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Long-Term Exposure to Ambient Air Pollution and Type 2 Diabetes in Adults

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Abstract

Purpose of Review We identified 24 publications from January 2010 until September 2018 in the peer-reviewed literature addressing the relationship of long-term air pollution exposures and type 2 diabetes-related morbidity and mortality among adults. We examine key methodological issues, synthesize findings, and address study strengths and limitations. We also discuss biological mechanisms, policy implications, and future research needed to address existing knowledge gaps.

Recent Findings In general, the studies included in this review employed rigorous methodology with large sample sizes, appropriate study designs to maximize available cohort study or administrative data sources, and exposure modeling that accounted for spatial patterns in air pollution levels. Overall, studies suggested increased risks of type 2 diabetes-related morbidity and mortality among adults associated with increased exposures; however, findings were not uniformly positive nor statistically significant.

Summary Current research is particularly limited regarding the biological mechanisms involved and the relationship between ozone and diabetes. Additionally, more research is needed to distinguish clearly the effects of nitrogen oxides from those of other pollutants and to identify potential subpopulations with greater susceptibility for certain pollutant exposures. A better understanding of the potential link between long-term ambient air pollution exposures and type 2 diabetes may provide opportunities for the reduction of health risks and inform future interventions for environmental protection and diabetes management.

Keywords Air pollution · Type 2 diabetes · Chronic exposures

Introduction

According to the World Health Organization, exposure to ambient air pollution is responsible for 4.2 million premature deaths worldwide every year [1•]. Ambient air pollution is a complex mixture of natural and synthetic substances, containing many chemical and biological constituents, in the form of gases and particulate matter released into and formed in the atmosphere. In addition to particulate matter, other major constituents of air pollution include ozone, nitrogen dioxide, sulfur dioxide, carbon monoxide, and lead [2]. Studies conducted over the last three decades have implicated exposure to ambient air pollution constituents to various adverse health effects, including cardiovascular disease, respiratory diseases, adverse pregnancy outcomes, cancer, and more recently, altered neurodevelopment [3–6]. Prior research has also shown that people with type 2 diabetes mellitus have higher risks of air pollution-related cardiovascular and respiratory outcomes compared with healthier populations [7, 8••, 9, 10]. There is

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also emerging evidence that increases in exposures to ambient air pollution may be associated with increased risks of type 2 diabetes morbidity and mortality among adults [11, 12].

The potential link between ambient air pollution and diabetes is of significant public health concern as the global health and economic burden from each of these is large and expected to increase. For example by 2030, diabetes is estimated to result in a global economic burden of $2.1 trillion USD and is projected to be the seventh leading cause of death worldwide [13]. Diabetes is a chronic disease that results from the body's inability to produce the insulin, which helps regulate the amount of glucose in the blood. The most common types of diabetes are type 1, type 2, and gestational diabetes. Type 1 diabetes results when the body cannot produce any insulin, while type 2 results when the body does not produce sufficient insulin. Type 2 diabetes is the most common type of diabetes and occurs most often among middle-aged and older adults [14]. While the exact biological mechanisms by which ambient air pollutants could increase an individual's risk of developing diabetes have not been clearly elucidated, several mechanisms have been proposed including impaired glucose metabolism and inflammation [15–17]. In addition, an animal study conducted by Sun et al. suggests linkages between particulate matter exposure and insulin resistance, supporting biologic plausibility [18].

In this review article, we examine peer-reviewed epidemiologic studies published from January 2010 until September 2018 that evaluated the role of long-term ambient air pollution exposures in the risk of type 2 diabetes-related morbidity and mortality among adults. We examine key methodological issues, synthesize findings, and address study strengths and limitations. We also discuss biological mechanisms, policy implications, and future research needed to address existing knowledge gaps.

Methods

The US National Library of Medicine's Pubmed database was originally searched in March, 2018, and a more systematic search developed by an experienced academic Public Health Librarian was conducted on September, 2018 to verify and update the results.

The initial search strategy combined 'diabetes' as a Medical Subject Headings (MeSH) term and keyword with the following MeSH terms and keywords for air pollution: 'air pollution', 'particulate matter', 'particulates', 'nitrogen oxides', 'nitrogen dioxide', 'ozone', and 'traffic air pollution.' Initial searches used the broad term 'air pollution'; however, given the majority of resulting abstracts focused on the specific pollutants aforementioned and for the purposes of addressing the principal air pollutants considered in regulatory policies, we employed the more specific pollutant terms in order to capture additional abstracts that did not appear under the broad term. The large number of articles and initial manual review of all identified abstracts lead us to add the following keywords to further the search focus: 'long-term' and 'chronic'. We excluded studies with keywords or MeSH terms of 'smoking' and 'tobacco'. Using filters, we limited our search to adult populations (to focus on type 2 diabetes), full articles, original research, and human studies published in English between 2010 and 2018. A manual search of abstracts was conducted to identify epidemiologic studies with a main research question/hypothesis and analyses addressing the relationship between type 2 diabetes and long-term exposure to air pollution.

Consequently, a similar search strategy was developed by an experienced academic Public Health Librarian (Appendix 1) based on the MeSH terms and keywords frequently used in the 21 articles identified through the first search. A total of 432 references were initially identified followed by a manual process of selection and screening titles and abstracts (Appendix 2). Full text manual screening of the 31 selected records resulted in a final set of 24 publications of 21 study populations.

We note that most publications reported results from several statistical models (e.g., adjusted for different confounders, sensitivity analyses). In this review, we attempt to present at least one fully adjusted model from the main analyses; however, our review is not an exhaustive nor comprehensive discussion of all results for each publication. For example, if results were reported for exposures modeled using different strategies, we may not have included results from each strategy, particularly if results were comparable.

Epidemiologic Study Design Strengths and Limitations

The 24 publications in this review focused on 21 study populations and were conducted in Europe, North America, and China (Table 1); only a limited number of studies focused on highly exposed populations. Global representation is likely limited due to the databases searched and use of English as the publication language, but also potentially due to the uneven availability of air quality monitoring throughout the world. The majority of the selected publications used cohorts, including five cohorts exclusively enrolling women and one study exclusively enrolled men [17, 22•, 23, 24•, 29•, 35, 40]. Among those studies using a cohort design, about half had follow-up periods of approximately 10 years or longer, which is a major strength for identifying cases of incident diabetes [20•, 21, 22•, 23, 24•, 29•, 34•, 35, 37, 40]. A few publications were cross-sectional analyses of a health survey [27, 31, 39]. The studies reviewed generally had large sample sizes (ranging from 1775 to 2,145,400), and as with many large epidemiologic studies, many of those included in our review

Table 1 Summary of study characteristics

Study	Population	Sample size	Diabetes definition	Exposure estimation
Andersen et al. 2012 [19]	Danish Diet Cancer and Health Study	51,818	One of: diabetes hospital discharge diagnosis, chiropody as a diabetic patient, blood glucose measures or diabetes medication purchase	Danish dispersion modeling system, annual mean
Bai et al. 2018 [20•]	Toronto Population-based Study	1,056,012	ICD codes for one hospital or two physician health claims	Land use regression for NO_2 and ultrafine particles
Brook et al. 2013 [21]	1991 Canadian Census Mortality Follow-up Study	2,145,400	Canadian Mortality Database coded by ICD	Long-term average $PM_{2.5}$ based on AOD, 10 km grid
Coogan et al. 2016a, 2016b; Jerrett et al. 2017 [22•, 23, 24•]	Black Women's Health Study, USA	43,003	Self-report with nested validation study	Hybrid land use regression and Bayesian Maximal Entropy for $PM_{2.5}$; Ozone: CMAQ and monitors; Land Use Regression and dispersion for NO2 and $PM_{2.5}$
Chen et al. 2013 [25]	Ontario Population-based Study	62,012	Ontario diabetes registry which uses ICD codes for one hospital or two physician health claims; validation study	Long-term average $PM_{2.5}$ based on AOD, 10 km grid
Clark et al. 2017 [26•]	British Columbia Population-based Study	380,738	ICD codes for one hospital or two physician health claims	Land use regression for NO, NO_2, $PM_{2.5}$, and black carbon, 30 m grid
Dijkema et al. 2011 [27]	Netherlands Population-based Survey	8018	Symptomology and glucose testing	Land use regression, GIS variables for traffic
Eze et al. 2014 [28]	Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA)	6392	One of: medication, self-reported, physician-diagnosis, blood glucose testing	Dispersion for PM_{10}, annual average with temporal adjustment, 200 m grid; hybrid land use regression and dispersion for NO_2
Hansen et al. 2016 [29•]	Danish Nurse Cohort	24,174	One of: diabetes hospital discharge diagnosis, chiropody as a diabetic patient, blood glucose measures or diabetes medication purchase	Danish dispersion modeling system, 5-year moving averages
Honda et al. 2017 [30]	National Social Life, Health, and Aging Project (NSHAP), USA	4121	One of: HbA1c value, self-reported medication	GIS-based spatio-temporal models, 6 km grid
Kramer et al. 2010 [17]	Study on the Influence of Air Pollution on Lung, Inflammation and Aging (SALIA), Germany	1775	Self-report diagnosis and treatment with validity and reliability studies	Land use regression for NO_2, $PM_{2.5}$, and soot, emission inventory fortraffic-related PM and NO_2, and averaged, monitoring data
Liu et al. 2016 [31]	China Health and Retirement Longitudinal Study (CHARLS)	11,847	Self-reported diabetes, and/or glucose testing and/or HbA1c value and/or medication	satellite-based spatial statistical mode for $PM_{2.5}$ plus Global Burden Model for ozone adjustment
O'Donovan et al. 2017 [32]	CHAMPIONS Study, United Kingdom	10,443	Glucose testing	Department for Environment Food & Rural Affairs, 2015 air modeling
Park et al. 2015 [33•]	Multi- Ethnic Study of Atherosclerosis (MESA), USA	5135	Glucose testing and medication	Hierarchical spatiotemporal models of $PM_{2.5}$ and NO_X, annual averages from 2000

Table 1 (continued)

Study	Population	Sample size	Diabetes definition	Exposure estimation
Pope et al. 2015 [34•]	American Cancer Society Cancer Prevention Study II Cohort	669,046	Death certificate ICD codes	Hybrid land use regression and Bayesian Maximal Entropy for $PM_{2.5}$
Puett et al. 2011 [35]	Health Professionals Follow-up Study (HPFS) and Nurses' Health Study (NHS), USA	HPFS 15,048 NHS 74,412	Probable: self-report diagnosis and treatment; confirmed: one of: blood glucose, symptoms, medication validity study	GIS-based spatiotemporal models
Qiu et al. 2018 [36]	Chinese Elderly Health Services Cohort	61,447	Self-report and receiving healthcare for prevalence; hospitalization records for incidence	Annual-mean surface extinction based on AOD regressed on annual ground-level ring $PM_{2.5}$
Raaschou-Nielsen et al. 2013 [37]	Danish Diet Cancer and Health Study	52,061	Danish Register of Causes of Death coded by ICD	Danish dispersion modeling system, annual mean; distance to major roads and traffic loads
Renzi et al. 2018 [38•]	Health Database in Rome	1,425,580	Qualified for free diabetes healthcare or ICD codes or medication validity study	Land use regression for $PM_{2.5}$, PM_{10}, NO_2 and others, annual averages; Ozone from an Eulerian chemical transport model,
Strak et al. 2017 [39]	2012 Dutch National Health Survey	289,703	Self-reported doctor diagnosis and medication questions validity study	Land use regression for $PM_{2.5}$,PM_{10}, NO_2 and others, annual average with temporal adjustment
To et al. 2015 [40]	Canadian National Breast Cancer Screening Study	29,549	ICD codes from three Canadian healthcare databases	Long-term average $PM_{2.5}$ based on AOD, 10 km grid
Weinmayr et al. 2015 [41]	Heinz Nixdorf Recall Study, Germany	3607	Self-reported physician diagnosis or medication or glucose testing	chemistry transport model (EURAD)

primarily used administrative data for defining type 2 diabetes (e.g., ICD codes from death certificates, hospitalization, or health care visits [17, 20•, 21, 25, 26•, 34•, 36, 37, 38•, 40]). While the use of administrative data has the potential of introducing bias due to misclassification of disease resulting from challenges inherent in health system coding, use of this type of data does offer higher power to detect effects due to the larger sample sizes these data afford.

Several other studies were survey-based, initially relying on self-reported physician diagnosis of diabetes. However, many of these studies employed additional methods in attempts to improve or examine diabetes assessment accuracy, including querying participants or health records for diabetes medication use and conducting nested validation studies [17, 22•, 23, 24•]. Other studies used a combination of information (e.g., treatment, biomarker measures, discharge diagnoses) and designated study participants as having diabetes if any of the information was suggestive of having the disease [19, 25, 28, 29•, 30, 31, 38•, 41]. Many studies used information from glucose testing, one of the measures included in the World Health Organization and American Diabetes Association diagnostic criteria [19, 27, 28, 29•, 31, 32, 33•, 35, 41•]. To provide information about the level of accuracy for diabetes assessment and to facilitate translation of epidemiological research to clinical guidelines, a comparison of outcome definitions with national or international diagnosis criteria is beneficial [e.g., 27, 31, 33•, 35, 42]. These standards require access to blood tests and symptomology reports, reflecting the challenges involved with obtaining specified laboratory testing (e.g., fasting for at least 8 h and using certified standardized assays) on specified criterion measures [43]. However, reliance on self-report or medical record report of physician diagnosis alone could lead to potential misclassification of disease given that the worldwide prevalence of undiagnosed type 2 diabetes has been estimated between 45 and 50% [44, 45]. Related to this, comparisons of self-report to biomedical measures tend to show low sensitivity (55–80%), but high specificity (84–98%) [46, 47]. Though self-report of physician diagnosis alone is typically highly specific, a study using information from a US cohort on atherosclerosis observed the magnitude of associations between known risk factors and self-reported diabetes were attenuated compared to using case definitions which included one or two of the following criteria: self-report, glucose testing, or medication. Differences in the strength of associations when defining diabetes with one versus two of the criteria were inconsistent [48].

Exposure Assessment

Overall, the majority of studies relied on exposure estimates from various modeling strategies that included dispersion factors such as land use and meteorology. If both particulate matter and nitrogen dioxide (NO_2) or nitrogen oxides were considered in the same study, investigators tended to use the same modeling strategy to estimate both exposures. However, some studies also included an additional model for one of the pollutants. For example, some studies used dispersion and land use regression modeling [22•, 28]. Generally, dispersion and spatiotemporal modeling were used to estimate particulate matter and NO_2 or nitrogen oxides exposures for cohort or national studies that had access to participant's residential addresses. These studies benefit from more highly spatially resolved information on air pollution exposure assessment as compared with the use of nearest monitors [19, 22•, 23, 28, 29•, 33•, 35, 37]. Spatiotemporal modeling was applied mostly in cohort studies that covered a range of cities/regional areas in the USA. The method was used to estimate NO_2 or nitrogen oxides and particulate matter exposures [30, 33•, 35]. Land use regression modeling was the most common exposure estimation procedure and was applied both in cohort studies and in population-based registry and health service studies, with many studies using this procedure for both NO_2 or nitrogen oxides and particulate matter exposure estimation [17, 20•, 22•, 23, 24•, 26•, 28, 34•, 38•, 39]. Two European studies employed air chemistry transport models, Weinmayr et al. for particulate matter estimation and Renzi et al. for ozone [38•, 41]. Renzi et al., one of the only two ozone studies, also used a dispersion modeling process for ozone estimation, while Jerrett et al. used the US Environmental Protection Agency Community Multiscale Air Quality System (an Eulerian chemical transport model) scaled to measured levels [24•, 38•]. Liu et al. used the global chemical transport model TM5 to adjust for ozone with particulate matter less than 2.5 $\mu g/m^3$ ($PM_{2.5}$) estimates [31, 49]. Two studies used information only from air quality monitors for $PM_{2.5}$ and for NO_2, while another study used monitors in addition to a spatiotemporal model [17, 30, 36]. Only national or regional large population-based studies primarily relying on health service usage and ICD coding for diabetes assessment, employed aerosol optical depth satellite data to characterize $PM_{2.5}$ exposures [20•, 25, 31, 36, 40]. A limitation of these methods is missingness in satellite observations due to cloud cover, though authors of the included studies accounted for missingness in their analyses in various ways. Only one study did not provide enough detail in the publication to identify the specific modeling process used for comparison to other studies [32].

As with all large ambient air pollution epidemiology studies, exposure estimation is necessary because personal exposure monitoring is neither available nor feasible. Thus, the spatial misalignment of monitors and study participants may lead to misclassification of exposure in various ways. There are of course limitations to each method of exposure estimation. In general, those that perform some form of spatial averaging are considered less susceptible to classical measurement error (referring to when instrument error or other non-

representative biases are imputed) as opposed to Berkson-type errors (those which, while they may lead to imprecision in health effect estimates, do not cause bias in said estimates). Study findings did not appear to be clearly connected with particular types of exposure assessment for particular pollutants. Levels of exposure estimates produced by modeling techniques and nearest monitor imputation methods were generally demonstrative of higher levels for densely populated, heavily trafficked urban areas and lower levels for suburban/rural areas. Overall, the strengths of these studies included generally well-considered and described exposure estimation methods with several studies using long time periods of available data. The consideration of dispersion factors and missingness of data as well as the inclusion of detailed information in publications is also necessary in future work, in order to evaluate the level of accuracy of the assessment, the sources considered, and whether background regional or local variation is included.

Pollutants: Potential Biological Mechanisms and Study Findings

The exact biological mechanisms by which ambient air pollution may be linked with diabetes have not been elucidated; however, experimental and epidemiologic research has investigated potential pathways. We present findings from the epidemiologic studies included in this review alongside this mechanistic work to enhance our examination of whether the literature suggests a relationship of type 2 diabetes-related morbidity or mortality in adults with exposures to particulate matter, NO_2 or nitrogen oxides, ozone, and other ambient air pollutants.

Particulate Matter

Experimental studies indicate that $PM_{2.5}$ could act as a mediator of endothelial dysfunction and insulin resistance (IR). In one animal study, exposure to $PM_{2.5}$ in combination with a high-fat diet was reported to increase fasting, postprandial glucose, insulin, and Homeostasis Model Assessment-IR similar to those observed with a high-fat diet over 24 weeks [50]. Elevated levels of tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), resistin, and leptin levels were also observed indicating a proinflammatory IR-resistant state. In another study by Sun et al. [18], there was supportive evidence of abnormal insulin signaling. Exposure to $PM_{2.5}$ in the absence of a high-fat diet has also been shown to increase HOMA-IR and postprandial glucose [51]. Limited epidemiology studies also report that exposure to ambient air pollution alters systemic biomarkers of inflammation [52, 53]. Another plausible biological mechanism includes endoplasmic reticulum (ER) stress [54]. In vitro studies have demonstrated that exposure to $PM_{2.5}$ can induce ER stress, and this may represent a pathophysiologically relevant mechanism linking particulate matter exposure with hepatic insulin resistance. In other experimental studies, $PM_{2.5}$ has been reported to decrease phosphorylation of Akt in the liver and skeletal muscle. Other changes observed included hepatic lipid deposition and decreased gluconeogenesis. In other research, $PM_{2.5}$ exposure was associated with alterations in IR and glucose homeostasis [55, 56]. Some experimental studies indicate that exposure to traffic-related fine and ultra fine particles (UFPs) and ozone trigger inflammation, oxidative stress, and biological pathways that promote metabolic IR [57–59].

Based on the long-term exposure epidemiology studies we reviewed, we found that particulate matter less than 10 $\mu g/m^3$ (PM_{10}) exposures were positively associated with prevalent diabetes in two out of three studies (Fig. 1) and with incident diabetes in four of five studies (Fig. 1), with two prevalent studies and two of the incident studies reaching levels of statistical significance [17, 28, 29•, 35, 38•, 39, 41]. Two of the incidence studies with positive findings were conducted among women only [17, 29•]. No obvious consistent differences among studies were observed (e.g., mean population age or outcome assessment differences for those with stronger findings). Notably, a null association was reported for the study with the largest sample size and highest average exposure [38•]. Contrary to other studies which included urban and suburban/rural areas, this study was conducted in a population dense, heavily trafficked city, and also reported statistically significant positive associations with traffic-related pollutants. Incident diabetes was also statistically significantly associated with living in close proximity to a major road in two of three studies [19, 27, 35]. Differences among studies could be due to differences in PM_{10} composition and sources. Findings for $PM_{2.5}$ exposures with diabetes prevalence and incidence were similar with the majority of studies showing positive associations, albeit with fewer studies reaching statistical significance (Fig. 1) [17, 25, 30, 31, 36, 40]. Several studies were conducted among only women and showed positive associations [17, 23, 29•]. Both diabetes-related mortality studies of particulate exposures reported statistically significant increased risk associated with higher long-term exposures to $PM_{2.5}$ [21, 34•]. No consistent pattern of differences among study methods, levels of exposure, or other factors we examined provide a clear explanation regarding the variations in findings. For UFPs, data are very limited in epidemiologic as well as animal studies [20•].

NO_2 or Nitrogen Oxides

NO_2 or nitrogen oxides are gaseous pollutants that often serve as a proxy for traffic-related pollution. Epidemiologic studies

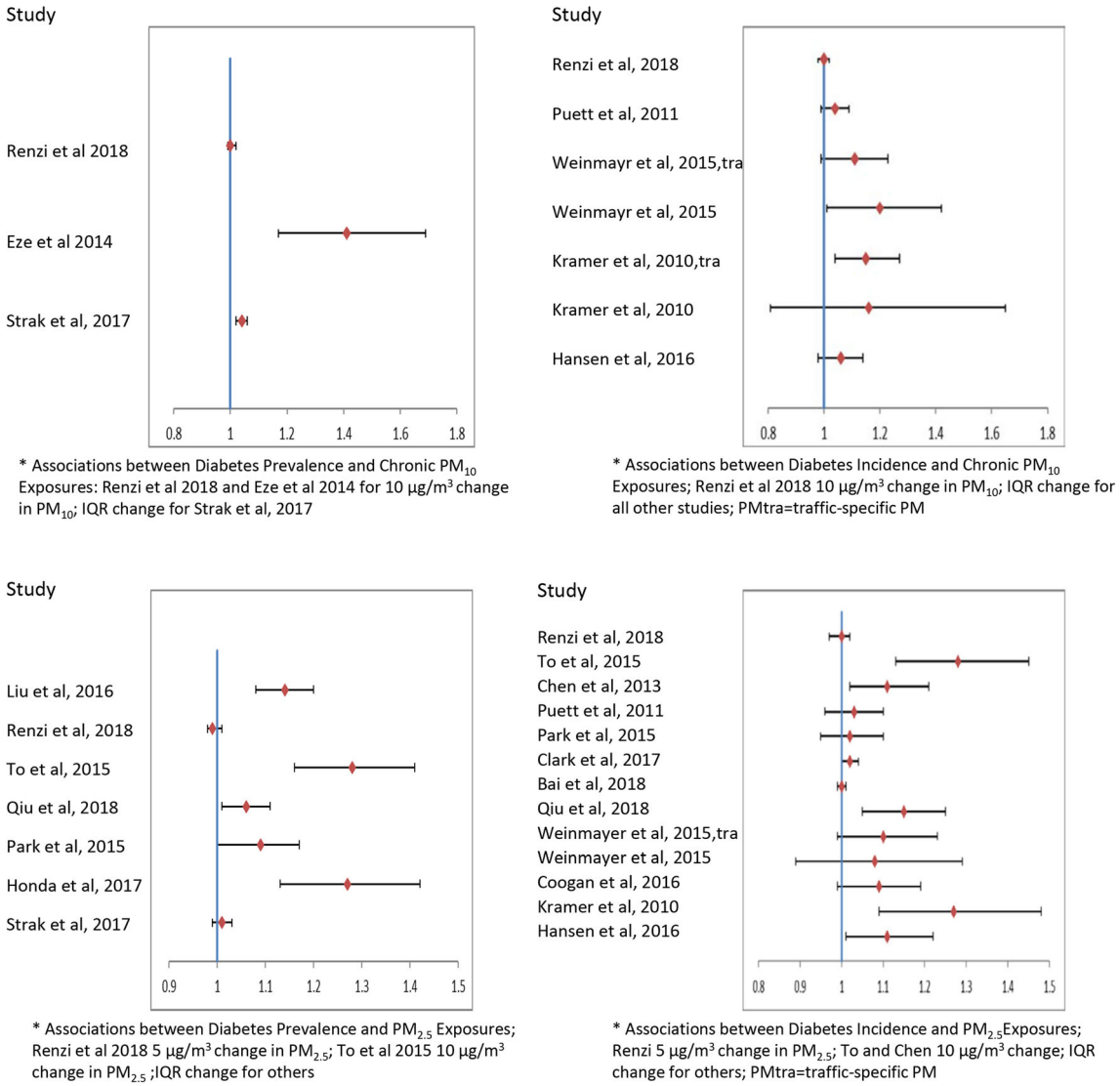

Fig. 1 Reported relative risks and 95%confidence intervals for fully-adjusted models of associations between type 2 diabetes and particulate matter exposures

of associations and toxicologic studies providing evidence for pathophysiologic pathways for NO_2 or nitrogen oxides are limited in part because these pollutants react with other pollutants, are correlated with other pollutants (positively and negatively), and are highly spatially variable; thus, both exposure estimation and distinguishing health outcomes specifically linked to NO_2 or nitrogen oxides from other pollutants are particularly challenging [24•, 60, 61, 62••]. While underscoring the limitations and need for additional mechanistic and toxicology studies examining the long-term impacts of NO_2 or nitrogen oxides, the review of evidence on health aspects of air pollution (REVIHAAP) Project: Technical Report suggests that current studies show some support for inflammation, airway hyperresponsiveness, and oxidative stress as potential pathophysiological mechanisms for adverse human health effects [62••]. Both oxidative stress and inflammation have been linked with insulin resistance and metabolic dysfunction.

Among the studies included in our review, positive associations were reported for all studies assessing long-term NO_2 or nitrogen oxide exposures, indicators of traffic-related pollution, with diabetes prevalence (Fig. 2) [28, 30, 38•, 39]. Findings for diabetes incidence with NO_2 were inconsistent, with about half of the studies reporting increasing risk with increasing exposures [17, 19, 20•, 29•]. An association between nitrogen oxides and incident diabetes was only supported by one (HR: 1.011, 95%CI: 1.003–1.019) of three studies examining the relationship [29•, 33•, 38•]. One study explored diabetes-related mortality and NO_2 exposures, reporting statistically significant increased risk with NO_2 exposures in the year prior to death and an attenuated but positive association with longer-term NO_2 exposures [37].

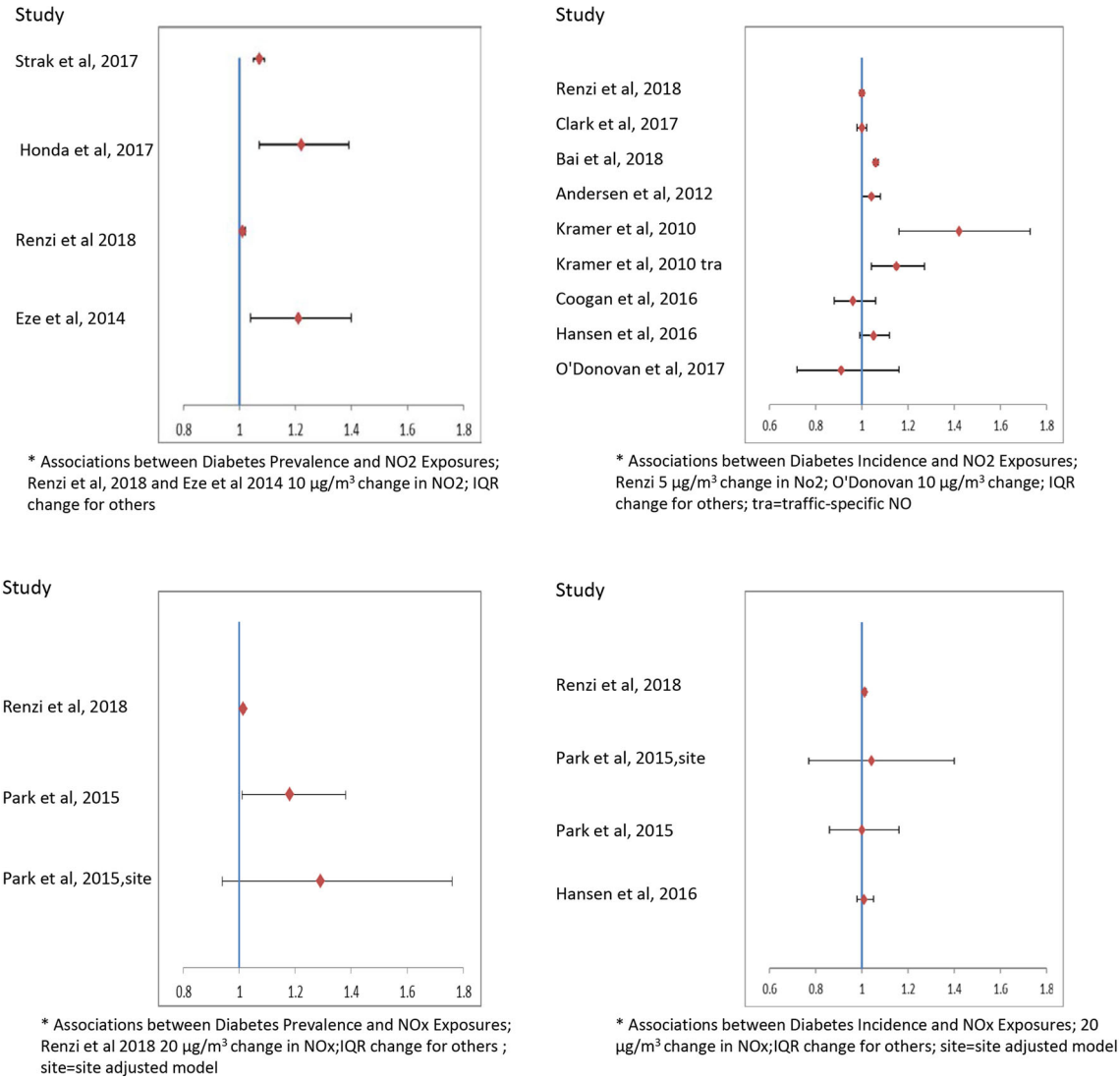

Fig. 2 Reported relative risks and 95%confidence intervals for fully-adjusted models of associations between type 2 diabetes and NO_2 and NO_x, and exposures

Ozone and Other Pollutants

Ozone, formed by photochemical reactions on emissions from fossil fuel combustion and industrial and vehicular activities, has been linked to poorer fasting glucose and insulin levels, and HOMA indices among older adults, with stronger associations observed among those with a history of diabetes or increased susceptibility to oxidative stress [63, 64]. One recent experimental study conducted by Vella et al. exposed rats to environmentally-relevant doses of ozone (0.8 ppm) and found that exposure induced whole-body insulin resistance and oxidative stress with associated endoplasmic reticulum (ER) stress, c-Jun N-terminal kinase (JNK) activation, and disruption of insulin signaling in skeletal muscle [59]. The authors also reported that subchronic exposure to ozone (0.25 ppm, 12 h/day for 4 days) led to pulmonary inflammation, oxidative stress, and insulin resistance. Vella et al. suggest that production of lung mediators that induce oxidative stress and subsequent activation of JNK activation in skeletal muscle could disrupt insulin-induced signaling and glucose uptake [59].

Thus, although biologically plausible, only two studies examined long-term ozone exposures with prevalent diabetes, reporting a null association and a weak inverse association [31, 38•]. Two studies reported statistically significant positive associations with incident diabetes. One study was conducted exclusively among women and the other study found stronger risks among women compared to men [24•, 38•].

Susceptible Subpopulations

Differences in human susceptibility to environmental exposures can be related to comorbid disease; demographic or anthropometric characteristics; genetics; race and ethnicity;

lifestyle, behaviors, and socioeconomic position. In general, the studies included in our review also considered whether differences in effects varied based on age group, sex, socioeconomic status, smoking, alcohol consumption, diet, comorbidities, and body mass index (BMI). Overall, consistent evidence of effect modification by any one of these factors or for any particular pollutant exposures/diabetes outcomes was limited, with the possible exception of differences based on age and sex.

Most studies examining age group differences reported none; however, a few studies reported observing higher risks among participants under 50 years of age compared to older groups for incident diabetes associated with exposure to UFPs, PM_{10} and with ozone [20•, 25, 38•]. These findings are noteworthy as type 2 diabetes incidence tends to increase with age, and recently, type 2 diabetes is becoming more common among youth [65–67].

Some studies also reported differences by sex, with few interactions statistically significant. Weinmayer et al. reported stronger risks among men for incident diabetes associated with PM_{10} and $PM_{2.5}$ exposures and Puett et al. for $PM_{2.5}$, while others reported stronger associations with $PM_{2.5}$ for women [25, 35, 36, 41]. Puett et al. reported a strong positive association between living within 50 m of a heavily traveled road compared to living more than 200 m from the road for women, but the same finding was not true for men [35]. Studies also reported stronger associations among women compared to men for incident or prevalent diabetes with higher NO_2 or nitrogen oxide exposures [19, 20•, 27, 33•].

Areas for Further Research

The implications of findings from the studies we examined are similar to those raised in previous reviews [68–71]. Well-designed epidemiologic studies of type 2 diabetes and long-term ambient air pollution exposures with rigorous methods and exposure assessment can inform clinical treatment practices and air quality regulatory guidelines. Large population-based studies with administrative data and cohort studies with more detailed information, including biomarkers and periodic follow-ups, are still needed to address inconsistent findings and areas with limited information, such as potential effect modification by sex and age for certain pollutants and associations in underrepresented groups (e.g., racial/ethnic minorities). Challenges may exist with regard to air pollution modeling, but additional well-designed and clearly reported studies in areas of high pollution and diabetes prevalence/incidence are needed to provide additional information about etiology and group differences. With respect to gaining further insights regarding higher risks among younger age groups, future studies will need careful consideration of age range inclusions and case definitions in order to gain information about type 2 diabetes in younger populations while avoiding potential misclassification by including type 1 diabetes cases, which is more common under age 30. Approximately half of the studies included in this review reported a mean/median age (typically at baseline) between 50 and 65 years with additional studies focused on populations with mean/median ages 70 and older, limiting numbers of younger study participants [17, 19, 20•, 25, 26•, 28, 29•, 30–32, 33•, 35–37, 40, 41•].

Administrative data and well-characterized cohort data that include biomarkers, symptomology, and medical treatment can enhance sensitivity as well as specificity of diabetes diagnosis. This is critical for ensuring type 2 diabetes outcome accuracy to reduce potential misclassification and bias in main association studies, potentially explaining some of the inconsistencies observed in findings across the studies reviewed. For example, in a study assessing the importance of diabetes case definitions used in epidemiologic research, Bielinski and colleagues reported that the magnitude of associations between known risk factors and diabetes varied depending on the criteria that were selected to identify diabetes cases [48]. Some studies included in this review addressed this issue by reporting results from sensitivity analyses conducted with multiple diabetes case assessment definitions [28, 35, 37].

In addition, better sensitivity and more comprehensive data are key for mechanistic studies, another area warranting further research. For example, studies have reported that statins, a class of drugs often prescribed by doctors to help lower cholesterol levels, reduced the risk of cardiovascular outcomes associated with particulate matter exposures, particularly among people with diabetes; a finding that has possible implications for diabetes studies if statin use in the population under study is unknown [72, 73]. Some of the cohort studies with more comprehensive biomarker data that were included in this review have embarked on initial mechanistic research. For example, Kramer and colleagues also examined the influence of an inflammatory biomarker on the relationship of incident diabetes and traffic-related long-term air pollutant exposures [17]. Eze et al. followed their main association study with mechanistically focused research, reporting an association between PM_{10} exposures and diabetes among individuals with pro-inflammatory candidate gene polymorphisms, providing further evidence for the inflammatory pathway [30, 74].

With regard to specific pollutants, epidemiologic data are very limited with respect to ultrafine particulates and ozone exposures. Prevalence and incidence association differences also suggest further research is needed with NO_2 and NOx exposures. Toxicological research on long-term NO_2 and nitrogen oxides exposures is severely limited. In epidemiologic studies, challenges clearly exist for distinguishing NO_2 or nitrogen oxides impacts from those of correlated pollutants. For example, Jerrett et al. examined and discussed the tradeoff between ozone and NO_2 levels (i.e., when one pollutant level is high, the other is low) [24•]. Thus, the more highly concentrated pollutant might mask the association with diabetes by

the other pollutant. The REVIHAAP Report also described that NO_2 is linked with particles and suggested that studies could include NO_2 and a particle mass indicator (e.g., ultrafines or black carbon) [62••].

Some of the studies included in this review investigated the impact of co-pollutants in predictive models compared with single pollutant models to demonstrate independent effects; however, challenges exist when these pollutants are correlated [e.g., 24•, 31, 35]. Most co-pollutants were other ambient air pollutants; however, noise is an important co-pollutant that has been linked with adverse health effects. The role of noise pollution is difficult to distinguish from air pollution. In this review, we included relevant findings from one study that focused primarily on noise, with air pollution treated as a co-pollutant [26•]. The authors reported that noise was associated with incident diabetes independent of air pollution, while the reverse situation was not observed. Findings from this and other studies in this small but growing body of work will provide important information with respect to whether each type of pollutant differentially impacts certain aspects of the diabetes pathway or certain subpopulations [75].

Studies in this review and rigorous methodological studies addressing the needs described above are important for supporting further policy and translational work in risk assessment and cost-benefit analyses which can more directly support air quality policies. Previous approaches for quantitatively incorporating population vulnerability and susceptibility in risk assessment have accounted for differences in baseline heath status using measures such as cause-specific death rates, hospital/emergency department visit rates, disease prevalence rates, and/or pollutant-specific differential relative risk estimates, which may serve as models for future diabetes and air pollution work [76–80, 81••].

Conclusions

In summary, the studies included in this review generally employed rigorous methodology with large sample sizes, appropriate study designs to maximize available cohort study or administrative data sources, and exposure modeling that accounted for air pollution dispersion factors. Overall, most studies for each pollutant/outcome reported increased risks associated with increased exposures; however, findings were not uniformly positive nor statistically significant. Further research is needed to provide a more comprehensive understanding for clinical treatment and air quality regulatory guidelines. Current research is particularly limited regarding the biological mechanisms involved, examining the relationship between ozone and diabetes, distinguishing NO_2 or nitrogen oxides effects from those of other pollutants, and identification of potential subpopulations with greater susceptibility for select pollutant exposures.

Compliance with Ethical Standards

Conflict of Interest Robin Puett received an honorarium and travel expenses to present part of this work at the Health Effects Institute Conference in April 2018. Lesliam Quiros-Alcala, Jessica Montresor-Lopez, Nedelina Tchangalova, Anindita Dutta, Devon Payne-Sturges and Jeff Yanosky each declare no potential conflicts of interest.

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.

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- •• Of major importance

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