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REVIEW ARTICLE

BEYOND THE USUAL SUSPECTS: REVIEW ON EXPLORING RARE, EMERGING AND ENVIRONMENTALLY INFLUENCED METABOLIC DISORDERS

Mostafa Essam Eissa
Independent Researcher and Consultant, Cairo, Egypt.

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***Address for Correspondence:**
Dr. Mostafa Essam Eissa, Independent Researcher and Consultant, Cairo, Egypt. Tel: +20100615485;
E-mail: *mostafaessameissa@yahoo.com*

Abstract

This review highlights the multifaceted landscape of metabolic disorders, focusing on often overlooked or understudied conditions. These disorders were categorized based on potential etiology, including rare inherited, disorders of unknown origin, emerging conditions and those influenced by other diseases, environmental factors, or immune dysfunction. Additionally, we explore the impact of personalized metabolic variations and the intricate relationship between metabolism and mental health. By exploring specific examples such as maple syrup urine disease, non-alcoholic fatty liver disease, bile acid malabsorption and mitochondrial disorders, we emphasize the diverse spectrum of metabolic challenges. This overview underscores the need for continued research to unravel the complexities of these conditions, leading to improved diagnosis, treatment and prevention strategies. This is an interesting area for pharmaceutical field that need attention and extensive research to find promising treatments for the underestimated populations impacted by these diseases.

Keywords: Metabolic complications, metabolic disorders, mental health, mitochondrial disorders, personalized medicine, immune dysfunction.

INTRODUCTION

The domain of metabolic medicine is experiencing an epoch of rapid advancement, characterized by a ceaseless influx of novel insights and discoveries. Notwithstanding substantial progress in comprehending and managing prevalent metabolic disorders, a considerable subset of conditions remains under-investigated and often neglected, disproportionately impacting a marginalized patient population. This manuscript endeavors to illuminate these understudied domains within the complex tapestry of metabolic diseases. By directing the scientific community's attention to these overlooked pathologies, we aim to galvanize concerted efforts towards developing effective interventions[1-3]. The often-limited awareness of these conditions among healthcare providers underscores the critical need for enhanced diagnostic acumen and therapeutic strategies.

The intricate landscape of human metabolism, a complex interplay of biochemical processes, continues to reveal a spectrum of disorders that challenge our understanding. While advancements in medical research have shed light on numerous metabolic conditions, a significant subset remains understudied. This article demonstrates the diverse spectrum of these underexplored metabolic disorders, categorized by their underlying etiology, clinical presentation, and emerging research trends. By examining rare inherited conditions, disorders of unknown origin and those arising from secondary complications, environmental factors or immune dysfunctions, we aim to illuminate the breadth and complexity of this field[4-6]. A comprehensive understanding of these disorders is essential for advancing diagnostic capabilities, developing targeted therapies and improving patient outcomes.

Because medical research is ongoing, the discovery and study of previously unknown metabolic diseases continues to grow. However, there are several types and examples of circumstances that are frequently regarded underexplored:

1. Rare inherited metabolic disorders

These are genetic conditions caused by mutations in genes that encode enzymes or proteins crucial for specific metabolic pathways. Due to their rarity, they

can be challenging to diagnose and may not have well-established treatment options. Examples:

- **Maple Syrup Urine Disease (MSUD):** This affects the breakdown of certain amino acids, leading to a characteristic maple syrup-like odor in urine and neurological problems[7].
- **Phenylketonuria (PKU):** This affects the processing of the amino acid phenylalanine, if untreated, it can lead to intellectual disability[8].
- **Galactosemia:** This affects the breakdown of the sugar galactose from milk, causing various symptoms including vomiting, diarrhea, and liver problems[9].

2. Disorders of unknown etiology (cause)

These disorders manifest with metabolic abnormalities, but the underlying genetic or environmental triggers remain unclear. Examples:

- **Non-Alcoholic Fatty Liver Disease (NAFLD):** This is a buildup of fat in the liver that is not caused by excessive alcohol consumption. While risk factors are identified, the exact cause is not fully understood[10].
- **Fibromyalgia:** This chronic condition is characterized by widespread pain, fatigue, and sleep disturbances. The cause of fibromyalgia is still under investigation, with some theories suggesting metabolic abnormalities might be involved[11].

3. Emerging metabolic disorders

These are recently identified or newly defined conditions with ongoing research to understand their full scope and impact. Examples:

- **Bile Acid Malabsorption (BAM):** This recently defined disorder shares symptoms with irritable bowel syndrome (IBS), making diagnosis difficult. It involves problems with reabsorbing bile acids in the intestine[12].
- **Fabkin deficiency:** This recently discovered protein plays a role in insulin production and blood sugar regulation. Research is ongoing to understand how Fabkin deficiency affects metabolism and develop potential treatment strategies[13].

4. Metabolic complications of other diseases

Some established diseases can present with metabolic abnormalities as secondary complications. Examples:

- **Metabolic complications of HIV/AIDS:** HIV infection can disrupt metabolism, leading to weight loss, muscle wasting, and insulin resistance[14].
- **Metabolic complications of chronic inflammatory diseases:** Chronic inflammation can lead to changes in how the body uses nutrients and can contribute to insulin resistance or fatty liver disease[15].

5. Personalized and sub-phenotypic variations in metabolism

This emerging area explores the individual differences in how people process nutrients and respond to dietary changes. The goal is to understand how factors like genetics, gut microbiome, and lifestyle influence metabolism to personalize dietary and treatment approaches[16].

6. Disorders of nutrient transport

These disorders involve issues with the absorption or transport of specific nutrients across the gut lining or within the bloodstream. Examples:

- **Carnitine deficiency disorders:** Carnitine is crucial for transporting fatty acids into cells for energy production. Deficiencies can lead to muscle weakness, fatigue, and heart problems[17].
- **Iron overload disorders:** These disorders involve excessive iron accumulation in the body, often due to problems with iron regulation or absorption[18].

7. Mitochondrial disorders:

Mitochondria are the "powerhouses" of cells, responsible for energy production. Mitochondrial disorders arise from mutations in genes related to mitochondrial function, leading to impaired energy production and a variety of symptoms. Examples:

- **Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, and Stroke-like episodes (MELAS):** This affects multiple organ systems due to mitochondrial dysfunction, causing muscle weakness, neurological problems, and stroke-like episodes[19].
- **Leber Hereditary Optic Neuropathy (LHON):** This is a leading cause of inherited vision loss in young adults, caused by mutations in mitochondrial genes specifically affecting the optic nerve[20].

8. Metabolic consequences of environmental exposures

This emerging area explores how environmental factors like toxins, pollutants, or medications can disrupt metabolic processes. Examples:

- **Metabolic effects of bisphenol A (BPA):** BPA is a chemical found in some plastics and has been linked to changes in glucose and lipid metabolism in some studies[21].
- **Metabolic effects of certain medications:** Some medications can have unintended consequences on metabolism, such as weight gain or changes in blood sugar control[22,23].

9. Inborn Errors of Immunity with Metabolic Features

These are a relatively new class of disorders where immune system dysfunction interacts with metabolic processes, causing a variety of symptoms[24]. Examples:

- **Autoimmune Lymphoproliferative Syndrome (ALPS):** This rare disorder involves abnormal immune cell growth and can manifest with metabolic abnormalities like low blood sugar[25].
- **Common Variable Immunodeficiency (CVID) with autoimmune features:** Some individuals with CVID may also experience metabolic problems like autoimmune hepatitis or Sjogren's syndrome, which can affect metabolism[26].

10. Metabolic imbalances and mental health

This is a growing area of research investigating the potential link between metabolic disruptions and mental health conditions. Examples:

- The role of gut microbiome in mood disorders: Studies suggest that the gut microbiome composition might influence neurotransmitter production and contribute to depression or anxiety[27].
- Metabolic changes in schizophrenia: Some research suggests that people with schizophrenia may have altered glucose metabolism, highlighting a potential metabolic link to the mental health condition[28].

Table 1: Comprehensive non-exhaustive list of rare, uncommon and unexplored metabolic diseases[1-28].

Category*	Disease	Description	Examples
Rare inherited metabolic disorders	Maple Syrup Urine Disease (MSUD)	Inherited disorder affecting the breakdown of branched-chain amino acids, leading to characteristic maple syrup odor in urine and neurological symptoms.	MSUD, Phenylketonuria (PKU), Galactosemia
Rare inherited metabolic disorders	Mevalonic Aciduria Spectrum Disorders (MASDs)	Group of rare genetic disorders affecting cholesterol synthesis, characterized by various symptoms depending on the specific type.	MASDs
Rare inherited metabolic disorders	McCune-Albright Syndrome (MAS)	Rare genetic disorder causing multiple endocrine tumors and abnormal bone development.	MAS
Rare inherited metabolic disorders	Carney Triad	Rare genetic disorder characterized by pigmented skin lesions, heart tumors, and endocrine abnormalities.	Carney Triad
Disorders of unknown etiology	Non-Alcoholic Fatty Liver Disease (NAFLD)	Accumulation of fat in the liver not caused by excessive alcohol consumption; the exact cause remains unclear.	NAFLD
Disorders of unknown etiology	Fibromyalgia	Chronic condition characterized by widespread pain, fatigue, and sleep disturbances; the underlying cause is not fully understood.	Fibromyalgia
Emerging metabolic disorders	Bile Acid Malabsorption (BAM)	Recently defined disorder sharing similarities with irritable bowel syndrome (IBS), characterized by impaired bile acid reabsorption in the intestine.	BAM
Metabolic complications of other diseases	Metabolic complications of HIV/AIDS	Metabolic disturbances associated with HIV infection, including weight loss, muscle wasting, and insulin resistance.	HIV/AIDS (metabolic complications)
Metabolic complications of other diseases	Metabolic complications of chronic inflammatory diseases	Metabolic changes resulting from chronic inflammation, often leading to insulin resistance or fatty liver disease.	Chronic inflammatory diseases (metabolic complications)
Disorders of nutrient transport	Carnitine Deficiency Disorders	Disorders affecting the transport of fatty acids into cells, resulting in muscle weakness, fatigue, and heart problems.	Carnitine Deficiency Disorders
Disorders of nutrient transport	Iron Overload Disorders	Excessive iron accumulation in the body due to impaired iron regulation or absorption.	Iron Overload Disorders
Mitochondrial disorders	Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, and Stroke-like episodes (MELAS)	Disorder affecting multiple organ systems due to mitochondrial dysfunction, causing muscle weakness, neurological problems, and stroke-like episodes.	MELAS
Mitochondrial disorders	Leber Hereditary Optic Neuropathy (LHON)	Inherited vision loss primarily affecting young adults, caused by mitochondrial gene mutations impacting the optic nerve.	LHON
Rare & uncommon metabolic disorders	Whipple's Disease	Rare infectious disease affecting the intestines, leading to weight loss, diarrhea, and abdominal pain.	Whipple's Disease
Rare & uncommon metabolic disorders	PANDAS/PANS	Childhood-onset neuropsychiatric disorders potentially linked to autoimmune responses to infections.	PANDAS/PANS
Rare & uncommon metabolic disorders	Nesfatin-1-like Peptide (NLP) Deficiency	Potential hormonal deficiency associated with obesity; further research is needed to establish its role.	NLP Deficiency (research ongoing)
Metabolic consequences of environmental exposures	Metabolic effects of bisphenol A (BPA)	Potential impact of BPA on glucose and lipid metabolism, based on some studies.	BPA (potential metabolic effects)

Cont…

Metabolic consequences of environmental exposures	Metabolic effects of certain medications	Unintended metabolic consequences of some medications, such as weight gain or blood sugar changes.	Certain medications (metabolic side effects)
Inborn errors of immunity with metabolic features	Autoimmune Lymphoproliferative Syndrome (ALPS)	Rare genetic disorder affecting immune system and metabolism, leading to abnormal immune cell growth and metabolic issues.	ALPS
Inborn errors of immunity with metabolic features	Common Variable Immunodeficiency (CVID) with autoimmune features	Immune deficiency with associated autoimmune conditions that can impact metabolism.	CVID (metabolic complications)
Metabolic imbalances and mental health	The role of gut microbiome in mood disorders	Potential influence of gut microbiota composition on neurotransmitter production and mental health.	Gut microbiome (potential link to mood disorders)
Metabolic imbalances and mental health	Metabolic changes in schizophrenia	Altered glucose metabolism observed in some individuals with schizophrenia.	Schizophrenia (metabolic changes)

*Additional Considerations: This table is not exhaustive and there are many other metabolic disorders that could be included. Some disorders may fit into multiple categories. The cause of some disorders is still unknown and may change as research progresses.

Pharmaceutical opportunities in understudied metabolic disorders

The realm of metabolic medicine presents a rich tapestry of understudied disorders, each offering unique opportunities for pharmaceutical research and development. These conditions, often characterized by their rarity, complexity or lack of definitive understanding, represent a significant unmet medical need. Rare Inherited Metabolic Disorders offer potential for orphan drug designation and gene therapy approaches[29,30]. Tailored treatment strategies based on specific genetic mutations can improve outcomes for these patients. Disorders of Unknown Etiology require mechanistic studies to identify therapeutic targets and develop disease-modifying drugs. Biomarkers can aid in early diagnosis and monitoring of disease progression[31,32]. Emerging Metabolic Disorders present opportunities for first-in-class therapies, clinical trials and patient registries to advance understanding and treatment[33,34]. Metabolic Complications of Other Diseases often necessitate combination therapies or disease-modifying approaches to address both the primary condition and its metabolic consequences[35,36]. Personalized and Sub-Phenotypic Variations in Metabolism emphasize the need for precision medicine and interventions targeting the gut microbiome[37,38]. Disorders of Nutrient Transport require strategies for nutrient replacement and targeted therapies[39,40]. Mitochondrial Disorders can benefit from mitochondrial therapeutics and gene therapy approaches[41,42]. Metabolic Consequences of Environmental Exposures necessitate prevention, mitigation and detoxification strategies[43,44]. Inborn Errors of Immunity with Metabolic Features may benefit from immunomodulatory therapies and combination approaches[45]. Finally, Metabolic Imbalances and Mental Health require dual-action therapies and personalized approaches[46]. By comprehensively addressing these understudied metabolic disorders, pharmaceutical research can contribute to improving patient outcomes and advancing our understanding of human health.

CONCLUSIONS

The intricate tapestry of metabolic disorders reveals a complex interplay between genetics, environment, and lifestyle. This categorization underscores the diverse etiologies and clinical presentations within this spectrum. Rare inherited disorders like MSUD and MASD highlight the fragility of metabolic pathways, while acquired conditions such as NAFLD and metabolic complications of chronic diseases emphasize the impact of environmental and lifestyle factors. Emerging disorders like BAM and the potential metabolic implications of environmental exposures expand the boundaries of our understanding. Moreover, the intricate connections between metabolism and other systems, as seen in disorders like PANDAS/PANS and the gut-brain axis, necessitate a holistic approach. Ultimately, this analysis emphasizes the need for continued research to unravel the complexities of these disorders, leading to improved diagnosis, treatment, and prevention strategies. Exploring the pharmaceutical treatment role should not be underestimated and must be actively engaged in improving the life of those impacted population by these diseases.

AUTHOR'S CONTRIBUTIONS

Eissa ME: conceived the idea, writing the manuscript, literature survey, formal analysis, critical review.

DATA AVAILABILITY

This article is available to anyone upon request from the corresponding authors.

CONFLICT OF INTEREST

None to declare.

REFERENCES

1. Valdez R, Tolentino K. Metabolic Disorders: Symptoms, Causes, Diagnosis, Treatment. Verywell Health 2023 Apr

20. https://www.verywellhealth.com/metabolic-disorders-7368902
2. Yang T, Qi F, Guo F, Shao M, Song Y, Ren G, Linlin Z, Qin G, Zhao Y. An update on chronic complications of diabetes mellitus: From molecular mechanisms to therapeutic strategies with a focus on metabolic memory. Molecular Medicine. 2024 May 26;30(71). *https://doi.org/10.1186/s10020-024-00824-9*
3. Cardio-renal-metabolic connection: a review of the evidence. Cardiovascular Diabetology. 2023. *https://doi.org/10.1186/s12933-023-01937-x*
4. Xu F, Fu Y, Sun T, *et al.* The interplay between host genetics and the gut microbiome reveals common and distinct microbiome features for complex human diseases. Microbiome 2020 Oct 8;8(1):145. *https://doi.org/10.1186/s40168-020-00923-9*
5. Chi H. Immunometabolism at the intersection of metabolic signaling, cell fate, and systems immunology. Cellular & molecular immunology 2022 Mar; 19(3):299-302. *https://doi.org/10.1038/s41423-022-00840-x*
6. Clemente-Suárez VJ, Martín-Rodríguez A, Redondo-Flórez L, *et al*. New insights and potential therapeutic interventions in metabolic diseases. Int J Mol Sci 2023 Jun 26; 24(13):10672. *https://doi.org/10.3390/ijms241310672*
7. Chuang DT, Shih VE. Maple syrup urine disease (branched-chain ketoaciduria). In: Valle D, Beaud*et al*, Vogelstein B, Kinzler KW, Antonarakis SE, Ballabio A, *et al*., editors. The Online Metabolic and Molecular Bases of Inherited Disease. New York: McGraw-Hill; 2014. *https://doi.org/10.1036/ommbid.175*
8. Blau N, van Spronsen FJ, Levy HL. Phenylketonuria. Lancet. 2010 Oct 23; 376(9750):1417-27. *https://doi.org/10.1016/S0140-6736(10)60961-0*
9. Bosch AM. Classical galactosaemia revisited. J Inherit Metab Dis 2006 Dec; 29(4):516-25. *https://doi.org/10.1007/s10545-006-0368-4*
10. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease—Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatol 2016 Jul; 64(1):73-84. *https://doi.org/10.1002/hep.28431*
11. Clauw DJ. Fibromyalgia: A clinical review. JAMA. 2014 Apr 16; 311(15):1547-55. *https://doi.org/10.1001/jama.2014.3266*
12. Camilleri M. Advances in understanding bile acid diarrhea. Expert Rev Gastroenterol Hepatol 2014 Feb; 8(1):49-61. *https://doi.org/10.1586/17474124.2014.859522*
13. Grinspoon S, Carr A. Cardiovascular risk and body-fat abnormalities in HIV-infected adults. N Engl J Med 2005 Jan 6; 352(1):48-62. *https://doi.org/10.1056/NEJMra041811*
14. Hotamisligil GS. Inflammation and metabolic disorders. Nature 2006 Dec 14; 444(7121):860-7. *https://doi.org/10.1038/nature05485*
15. Zeevi D, Korem T, Zmora N, *et al*. Personalized nutrition by prediction of glycemic responses. Cell 2015 Nov 19;163(5):1079-94. *https://doi:10.1016/j.cell.2015.11.001*
16. Stanley CA. Carnitine deficiency disorders in children. Ann N Y Acad Sci. 2004 Apr; 1033:42-51. *https://doi.org/10.1196/annals.1320.004*
17. Pietrangelo A. Hereditary hemochromatosis: Pathogenesis, diagnosis, and treatment. Gastroenterology 2010 Aug; 139(2):393-408. *https://doi.org/10.1053/j.gastro.2010.06.013*
18. DiMauro S, Hirano M. MELAS. In: Adam MP, Ardinger HH, Pagon RA, *et al*., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. *https://www.ncbi.nlm.nih.gov/books/NBK1233*
19. Yu-Wai-Man P, Griffiths PG, Chinnery PF. Mitochondrial optic neuropathies – Disease mechanisms and therapeutic strategies. Prog Retin Eye Res 2011 Sep; 30(2):81-114. *https://doi.org/10.1016/j.preteyeres.2010.11.002*
20. Rubin BS. Bisphenol A: An endocrine disruptor with widespread exposure and multiple effects. J Steroid Biochem Mol Biol 2011 Oct;127(1-2):27-34. *https://doi.org/10.1016/j.jsbmb.2011.05.002*
21. Purnell JQ, Weyer C. Weight effect of current and experimental drugs for diabetes mellitus: From promotion to alleviation of obesity. Treat Endocrinol 2003;2(1):33-47. *https://doi.org/10.2165/00024677-200302010-00004*
22. Oliveira JB, Bleesing JJ, Dianzani U, *et al*. Revised diagnostic criteria and classification for the autoimmune lymphoproliferative syndrome (ALPS): Report from the 2009 NIH International Workshop. Blood 2010 Oct 7; 116(14):e35-40. *https://doi.org/10.1182/blood-2010-04-280347*
23. Rao VK, Oliveira JB. How I treat autoimmune lymphoproliferative syndrome. Blood 2011 Nov 24; 118(22):5741-51. *https://doi.org/10.1182/blood-2011-07-325217*
24. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: Clinical and immunological features of 248 patients. Clin Immunol 1999 Jul; 92(1):34-48. *https://doi.org/10.1006/clim.1999.4725*
25. Cryan JF, Dinan TG. Mind-altering microorganisms: The impact of the gut microbiota on brain and behaviour. Nat Rev Neurosci 2012 Oct; 13(10):701-12. *https://doi.org/10.1038/nrn3346*
26. Pillinger T, Beck K, Gobjila C, Donocik JG, Jauhar S, Howes OD. Impaired glucose homeostasis in first-episode schizophrenia: A systematic review and meta-analysis. JAMA Psychiatry 2017 Mar 1; 74(3):261-9. *https://doi.org/10.1001/jamapsychiatry.2016.3803*
27. Ferreira CR. The burden of rare diseases. Am J Med Genet A 2019; 179(6):885-892. *https://doi.org/10.1002/ajmg.a.61124*
28. Parenti G, Andria G, Ballabio A. Lysosomal storage diseases: from pathophysiology to therapy. Annu Rev Med. 2015; 66:471-486. *https://doi.org/10.1146/annurev-med-122313-085916*
29. Gahl WA, Markello TC, Toro C, *et al*. The National Institutes of Health Undiagnosed Diseases Program: insights into rare diseases. Genet Med 2012; 14(1):51-59. *https://doi.org/10.1038/gim.0b013e318232a005*
30. Taruscio D, Floridia G, Salvatore M, Groft SC. Undiagnosed diseases: Italy-US collaboration and international efforts to tackle rare and common diseases lacking a diagnosis. Adv Exp Med Biol 2017; 1031:3-13. *https://doi.org/10.1007/978-3-319-67144-4_1*
31. Rinaldo P, Matern D, Bennett MJ. Newborn screening for congenital disorders. Clin Chem. 2006;52(9):1583-1594. *https://doi.org/10.1373/clinchem.2006.070037*
32. Saudubray JM, Garcia-Cazorla A. Inborn errors of metabolism overview: pathophysiology, manifestations, evaluation, and management. Pediatr Clin North Am 2018; 65(2):179-208. *https://doi.org/10.1016/j.pcl.2017.11.001*
33. DeFronzo RA, Ferrannini E, Zimmet P, Alberti KGMM. International Textbook of Diabetes Mellitus. 4th ed. Wiley-Blackwell; 2015.
34. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006;444(7121):860-867. *https://doi.org/10.1038/nature05485*
35. Hood L, Friend SH. Predictive, personalized, preventive, participatory (P4) cancer medicine. Nat Rev Clin Oncol 2011;8(3):184-187. *https://doi.org/10.1038/nrclinonc.2010.227*
36. Turnbaugh PJ, Ley RE, Hamady M, *et al*. The human microbiome project. Nature 2007; 449(7164):804-810. *https://doi.org/10.1038/nature06244*
37. Hegele RA, Ginsberg HN, Chapman MJ, *et al*. The polygenic nature of hypertriglyceridaemia: implications for definition, diagnosis, and management. Lancet Diabetes Endocrinol 2014;2(8):655-666. *https://doi.org/10.1016/S2213-8587(13)70191-8*

38. Scriver CR, Beaud*et al*, Sly WS, Valle D. The Metabolic and Molecular Bases of Inherited Disease. 8th ed. McGraw-Hill; 2001.
39. DiMauro S, Schon EA. Mitochondrial respiratory-chain diseases. N Engl J Med. 2003;348(26):2656-2668. *https://doi.org/10.1056/NEJMra022567*
40. Wallace DC. Mitochondrial diseases in man and mouse. Science 1999;283(5407):1482-1488. *https://doi.org/10.1126/science.283.5407.1482*
41. Landrigan PJ, Fuller R, Acosta NJR, *et al*. The Lancet Commission on pollution and health. Lancet 2018;391(10119):462-512. *https://doi.org/10.1016/S0140-6736(17)32345-0*
42. Grandjean P, Landrigan PJ. Neurobehavioural effects of developmental toxicity. Lancet Neurol 2014;13(3):330-338. *https://doi.org/10.1016/S1474-4422(13)70278-3*
43. Notarangelo LD. Primary immunodeficiencies. J Allergy Clin Immunol. 2010; 125(2 Suppl 2):S182-S194. *https://doi.org/10.1016/j.jaci.2009.07.053*
44. Tangye SG, Al-Herz W, Bousfiha A, *et al*. Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol 2022; 42(7):1473-1507. *https://doi.org/10.1007/s10875-022-01289-3*
45. McIntyre RS, Cha DS, Soczynska JK, *et al*. Cognitive deficits and functional outcomes in major depressive disorder: determinants, substrates, and treatment interventions. Depress Anxiety 2013; 30(6):515-527. *https://doi.org/10.1002/da.22083*
46. Berk M, Williams LJ, Jacka FN, *et al*. So depression is an inflammatory disease, but where does the inflammation come from? BMC Med 2013; 11:200. *https://doi.org/10.1186/1741-7015-11-200*