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Type 2 Diabetes Mellitus and Alzheimer's Disease: Overlapping Biologic Mechanisms and Environmental Risk Factors

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Abstract

Purpose of review—A number of studies over the past two decades have suggested that Type 2 diabetes mellitus (T2DM) patients are at an increased risk of Alzheimer's disease (AD). Several common molecular pathways to cellular and metabolic dysfunction have been implicated in the etiology of both diseases. Here, we review the emerging evidence from observational studies that investigate the relationship between T2DM and AD, and of shared environmental risk factors, specifically air pollution and pesticides, associated with both chronic disorders.

Recent findings—Particulate matter and traffic-related air pollution have been widely associated with T2DM, and multiple studies have associated exposures with AD or cognitive function. Organochlorine (OC) and organophosphate (OP) pesticides have been associated with T2DM in multiple independent populations. Two populations have observed increased risks for OC and OP exposure and AD. Other studies, limited in exposure assessment, have reported increased risk of AD with any pesticide exposure assessments.

Summary—This may suggest shared pathogenic pathways between environmental risk factors, T2DM, and AD. Research focusing on exposures related to both T2DM and AD could provide new disease insights on shared mechanisms and help shape innovative preventative measures and policy decisions.

Keywords

Type 2 Diabetes Mellitus; Alzheimer's disease; Environment; Air pollution; Pesticides

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Compliance with Ethical Standards

Conflict of Interest

Kimberly C. Paul, Michael Jerrett, and Beate Ritz declare that they have no conflict 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.

Introduction

Type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD) are both age-related disorders. A number of studies over the past two decades have suggested that T2DM patients are at an increased risk of AD. This has profound health implications, as virtually all countries will face the challenges of increasingly aging populations in the coming decades[1]. With the expected growth in elderly populations, by 2030, the prevalence of AD is estimated to double to nearly 65.7 million people worldwide[2] and T2DM, among the fastest growing chronic disease epidemics currently, is expected to affect 552 million people[3].

Several common molecular pathways to cellular and metabolic dysfunction have been implicated in the etiology of both diseases. Observational studies are also increasingly linking exposure to overlapping environmental factors in both diseases, including lifestyle factors, smoking, diet, and physical activity, and environmental/occupational toxicants, air pollution, pesticides, and heavy metals. This may suggest shared pathogenic pathways between T2DM and AD, with T2DM, which occurs on average earlier in life than AD, exacerbating neuronal and metabolic dysfunction, further increasing the risk of developing AD. In this article, we review the emerging evidence from observational studies that investigate the relationship between T2DM and AD, and of shared environmental risk factors, specifically air pollution and pesticides, associated with both chronic disorders.

Type 2 Diabetes Mellitus and Alzheimer's Disease

Overlapping Pathways of Dysfunction

The relationship between T2DM and AD is complex. Over the past twenty years, many researchers have investigated underlying links between T2DM and AD, especially with respect to disease mechanisms[4].

AD can only be diagnosed definitively by the presence of neurofibrillary tangles and neuritic plaques consisting of protein accumulations of β-amyloid peptide and tau in the postmortem brain. AD symptoms, primarily memory loss, difficulty with familiar tasks or planning, and confusion, are thought to result from impaired synaptic function, though how β-amyloid and tau contribute to synaptic dysfunction and loss is not fully understood[5]. T2DM is caused by insulin deficiency. This deficiency may be attributed to several pathologies, including insufficient insulin supply due to flawed insulin secretion, reduced insulin-secreting β-cell mass, and impaired insulin sensitivity in peripheral metabolic organs (e.g. liver or muscle)[4].

Insulin and leptin are hormones involved in T2DM. Both not only have major peripheral functions in maintaining blood sugar homeostasis, influencing food intake, and energy expenditure, but they also influence brain function considerably[4]. Insulin and leptin have been shown to regulate neuronal and synaptic function in different regions of the brain, protect neurons against neurodegeneration and cell death, and affect cognition and behavior[6–9].

Moreover, these hormones have also been shown to regulate β-amyloid levels by modulating β-amyloid production, through action on the β-site of amyloid precursor protein cleaving

enzyme (BACE), and β-amyloid degradation, through β-amyloid degrading enzymes such as insulin-degrading enzyme[10–13]. These findings support the idea that brain insulin resistance and insulin deficiency may contribute to AD. A recent APP23 transgenic mouse model[14] was the first to integrate spontaneous diabetes, insulin, and leptin resistance with AD, and has provided strong experimental evidence that T2DM and AD share common cellular and molecular mechanisms (for a discussion of the rodent model see Takeda et al[14]; Han and Li[4]).

There are other pathways to pathogenesis than insulin resistance and deficiency which link T2DM and AD, including inflammation, mitochondrial dysfunction, chronic oxidative stress, and increased advanced glycation end products (AGEs) to name a few[15]. For example, pollutants can cause oxidative stress in the lungs, which may lead to systemic pro-inflammatory and autonomic responses. This is linked to not only insulin resistance, but numerous adverse health effects[16,17]. Reciprocal action between these pathways may also potentially escalate events that lead to pathogenesis. See Figure 1 as an overview of proposed mechanistic pathways linking T2DM and AD.

Epidemiologic Evidence

The first study to report that T2DM increases the risk of developing AD was the Rotterdam cohort of over 6,000 subjects in the Netherlands (1999)[18]. Since, epidemiologic evidence has been accumulating in support of a link, though not all results are unequivocal.

Focusing on longitudinal studies only, 17 studies have investigated the influence of T2DM on the incidence of AD (Table 1). The largest was conducted by Katon et al[19] using data linkage in the Danish National Patient Register, one of the world's oldest nationwide health registries, representing both clinical in- and out-patients and 90% of the Danish population[20]. Among nearly 2.5 million people ≥50 years of age without dementia (2007-2013), including 223,174 T2DM patients, 59,663 individuals (2.4%) developed dementia over a 5-year follow-up period. This reflected a small T2DM-related increase in the risk of AD (HR = 1.06, 95%CI = 1.01, 1.11), while comorbid T2DM/depression was associated with a larger HR for AD (HR = 1.46, 95% CI = 1.37, 1.55)[19]. In Taiwan, researchers used a random sample of the National Health Insurance Research Database Registry, which includes nearly all citizens of Taiwan since 1995 (99.99%). More than 1.2 million people, including 615,532 T2DM patients, were included in the study. The authors identified 8,488 (0.69%) incident AD patients (2000-2008), corresponding to a HR of 1.45 (95% CI =1.38, 1.52)[21]. National insurance data from nearly 500,000 men in South Korea further corroborated both findings (1993-2006). In this study, T2DM was associated with a 60% increase in AD risk (HR = 1.60, 95% CI = 1.29, 1.98)[22].

Although National Hospital or Insurance Registry data provide many benefits, most notably the large, representative, and nationwide samples, they are often limited in some key aspects. For example, disease status is often based on hospital discharge records and ICD codes designated for insurance purposes. Also, measurement of crucial confounders beyond age, sex, and some medical factors are generally unavailable, including education, smoking, BMI, and physical activity.

Several smaller cohorts with more detailed confounder and outcome information have also reported T2DM to be associated with an increased AD risk, including the Honolulu-Asia Aging Study (Risk Ratio (RR) = 1.80, 95% CI=1.10, 2.92)[23], the Vantaa Study in Finland (RR = 2.45, 95% CI=1.33, 4.52)[24] and the Hisayama Study in Japan (RR = 2.05, 95% CI=1.18, 3.57)[25] (Table 1).

Some cohorts, including the Framingham (RR=1.15, 95% CI=0.65, 2.05)[26] and Canadian Study of Health and Aging (RR=1.30, 95% CI=0.83, 2.03)[27], have reported no association between T2DM and AD (Table 1). Although both did estimate small positive risks, the 95% CIs included the null value. In fact, out of the 17 longitudinal studies, only one did not report a positive point estimate, the OCTO-Twin Study, which had a relatively small sample size (n=702; RR=0.83, 95% CI=0.46, 1.48). A meta-analysis from 2013 summarizing the data from 15 longitudinal studies, reported a pooled adjusted risk ratio of 1.57 (95% CI=1.41, 1.75) between T2DM and AD, and a population-attributable risk of 8%[28].

While both biologic mechanisms and epidemiologic evidence strongly support a link between T2DM and AD, the studies mentioned do not assess how ubiquitous environmental exposures may influence this relationship, either as confounders, should T2DM mediate the relationship between exposure and AD, or effect modifiers, assessed with statistical interactions.

Environmental Risk Factors, Type 2 Diabetes Mellitus, and Alzheimer's Disease

Awareness is growing that many age-related diseases share common environmental risk factors. For example, smoking and physical inactivity are established risk factors for many chronic diseases, including T2DM and AD. Environmental toxicant exposures are increasingly recognized as falling in this category, i.e. they affect many health endpoints. Air pollution, for example, has been widely associated with cardiovascular events, T2DM, cancers, and more recently with neurodegenerative diseases[29–32]. Similarly, the organochlorine DDT is linked to cancer, T2DM, and cognitive deficits/AD[33,34]. Some exposures are more or less ubiquitous in certain communities, such as traffic-related air pollution (TRAP) in urban communities and pesticides from agricultural applications in rural environments.

One explanation may be that exposures induce shared pathophysiologic mechanisms, including those mentioned above, inflammation, oxidative stress, and insulin deficiencies. Air pollution and pesticide exposures in particular have been widely associated with such pathways. Table 2 briefly outlines findings from a sample of the vast literature linking these exposures with shared pathways for T2DM and AD. Given the ubiquity of air pollution and pesticide use and the strong experimental evidence linking exposures with shared pathophysiologic mechanisms, this review will focus on air pollution and pesticides and both disorders.

Understanding how shared T2DM/AD risk factors contribute to comorbid disease patterns could provide insight into underlying etiologic pathways and ultimately environmental

policy and prevention targets. In the following section, we will review the observational studies that have investigated the relationship between air pollutants and pesticides and both T2DM and AD.

Particulate Matter and Traffic-related Air Pollution

Air pollution is a complex mixture of compounds from different sources, including combustion, industrial, or agricultural, such as particulate matter (PM), ozone, carbon monoxide, sulfur and nitrogen oxides, methane, volatile organic compounds (e.g., benzene, toluene, and xylene), and metals (e.g., lead, manganese, vanadium, iron)[32]. In recent years, several major epidemiologic studies have reported positive associations between air pollutants and T2DM and AD or cognitive decline. In this review, we will however focus on the associations for exposures most commonly studied, that is particulate matter (PM, <2.5 μm (PM2.5) or <10 μm (PM10)) and TRAP, often assessed via a surrogate, nitrogen dioxide (NO_2) or black carbon.

Type 2 Diabetes

An association between air pollution and T2DM was first reported in 2008 in a Canadian population of 4,182 women, assembled from the Ontario Health Insurance database[35]. Using field measurements and a land use regression (LUR) model, a positive relationship between NO_2 and T2DM was estimated (OR=1.04 per 1 ppb increase in NO_2, 95% CI=1.00, 1.08). Since this initial study, 10 longitudinal cohort studies have investigated the link with T2DM, using different measures for air pollution: NO_2[35–41], PM2.5[36,41–45] and/or PM10[38,40,44,45] (we did not review cross-sectional or case-control studies). Table 3 outlines the findings of these studies.

While not every study investigating PM2.5 reported statistically significant associations, the 7 longitudinal studies all reported positive point estimates for the influence of PM2.5 on T2DM. For example, the Nurses' Health Study, with 74,412 female participants and 3,784 incident T2DM cases, reported an HR of 1.21 per IQR (95% CI=1.00, 1.46), while the all-male Health Professionals Follow-up Study (HPFS) estimated an HR of 1.52 per IQR (95% CI=0.93, 2.47)[44]. It should be noted that for a large number of participants in the HPFS, residential geocode information was missing, and instead the workplace address was used. Consequently exposure misclassification is possible and non-differential misclassification would have biased associations toward the null[44]. Other studies, with arguably less selective study populations and thus greater generalizability, also found increases in T2DM risk with PM2.5 exposures. These include two large Canadian studies, the 1991 Canadian Census Mortality Follow-Up Study with a sample size of over 2.1 million, which modeled T2DM mortality (HR=1.49 per 10-ug/m3 (1.37, 1.62))[42], and the National Population Health and Canadian Community Health Survey with 62,012 respondents (HR=1.11 per 10-ug/m3 (1.02, 1.21))[43].

Similar results were found in studies investigating PM10. All 5 longitudinal studies reported positive point estimates (Table 3); but only in the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults did the findings reach statistical significance. In the

Swiss sample, with 6,392 participants and 315 incident T2DM cases, the authors report a 40% increased risk of T2DM per IQR of PM10 (OR=1.40; 95% CI=1.17, 1.69)[40].

NO_2 was the initial pollutant investigated by Brook et al[35]. Since this report, 6 additional longitudinal investigations have been published. Of these studies (Table 3), only the Multi-Ethnic Study of Atherosclerosis did not find an association between NO_2 and T2DM incidence (HR=1.04 per IQR; 95% CI=0.77, 1.40). Though the same study found an increased risk between NO_2 and prevalent T2DM (OR = 1.18 per IQR; 95% CI: 1.01, 1.38)[41]. The effect sizes estimated by the other 5 studies ranged from 1.04 (1.00, 1.08) to 1.42 (1.16, 1.73) (Table 3).

A pooled meta-analysis of the studies published before 2014 reported elevated risks for T2DM from long-term exposures to higher levels of NO_2 (meta-analysis RR=1.11 per 10 μg/m3 increment, 95% CI 1.07–1.16), PM2.5 (meta-analysis RR=1.39 per 10 μg/m3 increment, 95% CI 1.14–1.68), and PM10 (meta-analysis RR=1.34 per 10 μg/m3 increment, 95% CI 1.22–1.47)[30]. A more recent meta-analysis (2015), which included case-control and cross-sectional studies as well as longitudinal studies, also reported a positive association for PM2.5 (meta-analysis RR=1.10 per 10 μg/m3 increment, 95% CI 1.02–1.18) and NO_2 (meta-analysis RR=1.08 per 10 μg/m3 increment, 95% CI 1.00–1.17). Furthermore, they found that associations were stronger in females[46]. Interestingly, AD disproportionately affects women[47].

Alzheimer's disease

Research targeting environmental risk factors for AD has largely focused on lifestyle. To date only a handful of longitudinal studies have investigated the role of air pollutants in AD. Therefore we opted to also review case-control studies of AD and longitudinal studies of cognitive decline among the elderly. Table 3 outlines the findings from these studies.

Some studies have linked air pollution and AD. Notably, two large prospective studies with PM2.5 exposure measures[48,49]. A Taiwanese study utilized the National Health Insurance Research Database, and routine air monitoring from the Taiwan Environmental Protection Agency (2000–2010)[48]. Among 95,690 study subjects, 1,399 were diagnosed with incident AD (2001–2010), and the authors found that those with higher PM2.5 exposures over follow-up were at more than twice the risk of developing AD (HR=2.38 per 4.43 ug/m3 increase; 95% CI=2.21, 2.56)[48]. Among 9.8 million Medicare enrollees from the Northeastern United States, PM2.5 exposure at baseline was associated with an increased risk of hospitalizations due to AD (HR=1.15 per 1 μg/m3; 95% CI=1.11, 1.19)[49]. Four additional longitudinal studies have reported a higher risk of incident cognitive decline with PM2.5 exposures in the United States, United Kingdom, and Germany[50–53] (see Table 3).

While none of the longitudinal studies reported on PM10 exposure and AD, a recent case-control study reported positive results. Among 249 AD patients and 497 controls in Taiwan, those in the highest tertile of PM10 exposure (based on a 12-year prior to onset exposure period) were found to be at over 4 times the risk of AD relative to those in the lowest tertile (OR=4.17; 95%=2.31, 7.54)[54]. Of interest is also that 30% of the AD cases in this study reported a history of T2DM compared and only 13% of controls[54]. Longitudinal studies of

cognitive decline have reported conflicting findings. The Whitehall II cohort (n=10,308) in London reported no association between cognitive decline and PM10[52]. While investigators using both the Nurses' Health Study Cognitive Cohort (highest vs lowest quintile β= −0.24, 95% CI: −0.040, −0.008)[50] and a smaller German cohort of elderly woman (β= −0.14 per IQR PM10; 95% CI: −0.26, −0.02)[53] reported faster cognitive decline with higher PM10 exposure.

The Betula cohort in Sweden investigated the influence of nitric oxides (NO_x) on AD. This cohort (n=1,806) reported 191 incident AD cases, and that NO_x was positively associated with the risk of AD (highest quartile of exposure vs lowest: HR=1.38, 95% CI=0.87, 2.19), but the 95% CI included the null value[55]. When the authors considered all causes of dementia (n=302), the estimated effects gained formal statistical significance (HR=1.43, 95% CI=1.00, 2.05)[55]. Another report, that relied on the large, population-wide National Health Insurance Research Database in Taiwan, similarly found that the highest quartile of NO_2 exposure relative to the lowest was associated with all cause dementia (HR=1.54, 95% CI=1.34, 1.77)[56]. And the German cohort of elderly woman mentioned above also linked NO_2 exposures with cognitive decline (β= −0.28 per 1 IQR NO_2; 95% C=−0.44, −0.12)[53].

While evidence implicating air pollution in T2DM or AD alone is somewhat strong and growing, few studies have investigated whether or how T2DM may modify the relationship between air pollution and cognition. This was explored in the Department of Veterans Affairs Normative Aging Study (n=680 men)[57] that evaluated the influence of black carbon (BC) exposure on cognitive function measured by the Mini-Mental State Examination (MMSE). When modeling MMSE ≤ 25, the authors observed a 30% increase in risk with each doubling of BC (OR=1.3, 95% CI=1.1, 1.6)[57]. Interestingly, they also suggested that the adverse effects of BC were concentrated in overweight and obese individuals (p-value for interaction=0.10); although, they did not find evidence for effect modification by T2DM specifically (p-value for interaction >0.10)[57]. While, these results are only suggestive of metabolic dysfunction modifying the effects of air pollution exposure on AD risk, the study was likely limited by its small number of participants with T2DM and MMSE ≤ 25.

Metabolic dysfunction modifying the influence of air pollution however has been shown for other outcomes, such as cardiovascular events. For example, a study using the Women's Health Initiative cohort to investigate the effects of PM2.5 on cardiovascular events reported that the risk for cardiovascular events associated with PM2.5 increased with increasing BMI (p for trend=0.003) and waist-to-hip ratio (p for trend=0.008)[58]. Moreover, several of the cohorts we have discussed above have implicated air pollutants in both T2DM and cognitive function, for example the Nurses' Health Study.

Pesticides

Pesticides represent a broad range of chemicals used for crop protection and agricultural food production, in homes and gardens, for roadway or building maintenance, and protection against insect-borne diseases in many countries. Pesticides are designed to impact living systems. Many have known acute health effects, and long-term health problems are increasingly recognized, even at low levels of exposure.

Certain pesticides relevant for this review are considered persistent organic pollutants (POPs), compounds with environmental persistence that are known to bio-accumulate. POPs have been studied since the 1970s, and many have since been banned due to their persistent properties impacting eco-systems, their documented bioaccumulation in the food chain and in turn human breast milk, and subsequently the many health concerns that have been raised[59]. The most prominent POP linked to T2DM is dioxin, a contaminant of the herbicide and war time chemical Agent Orange[60]. As a result, T2DM is listed by the U.S. Department of Veterans Affairs as a presumptive disease in Vietnam Veterans who handled these chemicals[60]. A workshop conducted by NIEHS (2013) reviewed 72 epidemiological studies that investigated associations of POPs with diabetes[61]. While studies were too heterogeneous to conduct a meta-analysis, the workshop members concluded that the overall evidence was sufficient for a positive association of some organochlorine POPs with T2DM, including trans-nonachlor, DDE (the metabolite of DDT), and dioxins and dioxin-like chemicals. But they also recommended to further evaluate causality in experimental models which might help shed new light on the pathogenesis of T2DM. Cognitive deficits due to organochlorine (OC) and organophosphate (OP) exposures have also been observed. While researchers are still trying to elucidate the mechanisms through which pesticides may cause T2DM and AD, especially in populations with low-level exposures, some compelling epidemiologic evidence exists for both T2DM and AD with OC and OP pesticide exposure. In the following section, we will discuss major studies investigating these agents.

Type 2 Diabetes

Studies linking low-level OC exposure to T2DM began in 1980, with an occupational study of 2,620 pesticide production workers. The study found a suggestive association between higher serum OC levels (specifically DDT, DDE, and dieldrin) and incident T2DM[62]. Since then a number of studies have replicated this finding (Table 4). Throughout the 2000s, a series of cross-sectional studies reported higher levels of different OC chemicals measured in human serum to be associated with risk of developing T2DM among multiple diverse populations, including population-based and occupational studies; for a review, see Evangelou et al[33]. These reports notably include the population-wide National Health and Examination Survey (NHANES) study in which higher plasma levels of 6 different POPs were associated with T2DM, including three OCs: Oxychlordane, trans-nonachlor, and mirex (summary measure of 6 POPs: ≥90th percentile vs < level of detection OR=37.7 (7.8, 182.0), p for trend <0.001)[63]. Subsequently, a number of cohort studies reported similar findings for OCs and also investigated OPs.

Most prominently, the Agricultural Health Study, which identified 1,176 incident T2DM cases among 31,787 licensed agriculture pesticide applicators, found that self-reported occupational exposure to two different OCs and four OPs was associated with T2DM risk (Table 4)[64]. Intriguingly, a study of the spouses of these applicators reported that, among farmers' wives who also personally mixed or applied pesticides, exposure to 3 OP pesticides and 1 OC pesticide was associated with a higher risk of T2DM[65]. The Great Lakes Consortium for the Health Assessment longitudinal cohort (n=435), measured serum DDE (an OC) at baseline, and found increasing levels to be associated with incident T2DM over the following 10 years (p for trend=0.008; tertile 3 vs 1: OR=7.1; 95% CI=1.6, 31.9)[66].

Likewise, the PIVUS cohort in Sweden, with 725 participants and 36 T2DM cases, linked higher levels of three OCs, HCB, DDE, and trans-nonachlor, with T2DM incidence after 5 years of follow-up (summary measure of the 3 OCs, quintile 5 vs 1: OR=3.4; 95% CI=1.0, 11.7)[67]. Additionally, two nested case-control studies, one within the Nurses' Health Cohort, measured multiple OCs, including HCB and trans-nonachlor, and found a number of difference OCs to be associated with T2DM[68,69] (see Table 4).

A systematic review of pesticides and T2DM included 22 studies and reported the top tertile of exposure to *any* type of pesticide (vs. bottom) to increase T2DM risk by nearly 60% (OR=1.58; 95% CI=1.32–1.90), and the OC pesticide specific summary OR was 1.68 (95% CI= 1.37–2.07)[33]. This meta-analysis found T2DM to be also associated with HCB, DDE, and trans-nonachlor individually. OPs were not specifically identified in this meta-analysis, but both studies that investigated OPs to date have found this exposure to be related to T2DM (Table 4).

Alzheimer's Disease

Table 4 outlines studies that investigated pesticides and AD or dementia. Few have relied on measured levels of pesticide metabolites in serum or plasma as has been common in T2DM studies. Instead, studies used occupational exposure questionnaires and self-report, which limited the ability to assess specific chemicals or chemical classes. Nevertheless, a small case-control study, which relied on 86 patients from the Alzheimer's Disease Research Center in Texas and 79 controls, measured serum DDE and found that higher serum levels were associated with 4 times the risk of AD (OR=4.18; 95%=2.54, 5.82)[70]. Furthermore, a large longitudinal cohort, consisting of 3,084 members of the agricultural community of Cache County, Utah, used occupational history questionnaires to assess OC and OP exposures[71]. In this cohort, 344 participants developed AD, and both OP (HR=1.53, 95% CI 1.05–2.23) and OC exposure (HR=1.49, 95% CI 0.99–2.24) was associated with an increased risk of AD. More recently, a Taiwanese group found that hospitalizations for acute OP poisoning were associated with an increased risk of all-cause dementia (HR=1.98; 95% CI, 1.59–2.47) when using the Nation Health Insurance Research Database[72].

Other studies of AD have relied on a measure of 'all' pesticides combined. Since 1994, when the Canadian Study of Health and Aging first reported higher occupational exposure to pesticides was associated with an increased risk of AD (OR=2.17; 95% CI=1.18, 3.99)[73], multiple other studies have followed. Another Canadian study, the Manitoba Study of Health and Aging (n=694) found no association with all pesticides (OR=1.45, 95% CI=0.57, 3.68) but an increased AD risk from fumigants/defoliants (OR=4.53, 95% CI=1.05, 17.09)[74]. A French study, PAQUID, reports exposure doubles the risk of AD (n=1507; RR=2.4; 95% CI=1.0, 5.6)[75]. Both conducted 5 year follow-ups and reported higher risk estimates for AD with occupational exposure. On the other hand, a small Canadian case-control study (n=67 pairs) that assessed residential proximity to pesticide use (record based) found no association with AD (OR=0.97; 95% CI=0.38, 2.41)[76]. A large cohort from the Netherlands also found no association between pesticides and AD-related mortality[77]. However, this study relied on death certificates to assess the outcome. AD is generally not considered a cause of death, and therefore often not listed on death certificates. Additionally, despite the

large study size, there were only a handful of death certificates with AD listed among those with occupational exposure (n=16)[77].

Interestingly, the nationwide study in Taiwan analyzing acute OP poisoning and AD hospitalizations also investigated whether or not T2DM modified this relationship and found that T2DM enhanced the risk of dementia in those with acute pesticide poisoning (HR= 2.95; 95%=2.02–4.31; p for interaction=0.03)[72].

Conclusions

Both biologic mechanisms and epidemiologic evidence strongly support a link between T2DM and AD. Collectively, environmental and occupational studies provide strong evidence that air pollution and pesticides are associated with an increased risk of T2DM, and there is suggestive evidence for a link with AD. We hypothesize that these shared environmental risk factors may initiate pathogenic events involved in both disorders, with T2DM exacerbating neuronal and metabolic dysfunction, further increasing the risk of developing AD. This is supported by the few studies reporting that metabolic dysfunction may modify the influence environmental exposures on health outcomes, including cognitive function.

The etiology of T2DM and AD is complex and heterogeneous. Researchers relying on both medical record data and aging cohorts have previously linked air pollutants and pesticides to both T2DM and cognition, sometimes in the same studies. In future research, T2DM should also be investigated as both a mediator and modifier between exposure and cognition. Furthermore, it is important to not only consider environmental factors generally, but also consider relevant features of exposures. This includes types of exposures, such as those discussed in this review, as well as mixtures of toxicants, and the timing of exposures.

Methods of ambient air pollution exposure assessment have been reviewed previously and have been steadily improving over the past decades[78,79]. For pesticides, a research challenge is to address a multitude of sources (e.g. occupational, home and gardening, diet, and proximity to agriculture), as well as a large number of different chemical compounds and classes that are changing over time. For some compounds, such as the POPs, biomarkers may be the best option. For other pesticides that do not bio-accumulate, such as OPs and permethrins, methods based on agricultural application records or job exposure matrices may be the best approach for assessing longer term exposure [80,81], but these need validation.

Additionally, with chronic diseases such as these, long term low-level exposures are likely important. Ambient monitoring for air pollution has become widespread in the United States since the 1990s, enabling future research of long-term exposures based on address histories. While publicly accessible databases of commercial pesticide use exist, such as the California Pesticide Use Reports, few countries record such information. However, researchers are developing methods to estimate historic environmental pesticide exposure based on land-use records to identify agriculture fields and residential address histories[82]. This may represent a good alternative approach for pesticide exposure assessment without requiring participant recall in countries that do not collect pesticide use records. A recent proposal to require

pesticide producers to conduct some post marketing ‘pesticidovigilance’ similar to pharmacovigilance employed in post approval marketing, use and monitoring of pharmaceuticals might also be an effective approach to assessing human health consequences from widespread pesticide exposures[83].

Ultimately, research thoughtfully considering environmental factors and the complexities of exposure assessment and focusing on exposures related to both T2DM and AD could be key to new disease insights on shared mechanisms and help shape innovative preventative measures and policy decisions. Such studies will ideally elaborate on the role of shared environmental risk factors contributing to these disorders, including but not limited to air pollution and pesticides, and consider how metabolic dysfunction may modify the impact of these exposures on cognitive decline.

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Abbreviations

DDT	dichlorodiphenyltrichloroethane
DDE	dichlorodiphenyldichloroethylene
HCB	hexachlorobenzene
ppb	parts per billion

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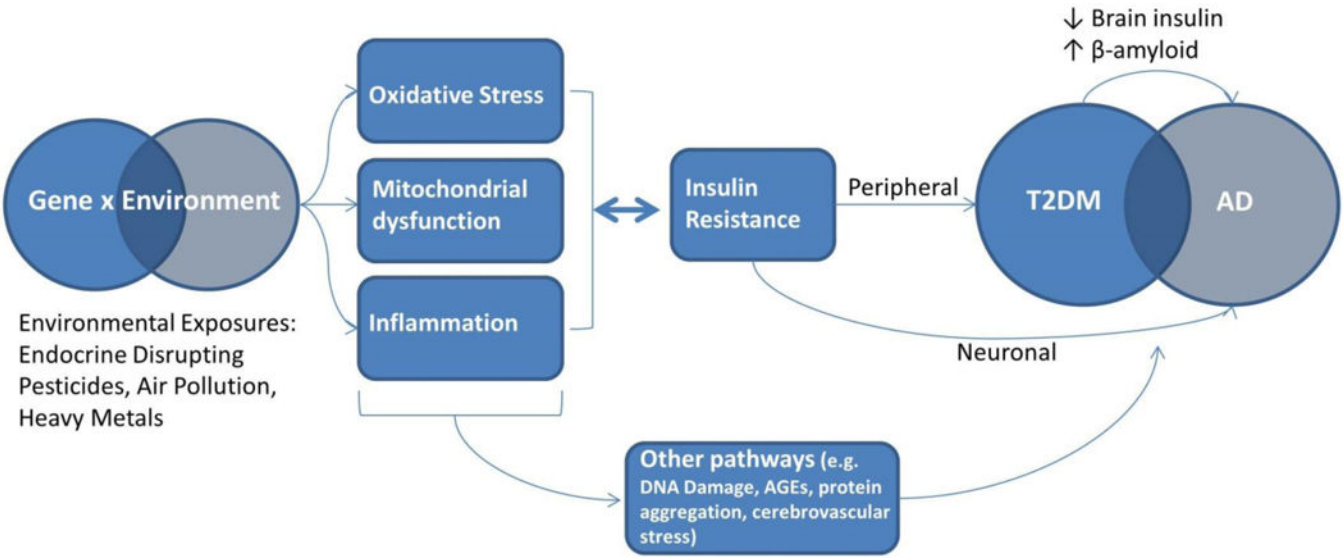

Figure 1.

Proposed underlying link between T2DM and AD, and mechanisms through which environmental toxicants induce pathogenesis.

Table 1

Recent longitudinal studies investigating the association between T2DM (exposure) and AD (outcome).

Study	Cohort	Country	n	T2DM Ascertainment	n	AD Ascertainment	Total	Main Results
Ott, 1999 [18]	Rotterdam Study	The Netherlands	692	Medication use or blood glucose	89	Clinical examination	6,370	RR=1.90 (1.18, 3.05)
MacKnight, 2002 [27]	CSHA	Canada	503	Medication use or blood glucose	267	Clinical examination	5,574	RR=1.30 (0.83, 2.03)
Hassing, 2002 [84]	OCTO-Twin Study	Sweden	108	Medical records	92	Clinical examination	702	RR=0.83 (0.46, 1.48)
Peila, 2002 [23]	HAAS	United States	900	Self-report or blood glucose	76	Clinical examination	2,592	RR=1.80 (1.10, 2.92)
Arvanitakis, 2004 [85]	Religious Order Study	United States	127	Medication use or self-report	151	Clinical examination	824	HR=1.65 (1.10, 2.47)
Xu, 2004 [86]	Kungsholmen Study	Sweden	114	Medical records or blood glucose	260	Clinical examination	1,301	HR=1.30 (0.90, 2.10)
Luchsinger, 2005 [87]	Medicare recipients, NYC	United States	230	Self-report	246	Clinical examination	1,381	HR=2.40 (1.80, 3.20)
Akomolafe, 2006 [26]	Framingham Study	United States	202	Medication use or self-report	237	Clinical examination	2,210	RR=1.15 (0.65, 2.05)
Raffaitin, 2009 [88]	Three-City Study	France	538	Medication use or blood glucose	134	Clinical examination	7,087	HR=1.15 (0.64, 2.05)
Al-Emam, 2010 [89]	University hospital referrals	Egypt	106	Medication use or self-report	137	Clinical examination	764	HR=1.53 (0.96, 2.45)
Ahtiluoto, 2010 [24]	Vantaa 85+ Study	Finland	131	Medical records or self-report	155	Clinical examination	553	HR=2.45 (1.33, 4.52)
Kimm, 2011 [22]	Male NHIC Enrollees	South Korea	33,350	Medical records	821	Medical records	490,445	HR=1.60 (1.29, 1.98)
Kimm, 2011 [22]	Female NHIC Enrollees	South Korea	18,261	Medical records	1,030	Medical records	358,060	HR=1.40 (1.15, 1.70)
Ohara, 2011 [25]	Hisayama Study	Japan	150	Oral glucose tolerance test	105	Clinical examination	1,017	HR=2.05 (1.18, 3.57)
Wang, 2012 [21]	BHNI Database	Taiwan	615,532	Medical records	8,488	Medical records	1,230,403	HR=1.45 (1.38, 1.52)
Huang, 2014 [90]	NHIRD	Taiwan	71,433	Medical records	612	Medical records	142,744	HR=1.76 (1.50, 2.07)
Katon, 2015 [19]	Danish National Register	Denmark	223,174	Medical records	59,663[a]	Medical records	2,454,532	HR=1.06 (1.01, 1.11); T2DM/depression: HR=1.46 (1.37, 1.55)

Abbreviations: AD=Alzheimer's disease; T2DM=Type 2 Diabetes Mellitus; RR=Risk Ratio; HR=Hazards Ratio; N/A=Not Available

Study Abbreviations: BHNI=Bureau of National Health Insurance;CSHA=Canadian Study of Health and Aging; HAAS=Honolulu-Asia Aging Study; NHIC=National Health Insurance Corporation; NHIRD=National Health Insurance Research Database

[a]Includes all forms of dementia, AD sample size alone was not provided; main results are for AD only – not all forms of dementia

Table 2

Examples of shared T2DM/AD pathophysiologic pathways associated with environmental exposures

Exposure	Shared Pathway	Outcomes
Air Pollution	Pulmonary inflammation resulting in systemic spread (elevated pro-inflammatory biomarkers including CRP, IL-6, TNF-α, and fibrogen)	↑ Systemic Inflammation; ↑ Oxidative Stress; ↑ Insulin Resistance
	Spread of ultrafine particles into the bloodstream	↑ Systemic Inflammation; ↑ Oxidative Stress; ↑ Vascular Dysfunction
	Alterations in endothelial function	↑ Insulin Resistance; ↑ Inflammation
	Endoplasmic reticulum stress/alterations in insulin transduction	↑ Protein Misfolding; ↑ Insulin Resistance
	Brown adipose tissue (BAT)-mediated thermogenesis	↑ Mitochondrial dysfunction; ↑ Oxidative Stress
Pesticides	Induction of inflammatory processes in the central system nervous, cardiac and pancreatic tissues; increase the secretion of pro-inflammatory cytokines (TNF-α, IL-6, etc.)	↑ Systemic Inflammation; ↑ Oxidative Stress; ↑ Insulin Resistance
	Induction of free radicals, lipid peroxidation, and impaired antioxidant status	↑ Systemic Inflammation; ↑ Oxidative Stress; ↑ Insulin Resistance
	Glucose metabolism disruptions/Hyperglycemia	↑ Insulin Resistance
	Dysfunction of insulin-secreting cells	↑ Insulin Resistance

Abbreviations: AD=Alzheimer's disease; T2DM=Type 2 Diabetes Mellitus;

Table 3

Recent epidemiologic studies investigating the association between air pollution and T2DM, AD, or cognition among adults/elderly

Outcome (Ascertainment)	Study, Cohort	Exposure Assessment	Exposure Location, Timing	Country	Study Type, Follow-up	Sample size		Main Results (per 1 IQR unless noted)
						Outcome	Total	
PM2.5								
T2DM (Medication use or blood glucose)	Puett, 2011, NHS[44]	EPA monitors/LUR	Residence, final two years of follow-up	United States	Longitudinal, 1989–2002	3,784	74,412	HR=1.21 (1.00, 1.46)
T2DM (Medication use or blood glucose)	Puett, 2011, HPFS[44]	EPA monitors/LUR	Residence, final two years of follow-up	United States	Longitudinal, 1989–2002	688	15,048	HR=1.52 (0.93, 2.47)
T2DM (Self-report)	Coogan, 2012, BWHS[36]	EPA monitors/Kriging model	Residence, 2000	United States	Longitudinal, 1995–2005	183	3,992	IRR=1.63 per 10 ug/m3 (0.78, 3.44)
Mortality from T2DM (Death Certificate)	Brook, 2013, 1991 Canadian Census Mortality[42]	Satellite sensing/Atmospheric model	Residence, 2001–2006	Canada	Longitudinal, 1991–2001	5,200	2,145,400	HR=1.49 per 10 ug/m3 (1.37, 1.62) [a]
T2DM (Registry)	Chen, 2013, NPHS Respondents[43]	Satellite sensing/Atmospheric model	Residence, 2001–2006	Canada	Longitudinal, 1996–2010	6,310	62,012	HR=1.11 per 10 ug/m3 (1.02, 1.21)
T2DM (Medication use or blood glucose)	Park, 2015, MESA[41]	EPA monitors/Spatio-temporal model	Residence, Baseline year	United States	Longitudinal, 2000–2002	622	5,135	HR=1.05 (0.87, 1.26)
T2DM (Medication use or blood glucose)	Weinmayr, 2015, Heinz Nixdorf Recall Study[45]	Chemistry transport model (EURAD)	Residence, 2001–2002	Germany	Longitudinal, 2000–2008	331	3,607	IRR=1.36 per 1-ug/m3 (0.98, 1.89)
AD (Medical records)	Jung, 2015, NHRID[48]	Taiwan EPA monitors	Residence, 2001–2010	Taiwan	Longitudinal, 2001–2010	1,399	95,690	HR=2.38 (2.21, 2.56)
Hospitalizations due to AD (Medical records)	Kioumourtzoglou, 2015, Medicare Enrollees[49]	EPA monitors, city averages	City averages, Yearly (time-varying)	United States	Longitudinal, 1999–2010	266,725	9.8 million	HR=1.15 per 1 μg/m3 (1.11, 1.19)
Cognitive Decline (Cognitive tests-Telephone)	Weuve, 2012, NHS Cognitive Cohort[50]	EPA monitors/Spatio-temporal model	Residence, 7–14 years	United States	Longitudinal, 1995–2008	N/A	19,409 women	Global Cognitive Score: Quintile 5 vs 1 β=−0.018 (−0.034, −0.002)
Cognitive Impairment (Cognitive test-Telephone)	Loop, 2013, REGARDS[51]	Satellite sensing & EPA monitors/Spatio-temporal model	Residence, Baseline year	United States	Longitudinal, 2003–2007	1,633	20,150	OR=1.26 (0.97, 1.64)
Cognitive Decline (Cognitive tests – In-person)	Tonne, 2014, Whitehall II[52]	London Monitors/KCLurban dispersion model	Residence, 4-yrs prior	United Kingdom	Longitudinal, 2002–2009	N/A	10,308	Standardized Memory Test: β =−0.04 (−0.07, −0.01)
Cognitive Decline (Cognitive tests-In-person)	Schikowski, 2015, SALIA[53]	Monitors/LUR	Residence, 2008–2009	Germany	Longitudinal, 1985–2009	N/A	789 women	CERAD-Plus test: β=−0.19 (−0.36, −0.02)
PM10								
T2DM (Self-report)	Kramer, 2010 SALIA[38]	Monitoring stations, nearest to residence	Residence, 1986–1990	Germany	Longitudinal, 1990–2006	87	1,775	HR=1.16 (0.81, 1.65)

Outcome (Ascertainment)	Study, Cohort	Exposure Assessment	Exposure Location, Timing	Country	Study Type, Follow-up	Sample size		Main Results (per 1 IQR unless noted)
						Outcome	Total	
T2DM (Medication use or blood glucose)	Puett, 2011, NHS [44]	EPA monitors/Spatio-temporal model	Residence, final two years of follow-up	United States	Longitudinal, 1989–2002	3,784	74,412	HR=1.13 (0.98, 1.29)
T2DM (Medication use or blood glucose)	Puett, 2011, HPFS[44]	EPA monitors/Spatio-temporal model	Residence, final two years of follow-up	United States	Longitudinal, 1989–2002	688	15,048	HR=1.27 (0.91, 1.77)
T2DM (Medication use or blood glucose)	Eze, 2014, SAPALDIA[40]	Dispersion model	Residence, 1 to 10-yr prior to follow-up	Switzerland	Longitudinal, 1991–2002	315	6392	OR=1.40 per 10 ug/m3 (1.17, 1.67)
T2DM (Medication use or blood glucose)	Weinmayr, 2015, Heinz Nixdorf Recall Study[45]	Chemistry transport model (EURAD)	Residence, 2001–2002	Germany	Longitudinal, 2000–2008	331	3,607	IRR=1.36 per 1-ug/m3 (0.97, 1.89)
AD (Clinical examination)	Wu, 2015, Neurology Clinic patients[54]	Taiwan EPA monitors/Spatio-temporal model	Residence, 1993–2006	Taiwan	Case-Control, 2007–2010	249	497	Tertile 3 vs 1 OR=4.17 (2.31, 7.54)
Cognitive Decline (Cognitive tests-Telephone)	Weuve, 2012, NHS Cognitive Cohort[50]	EPA monitors/Spatio-temporal model	Residence, 7–14 years	United States	Longitudinal, 1995–2008	N/A	19,409 women	Global Cognitive Score: Quintile 5 vs 1 β=−0.024 (−0.040, −0.008)
Cognitive Decline (Cognitive tests – In-person)	Tonne, 2014, Whitehall II [52]	London Monitors/KCLurban dispersion model	Residence, 4-yrs prior	United Kingdom	Longitudinal, 2002–2009	N/A	10,308	Reasoning Test: β=−0.01 (−0.03, 0.01)
Cognitive Decline (Cognitive tests – In-person)	Schikowski, 2015, SALIA[53]	Monitors/LUR	Residence, 2008–2009	Germany	Longitudinal, 1985–2009	N/A	789 women	CERAD-Plus test: β=−0.14 (−0.26, −0.02)
NO_2								
T2DM (Medical records)	Brook, 2008, Respiratory clinic patients[35]	Field measurements/LUR	Residence, 2002 & 2004	Canada	Longitudinal, 1992–1999	630	4,182 women	OR=1.04 per 1 ppb (1.00, 1.08)
T2DM (Self-report)	Kramer, 2010, SALIA[38]	Monitors/LUR	Residence, 2002	Germany	Longitudinal, 1990–2006	87	1775	HR=1.42 (1.16, 1.73)
T2DM (Self-report)	Coogan, 2012, BWHS[36]	Monitors/LUR	Residence, 2006	United States	Longitudinal, 1995–2005	183	3992	IRR=1.25 (1.07, 1.46)
T2DM (Medical records)	Andersen, 2012, Danish Diet, Cancer, and Health cohort[37]	Danish AirGIS human exposure modeling system	Residence, Yearly (time-varying)	Denmark	Longitudinal, 1993–2006	2,877	51,818	HR=1.04 (1.00, 1.08)
T2DM (Medication use or blood glucose)	Weinmayr, 2012, Heinz Nixdorf Recall Study [39]	Chemistry transport model (EURAD)	Residence, 1-yr prior to dx	Germany	Longitudinal, 2000–2008	309	3,424	IRR= 1.11 (1.00, 1.22)
T2DM (Medication use or blood glucose)	Eze, 2014, SAPALDIA[40]	Monitors/Hybrid dispersion model plus LUR	Residence, 1 to 10-yrs prior to follow-up survey	Switzerland	Longitudinal, 1991–2002	315[b]	6392	OR=1.19 per 10 ug/m3 (1.03, 1.38)
T2DM (Medication use or blood glucose)	Park, 2015, MESA[41]	EPA monitors/Spatio-temporal model	Residence Baseline year	United States	Longitudinal, 2000–2002	622	5,135	HR=1.04 (0.77, 1.40)
AD (Clinical examination)	Oudin, 2016, Betula Study[55]	Monitors/LUR	Residence, Baseline year	Sweden	Longitudinal, 1993–2014	191	1,806	Quartile 4 vs 1 HR=1.38 (0.87, 2.19); All cause dementia: HR=1.43 (1.00, 2.05)

Outcome (Ascertainment)	Study, Cohort	Exposure Assessment	Exposure Location, Timing	Country	Study Type, Follow-up	Sample size		Main Results (per 1 IQR unless noted)
						Outcome	Total	
Dementia (Medical records)	Chang, 2014, NHIRD[56]	Taiwan EPA monitors, nearest to clinic	Clinic, 1998–2010	Taiwan	Longitudinal, 2000–2007	1,720	29,547	Quartile 4 vs 1 HR=1.54 (1.34, 1.77)
Cognitive Decline (Cognitive tests-In-person)	Schikowski, 2015, SALIA[53]	Monitors/LUR	Residence, 2008–2009	Germany	Longitudinal, 1985–2009	N/A	789 women	CERAD-Plus test: β=−0.28 (−0.44, −0.12)

[a] Modeling mortality among subjects with T2DM code as an underlying cause

[b] Prevalent diabetes

N/A=Not Applicable, outcome is a continuous measure of cognitive decline; EPA=Environmental Protection Agency; EURAD= European Air Pollution Dispersion model; LUR= Land Use Regression

Studies: NHS= Nurses' Health Study; HPFS=Health Professionals Follow-Up Study; NPHS=National Population Health Survey; SALIA= Study on the Influence of air pollution on Lung function, Inflammation and Aging; SAPALDIA= Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults; REGARDS= Reasons for Geographic And Racial Differences in Stroke; MESA= Multi-Ethnic Study of Atherosclerosis; BWHS= Black Women's Health Study; NHRID= National Health Insurance Research Database

Table 4

Recent epidemiologic studies investigating the association between selective pesticides and T2DM or AD

Outcome (Ascertainment)	Study, Cohort	Exposure Assessment	Exposure Location, Timing	Country	Study Type	Sample size		Main Results
						Outcome	Total	
T2DM (Medication use or blood glucose)	Lee, 2006, NHANES[63]	6 OCs/POPs, Measured	Serum, Baseline	United States	Cross-Sectional, 1999–2002	217	2,016	6 POPs Summary: ≥90th vs < LOD OR=37.7 (7.8, 182.0), p for trend <0.001
T2DM (Self-report)	Montgomery, 2008, AHS[64]	OCs, Self-report	Occupational, Lifetime	United States	Longitudinal, 1993–2003	1,176	31,787	Ever vs Never: Chlordane: OR=1.16 (1.01, 1.34); Heptachlor: OR=1.20 (1.01, 1.43)
T2DM (Self-report)	Montgomery, 2008, AHS[64]	OPs, Self-report	Occupational, Lifetime	United States	Longitudinal, 1993–2003	1,176	31,787	Ever vs Never: Coumaphos: OR=1.26 (1.03, 1.55); Phorate OR=1.22 (1.06, 1.42); Terbufos OR=1.17 (1.02, 1.35); Trichlorfon OR=1.85 (1.03, 3.33)
T2DM (Self-report)	Turyk, 2009, Great Lakes Consortium[66]	DDE, Measured	Serum, Change over follow-up	United States	Longitudinal, 1994–2005	36	435	Tertile 2 vs 1: OR=5.5 (1.2, 25.1); Tertile 3 vs 1: OR=7.1 (1.6, 31.9); p for trend=0.008
T2DM (Medication use or blood glucose)	Lee, 2010, CARDIA[68]	8 OCs, Measured	Serum, Year 2	United States	Nested Case-control, 1987–2006	90	90	Quartile 4 vs 1: Oxychordane: OR=2.6 (1.0, 7.0); trans-Nonachlor: OR=3.7 (1.2, 11.0)
T2DM (Medication use or blood glucose)	Lee, 2011, PIVUS[67]	3 OCs, Measured	Plasma, Baseline	Sweden	Longitudinal, 2001–2009	36	725	3 OCs Summary: Quintile 5 vs 1 OR=3.4 (1.0, 11.7)
T2DM (Self-report)	Wu, 2013, NHS[69]	3 OCs, Measured	Plasma, Baseline	United States	Nested Case-control, 1989–2008	48	1,095	Tertile 3 vs 1: HCBs: OR=3.59 (1.49, 8.64); DDE: OR=1.58 (0.69, 3.59); DDT: OR=1.06 (0.49, 2.28)
T2DM (Self-report)	Starling, 2014, AHS Spouses[65]	OPs, Self-report	Occupational, Lifetime	United States	Longitudinal, 1993–2007	688	13,637 women	Ever vs never: Fonofos HR=1.56 (1.11, 2.19); Phorate HR=1.57 (1.14, 2.16); Parathion HR=1.61 (1.05, 2.46)
T2DM (Self-report)	Starling, 2014, AHS Spouses[65]	OCs, Self-report	Occupational, Lifetime	United States	Longitudinal, 1993–2007	688	13,637 women	Ever vs never: Dieldrin HR=1.99 (1.12, 3.54)
AD (Clinical examination)	McDowell, 1994, CSHA[73]	All pesticides, Self-report	Occupational, Lifetime	Canada	Case-Control, 1991	258	535	OR=2.17 (1.18, 3.99)
AD (Clinical examination)	Tyas, 2001, MSHA[74]	All pesticides/fertilizers, Self-report	Occupational, Lifetime	Canada	Longitudinal, 1991–1997	36	694	RR = 1.45 (95% CI 0.57–3.68)
AD (Clinical examination)	Gauthier, 2001, SLSJ[76]	All pesticides, Record based	Residence, 1971–1991	Canada	Case-Control	67	134	Herbicides: OR=1.07 (0.39, 2.54); Insecticides: OR=1.62 (0.64, 4.11); Pesticides: OR=0.97 (0.38, 2.41)
AD (Clinical examination)	Baldi, 2003, PAQUID[75]	All pesticide, JEM	Occupational, Lifetime	France	Longitudinal, 1992–1998	96	1,507 men	RR=2.4 (1.0, 5.6)

Outcome (Ascertainment)	Study, Cohort	Exposure Assessment	Exposure Location, Timing	Country	Study Type	Sample size		Main Results
						Outcome	Total	
AD (Clinical examination)	Hayden, 2010, CCMS[71]	OPs, Self-report	Occupational, Lifetime	United States	Longitudinal, 1995–2005	344	3,084	HR=1.53 (1.05, 2.23)
AD (Clinical examination)	Hayden, 2010, CCMS[71]	OCs, Self-report	Occupational, Lifetime	United States	Longitudinal, 1995–2005	344	3,084	HR=1.49 (0.99, 2.24)
AD Prevalence (Medical records)	Parron, 2011, Andalusian Districts[91]	All pesticides, Record based	District wide, 2001	Spain	Ecologic, 1985–2005	3529	17,429	High exposure vs low: OR=2.10 (1.96, 2.25)
AD (Clinical examination)	Richardson, 2014, AD Research Centers Patients[70]	DDE, Measured	Serum, Baseline	United States	Case-Control, 2002–2008	86	165	OR=4.18 (2.54, 5.82)
AD-related Mortality (Medical records)	Koeman, 2015, NLCS[77]	All pesticides, JEM	Occupational, Lifetime	Netherlands	Longitudinal, 1986–2003	113	2,098 men	Herbicides: OR=0.70 (0.24, 2.02); Insecticides: OR=0.87 (0.40, 1.90); Pesticides: OR=0.86 (0.40, 1.88)
Dementia (Medical Records)	Lin, 2015, NHIRD[72]	Acute OP poisoning, Medical records	N/A	Taiwan	Longitudinal, 2000–2011	507	48,126	HR=1.98 (95% CI, 1.59–2.47)

JEM=Job Exposure Matrix; LOD=Limit of Detection; N/A=Not applicable, exposure is acute OP poisoning based on hospital records.

Studies: NHANES= National Health and Examination Survey; AHS= Agricultural Health Study; CARDIA=Coronary Artery Risk Development in Young Adults cohort; PIVUS=The Prospective Investigation of the Vasculature in Uppsala Seniors study; NHS= Nurses' Health Cohort; PAQUID=Personnes Agées Quid; CHSA= The Canadian Study of Health and Aging; MSHA= Manitoba Study of Health and Aging; SLSJ= Saguenay–Lac Saint-Jean region study; CCME= Cache County Memory Study; NLCS= The Netherlands Cohort Study; NHIRD=National Health Insurance Research Database