ISSN: 0975 -8542

Journal of Global Pharma Technology

Available Online at: www.jgpt.co.in

RESEARCH ARTICLE

Anorexia in Childhood

Ekaterina Zenia*, Alexandr Tsymbal, Aleksandr Kruchinkin

I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russian Federation.

***Corresponding Author: Ekaterina Zenia**

Abstract

Over the past three decades, there has been a tendency to shift anorexia nervosa towards a younger age. It is necessary to identify a possible relationship between mental illness and the presence of anorexia. The purpose of the study is to comparatively examine the clinical, gastroenterological and psychopathological features of the development of anorexia nervosa in children with diagnosed mental disorders (autism, childhood schizophrenia). In 2008-2018, at the base of the Moscow Scientific Center for Mental Health and the Children's Psychiatric Clinic No. 6 (Russian Federation), 167 patients were selected, divided into two groups according to the diagnosis. The first included 90 children with a diagnosis of autism, the second - 77 children with a diagnosis of childhood schizophrenia. Children were observed from 3 months of age until they reach 10 years of age. At 8 years old, the children underwent gastroenterological examination. The frequency of occurrence of deviations in eating behavior was recorded. Used abdominal ultrasound, as well as esophagogastroduodenoscopy. In the group of children with autism aged 8-10 years, the total number of eating disorders is gradually decreasing, 2-2.5 times less than 1-3 years ($p = 0.001$). The incidence rate of anorexia was 70%. Also recorded a decrease in the frequency of occurrence of violations. At 1-3 years on average, the frequency of occurrence of eating disorders was at the level of one third of cases. At the age of 8-10 years, this indicator decreased by 6-15 times ($p = 0.001$). In the second group, children with schizophrenia, the manifestation of eating disorders occurs later, at 4-6 months of life. By 1-3 years, the frequency of occurrence of deceleration of chewing and swallowing increases 2 times ($p = 0.05$). At 8-10 years, these eating disorders develop into persistent phobias. Anorexia is recorded in 90% of cases. At 1-3 years of age, eating behavior changes: bulimia and vomitomania appear. The consequence of this is a decrease in body weight. Despite the fact that at the age of 8-10 years in the second group, many disorders are 2-4 times less likely ($p = 0.001$) than at 1-3 years, some (bulimia) can remain with the same frequency. Esophagitis and reflux in the esophagus are 3–7 times more likely to occur compared to cardia and erosion ($p = 0.05$ and $p = 0.001$). Gastroduodenitis and reflux were most often diagnosed in the stomach, 2 times more often than gastritis ($p = 0.05$), 6 times more often than erosion ($p = 0.001$), 10 times more than mucosal proliferation. Damage was found to occur to the gastrointestinal tract in children with anorexia nervosa in almost all of its departments. A group of patients with autism has a high percentage of anorexia (70%), with a predominance of eating disorders such as active or passive refusal to eat. In the group of patients with schizophrenia, anorexia is more common (90%), but eating disorders, edible substances, vomitomania, bulimia dominated among eating disorders. Gastroenterological examination revealed a number of diseases of the gastrointestinal tract, among which esophagitis (37%), gastroduodenitis (41%) and reflux (47%) predominated. The revealed age-related features of the development of eating disorders will allow establishing the disease in time and taking measures to cure it.

Key words: *Anorexia nervosa, Autism, Schizophrenia, Bulimia, Womitomania, Eating disorders.*

Introduction

In recent years, anorexia has become an increasingly common occurrence. Thus, up to 1.5% of females and up to 0.3% of males suffers from this disease [1]. Among the causes of the disease, one can single out mental factors, disorders related to the endocrine system, and digestive problems [2]. The first case of the disease was described back in the late 17th century by the English physician Morton, who described anorexia as a "nervous consumption". Actually, the term "anorexia nervosa" was proposed somewhat later by W. Gull. Despite the fact that initially, from the moment of description,

cases of anorexia were single and kept at approximately the same level (in Europe), in the last three decades, the incidence of anorexia has begun to increase. Anorexia also has a gender predisposition - among women this disease is fixed 5 times more often than among men [3]. A shift towards rejuvenation of this disease also becomes noticeable when the average age of patients becomes closer to adolescence [4].

Psycho-social factors are important for the occurrence of anorexia. So, in connection with the increase in the number of cases of obesity in developed countries (USA, European Union and others), diets that are actively popularized in the media and Internet resources are becoming especially popular for young people. A sharp shift in the quantity and quality of food causes the physiological stress of the body, which can ultimately lead to irreversible consequences, including anorexia [5].

For children and adolescents, the timely detection of signs of anorexia is especially important, since in the case of its development in humans, their individual genetic program is not fully implemented. This underdevelopment can persist in adulthood, and even worsen under the influence of adverse environmental factors [6].

The above risk factors for the development of anorexia nervosa can be divided into the following groups: a) factors of genetic origin; b) biological factors; c) family risk factors; d) individual and personal risk factors. Factors of the first risk group are localized on the 1st and 13th chromosomes. These include the HTR2A gene that controls the 5-HT2A serotonin receptor. At the hypothalamic level, nutritional behavior is determined by the cerebral neutrophic factor gene.

Through regulation of serotonin concentration, a predisposition to anorexia is determined. Implementation of disorders at the genetic level can be carried out in several ways: the development of an affective or anxious syndrome, belonging to a certain type of personality, as well as with an unbalanced diet or experienced stress [7]. The biological risk factor is mainly associated with obesity and associated processes. So, with the development of functional disorders of neurotransmitters, such as serotonin, dopamine and norepinephrine, an eating disorder occurs. This is primarily manifested in the development of deposits of adipose tissue. The lipocytes that form the basis of adipose tissue are capable of producing leptin, a substance of hormonal origin. Leptin interacts with the hypothalamus by sending saturation information there [8]. The third group of factors is mainly related to heredity - the presence of relatives (parents), also suffering from eating disorders, including anorexia nervosa, as well as bulimia and obesity. These factors manifest themselves in childhood and adolescence.

Among personality factors, the main cause of anorexia is perfectionism. Perfectionism can be a phenotypic reflection of deeper, genetic factors predisposing to anorexia nervosa. Personal-individual factors also include self-doubt, confidence in one's inferiority, low level of self-esteem, as well as some features of the hysterical nature of the person. Other equally important factors include cultural. The media image of thinness as an ideal of beauty can have the most devastating consequences [9].

This factor is especially active in developed countries. Severe stress caused by physical or sexual abuse, the death of loved ones, can also contribute to the development of anorexia nervosa. Finally, the last of the risk factors is age-related. The risk group primarily includes adolescents. With endocrine system rearrangements characteristic at this age, a conscious desire to reduce body weight, through fasting or special diets, is possible [10].

Anorexia was established to be also caused by impaired connections in the brain. In particular, when the connections between neurons in the parts of the brain responsible for processing visual information are weakened, all patients perceive themselves as overweight people [11].

There are 4 main types of eating disorders known. These include: a) Mericism or chewing-regurgitation disorder; b) anorexia nervosa, developing in infancy (or infantile anorexia); c) eating disorders associated with chronic eating of inedible substances; d) insufficient development of eating behavior [12]. Disorders of the first type occur with the same frequency in boys and girls. They are characterized by a combination of belching, chewing and swallowing food, but without pronounced pathologies of the

gastrointestinal tract. The consequence of this is the observed decrease in body weight.

This pathology begins, as a rule, from 3 months of life and can last up to 2-6 years, inclusive. The reasons for this are in the attention to the child from the mother - his redundancy or insufficiency. Moreover, with an excess of maternal attention and under its influence, chewing gum can be an enhancement of the behavior model, and with a lack of it, on the contrary, it can be a means of attracting attention. Some evidence suggests that the ruminant reflex is associated with the level of endorphins in the infant's blood [13].

With enough attention from the mother, the level of endorphins corresponds to the norm, with a deficiency; the chewing process stimulates the production of endorphins. With Mericism, some pathologies of the gastrointestinal tract, in particular, umbilical hernias may occur.

In a number of cases, it was possible to overcome Mericism by feeding through a probe, and in the presence of regurgitation urges and a hernia, surgical intervention and the subsequent connection of the mother to feeding were used. With this form of anorexia, weight loss of up to 20% of total body weight is possible. The second type, infantile anorexia, includes a complex of symptoms: malnutrition or refusal of food, selectivity in its choice. Refusal of food can be active or passive.

These symptoms appear shortly after birth [14]. Passive rejection manifests itself in the fact that the baby does not wake up while feeding, or does not show any interest in food. Food can linger in the oral cavity for long periods of time - up to 45-50 minutes, with a slowdown in chewing and swallowing movements.

Active refusal begins a little later, during complementary foods, when food is spit out, dishes with food are scattered, and increased attention is paid to approaching a spoon with food. If selectivity is present, it is expressed in the form of rejection of products of a certain color, for example, red or yellow, or in the preference of certain types of products, for example, eggs or dairy products. Infantile anorexia nervosa can occur in infancy for an extended period of three months [15]. Other, less prolonged cases of decreased appetite are attributed to changes in diet, rest, etc. The development of infant anorexia may occur in the absence of control by the mother in the amount of milk consumed. Of paramount importance in this case is the lack on the part of the mother of the ability to distinguish between signs given through crying or crying by the child. Anorexia of this type is very common. If at the age of six months, about 5% of children had signs of anorexia and 10% were with food whims, then by 3 years these indicators were 33% and 25%, respectively [16].

Thus, in this age period there is the greatest risk of the occurrence and subsequent progression of anorexia nervosa. In infantile anorexia, there are three main forms - dysthymic, regurgitational, and anorexia associated with passive or active refusal of food [17]. Constant eating of inedible substances is observed with equal frequency in boys and girls of 1-2 years old and, as a rule, disappears with time. Finally, nutritional underdevelopment was noted before the age of 1 year and, as a rule, does not cause severe pathologies.

Despite the well-established classification of various forms of anorexia in children, available studies do not sufficiently cover aspects such as disorders of the gastrointestinal tract, as well as age and clinical features of anorexia in early childhood and the possibility of its early diagnosis [18, 21]. There is only fragmentary information about eating disorders in early childhood, including in children with mental disorders [22].

There is a need to trace the relationship between mental illness and the presence of anorexia. This determined the relevance of this work. The purpose of this study is to study the clinical, gastroenterological and psychopathological features of the development of anorexia in children with mental disorders (autism and childhood schizophrenia).

Material and Research Methods

Material

The studies were conducted in 2008-2018 on the basis of the Scientific Center for Mental Health and Children's Psychiatric Clinic No. 6 (Moscow, Russian Federation). A total of 167 patients were examined. The first group included patients with a diagnosis of

childhood autism (90 children), the second group included 77 children with a diagnosis of childhood schizophrenia. The first disease corresponds to code F84.0, the second to code F20.8 according to the ICD-10 classifier. Both groups were examined over 10 years, from birth to 10 years. The first group included 56 girls and 34 boys, the second - 51 girls and 26 boys. Upon reaching 8 years of age, patients (all girls from both groups, randomly selected) additionally underwent a comprehensive gastroenterological examination.

All types of studies were carried out exclusively with the consent of the parents of children, or children from the age of 6, while they were in the hospital or at the examination. At the same time, both parties signed an agreement on non-disclosure of information about the identity of the child. During the research, no ethical rules were violated; all observations and manipulations were carried out according to the medical ethics of behavior with the patient.

Research Methods

In each group of children, the frequency of occurrence (in % of the total number of children in the group) of any symptom was recorded: refusal of food, gag reflex, etc. During gastroenterological examination, general clinical studies were performed (general biochemical analysis of blood, electrocardiogram). In addition, specialized examinations were performed: abdominal ultrasound, esophagogastroduodenoscopy, as well as a urease test for the presence of Helicobacter pylori.

Statistical Analysis

To process the obtained data, we used the statistics package for Microsoft Excel 2010, as well as the program Past v. 3.0 When comparing differences between characters and groups, we used a two-sample t-test for independent (in case of intra-group comparisons) and dependent (in case of intra-group differences between the frequency of occurrence of the trait and also between different ages in the same group) variables. Differences are significant at $p = 0.05$ (minimum threshold), differing levels are negotiated separately.

Results

Psychosomatic Research

It was established that in group 1 (autism) the number of eating disorders was maximal in the 1st-3rd year of life (Table 1). The number of eating disorders at this age amounted to one third of the total number of violations for the entire study period.

Table 1: Deviations in eating behavior in children with a diagnosis of autism (3 months - 10 years), group 1

Age	Type of deviation in eating behavior + The frequency of occurrence of the sign,%	The number of recorded signs for a given age
3 months	70 (anorexia) +14 (lack of interest in breastfeeding)	2
4-6 months	41 (swallowing slowing down) + 20 (active rejection of breastfeeding) + 49 (resistance to introducing new types of foods into the diet) + 25 (regurgitation) + 40 (active rejection of feeding)	5
1-3 years	45 (swallowing and uniform food) + 60 (eating foods of the same type and color) + 32 (refusing certain foods) + 17 (preferring one type of food)	4
4-7 years	32 (refusal to eat) + 21 (aversion to smell and type of food) + 37 (tearfulness at sight of food)	3
8-10 years	5 (eating homogeneous food) + 4 (selectivity in food choice)	2
Sum of signs	13	13

Further, as they grow older, at 8-10 years old, the total number of eating disorders decreases, 2-2.5 times less than that in 1-3 years ($p = 0.001$). The frequency of occurrence

of violations is also reduced. If in early childhood the average frequency of occurrence of eating disorders was at least one third of cases, then in 8-10 years this indicator decreased by 6-15 times (p = 0.001). If in 1-3 years there is a high frequency of occurrence of such signs as the use of food that is homogeneous in consistency and selectivity in choosing the type of food, then by the age of 8-10 years, the same violations are found 8-10 times less often (p = 0.001). Thus, it can be noted that in group 1, as they mature, the occurrence and number of recorded eating disorders are declining. Anorexia was found in the vast majority of infants (Table 1), which indicates the primacy of this disease and the fact that anorexia can provoke other eating disorders. Based on the data obtained, it can be argued that in children with autism eating disorders are reversible, gradually decreasing as they grow older. In the second group (the childhood form of schizophrenia), more severe, pathological forms of eating disorders, such as vomitomania, the development of food phobias, bulimia, were recorded (Table 2).

Table 2: Deviations in eating behavior in children with a diagnosis of childhood forms of schizophrenia (3 months - 10 years), group 2

Age	Type of deviation in eating behavior + The frequency of occurrence of the sign,%	The number of recorded signs for a given age
4-6 months	19 (swallowing slowing down) + 25 (weight loss) + 5 (diagnosis of postnatal nutritional malnutrition of the second degree) + 10 (initiation of regurgitation) + 28 (refusal of food)	4
1-3 years	33 (swallowing and chewing slowing down) + 90 (anorexia) + 47 (overweight) + 19 (acceleration of puberty)	4
4-7 years	51 (eating inedible substances) + 19 (eating feces and handling) + 37 (crying at sight of food)	2
8-10 years	39 (bulimia) + 14 (the appearance of phobias) + vomitomania (9) + weight loss (19)	4
Sum of signs	14	14

Firstly, the appearance of obvious eating disorders occurs here a little later, at 4-6 months of life. By 1-3 years, a 2-fold increase in the frequency of occurrence of some disorders was recorded, for example, slowing of chewing and swallowing, with food retained in the oral cavity (p = 0.05). At 8–10 years of age, persistent phobias and anorexia appear which was recorded in almost all patients at 1–3 years old and is replaced by bulimia and vomitomania, followed by a decrease in body weight.

Despite the fact that at 8-10 years, most disorders occur with a frequency of 2-4 times less often (p = 0.001), some (bulimia) can remain at the same level, provoking the development of eating disorders in the future. At 3-5 years, the dominant tendency in the 2nd group is eating inedible substances (including feces). Another feature is the joyful mood that accompanied both these actions and the process of taking ordinary food. The latter has always been characterized by sloppiness, sloppiness, with scattering of food in all directions. At the age of 8-10 years, mood swings were noted, from depressed and depressed to upbeatly cheerful. These differences coincide with changes in eating behavior.

The recorded phobias related exclusively to food. For example, there was a fear of food poisoning or infection by any parasites, while exclusively freshly prepared and just bought food was consumed. In case of forced feeding, the patients caused vomiting. The further development of children from the second group was reduced to the appearance of delusional syndrome in adolescence, an increase in dry skin, a sharp decrease in body weight, the appearance and strengthening of autistic features.

In general, the types of eating disorders in both groups were different, but anorexia was present in early childhood with almost the same frequency. This indicates the

importance of diagnosing this disease in the early stages, since in both groups it provokes the development of other, often dangerous eating disorders.

Gastroenterological Studies

Among the signs of anorexia in patients, amenoria, asthenia, and body mass deficiency predominated (Fig. 1A). If the first three signs are presented in all examined patients, then the rest (dry skin and others) are found 2-3 times less often (p = 0.001).

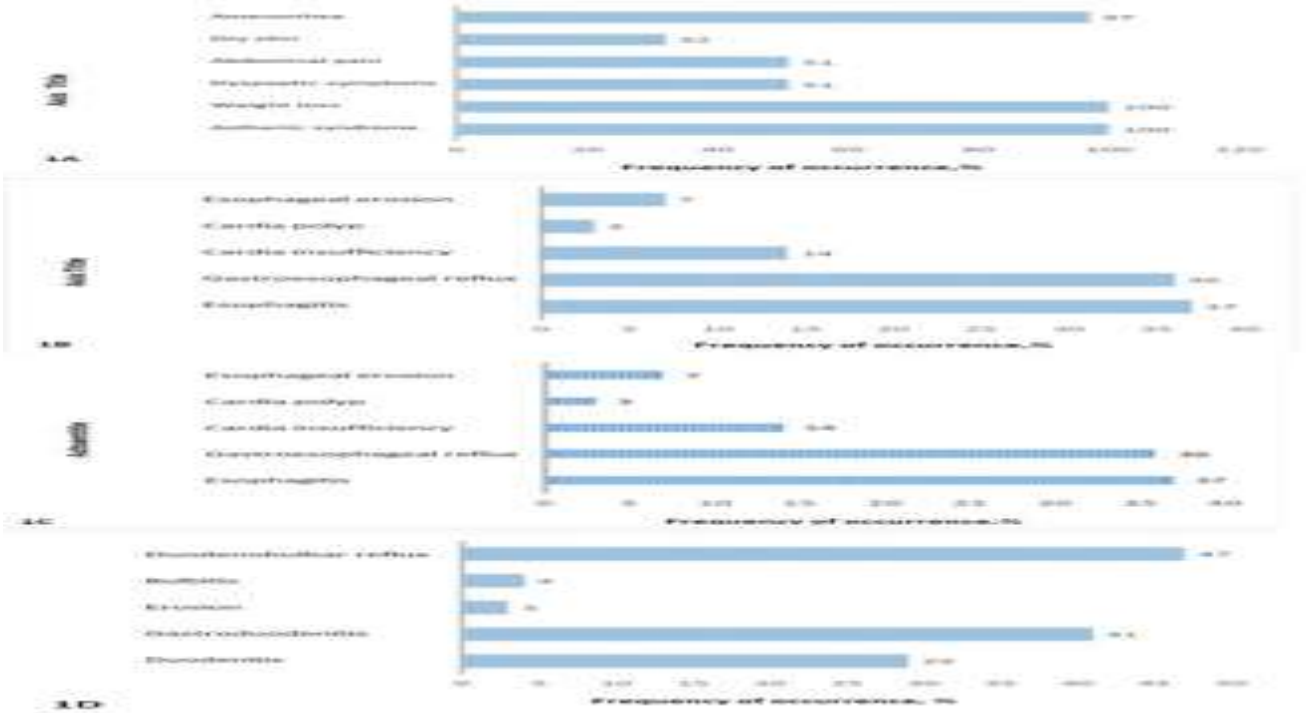

Figure 1: Clinical manifestations of anorexia nervosa (1A) and the frequency of lesions of the esophagus (1B), stomach (1C) and duodenum (1D) in the observed children with anorexia

The detected signs of esophagitis and reflux in the esophagus (Fig. 1B) indicate the development of gastroesophageal reflux disease. In addition, the presence of polyps was detected, as well as numerous erosions. In the esophagus, esophagitis and reflux were 3-7 times more likely to occur compared with other lesions, such as cardia and erosion (respectively, p = 0.05 and p = 0.001). Gastroduodenitis and reflux prevailed in the stomach, which were 2 times more common than gastritis (p = 0.05), 6 times more likely than erosion (p = 0.001), and 10 times more likely than mucosal proliferation (Fig. 1B). In the duodenum (Fig. 1D), gastroduodenitis and reflux also prevailed, moreover in approximately the same proportions as in the stomach. The remaining lesions were less common - duodenitis was 1.5 times less likely (p = 0.05), and bulbitis and erosion were 10 times less likely (p = 0.001)

It should be added that in one third of children with anorexia, a lesion was found in all the examined sections of the gastrointestinal tract - namely, the esophagus, stomach and 12 duodenal ulcers. The test for the presence of Helicobacter pylori gave positive results in 85% of cases. Thus, we can talk about the complex negative impact of the effects of anorexia on the body - both at the anatomical level and at the level of infection with bacterial infections.

The results of abdominal ultrasound showed an increase in the size of the pancreas (95% of cases), heterogeneity of the structure of its tissue (87%), an increase in the thickness of the walls of the gallbladder (64%), and liver hepatosis of varying severity (12%). A blood test showed generally normal results. Deviations were in the direction of hypoglycemia (55%, less than 2.8 mmol per 1 liter), increased to 7-10 mmol per 1 liter of cholesterol content.

Discussion

The main external manifestation of anorexia is the general depletion of the body [23]. Body weight loss rates can range from 20 to 50% [24]. At the same time, different indicators of changes in body weight affect differently the body as a whole. For example, with a weight loss of 25-30%, a pathological change in the endocrine system is noted [25]. Further, with a loss of 40-50%, ion exchange is disturbed [26].

The degradation process reaches a new fundamental level - interactions between macromolecules (transport proteins) and ions. If you refuse food, there is a decrease in blood sugar, up to a hypoglycemic coma. Women suffering from anorexia nervosa have

a lower thyroxine hormone compared to healthy ones [27]. At the social level, patients suffering from anorexia nervosa are able to maintain normal performance for a long time, and even engage in physical exercises. Well-being, according to such patients, they have satisfactory. There is a decrease in the secretion of sex hormones, which, in fact, returns fully adult people to the prepubertal period. Many of them need subsequent restoration of reproductive health.

A consequence of the lack of sex hormones is also the development of osteoporosis. It should be noted that anorexia nervosa usually occurs against the background of a conscious restriction of food intake by the patient [28]. In the case of anorexia in children, the prognosis is usually more favorable.

The main part of the disorders associated with eating disorder, as a result of reaching x years of age, as a rule, disappears. The foundations for anorexia are laid as early as infancy, when, with a violation of the instinct of sucking, eating disorders can develop at an older age [29]. This is also shown by our studies - and violations at the mental level entail those at the anatomical and morphological level. Most often, the reason for the occurrence of eating disorders lies in the lack of proper attention from the mother to the child [30]. Our study showed that damage to the gastrointestinal tract in children with anorexia nervosa can occur in almost all of its departments. Anorexia is triggered by a stressful situation, which, ultimately, is reflected in the presence of pathological processes in the digestive organs. Due to the lack of activity in the digestive tract, over time, almost all patients noted the development of pain. The pain syndrome is chronic, and according to some reports, it can lead patients to suicidal actions [31]. A particularly vulnerable group is children up to 1-3 years old, as well as patients diagnosed with childhood schizophrenia [32]. The data obtained indicate the need for further detailed study of anorexia nervosa in children.

Conclusions

A group of patients with autism showed a high percentage of infant form of anorexia (70%), with a predominance of eating disorders such as active or passive refusal to eat, refusal to breastfeed, or manifestation of food selectivity. In the group of patients with childhood forms of schizophrenia, a higher percentage of anorexia nervosa disease was noted (90%), but eating disorders, inedible substances, vomitomania, bulimia prevailed among eating disorders.

The group of patients with schizophrenia at the age of 10 years had higher rates of pathological eating disorders. Gastroenterological examination revealed a number of diseases of the gastrointestinal tract, among which esophagitis (37%), gastroduodenitis (41%) and reflux (47%) predominated. The revealed age-related features of the development of eating disorders will allow establishing the disease in time and taking measures to cure it.

References

1. Arcelus J, Mitchell AJ, Wales J, Nielsen S (2011) Mortality rates in patients with anorexia nervosa and other eating disorders: a meta-analysis of 36 studies. Archives of general psychiatry, 68(7): 724-731.
2. Association AP (2013) Diagnostic and Statistical Manual of Mental Disorders, 5th ed.; American Psychiatric Association: Washington, DC, USA.
3. Culbert KM, Racine SE, Klump KL (2015) Research Review: What we have learned about the causes of eating disorders-a synthesis of sociocultural, psychological, and biological research. Journal of Child Psychology and Psychiatry, 56(11): 1141-1164.
4. Duncan L, Yilmaz Z, Gaspar H, Walters R, Goldstein J, Anttila V, Ripke S (2017) Eating Disorders Working Group of the Psychiatric Genomics Consortium. Significant locus and metabolic genetic correlations revealed in genome-wide association study of anorexia nervosa. American Journal of Psychiatry, 174: 850-858.
5. Demontis D, Walters RK, Martin J, Mattheisen M, Als TD, Agerbo E, Cerrato F (2019) ADHD Working Group of the Psychiatric Genomics Consortium (PGC);

Early Life course & Genetic Epidemiology (EAGLE) Consortium; 23andMe Research Team. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. Nature Genetics, 51(1): 63-75.

6. Ilyas A, Hübel C, Stahl D, Stadler M, Ismail K, Breen G, Kan C (2018) The metabolic underpinning of eating disorders: A systematic review and meta-analysis of insulin sensitivity. Molecular and cellular endocrinology, 497: 110-307.
7. Focker M, Timmesfeld N, Scherag S, Knoll N, Singmann P, Wang-Sattler R, Adamski J (2012) Comparison of metabolic profiles of acutely ill and short-term weight recovered patients with anorexia nervosa reveals alterations of 33 out of 163 metabolites. Journal of psychiatric research, 46(12): 1600-1609.
8. Da Luz FQ, Hay P, Touyz S, Sainsbury A (2018) Obesity with comorbid eating disorders: Associated health risks and treatment approaches. Nutrients, 10(7): 829.
9. Abraham TM, Massaro JM, Hoffmann U, Yanovski JA, Fox CS (2014) Metabolic characterization of adults with binge eating in the general population: the Framingham Heart Study. Obesity, 22(11): 2441-2449.
10. Herle M, De Stavola B, Hübel C, Abdulkadir M, Santos Ferreira D, Loos RJF, Micali N (2019) Eating behaviours in childhood and later eating disorder behaviours and diagnoses: a longitudinal study. British Journal of Psychiatry.
11. Yilmaz Z, Gottfredson NC, Zerwas SC, Bulik CM, Micali N (2019) Developmental premorbid body mass index trajectories of adolescents with eating disorders in a longitudinal population cohort. Journal of the American Academy of Child & Adolescent Psychiatry, 58(2): 191-199.
12. Hussain AA, Hübel C, Hindborg M, Lindkvist E, Kastrup AM, Yilmaz Z, Sjögren JM (2019) Increased lipid and lipoprotein concentrations in anorexia nervosa: A systematic review and meta- analysis. International Journal of Eating Disorders, 52(6): 611-629.
13. Micali N, Field AE, Treasure JL, Evans DM (2015a) Are obesity risk genes associated with binge eating in adolescence?. Obesity, 23(8): 1729-1736.
14. Micali N, De Stavola B, Ploubidis G, Simonoff E, Treasure J, Field AE (2015b) Adolescent eating disorder behaviours and cognitions: gender-specific effects of child, maternal and family risk factors. The British Journal of Psychiatry, 207(4): 320-327.
15. Field AE, Sonneville KR, Micali N, Crosby RD, Swanson SA, Laird NM, Horton NJ (2012) Prospective association of common eating disorders and adverse outcomes. Pediatrics, 130(2): e289-e295.
16. Micali N, Solmi F, Horton NJ, Crosby RD, Eddy KT, Calzo JP, Field AE (2015c) Adolescent eating disorders predict psychiatric, high-risk behaviors and weight outcomes in young adulthood. Journal of the American Academy of Child & Adolescent Psychiatry, 54(8): 652-659.
17. Baskaran C, Eddy KT, Miller KK, Meenaghan E, Misra M, Lawson EA (2016) Leptin secretory dynamics and associated disordered eating psychopathology across the weight spectrum. European Journal of Endocrinology, 174(4): 503-12.
18. Townsend MK, Clish CB, Kraft P, Wu C, Souza AL, Deik AA, Wolpin BM (2013) Reproducibility of metabolomic profiles among men and women in 2 large cohort studies. Clinical chemistry, 59(11): 1657-1667.
19. Pinto J, Domingues MRM, Galhano E, Pita C, do Céu Almeida M, Carreira IM, Gil AM (2014) Human plasma stability during handling and storage: impact on NMR metabolomics. Analyst, 139(5): 1168-1177.
20. Kim K, Mall C, Taylor SL, Hitchcock S, Zhang C, Wettersten HI, Weiss RH (2014) Mealtime, temporal, and daily variability of the human urinary and plasma metabolomes in a tightly controlled environment. PloS one, 9(1): e86223.
21. Carayol M, Licaj I, Achaintre D, Sacerdote C, Vineis P, Key TJ, Ferrari P (2015) Reliability of serum metabolites over a two-year period: a targeted metabolomic approach in fasting and non-fasting samples from EPIC. PloS one, 10(8): e0135-437.

22. Townsend MK, Bao Y, Poole EM, Bertrand KA, Kraft P, Wolpin BM, Tworoger SS (2016) Impact of pre-analytic blood sample collection factors on metabolomics. Cancer Epidemiology and Prevention Biomarkers, 25(5): 823-829.

23. Fraser A, Macdonald-Wallis C, Tilling K, Boyd A, Golding J, Davey Smith G, Ring S (2013) Cohort profile: the Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. International journal of epidemiology, 42(1): 97-110.

24. Boyd A, Golding J, Macleod J, Lawlor DA, Fraser A, Henderson J, Davey Smith G (2013) Cohort profile: the 'children of the 90s'-the index offspring of the Avon Longitudinal Study of Parents and Children. International journal of epidemiology, 42(1): 111-127.

25. Emmett PM, Jones LR, Northstone K (2015) Dietary patterns in the avon longitudinal study of parents and children. Nutrition reviews, 73(3): 207-230.

26. Wurtz P, Kangas AJ, Soininen P, Lawlor DA, Davey Smith G, Ala-Korpela M (2017) Quantitative serum nuclear magnetic resonance metabolomics in large-scale epidemiology: a primer on-omic technologies. American journal of epidemiology, 186(9): 1084-1096.

27. Wurtz P, Kangas AJ, Soininen P, Lehtimäki T, Kähönen M, Viikari JS, Ala-Korpela M (2013) Lipoprotein subclass profiling reveals pleiotropy in the genetic variants of lipid risk factors for coronary heart disease: a note on Mendelian randomization studies. Journal of the American College of Cardiology, 62(20): 1906-1908.

28. Wang Q, Ferreira DLS, Nelson SM, Sattar N, Ala-Korpela M, Lawlor DA (2018) Metabolic characterization of menopause: cross-sectional and longitudinal evidence. BMC medicine, 16(1): 1-12.

29. Wang Q, Wurtz P, Auro K, Mäkinen VP, Kangas AJ, Soininen P, Salmi M (2016) Metabolic profiling of pregnancy: cross-sectional and longitudinal evidence. BMC medicine, 14(1): 205.

30. Ferreira DLS, Williams DM, Kangas AJ, Soininen P, Ala-Korpela M, Smith GD, Lawlor DA (2017) Association of pre-pregnancy body mass index with offspring metabolic profile: Analyses of 3 European prospective birth cohorts. PLoS medicine, 14(8): e1002376.

31. Santos Ferreira DL, Maple HJ, Goodwin M, Brand JS, Yip V, Min JL, Ring S (2019) The Effect of pre-analytical conditions on blood metabolomics in epidemiological studies. Metabolites, 9(4): 64.

32. Wasserstein RL, Lazar NA (2016) The ASA statement on p-values: context, process, and purpose. Journal of the American Statistical Association, 70: 129-131.

