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Complex chronic diseases have a common origin

Whitepaper

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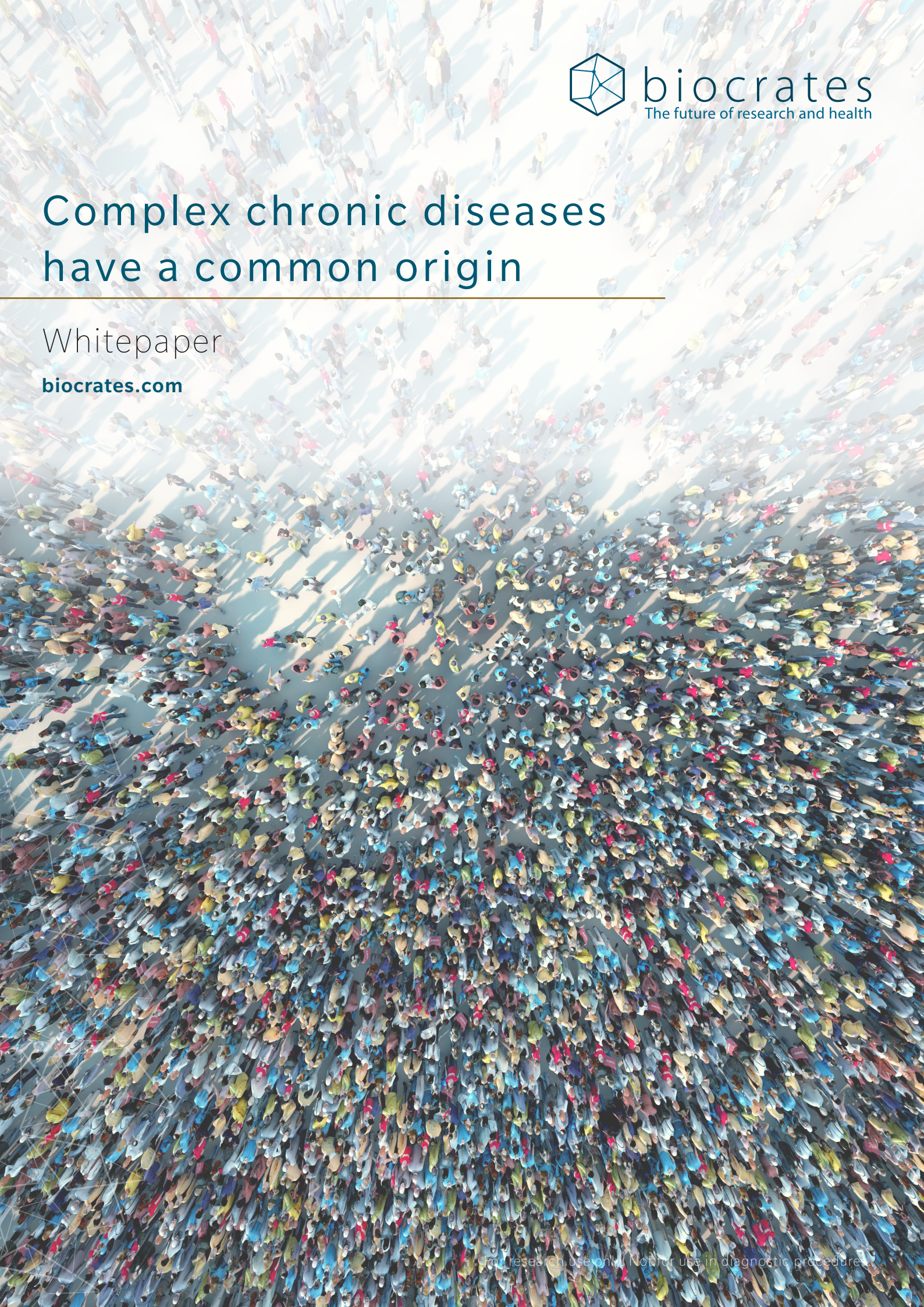

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Complex chronic diseases have a common origin

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Keywords | complex chronic diseases, Western-style diet, metabolic disease models

Abbreviations | AD: Alzheimer's disease, BA: bile acid, BCAA: branched-chain amino acid, IBD: inflammatory bowel disease, IEC: intestinal epithelial cell, LPS: lipopolysaccharide, MDD: major depressive disorder, MS: multiple sclerosis, NAFLD: non-alcoholic fatty liver disease, PUFA: polyunsaturated fatty acid, SCFA: short-chain fatty acid, T1D: type 1 diabetes, T2D: type 2 diabetes, TG: triglyceride, WSD: Western-style diet

What you'll learn

Focusing exclusively on genomics, proteomics, and microbiomics leaves a critical gap in our understanding of complex chronic diseases. Despite painstaking efforts, scientists and clinicians often struggle to predict disease trajectory and identify early markers, leading to costly studies that yield disappointing results. Metabolomics can close the gap and revolutionize complex chronic disease research.

While genomics and proteomics provide essential data, metabolomics sheds light on the interplay between genetics, microbiome, and environmental factors such as nutrition. These insights improve our understanding of complex chronic disease progression and early diagnostics, two areas that are pivotal to achieving the level of precision medicine needed for effective interventions. Without metabolomics, these invaluable discoveries will remain out of reach.

In this whitepaper you'll discover how to:

- Gain a **holistic understanding** of complex chronic diseases through metabolism
- **Increase the power of your study** by combining other omics with metabolomics to reveal associations out of reach for other omics alone.
- **Focus on what matters** in your subjects' phenotype and obtain detailed descriptions of disease metabolism providing substantial advantage
- **Learn** about metabolites and pathways driving progression to complex chronic diseases
- Uncover the metabolites that will **enable earlier disease detection**
- **Build better cohorts** with improved participant selection by exploiting knowledge of metabolism to maximize study impact and significance

Endowed with this knowledge, you have the opportunity to revolutionize your research approach. Engage further by booking a demo with our expert team, where we'll explore how to best integrate metabolomics into your project. Together, let's pave the way for breakthroughs in understanding, preventing, diagnosing, and finally curing complex chronic diseases.

Abstract

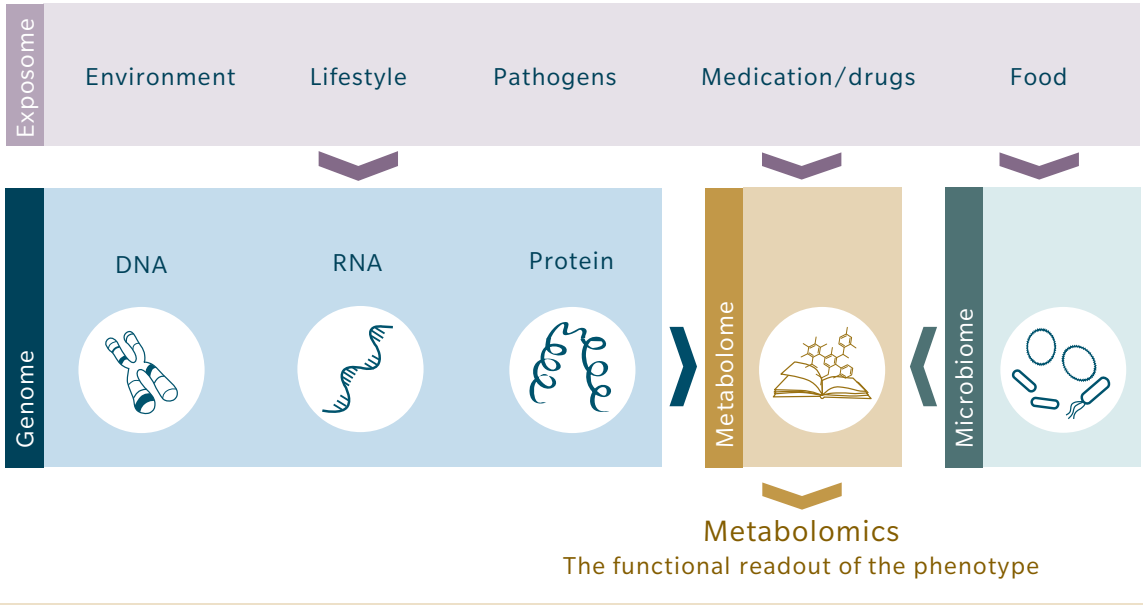
In spite of substantial research funding over the past three decades, the prevalence of complex chronic diseases continues to rise, while efficient therapies and preventive actions remain elusive. This white paper provides a new perspective on complex chronic diseases traditionally studied separately: Alzheimer's, depression, multiple sclerosis, inflammatory bowel disease, type 1 diabetes, and cancers, by examining them through the prism of metabolomics.

Metabolism is the missing link to explain the etiology of diseases that genomics alone cannot address. A growing body of evidence pointing to the Western-style diet (WSD), obesity and metabolic disease as risk factors for complex chronic diseases underlines the need for a metabolic perspective in studying these conditions. Rather than viewing it as a consequence of disease, **metabolism should be recognized as a driving force of complex chronic diseases**. To this end, we have constructed a metabolic model for each disease, beginning with the metabolites supplied by the WSD, their impact on gut microbiome composition, the shift in microbiome-derived metabolites, and their link to the metabolomic profile observed in patients with the disease.

These models of priming for complex chronic diseases confirm the significance of the gut microbiome for many conditions, reveals new potential druggable targets, and provides a proof-of-principle for the broader use of metabolomics in the study of complex chronic diseases.

Box 1 | Definitions

Complex chronic disease | Multi-factorial disease caused by a combination of genetic and environmental factors. Even if genetic variation is identified, it is not sufficient to explain the heritability or the etiology of the disease. Other factors pertaining to the exposome come into play.
Exposome | External factors the body is exposed to and that influence health. These include diet, pharmaceuticals, pathogens, and lifestyle factors.
Microbiome | The collection of microorganisms that live in and on our body. The microbiome contributes to human physiology, both in health and in disease, via messaging by metabolites.
Metabolomics | The omic at the crossroads of genetics, microbiome, and exposome. Metabolomics is a functional readout of the phenotype, and the best-suited omic to investigate complex chronic diseases.



1. Overview of the complex chronic disease epidemic

Demographics of complex chronic diseases

The bleak perspective of a patient who was just diagnosed with type 2 diabetes (T2D), multiple sclerosis (MS) or inflammatory bowel disease (IBD) is that some of their symptoms will be managed therapeutically while their condition will slowly but surely progress towards increasing deterioration of their organs. This focus on reaction rather than prevention has cost public health systems all over the world billions of dollars and provides little comfort for the patients and their relatives. Understanding the true origin of complex chronic diseases offers the hope to not only provide better care to patients with better-adapted therapies, but also to prevent the onset of disease in certain patients and unburden our health care systems.

Worldwide, the increase in prevalence of complex chronic diseases in the last decades has greatly surpassed the increase in the global population (figure 1) This trend is well-known for metabolic conditions such as T2D and obesity, but it is also a reality for diseases once thought to have little to do with metabolism, such as dementia and cancers. Of note, metabolic diseases such as T2D and non-alcoholic fatty liver disease (NAFLD) are risk factors or even precursors of other complex chronic diseases.

As discussed in each disease section, the Western-style diet (WSD) and its metabolites can be traced to the onset of these diseases, with patterns of disease associated with Western lifestyles, including obesity and diabetes, being replicated across the globe. In China, a country with a late adoption of Western lifestyles, the prevalence of diabetes has increased from 2.5% in 1994 (1) to more than 12% in 2023 (2), and around half of the adult Chinese population now has diabetes or pre-diabetes. Obesity is also a growing public health concern with over a fifth of the Chinese population afflicted by metabolic syndrome (3) and a third by NAFLD (4).

Inevitably, conditions linked to these metabolic diseases are likely to follow. China already has over 15 million people with dementia (5) and half a million new colorectal cancers each year (6). Like China, similar disease patterns are developing in India, with 77 million people diagnosed with diabetes – up from 26 million in 1990 (7) – along with nearly 25 million more with pre-diabetes (8). More than 135 million people are obese (9) and nearly a third of adults are thought to have metabolic syndrome (10). Thus, although these metabolic diseases are traditionally linked with a Western lifestyle, they now affect a growing part of the world at risk of becoming afflicted increasingly by complex chronic diseases.

Differences between ethnic groups show Asian populations have a greater prevalence of metabolic disease than white populations. Recent estimates show nearly three times as many Asian women in the United States have metabolic syndrome than white women, while Asian men are twice as likely as white men to be diagnosed (11). For example, Asian adults are three times more likely to suffer from pre-diabetes than white adults, even when they are a healthy weight (12). However, a recent study showed that the relationships between weight loss (BMI reduction) and remission/relapse for subjects with T2D are different in the Japanese and Western populations (13).

Sex is also an important risk factor for many complex chronic diseases. Dementia (32), depression (33), MS (34), and obesity (35) are more prevalent in women, while colorectal cancer (36), NAFLD (37), and T2D (38) are more common in men. There is little consensus on whether there are sex differences with regards to metabolic syndrome.

Metabolic imbalance as a risk factor for complex chronic diseases

Subjects with metabolic diseases are more likely to have depression (39), to develop dementia (40, 41), and to be diagnosed with cancer (42), including breast (43) and colorectal (44) cancer – two of the most prevalent cancers globally. In 2020, there were around 2.3 million new cases of breast cancer worldwide (45), and around 1.9 million new colorectal cancer cases (46): numbers that are expected to

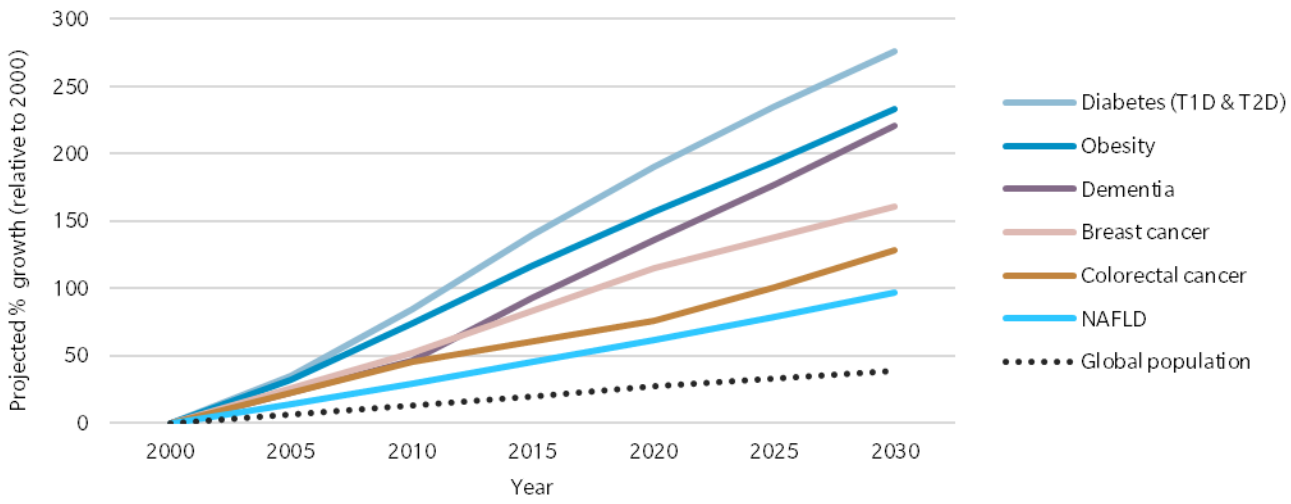


Figure 1: Complex chronic diseases have higher prevalence growth rates than the global human population. References: diabetes (14–17), obesity (18–21), dementia (22–25), breast cancer (26–28), colorectal cancer (26, 28, 29), NAFLD (30), global population (31).

rise to 3 million (45) and 3.2 million (46), respectively by 2040.

Advanced forms of metabolic disease that affect the liver (NAFLD) or the pancreas (T2D) are associated with all the modern complex diseases. NAFLD increases the risk of depression (47, 48), dementia (49), and cancers (50). Around 12% of cancers in men and 13% in women are estimated to be attributable to obesity (51), and midlife obesity is now ranked as the top modifiable risk factor for dementia in the US (52). Worldwide, NAFLD is also present in up to a third of subjects with IBD (53). T2D significantly increases the risk of dementia (54) and cancer (55), and has been found to increase the risk of MS (56). Both obesity (57) and T2D (58) increase the risk of depression. T2D is also common in subjects with IBD (59, 60).

Clearly these statistics represent worrying situations for the individuals affected, but they also point to a growing burden for healthcare systems and resources. This burden extends beyond healthcare, affecting social care services, workforce participation and investment in public services.

Box 2 | WSD hallmark nutrients

Although current lifestyle trends in Western countries emphasize the importance of eating "healthy", a continuous rise in foods high in fat and sugar as major components of the diet is observed in these countries, which has thus been named the Western-style diet (WSD).

The WSD is characterized by high intakes of refined sugars (sweets and soft drinks), unhealthy fats (high intake of saturated fats and omega-6 fatty acids), processed meats (especially red meat), refined grains, high-fat dairy products, salt, eggs, and starchy vegetables like potatoes and corn (61-65). These foods are often processed, refined, fried, and pre-packaged, with added sugars or emulsifiers.

At the same time, the WSD is associated with low intake of unprocessed vegetables and fruits, whole grains, fish, nuts, and seeds. Thus, despite an overall over-consumption of food in relation to energy expenditure, the WSD lacks in fiber, vitamins, minerals, and beneficial plant-derived metabolites such as antioxidants (61, 66, 67), replicating aspects of malnutrition observed in low-income countries.

2. The Western-style diet as a common origin to complex chronic diseases

Association of complex diseases with the WSD

Although it is widely acknowledged that consumption of a high-fat, high-sugar diet such as the WSD contributes to advanced metabolic diseases such as T2D and NAFLD, causal links to other complex chronic diseases have been harder to find. The advent of genomics has facilitated the investigation of genetic pre-disposition for all major complex conditions, leading to the identification of single nucleotide polymorphisms (SNPs) that help treat and sometimes prevent the disease. But for most people, the drivers of complex chronic diseases are non-genetic factors.

In this paper, we discuss evidence of the role of the WSD in the etiology of complex chronic diseases, from cancers to neurological, psychological, and autoimmune diseases. Starting with the hallmark metabolites of a WSD (61–67) (described in box 2) and their effects on the gut microbiome, we investigate the links between WSD and complex chronic diseases, using metabolomics as a primary readout to provide the alternative generation of druggable targets that are urgently needed slow their progression.

Core hypothesis | Complex chronic diseases have a common origin

The WSD is typically low in fiber, rich in carbohydrates and rich in fats that are low in PUFAs (see box 2). A WSD leads to changes in the microbiome and, over decades of exposure, to a disturbance of (metabolic) homeostasis. We propose that these changes create an unfavorable environment that prompts the development of early-stage metabolic disease leading to insulin resistance.

Once insulin resistance has settled in, energy metabolism is disturbed, leading to intracellular malnutrition. Consequently, multiple lines of dysfunction can be activated, including hyperinsulinemia-driven inflammation and systemic reprogramming of cell metabolism and of mitochondrial function. With the altered microbiome as a driving force of this transition, the WSD primes our organs for dysfunction, leading to a broad range of complex chronic diseases with a common origin. These steps are depicted in figure 2 and further discussed in the next paragraphs.

① The WSD shapes the gut microbiome

Diet affects the composition of the gut microbiome rapidly and reproducibly (68). Although effects of dietary intervention can be seen within a few hours, microbiome and metabolome profiles can take longer to stabilize (69) (figure 3).

The hallmark nutrients of the WSD (box 2) have multiple effects on the gut microbiome. Consumption of **added sugars and fats** increases the ratio of *Firmicutes* to *Bacteroidetes* in the gut microbiome. It also increases gut permeability, which allows lipopolysaccharide (LPS) derived from Gram-negative bacteria to enter the circulation (endotoxemia), and promotes systemic inflammation (70–73) .

Saturated fatty acids are an important part of a balanced diet, but quantity and quality are major determinants of the magnitude of gut permeability and postprandial inflammation (74, 75). Animal-derived fats are particularly rich in saturated fatty acids such as palmitic or stearic acid that can elicit cytotoxic effects at high concentrations (76). Both dietary cholesterol and palmitic acid promote inflammation (77). **Refined oils** lack the antioxidants present in non-refined plant oils (78), and their consumption promotes gut dysbiosis, gut permeability, and inflammation (79, 80). Processed fats and refined oils, even when rich in PUFAs, often contain a high fraction of *trans* fats and a low omega-3 to omega-6 fatty acids ratio, again associated with post-prandial inflammation (81–83).

However, it is not the fat content of the diet that causes intestinal inflammation: it is the **lack of fiber** that accompanies a high-fat diet (84). Processed grains and related foods have considerably less fiber than whole grains and other fiber-rich plants.

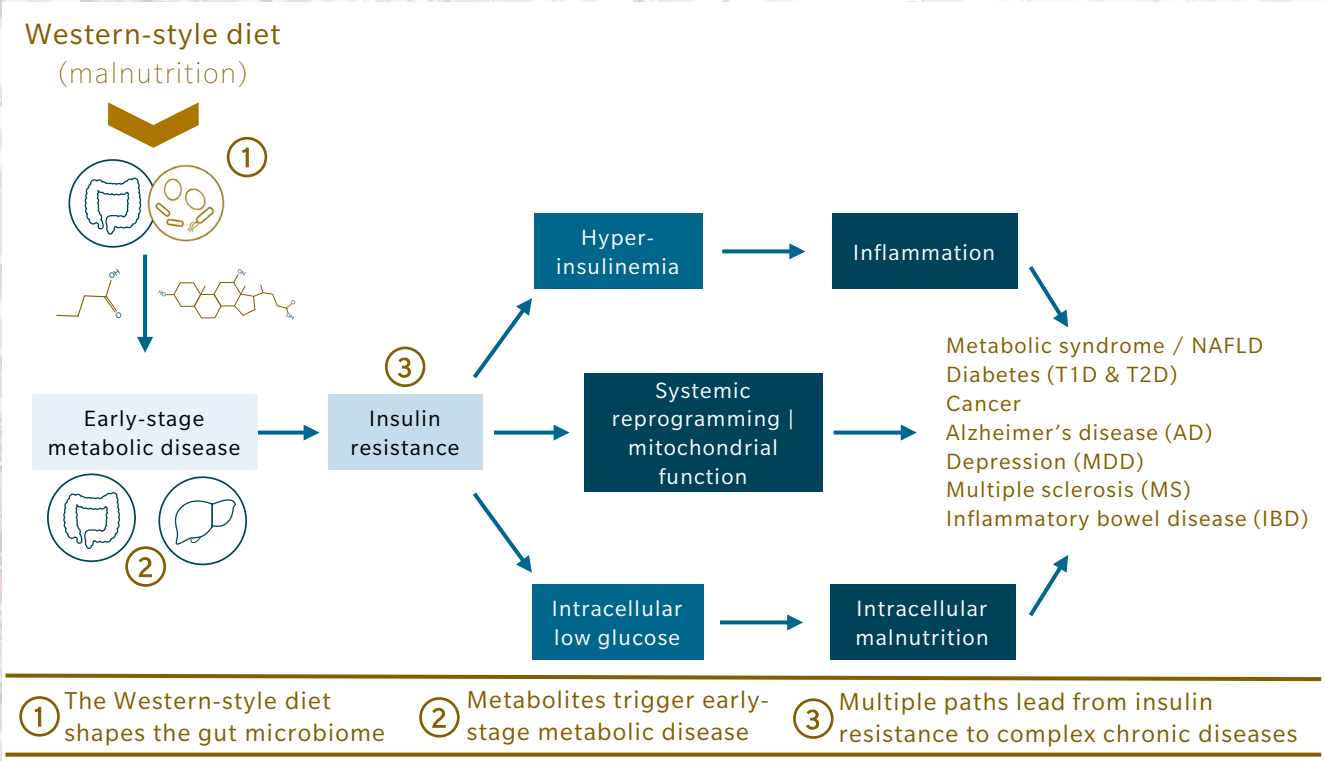


Figure 2: Complex chronic diseases have a common origin | Core hypothesis. The Western-style diet and altered gut microbiome drive a gradual progression towards organ dysfunction leading to early-stage metabolic disease and insulin resistance, both of which are underlying conditions of complex chronic diseases.

When fermented by the gut microbiome, fiber is a source of short-chain fatty acids (SCFA), which are key protective metabolites for the gut epithelium and are also taken up by the host. The WSD applies selective pressure on intestinal bacteria that, combined with low fiber intake, results in low levels of intestinal SCFA, especially acetate, propionate and butyrate (85).

② Metabolites as triggers of early-stage metabolic disease

The body has evolved to adapt its metabolism to survive long-lasting famines. However, in times of over-nutrition, this system backfires and converts excess sugars and fats into triglycerides (TGs). These accumulate in adipose tissue and in organs such as the liver and pancreas, leading to obesity and metabolic diseases characterized by organ dysfunction (e.g., NAFLD and T2D). The WSD alters the levels of several classes of metabolites, both by directly contributing to endogenous metabolite pools and through an indirect effect via gut microbiome metabolism.

Metabolites from WSD nutrients

Sucrose, also known as saccharose or table sugar, is broken down into glucose and fructose. **Glucose** can be used as energy in glycolysis. When the dietary pool of glucose exceeds glycolytic capacity, excess glucose is stored as glycogen or converted into fatty acids, particularly palmitic acid, which is a C16 fatty acid shorter than most sourced from the diet. Consequently, in presence of excess glucose levels, TGs with saturated and short fatty acyl groups tend to accumulate.

Unlike glucose, **fructose** is not used as fuel. Instead, it is directly converted to fatty acids in a process that happens exclusively in the liver (86, 87). This is why the consumption of sweeteners enriched in fructose (like the high-fructose corn syrup found in sugary beverages and sweets) is associated with NAFLD (72). Overconsumption of fructose is linked to a systemic pro-inflammatory status, cortisol hyperactivation, increased visceral adiposity, and insulin resistance (88). Processed grains and **simple carbohydrates** are particularly energy-dense with high glycemic indexes, provoking a fast rise in blood glucose (89). Consumption of high calorie foods over short periods, together with spikes in plasma glucose and insulin, promotes rapid weight gain compared to more balanced diets (90). These recurring spikes in insulin production also promote insulin resistance.

Dietary fats are emulsified by bile acids, enzymatically hydrolyzed in the intestine into free fatty acids and monoglycerides (MGs), and absorbed by enterocytes. In a healthy diet, the TGs formed to transport these fatty acids across the body contain long-chained and highly unsaturated fatty acids. In contrast, TGs produced from a WSD contain more saturated fatty acids. Elevated TGs with saturated and shorter-chained fatty acids (from glucose-derived fatty acids as described above) have been implicated as a major driver of T2D (91). During prolonged consumption of a WSD, high levels of saturated and oxidized fatty acids disturb the fluidity of cell membranes, making them more sensitive to disturbance, leading to low grade chronic inflammation and inducing repair processes (92). This also affects the membranes of intracellular organelles, including mitochondria. Unsurprisingly, a high-fat diet is linked to abnormal mitochondrial biogenesis, which may indicate mitochondrial dysfunction. Increased free radical production, inflammation, and insulin resistance may follow (93, 94).

The **branched-chain amino acids** (BCAAs), leucine and valine, act as insulin analogues by modulating the mammalian target of rapamycin (mTOR) system, inducing insulin secretion (95). Thus, it is no surprise that BCAAs have been identified as a causal factor in T2D pathogenesis and insulin resistance. Elevated serum levels of BCAAs form part of a signature that can identify individuals at risk of developing T2D (96). In addition, elevated BCAA blood levels are associated with an increased body-mass index (BMI) and obesity (97). Increased circulating TG levels and insulin analogue BCAAs converge to increase insulin secretion. Similar to alcohol, where constant exposure leads to de-sensitization to alcohol, chronically high insulin levels can lead to a build-up of insulin resistance (98)

Metabolites from the gut microbiome

Metabolic modeling of the human gut microbiome suggests that diet-induced changes in amino acid levels are not only due to amino acid quantities in the diet itself, but are also a function of the gut microbiome's composition and metabolic activity (99) (figure 3). The essential amino acid tryptophan is an important substrate for intestinal metabolic reactions. Gut bacteria can convert tryptophan into several products, including serotonin, which acts as an enterosyne on the enteric nervous system and contributes to the gut-brain axis. Other downstream products include indole and **indole derivatives**, which have varying effects on the intestine and host physiology, and **kynurenine** and related immunomodulators (100). The ratio of kynurenine to tryptophan levels in blood can be used as a marker of inflammation and is increased in several inflammatory conditions (101).

Bile acid (BA) synthesis is the result of both host and microbial metabolism. Bacteria of the intestinal microbiome convert part of the primary BA pool into secondary BAs, with varying relative concentrations of BAs along the intestinal tract. In the intestinal lumen, BAs bind dietary fats to facilitate their absorption. Secondary BAs such as deoxycholic acid (DCA) are excellent planar two-dimensional soaps not only useful to absorb dietary fat but also very efficient at intercalating within membranes (102). About 95% of BAs are reabsorbed from the large intestine and recycled in the enterohepatic circulation, with up to 35% being secondary BAs. Changes in the proportion of secondary to primary BAs (e.g., due to dysbiosis) can affect the host's physiology. This is because BAs have hormone-like effects on signaling pathways, in particular as ligands of multiple nuclear receptors including TGR5 and the farnesoid X receptor (FXR). Functional FXR is expressed in a wide range of tissues including brain neurons, the adrenal cortex,

and pancreatic β cells. FXR governs the expression of genes related to energy metabolism, BA metabolism, insulin signaling (103), immune cell regulation (104–106), mitochondrial physiology (107), and stability of the tumor suppressor protein p53 (108). An imbalance in secondary and primary BAs also affects membranes, especially those with disrupted fluidity caused by a high proportion of saturated and oxidized fatty acids. These membranes may become more susceptible to disruption by secondary BAs, contributing to inflammation, repair processes, and the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) through disruption of the mitochondrial respiratory chain.

The **short-chain fatty acids** (SCFAs) acetate and butyrate are major energy carriers and serve as the main energy source of intestinal epithelial cells (IECs) (109). These cells produce a protective mucous layer and form a barrier between intestinal contents and the rest of the organism that is compromised when gut permeability increases. The SCFA propionate helps regulate macrophages from the innate immune system and is involved in the activation of regulatory T cells (Treg) (110, 111). A WSD that is low in SCFAs promotes IEC dysfunction, causing a reduction in mucous layer thickness and a loss of barrier function (112). Consequently, decreased SCFA levels contribute to a "leaky gut" condition - allowing pathogens and toxins such as LPS to enter the body, trigger the innate immune system, and cause inflammation. Increased permeability also means that oxygen is allowed to diffuse into the gut and further contribute to dysbiosis by promoting oxidative processes and oxygen-consuming bacteria in a normally fermentation-driven/hypoxic environment.

In summary, metabolites are powerful effectors of biology, both through their direct interactions with cell structures and through signaling. Sugars, fats, and other metabolites extracted from our food can weaken membranes and challenge the gut microbiome. TGs and secondary BAs compromise lipid membranes. The lack of SCFAs creates a highly inflamed environment in the gut that puts extra pressure on the microbiome. The situation is made worse by progressive insulin resistance, which results from the chronic release of insulin in response to glucose and BCAA signaling described above.

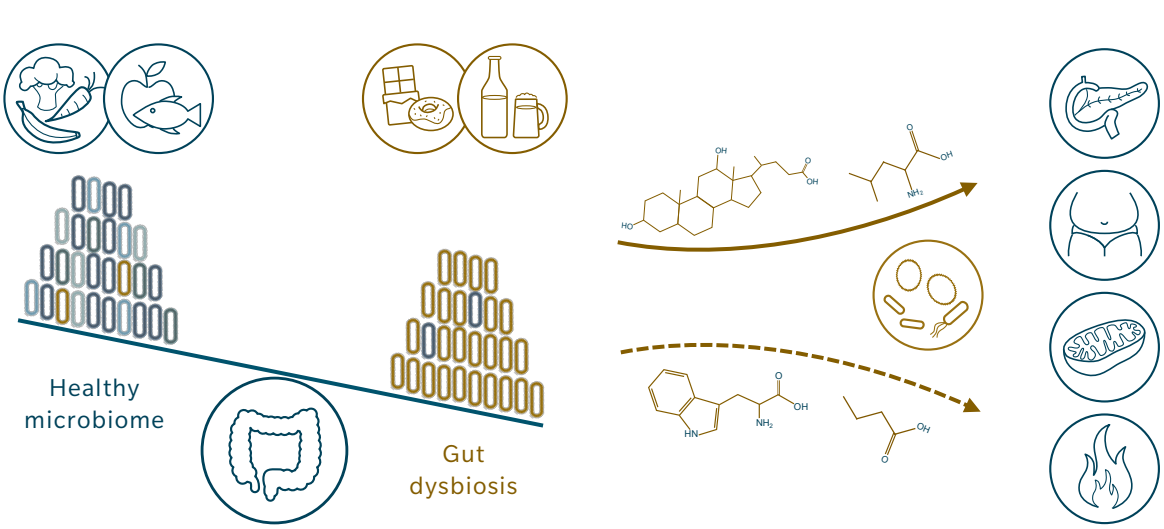


Figure 3: Interplay between WSD and microbiome priming for complex chronic diseases. The WSD causes changes in microbiome composition resulting in characteristic metabolic profiles that point to mechanisms of early-stage metabolic disease, intracellular metabolic changes, mitochondrial dysfunction, and inflammation.

③ Multiple paths lead from insulin resistance to complex chronic diseases

Hyperinsulinemia and inflammation

With a well-functioning pancreas, insulin resistance promotes insulin secretion due to high circulating glucose levels, which act as a signal for insulin release from pancreatic β cells. This leads to hyperinsulinemia, which does not resolve insulin resistance in organs that have already developed resistance to insulin.

However, it enhances insulin signaling in other organs and triggers inflammation, insulin secretion and secretion of TGs into circulation, contributing to a pro-inflammatory phenotype (113). This state is characterized by strong pro-inflammatory signaling by cytokines such as interleukin 6 (IL-6) and is a precursor state of T2D.

WSD-induced obesity alters metabolic and endocrine function of adipose tissue and leads to an increased release of fatty acids and adipocytokines. This is associated with persistent, chronic low-grade inflammation in the adipose tissue and other metabolic organs like pancreas and liver (114, 115).

Intracellular malnutrition

Chronic insulin resistance means that glucose cannot enter cells through insulin-dependent transporters, resulting in intracellular malnutrition for certain cells, even in a glucose-rich environment. In parallel, saturated and oxidized fatty acids and secondary BAs disrupt organelle and cell membranes, necessitating anabolic metabolism for maintenance and repair.

These energy-demanding mechanisms exert additional pressure on cells. In response to this stress, cells use compensatory mechanisms to overcome energy deficits and ensure survival.

These include increased insulin secretion (as described above), overexpression of glucose transporters (GLUT, both insulin-dependent and -independent), which are a key characteristic of cancer cells, and metabolic reprogramming that redirects other pathways towards anabolic metabolism (e.g., glutaminolysis and fatty acid oxidation) to generate alternative energy carriers such as glutamate and SCFA). Due to the deficiency of SCFAs in a WSD, fatty acids are a primary source of energy, and their oxidation relies on mitochondria.

Mitochondrial overload and dysfunction

The pro-inflammatory environment created by the WSD, in which mitochondrial membranes are structurally compromised by saturated and oxidized fatty acids and secondary BAs, contributes over time to the dysfunction and incomplete oxidation of fatty acids. This leads to elevated levels of diverse acylcarnitine mixtures released in the blood. Unsurprisingly, a high-calorie, high-carbohydrate diet has been associated with mitochondrial dysfunction (116).

Conclusions

Over the course of decades, the specific metabolite composition of the WSD and resulting changes in the microbiome contribute to insulin resistance. In this state, inflammation, metabolic reprogramming, and mitochondrial dysfunction predispose the body to organ-level dysfunction. As a result, various complex chronic diseases can emerge, originating from this shared underlying cause.

Elucidating the interactions between the WSD, the microbiome, and the body with metabolomics helps to understand and predict the impact of external influences on health and disease. Just as genomics helps us understand a person's genetic pre-disposition, metabolomics holds the key to their metabolic state, with considerable implications for our understanding of disease and personalized diagnosis and therapy.

3. Metabolic diseases

Metabolic diseases are conditions where energy metabolism is disturbed. Among the most prevalent are metabolic syndrome, T2D, and NAFLD, all of which have been associated with the WSD for decades. One possible reason for the apparent lack of effective treatments and policies may be the persistent belief that the WSD simply results in an excess of calories that can be offset by exercise. In this section, we briefly introduce these metabolic diseases and discuss how the hallmark nutrients and metabolites associated with a WSD impact homeostasis beyond energy metabolism.

WSD and metabolic diseases

Consumption of ultra-processed food increases the risk of **obesity** (117). Adherence to a WSD is associated with a higher BMI (118, 119). The WSD has a disruptive effect on the microbiome, altering the healthy balance of CD4+ T helper cells and promoting adipose tissue deposition independently of caloric intake (120). The WSD disrupts satiety sensing by impairing the active transport of the satiety-regulating hormones leptin and grehlin through the blood-brain barrier (121). Chronic exposure to LPS further diminishes the effect of the satiety-inducing gut peptide cholecystokinin and leptin signaling (122, 123). Thus, the WSD promotes a continuous increase in caloric intake over time in several ways, with obesity as a predictable consequence.

Obesity seems to play a mediating role in the relationship between elevated inflammatory markers and depression (124), with each of these factors potentially increasing the risk for the other two. Furthermore, obesity increases the chance for cognitive decline and Alzheimer's disease (125). **Metabolic syndrome** is estimated to affect over a billion people worldwide, accounting for around a quarter of the world's population (126). Around 35% of the US population suffers from metabolic syndrome (127). Varying definitions of metabolic syndrome worldwide make it difficult to measure global prevalence, but it is thought to parallel trends observed in obesity and T2D (126). As risk factors accumulate, individuals progress from stage I to III, with an increased chance of developing insulin resistance.

Following a Mediterranean or similar "healthy" dietary pattern reduces the risk of developing metabolic syndrome, while following a WSD pattern increases this risk (128, 119). The consumption of emulsifiers is also positively correlated with metabolic syndrome (129). Of an estimated 463 million people living with **T2D** worldwide, half are unaware of their condition (16). T2D is no longer considered a single disease, but rather an umbrella diagnosis comprising multiple disease types that differ, among other things, in the importance of dysregulated amino acid metabolism (130). Besides high carbohydrate intake, feeding patterns with multiple snacks and insulin spikes throughout the day contribute to the development of insulin resistance and T2D. Protein intake also stimulates insulin secretion, and increased meat consumption is associated with increased risk for T2D, although the molecular links are not yet fully understood (131, 132).

By 2040, over half the adult population may suffer from **NAFLD** (30). Dietary fructose is widely acknowledged to contribute to the etiology of NAFLD (133), as fructose cannot readily be metabolized by most cells and its processing relies on metabolism in the liver where excess glucose is also stored as glycogen and TGs.

Nutritional interventions have been studied to try to prevent or reverse the effects of the WSD. Caloric restriction was found to have positive effects on lipid dysregulation, along with anti-inflammatory effects (134–136). A Mediterranean diet, rich in high-quality unsaturated fats, appears to be superior to a low-fat diet in improving metabolic syndrome-related risk profiles (137).

Unsurprisingly, the pathophysiology of metabolic diseases is closely linked to metabolite levels. Nutrition plays a major role, both as a direct source of metabolites and as a trigger for internal metabolic changes in the host and gut microbiome. More detail is provided in the following paragraphs and in table 1.

Metabolites from WSD nutrients

Consumption of **emulsifiers** positively correlates with obesity (129), probably because they facilitate absorption of fats in the gut. Therefore, an excess of free fatty acids and a lack of PUFAs are considered primary contributors to metabolic diseases (138). However, the list of lipid classes affected in the pathogenesis of metabolic diseases is long and includes phospholipids, PUFA-derived lipid mediators like prostaglandins, and cholesterol derivatives like cholesteryl esters.

BCAAs have been consistently associated with T2D and T2D risk in European (139), Asian (140), and North American (141) populations. Mendelian randomization studies found causal links between BCAA levels, insulin resistance and T2D (139). Consistent with their role as insulin analogues, BCAAs are deeply involved in the mechanics of metabolic diseases (142) and were reported to associate with reduced insulin secretion (143), an important factor for the conversion from pre-diabetes to diabetes. Of note, the association between dietary uptake of BCAAs and T2D is contingent on genetic predisposition (144).

Lower levels of **glycine** are associated with pre-diabetes (145). The association between glycine metabolism and insulin resistance has been comprehensively reviewed (146). Glycine supplementation has thus been suggested to reduce the risk of insulin resistance and T2D. Among others, anti-inflammatory effects and modulation of glucagon-like peptide 1 (GLP-1) as well as glucagon release have been described as potential pathways through which glycine affects T2D risk. Glycine has also been suggested to counteract the effects of dietary fructose (147), making it a metabolite of interest in the study of therapeutic approaches to NAFLD (148).

Dietary **sugars** are a well-known cause of obesity that also works against immune-mediated protection against metabolic syndrome (149). Considering that intestinal glucose concentrations are not increased by a high-sugar diet (150), this suggests an indirect effect of dietary sugars on other signal transduction pathways via a metabolic route.

Metabolites	Effects	Levels in WSD
Sugars Sweeteners	Insulin signaling, storage as TGs, microbiome re-modelling	Excess of glucose, fructose, but also sweeteners
Lipids	Storage as TGs, membrane fluidity, inflammation signaling	Excess of lipids with low saturation fatty acids
Emulsifiers (e.g., lecithin)	Membrane disruption, leaky gut, inflammation	Excess from diet
Branched-chain amino acids (BCAAs)	Insulin signaling	Excess from both diet and microbiome metabolism
Bile acids (BAs)	Membrane disruption, regulation of gene expression and signalling	Excess secondary BAs Shift of secondary to primary BAs ratio
Short-chain fatty acids (SCFAs)	Gut health, immune regulation, signaling	Low due to lack of fiber / substrate for SCFA synthesis
Lipopolysaccharides (LPS)	Immune training, inflammation	Shift from LPS-6 to LPS-4/5
Indoles	Mixed beneficial/deleterious effects	Shift towards inflammation-related
Uremic toxins (e.g., TMA, p-cresol, ...)	Accumulation and poor renal filtration	Excess due to both diet and microbiome metabolism

Table 1: Metabolites involved in priming for complex chronic diseases. These metabolites can come directly from the WSD (ocher), be products of metabolism by the microbiome (blue), or both (green). TMA: trimethyl amine, TGs: triglycerides.

Metabolites from the gut microbiome

The interaction between host and gut microbiome has been investigated and reviewed extensively in the context of metabolic syndrome (151, 152), T2D (153) and overall metabolic health (154, 155). Much of this research uses metabolomics to explain microbiome-host interactions on a functional level.

Tryptophan levels associate with stages of T2D, from high levels in early stages to levels lower than control at advanced stages (156). Levels of tryptophan and **kynurenine**, but not serotonin, are increased in pediatric obesity and prediabetes (157). Although a rise in tryptophan levels is associated with early stages of metabolic syndrome, dietary tryptophan is associated with reduced risk of developing the disease (158). This discrepancy may be explained by differences in gut microbiome. In human cells, the enzymes indoleamine 2,3-dioxygenase (IDO) and tryptophan-2,3-dioxygenase (TDO) commit tryptophan to the kynurenine pathway, influencing inflammation signaling. IDO inhibition has been discussed in a wide variety of chronic diseases including metabolic diseases (159, 160). However, deleterious effects of inhibiting tryptophan metabolism in metabolic diseases have also been reported (161).

As mentioned in section 2, **BAs** are ligands of several nuclear receptors, including FXR. FXR is a key regulator of mechanisms related to energy homeostasis, including glucose, TG, and cholesterol metabolism. In routine clinical biochemistry, BAs are typically measured as a sum, but primary and secondary BAs have very different actions on FXR: several primary BAs are potent agonists, some have no affinity at physiological levels, and several secondary BAs have antagonistic effects (162, 163). In NAFLD, total BA levels are increased but hepatic FXR signaling is down-regulated. This is likely due to an increased proportion of FXR-antagonist secondary BA deoxycholic acid (DCA), while the proportion of FXR-agonist primary (i.e. liver-produced) BA chenodeoxycholic acid (CDA) is reduced (164).

The release of satiety-inducing gut peptides is hindered in the absence of **SCFA** (165). The presence of many – but not all – strains of butyrate-producing bacteria associates with insulin homeostasis (166). Production of butyrate is decreased in T2D subjects (167). Acetate can be protective against NAFLD via its effects on hepatic fatty acid receptors (168).

Tryptophan is metabolized by the gut microbiome into several metabolites, including **indole** derivatives. 3-indoleacetic acid (3-IAA) associates with low-grade inflammation in long-term overweight subjects (169). The levels of 3-indolepropionic acid (3-IPA), produced by commensal bacteria such as selected *Clostridium* species, are inversely associated with the incidence of T2D (170). Dietary intervention with the Mediterranean diet can increase concentrations of 3-IPA (171–173) and supplementation with 3-IPA restores metabolic function in obese subjects by improving gut barrier function (174).

Trimethyl amine oxide (**TMAO**) is a metabolite synthesized by the liver from the microbial metabolite trimethyl amine (TMA) and has been extensively studied as a risk factor for cardiovascular disease. In a study of coronary heart disease, TMAO levels were associated with metabolic syndrome (175), potentially providing a mechanistic link to explain the increased risk of individuals with metabolic syndrome, NAFLD, and T2D for cardiovascular events. However, the debate around the importance of TMAO has not settled, as showcased by the conflicting results regarding the link between TMAO levels and mortality risk (176, 177).

Consequences of insulin resistance

Owing to excessive consumption of refined sugars, problems of insulin regulation are at the core of metabolic diseases. Issues in metabolism and storage of the excess sugars and fats are typical of the WSD. The balance of pro- and anti-inflammatory stimuli induced by changes in lipid metabolism is an important contributor to the progression of metabolic diseases (178, 179). The interplay between metabolism and **inflammation** is sometimes called "metaflammation", with lipid mediators derived from PUFAs and hormones such as leptin and insulin regarded as major drivers (180).

Mitochondrial dysfunction is another common culprit in metabolic diseases (181–188). Relevant examples include changes in mitochondrial metabolism in pancreatic β cells in diabetes (189), in hepatocytes in NAFLD (190), and in adipose tissue

Disturbance	Metabolomic markers	Mechanism
Inflammation	Increased Kyn/Trp ratio	Trp committed to kynurenine signalling related to inflammation
	Increased LPC/PC ratio	Arachidonic acid released from membrane phospholipids causes increase in LPC and decrease in PC
Mitochondrial dysfunction	Increased AC levels in blood	Released from partly processed fatty acids in mitochondrial β oxidation
Intracellular malnutrition	Reduced intra-cellular glucose	Lack of transporters in spite of high levels of circulating glucose
	Lack of SCFAs as energy source (gut lumen)	Low fiber diet + altered microbial species

Table 2: Metabolic markers of WSD-induced disturbances.

of obesity (191). Changes in mitochondrial metabolism appear to also be associated with typical T2D-related endpoints, as shown by recent findings of altered TCA cycle activity in a model of diabetic cardiomyopathy (192), altered mitochondrial dynamics in podocytes, essential renal cells associated with diabetic kidney disease (193), an involvement of mitochondria in metabolic myopathy (194) and endothelial dysfunction in obesity (195).

Glutaminolysis has also been associated with the progression from NAFLD to non-alcoholic steatohepatitis (NASH) (196). There is also ample evidence for the involvement of altered mitochondrial β oxidation of fatty acids in the pathogenesis of metabolic diseases. For example, carnitine palmitoyltransferase 1 (CPT1), a mitochondrial membrane protein that performs the initial step to enable β oxidation of fatty acids via acylcarnitines, has recently been found to be involved in a cross-talk between liver and adipose tissue in hepatic steatosis (197), as well as in the regulation of blood glucose levels by glucagon (198). Recent findings also found a role for macrophages in the interplay between adipocyte mitochondrial metabolism and gut microbiome (199).

Metabolic markers of these three routes towards complex chronic diseases are described throughout the disease-specific sections, with recurring changes summarized in table 2.

4. Priming for cancer

Cancer is traditionally seen as the result of mutations in oncogenes and tumor suppressor genes or of the instability of the genome. As a result, treatment decisions are often based on the genetic landscape of the tumor. However, ~95% of cancers are of somatic origin, and only 5-10% are inherited (55, 200). Thus, in the vast majority of cases, the risk for developing cancer cannot be predicted by genetic screening. Environmental and lifestyle factors can also favor the development of cancer, as exemplified by the well-established association between smoking and lung and throat cancers.

Diet and its effect on BMI have become a factor of interest in oncology, as obesity is known to associate with the onset of several types of cancer (201). Moreover, thousands of different genetic alterations, ranging from tens of thousands of SNPs to millions of mutations, are known to affect genes beyond the reduced set of oncogenes and tumor suppressor genes. Thus, most mutations are "passenger mutations", i.e. somatic mutations that do not directly lead to cancer. Even within the same tumor mass, there can be great genetic heterogeneity (202), which makes cancer a complex disease from a genetic point of view.

However, at the metabolic level, the picture could be much simpler. Here, we propose a model of WSD-driven metabolic reprogramming that leads

to a pre-cancerous state favoring the occurrence and persistence of genetic mutations at the origin of several cancer types.

Genetically, cancer is a complex disease

It is thought that any given tumor harbors between two and eight driver mutations which confer a selective growth advantage, with half of them arising even before tumor initiation. With over 1,000 tumor suppressor genes and over 800 oncogenes described to date, loss-of-function mutations in tumor suppressors and gain-of-function mutations in oncogenes inevitably have broad metabolic consequences. In oncogenes like Myc, Ras, PI3 kinase or in tumor suppressors like p53 or AMP kinase, many of these mutations increase glucose uptake by overexpression of GLUT transporters (203). This enhances metabolization to lactate through aerobic glycolysis, irrespective of oxygen availability – a phenomenon known as the Warburg effect. In addition, oncogenes like Ras and Myc promote glutamine metabolism to fuel the TCA cycle. Thus, driver mutations induce metabolic reprogramming that converges on heightened uptake and utilization of nutrients, resulting in a reduced dependence on extracellular growth factors. These driver mutations switch on an anabolic program, which is usually seen only in highly proliferating cells, for example, during wound healing.

Metabolically, cancer is a simple disease

From a metabolic point of view, cancer is characterized by the activation of three major pathways that are commonly reprogrammed to support the growth, proliferation, and survival of the cancer cell (204); namely aerobic glycolysis, glutaminolysis and one-carbon metabolism. In figure 4, we propose a metabolic model that investigates the triggers originating directly in the WSD, and those arising from the modified microbiome. Together, these place cells in a pre-cancerous state where metabolism is reprogrammed to provide a hyper-proliferative environment driven by enhanced anabolic metabolism.

① Insulin resistance and inflammation

The WSD, and specifically high levels of **TGs** and **BCAAs**, leads to a chronic state of insulin resistance where glucose cannot enter cells. This constitutes a state of cellular malnutrition for cells that rely primarily on glycolysis for their energy demand, even in a glucose-rich environment. Insulin resistance is closely associated with inflammation and a disrupted cellular membrane environment, which necessitates repair processes that rely on anabolic cell metabolism to provide the necessary building blocks and energy.

② Mitochondrial dysfunction and DNA damage

In addition to their membrane-disrupting effects, **secondary BAs** promote genomic instability through multiple mechanisms. These include oxidative damage to DNA via reactive oxygen and nitrogen species **(ROS/RNS)** and damage to mitochondria and the endoplasmic reticulum. Other mechanisms include activation of several plasma membrane enzymes, such as NAD(P)H oxidases and phospholipase 2 (PLA2), which lead to an increase in the micronucleus rate, and chromosome aneuploid mutations (205). In addition, DCA can disrupt several DNA mismatch repair enzymes, such as anaphase promoting complex (APC) and p53, by inducing mutations (205, 108). The disruption of DNA mismatch repair function results in microsatellite instability within the genome (206).

Driver mutations in mitochondrial DNA (mtDNA) are highly prevalent, and are detected in primary, recurrent, and metastatic tumors (207). However, the presence of these mutations alone is not causative. This has been demonstrated through nuclear transfer experiments, where nuclei of cancer cells bearing mtDNA mutations are exchanged with non-cancerous healthy cells. The experiments show that a cancer cell nucleus does not transform the enucleated healthy cell cytoplasm, and instead results in an apparently healthy cell without abnormal morphology, proliferation, or migration properties. However, transfer of the healthy nucleus into enucleated cancer cytoplasm bearing mtDNA mutations results in a pro-metastatic transformation (208).

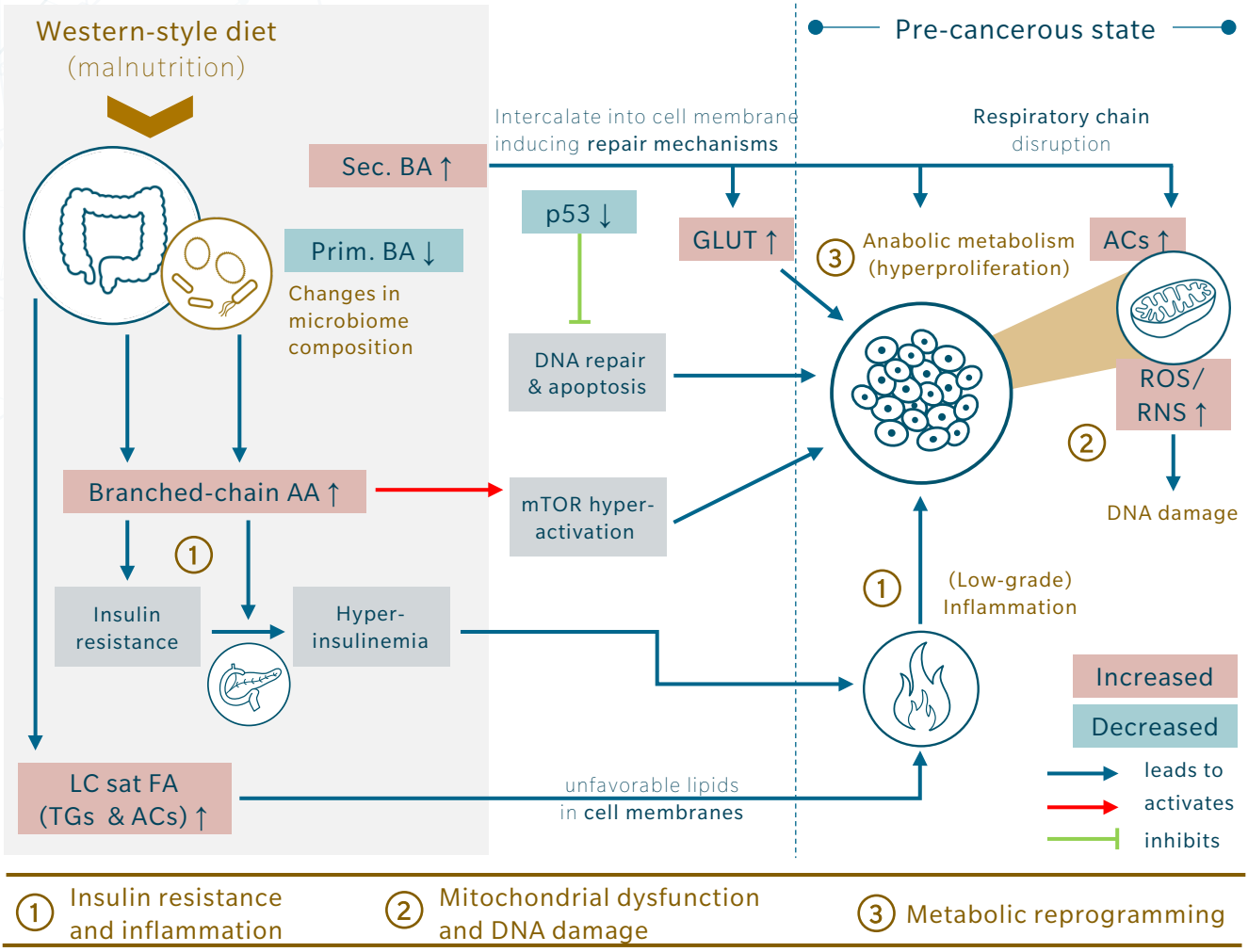


Figure 4: Metabolic model for pre-cancerous state. AA: amino acids, ACs: acylcarnitines, BA: bile acids, GLUT: glucose transporter, LC sat FA : long-chain saturated fatty acids, ROS/RNS: reactive oxygen and nitrogen species.

Shifting the energy source from glucose to fatty acids to compensate the high energy deficit of a cancerous cell leads to an overload of mitochondria. This high demand for fatty acid oxidation becomes problematic in an environment where mitochondrial membranes and respiratory chain activity are compromised (due to the effects of secondary BAs). This results in the accumulation of complex mixtures of unprocessed **acylcarnitines**, which are then released in the blood.

③ Metabolic reprogramming

In the absence of intracellular glucose, other mechanisms take over to maintain cellular integrity and functions. This reprogrammed anabolic cell metabolism supports cell survival, but is also a robust source of energy for the growth, proliferation, and survival of the cell if it becomes cancerous. Three pathways are activated to supply the required energy: aerobic glycolysis, glutaminolysis and one-carbon metabolism.

Activating **aerobic glycolysis** – the Warburg effect – generates energy by metabolizing glucose into lactate. Although aerobic glycolysis produces only two ATP molecules per glucose molecule (compared to 26 ATP molecules through catabolic metabolism in the TCA cycle and mitochondrial respiration), it is considered the primary fuel for cancer cells. This pathway supports the biosynthesis of macromolecules needed for cell proliferation, such as amino acids for proteins, fatty acids for lipids, and nucleotides for nucleic acids. An anabolic cell processes

up to 200 times more glucose than a cell with a catabolic metabolism. In addition, in cells with mutated or degraded p53 (e.g., via the action of secondary BAs), the up-regulation of GLUT expression enables excessive uptake of glucose, so that glycolysis produces NADH faster than it can be transported to mitochondria (209). This is the case in over 50% of human cancers (210). These findings reveal that the main hallmark of cancer, glucose fermentation, is a secondary consequence of metabolite transporter saturation rather than the metabolic driver of cellular proliferation (209).

Glutaminolysis relies on the amino acid glutamine as the primary energy source and synthesizes building blocks and antioxidants. These antioxidants are required to maintain redox balance in the highly oxidative environment generated by cancer cell metabolism. One-carbon metabolism also contributes to the pool of building blocks, primarily using the amino acids serine and glycine as substrates. This pathway is especially important for generating antioxidants and methyl group donors from methionine, an amino acid needed for multiple processes, including epigenetic methylation of newly synthesized DNA and histones.

Conclusions

Our metabolic model proposes a mechanism for cancer priming that produces the hallmarks of the disease, including inflammation, anabolic cell metabolism and DNA damage. This supports the view that cancer needs a disturbed and imbalanced cellular environment to manifest. This suggests that somatic evolution, the accumulation of mutations over time, is not the primary driver of disease manifestation, but rather the consequence of disrupted metabolic processes.

5. Neuropsychological diseases

Alzheimer's disease (AD)

AD is a progressive neurodegenerative disease with no established treatment to halt or reverse disease progression. By 2030, an estimated 78 million people will have dementia worldwide, rising to 139 million by 2050 (25), with a higher prevalence in women (32). Risk factors for AD include metabolic disease (41, 40), NAFLD (49) and T2D (54), with obesity in midlife now ranked as the top modifiable risk factor for dementia in the US (52). Although genetic factors that predispose to AD are well established, adherence to a Mediterranean diet is associated with a lower risk of dementia, independent of genetic risk such as apolipoprotein E (APOE) genotype (211).

In brain tissue, AD is characterized by the accumulation of amyloid beta plaques and tau protein neurofibrillary tangles, synaptic loss, and brain volume reduction. The "amyloid beta theory" postulates that the origin of AD lies in a defect in amyloid beta synthesis and disposal. This has driven AD research for the last 30 years without any significant breakthroughs to improve the prognosis of AD patients. Recent research has explored other factors, including factors that could cause the eventual accumulation of amyloid beta and tau protein in the brain as a secondary mechanism.

As discussed in section 2, long-term adherence to a WSD (i.e., a diet rich in sugars and fats, but low in fibers and long chain PUFAs) leads to unfavorable lipid composition causing low grade inflammation, which has been shown to reduce cell membrane fluidity (92) and influence AD pathophysiology (212). There is mounting evidence for a role of the WSD on age-related inflammation ("inflammaging"), permeabilization of the blood-brain barrier, amyloid and tau accumulation, and memory impairment (213). Adhering to other diets such as the Korean national nutritional guidelines can reduce the risk for developing AD (214).

In this section, we discuss findings from metabolomic studies that investigated novel hypotheses on the etiology of AD. Rather than AD beginning with a problem in amyloid beta and tau synthesis or clearance, could metabolism be a culprit in the onset and progression of AD? Our metabolic model of AD is presented in figure 5.

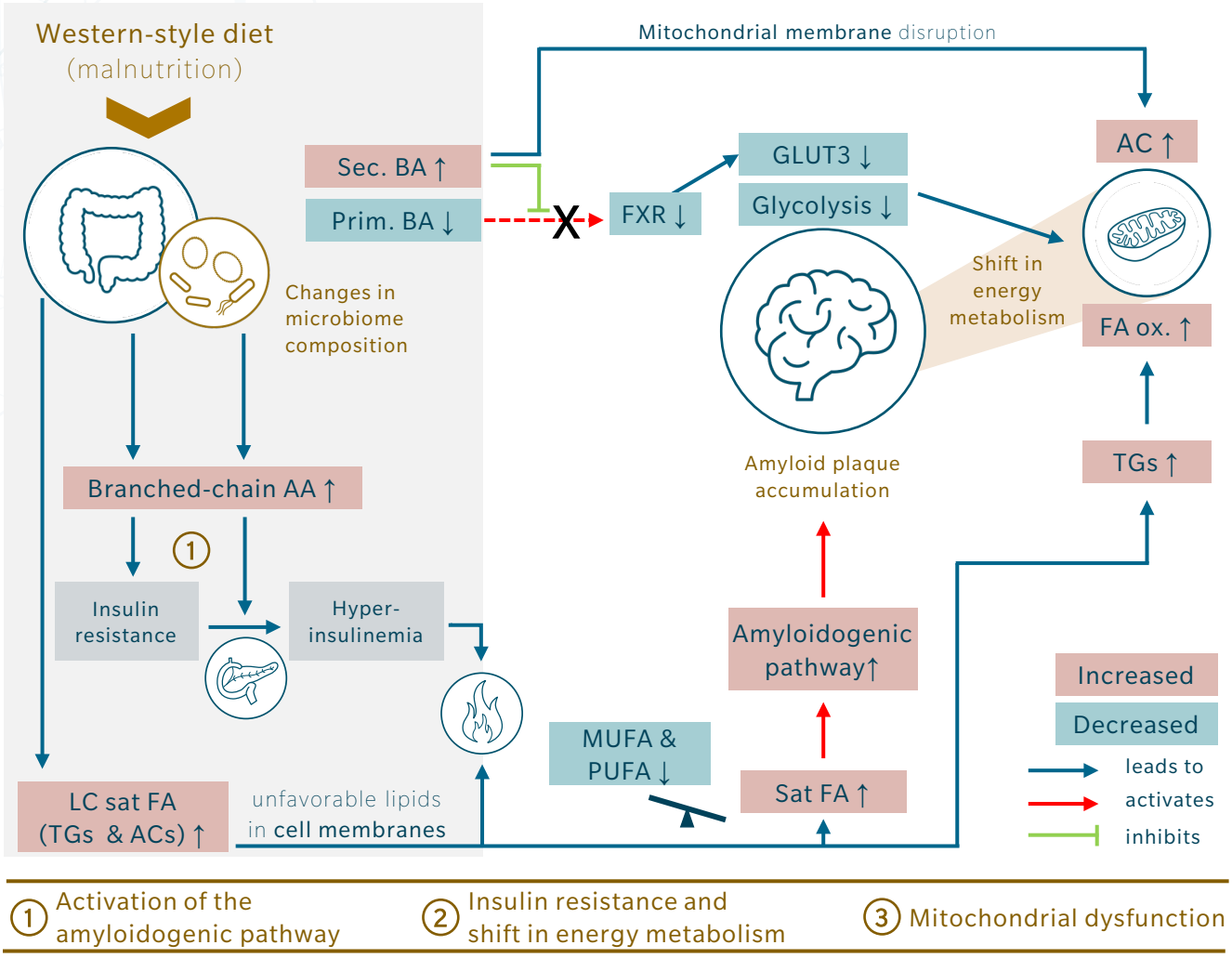


Figure 5: Metabolic model of Alzheimer's disease. AA: amino acids, ACs: acylcarnitines, BA: bile acids, FA ox.: fatty acid oxidation, FXR: farnesoid X receptor, GLUT3: glucose transporter 3, (LC) sat FA : (long-chain) saturated fatty acids, MUFA: mono-unsaturated fatty acids, PUFA: poly-unsaturated fatty acids, ROS/RNS: reactive oxygen and nitrogen species, TGs: triglycerides.

1 Activation of the amyloidogenic pathway

Recent advances in lipidomics have facilitated the study of the exact lipid composition of membranes in the brain together with post-translational processing of the amyloid precursor protein (APP). APP is cleaved by three groups of secretases (alpha-, beta-, and gamma-) that are all trans-membrane proteins influenced by membrane lipid composition. Of note, the fatty acid composition of membrane lipids influences the selection of amyloidogenic or non-amyloidogenic processing of APP (215). In membranes rich in mono- and poly-unsaturated fatty acids, alpha-secretases and the non-amyloidogenic pathway are favored. In contrast, when membranes are rich in **saturated and oxidized fatty acids**, beta- and gamma-secretases are activated, resulting in the synthesis of amyloid beta that can aggregate to form plaques. Following these findings, one of the hallmarks of AD, amyloid beta plaques, can be understood as the consequence of perturbation of membrane composition rather than as a driver of the disease.

This would explain why all attempts to develop game-changing drugs targeting amyloid plaques

have failed to deliver convincing results.

Disturbances in membranes lipids in AD are supported by an analysis of three cohorts within the Alzheimer's Disease Neuroimaging Initiative (ADNI) that demonstrated changes in **phospholipid** levels as early metabolic events in AD pathophysiology, citing changes in membrane composition as a probable explanation (216). Changes in amino acids and acylcarnitines were associated with later stages of AD pathophysiology. These stage-dependent biomarkers in AD are a likely reason why replication of AD biomarker signatures with independent cohorts have been difficult to come by.

② Insulin resistance and shift in energy metabolism

Elevated **TG** levels with saturated fatty acyl chains and **BCAAs** with insulin-like properties (98) are strongly associated with T2D and BMI (91, 139). Epidemiological studies have shown that high blood glucose levels and peripheral insulin resistance are risk factors for AD (217), even though the brain glucose supply – the main energy source of the brain – depends on an insulin-independent glucose transporter, GLUT3.

Analysis of post-mortem brain tissues revealed high tissue glucose levels, a lower glycolytic flow, and significantly less **GLUT3** transporters than in healthy controls (218), suggesting that the reduced expression of glucose transporters creates a need for the brain to utilize different sources than glucose for energy production. This hypothesis of altered energy metabolism as a hallmark of AD pathogenesis was confirmed in a large-scale proteomics study (219). To compensate for the constant energy need, cell metabolism shifts from glycolysis to **fatty acid oxidation**. The peripheral insulin resistance leads to increased TG secretion from the adipose tissue, which sustains the high energy demand of the brain. Due to the commonalities with type 1 and type 2 diabetes, the term "type 3 diabetes" was proposed to describe brain-specific abnormalities in insulin signaling associated with AD (220, 221).

Excess **BCAAs** are associated with obesity and insulin resistance. They also affect brain biochemistry, as circulating levels of BCAAs inhibit the uptake of other amino acids in the brain, altering the production of various neurotransmitters (222). High-BCAA diets have also been associated with lower cortical levels of threonine and tryptophan, with a negative impact on cognition (223).

BA synthesis has been shown to be affected in AD (224). We propose **secondary BAs** as the driving force for the down-regulation of GLUT3 expression in the brain. As introduced in section 2, besides their role in fat absorption secondary BAs are also important signaling molecules. In particular, as ligands of FXR, primary and secondary BAs can have opposing effects on energy homeostasis, innate immunity, and BA metabolism (162). Interestingly, secondary/primary BAs ratio in brain tissue and blood positively correlates with cognitive decline (225). This ratio also correlates with the classical A/T/N AD biomarkers (226).

Increased secondary BAs may therefore inhibit neuronal FXR, and result among other changes in energy homeostasis, in the down-regulation of GLUT3 expression, leading to an incremental intracellular malnutrition. When glycolysis cannot be performed, compensatory processes shift energy supply towards fatty acid oxidation, increasing the demand on mitochondrial metabolism.

③ Mitochondrial dysfunction

Satisfying the brain's energy demands with fatty acid oxidation instead of glycolysis increases the demand on mitochondria. When combined with the membrane disruptions caused by secondary BAs and saturated TGs, this environment can easily lead to overload, mitochondrial dysfunction, and incomplete fatty acid oxidation. Such metabolic impairments can be detected in the blood as a complex mixture of **acylcarnitines**, another marker of late-stage AD (216).

This model suggests that at least some part of AD pathology may be of metabolic origin and caused by malnutrition in the brain, and supports the reclassification for AD as type 3 diabetes.

Major depressive disorder (MDD)

The first written accounts of depression date back to Mesopotamia, more than 3800 years ago (227). Today, depression is estimated to affect over 280 million people worldwide (228). Major depressive disorder (MDD) is the clinical term for this diverse group of diseases. Because of this heterogeneity, finding the most suitable therapy for each patient involves a process of trial and error, with a high cost for the patient in terms of side effects and strain (229). Most therapies target what was believed to be the primary culprit in MDD: disrupted serotonin communication between neurons. But this "monoamine hypothesis" is now heavily criticized (230).

First-line medication such as selective serotonin reuptake inhibitors (SSRIs) typically only work for half of MDD patients. New generations of drug candidates such as ketamine have the potential to bring solace to a fraction of "treatment-resistant" patients (231). But with 50% of depressed patients still without successful treatment, there is an urgent need for better therapeutic options (232). The heterogeneity of MDD profiles is evident in the psychological presentation of the disease, its pathophysiology and metabolomic profiles (233), and must be addressed by precision medicine.

Numerous prospective studies have shown an association between the WSD and depression. Longitudinal studies have shown an increased risk of depression associated with hallmarks of the WSD such as sweetened beverages, processed foods, and high-sugar/high-fat foods (234). Conversely, these studies also found an inverse association between "healthy" diets (e.g., Mediterranean and Japanese diets) and the risk of depression, suggesting a potential avenue for nutritional intervention to prevent or improve symptoms of depression.

In line with these findings, a 2023 study based on National Health and Nutrition Examination Study (NHANES) data collected in the US showed an inverse association of food fiber content with depressive symptoms (235). This supports the notion that adopting a healthier diet and cultivating a balanced microbiome can prevent and/or reverse symptoms of depression. Notably, a Mediterranean diet supplemented with nuts was found to reduce the risk of depression in subjects with T2D (236). However, the association was not significant when combining subjects with and without T2D, suggesting that diet has a greater impact on depression for subjects with an advanced metabolic condition.

Indeed, risk factors for MDD include obesity (57) and cardiometabolic diseases such as T2D (58) and NAFLD (48, 47). Although the link between MDD and metabolic syndrome is less clear, adiposity-driven inflammation has been suggested as a driving force in the development of depressive disorders (237). More drastic dietary interventions such as calorie restriction have also been investigated, resulting in a regression of symptoms of mood disorders, including MDD, upon intermittent fasting and reduced calorie intake (238, 239).

Brain glucose metabolism

Brain imaging using positron emission tomography has revealed decreased glucose metabolism and impaired functional connectivity in specific brain regions in a small set of MDD subjects without anti-depressive treatment (240). An epigenetic study comparing circulating cells of MDD subjects to controls identified hyper-methylation of the gene encoding the insulin-independent glucose transporter GLUT1 (241). This epigenetic modification favors silencing of gene expression and a decrease GLUT1 expression. Methylation for the GLUT4 gene (insulin-dependent glucose transporter) was unaffected.

However, after a 6-week anti-depressive treatment, methylation returned to control levels in individuals who responded to treatment, but not in non-remitters where GLUT1 methylation was maintained. This indicates a reversible mechanism associated with treatment efficacy and depressive symptoms. While these results were observed in circulating cells and not in brain tissue, they suggest a differential regulation of glucose transport in MDD versus control subjects.

In a 2022 study, multiple kernel learning applied to imaging of brainstem regions with increased metabolic activity, specifically glucose metabolism, predicted reward dependence but not novelty seeking or harm avoidance in subjects with treatment-resistant depression (242). In a mouse model, ketamine was shown to ameliorate depressive-like

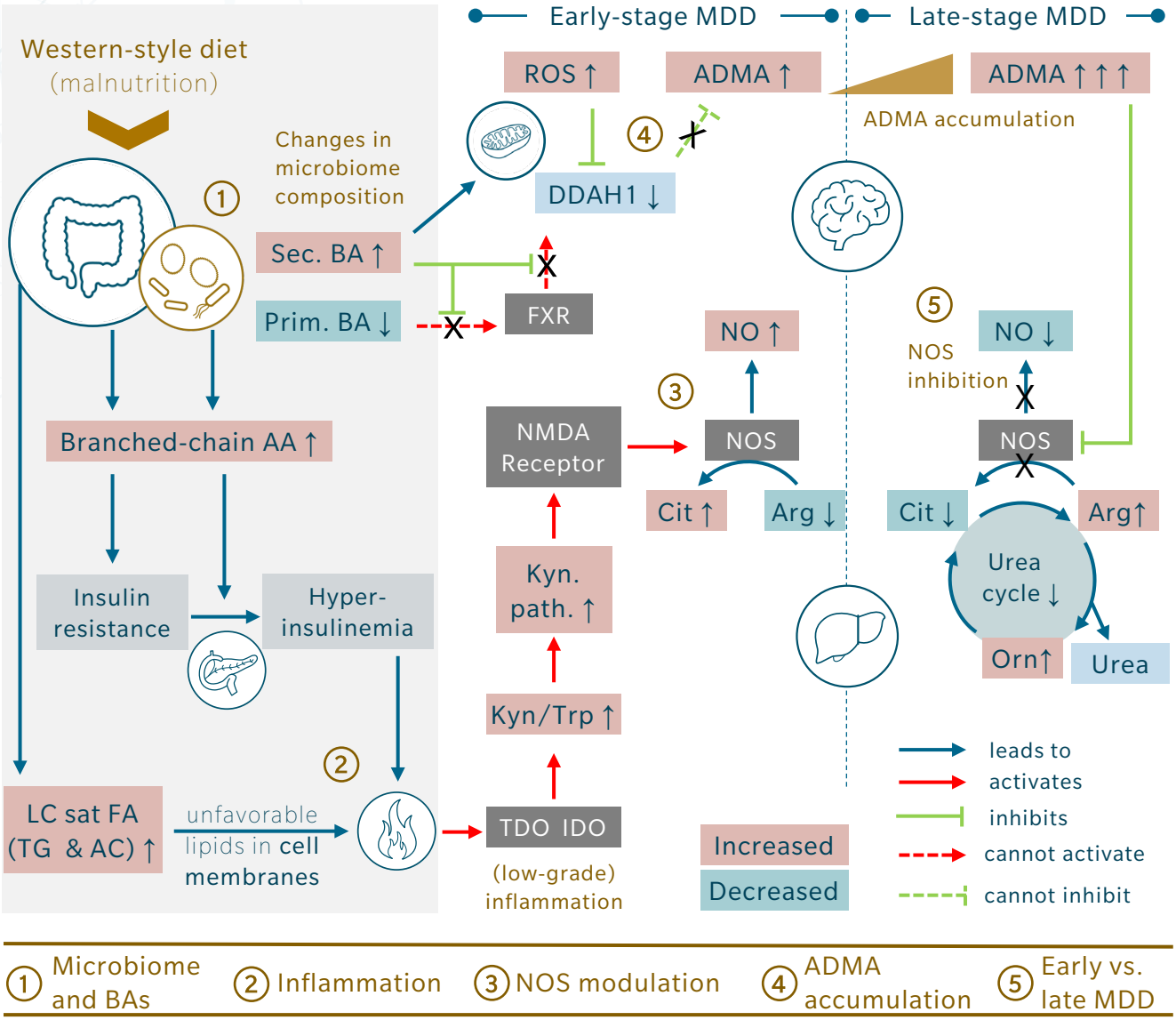


Figure 6: Metabolic model of depression (MDD). AA: amino acids, ADMA: asymmetric dimethyl arginine, Arg: arginine, BA: bile acids, Cit: citrulline, DDAH1: dimethylarginine dimethylaminohydrolase 1 enzyme, FXR: farnesoid X receptor, Kyn/Trp: kynurenine/ tryptophan ratio, LC sat FA: long-chain saturated fatty acids, MDD: major depressive disorder, NMDA receptor: N-methyl-D-aspartate receptor, NO: nitric oxide, NOS: NO synthase, Orn: ornithine, ROS: reactive oxygen species, TDO IDO: tryptophan 2,3-dioxygenase and/or indoleamine 2,3-dioxygenase enzyme.

behavior by increasing glucose uptake in the prefrontal cortex via GLUT3-mediated transport (243). Although our understanding is still developing, these findings point to a role of glucose metabolism in MDD and as an avenue for treatment.

In this section, we used findings from metabolomic studies to investigate novel hypotheses on the etiology of MDD and build the metabolic model of depression presented in figure 6. Besides its direct effects on nutrient supply and cardiometabolic diseases, diet also has a large impact on another culprit in depression: the microbiome.

1 Microbiome and bile acids

As described in section 2, the WSD influences the metabolome directly and through its impact on the gut microbiome. Gut microbiome alpha-diversity is negatively associated with depressive symptoms

(244). A study of mood disorders in obese patients demonstrated a link between microbiota-generated metabolites and mood alterations (245). A microbiome genome-wide association study identified several bacterial strains that influence BA metabolism as associating with depression (246, 247). *Morganella* was identified by Mendelian randomization as a potential cause of depression (248). Levels of **secondary BAs** derived from lithocholic (LCA) and deoxycholic (DCA) acids were decreased in MDD subjects compared to controls (249).

A 2022 gut microbiome-wide association study identified associations of 13 microbial taxa with depressive symptoms in an exploratory set of 1,054 subjects from the Rotterdam Study cohort and a validation set of 1,539 subjects from the Amsterdam HELIUS cohort (244). Mendelian randomization suggested a causal link between MDD and *Eggerthella*. This bacterial strain was found to be increased in patients with depression and anxiety, and contributes to several microbial metabolic pathways, including BA oxidation (247). Administration of probiotics for 8 weeks has been shown to improve depressive symptoms, decrease markers of insulin resistance and inflammation, and increase circulating levels of the antioxidant glutathione (250). In addition, several types of antidepressant treatments have been shown to affect the gut microbiota, while certain bacterial strains could be limiting drug efficacy (251).

② Inflammation

Inflammation is a recognized underlying factor in MDD that can be linked to obesity, but also occurs in patients with lower BMIs (237). The links between BMI, insulin levels and depression are intertwined since childhood (252) and can limit the action of therapeutic interventions (253). In a large meta-analysis of insulin resistance in MDD subjects, insulin resistance was identified as an underlying characteristic of MDD patients that was neither improved by effective antidepressant treatments nor by remission (254).

MDD patients generally have lower circulating levels of **BCAAs** than healthy controls (255, 256), with dietary intake of BCAAs being inversely associated with depression score (257). Blood BCAA levels are determined by dietary intake and synthesis by gut microbiota. Indeed, an analysis of 298 healthy individuals from the cross-sectional KarMeN study showed that BCAA intake explains only around a third of BCAA variation in blood (258). Hence, it is possible that specific effects on the microbiome may contribute to the lower BCAA levels observed in MDD subjects.

Inflammation activates the kynurenine pathway, which often results in an increase in the **kynurenine/tryptophan ratio** in blood metabolic profiles (259). This activation diverts tryptophan to the synthesis of kynurenine and its downstream metabolites. SNPs in IDO and other kynurenine metabolism enzymes have been identified in subjects with depression (260, 261). Multiple studies have identified lower tryptophan, higher kynurenine, and higher kynurenine/tryptophan ratio values in subjects with depression, both in cerebrospinal fluid and in blood (262). The ratio of downstream metabolites kynurenic acid (KYNA) and quinolinic acid (QUIN) is reduced in the serum of MDD subjects, and inversely correlated with anhedonia (263). In the same study, **KYNA/QUIN** was correlated with the duration of remission in former MDD subjects, suggesting a role for these kynurenine derivatives in the progression of the disease.

③ NOS modulation

In the brain, KYNA and QUIN have antagonistic effects on signaling through the N-methyl-D-aspartate (NMDA) receptor. KYNA inhibits the NMDA receptor and is considered neuroprotective while QUIN has the opposite effect and is considered neurotoxic. In neuron membranes, the NMDA receptor influences **nitric oxide** (NO) synthesis with consequences on synaptic plasticity, long-term potentiation and vascular tone regulation. NO synthesis results from the conversion of **arginine** to **citrulline**, and NOS activity is regulated through various mechanisms, including competition for the NOS active site by arginine derivatives.

④ ADMA accumulation

Asymmetric dimethylarginine (ADMA) is a methylated form of arginine and potent NOS inhibitor. In a case-control longitudinal study comparing

plasma metabolite levels of 460 MDD subjects to 895 healthy controls, ADMA, arginine, and ornithine levels were increased, while citrulline levels and NOS activity (as estimated by the citrulline/arginine ratio) were decreased (264, 265). Arginine methylation serves as a post-translational modification of proteins, and methylated arginines are released upon protein degradation in the proteasome. ADMA accumulates in the bloodstream unless the metabolite is excreted (typically only about 5% of total ADMA under physiological conditions) or degraded by the enzyme dimethylarginine dimethylaminohydrolase-1 (DDAH1). DDAH1 activity is regulated by reactive oxygen species (ROS) and the nuclear receptor FXR.

Studies exploring BA metabolism in MDD have suggested a decrease in **secondary BAs**, although Mendelian randomization studies have found that changes in microbiome strains associated with these changes in secondary BA levels may be a consequence rather than a cause of MDD. Thus, it is difficult to distinguish between microbiome changes that are causal to MDD and those resulting from MDD. It is likely that both occur at different times, contributing to the complexity and variety of MDD presentations.

⑤ Early vs. late MDD

We propose that in the early stages of MDD, the metabolic and microbiome environment allows for FXR activation, DDAH1 expression and ADMA degradation, allowing kynurenine metabolites such as QUIN to activate the NMDA receptor and nNOS in neurons. This would result in only minimal ADMA accumulation that still allows a **high production of NO**, leading to habituation.

In later stages, where there are changes in microbiome, BCAA and BA profiles, feedback mechanisms to counteract excessive NO production may kick in. This could impair DDAH1-mediated degradation of ADMA, leading to greater ADMA accumulation and **inhibition of NOS** through allosteric competition with arginine for the enzyme's catalytic site (266, 267).

This mechanism would be independent of the effects of kynurenine metabolites on the NMDA receptor, as ADMA directly interferes with the availability of arginine for NO synthesis by NOS. Consequently, NO production would be reduced, which would be particularly challenging in individuals habituated to higher NO levels in earlier stages of the disease.

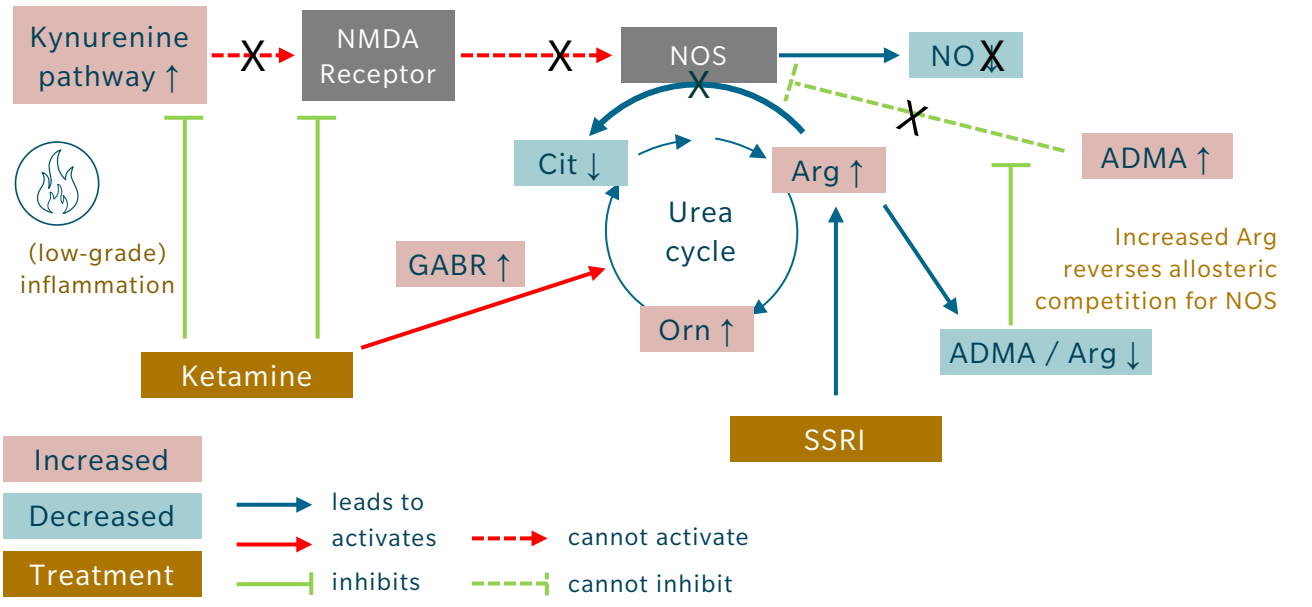


Figure 7: Metabolic model of depression explains effects of anti-depressants. ADMA: asymmetric dimethyl arginine, Arg: arginine, Cit: citrulline, GABR: global arginine bioavailability ratio [Arg / (Orn + Cit)], NMDA receptor: N-methyl-D-aspartate receptor, NO: nitric oxide, NOS: NO synthase, Orn: ornithine, SSRI: selective serotonin reuptake inhibitor.

This model helps explain conflicting findings in depression research that support both elevated and reduced NO production and NOS activity in MDD (reviewed by Joca et al. (268).

NOS expression is not limited to brain tissue. An inducible form of NOS (iNOS) is expressed in other organs such as the liver, where its substrate and product (arginine and citrulline, respectively) undergo the opposite reaction in the **urea cycle**. This pathway is essential to nitrogen balance and results in the synthesis of nitrogen-rich urea for urinary excretion. In MDD, elevated circulating arginine levels and decreased citrulline levels suggest that arginine processing may be inhibited by urea cycle enzymes, in addition to the NOS inhibition discussed above.

Metabolic impact of pharmacological interventions

Interestingly, metabolomic studies focusing on the effects of anti-depressants have shown that SSRIs increase arginine levels, resulting in a decrease of the **ADMA/arginine ratio** (225) (figure 7).

This could support symptom improvement by reversing the allosteric competition for NOS to benefit arginine, even though ADMA levels remain unchanged. Similarly, metabolomics has shown that ketamine causes a marked reduction in inflammation (including decreased **kynurenine/tryptophan ratio**), and shows signs of urea cycle reactivation with an increased global arginine bioavailability ratio (**GABR**, ratio of arginine/(ornithine+citrulline)) (269, 270). These effects of both ketamine and SSRIs, may help mitigate the effects of ADMA as an inhibitor of NOS, but without addressing the high levels of ADMA (figure 7).

Thus, our metabolic model of MDD reveals a role for the arginine metabolite ADMA that has been only indirectly addressed by several generations of anti-depressant medication. Targeting ADMA metabolism may present a promising new avenue for future MDD treatments and a new hope for MDD patients who do not respond to current pharmacological approaches.

6. Autoimmune diseases

Priming for autoimmunity

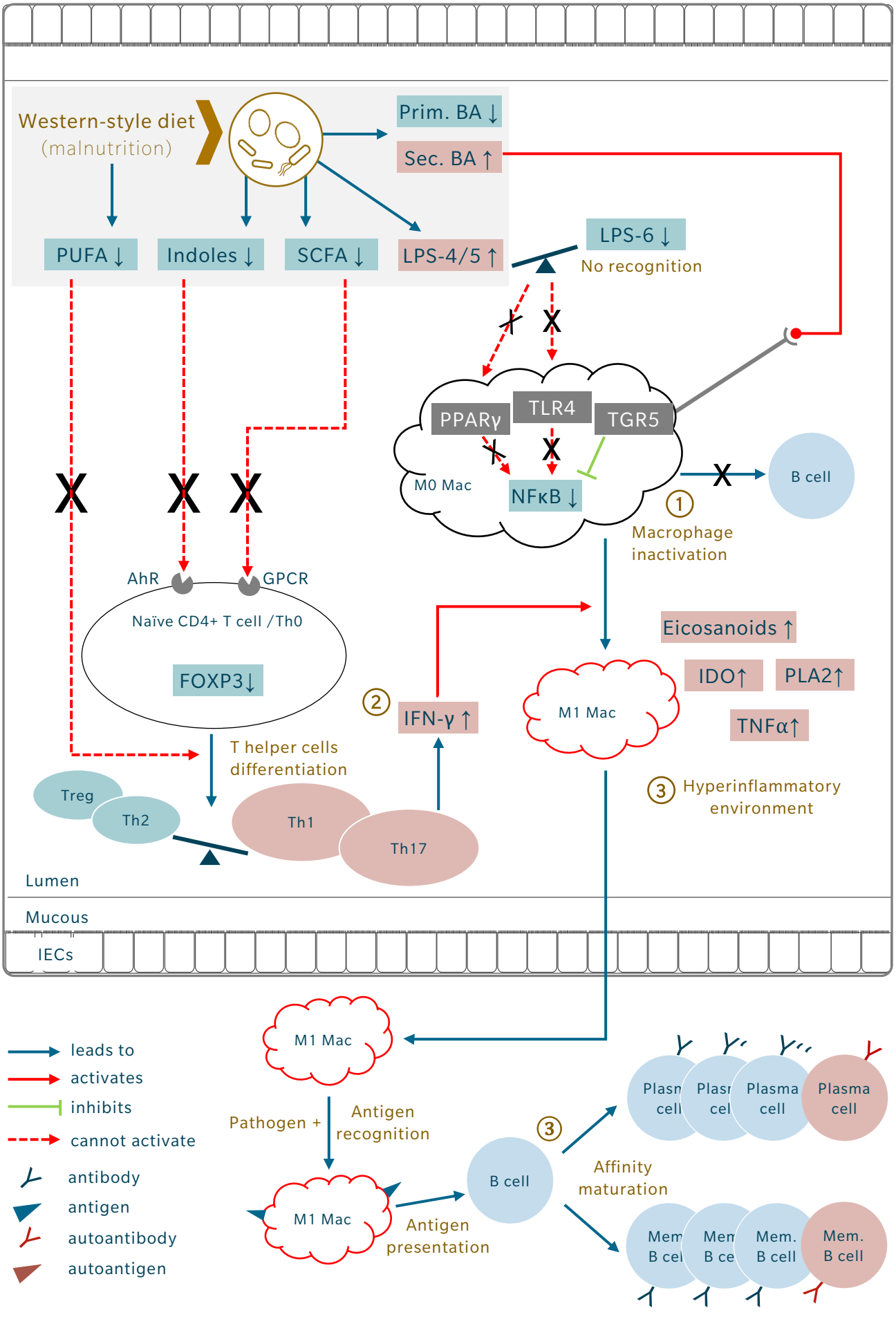
It is widely accepted that genetic factors contribute to the development of autoimmune diseases. However, since many humans with risk variants do not develop disease, these factors can only be one piece of the puzzle. One key characteristic of autoimmune diseases is the development of autoreactive T cells and B cells that produce antibodies targeting the body's own tissues (the self), known as autoantibodies. These autoantibodies can be generated via two routes: (i) in response to self-antigen presentation resulting from tissue damage or (ii) during affinity maturation, the physiological process in which B cells are selected based on their ability to produce antibodies with the highest affinity for a specific antigen, which is used to train the immune system.

While each autoimmune disease has its own unique set of susceptibility genes, one commonality in inflammatory bowel disease (IBD), multiple sclerosis (MS), and type 1 diabetes (T1D) is the presence of susceptibility loci that affect antigen presentation to T and B cells. In autoimmune diseases, affinity maturation wrongly selects B cells that target the self's structures instead of pathogens. These cells can be amplified and/or stored for years until reactivated through an additional trigger, which leads to an immune attack against the self.

The metabolic models described in this section each begin with the same three steps detailed in figure 8.

① Innate immune system suppression

The innate immune system plays a crucial role in presenting antigens to B cells. For example, in the gut, presentation of hexa-acylated LPS (**LPS-6**) contributes to innate immune system training through efficient pathogen recognition and activa-



1 Innate immune system suppression	2 Shift to pro-inflammatory T helper cells	3 Hyperinflammatory environment

tion of the receptor TLR4. By contrast, presentation of tetra- or penta-acylated LPS (**LPS-4/5**) contributes to an inhibition of the transcription factor NF-κB in macrophages, suppressing the innate immune system, with effects on immune system training and maturation (271).

LPS-6 also primes macrophages to respond to a secondary stimulus by triggering the hydrolysis of phospholipids and mobilization of **arachidonic acid** from membrane phospholipids by PLA2 (272). Arachidonic acid, a PUFA, is subsequently used for synthesis of lipid mediators (eicosanoids) and NF κ-B activation, via its agonistic effects on the transcription factor PPAR-γ (273). Interestingly, a characteristic observed in children who later develop autoimmune diseases such as IBD and T1D is a low abundance of plasma lysophospholipids (e.g., lysophosphatidylcholines (LPCs), lysophosphatidylethanolamines (LPEs)) and arachidonic acid, which increase prior to seroconversion (274, 275). These results support the notion that autoimmune preconditioning involves delayed maturation of the innate immune system.

The metabolic hallmarks of a WSD discussed in section 2 further contribute to the suppression of the innate immune system. Inflammation and its effect on tryptophan metabolism can lead to NF-κB inhibition (276). In addition, excess levels of the **secondary BA**, DCA, inhibit NF-κB (277). The suppression of the innate immune system and its impaired maturation result from a **triple inhibition of NF-κB in macrophages**, through inactivation of PPAR-γ, LPS-4/5-mediated effects on the TLR4 receptor, and secondary BA-induced activation of the TGR5 receptor.

② Shift to pro-inflammatory T helper cells

The WSD also affects the lymphoid cells of the adaptive immune system, both directly, through nutritional content (or lack thereof) and indirectly, through its impact on the microbiome, resulting in an imbalance that favors pro-inflammatory T cells. Treg cell differentiation is affected by dietary factors via the FOXP3 transcription factor, which is activated by **PUFAs** and inhibited by **TGs** (278). In addition, **SCFAs** and **indoles** promote Treg differentiation and immunoregulatory function by serving as ligands for the cell surface receptors GPCR and AhR, respectively (279). Prolonged adherence to a diet rich in sugars and saturated fatty acids and poor in fiber, as is common in WSD, results in the accumulation of TGs and depletion of PUFAs and SCFAs. This can reduce FOXP3 expression, prevent naïve CD4+ T cells/Th0 cells differentiation towards Treg, and shift the balance of T helper cell differentiation toward pro-inflammatory Th1 and Th17 cells that release interferon-gamma (**IFN-γ**) (280). At high levels, IFN-γ can overcome the inhibition of NF-κB, prompting **activation of improperly trained macrophages** into a pro-inflammatory M1 state. These activated M1 macrophages exacerbate the inflammation induced by WSD and IFN-γ by producing pro-inflammatory **eicosanoids** and the cytokine **TNF-α**, resulting in a hyperinflammatory environment.

③ Hyperinflammatory environment

An activated but untrained immune system that is devoid of anti-inflammatory regulatory mechanisms and exists in a hyperinflammatory environment will be prone to **mistakes in immune training**. These may be amplified during affinity maturation, particularly in subjects who are genetically predisposed to mistakes in antigen presentation. As a result, faulty antibodies that target the self rather than pathogens can be generated and stored. These misguided antibodies may remain dormant for years or even decades, as seems to be the case in conditions like MS.

In the next section, we describe how this process

Figure 8 (page 25): Metabolic model of priming for autoimmunity. AhR: aryl hydrocarbon receptor, BA: bile acids, FOXP3: forkhead box P3 protein, GPCR: G-protein coupled receptor, IDO: indoleamine 2,3-dioxygenase enzyme, IFNγ: interferon-γ, LPS: lypopolysaccharide, M0 Mac: inactive macrophage, M1 Mac: activated macrophage, NFκB: nuclear factor kappa-light-chain-enhancer of activated B cells, PLA2: phospholypase A2 enzyme, PPARγ: peroxisome proliferator-activated receptor γ, PUFA: polyunsaturated fatty acid, SCFA: short-chain fatty acid, TGR5: Takeda-G-protein-receptor-5, TLR4: toll-like receptor 4, TNFα: tumor necrosis factor α.

primes the immune system for training errors through the WSD and its effect on the microbiome, and how this connects to the pathophysiology of IBD, MS, and T1D.

Inflammatory bowel disease (IBD)

IBD is characterized by chronic inflammation of the gastrointestinal (GI) tract resulting from aberrant interactions between the gut microbiome and the host's immune system. It is estimated that 5 million people worldwide suffer from IBD (2019), with an equivalent impact on males and females. Prevalence of IBD has grown 12.5% in the last decade, disproportionately affecting higher income countries (281). Although IBD is a highly heterogenous disease, it is often studied either as a group or by distinguishing between ulcerative colitis (UC) and Crohn's disease (CD), which present with localized effects in the colon and GI tract, respectively. The two conditions share many characteristics, making them difficult to distinguish in some cases.

While the genetic component of IBD is well established, many subjects with risk variants do not develop the disease, as a **microbial trigger** is required for the effects to manifest. The genetic susceptibility loci for IBD are diverse, including genes related to autophagy, intestinal barrier maintenance, immune cell function (279), and mitochondrial homeostasis (282).

As detailed in section 2, the WSD alters gut microbiota and leads to chronic, low-grade systemic inflammation (283) – a suspected risk factor for autoimmune diseases implicated in the pathogenesis of rheumatoid arthritis (284), MS (285), and IBD (286). Although causal links are yet to be confirmed, there is growing suspicion that the WSD and obesity affect the onset and course of IBD (287), particularly as prevalence is rising in various countries alongside the increased adoption of Western lifestyles (288). An estimated 15-40% of patients with IBD are obese (289) with obesity occurring as a comorbidity, particularly in CD (290). In fact, the WSD has recently been proposed as the most ubiquitous factor in the development of IBD (291, 292).

Accordingly, NAFLD (53) and diabetes (60, 59) occur frequently with IBD. Various dietary interventions have been somewhat effective in altering microbiome composition, reducing inflammation, and inducing clinical remission in IBD patients, including the Mediterranean diet, exclusive enteral nutrition (EEN), anti-inflammatory diets, and the low-fermentable oligo-, di-, mono-saccharides and polyols (FODMAP) diet (293–296), further demonstrating the critical role of diet and inflammation in the development of IBD.

We propose the metabolic model of IBD presented in figure 9, starting after the priming steps presented in figure 8.

① Priming for autoimmunity

Evidence for the role of immunostimulatory **LPS** and innate immune inactivation in IBD development includes the findings that LPS levels from house dust samples are lower for children with IBD than healthy controls (297). In IBD, WSD-induced dysbiosis increases mucolytic bacteria and reduces SCFA-producing bacteria (293–296), consistent with the lower **SCFA** levels observed in plasma/serum and stool from IBD patients (298–300). SCFAs are important for immune regulation, gut barrier function, and metabolic homeostasis, all of which are affected in IBD. IBD microbiomes have higher levels of bacteria that produce hydrogen disulfide, which damages intestinal epithelial cells (IECs) and induces mucosal inflammation (301, 293). Collectively, this contributes to a thinning of the protective mucous layer and a weakening of the epithelial barrier.

As IBD is characterized by inflammation within the GI system, it is not surprising that IBD patients display elevated levels of pro-inflammatory IL-6/12, IL-1β, and TNF-α, (302, 303) in plasma and stool. The levels of other small molecules and lipids also reflect the pro-inflammatory environment. For example, the **kynurenine/tryptophan ratio** is elevated in the blood of IBD patients, due to increased levels of kynurenine and reduced levels of tryptophan (304–309). This is attributed to increased activity of the IDO enzyme and is reflective of the inflammatory environment. Stool and blood samples from IBD patients exhibit reduced levels of microbiome-associated tryptophan catabolites, such as indole-derived **3-IPA** and **indoxyl sulfate** (310, 299, 311). Because tryptophan levels

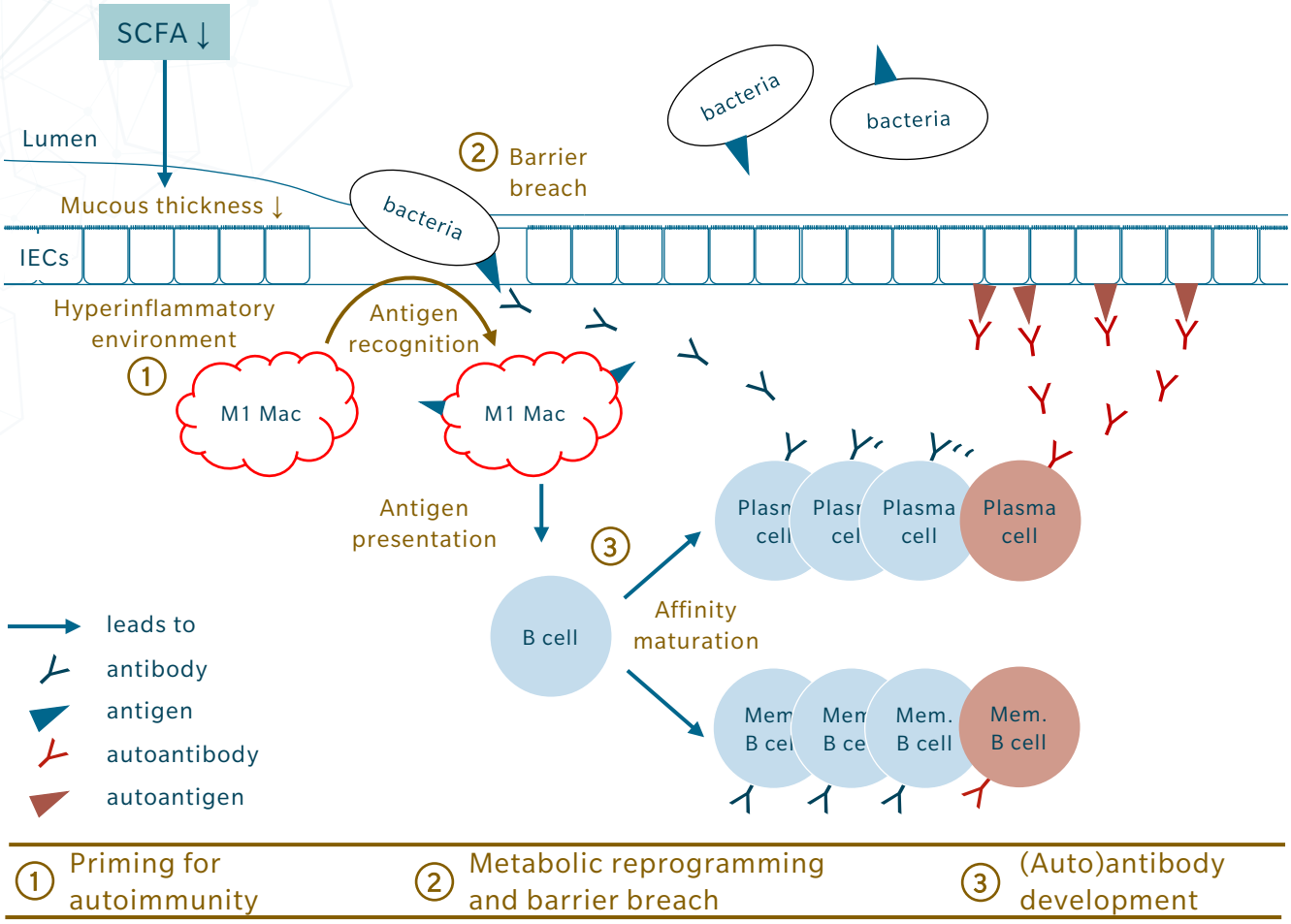


Figure 9: Metabolic model of IBD. IECs: intestinal epithelial cells, M1 Mac: activated macrophage, Mem. B cell: memory B cell, SCFA: short-chain fatty acids.

are elevated in the feces of IBD patients (312, 313, 305), these reduced indole levels may result from microbiome dysbiosis and/or insufficient time to metabolize tryptophan, though the upregulation of IDO activity may contribute as well.

The levels of pro- and anti-inflammatory lipids provide further hints into the mechanisms that exacerbate inflammation in IBD. Studies consistently highlight alterations in plasma and stool levels of **phospholipids** and **sphingolipids**, including sphingomyelins (SM) and ceramides (314, 308, 303, 315, 309, 298, 310, 316, 317). Consistent with the effects of the WSD, a common trend among IBD patients is the accumulation of **TGs** (316, 318, 315, 303) and depletion of circulating **PUFAs** (318, 310, 314, 317, 311). The depletion of PUFAs is particularly relevant given their role as precursors of lipid mediators of inflammatory processes such as **eicosanoids** and **resolvins**. Omega-3 PUFAs (eicosapentaenoic acid, docosahexaenoic acid) have anti-inflammatory functions, while omega-6 PUFAs (arachidonic acid, linoleic acid) are pro-inflammatory. Both omega-3 and omega-6 PUFAs are reduced in IBD serum (318). Higher levels of **eicosanoids** are present in inflamed colonic mucosa of adult UC patients and correlate with the severity of inflammation (319).

Among the ceramides altered in IBD patients, one **lactosylceramide** (LacCer) species in particular was discovered as a uniquely elevated pro-inflammatory lipid in serum (314) and tissue biopsies (309) of pediatric IBD patients. LacCer synthesis is mediated by TNF-α, and is known to activate PLA2, which hydrolyzes membrane-bound phosphatidylcholines (PCs) and phosphatidylethanolamines

(PEs), releasing lysophospholipids and arachidonic acid that is used for eicosanoid synthesis (314).

Interestingly, it was postulated that disease onset is associated with reduced PLA2 activity, after observing decreased levels of lysophospholipids and PUFAs in inflamed biopsies of children with incident IBD (309). This differed from observations in adult populations of patients with more advanced disease (309). Given the role of LacCer in PLA2 activation and observations of LacCer in tissue but not circulating serum, it is reasonable to speculate that the PLA2 activity enhancement was soon to follow.

Collectively, these findings support our metabolic model of IBD. The lack of stimulation by LPS primes the immune system in early stages of autoimmune diseases, resulting in low PLA2 activity, whereas its activity is increased upon subsequent hyperactivation of the immune system.

② Metabolic reprogramming and barrier breach

IECs form a barrier against the luminal environment. They selectively absorb nutrients including sugars, amino acids, and minerals via ATP-dependent transporters. In IECs, the primary energy source is SCFAs that enter the TCA cycle and provide the cofactors necessary for ATP synthesis in the mitochondrial respiratory chain. Therefore, the efficient functioning of mitochondria is essential for IECs to absorb nutrients.

The importance of mitochondrial function is even more apparent during immune cell recruitment, which increases energy demands. This results in a preferential enhancement of mitochondrial β-oxidation, as evidenced by depleted levels of **fatty acids** and accumulation of **acylcarnitines** in plasma samples from newly diagnosed pediatric IBD patients (305, 314). Inflamed tissue biopsy samples also revealed reduced **tryptophan** and **NAD+** levels, with increased levels of **nicotinamide** (NAM) (320, 309). Independent reports of increased serum levels of the precursor, **quinolinic acid** (307), suggest that depletion of NAD+ in tissues are due to high energy demands and mitochondrial dysfunction, rather than deficiency in its production.

Since 1980, a longstanding hypothesis has been that IBD is an "energy deficiency disease" (321). Evidence accumulated over the years supports this hypothesis, particularly reports of impaired mitochondrial function and dysregulation of metabolic pathways resulting from altered host-microbiome interactions and inflammatory signaling. Metabolic profiling of IBD patients with more advanced disease and inflammation have consistently demonstrated elevated **lactate** levels in plasma and stool and reduced plasma levels of **TCA intermediates** (300, 322, 323, 304, 298).

Collectively, these results indicate that disease progression coincides with metabolic reprogramming and mitochondrial dysfunction. Prolonged exposure to the WSD challenges the cell membranes with an unfavorable lipid composition. Intercalated **secondary BAs** induce repair processes that favor anabolic cell metabolism. Meanwhile, a scarcity of **SCFAs** denies IECs their preferred energy source and hinders mitochondrial biogenesis, since SCFA promote mitochondrial biogenesis via activation of the transcription factor PGC1α, which leads to an energy deficit (282). Lack of PGC1α activation also suppresses PPAR-γ signaling in IECs, prompting a shift from β-oxidation to anaerobic glycolysis. To close the energy gap, glucose is imported to IECs from the lumen by glucose transporters. In this anabolic-like status, the availability of redox equivalents is limited. Consequently, an overflow of glycolytic intermediates may be secreted as lactate, since the transporter in the reduced number of mitochondria reach saturation (209), as discussed in the cancer section. Reduced levels of TCA intermediates in both IBD tissue biopsies and blood (323, 309) support this view. These conditions hinder the processing of pyruvate through the TCA cycle, making lactate the primary product of glucose degradation through anaerobic glycolysis (324).

In response to lactate production, monocarboxylate transporters (MCT) secrete lactate to limit acidification of the intracellular environment. Two such transporters are MCT1 and MCT4, which function synergistically due to their distinct substrate preferences. Specifically, MCT4 exports lactate produced during cytoplasmic anaerobic glycolysis, while MCT1 imports lactate for use as an energy substrate in mitochondrial oxidative phosphoryla-

tion (325). Interestingly, in the context of IBD, independent reports have demonstrated that MCT4 is overexpressed (326), whereas MCT1 and several β-oxidation genes are down-regulated in IECs in response to TNF-α and IFN-γ (327, 328). The activity of these transporters explains the elevated levels of lactate in plasma and reduced levels in colon tissue biopsies of IBD patients (329). This is further emphasized by the reduced levels of fumarate in IBD tissue biopsies (323). Additionally, IBD microbiomes exhibit an overrepresentation of lactate-producers, rather than consumers (330, 331), further contributing to the elevated levels of lactate in stool and plasma.

Glucose absorption can be Na-dependent or -independent. The sodium required for glucose absorption typically comes from ATP-dependent transport via the Na/K ATPase pump. In our model, this would be limited by ATP availability due to mitochondrial dysfunction. Interestingly, in subjects with obesity and T2D, the expression of Na-independent and insulin-independent glucose transporter GLUT2 is stabilized at the apical membrane of IECs, while Na-dependent transport through SGLT1 continues. As a result, IECs are flooded with glucose that can be transported into the blood or serve as substrate for glycolysis (332). Metabolic profiling has shown that extracellular glucose is abundantly available, as evidenced by increased glucose levels in blood and stool from IBD patients (322, 323, 300).

When mitochondrial function is compromised and ATP levels are insufficient for Na-dependent glucose transport, GLUT2 becomes the primary means of glucose uptake. In stressful environments like this, epithelial cells can deviate from their main functions, including ATP-dependent transport and barrier function. This weakens the tight junctions responsible for barrier integrity, and increases lactate synthesis and excretion (333). Moreover, since mitochondrial functions control IEC renewal and shedding (282), this sets the stage for continued damage to the gut barrier, allowing commensal bacteria to breach the barrier.

The lactate overproduction and loss of mitochondrial function comes at the expense of oxygen consumption. Extracellular secretion of lactate contributes to a lower pH in the intestinal lumen and locally suppresses the immune system, causing inflammation and reduced tolerance to commensal species. Under these conditions, there is a preference for the colonization of pathobionts over beneficial commensal species, as facultative anaerobes are favored over rather than the native obligate anaerobes (298, 299).

Bile acids

Studies on patients with active and later-stage IBD consistently reveal elevated primary BA levels and reduced secondary BA levels in plasma and stool (298, 299, 334, 305, 302). There are larger discrepancies in BA trends among newly diagnosed patients, though BA profiles for these patients are quite limited. Secondary BAs appear to be elevated in plasma, urine, and stool of patients in early disease stages or in remission (309, 335, 336), while primary BAs are lower (336, 309, 310, 337). A significant limitation of many studies is that participant diets are often standardized, due to study design or prescribed dietary interventions. Therefore, they do not always reflect the normal dietary habits (such as WSD) that can predispose patients to the disease and trigger relapse. Thus, while the dynamics of BA fluctuations after disease onset are well established, the pre-conditioning events that preface these changes need further exploration.

A recent study examined the impact of microbiome community structures and fecal BA profiles on response to dietary intervention among pediatric CD patients (336). The baseline profiles of patients that achieved sustained remission or no remission were dominated by secondary BAs. Conversely, those who achieved non-sustained remission had primary BA dominant profiles, associated with decreased alpha diversity, lower levels of *Firmicutes* and *Bacteroidetes* and higher levels of *Proteobacteria*. While baseline disease activity was low (and comparable) for all groups, those who sustained remission had much less GI inflammation. Taken together, these findings support our model, showing that the early stages of IBD correspond with fecal profiles dominated by secondary BAs. Yet, inflammation-induced microbiome changes induce a shift to predominantly primary BAs. This suggests that dietary interventions to overcome the damage imposed by the WSD are most effec-

tive earlier in the disease course (336).

The inconsistent BA trend among patients in early stages of IBD suggests a **shift in BA pools** during disease progression. This is reinforced by the understanding that IBD microbiomes are largely heterogeneous, and that disease onset and relapse coincide with inflammation-associated shifts in microbiome composition.

Reduced FXR expression has been shown in the early stage of IBD, likely due to low levels of FXR agonists. As FXR influences BA synthesis, this can lead to overproduction of primary BAs in the liver. Subsequent inflammation-induced dysbiosis results in underrepresentation of microbial species that convert primary BAs to secondary BAs. This is supported by results obtained while examining the impact of anti-TNF-α treatment on the progression of hepatic steatosis in CD patients where TNF-α inhibition was associated with reduced steatosis, lower serum TG levels, activation of FXR signaling, and changes in microbiome composition, including increased levels of *Firmicutes* (316). Species of the *Firmicutes* phylum are commensal anaerobes that contribute to SCFA and secondary BA pools.

In IBD patients with active disease, fecal BA levels correlate with intestinal microbiome composition and serum cytokines (338, 302). Specifically, primary BAs positively correlate with IBD-associated microbes, and negatively correlate with healthy microbes, while the inverse is true for secondary BAs. Primary BAs also correlate strongly with IL-1α and TNF-α. Conversely, secondary BAs negatively correlate with these cytokines, as well as IL-1β and IL-6 (302). This can be partially attributed to the depleted levels of the secondary BA, LCA, in plasma and stool (302, 334, 299, 298). Importantly, LCA is the main BA agonist of the vitamin D receptor (VDR), which is known to control Th1 responses and inhibit TNF α- and IFN-γ production (104). As expected, VDR is down-regulated in IBD patients, thus contributing to the pro-inflammatory environment (302).

The priming and hyperactivation of the immune system, the mucosal thinning and the weakening of the epithelial barrier sets the stage for genetically susceptible patients to develop autoantibodies that cause further damage.

③ (Auto)antibody development

As an autoimmune disease, IBD is characterized by the production of antibodies with specificity against the human host (autoantibodies). These include perinuclear anti-neutrophil cytoplasmic antibody (pANCA), and antibodies against exocrine pancreas (PAB) or intestinal goblet cells (GAB) (339). IBD is also characterized by antibodies against the gut microbiome. Both antimicrobial antibodies and autoantibodies are known to precede disease onset and clinical diagnosis (340–342), and antimicrobial antibodies are detected even before biomarkers of impaired gut barrier function and subclinical gut inflammation (343).

Under normal conditions, commensal bacteria are maintained in the vicinity of the mucosal barrier by secretory immunoglobulin A (IgA). These preferential colonization niches promote the symbiotic relationship between microbiome and host. However, when the mucous layer becomes thin, commensal species can breach the mucosal barrier. At this point, the activated and untrained immune system launches the attack against these beneficial bacteria that results in the development of antibodies against these species.

Loss of tolerance to beneficial commensal bacteria, coupled with a hyper-inflammatory environment, allows pathogens to flourish. Indeed – particularly during active disease states – IBD microbiomes are characterized by a reduced abundance of obligate anaerobic bacteria and a higher abundance of pathobionts/facultative anaerobes, including *Proteobacteria* and select members of *Bacteroidetes*. These conditions further exacerbate inflammation and tissue damage, thus setting the stage for the development of autoantibodies. This may be due either to presentation of self-antigens arising from tissue damage, or to affinity maturation – as seen with the pANCA autoantibody, which arises from cross-reactivity to microbial antibodies (344).

Multiple sclerosis (MS)

MS is a demyelinating disease that can result in a broad spectrum of symptoms, ranging from motor and sensory dysfunctions to autonomic and neurological problems. Prevalence of MS is rising globally (345). Growing evidence suggests that child-

hood obesity is a major risk factor for developing the disease (346, 347). At the cellular level, MS is characterized by the loss of the myelin sheath, the lipid-rich covering that surrounds neurons of the brain and spinal cord to enable the quick propagation of action potentials along axons. The main lipid constituents of myelin are **phospholipids** (PE, PC, phosphatidylserine (PS), SM, plasmalogens), **galactocerebroside**, and **cholesterol** (348).

In figure 10, we propose a three-step metabolic model of MS where the hyperinflammatory environment described in figure 8 increases the likelihood of propagation of autoantibodies associated with the disease.

① Priming for autoimmunity

While there appears to be no significant differences in the alpha- and beta-diversity of the microbiome in MS and control subjects (349), several taxa are depleted in MS patients' stool samples, including SCFA-producing bacteria such as ***Butyricimonas***. Experiments in a spontaneous mouse model of MS suggest a major role for the gut microbiome in MS etiology, with the gut microbiome and myelin autoantigens cooperating to trigger demyelination by the immune system (350). The same group showed that transferring fecal microbiota from MS subjects to mice increased the incidence of CNS-specific autoimmunity in transgenic mice expressing a T cell receptor with an autoantigen targeting myelin (351).

In MS, there is a depletion in the number and function of Treg cells, including an impaired capacity to suppress effector T cells (352, 353). This **shifts the differentiation of naïve CD4+ T cells/Th0**

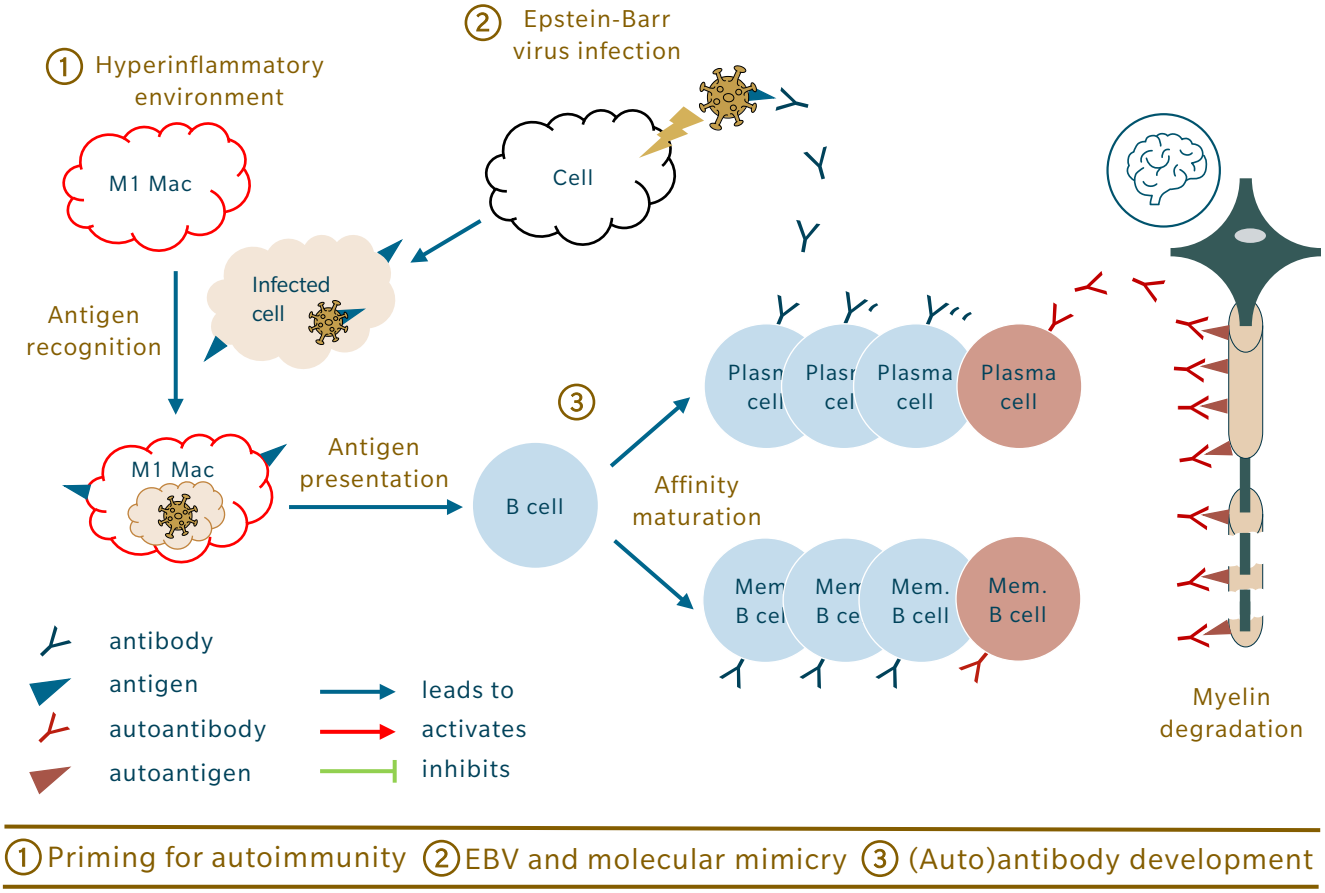


Figure 10: Metabolic model of multiple sclerosis. EBV: Epstein-Barr virus, M1 Mac: activated macrophage, Mem. B cell: memory B cell.

cells towards pro-inflammatory Th17 and Th1 cells (354). This is exacerbated by a hyperinflammatory environment. Studies suggest metabolic intervention can improve disease trajectory in MS patients. For example, supplementing with the SCFA propionic acid has been shown to reverse the Treg/Th17 balance and improve Treg cell activation (349).

② Epstein-Barr virus (EBV) and molecular mimicry

The root cause of MS remains elusive. Multiple epidemiology studies suggest the Epstein-Barr virus (EBV) may play a role in disease development (355). EBV is usually contracted in childhood or adolescence, whereas the onset of MS typically occurs later in life, between ages 20 and 50. A 2022 longitudinal study of over 10 million young adults in the US military found that the risk of developing MS increased 32-fold after EBV infection (356). Of the 801 individuals who developed MS, only one had no trace of EBV infection before MS onset. In the same study, a marker of neuroaxonal degeneration appeared in the blood of the subjects only after they developed antibodies against EBV.

Our model for the priming of the immune system to promote autoimmune diseases offers a plausible explanation for this delayed effect. As noted, the WSD promotes errors in immune training by inactivating the innate immune response and disrupts affinity maturation by establishing a hyperinflammatory environment. This weakening of the innate immune system would foster the selection of B cells that produce autoantibodies in place of EBV-directed antibodies. In a study of the reactivity of B cells of MS subjects, high-affinity **molecular mimicry was identified between the EBV protein EBNA1 and the myelin protein GlialCAM** (357), meaning that the structures of parts of these two proteins were highly similar.

③ (Auto)antibody development

During affinity maturation, antibody testing selects B cells that express antibodies with the highest affinity to the target antigen. This can introduce antibodies that accidentally react against other proteins in the body. Under normal circumstances, the affinity maturation process would identify and eliminate such errors, but in an environment where immune training errors may have occurred in infancy, and in a state of hyperinflammation, errors become more likely and difficult to correct.

The autoreactive B cells can differentiate into plasma cells, which immediately release their antibodies to fight infection, or into memory B cells, which remain dormant until re-exposure to the antigen. The re-activation of stored memory B cells expressing autoantibodies could explain the delay in autoimmunity after EBV infection. The **trigger for re-activation** could come from the release of EBV stored in reservoirs or from an over-reaction of the immune system. Interestingly, EBV typically establishes reservoirs in memory B cells and epithelial cells to evade the immune system, making EBV a risk factor for several types of cancer, including lymphoma, gastric, nasopharyngal and vitreoretinal carcinomas (358).

Supplementing SCFA in MS

In MS, propionic acid blood and feces levels are low and the gut microbiome is altered, particularly after a relapse. Interestingly, the levels of other SCFAs butyric acid and acetic acid are comparable to healthy control levels. Supplementation with propionic acid can change the fecal pH and influence the dynamics of the gut microbiome. A 14-day supplementation with **propionic acid** increased the proportion of Treg (FOXP3+ cells), restored Treg/Th17 balance, led to a gain in Treg function, and increased production of the anti-inflammatory cytokine IL-10 (349). Propionic acid also improved Treg cell mitochondria function and morphology.

Type 1 diabetes (T1D)

T1D is a chronic autoimmune disease affecting women and men equally in which the pancreas produces little to no insulin due to the destruction of insulin-producing pancreatic β cells. In 2019, approximately 22 million individuals were living with T1D worldwide, an increase of 25% within a decade. (281). While T1D can occur at any age, it most commonly develops in childhood (359). Several genetic polymorphisms are associated with T1D and put individuals at varying degrees of risk for developing autoantibodies and/or progression to clinical disease. While the strongest genetic

risk factors occur in the human leukocyte antigen (HLA) gene complex, only 3-10% of those with HLA-susceptibility develop T1D (360). Thus, environmental factors also play a key role in disease progression.

We propose the metabolic model of T1D presented in figure 11, starting after the priming steps presented in figure 8.

① Priming for autoimmunity

In line with our model of autoimmune disease priming, children who develop T1D exhibit a transcriptomic signature characterized by upregulation of interferon (IFN) signaling and innate immune response prior to autoantibody development (361). Genetic risk for autoimmunity has been associated with changes in microbiome dysbiosis but many

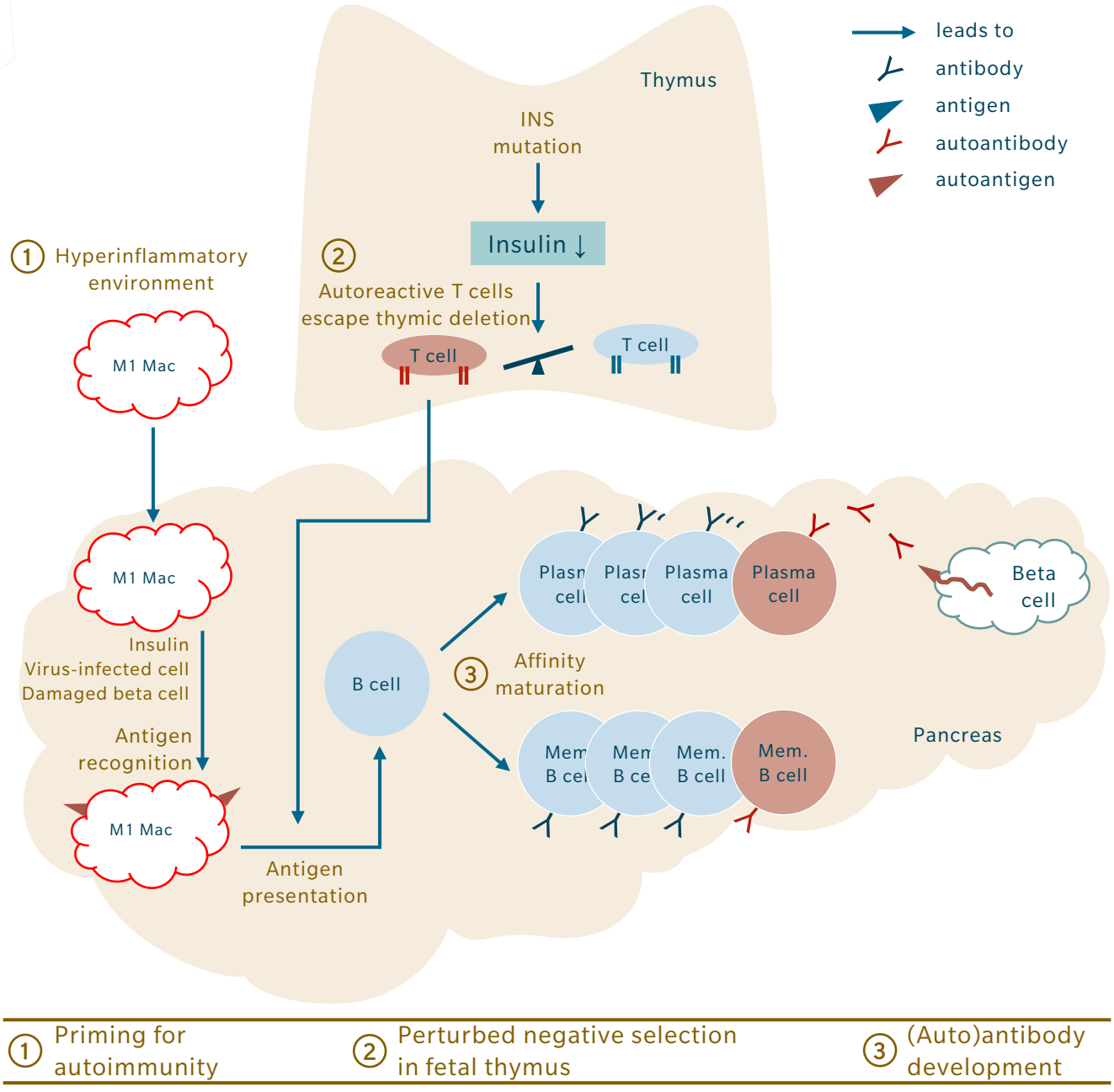


Figure 11: Metabolic model of type 1 diabetes. INS: insulin gene, M1 Mac: activated macrophage, Mem. B cell: memory B cell.

environmental factors have also been explored as potential drivers of T1D, including diet, viral infection, and birth mode (362). As the first stages of microbial exposure determine microbiota composition and influence overall metabolism and immunomodulation, early dysbiosis can have long-term effects on immune function and T1D risk (362). Birth weight and gestational age significantly impact the cord blood metabolome of infants at risk for autoimmune diseases (274). In addition, higher BMI at birth is associated with increased susceptibility to T1D (363).

From an early age, diet has been a potential culprit in T1D progression and autoimmunity against islets, the region of the pancreas where β cells are concentrated. Studies have shown that breastfeeding may confer a protective effect on the child, due to bioactive molecules in breast milk that modulate GI and immune function and the microbiome (362). In fact, many of the same microbial species that confer protection against T1D through **LPS-6** are also enriched in breastfed infants compared to formula-fed infants (362, 271). This provides a link to the delayed immune maturation described in our priming model.

The consumption of fish-derived fatty acids during breastfeeding and infancy may be protective against β cell autoimmunity. Higher ratios of omega 6 to omega 3 fatty acids (such as the **arachidonic acid/docohexaenoic acid ratio**) are associated with increased risk of autoimmunity (361). Breastfeeding may also offer indirect protection by avoiding early exposure to foreign food antigens such as gluten and bovine insulin, which are present in formula. These antigens trigger cytokine release which induces inflammation and affects the microbiome, thus increasing gut permeability (362).

The microbiome plays a major role in T1D. Children who develop T1D have a depletion in SCFA-producing bacteria (364). Prior to seroconversion (when autoantibodies can be detected in the patient's blood), children have elevated serum levels of **BCAAs** and associated alterations in their corresponding **keto acids** (275). BCAA levels remain elevated in serum and stool between seroconversion and the onset of clinical disease, and seroconversion reflects a point at which the levels of serum **TGs** rise and remain elevated (365, 366). As described in section 2, BCAAs act as insulin analogues and can induce insulin resistance at chronically high levels. Interestingly, an inverse trend has been observed for **ascorbic acid**, which is known to inhibit insulin secretion (367, 368). The prolonged elevation of BCAAs, together with the depletion of ascorbic acid and insulin secretion mediated by the secondary BA **LCA** all point to a temporary hyper-insulinemia phenotype which would cause β cell damage and ultimately, insulin resistance.

Individuals who progress to T1D experience a distinct shift in their microbiome composition after seroconversion. This is associated with an overabundance of detrimental microbiome species and lower abundance of bacterial species that are depleted during inflammatory states (365). Microbiome analysis indicates that species present in the gut of T1D progressors are more auxotrophic, with upregulated GLUT transporters and downregulated amino acid biosynthesis pathways (365). As in IBD, this suggests that the onset of inflammation and autoimmunity induces further dysbiosis of the microbiome.

Insulin resistance results in hyperglycemia, which inhibits glycolysis, reducing pyruvate levels and thereby downregulating the TCA cycle. Accordingly, infants who go on to develop T1D have high levels of **pyruvate**, which decrease upon seroconversion, alongside a reduction in previously elevated levels of **TCA intermediates** and **amino acids** (369). Additionally, low levels of certain **fatty acids** in early infancy are likely indicative of increased energy demand in T1D progressors (370). These metabolic patterns appear to signal a transition from catabolic to anabolic metabolism, perhaps due to the depletion of reducing equivalents and resulting ER/oxidative stress.

Metabolites play a significant role in T cell regulation. As described for IBD, the secondary BA, LCA, is a known agonist of TGR5, leading to downregulation of NF-κB in dendritic cells (DCs) and macrophages and reducing production of proinflammatory cytokines. *In vitro* studies have shown that LCA pre-treatment of DCs reduces the abundance of Th1 and Th17 cells, as well as IFN-γ (371). Interestingly, **downstream LCA metabolites** have a differ-

ent effect, shifting naïve CD4+ T cells/Th0 cells away from Th17 differentiation and towards Treg differentiation via upregulation of FOXP3 (372). These LCA metabolites are produced by bacterial species such as *Eggerthella* that are underrepresented in T1D patients (365, 373), although it has been suggested that this bacterial strain may activate Th17 cells (373).

The agonistic effects of LCA on the TGR5 receptor also promote insulin release from β cells, due to the role of TGR5 in mediating the release of GLP-1 (374). After seroconversion, T1D progressors exhibit decreased LCA levels and increased SM levels in stool – both of which associate with an overabundance of detrimental microbiome species (365). A recent study investigated the role of microbiome-mediated BA metabolism on progression to autoimmunity (375). It revealed that children who develop multiple islet autoantibodies had lower levels of **conjugated BAs** in early life and lower levels of secondary BAs at seroconversion (in serum and stool) due to microbiome dysbiosis and dysfunction of bile acid metabolizing ability, which was corrected after autoantibody development (375).

Altogether, these findings support our model of autoimmune disease priming. In early stages, LCA accumulation contributes to delayed immune maturation and promotes insulin secretion, potentially adding stress to β cells. The microbiome dysbiosis that follows induction of autoimmunity causes LCA levels to drop, which further promotes the immune response and inflammatory environment.

Choline is another metabolite of interest. **Choline** controls the secretion of TG-containing VLDL-protein particles, and its absence results in depletion of serum **TGs** and their hepatic accumulation. Choline deficiency may also explain decreased levels of TGs in T1D progressors at birth and during infancy (275). Children who are at high risk of developing and/or who develop T1D exhibit lower circulating levels of PCs, particularly **PUFA-PCs**, and **SMs** at birth, which inversely correlate to HLA risk genotypes (275, 274). As choline is a building block for both and its metabolism is microbiome-dependent, this suggests that T1D progressors are choline-deficient at birth, due to microbiome modulation resulting from the mother's diet during pregnancy. From birth through autoantibody development, T1D progressors consistently present with depletions of ether phospholipids (**PC and PE plasmalogens**) that protect cells from oxidative damage. As pancreatic β cells are particularly sensitive to metabolic and oxidative stress, the loss of these antioxidant phospholipids likely renders β cells even more susceptible to oxidative damage that may arise in response to a pro-inflammatory environment (275). Consistent with chronically low PC levels, the levels of pro-inflammatory **LPCs** increase prior to seroconversion (275), likely due to PLA2 activity. This is supported by the finding that elevated levels of proinflammatory **eicosanoids** are observed in peripheral blood mononuclear cells (PBMC) isolated from progressors prior to seroconversion (376). Altogether, this suggests that choline deficiency (modulated by microbiome dysbiosis) is the root cause of low PC levels. However, consistent depletion of PCs is a byproduct of PLA2 activity that occurs upon activation of the immune system and contributes to the hyperinflammatory environment.

The depletion of PC and SM may also be attributed to exposure to environmental triggers, particularly **perfluoroalkyl substances** (PFAS). Maternal PFAS exposure results in altered BA levels, as well as decreases in PC, SM, and the SM precursors, **serine** and **palmitic acid**, in the cord blood of high-risk infants (374). These trends are consistent with those observed in separate studies on T1D progressors, as described above for the PC and SM profiles. PFAS exposure led to decreased serum levels of **primary BAs**, cholic acid (CA) and chenodeoxycholic acid (CDCA), and an accumulation of the secondary BA, **LCA**, in infants prior to seroconversion (374). While PFAS share structural similarities with fatty acids, they are believed to function like BAs, including their enterohepatic circulation. It is possible that PFAS influence SM levels directly, or indirectly by influencing the BA levels that support the absorption of dietary lipids. Secondary BAs, especially LCA, are known to cause depletion of circulating lipids, such as PC and SM (275, 374). Through their influence on BA absorption, PFAS appear to affect lipid absorption, which leads to immune modulation.

② Perturbed negative selection in fetal thymus

Some T1D patients have genetic polymorphisms in the insulin gene (*INS*) that result in reduced insulin expression in the fetal thymus (361), where the process of negative selection of T cells occurs. During **negative selection**, self-antigens are presented to naïve CD4+ T cells/Th0 cells and any autoreactive T cells that have a high affinity for the self-antigen undergo apoptosis to avoid autoimmunity. Reduced insulin expression in the fetal thymus limits the substrate available for negative selection, allowing insulin-reactive T cells to escape to the periphery (377). In line with this, *INS* variants that increase thymic insulin expression are protective against T1D (378).

③ (Auto)antibody development

Autoreactive T cells from the thymus and macrophages activated in the gut during priming can be transported through the circulation to the pancreatic lymph nodes and islets. There, they can work together to present autoantigens against insulin and islet molecules from damaged β cells and help B cells differentiate into plasma cells for autoantibody production.

Several factors may contribute to β cell damage, all of which converge on a hyperinflammatory environment and an increased demand for insulin. The WSD pre-conditioning sets the stage for basal inflammation, and its impact on the microbiome results in a loss of gut barrier function, which can provoke further inflammation. Moreover, these antigens may have cross-reactivity with self-antigens specific to T1D development.

Antigens resulting from viral infection have attracted interest here. While there is limited evidence for a role of viral infection – and particularly, molecular mimicry of viral antigens – in T1D pathogenesis, it certainly remains a possibility. Specifically, enterovirus infections have been implicated in T1D pathogenesis (379). Cross-reactivity has been reported between an enterovirus peptide and the IA-2 islet antigen epitope, and antibodies against enterovirus are reported to recognize islet antigen epitopes. It is known that enterovirus infections can reactivate other dormant viruses (380). Interestingly, a key DNA-binding protein from cytomegalovirus can cross-react with GAD65-specific T cells (381). Yet, the timing of enterovirus infections as triggers for T1D development is inconsistent. Some studies report infections at or just prior to diagnosis, while others report infections prior to appearance of autoantibodies (382). Further search is needed to determine whether affinity maturation of viral antigens has a role in T1D pathogenesis. In any case, viral infections may also be implicated in T1D development as they increase the demand for insulin due to heightened energy requirements to fight off infection (382, 383, 362).

Rather than competing to explain the shift to progressor status, these **different triggers** may reflect a variety of ways to reach a T1D disease in subjects that were primed for autoimmunity in infancy, which may be reflected in the heterogeneity of presentations in T1D subjects (379).

Prevention of autoimmunity is key to tackle T1D. Based on our metabolic model, we suggest **propionic acid supplementation** similar to that described in the MS section. Supplementation with this SCFA in genetically pre-disposed high-risk infants would likely have the following positive effects on the recipients: shift pH in stool, favoring SCFA-producing gut bacteria; offer a substrate for IECs, helping to maintain barrier integrity; and promote anti-inflammatory signaling by increasing functional Treg cells and reducing Th1 and Th17 cells.

Given that the first 18 months of life are the most vulnerable for T1D manifestation, propionic acid could reactivate the innate immune system and help prevent triggers causative for autoimmunity.

7. Conclusions

Recognizing that complex chronic diseases have a common origin unlocks new strategies that offer real hope for early diagnosis, improved treatment, and prevention of these diseases (figure 12). The metabolic models introduced in this white paper demonstrate the relevance of metabolomics to identify mechanisms that lead to each disease's phenotype, and its potential to uncover new potentially druggable targets based on metabolic changes.

Modelling the entirety of a disease's pathophysiology is outside of the scope of this white paper. We have deliberately narrowed the scope of our models to the aspects of the diseases that can be addressed with metabolomics. This allows us to demonstrate the power of metabolomics and present it as a tool of choice to address diseases with a heterogeneous presentation, such as depression, MS, and IBD, where metabolic profiling provides a level of phenotypic detail out of reach for genomics.

Taking diet and other environmental factors into account is essential to avoid bias in epidemiological research. However, if diet and its impact on the microbiome are a driving force of disease, they should not merely be treated as a confounding factor by statistical analysis. Rather, we should use metabolic profiling to dive deep into the consequences of diet, including its nutritional composition, its effects on the microbiome and its impact on our organs.

A better understanding of the pathophysiology of complex chronic diseases will pave the way for the next generation of therapeutic, diagnostic, and preventive approaches, with metabolomics-based precision medicine at its core.

As this white paper has demonstrated, metabolomics can reveal relevant important insights for complex chronic disease prevention, earlier diagnoses, and more effective patient care. To explore how metabolomics could support your research, book a demo with our experts.

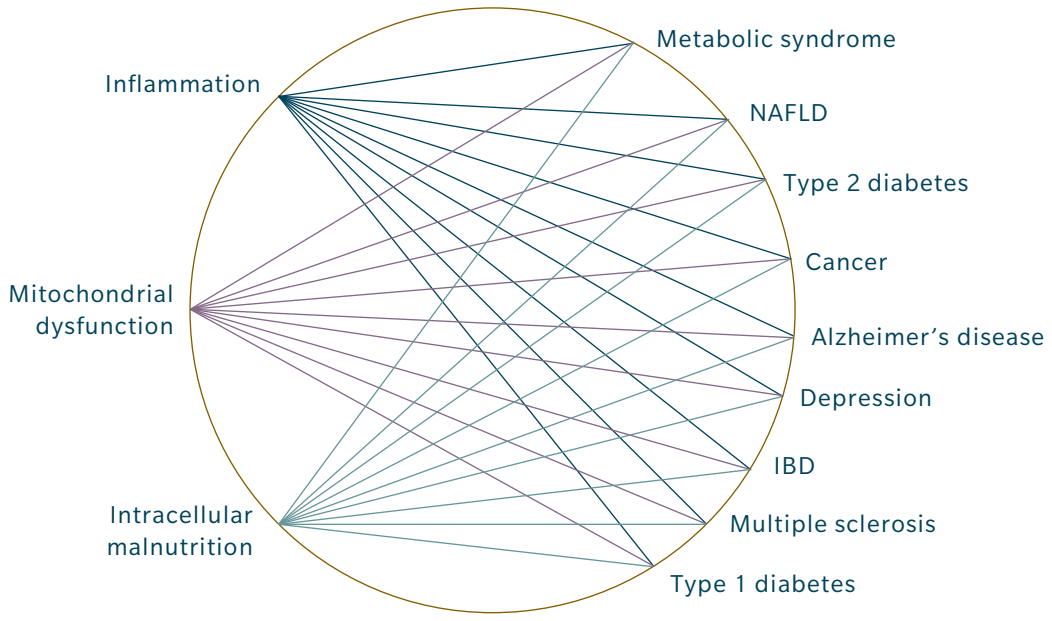


Figure 12: Complex chronic diseases share common mechanisms that lead to different pathologies.

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