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Ambient and Traffic-Related Air Pollution Exposures as Novel Risk Factors for Metabolic Dysfunction and Type 2 Diabetes

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Abstract

Purpose of Review—Diabetes mellitus is a top contributor to the global burden of mortality and disability in adults. There has also been a slow, but steady rise in prediabetes and type 2 diabetes in youth. The current review summarizes recent findings regarding the impact of increased exposure to air pollutants on the type 2 diabetes epidemic.

Recent Findings—Human and animal studies provide strong evidence that exposure to ambient and traffic-related air pollutants such as particulate matter (PM), nitrogen dioxide (NO_2), and nitrogen oxides (NO_x) play an important role in metabolic dysfunction and type 2 diabetes etiology. This work is supported by recent findings that have observed similar effect sizes for increased exposure to air pollutants on clinical measures of risk for type 2 diabetes in children and adults. Further, studies indicate that these effects may be more pronounced among individuals with existing risk factors, including obesity and prediabetes.

Summary—Current epidemiological evidence suggests that increased air pollution exposure contributes to alterations in insulin signaling, glucose metabolism, and beta (β)-cell function. Future work is needed to identify the specific detrimental pollutants that alter glucose metabolism. Additionally, advanced tools and new areas of investigation present unique opportunities to study the underlying mechanisms, including intermediate pathways, that link increased air pollution exposure with type 2 diabetes onset.

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Compliance with Ethical Standards

Conflict of Interest

Tanya L. Alderete, Zhanghua Chen, Claudia M. Toledo-Corral, Zuelma A. Contreras, Jeniffer S. Kim, Rima Habre, Leda Chatzi, and Frank D. Gilliland declare no conflicts of interest.

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Keywords

air pollution; type 2 diabetes; insulin resistance; beta-cell function

Introduction

The prevalence of diabetes mellitus remains high and is a top contributor to the global burden of mortality and disability [1]. Although type 2 diabetes has been traditionally regarded as an adult disease, there has been a slow yet steady increase in youth. For example, by 2050 the number of youth with type 2 diabetes is projected to increase 4-fold [2,3], illustrating that prevention of type 2 diabetes over the life course is an enormous public health priority. While studies have shown that type 2 diabetes is strongly linked with traditional risk factors such as poor diet and low physical activity and socio-economic status, recent work suggests that ambient and traffic-related air pollution exposures may also play an important role in disease development. The detrimental impact of air pollution exposure on chronic respiratory, cardiovascular, and cerebrovascular morbidity and mortality has been extensively studied [4–6], but the relationship between exposure to air pollutants and type 2 diabetes risk is a relatively new field of study in the past decade. This targeted review provides an update of the most recent epidemiological findings regarding the impact of air pollution exposure on diabetes morbidity in adults and children between the years 2012 and 2017.

Type 2 diabetes is characterized by high peripheral glucose concentrations caused by insulin resistance and a relative deficiency of insulin secretion from pancreatic beta (β)-cells to compensate insulin resistance. In clinical practice, the diagnosis of pre-diabetes and type 2 diabetes is made based upon blood markers of altered glucose metabolism, which include elevated levels of fasting glucose, post-prandial glucose, or glycated hemoglobin (HbA1c). Additionally, insulin resistance, hyperinsulinemia, and β-cell dysfunction can serve as early indicators of risk for developing type 2 diabetes. Collectively, these metabolic markers assist researchers and clinicians in monitoring individual risk for developing type 2 diabetes and present opportunities for early intervention. In this review, the term “metabolic dysfunction” has been used to encompass these metabolic markers as they relate to type 2 diabetes progression.

Methods

In this narrative review, we performed a comprehensive review of the literature between 2012–2017. Searches were performed in August 2017. PubMed database was searched for articles that contained the terms in the title and/or abstract that were relevant to the current review. The terms included: “air pollution” AND (“diabetes,” or “type 2 diabetes,” or “prediabetes,” or “metabolic dysfunction,” or “fasting glucose,” or “fasting insulin,” or “insulin resistance,” or “insulin sensitivity,” or “HOMA-IR,” or “beta-cell function,” or “HbA1c”). We also examined bibliographies of relevant articles, and papers previously known to the authors. This resulted in 170 articles from PubMed that were further evaluated for their relevance. Of these, we included 21 articles for diabetes prevalence or incidence, 6

articles on risk factors for type 2 diabetes among children, and 14 articles on risk factors for type 2 diabetes in adults.

Air pollution and diabetes morbidity in adults

Between 2012 and 2017, thirteen studies have examined the associations between chronic ambient and/or traffic-related air pollution exposures and diabetes morbidity in adults (Table 1). Eleven of these thirteen cross-sectional studies observed positive associations between diabetes prevalence and air pollutants, predominantly with particulate matter (including PM less than 10 [PM_{10}] and 2.5 micrometers [$PM_{2.5}$]), NO_2, nitrogen oxides (NO_x) [7–19]. Additionally, two of these studies examined traffic density and proximity to roadways as proxies for residential traffic-related air pollution exposure. One of these studies observed a positive association between diabetes prevalence and self-reported traffic density perception, yet the other did not find an association between diabetes and proximity to major roads [7,17]. Most longitudinal studies in adults [20–25], but not all [19,26,27], provide evidence that increased exposure to air pollution contributes to diabetes incidence. For example, cohort studies in Denmark and Germany found that exposure to pollutants, including PM, NO_2, and traffic-related air pollutants (i.e. traffic density, distance to roadways), were associated with an elevated risk for developing diabetes [21,23]. Furthermore, results from the German cohort indicated that traffic exposures may account for the largest detrimental effects on metabolic risk where traffic- specific fine particulate matter ($PM_{2.5}$) derived from a source-specific dispersion and chemistry transport model was more strongly associated with incident diabetes than total $PM_{2.5}$ [23]. Lastly, only one longitudinal study found an increased risk of diabetes with greater ozone (O_3) exposure among African-American women [25]. Among these recent studies, there appears to be specific subgroups that are more vulnerable to the effects of air pollution exposure, including nonsmokers, obese women, physically active older adults and those with heart disease [20,21]. Further, many of the studies that found positive associations between diabetes and traffic-related or ambient air pollution were in female-only cohorts or reported stronger effect sizes in women [19–22,24,25,28].

Air pollution and metabolic dysfunction among adults

Beyond diabetes morbidity, recent studies indicate that exposure to air pollutants may negatively impact early indicators of metabolic dysfunction (Table 2). Among fourteen recent reports, nine cross-sectional studies found that increased exposure to three ambient air pollutants (PM, NO_2, and NO_x) were associated with fasting blood levels of glucose, insulin, homeostatic model assessment of insulin resistance (HOMA-IR), and/or HbA1c [11,12,28–34]. In a large study among 11,847 Chinese adults, exposure to $PM_{2.5}$ was estimated using a spatial model incorporating satellite remote sensing data and an interquartile range increase in $PM_{2.5}$ exposure (41.1 $\mu g/m^3$) in the 10 months prior to blood testing was associated with an elevated fasting glucose (4.68 mg/dL) and HbA1c (0.08%) [12]. Another study in 1,023 predominantly obese Mexican-American women found that up to 58 days of cumulative lagged exposure to $PM_{2.5}$ was associated with higher fasting insulin and glucose levels as well as HOMA-IR [28]. In addition to ambient pollutants, distance to major roadways has been used as a proxy of residential exposure to the complex mixture of traffic pollutants.

Among 371 Chinese men and women, those living within 50 meters of a major road had 1.30 times higher HOMA-IR and 1.95 μU/ml higher fasting insulin levels compared to those living more than 200 meters away, yet fasting glucose levels did not differ between these two groups [30]. In a study among 363 women from Germany, land-use regression was used to asses exposures to NO_2 and NO_x 10 to 20 years prior their clinical visit, which were found to be positively associated with impaired glucose tolerance (2-hour glucose levels ≥140–199 mg/dL) [34]. To date, only one adult study has used robust measures of risk factors for type 2 diabetes [28], which includes whole-body insulin sensitivity (S_I) and β-cell function from a frequently sampled intravenous glucose tolerance test (FSIVGTT) with minimal modeling [35]. This study found that short-term ambient exposure to $PM_{2.5}$ and NO_2 (two-months and up to 37 days prior to testing, respectively) was associated with lower S_I among the 1,023 Mexican-American previously described [28]. Results from this study were robust to multi-pollutant models and further indicated that $PM_{2.5}$ may have a larger effect on insulin resistance among those with increased obesity [28]. Although this study found strong inverse associations between ambient pollutants and S_I, exposure to $PM_{2.5}$ and NO_2 was not associated with β-cell function. Overall, results from these studies suggest that increased exposure to ambient and traffic-related air pollutants have adverse effects on altered glucose metabolism through insulin-dependent pathways.

Numerous studies have shown that increased exposure to air pollutants is associated with measures of type 2 diabetes risk, yet it remains uncertain as to whether these associations are independent of pre-existing states of metabolic dysfunction in susceptible populations. Four recent studies examined this question by conducting stratified analyses based on metabolic health [11,31–33] or restricting to a population of participants with metabolic syndrome (MetS), which is a constellation of metabolic complications associated with insulin resistance [29]. In one of the largest studies of this kind, researchers examined 73,117 adults in southern Israel. Results from this study found that average three-month concentrations of PM_{10}, but not one- to seven-day exposure, was associated with increased fasting glucose levels and HbA1c. Positive associations were observed amongst all participants; however, the strongest association was present in diabetic patients where an interquartile range increase in PM_{10} (20 $\mu g/m^3$) and $PM_{2.5}$ (7 $\mu g/m^3$) was associated with a 3.6% and 2.9% increase in HbA1c, respectively [31]. A German cohort study examined associations between an array of pollutants (e.g., PM_{10}, $PM_{2.5}$, NO_2, NO_x) in 2,944 participants who did not have diabetes, had prediabetes (impaired fasting glucose: ≥100–125 mg/dL or impaired glucose tolerance), or had diabetes. Among all participants, PM_{coarse} ($PM_{2.5-10}$), PM_{10}, $PM_{2.5}$, NO_2, and NO_x were each associated with HOMA-IR and fasting insulin levels. In a stratified analysis, the effect sizes for these pollutants were much larger and highly statistically significant among those with prediabetes compared to those who were normal in fasting glucose concentrations [32]. Further, no associations were observed between air pollutants and HbA1c levels, and only increased $PM_{2.5}$ and NO_2 exposure were modestly associated with higher fasting glucose levels among all participants [32]. In another study, prior 3-month NO_2 exposure was associated with fasting glucose levels among 131,882 adults, yet the effect sizes of these associations differed by glycemic status. For example, a 6.4 ppb (parts per billion) increase in NO_2 exposure (24–72 hours prior to testing) was associated with a 0.4%, 0.6%, and 1.1% increase in fasting glucose levels among those with

normal glucose, impaired fasting glucose, and diabetes, respectively [33]. In a large cohort of 4,121 older United Sates (U.S.) adults, 2–5 year moving averages of $PM_{2.5}$ and NO_2 exposure was associated with higher HbA1c levels in diabetic participants, while only NO_2 was significantly associated with HbA1c in non-diabetic participants [11]. Additionally, significant dose response relationships were identified for both pollutants in diabetic participants and only for NO_2 in non-diabetic participants [11]. Finally, in 65 nonsmoking adults with MetS from Beijing, four- and five-day exposure lags to exposure to ambient $PM_{2.5}$ were significantly associated with an increased HOMA-IR. Specifically, a one-standard deviation (SD) increase in $PM_{2.5}$ (67.2 $\mu g/m^3$) exposure that was estimated from urban and local monitor sites was associated with a 0.22 unit increase in HOMA-IR [29]. Results from these studies suggest that individuals with underlying type 2 diabetes risk may be more susceptible to air pollution exposure by exacerbating insulin resistance and/or impairing insulin signaling. However, additional studies are needed in order to determine how such exposures impact whole body S_I and β-cell function among susceptible populations. Despite this, associations between increased air pollution exposure and metabolic dysfunction have been observed in healthy populations, suggesting that air pollutants play an important role in type 2 diabetes development and progression.

Recent literature suggests that increased exposure to air pollutants negatively alters glucose metabolism. However, such cross-sectional studies are limited in that they are unable to determine causality. As such, longitudinal and intervention studies provide additional evidence, suggesting a causal role of air pollutants in type 2 diabetes. For example, four recent longitudinal studies [16,36–38] and one intervention study [39] found that PM_{10} and NO_2 exposures negatively impacted metabolic health, including fasting glucose and MetS. In 27,685 Chinese adults, associations between 4-day average PM_{10} and NO_2 exposure with fasting glucose levels were examined over four years of follow-up. This study found that a 100 $\mu g/m^3$ increase in PM_{10} and NO_2 was associated with 1.98 mg/dL and 9.6 mg/dL increase in fasting glucose levels, respectively. Furthermore, the effects of air pollutants on fasting glucose levels were stronger in females, the elderly, and overweight participants [36]. Amongst 3,769 participants, the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults revealed that per every 10 μ/m^3 increase in 10-year mean PM_{10} the odds for developing MetS increased between 18–72% depending on the MetS definition. Interestingly, amongst all the MetS components these associations appeared to be driven by impaired fasting glucose [16]. Another study followed 551 nondiabetic US adults for a median of 2 years and found that an interquartile range increase in 1-, 7-, and 28-day $PM_{2.5}$ exposure was associated with 0.6 mg/dL, 1.0 mg/dL, and 0.9 mg/dL higher fasting glucose level, respectively. The same $PM_{2.5}$ exposures were associated with 13%, 27%, and 32% higher odds of impaired fasting glucose respectively [37]. The same group of researchers investigated 587 men with visits every 3–7 years (average number of visits: 2) in an effort to examine associations between $PM_{2.5}$ and MetS as well as its components. This study found that a 1-$\mu g/m^3$ increase in mean annual $PM_{2.5}$ concentrations were associated with a 1.1 times higher risk of developing MetS and a 1.2 times higher risk of having an elevated fasting blood glucose level (defined as ≥100 mg/dL or medication to treat elevated blood glucose) [38]. Notably, an intervention study among 25 healthy adults in rural Michigan found that a 10 $\mu g/m^3$ increase in sub-acute $PM_{2.5}$ exposure for 5 consecutive days (with 4–5

hours/day of ambient exposures in an urban environment) was associated with increased HOMA-IR [39]. Results from these studies provide strong evidence that $PM_{2.5}$ and NO_2 exposures contribute to glucose dysregulation.

Air pollution and metabolic dysfunction among children

Meanwhile, early onset type 2 diabetes in children and youth is increasingly prevalent [40] with a heightened risk of microvascular and macrovascular complications in adult life [41]. There has been a growing body of evidence linking ambient and traffic-related air pollution exposures with metabolic dysfunction in children (Table 3). Of these, three cross-sectional studies found that increased exposure to ambient and traffic-related air pollution was associated with higher fasting insulin levels and higher HOMA-IR [42–44]. For example, among 837 adolescents from Germany, average prior year exposure to PM_{10} and NO_2 was associated with increased HOMA-IR where a 2-SD increase in PM_{10} (6.7 $\mu g/m^3$) and NO_2 (8.9 $\mu g/m^3$) were each associated with 11.4% higher HOMA-IR. Interestingly, in a multi-pollutant model including $PM_{2.5}$ and NO_2, only NO_2 exposure remained significantly associated with HOMA-IR [42]. In an earlier study in 397 German children, the same group found that HOMA-IR increased by 17.0% and 18.7% for every 2-SD increase in ambient NO_2 (6 $\mu g/m^3$) and PM_{10} (3.7 $\mu g/m^3$) exposure, respectively. Additionally, proximity to the nearest major road increased HOMA-IR by 7.2% per 500 meters [44]. The third cross-sectional study examined 54 children from the Mexico City Metropolitan Area (MCMA) and compared them to 26 controls matched on age, sex, weight, height, BMI, and socioeconomic status. Importantly, this control group lived in areas of Mexico with air pollution levels at or below air quality attainment levels. Compared to control children, MCMA children had higher fasting glucose levels but did not differ in fasting insulin levels or HOMA-IR [43]. Lastly, intervention studies provide additional evidence that air pollutants have negative effects on glucose homeostasis. For example, a clinical intervention study of 75 obese adolescents examined the metabolic benefits of laparoscopic adjustable gastric banding in the context of exposure to air pollutants. This study found that increased exposure to $PM_{2.5}$ and NO_2 attenuated the magnitude of HbA1c reduction, a known metabolic benefit of gastric banding [45]. As such, studies in children indicate that exposure to air pollutants may disrupt glucose homeostasis and/or hinder preventive methods to improve glucose metabolism.

To our knowledge, only two studies in children have investigated the impact of increased air pollution exposure using the FSIVGTT with minimal modeling in order to describe S_I, acute insulin response to glucose (AIR_g), and β-cell function [46,47]. The first was a cross-sectional study among 429 overweight and obese African American and Latino children living in urban Los Angeles, California. This study found that higher prior year exposure to ambient and traffic-related air pollutants was positively associated with adverse effects on glucose metabolism independent of body fat percent. For example, a 1-SD increase in $PM_{2.5}$ exposure (5.2 $\mu g/m^3$) was associated with 25.0% higher fasting insulin, 8.3% lower S_I, 14.7% higher AIR_g, and 1.7% higher fasting glucose. Similar associations were observed for increased NO_2 exposure. Additionally, a 1-SD increase in traffic-related air pollution exposure from non-freeway roads (4.8 ppb of NO_x) was also associated with 12.1% higher fasting insulin, 6.9% lower S_I, 10.8% higher AIR_g, and 0.7% higher fasting glucose [46]. A

recent longitudinal study built on this work by examining a cohort of 314 overweight and obese Latino youth from urban Los Angeles, California that was followed for an average of 3.4 years [47]. Results from this study found that higher NO_2 and $PM_{2.5}$ exposure over follow-up was associated with faster declines in S_I and β-cell function. As an example, a 1-SD increase in NO_2 exposure (5 ppb) over follow-up was associated with a 13% lower S_I and 13% lower β-cell function at age 18 years [47]. Although these studies included only overweight and obese minority youth, their results suggest that increased air pollution exposure affects the underlying pathophysiology of type 2 diabetes, including insulin resistance and β-cell dysfunction in children.

Mechanisms linking air pollution with metabolic dysfunction

While the exact mechanisms underlying the associations between increased air pollution exposure and greater risk of type 2 diabetes remain uncertain, most hypothesized mechanisms include inflammatory or oxidative-stress responses. Exposure-induced inflammation in the lungs, may lead to spill-over of pro-inflammatory cytokines and chemokines to other tissues [48–54] or it may trigger neuronal responses in the brain. Either can cause a cascade of events that may lead to metabolic dysfunction. Additionally, PM components such as transition metals and lipopolysaccharides may penetrate into the systemic vasculature and/or activate toll-like receptors, [55] leading to increased inflammation. Exposure to air pollutants may also alter basal metabolism, including increased white adipose tissue accumulation relative to metabolically active brown adipose tissue, [56,57] inhibition of lipolysis [58], and/or increased adipose tissue inflammation [59]. Finally, inhaled or ingested PM can result in intestinal inflammation and increasing metabolic susceptibilities. These hypothesized mechanisms are largely derived from animal studies and suggest that the effects of increased air pollution exposure on diabetes etiology are complex and multifactorial.

Diabetes is characterized by an altered metabolism of key molecules and pathways that regulate insulin sensitivity and glycemic control. Metabolomics studies [60] suggest that exposure to air pollutants may alter these molecules and/or endogenous metabolites, which may contribute to increased inflammation and diabetes development. In a cohort of cardiac catheterization patients in the U.S. [61], researchers found that one-day lagged exposure to $PM_{2.5}$ and O_3 was associated with changes in amino acid concentrations of the glycineornithine-arginine metabolic axis, as well as increased levels of medium- and long-chain acylcarnitines, which indicated the involvement of oxidative stress [62] and mitochondrial dysfunction [63]. Another study in London [64] found that higher long-term exposure to PM_{10} and $PM_{2.5}$ was associated with lower levels of asparagine and glycine. Interestingly, decreased glycine concentrations and increased levels of acylcarnitines have been related with insulin resistance and increased risk of type 2 diabetes [63,65–67]. In addition, a meta-analysis of targeted metabolomics across four cohorts in Germany [61] suggested that higher lagged 5-day averaged exposure to $PM_{2.5}$, NO_2, and O_3 were associated with higher levels of lysophosphatidylcholines, which are associated with oxidative stress and increased oxidation of LDL [68]. Finally, non-targeted metabolomics studies of O_3 suggest that acute (0–1 hour lagged) exposure can rapidly increase lipolysis and incomplete fatty acid oxidation in rats and humans [69,70]. Evidence in rats also suggest

that short- and long-term exposure to air pollutants, including $PM_{2.5}$ and O_3, can increase lipid peroxidation and result in dyslipidemia and insulin resistance [69,71–73]. Overall, metabolomic studies suggest that $PM_{2.5}$, NO_2, and O_3 exposure may contribute to metabolic dysfunction.

The neuroendocrine system may also play a role in air pollution-induced metabolic dysfunction via central nervous system (CNS) activation and downstream effects on psycho-behavioral pathways. A recent study in mice found that weight gain resulting from exposure to diesel exhaust was paralleled by changes in neuro-inflammation and neuronal structure in cognitive and emotional brain areas, suggesting that air pollution exposure directly alters the CNS [74]. It has also been shown that hunger and satiety signals interact with the hypothalamus to regulate energy status, feeding behaviors, and metabolism [75]. Moreover, air pollution may also act on the hypothalamus-pituitary-adrenal (HPA) system to alter the hormonal stress response [76]. In rats, for example, it has been shown that acute O_3 exposure induces the activation of nucleus tractus solitarius neurons through the vagal nerves and promotes neuronal activation in stress-responsive regions of the CNS [77]. In humans, acute O_3 exposure resulted in increased serum corticosterone and cortisol as well as lipid dysregulation [70]. These studies suggest O_3-induced effects on the stress response through the CNS, which may ultimately affect metabolic regulation.

An emerging area of research suggests that increased exposure to air pollution may alter the composition and/or function of the gut microbiome where particles may reach the intestine through inhalation and diffusion from the lungs into systemic circulation or ingestion of inhaled particles following mucociliary clearance from the airways [78–81]. For example, studies in rodents have shown that ingestion of airborne sources of PM alter the gut microbiome and increase intestinal inflammation [82–84]. Studies in mice also indicate that exposure to PM alters resident bacteria, promotes intestinal inflammation, disrupts gut barrier integrity, and increases gut bacterial translocation [81,84,85]. As such, exposure-induced alterations in the gut microbiome may decrease gut barrier integrity, resulting in increased gut bacterial translocation, and a chronic low-grade level of inflammation that has been linked with insulin resistance and decreased glucose utilization [86–88]. Studies examining associations between air pollution exposure and chronic intestinal disease further support effects of air pollution on the gut [78]. One study found that adolescents who lived in regions with greater NO_2 concentrations were more likely to be diagnosed with Crohn's disease [89] and when indicators of air pollution (NO_2, $PM_{2.5}$) were elevated, adolescents and young adults visited emergency rooms more often for intestinal bowel disease-related pain [90]. Recently, work in overweight and obese adolescents found that increased exposure to traffic-related air pollutants was correlated with gut bacterial taxa and fasting glucose levels, suggesting that exposure to air pollutants may contribute to metabolic dysfunction through alterations in the gut microbiota [91]. Lastly, the gut and CNS have strong connections via the gut-brain axis, which is comprised of multiple sensing and signaling pathways that are thought to convey enteric signals to the brain. These signals can be mediated by the composition of the gut microbiome through alterations in the HPA axis in the form of gut hormones, through microbial-derived neurotransmitters, and/or gut bacterial translocation that may result in increased levels of systemic inflammation and increased risk of type 2 diabetes [92].

Conclusions

Human and animal studies provide strong evidence that short- and long-term exposures to ambient and traffic-related air pollutants, namely PM, NO_2, NO_x, play a role in glucose metabolism and type 2 diabetes etiology. This work is supported by recent findings that have observed similar effect sizes for increased exposure to air pollutants on clinical measures of risk for type 2 diabetes in children and adults. Emerging evidence also indicates that exposure to air pollutants has stronger effects in susceptible populations, including females and those with obesity and existing metabolic dysfunction. Despite recent advances in our understanding of the effects of air pollution exposure on human health, few long-term follow-up studies have examined the chronic and dynamic impacts of air pollution on increased diabetes risk. Additionally, most recent epidemiological studies have relied on air pollution exposure estimated from central monitors and/or model predictions. In order to fully understand the mechanics linking air pollution exposure with risk for type 2 diabetes, future studies should characterize the sources of air pollution exposure taking into account the multipollutant nature of the mixture and its varying chemical composition and physical properties that could lead to differential toxicity. Beyond these approaches, advanced tools (e.g., metabolomics) and new areas of investigation such as the CNS and the microbiome present distinct opportunities to generate additional evidence for causality by constructing the potential biological pathways linking air pollution exposure with type 2 diabetes. In summary, the strength of the current evidence linking air pollution exposure with metabolic dysfunction and diabetes risk warrants broader thinking about including the environment in the prevention and treatment of diabetes.

REFERENCES

(• Important reference and • • Very important reference within past 3 years)

1. Vos T, Allen C, Arora M, Barber RM, Bhutta ZA, Brown A, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016; 388:1545–602. The Author(s) Published by Elsevier Ltd This is an Open Access article under the CC BY license. [PubMed: 27733282]
2. Dabelea D, Mayer-Davis EJ, Saydah S, Imperatore G, Linder B, Divers J, et al. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. JAMA American Medical Association. 2014; 311:1778–86.
3. Imperatore G, Boyle JP, Thompson TJ, Case D, Dabelea D, Hamman RF, et al. Projections of type 1 and type 2 diabetes burden in the U.S. population aged <20 years through 2050: dynamic modeling of incidence, mortality, and population growth. Diabetes Care American Diabetes Association. 2012; 35:2515–20.
4. Ljungman PL, Mittleman MA. Ambient Air Pollution and Stroke. Stroke. 2014; 45:3734–41. [PubMed: 25300971]
5. Koulova A, Frishman WH. Air Pollution Exposure as a Risk Factor for Cardiovascular Disease Morbidity and Mortality. Cardiology in Review. 2014; 22:30–6. [PubMed: 24304808]
6. Sava F, Carlsten C. Respiratory health effects of ambient air pollution: an update. Clin Chest Med. 2012; 33:759–69. [PubMed: 23153614]
7. Dzhambov A, Dimitrova D. Exposures to road traffic, noise, and air pollution as risk factors for type 2 diabetes: A feasibility study in Bulgaria. Noise Health. 2016; 18:133–11. [PubMed: 27157686]

8. O'Donovan G, Chudasama Y, Grocock S, Leigh R, Dalton AM, Gray LJ, et al. The association between air pollution and type 2 diabetes in a large cross-sectional study in Leicester_ The CHAMPIONS Study. Environ Int Elsevier. 2017; 104:41–7.

9. Strak M, Janssen N, Beelen R, Schmitz O, Vaartjes I, Karssenberg D, et al. Long-term exposure to particulate matter, NO2 and the oxidative potential of particulates and diabetes prevalence in a large national health survey. Environ Int Elsevier. 2017; 108:228–36.

10. Sohn D, Oh H. Gender-dependent Differences in the Relationship between Diabetes Mellitus and Ambient Air Pollution among Adults in South Korean Cities. Iran J Public Health. 2017; 46:293–300. [PubMed: 28435814]

11. Honda T, Pun VC, Manjourides J, Suh H. Associations between long-term exposure to air pollution, glycosylated hemoglobin and diabetes. International Journal of Hygiene and Environmental Health. 2017; 220:1124–32. [PubMed: 28712959]

12•. Liu C, Yang C, Zhao Y, Ma Z, Bi J, Liu Y, et al. Associations between long-term exposure to ambient particulate air pollution and type 2 diabetes prevalence, blood glucose and glycosylated hemoglobin levels in China. Environ Int. 2016; 92–93:416–21. Large, cross-sectional study (n=11,847) conducted in China with relatively high pollution levels. Results suggest that long-term exposures to ambient $PM_{2.5}$ were associated with higher risk of type 2 diabetes. These findings suggest that air pollution exposures impact type 2 diabetes risk in high polluted areas. Notably, similar findings were also observed in Europe and North America, where air pollution levels are relatively low.

13. Requia WJ, Adams MD, Koutrakis P. Science of the Total Environment. Vol. 584–585. Elsevier B.V; 2017. Association of PM2.5 with diabetes, asthma, and high blood pressure incidence in Canada: A spatiotemporal analysis of the impacts of the energy generation and fuel sales; 1077–83.

14. To T, Zhu J, Villeneuve PJ, Simatovic J, Feldman L, Gao C, et al. Chronic disease prevalence in women and air pollution—A 30-year longitudinal cohort study. Environ Int Elsevier Ltd. 2015; 80:26–32.

15. Mazidi M, Speakman JR. Sci Rep. Springer US; 2017. Ambient particulate air pollution (PM2.5) is associated with the ratio of type 2 diabetes to obesity; 1–8.

16. Eze IC, Schaffner E, Fischer E, Schikowski T, Adam M, Imboden M, et al. Long-term air pollution exposure and diabetes in a population-based Swiss cohort. Environ Int The Authors. 2014; 70:95–105.

17. Lazarevic N, Dobson AJ, Barnett AG, Knibbs LD. Long-term ambient air pollution exposure and self-reported morbidity in the Australian Longitudinal Study on Women's Health: a cross-sectional study. BMJ Open. 2015; 5:e008714–10.

18. Chien L-C, Alamgir H, Yu H-L. Science of the Total Environment. Vol. 508. Elsevier B.V; 2015. Spatial vulnerability of fine particulate matter relative to the prevalence of diabetes in the United States; 136–44.

19••. Park SK, Adar SD, O'Neill MS, Auchincloss AH, Szpiro A, Bertoni AG, et al. Long-term exposure to air pollution and type 2 diabetes mellitus in a multiethnic cohort. Am J Epidemiol. 2015; 181:327–36. A large multiethnic, prospective study (n=5,839) across six sites in the United States, which found long-term exposures to NO_2 and $PM_{2.5}$ were associated with a higher prevalence of type 2 diabetes across all sites. However, the longitudinal associations between long-term exposures to NO_2 and $PM_{2.5}$ and type 2 diabetes incidence were largely nonsignificant in across study sites. [PubMed: 25693777]

20••. Hansen AB, Ravnskjær L, Loft S, Andersen KK, Bräuner EV, Baastrup R, et al. Long-term exposure to fine particulate matter and incidence of diabetes in the Danish Nurse Cohort. Environ Int The Authors. 2016; 91:243. 50. Large prospective cohort study among 28,731 female nurses in Denmark. Results indicate that long-term exposures to $PM_{2.5}$ were associated with greater diabetes incidence from year 1993–2013. No significant associations were observed for NO_2, PM_{10} and NO_x exposures. The associations with $PM_{2.5}$ were larger in non-smokers and obese participants.

21. Andersen ZJ, Raaschou-Nielsen O, Ketzel M, Jensen SS, Hvidberg M, Loft S, et al. Diabetes incidence and long-term exposure to air pollution: a cohort study. Diabetes Care American Diabetes Association. 2012; 35:92–8.

22. Chen H, Burnett RT, Kwong JC, Villeneuve PJ, Goldberg MS, Brook RD, et al. Risk of incident diabetes in relation to long-term exposure to fine particulate matter in Ontario, Canada. Environ Health Perspect. 2013; 121:804–10. [PubMed: 23632126]

23. Weinmayr G, Hennig F, Fuks K, Nonnemacher M, Jakobs H, Möhlenkamp S, et al. Long-term exposure to fine particulate matter and incidence of type 2 diabetes mellitus in a cohort study: effects of total and traffic-specific air pollution. Environ Health. 2015; 14:53. [PubMed: 26087770]

24. Coogan PF, White LF, Jerrett M, Brook RD, Su JG, Seto E, et al. Air pollution and incidence of hypertension and diabetes mellitus in black women living in Los Angeles. Circulation. 2012; 125:767–72. [PubMed: 22219348]

25. Jerrett M, Brook R, White LF, Burnett RT, Yu J, Su J, et al. Ambient ozone and incident diabetes: A prospective analysis in a large cohort of African American women. Environ Int Elsevier Ltd. 2017; 102:42–7.

26. Eze IC, Foraster M, Schaffner E, Vienneau D, Héritier H, Rudzik F, et al. Long-term exposure to transportation noise and air pollution in relation to incident diabetes in the SAPALDIA study. International Journal of Epidemiology. 2017; 46:1115–25. [PubMed: 28338949]

27. Coogan PF, White LF, Yu J, Burnett RT, Marshall JD, Seto E, et al. Long term exposure to NO2 and diabetes incidence in the Black Women's Health Study. Environ Res Elsevier. 2016; 148:360–6.

28••. Chen Z, Salam MT, Toledo-Corral C, Watanabe RM, Xiang AH, Buchanan TA, et al. Ambient Air Pollutants Have Adverse Effects on Insulin and Glucose Homeostasis in Mexican Americans. Diabetes Care. 2016; 39:547–54. First adult study to examine ambient air pollution exposure with robust measures of insulin sensitivity estimated from a FSIVGTT. Results indicate that short-term and long-term exposures to $PM_{2.5}$ were associated with lower insulin sensitivity as well as higher fasting glucose and dyslipidemia. [PubMed: 26868440]

29. Brook RD, Sun Z, Brook JR, Zhao X, Ruan Y, Yan J, et al. Extreme Air Pollution Conditions Adversely Affect Blood Pressure and Insulin Resistance: The Air Pollution and Cardiometabolic Disease Study. Hypertension American Heart Association, Inc. 2016; 67:77–85.

30. Jiang S, Bo L, Gong C, Du X, Kan H, Xie Y, et al. Traffic-related air pollution is associated with cardio-metabolic biomarkers in general residents. Int Arch Occup Environ Health. 2016; 89:911–21. [PubMed: 27084335]

31. Yitshak Sade M, Kloog I, Liberty IF, Schwartz J, Novack V. The Association Between Air Pollution Exposure and Glucose and Lipids Levels. J Clin Endocrinol Metab. 2016; 101:2460–7. [PubMed: 27218271]

32•. Wolf K, Popp A, Schneider A, Breitner S, Hampel R, Rathmann W, et al. Association Between Long-term Exposure to Air Pollution and Biomarkers Related to Insulin Resistance, Subclinical Inflammation, and Adipokines. Diabetes. 2016; 65:3314–26. Large cross-sectional study (n=2,944) in German adults where air pollution levels are relatively low. Results show that higher long-term exposures to a wide spectrum of ambient and traffic- related air pollutants (e.g., NO_2, NOx, $PM_{2.5}$ and PM_{10}) were associated with higher fasting *glucose, HOMA-IR and leptin. Notably, the associations were strongest among prediabetic participants*. [PubMed: 27605624]

33•. Sade MY, Kloog I, Liberty IF, Katra I, Novack L, Novack V. Air Pollution and Serum Glucose Levels: A Population-Based Study. Medicine (Baltimore). 2015; 94:e1093. A large (n=27,685) longitudinal study in China that indicates that acute exposures (prior 0–3 day average) to NO_2, PM_{10}, SO_2 were associated higher fasting glucose, a clinical marker of glucose metabolism dysfunction. [PubMed: 26166095]

34. Teichert T, Vossoughi M, Vierkötter A, Sugiri D, Schikowski T, Schulte T. , et al. Association between Traffic-Related Air Pollution, Subclinical Inflammation and Impaired Glucose Metabolism: Results from the SALIA Study. In: Targher G, editorPLoS ONE. Vol. 8. Public Library of Science; 2013. e83042

35. Bergman RN. Lilly lecture 1989. Toward physiological understanding of glucose tolerance. Minimal-model approach. Diabetes. 1989; 38:1512–27. [PubMed: 2684710]

36•. Chen L, Zhou Y, Li S, Williams G, Kan H, Marks GB, et al. Air pollution and fasting blood glucose: A longitudinal study in China. Sci Total Environ. 2016; 541:750–5. A large longitudinal

study that shows that NO_2, PM_{10}, SO_2 were associated with fasting glucose, a clinical marker of glucose metabolism dysfunction. [PubMed: 26433332]

37. Peng C, Bind M-AC, Colicino E, Kloog I, Byun H-M, Cantone L, et al. Particulate Air Pollution and Fasting Blood Glucose in Nondiabetic Individuals: Associations and Epigenetic Mediation in the Normative Aging Study, 2000–2011. Environ Health Perspect. 2016; 124:1715–21. [PubMed: 27219535]
38. Wallwork RS, Colicino E, Zhong J, Kloog I, Coull BA, Vokonas P, et al. Ambient Fine Particulate Matter, Outdoor Temperature, and Risk of Metabolic Syndrome. Am J Epidemiol. 2017; 185:30–9. [PubMed: 27927620]
39. Brook RD, Xu X, Bard RL, Dvonch JT, Morishita M, Kaciroti N, et al. Reduced metabolic insulin sensitivity following sub-acute exposures to low levels of ambient fine particulate matter air pollution. Sci Total Environ. 2013; 448:66–71. [PubMed: 22901427]
40. Mayer-Davis EJ, Lawrence JM, Dabelea D, Divers J, Isom S, Dolan L, et al. Incidence Trends of Type 1 and Type 2 Diabetes among Youths, 2002–2012. N Engl J Med. 2017; 376:1419–29. [PubMed: 28402773]
41. Eppens MC, Craig ME, Cusumano J, Hing S, Chan AKF, Howard NJ, et al. Prevalence of diabetes complications in adolescents with type 2 compared with type 1 diabetes. Diabetes Care. 2006; 29:1300–6. [PubMed: 16732012]
42. Thiering E, Markevych I, Brüske I, Fuertes E, Kratzsch J, Sugiri D, et al. Associations of Residential Long-Term Air Pollution Exposures and Satellite-Derived Greenness with Insulin Resistance in German Adolescents. Environ Health Perspect. 2016; 124:1291–8. [PubMed: 26863688]
43. Calderón-Garcidueñas L, Franco-Lira M, D'Angiulli A, Rodríguez-Díaz J, Blaurock-Busch E, Busch Y, et al. Mexico City normal weight children exposed to high concentrations of ambient PM2. show high blood leptin and endothelin-1, vitamin D deficiency, and food reward hormone dysregulation versus low pollution controls. Relevance for obesity and Alzheimer disease. Environ Res. 2015; 140:579–92. [PubMed: 26037109]
44. Thiering E, Cyrys J, Kratzsch J, Meisinger C, Hoffmann B, Berdel D, et al. Long-term exposure to traffic-related air pollution and insulin resistance in children: results from the GINIplus and LISAplus birth cohorts. Diabetologia. 2013; 56:1696–704. [PubMed: 23666166]
45•. Ghosh R, Gauderman WJ, Minor H, Youn HA, Lurmann F, Cromar KR, et al. Air pollution, weight loss and metabolic benefits of bariatric surgery: a potential model for study of metabolic effects of environmental exposures. Pediatr Obes. 2017 The only current intervention study in children showing an attenuation of the metabolic benefits associated with bariatric surgery with increased air pollution exposure.
46•. Toledo-Corral CM, Alderete TL, Habre R, Berhane K, Lurmann FW, Weigensberg MJ, et al. Effects of air pollution exposure on glucose metabolism in Los Angeles minority children. Pediatr Obes. 2016; 312:1218. First cross-sectional study in children examining the associations of chronic exposures to ambient and traffic-related air pollutants with type 2 diabetes-related quantitative traits including robust measures of insulin sensitivity estimated from a FSIVGTT.
47••. Alderete TL, Habre R, Toledo-Corral CM, Berhane K, Chen Z, Lurmann FW, et al. Longitudinal Associations Between Ambient Air Pollution With Insulin Sensitivity, β-Cell Function, and Adiposity in Los Angeles Latino Children. Diabetes. 2017; 66:1789–96. First longitudinal study to examine ambient air pollutants (NO_2 and $PM_{2.5}$) with robust measures of insulin sensitivity and β-cell function estimated by FSIVGTT. Results indicate that long-term exposures to NO_2 and $PM_{2.5}$ were associated with faster declines in insulin sensitivity and β-cell function among overweight and obese children. [PubMed: 28137791]
48. Nemmar A. Circulation. Vol. 105. American Heart Association, Inc; 2002. Passage of Inhaled Particles Into the Blood Circulation in Humans; 411–4.
49. Tamagawa E, Bai N, Morimoto K, Gray C, Mui T, Yatera K. , et al. Am J Physiol Lung Cell Mol Physiol. Vol. 295. American Physiological Society; 2008. Particulate matter exposure induces persistent lung inflammation and endothelial dysfunction; L79–85.
50. Happo MS, Salonen RO, Hälinen AI, Jalava PI, Pennanen AS, Kosma VM, et al. Dose and time dependency of inflammatory responses in the mouse lung to urban air coarse, fine, and ultrafine particles from six European cities. Inhal Toxicol. 2007; 19:227–46. [PubMed: 17365027]

51. van Eeden SF, Tan WC, Suwa T, Mukae H, Terashima T, Fujii T, et al. Cytokines involved in the systemic inflammatory response induced by exposure to particulate matter air pollutants (PM(10)). Am J Respir Crit Care Med. 2001; 164:826–30. [PubMed: 11549540]
52. Dadvand P, Nieuwenhuijsen MJ, Agustí À, de Batlle J, Benet M, Beelen R, et al. Air pollution and biomarkers of systemic inflammation and tissue repair in COPD patients. Eur Respir J. 2014; 44:603–13. [PubMed: 24558180]
53. Fry RC, Rager JE, Zhou H, Zou B, Brickey JW, Ting J, et al. Individuals with increased inflammatory response to ozone demonstrate muted signaling of immune cell trafficking pathways. Respir Res BioMed Central. 2012; 13:89.
54. González-Guevara E, Martínez-Lazcano JC, Custodio V, Hernández-Cerón M, Rubio C, Paz C. Exposure to ozone induces a systemic inflammatory response: possible source of the neurological alterations induced by this gas. Inhal Toxicol. 2014; 26:485–91. [PubMed: 24987980]
55. Rajagopalan S, Brook RD. Air pollution and type 2 diabetes: mechanistic insights. Diabetes. 2012; 61:3037–45. [PubMed: 23172950]
56. Xu X, Liu C, Xu Z, Tzan K, Zhong M, Wang A, et al. Long-term exposure to ambient fine particulate pollution induces insulin resistance and mitochondrial alteration in adipose tissue. Toxicol Sci. 2011; 124:88–98. [PubMed: 21873646]
57. Xu X, Yavar Z, Verdin M, Ying Z, Mihai G, Kampfrath T. , et al. Arteriosclerosis, Thrombosis, and Vascular Biology. Vol. 30. Lippincott Williams & Wilkins; 2010. Effect of early particulate air pollution exposure on obesity in mice: role of p47phox; 2518–27.
58. Irigaray P, Ogier V, Jacquenet S, Notet V, Sibille P, Mejean L, et al. Benzo[a]pyrene impairs beta-adrenergic stimulation of adipose tissue lipolysis and causes weight gain in mice. A novel molecular mechanism of toxicity for a common food pollutant. FEBS J. 2006; 273:1362–72. [PubMed: 16689925]
59. Sun Q, Yue P, Deiuliis JA, Lumeng CN, Kampfrath T, Mikolaj MB, et al. Ambient air pollution exaggerates adipose inflammation and insulin resistance in a mouse model of diet-induced obesity. Circulation. 2009; 119:538–46. [PubMed: 19153269]
60. Sas KM, Karnovsky A, Michailidis G, Pennathur S. Metabolomics and diabetes: analytical and computational approaches. Diabetes. 2015; 64:718–32. [PubMed: 25713200]
61. Breitner S, Schneider A, Devlin RB, Ward-Caviness CK, Diaz-Sanchez D, Neas LM, et al. Associations among plasma metabolite levels and short-term exposure to PM2 and ozone in a cardiac catheterization cohort. Environ Int. 2016; 97:76–84. [PubMed: 27792908]
62. Sourij H, Meinitzer A, Pilz S, Grammer TB, Winkelmann BR, Boehm BO, et al. Arginine bioavailability ratios are associated with cardiovascular mortality in patients referred to coronary angiography. Atherosclerosis. 2011; 218:220–5. [PubMed: 21632053]
63. Schooneman MG, Vaz FM, Houten SM, Soeters MR. Acylcarnitines: reflecting or inflicting insulin resistance? Diabetes. 2013; 62:1–8. [PubMed: 23258903]
64. Menni C, Metrustry SJ, Mohney RP, Beevers S, Barratt B, Spector TD, et al. Circulating levels of antioxidant vitamins correlate with better lung function and reduced exposure to ambient pollution. Am J Respir Crit Care Med. 2015; 191:1203–7. [PubMed: 25978575]
65. Wang-Sattler R, Yu Z, Herder C, Messias AC, Floegel A, He Y, et al. Novel biomarkers for pre-diabetes identified by metabolomics. Mol Syst Biol. 2012; 8:615. [PubMed: 23010998]
66. Ferrannini E, Natali A, Camastra S, Nannipieri M, Mari A, Adam K-P, et al. Early metabolic markers of the development of dysglycemia and type 2 diabetes and their physiological significance. Diabetes. 2013; 62:1730–7. [PubMed: 23160532]
67. Floegel A, Stefan N, Yu Z, Mühlenbruch K, Drogan D, Joost H-G, et al. Identification of serum metabolites associated with risk of type 2 diabetes using a targeted metabolomic approach. Diabetes. 2013; 62:639–48. [PubMed: 23043162]
68. Zhao Y-Y, Wang H-L, Cheng X-L, Wei F, Bai X, Lin R-C. , et al. Sci Rep. Vol. 5. Nature Publishing Group; 2015. Metabolomics analysis reveals the association between lipid abnormalities and oxidative stress, inflammation, fibrosis, and Nrf2 dysfunction in aristolochic acid-induced nephropathy; 12936

69. Miller DB, Karoly ED, Jones JC, Ward WO, Vallanat BD, Andrews DL, et al. Inhaled ozone (O3)-induces changes in serum metabolomic and liver transcriptomic profiles in rats. Toxicol Appl Pharmacol. 2015; 286:65–79. [PubMed: 25838073]
70. Miller DB, Ghio AJ, Karoly ED, Bell LN, Snow SJ, Madden MC, et al. Ozone Exposure Increases Circulating Stress Hormones and Lipid Metabolites in Humans. Am J Respir Crit Care Med. 2016; 193:1382–91. [PubMed: 26745856]
71. Kodavanti UP. Air pollution and insulin resistance: do all roads lead to Rome? Diabetes. 2015; 64:712–4. [PubMed: 25713198]
72. Vella RE, Pillon NJ, Zarrouki B, Croze ML, Koppe L, Guichardant M, et al. Ozone Exposure Triggers Insulin Resistance Through Muscle c-Jun N-Terminal Kinase Activation. Diabetes. 2015; 64:1011–24. [PubMed: 25277399]
73. Wei Y, Zhang J, Li Z, Gow A, Chung KF, Hu M, et al. Chronic exposure to air pollution particles increases the risk of obesity and metabolic syndrome: findings from a natural experiment in Beijing. The FASEB Journal. 2016; 30:2115–22. [PubMed: 26891735]
74. Bolton JL, Smith SH, Huff NC, Gilmour MI, Foster WM, Auten RL, et al. Prenatal air pollution exposure induces neuroinflammation and predisposes offspring to weight gain in adulthood in a sex-specific manner. FASEB J. 2012; 26:4743–54. [PubMed: 22815382]
75. Elmquist JK, Scherer PE. JAMA. Vol. 308. American Medical Association; 2012. The cover. Neuroendocrine and endocrine pathways of obesity; 1070–1.
76. Kodavanti UP. Stretching the stress boundary: Linking air pollution health effects to a neurohormonal stress response. Biochim Biophys Acta. 2016; 1860:2880–90. [PubMed: 27166979]
77. Gackière F, Saliba L, Baude A, Bosler O, Strube C. Ozone inhalation activates stress-responsive regions of the CNS. Journal of Neurochemistry. 2011; 117:961–72. [PubMed: 21466555]
78. Beamish LA, Osornio-Vargas AR, Wine E. J Crohns Colitis. Vol. 5. The Oxford University Press; 2011. Air pollution: An environmental factor contributing to intestinal disease; 279–86.
79. Möller W, Häussinger K, Winkler-Heil R, Stahlhofen W, Meyer T, Hofmann W, et al. Mucociliary and long-term particle clearance in the airways of healthy nonsmoker subjects. J Appl Physiol. 2004; 97:2200–6. [PubMed: 15347631]
80. Nemmar A, Hoet PM, Vanquickenborne B, Dinsdale D, Thomeer M, Hoylaerts MF. , et al. Circulation. Vol. 105. Am Heart Assoc; 2002. Passage of inhaled particles into the blood circulation in humans; 411–4.
81. Salim SY, Kaplan GG, Madsen KL. Air pollution effects on the gut microbiota: a link between exposure and inflammatory disease. Gut Microbes. 2014; 5:215–9. [PubMed: 24637593]
82. Dybdahl M. DNA adduct formation and oxidative stress in colon and liver of Big Blue(R) rats after dietary exposure to diesel particles. Carcinogenesis. 2003; 24:1759–66. [PubMed: 12919963]
83. Kish L, Hotte N, Kaplan GG, Vincent R, Tso R, Gänzle M. , et al. PLoS ONE. Vol. 8. Public Library of Science; 2013. Environmental particulate matter induces murine intestinal inflammatory responses and alters the gut microbiome; e62220
84. Mutlu EA, Engen PA, Soberanes S, Urich D, Forsyth CB, Nigdelioglu R, et al. Particulate matter air pollution causes oxidant-mediated increase in gut permeability in mice. Part Fibre Toxicol. 2011; 8:19. [PubMed: 21658250]
85. Kish L, Hotte N, Kaplan GG, Vincent R, Tso R, Gänzle M, et al. Environmental particulate matter induces murine intestinal inflammatory responses and alters the gut microbiome. PLoS ONE. 2013; 8:e62220. [PubMed: 23638009]
86. Shen J, Obin MS, Zhao L. The gut microbiota, obesity and insulin resistance. Mol Aspects Med. 2013; 34:39–58. [PubMed: 23159341]
87. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 2006; 444:1027–31. [PubMed: 17183312]
88. Amar J, Lange C, Payros G, Garret C, Chabo C, Lantieri O. , et al. Blood microbiota dysbiosis is associated with the onset of cardiovascular events in a large general population: the D .S.I.R. study. In: Bayer A, editorPLoS ONE. Vol. 8. 2013. e54461

89. Kaplan GG, Hubbard J, Korzenik J, Sands BE, Panaccione R, Ghosh S, et al. The inflammatory bowel diseases and ambient air pollution: a novel association. Am J Gastroenterol. 2010; 105:2412–9. [PubMed: 20588264]

90. Kaplan GG, Szyszkowicz M, Fichna J, Rowe BH, Porada E, Vincent R. , et al. Non-Specific Abdominal Pain and Air Pollution: A Novel Association. In: Amre D, editorPLoS ONE. Vol. 7. 2012. e47669

91. Alderete TL, Jones RB, Chen Z, Kim JS, Habre R, Lurmann F, et al. Exposure to traffic-related air pollution and the composition of the gut microbiota in overweight and obese adolescents. Environ Res. 2017; 161:472–8.

92. Lerner A, Neidhöfer S, Matthias T. The Gut Microbiome Feelings of the Brain: A Perspective for Non-Microbiologists. Microorganisms. 2017:5.

Table 1

Summary of recent studies between ambient and traffic-related exposures with type 2 diabetes incidence or prevalence

Reference	Study Design	Location	Sample Size	Pollutants	Main Findings
Eze et. al. (2017)	Longitudinal	Switzerland	2,631	NO_2	An IQR increase in NO_2 (15 μg/m^3) was not associated with incident diabetes [RR=0.87, 95%CI: 0.62, 1.21].
Honda et. al. (2017)	Cross-sectional	United States	4,121	$PM_{2.5}$, NO_2	An IQR increase in one-year moving average $PM_{2.5}$ (3.9 μg/m^3) was associated with diabetes prevalence [POR= 1.35, 95% CI: 1.19, 1.53]. An IQR increase in NO_2 (8.6 ppb) was associated with diabetes prevalence [POR=1.27, 95% CI: 1.10, 1.48].
Jerrett et. al. (2017)	Longitudinal	United States	43,003	O_3	An IQR increase in O_3 (6.7 ppb) was associated with incident T2D [HR=1.18, 95%CI: 1.04, 1.34].
Mazidi et. al. (2017)	Cross- sectional/ecologic	United States	3106 counties or equivalents from the continental USA, reflecting a population of ~170 million adults	$PM_{2.5}$	Average $PM_{2.5}$ (μg/m^3) explained 8.3% of the residual variation in T2D prevalence in males ($P < 0.0001$) and 11.5% in females ($P < 0.0001$) after correcting for obesity, race, poverty, education and temperature,
O'Donovan et. al. (2017)	Cross-sectional	United Kingdom	10,443	$PM_{2.5}$, PM_{10}, NO_2	NO_2 (μg/m^3) was not associated with T2D prevalence after adjustment for demographic factors [OR= 1.08; 95% CI: 0.91, 1.29], further adjustment for lifestyle factors [1.10, 95% CI: 0.92, 1.32], and further adjustment for neighborhood green space [OR=0.91, 95% CI: 0.72, 1.16]. $PM_{2.5}$ and PM_{10} were not significantly associated with T2D prevalence (p-value >0.05).
Requia et. al. (2017)	Cross- sectional/ecologic	Canada	117 health regions	$PM_{2.5}$	A 2-year increase of 10 μg/m^3 in $PM_{2.5}$ was associated with a 5.43% increase in incidence of diabetes [95%CI: 2.28%, 12.53%].
Sohn et. al. (2017)	Cross-sectional	South Korea	96,608	PM_{10}, SO_2	Exposure to PM_{10} (μg/m^3) and SO_2 (10^{-3} ppm) was associated with the prevalence of T2D among women [OR=1.01, 95%CI: 1.003, 1.013; OR=1.032, 95% CI: 1.004, 1.062, respectively], but not among men [OR=1.003, 95% CI: 0.998, 1.008; OR=0.98, 95% CI: 0.952, 1.006].
Strak et. al. (2017)	Cross-sectional	Netherlands	387,195	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, NO_2, OP^{DDT}, OP^{ESR}	All pollutants, except $PM_{2.5}$, were associated with diabetes prevalence. An IQR increase in NO_2 (7.76 μg/m^3) and OP^{DTT} (0.28 nmol DTT/min/m^3) was associated with diabetes prevalence [OR=1.07, 95%CI:1.05, 1.09; 1.08, 95% CI: 1.05, 1.10, respectively].
Coogan et. al. (2016)	Longitudinal	United States	43,003	NO_2	NO_2 was not associated with diabetes incidence (p-value >0.05).
Dzhambov et. al. (2016)	Cross-sectional	Plovdiv, Bulgaria	513	$PM_{2.5}$, BaP, traffic density	No significant associations with T2D for any pollutants (p-value >0.05).

Reference	Study Design	Location	Sample Size	Pollutants	Main Findings
Hansen et. al. (2016)	Longitudinal	Denmark	24,174	PM_{10}, $PM_{2.5}$, NO_x, NO_2	An IQR increase in $PM_{2.5}$ (3.1 μg/m^3) increased diabetes incidence [HR=1.11, 95% CI: 1.02, 1.22]. An IQR increase in PM_{10} (2.8 μg/m^3) [HR=1.06, 95% CI: 0.98, 1.14], NO_2 (7.5 μg/m^3) [HR=1.05, 95%CI: 0.99, 1.12] and NO_X (10.2 μg/m^3) [HR=1.01, 95% CI: 0.98, 1.05] was weakly associated with diabetes incidence. Associations with $PM_{2.5}$ enhanced in non-smokers, obese women, and heart disease patients.
Lazarevic et. al. (2015)	Cross-sectional	Australia	26,991	NO_2, distance to major/minor road	No significant associations were found between any pollutant and diabetes prevalence (p-value >0.05).
Liu et. al. (2016)	Cross-sectional	China	11,847	$PM_{2.5}$	An IQR increase in $PM_{2.5}$ (41.1 μg/m^3) was associated with increased T2D prevalence [PR: 1.14, 95% CI: 1.08, 1.20].
Park et. al. (2015)	Longitudinal	6 US sites *	5,839	$PM_{2.5}$, NO_x	An IQR increase in $PM_{2.5}$ (2.43 μg/m^3) and NO_x (47.1 pbb) was associated with T2D prevalence [OR=1.09, 95%CI: 1.00, 1.17; OR=1.18, 95% CI: 1.00, 1.38, respectively].
To et. al. (2015)	Cross-sectional	Canada	29,549	$PM_{2.5}$	A 10 μg/m^3 increase in $PM_{2.5}$ was associated with diabetes [PR=1.28, 95% CI: 1.16, 1.41]. Risks elevated in the obese.
Weinmayr et. al. (2015)	Longitudinal	Germany	3,607	PM_{10}, $PM_{2.5}$	An increase of 1 μg/m^3 in PM_{10} [RR=1.05, 95% CI: 1.00, 1.10) and $PM_{2.5}$ [RR=1.03, 95% CI: 0.95, 1.12] was associated with incident T2D. Traffic- specific PM_{10} and $PM_{2.5}$ were more strongly associated with T2D [RR=1.36, 95%CI: 0.98, 1.89; RR=1.36, 95% CI: 0.97, 1.89, respectively]. Individuals closer than 100m to busy road had a higher risk of incident T2D [RR=1.37, 95% CI: 1.04, 1.81].
Chien et. al. (2014)	Cross- sectional/ecologic	United States	3109 counties in the 48 contiguous states	$PM_{2.5}$	An increase in 1 μg/m^3 $PM_{2.5}$ increased the relative risk percentage for diabetes from −5.47 (95% credible interval: −6.14, −4.77) to 2.34% (95% credible interval: 2.01, 2.70) where 1323 of 3109 counties (42.55%) displayed diabetes vulnerability with significantly positive risk percentages.
Eze et. al. (2014)	Cross-sectional	Switzerland	6,392	PM_{10}, NO_2	PM_{10} and NO_2 were associated with prevalent diabetes [OR= 1.40, 95% CI: 1.17, 1.67; OR=1.19, 95% CI: 1.03, 1.38, respectively] per 10 μg/m^3 increase in average home outdoor level.
Chen et. al. (2013)	Longitudinal	Ontario, Canada	62,012	$PM_{2.5}$	A 10 μg/m^3 increase in $PM_{2.5}$ was associated with incident diabetes 1.11 (95% CI:1.02, 1.21).
Andersen et. al. (2012)	Longitudinal	Denmark	57,053	NO_2, traffic density/proximity	An IQR increase in NO_2 (4.9 μg/m^3) was associated with confirmed diabetes incidence [HR=1.04, 95% CI:1.00–1.08]. Traffic load within 100 m was associated with confirmed diabetes incidence [HR=1.02, 95%CI: 1.00, 1.04]. NO_2 effects were enhanced in nonsmokers, [HR=1.12, 95% CI: 1.05, 1.20] and physically active people [HR=1.10, 95% CI:1.03, 1.16].

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Reference	Study Design	Location	Sample Size	Pollutants	Main Findings
Coogan et. al. (2012)	Longitudinal	Los Angeles, California	3,992	NO_x, $PM_{2.5}$	A 10 μg/m^3 in $PM_{2.5}$ and an IQR increase in NO_x (12.4 parts ppb) was associated with diabetes [IRR=1.63, 95% CI: 0.78, 3.44; IRR=1.25, 95% CI: 1.07, 1.46, respectively].

Summarizes the main findings from studies in adults between 2012 and 2017 that were included in this review. Bap: benzo alpha pyrene, CI: confidence interval, DTT: dithiothreitol, HR: hazard ratio, IQR: interquartile range, IRR: incidence rate ratio, nmol: nanomole, NO_2: nitrogen dioxide, NO_X: nitrogen oxide, O_3: ozone, OP^{DTT}: oxidative potential dithiothreitol OP^{ESR}: oxidative potential electron spin resonance, OR: odds ratio, PM: particulate matter, POR: prevalence, ppb: parts per billion, ppm: parts per million, PR: prevalence ratio, RR: risk ratio, SO_2: sulfur dioxide, T2D: type 2 diabetes.

*Six US sites included Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; New York, New York; St. Paul, Minnesota

Table 2

Summary of recent adult studies that found significant associations between ambient and traffic-related exposures with metabolic dysfunction

Reference	Study Design	Location	Sample Size	Pollutants with Significant Associations*	Main Findings
Honda et. al. (2017)	Longitudinal	USA (Regions: North Atlantic, South, Great Lakes region, Plains States, Pacific)	4,121	$PM_{2.5}$, NO_2	↑ HbA1c
Wallwork et. al. (2017)	Longitudinal	Eastern Massachusetts, southern New Hampshire, and southern Maine, USA	587	$PM_{2.5}$	↑ Fasting glucose, ↑ Hypertriglyceridemia, ↑ Risk of developing metabolic syndrome
Brook et (2016)	Panel study (longitudinal)	Beijing Area, China	65	$PM_{2.5}$, BC	↑ HOMA-IR
Chen L et. al. (2016)	Longitudinal	Kailuan community, Tangshan City, China	27,685	NO_2, PM_{10}, SO_2	↑ Fasting glucose
Chen Z et. al. (2016)	Cross-sectional	Southern California, USA	1,023	NO_2, $PM_{2.5}$	↑ Fasting glucose, ↑ Fasting insulin, ↑ HOMA-IR, ↓S_I, ↓ HDL-to-LDL cholesterol ratio
Jiang et. al. (2016)	Cross-sectional	Urban residential area in Shanghai, China	371	$PM_{2.5}$, Residential distance to major road	↑ Fasting insulin, ↑ HOMA-IR, ↑ LDL-C
Liu et. al. (2016)	Cross-sectional	China (nationally representative sample)	11,847	$PM_{2.5}$	↑ Fasting glucose, ↑HbA1C
Peng et. al. (2016)	Longitudinal	Greater Boston Area, MA, USA	551	$PM_{2.5}$	↑ Fasting glucose, ↑ Odds of IFG
Sade et. al. (2016)	Cross-sectional	southern Israel	73,117	PM_{10}, $PM_{2.5}$	↑ Fasting glucose, ↑ HbA1C, ↑ LDL, ↑ TAG, ↓ HDL
Wolf et. al. (2016)	Cross-sectional	Augsburg, Germany and two adjacent rural counties (southern Germany)	2,944	PM_{10}, PM_{coarse},$PM_{2.5}$, NO_2, NO_x	↑ HOMA-IR, ↑ Fasting glucose, ↑Fasting insulin
Eze et. al. (2015)	Cross-sectional	Eight Swiss communities representing a wide range of environmental conditions in Switzerland	3,769	PM_{10},	↑ Odds of MetS-W, MetS-I and MetS-A, ↑ Impaired fasting glycemia,
Sade et. al. (2015)	Longitudinal	southern Israel	131,882	NO_2, SO_2	↑ Fasting glucose
Brook et. al. (2013)	Experimental	Michigan, USA	25	Environmental Mixture (only $PM_{2.5}$ measured)	↑ HOMA-IR, ↓ Heart rate variability
Teichert et. al. (2013)	Cross-sectional	North-Rhine Westphalia (West Germany)	363	NO_2, NO_x	↑ Odds impaired glucose metabolism (IFG+T2D)

Summarizes the main findings from adult studies between 2012 and 2017 that were included in this review. Pollutants listed are those found to be significantly associated with at least one measure of metabolic dysfunction. BC: black carbon, HbA1c: hemoglobin A1C, HDL: high density lipoprotein, HOMA-IR: homeostatic model assessment of insulin resistance, IFG: impaired fasting glucose, LDL: low density lipoprotein, NO_2: nitrogen dioxide, PM: particulate matter, S_I: insulin sensitivity, SO_2: sulfur dioxide, TAG: triglycerides; MetS: metabolic syndrome, T2D: type 2 diabetes.

*Statistically significant associations at a p-value <0.05.

Table 3

Summary of recent studies in children that found significant associations between ambient and traffic-related exposures with metabolic dysfunction

Reference	Study Design	Location	Sample Size	Pollutants with Significant Associations*	Main Findings
Alderete et. al. (2017)	Longitudinal	Los Angeles, CA, USA	314	NO_2, $PM_{2.5}$	↓ S_I, ↓ β-cell function (DI)
Ghosh et. al. (2017)	Prospective /Intervention	New York Area, USA	75	NO_2, $PM_{2.5}$	↓ Metabolic benefits (e.g., HbA1c) of laparoscopic adjustable gastric banding
Thiering et. al. (2016)	Cross-sectional	Southern and Western Germany	837	PM_{10}, NO_2	↑ HOMA-IR
Toledo-Corral & Alderete et. al. (2016)	Cross-sectional	Los Angeles, CA, USA	429	$PM_{2.5}$, NO_2, NO_X	↑ Fasting glucose, ↓ Fasting insulin, ↓ S_I, ↑ AIR_g
Caldero n -Garciduen as et. al. (2015)	Cross-sectional	Mexico City Metropolitan Area (MCMA) and Polotitlán, Mexico (Control City)	54 MCMA and 26 Controls	Matched case vs. control for high vs. low exposure in Mexico	Compared to control children, MCMA had ↑ Fasting glucose levels
Thiering et. al. (2013)	Cross-sectional	Munich, South Germany, and Wesel, West Germany,	397	NO_2, $PM_{2.5}$, Proximity to Roadway	↑ HOMA-IR

Summarizes the main findings from studies in children between 2012 and 2017 that were included in this review. Pollutants listed are those found to be significantly associated with at least one measure of metabolic dysfunction. AIR_g: acute insulin response to glucose, DI: disposition index, HbA1c: hemoglobin A1C, HOMA-IR: homeostatic model assessment of insulin resistance, NO_2: nitrogen dioxide, PM: particulate matter, S_I: insulin sensitivity, MCMA: Mexico City Metropolitan Area.

*Statistically significant associations at a p-value <0.05.