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Understanding The Exposome In Type 2 Diabetes: Integrating Lifestyle Behaviors And Environmental Pollutants In Disease Risk And Prevention

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Abstract

The exposome, encompassing the totality of environmental, lifestyle, and biological exposures across the life course, offers a comprehensive framework for understanding the multifactorial etiology of type 2 diabetes (T2D). This review synthesizes evidence on the interplay between external exposures (e.g., pollutants, diet, socioeconomic status), internal domains (e.g., microbiome, metabolic alterations), and biological mechanisms (e.g., oxidative stress, hormonal disruption, epigenetic regulation) that collectively influence T2D risk. Technological advances, including geospatial tools, wearable devices, and multi-omics integration, are reshaping exposome research, enabling precise exposure assessment and mechanistic insight. Moreover, we highlight the modifying roles of socioeconomic status and education, the gut microbiome, and transgenerational influences in shaping T2D susceptibility. Public health strategies emphasizing lifestyle modification, environmental risk reduction, and equity-focused interventions remain central to prevention, while translation of exposome insights into policy and precision public health offers new opportunities. Finally, we outline future research directions, emphasizing artificial intelligence–driven analytics, longitudinal and multi-generational studies, and methodological innovations to bridge existing gaps. Collectively, this review underscores the importance of a systems-level, exposome-informed approach to mitigate the growing burden of T2D globally.

Keywords: *Exposome, type 2 diabetes, oxidative stress, gut microbiome, precision public health*

1. INTRODUCTION

Type 2 diabetes mellitus (T2D) has emerged as one of the most urgent public health concerns of the 21st century, with prevalence rising at an alarming rate in nearly all regions of the world. According to the **Global Burden of Disease (GBD) 2021 study**, approximately 529 million people were living with diabetes in 2021, and this number is projected to exceed 1.31 billion by 2050—more than doubling within three decades (Ong et al., 2023). The **International Diabetes Federation (IDF)** provides parallel estimates, reporting that roughly 1 in 9 adults, or about 590 million individuals, currently live with diabetes, with projections reaching 853 million by 2050 (IDF, 2024/2025). The majority of these cases are T2D, which not only accounts for the largest share of the global diabetes burden but is also driving much of the observed growth in prevalence. Alarmingly, the steepest relative increases are projected for low- and middle-income countries (LMICs), where rapid urbanization, economic transition, and lifestyle shifts are accelerating the epidemic (Ong et al., 2023).

The economic and societal costs of T2D are equally profound. Global healthcare expenditure attributable to diabetes reached US$966 billion in 2021, representing a 316% increase since 2007 (IDF, 2021). By 2024, annual costs surpassed US$1 trillion (IDF, 2025). These expenditures include not only direct medical care but also indirect costs from reduced productivity, disability, and premature mortality. Furthermore, T2D is a major cause of cardiovascular disease, kidney failure, and vision loss, making it a key contributor to years of life lost and disability-adjusted life years (DALYs) worldwide (GBD 2021 Diabetes Collaborators, 2023). This epidemiological and economic evidence underscores that T2D is not merely a clinical issue but a global systems-level challenge requiring comprehensive prevention and management strategies.

While genetic susceptibility plays a role in T2D pathogenesis, genome-wide association studies (GWAS) suggest that genetic variation explains only a modest proportion of disease risk, generally between 15% and 45% (Beulens et al., 2022). The remainder is attributable to modifiable environmental and behavioral determinants. Lifestyle factors—such as dietary quality, physical activity, sedentary behavior, tobacco use, alcohol consumption, sleep patterns, and psychosocial stress—are among the most significant drivers of risk (Yang et al., 2020; Cappuccio et al., 2010; Gan et al., 2015). For instance, adherence to dietary patterns rich in whole grains, vegetables, fruits, and healthy fats is associated with a substantially lower risk of T2D, whereas diets high in processed meats, refined carbohydrates, and added sugars confer substantial risk (Ley et al., 2014). Regular physical activity improves insulin sensitivity and reduces T2D incidence, while prolonged sedentary time increases risk even in otherwise active individuals (Booth et al., 2017).

Beyond lifestyle, a growing body of research implicates environmental exposures in T2D etiology. Long-term exposure to ambient air pollution—particularly fine particulate matter ($PM_{2.5}$) and nitrogen dioxide (NO_2)—has been associated with increased insulin resistance and higher incidence of T2D, with hazard ratios around 1.10 per 10 $\mu g/m^3$ increase in $PM_{2.5}$ (Yang et al., 2020). Endocrine-disrupting chemicals (EDCs) such as bisphenol A, phthalates, and persistent organic pollutants interfere with hormonal regulation of glucose metabolism (Heindel et al., 2015). Heavy metals including arsenic, cadmium, and mercury contribute to oxidative stress, mitochondrial dysfunction, and β-cell damage. Other exposures—such as chronic noise, artificial light at night, urban heat islands, and limited access to green space—further compound T2D risk through stress activation, circadian disruption, and reduced opportunities for physical activity (Beulens et al., 2022).

Importantly, these determinants rarely act in isolation. They cluster and interact in complex ways: socioeconomic disadvantage can simultaneously constrain access to healthy food, increase environmental pollutant exposure, and limit healthcare access. Early-life exposures—such as maternal malnutrition, environmental toxins, and adverse social environments—can leave long-lasting biological imprints through epigenetic modifications, altered metabolic programming, and microbiome changes, creating a trajectory of heightened vulnerability in adulthood (Gluckman et al., 2011). Such complexity challenges reductionist approaches and calls for integrative frameworks capable of capturing the cumulative, concurrent, and interactive effects of diverse exposures over the life course.

The **exposome**, introduced by Wild (2005, 2012), offers such a framework by encompassing the totality of environmental exposures from conception onwards. Conceptually, it is the environmental counterpart to the genome, aiming to account for all non-genetic influences on health and disease. The exposome is typically divided into three interrelated domains: the **general external domain** (socioeconomic status, psychosocial factors, climate, urban design), the **specific external domain** (individual behaviors, occupational exposures, pollutants, infections), and the **internal domain** (endogenous biological responses such as inflammation, metabolism, oxidative stress, microbiome composition, and epigenetic regulation) (Wild, 2012; Rappaport & Smith, 2010; Rappaport, 2011).

Methodological advances in exposome research have enabled high-dimensional, integrative assessments of multiple exposures simultaneously. These include exposome-wide association studies (ExWAS), untargeted metabolomics for "blood exposome" profiling, geospatial modeling of environmental hazards, and wearable devices for personal exposure monitoring (Rappaport, 2018). Applied to T2D, the exposome perspective recognizes that lifestyle behaviors themselves are exposures embedded within broader social and environmental contexts, and that environmental hazards may exacerbate the effects of unhealthy behaviors. For example, the metabolic harm from poor diet may be amplified by co-exposure to air pollution, while circadian disruption from shift work may interact with obesogenic environments to further elevate T2D risk (Beulens et al., 2022).

The objective of this review is to apply the exposome framework to the understanding of T2D etiology. Specifically, it aims to (i) conceptualize the integration of lifestyle behaviors and environmental pollutants within the three-domain exposome model, (ii) synthesize and critically appraise epidemiological evidence on their individual and combined effects, (iii) examine biological mechanisms underpinning these associations, (iv) review methodological advances in measuring and analyzing complex exposure mixtures, and (v) discuss implications for public health policy and precision prevention strategies. By moving beyond single-exposure paradigms, this review seeks to provide researchers, clinicians, and policymakers with a comprehensive, systems-level perspective for addressing the escalating global burden of T2D.

2. The Exposome: Conceptual Framework

2.1. Definition and Evolution of the Exposome Concept

The term **"exposome"** was first introduced by Christopher Wild in 2005 to capture the *totality of environmental exposures*—both chemical and non-chemical—that an individual experiences from conception to death (Wild, 2005). Wild's argument was grounded in a recognition that while the **Human Genome Project** had revolutionized our understanding of genetic contributions to disease, the non-genetic component—the vast and complex landscape of environmental determinants—remained poorly characterized. This imbalance, he noted, risked skewing research priorities toward genomics at the expense of environmental health, despite overwhelming evidence that chronic diseases such as cancer, cardiovascular disease, and type 2 diabetes mellitus (T2D) are driven by an interplay of genetic and environmental factors.

Initially, the exposome was proposed as a conceptual counterweight to the genome: where the genome is largely static across the lifespan, the exposome is **dynamic**, shaped by ongoing interactions with diet, physical activity, pollutants, stressors, occupational hazards, and social environments (Wild, 2012). Over the past decade, the definition has evolved into a **structured framework** for research. Rappaport and Smith (2010) refined Wild's original idea by distinguishing between *external* and *internal* domains of the exposome, thus linking the measurable biological consequences of environmental exposures with their sources. This conceptual evolution was accompanied by methodological advances—particularly in high-throughput biomonitoring, omics technologies, and geospatial analytics—that have transformed the exposome from a theoretical ideal into an **operationalizable research paradigm** (Miller & Jones, 2014; Rappaport, 2018).

Modern exposome science now emphasizes **life-course epidemiology**, recognizing that exposures accumulate over time and that certain **critical windows**—such as fetal development, early childhood, adolescence, and midlife—are periods of heightened vulnerability. It also acknowledges that exposures do not occur in isolation but as part of complex mixtures, often interacting in synergistic or antagonistic ways. This recognition has driven a shift toward **systems-level approaches** in epidemiology, with the exposome serving as the central integrative concept.

2.2. The Three Domains of the Exposome

The exposome is typically divided into **three interrelated domains**—internal, specific external, and general external—each representing different layers of the environmental influence on health (Wild, 2012) as shown in Figure 1 and Table 1. These domains are not siloed; instead, they interact continuously, with exposures in one domain often influencing or modulating those in another.

Figure 1. The Exposome Framework in Type 2 Diabetes

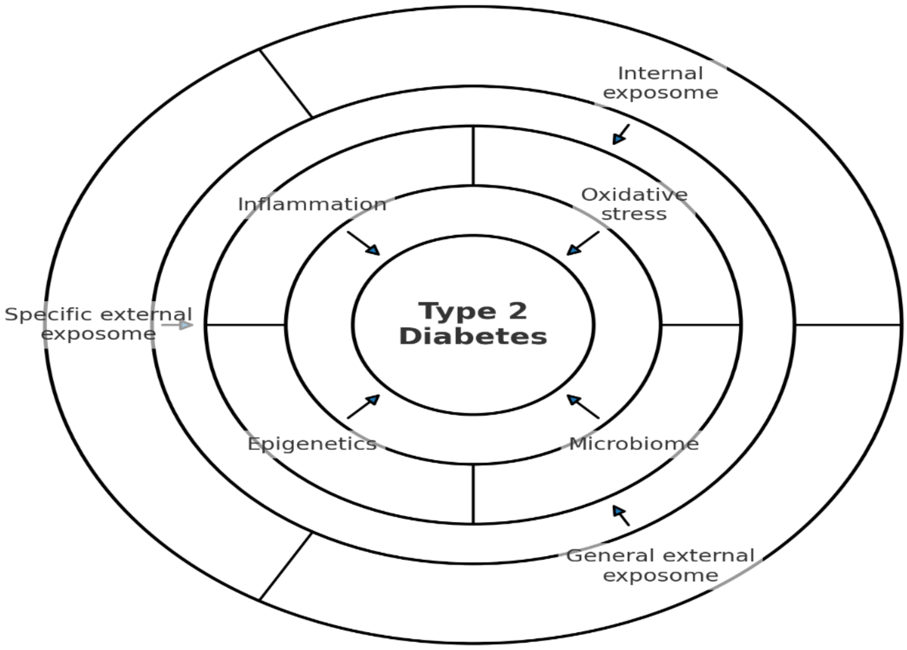

Table 1. Exposome Domains and Their Contributions to Type 2 Diabetes

Exposome Domain	Key Factors / Exposures	Mechanistic Links to T2D	Example Studies
Internal Exposome	- **Gut microbiome**: Microbial composition, diversity, and metabolites (e.g., short-chain fatty acids). - **Metabolism**: Glucose,	- **Gut dysbiosis** alters production of metabolites that regulate insulin sensitivity and inflammation. - **Hormonal imbalance** (e.g., hyperinsulinemia, leptin	- **Qin et al., 2012** showed gut microbial dysbiosis in T2D patients, highlighting altered butyrate-producing species. - **Kootte et al., 2017** demonstrated that fecal

	lipid, and amino acid homeostasis. - **Hormones**: Insulin, glucagon, adipokines, and incretins.	resistance) drives insulin resistance and obesity. - **Metabolic shifts** contribute to impaired glucose tolerance and systemic inflammation.	microbiota transplantation from lean donors improved insulin sensitivity in metabolic syndrome.
Specific External Exposome	- **Environmental pollutants**: Air pollution (PM2.5), endocrine-disrupting chemicals (e.g., BPA, phthalates). - **Diet**: High sugar, high-fat intake; low fiber and micronutrient deficiencies. - **Physical activity**: Sedentary lifestyle vs. regular exercise. - **Infections**: Viral and bacterial exposures that affect immune pathways.	- **Pollutants** induce oxidative stress and β-cell damage, impairing insulin secretion. - **Poor diet** contributes to obesity, dyslipidemia, and insulin resistance. - **Sedentary lifestyle** reduces glucose uptake by muscles and promotes fat accumulation. - **Chronic infections** activate immune pathways, leading to low-grade inflammation.	- **Rajagopalan et al., 2021** linked air pollution to systemic inflammation and metabolic dysfunction, increasing T2D incidence. - **Song et al., 2020** reported that Western-style diets enriched in processed foods significantly increased T2D risk through obesity-related pathways.
General External Exposome	- **Socioeconomic status (SES)**: Income, occupation, and living conditions. - **Education**: Health literacy, awareness of nutrition and lifestyle risks. - **Built environment**: Urbanization, access to green spaces, food deserts, walkability.	- **Low SES** is associated with limited access to healthy foods, safe environments, and healthcare services. - **Educational disadvantage** reduces awareness of preventive measures and adherence to healthy behaviors. - **Built environment factors** shape opportunities for physical activity, stress exposure, and diet quality.	

2.2.1. Internal Exposome

The **internal exposome** refers to *endogenous* biological processes that occur within the body as a consequence of, or in response to, external exposures. It encompasses **metabolites**, **hormones**, **lipid mediators**, **oxidative stress markers**, **immune and inflammatory profiles**, and **epigenetic modifications**—all of which can be measured through biological sampling (Miller & Jones, 2014). The internal exposome also includes **microbiome composition and function**, which are increasingly recognized as pivotal mediators of metabolic health (Gilbert et al., 2018).

In the context of T2D, internal exposome measures can capture biological perturbations linked to chronic exposure to air pollution, poor diet, or psychosocial stress. For example, long-term exposure to fine particulate matter ($PM_{2.5}$) is associated with elevated systemic inflammation and oxidative stress, evidenced by higher circulating levels of C-reactive protein, interleukin-6, and lipid peroxidation products (Brook et al., 2010). Similarly, dietary patterns leave distinct signatures in the metabolome: high-fiber diets increase short-chain fatty acids beneficial for insulin sensitivity, while high saturated-fat diets elevate pro-inflammatory lipid species (Zheng et al., 2020). These biomarkers act as **biological fingerprints** of cumulative exposures and provide mechanistic insight into disease pathways.

2.2.2. Specific External Exposome

The **specific external exposome** includes identifiable, measurable exposures that occur at the individual level. These encompass **dietary intake**, **physical activity patterns**, **tobacco and alcohol consumption**, **occupational hazards**, **infectious agents**, and **chemical pollutants** such as heavy metals, pesticides, and endocrine-disrupting chemicals (EDCs) (Rappaport & Smith, 2010). Such exposures can be quantified using self-report, environmental monitoring, wearable sensors, or biomonitoring of relevant biomarkers.

For T2D, specific external exposures have well-documented causal or contributory roles. Long-term exposure to $PM_{2.5}$ has been linked to increased insulin resistance and elevated T2D incidence (Yang et al., 2020). Persistent organic pollutants, including polychlorinated biphenyls (PCBs) and certain pesticides, have been associated with impaired glucose tolerance and β-cell dysfunction (Heindel et al., 2015). Dietary exposures—whether beneficial (Mediterranean diet) or harmful (Western diet)—also fall within this domain, as do physical inactivity and circadian disruption from shift work (Gan et al., 2015).

2.2.3. General External Exposome

The **general external exposome** comprises *broad contextual factors* that shape the nature, intensity, and distribution of more specific exposures. These include **socioeconomic status (SES)**, **educational attainment**, **psychosocial stress**, **cultural norms**, **built environment characteristics** (walkability, green space availability, transport infrastructure), **climate**, and **political or regulatory environments** (Wild, 2012; Nieuwenhuijsen, 2016).

In T2D epidemiology, the general external domain plays a critical role in shaping exposure disparities. For example, low-SES communities often experience higher exposure to environmental pollutants, limited access to healthy foods, and reduced opportunities for physical activity—creating a "triple burden" of disadvantage (Beulens et al., 2022). Urban heat islands can exacerbate heat stress, impairing insulin sensitivity and metabolic control, while noise pollution and lack of green space may elevate stress hormones and reduce opportunities for restorative activity (Hackett & Steptoe, 2017). The general external exposome thus provides the **social and environmental context** within which specific exposures and internal responses occur.

2.3. Relevance of the Exposome to Metabolic Diseases

The exposome framework is particularly well-suited to addressing metabolic diseases such as T2D because these conditions are driven by **complex, multifactorial interactions** over extended timeframes. T2D is characterized by a protracted preclinical phase involving progressive insulin resistance, compensatory hyperinsulinemia, β-cell stress, and eventual failure (Tabák et al., 2012). A wide array of exposures—ranging from obesogenic diets and sedentary lifestyles to air pollution and psychosocial stress—can influence these processes, often through overlapping biological pathways such as **systemic inflammation**, **oxidative stress**, **endocrine disruption**, and **altered circadian regulation**.

Moreover, the **life-course approach** embedded in the exposome recognizes that metabolic risk is shaped not only by current exposures but also by **earlier life experiences**, including prenatal and early postnatal environments (Gluckman et al., 2011). For instance, maternal malnutrition, gestational exposure to EDCs, or early-life air pollution exposure can program metabolic pathways in ways that predispose individuals to T2D decades later (Barouki et al., 2012). This perspective aligns closely with the **developmental origins of health and disease (DOHaD)** paradigm, offering a unifying framework to link diverse lines of evidence.

2.4. Integrating Lifestyle and Environmental Factors within the Exposome Model

One of the most powerful features of the exposome framework is its ability to integrate **lifestyle behaviors** and **environmental exposures** into a single analytic model, allowing for a more realistic representation of real-world risk environments. In practice, this means examining how physical activity, diet, smoking, and sleep patterns interact with exposures such as air pollution, EDCs, and urban design to shape T2D risk.

For example, physically active individuals may mitigate some of the harmful metabolic effects of air pollution through improved cardiorespiratory fitness and antioxidant defenses (Pope et al., 2016). Conversely, an unhealthy diet high in refined carbohydrates and saturated fats may potentiate the metabolic toxicity of EDCs by promoting adiposity and systemic inflammation (Heindel et al., 2015).

Methodologically, integrating these domains requires **advanced statistical tools** capable of modeling high-dimensional, correlated exposures, such as Bayesian kernel machine regression (BKMR), weighted quantile sum regression, and network analysis (Bobb et al., 2015). Recent advances in **wearable sensors**, **remote sensing**, **mobile health technologies**, and **biomarker discovery** have made it possible to capture both behavioral and environmental exposures at high temporal and spatial resolution (Nieuwenhuijsen, 2016).

From a public health standpoint, this integrated perspective highlights the necessity of **dual intervention strategies**: targeting behavioral change at the individual level while implementing **structural and environmental reforms**—such as air quality improvements, chemical regulation, urban greening, and equitable access to healthy foods. Such strategies are consistent with the exposome's **holistic vision** for preventing complex chronic diseases like T2D.

3. Lifestyle Behaviors and Type 2 Diabetes Risk

3.1. Diet and Nutritional Patterns

3.1.1. High-Calorie and High-Sugar Diets

The habitual consumption of **sugar-sweetened beverages (SSBs)** and energy-dense foods rich in rapidly absorbable carbohydrates plays a pivotal role in the pathogenesis of type 2 diabetes (T2D). These dietary exposures induce a cascade of **hepatic metabolic disturbances**. Specifically, high fructose and glucose intake promotes **de novo lipogenesis** (DNL) in the liver, leading to the accumulation of **intrahepatic diacylglycerol (DAG)**. DAG activates **protein kinase C epsilon (PKCε)**, a critical serine kinase that disrupts insulin receptor tyrosine kinase activity, thereby suppressing insulin signaling in hepatocytes. This impairment leads to **hepatic insulin resistance**, a central feature in the pathophysiology of T2D (Samuel & Shulman, 2012).

At the **population level**, epidemiological studies strongly support this mechanistic link. A large meta-analysis of prospective cohort studies found that each additional daily serving of SSBs is associated with an ~**18% increased risk of T2D**, independent of adiposity (Imamura et al., 2015). This suggests that the diabetogenic effects of SSBs cannot be fully explained by weight gain alone but also involve **direct metabolic toxicity**. Similarly, findings from the **EPIC-InterAct study**, a large European cohort of over 350,000 participants, revealed a **hazard ratio of approximately 1.18 per 12-oz daily serving** of SSBs, further confirming their robust association with diabetes risk (Romaguera et al., 2013).

Notably, the apparent risk from **artificially sweetened beverages (ASBs)** is less consistent. When adjusting for adiposity and reverse causation (i.e., individuals with high metabolic risk consuming ASBs in response to pre-diabetic states), the associations largely attenuate, suggesting that ASBs may not exert the same biological harm as SSBs but may still serve as **markers of underlying risk behaviors or reverse causality** (Romaguera et al., 2013).

At the **molecular level**, fructose metabolism is particularly implicated in this process. Unlike glucose, which is tightly regulated by **phosphofructokinase**, fructose bypasses this checkpoint and is metabolized primarily by **ketohexokinase-C (KHK-C)** in hepatocytes. This leads to rapid phosphorylation of fructose, **ATP depletion**, increased production of **uric acid**, and accelerated conversion into **triglycerides and DAG** (Ishimoto et al., 2012; Lanaspa et al., 2012). Experimental evidence in **murine models** and **in vitro hepatocyte studies** implicates KHK-C in fructose-induced **hepatic steatosis, oxidative stress, and insulin resistance**. Furthermore, uric acid generated in this pathway can impair endothelial function and stimulate **oxidative stress**, further compounding metabolic risk (Lanaspa et al., 2012).

3.1.2. Dietary Fiber and Whole Food Consumption

Dietary fiber and whole food consumption constitute one of the most **robust protective exposures** within the **lifestyle dimension of the exposome** against type 2 diabetes (T2D). Unlike macronutrients such as sugars and refined carbohydrates, which exacerbate metabolic stress, fiber-rich diets consistently demonstrate protective associations across mechanistic, clinical, and epidemiological studies. Fiber is classified into **soluble** forms (e.g., pectin, β-glucans, gums, inulin) and **insoluble** forms (e.g., cellulose, hemicellulose, lignin). Soluble fibers dissolve in water to form viscous gels that slow gastric emptying and nutrient absorption, while insoluble fibers add bulk to intestinal contents, modulate peristalsis, and enhance toxin elimination. Both types influence metabolic pathways relevant to glucose homeostasis, insulin sensitivity, and systemic inflammation. Crucially, in the **exposome framework**, dietary fiber also functions as a mediator of **environmental pollutant detoxification**, reducing the systemic bioavailability of harmful xenobiotics such as heavy metals, pesticides, and endocrine-disrupting chemicals (EDCs).

3.1.2.1. Epidemiological Evidence and Dose–Response Patterns

A large body of epidemiological evidence confirms the inverse association between dietary fiber intake and T2D risk. A **meta-analysis of 19 prospective studies** found that individuals with the highest fiber consumption had a **20–30% lower risk of T2D** compared to those with the lowest intake (Yao et al., 2014). Importantly, this relationship is dose-dependent: every **10 g/day increase in total fiber intake** reduces T2D incidence by approximately **11%**, independent of adiposity, age, and physical activity (Yao et al., 2014). These findings are supported by the **EPIC-InterAct study**, which tracked 340,000 participants across eight European countries and demonstrated that dietary fiber intake—particularly from cereal sources—was strongly associated with reduced

T2D risk (InterAct Consortium, 2015). Similar protective effects have been observed in Asian cohorts, such as the Shanghai Women's Health Study, where higher intakes of legumes and vegetable-based fiber were inversely associated with diabetes incidence (Villegas et al., 2008). These data confirm that the metabolic benefits of fiber are **globally consistent**, strengthening its role as a central protective factor in the diabetes exposome.

3.1.2.2. Glycemic Regulation, Insulin Dynamics, and β-cell Preservation

Dietary fiber improves **glycemic regulation** by attenuating postprandial glucose and insulin excursions. Soluble fibers increase chyme viscosity, delay carbohydrate digestion, and reduce the rate of glucose absorption, which leads to **lower glycemic load** and **decreased insulin demand** (Chandalia et al., 2000). By blunting postprandial hyperglycemia, high-fiber diets reduce **glucotoxicity** and **lipotoxicity**, which are central drivers of β-cell dysfunction (Samuel & Shulman, 2012). Importantly, clinical trials confirm that high-fiber diets improve both **fasting plasma glucose** and **glycated hemoglobin (HbA1c)**, even in patients with established diabetes. In one landmark study, patients consuming **50 g/day of dietary fiber** showed a **10% reduction in fasting glucose** and a significant decline in plasma insulin requirements, independent of weight loss (Chandalia et al., 2000). Fiber-rich foods also stimulate **satiety hormones** such as **GLP-1** and **PYY**, which act on the hypothalamus to suppress appetite and reduce energy intake, contributing to long-term weight regulation (Cani et al., 2008). Thus, dietary fiber acts as a **dual regulator**: directly lowering glycemic stress and indirectly reducing obesity-related diabetes risk.

3.1.2.3. Gut Microbiota, SCFAs, and Crosstalk with Pollutants

A rapidly growing area of research emphasizes the role of dietary fiber in **modulating the gut microbiota**, a key exposome interface. Non-digestible fermentable fibers serve as substrates for colonic bacteria, leading to the production of **short-chain fatty acids (SCFAs)** such as acetate, propionate, and butyrate. These SCFAs exert **systemic metabolic effects**: butyrate enhances colonic barrier integrity, reducing **metabolic endotoxemia** (leakage of lipopolysaccharides into the bloodstream), propionate regulates hepatic gluconeogenesis, and acetate influences central appetite pathways (Morrison & Preston, 2016). In parallel, SCFAs activate **G-protein coupled receptors (GPR41/43)**, which stimulate GLP-1 secretion and improve insulin sensitivity (Cani et al., 2008).

This microbiota-mediated mechanism also has relevance for **environmental pollutant exposure**. A healthy, fiber-driven microbiome enhances detoxification by altering xenobiotic metabolism, binding carcinogens, and reducing intestinal absorption of **toxic metals (arsenic, cadmium, lead)** and **persistent organic pollutants (POPs)**. By strengthening barrier function, fiber indirectly protects against translocation of environmental toxicants into systemic circulation (Lee et al., 2014). In this way, the **microbiome-fiber axis** serves as a protective mediator at the intersection of **dietary and environmental exposures** in the T2D exposome.

3.1.2.4. Fiber as a Detoxifying Agent Against Environmental Pollutants

Beyond microbiome interactions, dietary fiber directly contributes to **toxin binding and excretion**. Certain soluble fibers (pectin, alginate) can **bind bile acids and hydrophobic organic pollutants**, increasing their fecal elimination (Rose & Holub, 2000). Insoluble fibers such as lignin act as **chelating agents**, binding heavy metals like cadmium and lead, thereby reducing their intestinal absorption. This is particularly relevant given that heavy metal exposures are increasingly recognized as diabetogenic through mechanisms of **oxidative stress, β-cell apoptosis, and impaired insulin signaling** (Tinkov et al., 2017). Similarly, endocrine-disrupting chemicals (EDCs) such as bisphenol A and phthalates, which are found in food packaging, can accumulate in adipose tissue and exacerbate insulin resistance. Diets high in fiber and whole foods may mitigate these risks by lowering the **bioavailability of pollutants** while simultaneously reducing consumption of **ultra-processed foods**, which are the major dietary sources of EDCs and pesticide residues (Heindel & Blumberg, 2019).

3.1.2.5. Whole Foods: Nutrient Synergies and Reduced Exposome Burden

While fiber supplements provide isolated benefits, the protective effect is most pronounced when fiber is consumed as part of **whole foods**, such as whole grains, legumes, vegetables, and fruits. Whole grains provide not only fiber but also **magnesium**, which plays a critical role in glucose transport, insulin receptor activity, and enzymatic function (Larsson & Wolk, 2007). Magnesium deficiency is associated with increased T2D risk, and whole grains represent one of the richest natural sources. In addition, whole grains and legumes provide **antioxidants, polyphenols, lignans, and phytosterols**, which reduce oxidative stress and inflammation (de Munter et al., 2007). These compounds also enhance the body's defense against pollutant-induced oxidative damage, demonstrating another **synergistic exposome interaction**. Epidemiological studies show that individuals in the highest quintile of whole grain intake have a **20–30% lower risk of T2D**, a finding consistent across Western and Asian cohorts (Aune et al., 2013). Furthermore, shifting toward whole-food diets inherently reduces reliance on processed, packaged, and pesticide-heavy foods, thus lowering **exposome-related pollutant exposures**. Clinical interventions consistently support the epidemiological evidence: replacing refined carbohydrates with fiber-rich foods leads to significant improvements in glycemic control, insulin sensitivity, lipid profiles, and inflammatory biomarkers (Ye et al., 2012). These effects are observed in both healthy individuals and patients with T2D. Importantly, the **global nutrition transition** toward refined grains, ultra-processed foods, and sugar-laden beverages has led to a parallel rise in T2D incidence, particularly in rapidly urbanizing low- and middle-income countries (Popkin, 2014). Populations traditionally consuming legume- and whole-grain–based diets (e.g., rural Asian and African communities) had historically low diabetes prevalence, but dietary Westernization has eroded this protection. In the context of the exposome, dietary fiber and whole foods represent a **dual shield**: mitigating endogenous risks (e.g., insulin resistance, β-cell failure, inflammation) while buffering against exogenous toxicant exposures (e.g., metals, POPs, EDCs). Promoting fiber-rich whole food diets thus offers a **comprehensive strategy for diabetes prevention** within an exposome framework, simultaneously targeting lifestyle and environmental risk factors.

3.1.3 Role of Dietary Patterns (Mediterranean, DASH, Plant-Based)

Dietary pattern analysis has increasingly gained recognition as a more reliable tool for understanding the relationship between diet and type 2 diabetes (T2D) compared to reductionist approaches that examine single nutrients in isolation. While early nutritional epidemiology often focused on macronutrient ratios such as carbohydrate-to-fat intake or individual components like fiber or saturated fat, it became evident that foods are consumed in complex combinations that interact synergistically within the human body. The concept of dietary patterns acknowledges this complexity by evaluating the **totality of the diet**, incorporating not only nutrient composition but also food preparation methods, cultural contexts, and lifestyle factors. This approach is particularly important in the study of T2D because the disease arises from the interplay of **metabolic dysfunction, systemic inflammation, oxidative stress, and environmental exposures**, all of which are influenced by habitual eating behaviors. Moreover, by analyzing whole patterns rather than isolated nutrients, researchers can better capture the **real-world exposome**—the totality of dietary and environmental exposures that shape disease risk throughout life (Hu, 2002; Mozaffarian, 2016).

Among dietary patterns, the **Mediterranean diet** has emerged as the most consistently protective against T2D. This dietary model, rooted in the traditional eating habits of Mediterranean countries, emphasizes abundant consumption of plant-based foods, particularly fruits, vegetables, legumes, whole grains, nuts, and seeds, with olive oil serving as the primary source of fat. Moderate intake of fish and poultry provides high-quality protein and omega-3 fatty acids, while red and processed meats are limited, and alcohol—primarily red wine—is consumed moderately with meals. Evidence from the **PREDIMED randomized controlled trial**, one of the most influential studies in nutritional science, showed that high-risk individuals adhering to the Mediterranean diet supplemented with either extra-virgin olive oil or mixed nuts experienced a **30% reduction in the incidence of T2D** compared to those following a conventional low-fat diet (Salas-Salvadó et al., 2011). Subsequent meta-analyses have consistently confirmed a **20–30% lower risk of T2D** among individuals with high adherence to the Mediterranean diet (Martínez-González et al., 2011; Schwingshackl et al., 2015). Mechanistically, the Mediterranean diet confers metabolic advantages by lowering postprandial glycemic load through its high fiber content, improving insulin sensitivity via monounsaturated fats from olive oil, and reducing systemic oxidative stress through polyphenol-rich foods such as extra virgin olive oil, red wine, and fruits. It also exerts favorable effects on the **gut microbiota**, promoting short-chain fatty acid (SCFA) production, which enhances metabolic flexibility and reduces low-grade inflammation (Gutiérrez-Díaz et al., 2016).

The **DASH (Dietary Approaches to Stop Hypertension) diet** also demonstrates protective associations with T2D, despite being initially designed to prevent hypertension. The DASH pattern emphasizes fruits, vegetables, whole grains, nuts, and low-fat dairy, while limiting sodium, red meats, and added sugars. Epidemiological evidence has linked adherence to the DASH diet with a significantly **reduced incidence of T2D**, with Jannasch et al. (2017) reporting up to a 20% reduction in risk in prospective cohort studies. Clinical interventions further highlight its capacity to improve insulin resistance, body weight, and glycemic control among individuals with metabolic syndrome (Azadbakht et al., 2011). The DASH diet's metabolic benefits derive from its **high intake of potassium, magnesium, and calcium**, nutrients that support vascular health and insulin secretion, as well as its

antioxidant-rich food base, which reduces oxidative stress and systemic inflammation. Furthermore, its emphasis on fresh, minimally processed foods lowers reliance on sodium-laden processed items, thereby indirectly reducing exposure to preservatives and food additives often implicated in metabolic disturbances. From an exposome perspective, the DASH diet reflects a **dual protection model**: it enhances micronutrient intake while limiting harmful dietary exposures such as excess sodium and chemical additives, both of which can interact with environmental stressors like air pollution to exacerbate cardiometabolic risk (Brook et al., 2018).

Plant-based diets represent another increasingly studied dietary model in the prevention of T2D. While definitions vary, they typically involve patterns where plant foods—whole grains, legumes, fruits, vegetables, nuts, and seeds—form the dietary foundation, and animal-derived foods are minimized or excluded. Large-scale prospective studies, such as the **Nurses' Health Study**, have shown that individuals adhering to a **healthy plant-based diet** rich in minimally processed plant foods had a **34% lower risk of developing T2D**, whereas adherence to an "unhealthy" plant-based diet dominated by refined grains, sugar-sweetened beverages, and fried foods was paradoxically associated with a **16% increased risk** (Satija et al., 2016). These findings underscore the importance of **diet quality within plant-based frameworks**. Mechanistically, plant-based diets reduce diabetes risk through multiple pathways: they increase intake of dietary fiber and resistant starch, which slow glucose absorption and enhance SCFA production in the gut; they lower consumption of heme iron, which contributes to oxidative stress and advanced glycation end-product formation; and they reduce saturated fat intake, improving insulin sensitivity. Additionally, diets high in phytochemicals, such as flavonoids and carotenoids, dampen inflammatory responses and enhance cellular antioxidant defenses. However, from an exposome perspective, poorly constructed plant-based diets may increase reliance on **ultra-processed plant foods**, including packaged meat substitutes and refined carbohydrate snacks, which introduce **new exposures such as emulsifiers, acrylamide, and plasticizers from packaging materials**. Thus, the plant-based dietary model illustrates the importance of distinguishing between **nutrient-dense, whole-food approaches** versus highly processed plant-derived diets that may undermine metabolic benefits.

Taken together, the Mediterranean, DASH, and high-quality plant-based diets all converge on **three unifying principles** that explain their consistent protective associations with T2D: a predominance of minimally processed plant foods, a restriction of red/processed meats and ultra-processed foods, and a favorable fatty acid profile rich in unsaturated fats. By simultaneously promoting **nutrient density and metabolic resilience** while reducing exposures to harmful dietary pollutants, these dietary models exemplify the integration of nutrition into the broader **exposome framework**. They highlight how **lifestyle behaviors and environmental pollutants are not separate risk domains but are instead deeply interwoven through dietary choices**. The Mediterranean diet minimizes exposure to food processing contaminants while enriching antioxidant and polyphenol intake, the DASH diet protects against sodium and additive-driven metabolic stress, and plant-based diets reduce intake of bioaccumulative pollutants found in animal fat while optimizing fiber and phytochemical consumption. In this way, dietary patterns do not simply represent cultural preferences or macronutrient distributions, but **powerful exposome-level interventions** that can be harnessed for precision prevention of type 2 diabetes.

3.2 Physical Activity and Sedentary Behavior

3.2.1 Mechanistic links to insulin sensitivity

Regular physical activity is one of the most powerful non-pharmacological interventions for improving insulin sensitivity and mitigating the risk of type 2 diabetes (T2D). At the molecular level, exercise enhances glucose uptake into skeletal muscle by upregulating **glucose transporter type 4 (GLUT4)** expression and promoting its translocation to the plasma membrane (Hawley & Lessard, 2008). This adaptation facilitates greater post-exercise glucose disposal and improved glycemic control. Importantly, glucose uptake during physical activity occurs via **insulin-independent mechanisms**, largely mediated by the activation of **AMP-activated protein kinase (AMPK)** and **calcium/calmodulin-dependent protein kinase (CaMK)** pathways (Richter & Hargreaves, 2013). These signaling cascades provide an immediate improvement in glucose utilization, independent of insulin, making physical activity especially relevant for individuals with insulin resistance.

Exercise also induces long-term adaptations in **mitochondrial biogenesis** and oxidative capacity, improving the efficiency of fatty acid oxidation and reducing intramyocellular lipid accumulation, which is a key driver of insulin resistance (Holloszy, 2005). Furthermore, physical activity lowers **visceral adiposity**, a metabolically active fat depot that secretes pro-inflammatory adipokines such as TNF-α and IL-6, both implicated in impaired insulin signaling (Pedersen & Saltin, 2015). Beyond adipose tissue, exercise exerts systemic anti-inflammatory effects by increasing the release of **myokines** (e.g., IL-6 in its anti-inflammatory role during exercise, irisin), which modulate cross-talk between skeletal muscle, liver, and adipose tissue, thereby improving whole-body metabolic homeostasis (Pedersen & Febbraio, 2012).

Another crucial pathway involves **endothelial function** and vascular health. Exercise stimulates nitric oxide (NO) bioavailability, enhancing skeletal muscle perfusion and glucose delivery. This vascular adaptation complements direct effects on muscle glucose uptake, creating a synergistic improvement in insulin sensitivity and overall metabolic health (Green et al., 2017). Collectively, these mechanisms demonstrate how physical activity acts as a systemic regulator of glucose metabolism, targeting multiple nodes in the pathophysiology of T2D.

3.2.2 Dose-response relationships

Large-scale epidemiological studies and meta-analyses confirm a **dose-response relationship** between physical activity and T2D incidence. Aune et al. (2015) found that individuals engaging in **150 minutes per week of moderate-intensity aerobic activity** experienced approximately a **26% reduction in T2D risk** compared to sedentary individuals. The risk reduction followed a curvilinear pattern, with the greatest benefits occurring when moving from inactivity to moderate activity, though additional gains persisted at higher activity volumes. Importantly, both **aerobic exercise** and **resistance training** contribute to T2D prevention. Resistance exercise specifically enhances lean muscle mass, which increases the tissue reservoir for glucose disposal and improves resting metabolic rate (Grontved et al., 2012).

Conversely, sedentary behavior has emerged as an **independent risk factor** for T2D, distinct from insufficient exercise. Prolonged sitting time, even among individuals meeting recommended physical activity levels, is linked to higher fasting glucose, insulin resistance, and T2D risk (Wilmot et al., 2012). Mechanistic evidence shows that prolonged sitting suppresses skeletal muscle lipoprotein lipase activity, impairing triglyceride clearance and HDL cholesterol production, while reducing glucose uptake (Hamilton et al., 2007). Intervention studies demonstrate that **frequent breaks in sitting with light activity** (e.g., 2–3 minutes of walking every 30 minutes) significantly reduce postprandial glucose and insulin excursions, supporting the concept that sedentary behavior and physical inactivity represent **distinct but interacting components** of diabetes risk (Dunstan et al., 2012).

From an exposome perspective, the impact of physical activity extends beyond energy balance and glucose metabolism to shaping systemic resilience against other environmental stressors, including inflammation, pollution-related oxidative stress, and psychosocial strain. Thus, promoting structured exercise and reducing sedentary time represent complementary and synergistic strategies for reducing the burden of T2D at both the biological and population level.

3.3 Tobacco Use and Alcohol Consumption

3.3.1 Smoking and β-cell dysfunction

Cigarette smoking is a **significant but underappreciated contributor to type 2 diabetes (T2D) risk**, supported by both epidemiological and mechanistic evidence. A comprehensive meta-analysis of 25 prospective cohort studies demonstrated that current smokers had a **44% higher risk** of developing T2D compared to non-smokers, while former smokers retained a **23% elevated risk**, highlighting both the detrimental effects of smoking and the long-term benefits of cessation (Willi et al., 2007). The diabetogenic impact of smoking is mediated through multiple interlinked biological mechanisms. Chronic smoking induces **systemic inflammation and oxidative stress**, increasing circulating levels of pro-inflammatory cytokines such as TNF-α and interleukin-6, which impair insulin receptor signaling and promote insulin resistance (Facchini et al., 1992). In addition, smoking exacerbates **endothelial dysfunction**, reducing nitric oxide bioavailability and impairing vascular reactivity, which compromises insulin-mediated glucose delivery to skeletal muscle (Wannamethee et al., 2001).

Beyond systemic effects, cigarette smoke and nicotine exert **direct toxic effects on pancreatic β-cells**, crucial for insulin secretion. Experimental studies have shown that nicotine exposure impairs β-cell function by inducing oxidative stress, mitochondrial dysfunction, and apoptosis in pancreatic islets (Benedict et al., 2012). Furthermore, smoking accelerates central adiposity and increases circulating free fatty acids, both of which synergistically reduce insulin sensitivity. The cumulative evidence thus suggests that smoking contributes not only to **insulin resistance** but also to **β-cell dysfunction**, amplifying the risk of progression from impaired glucose tolerance to overt T2D. Importantly, the dose-response relationship indicates that heavier smoking correlates with greater risk, whereas quitting smoking significantly reduces T2D incidence, though former smokers may carry residual risk for several years post-cessation (Pan et al., 2015).

3.3.2 Alcohol's dual role in T2D risk

In contrast to smoking, the relationship between **alcohol consumption and T2D risk** is complex and often described as **J-shaped**. Moderate alcohol consumption—typically defined as up to **one drink per day for women and two drinks per day for men**—has been consistently associated with a **reduced risk of T2D** compared to abstainers. A meta-analysis of 20 cohort studies involving over 477,000 participants found that light-to-moderate drinkers had a **30–40% lower risk of T2D** (Baliunas et al., 2009). Mechanistically, moderate alcohol intake has been shown to **improve insulin sensitivity**, enhance glucose uptake, and increase high-density lipoprotein (HDL) cholesterol levels, all of which provide metabolic protection (Koppes et al., 2005). Moreover, ethanol at low doses stimulates adiponectin secretion, an insulin-sensitizing adipokine, further reducing metabolic risk (Beulens et al., 2006).

However, **heavy or binge drinking exerts the opposite effect**, markedly increasing T2D risk. Excessive alcohol intake contributes to **hepatic steatosis, hepatotoxicity, and pancreatitis**, which impair both insulin action and insulin secretion. Chronic heavy drinking is also associated with **weight gain, elevated triglycerides, and increased inflammation**, all of which accelerate insulin resistance (Seike et al., 2008). Importantly, the net effect of alcohol depends not only on **quantity** but also on **drinking patterns** (e.g., regular vs. binge), the **type of alcoholic beverage** (wine appears more protective than beer or spirits due to its polyphenolic content), and individual metabolic context (e.g., obesity, hypertension, or genetic predisposition) (Carlsson et al., 2005). For example, in populations with high prevalence of obesity or metabolic syndrome, even moderate alcohol consumption may exacerbate risk.

Collectively, the evidence suggests that while **light-to-moderate alcohol consumption may confer some protective metabolic effects**, public health recommendations should remain cautious, as the threshold for harm is highly individual and the risks of alcohol—including liver disease, cancer, and cardiovascular harm—often outweigh potential benefits. Thus, unlike smoking, which is unequivocally harmful for diabetes risk, alcohol presents a nuanced picture where **dose, pattern, and context determine its role** in T2D pathogenesis.

3.4 Sleep Patterns and Psychological Stress

3.4.1 Circadian Rhythm Disruption

Sleep is one of the most critical yet often underestimated determinants of metabolic homeostasis. Both insufficient sleep (<6 hours/night) and prolonged sleep (>9 hours/night) have been shown to significantly increase the risk of developing type 2 diabetes (T2D), creating a **U-shaped relationship** between sleep duration and disease incidence (Cappuccio et al., 2010). Short sleep duration has direct effects on **glucose metabolism**, including reduced insulin sensitivity, impaired pancreatic β-cell responsiveness, and elevated postprandial glucose levels (Spiegel et al., 1999). Mechanistically, sleep restriction leads to **neuroendocrine alterations**, such as decreased leptin and increased ghrelin levels, which enhance appetite and caloric intake, promoting obesity—a major risk factor for T2D (Taheri et al., 2004).

On the other end of the spectrum, long sleep duration has also been associated with increased T2D risk, possibly mediated by underlying health conditions such as **depression, low physical activity, systemic inflammation, and obstructive sleep apnea** (Cappuccio et al., 2010). These comorbidities contribute to weight gain, insulin resistance, and impaired glucose tolerance. Importantly, both insufficient and excessive sleep are linked to **low-grade systemic inflammation**, as evidenced by elevated levels of C-reactive protein and interleukin-6, which further exacerbate insulin resistance (Patel et al., 2009).

Beyond sleep duration, **circadian rhythm disruption** plays a central role in diabetes pathogenesis. Circadian misalignment—common among **shift workers, frequent travelers, and individuals with irregular sleep schedules**—alters the timing of endogenous hormonal secretion. Laboratory studies have demonstrated that circadian misalignment reduces **nocturnal melatonin**, elevates **evening cortisol**, and impairs insulin secretion and sensitivity independent of sleep duration (Scheer et al., 2009). Notably, melatonin regulates pancreatic β-cell function, and genetic variants in **MTNR1B** (melatonin receptor 1B) predispose individuals to greater β-cell dysfunction and higher fasting glucose, especially when combined with shift work (Bonnefond et al., 2010).

Epidemiological studies corroborate these findings. A large meta-analysis reported that **night shift workers face a 9–40% higher risk of T2D**, with longer exposure duration and more frequent shift rotations associated with progressively higher risk (Gan et al., 2015). Furthermore, individuals with irregular sleep timing experience **reduced insulin sensitivity, increased adiposity, and higher HbA1c**, highlighting the impact of not just sleep quantity but also circadian stability on metabolic health (Reutrakul & Knutson, 2015).

Taken together, the evidence indicates that both **sleep duration and circadian alignment are key determinants of metabolic health**. Sleep and circadian optimization should therefore be considered essential preventive and therapeutic strategies for reducing T2D risk.

3.4.2 Chronic Stress and Hormonal Imbalance

While sleep disturbances directly impair glucose metabolism, **chronic psychological stress** also represents a significant modifiable risk factor for T2D. Stress activates the **hypothalamic–pituitary–adrenal (HPA) axis**, resulting in elevated cortisol secretion. Cortisol promotes **hepatic gluconeogenesis, lipolysis, and central fat deposition**, thereby inducing insulin resistance (Hackett & Steptoe, 2017). Chronic cortisol elevation further damages pancreatic β-cell function, worsening glycemic control (Heraclides et al., 2009).

Simultaneously, stress triggers **sympathetic nervous system (SNS) activation**, increasing circulating catecholamines (epinephrine and norepinephrine). While acutely adaptive, prolonged SNS hyperactivation causes sustained elevations in glucose and free fatty acids, leading to **lipotoxicity, β-cell apoptosis, and impaired insulin action** (Black, 2003). This dual activation of the HPA axis and SNS creates a **neuroendocrine environment highly conducive to insulin resistance and T2D development**.

Epidemiological studies consistently support these mechanisms. The **Whitehall II cohort** showed that individuals with chronic work-related stress had a nearly **2-fold increased risk of incident T2D**, independent of BMI and lifestyle factors (Heraclides et al., 2009). Another meta-analysis demonstrated that **psychological distress, including depression and anxiety, significantly increases T2D risk**, mediated partly through behavioral pathways such as poor diet, low physical activity, and disturbed sleep (Hackett & Steptoe, 2017). Importantly, chronic stress interacts with socioeconomic and psychosocial determinants: individuals with **low social support, financial strain, or adverse childhood experiences** are more vulnerable to stress-induced T2D (Surwit et al., 2002).

Moreover, stress-related sleep disturbances create a **bi-directional cycle**: stress reduces sleep quality and duration, while poor sleep further enhances stress hormone secretion and emotional dysregulation, jointly amplifying metabolic dysfunction (Chandola et al., 2006). Emerging evidence also suggests that stress-induced epigenetic modifications, including DNA methylation of HPA-axis-related genes, may have long-term consequences on glucose metabolism and intergenerational transmission of T2D risk (Hackett & Steptoe, 2017).

Thus, chronic psychological stress not only serves as an independent risk factor for T2D but also **synergistically interacts with sleep disruption**, creating a vicious cycle of metabolic dysregulation. This evidence underscores the need for **integrated lifestyle interventions**—including stress management techniques such as mindfulness-based stress reduction, cognitive-behavioral therapy, and workplace policy changes—alongside sleep hygiene practices to mitigate diabetes risk.

4. Environmental Pollutants and Type 2 Diabetes Risk

Environmental exposures are increasingly recognized as important determinants of type 2 diabetes mellitus (T2D), complementing traditional risk factors such as obesity, diet, and physical inactivity. Among environmental hazards, **air pollution** has emerged as a particularly concerning contributor due to its global prevalence and strong links with metabolic diseases. Both long-term and short-term exposure to common air pollutants—especially **fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2), and ground-level ozone (O_3)**—have been consistently associated with a higher incidence of T2D (Eze et al., 2015; Liu et al., 2019). The mechanisms underlying this association involve **systemic inflammation, oxidative stress, endothelial dysfunction, and impaired glucose-insulin homeostasis** (Brook et al., 2010; Rajagopalan & Brook, 2012).

4.1. Air Pollution

4.1.1. $PM_{2.5}$, NO_2, and Ozone Exposure

Air pollution has emerged as a critical environmental determinant of metabolic disorders, including type 2 diabetes mellitus (T2D). Among pollutants, fine particulate matter ($PM_{2.5}$, particles ≤2.5 μm in aerodynamic diameter), nitrogen dioxide (NO_2), and ozone (O_3) are the most consistently linked to diabetes risk in epidemiological studies. Large-scale prospective cohort studies and meta-analyses have demonstrated a significant association between chronic $PM_{2.5}$ exposure and T2D incidence. For instance, a meta-analysis of 13 cohort studies reported that every 10 $\mu g/m^3$ increase in $PM_{2.5}$ exposure is associated with a 13% increased risk of developing T2D (Eze et al., 2015). Similarly, data from the U.S.-based Nurses' Health Study and Health

Professionals Follow-Up Study found that individuals in areas with higher $PM_{2.5}$ concentrations had a 15–20% higher risk of T2D, independent of traditional lifestyle risk factors (Puett et al., 2011).

Nitrogen dioxide (NO_2), a major traffic-related pollutant, has also been consistently linked to diabetes risk. A meta-analysis of 12 studies found that long-term exposure to NO_2 increased T2D incidence by approximately 8% per 10 $\mu g/m^3$ increment (Eze et al., 2015). NO_2 is not only a marker of traffic-related air pollution but also directly contributes to systemic oxidative stress and airway inflammation, both of which exacerbate insulin resistance.

Ozone (O_3), though less studied in this context, has been shown to impair glucose homeostasis. Experimental studies in mice demonstrate that acute and chronic O_3 exposure leads to hyperglycemia, insulin resistance, and increased adipose inflammation (Vella et al., 2015). Epidemiological evidence, such as the Multi-Ethnic Study of Atherosclerosis (MESA), also indicates that higher ozone levels are associated with poorer glycemic control and increased diabetes prevalence, particularly in urban populations exposed to complex mixtures of pollutants (Chan et al., 2018). Collectively, these findings underscore that chronic exposure to ambient air pollutants, especially $PM_{2.5}$, NO_2, and ozone, contributes significantly to diabetes risk beyond traditional lifestyle factors like diet and physical inactivity.

4.1.2. Mechanisms: Oxidative Stress and Inflammation

The biological mechanisms linking air pollution to T2D development primarily involve **oxidative stress, systemic inflammation, and endothelial dysfunction**. Fine particulate matter ($PM_{2.5}$) penetrates deep into the alveoli, enters the bloodstream, and generates reactive oxygen species (ROS). This oxidative burden disrupts redox homeostasis, leading to lipid peroxidation, DNA damage, and mitochondrial dysfunction in insulin-sensitive tissues such as skeletal muscle, liver, and adipose tissue (Brook et al., 2010). Chronic oxidative stress impairs insulin signaling pathways, particularly through serine phosphorylation of insulin receptor substrate proteins, which reduces glucose uptake by skeletal muscle and promotes hepatic gluconeogenesis.

Air pollution also triggers systemic inflammation. Inhaled particles activate pulmonary macrophages and epithelial cells, releasing pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) into circulation (Rajagopalan & Brook, 2012). These cytokines induce low-grade chronic inflammation, a hallmark of T2D pathogenesis, which exacerbates insulin resistance in peripheral tissues and promotes β-cell dysfunction. For example, experimental studies have shown that mice exposed to concentrated $PM_{2.5}$ exhibit elevated inflammatory cytokines, increased visceral adiposity, and glucose intolerance (Sun et al., 2009).

Another critical mechanism is **endothelial dysfunction**. $PM_{2.5}$ and NO_2 impair nitric oxide bioavailability, reducing vasodilation and impairing blood flow to skeletal muscle, thereby limiting glucose disposal. Endothelial dysfunction further promotes vascular inflammation and accelerates atherosclerosis, compounding metabolic complications. Additionally, ozone exposure exacerbates insulin resistance by increasing systemic oxidative stress and altering adipokine profiles, such as reduced adiponectin and increased leptin, which dysregulate energy balance and glucose metabolism (Vella et al., 2015).

Taken together, chronic exposure to air pollutants leads to a vicious cycle of oxidative stress, inflammation, adipose dysfunction, and vascular impairment, all of which converge on insulin resistance and β-cell dysfunction, ultimately increasing the risk of type 2 diabetes.

4.2 Endocrine-Disrupting Chemicals (EDCs)

4.2.1 Bisphenols, phthalates, and organochlorines

Across continents, biomonitoring consistently detects **bisphenols (e.g., BPA, BPS, BPF), phthalates (e.g., DEHP, DBP, DiNP metabolites), and organochlorines** (e.g., DDT/DDE, PCBs, dioxins) in human tissues. These chemicals are linked to higher odds of **insulin resistance and incident T2D** in prospective cohorts and meta-analyses, while experimental models show convergent effects on glucose homeostasis. For **bisphenol A (BPA)** specifically, multiple meta-analyses and pooled analyses associate higher BPA concentrations with **greater T2D risk and insulin resistance** after adjustment for adiposity and lifestyle, supporting a diabetogenic signal at environmentally relevant doses (Hwang et al., 2018; Farrugia et al., 2021). Substitution chemicals **BPS and BPF** are not metabolically inert: in vitro and in vivo work shows they perturb β-cell ion-channel activity and insulin secretion in the **nanomolar** range, similar to BPA (Marroquí et al., 2021; Soriano et al., 2012). For **phthalates**, a recent meta-analysis concluded that exposure is **positively associated with diabetes** and with intermediate phenotypes such as **insulin resistance**; mechanistically, phthalate metabolites (e.g., **MEHP**) activate **PPARα/γ** and drive adipogenesis and lipid dysregulation, plausibly worsening insulin sensitivity (Zhang et al., 2022; Hao et al., 2012; Feige et al., 2010). Regarding **organochlorines/POPs**, extensive epidemiology (including nested case–control and cohort studies) and authoritative reviews link **low-dose, chronic exposure** to **T2D**; these lipophilic chemicals bioaccumulate in adipose tissue and show **non-monotonic** or mixture effects that complicate causal inference but consistently point in a harmful direction (Lee et al., 2014; Evangelou et al., 2016; Wolf et al., 2019). Complementing human data, animal and dietary exposure studies demonstrate that **POPs mixtures** precipitate **insulin resistance, hepatic steatosis, and adipose inflammation**, thereby offering biological plausibility for the epidemiologic signal (Ruzzin et al., 2010; Ibrahim et al., 2011). (Hwang et al., 2018; Farrugia et al., 2021; Marroquí et al., 2021; Soriano et al., 2012; Zhang et al., 2022; Hao et al., 2012; Feige et al., 2010; Lee et al., 2014; Evangelou et al., 2016; Wolf et al., 2019; Ruzzin et al., 2010; Ibrahim et al., 2011).

4.2.2 Disruption of insulin signaling

EDCs disrupt insulin signaling via complementary, tissue-specific mechanisms that converge on **insulin resistance and β-cell dysfunction**. In **pancreatic β-cells**, **BPA** mimics 17β-estradiol and engages **ERα/ERβ and membrane estrogenic pathways**. At **~1 nM**, BPA **rapidly closes K_ATP channels**, increases Ca^{2+} influx, and **acutely increases insulin secretion**; with ongoing exposure, this produces **hyperinsulinemia** followed by **peripheral insulin resistance** and altered insulin content—effects reproduced in mouse and human islets and abolished in ERβ-deficient cells (Alonso-Magdalena et al., 2006, 2008; Soriano et al., 2012; Martínez-Piñña et al., 2019). Replacement bisphenols (**BPS/BPF**) similarly modulate β-cell ion-channel expression and secretion via estrogen receptors and G-protein–coupled ER (**GPER**), indicating **class** rather than **single-compound** risk (Marroquí et al., 2021; Babiloni-Chust et al., 2022). In **insulin-responsive tissues** (muscle, liver, adipose), bisphenols and phthalates induce **oxidative and ER stress**, activate **JNK/IKKβ**, and promote **serine phosphorylation of IRS-1**, thereby **blunting PI3K–AKT signaling** and GLUT4 translocation; phthalate metabolites additionally **activate PPARγ/RXR**, re-programming adipocyte differentiation and lipid storage and contributing to **systemic insulin resistance** (Sargis, 2014; Hao et al., 2012; Feige et al., 2010; Heindel & Blumberg, 2017). **Organochlorines** (e.g., **PCBs, DDT/DDE, dioxins**) engage receptors such as **AhR** and **PXR**, induce **mitochondrial dysfunction**, and precipitate **adipose inflammation** with reduced **adiponectin**, collectively impairing insulin action and β-cell function; controlled exposure and dietary studies in rodents demonstrate that **real-world POPs mixtures** are sufficient to cause **insulin resistance** and steatosis (Lee et al., 2014; Ruzzin et al., 2010; Ibrahim et al., 2011; Kim et al., 2019). Epigenetic alterations (e.g., **DNA methylation** changes in metabolic genes) and **non-monotonic dose–responses** further characterize many EDCs, highlighting **windows of susceptibility** (developmental, perinatal) and the importance of mixture-aware risk assessment (Lee et al., 2014; Kassotis et al., 2019). In aggregate, these pathways establish **biological plausibility** for EDC-diabetogenicity, aligning **human** and **experimental** evidence across chemical classes. (Alonso-Magdalena et al., 2006, 2008; Soriano et al., 2012; Martínez-Piñña et al., 2019; Marroquí et al., 2021; Babiloni-Chust et al., 2022; Sargis, 2014; Hao et al., 2012; Feige et al., 2010; Heindel & Blumberg, 2017; Lee et al., 2014; Ruzzin et al., 2010; Ibrahim et al., 2011; Kim et al., 2019; Kassotis et al., 2019).

4.3 Heavy Metals and Metalloid Exposure

Heavy metals and metalloids represent a critical dimension of the exposome framework in understanding environmental contributions to Type 2 Diabetes Mellitus (T2D). Unlike nutrients, these toxic elements are non-essential, persistent in biological systems, and capable of bioaccumulation. Epidemiological evidence and mechanistic studies have demonstrated that chronic exposure to metals such as arsenic, cadmium, mercury, and lead significantly increases T2D risk by impairing insulin signaling, inducing mitochondrial dysfunction, and promoting oxidative stress and inflammation. Below, each major metal is reviewed in detail with respect to its environmental sources, biological mechanisms, and role in diabetogenesis.

4.3.1 Arsenic

Arsenic, a metalloid widely present in contaminated groundwater, pesticides, and industrial waste, is one of the most extensively studied toxicants in relation to T2D. Populations in South Asia, Latin America, and parts of the United States (notably Bangladesh, India, and Mexico) are exposed to high arsenic levels through drinking water (Naujokas et al., 2013). Epidemiological studies consistently report that chronic exposure to inorganic arsenic (iAs) is associated with increased risk of T2D. A large prospective cohort in Bangladesh demonstrated a dose-dependent association between water arsenic concentrations and incident T2D, with adjusted hazard ratios up to 1.6 for the highest exposure quartile (Chen et al., 2010).

At the mechanistic level, arsenic exerts diabetogenic effects through multiple pathways. First, it impairs pancreatic β-cell function by reducing insulin transcription and secretion, partly mediated through oxidative stress–induced mitochondrial injury (Díaz-Villaseñor et al., 2008). Second, arsenic exposure activates stress kinases such as JNK and p38 MAPK, which disrupt insulin receptor substrate (IRS) signaling, leading to peripheral insulin resistance (Paul et al., 2007). Furthermore, arsenic metabolites (monomethylated and dimethylated arsenic species) have been shown to generate reactive oxygen species (ROS), causing DNA damage, lipid peroxidation, and apoptosis of β-cells (Pi et al., 2010). Arsenic also perturbs adipokine balance, reducing adiponectin levels, which further exacerbates insulin resistance.

4.3.2 Cadmium

Cadmium is a highly toxic heavy metal with a biological half-life exceeding 20 years, making even low-level chronic exposure clinically significant. Major sources include cigarette smoke, industrial emissions, and consumption of contaminated rice, cereals, and shellfish (Jarup & Akesson, 2009). Epidemiological studies demonstrate strong associations between urinary cadmium levels and T2D prevalence. A Korean cohort reported that individuals in the highest quartile of urinary cadmium had a 35% increased odds of T2D (Moon, Guallar, & Navas-Acien, 2013).

Mechanistically, cadmium induces diabetes through multiple interlinked processes. It accumulates in the pancreas, liver, and kidneys, where it induces mitochondrial dysfunction and ROS generation (Satarug et al., 2010). Cadmium exposure reduces GLUT4 translocation in skeletal muscle, impairing glucose uptake (Wang et al., 2015). At the β-cell level, cadmium displaces zinc ions in insulin granules, impairing insulin processing and secretion (Elinder et al., 1985). In addition, cadmium acts as an endocrine disruptor by activating estrogen receptor pathways, contributing to metabolic dysregulation. Chronic cadmium exposure also promotes low-grade inflammation via NF-κB activation, which further aggravates insulin resistance (Tinkov et al., 2017).

4.3.3 Mercury

Mercury, particularly in its organic form (methylmercury), bioaccumulates in fish and seafood, while inorganic mercury exposure arises from dental amalgams, mining, and industrial processes. Mercury is a potent neurotoxin, but growing evidence links it with metabolic dysfunction as well. Cross-sectional studies have shown associations between blood mercury levels and impaired fasting glucose and insulin resistance (He et al., 2013). Although some population studies yield mixed results due to confounding from fish consumption (which provides protective omega-3 fatty acids), meta-analyses suggest that mercury exposure may increase T2D risk, especially at higher exposure levels (Sun et al., 2014).

Mechanistically, mercury has a high affinity for sulfhydryl groups, leading to inhibition of antioxidant enzymes such as glutathione peroxidase and superoxide dismutase, thereby enhancing oxidative stress (Houston, 2011). Mercury disrupts mitochondrial electron transport chain (ETC) complexes, particularly complex II and III, reducing ATP production and enhancing ROS leakage (Farina et al., 2011). In pancreatic β-cells, this oxidative damage triggers apoptosis and reduced insulin secretion. Mercury also induces immune dysregulation by increasing pro-inflammatory cytokine secretion (IL-6, TNF-α), thereby contributing to systemic insulin resistance (Rafiei et al., 2017).

4.3.4 Lead

Lead exposure, though declining in many countries after the removal of leaded gasoline, remains a significant global health problem due to contaminated soil, water pipes, paints, and batteries. Chronic lead exposure is linked with multiple cardiometabolic outcomes, including hypertension and renal dysfunction. Recent studies have highlighted its role in T2D pathogenesis. A large U.S. NHANES analysis reported a positive association between blood lead levels and both fasting plasma glucose and HbA1c, independent of age, BMI, and lifestyle factors (Lee et al., 2018).

At the molecular level, lead disrupts calcium signaling in β-cells, impairing insulin secretion (Tchounwou et al., 2012). It also accumulates in mitochondria, where it interferes with ETC enzymes and enhances ROS production (Ercal et al., 2001). Lead exposure promotes chronic inflammation through increased production of TNF-α and IL-1β, which induce insulin resistance in adipose and muscle tissue. Additionally, epigenetic modifications such as DNA methylation changes in glucose metabolism–related genes have been observed in lead-exposed populations, suggesting long-term intergenerational effects (Goodrich et al., 2016).

4.3.5 Mitochondrial Dysfunction and Oxidative Damage

Mitochondria orchestrate ATP production, redox balance, lipid oxidation, and apoptotic signaling—functions that are **indispensable for glucose-stimulated insulin secretion (GSIS) in β-cells** and for **insulin-stimulated glucose disposal in muscle and liver**. In β-cells, nutrient metabolism must generate a robust **ATP/ADP rise** to close K_ATP channels, depolarize the membrane, open voltage-gated Ca^{2+} channels, and trigger exocytosis; any deficit in oxidative phosphorylation or excess mitochondrial reactive oxygen species (mtROS) directly blunts GSIS (Rorsman & Ashcroft, 2018; Lenzen, 2008). In insulin-responsive tissues, **mtROS and lipid-derived ROS** activate stress kinases (JNK/IKKβ), promote **serine phosphorylation of IRS-1**, and impair **PI3K–AKT signaling**, producing insulin resistance even when bulk oxidative capacity appears preserved (Houstis et al., 2006; Fazakerley et al., 2018). Heavy metals and metalloids (arsenic, cadmium, mercury, lead) converge on mitochondria through **direct inhibition of respiratory chain components, thiol/selenol binding, disruption of Ca^{2+} handling, and damage to mitochondrial DNA (mtDNA) and membranes**, creating a high-oxidant milieu that propagates local organelle damage into cell- and tissue-level insulin defects (Eguchi et al., 2021; Zong et al., 2024).

4.3.5.1. β-cell–specific vulnerabilities to oxidative injury

Pancreatic β-cells are unusually **poorly endowed with antioxidant enzymes** (low catalase and glutathione peroxidase relative to other tissues), which means **modest increases in mtROS** have outsized effects on membrane potential (ΔΨm), ATP generation, and viability (Lenzen, 2008; Eguchi et al., 2021). Persistent oxidant pressure **depolarizes ΔΨm**, triggers **mitochondrial permeability transition pore (mPTP) opening**, releases **cytochrome-c**, and activates caspases, culminating in **apoptosis** and **loss of insulin secretory capacity**. Metals exacerbate each of these steps (Chen et al., 2006; Chang et al., 2013). Functionally, this converts early hypersecretion (compensatory, stress-driven GSIS perturbations) into **β-cell failure**, a hallmark of T2D progression.

4.3.5.2. Insulin-target tissues: redox signaling to insulin resistance

In skeletal muscle and liver, **mtROS is a proximal driver of insulin resistance**. Redox-sensitive kinases (JNK, IKKβ) and transcriptional programs (NF-κB) blunt insulin signaling, while oxidized lipids (e.g., 4-HNE) modify insulin-pathway proteins and membrane dynamics, curtailing **GLUT4 translocation** and enhancing **hepatic gluconeogenesis** (Houstis et al., 2006; Fazakerley et al., 2018). Mitochondria also communicate damage via **danger signals**—oxidized **mtDNA** and **cardiolipin**—that activate the **NLRP3 inflammasome**, reinforcing systemic insulin resistance and β-cell stress (Eguchi et al., 2021; Zong et al., 2024).

4.3.5.3. Metal-specific mitochondrial "hits":

- **Arsenic (iAs; MMA^{3+}/DMA^{3+} metabolites):** Trivalent arsenicals **bind vicinal thiols** (e.g., lipoic acid), inhibit **pyruvate dehydrogenase** and **ETC enzymes**, elevate **mtROS**, and derail the **SIRT3–FOXO3a–MnSOD** antioxidant axis (Fu et al., 2010; Divya et al., 2015). The result is **ATP shortfall** and **excess oxidants**, which suppress GSIS and insulin action. In adipocytes and myotubes, arsenic impairs **AKT** signaling and **glucose uptake**, linking mitochondrial stress directly to peripheral insulin resistance (Divya et al., 2015).
- **Cadmium (Cd):** Cd gains entry via **ZIP8/ZIP14** transporters (SLC39A8/SLC39A14), accumulates in β-cells, and **binds protein thiols** in respiratory complexes, promoting **mtROS**, **mPTP opening**, **cytochrome-c release**, **caspase-3 activation**, and **β-cell apoptosis** (He et al., 2009; Jenkitkasemwong et al., 2012; Chang et al., 2013). In hepatocytes and myocytes, Cd blunts **IRS-1/PI3K/AKT** and favors **gluconeogenesis**, while human islets show **selective Cd accumulation**, aligning mechanism with epidemiology (El Muayed et al., 2012; Filippini et al., 2022).
- **Mercury (MeHg; Hg^{2+}):** Mercury **reacts with thiol/selenol groups**, depletes **glutathione**, inhibits **complex II/III**, collapses **ΔΨm**, and triggers **caspase-dependent apoptosis** in β-cells; it also suppresses **PI3K–AKT** signaling (Chen et al., 2006; Chen et al., 2010). Selenium status and fish-derived nutrients modify toxicity—critical contextual factors when interpreting cohort findings (Mozaffarian et al., 2013).
- **Lead (Pb):** Pb perturbs **mitochondrial Ca^{2+} handling** (exaggerating Ca^{2+}-driven ROS generation), inhibits dehydrogenases, increases **mtROS**, and impairs **bioenergetics**. In β-cells, this translates to **reduced insulin release**; in muscle/liver, to redox-driven insulin resistance. Co-exposure with Cd magnifies mitochondrial injury and metabolic toxicity (Leff & Tiffany-Castiglioni, 2018; Jin et al., 2024; Yimthiang et al., 2022).

4.3.5.4. Oxidative damage: molecular substrates and signaling nodes

mtROS (superoxide, H_2O_2) oxidizes **cardiolipin**, **ETC proteins**, and **mtDNA**, creating a feedback loop of respiratory inefficiency and further ROS. Oxidative adducts such as **4-hydroxynonenal (4-HNE)** and **malondialdehyde (MDA)** covalently modify insulin-pathway proteins and SNARE machinery for exocytosis. Redox-sensitive transcriptional programs—**Nrf2 antioxidant response**, **NF-κB inflammation**, and **CHOP (ER stress)**—are dysregulated by metals, fostering a **pro-inflammatory milieu** that cements insulin resistance (Eguchi et al., 2021; Zong et al., 2024). In β-cells, suppression of **MnSOD/SOD2** and **GPx** and hyperacetylation of mitochondrial enzymes (when **SIRT3** is functionally compromised) intensify vulnerability (Divya et al., 2015).

4.3.5.5. Organelle quality control: dynamics, mitophagy, and UPRmt

Metal-induced oxidative stress deranges **mitochondrial dynamics**—shifting toward **excess fission** (DRP1/FIS1) and limiting **fusion** (MFN1/2, OPA1)—fragmenting the network and lowering respiratory efficiency. At the same time, damage-laden mitochondria should be cleared by **PINK1/Parkin-mediated mitophagy**; when mtROS is excessive or persistent, **mitophagy is insufficient**, allowing dysfunctional organelles to accumulate and perpetuate insulin resistance and β-cell dysfunction (Zong et al., 2024; Eguchi et al., 2021). The **mitochondrial unfolded protein response (UPRmt)** attempts to restore proteostasis but can be overwhelmed by ongoing metal exposure. These defects integrate with **ER stress** and impaired **mitochondria-associated membranes (MAMs)**, further disrupting Ca^{2+} exchange and insulin signaling.

4.3.5.6. Human signals: biomarkers and translational evidence

Human studies link metal exposure to **circulating and urinary oxidative damage markers** (e.g., **8-oxo-dG**, **F_2-isoprostanes**), **lower antioxidant capacity**, and **worse glycemic indices**. In diabetes-relevant cohorts, **urinary/blood metals** correlate with **insulin resistance surrogates** (HOMA-IR, TyG index) and with redox/inflammatory markers, consistent with the mitochondrial-oxidative axis (Filippini et al., 2022; Jin et al., 2024; Menke et al., 2016). Importantly, **human islets** demonstrate **cadmium accumulation**, directly tying real-world exposure to β-cell mitochondrial liability (El Muayed et al., 2012).

4.3.5.7. Modifiers and reversibility: nutrition, signaling, and lifestyle

Nutritional modifiers (e.g., selenium for mercury, zinc for cadmium competition, folate/B-vitamins for arsenic methylation) can mitigate mitochondrial and redox injury (Maull et al., 2012; He et al., 2009; Jenkitkasemwong et al., 2012). **SIRT3/FOXO3a/MnSOD** axis support—experimentally via metformin or targeted antioxidants—can **restore ΔΨm** and **reduce mtROS** in arsenic and cadmium models (Divya et al., 2015). **Physical activity** enhances mitochondrial biogenesis (PGC-1α), improves redox buffering, and may attenuate metal-induced insulin resistance, underscoring the **exposome–behavior interplay** (Fazakerley et al., 2018). At the exposure level, **source control** (water treatment for arsenic, smoking cessation for cadmium, low-Hg/high-n-3 seafood choices, lead remediation) reduces the upstream oxidant load.

4.4. Occupational and Residential Exposures

Urbanization concentrates environmental stressors—disrupted light–dark cycles, thermal extremes, and chronic noise—alongside occupational demands that misalign circadian timing. Within an exposome framework, these exposures **co-occur, interact, and cluster** socio-spatially (e.g., near transport corridors, dense urban cores, and in shift-work dominated sectors), amplifying pathways to insulin resistance and β-cell dysfunction via **circadian disruption, sleep fragmentation, neuroendocrine stress signaling, oxidative/inflammatory activation, and behavioral displacement** (e.g., reduced physical activity on hot or noisy nights). Robust cohort studies and human laboratory experiments now tie these conditions to impaired glucose tolerance, higher incident T2D, and worse glycemic outcomes, independent of traditional risk factors (Pan et al., 2011; Gan et al., 2015; Scheer et al., 2009; Zheng et al., 2023; Sørensen et al., 2012).

4.4.1. Shift work and light-at-night (LAN)

4.4.1.1. Epidemiology and dose–response

Shift work—especially rotating night shifts—shows a consistent association with T2D. In two large U.S. Nurses' Health cohorts (177,000+ women), **longer duration of rotating night shift work** predicted higher T2D incidence, partially mediated by weight gain (Pan et al., 2011). Meta-analyses confirm elevated diabetes risk in shift workers (Gan et al., 2015; Gao et al., 2020), with **stronger effects for rotating schedules** versus permanent nights, and signals of **sex differences** and **exposure duration** effects (Gan et al., 2015). Lifestyle and shift work are **additive**: in nurses, rotating night shifts combined with an unhealthy lifestyle conferred the largest T2D risks (Shan et al., 2018).

Light at night (LAN)—both **indoor light during sleep** and **outdoor light infiltrating bedrooms**—is increasingly implicated in dysglycemia. A national Chinese study reported that greater **outdoor LAN** was associated with **poorer glucose homeostasis and higher diabetes prevalence** (Zheng et al., 2023). A complementary line of evidence shows **gestational diabetes** (GDM) risks rising with higher outdoor LAN (Sun et al., 2024), consistent with a broader literature linking LAN to adverse metabolic profiles (Baek & Lee, 2024).

4.4.1.2. Human mechanistic evidence (circadian misalignment, sleep & autonomic arousal)

Stringent **in-laboratory** protocols establish **causality** from circadian misalignment to impaired glucose handling. Forced circadian misalignment **reduces insulin sensitivity and glucose tolerance** within days (Scheer et al., 2009), and experiments disentangling circadian phase from sleep/wake show **intrinsic evening reductions in glucose tolerance** (Morris et al., 2015). One-night exposure to **moderate indoor light (~100 lux) during sleep** raises **sympathetic activity and next-morning insulin resistance**, despite equivalent sleep duration (Mason et al., 2022). Collectively, these data map a **plausible chain**: LAN → **melatonin suppression**, **autonomic activation**, and **sleep architecture disruption** → impaired **β-cell responsiveness** and **peripheral insulin signaling**—mechanisms that align with the epidemiology of shift work–related T2D.

4.4.1.3. Exposome considerations and mitigation

Within cities, **LAN, noise, and heat** co-occur; thus, models should **co-adjust** for these exposures and for air pollution to reduce confounding. Practical mitigations include **predictable shift rotations**, **forward-rotating schedules**, **strategic meal timing** (avoid heavy caloric intake on circadian night), **melanopic-aware lighting** (dim, warm light in pre-sleep windows), **blackout curtains/eye masks**, and **LAN reduction** in bedrooms; at workplace scale, **task lighting** tuned to time-of-day and **protected dark intervals** may attenuate risk (Shan et al., 2018; Mason et al., 2022; Baek & Lee, 2024).

4.4.2. Urban heat islands and noise pollution

4.4.2.1. Urban heat islands (UHI): thermal stress, sleep, and glycemic control

UHI intensifies nighttime heat, limiting physiological cooling and recovery; environmental agencies explicitly note **persistent nocturnal warmth** as a key health risk amplifier (CalEPA, 2023). Large global datasets show that **hotter nights shorten sleep** (by ~14 minutes on very warm nights), with disproportionate effects in older and lower-income populations—groups already at elevated metabolic risk (Minor et al., 2022). Systematic reviews confirm that **higher ambient temperatures degrade sleep quality and duration worldwide**, a **biologically plausible** pathway linking heat to metabolic dysregulation (Chevance et al., 2024). In people with diabetes, **heatwaves** raise **mortality** (~18%) and **morbidity** (~10%) risks, and acute heat links to **hospitalizations for DKA/HHS** and **serious hypoglycemia** (Moon et al., 2021; Miyamura et al., 2022; Diabetes Care, 2023). Urban analyses further show **greater cardiovascular heat-attributable admissions** in **high-UHI neighborhoods**, with diabetes status a vulnerability stratum—underscoring **place-based, inequitable exposure** (Cleland et al., 2023; Hsu et al., 2021). Mechanistically, **nocturnal heat** erodes **slow-wave sleep**, elevates **sympathetic tone** and **cortisol**, dehydrates and concentrates glucose, and **reduces physical activity** the following day—all unfavorable for insulin action. Thermal physiology also intersects with metabolism via **brown adipose tissue (BAT)**; temperature manipulations that enhance BAT can improve **insulin sensitivity**, highlighting a **thermoregulatory–metabolic** interface (Lee et al., 2014; Iwen et al., 2017).

Mitigation within the exposome includes **cool-roof/cool-pavement programs**, **urban greening/tree canopy expansion**, **heat-health warning systems**, **night-cooling ventilation**, and **bedroom temperature targets** (e.g., <24–25 °C) to preserve sleep and glycemic stability; public health messaging should prioritize **at-risk, heat-exposed communities** (CalEPA, 2023; Cleland et al., 2023).

4.4.2.2. Environmental noise: autonomic arousal, sleep fragmentation, and insulin resistance

Transportation noise (road, rail, aircraft) is independently associated with **incident diabetes** in European and North American cohorts after adjustment for air pollution and socioeconomic factors (Sørensen et al., 2012; Eze et al., 2017; Shin et al., 2020). A **systematic review/meta-analysis of cohort studies** indicates higher T2D risk

per 10 dB increase in road traffic noise (Wu et al., 2023), and an updated **nationwide cohort** found **diabetes mortality** increased with **road and rail noise**, extending the evidence from incidence to lethality (Vienneau et al., 2024).

Mechanistically, **chronic noise** activates **sympathetic and HPA-axis** pathways, causing **nocturnal arousals, endothelial oxidative stress, inflammation (e.g., NF-κB activation), and metabolic derangements**—biological routes long established for cardiovascular outcomes and increasingly supported for metabolic disease (Münzel et al., 2018; Hahad et al., 2023). Experimental work shows **noise exposure exacerbates insulin resistance and glucose intolerance** in rodent models, particularly when combined with a high-fat diet, mirroring human co-exposure realities (Liu et al., 2018). Importantly, **noise and LAN** jointly **fragment sleep**, and **noise often co-varies with air pollution**, warranting **mixture-aware modeling** in exposome studies (Eze et al., 2017; Wu et al., 2023).

Mitigation spans **source controls** (quiet road surfaces, traffic speed/calming, aircraft flight-path/night-curfew policies), **pathway measures** (noise barriers, building envelope upgrades), and **receiver strategies** (bedroom re-orientation, sound-insulating windows, white-noise masking). For **clinical practice**, screening noise/LAN/heat in social–environmental histories and delivering **sleep hygiene**, **bedroom darkness**, **evening light-reduction**, **cool-sleep guidance**, and **shift-schedule counseling** can be integrated into **diabetes prevention and management pathways** (Mason et al., 2022; Shan et al., 2018; CalEPA, 2023).

5. Interaction Between Lifestyle and Environmental Risk Factors

5.1 Synergistic and Antagonistic Effects

Lifestyle behaviors (dietary patterns, physical activity, smoking, alcohol, sleep/circadian regularity) and environmental pollutants (air pollution, EDCs, metals, heat, noise, light-at-night) often co-occur, act on *shared biological pathways* (oxidative stress, systemic inflammation, endothelial dysfunction, autonomic/circadian disruption), and can therefore *amplify* or *buffer* each other's effects on type 2 diabetes (T2D) risk. This is the essence of the exposome: totality of exposures and their interdependencies across time (Rajagopalan & Brook, 2012). Interactions can be **synergistic** (risk greater than the sum of parts)—for example, adiposity magnifying the diabetogenic impact of air pollution—or **antagonistic** (one factor mitigating another)—for example, nutrient patterns dampening pollution-induced oxidative injury. Cutting-edge mixture models (e.g., Bayesian kernel machine regression; quantile g-computation) now make these non-linear, non-additive relations empirically tractable in cohort data.

Adiposity as an amplifier of air-pollution–diabetes associations (synergy). In a 378,000-participant UK Biobank analysis, obesity *modified* the joint effect of long-term $PM_{2.5}$, NO_2, and traffic noise on incident T2D: hazard ratios were substantially larger among participants with obesity, while a polygenic risk score showed weaker or null modification (Li et al., 2021). This pattern—*higher inhaled dose, greater systemic inflammation, lipotoxic milieu*—fits a shared-pathway model (Li et al., 2021; Rajagopalan & Brook, 2012). Practically, obesity creates a "biological susceptibility" that converts background urban exposures into clinically meaningful diabetogenic load (Li et al., 2021).

Diet quality as a buffer of pollution toxicity (antagonism), from cohort evidence to intervention. Two complementary strands of evidence support a protective interaction of dietary quality with air pollution.

(1) **Cohort-level effect modification:** In the Multi-Ethnic Study of Atherosclerosis, greater adherence to a Mediterranean-style diet *attenuated* the association between chronic air-pollution exposure and incident cardiovascular disease, plausibly via antioxidant and anti-inflammatory nutrient profiles (Lim et al., 2019)—mechanisms relevant to insulin resistance and T2D pathogenesis. In a large Chinese cohort, higher **dietary diversity** weakened the $PM_{2.5}$–T2D association, indicating that heterogeneous, minimally processed food patterns may buffer pollution-related diabetogenic effects (Zheng et al., 2024).

(2) **Human intervention signals:** In a randomized crossover trial, **B-vitamin supplementation** (folate, B_6, B_{12}) *attenuated $PM_{2.5}$-induced epigenetic changes* in circulating cells—mechanistic hallmarks of pollution-triggered oxidative stress and inflammatory signaling (Zhong et al., 2017). A separate human exposure study showed **olive oil or fish-oil supplementation** blunted vascular dysfunction after concentrated ambient particle exposure (Tong et al., 2015). Together, these data triangulate from mechanism to population: nutrient-dense, antioxidant-rich dietary patterns *antagonize* pollution toxicity relevant to glucose homeostasis.

Physical activity: benefits dominate—but context matters. Modeling and cohort analyses indicate the **health benefits of regular physical activity generally outweigh air-pollution harms**, even in fairly polluted cities (Tainio et al., 2016). That said, micro-environment strategies (e.g., parks/greenways, off-peak training) can *optimize the* *benefit–risk balance*; in cardiopulmonary trials, exercising in cleaner microenvironments yields greater vascular and respiratory gains than along high-traffic corridors (Tainio et al., 2016; mechanistic consistency with Tong et al., 2015). From a diabetology perspective, prioritizing **timing, location, and intensity** of activity during lower-pollution periods is an interaction-aware prevention strategy.

Psychosocial stress and social context amplify pollution effects (synergy). Chronic psychosocial stress elevates HPA-axis and sympathetic outputs that worsen insulin resistance; stress also increases vulnerability to pollution-induced oxidative and inflammatory injury. Epidemiologic work suggests *perceived or chronic stress modifies air-pollution associations* with cardiometabolic indicators (Chen et al., 2021; Mehta et al., 2015), supporting a "double-jeopardy" model wherein disadvantaged, high-stress populations experience stronger pollution–metabolic links.

Nutritional one-carbon status modifies arsenic toxicity (antagonism) with implications for diabetes. In randomized trials in Bangladesh, **folic acid supplementation** enhanced arsenic methylation and **lowered blood arsenic** by ~14%, reducing the more toxic monomethyl-arsenic fraction (Gamble et al., 2007; Bozack et al., 2019). Because chronic arsenic exposure impairs insulin signaling and β-cell function, nutritional support of methylation represents a plausible *antagonistic* lever to lower diabetes risk in exposed settings (Spratlen et al., 2018).

Smoking and metals: behavioral–toxicant synergy. Smoking markedly increases **cadmium** body burden, and cadmium exposure has been linked—though heterogeneously—to higher risks of T2D and metabolic dysfunction, with stronger signals at greater doses and in women (Filippini et al., 2022; Yimthiang et al., 2022). Here, *smoking behavior* potentiates a *toxicant exposure*, creating synergy for renal and metabolic injury (Yimthiang et al., 2022). Conversely, **selenium** biochemistry illustrates antagonism with **mercury** via high-affinity selenol–mercury binding and restoration of selenoprotein antioxidant functions (Chen et al., 2006; Spiller, 2021), though the selenium–diabetes relation itself appears **U-shaped**, warranting caution (Cardoso et al., 2021; Casanova-Páez & Lee, 2023).

Green infrastructure as an interaction-aware, multi-exposure buffer (antagonism). Residential **greenness** correlates with lower T2D incidence in longitudinal syntheses (18–21% lower odds/incidence with higher greenness), plausibly via *reduced air/noise/heat*, *better sleep*, and *more physical activity* (Ccami-Bernal et al., 2023; Feyissa et al., 2024; Doubleday et al., 2022). Greenness therefore operates as a *contextual antagonist* of multiple environmental stressors while promoting healthy behaviors—an exposome-level prevention tool.

Mixture-aware methods to detect and quantify interactions. Beyond single-exposure models, **Bayesian kernel machine regression (BKMR)** flexibly captures high-order, non-linear interactions across co-exposures (e.g., $PM_{2.5}$+NO_2+noise+metals) and behaviors. **Quantile g-computation** efficiently estimates joint effects of exposure bundles with interpretable weights. These approaches better reflect the exposome's reality and have been increasingly applied in metabolic epidemiology to move past oversimplified additive assumptions (methodological reviews commonly recommend BKMR and q-gcomp for complex mixtures).

Practice and policy implications—designing interaction-aware prevention.

Individual-level: Pair **dietary quality** (Mediterranean/DASH, adequate B-vitamins/folate) with **strategic physical activity** (timed to lower pollution, in green spaces) to *antagonize* pollution effects (Lim et al., 2019; Zhong et al., 2017; Tainio et al., 2016). Address **sleep/stress**, especially in shift workers where lifestyle changes show super-additive risk reductions (Shan et al., 2018). In arsenic-exposed areas, support **one-carbon nutrients** to reduce arsenic body burden (Gamble et al., 2007; Bozack et al., 2019).

Built environment & policy: Expand **urban greening** and **active-travel networks** to concurrently reduce pollution/noise/heat exposure and enable physical activity, leveraging a systemic antagonist to multiple hazards (Ccami-Bernal et al., 2023; Feyissa et al., 2024).

Research: Routine testing for **effect modification** (e.g., by BMI, diet quality, stress) and deployment of **mixture models** is essential to quantify real-world synergistic and antagonistic dynamics.

5.2. Modifying Effects of Socioeconomic Status and Education

Conceptual frame (exposome and social determinants). Socioeconomic status (SES)—capturing education, income, wealth, occupation, and neighborhood context—shapes type 2 diabetes (T2D) risk through three interlocking pathways: (i) **differential exposure** to harmful environments (e.g., higher air/noise pollution, urban heat, light-at-night, limited greenness and healthy food access); (ii) **differential susceptibility** via chronic psychosocial stress and *allostatic load* that amplify inflammatory and neuroendocrine dysregulation; and (iii) **differential capacity to respond** (health literacy, material resources, access to prevention and care) that governs whether healthy behaviors and clinical advice can be enacted. Large cohorts consistently show graded, inverse associations between SES/education and incident T2D, with portions of the gradient mediated by adiposity and lifestyle but with additional contribution from inflammation and stress biology—underscoring SES and education as *modifiers* of both lifestyle and environmental risks in an exposome framework (Lee et al., 2011; Stringhini et al., 2012; Stringhini et al., 2013).

Differential exposure: where people live and work changes what they breathe, hear, and feel. Compared with affluent or highly educated groups, lower-SES or historically marginalized communities experience **higher long-term exposure to ambient $PM_{2.5}/NO_2$**, **greater heat island intensity**, and **more transportation noise**—a clustering of urban stressors that converges on insulin resistance pathways (oxidative stress, endothelial dysfunction, sleep/circadian disruption). Population-scale analyses in the U.S. show that racial–ethnic disparities in $PM_{2.5}$ exposures exceed—and are not explained by—income gaps, pointing to structural and spatial mechanisms that concentrate pollution in specific communities (Tessum et al., 2021). Neighborhood-level analyses likewise document disproportionate **urban heat burden** among lower-income and minority residents, a pattern with downstream metabolic implications through sleep loss and autonomic activation (Hsu et al., 2021). For **noise**, systematic reviews and small-area studies across Europe and the U.K. consistently find **higher environmental noise levels in socioeconomically deprived neighborhoods**, adding an often-overlooked cardiometabolic stressor to the SES gradient (Dreger et al., 2019; Dale et al., 2015). Together, these data establish SES as an upstream driver of *co-exposure profiles* that raise T2D risk even before individual behavior is considered.

Differential susceptibility: stress biology and inflammation magnify the same exposures. Beyond exposure differences, **lifecourse socioeconomic disadvantage** confers *biologic vulnerability* to diabetes. In the Whitehall II cohorts, chronic low SES from childhood through adulthood predicted incident T2D; **serial C-reactive protein and interleukin-6 measurements explained a substantial portion of this association**, indicating that **inflammation and stress** are key intermediates of social disadvantage on diabetogenesis (Stringhini et al., 2013). A complementary analysis showed that **modifiable behaviors and adiposity** explained about half of the SES–T2D gradient, leaving a sizeable residual attributable to pathways like inflammation and stress (Stringhini et al., 2012). These findings align with broader evidence that **neighborhood deprivation** and **allostatic load** track together, providing a mechanistic link between social context and metabolic disease risk.

Education as a modifier of genetic and environmental risk. Education does more than signal SES; it appears to **buffer risk** by altering exposures, resources, and decision-making capacity. In UK Biobank, **higher educational attainment attenuated polygenic susceptibility to T2D and related risk factors on the additive scale**, suggesting that educational resources and cognition/skills can offset biological risk (Carter et al., 2022). Related work in the U.S. Health and Retirement Study points in the same direction—**education mitigates genetic vulnerability to T2D/obesity**, particularly at higher risk quantiles (Liu & Guo, 2015). Education also supports **health literacy**; in clinical cohorts, **inadequate literacy** was associated with **worse glycemic control and diabetes outcomes**, demonstrating a pragmatic pathway from education to day-to-day self-management (Schillinger et al., 2002).

SES modifies the impact of work organization and time use. The same "dose" of work-related stress may not have the same metabolic impact across SES groups. In a pooled meta-analysis, **long working hours** were associated with incident T2D **only in lower-SES participants**, highlighting how economic constraints and reduced recovery resources convert occupational demand into metabolic disease (Kivimäki et al., 2015). This SES modification dovetails with evidence that **shift work** and **light-at-night** (more common in certain occupations) worsen insulin sensitivity and raise T2D risk, particularly when paired with unhealthy lifestyle—a combination more prevalent in socioeconomically constrained contexts (Shan et al., 2018).

Food insecurity and neighborhood socioeconomic environment: interaction with lifestyle risk. Food insecurity—a concentrated feature of low-SES settings—is consistently linked to higher T2D prevalence and poorer glycemic outcomes and clusters with obesogenic food environments that impede adherence to recommended dietary patterns (Beltrán et al., 2022; Mujahid et al., 2023). Neighborhood-level SES also predicts *incident* T2D; in a large New York City study, **lower neighborhood socioeconomic environment** was associated with higher T2D risk, with food outlet profiles mediating part of the effect—an exposome-consistent pathway in which place-based features alter **diet quality**, **sleep**, and **activity** in tandem (Thorpe et al., 2022; Mujahid et al., 2023).

Effect modification of environmental hazards by SES: examples for air and noise. In air-pollution epidemiology, **associations are often stronger in lower-SES strata**, plausibly due to co-morbid stress, diet, and housing conditions that heighten **oxidative/inflammatory responses**—a pattern synthesized in global reviews (Hajat et al., 2015). For **transportation noise**, European cohorts link chronic exposure to **incident diabetes** and, more recently, to **diabetes mortality**; because **noise exposure is socially patterned**, the same decibels can translate into greater glycemic harm in deprived communities (Sørensen et al., 2012; Vienneau et al., 2024; Dreger et al., 2019). These examples illustrate **true interaction** (biologic susceptibility and co-exposures) layered on top of **exposure inequality** (environmental injustice).

Implications for prevention and methods. From a prevention standpoint, SES and education should be **pre-specified effect modifiers** when quantifying the diabetes impacts of **air pollution, noise, heat, LAN, EDCs, and metals**; modern mixture frameworks (e.g., **BKMR**, **quantile g-computation**) can estimate **joint effects** while testing **interaction by SES/education**. Practically, **raising diet quality** (and addressing food insecurity), **preserving sleep**, and **facilitating safe physical activity** in high-deprivation neighborhoods may *antagonize* pollution/noise/heat effects; **patient education** and **literacy-tailored self-management** can amplify benefits; and **regulatory/urban design actions** that reduce exposures in disadvantaged areas directly shrink the risk gradient (Mujahid et al., 2023; Hsu et al., 2021).

5.3. Gene–Environment–Lifestyle Interactions in T2D

Type 2 diabetes (T2D) is highly polygenic, with hundreds of common variants each conferring modest effects that act through β-cell function, insulin action, adiposity, and circadian/metabolic pathways. In practice, genetic risk does not operate in a vacuum: lifestyle and environmental exposures modify the phenotypic expression of inherited risk, while genetic architecture can determine vulnerability to specific exposures—an exposome perspective that integrates genomes, behaviors, and environments over time (Ben-Shlomo & Kuh, 2002). Contemporary cohort analyses show that high diet quality and healthy lifestyle are associated with substantially lower absolute T2D risk **at every level of polygenic risk**, and formal tests often find limited or no multiplicative gene×diet interaction—implicating primarily **additive** risk reduction that benefits even those at highest genetic risk (Merino et al., 2022). Conceptually, this means that genetic liability determines *baseline susceptibility*, while lifestyle and environmental levers shift risk across that baseline; methodologically, it also cautions that interaction tests are power-hungry and susceptible to exposure misclassification—particularly relevant for complex, dynamic exposures like diet and physical activity. (Ben-Shlomo & Kuh, 2002; Merino et al., 2022.) Oxford Academic

Several well-characterized gene×lifestyle examples illustrate mechanism-anchored interactions relevant to T2D. First, the adiposity locus **FTO**: a large meta-analysis (>218,000 participants) showed that higher physical activity **attenuates** the BMI-increasing effect of FTO by ~27%, a clinically meaningful modification of a core upstream determinant of insulin resistance (Kilpeläinen et al., 2011). Second, **TCF7L2**—a canonical β-cell gene: in the randomized **Diabetes Prevention Program**, risk genotypes predicted progression to diabetes through impaired insulin secretion, but both intensive lifestyle and metformin **reduced absolute risk across genotypes** (no significant genotype×intervention multiplicative interaction), underscoring that prevention works even in those with high genetic susceptibility (Florez et al., 2006). Third, circadian biology provides a clear gene×behavior example: variants at **MTNR1B** (melatonin receptor 1B) amplify the deleterious glycemic effects of eating when endogenous melatonin is high—**late dinner worsened glucose tolerance in MTNR1B risk-allele carriers but not in non-carriers** in a randomized crossover trial; pharmacologic melatonin similarly impaired glucose tolerance preferentially in carriers (Lopez-Mínguez et al., 2017; Kampmann et al., 2021). Collectively, these data show that activity timing, meal timing, and sleep biology are axes where **behavioral choice** and **genotype** intersect to shape glycemic responses. (Kilpeläinen et al., 2011; Florez et al., 2006; Lopez-Mínguez et al., 2017; Kampmann et al., 2021.) Florez LabPMCWiley Online Library

Gene×**environmental pollutant** interactions are an emerging pillar of the T2D exposome. For arsenic, inter-individual differences in **inorganic arsenic methylation**—strongly influenced by **AS3MT** variants—govern internal dose of toxic metabolites (e.g., monomethylarsonic acid), which have been linked to cardiometabolic toxicity. Genetic variation in AS3MT and one-carbon metabolism pathways modifies arsenic biotransformation phenotypes in humans, plausibly altering diabetes risk at a given exposure (Agusa et al., 2011). Similarly, circadian genes (e.g., **MTNR1B**) may act as *environmental sensors* that transduce light-at-night/meal-timing exposures into pancreatic β-cell signaling changes, yielding **gene×light/behavior** interactions relevant to shift-work/ALAN contexts described elsewhere in this review. Mechanistically anchored G×E studies underscore the value of

integrated omics, repeated exposure assessment, and ancestry-inclusive sampling to detect and interpret interactions. (Agusa et al., 2011; Lopez-Mínguez et al., 2017.) MDPIPMC

5.4. Life-course Perspective: Early-life vs. Adult Exposures

A life-course approach distinguishes **critical/sensitive periods**, **exposure accumulation**, and **chains of risk** to explain how early and later exposures combine to shape T2D risk trajectories (Ben-Shlomo & Kuh, 2002). Pivotal human "natural experiments" demonstrate durable biological imprints of early adversity. Individuals conceived during the **Dutch Hunger Winter (1944–45)** exhibit persistent epigenetic alterations decades later—e.g., lower methylation at the **IGF2** differentially methylated region 60 years post-exposure (Heijmans et al., 2008) and broader timing-specific methylation changes across metabolic and inflammatory loci (Tobi et al., 2009; 2014), some mediating associations with adult metabolic phenotypes (Tobi et al., 2018). In parallel, **intrauterine exposure to maternal diabetes**—independent of inherited genotype—raises offspring risk of diabetes and obesity (discordant-sibship analyses in the Pima Indians), implicating hyperglycemia-induced programming of β-cell function and adiposity that perpetuates intergenerational risk (Dabelea et al., 2000). Together, these findings validate the DOHaD paradigm for glycemic disease and argue that **periconceptional and fetal windows** are particularly sensitive periods for long-lived metabolic programming. (Ben-Shlomo & Kuh, 2002; Heijmans et al., 2008; Tobi et al., 2009; 2014; Tobi et al., 2018; Dabelea et al., 2000.)
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Early-life **environmental** exposures also map onto glycemic phenotypes. Prenatal and childhood exposure to **traffic-related air pollution** has been associated with higher insulin resistance and adverse metabolic biomarkers in children and adolescents (e.g., German birth cohorts and the Southern California Children's Health Study), suggesting both **priming** and **early manifestation** of insulin resistance (Thiering et al., 2013; 2016; Zhang A. L. et al., 2021). In pregnancy, multipollutant time-window analyses indicate that higher **$PM_{2.5}/NO_2$** exposures are linked with greater risk of **gestational diabetes**, a powerful antecedent of later maternal and offspring dysglycemia (Niu et al., 2023). Mechanistically, sustained oxidative stress, low-grade inflammation, endothelial dysfunction, and autonomic imbalance provide convergent pathways from air pollutants to impaired insulin signaling—biologic themes that reappear in adult studies of pollution and incident T2D. (Thiering et al., 2013; 2016; Niu et al., 2023; Zhang A. L. et al., 2021.) PMC+1Environmental Health PerspectivesThe Lancet

Critically, **adult** exposures remain potent and modifiable—even in those already "programmed" by early-life conditions—supporting an **accumulation-of-risk** model. Controlled circadian misalignment studies show that shifting behavioral schedules out of phase with endogenous clocks acutely impairs glucose tolerance and insulin sensitivity (Morris et al., 2015), while in free-living settings meal timing intersects with **MTNR1B** genotype to worsen evening glycemia (Lopez-Mínguez et al., 2017). Long-term ambient and traffic-related air pollution also tracks with **incident T2D** in adults, consistent with persistent oxidative/inflammatory signaling (Krämer et al., 2010). Thus, **later-life interventions**—sleep regularity, earlier main meals, physical activity, pollution reduction, weight control—can **partially counter** early-life liabilities and reduce population risk, even absent strong statistical G×E interactions. (Morris et al., 2015; Lopez-Mínguéz et al., 2017; Krämer et al., 2010.) PMC+1Environmental Health Perspectives

Finally, life-course models emphasize **context**, including social and built environments that co-expose individuals to unhealthy diet, inactivity, light-at-night, heat, noise, and pollution. Recent nationwide cohort work shows that **area-level deprivation** independently elevates T2D risk and compounds polygenic susceptibility—an example of how **social exposures** shape both baseline risk and the *expression* of genetic risk across adulthood (Diabetes Care, 2023). These observations reinforce the core exposome message: **what we inherit, what we do, and what we breathe/ingest are braided over time**; effective prevention requires interventions at **multiple life stages** and across **multiple layers** of exposure. (Diabetes Care, 2023).

6. Methods for Assessing the Exposome

The exposome represents the totality of environmental exposures that an individual experiences throughout the life course, and its assessment requires diverse methodological strategies. Unlike single-exposure epidemiological studies, exposome approaches integrate multiple exposures, their interactions, and temporal variability. To effectively capture the complexity of environmental determinants of Type 2 Diabetes (T2D), researchers have employed traditional epidemiological designs, high-dimensional statistical frameworks such as exposome-wide association studies (ExWAS), and molecular-level assessments using biomonitoring and biospecimen analysis.

Together, these approaches help elucidate pathways linking environmental exposures with metabolic health outcomes.

6.1. Traditional Epidemiological Approaches

Traditional epidemiological approaches, such as **prospective cohort studies, case-control studies, and cross-sectional surveys**, have long been the cornerstone of exposure-disease assessment. These methods often focus on single or a limited set of exposures (e.g., air pollution, occupational risk factors, or dietary patterns) and relate them to incident T2D risk using statistical models adjusted for confounders (Hu, 2011; Pan et al., 2011).

For instance, large-scale cohorts such as the **Nurses' Health Study (NHS)** and **European Prospective Investigation into Cancer and Nutrition (EPIC)** have provided critical evidence on associations between air pollutants, shift work, and metabolic disease (Sørensen et al., 2012; Pan et al., 2011). These designs benefit from **temporal sequencing**, allowing assessment of causality, and enable investigation of dose-response relationships. However, they face limitations such as exposure misclassification, residual confounding, and limited capacity to capture **multiple simultaneous exposures** that are often intercorrelated in real-world settings (Wild, 2012).

Traditional approaches thus form the **foundation of exposome science**, but require integration with modern tools to manage complexity and interactions inherent in the totality of exposures.

6.2. Exposome-Wide Association Studies (ExWAS)

Exposome-Wide Association Studies (ExWAS) represent an extension of the genome-wide association study (GWAS) framework into the environmental domain. ExWAS systematically evaluates associations between a broad set of exposures (e.g., air pollutants, noise, chemicals, diet, lifestyle) and health outcomes, including T2D, in a hypothesis-free manner (Patel & Manrai, 2015).

This approach leverages **high-throughput environmental exposure data**, statistical correction for multiple testing (e.g., false discovery rate), and integration with **omics layers** such as metabolomics or epigenomics. For example, studies within the **HELIX (Human Early Life Exposome) project** have applied ExWAS to identify critical early-life exposures linked with cardiometabolic health (Vrijheid et al., 2014). Similarly, **Patel et al. (2010)** pioneered ExWAS in T2D by screening hundreds of environmental factors in relation to disease outcomes, highlighting previously unrecognized risk factors.

While ExWAS provides a scalable framework for exposure discovery, challenges include high correlation among exposures, risk of false positives, and the need for **integrated statistical models** (e.g., Bayesian hierarchical modeling or environment-wide interaction studies, EWIS) to capture **synergistic and antagonistic effects** (Robinson et al., 2023). Nevertheless, ExWAS remains a key methodological advancement in uncovering the exposome's contribution to T2D.

6.3. Biomonitoring and Biospecimen Analysis

Biomonitoring, which involves the **measurement of chemicals, metabolites, and biomarkers in biological specimens**, provides the most **direct and individualized assessment of internal exposure** (CDC, 2022). Biological matrices commonly used include blood, urine, saliva, hair, nails, and adipose tissue, each reflecting different windows of exposure (Angerer et al., 2007). For example, **urinary bisphenol A (BPA)** and **phthalate metabolites** have been widely studied in relation to insulin resistance and T2D (Sun et al., 2014). Similarly, blood concentrations of **heavy metals** such as arsenic, cadmium, and lead have been quantified to link environmental toxicants with mitochondrial dysfunction and diabetes risk (Menke et al., 2016).

Biospecimen analysis is also crucial for **integrating exposomics with omics technologies**, such as **metabolomics, epigenomics, and proteomics**, allowing mechanistic insights into how exposures alter biological pathways leading to T2D (Rappaport & Smith, 2010). Advances in **high-resolution mass spectrometry (HRMS)** and **non-targeted metabolomics** have facilitated the detection of thousands of exogenous and endogenous molecules, providing an untargeted window into the internal exposome (Miller & Jones, 2014).

Nonetheless, challenges remain, including issues of biomarker half-life, intra-individual variability, and the need for **standardized protocols** for sample collection and analysis (Dennis et al., 2017). Despite these challenges, biomonitoring represents a cornerstone for exposome assessment, especially when combined with **geospatial data and personal exposure sensors** for a multidimensional view of risk.

6.4. Geospatial and Remote Sensing Tools

Geospatial and remote sensing technologies have become indispensable in exposome research because they allow investigators to quantify environmental exposures across space and time at unprecedented scales. Geographic Information Systems (GIS) enable the integration of spatial data such as land use, traffic density, green space distribution, and proximity to pollution sources with health outcomes, thereby providing a fine-grained exposure assessment (Browning & Rigolon, 2019). Satellite-based remote sensing adds another dimension by capturing large-scale environmental determinants, including air pollution ($PM_{2.5}$, NO_2), vegetation indices such as NDVI, land surface temperature, and urban heat island effects (Brochu et al., 2019; Hsu et al., 2021).

These tools provide temporal continuity, helping track exposures that fluctuate over time, such as air quality and climate variability. Remote sensing is particularly valuable for population-wide studies in regions where ground-based monitoring networks are sparse. For example, the integration of satellite aerosol optical depth (AOD) data with atmospheric models has been used to estimate global $PM_{2.5}$ levels linked to cardiometabolic risks, including type 2 diabetes (Shaddick et al., 2020). Additionally, combining geospatial data with personal health records supports a contextualized exposome framework, linking environmental determinants with socio-demographic variables and lifestyle risk factors. However, limitations remain, including spatial resolution challenges in urban microenvironments and potential exposure misclassification when assigning exposures at the residential level instead of accounting for daily mobility (Robinson et al., 2018).

6.5. Wearable Devices and Digital Health Tools

Recent advances in wearable devices and mobile health (mHealth) technologies have revolutionized how exposures are captured at the individual level. These tools provide real-time, personalized data on physical activity, sleep, circadian rhythms, stress, and physiological responses, complementing traditional epidemiological exposure measurements (de Nazelle et al., 2021). Wearable sensors can also directly measure environmental exposures such as noise, air pollutants (e.g., $PM_{2.5}$, VOCs), and UV radiation during daily activities, reducing reliance on static monitoring stations (Korsmo-Haugen et al., 2021).

Smartphones, equipped with GPS, accelerometers, and integrated health apps, act as powerful digital phenotyping platforms, enabling the capture of spatiotemporal behavioral data and linking them with environmental conditions (Onnela & Rauch, 2016). For example, GPS-enabled wearables have been applied to assess physical activity in green versus urbanized environments, helping quantify the restorative effects of natural environments within the exposome framework (Klepeis et al., 2020).

In metabolic health research, continuous glucose monitors (CGMs) and wearable heart rate variability (HRV) trackers provide insights into physiological stress and glycemic responses under varying environmental exposures. Despite their strengths, challenges include device accuracy, data interoperability, participant adherence, and privacy concerns regarding large-scale digital health data collection (Wright et al., 2022).

6.6. Integrating Multi-omics Data into Exposome Research

One of the most transformative advancements in exposome science is the integration of multi-omics approaches—including genomics, epigenomics, transcriptomics, proteomics, metabolomics, and microbiomics—to provide a mechanistic understanding of how environmental exposures interact with biological pathways. By linking external exposures with internal molecular signatures, multi-omics allows researchers to bridge the gap between environmental factors and disease etiology (Patel & Manrai, 2015).

Metabolomics, in particular, plays a central role in exposome research by capturing small-molecule signatures that reflect both external exposures and internal metabolic responses. This has been applied in identifying metabolites associated with air pollution, endocrine-disrupting chemicals, and diet-related exposures in relation to type 2 diabetes and obesity risk (Walker et al., 2019). Similarly, epigenomics helps elucidate how long-term exposures, such as heavy metals or persistent organic pollutants, alter DNA methylation patterns that influence insulin sensitivity and beta-cell function (Vrijens et al., 2022).

The integration of multiple omics layers enables systems-level modeling of the exposome, facilitating the discovery of biomarkers and exposure-response pathways. Advanced computational methods, including machine learning, Bayesian networks, and causal inference models, are increasingly used to integrate heterogeneous datasets from omics, epidemiology, and environmental monitoring (Li et al., 2022). The ultimate goal is to build predictive exposome profiles that capture gene–environment–lifestyle interactions across the life course. Nonetheless, key challenges include high dimensionality, the need for harmonization across platforms, and the requirement for longitudinal datasets that can disentangle causality from correlation.

7. Mechanistic Pathways Linking Exposures to T2D

7.1. Oxidative stress and chronic inflammation

A central axis through which many lifestyle and environmental exposures promote type 2 diabetes (T2D) is redox imbalance, with reactive oxygen species (ROS) serving as both triggers and effectors of insulin resistance and β-cell dysfunction. Causal evidence in humans and model systems shows that ROS can directly impair insulin action via serine phosphorylation of insulin receptor substrate proteins (e.g., IRS-1), activation of stress kinases (JNK, IKKβ), and inhibition of PI3K–Akt signaling in metabolic tissues (skeletal muscle, liver, adipose) (Houstis et al., 2006; Solinas & Becattini, 2016). In clamp-based human studies and cellular models, experimentally elevating ROS is sufficient to create insulin resistance, whereas antioxidant or genetic attenuation of stress-kinase signaling restores insulin responsiveness, establishing a mechanistic link beyond association (Houstis et al., 2006; Solinas & Becattini, 2016).

At the molecular level, major ROS sources include mitochondrial electron-transport leakage, NADPH oxidases, and (in some exposures) xanthine oxidase; these activate redox-sensitive nodes such as JNK and NF-κB. The resulting transcriptional program promotes pro-inflammatory cytokines (TNF-α, IL-6), chemokines, and endoplasmic reticulum (ER) stress, which together blunt insulin signaling and alter substrate use in muscle and liver (Hotamisligil, 2017; Newsholme et al., 2019). Adipose tissue macrophage infiltration is both a cause and consequence of this state, sustaining “metaflammation” characteristic of obesity and T2D (Hotamisligil, 2017).

Environmental components of the exposome can initiate the same redox-inflammatory cascade. Fine particulate matter ($PM_{2.5}$) and traffic-related mixtures generate pulmonary and systemic oxidative stress, induce endothelial dysfunction, and impair insulin signaling (e.g., reduced vascular insulin responses) within days to weeks (Haberzettl et al., 2016). Long-term exposure is linked to incident T2D and its progression, with oxidative stress and inflammation repeatedly implicated as dominant pathways in human cohorts and translational studies (Lim et al., 2019; Gangwar et al., 2020; Wu et al., 2022).

The gut–immune interface provides a complementary redox–inflammatory conduit. Diets high in fat and low in fiber can increase circulating lipopolysaccharide ("metabolic endotoxemia"), activating TLR4/CD14-dependent inflammatory signaling and precipitating hepatic insulin resistance even in the absence of overt adiposity changes (Cani et al., 2007). Targeting downstream inflammatory mediators can improve glycemic control: IL-1 blockade with anakinra improved β-cell function and HbA1c in T2D, underscoring the pathogenic role of cytokine-driven islet inflammation (Larsen et al., 2007). (Notably, broad anti-inflammatory strategies do not uniformly prevent new-onset diabetes, emphasizing pathway-specific heterogeneity).

β-cells are especially vulnerable to oxidative and ER stress because they express relatively low levels of catalase and glutathione peroxidase. Oxidative load drives loss of β-cell identity (decreased PDX1, MAFA), activation of the thioredoxin-interacting protein (TXNIP)–NLRP3 inflammasome axis, and IL-1β-mediated dysfunction and apoptosis—events documented in human islets and in vivo models (Robertson, 2007; Oslowski et al., 2012; Leenders et al., 2021; Choi et al., 2023). These observations link hyperglycemia-induced ER stress (glucotoxicity) to inflammasome activation and progressive insulin secretory failure, integrating metabolic and inflammatory stress into a single β-cell death pathway (Oslowski et al., 2012; Choi et al., 2023).

Collectively, these data position oxidative stress as a unifying mechanism through which multiple exposome components—air pollution, obesogenic diets, psychosocial stress via stress-kinase activation, and even certain chemicals—converge on immune and stress pathways to degrade insulin action and β-cell viability. The causal chain runs from exposure → ROS/ER stress → JNK/NF-κB and inflammasome activation → tissue-level insulin resistance and β-cell failure (Houstis et al., 2006; Hotamisligil, 2017; Solinas & Becattini, 2016; Oslowski et al., 2012).

7.2. Hormonal disruption and insulin resistance

Hormonal axes translate many exposures into metabolic phenotypes, creating gene–environment–lifestyle contingencies that affect insulin sensitivity and secretion. One pillar is the hypothalamic–pituitary–adrenal (HPA) axis. Chronic psychological stress elevates glucocorticoids, which (via glucocorticoid receptor signaling) increase hepatic gluconeogenesis, antagonize insulin-stimulated glucose uptake in muscle and adipose tissue, redistribute fat centrally, and impair β-cell function—changes that are well-characterized mechanistically and clinically (Hackett & Steptoe, 2017; Geer & Islam, 2014; Beaupere et al., 2021; Li et al., 2022). These effects are potentiated by co-exposures (e.g., sleep loss, circadian disruption, noise), illustrating how psychosocial and physical stressors within the exposome can converge on glucocorticoid biology to produce insulin resistance (Hackett & Steptoe, 2017; Li et al., 2022).

Circadian hormone signaling is a second pillar. Controlled laboratory studies disentangle circadian phase from behavior and show that: (i) glucose tolerance is intrinsically lower in the biological evening due to reduced early-phase insulin secretion, and (ii) circadian misalignment independently reduces insulin sensitivity—even when sleep and meals are held constant (Scheer et al., 2009; Morris et al., 2015). Melatonin signaling intersects with these effects: genetic variation at MTNR1B (e.g., rs10830963) associates with higher fasting glucose, reduced β-cell function, and greater T2D risk, and acute melatonin administration can transiently impair glucose tolerance in some contexts (Karamitri & Jockers, 2019; Zhu et al., 2023). Because artificial light at night, rotating shift schedules, and late eating shift melatonin profiles, these environmental/lifestyle exposures can act as hormonal disruptors of glucose homeostasis (Morris et al., 2015; Karamitri & Jockers, 2019; Zhu et al., 2023).

Endocrine-disrupting chemicals (EDCs) represent a third hormonal channel. Several classes—including bisphenols, phthalates, persistent organochlorines, and some PFAS—interact with nuclear receptors (ER/AR, PPARα/γ), influence glucocorticoid and thyroid signaling, and perturb adipokines and incretin pathways, thereby promoting adipogenesis, ectopic fat, and insulin resistance (Papalou et al., 2019). Meta-analytic and systematic reviews report associations between urinary phthalate metabolites and impaired insulin sensitivity or T2D, and between BPA or persistent organic pollutants and diabetes risk, with experimental models demonstrating rapid non-genomic effects on β-cells and interference with insulin signaling (Radke et al., 2019; Farrugia et al., 2021; Papalou et al., 2019). Although exposure–outcome certainty varies by chemical, the mechanistic plausibility—via receptor-mediated hormonal disruption and oxidative stress—aligns with observed epidemiology (Papalou et al., 2019; Farrugia et al., 2021).

These hormonal pathways do not operate in isolation: they integrate with redox and inflammatory signaling. For example, glucocorticoids can increase ceramide synthesis, worsening insulin resistance downstream of stress kinases; melatonin–β-cell signaling interfaces with cAMP/PKA and K_ATP channel activity; and EDC-PPARγ activation skews adipocyte endocrine function (adiponectin↓, leptin↑), reinforcing inflammatory loops (Li et al., 2022; Karamitri & Jockers, 2019; Papalou et al., 2019). In exposome terms, mixtures of psychosocial stress, circadian disruption, and chemical exposures can therefore exhibit additivity or synergy at shared hormonal and inflammatory nodes that regulate insulin action and secretion.

7.3. Epigenetic Modifications and Gene Expression

Epigenetic mechanisms—DNA methylation at cytosine–guanine dinucleotides (CpGs), post-translational histone modifications, chromatin remodeling, small and long non-coding RNAs, and epitranscriptomic marks such as N^6-methyladenosine (m^6A)—provide a biologically plausible route by which the exposome (diet, physical activity, pollutants, psychosocial stressors) can induce durable, tissue-specific shifts in gene expression without altering DNA sequence. In type 2 diabetes (T2D), human data from pancreatic islets, skeletal muscle, adipose tissue, liver, and blood now consistently show epigenetic dysregulation linked to impaired insulin secretion and insulin resistance and, critically, demonstrate that many marks are dynamic and modifiable by lifestyle or environmental change (e.g., exercise, diet, weight loss). (Ling & Rönn, 2019).

7.3.1. Epigenetic alterations in human pancreatic islets

Epigenome-wide analyses in human islets reveal thousands of differentially methylated CpG sites in donors with T2D, often located in enhancers and regions bound by β-cell transcription factors. These changes correlate with altered expression of genes that govern mitochondrial dynamics and stimulus-secretion coupling (e.g., **RHOT1/MIRO1**, **TBC1D4**, **FOXP1**) and with impaired insulin secretion; experimental silencing of RHOT1 in β-cells reduces ATP/ADP ratio, Ca^2+ flux, respiration, and insulin release—implicating methylation-linked mitochondrial dysfunction in T2D pathogenesis (Rönn et al., 2023). Earlier work mapped 1,649 differentially methylated CpGs across 853 genes in T2D islets, including **TCF7L2**, **FTO**, and **KCNQ1**; >100 targets showed concordant methylation–expression shifts, and functional assays confirmed direct effects on β-cell exocytosis and glucagon secretion (Dayeh et al., 2014). These studies collectively support a causal chain from islet methylation changes → transcriptional remodeling → secretory defects. (Rönn et al., 2023; Dayeh et al., 2014).

7.3.2. Blood DNA methylation markers that predict incident T2D

Because obtaining islets in vivo is impractical, blood DNA methylation has been tested as a risk biomarker. In the EPIC-Norfolk prospective cohort, an epigenome-wide association study (EWAS) identified CpGs whose methylation levels at baseline predicted future T2D independent of conventional risk factors; results overlapped with loci such as **ABCG1** and **TXNIP**, which have repeatedly emerged across cohorts and ethnicities as predictive of incident T2D (Cardona et al., 2019; Fraszczyk et al., 2022; Dayeh et al., 2016). Although tissue specificity limits mechanistic inference from blood, convergence on lipid metabolism (**ABCG1**, **SREBF1**) and redox/glucose-sensing (**TXNIP**) pathways strengthens biological plausibility.

7.3.3. Lifestyle and environmental modulation of the epigenome

Exposures central to the T2D exposome rapidly remodel epigenetic marks. A single session of high-intensity exercise induces promoter hypomethylation at **PPARGC1A (PGC-1α)**, **PDK4**, and **PPARδ** in human muscle, with concomitant transcriptional activation; intensity matters (no effect at ~40% VO_2max), demonstrating dose–response and reversibility (Barrès et al., 2012; McGee & Hargreaves, 2017). Weight-loss/bariatric surgery is likewise followed by widespread, depot-specific methylation reprogramming in adipose tissue and blood, paralleling improvements in insulin sensitivity—again indicating plasticity of diabetes-relevant epigenetic marks in response to environmental change (Talukdar et al., 2022; Fraszczyk et al., 2020).

Ambient pollutants can also reshuffle methylomes: controlled and observational studies show short-term traffic-related particulate exposure reduces repeated-element methylation in blood, and broader reviews document pollutant-linked methylation and histone changes across candidate loci and pathways (Baccarelli & Bollati, 2009; Madrigano et al., 2009; Rider et al., 2019). Although diabetes-specific mediation remains under active study, these findings cement a mechanistic bridge from environmental toxicants to gene regulation relevant for metabolic disease.

7.3.4. Non-coding RNAs and epitranscriptomics

Diabetes-relevant microRNAs (miRNAs) add a layer of post-transcriptional control. **miR-375**, one of the most abundant β-cell miRNAs, restrains exocytosis and insulin secretion; its intra-islet abundance and export to HDL respond to glucose and secretory cues, and circulating miR-375 is a candidate biomarker of β-cell stress/death (Eliasson, 2017; Sedgeman et al., 2019; Erener et al., 2013). In insulin-target tissues, the **miR-29** family promotes insulin resistance by dampening **AKT** signaling and reducing **GLUT4 (SLC2A4)** and oxidative metabolism; miR-29 antagonism improves hepatic and muscle insulin sensitivity in preclinical models (He et al., 2007; Hung et al., 2019; Dalgaard, 2022).

Beyond DNA and miRNA, m^{6A}/m^{6Am} RNA modifications orchestrated by "writers" (METTL3/14), "erasers" (FTO/ALKBH5), and "readers" (e.g., IGF2BP proteins) regulate RNA stability, splicing, and translation in β-cells, liver, and adipose tissue. Dysregulated m^6A machinery is reported in human diabetic islets and liver; in mouse models, hepatocyte Mettl3 deletion improves insulin sensitivity and reduces lipogenesis, highlighting epitranscriptomic control of metabolic programs (Benak et al., 2023).

7.3.5. Diet–microbiome–epigenome crosstalk

Microbiota-derived short-chain fatty acids (SCFAs)—especially butyrate—are endogenous histone deacetylase (HDAC) inhibitors and/or histone acyl donors that reshape chromatin accessibility and inflammatory tone. Butyrate and propionate inhibit HDAC activity at physiologic concentrations, upregulate **PGC-1α** and mitochondrial antioxidant genes in myotubes/endothelium, and promote epithelial barrier and anti-inflammatory programs, mechanistically linking fiber-rich diets and microbial metabolism to host epigenetic regulation relevant to T2D (Chang et al., 2014; Silva et al., 2018; Chriett et al., 2019; Korsten et al., 2023; Nshanian et al., 2025).

Implication for the exposome framing: Taken together, these findings show that lifestyle and environmental exposures leave measurable, often reversible, epigenetic "footprints" in insulin-secreting and insulin-responsive tissues that track with mitochondrial function, inflammation, and glucose homeostasis. This mechanistic plasticity provides both (i) biomarkers for exposure and early disease risk (e.g., blood methylation panels) and (ii) intervention targets (exercise, diet, pollutant mitigation) to re-tune gene expression networks toward metabolic resilience. (Ling & Rönn, 2019; Cardona et al., 2019; Rönn et al., 2023).

7.4. Gut Microbiome Alterations

7.4.1. Diabetes-associated dysbiosis and functional signatures

Across diverse cohorts, T2D is linked to reduced abundance of butyrate-producing taxa (e.g., *Faecalibacterium*, *Roseburia*) and enrichment of opportunistic/pathobiont lineages, though effect sizes vary by geography, medication use, and diet. Functionally, T2D microbiomes display decreased SCFA-biosynthetic capacity and increased microbial pathways for branched-chain amino acids (BCAAs) and trimethylamine (TMA) production, metabolites tied to insulin resistance and cardiometabolic risk (Gurung et al., 2020; Pedersen et al., 2016; Barlow et al., 2023).

Mechanistically, multiple gut–host axes are implicated. First, fewer SCFA producers → lower colonic butyrate → weaker HDAC inhibition/G-protein–coupled receptor (GPR41/43) signaling, diminished GLP-1 secretion, impaired epithelial barrier, and heightened mucosal inflammation—processes that foster hepatic and peripheral insulin resistance. Second, lipopolysaccharide (LPS) translocation ("metabolic endotoxemia") activates innate immunity and disrupts insulin signaling. Third, microbial BCAA biosynthesis associates with elevated circulating BCAAs, mTOR/S6K activation, and insulin resistance in muscle; colonization of germ-free mice with **Prevotella copri** increases BCAAs and worsens glucose tolerance (Pedersen et al., 2016).

7.4.2. Interventional and causality-oriented evidence

Causality is supported by human and animal interventions. In a randomized, controlled crossover study, fecal microbiota transplantation (FMT) from lean donors improved peripheral insulin sensitivity in individuals with metabolic syndrome, particularly those with low baseline diversity—demonstrating transferable insulin-sensitizing functions (Vrieze et al., 2012). In an open-label, mechanistically rich trial in T2D, a high-fiber diet tailored to enrich acetate- and butyrate-producing consortia increased fecal SCFAs, restored SCFA producers (e.g., *Faecalibacterium prausnitzii*, *Roseburia*), elevated GLP-1, and significantly improved HbA1c relative to control, linking diet → microbiota → metabolite → endocrine pathways (Zhao et al., 2018). Medication is a major modifier: metformin consistently reshapes the gut community (e.g., increases *Escherichia/Shigella*, *Akkermansia*), confounding cross-sectional T2D–microbiome associations and likely mediating part of its glucose-lowering effect via microbial pathways (Forslund et al., 2015; Wu et al., 2017).

7.4.3. Exposome influences on the microbiome

Dietary patterns (fiber vs. ultra-processed foods), artificial sweeteners, and environmental stressors modulate microbiota composition and function. Artificial sweeteners can induce glucose intolerance in a microbiome-dependent manner in humans and mice, underscoring how non-nutritive additives in the diet interact with microbial pathways to influence glycemic control (Suez et al., 2014). More broadly, the exposome can act on the microbiome to alter SCFA production, bile acid pools (FXR/TGR5 signaling), barrier integrity, and immunometabolic axes that converge on insulin sensitivity.

Within an exposome framework, the gut microbiome is both a mediator and a modifier of lifestyle/environmental effects on T2D. Microbial metabolites (SCFAs, BCAAs, bile acids) interface directly with host epigenetic and endocrine mechanisms—e.g., SCFA-driven HDAC inhibition and incretin release—providing mechanistic levers for prevention (fiber-rich, minimally processed diets; selective prebiotics/probiotics; exposure reduction) and therapy (microbiome-targeted interventions, medication–microbiome synergy). (Gurung et al., 2020; Zhao et al., 2018; Forslund et al., 2015).

Figure 2. Biological Mechanisms Linking Exposures to T2D

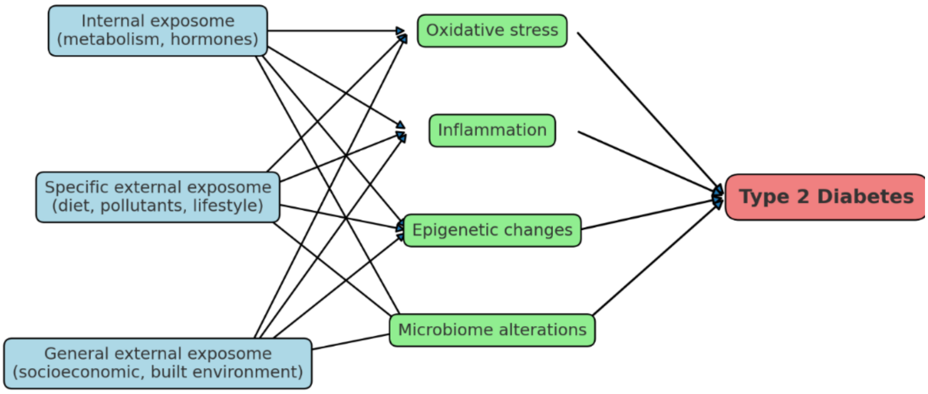

Table 2. Biological Mechanisms Linking Exposome to Type 2 Diabetes (Elaborated)

Mechanism	Pathway / Biomarkers	Representative Exposures	Mechanistic Link to T2D (brief)	Evidence
Oxidative stress	↑ROS; lipid peroxidation (MDA, F_2-isoprostanes/8-iso-$PGF_{2\alpha}$); protein carbonyls; DNA oxidation (8-OHdG); antioxidant status (GSH/GSSG, SOD, catalase, GPx); NOX2/mitochondrial ROS	**Air pollution** ($PM_{2.5}$/ozone/NO_2), tobacco smoke; **processed/high-fructose/high-fat diets**; heavy metals (As, Cd); sleep loss	Excess ROS impairs insulin receptor signaling (IRS/PI3K/AKT), damages β-cells (low antioxidant reserves), and amplifies inflammatory cascades—driving insulin resistance and β-cell failure	Reviews/meta: oxidative stress is central to T2D pathogenesis and complications; hyperglycemia and mitochondrial dysfunction amplify ROS; β-cell vulnerability documented.

Inflammation	Cytokines: TNF-α, IL-6, IL-1β; NF-κB, JNK, IKKβ activation; hs-CRP; immune cell infiltration (M1 macrophages in adipose)	**Adiposity/overnutrition**; **air pollution**; **heavy metals**; psychosocial stress; endotoxemia (LPS)	Chronic low-grade inflammation disrupts insulin signaling (serine phosphorylation of IRS), alters adipokines (↓adiponectin, ↑leptin, resistin), and promotes hepatic gluconeogenesis and lipotoxicity	Seminal frameworks and updates link nutrient/exposure-triggered NF-κB/JNK signaling to insulin resistance and T2D; integrative human+animal evidence.
Epigenetic modifications	DNA methylation (e.g., **PPARGC1A, TXNIP, ABCG1** loci); histone marks (H3K27ac/H3K9me3); chromatin remodeling; non-coding RNAs (miR-29, miR-375)	**Maternal diet/overnutrition** or **undernutrition**; **endocrine disruptors/toxins**; persistent stress; early-life famine/overnutrition	Stable, exposure-responsive epigenetic changes in islets, liver, muscle, adipose alter metabolic gene programs → reduced mitochondrial function, impaired insulin secretion/sensitivity; some marks are reversible with lifestyle	Authoritative reviews in humans show altered methylation/histone patterns in obesity/T2D tissues; epigenetics is a key link from environment to phenotype.
Endocrine disruption	Insulin/GLUT4 pathway (IRS-1/AKT); estrogen receptor (ER) and PPARγ signaling; cortisol/HPA-axis dysregulation; β-cell Ca^{2+} handling	**BPA and analogs, phthalates, organophosphate/pyrethroid pesticides**	EDCs mimic/hijack hormone signaling: reduce insulin sensitivity and secretion; promote adipogenesis; alter hepatic lipid/glucose metabolism; pregnancy exposure programs maternal/offspring glucose intolerance	Experimental and translational studies: BPA impairs glucose tolerance, increases insulin resistance and lipids; pregnancy exposure has lasting metabolic effects; reviews consolidate endocrine and metabolic impacts.
Microbiome alterations	Community structure (α/β diversity); butyrate producers (e.g., *Roseburia*, *Faecalibacterium*); **SCFAs** (acetate/propionate/butyrate); **LPS** (metabolic endotoxemia); bile acids	**Dietary patterns** (low fiber, high fat/sugar), **antibiotics**, emulsifiers; infections; early-life feeding	Dysbiosis reduces SCFA-mediated GLP-1 signaling and gut barrier integrity; ↑LPS/TLR4 activation → inflammation; altered bile acid pools affect hep	

8. Public Health and Policy Implications

8.1. Preventive strategies targeting lifestyle behaviors

High-impact diabetes prevention at the population level starts with evidence-based lifestyle programs and supportive food and activity environments. The U.S. Diabetes Prevention Program (DPP) randomized trial established that intensive lifestyle change (dietary quality, ≥150 min/week physical activity, ~7% weight loss) cut incident T2D by 58% over 2.8 years versus placebo, outperforming metformin (31% reduction) among adults with impaired glucose tolerance; risk reductions persisted (27% for lifestyle; 18% for metformin) over 15 years in the DPP Outcomes Study, albeit attenuated, underscoring the need for durable delivery models. These trials are the foundation for health-system and payer adoption (e.g., the U.S. Medicare Diabetes Prevention Program) and for guideline recommendations to screen at-risk adults and refer those with prediabetes to proven preventive interventions. Scaling requires reimbursement, quality standards, culturally tailored curricula, and hybrid/virtual delivery to improve reach and adherence, particularly in underserved groups. (Knowler et al., 2002; Diabetes Prevention Program Research Group, 2015; CMS MDPP program; USPSTF 2021 recommendation).

Fiscal and regulatory nutrition policies can shift diets toward diabetes-protective patterns at population scale. Taxes on sugar-sweetened beverages (SSBs) have repeatedly reduced purchases of taxed drinks (e.g., Mexico's 1 peso/L excise tax ≈10% price increase led to a ~6% average decline in year 1, with larger reductions over time and among lower-income households; Berkeley, CA saw ~10% declines in SSB sales and increased water sales after a 1 ¢/oz tax). Such policies can be paired with healthy-food subsidies, procurement standards (schools, hospitals), front-of-pack labeling, trans-fat elimination (REPLACE), and sodium targets—elements the WHO identifies as highly cost-effective "Best Buys" for NCD prevention. (Colchero et al., 2016; Madsen, 2019; CDC/WHO Best Buys & REPLACE).

Built-environment and transport policies that make active choices the easy choices—safe walking/cycling networks, connected land-use, greenspace and park investments—raise routine physical activity and deliver double dividends for cardiometabolic health and air-pollution mitigation. WHO's Global Action Plan on Physical Activity (GAPPA) details cross-sector actions to reduce physical inactivity by 15% by 2030; systematic reviews show that park renovations, pocket parks, and cycling/walking infrastructure measurably increase population activity. Co-benefits include lower traffic emissions, noise, and heat exposure, reinforcing the exposome focus on multisector determinants. (WHO GAPPA; Zhang et al., 2022).

8.2. Reducing environmental pollutant exposure at the population level

Air-quality regulation remains a cornerstone for diabetes-relevant exposure control. WHO's 2021 Air Quality Guidelines recommend annual $PM_{2.5}$ ≤ 5 $\mu g/m^3$ and NO_2 ≤ 10 $\mu g/m^3$ to minimize cardiometabolic risk. In 2024 the U.S. EPA tightened the annual $PM_{2.5}$ standard from 12 to 9 $\mu g/m^3$—projected to avert thousands of premature deaths and reduce chronic disease burden. Cities and countries operationalize these standards through emissions controls (industry, power, transport), low-/ultra-low-emission zones, electrified transit, and clean-household energy transitions (to cut household $PM_{2.5}$ in settings reliant on solid fuels). (WHO 2021 AQG; U.S. EPA 2024 $PM_{2.5}$ rule; WHO household energy guidance).

Noise and light-at-night (LAN) policies are increasingly relevant given links to metabolic dysregulation. WHO's Environmental Noise Guidelines (2018) set health-based exposure recommendations and call for transport-noise action plans (speed reductions, quiet road surfaces/tires, barriers, and façade insulation). For outdoor LAN, municipalities can adopt "dark-sky" ordinances (full cut-off fixtures, lower correlated color temperature, adaptive dimming) and use physiology-informed metrics such as melanopic equivalent daylight illuminance (CIE S 026) to minimize circadian disruption while maintaining safety. (WHO 2018 noise guidelines; EEA noise directive; DarkSky/IDA guidance; CIE S 026).

Heat-risk management is now essential for diabetes prevention and control because heat amplifies glycemic instability, dehydration risk, and cardiometabolic stress. WHO and regional partners recommend Heat-Health Action Plans (HHAPs) with early warnings, targeted outreach to high-risk patients (including people with T2D), cooling access, workplace protections, and long-term urban-form solutions (cool roofs/pavements, shade trees). EPA's Urban Heat Island Compendium and WHO/EEA briefs summarize effective, scalable measures; national guidance (e.g., India's National Action Plan on Heat-Related Illnesses) illustrates institutionalization. (WHO HHAP guidance; EEA/Climate-ADAPT; U.S. EPA compendium; MoHFW India).

Chemical exposure control requires both source-specific regulation and biomonitoring-informed policy. The EU HBM4EU initiative has shown how human biomonitoring can inform regulatory action (e.g., PFAS, phthalates, bisphenols), while in the U.S. the 2024 EPA National Primary Drinking Water Regulation set enforceable PFAS limits (MCLs of 4 ppt for PFOA and PFOS, with hazard index for mixtures), plus Superfund designations to accelerate remediation—policies expected to curb internal PFAS loads over time. (HBM4EU policy briefs and synthesis; U.S. EPA 2024 PFAS rules).

8.3. Health equity considerations in exposome research and action

The exposome emphasizes that social and environmental risks cluster: communities with fewer resources often face higher $PM_{2.5}$, traffic-related NO_2, heat-island intensity, noise, and LAN, compounding lifestyle barriers (food deserts, unsafe streets) and generating disproportionate diabetes risk. Large U.S. analyses document higher $PM_{2.5}$ exposures among people of color across income strata; urban heat-island intensity also disproportionately affects marginalized neighborhoods, reinforcing thermal stress and sleep disruption. Equity-centered policy uses screening and mapping tools (e.g., EPA EJSCREEN; the Climate & Economic Justice Screening Tool methodology) to direct investments—tree canopy, cooling, clean mobility, indoor air quality upgrades, and diabetes-prevention services—toward the most burdened areas, consistent with "Health in All Policies." (Tessum et al., 2021; Hsu et al., 2021; EPA EJSCREEN; CEJST methodology; WHO HiAP/Helsinki Statement).

Equitable diabetes prevention also relies on removing access barriers. Policy levers include universal coverage for DPP-like programs (e.g., MDPP), transportation and childcare supports, culturally and linguistically tailored delivery, and integration with social services. The USPSTF's 2021 recommendation to screen adults aged 35–70 years with overweight/obesity and "offer or refer" to effective preventive interventions provides a payer-agnostic entry point; CMS coverage and allowance of distance-learning delivery can help close gaps, but uptake remains uneven—requiring targeted financing and community partnerships. (USPSTF 2021; CMS MDPP and program updates; implementation analyses).

8.4. Translating exposome findings into policy and practice

Turning exposome science into action entails (i) better exposure measurement, (ii) causal inference for mixtures, and (iii) governance that links evidence to regulation and clinical/public-health workflows. National Academies reports have outlined modernization of risk assessment and exposure science, advocating the integration of biomonitoring, high-resolution spatiotemporal exposure models, and systems approaches to support timely decisions. Europe's HBM4EU demonstrates policy-facing indicators (e.g., reference values, risk contextualization) that regulators can directly use; the U.S. Human Health Exposure Analysis Resource (HHEAR) provides shared laboratory and data-science infrastructure to harmonize biospecimen assays and link omics-enabled exposure profiling with health outcomes across cohorts. Health Impact Assessment (HIA) and "Health in All Policies" frameworks operationalize cross-sector decision-making so that transport, housing, energy, and lighting choices are evaluated for metabolic and broader NCD impacts before implementation. (National Academies 2017; HBM4EU indicators and synthesis; NIEHS HHEAR; WHO HiAP).

Finally, sustained implementation requires robust surveillance and evaluation. Pollution-and-health assessments (e.g., Lancet Commission updates) keep attention on disease and economic burdens; pairing health surveillance with regulatory monitoring (air/noise/heat/chemical dashboards) and open data enables adaptive management and accountability. Embedding geocoded exposure metrics into electronic health records could support risk-stratified screening (e.g., earlier diabetes screening in high-exposure neighborhoods) and targeted referral to prevention services—an exemplar of exposome-informed precision public health. (Lancet Commission update; WHO/EEA heat-health surveillance resources).

9. Future Directions in Exposome and T2D Research

9.1. Integrating Big Data and Artificial Intelligence

The next decade of type 2 diabetes (T2D) exposome research will be defined by **data integration at scale**—linking high-frequency personal sensing, geospatial exposures, biospecimen biomonitoring, and health records—together with **fit-for-purpose machine learning (ML) and causal inference**. Several international platforms already point the way. In Europe, **EXPANSE** is building a continent-wide *urban exposome* with >55 million residents, standardized exposure models (air/noise/greenspace/food environment), and analytic pipelines that explicitly support cardiometabolic research (van Nunen et al., 2023; Hoek et al., 2023). In the U.S., **HHEAR** (the NIEHS Human Health Exposure Analysis Resource) provides centralized laboratory analysis of chemicals and multi-omics plus a data center that harmonizes exposure and health datasets for hypothesis generation and replication (HHEAR Program, 2024a; 2024b; 2024c). Methodologically, exposome-specific roadmaps emphasize **federation of data** (bringing algorithms to the data) and **interoperability/FAIR** data standards to address privacy, governance, and reproducibility across jurisdictions (Zheng et al., 2023; Manrai et al., 2022; Wilkinson et al., 2016). These are essential for multi-site T2D studies where exposures (e.g., air pollution, endocrine disruptors) and covariates (diet, activity, access to care) vary systematically by place and time.

On the analytics side, future T2D work should treat exposures as **correlated mixtures** and environments as **complex systems**. Established mixture methods—**Bayesian Kernel Machine Regression (BKMR)** for nonlinear, high-order interactions; **weighted quantile sum (WQS)** regression for "bad-actor" identification; and **quantile g-computation** for directional-agnostic joint effects—are increasingly used to model cardiometabolic risk (Bobb et al., 2015; Carrico et al., 2015; Keil et al., 2020; Schmidt et al., 2020). Causal extensions (e.g., **BKMR–causal mediation**) can decompose how mixtures act through adiposity, inflammation or epigenetic intermediates on glycemia (Devick et al., 2022). In parallel, domain reviews outline how **AI/ML**—including deep representation learning for high-dimensional exposure panels, graph models for exposure networks, and semi-supervised learning for sparse chemicals—can accelerate signal discovery if paired with rigorous validation and transparency (Isola et al., 2024; Baccarelli et al., 2023). To keep models clinically meaningful, reporting frameworks from clinical AI should be adopted—**TRIPOD-ML** for prediction modeling and **CONSORT-AI/SPIRIT-AI** for trial-adjacent designs—together with strict external validation across places and subpopulations (Collins et al., 2023; Liu et al., 2020; Riveros et al., 2020). Finally, **target-trial emulation** and modern causal design should be embedded into ML pipelines so that *associations* between exposome features and T2D are distinguished from *intervention-relevant* effects (Hernán & Robins, 2020; Hernán & Robins, 2016; Fu et al., 2023).

9.2. Longitudinal and Multi-generational Studies

Life-course and **intergenerational** designs are indispensable to disentangle how time-varying exposures program T2D risk. The NIH **ECHO** program brings together dozens of pregnancy/birth cohorts with harmonized assessments of environmental, behavioral, and social determinants, plus linkable biospecimens for multi-omics—an ideal substrate for exposome-to-glycemia pathways from in utero through adolescence (ECHO, 2025; Park et al., 2024). Multi-generation cohorts such as **ALSPAC** (G0 mothers, G1 offspring, and growing G2 grandchildren) enable tests of cross-generation effects and timing (periconceptional vs. second/third trimester) relevant to later metabolic disease (Boyd et al., 2013; Lawlor et al., 2019). Human "natural experiments" demonstrate lasting **epigenetic marks** after early-life adversity: individuals conceived during the **Dutch Hunger Winter** show persistent DNA methylation differences (e.g., *IGF2*), with mediation analyses linking famine exposure to higher adult BMI and triglycerides via specific CpGs including *TXNIP* (Heijmans et al., 2008; Tobi et al., 2014; Tobi et al., 2018). Clinically, intrauterine hyperglycemia and maternal obesity increase offspring T2D risk independent of genetics, as shown in sibling-comparison studies in the Pima and in multiethnic cohorts (Dabelea et al., 2000; Dabelea et al., 2008).

9.3. Personalized Prevention and Precision Public Health

Evidence increasingly supports **risk-stratified prevention** that joins genetics, lifestyle, and environmental exposures. Large prospective cohorts show that **high diet quality lowers T2D risk across all genetic risk strata**, arguing that lifestyle remains beneficial even at high polygenic risk (Merino et al., 2022). For prediction, **polyexposure scores** (capturing diet, activity, sleep, psychosocial stress, neighborhood context, and environmental chemicals) can match or **outperform polygenic scores** for T2D classification in multi-ancestry populations, underscoring the preventive leverage of modifiable factors (Akhtari et al., 2023; He et al., 2021). A precision-environmental-health framework proposes tailoring interventions to exposure profiles (e.g., air-pollution reduction + shift-work scheduling + sleep/ALAN mitigation) while embedding *implementation science* for equitable uptake (Baccarelli et al., 2023; Khoury et al., 2016).

9.4. Addressing Methodological Gaps and Biases

Future exposome–T2D work must directly confront **measurement error, batch effects, selection bias, and transportability**. Exposure misclassification (e.g., spatial smoothing of $PM_{2.5}$, single-time-point chemicals) typically **biases effects toward the null** and inflates uncertainty; prospective designs should incorporate **repeat measures**, calibration sub-studies, and measurement-error correction (Edwards & Keil, 2017; Samoli et al., 2020; Katsouyanni, 2022). In multi-omics, **batch effects** can overwhelm true biological signal; recent benchmarking shows that careful design (randomization across plates) plus **post-hoc harmonization** (e.g., ComBat variants, TAMPOR) improves downstream differential analyses and predictive modeling (Yu et al., 2023; Yu et al., 2024; Dammer et al., 2023). To detect hidden confounding, **negative controls** (exposure or outcome) should be routine, and **DAG-based** study specification with **target-trial emulation** should mitigate immortal-time and prevalent-user biases when linking exposures to diabetes onset or control (Lipsitch et al., 2010; Hernán & Robins, 2020; Fu et al., 2023). For highly correlated exposures, mixture methods (BKMR, WQS, quantile g-computation) reduce model misspecification, and causal extensions can parse mediated pathways (Bobb et al., 2015; Carrico et al., 2015; Keil et al., 2020; Devick et al., 2022). Finally, **external validity** and **equity** require transparent reporting (STROBE; GREEN under development), *a priori* transportability plans, and inclusion of under-represented populations to avoid widening disparities (von Elm et al., 2007; GREEN guideline in development; Bareinboim & Pearl, 2016; Westreich et al., 2017).

10. Conclusion:

Understanding type 2 diabetes through the lens of the exposome highlights the intricate interactions between environmental exposures, lifestyle determinants, biological processes, and social inequities. Evidence synthesized in this review demonstrates that factors such as oxidative stress, chronic inflammation, hormonal imbalance, epigenetic modifications, and gut microbiome alterations serve as key mechanistic pathways linking exposures to T2D development. At the same time, socioeconomic and educational disparities modify risk trajectories, underscoring the importance of equity-focused interventions. Emerging technologies—including geospatial analytics, wearable sensors, and multi-omics platforms—are revolutionizing exposure assessment and enabling personalized risk profiling. However, significant challenges remain, including methodological biases, fragmented data integration, and limited translation of findings into clinical and policy frameworks. Future research should prioritize longitudinal and multi-generational approaches, harness artificial intelligence to manage big data, and move toward precision public health strategies tailored to individual and community needs. Ultimately, advancing an exposome-informed paradigm has the potential not only to deepen mechanistic understanding of T2D but also to shape proactive, equitable, and evidence-based prevention and policy measures to curb the global diabetes epidemic.

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