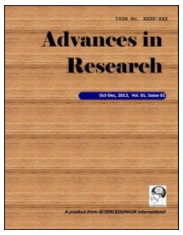

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Association between Air Pollutant Emissions and Type 1 Diabetes Incidence in European Countries

Agostino Di Ciaula[1*]

[1]*Division of Internal Medicine, Hospital of Bisceglie (ASL BAT),Via Bovio, 76011 Bisceglie (BAT), Italy.*

Author's contribution

This whole work was carried out by the author ADC.

Original Research Article

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ABSTRACT

Aims: The rise of Type 1 diabetes (T1D) incidence throughout Europe is only partially due to genetic factors, and the possibility that it may be affected by the amount of pollutant emissions has not been checked, until now.
Methodology: T1D incidence data among children from 16 European Countries (1990-2010) were collected (literature review) and analysed according to the nationwide amount of pollutant emissions (European Environmental Agency: particulate matter<10µm, PM10; nitrogen oxides, NOx; non-methane organic volatile compounds, VOCs; sulphur oxides, SOx; ammonia) in the same Nations/time periods. Pollutants were categorized by tertiles of emissions, and odds ratio (ORs) of T1D incidence were calculated.
Results: T1D incidence increased with time in all populations, and was positively correlated with the nationwide emissions of PM10 (P=0.03), NOx (P=0.0004), VOCs (P=0.009). Countries in the high tertile of PM10, NOx and VOCs emissions had higher ORs of T1D incidence than those in the low tertile, and mean T1D incidence was greater in Countries in the high- than in those in the medium or low tertile of PM10, NOx and VOCs emissions. T1D incidence was two-folds higher if two or more pollutants coexisted in the upper tertile of emissions.
Conclusion: The burden of specific pollutants might affect the extent of T1D incidence among European children, possibly triggering the development of disease by epigenetic mechanisms in genetically susceptible individuals. Thus, T1D might be considered, at least in part, a preventable condition. Further studies pointing to deeply explore this

**Corresponding author: E-mail: agostinodiciaula@tiscali.it;*

hypothesis are needed, also considering that primary prevention policies acting through a marked abatement of pollutant emissions might strongly attenuate T1D incidence throughout Europe.

Keywords: Type 1 diabetes; environmental pollution; Particulate Matter (PM10); Nitrogen Oxides (NOx); Volatile Organic Compounds (VOCs).

1. INTRODUCTION

Type 1 diabetes (T1D) is an autoimmune disease characterized by formation of autoantibodies, islet specific T-cells and inflammatory destruction of the beta-cells [1]. This process is determined by a complex interplay between genetic [2,3] and environmental factors [4], which may possibly start the process leading to the destruction of the beta cells and the onset of diabetes [1], mainly through epigenetic pathways [5].

The incidence of T1D in paediatric age has been reported to rapidly increase in many European countries [6,7], with an increment rate of about 3% per year [7]. This rise, particularly evident in the age group of 0-5 years [8], seems not to be uniform in different European Countries [7].

It has been observed that the constantly increasing incidence of T1D over a relatively small period of time cannot be explained by shifts in genetic susceptibility alone, and that only a minority of genetically susceptible children progress to clinical disease [9-11], suggesting a critical role for environmental factors (also pre-birth) [4,11,12] and environment-gene interaction [13].

Among environmental factors, however, although possible links between T1D and a number of maternal, microbiological and nutritional conditions [12] (in particular maternally derived gut microbiota [14] or variations of intestinal microbiota [15,16]) have been suggested, the possibility that chronic exposure to a comprehensive panel of widely diffused air pollutants may influence T1D incidence in paediatric age has not been checked, until now.

In fact, a link between chronic pollution, type 2 diabetes [17] and insulin resistance in children [18, 19] has been previously explored, but scarce observations about the relationship between toxic pollutants and T1D onset (in particular ozone and sulphate [20], nitrates, nitrites, N-nitroso compounds, persistent organochlorine pollutants [21,22], heavy metals [23-25]) have been reported, and epigenetic mechanisms [13,26] have been hypothesized.

Thus, aim of the present study is to verify the existence of possible relationships between T1D incidence in European children from different Countries, and the nationwide burden of the more diffused air pollutants, during a wide time period.

2. MATERIALS AND METHODS

We examined available data about the incidence of T1D in paediatric age in European Countries, and the global amount of pollutant emissions in the same Nations and in the same time periods, in order to explore the time-course of T1D incidence and possible links with a panel of specific and widely diffused air pollutants.

Incidence data were collected by a systematic literature review (PubMed). Included in the analysis were works on T1D incidence selected by the following criteria: 1) the study period was ≥2 years; 2) the study considered the overall age-standardized incidence of T1D (per 100,000 per year) in European Countries and in paediatric age; 3) the study was based on a nationwide dataset.

Only works considering study periods starting from the year 1990 were taken into account, due to the lack of information about countrywide pollutant emissions before this year.

Altogether, 12 studies considering T1D incidence in 16 European Countries (three studies considered T1D incidence in more than one Country) met the inclusion criteria and were considered in the analysis (Table 1).

In the selected studies, the mean time period considered for T1D incidence assessment in each Country was 4 years (range 2-8 years). The whole period considered in the analysis was 20 years (from 1990 to 2010). Only one study explored T1D incidence in different time intervals until 2012 [33]. In this case, all data were employed to analyse the incidence trend over time, while only data from 1996 to 2008 were used in the analysis of the relationships between T1D incidence and pollutant emissions.

In the case of different studies examining similar time periods in the same Country, data from the study with the shortest period were excluded from the analysis, in order to avoid time overlapping and correlation bias.

Data about pollutant emissions were derived from the European Environmental Agency (EEA) and Eurostat database (last update October 7, 2013) and measured as Tonnes of emissions per year, considering total sectors of emissions for each pollutant and for the national territory, in the period 1990-2010.

Median emissions in selected periods (corresponding to T1D incidence time periods in each Country) were thereafter calculated for the following pollutants: Particulate matter <10μm (PM10), nitrogen oxides (NOx), non-methane organic volatile compounds (VOCs), sulphur oxides (SOx) and ammonia.

The correlation between the amount of pollutant emissions and T1D incidence was assessed by Spearman's rank correlation coefficient.

Possible spatial autocorrelation of T1D incidence rates in the examined periods and the assumption of conditional independence were verified by Bayesian conditionally autoregressive regression models (CAR models) and the global Moran's I test, employing the R Package CARBayes [36].

We categorized each pollutant according to tertiles of emissions in the entire study period (low, medium and high pollutant emissions). Frequencies of categorical variables and medians or means and standard errors of continuous variables were subsequently calculated, as appropriate.

Table 1. Meanage-standardized incidence of T1D (per 100,000 per year) in children from 16 European Countries

Country	Time Period	Age Range (Years)	T1D Incidence	Reference
Austria	1990-1994	0-14	9.6	[27]
	1994-1998	0-15	9.9	[7]
	1999-2003	0-15	13.3	[7]
	2004-2008	0-15	17.5	[7]
Croatia	1995-2003	0-15	9.1	[28]
Cyprus	1990-1994	0-15	10.5	[29]
	1995-1999	0-15	10.5	[29]
	1999-2004	0-15	14.9	[29]
Czech Republic	1994-1998	0-15	11.5	[7]
	1999-2003	0-15	17	[7]
	2004-2008	0-15	19.3	[7]
Denmark	1999-2003	0-15	22.6	[7]
	2004-2008	0-15	25.1	[7]
Estonia	1990-1994	0-14	10.5	[27]
	1991-1998	0-14	12.3	[30]
	1999-2006	0-15	17.2	[31]
Finland	1990-1994	0-14	36.5	[27]
	1991-1998	0-14	40.8	[30]
Latvia	1990-1992	0-14	5.9	[27]
	1991-1998	0-14	7.4	[30]
Lithuania	1990-1994	0-14	7.4	[27]
	1991-1998	0-14	7.8	[30]
	1994-1998	0-15	8.2	[7]
	1999-2003	0-15	10.3	[7]
	2004-2008	0-15	14.2	[7]
Malta	2006-2010	0-14	21.86	[32]
Norway	1996-2004	0-15	28.4	[33]
	2004-2008	0-15	32.8	[7]
	2004-2012	0-15	32.7	[33]
Slovakia	1990-1994	0-14	8.5	[27]
Slovenia	1990-1994	0-14	7.9	[27]
	1994-1998	0-15	9.2	[7]
	1999-2003	0-15	11.1	[7]
	2004-2008	0-15	14.6	[7]
	1998-2010	0-18	12.5	[34]
Sweden	1990-1994	0-14	27.5	[27]
	1993-1995	0-14.9	29.9	[6]
	1996-1998	0-14.9	32.7	[6]
	1999-2001	0-14.9	35.4	[6]
	2002-2004	0-14.9	42.5	[6]
	2005-2007	0-14.9	43.9	[6]
Switzerland	1994-1998	0-15	8.3	[7]
	1999-2003	0-15	11	[7]
	2004-2008	0-15	13.1	[7]
Netherlands	1996-1999	0-14	18.6	[35]

To calculate odds ratios and confidence intervals for T1D incidence associated with emissions of specific pollutants, we fit separate logistic regression models with T1D incidence as the dependent variable and tertiles of each pollutant as the independent variable.

Kruskal-Wallis analysis of variance by ranks (followed by Multiple-comparison Z-value test**)** or Mann-Whitney U-test were employed to compare differences among groups, as appropriate.

Data are expressed as medians (range) or mean ± standard errors (SE), as appropriate. P values<0.05 were considered statistically significant for all analysis.

3. RESULTS AND DISCUSSION

In the whole observation period, T1D incidence rose with time across Europe in all paediatric populations, with mean values ranging from 5.9 (Latvia, period 1990-1992) to 43.9 (Sweden, period 2005-2007) per 100,000 a year (Table 1 and Fig. 1).

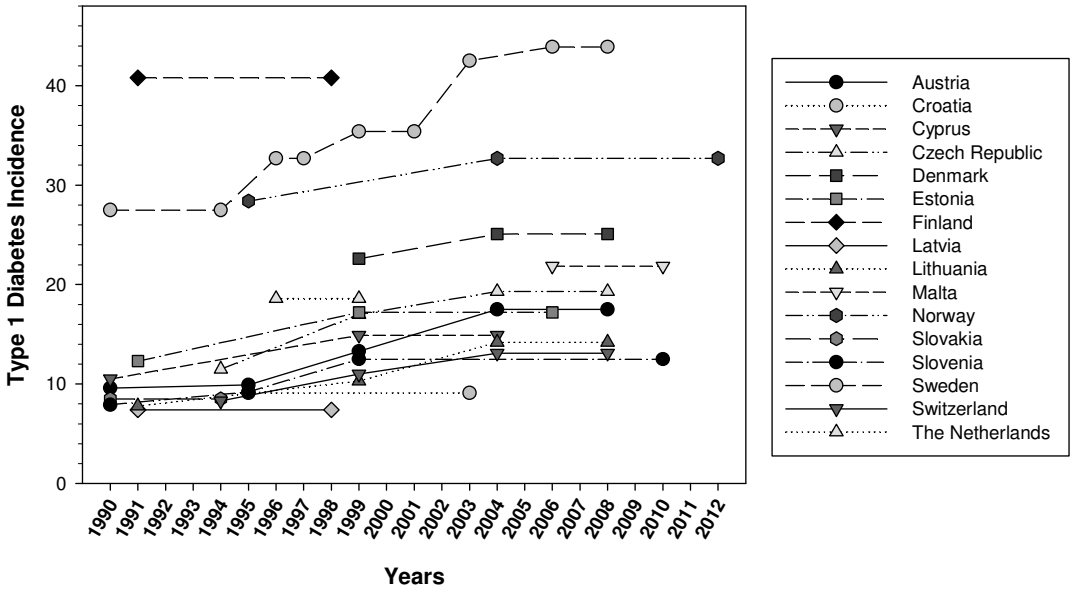

Fig. 1. Time variations of age-standardized incidence of type 1 diabetes in children from 16 European Countries. Incidence data were recorded at various time intervals in the period 1990-2012, and were combined after a systematic literature review considering 12 studies (see Table 1). Data for boys and girls have been pooled

T1D incidence in different countries correlated with both population size (ρ= 0.337, P=0.02) and Country area (Km2, ρ=0.86, P=0.001).

The trend of pollutant emissions over the two decades in the whole group of Countries was towards a reduction (Fig. 2), although the decrement (2010 *vs* 1990) was statistically significant only in the case of VOCs and SOx but not for PM10, NOx and ammonia (Table 2).

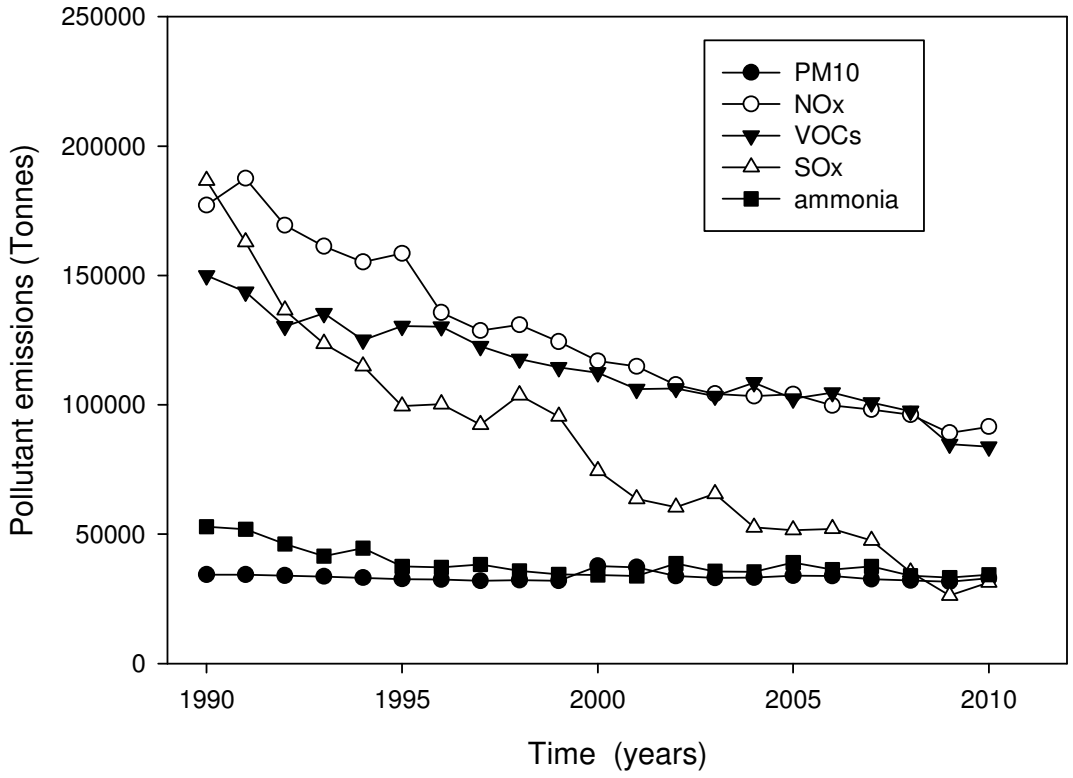

Fig. 2. Time variations of pollutant emissions (total sector of emissions for each pollutant) recorded in 16 European Countries from 1990 to 2010. Symbols indicate medians for each pollutant in the whole group of countries per year

Table 2. Pollutant emissions in the whole group of European Countries in the years 1990 and 2010

	PM10 (ton)	NOx (ton)	VOCs (ton)	Ammonia (ton)	SOx (ton)
1990	34314.5 (1026-78690)	177112 (12632-744840)	150011 (6852-479860)	52864 (1860-354828)	186636.5 (19491-1875847)
2010	32956.5 (1240-54599)	91511 (19135-385150)	83693.5 (2787-185511)	34351 (1502-121749)	31397 (9052-170275)
Difference	- 4 %	- 48.3 %	- 44.2 %	- 35 %	- 83.2 %
P	NS	NS	0.04	NS	0.0006

Data are medians (range). Statistical differences were tested by Mann-Whitney U-test.

T1D incidence in European Countries was significantly and positively correlated with the nationwide amount of VOCs (ρ= 0.49, P=0.009), NOx (ρ= 0.57, P=0.0004) and PM10 (ρ= 0.36, P= 0.03) emissions (Fig. 3), but not with SOx and ammonia emissions (P=NS, data not shown).

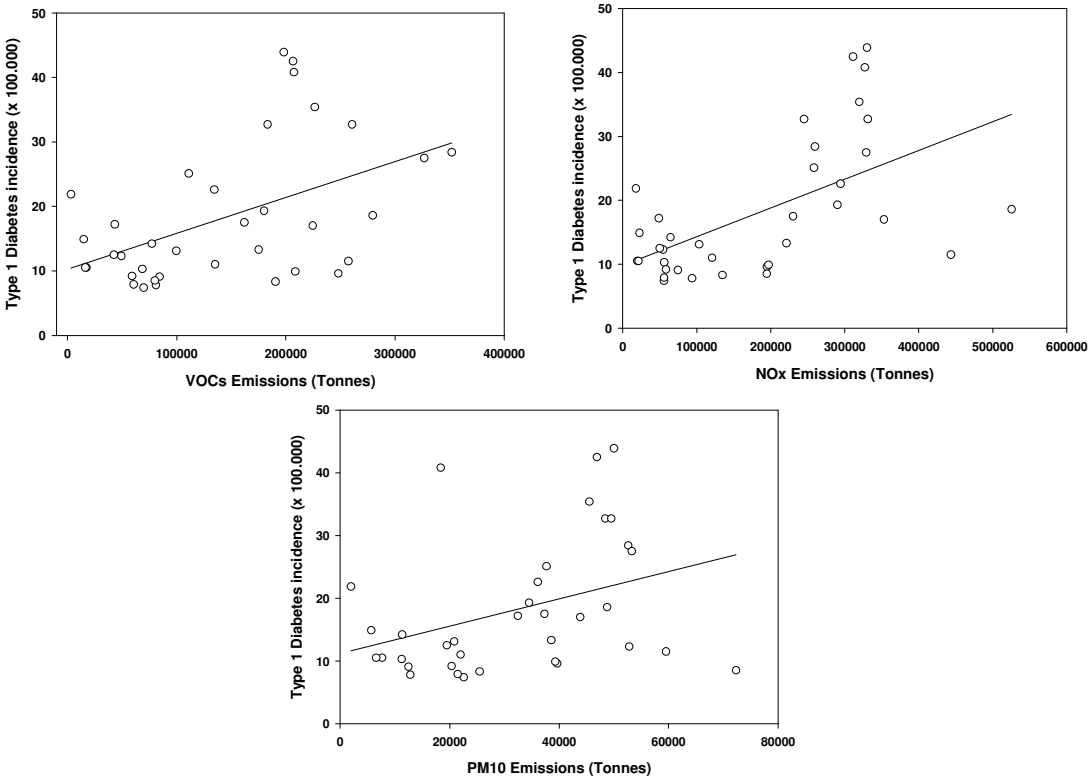

Fig. 3. Correlation between the amount of VOCs (ρ= 0.49, P=0.009), NOx (ρ= 0.57, P=0.0004) and PM10 (ρ= 0.36, P=0.03) emissions (total sector of emissions for each pollutant in each country) and age-standardized incidence of type 1 diabetes in children from 16 European Countries. The amount of pollutant emissions and type 1 diabetes incidence were calculated for each country in the same years

Incidence rates showed no spatial autocorrelation.

Countries in the higher tertile of VOCs, NOx and PM10 emissions had significantly higher odds of T1D incidence (1.20 [1.03-1.38], 1.20 [1.03-1.39] and 1.24 [1.05-1.46], respectively) than those in the reference (low emission) group (Fig. 4). Odds of T1D incidence were also significantly higher for Countries in the medium (but not high) tertile of ammonia and SOx (1.15 [1.0-1.3] and 1.16 [1.2-1.3], respectively), as compared with the reference group.

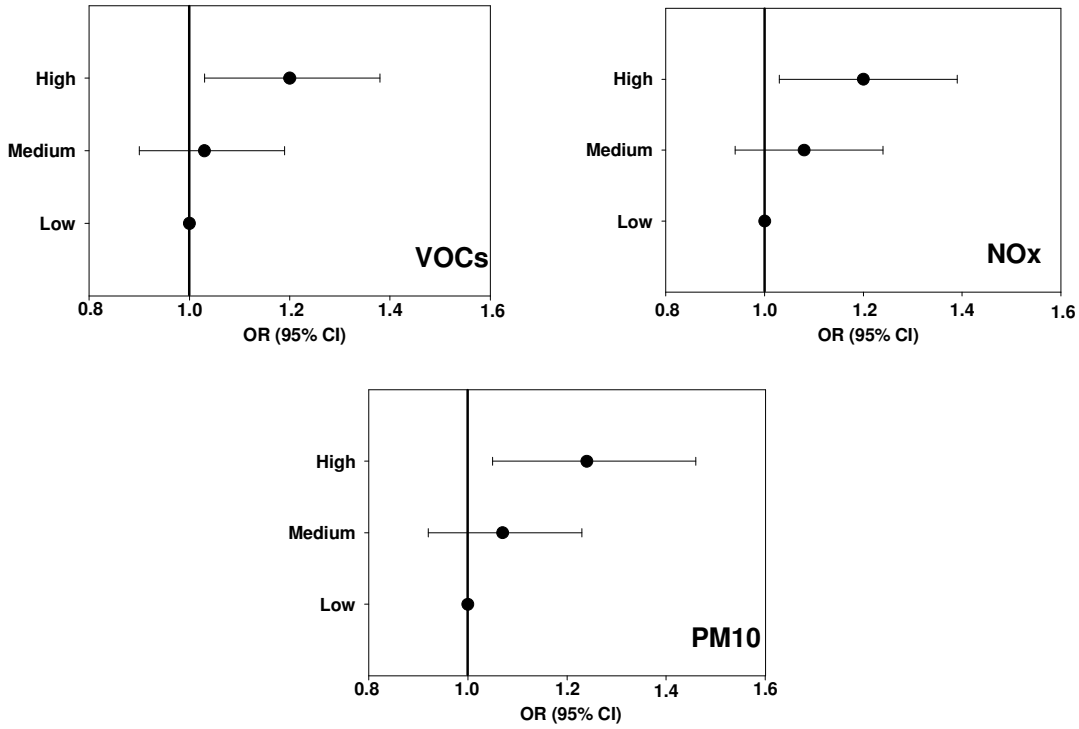

Fig. 4. Odds ratios and confidence intervals of T1D incidence in 16 European countries grouped according to tertile of VOCs, NOx and PM10 emissions (total sector of emissions for each pollutant in each country). Values were calculated by logistic regression models, with T1D incidence as the dependent variable and tertiles of each pollutant (low, medium and high pollutant emissions) as the independent variable

Mean incidence of T1D in paediatric age was significantly higher in Countries with high- than in those with medium or low global amount of VOCs, NOx and PM10 emissions (Fig. 5).

In order to verify the cumulative effect of multiple pollutants on T1D incidence, Countries and incidence data were grouped according to the number of pollutants coexisting in the upper tertile of emissions. The mean T1D incidence was about two-folds higher in Countries with two (23.5±3.9) and three or more (27.6±2.9) pollutants in the upper tertile, as compared to those with one (12.4±3.9) or no pollutant (13.3±2.1) in the upper tertile of emissions (P=0.003, Kruskal-Wallis One-Way ANOVA on Ranks and Multiple-Comparison Z-value test) (Fig. 6).

Results from this study support the rise of T1D incidence among European children, and document a correlation between the burden of the nationwide emissions of specific pollutants (mainly PM10, NOx, VOCs) and T1D incidence in paediatric age, with increased odds of T1D incidence in Countries with the highest pollutant emissions.

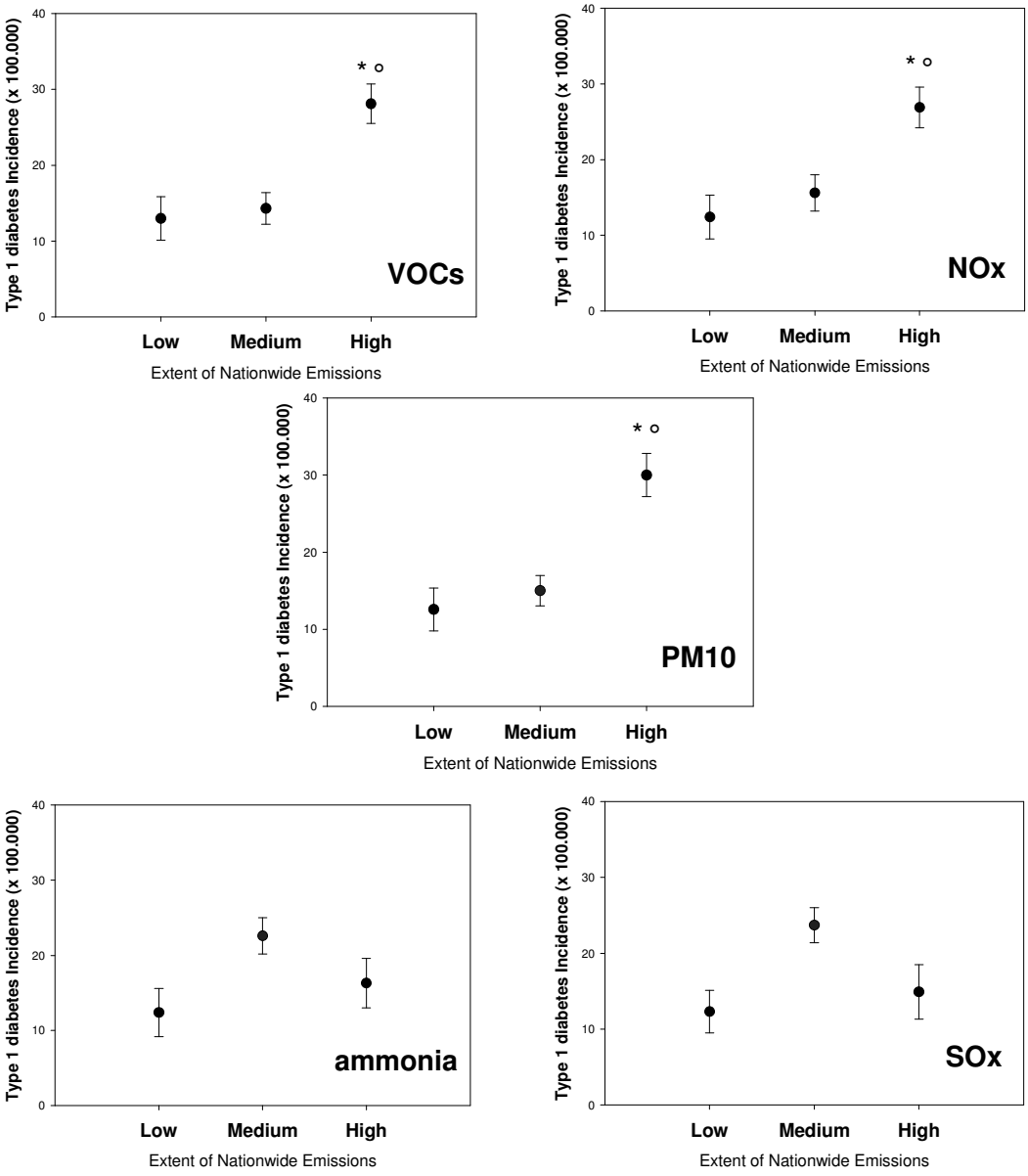

Fig. 5. Type 1 diabetes incidence in paediatric age in 16 European countries grouped according to tertiles (low, medium, high) of NOx, PM10, VOCs, ammonia and SOx emissions. Total sector of emissions was considered for each pollutant in each country. The amount of pollutant emissions and mean Type 1 Diabetes incidence were calculated for each country in the same time period. Data are means ± SE

**P<0.05 vs countries with low emissions; °P<0.05 vs countries with medium emissions (Kruskal-Wallis analysis of variance by ranks followed by Multiple-comparison Z-value test)*

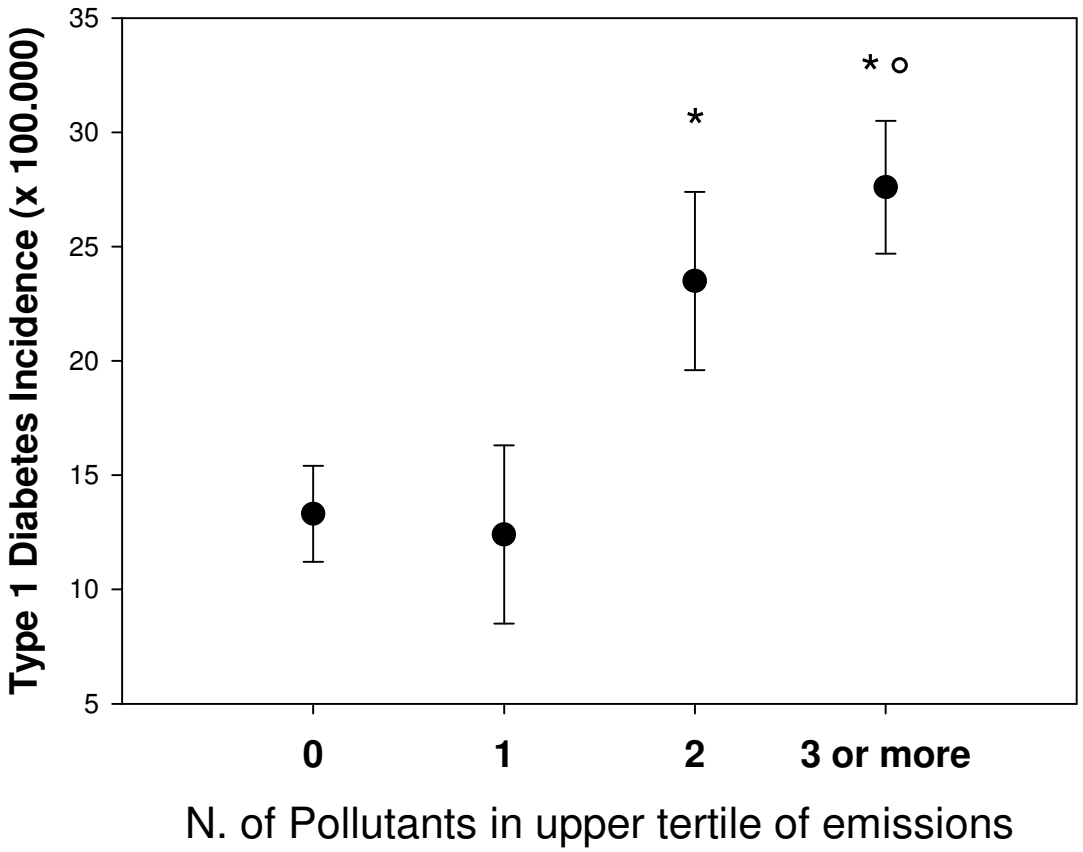

Fig. 6. Type 1 Diabetes incidence (paediatric age) in 16 European countries grouped according to the number of pollutants coexisting in the upper tertile of emissions. Data are means ± SE

**P<0.05 vs no pollutant in the upper tertile of emissions;*
°P<0.05 vs one pollutant in the upper tertile of emissions (Kruskal-Wallis One-Way ANOVA on Ranks and Multiple-Comparison Z-value test)

To the best of our knowledge, no study has yet investigated the relationship between the emission of a comprehensive panel of specific air pollutants and T1D incidence at a continental level. The present study considered the role of a broad set of air pollutants in 16 European Countries, through a wide time period (20 years).

Although genetic susceptibility is a well recognized risk factor for the onset of T1D [2,3], it cannot fully explain the epidemiological trend confirmed by this and other studies [6,7,35], since the observed rise in T1D incidence seems not to be paralleled by an increment in the frequency of the major genetic risk factors [3], some of which have been, at contrary, reported as progressively decreasing [37].

It has been previously well documented that not all genetically susceptible subjects develop the disease, as the concordance rate among monozygotic twins ranges from 13 to 67.7%, and is approximately 6% in siblings [9-11]. The absence of a complete concordance in twin

pairs (up to the 87% of cases) may be considered the major evidence supporting the crucial role of environmental factors in the onset of T1D in genetically susceptible subjects.

The links between T1D onset and the environment have been previously investigated considering a number of factors, none of which has yet been convincingly implicated in the aetiology of this chronic autoimmune disease [11,12]. Among these factors, environmental pollution still remains scarcely explored, until now, although it has been linked with other autoimmune diseases [38] such as rheumatic diseases [39], thyroid diseases [40], systemic lupus erythematosus [41] and with type 2 diabetes [17].

Air pollution is a heterogeneous mixture of gases and solid particles in the air, each component having its own potential effect on the human body and, of note, the foetal period is a vulnerable period for toxic substances, in particular considering the immune system development, which might be strongly affected by maternal exposure [42].

Systemic inflammation chronically induced by air pollutants has been indicated as the underlying biological mechanism linking air pollution with type 2 diabetes [17], also considering that chronic exposure to environmental chemical is able to induce a marked oxidative stress through a direct effect on lipids and proteins, or indirectly through the activation of intracellular oxidant pathways [43,44], contributing to insulin resistance in children [18].

However, on the contrary from type 2 diabetes and from insulin resistance, limited observations regarding possible links between T1D onset and specific pollutants have been reported, until now. Higher intake of nitrates, nitrites, N-nitroso compounds and persistent organochlorine pollutants [21,22] have been previously associated with increased risk of T1D, and a possible influence of some heavy metals like chromium [23], cadmium [24] and lead [25] has also been suggested, but the data were limited or inconsistent [21,22]. The effects of heavy metals, in particular, have been previously explored in type 2 diabetes [45,46] but the possibility of their involvement in T1D onset needs to be investigated by specific further studies.

Since air pollution is characterized by a complex combination of pollutants, the epidemiologic effect of a single pollutant is difficult to separate. Data from the present study indicate a possible role, in terms of T1D incidence, for PM10, NOx and VOCs, as compared with SOx and ammonia emissions. Interestingly, however, a cumulative effect of multiple pollutants on the onset of T1D is evident, since results showed a two-fold higher mean T1D incidence in children living in Countries where three or more pollutants were simultaneously located in the upper tertile of emissions, as compared to those with one or no pollutant in the highest tertile.

In paediatric age, it has been previously reported a significant link between air pollution, oxidative stress and insulin resistance in exposed children [19] and, interestingly, a recent prospective German study confirmed great levels of insulin resistance in school-aged children highly exposed to PM10 and NO_2 air pollution [18]. Furthermore, *in utero* exposure to VOCs may have a marked influence on the immune status of the newborn child [47].

It has been also described that cumulative exposure to ozone and sulphate in ambient air may predispose to the development of T1D in children [20]. Although ozone was not directly considered in our study, it has to be underlined that the amount of NOx emission is the main factor causing ozone pollution [48].

Epigenetics has been highlighted as the key factor in the onset of several diseases, as a consequence of exposure to toxic agents [49] occurring *in utero* before birth [50,51]. They occur when the function of a gene is altered by various mechanisms, although its DNA sequence remains stable [50]. Thus, the epigenome is actually considered the major pathway by which the environment influences phenotype expression and disease onset [5,13], since heritable epigenetic changes may disrupt the normal functioning of genes by affecting their expression, without changes in the DNA sequence.

This seems also the case of T1D [13,26]. In fact, a number of epigenetic changes, mainly in terms of DNA methylation, [52], variations in histone post-translational modifications [53], and microRNA regulation [54,55], have been linked to the onset of T1D in paediatric age.

T1D is an autoimmune disease mediated by T-cells, which promote a destruction of the majority of insulin-secreting beta-cells in the pancreatic islets [1]. Interestingly, from this point of view, several observations point to an epigenetic control of T-cell differentiation [56,57], and prospective studies suggest that the development of islet autoimmunity may occur at any point from early life (during the first years) [58] throughout childhood [59].

In utero exposure to toxicants strongly affects the development of the immune system. It has been shown in newborns from the Czech Republic that living in a highly polluted urban area was related to a lower percentage of CD4+ T-lymphocytes and a lower CD4 +/CD8+ ratio but a higher percentage of NK cells [60], and that prenatal maternal exposure to polycyclic aromatic hydrocarbons (PAHs) and fine particulate matter was linked with a lower percentages of CD3+, CD4+ and CD8+ T-lymphocytes, and with a higher percentage of CD19+ B-lymphocytes [61].

It has been also observed that blood lymphocyte immunophenotype distribution in newborns is significantly affected, even at low air pollutants levels, by maternal exposure (before and during pregnancy) to PM10, NO_2 [62] and VOCs [47,62], the same pollutants whose nationwide amount, according to our results, was significantly related to T1D incidence.

According to results from the present study, the odds of T1D incidence were significantly higher in Countries with the highest PM10, NOx and VOCs emissions, than in those placed in the reference group. Although the odds were relatively low (from 1.18 to 1.23), it has to be underlined that the entire population is exposed to these pollutants (even during early *in utero* life) and, thus, the public health effect might be quite large, as suggested by epidemiological data in the more polluted Nations.

Our data show that T1D incidence correlated with both population size in different countries and country area. Thus, it might be argued that a large amount of people can generate high pollution levels and, in turn, more T1D. Of note, however, results from the present study support the hypothesis that this might only be true for some (PM10, VOCs, NOx) but not all pollutants, underlying the potential role of specific emissions of the onset of T1D.

Results showed a trend towards a progressive decrement in pollutant emissions throughout Europe. However, this reduction is only significant for two (i.e. VOCs and SOx) out of five explored pollutants and seems not to be able to appreciably attenuate the progressive rise in T1D incidence which, on the other hand, may also be influenced by other chemicals (i.e. BPA [63] and/or other endocrine disruptors [64]) and by environmental factors different from air pollution [11,12].

The pollutant reduction in the last two decades was virtually absent in the case of PM10 and it was not significant for NOx. Interestingly, it has to be underlined that no apparent threshold exists below which the link between particulate [65] and NOx [66] emissions and adverse health effects no longer applies. Hence, a biological effect of these pollutants might also be evident in the case of moderate exposure, also considering the cumulative effects of the combined exposure to multiple pollutants.

4. CONCLUSION

In conclusion, the present study suggests the possibility that the global burden of some, but not all environmental pollutants (predominantly PM10, NOx, VOCs, also considering combined exposure to multiple pollutants) might have a critical role in the determination of T1D incidence in paediatric age throughout Europe. Pollution by specific toxicants might possibly trigger the development of T1D in genetically susceptible subjects, mainly through epigenetic mechanisms.

Future studies are needed, in order to verify if the major role of epigenome in the interplay between environment and genome expression (and, subsequently, the onset of T1D) might be used as a novel tool for both early diagnosis (identification of epigenetic markers for human diseases, i.e. micro-RNAs [54,55]) and therapeutic approaches, since a potential cure can arise by reversing the epigenetic effects, mainly in terms of enzyme activity.

Finally, our evidences support the hypothesis that childhood diabetes may be considered, at least in part, a preventable condition. Thus, primary prevention policies acting through a marked abatement of pollutant emissions might attenuate future T1D incidence throughout Europe.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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