Research Article

Integrated Assessment of Gut Microbiota, Liver Function, and Metabolic Health Among Adolescents: Implications For Preventive Medicine

Dr. Manabendra Nayak[1], Dr Dipak Kumar Boro[2], Dr Binisha C[3], Dr Bharat Agravat[4], Dr Kartavya Agravat[5], Dr. Himanshu Jha[6]

[1]HOD Dept of Medicine Down Town Hospital Guwahati, Post Graduate Teacher of Medicine NBEMS, Internal Medicine, Passout under Gauhati University, Email: dr.mnayak@yahoo.co.in
[2]Classified Specialist Medicine, Command Hospital Air Force Bangalore, Email- dipakkumar365@gmail.com
[3]Assistant Professor, Kaumarabhritya, Parul University, Email ID: chothayothbinisha@gmail.com , Orcid ID:0009-0003-8970-8231
[4]Dental Surgeon, Gujarat University, Email Id: agravatresearch@gmail.com
[5]Dental Surgeon, Karnavati University, Email- dragravatthesis@gmail.com
[6]DNB PGT, Family Medicine, Family medicine, Down Town Hospital Guwahati, Email I'd: DRHJ37@GMAIL.COM

Abstract

Adolescence represents a critical developmental window during which disturbances in metabolic regulation may establish long-term trajectories toward obesity, insulin resistance, dyslipidemia, and fatty liver disease. Growing evidence implicates the gut microbiome as a key mediator of these processes through its effects on nutrient metabolism, intestinal barrier integrity, microbial metabolite production, bile acid signalling, inflammation, and hepatic lipid homeostasis. This review evaluates the interrelationship between gut microbiota, liver function, and metabolic health in adolescents and examines its relevance to preventive medicine. Peer-reviewed literature published between 2020 and 2026 addressing adolescent microbiome characteristics, hepatic dysfunction, metabolic abnormalities, associated mechanisms, and microbiome-targeted interventions was critically synthesised. Current evidence indicates that altered microbial diversity, taxonomic composition, and functional activity are associated with obesity, impaired glucose regulation, dyslipidemia, and hepatic steatosis. These relationships are further shaped by diet, adiposity, endocrine status, environmental exposures, and host susceptibility, emphasizing the multifactorial nature of the gut–liver–metabolic axis. Dietary modification and other microbiome-oriented approaches show preventive potential, but microbial biomarkers and targeted therapies remain insufficiently validated for routine clinical use. Integrating microbiome data with anthropometric, metabolic, and hepatic assessments may improve early risk stratification. Longitudinal and interventional studies are needed to establish causality and determine whether microbiome-informed prevention provides sustained clinical benefit beyond conventional lifestyle-based strategies.

Keywords: Adolescents, Gut–Liver Axis, Gut Microbiota, Metabolic Health, Preventive Medicine

1. Introduction

Adolescents are a sensitive developmental window, where hepatic and cardiometabolic health may be impacted by metabolic, hormonal and behavioural changes (Jian et al. 2021). As more young people are becoming overweight and obese, so has the awareness of children and adolescents with metabolic dysfunction-associated fatty liver disease and associated metabolic abnormalities (Le Garf et al., 2021). Fatty liver disease in children is clinically relevant due to its relationship with other metabolic abnormalities such as adiposity, glucose regulation disorders, lipid metabolism, and systemic metabolic function (Vimalesvaran et al., 2024). It is therefore recommended to use pediatric definitions of metabolic fatty liver disease that include evidence of metabolic dysfunction and not just hepatic steatosis (Eslam et al., 2021). Standardised assessment and management strategies for pediatric metabolic dysfunction-associated fatty liver disease (P-MAFLD) are further emphasised in more recent multidisciplinary recommendations. Standardised assessment and management strategies for pediatric metabolic dysfunction-associated fatty liver disease (P-MAFLD) are also highlighted in more recent multidisciplinary recommendations (Zhang et al., 2024).

The gut microbiota has become an important part of the biological regulation of metabolism and host health (Fan & Pedersen, 2021). Intestinal microorganisms are involved in the metabolism of nutrients, energy harvest, production

of short-chain fatty acids, transformation of bile acids and preservation of intestinal barrier integrity and regulation of immune responses (Fan & Pedersen, 2021). These physiological processes can be affected by changes in microbial composition and function, which can lead to metabolic dysfunction (Fan & Pedersen, 2021). In addition, increased permeability of the intestine could allow the passage of microbial products into the portal circulation, and so stimulate the liver to be exposed to pro-inflammatory signals (Fan & Pedersen, 2021). These mechanisms suggest a biological mechanism for the gut–liver axis and its possible role in hepatic steatosis and metabolic disease (Fan & Pedersen, 2021).

Recent research in children has shown links between changes in the gut microbiota and metabolic disorders linked to obesity (Cho, 2022). The differences in the microbial composition and metabolic activity have been reported between obese children and metabolically healthier children (Yuan et al., 2021). Metabolically associated fatty liver disease (MAFLD) has also been associated with distinct differences in the gut microbial composition compared with the controls (Ji et al., 2024). Microbiota analysis by metagenomics of stool samples in children and adolescents has revealed an association between the presence of Megamonas species and nonalcoholic fatty liver disease (NALFD) (Megamonas species with nonalcoholic fatty liver disease in children and adolescents, 2022). Similar gut microbiota changes have been observed in adolescents with fatty liver disease and metabolic and hepatic abnormalities (Amrousy et al., 2024). There is also emerging evidence that early metabolic dysfunction and hepatic steatosis (HFE) may result in changes to microbial metabolite profiles in adolescents (Zeber-Lubecka et al., n.d.). These results indicate that functional changes within the microbial community can offer more information than just taxonomy (Zeber-Lubecka et al., n.d.).

The composition of gut microorganisms and metabolic status of children and adolescents is largely influenced by diet (Jian et al., 2021). Healthy gut microbiota-related diets could also be linked with a healthier hepatic metabolic profile (Kamrani et al., 2026). Children and adolescents who are overweight or obese with a higher Dietary Index for Gut Microbiota are less likely to have metabolic dysfunction-associated fatty liver disease (Kamrani et al., 2026). It may also be that the microbial developmental trajectory in early life can affect the developmental trajectory later in life when interacting with dietary or environmental exposures and other ecological factors (Jian et al., 2021). These findings further demonstrate the importance of the adolescent period as a window for microbiota and metabolic risk prevention.

However, gut microbiota, liver function and metabolic health are often studied clinically and biologically separately, in spite of compelling evidence (Fan & Pedersen, 2021). This piecemeal approach could hinder the understanding of the interaction between microbial and hepatic disorders and systemic metabolic disorders that occur during adolescence (Vimalesvaran et al., 2024). A holistic evaluation of all these areas could lead to better identification of early biological and metabolic markers for future disease risk (Zeber-Lubecka et al., n.d.). This approach could also assist in recognising diet and lifestyle factors that could be included in the prevention strategies for high-risk adolescents (Kamrani et al., 2026). It may therefore be beneficial to consider the gut microbiota–liver–metabolic axis as a whole to better stratify risk for early intervention and prevention of chronic metabolic and liver disease.

1.1 Objectives of the review

This review evaluates the interrelationship between gut microbiota, liver function, and metabolic health in adolescents. It examines microbial alterations associated with obesity, insulin resistance, dyslipidemia, and metabolic dysfunction-associated fatty liver disease. The review also explores key biological mechanisms linking the gut–liver axis with metabolic dysfunction and identifies modifiable dietary and lifestyle factors relevant to prevention. It further assesses the potential role of microbiome-related markers and interventions in early risk stratification and preventive medicine.

2. Review

2.1 Gut Microbiota Development And Characteristics During Adolescence

During childhood and early adolescence, the gut microbiota is still developing and shaped by environmental exposures, host characteristics, diet and lifestyle (Moran-Ramos et al., 2020). During this time, microbial composition

is also linked to metabolic health, suggesting that microbiome development may be a reflection of the differences in host metabolic phenotype (Alcazar et al., 2022). The fact that obesity complicates the scenario further makes it necessary to consider that children with a similar adiposity may have different microbial patterns depending on their metabolic status (Alcazar et al., 2022). There is also adult evidence connecting visceral adiposity to the metabolic and microbial traits, but it is unclear to what extent these can be applied to adolescents (U-Din et al., 2024).

Diet is an important modifiable factor for microbial ecology as it can affect the availability of substrates and production of microbial metabolites (Bonsembiante et al., 2022). Adolescent exposure to an experimental high fructose diet (HFD) results in different alterations of hepatic metabolism and gut microbial population in both sexes, indicating developmental sensitivity to dietary influence (Bhat et al., 2021). Fungal communities in early life could also play a role in later regulation of metabolism, but this evidence is mostly drawn from experimental models (Gutierrez et al., 2025). Additionally, prebiotic and probiotic interventions provide further evidence that microbial communities can be programmed with nutritional interventions (Bock et al., 2024). It is therefore important to consider a healthy adolescent microbiome as the result of an interplay between microbial taxa and age, diet, adiposity, metabolic status and environmental exposure, not just one microbial taxa (Moran-Ramos et al., 2020). The table below (Table 1) details some key influences on the development of microbes in adolescents, including those from their hosts, their diet, and their environment.

Table 1. Key determinants shaping the adolescent gut microbiome and their metabolic implications

Domain	Key point	Relevance	Reference
Microbiota maturation	Gut microbiota continues to develop during childhood and early adolescence under environmental, dietary, and host influences.	Adolescence is a dynamic period for microbiome-related metabolic programming.	Moran-Ramos et al. (2020)
Metabolic phenotype	Microbial profiles differ according to metabolic health, even among children with similar adiposity.	May help explain metabolic heterogeneity in pediatric obesity.	Alcazar et al. (2022)
Visceral adiposity	Visceral fat is associated with metabolic and microbial characteristics in adults.	Supports adiposity–microbiome interactions, with cautious adolescent extrapolation.	U-Din et al. (2024)
Dietary influence	Nutrient composition modifies microbial substrate availability and metabolite production.	Identifies diet as a major modifiable determinant of microbial ecology.	Bonsembiante et al. (2022)
High-fructose exposure	Adolescent fructose exposure alters hepatic metabolism and microbiota in experimental models.	Suggests developmental sensitivity to diet–microbiome interactions.	Bhat et al. (2021)
Gut mycobiome	Early fungal communities may influence later metabolic regulation.	Extends metabolic research beyond bacterial microbiota.	Gutierrez et al. (2025)
Microbiome modulation	Prebiotics and probiotics can modify microbial composition and function.	Supports potential nutritional microbiome-targeted strategies.	Bock et al. (2024)
Healthy microbiome concept	Microbial health depends on age, diet, adiposity, metabolism, and environment.	Single taxa should not define a healthy adolescent microbiome.	Moran-Ramos et al. (2020)

2.2 The Gut–Liver Axis: Biological and Physiological Interconnections

The gut–liver axis is a bidirectional relationship between gut microbial activity and liver metabolism and immune regulation (Vallianou et al., 2021). The liver is directly exposed to the intestinally derived nutrients, microbial metabolites and microbial products via portal circulation (Pan et al., 2021). This exposure is controlled by the integrity of the intestinal barrier, while an increase in its permeability could allow for microbial translocation and induce inflammatory and metabolic responses in the liver (Bonsembiante et al., 2022). The metabolites produced by the microbiota also affect liver energy control, systemic metabolic signalling, and lipid metabolism (Vallianou et al., 2021).

The role of bile acids is crucial in this interaction, as the intestinal microorganisms turn the primary bile acids into secondary bile acids that have metabolic signalling activities (Yu et al., 2021). Microbiota-dependent bile acid metabolism is disrupted in children with nonalcoholic fatty liver disease, as evidenced by decreases in secondary bile acid profiles (Yu et al., 2021). Pediatric fatty liver disease is also linked to an altered gut microbiome, which is also correlated with metabolic abnormalities involving glucose, lipid and water–electrolyte metabolism (Pan et al., 2021). Nutrition influences gut–liver interactions through changes in microbial ecology and hepatic substrate metabolism, so it is an important regulator of gut–liver interactions (Bonsembiante et al., 2022). Gut–liver mechanisms can also lead to long-lasting influences on liver function after developmental exposures (Li et al., 2025). Microbiological changes and the production of metabolites may alter this network with a variable clinical response to prebiotics and probiotics (Bock et al., 2024).

2.3 Gut Microbiota and Liver Function in Adolescents

Increasingly, gut microbial changes have been linked to hepatic and systemic metabolic dysfunction in paediatric fatty liver disease (FLD) (Pan et al., 2021). Obesity related children also showed different microbial patterns, depending on metabolic health, indicating that dysbiosis might be associated with metabolic dysfunction, not just with obesity (Alcazar et al., 2022). Nutritional factors are relevant since the composition of the diet can also affect the intestinal microbial ecology and the hepatic accumulation of lipids (Bonsembiante et al., 2022).

Points of dysbiosis–hepatic dysfunction connections are the changes in production of microbial metabolites, intestinal permeability, inflammatory signaling and disruption of bile acid metabolism (Vallianou et al., 2021). Microbiota-dependent metabolic activity is impaired in pediatric nonalcoholic fatty liver disease (NAFLD) as evidenced by reduced secondary bile acid profiles (Yu et al., 2021). In addition to altered glucose and lipid metabolism, microbial alterations also contribute to the integration of liver dysfunction into a metabolic phenotype (Pan et al., 2021).

The adolescent intestinal microbiome is modifiable through microbiome-targeted interventions (Leong et al., 2020). FMT has been shown to result in metabolically significant changes in the gut microbiome of children and adolescents with obesity, and long-term follow-up studies have shown that the effects of FMT are persistent (Wilson et al., 2025). Prebiotic and probiotic approaches are less invasive and show varying clinical efficacy (Bock et al., 2024). Future studies of adolescents should involve microbial profiling along with liver enzymes, imaging, bile acid, and metabolic biomarkers to aid in early hepatic risk assessment (Pan et al., 2021). In summary, important dysbiosis-related hepatic and metabolic pathways are presented in Figure 1.

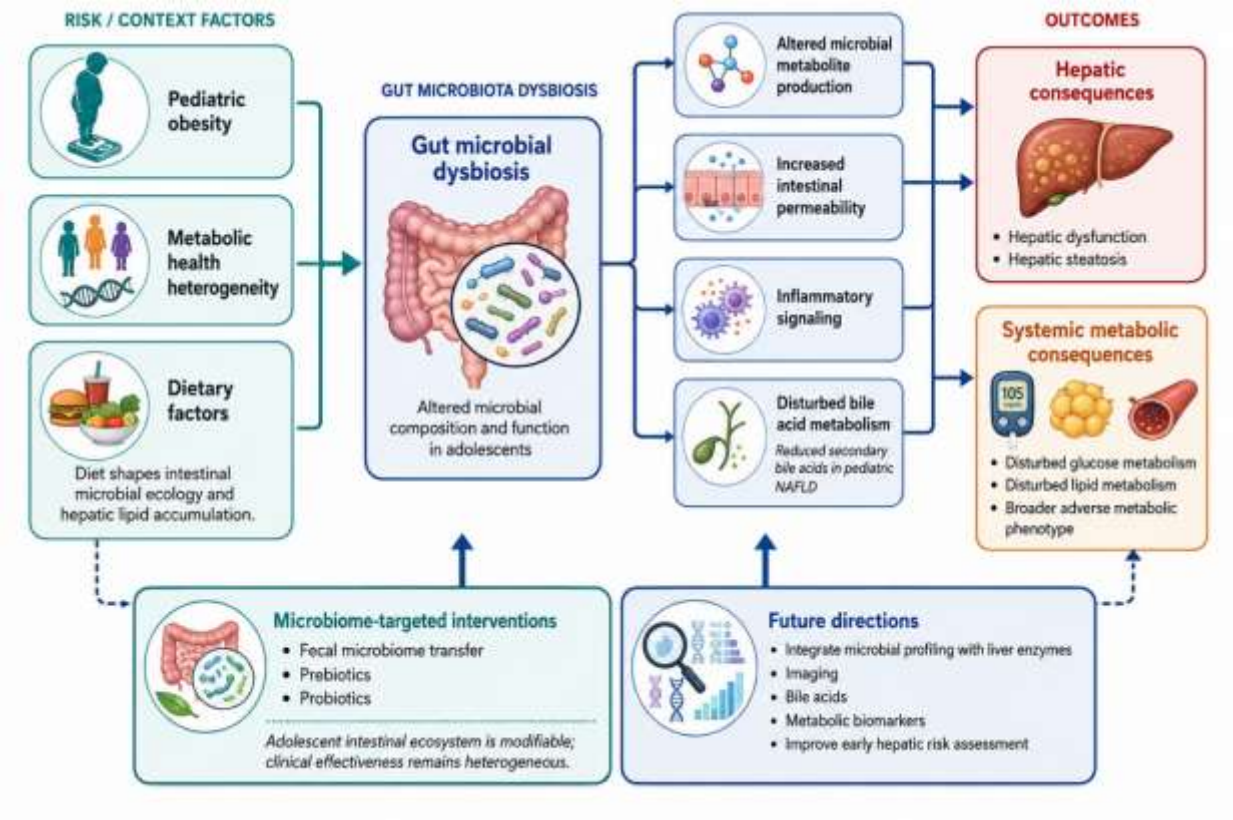

Figure 1. Gut Dysbiosis and Hepatic–Metabolic Dysfunction in Adolescents

2.4 Microbial Signatures and Adolescent Obesity

The gut microbiota has been gaining attention as a significant contributor to pediatric obesity and associated metabolic defects. Children and adolescents who are overweight or obese have differences in microbial diversity and community composition as well as functional pathways when compared to metabolically healthy children (Zhang & Dang, 2022). Such differences could affect the energy balance of the host by altering the fermentation of nutrients, energy extraction and production of metabolites, affecting metabolic signalling (Sankararaman et al., 2023). The concept of pediatric obesity should thus be considered to be a complex interplay of adiposity, diet, host metabolic activity, and microbiome rather than simply overconsumption of energy (Akagbosu et al., 2022).

Feed composition is a significant modifier of these effects, as the amount and composition of food consumed, and the nature of feeding, can alter microbial communities and responses to food (Zhang et al., 2021). Some food additives are also known to affect intestinal homeostasis and metabolic pathways that are linked to obesity and steatotic liver disease, but human evidence is limited (Jarmakiewicz-Czaja et al., 2025). SCFAs can also potentially affect appetite control, gut health, and energy utilisation (Zhang & Dang, 2022).

Adolescent endocrine disorders give a glimpse of interactions between the microbiome and metabolism. Polycystic ovary syndrome (PCOS) in obese adolescents is associated with a change in the microbial diversity and abundance of the taxa (Jobira et al., 2020). Additionally, the metabolic disorders shown in the microbiota following random metabolic treatments in adolescent girls with PCOS point to the gut ecosystem's sensitivity to host physiology changes (Garcia-Beltran et al., 2021).

2.5 Insulin Resistance and Glucose Homeostasis

Insulin resistance is a key metabolic feature of paediatric obesity and a significant risk factor for the future development of cardiometabolic disease. In children and adolescents with obesity, the gut microbiota is linked to obesity markers of insulin resistance (Orsso et al., 2021). The interactions are biologically plausible as metabolites

from the microbiota in the gut affect glucose metabolism, inflammatory responses, and intestinal barrier integrity (Sankararaman et al., 2023).

Short-chain fatty acids are of particular importance since they affect intestinal, hepatic and endocrine pathways related to glucose homeostasis (Zhang & Dang, 2022). Another potential mechanism is bile acid transformation by gut microorganisms; bile acid signalling is involved in the regulation of glucose metabolism, lipids, and gut–liver communication (Barber et al., 2023). Disruption of these pathways may thus be linked to the metabolic changes seen with obesity and fatty liver disease.

The case of adolescent polycystic ovary syndrome (PCOS) is an example of how these three things can occur together: insulin resistance, endocrine dysfunction, and changes in the microbes. Thus, obese adolescents with polycystic ovary syndrome have dysbiosis in their gut microbiome linked to metabolic and hormonal features (Jobira et al., 2020). Randomised treatment studies also indicate that endocrine-metabolic status can be ameliorated while gut microbial composition changes (Garcia-Beltran et al., 2021). Experimental Cad exposure also affects microbiota and metabolomic profile, but this information needs to be confirmed in human adolescents (Yang et al., 2021). Table 2 presents an overview of the important microbial pathways related to insulin resistance and glucose homeostasis.

Table 2. Microbiome and Insulin Resistance in Adolescents

Domain	Key finding	Metabolic relevance	Reference
Insulin resistance	Microbial composition and functional pathways are associated with insulin-resistance markers in pediatric obesity.	Links dysbiosis with early metabolic impairment.	Orsso et al. (2021)
Microbial metabolites	Gut-derived metabolites influence glucose regulation, inflammation, and intestinal barrier function.	Provides a mechanistic basis for microbiome–glucose interactions.	Sankararaman et al. (2023)
Short-chain fatty acids	SCFAs interact with intestinal, hepatic, and endocrine pathways involved in glucose homeostasis.	May influence insulin sensitivity and metabolic signalling.	Zhang & Dang (2022)
Bile acid signaling	Microbial bile acid transformation affects glucose and lipid regulation and gut–liver communication.	Connects dysbiosis with broader metabolic dysfunction.	Barber et al. (2023)
PCOS-related dysbiosis	Adolescents with obesity and PCOS show altered microbial biodiversity associated with metabolic and hormonal features.	Demonstrates interaction among dysbiosis, insulin resistance, and endocrine dysfunction.	Jobira et al. (2020)

Treatment-related changes	Improvement in endocrine-metabolic status can occur alongside changes in microbial composition.	Suggests microbiome responsiveness to metabolic intervention.	Garcia-Beltran et al. (2021)
Environmental exposure	Cadmium alters microbiota and metabolomic profiles in experimental adolescent models.	Highlights potential environmental modulation of metabolic pathways.	Yang et al. (2021)

2.6 Lipid Metabolism and Cardiometabolic Risk

In summary, the gut microbiome is known to impact lipid homeostasis via various mechanisms, including bile acid metabolism, production of microbial metabolites, use of dietary energy, and hepatic lipid handling (Barber et al., 2023). Imbalances in these processes can be associated with dyslipidemia, insulin resistance, obesity, and steatotic liver disease and establish a connection between the intestinal microbial ecology and overall cardiometabolic risk (Sankararaman et al., 2023). Microbial metabolites can also regulate lipid synthesis, oxidation, storage, and inflammatory pathways in metabolic dysfunction (Zhang & Dang, 2022).

The relationship between the microbiome and lipids is especially important in adolescents who are obese and have hepatic steatosis. The gut microbial features have been investigated in combination with PNPLA3 rs738409 in obese children with NAFLD, suggesting a potential interaction between the PNPLA3 variant and the gut flora (Monga Kravetz et al., 2020). Microbial structure and host lipid metabolism are also modified by dietary patterns, which modify this network (Zhang et al., 2021). Other food additives are also likely to impact the intestinal homeostasis and pathways involved in steatotic liver disease, though there is limited prospective evidence (Jarmakiewicz-Czaja et al., 2025).

Fungal communities are other components in the intestinal ecosystem that can affect the regulation of the immune and metabolic system (Gutierrez & Arrieta, 2021). Exposure to toxicants can also dysregulate microbiota and change lipid and organ-function markers (Yang et al., 2021). Thus, adiposity, lipid profile, glucose regulation, hepatic status, diet, genetics and microbial characteristics should be taken into consideration in the assessment of the adolescent cardiometabolic status.

2.7 Modifiable Determinants of the Adolescent Gut–Liver–Metabolic Axis

Nutrient and lifestyle factors play a crucial role in the modifiable factors affecting the gut–liver–metabolic axis in adolescents. The composition of the diet may influence the structure of the microorganisms, the production of metabolites, the handling of lipids in the liver and the regulation of systemic metabolism (Hamamah et al., 2024). The quality of carbohydrates is especially important as fermentable and refined carbohydrates can impact the metabolism and pathways of microorganisms that involve hepatic steatosis (Park et al., 2021). Foods from a Mediterranean lifestyle might help provide metabolic benefits due to increased consumption of plant foods, fibre, unsaturated fats and nutrients with high antioxidant content (Gantenbein & Kanaka-Gantenbein, 2021).

Fatty liver disease is a condition that can be particularly problematic for adolescents, and they might have a greater risk of interactions between their diet, microbes, and lipid metabolism (Kurhaluk et al., 2026). In children, it has been demonstrated that hepatic fat accumulation can be accompanied by dysbiosis, due to alterations in intestinal permeability, inflammatory signalling, and production of microbial metabolites (Tokuhara, 2021). Children and adolescents with NAFLD have been linked to particular taxa, such as Megamonas species, but it is not clear whether these are causal. (Zhou et al., 2022).

This axis may be further modified by other exposures. Microbial disturbances and pathways involved in steatotic liver disease (SLD) could affect nicotine-related oxidative stresses (Mignini et al., 2024). PCOS is also representative of the correlation between intestinal dysbiosis and endocrine-metabolic dysfunction in younger populations, as was showcased by Li et al. (2025). Therefore, 'dietary quality', maintenance of healthful body weight, regular physical activity and avoidance of harmful exposures should be the primary focus of preventive strategies, and microbiome findings should complement these efforts, but not be used as standalone clinical targets. The factors shown in Figure 2 are some of the modifiable factors associated with gut–liver–metabolic health.

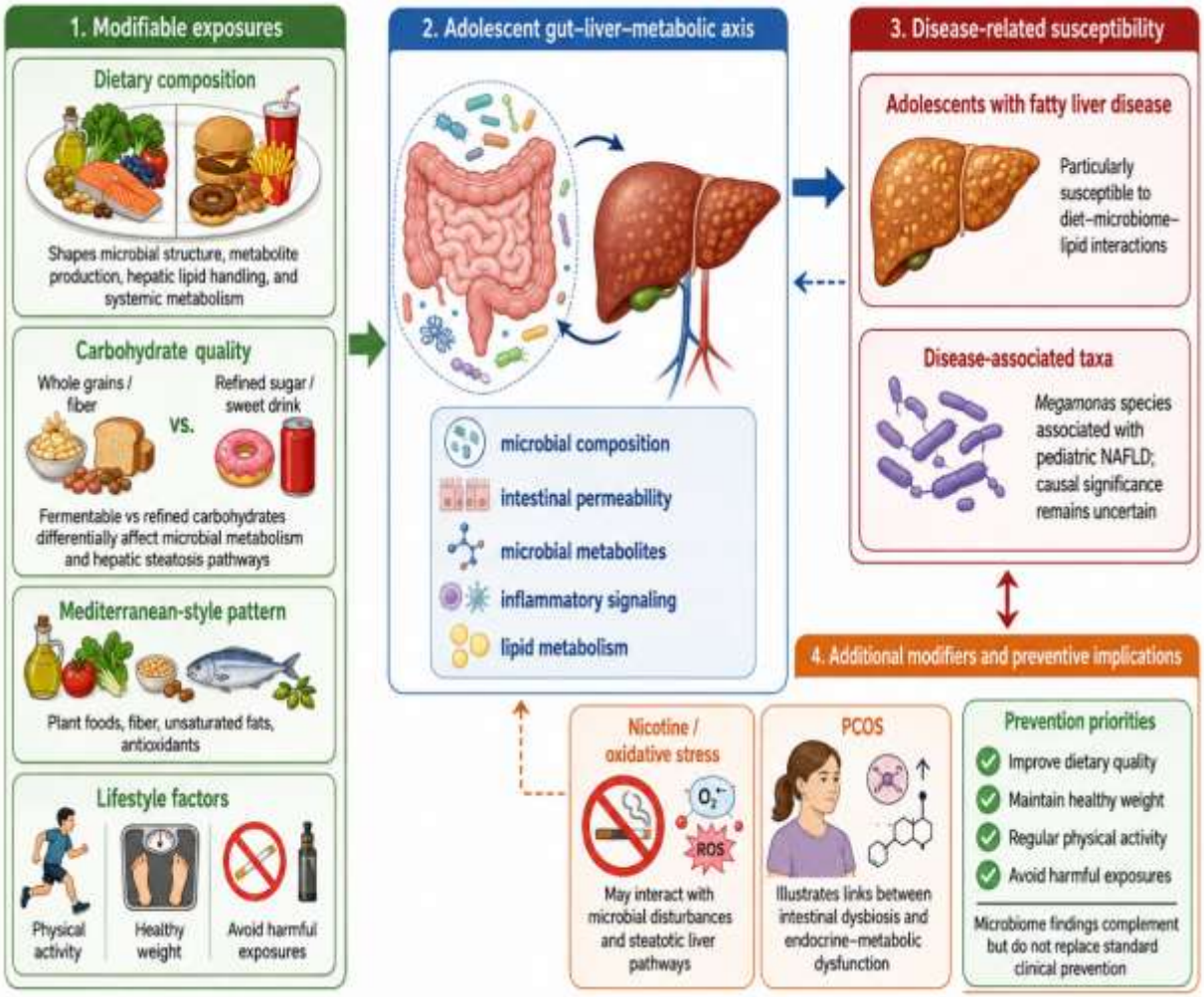

Figure 2. Modifiable Determinants of the Adolescent Gut–Liver–Metabolic Axis

2.8 Preventive and Microbiome-Targeted Strategies

The primary goal for preventing adolescent metabolic and hepatic dysfunction should be to prevent chronic liver injury and cardiometabolic abnormalities by addressing modifiable exposures before they occur. The dietary modification is a practical first-line treatment, as the composition of the diet affects the ecology of intestinal bacteria, hepatic lipid metabolism and the systemic metabolic signalling (Hamamah et al., 2024). The Mediterranean dietary patterns are of particular interest because plant-based diets, the intake of fibre, unsaturated fat and the consumption of antioxidant compounds have been linked to beneficial metabolic effects (Gantenbein & Kanaka-Gantenbein, 2021). Further reducing the negative microbiome–metabolic interactions associated with hepatic fat accumulation could be achieved by improving the quality of carbohydrates (Park et al., 2021).

Prevention using a microbiome approach is still in its nascent phase and not yet considered standard care. Microbial dysbiosis has been linked to PFLD, and efforts to restore microbial balance or function should be investigated to treat the disease in children (Tokuhara, 2021). Concurrently targeting lipid metabolism and microbial composition could be especially important in adolescents who are at risk for obesity or early FLD (Kurhaluk et al., 2026). In the future, disease-associated taxa like Megamonas could be used as part of a microbiome-based risk stratification, but this needs to be validated in a prospective study and standardised analytical methods (Zhou et al., 2022).

In addition, based on evidence from PCOS, modulation of the microbiome could also influence endocrine and

metabolic pathways (Li et al., 2025). Nicotine exposure avoidance could also decrease oxidative and metabolic stress, which is linked to steatotic liver disease (Mignini et al., 2024). Preventive medicine should thus include proven dietary and behavioural strategies along with new microbiome-based strategies, but not use unvalidated microbial markers for clinical intervention. The key preventive and microbiome-focused strategies are summarised in Table 3.

Table 3. Preventive Strategies Targeting Adolescent Gut–Liver–Metabolic Health

Preventive domain	Key approach	Clinical relevance	Reference
Dietary modification	Improve overall nutrient quality to influence microbial ecology and hepatic metabolism.	Practical first-line preventive strategy.	Hamamah et al. (2024)
Mediterranean-style diet	Emphasise plant foods, fibre, unsaturated fats, and antioxidants.	Supports favourable metabolic profiles.	Gantenbein & Kanaka-Gantenbein (2021)
Carbohydrate quality	Reduce refined carbohydrates and improve fermentable carbohydrate intake.	May lessen adverse microbiome–metabolic interactions.	Park et al. (2021)
Microbiome modulation	Restore or support microbial balance in pediatric fatty liver disease.	Emerging preventive target, not yet standard care.	Tokuhara (2021)
Diet–lipid–microbiome strategy	Target microbial composition and lipid metabolism simultaneously.	Particularly relevant in obesity and early fatty liver disease.	Kurhaluk et al. (2026)
Microbial risk markers	Evaluate taxa such as Megamonas for risk stratification.	Requires prospective validation before clinical use.	Zhou et al. (2022)
Endocrine–microbiome interactions	Consider microbiome involvement in PCOS-related metabolic dysfunction.	Broadens prevention beyond hepatic disease alone.	Li et al. (2025)
Harmful exposure reduction	Avoid nicotine-related oxidative and metabolic stress.	Supports hepatic and metabolic prevention.	Mignini et al. (2024)

2.9 Limitations and Future Directions

The existing data regarding the gut microbiota – liver – metabolic axis in adolescent subjects are limited by significant methodological variability between studies, including the sequencing methods used, dietary assessment, population features, and the definition of metabolic and hepatic dysfunction. Most of the studies are cross-sectional, which restricts temporal and causal inference; and small samples and geographically confined samples make it difficult to draw external conclusions. Other factors like pubertal stage, sex, adiposity, medication exposure, socioeconomic context and lifestyle behaviours can significantly impact microbial composition; however, these factors are not always measured or accounted for. In addition, there are variable sample collection, bioinformatic pipelines, taxonomic resolution and outcome reporting, complicating comparisons across studies. Mechanistic interpretation is also somewhat limited by adult and animal research, the latter of which may not adequately reflect the physiology of adolescents.

More studies are needed with large, prospective, multicenter cohorts that have a standardised microbiome sampling and harmonised metabolic and hepatic phenotyping. Incorporating metabolomics, bile acid profile, inflammatory markers, liver imaging, insulin resistance indexes, and lipid parameters with metagenomics will facilitate biological

interpretation. Randomised intervention studies to assess the sustained clinical benefit of dietary modification, prebiotics, probiotics and other microbiome-directed strategies are warranted. Eventually, validated multi-omics signatures could be used to stratify patients at the onset of treatment, but the signatures need to be reproducible and cost-effective, and there must be a clear added value over the known metabolic markers to be used clinically.

Conclusion

Disturbances in gut microbiome are consistently linked to liver and metabolic changes in adolescents, highlighting the gut–liver–metabolic axis as a clinically relevant approach for early risk identification. The evidence suggests microbial dysbiosis is associated with obesity, insulin resistance, dyslipidaemia and fatty liver disease via interacting pathways that involve microbial metabolites, bile acid signalling, intestinal permeability, inflammation, and hepatic lipid handling. The complex regulation of metabolism during adolescence is further complicated by these relationships, which are influenced by diet, adiposity, lifestyle, environmental exposures, and host susceptibility. Although there is some potential for microbiome intervention to be a preventative measure, this evidence is not yet sufficient to use microbial biomarkers or microbiome-directed treatment in routine clinical practice. An integrated assessment that integrates anthropometric parameters, metabolic parameters, liver parameters and microbiome parameters could be useful in identifying adolescents at high risk. Longitudinal studies and interventions will confirm whether specific microbial signatures are reproducible and if changing the microbiome could yield long-term benefits in hepatic and metabolic outcomes in addition to known lifestyle measures for prevention.

References

1. Akagbosu, C. O., Nadler, E. P., Levy, S., & Hourigan, S. K. (2022). The role of the gut microbiome in pediatric obesity and bariatric surgery. International journal of molecular sciences, 23(23), 15421.
2. Alcazar, M., Escribano, J., Ferré, N., Closa-Monasterolo, R., Selma-Royo, M., Feliu, A., ... & Balcells, E. (2022). Gut microbiota is associated with metabolic health in children with obesity. Clinical Nutrition, 41(8), 1680-1688.
3. Amrousy, D. E., Ashry, H. E., Maher, S., Elsayed, Y., & Hasan, S. (2024). Non-alcoholic fatty liver disease and the gut microbiota in adolescents: is there a relationship?. BMC pediatrics, 24(1), 779.
4. Barber, T. M., Hanson, P., & Weickert, M. O. (2023). Metabolically associated fatty liver disease and the gut microbiota. Endocrinology and Metabolism Clinics, 52(3), 485-496.
5. Bhat, S. F., Pinney, S. E., Kennedy, K. M., McCourt, C. R., Mundy, M. A., Surette, M. G., ... & Simmons, R. A. (2021). Exposure to high fructose corn syrup during adolescence in the mouse alters hepatic metabolism and the microbiome in a sex-specific manner. The Journal of physiology, 599(5), 1487-1511.
6. Bock, P. M., Martins, A. F., & Schaan, B. D. (2024). Understanding how pre-and probiotics affect the gut microbiome and metabolic health. American Journal of Physiology-Endocrinology and Metabolism.
7. Bonsembiante, L., Targher, G., & Maffeis, C. (2022). Non-alcoholic fatty liver disease in obese children and adolescents: a role for nutrition?. European journal of clinical nutrition, 76(1), 28-39.
8. Cho, K. Y. (2022). Association of gut microbiota with obesity in children and adolescents. Clinical and experimental paediatrics, 66(4), 148.
9. Eslam, M., Alkhouri, N., Vajro, P., Baumann, U., Weiss, R., Socha, P., ... & George, J. (2021). Defining paediatric metabolic (dysfunction)-associated fatty liver disease: an international expert consensus statement. The lancet Gastroenterology & hepatology, 6(10), 864-873.
10. Fan, Y., & Pedersen, O. (2021). Gut microbiota in human metabolic health and disease. Nature Reviews Microbiology, 19(1), 55-71.
11. Gantenbein, K. V., & Kanaka-Gantenbein, C. (2021). Mediterranean diet as an antioxidant: the impact on metabolic health and overall wellbeing. Nutrients, 13(6), 1951.
12. Garcia-Beltran, C., Malpique, R., Carbonetto, B., González-Torres, P., Henares, D., Brotons, P., ... & Ibanez, L. (2021). Gut microbiota in adolescent girls with polycystic ovary syndrome: effects of randomized

treatments. Pediatric Obesity, 16(4), e12734.
13. Gutierrez, M. W., & Arrieta, M. C. (2021). The intestinal mycobiome as a determinant of host immune and metabolic health. Current opinion in microbiology, 62, 8-13.
14. Gutierrez, M. W., van Tilburg Bernardes, E., Ren, E., Kalbfleisch, K. N., Day, M., Lameu, E. L., ... & Arrieta, M. C. (2025). Early-life gut mycobiome core species modulate metabolic health in mice. Nature Communications, 16(1), 1467.
15. Hamamah, S., Iatcu, O. C., & Covasa, M. (2024). Dietary influences on gut microbiota and their role in metabolic dysfunction-associated steatotic liver disease (MASLD). Nutrients, 17(1), 143.
16. Jarmakiewicz-Czaja, S., Sokal-Dembowska, A., & Filip, R. (2025). Effects of selected food additives on the gut microbiome and metabolic dysfunction-associated steatotic liver disease (MASLD). Medicina, 61(2), 192.
17. Ji, J., Sun, J., Li, J., Xie, J., Xi, B., & Zhao, M. (2024). Altered gut microbiome associated with metabolic-associated fatty liver disease in Chinese children. Clinical Nutrition, 43(1), 187-196.
18. Jian, C., Carpén, N., Helve, O., de Vos, W. M., Korpela, K., & Salonen, A. (2021). Early-life gut microbiota and its connection to metabolic health in children: Perspective on ecological drivers and need for quantitative approach. EBioMedicine, 69.
19. Jobira, B., Frank, D. N., Pyle, L., Silveira, L. J., Kelsey, M. M., Garcia-Reyes, Y., ... & Cree-Green, M. (2020). Obese adolescents with PCOS have altered biodiversity and relative abundance in gastrointestinal microbiota. The Journal of Clinical Endocrinology & Metabolism, 105(6), e2134-e2144.
20. Kamrani, F., Nikparast, A., Tabatabaeyan, A., Etesami, E., Rohani, P., & Asghari, G. (2026). Dietary Index for Gut Microbiota and the Odds of Metabolic Dysfunction-Associated Fatty Liver Disease in Overweight and Obese Children and Adolescents: A Cross-Sectional Study. Health Science Reports, 9(6), e72640.
21. Kurhaluk, N., Mazur, Z., Kołodziejska, R., & Tkaczenko, H. (2026). Gut microbiota, diet and lipid metabolism in adolescents with NAFLD and their role in preventive strategies. International Journal of Molecular Sciences, 27(8), 3511.
22. Le Garf, S., Negre, V., Anty, R., & Gual, P. (2021). Metabolic fatty liver disease in children: a growing public health problem. Biomedicines, 9(12), 1915.
23. Leong, K. S., Jayasinghe, T. N., Wilson, B. C., Derraik, J. G., Albert, B. B., Chiavaroli, V., ... & Cutfield, W. S. (2020). Effects of fecal microbiome transfer in adolescents with obesity: the gut bugs randomized controlled trial. JAMA network open, 3(12), e2030415.
24. Li, C., Cheng, D., Ren, H., & Zhang, T. (2025). Unraveling the gut microbiota's role in PCOS: a new frontier in metabolic health. Frontiers in Endocrinology, 16, 1529703.
25. Li, Y., Xu, W., Kong, X., Dong, Y., An, M., Guan, Y., ... & Niu, Y. (2025). A Moderately High-Protein Diet During the Critical Development Period Protects Hepatic Functional Integrity and Improves Metabolic Health in Middle-Aged Offspring via the Gut–Liver Axis. Molecular Nutrition & Food Research, 69(20), e70169.
26. Mignini, I., Galasso, L., Piccirilli, G., Calvez, V., Termite, F., Esposto, G., ... & Zocco, M. A. (2024). Interplay of oxidative stress, gut microbiota, and nicotine in metabolic-associated steatotic liver disease (MASLD). Antioxidants, 13(12), 1532.
27. Monga Kravetz, A., Testerman, T., Galuppo, B., Graf, J., Pierpont, B., Siebel, S., ... & Santoro, N. (2020). Effect of gut microbiota and PNPLA3 rs738409 variant on nonalcoholic fatty liver disease (NAFLD) in obese youth. The Journal of Clinical Endocrinology & Metabolism, 105(10), e3575-e3585.
28. Moran-Ramos, S., Lopez-Contreras, B. E., Villarruel-Vazquez, R., Ocampo-Medina, E., Macias-Kauffer, L., Martinez-Medina, J. N., ... & Canizales-Quinteros, S. (2020). Environmental and intrinsic factors shaping gut microbiota composition and diversity and its relation to metabolic health in children and early adolescents: A population-based study. Gut microbes, 11(4), 900-917.

29. Orsso, C. E., Peng, Y., Deehan, E. C., Tan, Q., Field, C. J., Madsen, K. L., ... & Haqq, A. M. (2021). Composition and functions of the gut microbiome in pediatric obesity: relationships with markers of insulin resistance. Microorganisms, 9(7), 1490.
30. Pan, X., Kaminga, A. C., Liu, A., Wen, S. W., Luo, M., & Luo, J. (2021). Gut microbiota, glucose, lipid, and water-electrolyte metabolism in children with nonalcoholic fatty liver disease. Frontiers in cellular and infection microbiology, 11, 683743.
31. Park, G., Jung, S., Wellen, K. E., & Jang, C. (2021). The interaction between the gut microbiota and dietary carbohydrates in nonalcoholic fatty liver disease. Experimental & Molecular Medicine, 53(5), 809-822.
32. Sankararaman, S., Noriega, K., Velayuthan, S., Sferra, T., & Martindale, R. (2023). Gut microbiome and its impact on obesity and obesity-related disorders. Current gastroenterology reports, 25(2), 31-44.
33. Tokuhara, D. (2021). Role of the gut microbiota in regulating non-alcoholic fatty liver disease in children and adolescents. Frontiers in Nutrition, 8, 700058.
34. U-Din, M., Ahmed, B. A., Syed, S. A., Ong, F. J., Oreskovich, S. M., Gunn, E., ... & Morrison, K. M. (2024). Characteristics of abdominal visceral adipose tissue, metabolic health and the gut microbiome in adults. The Journal of Clinical Endocrinology & Metabolism, 109(3), 680-690.
35. Vallianou, N., Christodoulatos, G. S., Karampela, I., Tsilingiris, D., Magkos, F., Stratigou, T., ... & Dalamaga, M. (2021). Understanding the role of the gut microbiome and microbial metabolites in non-alcoholic fatty liver disease: current evidence and perspectives. Biomolecules, 12(1), 56.
36. Vimalesvaran, S., Vajro, P., & Dhawan, A. (2024). Pediatric metabolic (dysfunction)-associated fatty liver disease: current insights and future perspectives. Hepatology international, 18(Suppl 2), 873-883.
37. Wilson, B. C., Zuppi, M., Derraik, J. G., Albert, B. B., Tweedie-Cullen, R. Y., Leong, K. S., ... & Cutfield, W. S. (2025). Long-term health outcomes in adolescents with obesity treated with faecal microbiota transplantation: 4-year follow-up. Nature Communications, 16(1), 7786.
38. Yang, J., Chen, W., Sun, Y., Liu, J., & Zhang, W. (2021). Effects of cadmium on organ function, gut microbiota and its metabolomics profile in adolescent rats. Ecotoxicology and Environmental Safety, 222, 112501.
39. Yu, J., Zhang, H., Chen, L., Ruan, Y., Chen, Y., & Liu, Q. (2021). Disease-associated gut microbiota reduces the profile of secondary bile acids in pediatric nonalcoholic fatty liver disease. Frontiers in cellular and infection microbiology, 11, 698852.
40. Yuan, X., Chen, R., McCormick, K. L., Zhang, Y., Lin, X., & Yang, X. (2021). The role of the gut microbiota on the metabolic status of obese children. Microbial cell factories, 20(1), 53.
41. Zeber-Lubecka, N., Czarnowski, P., Ziemska-Legięcka, J., Wierzbicka-Rucińska, A., Jańczyk, W., Michałkiewicz, J., ... & Ostrowski, J. Gut microbiota-metabolite alterations associated with early metabolic dysfunction and hepatic steatosis in adolescents. Computational and Structural Biotechnology Journal.
42. Zhang, L., El-Shabrawi, M., Baur, L. A., Byrne, C. D., Targher, G., Kehar, M., ... & Zheng, M. H. (2024). An international multidisciplinary consensus on pediatric metabolic dysfunction-associated fatty liver disease. Med, 5(7), 797-815.
43. Zhang, S., & Dang, Y. (2022). Roles of gut microbiota and metabolites in overweight and obesity of children. Frontiers in endocrinology, 13, 994930.
44. Zhang, Z., Chen, X., Loh, Y. J., Yang, X., & Zhang, C. (2021). The effect of calorie intake, fasting, and dietary composition on metabolic health and gut microbiota in mice. BMC biology, 19(1), 51.
45. Zhou, J., Zhang, Q., Zhao, Y., Zou, Y., Chen, M., Zhou, S., & Wang, Z. (2022). The relationship of Megamonas species with nonalcoholic fatty liver disease in children and adolescents revealed by metagenomics of gut microbiota. Scientific Reports, 12(1), 22001.