Diabetes, Metabolic Syndrome and Obesity

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Endocrine Disruptors, Gut Microbiota, and Type 2 Diabetes: Bridging Mechanisms to Probiotic-Based Therapeutic Approaches

Shun-Man Cheung[1], Chi-Yung Cheng[2], Vinoth Kumar Ponnusamy[3–5], Kai-Fan Tsai[6], Chia-Te Kung[2,7], Wan-Ting Huang[8], Huey-Ling You[8], Shau-Hsuan Li[6], Wen-Chin Lee[6], Fu-Jen Cheng[2,9], Venkata Chaithanya[2]

[1]Department of Physical Medicine and Rehabilitation, Taitung MacKay Memorial Hospital, Taitung, Taiwan; [2]Department of Emergency Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan; [3]Department of Medicinal and Applied Chemistry, Kaohsiung Medical University (KMU), Kaohsiung, Taiwan; [4]Research Center for Precision Environmental Medicine, Kaohsiung Medical University (KMU), Kaohsiung, Taiwan; [5]Department of Medical Research, Kaohsiung Medical University Hospital (KMUH), Kaohsiung, Taiwan; [6]Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan; [7]Department of Emergency Medicine, Jen-Ai Hospital, Taichung, Taiwan; [8]Department of Laboratory Medicine, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan; [9]Institute for Translational Research in Biomedicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan

Correspondence: Fu-Jen Cheng; Venkata Chaithanya, Department of Emergency Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, No. 123, Dapi Road, Niaosong Township, Kaohsiung County, 833, Taiwan, Email a0953283092@yahoo.com.tw; s12273@cgmh.org.tw; chaithu280298@gmail.com

Diabetes, Metabolic Syndrome and Obesity downloaded from https://www.dovepress.com/
For personal use only.

Abstract: Genetic and lifestyle factors alone cannot explain the rising global burden of type 2 diabetes mellitus (T2DM). Growing evidence implicates endocrine-disrupting chemicals (EDCs) found in plastics, pesticides, food packaging, industrial products, and contaminated water as significant environmental contributors to metabolic dysfunction. EDCs, including bisphenol A (BPA), phthalates, per- and polyfluoroalkyl substances (PFAS), persistent organic pollutants (POPs), and heavy metals, have been associated with insulin resistance, pancreatic β-cell dysfunction, oxidative stress, mitochondrial impairment, chronic inflammation, and epigenetic modifications that collectively promote T2DM pathogenesis. The gut microbiota has emerged as a potential mediator of EDC-associated metabolic disruption, whereby chemical exposures may alter microbial diversity, disturb the *Firmicutes/Bacteroidetes* ratio, impair short-chain fatty acid production, decrease intestinal barrier integrity, driving metabolic endotoxemia and systemic inflammation. This narrative review examines the major EDCs associated with diabetes, their molecular and metabolic mechanisms of action, and their interactions with the gut microbiota, drawing on current experimental and epidemiological evidence. Special emphasis is placed on probiotic supplementation as an emerging therapeutic strategy targeting the EDC–gut microbiota–metabolic axis. Current evidence for probiotics in EDC-associated metabolic dysfunction is predominantly preclinical, with studies suggesting improvements in microbial homeostasis, pancreatic oxidative damage, and glucose metabolism. However, available evidence remains heterogeneous and human clinical trials specifically examining probiotic intervention in EDC-exposed populations at risk of T2DM remain absent, representing a fundamental translational gap that future research must urgently address. Advancing precision medicine approaches, integrating microbiome profiling, metabolomics, epigenetic analysis, and coordinated efforts across toxicology, clinical medicine, and public health, will be essential to reducing the growing global burden of environmentally driven type 2 diabetes.

Keywords: type 2 diabetes mellitus, endocrine-disrupting chemicals, gut microbiota, probiotics, bisphenol a

Introduction

The growing global prevalence of type 2 diabetes mellitus (T2DM) has emerged as one of the most pressing public health challenges of the twenty-first century. Diabetes mellitus is a chronic metabolic disease characterised by prolonged hyperglycemia resulting from deficient insulin secretion, impaired insulin action, or both, and is responsible for significant cardiovascular, renal, neurological, and immune complications that collectively impose a substantial burden of morbidity and mortality worldwide. According to the International Diabetes Federation, the global diabetes burden is projected to increase

https://doi.org/10.2147/DMSO.S636877
Received: 30 June 2026
Accepted: 7 September 2026
Published: 7 October 2026

© 2026 Cheung et al. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php and incorporate the Creative Commons Attribution – Non Commercial (unported, v4.0) License (http://creativecommons.org/licenses/by-nc/4.0/). By accessing the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, please see paragraphs 4.2 and 5 of our Terms (https://www.dovepress.com/terms.php).

significantly in the coming decades, presenting an unprecedented challenge for health systems everywhere.[1] While traditional risk factors such as sedentary lifestyles, unhealthy diets, and genetic predisposition are well-established, but they are insufficient to fully explain the rapid worldwide surge in metabolic disorders. The burden of disease has consequently increased and a shift in focus has occurred to those factors that are related with diet, physical activity, obesity, and genetics, causing metabolic changes as well as the endocrine system of the body.[2] Among these environmental factors, endocrine-disrupting chemicals (EDCs) have emerged as a key factor in metabolic abnormalities and diabetes pathogenesis.

Endocrine disruptors are exogenous natural or synthetic substances that affect hormonal signalling pathways and disrupt hormonal homeostasis.[3] These chemicals are predominantly used in industrial processing in industrial plants as well as in consumer products where human beings may be exposed to them through contaminated food, drinking water, air, household dust, cosmetics, and food packaging materials. Some common endocrine disruptors may be bisphenol A (BPA), phthalates, per- and polyfluoroalkyl substances (PFAS), dioxins, pesticides, polychlorinated biphenyls (PCBs), and heavy metals.[4] The endocrine system manages several physiological events, such as glucose metabolism, lipid homeostasis, growth, reproduction, and immune function, by hormonal signaling. Environmental chemicals can interfere with these pathways, may cause metabolic disorders and endocrine diseases. Previous epidemiological and experimental studies have shown that EDC exposure is associated with insulin resistance, obesity, pancreatic β-cell dysfunction, oxidative stress, inflammation, mitochondrial dysfunction and glucose metabolism abnormalities. These are critical for the development of diabetes mellitus.[2] Some endocrine disruptors function as obesogens, promoting adipocyte differentiation and lipid accumulation, with increased risk of obesity and metabolic syndrome.[5] Compounding these concerns are the persistence and bioaccumulation of many EDCs in biological tissues; their lipophilic properties and long biological half-lives allow sustained accumulation in adipose tissue, and their biological activity at low concentrations, often yielding non-monotonic dose-response relationships, considerably complicates toxicological risk assessment.[6] Importantly, human exposure to EDCs rarely occurs in isolation. Individuals are commonly exposed to complex mixtures of environmental chemicals through multiple sources and exposure routes across the life course. The exposome concept, which encompasses the totality of environmental exposures experienced by an individual over the life course, provides a useful framework for understanding these cumulative and interacting exposures.[7] Such combined exposures may occur simultaneously or sequentially and may produce additive, synergistic, or antagonistic effects that are not adequately captured by studies examining individual chemicals alone. The assessment of cumulative environmental risks is further complicated by differences in exposure duration, frequency, timing, concentration, and the interactions among multiple exposure constituents.[8] Considering these cumulative and mixed exposures is therefore important for understanding real-world environmental risks and their potential contribution to metabolic dysfunction and T2DM. Recent advances in the study of gut microbiomes, point to the involvement of gut microbiota in the metabolic dysfunction induced by EDC. The gut microbiota is essential in the maintenance of gut barrier integrity, nutrient metabolism, immune regulation and overall host physiological balance. For example, there is increasing evidence that exposure to endocrine disruptors alters the composition and diversity of intestinal microbiota, causes dysbiosis, increased permeability in gut membrane, endotoxemia, and a low level of chronic inflammation.[9,10] These disturbances may contribute to individuals with insulin sensitivity and insulin resistance. Furthermore, gut microorganisms are able to biotransform endocrine disrupters into altered biological activities of metabolites, which in turn may modulate their toxicity and metabolic consequences. Notably, changes in the *Firmicutes/Bacteroidetes* ratio and reduced abundance of beneficial short-chain fatty acid (SCFA)-producing bacteria have been consistently associated with obesity, insulin resistance, and diabetes progression,[11] supporting the potential involvement of the microbiota–gut–endocrine axis in environmentally associated metabolic disease.

Despite growing evidence linking EDC to metabolic disorders, important gaps remain in the integration and interpretation of the available evidence. Existing studies have frequently focused on individual EDCs or isolated molecular pathways, whereas the complex interactions among EDC exposure, gut microbiota dysbiosis, epigenetic modifications, inflammation, and metabolic dysfunction have not been comprehensively integrated.[12,13] In particular, a unified mechanistic framework linking EDC exposure, gut microbiota disruption, and diabetes remains insufficiently established. Furthermore, although probiotics have emerged as a promising strategy for restoring gut microbial homeostasis and improving metabolic outcomes, their potential role in mitigating EDC-induced diabetogenic effects remains insufficiently explored and the available evidence is largely preclinical.[14] Therefore, this narrative review aims to integrate current evidence on the relationship between EDC exposure, gut dysbiosis and T2DM, with particular emphasis on the mechanisms linking to environmental exposure to insulin

resistance, inflammation, β-cell and metabolic dysfunction. The review further evaluates the emerging evidence for probiotic-based interventions as a targeted microbiota and identifies important limitations and priorities for future research.

Methods

Review Design and Literature Search

This study was conducted as a narrative review to synthesize current evidence regarding the relationships among endocrine-disrupting chemical exposure, gut microbiota alterations, metabolic dysfunction, and type 2 diabetes mellitus, with particular emphasis on probiotic-based interventions. Relevant literature was identified through searches of PubMed and Google Scholar conducted in 2026. The search strategy included combinations of terms related to "endocrine-disrupting chemicals", "EDCs", "bisphenol A", "phthalates", "PFAS", "persistent organic pollutants", "heavy metals", "gut microbiota", "gut dysbiosis", "intestinal barrier", "metabolic dysfunction", "insulin resistance", "type 2 diabetes", "probiotics", and "microbiome".

Study Selection and Evidence Synthesis

Studies were considered relevant when they examined associations or potential mechanisms linking EDC exposure with metabolic dysfunction, T2DM, or gut microbiota alterations, or evaluated microbiota-targeted interventions relevant to EDC-associated metabolic effects. Experimental, epidemiological, clinical, and relevant review studies were considered to provide evidence across mechanistic and translational domains. Studies unrelated to EDC exposure, gut microbiota, metabolic outcomes, or the objectives of this review were excluded.

Endocrine-Disrupting Chemicals

Environmental pollutants that disrupt the normal functions of the endocrine system and adversely affect metabolic, reproductive, neurological, and immunological processes are labelled as endocrine-disrupting substances. Since large-scale industrial production and the widespread use of synthetic chemicals in the last couple of decades, human exposure to endocrine-disrupting chemicals has expanded tremendously. These substances are common in plastics, pesticides, cosmetics, food packaging, industrial goods, and contaminated water sources. Because these chemicals are associated with a range of chronic conditions, including type 2 diabetes, obesity, thyroid disorders, infertility, and cancer, chronic exposure to these substances is a matter of major public health concern.[15,16] These substances may disrupt endocrine homeostasis and physiological regulation by changing hormone production, secretion, transport, receptor binding, metabolism, or elimination.[17]

Hormone-producing glands like the pancreas, thyroid, adrenal, pituitary, ovaries, and testes make up the endocrine system. These glands create hormones that control vital biological functions such as energy, immunological response, growth, reproduction, and glucose metabolism. By interacting with hormonal receptors or signaling pathways, EDCs interfere with these processes.[18]

Endocrine disruptors, in contrast to common toxic compounds, exhibit biological activity even at very low concentrations and frequently display non-monotonic dose–response relationships, where the magnitude or direction of the biological response varies across the dose range, making their toxicological evaluation particularly challenging. Importantly, low-dose responses may not necessarily be predicted by effects observed at higher doses, emphasizing the need to consider exposure levels relevant to human environmental exposure. However, doses used in experimental animal studies may differ substantially from typical human exposure levels. Therefore, the metabolic effects reported in experimental studies should be interpreted in the context of dose relevance and exposure conditions when assessing their potential implications for human health.[19,20] Table 1 summarises the Endocrine-Disrupting Chemical Classes, Exposure Sources, Metabolic Effects, and Gut Microbiome Effects.

Hormonal Interference

The main mechanism that endocrine disruptors cause biological and toxicological consequences is through hormonal influence. Many EDCs function as hormone mimics or antagonists because they structurally resemble endogenous hormones. These substances bind to thyroid hormone receptors, glucocorticoid receptors, estrogen receptors, androgen receptors, and peroxisome proliferator-activated receptors (PPARs), changing gene expression and hormonal signalling.[17]

Table 1 Summary of Major Endocrine-Disrupting Chemical Classes, Exposure Sources, Metabolic Effects, and Gut Microbiome Effects

EDC Class	Exposure Sources	Mechanisms	Metabolic Effects	Gut Microbiome Effects	Key Evidence Gaps	References
BPA	Plastics, food packaging and consumer products	Endocrine signaling disruption, oxidative stress, mitochondrial dysfunction and β-cell dysfunction	Insulin resistance, impaired glucose homeostasis, obesity and T2DM	Altered microbial composition and diversity, increased intestinal permeability and metabolic endotoxemia	Human evidence directly linking BPA-related microbiome changes to T2DM remains limited	[21–29]
Phthalates	Cosmetics, food packaging, detergents and personal-care products	Endocrine and metabolic signaling disruption, oxidative stress and altered insulin sensitivity	Obesity, dyslipidemia, insulin resistance and T2DM	Evidence for microbiome-mediated effects remains limited	Human and mechanistic evidence remains heterogeneous	[30–32]
PFAS	Food packaging, contaminated water, non-stick products, textiles and firefighting foams	PPAR signaling, altered lipid and glucose metabolism, oxidative stress and inflammation	Altered glucose and lipid metabolism, obesity, insulin resistance and metabolic dysfunction	Evidence for gut microbiome involvement is emerging but remains limited	Findings vary by individual PFAS, sex and population	[33–37]
POPs	Contaminated food and environmental/ occupational exposure	Endocrine disruption, oxidative stress, mitochondrial dysfunction and altered metabolic signaling	Obesity, insulin resistance and altered glucose and lipid metabolism	Evidence regarding gut microbiome effects remains limited and requires further investigation	Mixture effects and long-term low-dose exposure require further investigation	[38–40]
Heavy metals	Contaminated water and food, industrial pollution, cigarette smoke and occupational exposure	Oxidative stress, mitochondrial dysfunction, altered insulin signaling and β-cell dysfunction	Impaired glucose homeostasis, insulin resistance and β-cell dysfunction	Cadmium can alter gut microbiota, disrupt intestinal tight-junction integrity and increase intestinal permeability	Human evidence for microbiome-mediated metabolic effects remains limited	[41–46]

Certain endocrine disruptors activate estrogen-dependent pathways by acting as estrogenic substances. For instance, Bisphenol A has estrogen-like properties that could interfere with glucose metabolism and insulin signalling.[47]

Interference with pancreatic β-cell function is a risk factor for diabetes mellitus, leading to impaired glucose homeostasis and reduced insulin secretion. Endocrine disruptors may also initiate oxidative stress and inflammatory pathways associated with metabolic dysfunction and insulin resistance. Such alterations in metabolism suggest that prolonged exposure to endocrine disruptors may significantly influence the pathophysiology of diabetes.[48]

Persistence and Bioaccumulation

Persistent organic pollutants (POPs), such as dioxins, polychlorinated biphenyls, and PFAS, are particularly harmful and they can remain in environmental and biological system because of their resistance to degradation[49,50] several lipophilic endocrine disruptors accumulate in the liver, adipose tissue, and other organs, prolonging internal exposure even after external exposure has declined.

Bioaccumulation refers to the accumulation of chemicals within living organisms over time. Dietary sources including fish, meat, and dairy products are among the foods that frequently expose humans to chronic endocrine disruptors.[51] However, the extent of bioaccumulation and its metabolic consequences vary according to the chemical's physicochemical properties, exposure duration, dose, and individual metabolic characteristics. These factors are particularly relevant when interpreting epidemiological associations between persistent EDC exposure and metabolic outcomes, because measured concentrations may reflect cumulative exposure rather than a single exposure event.

Routes of Exposure

Endocrine-disrupting chemicals can enter the human body through a variety of routes, including as ingestion, inhalation, dermal absorption, and occupational exposure. The most common route is thought to be ingestion, primarily through

contaminated food and water. Chemicals can also be introduced into food products from non-stick cookware, canned food linings, plastic containers, and food packaging during heating.[52] Industrial emissions, cigarette smoke, household dust, and contaminated air can release endocrine disruptors in an inhaled form. Inside the house, phthalates and BPA can be very high, so they can be inhaled and absorbed into the bloodstream.[53–55] Another major mode of exposure is dermal absorption, particularly from BPA-containing cosmetics, personal hygiene products, detergents, insecticides, and thermal paper receipts. Occupational workers have frequent exposure to waste processing, chemical manufacturing, plastics, and agriculture sectors.[56] Also, mothers transfer the endocrine disruptor during pregnancy and lactation may also risk exposing developing fetuses and newborns to these substances at critical developmental period. Research have linked early exposures to endocrine disruptors with long-term metabolic disorders and endocrine problems in adulthood.[57] However, Rundle et al reported that children born to mothers who were most exposed to polycyclic aromatic hydrocarbons during pregnancy had higher body weights at five and seven years old.[58] The comprehensive dispersion, durability, and multiple exposure pathways of endocrine disruptors mean they represent important environmental risk factors for metabolic diseases such as diabetes mellitus.

Major Endocrine-Disrupting Chemicals Associated with Diabetes

The most extensively studied endocrine disruptors associated with diabetes are bisphenol A, phthalates, per- and polyfluoroalkyl substances, persistent organic pollutants, and heavy metals.[21,38] Table 2 summarises the association between Endocrine-Disrupting Chemicals and type 2 Diabetes Mellitus.

Bisphenol A

BPA is a powerful endocrine disruptor that can affect insulin secretion, pancreatic β-cell function, estrogen receptor signalling, and glucose homeostasis, according to growing experimental, epidemiological, and clinical data.[22,66]

Table 2 Epidemiological Studies Investigating the Association Between Endocrine-Disrupting Chemicals and Type 2 Diabetes Mellitus

S. no	Study Design/ Population	Exposure Assessed	Key Findings	Reference
1	Case-control study; 30 T2DM and 30 controls	Serum BPA	BPA levels were significantly higher in T2DM patients and correlated with poor glycemic control and insulin resistance. BPA was associated with inflammation, cellular senescence, and shortened telomeres.	[24]
2	Clinical study; 120 T2DM patients with vascular complications	Serum and urinary BPA	Elevated BPA levels were associated with vascular complications in T2DM. BPA correlated with inflammatory markers and vascular calcification-related genes.	[28]
3	Prospective cohort; 755 participants followed for 9 years	Urinary BPA-G and BPS-G	Higher BPA and BPS exposure increased the risk of incident T2DM. BPS exposure showed a strong positive association with diabetes development.	[29]
4	Case-control study; 251 T2DM cases and 251 controls	Urinary BPA, BPAF, and BPS	BPAF and BPS levels were positively associated with T2DM risk. BPA showed a nonlinear association with diabetes.	[59]
5	Nested case-control study; 5-year follow-up	Serum BPA	BPA levels were associated with fasting glucose but not with future T2DM incidence. No significant association with insulin resistance was observed.	[60]
6	Prospective community-based study; 2209 participants	Urinary BPA	BPA exposure alone was not significantly associated with T2DM incidence. Genetic susceptibility modified the effect of BPA on fasting glucose levels.	[61]
7	Cross-sectional study; 20 T2DM and 131 healthy adults	Urinary mono-ClBPA and BPA	Mono-ClBPA was significantly associated with increased odds of T2DM. Total BPA showed no significant association with diabetes.	[62]
8	Cross-sectional study; 239 Iranian adults	Urinary BPA	Higher urinary BPA levels were strongly associated with T2DM and elevated HbA1c. BPA exposure was independent of traditional diabetes risk factors.	[63]
9	Cross-sectional study; 3423 Chinese adults	Urinary BPA	No clear overall association was observed between BPA and T2DM. Some BPA quartiles showed slightly increased diabetes risk.	[64]

(*Continued*)

https://doi.org/10.2147/DMSO.S636877

Table 2 (Continued).

S. no	Study Design/ Population	Exposure Assessed	Key Findings	Reference
10	Nested case-control study; 1006 T2DM cases and 1006 controls	Serum phthalates (PAEs)	No significant association was found in the overall population. Current alcohol drinkers with higher DnBP and ΣLMW exposure showed increased T2DM risk.	[30]
11	Case-control study; 250 T2DM and 250 controls	Urinary phthalate metabolites	Most urinary phthalate metabolites were positively associated with T2DM. Phthalate exposure was also associated with increased fasting glucose and HbA1c.	[32]
12	Cross-sectional study; 571 Taiwanese adults	Serum PFAS (PFOS, PFOA, PFNA, PFUA)	PFOS exposure was associated with impaired glucose homeostasis and higher diabetes prevalence. PFOA, PFNA, and PFUA showed possible protective associations.	[34]
13	Cross-sectional NHANES study; 7904 adults	Serum PFAS	Higher serum PFOA was positively associated with diabetes prevalence in men. No significant association was found for PFOS, PFHxS, or PFNA.	[35]
14	Cohort study; 32,254 residents and workers exposed to PFOA	Serum PFOA	No association was found between cumulative PFOA exposure and incident T2DM. Fasting glucose levels were also not associated with PFOA exposure.	[36]
15	Prospective nested case-control study; 124 case-control pairs	Plasma PFAS	PFAS exposure showed overall inverse or non-significant associations with T2DM risk. Long-term PFAS exposure was associated with lower insulin resistance.	[37]
16	Prospective Diabetes Prevention Program study; 957 participants	Plasma PFAS	PFOS and PFOA were associated with higher HOMA-IR, HOMA-β, and HbA1c at baseline. However, no strong association with incident diabetes was observed during follow-up.	[65]
17	Systematic review of 72 epidemiological studies	Persistent organic pollutants	Evidence suggested positive associations between organochlorine POPs and T2DM. Evidence for PFAS and brominated compounds remained inconsistent.	[39]
18	Cross-sectional study; 386 adults from Southern Spain	Organochlorine pesticides and PCBs	Higher adipose tissue levels of p,p'-DDE and β-HCH were associated with increased diabetes risk. Associations varied according to BMI and exposure level.	[40]
19	Experimental study in mice	Arsenic	Arsenic exposure caused oxidative stress, inflammation, and pancreatic β-cell dysfunction, which interfered with glucose metabolism	[42]
20	Cohort study; Pakistani population	Lead	Lead exposure was significantly associated with fasting blood glucose and glycated hemoglobin levels, suggesting that chronic Pb exposure may contribute to impaired glucose regulation and diabetes mellitus.	[44]
21	Prospective cohort study; American young adults	Mercury	Individuals with the highest mercury exposure had a 65% greater risk of developing diabetes than those with the lowest exposure. Higher mercury exposure was also associated with reduced pancreatic β-cell function, indicating impaired insulin secretory capacity.	[45]
22	Experimental study in mice	Cadmium (Cd)	Cadmium exposure altered gut microbiota composition and disrupted intestinal tight-junction proteins, including ZO-1, ZO-2, JAM-A, occludin, and claudin-1, resulting in increased intestinal permeability and impaired gut-barrier function.	[46]

Significant correlations between BPA exposure and insulin resistance, hyperinsulinemia, elevated HbA1c levels, obesity, metabolic syndrome, and diabetes progression were further confirmed by later studies and meta-analyses.[4,66] The first cross-sectional evidence linking elevated urinary BPA concentrations with type 2 diabetes and related metabolic disorders was published by Lang et al in 2008.[23] In another study by soundarajan et al Serum BPA levels were significantly higher in patients with T2DM compared to individuals with normal glucose tolerance, indicating a possible role of BPA in diabetes development. The association was more prominent in females, suggesting potential gender-specific susceptibility to BPA-induced metabolic disturbances.[24] Several epidemiological studies found higher BPA and chlorinated BPA levels to be associated with type 2 diabetes.[25,62,67] For a more precise study of the endocrine disruptors and the molecular mechanisms of these molecules, animal studies have provided important experimental evidence in understanding their diabetogenic role. For example, rodent and other animal studies have found that exposure to chemicals like bisphenol A could cause metabolic abnormalities in rats that may resemble type 2 diabetes.[26] Studies show BPA exposure during pregnancy and early development can cause glucose intolerance, insulin resistance, obesity, and pancreatic β-cell dysfunction in offspring. BPA-exposed mice have altered insulin

signalling pathways, oxidative stress, mitochondrial malfunction, and inflammatory activation in metabolic tissues.[27] Insulin signaling is impaired due to BPA-induced oxidative stress, mitochondrial dysfunction, inflammatory cytokine release, and sex-related metabolic impact has been recorded. A clinical study by Mohanraj et al involving patients with T2DM-associated vascular complications exhibited significantly higher serum and urinary BPA levels than controls. Elevated BPA concentrations were associated with altered expression of genes and inflammatory mediators involved in vascular calcification and inflammation, suggesting a potential link between BPA exposure and diabetic vascular complications.[28] Epidemiological studies investigating the association between BPA exposure and T2DM have produced mixed findings. Several prospective and case-control studies reported that higher urinary concentrations of BPA and its analogs, particularly bisphenol S and bisphenol AF, were associated with an increased risk of incident T2DM and poorer glycemic outcomes, including elevated fasting glucose and HbA1c levels.[29,59,63] In contrast, some longitudinal and community-based studies found no significant association between BPA exposure and future diabetes incidence, although BPA was associated with fasting glucose levels and its metabolic effects appeared to be modified by genetic susceptibility.[60,61,64] Overall, current evidence suggests that BPA and its substitutes may contribute to T2DM development, but the strength and consistency of these associations vary across populations, study designs, and exposure assessment methods.

In addition, gut permeability, metabolic endotoxemia, change in gut microbial diversity, and disturbance of *Firmicutes/Bacteroidetes* ratio have all been associated with BPA exposure,[68,69] suggesting that gut microbiota dysbiosis may be a central pathophysiological contributor to the development of diabetes and chronic inflammation.

Phthalates

Phthalates are plasticizers used in cosmetics, detergents, food packaging materials, medical equipment, and personal care items. Recent epidemiological studies have shown a link between phthalate intake and dyslipidemia, obesity, insulin resistance, and a high risk of diabetes.[38] Zhang et al reported no overall significant association between phthalate exposure and diabetes risk in the general population, analyzing 1006 diabetes cases and 1006 matched controls. Nevertheless, in current alcohol drinkers, exposure to elevated concentrations of specific phthalates, especially DnBP, ΣDBP, and ΣLMW, has been linked to a significantly increased risk of type 2 diabetes, further suggesting that alcohol drinkers may be at greater risk of the negative metabolic effects of phthalates.[30] In another case control study in China with 250 patients with T2DM and 250 controls, urinary phthalate metabolite concentration was found to be significantly related to type 2 diabetes mellitus, fasting blood glucose (FBG), and glycated hemoglobin (HbA1c) levels. Although one specific finding was negative for some secondary metabolites, most phthalate metabolites had positive relationships with the risk of type 2 diabetes. The study also reported that these correlations differed by age, sex, and BMI, suggesting that exposure to phthalates may have differential influencing effects on glucose metabolism in the demographic groups. Phthalate intake has associated with increased waist circumference, obesity, inflammation, and insulin resistance in both adults and children. Long-term exposure to persistent organic pollutants and air pollutants is also linked to a higher risk of diabetes and cardiovascular problems, according to epidemiological studies.[31,32]

Per- and Polyfluoroalkyl Substances

Highly persistent synthetic chemicals labeled per- and polyfluoroalkyl substances are found in food packaging materials, waterproof textiles, firefighting foams, and nonstick cookware. PFAS are frequently referred to as "forever chemicals" because of their resistance to breakdown. The main ways that humans are exposed are through contaminated food, water, dust in the home, and contact at work.[70]

Recent studies have demonstrated significant associations between PFAS exposure and impaired glucose metabolism, insulin resistance, obesity, and metabolic syndrome. PFAS alter lipid metabolism, mitochondrial function, and endocrine signaling pathways including PPAR activation. Increased oxidative stress and inflammatory cytokine production further contribute to metabolic dysfunction associated with PFAS exposure.[71]

Cardenas et al (2017) demonstrated that elevated serum PFAS concentrations related to long-term weight gain and hip circumference. The Diabetes Prevention Program trial (957 participants) showed a 1.80 kg increase in body weight and 1.03 cm increase in hip girth at each doubling of total PFAS concentration over 9 years in the placebo group, but showed

no significant changes for participants receiving lifestyle intervention, indicating that lifestyle modification may counteract the obesogenic effects of PFAS exposure.[33]

A cross-sectional study by Su et al reported that higher concentrations of the PFAS compound PFOS were positively associated with impaired glucose homeostasis and increased diabetes prevalence, whereas other PFAS compounds, including PFOA, PFNA, and PFUA, demonstrated inverse associations with glucose intolerance and diabetes risk.[34] In another cross-sectional analysis based on data from the National Health and Nutrition Examination Survey reported that elevated serum PFOA levels were significantly associated with diabetes among men, whereas no such association was observed in women.[35] In contrast, some studies reported no significant association between circulating PFAS concentrations and type 2 diabetes,[36,37,65] although studies conducted specifically among women more frequently demonstrated positive associations.[72]

Persistent Organic Pollutants

Lipophilic environmental pollutants with extended biological half-lives and bioaccumulation in adipose tissue are referred to as persistent organic pollutants. Polychlorinated biphenyls, dioxins, organochlorine insecticides, and flame retardants are among the main POPs. Contaminated food items, particularly fatty fish, meat, and dairy products, are the primary source of exposure.[21]

According to a review by Taylor et al, there is enough data to show a positive correlation between type 2 diabetes and several organochlorine persistent organic pollutants, specifically DDE, PCBs, dioxins, and trans-nonachlor. On the other hand, non-organochlorine POPs such brominated chemicals and perfluoroalkyl acids showed weaker correlations.[39]

Serum POP concentrations are strongly correlated with a higher incidence of type 2 diabetes, according to recent epidemiological research.[40] POPs interfere with aryl hydrocarbon receptor (AhR) signaling, oxidative stress pathways, mitochondrial activity, and inflammatory responses, thereby contributing to metabolic dysfunction.[73] In animal study 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) exposure induces insulin resistance and diabetes.[74] Chronic accumulation of POPs in adipose tissue further aggravates obesity-associated inflammation and endocrine disruption.

Heavy Metals

Lead, cadmium, mercury, arsenic, and other heavy metals are significant environmental contaminants linked to metabolic and endocrine problems. Contaminated drinking water, industrial pollutants, cigarette smoke, food items, and occupational exposure are all ways that humans are exposed. Chronic exposure to heavy metals has been associated with altered insulin signaling, β-cell dysfunction, oxidative stress, and mitochondrial dysfunction.[41]

One of the heavy metals that has been investigated the most in relation to diabetes is arsenic. According to recent research, exposure to arsenic causes oxidative stress, inflammation, and pancreatic β-cell dysfunction, all of which interfere with glucose metabolism.[42]

Lead exposure has also emerged as an important risk factor for metabolic dysfunction and T2DM. Experimental studies suggest that lead impairs glucose homeostasis by disrupting calcium-dependent insulin secretion from pancreatic β-cells through interference with voltage-gated calcium channels. In addition, lead-induced generation of reactive oxygen species (ROS) promotes oxidative stress, pancreatic damage, and reduced insulin sensitivity.[43] A study conducted in a Pakistani population reported a significant association between lead (Pb) exposure and both fasting blood glucose and glycated hemoglobin levels, suggesting that chronic Pb exposure may contribute to the development of diabetes mellitus.[44] Collectively, these findings indicate that lead exposure may impair glucose regulation through both direct effects on pancreatic β-cell function and indirect effects mediated by oxidative stress and metabolic dysfunction, highlighting lead as a potential environmental contributor to T2DM development.

Mercury, particularly in its organic form methylmercury, exerts diabetogenic effects through mechanisms distinct from those of other heavy metals. Methylmercury has a high affinity for selenium-containing proteins and disrupts the activity of antioxidant selenoenzymes such as glutathione peroxidase and thioredoxin reductase, resulting in mitochondrial dysfunction, excessive oxidative stress, and pancreatic β-cell injury. These effects impair insulin secretion and glucose homeostasis. Supporting these mechanistic findings, a prospective cohort study involving American young adults reported that individuals with the highest mercury exposure had a 65% greater risk of developing diabetes than those with the lowest exposure levels,

while higher mercury concentrations were also associated with reduced pancreatic β-cell function, indicating impaired insulin secretory capacity.[45]

Diabetes mellitus is associated with exposure to cadmium and arsenic which have been shown to impair glucose metabolism and disturb hepatic glucose homeostasis. These heavy metals lowered the activity of enzymes critical for glycolysis, glycogenesis, and gluconeogenesis, resulting in dysregulation of blood glucose levels and metabolic dysfunction. They also reduced antioxidant defense mechanisms and increased reactive oxygen species production, resulting in oxidative stress and damage to the pancreas, liver, kidney, and muscle tissues.[75] Cadmium (Cd) exposure significantly disrupts the integrity of the intestinal barrier and alters the gut microbiota composition in an experiment with mice by Liu et al In intestinal epithelial cells, cadmium exposure lowered the expression and shifted the positioning of tight junction proteins, including ZO-1, ZO-2, JAM-A, occludin, and claudin-1. The function of the gut barrier and intestinal were negatively affected by these changes, which increased intestinal permeability[46] cadmium is known to induce excessive intracellular reactive oxygen species generation and mitochondrial dysfunction, leading to oxidative stress-mediated damage to intestinal epithelial cells. Elevated ROS levels activate redox-sensitive signaling pathways, including NF-κB and mitogen-activated protein kinase (MAPK) cascades, which suppress the expression and proper assembly of tight junction proteins such as ZO-1, occludin, and claudins. Consequently, disruption of epithelial tight junctions increases paracellular permeability, facilitating the translocation of bacterial endotoxins such as lipopolysaccharide (LPS) into the circulation and promoting chronic low-grade inflammation, metabolic endotoxemia, and insulin resistance.[76,77] These findings suggest that cadmium-induced oxidative stress and gut barrier dysfunction represent important mechanistic links between heavy metal exposure, gut dysbiosis, and T2DM pathogenesis.

Sex-Specific Effects of EDC Exposure

Sex-specific differences may modify the metabolic effects of EDC exposure. Epidemiological studies have reported sex-dependent associations for several EDCs, although the direction and magnitude of these differences vary according to the chemical, metabolic outcome, and study population. For BPA, associations with insulin levels, β-cell function, and insulin resistance have been reported to be stronger among men than women in a population-based analysis of US adults.[66] For PFAS, the evidence is more heterogeneous. A population-based study reported female-specific associations between several PFASs and insulin- and sex-hormone-related measures, with n-PFOA and PFHxS contributing substantially to the observed mixture associations in women.[78] In contrast, another NHANES-based study reported a positive association between serum PFOA and diabetes prevalence in men, but not women.[35] Conversely, two population-based Swedish cohorts reported an inverse association between PFOA and prevalent diabetes and changes in fasting glucose among women, together with a significant sex interaction.[79] These findings indicate that the direction and magnitude of sex modification may differ according to the individual EDC, metabolic outcome, exposure level, and study population. Such differences may reflect sex-related variation in hormone signaling, body composition, metabolism and elimination of EDCs, as well as differences in exposure sources and patterns. The available evidence remains inconsistent, and differences in study populations, exposure levels, outcome definitions, and potential confounding factors limit direct comparison across studies. Therefore, sex should be considered an important potential effect modifier in future epidemiological and mechanistic investigations of EDC-related metabolic dysfunction.

Potential Confounding and Reverse Causation

Interpretation of associations between EDC exposure and metabolic disease requires consideration of potential confounding and reverse causation. Obesity and diabetes may themselves influence the internal distribution, metabolism, and elimination of certain EDCs. For example, changes in adipose tissue mass may affect the distribution and storage of lipophilic chemicals, while metabolic dysfunction may alter the clearance of some compounds. Consequently, higher measured concentrations of EDCs in individuals with obesity or diabetes may not necessarily reflect greater external exposure alone. In addition, factors such as age, sex, body mass index, diet, smoking, physical activity, socioeconomic status, and co-exposure to other chemicals may influence both EDC exposure and metabolic outcomes. Therefore, associations observed in observational studies should be interpreted cautiously.

Molecular Mechanisms Linking Endocrine-Disrupting Chemicals and Diabetes

Insulin Resistance

Insulin resistance is one of the most important mechanisms linking endocrine disruptors with diabetes mellitus. Under physiological conditions, insulin activates insulin receptor substrate (IRS)-1/2, phosphatidylinositol-3 kinase (PI3K), and protein kinase B (Akt) signalling pathways that regulate glucose uptake and metabolism. Following insulin receptor activation, IRS-1 undergoes tyrosine phosphorylation, which activates PI3K, leading to Akt activation. Activated Akt in turn facilitates the translocation of glucose transporter type 4 (GLUT4)-containing vesicles from intracellular storage compartments to the plasma membrane of skeletal muscle and adipose cells, thereby facilitating glucose uptake and maintaining glucose homeostasis.[80,81] EDCs including BPA, PFAS, and phthalates impair IRS-1/PI3K/Akt signalling and reduce glucose transporter type 4 translocation in skeletal muscle and adipose tissue, thereby decreasing glucose uptake and increasing hyperglycemia.[82]

Several EDCs have also been reported to activate stress-responsive kinases such as c-Jun N-terminal kinase (JNK), inhibitor of nuclear factor kappa-B kinase (IKKβ), and p38 MAPK, resulting in serine phosphorylation of IRS proteins and attenuation of insulin signalling.[83,84] Reduced adiponectin secretion and increased leptin resistance induced by endocrine disruptors further aggravate insulin resistance and metabolic dysfunction.[85,86] Mitochondrial dysfunction and increased reactive oxygen species production may exacerbate insulin resistance by promoting oxidative stress and lipid accumulation in metabolic tissues.[87] Impaired insulin sensitivity is also a result of mitochondrial malfunction, which increases lipid accumulation in metabolic tissues and reduces ATP production. Thus, long-term low-dose EDC exposure has been closely linked to poor glucose homeostasis and a higher risk of type 2 diabetes.[88]

Pancreatic β-Cell Dysfunction

Pancreatic β-cells are particularly vulnerable to endocrine disruptor-induced damage due to their limited antioxidant capacity. Recent studies show that BPA, PFAS, and phthalates reduce insulin production by causing oxidative stress, mitochondrial injury, calcium dysregulation, and endoplasmic reticulum stress.[89]

EDCs alter mitochondrial membrane potential and reduce the amount of ATP needed to produce glucose-stimulated insulin secretion. Persistent exposure stimulates apoptotic signaling pathways through caspase activation, Bax/Bcl-2 imbalance, and DNA fragmentation, resulting in a loss of β-cell and insulin synthesis.[88] Endocrine disruptors can disrupt β-cell physiology by affecting calcium signaling, insulin gene transcription, and mitochondrial membrane integrity.[22] Experimental studies additionally indicate that endocrine disruptors alter transcription factors involved in pancreatic development and insulin gene expression, thereby impairing β-cell identity and long-term glucose regulation.

Oxidative Stress and Mitochondrial Dysfunction

Oxidative stress is a major mechanism underlying EDC-induced metabolic dysfunction. Endocrine disruptors increase the production of reactive oxygen species, including superoxide anions, hydroxyl radicals, and hydrogen peroxide, resulting in oxidative damage to proteins, lipids, and DNA.[90]

Mitochondria are important targets of endocrine disruptor toxicity. Impaired mitochondrial electron transport chain activity enhances ROS generation and reduces ATP synthesis, thereby impairing insulin signaling and glucose metabolism. Excess ROS also activates redox-sensitive pathways including NF-κB, MAPKs, and Nrf2/Keap1 signaling, which contribute to chronic inflammation and insulin resistance.[91]

Lipid peroxidation and mitochondrial injury induced by EDCs further aggravate pancreatic β-cell dysfunction and endothelial damage associated with diabetes complications. Recent evidence suggests that mitochondrial oxidative stress induced by endocrine disruptors is strongly associated with impaired metabolic flexibility and progression of insulin resistance.[92]

Chronic Inflammation

Chronic low-grade inflammation is a hallmark of obesity and type 2 diabetes and plays a critical role in endocrine disruptor-induced metabolic dysfunction. Exposure to EDCs stimulates production of inflammatory cytokines including tumor necrosis

factor-alpha, interleukin-6, interleukin-1β, and monocyte chemoattractant protein-1 (MCP-1).[93] EDC exposure induces oxidative stress, lipotoxicity, and Damage-associated molecular patterns (DAMPs) that activate toll-like receptor 4 (TLR4) signaling in adipocytes, macrophages, and hepatocytes. When TLR4 is activated, it recruits adaptor proteins such as myeloid differentiation primary response protein 88, leading to activation of the IκB kinase (IKK) complex. Activation of IKK phosphorylates inhibitor of κB, targeting it for degradation and releasing nuclear factor-kappa B for translocation into the nucleus. The nuclear NF-κB subsequently upregulates transcription of pro-inflammatory cytokines such as TNF-α, IL-6, IL-1β, and MCP-1, leading to accentuated local and systemic inflammatory responses.[94]

Activation of NF-κB and toll-like receptor (TLR2/TLR4) signaling pathways impairs insulin receptor signaling through inhibitory phosphorylation of IRS proteins. Macrophage infiltration into adipose tissue and liver amplifies inflammatory responses and contributes to adipose dysfunction and hepatic insulin resistance.[95]

Epigenetic Modifications

Recent evidence indicates that endocrine disruptors induce persistent epigenetic modifications that influence metabolic disease susceptibility. Epigenetic mechanisms include DNA methylation, histone modification, chromatin remodeling, and dysregulation of microRNAs involved in glucose metabolism and insulin signalling.[96] Environmental toxicants can alter the methylation status of genes involved in insulin signalling, glucose metabolism, inflammation, and pancreatic β-cell function, thereby promoting insulin resistance and metabolic dysfunction.[97,98]

Increased DNA methylation of the *PDX1* gene in pancreatic islets has been associated with reduced insulin secretion and impaired β-cell activity in T2DM patients.[99] Similarly, Liu et al (2021) reported that abnormal epigenetic regulation of *PDX1* contributes significantly to pancreatic dysfunction and glucose intolerance.[100]

Beyond gene-specific methylation changes, BPA has been shown to induce epigenetic alterations at the genome-wide level. Miao et al reported that occupational BPA exposure was significantly associated with LINE-1 hypomethylation in human spermatozoa, with urinary BPA concentrations inversely correlated with LINE-1 methylation levels.[101] Because LINE-1 methylation is widely regarded as a surrogate marker of global DNA methylation status, these findings suggest that BPA exposure may induce widespread epigenetic reprogramming extending beyond individual genes and potentially affecting broader regulatory networks involved in metabolic homeostasis and disease susceptibility.[102]

Additionally, environmental pollutants and EDC exposure cause histone acetylation and deacetylation abnormalities leading to altered chromatin structure and activation of inflammatory pathways such as PI3K/Akt and MAPK signaling.[103] These pathways are highly connected to oxidative stress, mitochondrial dysfunction, and chronic inflammation, all of which contribute to progress of diabetes. In addition, EDC-mediated diabetes problems have been associated with non-coding RNAs including MALAT1 and miR-21 which regulate fibrosis, inflammatory responses, and cellular stress pathways.[104] These results indicate that environmental toxicants may cause insulin resistance, β-cell dysfunction, and T2DM through epigenetic changes. Figure 1 depicts the potential pathways linking Endocrine-Disrupting Chemical exposure to obesity and type 2 diabetes.

Gut Microbiota and Endocrine Disruptors

The gut microbiota has been recently recognized as a major regulator of metabolic health, associated with obesity, insulin resistance, and type 2 diabetes. Recent studies have reported that endocrine-disrupting chemicals alter gut microbial communities, and their diversity and activity are modulated by EDCs; the gut microbiota is known to play a role by microbiome-mediated pathways to affect metabolic dysfunction that result in metabolic imbalance via microbiome pathways. Thus, affecting glucose homeostasis and insulin sensitivity. Bacteria, fungi, viruses, and archaea are all key microbes facilitating digestion, absorption of nutrients, the immune system, production of vitamins, and maintaining gut barrier.[105] *Firmicutes* and *Bacteroidetes* are the essential bacterial phyla in the human gut, followed by *Actinobacteria* and *Proteobacteria* in lower proportions. A good microbial environment is crucial for metabolic control and immune system modulation. The gut microbiota particularly produces metabolites, including short-chain fatty acids such as acetate, propionate, and butyrate, that facilitate glucose metabolism, lipid metabolism, appetite, and inflammatory responses.[106]

 https://doi.org/10.2147/DMSO.S636877

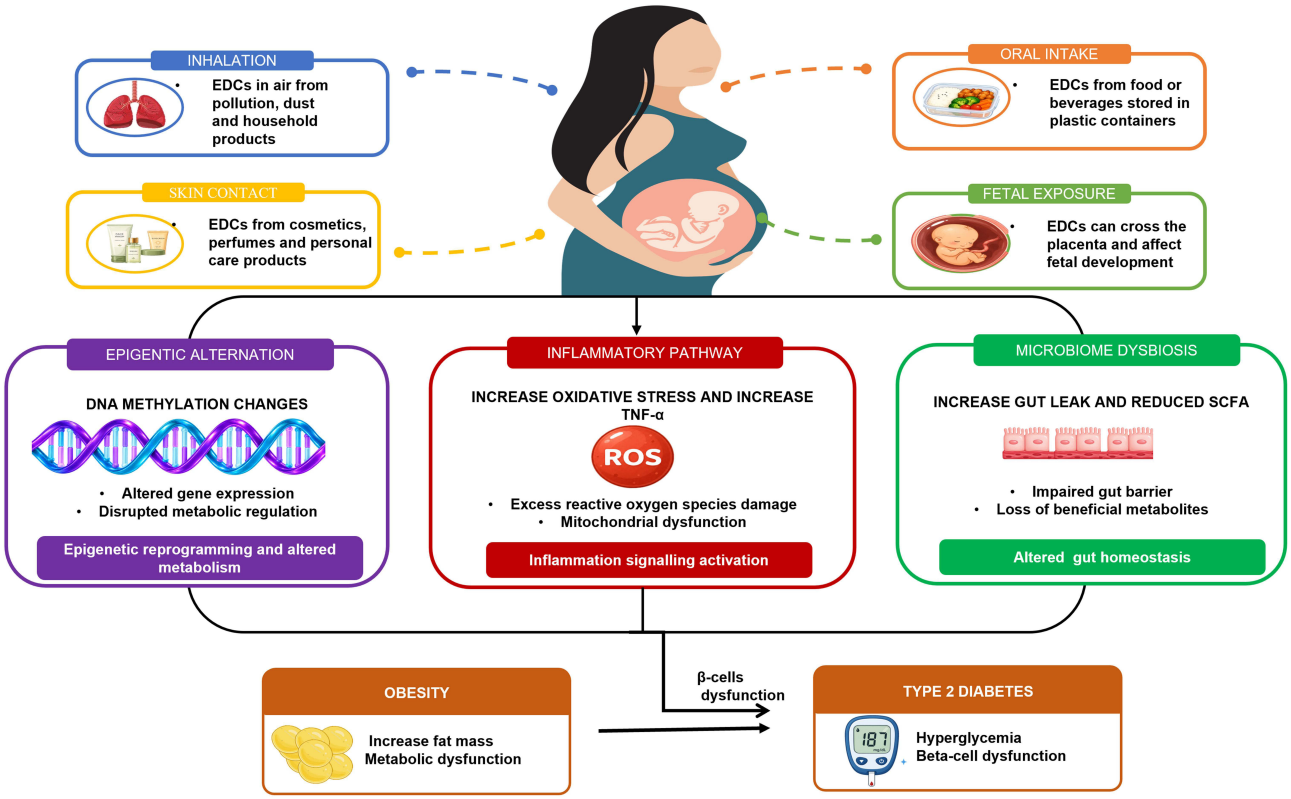

Figure 1 Potential pathways linking endocrine-disrupting chemical (EDC) exposure to obesity and type 2 diabetes mellitus. EDCs may enter the body through inhalation, oral intake, skin contact, and prenatal exposure. Exposure may contribute to metabolic dysfunction through interconnected pathways involving epigenetic alterations, oxidative stress and inflammation, and gut microbiota dysbiosis. These alterations may promote increased fat accumulation, metabolic dysfunction, hyperglycemia, and β-cell dysfunction, ultimately contributing to the development of type 2 diabetes mellitus.
Abbreviations: EDC, endocrine-disrupting chemical; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-alpha; SCFA, short-chain fatty acid.

Several health issues, including diabetes, insulin resistance, obesity and chronic inflammation, have been linked to an imbalance of microbes in the gut. Alterations in the *Firmicutes/Bacteroidetes* ratio and reduced populations of beneficial SCFA-producing bacteria are commonly observed in metabolic disorders.

EDC-Induced Gut Dysbiosis

Endocrine-disrupting chemicals significantly influence gut microbial composition and diversity. Chronic exposure to BPA, phthalates, PFAS, pesticides, and heavy metals may alter the relative abundance of beneficial and pathogenic bacterial species, resulting in gut dysbiosis.[12]

Several studies have demonstrated that EDC exposure alters the *Firmicutes/Bacteroidetes* ratio, which is frequently associated with obesity and metabolic syndrome. Increased *Firmicutes* abundance may enhance energy extraction from food and promote adiposity, whereas reductions in *Bacteroidetes* may impair carbohydrate metabolism and SCFA production.[13]

EDCs also reduce populations of beneficial bacteria such as *Lactobacillus* and *Bifidobacterium*, while increasing opportunistic pathogenic bacteria. Such alterations have been proposed to impair intestinal barrier integrity and increase gut permeability, commonly referred to as “leaky gut”. Increased intestinal permeability allows translocation of bacterial endotoxins such as lipopolysaccharides into systemic circulation, leading to metabolic endotoxemia and chronic inflammation.[107]

In addition, endocrine disruptors interfere with microbial metabolism and bile acid regulation. Reduced production of SCFAs may impairs glucose homeostasis, insulin sensitivity, and anti-inflammatory signaling pathways. Butyrate deficiency may also weaken intestinal epithelial integrity and increase inflammatory responses.[108]

Recent evidence suggests that EDC-induced dysbiosis extends beyond broad alterations in the *Firmicutes/Bacteroidetes* ratio and involves specific microbial taxa associated with metabolic health. Experimental studies have demonstrated that exposure to bisphenol A and other EDCs significantly alters the abundance of key bacterial genera and species in a sex- and age-dependent manner. Javurek et al reported that BPA and ethinyl estradiol exposure increased the abundance of *Akkermansia*, *Prevotellaceae*, *Bacteroides*, *Erysipelotrichaceae*, *Methanobrevibacter*, and *Sutterella*, microbial taxa previously associated with obesity, inflammatory bowel disease, and metabolic disorders.[109] Notably, BPA-induced microbial alterations appear to differ between sexes, with male mice exhibiting a greater enrichment of *Prevotellaceae* compared with females. Lai et al further demonstrated that juvenile female mice exposed to BPA exhibited increased abundance of *Turicibacter*, *Oscillospira*, *Ruminococcus*, *Jeotgalicoccus*, and members of the *Lachnospiraceae* family, suggesting that EDC-induced microbial perturbations may contribute to immune dysregulation and diabetes susceptibility.[110] In a rabbit model, Reddivari et al showed that perinatal BPA exposure significantly reduced beneficial SCFA-producing taxa, including members of the *Ruminococcaceae* family, *Oscillospira* spp., and *Odoribacter* spp., resulting in decreased SCFA production and elevated circulating lipopolysaccharide concentrations. The same study reported that increased abundance of *Methanobrevibacter* spp. was associated with enhanced intestinal permeability and chronic hepatic and colonic inflammation.[111] Supporting these findings, Koestel et al, observed positive correlations between serum BPA concentrations and increased abundance of *Bacteroides ovatus*, *Prevotella* spp., *Ruminococcus* spp., and *Cetobacterium somerae* in dogs[112] indicating that BPA-induced microbial alterations occur across multiple species. Collectively, these microbial alterations promote gut barrier dysfunction, chronic inflammation, impaired SCFA production, insulin resistance, and ultimately the progression of type 2 diabetes.

Gut Microbiota in Diabetes

Gut microbiota plays a central role in the development of insulin resistance and type 2 diabetes through regulation of inflammatory pathways, glucose metabolism, and host energy balance. Dysbiosis alters microbial metabolite production and promotes systemic inflammation associated with metabolic dysfunction.[113]

One of the major mechanisms linking gut microbiota with diabetes is metabolic endotoxemia. Increased intestinal permeability allows LPS derived from gram-negative bacteria to enter circulation and activate toll-like receptor-4 signaling pathways. Activation of inflammatory mediators including nuclear factor-kappa B, tumor necrosis factor-alpha, and interleukin-6 contributes to insulin resistance and chronic low-grade inflammation.[114]

Reduced abundance of SCFA-producing bacteria is another important feature of diabetic dysbiosis. SCFAs, especially acetate, propionate, and butyrate, activate G protein-coupled receptors and other signalling pathways.[115,116] SCFAs also suppress inflammatory signalling and promote regulatory immune responses. Butyrate serves as a primary energy source for intestinal epithelial cells and helps maintain gut barrier integrity by strengthening tight junction proteins and reducing intestinal permeability.[106] Changes in the metabolism of bile acids due to intestinal dysbiosis play an additional role in metabolic dysfunctions.[117,118]

Increasing data demonstrate that endocrine-disrupting chemical cause metabolic dysfunction via gut microbiota-mediated pathways. EDC-induced dysbiosis affects the *Firmicutes/Bacteroidetes* ratio, decreases beneficial SCFA-producing bacteria, raises intestinal permeability, and promotes metabolic endotoxemia and chronic inflammation. These changes provide a considerable contribution to insulin resistance, obesity, and diabetes progression.

Bile Acid–FXR/TGR5 Signaling in Metabolic Regulation

In addition to SCFAs, bile acids serve as important signaling molecules linking the gut microbiota to host metabolism. Intestinal microorganisms regulate the conversion of primary bile acids into secondary bile acids, which function as ligands for the farnesoid X receptor (FXR) and Takeda G-protein-coupled receptor 5 (TGR5). Dysbiosis-induced alterations in bile acid composition can disrupt FXR signaling in both the intestine and liver. Abnormal FXR activation impairs fibroblast growth factor 19 -mediated feedback regulation, resulting in increased hepatic gluconeogenesis and elevated expression of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase, thereby increasing hepatic glucose output and promoting hyperglycemia. Furthermore, activation of TGR5 on intestinal enteroendocrine L-cells stimulates secretion of glucagon-like peptide-1, enhancing insulin secretion, improving insulin sensitivity, and reducing postprandial glucose excursions.[119,120] Therefore, EDC-induced

alterations in gut microbial communities may contribute to metabolic dysfunction through disruption of the bile acid–FXR/TGR5 signaling axis, providing an additional mechanistic link between gut dysbiosis and T2DM progression.

Probiotics as a Therapeutic Strategy Against EDC-Induced Metabolic Disruption in Type 2 Diabetes

The interplay between endocrine-disrupting chemicals, gut microbiota dysbiosis, and type 2 diabetes mellitus has prompted growing interest in probiotic supplementation as a potential protective strategy. EDCs are increasingly recognized as microbiota-disrupting chemicals, and their capacity to alter gut microbial composition, reduce microbial diversity, impair short-chain fatty acid production, and promote gut barrier dysfunction creates a pathological environment conducive to insulin resistance and metabolic disease.[121] Probiotic intervention targeting this EDC–microbiota–metabolic axis therefore represents a biologically plausible and emerging therapeutic approach.

The most direct experimental evidence linking probiotics, EDC exposure, and T2DM comes from the work of Baralić et al (2020, 2021), Their initial in vivo study demonstrated that a multi-strain probiotic containing *Saccharomyces boulardii*, *Lactobacillus rhamnosus*, and *Lactobacillus plantarum* LP 6595, and *Lactobacillus plantarum* HEAL9 strains attenuated the toxic effects of a combined exposure to bis(2-ethylhexyl) phthalate, dibutyl phthalate, and bisphenol A in Wistar rats, with significant protective effects on serum glucose levels, lipid status, liver and kidney function, hormonal parameters, and systemic inflammation.[122] Their subsequent bioinformatics-integrated in vivo study further identified 44 mutual genes shared between DEHP, DBP, and BPA co-exposure and T2DM pathogenesis, with apoptosis and oxidative stress highlighted as the predominant mechanistic pathways. Crucially, the multi-strain probiotic ameliorated mixture-induced redox status changes, including total oxidative status, superoxide dismutase, and sulfhydryl group alterations in rat pancreatic tissue, suggesting a direct protective effect on pancreatic beta-cell integrity.[123] These findings are particularly noteworthy given that combined EDC exposures through real-world dietary routes are the norm rather than the exception, and that mixture toxicity may produce more pronounced metabolic perturbations than single-chemical exposures. Beyond phthalates and BPA, probiotic therapy has also demonstrated protective efficacy against Polybrominated Diphenyl Ether -induced metabolic reprogramming. A 2024 study by Curras-Collazo et al demonstrated for the first time that maternal supplementation with *Limosilactobacillus reuteri* protected offspring against PBDE-induced dysregulation of glucose homeostasis in a sex-dependent manner, acting through restoration of gut microbiome richness and diversity.[14] These findings are consistent with the known anti-inflammatory and antioxidant properties of *Lactobacillus* strains, which protect insulin-secreting cells and maintain gut barrier integrity. Mechanistically, probiotic supplementation may counteract EDC-induced metabolic dysfunction through several interconnected pathways. One of the earliest consequences of EDC exposure is disruption of intestinal barrier integrity, characterized by reduced expression of tight junction proteins such as zonula occludens-1, occludin, and claudin-1, leading to increased intestinal permeability and translocation of lipopolysaccharide into the circulation. Certain *Lactobacillus* strains, particularly *L. rhamnosus* and *L. plantarum*, have been shown to restore tight junction protein expression, reinforce epithelial barrier function, and reduce endotoxemia, thereby limiting activation of inflammatory pathways associated with insulin resistance.[124,125] Probiotics also promote recovery of SCFA-producing bacteria, including butyrate-producing taxa that are frequently depleted following EDC exposure. Restoration of SCFA production contributes to improved glucose homeostasis through activation of G-protein-coupled receptors GPR41 and GPR43 on intestinal enteroendocrine cells, stimulating secretion of glucagon-like peptide-1 and peptide YY, enhancing insulin sensitivity, and improving energy metabolism.[126,127] Furthermore, butyrate functions as a potent histone deacetylase (HDAC) inhibitor, suppressing transcription of pro-inflammatory genes and attenuating activation of the nuclear factor-kappa B signaling pathway. Through these actions, probiotics reduce the production of inflammatory mediators such as TNF-α, IL-6, and IL-1β, thereby alleviating chronic low-grade inflammation that contributes to T2DM pathogenesis.[128] At the mechanistic level, certain probiotic strains have also been shown to directly degrade EDCs; notably, *Lactobacillus reuteri* was found to degrade BPA at a rate of up to 69.83%, while *Bifidobacterium breve* and *Lactobacillus casei* reduced intestinal BPA absorption by facilitating fecal excretion, with probiotic-supplemented rats demonstrating 2.4-fold greater BPA excretion compared to controls.[129,130] This capacity for direct EDC biotransformation adds an additional dimension to the therapeutic potential of probiotics beyond mere microbiota modulation. In the context of T2DM independent of EDC exposure, probiotic supplementation has been shown to

improve glucose metabolism, reduce insulin resistance, enhance SCFA production, lower inflammatory markers including hsCRP, and improve lipid profiles.[131–133] The convergence of these mechanisms with those disrupted by EDC exposure suggests a strong rationale for probiotic use specifically in EDC-exposed populations at risk of T2DM. However, it is important to acknowledge that the current evidence base remains predominantly preclinical, derived from animal models and in vitro studies. Human clinical trials specifically examining probiotic intervention in EDC-exposed populations with metabolic outcomes are largely absent, representing a critical gap in the literature that future research must address. Next-generation probiotics and live biotherapeutics targeting the EDC–gut microbiota–metabolic axis are an emerging frontier, and sex-specific differences in microbiome responses to such interventions warrant further investigation. Figure 2 depicts the role of probiotics in attenuating EDC-Induced type 2 Diabetes. Table 3 summarises the probiotics, EDC's and type 2 diabetes.

Conclusion

The escalating global prevalence of type 2 diabetes can no longer be attributed solely to genetic and lifestyle, as mounting evidence increasingly implicates environmental endocrine-disrupting chemicals as significant contributors to metabolic dysfunction. EDCs such as phthalates, bisphenol A, persistent organic pollutants, and heavy metals interfere with hormonal signaling, glucose homeostasis, lipid metabolism, and pancreatic β-cell function through multiple converging mechanisms including oxidative stress, mitochondrial impairment, chronic low-grade inflammation, and insulin resistance. The gut microbiome has emerged as a critical mediator of EDC-induced metabolic dysregulation, with chemical exposures disturb microbial diversity, alter *Firmicutes/Bacteroidetes* ratios, impair short-chain fatty acid production, and compromise intestinal barrier integrity, collectively driving metabolic endotoxemia and perpetuating inflammatory cascades that undermine glucose metabolism. The complexity of these interactions is further amplified in real-world conditions, where humans are not exposed to single compounds in isolation but rather to complex mixtures of

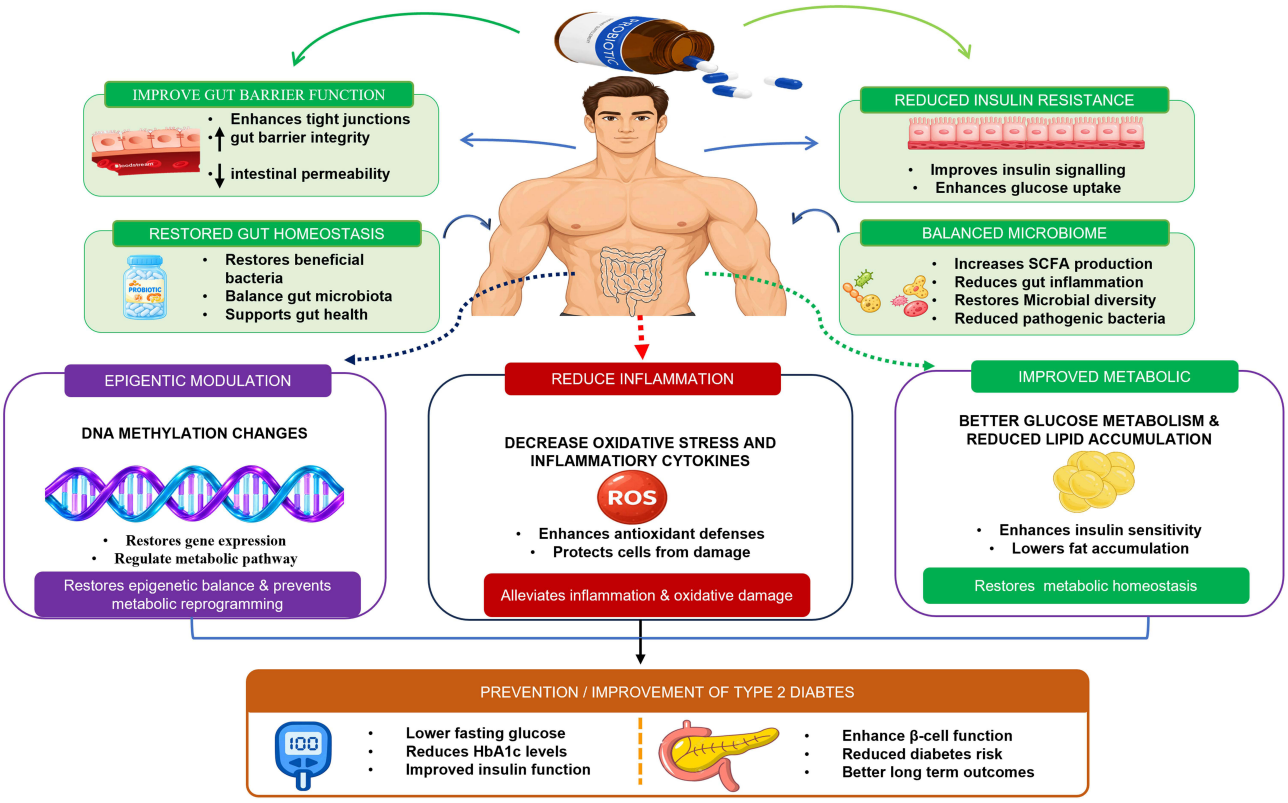

Figure 2 Role of probiotics in attenuating EDC-Induced metabolic dysfunction and type 2 diabetes. Probiotic supplementation may modulate the EDC–gut microbiota–metabolic axis by improving gut barrier function, restoring microbial homeostasis, reducing insulin resistance, modulating epigenetic alterations, and attenuating inflammation and oxidative stress. These effects may contribute to improved glucose metabolism, reduced lipid accumulation, and restoration of metabolic homeostasis, potentially supporting the prevention or improvement of type 2 diabetes.
Abbreviations:EDC, endocrine-disrupting chemical; ROS, reactive oxygen species; SCFA, short-chain fatty acid; HbA1c, glycated hemoglobin.

https://doi.org/10.2147/DMSO.S636877

Table 3 Studies on Probiotics, Gut Microbiota, and EDC-Induced Metabolic Alterations in Type 2 Diabetes

Study Type	EDC	Probiotic Strain(s)	Model	Key Findings	Metabolic Outcome	Ref
EDC+ Probiotic + T2DM Studies						
Animal	DEHP, DBP, BPA mixture	*S. boulardii, L. rhamnosus, L. plantarum* (multi-strain)	Wistar rats	Probiotic attenuated mixture-induced systemic inflammation; protected liver, kidney, lipid status, and serum glucose; annulled hormonal and biochemical changes	Reduced serum glucose, improved lipid profile	[122]
Animal	DEHP, DBP, BPA mixture	*S. boulardii, L. rhamnosus, L. plantarum* (multi-strain)	Wistar rats + bioinformatics	44 mutual genes linked to T2DM identified; apoptosis and oxidative stress as key mechanisms; probiotic ameliorated redox changes (TOS, SOD, SH groups) in pancreatic tissue	Pancreatic beta-cell protection, reduced oxidative stress	[123]
Animal	PBDEs (DE-71 mixture)	*Limosilactobacillus reuteri* (LR)	C57BL/6N mice (maternal–offspring)	Maternal LR supplementation protected gut microbiome diversity, restored glucose homeostasis in offspring; effects were sex-dependent; mitigated PBDE-induced leptin reduction	Improved glucose homeostasis, restored microbial diversity	[14]
EDC Degradation/elimination by probiotics						
In vitro	BPA	*Lactobacillus reuteri*	In vitro	Direct BPA degradation rate up to 69.83% demonstrated; cell-surface hydrophobicity implicated in adsorption mechanism	Direct EDC biotransformation	[129]
Animal	BPA	*Bifidobacterium breve, Lactobacillus casei*	Wistar rats	Probiotics reduced intestinal BPA absorption; fecal BPA excretion was 2.4× higher in probiotic group; BPA blood AUC significantly decreased	Reduced systemic BPA burden	[130]

environmental contaminants that may exert additive or synergistic toxic effects, as evidenced by experimental findings demonstrating that co-exposure to DEHP, DBP, and BPA produced more pronounced oxidative damage in pancreatic tissue than individual exposures alone. These observations underscore the urgent need to move beyond single-chemical risk assessment frameworks and adopt a more integrative approach to understanding the cumulative metabolic burden imposed by environmental exposures across the life course.

Two foundational gaps constrain progress in this field. First, no unified mechanistic framework currently exists to explain how EDC-induced microbiome disruption and direct endocrine interference converge to drive metabolic dysfunction. Existing studies address these axes separately rather than as an integrated system. Second, the near-total reliance on cross-sectional designs means that the temporal sequence between EDC exposure, microbiome alteration, and type 2 diabetes onset remains unestablished in human populations. Closing these gaps requires longitudinal cohort studies and multi-omics integration capable of capturing early biomarkers of metabolic risk, alongside mechanistic investigations to validate microbiome-based therapeutic targets. Human clinical trials evaluating probiotic interventions specifically in EDC-exposed populations remain lacking. The absence of human clinical evidence represents a fundamental translational gap between preclinical promise and actionable clinical recommendations, and underscores the urgency of rigorously designed trials in this area. Future research should therefore prioritize well-designed longitudinal and interventional studies, alongside individualized microbiome and metabolic profiling, to determine whether microbiota-targeted strategies can translate into clinically meaningful prevention or treatment of environmentally associated T2DM.

Data Sharing Statement

Data sharing is not applicable to this article as no data were created or analysed in this study.

Acknowledgments

This research was supported in part by the research grants from the Kaohsiung Chang Gung Memorial Hospital (grant number CMRPG8Q0772). The sponsor played no role in the study design, data collection, analysis, interpretation, writing of the report, or decision to submit the article for publication.

Author Contributions

Shun-Man Cheung, Chi-Yung Cheng, Chia-Te Kung and Venkata Chaithanya: Investigation, methodology, formal analysis, software, visualization, validation, and writing—original draft.

Kai-Fan Tsai, Wan-Ting Huang, Huey-Ling You and Shau-Hsuan Li: re-sources, visualization and writing—review and editing.

Wen-Chin Lee, Fu-Jen Cheng and Vinoth Kumar Ponnusamy: conceptualization, investigation, resources, supervision, and writing—review and editing.

All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

No funding was received for this study.

Disclosure

The authors declare no conflicts of interest.

References

1. IDF Diabetes Atlas Scientific Papers and Posters. IDF Diabetes Atlas. Available from: https://diabetesatlas.org/scientific-papersand-posters/. Accessed August 26, 2026.
2. Velmurugan G, Ramprasath T, Gilles M, Swaminathan K, Ramasamy S. Gut microbiota, endocrine-disrupting chemicals, and the diabetes epidemic. *Trends Endocrinol Metab*. 2017;28(8):612–625. doi:10.1016/j.tem.2017.05.001
3. Hampl R, Stárka L. Endocrine disruptors and gut microbiome interactions. *Physiol Res*. 2020;69(Suppl 2):S211. doi:10.33549/physiolres.934513
4. Song Y, Chou EL, Baecker A, et al. 内分泌干扰物, 2 型糖尿病危险因素以及糖尿病相关代谢特征: 一项系统回顾与 meta 分析 [Endocrine-disrupting chemicals, risk of type 2 diabetes, and diabetes-related metabolic traits: a systematic review and meta-analysis]. *J Diabetes*. 2016;8(4):516–532.
5. Heindel JJ, Newbold R, Schug TT. Endocrine disruptors and obesity. *Nat Rev Endocrinol*. 2015;11(11):653–661. doi:10.1038/nrendo.2015.163
6. La Merrill MA, Vandenberg LN, Smith MT, et al. Consensus on the key characteristics of endocrine-disrupting chemicals as a basis for hazard identification. *Nat Rev Endocrinol*. 2020;16(1):45–57. doi:10.1038/s41574-019-0273-8
7. Cui Y, Balshaw DM, Kwok RK, Thompson CL, Collman GW, Birnbaum LS. The exposome: embracing the complexity for discovery in environmental health. *Environ Health Perspect*. 2016;124(8):A137. doi:10.1289/EHP412
8. Sexton K, Hattis D. Assessing cumulative health risks from exposure to environmental mixtures-three fundamental questions. *Environ Health Perspect*. 2007;115(5):825.
9. Fabozzi G, Rebuzzini P, Cimadomo D, et al. Endocrine-disrupting chemicals, gut microbiota, and human (in) fertility-it is time to consider the triad. *Cells*. 2022;11(21):3335.
10. Gálvez-Ontiveros Y, Páez S, Monteagudo C, Rivas A. Endocrine disruptors in food: impact on gut microbiota and metabolic diseases. *Nutrients*. 2020;12(4):1158. doi:10.3390/nu12041158
11. Liu N, Yan X, Lv B, et al. A study on the association between gut microbiota, inflammation, and type 2 diabetes. *Appl Microbiol Biotechnol*. 2024;108(1):213. doi:10.1007/s00253-024-13041-5
12. Rosenfeld CS. Gut dysbiosis in animals due to environmental chemical exposures. *Front Cell Infect Microbiol*. 2017;7:396. doi:10.3389/fcimb.2017.00396
13. Claus SP, Guillou H, Ellero-Simatos S. The gut microbiota: a major player in the toxicity of environmental pollutants? *NPJ Biofilms Microbiomes*. 2016;2(1):16003. doi:10.1038/npjbiofilms.2016.3
14. Denys ME, Kozlova EV, Liu R, et al. Maternal probiotic supplementation protects against PBDE-induced developmental, behavior and metabolic reprogramming in a sexually dimorphic manner: role of gut microbiome. *Arch Toxicol*. 2025;99(1):423–446. doi:10.1007/s00204-024-03882-4
15. Birnbaum LS, Fenton SE. Cancer and developmental exposure to endocrine disruptors. *Environ Health Perspect*. 2003;111(4):389. doi:10.1289/ehp.5686
16. Kumar M, Sarma DK, Shubham S, et al. Environmental endocrine-disrupting chemical exposure: role in non-communicable diseases. *Front Public Health*. 2020;8:553850.
17. Casals-Casas C, Desvergne B. Endocrine disruptors: from endocrine to metabolic disruption. *Annu Rev Physiol*. 2011;73(1):135–162. doi:10.1146/annurev-physiol-012110-142200
18. Schug TT, Janesick A, Blumberg B, Heindel JJ. Endocrine disrupting chemicals and disease susceptibility. *J Steroid Biochem Mol Biol*. 2011;127(3–5):204–215. doi:10.1016/j.jsbmb.2011.08.007
19. Birnbaum LS. Environmental chemicals: evaluating low-dose effects. *Environ Health Perspect*. 2012;120(4):a143. doi:10.1289/ehp.1205179
20. Melnick R, Lucier G, Wolfe M, et al. Summary of the National toxicology program's report of the endocrine disruptors low-dose peer review. *Environ Health Perspect*. 2002;110(4):427.
21. Lee S, Lim Y, Kang Y, Jung K, Jee S. The association between blood concentrations of PCDD/DFs, DL-PCBs and the risk of type 2 diabetes mellitus and thyroid cancer in South Korea. *Int J Environ Res Public Health*. 2022;19(14):8745. doi:10.3390/ijerph19148745

22. Martínez-Pinna J, Sempere-Navarro R, Medina-Gali RM, et al. Endocrine disruptors in plastics alter β-cell physiology and increase the risk of diabetes mellitus. *Am J Physiol-Endoc M*. 2023;324(6):E488–E505. doi:10.1152/ajpendo.00068.2023
23. Lang IA, Galloway TS, Scarlett A, et al. Association of urinary bisphenol a concentration with medical disorders and laboratory abnormalities in adults. *JAMA*. 2008;300(11):1303–1310.
24. Soundararajan A, Prabu P, Mohan V, Gibert Y, Balasubramanyam M. Novel insights of elevated systemic levels of bisphenol-A (BPA) linked to poor glycemic control, accelerated cellular senescence and insulin resistance in patients with type 2 diabetes. *Mol Cell Biochem*. 2019;458 (1):171–183. doi:10.1007/s11010-019-03540-9
25. Shankar A, Teppala S. Relationship between urinary bisphenol a levels and diabetes mellitus. *J Clin Endocrinol Metab*. 2011;96 (12):3822–3826. doi:10.1210/jc.2011-1682
26. Angle BM, Do RP, Ponzi D, et al. Metabolic disruption in male mice due to fetal exposure to low but not high doses of bisphenol a (BPA): evidence for effects on body weight, food intake, adipocytes, leptin, adiponectin, insulin and glucose regulation. *Reprod Toxicol*. 2013;42:256–268. doi:10.1016/j.reprotox.2013.07.017
27. Wei J, Lin Y, Li Y, et al. Perinatal exposure to bisphenol a at reference dose predisposes offspring to metabolic syndrome in adult rats on a high-fat diet. *Endocrinology*. 2011;152(8):3049–3061. doi:10.1210/en.2011-0045
28. Mohanraj N, Prasanth S, Rajapriya P, et al. Bisphenol a accelerates the vascular complications in patients with type 2 diabetes mellitus through vascular calcification-a molecular approach. *Int Arch Occup Environ Health*. 2023;96(9):1291–1299.
29. Rancière F, Botton J, Slama R, et al. Exposure to bisphenol a and bisphenol S and incident type 2 diabetes: a case-cohort study in the French cohort DESIR. *Environ Health Perspect*. 2019;127(10):107013.
30. Zhang S, Cheng X, Jia C, et al. Association of serum phthalates exposure with incident type 2 diabetes risk in Chinese population: a nested case-control study. *Ecotoxicol Environ Saf*. 2023;265:115493.
31. Airaksinen R, Rantakokko P, Eriksson JG, Blomstedt P, Kajantie E, Kiviranta H. Association between type 2 diabetes and exposure to persistent organic pollutants. *Diabetes Care*. 2011;34(9):1972–1979. doi:10.2337/dc10-2303
32. Duan Y, Sun H, Han L, Chen L. Association between phthalate exposure and glycosylated hemoglobin, fasting glucose, and type 2 diabetes mellitus: a case-control study in China. *Sci Total Environ*. 2019;670:41–49. doi:10.1016/j.scitotenv.2019.03.192
33. Cardenas A, Hauser R, Gold DR, et al. Association of perfluoroalkyl and polyfluoroalkyl substances with adiposity. *JAMA Netw Open*. 2018;1 (4):e181493. doi:10.1001/jamanetworkopen.2018.1493
34. Su TC, Kuo CC, Hwang JJ, Lien GW, Chen MF, Chen PC. Serum perfluorinated chemicals, glucose homeostasis and the risk of diabetes in working-aged Taiwanese adults. *Environ Int*. 2016;88:15–22. doi:10.1016/j.envint.2015.11.016
35. He X, Liu Y, Xu B, Gu L, Tang W. PFOA is associated with diabetes and metabolic alteration in US men: National Health and Nutrition Examination Survey 2003-2012. *Sci Total Environ*. 2018;625:566–574. doi:10.1016/j.scitotenv.2017.12.186
36. Karnes C, Winquist A, Steenland K. Incidence of type II diabetes in a cohort with substantial exposure to perfluorooctanoic acid. *Environ Res*. 2014;128:78–83. doi:10.1016/j.envres.2013.11.003
37. Donat-Vargas C, Bergdahl IA, Tornevi A, et al. Perfluoroalkyl substances and risk of type II diabetes: a prospective nested case-control study. *Environ Int*. 2019;123:390–398.
38. Kim B, Park B, Kim CH, Kim S, Park B. Association between endocrine-disrupting chemical mixture and metabolic indices among children, adolescents, and adults: a population-based study in Korea. *Environ Pollut*. 2022;315:120399. doi:10.1016/j.envpol.2022.120399
39. Taylor KW, Novak RF, Anderson HA, et al. Evaluation of the association between persistent organic pollutants (POPs) and diabetes in epidemiological studies: a national toxicology program workshop review. *Environ Health Perspect*. 2013;121(7):774.
40. Arrebola JP, Pumarega J, Gasull M, et al. Adipose tissue concentrations of persistent organic pollutants and prevalence of type 2 diabetes in adults from Southern Spain. *Environ Res*. 2013;122:31–37.
41. Wang L, Liu X, Xiang C, et al. Exploring the mechanism link between endocrine disrupting chemicals and metabolic diseases: observational and GWAS evidence. *Ecotoxicol Environ Saf*. 2026;309:119742.
42. Liu S, Guo X, Wu B, Yu H, Zhang X, Li M. Arsenic induces diabetic effects through beta-cell dysfunction and increased gluconeogenesis in mice. *Sci Rep*. 2014;4(1):6894. doi:10.1038/srep06894
43. Leff T, Stemmer P, Tyrrell J, Jog R. Diabetes and exposure to environmental lead (pb). *Toxics*. 2018;6(3):54. doi:10.3390/toxics6030054
44. Feezan A, Afzal S, Shoaib SM, et al. Impact of lead and nickel contamination on metabolic health: associations with diabetes mellitus in a Pakistani cohort. *Emerg Contam*. 2025;11(1):100419.
45. He K, Xun P, Liu K, Morris S, Reis J, Guallar E. Mercury exposure in young adulthood and incidence of diabetes later in life: the CARDIA trace element study. *Diabetes Care*. 2013;36(6):1584–1589. doi:10.2337/dc12-1842
46. Liu Y, Li Y, Xia Y, Liu K, Ren L, Ji Y. The dysbiosis of gut microbiota caused by low-dose cadmium aggravate the injury of mice liver through increasing intestinal permeability. *Microorganisms*. 2020;8(2):211. doi:10.3390/microorganisms8020211
47. Alonso-Magdalena P, Vieira E, Soriano S, et al. Bisphenol a exposure during pregnancy disrupts glucose homeostasis in mothers and adult male offspring. *Environ Health Perspect*. 2010;118(9):1243.
48. Thayer KA, Heindel JJ, Bucher JR, Gallo MA. Role of environmental chemicals in diabetes and obesity: a National toxicology program workshop review. *Environ Health Perspect*. 2012;120(6):779. doi:10.1289/ehp.1104597
49. Darbre PD. Overview of air pollution and endocrine disorders. *Int J Gen Med*. 2018:191–207.
50. Lind PM, Lind L. Endocrine-disrupting chemicals and risk of diabetes: an evidence-based review. *Diabetologia*. 2018;61(7):1495–1502. doi:10.1007/s00125-018-4621-3
51. Meeker JD. Human epidemiologic studies of exposure to endocrine-disrupting chemicals and altered hormone levels. *Endocr-Disrupting Chemicals Food*. 2009:36–57.
52. Rudel RA, Gray JM, Engel CL, et al. Food packaging and bisphenol a and bis (2-ethyhexyl) phthalate exposure: findings from a dietary intervention. *Environ Health Perspect*. 2011;119(7):914.
53. Salthammer T, Zhang Y, Mo J, Koch HM, Weschler CJ. Assessing human exposure to organic pollutants in the indoor environment. *Angew Chem Int Ed*. 2018;57(38):12228–12263. doi:10.1002/anie.201711023
54. Weschler CJ, Salthammer T, Fromme H. Partitioning of phthalates among the gas phase, airborne particles and settled dust in indoor environments. *Atmos Environ*. 2008;42(7):1449–1460. doi:10.1016/j.atmosenv.2007.11.014

55. Dang H, Zhang P, Zheng J, Chen S, Wei W, Wang X. Long-term inhalation exposure: a model for phthalate accumulation in the respiratory tract. *Ecotoxicol Environ Saf*. 2024;286:117207. doi:10.1016/j.ecoenv.2024.117207
56. Anderson SE, Meade BJ. Potential health effects associated with dermal exposure to occupational chemicals. *Environ Health Insights*. 2014;8: EHI–S15258.
57. Heindel JJ, Blumberg B, Cave M, et al. Metabolism disrupting chemicals and metabolic disorders. *Reprod Toxicol*. 2017;68:3–33. doi:10.1016/j.reprotox.2016.10.001
58. Rundle A, Hoepner L, Hassoun A, et al. Association of childhood obesity with maternal exposure to ambient air polycyclic aromatic hydrocarbons during pregnancy. *Am J Epidemiol*. 2012;175(11):1163–1172.
59. Duan YiShuang DY, Yao YiMing YY, Wang Bin WB, et al. Association of urinary concentrations of bisphenols with type 2 diabetes mellitus: a case-control study; 2018.
60. Shu X, Tang S, Peng C, et al. Bisphenol a is not associated with a 5-year incidence of type 2 diabetes: a prospective nested case-control study. *Acta Diabetol*. 2018;55(4):369–375.
61. Bi Y, Wang W, Xu M, et al. Diabetes genetic risk score modifies effect of bisphenol a exposure on deterioration in glucose metabolism. *The J Clin Endocrinol*. 2016;101(1):143–150.
62. Andra SS, Kalyvas H, Andrianou XD, Charisiadis P, Christophi CA, Makris KC. Preliminary evidence of the association between monochlorinated bisphenol a exposure and type II diabetes mellitus: a pilot study. *J Environ Sci Health Part A*. 2015;50(3):243–259. doi:10.1080/10934529.2015.981111
63. Ahmadkhaniha R, Mansouri M, Yunesian M, et al. Association of urinary bisphenol a concentration with type-2 diabetes mellitus. *J Environ Health Sci Eng*. 2014;12(1):64.
64. Ning G, Bi Y, Wang T, et al. Relationship of urinary bisphenol a concentration to risk for prevalent type 2 diabetes in Chinese adults: a cross-sectional analysis. *Ann Intern Med*. 2011;155(6):368–374. doi:10.7326/0003-4819-155-6-201109200-00005
65. Cardenas A, Gold DR, Hauser R, et al. Plasma concentrations of per-and polyfluoroalkyl substances at baseline and associations with glycemic indicators and diabetes incidence among high-risk adults in the diabetes prevention program trial. *Environ Health Perspect*. 2017;125(10):107001.
66. Beydoun HA, Khanal S, Zonderman AB, Beydoun MA. Sex differences in the association of urinary bisphenol-A concentration with selected indices of glucose homeostasis among US adults. *Ann Epidemiol*. 2014;24(2):90–97.
67. Aekplakorn W, Chailurkit L, Ongphiphadhanakul B. 在泰国人群中血清双酚丙烷与糖尿病的关系, 2009 年第 4 次全国健康调查研究 [Relationship of serum bisphenol a with diabetes in the Thai population, National Health Examination Survey IV, 2009]. *J Diabetes*. 2015;7(2):240–249.
68. Ma N, Ma D, Liu X, et al. Bisphenol P exposure in C57BL/6 mice caused gut microbiota dysbiosis and induced intestinal barrier disruption via LPS/TLR4/NF-κB signaling pathway. *Environ Int*. 2023;175:107949.
69. Liu R, Cai D, Li X, et al. Effects of bisphenol a on reproductive toxicity and gut microbiota dysbiosis in male rats. *Ecotoxicol Environ Saf*. 2022;239:113623.
70. Ma CX, Ma XN, Li HL, Mauricio D, Fu SB. Endocrine-disrupting chemicals exposure: cardiometabolic health risk in humans. *Cardiovasc Diabetol*. 2025;24(1):381. doi:10.1186/s12933-025-02938-8
71. Li Z, Deng L, Zhang Y. Environmental pollutants as emerging disruptors of thyroid function: mechanisms and early-life risks. *Ecotoxicol Environ Saf*. 2026;309:119581. doi:10.1016/j.ecoenv.2025.119581
72. Mancini FR, Rajaobelina K, Praud D, et al. Nonlinear associations between dietary exposures to perfluorooctanoic acid (PFOA) or perfluorooctane sulfonate (PFOS) and type 2 diabetes risk in women: findings from the E3N cohort study. *Int J Hyg Environ Health*. 2018;221(7):1054–1060.
73. Hwang HJ, Dornbos P, Steidemann M, Dunivin TK, Rizzo M, LaPres JJ. Mitochondrial-targeted aryl hydrocarbon receptor and the impact of 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin on cellular respiration and the mitochondrial proteome. *Toxicol Appl Pharmacol*. 2016;304:121–132. doi:10.1016/j.taap.2016.04.005
74. Wang H, Wang J, Zhu Y, Yan H, Lu Y. Effects of different intensity exercise on glucose metabolism and hepatic IRS/PI3K/AKT pathway in SD rats exposed with TCDD. *Int J Environ Res Public Health*. 2021;18(24):13141. doi:10.3390/ijerph182413141
75. Javaid A, Akbar I, Javed H, et al. Role of heavy metals in diabetes: mechanisms and treatment strategies. *Crit Rev Eukaryot Gene Expr*. 2021;31(3).
76. Thévenod F, Lee WK. Cadmium and cellular signaling cascades: interactions between cell death and survival pathways. *Arch Toxicol*. 2013;87(10):1743–1786. doi:10.1007/s00204-013-1110-9
77. Prozialeck WC, Edwards JR. Mechanisms of cadmium-induced proximal tubule injury: new insights with implications for biomonitoring and therapeutic interventions. *J Pharmacol Exp Ther*. 2012;343(1):2–12. doi:10.1124/jpet.110.166769
78. Yang LX, Zhai J, Chen ZJ, Du Y. Female-specific associations of serum perfluoroalkyl and polyfluoroalkyl substances with sex hormonal/insulin dysregulation: an integrated population-based study. *Ecotoxicol Environ Saf*. 2025;298:118273. doi:10.1016/j.ecoenv.2025.118273
79. Dunder L, Salihovic S, Elmståhl S, Lind PM, Lind L. Associations between per-and polyfluoroalkyl substances (PFAS) and diabetes in two population-based cohort studies from Sweden. *J Expo Sci Environ Epidemiol*. 2023;33(5):748–756. doi:10.1038/s41370-023-00529-x
80. van Gerwen J, Shun-Shion AS, Fazakerley DJ. Insulin signalling and GLUT4 trafficking in insulin resistance. *Biochem Soc Trans*. 2023;51(3):1057–1069. doi:10.1042/BST20221066
81. Yunn NO, Kim J, Ryu SH, Cho Y. A stepwise activation model for the insulin receptor. *Exp Mol Med*. 2023;55(10):2147–2161. doi:10.1038/s12276-023-01101-1
82. Chen H, Li J, Zhang Y, et al. Bisphenol F suppresses insulin-stimulated glucose metabolism in adipocytes by inhibiting IRS-1/PI3K/AKT pathway. *Ecotoxicol Environ Saf*. 2022;231:113201.
83. Chandrasekaran P, Weiskirchen R. Cellular and molecular mechanisms of insulin resistance. *Curr Tissue Microenviron Rep*. 2024;5(3):79–90. doi:10.1007/s43152-024-00056-3
84. Sadeghi A, Niknam M, Momeni-Moghaddam MA, et al. Crosstalk between autophagy and insulin resistance: evidence from different tissues. *Eur J Med Res*. 2023;28(1):456. doi:10.1186/s40001-023-01424-9

85. Copps KD, White MF. Regulation of insulin sensitivity by serine/threonine phosphorylation of insulin receptor substrate proteins IRS1 and IRS2. *Diabetologia*. 2012;55(10):2565–2582. doi:10.1007/s00125-012-2644-8
86. Schulz MC, Sargis RM. Inappropriately sweet: environmental endocrine-disrupting chemicals and the diabetes pandemic. *Adv Pharmacol*. 2021;92:419–456.
87. Hinault C, Caroli-Bosc P, Bost F, Chevalier N. Critical overview on endocrine disruptors in diabetes mellitus. *Int J Mol Sci*. 2023;24(5):4537. doi:10.3390/ijms24054537
88. He K, Chen R, Xu S, et al. Environmental endocrine disruptor-induced mitochondrial dysfunction: a potential mechanism underlying diabetes and its complications. *Front Endocrinol*. 2024;15:1422752.
89. Zhao Y, Ou Y. Environmental endocrine-disrupting chemicals, pancreatic β-cells, and type 2 diabetes mellitus. *Clin Endocrinol*. 2026;104 (2):79–91. doi:10.1111/cen.70050
90. Gao C, He H, Qiu W, et al. Oxidative stress, endocrine disturbance, and immune interference in humans showed relationships to serum bisphenol concentrations in a dense industrial area. *Environ Sci Technol*. 2021;55(3):1953–1963.
91. Liu S, Liu J, Wang Y, Deng F, Deng Z. Oxidative stress: signaling pathways, biological functions, and disease. *MedComm*. 2025;6(7):e70268. doi:10.1002/mco2.70268
92. Chen J, Song P, Li C, et al. Endocrine disrupting chemicals exposure and health: an umbrella review. *J Australas Coll Nutritional Environ Med*. 2026;45(1):8–22.
93. Liu Z, Lu Y, Zhong K, Wang C, Xu X. The associations between endocrine disrupting chemicals and markers of inflammation and immune responses: a systematic review and meta-analysis. *Ecotoxicol Environ Saf*. 2022;234:113382. doi:10.1016/j.ecoenv.2022.113382
94. Cano R, Pérez JL, Dávila LA, et al. Role of endocrine-disrupting chemicals in the pathogenesis of non-alcoholic fatty liver disease: a comprehensive review. *Int J Mol Sci*. 2021;22(9):4807.
95. Kim JJ, Sears DD. TLR4 and insulin resistance. *Gastroenterol Res Pract*. 2010;2010(1):212563.
96. Nettore IC, Franchini F, Palatucci G, Macchia PE, Ungaro P. Epigenetic mechanisms of endocrine-disrupting chemicals in obesity. *Biomedicines*. 2021;9(11):1716. doi:10.3390/biomedicines9111716
97. Pinney SE, Simmons RA. Epigenetic mechanisms in the development of type 2 diabetes. *Trends Endocrinol Metab*. 2010;21(4):223–229. doi:10.1016/j.tem.2009.10.002
98. Rahmani S, Khalili NP, Khan F, Hassani S, Ghafour-Boroujerdi E, Abdollahi M. Bisphenol A: what lies beneath its induced diabetes and the epigenetic modulation? *Life Sci*. 2018;214:136–144. doi:10.1016/j.lfs.2018.10.044
99. Yang BT, Dayeh TA, Volkov PA, et al. Increased DNA methylation and decreased expression of PDX-1 in pancreatic islets from patients with type 2 diabetes. *Mol Endocrinol*. 2012;26(7):1203–1212. doi:10.1210/me.2012-1004
100. Liu J, Lang G, Shi J. Epigenetic regulation of PDX-1 in type 2 diabetes mellitus. *Diabetes Metabolic Syndr Obes*. 2021:431–442.
101. Miao M, Zhou X, Li Y, et al. LINE-1 hypomethylation in spermatozoa is associated with bisphenol a exposure. *Andrology*. 2014;2(1):138–144. doi:10.1111/j.2047-2927.2013.00166.x
102. Tian Y, Zhou X, Miao M, et al. Association of bisphenol a exposure with LINE-1 hydroxymethylation in human semen. *Int J Environ Res Public Health*. 2018;15(8):1770.
103. Zhou H, Lv X, Liang Y, Yu D, Wang W. Epigenetic regulation in a high-sugar environment. *Int J Mol Med*. 2026;57(5):131.
104. Matarid TR, Rayan M, Hussein OJ, Abunada HH, Maayah ZH, Korashy HM. Exploring the link between environmental chemical exposures and epigenetic modifications in diabetes mellitus: a review. *Biomolecules Biomed*. 2025;25(12):2607. doi:10.17305/bb.2025.11801
105. Kho ZY, Lal SK. The human gut microbiome-a potential controller of wellness and disease. *Front Microbiol*. 2018;9:356589.
106. Canfora EE, Meex RCR, Venema K, Blaak EE. Gut microbial metabolites in obesity, NAFLD and T2DM. *Nat Rev Endocrinol*. 2019;15 (5):261–273. doi:10.1038/s41574-019-0156-z
107. DeGruttola AK, Low D, Mizoguchi A, Mizoguchi E. Current understanding of dysbiosis in disease in human and animal models. *Inflamm Bowel Dis*. 2016;22(5):1137–1150. doi:10.1097/MIB.0000000000000750
108. Tilg H, Zmora N, Adolph TE, Elinav E. The intestinal microbiota fuelling metabolic inflammation. *Nat Rev Immunol*. 2020;20(1):40–54. doi:10.1038/s41577-019-0198-4
109. Javurek AB, Spollen WG, Johnson SA, et al. Effects of exposure to bisphenol a and ethinyl estradiol on the gut microbiota of parents and their offspring in a rodent model. *Gut Microbes*. 2016;7(6):471–485. doi:10.1080/19490976.2016.1234657
110. Lai KP, Chung YT, Li R, Wan HT, Wong CKC. Bisphenol a alters gut microbiome: comparative metagenomics analysis. *Environ Pollut*. 2016;218:923–930. doi:10.1016/j.envpol.2016.08.039
111. Reddivari L, Veeramachaneni DNR, Walters WA, et al. Perinatal bisphenol a exposure induces chronic inflammation in rabbit offspring via modulation of gut bacteria and their metabolites. *mSystems*. 2017;2(5):10–1128. doi:10.1128/mSystems.00093-17
112. Koestel ZL, Backus RC, Tsuruta K, et al. Bisphenol a (BPA) in the serum of pet dogs following short-term consumption of canned dog food and potential health consequences of exposure to BPA. *Sci Total Environ*. 2017;579:1804–1814. doi:10.1016/j.scitotenv.2016.11.162
113. Zhao L, Zhang F, Ding X, et al. Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes. *Science*. 2018;359 (6380):1151–1156. doi:10.1126/science.aao5774
114. Cani PD, Bibiloni R, Knauf C, et al. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. *Diabetes*. 2008;57(6):1470–1481.
115. Fan Y, Pedersen O. Gut microbiota in human metabolic health and disease. *Nat Rev Microbiol*. 2021;19(1):55–71. doi:10.1038/s41579-020-0433-9
116. Layden BT, Angueira AR, Brodsky M, Durai V, Lowe WL. Short chain fatty acids and their receptors: new metabolic targets. *Transl Res*. 2013;161(3):131–140. doi:10.1016/j.trsl.2012.10.007
117. Li Z, Yuan H, Chu H, Yang L. The crosstalk between gut microbiota and bile acids promotes the development of non-alcoholic fatty liver disease. *Microorganisms*. 2023;11(8):2059. doi:10.3390/microorganisms11082059
118. Qi Y, Jiang C, Cheng J, et al. Bile acid signaling in lipid metabolism: metabolomic and lipidomic analysis of lipid and bile acid markers linked to anti-obesity and anti-diabetes in mice. *Biochim et Biophys Acta*. 2015;1851(1):19–29.
119. Taoka H, Yokoyama Y, Morimoto K, et al. Role of bile acids in the regulation of the metabolic pathways. *World J Diabetes*. 2016;7(13):260.

120. Chiang JYL, Pathak P, Liu H, Donepudi A, Ferrell J, Boehme S. Intestinal farnesoid X receptor and takeda G protein couple receptor 5 signaling in metabolic regulation. 2017;35(3):241–245. doi:10.1159/000450981
121. Aguilera M, Gálvez-Ontiveros Y, Rivas A. Endobolome, a new concept for determining the influence of microbiota disrupting chemicals (MDC) in relation to specific endocrine pathogenesis. *Front Microbiol*. 2020;11:578007. doi:10.3389/fmicb.2020.578007
122. Baralić K, Živančević K, Javorac D, et al. Multi-strain probiotic ameliorated toxic effects of phthalates and bisphenol a mixture in Wistar rats. *Food Chem Toxicol*. 2020;143:111540. doi:10.1016/j.fct.2020.111540
123. Baralić K, Živančević K, Jorgovanović D, et al. Probiotic reduced the impact of phthalates and bisphenol a mixture on type 2 diabetes mellitus development: merging bioinformatics with in vivo analysis. *Food Chem Toxicol*. 2021;154:112325. doi:10.1016/j.fct.2021.112325
124. Gou HZ, Zhang YL, Ren LF, Li ZJ, Zhang L. How do intestinal probiotics restore the intestinal barrier? *Front Microbiol*. 2022;13:929346.
125. Chelakkot C, Ghim J, Ryu SH. Mechanisms regulating intestinal barrier integrity and its pathological implications. *Exp Mol Med*. 2018;50 (8):1–9. doi:10.1038/s12276-018-0126-x
126. Corrêa-Oliveira R, Fachi JL, Vieira A, Sato FT, Vinolo MAR. Regulation of immune cell function by short-chain fatty acids. *Clin Transl Immunol*. 2016;5(4):e73. doi:10.1038/cti.2016.17
127. Lee DH, Kim MT, Han JH. GPR41 and GPR43: from development to metabolic regulation. *Biomed Pharmacother*. 2024;175:116735. doi:10.1016/j.biopha.2024.116735
128. Dang G, Wu W, Zhang H, Everaert N. A new paradigm for a new simple chemical: butyrate & immune regulation. *Food Funct*. 2021;12 (24):12181–12193.
129. Ju J, Shen L, Xie Y, et al. Degradation potential of bisphenol a by Lactobacillus reuteri. *Lwt*. 2019;106:7–14. doi:10.1016/j.lwt.2019.02.022
130. Oishi K, Sato T, Yokoi W, Yoshida Y, Ito M, Sawada H. Effect of probiotics, Bifidobacterium breve and Lactobacillus casei, on bisphenol a exposure in rats. *Biosci Biotechnol Biochem*. 2008;72(6):1409–1415. doi:10.1271/bbb.70672
131. Chaithanya V, Kumar J, Vajravelu Leela K, Ram M, Thulukanam J. Impact of multistrain probiotic supplementation on glycemic control in type 2 diabetes mellitus-randomized controlled trial. *Life*. 2024;14(11):1484. doi:10.3390/life14111484
132. Firouzi S, Majid HA, Ismail A, Kamaruddin NA, Barakatun-Nisak MY. Effect of multi-strain probiotics (multi-strain microbial cell preparation) on glycemic control and other diabetes-related outcomes in people with type 2 diabetes: a randomized controlled trial. *Eur J Nutr*. 2017;56 (4):1535–1550. doi:10.1007/s00394-016-1199-8
133. Mazloom Z, Yousefinejad A, Dabbaghmanesh MH. Effect of probiotics on lipid profile, glycemic control, insulin action, oxidative stress, and inflammatory markers in patients with type 2 diabetes: a clinical trial. *Iran J Med Sci*. 2013;38(1):38.

Diabetes, Metabolic Syndrome and Obesity

Dovepress
Taylor & Francis Group

Publish your work in this journal

Diabetes, Metabolic Syndrome and Obesity is an international, peer-reviewed open-access journal committed to the rapid publication of the latest laboratory and clinical findings in the fields of diabetes, metabolic syndrome and obesity research. Original research, review, case reports, hypothesis formation, expert opinion and commentaries are all considered for publication. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: https://www.dovepress.com/diabetes-metabolic-syndrome-and-obesity-journal