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An ecological study shows increased prevalence of autism spectrum disorder in children living in a heavily polluted area

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The burden of autism spectrum disorder (ASD) is increasing worldwide with genetic, epigenetic, and environmental factors being possibly responsible for the observed epidemiological figures. In the setting of environmental exposure, the city of Taranto, in Southern Italy, represents an interesting case study as it hosts well inside the city one of the biggest steel plants in Europe. This is a cross-sectional ecological study carried out in the year 2020 in the province of Taranto designed to estimate the burden of ASD in the municipalities of Taranto and Statte, classified as high environmental risk areas (Contaminated Site of National Interest—SIN), compared to the other 27 municipalities of the same province. Differences have been evaluated using the Chi Square Test. Children aged 6–11 years identified in SIN municipalities had a statistically significant higher prevalence of ASD than children of other municipalities (9.58 vs. 6.66/1000 respectively, $p = 0.002$). No statistically significant difference was observed for the 12–18 years group (3.41 vs. 2.54/1000, $p = 0.12$). The findings observed in this study are suggestive of the association between urban residential proximity to industrial facilities emitting air pollutants and higher ASD prevalence.

Keywords Children, Autism spectrum disorder (ASD), Taranto, Prevalence, Pollution, Steel

Abbreviations

ASD	Autism spectrum disorder
DL-PCB	Dioxin-like polychlorinated biphenyls
HFA	High-functioning autism
IQ	Intelligence quotient
PAHs	Polycyclic aromatic hydrocarbons
PCDD	Polychlorinated dibenzo-p-dioxins
PCDF	Polychlorinated dibenzofurans
PM	Particulate matter
SIN	Contaminated Site of National Interest
TEQ	The toxic equivalents

The prevalence of neurodevelopmental disorders, including autism spectrum disorders (ASD), has registered an increase worldwide, although showing a high variability in different regions or countries[1]. In Italy an estimated prevalence of 1 out of 77 children (aged 7–9 years) has been calculated based on local studies[2], being 4.4 times higher in males than in females[3].

Neurodevelopmental disorders including ASD are supposed to have multifactorial origin, with recognized genetic and environmental triggers[4]. The highest vulnerability for neurodevelopmental disorders occurs from foetal life through early childhood. It is during this period that exposure to neurotoxic chemicals, even at doses resulting in little or no adverse effects in adults, can interfere with ongoing normal neurological development

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resulting in permanent brain damage[5]. In recent decades, large and rapid industrialization and other human activities have led to the emission of pollutants with neurotoxic potential into the air, water and soil, causing environmental pollution. Therefore, in some areas of the planet people have been chronically exposed to a mixture of these chemicals, potentially resulting in a considerable risk to human health. While neurotoxic substances act individually, co-exposure may lead to increased neurotoxicity compared to single agent exposure due to synergistic action[6–8].

Increasing scientific evidence links ASD to environmental exposures in the frame of an interaction with genetic factors[9]. Specifically, epigenetic modifications of gene expression by toxic chemicals might represent the mechanism of this gene-environment interaction[10]. Exposure to environmental toxins can also increase disease rates in subsequent generations not directly exposed, thus producing an effect of transgenerational toxicology[11]. The substances potentially questioned for causing ASD in case of exposures during foetal life and early childhood include heavy metals[12–14], endocrine disruptors, including pesticides[15], and atmospheric particulates[16].

The province of Taranto, located in southern Italy, is the fourth province in the Puglia region in terms of both area and population. The area of Taranto hosts, in proximity of the resident population, the biggest single-site integrated steel plant in Europe. The municipalities of Taranto and Statte are classified as high environmental risk areas (Contaminated Site of National Interest–SIN) by the Italian Ministry of Environment because of several polluting sources such as a large steel plant, a refinery, the harbor and both controlled and illegal waste dumps. Contaminated Site of National Interest are identified in relation to the characteristics of the site, the quantities and dangers of the pollutants present, the importance of the impact on the surrounding environment in terms of health and ecological risk, as well as damage to cultural and environmental heritage. (Art. 252, paragraph 1 of Legislative Decree 152/06 and subsequent amendments)[17].

The aim of this study was to evaluate the prevalence of ASD in the Province of Taranto, Italy, comparing the findings of the two highly polluted municipalities of Taranto and Statte with the other less polluted nonindustrial 27 municipalities of the same Province.

Methods

This cross-sectional ecological study was carried out in the year 2020 in the province of Taranto, which has a total population of 576,000 inhabitants (Fig. 1) distributed in 29 municipalities (189,000 in Taranto city, 13,000 in Statte and 374,000 in the other towns).

The prevalence of ASD in Taranto and its province was estimated in the year 2020 according to a validated methodology, described in a study carried out in the province of Lecce, an area located in Apulia Region bordering the province of Taranto[18]. In Italy each child diagnosed with ASD receives specific school support by a dedicated teacher. All the diagnostic and supportive costs are fully covered by the National Health System and by the Ministry of Education. Therefore, the ASD diagnoses were based on official data referring to the number of students individually supported by a dedicated teacher due to diagnosis of ASD and confirmed by the local health authority established in each province. This methodological approach has been chosen because local health authorities do not have a centralized database of ASD diagnoses performed by their neuropsychiatric services, while the school office in each province is able to provide this kind of data for all the municipalities belonging to the same province.

According to the Italian Law No. 104/1992, children with any type of disability or emotional and behavioural difficulties must regularly attend ordinary classes at all levels of compulsory education from primary to the
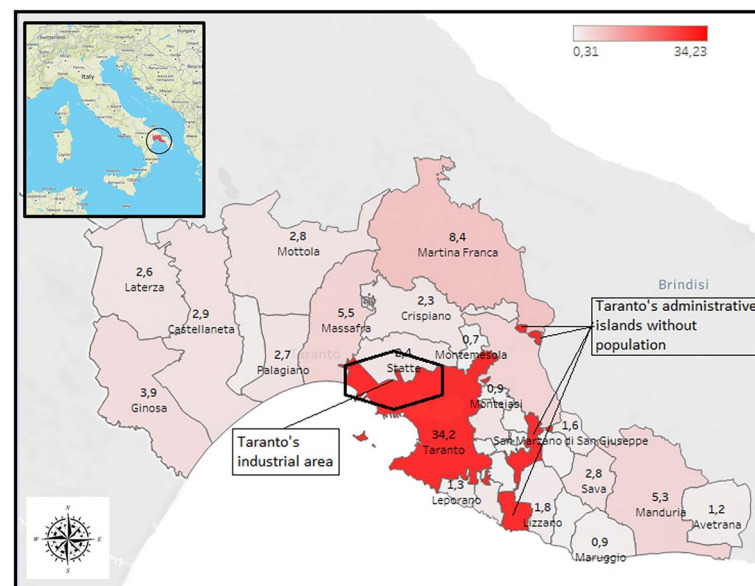

Figure 1. The province and the city of Taranto—share of total population (%).

second year of high school (at least until 15 years old, with the possibility to continue up to the age of 18). To receive individual teacher support for their schoolchildren with ASD, parents must obtain a specific certification issued by the school office after the diagnosis of ASD performed by neuropsychiatric services of the local health authority. Therefore, instead of referring to the data scattered in the different local neuropsychiatric services, which are very complex to get and group together, we have referred to the school office database in a completely anonymous way as a surveillance system.

As shown by a previous study in Italy, for children aged 6 years or more the school dataset contains at least 95% of all diagnoses performed by neuropsychiatric services, thus also useful for epidemiological purposes[18]. This methodological approach enabled us to estimate the prevalence of ASD in children aged 6–18 years who attend primary and secondary schools in the province of Taranto and need the individual support provided by the Italian State Law No. 104/1992 following any ASD diagnosis. Data from children below the age of 6 were excluded for several reasons: the diagnosis of ASD is in some cases definitively confirmed only at 5 years of age, some children with ASD do not attend pre-schools or remain outside the public education system until the beginning of compulsory school at age 6, and finally because the previous study carried out in the province of Lecce showed that the methodology adopted underestimates data for children under 6 years of age[18].

Statistical analysis

The prevalence of ASD was calculated as the ratio between the number of children 6–18 years individually supported by a dedicated teacher due to diagnosis of ASD and the total population 6–18 years residing in the area, per 1000 population. Data are presented for the whole population, for two different age groups (6–11 years and 12–18 years) and by sex. The 95% Confidence Interval of prevalence data was calculated using the SAS software, Version 9.4 (SAS Institute Inc., Cary, NC, USA).

To evaluate the possible impact of living in highly polluted vs less polluted setting on ASD diagnosis, two areas were compared: the municipalities of Taranto and Statte, classified by the Italian Ministry of Environment as SIN vs all the other municipalities belonging to the Province of Taranto. Differences have been evaluated using the Chi Square Test. The same statistical methodology was used to compare data collected in a previous study carried out in the province of Lecce with data above-described areas.

Figure 1 was created by Stefano Cervellera with the use of the software Tableau Desktop 2023, realese 1.

Ethical considerations

Ethical Committee approval was not requested according to the Italian Law since the General Authorization to Process Personal Data for Scientific Research Purposes (Authorization no. 101/2018) declared that retrospective archive studies that use ID codes, preventing the data from being traced back directly to the data subject, do not need ethics approval[19].

As this was retrospective archive study, no formal informed consent was required. Rules and protocols on data collection and processing of Internal review board of the Institute for Maternal and Child Health—IRCCS Burlo Garofolo were strictly followed. With the support of the school office of the province of Taranto, using only total numerical data by municipality or by school, these data could in no way be traced back to individual identifiers. All methods were carried out in accordance with relevant guidelines and regulations.

Results

Overall, in the study period, 344 children and adolescents aged 6–18 years with ASD were identified in the Province of Taranto in a total residing population of 70,325 children of the same age range.

Table 1 shows the absolute number and the prevalence of ASD per 1000 children by age groups (6–11; 12–18 years old) in the Province of Taranto.

The overall prevalence of ASD was 4.89 per 1000 children, with higher values in the 6–11 year group and a significant decrease in the 12–18 year group.

A total of 291 children were male (prevalence 8.09 per 1000) and 53 were female (prevalence 1.54 per 1000) with a male:female ratio of 5:1. The male:female ratio was higher in the 12–18 year group (6:1) (Table 2).

Children aged 6–11 years identified in SIN municipalities (Taranto and Statte) had a statistically significant higher prevalence of ASD than children of other municipalities (9.58 vs. 6.33 per 1000 respectively, $p = 0.002$). No statistically significant difference was observed for the 12–18 year group (3.41 vs. 2.54 per 1000, $p = 0.12$) (Table 3). The overall (6–18 years) RR for ASD diagnosis in the SIN municipalities vs other municipalities was 1.45 (95% CI 1.18–1.80) and 1.51 (95% CI 1.17–1.96) for children 6–11 years of age.

The comparison with data collected in a previous study[18] with the same methodology in a neighbouring low-pollution area (province of Lecce) does not present any evidence of statistically significant differences in the prevalence in the municipalities of the province of Taranto outside the SIN (other municipalities) and in the province of Lecce (for the 6–11 years group 6.33 vs. 5.86 per 1000, respectively, $p = 0.490$; for the 12–18 years

Age groups	ASD cases (number)	Total population (number)	Prevalence per 1000	P value
6–11 years	231	30,757	7.51	< 0.0001
12–18 years	113	39,568	2.86	
6–18 years	344	70,325	4.89	–

Table 1. Number of cases and prevalence of ASD in the Province of Taranto by age group.

Age groups	Sex	ASD cases (number)	Total population (number)	Prevalence per 1000	P value
6–11 years	Female	38	14,885	2.55	<0.0001
	Male	193	15,872	12.16	
12–18 years	Female	15	19,486	0.77	<0.0001
	Male	98	20,082	4.88	
6–18 years	Female	53	34,371	1.54	<0.0001
	Male	291	35,954	8.09	

Table 2. Number of cases and prevalence of ASD in the Province of Taranto by age group and sex.

Age groups	Area	SDA cases (number)	Total population (number)	Prevalence per 1000	P value
6–11 years	SIN municipalities	107	11,171	9.58	0.002
	Other municipalities	124	19,586	6.33	
12–18 years	SIN municipalities	49	14,382	3.41	0.120
	Other municipalities	64	25,186	2.54	
6–18 years	SIN municipalities	156	25,553	6.10	0.001
	Other municipalities	188	44,772	4.20	

Table 3. Number of cases and prevalence of ASD in the Province of Taranto by age group and area.

group 2.54 vs. 2.10, respectively, $p = 0.220$). Differences between the province of Lecce and the SIN municipalities are statistically significant (for the 6–11 year group $p < 0.0001$; for the 12–18 year group $p = 0.004$) (Fig. 2).

Discussion

This study shows that in a highly polluted area the prevalence of ASD was higher than in the other non-polluted municipalities of the same province, especially for 6–11 year old children (Fig. 2).

The association between urban residential proximity to industrial facilities emitting air pollutants and higher ASD prevalence has already been established in another study[20].
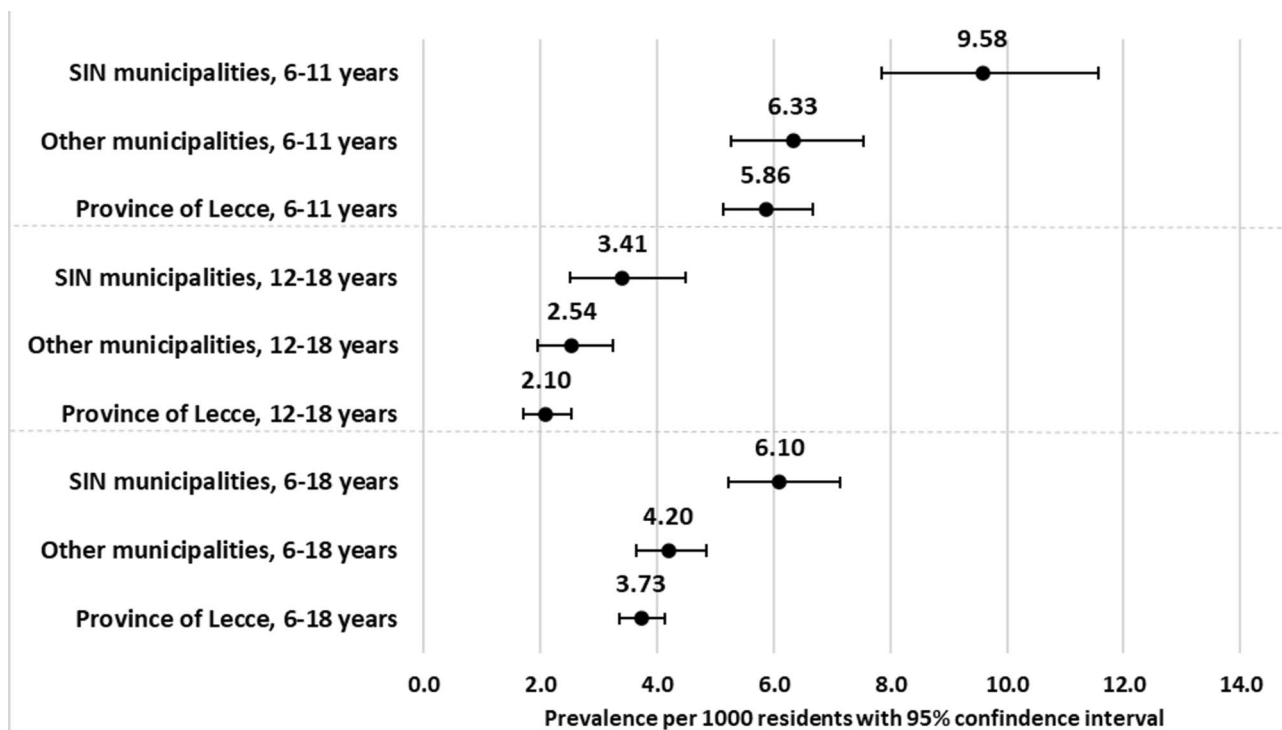

Figure 2. Comparison of the prevalence of ASD between the SIN municipalities, other municipalities of the province of Taranto and the province of Lecce.

These data are also consistent with what has been observed in one of the most investigated cohorts, such as that of Duisburg, Germany, in the Ruhr District. The "Duisburg cohort" is comprised of children delivered by 234 healthy women who were exposed during pregnancy to the pollutants released in the industrial area where they lived, in which there is also an integral cycle steel plant. This study demonstrated the presence of polychlorinated dibenzo-p-dioxins (PCDD), polychlorinated dibenzofurans (PCDF) and dioxin-like polychlorinated biphenyls (DL-PCB) in the blood of mothers during the period of pregnancy, as well as the contamination of their breast milk by dioxins[21]. The study of the children born from those pregnancies highlighted abnormalities and neurodevelopmental damage, and in particular autistic traits diagnosed at the age of 10 in children[22]. The relationship between high levels of dioxins in breast milk and autistic traits was also found in a sample of Vietnamese children[23]. The relationship with urinary polycyclic aromatic hydrocarbons (PAHs) metabolites and autistic traits was found in a sample of Chinese children[24].

To our knowledge, this is the first study comparing the prevalence of ASD in a highly polluted setting versus other less polluted non-industrial municipalities of the same limited geographical area.

Remarkably, data on the prevalence of ASD outside the SIN area are similar to those reported by a previous study carried out in an area located in the same region, the province of Lecce, bordering the province of Taranto[18]. Furthermore, considering the different methodologies and target populations, the prevalence data recorded in the province of Taranto are also similar to those recorded in other studies conducted in both Italy and Europe[1,25]. In a recent systematic umbrella review the Global Burden of Diseases global estimate for ASD was 0.4% (95% UI: 0.3–0.5) with a higher prevalence of 0.7% (95% UI: 0.6–0.8) estimated for High Income Countries[26]. On the other hand, the prevalence of ASD in the polluted area of the SIN is confirmed to be higher from those recorded in these studies.

The male/female ratio in ASD prevalence is consistent with data published in literature[18,27].

Consistent with data published by Imbriani et al., the prevalence of ASD has shown a significant decrease from younger to older age groups, indicating a possible increase in attention to ASD symptoms and access to surveillance and care systems over the past few years, as well as a possible increase in the incidence of the condition, especially in younger children[18]. Furthermore, this could be attributed to the fact that some children with ASD may not attend high schools (the school dropout rate in Taranto among 14–18 year-old is 17.6%), and that high schools are not uniformly distributed in urban areas as primary schools are.

The study area (municipalities of Taranto and Statte) is characterized by the presence, just 200 m away from the closest houses, of a large industrial area hosting the biggest single-site integrated steel plant in Europe, with the capacity of creating new steel straight from raw materials.

The municipality of Taranto is downwind from the industrial area, representing a further risk factor for human health[28]. It has been shown that pollutants released into the environment because of steel production particularly affect the city on the windiest days[29]. Mortality/morbidity excesses were detected in residents living in districts near the industrial area, for several pathologies including cancer, cardiovascular, and respiratory diseases[30,31]. It is noteworthy that in the city the overall mortality varies accordingly to the fluctuations in the concentration of industrial dust[32].

Remarkably, this study takes place in an area recognized as heavily polluted and investigated over the years by several studies that document both the high degree of pollution and the health risk. As a matter of fact, beyond the link between specific pollutants and ASD, the amount and the quality of evidence about the environmental contamination makes the SIN area a unique setting.

In Taranto the soil of the neighborhoods closest to the industrial area of the city is contaminated by heavy metals, PCB and PAHs[33–35]. Heavy metals and PAHs are much higher in city dust than in a rural site in the province[36]. The contamination of fish and mussels in the Mar Piccolo and in the sheep grazing in the 20 km around the city has been also documented[37–41]. The biomonitoring studies carried out on the hair, urine, blood and maternal milk of the citizens living in Taranto have shown a coherent picture of widespread contamination by dioxins and heavy metals. A significant difference was observed in the concentration of dioxins and PCBs in the breast milk of women residing in the cities of Taranto and in Statte compared to women residing in the province (municipalities of the province located 30 km from the SIN area). In the women from Taranto a significant increase was observed in the concentration of certain dioxins. The 2,3,4,7,8-P5CDF based on literature data, can be considered a marker of metallurgical industrial activities[42]. A previous study on 15 breast milk samples showed a prevalence of PCDFs, typical industrial pollutant markers, compared to PCDDs (2,3,4,7,8-PeCDF the most abundant congener). The toxic equivalents (TEQ in picogram per gram of fat) of four breast milk samples were far above the legal limit for human consumption (3.0 pg/g)[43]. Similarly, blood biomonitoring studies indicate significantly higher concentrations of PCDDs and PCDFs in women living in industrial areas compared to rural areas. Elevated levels of heavy metals have also been detected in the follicular fluid and urine of women from Taranto, with an excessive concentration of heavy metals in their hair[44–47]. Another study on agricultural workers in Taranto's province shows that dioxin and PCB blood levels vary with proximity to the industrial zone, suggesting differential impacts of industrial emissions. Age is a strong predictor of blood levels of organochlorine contaminants, with PCDF levels particularly influenced by the location of farms relative to industrial zones[48]. The exposure of children to pollutants is greater than adults due to the hand-to-mouth behaviour typical of the first years of life, the greater cutaneous absorption as well as to the higher volume of air and food that children encounter through feeding and breathing[49].

Increasing scientific evidence links ASD to environmental exposures in the frame of an interaction with genetic factors. The emissions of the steel plant, that are prevalent compared to other sources in the industrial area, include most of the substances (PM, heavy metals, and endocrine disruptors) that scientific literature recognizes as possibly involved in ASD development[22,24,50–52].

In Taranto, a sample of 299 healthy children between the ages of 6 and 11 years old was classified according to the incremental distance of their residence from the industrial area. Urinary arsenic, cadmium and hair

manganese resulted inversely related to the distance from the industrial emission source, while blood Pb levels show a non-significant decreasing trend. A reduction in intelligence quotient (IQ) of about 15 points was found in children and adolescent who live closer to the industrial area compared to those who live further away, with data corrected for the mother's socioeconomic status and cognitive skills[53]. Moreover, increased hyperactivity and psychopathological traits, impaired social behaviour and increased risk of autism were reported in children living in the neighbourhoods close to industrial emissions[54]. These findings are similar to those observed in our study.

While the strength of our study is its setting in an area recognized as heavily polluted and investigated over the years, it should be also highlighted that the entire population under consideration inhabits a small territory of only 2467.35 km². This group is ethnically and genetically homogeneous, sharing similar lifestyles, behavioral attitudes, and cultural backgrounds, and all reside within the same natural environment.

Among the limitations of our study are those attributable to the methodology approach used for data collection based on school records. This methodology can underestimate the phenomenon because it is not able to include high-functioning autism (HFA) forms, which occur when a child does not present intellectual disabilities, but only deficits in communication, emotional expression and social interactions or obsessive symptoms. These HFA conditions are usually diagnosed in adolescence and do not require specific support at school. On the other hand, as already shown[18], the school dataset contains at least 95% of all diagnoses made by neuropsychiatric services.

Furthermore, due to the methodology used for data collection, it is impossible to know the exact place and length of residence of each child, with a lack of data about population mobility. Despite this, the province of Taranto is composed of urban agglomerations that are distant various kilometers from each other, with no school bus service for schools outside the catchment area. Furthermore, in Italy, at the time of enrollment in primary school, priority is given to children within the catchment area, and children enrolled in primary schools outside their municipality of residence do not enjoy certain benefits, such as the use of the school canteen. All of this makes it rare for a child to attend school outside their municipality of residence, and therefore it is unlikely to be a confounding factor for our study.

A possible error determined by the different socio-economic status of families cannot be fully ruled out but seems unlikely in this school age group, and in the social context of the province which is not known for significant income differences between the two areas[55].

Finally, it may be speculated that family pediatricians and teachers caring for children in the SIN may have been aware of the environmental risks, thus performing more careful evaluations. While this bias cannot be completely ruled out it seems unlikely since the difference between the two populations did not change over the last ten years, starting from a period in which the awareness of the problem was much less. Furthermore, we believe that even in the presence of greater sensitivity in the SIN area this is unlikely to explain the statistically significant differences highlighted between the two different areas. It is unlikely that the children's cognitive problems escape the teachers, who work as a team for reporting them. On the contrary there could be an underestimation in the SIN area in case of denial of the problem by parents after the teacher's report, particularly in the areas of lower socio-economic level present in the SIN.

Causal conclusions cannot be drawn without caution as autism and subclinical autistic behavior are of complex, multifactorial origin and likely not attributable to a single cause. Furthermore, in the age group 12–18 years, the 95% confidence intervals of prevalence data calculated for the 3 areas under study overlap and this may indicate that the statistically significant differences observed may only have been achieved due to the large sample size. However, given the largely consistent results across the many studies that have explored aspects of air pollution and ASD, we can consider the role of pollutants present in the study area as responsible for the greater incidence of ASD to be plausible. Thus, while questions remain about which specific component of air pollution is the most relevant, this study reinforces the hypothesis of an association between air pollution exposure and ASD.

The findings observed in this study are suggestive of the association between urban residential proximity to industrial facilities emitting air pollutants and higher ASD prevalence.

These data add to the body of knowledge that heavy industrial pollution represents a challenge for children representing an important and clear near-term public health priority.

Data availability
The datasets used and/or analysed during the current study availabre from the corresponding author on reasonable request.

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Author contributions

A.M. and A.G.S. conceptualized and designed the study, drafted the initial manuscript, collected data and critically, assisted with the interpretation of the results, reviewed and revised the manuscript. M.G., L.R., S.C., M.P.R. designed the data collection instruments, collected data, carried out the initial analyses, interpreted the results, developed the statistical methods and critically revised the manuscript. E.B., C.N. assisted with the interpretation of the results, critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Additional information

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