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Research Article

Climate Change, Pollution and Related Effect in Some Neurological Condition like Autism Spectrum Disorders and Related Pathology. A Sociological Neuro Toxicological Analisys: State Of Evidence

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Abstract

Aim of this research work is to verify the influence on some environmental factors in some neuro-developmental phases and the effect related a reverse of the increase of concentration of some toxic movens.

Keywords: Climate Change , Pollution , Toxicology, Neurology , Neruscience , Autism , Environmental Factors

Introduction

Many article and research investigated the role played by some toxicological movens in autistic spectrum disorder and this can be easily obtained using PUBMED or other biomedical database.

In this kind of disorder the environmental factor are investigated like genetic or other endogenous factor.

Environmental pollution related also to climate change produce an unbalance in some air composition.

The neurotoxicology of some level of molecules like : co2, co ,NO , NO2 , O3, SO2 and other in the air is

Currently studied by all world toxicologist.

An analysis of what happen in last centuries by human factor in increase air pollution can be interesting

To correctly set our future (Figures 1-4).

According NATIONAL GEOGRAFIC: "Air pollution is a mix of particles and gases that can reach harmful concentrations both outside and indoors. Its effects can range from higher disease risks to rising temperatures. Soot, smoke, mold, pollen, methane, and carbon dioxide are a just few examples of common pollutants.

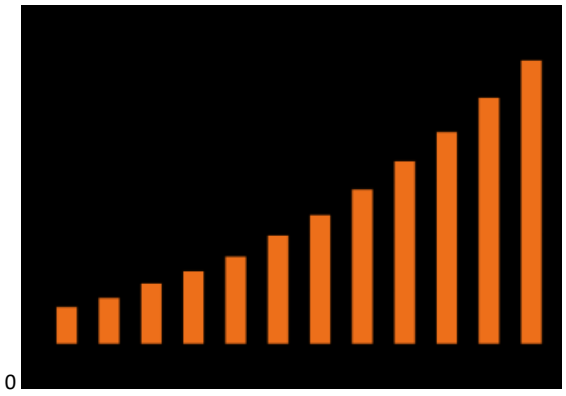


Figure 1: Reports of autism cases per 1,000 children grew dramatically in the U.S. from 1996 to 2007

In the U.S., one measure of outdoor air pollution is the Air Quality Index, or AQI which rates air conditions across the country based on concentrations of five major pollutants: ground-level ozone, particle pollution (or particulate matter), carbon monoxide, sulfur dioxide, and nitrogen dioxide. Some of those also contribute to indoor air pollution, along with radon, cigarette smoke, volatile organic compounds (VOCs), formaldehyde, asbestos, and other substances. Humans have pumped enough carbon dioxide into the atmosphere over the past 150 years to raise its levels higher than they have been for hundreds of thousands of years

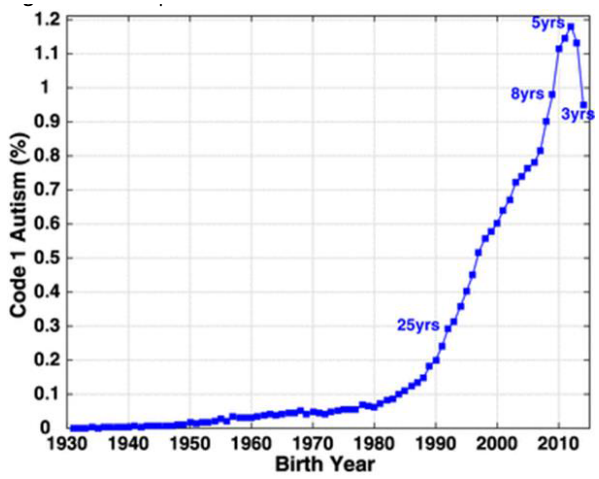


Figure :2 autism prevalence in California.

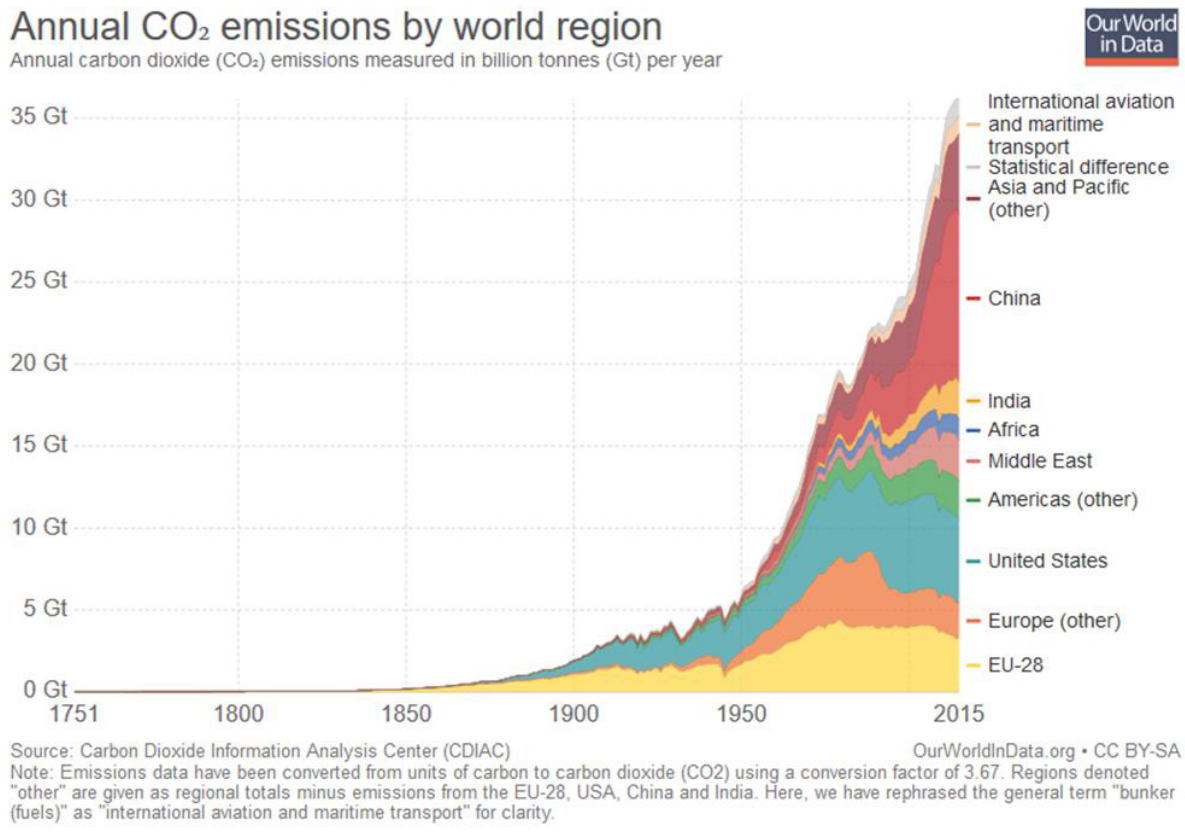
Other greenhouse gases include methane —which comes from such sources as landfills, the natural gas industry, and gas emitted by livestock—and chlorofluorocarbons (CFCs), which were used in refrigerants and aerosol propellants until they were banned in the late 1980s because of their deteriorating effect on Earth's ozone layer. Another pollutant associated with climate change is sulfur dioxide, a component of smog. Sulfur dioxide and closely related chemicals are known primarily as a cause of acid rain. But they also reflect light when released in the atmosphere, which keeps sunlight out and creates a cooling effect. Volcanic eruptions can spew massive amounts of sulfur dioxide into the atmosphere, sometimes causing cooling that lasts for years." https://www.nationalgeographic.com/environment/global-warming/pollution/ (Figures 4-8).

Material and Methods

Whit an observational methods some relevant scientific literature is evaluated in order to produce a global

Conclusion related also to the experimental project hypothesis.

All the reference are in scientific database like PUBMED.



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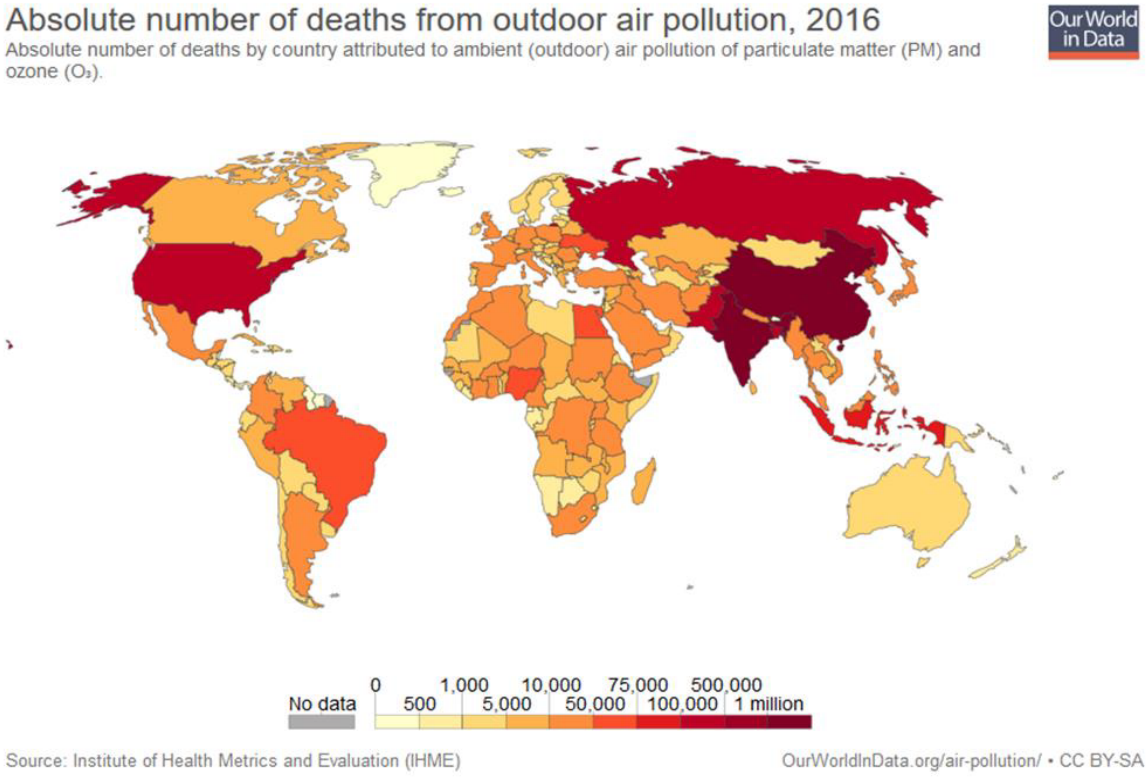

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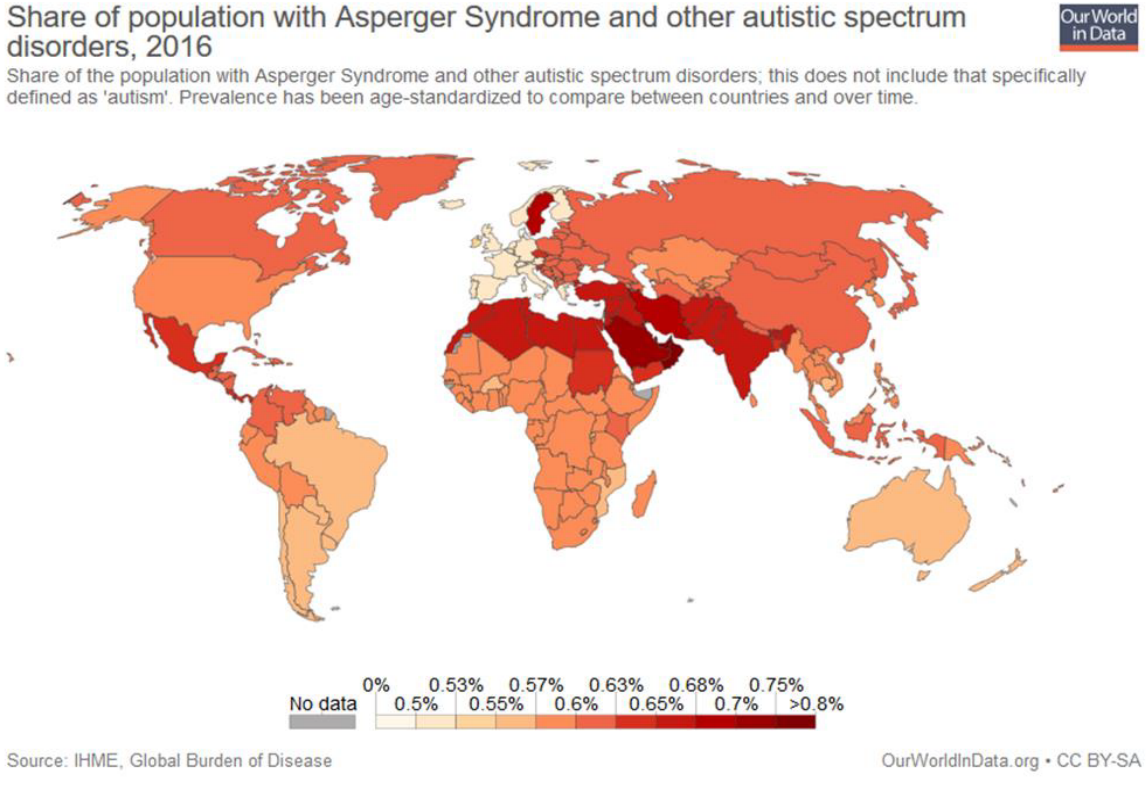

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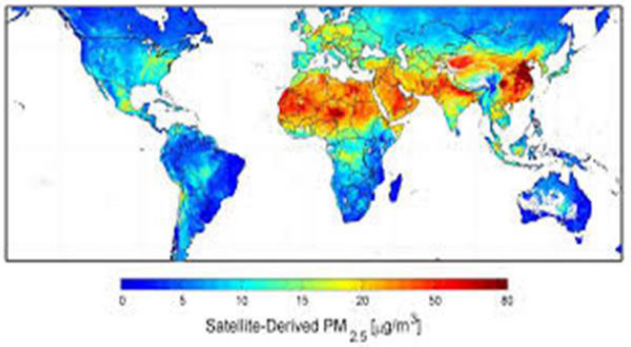

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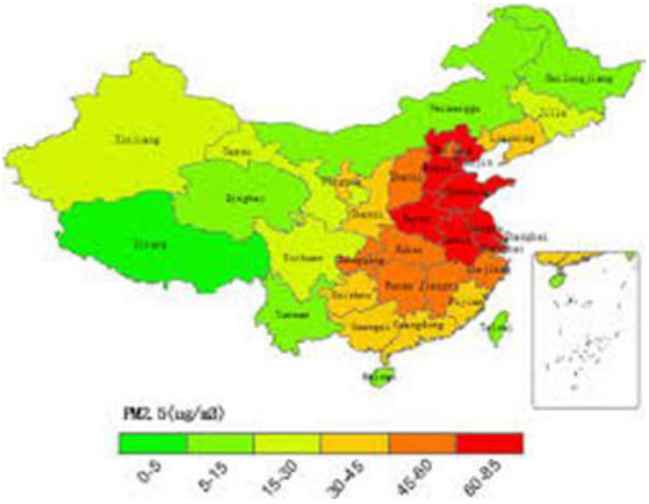

Figure 7: CHINA PM 2,5 POLLUTION.

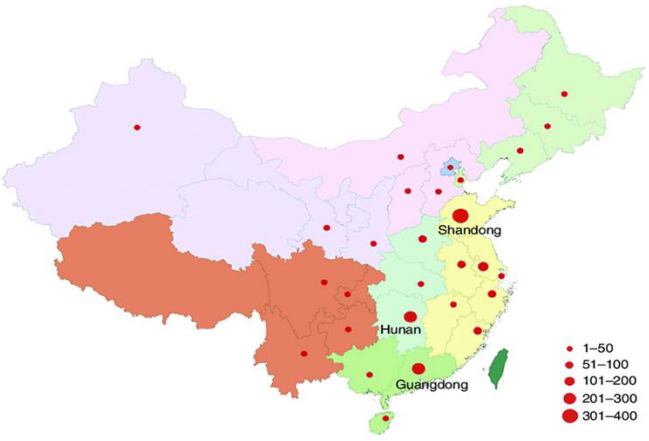

Figure 8 : CHINA BIRTHPLACE DISTRIBUTION OF ASD.

Results

From literature

Am J Epidemiol. 2018 Apr 1;187(4):717-725. doi: 10.1093/aje/kwx294.

Traffic-Related Air Pollution and Autism Spectrum Disorder: A Population-Based Nested Case-Control Study in Israel.

Raz R1, Levine H1, Pinto O2, Broday DM3, Yuval3, Weisskopf MG4.

"Accumulating evidence suggests that perinatal air pollutant exposures are associated with increased risk of autism spectrum disorder (ASD), but evidence for traffic pollutants outside the United States is inconclusive. We assessed the association between nitrogen- dioxide, a traffic pollution tracer, and risk of ASD. We conducted a nested case-control study among the entire population of children born during 2005-2009 in the central coastal area of Israel. Cases were identified through the National Insurance Institute of Israel (n = 2,098). Controls were a 20% random sample of the remaining children (n = 54,191). Exposure was based on an optimized dispersion model. We estimated adjusted odds ratios and 95% confidence intervals using logistic regression and a distributed-lag model. In models mutually adjusted for the 2 periods, the odds ratio per 5.85-parts per billion (ppb) increment of nitrogen dioxide exposure during pregnancy (median, 16.8 ppb; range, 7.5-31.2 ppb) was 0.77 (95% confidence interval: 0.59, 1.00), and the odds ratio for exposure during the 9 months after birth was 1.40 (95% confidence interval: 1.09, 1.80). A distributed-lag model revealed reduced risk around week 13 of pregnancy and elevated risk around week 26 after birth. These findings suggest that post-natal exposure to nitrogen dioxide in Israel is associated with increased odds of ASD, and prenatal exposure with lower odds. The latter may relate to selection effects [1].

Pagalan L et al

The etiology of ASD is poorly understood, but prior studies suggest associations with airborne pollutants.

Objective

To evaluate the association between prenatal exposures to airborne pollutants and ASD in a large population-based cohort.

This population-based cohort encompassed nearly all births in Metro Vancouver, British Columbia, Canada, from 2004 through 2009, with follow-up through 2014. Children were diagnosed with ASD using a standardized assessment with the Autism Diagnostic Interview-Revised and Autism Diagnostic Observation Schedule. Monthly mean exposures to particulate matter with a diameter less than 2.5 μm (PM2.5), NO, NO2 at the maternal residence during pregnancy were estimated with temporally adjusted, high-resolution land use regression models. The association between prenatal air pollution exposures and the odds of developing ASD was evaluated using logistic regression adjusted for child sex, birth month, birth year, maternal age, maternal birthplace, and neighborhood-level urbanicity and income band. Data analysis occurred from June 2016 to May 2018

In a population-based birth cohort, we detected an association between exposure to NO and ASD but no significant association with PM2.5 and NO2 [2].

Marc G. Weisskopf et al

"The direction and magnitude of the association between perinatal air pollution exposures and risk of ASD has been relatively consistent across several studies in different settings.

SES and residence-related factors are the elements most likely to confound this association, and they can be difficult potential confounders to completely capture and rule out. 2 of the most recent studies of air pollution and ASD, found associations specific to the 3rd trimester of pregnancy, with null associations for the 1st trimester when both were estimated simultaneously. This exposure-window specificity of findings is an important new contribution and implies that uncontrolled confounding by exposures that do not vary over the time frame examined—such as SES and residence-related factors—cannot account for the estimate seen with 3rd trimester exposure. Given the largely consistent results across the many studies that have explored aspects of air pollution and ASD, the new findings of exposure-window-specific effects suggest either that time-invariant confounding is not as problematic as we might think, or that studies have done a reasonable job of accounting for them. the use of ambient concentrations rather than personal exposure measures also helps avoid confounding by behavioral differences that could impact personal exposure levels. Thus, while questions still remain about which specific component of air pollution (although there could be several) is the most relevant, we believe the overall evidence for a causal association between exposure to air pollution and risk of ASD is increasingly compelling [3].

Lucio G. Costa et

"While several chemicals present in the environment or in the diet have been considered and studied for potential developmental neurotoxicity, little had been done until recently in this regard for chemicals present in the air. Yet, the air we breathe seems a logical potential source of exposure for chemicals which may exert neurotoxicity or developmental neurotoxicity. Though attention has been limited for several decades only to effects on the respiratory system, and more recently on the cardiovascular system, evidence has been accumulating during the past several years providing strong support to the notion that exposure to high levels of air pollution, very common in many cities all around the world, is associated with damage to the CNS. Human and animal studies have evidenced a series of common adverse effects of air pollution (particularly traffic-related), with oxidative stress and neuro-inflammation emerging as the hallmark biochemical effects, and clinical manifestations which included a variety of behavioral alterations.

As the developing nervous system is particularly sensitive to toxic insult , the issue of developmental neurotoxicity of air pollution is especially relevant. Particularly troublesome is the suggestion that air pollution may contribute to the etiopathology of neuro-developmental diseases whose incidence seems to be increasing in the global populations. This review has focused on ASD, which have been the most studied in this regard, but other disorders such as early onset schizophrenia, or attention deficit hyperactivity disorder, also need to be considered. Measures to decrease emissions leading to poor air quality are the obvious first choice to pursue in order to protect human health. However, further studies aimed at better characterizing the effects of air pollution on the CNS, its underlying mechanisms, and its role in the etiology of neuro-developmental diseases are certainly warranted. In particular, the possibility that sexes may be differentially affected by air pollution, with males being more susceptible, needs to be further investigated, in light of the higher incidence of neuro-developmental disorders (e.g. ASD) in males . In addition, gene-environment interactions still need to be investigated in the context of exposure to high air pollution and effects on the CNS, as developmental abnormalities are likely to be manifest only or especially in susceptible individuals. In this respect, there is the need for experimental studies utilizing transgenic animal models of certain neuro-developmental disorders (e.g. the reelin heterozygote mouse for ASD) or other transgenic animals addressing specific mechanistic hypotheses (e.g. the Gclm+/− mouse). Markers of genetic susceptibility should also be incorporated in human epidemiological studies, something that has been missing so far. Last but not least, these studies should provide important novel information for therapeutic interventions involving for examples, anti-inflammatory and/or anti-oxidant compounds, drugs that inhibit microglia activation, or others that facilitate GABAergic neurotransmission [4].

Padideh Karimi et al

"Currently, epigenetic and its complex mechanisms are presented as the most momentous mediator in the environment and genome interactions. Environmental factors can affect the quality and quantity of gene expression without changing the DNA sequence through epigenetic mechanisms, including DNA methylation, changes in histone proteins, and expression of noncoding RNAs. This way, they can be transferred to the next cellular generation or even the next organism generation. As a result, exposure to harmful environmental factors can change the expression of developmental key genes in critical periods of embryo formation and increases the risk of genomic imprinting diseases such as autism.

None of the environmental factors is sufficient to yield autism, but rather a collection of them can be involved in the incidence of autism

Autism is a multifactorial neuro-developmental disorder which is caused by genetic and environmental factors. The prevalence of autism has been increased over the last decades. About every disorder, prevention is more important than cure. Among the risk factors of autism, environmental ones attracted the attention of most of the scientists because prevention is possible by avoiding from them.

There are a lot of environmental risk factors which influence autism pathogenesis by their epigenetic effects. These factors are divided into three categories, included prenatal, natal, and postnatal risk factors. Each category allocates to the specific period of neonate development. A collection of these factors is involved in the pathogenesis of autism [5].

Frederica P. Perera

"Data are more limited for neuro-developmental effects than for birth outcomes and respiratory illness. However, air pollutants have been linked to an array of neuro-developmental disorders in children. For example, in our cohort studies in New York City and Krakow, Poland, prenatal exposure to PAHs was associated with developmental delay, reduced IQ, symptoms of anxiety, depression, and inattention, ADHD , and reductions in brain white matter surface in children . We observed significant interactions between prenatal PAH exposure and material hardship on IQ and between prenatal PAH exposure and maternal demoralization on behavioral problems . Research in Tongliang, China, found that, compared with a cohort born before the closure of a centrally

located coal power plant, a cohort conceived after plant closure had significantly lower cord blood levels of PAH–DNA adducts and higher levels of brain-derived neurotrophic factor (BDNF), a protein important in early brain development . A small study comparing school-age children in Mexico City with those in a less-polluted area of Mexico found that the cognitive deficits in highly exposed children matched the localization of the volumetric differences detected in the brain . Other studies have linked roadway proximity or traffic particles to decreased cognitive function .Early-life exposures to traffic-related pollution, $PM_{2.5}$, PAHs, and O_3 are associated with a multiplicity of effects on the developing fetus and child, which can have long-term consequences for child healthThere is some emerging evidence that prenatal exposure to traffic-related air pollutants and $PM_{2.5}$ may be a risk factor for ASD [6].

Yu-Chi Chang et

Escalating prevalence of ASD in recent decades has triggered increasing efforts in understanding roles played by environmental risk factors as a way to address this widespread public health concern. Several epidemiological studies show associations between developmental exposure to traffic-related air pollution and increased ASD risk. In rodent models, a limited number of studies have shown that developmental exposure to ambient ultrafine particulates or diesel exhaust (DE) can result in behavioral phenotypes consistent with mild ASD. We performed a series of experiments to determine whether developmental DE exposure induces ASD-related behaviors in mice.

C57Bl/6J mice were exposed from embryonic day 0 to postnatal day 21 to 250–300 $\mu g/m^3$ DE or filtered air (FA) as control. Mice exposed developmentally to DE exhibited deficits in all three of the hallmark categories of ASD behavior: reduced social interaction in the reciprocal interaction and social preference tests, increased repetitive behavior in the T-maze and marble-burying test, and reduced or altered communication as assessed by measuring isolation-induced ultrasonic vocalizations and responses to social odors.

These findings demonstrate that exposure to traffic-related air pollution, in particular that associated with diesel-fuel combustion, can cause ASD-related behavioral changes in mice, and raise concern about air pollution as a contributor to the onset of ASD in humans [7].

Richard J. Levy

"Prenatal low concentration CO exposure impacts rodent fetal growth and neuro-development

"A number of experimental studies in rodents have demonstrated that chronic prenatal CO exposure yielding up to 16% COHb results in impaired memory, learning, and behavior in offspring (De Salvia, 1995; Fechter, 1980; Giustino, 1999). Such investigations were designed to mimic fetal CO exposure encountered with maternal smoking during pregnancy as well as gestational exposure to industrial and ambient air pollution (De Salvia, 1995; Fechter, 1980; Giustino, 1999). As with cigarette smoking during pregnancy in humans, exposure to 150 ppm CO during gestation yielded maternal COHb levels of 15% and resulted in lower birth weight and reduced rates of growth in newborn rats (Fechter, 1980). Prenatal CO exposure also impaired behavior in these animals as assessed with negative geotaxis and homing tests (Fechter, 1980). Maternal inhalation of 75 or 150 ppm CO during gestation was shown to increase COHb in pregnant rat dams to levels that approximate those seen in cigarette smokers (means of 7.3% and 16.08%, respectively) and resulted in abnormal habituation and working memory in prenatally exposed juvenile male rats while sparing motor activity . exposure to 150 ppm CO during pregnancy (resulting in maternal COHb levels of 15%) led to impaired acquisition of a 2-way active avoidance task in male rats tested at 3 months of age (De Salvia, 1995). Importantly, this defect in learning and memory was permanent and persisted into late adulthood (De Salvia, 1995) [8].

Amy E. Kalkbrenner et al

"We included participants of a U.S. family-based study [the Autism Genetic Resource Exchange (AGRE)] who were born between 1994 and 2007 and had address information. We assessed associations between average annual concentrations at birth for each of 155 air toxics from the U.S. EPA emissions-based National-scale Air Toxics Assessment and *a*) ASD diagnosis (1,540 cases and 477 controls); *b*) a continuous measure of autism-related traits, the Social Responsiveness Scale (SRS, among 1,272 cases and controls); and *c*) a measure of autism severity, the Calibrated Severity Score (among 1,380 cases). In addition to the individual's air toxic level, mixed models (clustering on family) included the family mean air toxic level, birth year, and census covariates, with consideration of the false discovery rate.

ASD diagnosis was positively associated with propionaldehyde, methyl *tert*-butyl ether (MTBE), bromoform, 1,4-dioxane, dibenzofurans, and glycol ethers and was inversely associated with 1,4-dichlorobenzene, 4,4′-methylene diphenyl diisocyanate (MDI), benzidine, and ethyl carbamate (urethane). These associations were robust to adjustment in 2-pollutant models. Autism severity was associated positively with carbon disulfide and chlorobenzene, and negatively with 1,4-dichlorobenzene. There were no associations with the SRS.

Some air toxics were associated with ASD risk and severity, including some traffic-related air pollutants and newly-reported associations, but other previously reported associations with metals and volatile organic compounds were not reproducible [9].

Adel Ghorani-Azam et al

"Air pollutants and their toxicities

Every material in the air which could affect human health or have a profound impact on the environment is defined as air pollutants. According to the World Health Organization (WHO), particle pollution, ground-level O3, CO, sulfur oxides, nitrogen oxides, and lead (Pb) are the six major air pollutants which harm human health and also the ecosystem. There are many pollutants of suspended materials such as dust, fumes, smokes, mists, gaseous pollutants, hydrocarbons, volatile organic compounds (VOCs), polycyclic aromatic hydrocarbons (PAHs), and halogen derivatives in the air which at the high concentrations cause vulnerability to many diseases including different types of cancers.[29,30,31,32] The most important air pollutants and their toxic effects on different human body organs and related diseases have been briefly described below.Air pollution is a major concern of new civilized world, which has a serious toxicological

impact on human health and the environment. It has a number of different emission sources, but motor vehicles and industrial processes contribute the major part of air pollution. According to the World Health Organization, six major air pollutants include particle pollution, ground-level ozone, carbon monoxide, sulfur oxides, nitrogen oxides, and lead. Long and short term exposure to air suspended toxicants has a different toxicological impact on human including respiratory and cardiovascular diseases, neuropsychiatric complications, the eyes irritation, skin diseases, and long-term chronic diseases such as cancer. Several reports have revealed the direct association between exposure to the poor air quality and increasing rate of morbidity and mortality mostly due to cardiovascular and respiratory diseases. Air pollution is considered as the major environmental risk factor in the incidence and progression of some diseases such as asthma, lung cancer, ventricular hypertrophy, Alzheimer's and Parkinson's diseases, psychological complications, autism, retinopathy, fetal growth, and low birth weight. There are some proven data which highlighted the role of air pollutants, especially traffic-related air pollution on the incidence of autism and its related disorders in fetus and children [10].

Mental Disorders and Disabilities Among Low-Income Children.

Prevalence of Autism Spectrum Disorder

"A notable pattern observed in both the SSI data and the special education service utilization data is the increase in the frequency of ASD and the concurrent decrease in the frequency of ID over the time period from 2004 to 2013 . These patterns could be explained in part by diagnostic substitution . Special education service use data and SSI data might be particularly sensitive to diagnostic substitution because both are benefit programs that generally require a diagnosis as a prerequisite for benefit or for service eligibility. The data presented here do not provide additional evidence to support a conclusion that diagnostic substitution is, a cause of the observed trends, but the trends observed in the SSI program are consistent with the possibility that there are children with developmental-cognitive-social impairments who were previously eligible for services or benefits on the basis of a diagnosis of ID or MR but who are more recently deemed eligible on the basis of a diagnosis of ASD [11].

Gillberg C et al

"The objective of this study was to establish rates of diagnosed ASDs in a circumscribed geographical region. The total population born in 1977-94, living in Göteborg in 2001, was screened for ASD in registers of the Child Neuropsychiatry Clinic. The minimum registered rate of autistic disorder was 20.5 in 10,000. Other ASDs were 32.9 in 10,000, including 9.2 in 10,000 with Asperger syndrome. Males predominated. In the youngest group (7-12 years), 1.23% had a registered diagnosis of ASD. There was an increase in the rate of diagnosed registered ASD over time; the cause was not determined. The increase tended to level off in the younger age cohort, perhaps due to Asperger syndrome cases missed in screening [12].

Fombonne E

"There is some uncertainty about the rate and correlates of autism.

About 23 epidemiological surveys of autism published in the English language between 1966 -98 were reviewed.

Over 4 million subjects were surveyed; 1533 subjects with autism were identified. The methodological characteristics of each study are summarized, including case definition, case-finding procedures, participation rates and precision achieved. the median prevalence estimate was 5.2/10000. Half the surveys had 95% confidence intervals consistent with population estimates of 5.4-5.5/10000. Prevalence rates significantly increased with publication year, reflecting changes in case definition and improved recognition; the median rate was 7.2/10 000 for 11 surveys conducted since 1989. The average male/female ratio was 3.8:1, varying according to the absence or presence of mental retardation. Intellectual functioning within the normal range was reported in about 20% of subjects. On average, medical conditions of potential causal significance were found in 6% of subjects with autism, with tuberous sclerosis having a consistently strong association with autism. Social class and immigrant status did not appear to be associated with autism. There was no evidence for a secular increase in the incidence of autism. In 8 surveys, rates for other forms of pervasive developmental disorders were 2 to 3 times higher than the rate for autism [13].

Chau-Ren Jung et al

"There is limited evidence that long-term exposure to ambient air pollution increases the risk of childhood ASD. The objective of the study was to investigate the associations between long-term exposure to air pollution and newly diagnostic ASD in Taiwan. We conducted a population-based cohort of 49,073 children age less than 3 years in 2000 that were retrieved from Taiwan National Insurance Research Database and followed up from 2000 through 2010. Inverse distance weighting method was used to form exposure parameter for ozone (O3), carbon monoxide (CO), nitrogen dioxide (NO2), sulfur dioxide (SO2), and particles with aerodynamic diameter less than 10 μm (PM10). Time-dependent Cox proportional hazards (PH) model was performed to evaluate the relationship between yearly average exposure air pollutants of preceding years and newly diagnostic ASD. The risk of newly diagnostic ASD increased according to increasing O3, CO, NO2, and SO2 levels. The effect estimate indicating an approximately 59% risk increase per 10 ppb increase in O3 level (95% CI 1.42–1.79), 37% risk increase per 10 ppb in CO (95% CI 1.31–1.44), 340% risk increase per 10 ppb increase in NO2 level (95% CI 3.31–5.85), and 17% risk increase per 1 ppb in SO2 level (95% CI 1.09–1.27) was stable with different combinations of air pollutants in the multi-pollutant models. Our results provide evident that children exposure to O3, CO, NO2, and SO2 in the preceding 1 year to 4 years may increase the risk of ASD diagnosis.

Exposure assessment

CO, NO, SO2 and PM10 monthly average data and Ozone monthly average of daily maximum value were obtained from 70 Taiwan Environmental Protection Agency (EPA) monitoring station on Taiwan's main island. All of these air pollutants measured hourly—CO by nondispersive infrared absorption, NO2 by chemiluminescence, O3 by ultraviolet absorption, SO2 by ultraviolet fluorescence, and PM10 by beta-gauge—and continuously.

The locations of the monitoring stations and air pollution

sources were identified and managed by geographic information system (GIS) . The monitoring data were integrated into yearly point data and interpolated to pollutant surfaces using inverse distance weighting method (IDW). For the IDW approach, we used suitable spatial resolution (100 m) and inverse squared distance (1/squared distance) weighted average of the three nearest monitors within 25 km to compute yearly mean concentration. the yearly air pollution data were assigned to individuals by post-code levels. The postal code typically corresponded to one block face in urban areas (mean±SD: 17±8.56 square kilometer) but was larger in rural areas (mean±SD: 154±104.39 square kilometer) with low population density. We averaged exposure to CO, NO2, O3, PM10, and SO2 over several years before newly diagnostic ASD: preceding 1 year, 2 years, 3 years, and 4 years.The risk of newly diagnostic ASD increased according to increasing O3, CO, NO2, and SO2 levels. The effect estimate indicating an approximately 59% risk increase per 10-ppb increase in O3 level, 37% risk increase per 10-ppb in CO, 343% risk increase per 10-ppb increase in NO2 level, and 18% risk increase per 1-ppb in SO2 level was stable with different combinations of air pollutants in the 2-pollutant models. The results provide evidence that children exposure to O3, CO, NO2, and SO2 in the preceding 1 year to 4 years may increase the risk of newly diagnostic ASD. A negative or weak association between the risk of newly diagnostic ASD and PM10 was found In conclusion, the present study found a statistically significant association between O3, CO, and NO2 exposure and newly diagnostic ASD with an exposure-response pattern. Our finding suggests that improve ambient air quality, especially in traffic-related air pollutants and O3, might decrease the risk of newly diagnostic ASD [14].

Volk HE et al

"Independent studies report association of autism spectrum disorder with air pollution exposure and a functional promoter variant (rs1858830) in the MET receptor tyrosine kinase (MET) gene. The Toxicological data find altered brain Met expression in mice after prenatal exposure to a model air pollutant. Our objective was to investigate whether air pollution exposure and MET rs1858830 genotype interact to alter the risk of autism spectrum disorder.

We studied about 252 cases of autism spectrum disorder and 156 typically developing controls from the Childhood Autism Risk from Genetics and the Environment Study. Air pollution exposure was assigned for local traffic related sources and regional sources (particulate matter, nitrogen dioxide, and ozone). MET genotype was determined by a direct resequencing.

Subjects with both MET rs1858830 CC genotype and high air pollutant exposures were at increased risk of autism spectrum disorder compared with subjects who had both the CG/GG genotypes and lower air pollutant exposures. There was evidence of multiplicative interaction between NO2 and MET CC genotype (P= 0.03) [15].

V. A. Otellin et al

"The responses of forming synapses in the rat neocortex to the actions of hypoxia in the early period of neonatal life (day 2) were studied. Immunocytochemical studies were used to detect synaptophysin and these results, along with electron microscopic studies, addressed the sensorimotor cortex in rat pups at 3, 5, and 10 days of postnatal development (using groups of 6–10 individuals) in an experimental group and a control group (intact animals). Immunocytochemical studies of control animal showed significant differences in the quantitative distribution of synaptophysin-positive structures in different layers of the neocortex during the early neonatal period of development (day 5). Perinatal hypoxia decreased the optical density of the immunocytochemical reaction product more than twofold, and this was accompanied by reductions in the density of synaptophysin-positive granules in all layers of the neocortex. electron-dense terminals, providing evidence of degenerative processes, were seen. The neuropil of the neocortex showed a sharp decrease in the number of growth cones, small processes, and forming synapses, along with a significant increase in the electron density of synaptic elements, especially postsynaptic membranes and densities. In experimental animals, increases in the numbers of growth cones and forming synaptic structures were seen only by postnatal day 10. Thus, the consequences of hypoxia during the early neonatal period, inducing impairments to synaptogenesis, persisted throughout the study period.

Experiments were performed using 2 groups of rats: group 1 consisted of animals subjected to hypoxia in a barochamber (experimental group); group 2 consisted of intact animals of the same age (control group). Animals were exposed to hypoxia on day 2 of postnatal development using a baro-chamber fitted with an automatic heater, a gas mix exchanger, and a gas flowmeter. The nitrogen-containing gas mix was prepared using a gas analyzer/exchanger . Experimental animals were placed in the barochamber for 1 h. During experiments, the oxygen level in the baro-chamber was 7.6–7.8%, the carbon dioxide concentration was 0.15–0.20%,and the nitrogen concentration was 91.8% at T = 21.3–23°C and normal total pressure. All procedures were performed in compliance with the "Regulations for Studies Using Experimental Animals. Results Immunocytochemical reactions for synaptophysin showed that on day 3 of postnatal development, layer I of the sensorimotor cortex in intact animals showed a high reaction product OD (0.154 ± 0.015), with lower levels in layers II–III. Immunopositive granules were located singly or in small groups of 2–6 granules on rare processes both in the neuropil and the plasmalemma of the bodies of isolated neurons. In the deep layers (V–VI) of the neocortex, synaptophysin reaction product OD increased sharply compared with that in layers II–III and was essentially identical in these layers, though it was slightly greater than the OD in layer I (0.176 ± 0.011). Numerous groupings of immunopositive granules were seen in the neuropil and on the plasmalemma of neuron bodies. On day 3 of postnatal development (1 day after hypoxia), experimental animals showed a lower synaptophysin reaction product OD in almost all layers of the neocortex than controls [16].

Raanan Raz et al

"Higher maternal exposure to PM2.5 during pregnancy, particularly the third trimester, was associated with greater odds of a child having ASD [17].

Heather E. Volk et al

"To examine the relationship between traffic-related air pollution (TRP), air quality, and autism.

This study includes data on 279 autism cases and 245

typically developing controls enrolled in the Childhood Autism Risks from Genetics and the Environment (CHARGE) Study in California. The mother's address from the birth certificate and addresses reported from a residential history questionnaire were used to estimate exposure for each trimester of pregnancy and first year of life. TRP was assigned to each location using a line-source air-quality dispersion model. Regional air- pollutant measures were based on the Environmental Protection Agency's Air Quality System data. Logistic- regression models compared estimated and measured pollutant levels for autism cases and typically developing controls Exposure to TRP, NO2, PM2.5, and PM10 during pregnancy and the first year of life was associated with autism [18].

Jung CR et al

"There is limited evidence that long-term exposure to ambient air pollution increases the risk of childhood ASD. The objective of the study was to investigate the associations between long-term exposure to air pollution and newly diagnostic ASD in Taiwan. We conducted a population-based cohort of 49,073 children age less than 3 years in 2000 that were retrieved from Taiwan National Insurance Research Database and followed up from 2000 through 2010. Inverse distance weighting method was used to form exposure parameter for ozone , carbon monoxide , nitrogen dioxide sulfur dioxide , and particles with aerodynamic diameter less than 10 μm (PM10). Time-dependent Cox proportional hazards (PH) model was performed to evaluate the relationship between yearly average exposure air pollutants of preceding years and newly diagnostic ASD. The risk of newly diagnostic ASD increased according to increasing O3, CO, NO2, and SO2 levels. The effect estimate indicating an approximately 59% risk increase per 10 ppb increase in O3 level (95% CI 1.42–1.79), 37% risk increase per 100 ppb in CO (95% CI 1.31–1.44), 340% risk increase per 10 ppb increase in NO2 level (95% CI 3.31–5.85), and 17% risk increase per 1 ppb in SO2 level (95% CI 1.09–1.27) was stable with different combinations of air pollutants in the multi-pollutant models. Our results provide evident that children exposure to O3, CO, NO2, and SO2 in the preceding 1 year to 4 years may increase the risk of ASD diagnosis [19].

Amy E. Kalkbrenner et al

"Results for the included studies showed elevated associations between autism and measures of mixed air pollutant exposures and diesel particulate matter and for the individual air pollutants PM2.5, PM10, and NO2, with less consistently elevated associations for NO, ozone, and CO . The size of the ORs was not consistent across studies, despite the standardized comparison of air pollutant concentrations that we calculated, for example, ORs were around 1.5 per 10 ppb increase in NO2 for the California CHARGE study , but only 1.04 for the California Department of Developmental Services study .Reasons for this different size in impact could reflect air pollutant differences between California regions, a greater degree of exposure measurement error in the DDS study, or that this research study adjusted for a possible mediating factor, gestational age, which did result in the attenuation of ORs for some air pollutants. For almost every pollutant and every study, associations were stronger for exposures in the 3rd- trimester of pregnancy and the 1st year of life compared to in earlier pregnancy Increasingly, studies that examine exposures by developmental time period suggest that all windows are not equal. Although evidence for a discrete developmental window of susceptibility for autism is in its early stages, results shown here suggest that early pregnancy may be a period of susceptibility to pesticides, whereas later pregnancy may be a period of susceptibility to criteria air pollutants. Different critical windows for different exposures is not unexpected given the various biological activities of environmental chemicals and the many, interwoven events of neuro-development, taking place during pregnancy and postnatal life, which, if disrupted, could manifest in autism symptoms Genetic Susceptibilities

It is likely that the autism risk associated with a given xenobiotic exposure will differ based on the child's genes or the mother's genes. Genetic poly-morphisms of possible relevance include those encoding proteins involved in the metabolism or biological activation of the xenobiotic, genes allowing improved resiliency to neuro-developmental damages, or genes that confer some degree of autism risk that, when combined with xeno-biotic damage, result in autism. Some examples of research in this area include a study demonstrating interaction between traffic-related air pollutants and a functional variant of the Met receptor tyrosine kinase (MET) gene with regard to autism risk,163 and a study finding no interaction between OP pesticide exposure and polymorphisms in the gene encoding the detoxifying enzyme, para-oxonase 1 (PON1) with autism risk.164 [20].

Norrice M Liu et. Al

Components of air pollution

"The major outdoor pollutants in urban areas are inhalable particulate matter (PM, measured as either PM less than 10 μm in aerodynamic diameter (PM10) or the even smaller PM2.5), nitrogen oxides (NOX, such as nitrogen dioxide, NO2), ozone , sulfur dioxide , carbon monoxide and hydrocarbons (HC). Sources of these include gasoline-powered and diesel-powered engines from vehicles, trains and, in port towns, ships (proximately PM, NOX), vehicle tyre and brake wear (PM), power stations and factories from coal combustion and biomass burning (PM, NOX and SO2), and wood burning heating that is increasingly popular, contributing up to 9% of PM in London during winter. For diesel motor engines, an important component of emissions is black carbon, that is, the fraction of PM that most strongly absorbs light—a component that is often called 'diesel soot'. Another pollutant, ozone, is formed by the reaction of NOX with carbon compounds called volatile organic compounds (VOCs) in the presence of sunlight. 2 of the most important VOCs emitted by vehicles are benzene and 1,3-butadiene. For emissions from diesel, there is a strong correlation between locally emitted PM10 and NOX,11 and it is reasonable to assume that, where diesel vehicles predominate, either metric is a good marker of exposure to the locally generated pollutant mix in urban areas There is emerging evidence that air pollution impacts on children's neurological system and development. associations between exposure to air pollutants and reduced IQ and neurocognitive ability such as working memory, autism and reduced brain-derived neurotrophic factor are widely reported [21].

Nelly D. Saenen et al

"Placental expression of BDNF and SYN1, 2 genes implicated in normal neuro-developmental trajectories, decreased with increasing in utero exposure to PM2.5. Future research studies

are needed to confirm our findings and evaluate the potential relevance of associations between PM2.5 and placental expression of BDNF and SYN1 on neuro-development. We provide the first molecular epidemiological evidence concerning associations between in utero fine particle air pollution exposure and the expression of genes that may influence - processes [22].

Lorna Wing

"For decades after Kanner's original paper on the subject was published in 1943, autism was generally considered to be a rare condition with a prevalence of around 2–4 per 10,000 children. Research studies carried out in the late 1990s and the present century reported annual rises in incidence of autism in pre-school children, based on age of diagnosis, and increases in the age-specific prevalence rates in children. Prevalence rates of up to 60 per 10,000 for autism and even more for the whole autistic spectrum were reported. Reasons for these increases are discussed. They include changes in diagnostic criteria, development of the concept of the wide autistic spectrum, different methods used in studies, growing awareness and knowledge among parents and professional workers and the development of specialist services, as well as the possibility of a true increase in numbers. Various environmental causes for a genuine rise in incidence have been suggested, including the triple vaccine for measles, mumps and rubella (MMR]. Not one of the possible environmental causes, including MMR, has been confirmed by independent scientific investigation, whereas there is strong evidence that complex genetic factors play a major role in etiology. The evidence suggests that the majority, if not all, of the reported rise in incidence and prevalence is due to changes in diagnostic criteria and increasing awareness and recognition of autistic spectrum disorders. Whether there is also a genuine rise in incidence remains an open question [23].

MMWR Surveill Summ. 2012 Mar 30;61(3):1-19.

Prevalence of autism spectrum disorders--Autism and Developmental Disabilities Monitoring Network, 14 sites, United States, 2008.

" 2008, the overall- estimated prevalence of ASDs among the 14 ADDM sites was 11.3 per 1,000 (one in 88) children aged 8 years who were living in these communities during 2008. Overall ASD prevalence estimates varied widely across all sites (range: 4.8-21.2 per 1,000 children aged 8 years). ASD prevalence estimates also varied widely by sex and by racial/ethnic group. Approximately 1 in 54 boys and one in 252 girls living in the ADDM Network communities were identified as having ASDs. Comparison of 2008 findings with those for earlier surveillance years indicated an increase in estimated ASD prevalence of 23% when the 2008 data were compared with the data for 2006 (from 9.0 per 1,000 children aged 8 years in 2006 to 11.0 in 2008 for the 11 sites that provided data for both surveillance years) and an estimated increase of 78% when the 2008 data were compared with the data for 2002 (from 6.4 per 1,000 children aged 8 years in 2002 to 11.4 in 2008 for the 13 sites that provided data for both surveillance years). Because the ADDM Network sites do not make up a nationally represent [24].

Catherine E. Rice et al

"Starting in the 1990s, the U.S. Department of Education's Office of Special Education and the California Department of Developmental Services (CA DDS) documented increases in the need for autism services. There is an annual count of children enrolled in special education services as an accountability measure required by the 1990 Individuals with Disabilities Education Act (IDEA) based on select eligibility categories for each state. Autism was not initially a category within the child count, but states were required to report autism beginning in 1991. The number of children classified as having autism and receiving special education services has increased since the early 1990s. the total numbers are still fewer than would be expected given current prevalence estimates. A special education label does not always match the medical diagnosis that a child may have to describe developmental challenges, and enrollment counts might not have provided a true prevalence of ASD as the special education system never was intended to serve a public- health surveillance role. These data are more useful in understanding variation in state-level special education criteria and services and examining barriers to timely identification

The CA DDS- administrative data have been used to evaluate trends among children receiving services for ASD, mainly those meeting criteria for autistic disorder.The CA DDS tracks service provision for five conditions (autism, epilepsy, cerebral palsy, intellectual disability, and intellectual disability-related conditions) across 21 regional centers. Data collection is passive in that a child must be brought to a CA DDS center and a parent or guardian must request an evaluation to determine if they meet eligibility criteria. Comparing births in 1990 with those in 2001 (followed to age ten), the cumulative- incidence of autism in the CA DDS rose 600 percent. There was substantial variability among the centers. About 200 percent of this increase could be explained by trends toward younger age at diagnosis, inclusion of more mild cases, changes in diagnostic criteria, and older ages of mothers. It has been estimated that about 50 percent of administrative autism prevalence increases in the CA DDS data could be explained by several identification factors, such as diagnostic changes in the use of intellectual disability (mental retardation), earlier age of diagnosis, social influence of people sharing information on ASDs; and potential risk indicators, like closely-spaced pregnancies and increasing parental age. A recent study indicates that these trends are due to factors that have changed in a linear fashion, aggregate among birth cohorts, and dis-proportionately impact more mild forms of ASD. At this point, changes over time related to diagnostic criteria, methods for ascertainment and some risk factors appear to explain part, but not all, of the increase in autism cumulative incidence in the CA DDS system. more complex methods are needed to evaluate the overlapping relationships between the different and yet unstudied factors as they relate to ASD prevalence changes [25].

William J. Barbaresi et al

"We first compiled a list of all developmental, psychiatric or neurologic diagnoses (n=80) ever applied to a group of 182 children with autistic disorder or pervasive developmental disorder, not otherwise specified, consistent with DSM-IV criteria, evaluated at Mayo Clinic from 1994 to 1998 . In addition to ASD, other common diagnoses included mental retardation, developmental delay, and language disorders. We reviewed the medical- records of these 182 subjects, transcribing every reference to symptoms of autism, and created a 20-page glossary

of phrases (our screening tool) consistent with the symptoms of autistic disorder as specified in DSM-IV.

We found the incidence of research-identified autism increased 8.2 fold, from 5.5 per 100,000 in 1980–1983 to 44.9 per 100,000 in 1995–1997. In the current study, we examined the incidence of clinical diagnoses of ASD in the same population, during the same years. We found that the incidence of clinical -diagnoses in the autism spectrum increased 22.1 fold, from 1.5 per 100,000 in 1980–1983 to 33.1 per 100,000 in 1995–1997. Thus, had we relied solely on clinical diagnoses, we would have reported lower incidence rates from 1976–1997. the apparent, relative increase in the incidence of autism would have been exaggerated (22.1 fold for clinical diagnoses versus 8.2 fold for research identified cases") [26].

Ondine S von Ehrenstein et al

"Autism risks were increased per interquartile-range increase in average concentrations during pregnancy of several correlated toxics mostly loading on one factor, including 1,3-butadiene (OR=1.59 [95% confidence interval=1.18–2.15]), meta/ para-xylene (1.51 [1.26–182]), other aromatic solvents, lead (1.49 [1.23–1.81]), perchloroethylene (1.40 [1.09–1.80]), and formaldehyde (1.34 [1.17–1.52]), adjusting for maternal age, race/ethnicity, nativity, education, insurance type, maternal birth place, parity, child sex, and birth year.

Risks for autism in children may increase following in utero exposure to ambient air toxics from urban traffic and industry emissions, as measured by community-based air -monitoring stations [27].

D A Rossignol et al

"The 3th -study enrolled 7603 children with autism matched to 10 controls per autism case. This research study reported a 12–15% estimated increase in the risk of autism for each increase in the interquartile range of ozone (OR=1.12; 95% CI, 1.06–1.19) and particulate matter <2.5 μm (PM2.5) in aerodynamic diameter (OR=1.15; 95% CI, 1.06–1.24) while controlling for the effect of each pollutant on the other pollutants The 4 th study was population based and contained 279 children with ASD and 245 controls, and reported that residences with the highest quartile of traffic-related air pollution were associated with ASD during gestation (OR=1.98; 95% CI, 1.20–3.31), including estimated exposures to PM2.5 (OR=2.08; 95% CI, 1.93–2.25), particulate matter <10 μm (PM10) in aerodynamic diameter (OR=2.17; 95% CI, 1.49–3.16) and nitrogen dioxide (OR=1.81; 95% CI, 1.37–3.09).30 A 5 th study of 325 children with ASD and 22 101 controls reported that perinatal exposure to the highest versus lowest quintile of air pollutants was significantly associated with an increased risk of ASD, including pooled metals (OR=1.5; 95% CI, 1.3–1.7), mercury (OR=2.0; 95% CI, 1.2–3.3), lead (OR=1.6; 95% CI, 1.1–2.3), nickel (OR=1.7; 95% CI, 1.1–2.5), manganese (OR=1.5; 95% CI, 1.1–2.2), diesel particulate (OR=2.0; 95% CI, 1.0–4.0) and methylene chloride (OR=1.8; 95% CI, 1.2–2.7) [28].

Von Ehrenstein OS e t al

"To examine associations between early developmental exposure to ambient pesticides and autism spectrum disorder.

Population based case-control study

California's main agricultural region, Central Valley, using 1998-2010 birth data from the Office of Vital Statistics.

2961 individuals with a diagnosis of autism spectrum disorder based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, revised (up to 31 December 2013), including 445 with intellectual disability comorbidity, were identified through records maintained at the California Department of Developmental Services and linked to their birth records. Controls derived from birth records were matched to cases 10:1 by sex and birth year.

Data from California state mandated Pesticide Use Reporting were integrated into a geographic information system tool to estimate prenatal and infant exposures to pesticides (measured as pounds of pesticides applied per acre/month within 2000 m from the maternal residence). 11 high use pesticides were selected for examination a priori according to previous evidence of neuro-developmental toxicity in vivo or in vitro (exposure defined as ever v never for each pesticide during specific developmental periods).

Odds ratios and 95% confidence intervals using multivariable logistic regression were used to assess associations between pesticide exposure and autism spectrum disorder (with or without intellectual disabilities) in offspring, adjusting for confounders.

Risk of autism spectrum disorder was associated with prenatal exposure to glyphosate (odds ratio 1.16, 95% confidence interval 1.06 to 1.27), chlorpyrifos (1.13, 1.05 to 1.23), diazinon (1.11, 1.01 to 1.21), malathion (1.11, 1.01 to 1.22), avermectin (1.12, 1.04 to 1.22), and permethrin (1.10, 1.01 to 1.20). For autism spectrum disorder with intellectual disability, estimated odds ratios were higher (by about 30%) for prenatal exposure to glyphosate (1.33, 1.05 to 1.69), chlorpyrifos (1.27, 1.04 to 1.56), diazinon (1.41, 1.15 to 1.73), permethrin (1.46, 1.20 to 1.78), methyl bromide (1.33, 1.07 to 1.64), and myclobutanil (1.32, 1.09 to 1.60); exposure in the first year of life increased the odds for the disorder with comorbid intellectual disability by up to 50% for some pesticide- substances.

Findings suggest that an offspring's risk of autism spectrum disorder increases following prenatal -exposure to ambient pesticides within 2000 m of their mother's residence during pregnancy, compared with offspring of women from the same agricultural region without such exposure. Infant exposure could further increase risks for autism spectrum disorder with comorbid intellectual disability [29].

Kalkbrenner AE et al

"Previous studies have reported associations of perinatal exposure to air toxics, including some metals and volatile organic compounds, with ASD.

Our goal was to further explore associations of perinatal air toxics with ASD and associated quantitative traits in high-risk multiplex families

We included participants of a U.S. family-based study [the Autism Genetic Resource Exchange (AGRE)] who were born between 1994 and 2007 and had address information. We assessed associations between average annual concentrations at birth for each of 155 air toxics from the U.S. EPA emissions-based

National-scale Air Toxics Assessment and a) ASD diagnosis (1,540 cases and 477 controls); b) a continuous measure of autism-related traits, the Social Responsiveness Scale (SRS, among 1,272 cases and controls); and c) a measure of autism severity, the Calibrated Severity Score (among 1,380 cases). In addition to the individual's air toxic level, mixed models (clustering on family) included the family mean air toxic level, birth year, and census covariates, with consideration of the false discovery rate.

ASD diagnosis was positively associated with propionaldehyde, methyl tert-butyl ether (MTBE), bromoform, 1,4-dioxane, dibenzofurans, and glycol ethers and was inversely associated with 1,4-dichlorobenzene, 4,4'-methylene diphenyl diisocyanate (MDI), benzidine, and ethyl carbamate (urethane). These associations were robust to adjustment in 2-pollutant models. Autism severity was associated positively with carbon disulfide and chlorobenzene, and negatively with 1,4-dichlorobenzene. There were no associations with the SRS.

Some air -toxics were associated with ASD risk and severity, including some traffic-related air pollutants and newly-reported associations, but other previously reported associations with metals and volatile organic compounds were not reproducible [30].

Costa LG ET AL

"Epidemiological and animal studies suggest that air pollution may negatively affect the central nervous system (CNS) and contribute to CNS diseases. Traffic-related air pollution is a major contributor to global air pollution, and diesel exhaust (DE) is its most important component.

"Several studies suggest that young individuals may be particularly susceptible to air pollution-induced neurotoxicity and that perinatal exposure may cause or contribute to developmental disabilities and behavioral abnormalities. In particular, a number of recent studies have found associations between exposures to traffic-related air pollution and autism spectrum disorders (ASD), which are characterized by impairment in socialization and in communication and by the presence of repetitive and unusual behaviors. The cause(s) of ASD are unknown, and while it may have a hereditary component, environmental factors are increasingly suspected as playing a pivotal role in its etiology, particularly in genetically susceptible individuals. Autistic children present higher levels of neuroinflammation and systemic inflammation, which are also hallmarks of exposure to traffic-related air pollution. Gene-environment interactions may play a relevant role in determining individual susceptibility to air pollution developmental neurotoxicity. Given the worldwide presence of elevated air pollution, studies on its effects and mechanisms on the developing brain, genetic susceptibility, role in neurodevelopmental disorders, and possible therapeutic interventions are certainly warranted [31].

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Toxic metal(loid)-based pollutants and their possible role in autism spectrum disorder.

Bjørklund G1, Skalny AV2, Rahman MM3, Dadar M4, Yassa HA5, Aaseth J6, Chirumbolo S7, Skalnaya MG8, Tinkov AA9.

"Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social interaction, verbal and non-verbal communication, and stereotypic behaviors. Many studies support a significant relationship between many different environmental factors in ASD etiology. These factors include increased daily exposure to various toxic metal-based environmental pollutants, which represent a cause for concern in public health. This article reviews the most relevant toxic metals, commonly found, environmental pollutants, i.e., lead (Pb), mercury (Hg), aluminum (Al), and the metalloid arsenic (As). Additionally, it discusses how pollutants can be a possible pathogenetic cause of ASD through various mechanisms including neuroinflammation in different regions of the brain, fundamentally occurring through elevation of the proinflammatory profile of cytokines and aberrant expression of nuclear factor kappa B (NF-κB). Due to the worldwide increase in toxic environmental pollution, studies on the role of pollutants in neurodevelopmental disorders, including direct effects on the developing brain and the subjects' genetic susceptibility and polymorphism, are of utmost importance to achieve the best therapeutic approach and preventive strategies [32].

Andreas M. Grabrucker

"Prenatal exposure to organophosphate pesticides such as diazinon and chlorpyrifos, agents that have been shown to be neurotoxic (Karr et al., 2007), may contribute to autism. A genetic predisposition seems to enhance vulnerability for these substances (Dufault et al., 2012). Additionally, a study found that women who are in the first 8 weeks of pregnancy in closer contact with the organochlorine pesticides dicofol and endosulfan due to their residential proximity to sprayed fields, are several times more likely to give birth to children with autism (Roberts et al., 2007). However, a limited number of cases and studies makes these findings hard to interpret and the concordance rate is not 100%, which suggests that a genetic predisposition might be necessary for a toxin to act as trigger (Szpir, 2006). Many symptoms are observed and many significant associations of environmental as well as genetic factors were found. What is missing so far is a hypothesis, unifying all those different factors chasing autism back to a single cause, for instance the disturbance of a specific synaptic pathway that is influenced by genetic and environmental factors. The fact that many autism-associated genes are interconnected and that also many environmental factors seem to be related and impact genetic factors makes this goal look achievable in the future. Like a necklace of pearls, where a cut between two single parts at a random position in the chain will lead to the drop of every pearl, the deregulation of this environmentally influenced genetic pathway at any level may results in autism. However, it is likely that the cut in the signaling chain might influence the occurrence and severity of specific features of autism [33]. Environ Res. 2016 Nov;151:763-776. doi: 10.1016/j.envres.2016.07.030. Epub 2016 Sep 5.

Flores-Pajot MC et al

"Genetic and environmental factors have been recognized to play an important role in autism. The possibility that exposure to outdoor air pollution increases the risk of autism spectrum disorder (ASD) has been an emerging area of research. Herein, we present a systematic review, and meta-analysis of published epidemiological studies that have investigated these associations.

We undertook a comprehensive search strategy to identify

studies that investigated outdoor air pollution and autism in children. Overall, seven cohorts and five case-control studies met our inclusion criteria for the meta-analysis. We summarized the associations between exposure to air pollution and ASD based on the following critical exposure windows: (i) first, second and third trimester of pregnancy, (ii) entire pregnancy, and (iii) postnatal period. Random effects meta-analysis modeling was undertaken to derive pooled risk estimates for these exposures across the studies.

The meta-estimates for the change in ASD associated with a 10μg/m3 increase in exposure in PM2.5 and 10 ppb increase in NO2 during pregnancy were 1.34 (95% CI:0.83, 2.17) and 1.05 (95% CI:0.99, 1.11), respectively. Stronger associations were observed for exposures received after birth, but these estimates were unstable as they were based on only two studies. O3 exposure was weakly associated with ASD during the third trimester of pregnancy and during the entire pregnancy, however, these estimates were also based on only two studies.

Our meta-analysis support the hypothesis that exposure to ambient air pollution is associated with an increased risk of autism. Our findings should be interpreted cautiously due to relatively small number of studies, and several studies were unable to control for other key risk factors [34].

Hideo Matsuzaki et al

"However, no single neurobiological factor currently dominates the mechanism, pathology and prevalence of autism. This suggests that interactions between multiple genes cause "idiopathic" autism but that epigenetic factors and exposure to environmental modifiers may contribute to variable expression of autism-related traits. Although these factors independently account for few cases, environmental factors may interact with genetic susceptibility to increase the likelihood of autism. For example, some data implicate a possible role of immune factors, including an increased family history of autoimmune diseases and presence of autoantibodies to neural antigens. Epidemiological studies have linked prenatal stress to increases in the incidence of neurodevelopmental disorders, including autism spectrum disorders, and these associations are often sex dependent.Autism often displays sex differences in prevalence, presentation, or therapeutic outcomes.The contribution of epigenetic modifications on the pathophysiology of autism has also been championed. Therefore, many studies have focused on genome imprinting as the research strategy [35].

Sylvie Tordjman et al

"Effects of exposure to air pollution during pregnancy in the first year of life deserve particular attention, especially because they might be mediated by epigenetic mechanisms as in valproate exposure. Epidemiological studies reported associations between autism and air pollution at the birth and early life residences. Thus, residential proximity to freeways in California within 309 m during the third trimester of pregnancy and at birth was found associated with a risk of ASD about twofold higher (88). Studies in animal models (rodents) and humans described developmental effects of air pollution following prenatal and early life exposure, such as altered neuronal differentiation, impaired cognitive functions, and white matter abnormalities . Given the male prevalence observed in autism, it is noteworthy that adult male mice but not females, showed increased depression-like responses and low resilience to stress in the tail suspension test following prenatal exposure to urban freeway nanoparticulate matter. In this line, Volk et al. found that exposure during pregnancy and the first year of life to traffic-related air pollution was associated with autism (DSM-IV and ICD-10 criteria based on the ADI-R and ADOS scales). Children residing in homes with the highest levels of modeled air pollution (>31.8 ppb) were three times as likely to have autism compared to children residing in homes with the lowest levels of exposure (<9.7 ppb). An increasing probability of autism was seen with increasing air pollution (nitrogen dioxide and particulate matter less than 2.5 and 10 μm in diameter: PM2.5 and PM10) with a plateau reached at a threshold above 25–30 ppb. Associations were reported for each trimester of pregnancy but the smallest magnitude of the effects was observed for the first trimester. Neurodevelopmental effects of prenatal and/or early life exposure to polycyclic aromatic hydrocarbons may be mediated by epigenetic effects. the results could also be affected by unmeasured confounding factors associated with both autism and exposure to traffic-related air pollution [36].

Kim D et al

"Autism spectrum disorder is a complex trait with a high degree of heritability as well as documented susceptibility from environmental factors. In this study the contributions of copy number variation, exposure to air pollutants, and the interaction between the two on autism risk, were evaluated in the population-based case-control Childhood Autism Risks from Genetics and Environment (CHARGE) Study. For the current investigation, we included only those CHARGE children (a) who met criteria for autism or typical development and (b) for whom our team had conducted both genetic evaluation of copy number burden and determination of environmental air pollution exposures based on mapping addresses from the pregnancy and early childhood. This sample consisted of 158 cases of children with autism and 147 controls with typical development. Multiple logistic regression models were fit with and without environmental variable-copy number burden interactions. We found no correlation between average air pollution exposure from conception to age 2 years and the child's CNV burden. We found a significant interaction in which a 1SD increase in duplication burden combined with a 1SD increase in ozone exposure was associated with an elevated autism risk (OR 3.4, $P < 0.005$) much greater than the increased risks associated with either genomic duplication (OR 1.85, 95% CI 1.25-2.73) or ozone (OR 1.20, 95% CI 0.93-1.54) alone. Similar results were obtained when CNV and ozone were dichotomized to compare those in the top quartile relative to those having a smaller CNV burden and lower exposure to ozone, and when exposures were assessed separately for pregnancy, the first year of life, and the second year of life [37]

Cynthia D Nevison

"The CDDS and IDEA data sets are qualitatively consistent in suggesting a strong increase in autism prevalence over recent decades. The quantitative comparison of IDEA snapshot and constant-age tracking trend slopes suggests that ~75-80% of the tracked increase in autism since 1988 is due to an actual increase in the disorder rather than to changing diagnostic criteria. Most of the suspected environmental toxins examined have flat or

decreasing temporal trends that correlate poorly to the rise in autism. Some, including lead, organochlorine pesticides and vehicular emissions, have strongly decreasing trends. Among the suspected toxins surveyed, polybrominated diphenyl ethers, aluminum adjuvants, and the herbicide glyphosate have increasing trends that correlate positively to the rise in autism [38].

Ritz B et al

"Previous ASD and air pollution studies focused on pregnancy exposures, but another vulnerable period is immediate postnatally. Here, we examined early life exposures to air pollution from the pre- to the postnatal period and ASD/ASD subtypes in the Danish population.

With Danish registers, we conducted a nationwide case-control study of 15,387 children with ASD born 1989-2013 and 68,139 population controls matched by birth year and sex identified from the birth registry. We generated air dispersion model (AirGIS) estimates for NO2, SO2, PM2.5 and PM10 at mothers' home from 9 months before to 9 months after pregnancy and calculated odds ratios (OR) and 95% confidence intervals (CI), adjusting for parental age, neighborhood socio-economic indicators, and maternal smoking using conditional logistic regression.

In models that included all exposure periods, we estimated adjusted ORs for ASD per interquartile range (IQR) increase for 9 month after pregnancy with NO2 of 1.08 (95% CI: 1.01, 1.15) and with PM2.5 of 1.06 (95% CI: 1.01, 1.11); associations were smaller for PM10 (1.04; 95% CI: 1.00, 1.09) and strongest for SO2 (1.21; 95% CI: 1.13, 1.29). Also, associations for pollutants were stronger in more recent years (2000-2013) and in larger cities compared with provincial towns/rural counties. For particles and NO2, associations were only specific to autism and Asperger diagnoses.

Our data suggest that air pollutant exposure in early infancy but not during pregnancy increases the risk of being diagnosed with autism and Asperger among children born in Denmark [39].

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"Studies of season of birth or season of conception can provide clues about etiology. We investigated whether certain months or seasons of conception are associated with increased risk of ASD , for which etiology is particularly obscure.

The study population comprises 6,604,975 children born from 1990 to 2002 in California. Autism cases (n = 19,238) were identified from 1990 through 2008 in databases of the California Department of Developmental Service, which coordinates services for people with developmental disorders. The outcome in this analysis was autism diagnosed before the child's sixth birth date. The main independent variables were month of conception and season of conception (winter, spring, summer, and fall). Multivariate logistic regression models were used to estimate odds ratios (ORs) with their 95% confidence intervals (CIs) for autism by month of conception.

Children conceived in December (OR = 1.09 [95% CI = 1.02 – 1.17]), January (1.08 [1.00 –1.17]), February (1.12 [1.04– 1.20]), or March (1.16 [1.08 – 1.24]) had higher risk of developing autism compared with those conceived in July. Conception in the winter season (December, January, and February) was associated with a 6% (OR = 1.06, 95% CI = 1.02 – 1.10) increased risk compared with summer.

Higher risks for autism among those conceived in winter months suggest the presence of environmental causes of autism that vary by season [40].

Experimental Project Hypotesys to Be Verified

It must be verified the dose response involving air pollution (animal model ?) and some neurodevelopmental disease to verify the effect of the increase of some air toxic molecules (even in little modify).

Discussion

After the analysis of reported literature is possible to say that some air pollutants or unbalances of air composition with increase of toxic component (carbon world and other) has been identified as neurodevelopmental negative factors.

Relevant the time of exposure (pre – post natal) and the dose response relationship tissue related

(nervous system development)

Conclusion

Is undeniable the role played by some air pollutant or unbalances in air composition with increase of the toxic component in neuro-developmental models we have see in this work.

Nothing to add : only is evident what kind of future we like for our sons.

Clarifications

This work is produced without any diagnostic or therapeutic intent only to produce new research hypotesis to be submit to the researcher .

This paper is produced under a toxicological approach

"Studies of season of birth or season of conception can provide clues about etiology. We investigated whether certain months or seasons of conception are associated with increased risk of autism spectrum disorders, for which etiology is particularly obscure.

Conflict Of Interest

NO

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