Editorial

Functional and metabolic burden of air pollution: relevance of early disease (prediabetes) stage for progression to overt diabetes mellitus

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The growing burden of diabetes mellitus has raised interest in uncovering disease susceptibility factors, in order to contain further increases in the burden (1). It is currently admitted that both genetic and environmental factors play a critical role in the disease occurrence and progression. Besides the traditional diabetes risk factors such as unhealthy lifestyles, obesity, and family history of diabetes, interest for emerging factors such as ambient air pollutants, has significantly increased in recent years. This is reflected in a number of studies recently summarized by our group and other investigators (2-4). While existing studies suggest a modest effect of exposure to ambient air pollutants on diabetes risk, the underlying mechanisms largely remain elusive. With regard to type 2 diabetes, the progression to clinically overt disease is determined by the interplay between insulin resistance and alteration of beta-cell secretory capacity (5). It has been suggested that air pollutants could possibly interfere with these pathophysiological derangements either directly or via multiple pathways including endothelial dysfunction, systemic inflammation, dysregulation of visceral adipose tissue, mitochondrial dysfunction, non-alcoholic steatohepatosis, among others (6).

In a recent study, Wolf *et al*. have undertaken to explore some of the pathways linking air pollution with diabetes risk, by investigating the association of long-term exposure to air pollutants including PM_{10}, PMcoarse, $PM_{2.5}$ and nitrogen oxides (NO_2 and NO_X) with insulin resistance using the homeostatic model assessment of insulin resistance (HOMA-IR) as a surrogate, subclinical inflammation using high-sensitivity C-reactive protein (hs-CRP), and leptin as a member of adipokines family (7). They also explored the effects of two traffic related indicators of air pollution (i.e., the traffic intensity on the nearest road, and traffic load on major roads within 100 m of the residence). The study was conducted among residents of Augsburg in Germany and in two rural counties in its neighborhood. Oral glucose tolerance test (OGTT) was performed in individuals not previously diagnosed with diabetes, and various stages of glucose tolerance including: normal glucose metabolism, new-onset diabetes, impaired fasting glucose, impaired glucose tolerance and the combination of the two latter states were defined. Average annual exposure to air pollutions was assessed in the framework of the ESCAPE project by land use regression models incorporating participants home addresses and long-term exposure to the investigated air pollutants (8). Hierarchical linear regression models were developed to minimize the effect of potential confounders and model selection used Bayesian information criterion after adjustment, when applicable, of traffic related parameters for background air pollution. Analyses were performed in the general population and replicated in each

of the metabolic states in a sensitivity analysis. Further analyses were conducted after minimizing the number of adjustments factors in the regression models, after exclusion of individuals with relatively elevated hs-CRP (>10 mg/dL) and those receiving glucose-lowering agents or statins, then patients treated with diuretics and/or beta-blockers (7).

In the overall sample, the majority (72%, n=2,155) had no diabetes and respectively 17% (n=496) and 11% (n=323) were diagnosed with prediabetes and diabetes mellitus. Using the difference between the 5th and 95th percentile as estimate of exposure, the authors reported a positive association between all air pollutants except $PM_{2.5}$ and traffic related covariates with HOMA-IR and insulin. A tendency was observed for $PM_{2.5}$ and NO_X with glucose, while leptin increased with nitrogen oxides accretion. There was no association between all pollutants or traffic related exposure with HbA1c or hs-CRP. In analyses stratified by status for glucose tolerance, the above associations were mostly apparent in the prediabetic group, while participants with diabetes and those without showed weak or no association.

The association of exposure to air pollution with insulin resistance, driven by the effect in people with prediabetes in the sample of Wolf and colleagues (7), suggests a contribution of air pollution to the initiation or potentiation of pathophysiological process from normal glucose tolerance to prediabetes, and subsequently to diabetes mellitus. Abnormal glucose metabolism (prediabetes) is already a major determinant of the progression to overt diabetes. This risk therefore seems to be accentuated upon exposure to air pollution, by the superimposed insulin resistance state reported by Wolf *et al*. and other investigators (7,9,10). Interestingly, this process seems to occur predominantly in an inflammatory environment. Indeed, hs-CRP, a biomarker of inflammation increased with higher exposure to most of the pollutants except $PM_{2.5}$ and road traffic associated indicators, and the association of air pollutants with insulin resistance attenuated after exclusion of participants with elevated hs-CRP (7). In line with this report, other inflammatory markers have been identified as key mediators of disease susceptibility associated with ambient air pollution (9,11). The lack of association with traffic load or intensity with the outcomes of interest, emphasizes the remaining work to clarify the link between road traffic proximity and diabetes mellitus (12,13).

The findings of Wolf and co-workers have to be interpreted in the context of some important study limitations, reflecting the methodological challenges involved in such undertaking. HOMA-IR is not the best predictor of insulin resistance (14), and whether results could have been different if a more accurate measure like the euglycemic hyperinsulinemic clamp was used, is unknown. However, clamps are very challenging procedures that are not directly applicable in large population-based surveys. Similarly, land-use regression (LUR) methods have got some limitations in approximating long-term exposure to air pollution, including the risk of exposure misclassification (15). Lastly, air pollution in the study was measured years after the measurements of the biomarkers (outcomes) of interest, and as such inference about the direction of the observed association is not strictly possible. Nevertheless, the study adds to the current literature, by further highlighting a possible role of exposure to air pollution in diabetes occurrence. Indeed, the most relevant study outcomes of Wolf and co-workers (HOMA-IR and leptin) have been associated with obesity, metabolic syndrome and a higher risk of diabetes mellitus (16,17).

The interest for exposure to air pollution in relation with diabetes and chronic diseases risk has relevance, particularly to inform population-based strategies to prevent further increases in the burden. With the rapid urbanization and industrialization of the developing world, an important segment of the global population is increasingly living in polluted environment. In parallel, either incidentally or through causal links, diabetes and other chronic diseases burden are rapidly increasing in those parts of the world. Whether effective interventions to improve air quality in those settings can lower diabetes and other diseases risk, should be actively investigated.

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aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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