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Environmental pollution and risk of type 2 diabetes mellitus: a short narrative review

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Summary

Background: *Exposure to air pollution (AP) and environmental noise influences the risk of cardiovascular diseases. These pollutants might also play a role in type 2 diabetes mellitus (T2DM).* **Objectives:** *To summarize the current evidence on the association between AP, noise and T2DM.* **Methods:** *We searched PubMed for pertinent literature up to March 17 2019, and summarized in a narrative review the 158 retrieved works.* **Results:** *In 2009, a first murine model suggested that air pollution might cause insulin-resistance. One of the most relevant ecological studies that followed showed concordant trends among diabetes prevalence and average concentrations of fine particulate (PM2.5) in US counties. In 2015, a robust meta-analysis estimated a RR of 1.10 (95%CI: 1.02-1.18) for 10 μg/m³ increase in PM2.5, and of 1.08 (1.00-1.17) for the same increase in nitrogen dioxide. Even exposures to increasing levels of ozone seem to be associated with higher incident cases of T2DM (+18% per 6.7 ppb). Studies on noise as well, although more limited, seem to indicate an association with an increased risk of T2DM.* **Discussion:** *Adequate control for confounders and potential effect modifiers is often highlighted as a critical aspect, together with uncertainty deriving from accurate definition of diagnosis. Open issues are related to critical exposure windows and the role of specific components of the pollution mixture in determining health effects. Current evidence seems to indicate an association between AP and T2DM, but some aspects still need to be elucidated. Greater uncertainty characterizes the association between noise and T2DM.*

Riassunto

«Inquinamento ambientale e rischio di diabete mellito di tipo 2: una breve revisione narrativa». **Introduzione:** *L'esposizione a inquinamento atmosferico (IA) e rumore ambientale influenza il rischio di patologie cardiovascolari. Tali inquinanti potrebbero avere un ruolo anche nell'insorgenza di diabete mellito di tipo 2 (DM2).* **Obiettivi:** *Sintetizzare le evidenze di letteratura ad oggi disponibili sull'associazione tra IA, rumore e DM2.* **Metodi:** *È stata condotta una ricerca in PubMed al 17 marzo 2019, sintetizzando in una revisione narrativa le evidenze dei 158 lavori individuati.* **Risultati:** *Nel 2009, un primo modello murino suggerisce come l'IA possa provocare insulino-resistenza. Seguono studi ecologici, di cui il più significativo mostra andamenti concordi tra prevalenza di diabete e concentrazioni medie di particolato fine (PM2.5) in contee statunitensi. Nel 2015, una robusta meta-analisi stima un RR di 1,10*

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(IC95%: 1,02-1,18) per incrementi di 10 μg/m³ di PM2.5, e di 1,08 (1,00-1,17) per analoghi incrementi di biossido di azoto. Anche esposizioni a livelli crescenti di ozono sembrerebbero comportare un incremento di casi incidenti di DM2 (+18% ogni 6,7 ppb). Le indagini condotte sul rumore, seppur più limitate, sembrano anch'esse indicare un'associazione con un aumentato rischio di DM2. **Discussione:** *L'incapacità di tenere adeguatamente conto di fattori confondenti e di potenziali modificatori d'effetto viene spesso segnalata come aspetto critico, insieme all'incertezza derivante dalla definizione della diagnosi. Problemi aperti riguardano l'individuazione di finestre di esposizione critiche e il ruolo delle specifiche componenti della miscela inquinante nel determinare effetti sulla salute. Le evidenze ad oggi disponibili sembrano indicare un'associazione tra IA e DM2, anche se rimangono aspetti da approfondire. Maggiore incertezza caratterizza l'associazione tra rumore e DM2.*

Introduction

The health effects of exposure to air pollution are well known, since many studies documented an association between both gaseous and particulate pollutants and health outcomes, especially respiratory and cardiovascular effects (3, 17). More recently, air pollution has been suggested to have a role also in metabolic dysfunction, and thus potentially increase the risk of type 2 diabetes mellitus (T2DM) (22).

Among other environmental pollutants, even exposure to noise (especially from aircrafts and road traffic) has been found to influence the risk of heart disease and stroke (12). However, evidences on the association between noise and diabetes are still inconsistent.

With the present narrative review, we aim to briefly summarize the current evidences on the association between environmental pollutants (especially air pollution and noise) and diabetes, and highlight criticisms and open issues on the topic.

Methods

We searched the electronic literature database PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) for pertinent literature up to March 17 2019. As this was meant to be a quick and narrative review on the topic of environmental pollution and T2DM, we decided to tailor our search using the following string: ("air pollution"[MeSH] OR "particulate matter"[MeSH] OR "nitrogen dioxide"[MeSH] OR ozone[MeSH] OR noise[MeSH]) AND "Diabetes Mellitus, Type 2"[MeSH]. We applied no filters for study design or language. We screened titles and abstracts for pertinence and retrieved potentially relevant articles as full texts.

Results

The PubMed search returned 158 publications. Some articles intercepting the topic dated back in the '90s, with no publication though directly addressing the link between exposure to environmental toxicants and T2DM. As a matter of fact, the works published between 1990 and 2008 mostly considered diabetic subjects as a hypersusceptible population where to study and better capture health effects (other than diabetes) associated with exposure to noise (14) or air pollution (8, 19).

In 2009, Sun and colleagues published the first article recovered by our search explicitly addressing, in a murine model, the question of whether air pollution is associated with T2DM (or related traits): they observed that a 6-month exposure at cumulative concentration levels of particulate matter with diameter less than or equal to 2.5 μm (PM2.5) induced insulin resistance in high-fat-fed nonatherosclerotic mice (24).

In the last decade, the interest for this topic has clearly increased, with a peak of articles between 2014 and 2016 (Figure 1).

In 2010, Pearson and colleagues published an ecological study assessing the relationship between PM2.5 annual mean levels and diabetes prevalence for the years 2004-2005, at the county level in the entire United States territory. In multivariate linear regression models (adjusted for socioeconomic covariates, behavioral risk factors, population density, and latitude), they observed a 0.78% increase

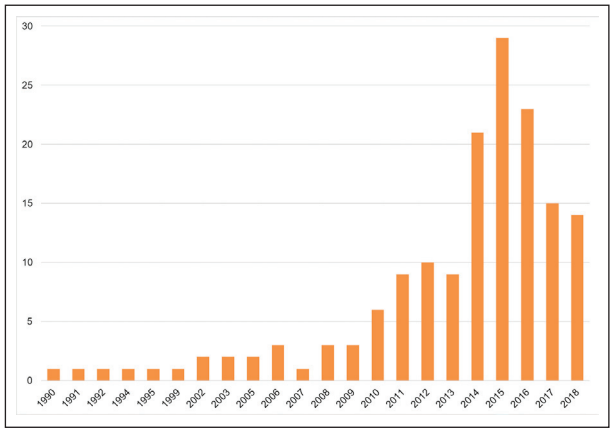

Figure 1 - PubMed results as of March 17 2019 for the search string: ("air pollution"[MeSH] OR "particulate matter"[MeSH] OR "nitrogen dioxide"[MeSH] OR ozone[MeSH] OR noise[MeSH]) AND "Diabetes Mellitus, Type 2"[MeSH]. X-axis: publication year; Y-axis: number of publications

(95% Confidence Interval [CI]: 0.39-1.25) in diabetes prevalence for each 10 μg/m^3 increase in PM2.5 concentration in 2004. Results in 2005 were comparable, with an estimated increase in diabetes prevalence equal to 0.81% (95%CI: 0.48-1.07). Interestingly, they found a similar association between increasing PM2.5 levels and diabetes prevalence after restricting the (univariate) analyses to counties with PM2.5 values below the 15 μg/m^3 limit set by the Environmental Protection Agency. Given the study design, the authors acknowledge the possibility of potential ecological biases.

In the following years, some more robust cohort studies have been published, also investigating the association between T2DM and air pollutants other than PM. For example, Andersen et al. followed over 57,000 participants of the Danish Diet, Cancer, and Health cohort between 1993-1997 and 2006, assessing the relationship between nitrogen dioxide (NO_2) exposure (estimated at the residential address since the early '70s) and incidence of diabetes (2). A 4% increase in diabetes was observed (95%CI: 1.00-1.08) per interquartile range (IQR) increase in NO_2 (4.9 μg/m^3), when restricting the analysis to confirmed diabetes cases in fully adjusted models.

Together with the work by Andersen and colleagues, an additional longitudinal study on NO_2 (16) and 3 others on PM2.5 (6, 7, 21) were considered in a sound meta-analysis by Eze and colleagues in 2015 (11). The pooled risk estimates for T2DM were equal to 1.10 (95%CI: 1.02-1.18) for 10 μg/m^3 increase in PM2.5 and 1.12 (95% CI: 1.05-1.19) for the same increase in NO_2. This latter estimate slightly decreased to 1.08 (95%CI: 1.00-1.17) when including in the analysis also results from two cross-sectional studies (5, 9). Interestingly, for both pollutants effects were more evident among females, with a risk ratio of 1.14 (95%CI: 1.03-1.26) for PM2.5 and of 1.15 (95%CI: 1.05-1.27) for NO_2.

Ozone was investigated too as potential environmental risk factor for T2DM. A large cohort study conducted on over 45,000 African American women living in metropolitan areas of the United States observed an 18% increased risk of incident diabetes (95%CI: 1.04-1.34) for an IQR increase of 6.7 ppb in ozone concentration. Interestingly, NO_2 seemed to act as effect modifier of the ozone-diabetes association, as higher hazard ratios for ozone levels were observed in areas with lower NO_2 (15).

Other than on diabetes itself, some other evidences have been produced, documenting an association between air pollution exposure and diabetes-related traits or preclinical factors, such as glycated hemoglobin, insulin resistance or glucose intolerance (26).

Finally, also environmental noise has been hypothesized to have a direct effect on the risk of diabetes. The only meta-analysis identified on the topic summarized evidences from five investigations on residential noise exposure and estimated a 19% increase in T2DM risk (95%CI: 1.05-1.35) for exposure levels (Lden) = 60-70 dB vs. Lden < 60 dB (10).

Discussion

The amount of studies investigating the association between exposure to air pollutants and risk of diabetes has been increasingly growing in the last 10 years. Although evidences produced so far suggest that air pollution may play a minor role on human health if compared to other factors (e.g. lifestyle or genetics), *"the pervasive, persistent, and lifelong exposure to air pollutants may arguably make this an important determinant of cardiometabolic health, especially in areas that have high levels of air pollution*" (23). This appears particularly clear if we consider, for example,

a recent large cohort study conducted on about 1.7 million US veterans with no previous history of diabetes. Using the Global Burden of Disease (GBD) study methodologies, the authors estimated that, in 2016, ambient PM2.5 contributed to about 3.2 million incident cases of diabetes worldwide (95% Uncertainty Interval [UI] 2.2-3.8) and that the age-standardized burden of incident diabetes attributable to PM2.5 per 100,000 population (Figure 2) was 40.4 (95%UI 29.7-51.1) globally (4).

Most of the reviews retrieved by our search try also to describe potential biological pathways underlying the association between air pollutants and diabetes: the main hypothesis relates to pollutants exacerbating an inflammatory status, with subsequent dysregulation of the glucose metabolism through several mechanisms (e.g. cytokine release, immune cells activation, altered glucose homeostasis through defective insulin signaling in tissues, etc.) (11, 23).

Some methodological aspects arise as critical in many of the works recovered by our search.

The first one is bias related to confounder adjustment: although most of the studies did adjust their models for basic T2DM risk factors (i.e. age, body mass index, socio-economic status, smoking, family history of diabetes, physical activity), some did not consider other elements, such as diet or environmental tobacco smoke (11). The relevance of properly adjusting for confounders is highlighted by the findings of a recent cross-sectional study by O'Donovan and colleagues. After collecting data from over 10,000 participants in three diabetes-screening studies in the UK, they found nitrogen dioxide and particulate matter concentrations to be associated with T2DM in unadjusted models. However, the observed associations were not consistent after further adjustment for demographic and lifestyle factors, and neighborhood green space (18).

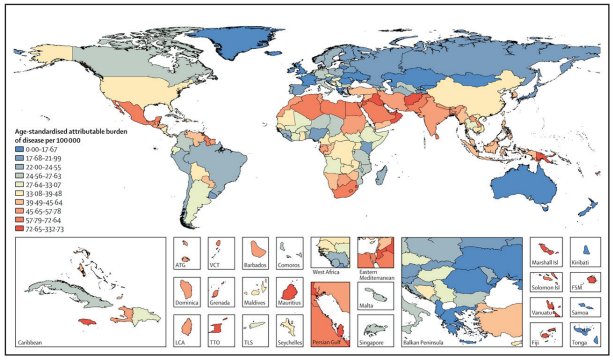

Figure 2: Age-standardized burden of incident diabetes attributable to PM2.5 per 100,000 population. List of abbreviations: ATG=Antigua and Barbuda; VCT=Saint Vincent and the Grenadines; LCA=Saint Lucia; TTO=Trinidad and Tobago; Isl=Island; FSM=Federated States of Micronesia; TLS=Timor-Leste. Adapted from Bowe et al., 2018 (4) under the CC BY 4.0 license.

Another critical point relates to bias due to outcome assessment: some studies relied on self-reported doctor-diagnosed diabetes (7, 9, 15), while others identified cases through linkage with established databases (2, 6). Both methods have limitations: relying on self-reported diagnoses entails the risk of disease misclassification, while record-linkage studies might bring to loss of cases, especially when the only informative source available is represented by hospital discharge registries.

As with most health effects associated with air pollution, even for T2DM an open question regards whether critical windows of exposure exist throughout the lifetime. To address this issue, Alderete and colleagues enrolled over 300 overweight and obese Latino children (8-15 years) and found that higher NO_2 and PM2.5 levels were associated with a faster decline in insulin sensitivity; they also observed NO_2 to negatively affect pancreatic β-cell function (1). Childhood exposure to ambient air pollution might thus be responsible for rapid metabolic dysfunction and contribute to the development of T2DM (20).

Another question regards what components of the pollutants mixture (especially particulate matter) play a role in influencing the risk of T2DM. To this extent, a study conducted in Hong Kong among residents aged 65 years or above observed an association between elemental carbon, organic carbon, nitrate, and nickel (out of 17 chemical components of PM) and daily emergency hospital admissions for T2DM (25). These findings thus suggest that PM constituents from combustion-related particles may be responsible for acute exacerbations of T2DM symptoms or complications.

Finally, other lifestyle and environmental factors (e.g. diet, noise) might act as effect modifiers of the air pollution-diabetes association. This has been

suggested, for example, by an experimental study conducted on male mice, which documented how exposure to PM2.5 potentiated T2DM development in high-fat diet (HFD)-fed mice if compared to mice only exposed to PM2.5, only treated with HFD, or to non-exposed non-treated referents (13).

Investigations on noise and T2DM still represent a small number of studies, and are characterized by a greater uncertainty and methodological challenges, especially for what concerns the heterogeneity of techniques applied to assess noise exposure (10).

Conclusions

The existing evidence indicates a positive association between air pollution and T2DM risk. Nonetheless, high-quality studies assessing dose-response effects are still needed to evaluate the role of the various pollutants, properly understand potential confounders and effect modifiers, and minimize the risk of bias.

Findings on the effects of noise on diabetes risk are still scarce and prevent firm conclusions.

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