**Attention Deficit/Hyperactivity-Disorder and obesity: a review and model of current hypotheses explaining their comorbidity**

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**1. Introduction**

Obesity is a growing societal problem. Its prevention and treatment are one of the biggest challenges of health care worldwide (Branca et al., 2007). The increasing incidence of obesity in children and adolescents is particularly worrying, because obesity is associated with subsequent risk of other conditions, such as hypertension, diabetes type II (Wabitsch et al., 2004), sleep apnea (Arens and Muzumdar, 2010), gall bladder disease (Larsson and Wolk, 2007), and psychosocial problems (Rosen-Reynoso et al., 2011), among others. Therefore, ongoing research aims to better understand and characterize the risk factors for obesity. In this context, the previously overlooked link between Attention-Deficit/Hyperactivity Disorder (ADHD) and increased risk of obesity in children, adolescents and adults is a relatively novel and interesting line of research.

ADHD, which affects around 5% school-age children worldwide (Polanczyk et al., 2007), is characterized by age inappropriate and impairing levels of inattention and/or hyperactivity-impulsivity (American Psychiatric Association, 2000; Scahill and Schwab-Stone, 2000). Children with ADHD have lower school achievements and less satisfying relationships with peers (Hanć and Brzezińska, 2009). The etiology of ADHD is multifactorial, including a complex interplay between genetic and environmental factors. Candidate genes for ADHD are related to neurotransmission and neuroplasticity (Banaschewski et al., 2010), as well as to cell adhesion and migration, neurogenesis, synaptic plasticity, inflammation, and apoptosis (Lee and Song, 2014). Environmental risk factors include smoking during pregnancy, prematurity, and low birth weight, among others (Faraone et al., 2015; Hanć et al., 2016a).

An increasing amount of evidence has shown, albeit not consistently, a significant association between ADHD and obesity (Cortese et al., 2016a; Nigg et al., 2016). The aim of this review is to provide a synthesis of the research aimed at explaining the mechanisms underlying the ADHD-obesity association and to build a comprehensive model based on current empirical evidence. We will consider in particular the following: genetic factors, fetal programming, executive dysfunctions, psychosocial stress, factors directly related to energy balance (i.e. a physical activity, sedentary behaviors, eating patterns) and sleep patterns alterations. The proposed division of mechanisms makes it possible to synthesize the results of all studies included in this review. The order in which the mechanisms are discussed is determined by the sequence of events in human ontogeny and leads through prenatal to postnatal phases of development, and from genes through epigenetic mechanisms to wide understood neurobehavioral phenotype and its interactions with environment.Overall, this set of mechanisms reflects the biopsychosocial model.

Before moving to the discussion of each of these factors, we will provide an overview of current evidence on the association between ADHD and obesity.

**2. Methods**

Although not intended as a formal systematic review, this review is based on a systematic and comprehensive search of pertinent articles retrieved via Medline and Scopus databases using a combination of the following terms in the title: *attention deficit hyperactivity disorder, ADHD, overweight, obesity, adiposity, fat*. The last search was performed on 20.10.2017. Twenty-nine articles that contribute to the explanations of the ADHD-obesity link (Table 1) were selected for the present review. The review is supplemented by the articles not directly focusing on the association between ADHD and obesity, when they added to the discussed hypotheses.

**3. Evidence on the association between ADHD and obesity**

The first evidence of an association between ADHD and obesity was provided by Altfas (2002) and Fleming and Levy (2002), pointing to a significantly increased prevalence (up to 50%) of ADHD in adults treated for obesity, especially of the class III, compared to non ADHD controls. Another seminal study by Holtkamp et al. (2004) showed that boys with ADHD had significantly higher BMI compared to a control group, and that overweight and obesity were more frequent in this group than in the general population. Since then, many studies have tested the co-occurrence of ADHD and obesity (see Table 2, summarizing the studies that analyzed the occurrence of overweight and obesity in children, adolescents and adults with ADHD). Better understanding the association between ADHD and obesity is of clinical relevance since it has been reported that screening for and treating previously unrecognized ADHD in individuals with obesity may positively impact obesity outcome. (REF) The increasing number of studies in the field has recently allowed for meta-analytic synthesis of their findings, addressing possible issues in terms of confounding factors.

Specifically, two meta-analyses have been published, providing somehow different conclusions. Cortese et al. (2016a) (pooling a total of 42) concluded for a significant ADHD-obesity association, regardless of a number of confounding factors, including age and gender. Nigg et al. (2016) (including 43 studies, only partially overlapping with those included by Cortese et al.) indicated a non-significant association in children, a possible clinically significant association in girls, and a significant association in adults. The two meta-analyses share similarities but are also characterized by differences in the methodological approach. They were both conducted in accordance with recommendations of the Meta-Analysis of Observational Reporting Items for Systematic Reviews and Meta-Analyses statement (Linerati et al., 2009). Both meta-analyses included studies in which the diagnosis of ADHD was established according to the criteria of the International Statistical Classification of Diseases and Related Health Problems (ICD) or Diagnostic and Statistical Manual of Mental Disorders (DSM) but also on the basis of medical records, or based on questions such as: "Did your doctor ever tell you that you have ADHD?". Thus, the two meta-analyzes included also cases in which ADHD has not been formally confirmed. However, a sensitivity analysis in Cortese et al. removing these studies confirmed the robustness of the findings. Both Cortese et al. and Nigg et al. defined the overweight and obesity on the basis of cut-off scores for body mass index (BMI) recommended by the International Obesity Task Force IOTF (Cole et al., 2000), the Centers for Disease Control and Prevention (CDC) (CDC, 2016) or the World Health Organization (WHO) (WHO, 2017). In both meta-analyses, the main outcomes was the odds ratio expressing the association between obesity and ADHD and they both controlled for medication, sex, age (children and adolescents or adults), socioeconomic status and comorbid disorders. However, unlike the work of Cortese et al., the meta-analysis of Nigg et al. included also studies reporting an association between BMI as a dimensional variable and ADHD measures. Additionally, Cortese et al. gathered unpublished data from study authors, that allowed them to calculate the prevalence of obesity in individuals with ADHD in studies not originally reporting it.

In terms of results, the meta-analyses of Cortese et al. and Nigg et al. had a similar overall pooled effect size for the association between ADHD and obesity, which was, respectively, OR = 1.30 and OR = 1.22. In both meta-analyses, the association between ADHD and obesity was stronger when restricting the analyses to studies including only individuals not pharmacologically treated (OR = 1.43 and OR = 1.30, respectively). Using a meta-regression analysis, Cortese et al. concluded that gender did not significantly impact the association between obesity and ADHD. Slightly different results were obtained by Nigg et al. Although they did not find significant differences between genders in the size of the effect, in a separate analysis they showed a significant association of ADHD with BMI in women (OR = 1.19) but not in men (OR = 1.10). In both meta-analyses, the ADHD-obesity association was stronger in adults (Cortese et al.: OR=1.55 and Nigg et al.: OR=1.37) than in youths (OR=1.20 and OR=1.13, respectively). However, differently from the Cortese et al. meta-analysis, the study by Nigg et al. showed no significant association between ADHD and obesity in pre-pubertal children and a monotonic increase in the incidence of obesity in successive age groups. Cortese et al. further reported that the incidence of obesity in individuals with ADHD (10.3%) was approximately 40% higher than in those without ADHD (7.4%) in children, and about 70% higher in adults with ADHD (28.2%) compared to those without ADHD (16.4%). An additional aspect assessed by Cortese et al. relates to possible effects of the pharmacological treatment of ADHD. They found that the prevalence of obesity among medicated individuals with ADHD (13.8%) was decreased for about 40% compared with those not medicated (19.2%). The association between ADHD and obesity in patients treated pharmacologically was not statistically significant. Additionally, Cortese et al. performed a separate analysis controlling for the impact of different methodological approaches used in studies. In all analyses, the relationship of ADHD with obesity remained statistically significant and the effect size increased with increasing rigor of adopted criteria for the research selection (e.g., for studies including formal diagnosis of ADHD and direct measure of height and weight OR=1.47, for clinical samples OR=1.61). In conclusion, the two meta-analyses indicate a significant association of ADHD with risk of obesity in adults, but they differ in relation to the magnitude of the association in children. Furthermore, the meta-analysis by Nigg et al. additionally suggests gender differences.

Although the sensitivity and subgroup analyses performed in the two meta-analysis allowed to gain insight on possible factors impacting the association between ADHD and obesity, the two meta-analyses were primarily aimed at establishing the degree of association, if any, between ADHD and obesity, rather than elucidating the mechanisms underlying the association. Understanding possible factors underpinning the association between ADHD and obesity is arguably the current priority in this field. The remaining part of this paper presents and critically discusses studies that attempted to gain insight into these mechanisms.

**4. Possible explanations of the ADHD-obesity association**

Since the risk of obesity increases in people with ADHD from childhood to adulthood, it is of relevance to search for mechanisms and factors operating specifically on the subsequent stages of ontogeny. It goes without saying that each of the factors that will be discussed in the next sections should not be seen in isolation; rather, they are clearly interlinked (eg, neuropsychological dysfunctions are accounted for, at least in part, by genetic factors).

***4.1 Genetic factors***

A recently published study found a familial co-aggregation of ADHD and obesity (Chen et al. 2017). The authors’ interpretation is that the disorders share familial risk factors, although the study could not address the specific characteristics of such factors. As stated by authors, family environment as well as pleiotropic genes may both contribute to the ADHD-obesity comorbidity. Indeed, studies so far have focused more on genetic risk factors rather than the environmental ones. In fact, a number of genes have been identified as involved both in ADHD and obesity. A first group of genes belongs to the *FTO set* (fat mass and obesity gene). *FTO* is strongly associated with risk of obesity, and alos modulates the symptoms of ADHD. There is evidence of a relationship between rs8050136 and rs9939609 alleles of *FTO* and low severity of ADHD as well as better performance on tests of executive functions (Choudhry et al., 2013a; Velders et al., 2012). ADHD symptoms have been showed to co-occurr also with mutations of the gene of brain melanocortin-4 receptor (*MC4R*), which is also responsible for the most common monogenic severe obesity and is involved in the regulation of appetite and energy homeostasis (Porfirio et al., 2015). A case report has also showed a co-occurrence of ADHD and hyperphagia with *MC4R* mutations (Aguirre Castaneda et al., 2016; Pott et al., 2013). Despite these promising results, in another study (Albayrak et al., 2013) assessing the relationship of risk alleles of obesity and ADHD, only two of tested 32 alleles related to obesity were significantly associated with ADHD: rs20696 in the *NUDT3* gene (nudix; nucleoside diphosphate linked moiety X-type motif) and rs6497416 in *GPRC5B* gene (intronic region of the gene coding the G protein-coupled receptor, family C, group 5, member B). Active NUDT3prevents somatic gene mutations (Safrany et al., 1998), while GPRC5B is homologous with the C receptors, which include the metabotropic glutamate receptors associated with ADHD (Elia et al., 2011).

Of note, some of candidate genes for ADHD are also related to increased risk for obesity, e.g.: polymorphisms of dopamine receptor *DRD2* (polymorphism rs1799732 and rs1800497), *DRD3* (rs6280) and *DRD4* (rs1800955, rs1800443, 48 VNTR), the dopamine transporter (*DAT* rs27072, rs463379, VNTR 3'-UTR), catechol-O-methyltransferase *COMT* (rs4680) presynaptic protein *SNAP25* (rs363039, rs363043, rs363050), serotonin receptor *5HTR2A* (rs17288723), and brain-derived neurotrophic factor *BDNF* (rs6265) (Ariza et al., 2012; Friedel et al., 2005; Hanć et al., 2016b; Kernie et al., 2000; Nakazato et al., 2003; Patte et al., 2016). One study has also shown a significant relationship of A1 (T) allele of the *ANKK1 Taq1A* (allele of lower binding capacity and lower density of DRD2 receptor influencing the decrease in dopaminergic signaling) to overeating (Patte et al., 2016). However, another study failed to detect significant differences in frequency of *ANKK1 Taq1A* and DRD4-7R between adults with or without obesity (Ariza et al., 2012).

There is also evidence of a significantly higher prevalence of obesity and eating disorders in heterozygous *Bdnf+/-* mice (*Brain Derived Neurotrophic Factor)* (Kernie et al., 2000) and reduced levels of BDNF in the serum of patients with eating disorders (Nakazato et al., 2003). However, no relationship of the assessed variants of *BDNF*, p.V66M and c-46C>T SNP, was found with obesity, eating disorders and ADHD in humans (Friedel et al., 2005). In the most recent study including an analysis of 14 polymorphisms (SNPs and VNTR), overweight in children and adolescents with ADHD was associated only with SNPs of 3 candidate genes, namely *DRD4* rs1800955, *SNAP25* rs363039, rs363043 and *5HTR2A* rs17288723 (Hanć et al., 2016b).

In summary, the studies of the genetic underpinnings of the ADHD-obesity relationship are inconclusive but overall they seem to suggest that a subgroup of the obesity genes increase the risk for ADHD and executive dysfunctions. Additionally, some candidate genes for ADHD, associated with the reward system, mood regulation and neuroplasticity, seem to increase the risk of obesity. Future studies testing specific gene variants associated with ADHD and obesity and their interaction with specific environmental conditions are needed.

***4.2 Fetal programming of ADHD-obesity shared phenotype***

According to some studies, the prenatal period could play a key role in the development both of neuropsychological characteristics associated with ADHD, and of subsequent obesity. Both conditions may indeed be considered in the light of the fetal programming hypothesis. This hypothesis is based on the observation that children with low birth weight (likely due to prenatal malnutrition) have a significantly greater weight gain than their peers with normal birth weight in subsequent development phases (Barker et al., 1989). This may be due to physiological and metabolic adaptations to adverse environmental conditions. Rapid weight gain in the post-natal phase could be understood then as an effect of adaptive development strategy programmed during the prenatal period (Gluckman and Hanson, 2005). This obviously may lead to obesity and metabolic syndrome in later phases of development (Casey, 2008). Since low birth weight is one of the risk factors for ADHD (Hultman et al., 2007), it is possible that fetal programming underlies a greater risk of obesity in this group (Hanć et al., 2015a). Accordingly, Odent (2010) suggests that ADHD and obesity are facets of the same disease, caused by the interaction of genes with factors affecting a child in the prenatal stage, such as maternal stress, maternal smoking and drinking alcohol during pregnancy, which have been associated with ADHD (Davis, 2010).

Fetal programming was tested as a possible mechanism underlying the ADHD-obesity relationship by Hanć et al. (2015a). Although in their sample low birth weight occurred more than twice as frequently in ADHD group than in the control group, ADHD remained significantly associated with overweight in analyses adjusted for birth weight. In several other studies (Aguirre Castaneda et al., 2016; Byrd et al., 2013; Hanć et al., 2012; Hanć et al., 2015b) the relation between ADHD and obesity remained statistically significant after controlling for birth weight. These studies exclude low birth weight as a factor associated with the phenotype of ADHD-obesity, but cannot ultimately disprove the role of fetal programming. The association between obesity and ADHD may be the result of epigenetic interaction between susceptibility genes and specific prenatal environmental factors, which is in line with the hypothesis proposed by Odent (2010). Environmental programming factors, however, are not as of yet well understood, though some evidence (Davis, 2010) indicates that they are associated with high levels of stress. In summary, this line of research seems promising and deserves to be further expanded.

***4.3 Neuropsychological characteristics of ADHD-obesity phenotype***

Genes that underpin the link between ADHD and obesity may contribute to deficits in executive functions, which may act as a common neuropsychological phenotype of both disorders. Executive functions are defined as functions involved in the regulation of behavior and adapting to novelty (Gilbert and Burgess, 2008; Lezak and Lilienfeld, 1995). They are top-down mental processes regulating attention when going on automatic processes or intuition is insufficient or impossible (Diamond, 2013). The core executive functions are: inhibition or inhibitory control, including self-control (behavioral inhibition) and interference control (selective attention and cognitive inhibition), working memory, and cognitive flexibility. In fact, these functions overlap each other and cooperate in controlling humans goal-oriented actions. The higher-ordered executive function, built from those above mentioned, include reasoning, problem solving and planning (Diamond, 2013).

Earlier studies have shown that the deficits in executive functions are linked with ADHD, albeit not all children with ADHD present with executive dysfunctions and executive dysfunctions are variable from child to child (Craig et al., 2016). Some studies in children and adolescents indicated common deficits in inhibitory control and impulsiveness both in obesity and ADHD. Deficits in the range of functions controlled by the orbitofrontal cortex (including attention functions) were observed in teenagers with obesity and this has also been confirmed by neuroimaging studies (Pauli-Pott et al., 2010; Reinert et al., 2013). However, only few studies have been conducted to test the hypothesis that executive dysfunction contribute to the ADHD-obesity relationship. Available studies, however, tend to suggest that the relationship may be mediated by inhibitory control dysfunctions resulting in impulsivity, deficits in response inhibition and attention deficits. In particular, one study showed significantly higher BMI associated with severe inattention, measured with Autism-Tics, ADHD, and other Comorbidities inventory (A-TAC) reflecting diagnostic criteria listed in the DSM-IV (Kerekes et al., 2015), in girls aged 12y. The low level of executive functions indicated by the Trail Making Test, Verbal Fluency Test and Color-Word Interference Test was associated with a higher BMI and a greater likelihood of being overweight/obese in another study (Graziano et al., 2012). Children with ADHD had also significantly increased odds of loss of control eating syndrome (LOC-ES) compared with control group (Reinblatt et al., 2015). LOC-ES was associated with deficits in response inhibition, measured by performance-based measures (the Go/No-Go Task) and parental ratings (the Behavior Regulation Inventory of Executive Function - BRIEF).

There are other studies, however, pointing to a lack of involvement of executive dysfunctions in the ADHD-obesity relationship. In one study, no significant association between inhibitory control measured with stop-signal task and overweight in children and adolescents with ADHD was reported (Fliers et al., 2013). The study by Choudhry et al. (2013b) found no differences among normal weight, overweight and obese children with ADHD in terms of neurocognitive indicators of Wechsler Intelligence Scale WISC-III (verbal IQ, performance IQ, full scale IQ), Wisconsin Card Sorting Test (assessing cognitive flexibility and set-shifting), Finger Windows subtest (evaluating visual-spatial working memory), Tower of London (planning, organization, problem-solving), Self-Ordered Pointing Test (working memory, planning, response inhibition), Stroop Test (cognitive flexibility, resistance to interference from outside stimuli), Continuous Performance Test (attention, response inhibition, impulse control), and motivation style tasks: Choice Delay Task and Task-engagement Traits. In another study on the relationship of *DRD4* rs1800955, *SNAP25* rs363039, rs363043 and *5HTR2A* rs17288723 with obesity in boys with ADHD (Hanć et al., 2016a), although the majority of the analyzed polymorphisms (13 of 14 polymorphisms) were associated with the level of performance in neuropsychological tests (Continuous Performance Test, Stroop Test, The Trail Making Test A and B, The Matching Familiar Figures Test, Verbal Fluency Test, the Ray-Osterrieth Complex Figure, and Wisconsin Card Sorting Test), no significant association was found between scores at the neuropsychological tests and obesity. The authors concluded that mechanisms (probably physiological) other than the executive functions deficits are involved in the development of obesity in these patients. Another explanation is based on “cool/hot” executive functions divergence. It should be pointed out that research on executive dysfunction in individuals with obesity/ADHD has mostly focused on the so called "cool executive functions" related to the control of thoughts, attention and actions, but working in laboratory conditions and measured by neuropsychological tests. “Cool” executive functions rely more on dorso- and ventrolateral prefrontal cortex (Diamond, 2013). On the other hand, investigation on "hot executive functions", related to self-regulation under emotional and motivational arousal in “real world” conditions, not “cool” laboratory situation (Diamond, 2013, Peterson and Welsh, 2014), has been downplayed. “Hot” executive functions engage more the medial prefrontal cortex (especially orbitofrontal) and parasympathetic part of autonomic nervous system (Diamond, 2013). It is possible that deficits in these “hot” functions (related to self-regulation in emotional arousal conditions) can be associated with a lower tolerance for hunger and a greater tendency towards high-calorie food. A preliminary study by Van der Oord and colleagues (2017) tested the hypothesis of reward/executive dysfunctioning (dual pathway model of ADHD) in a sample of adults with obesity. Although no significant differences were found between individuals with and without obesity on the outcome measures, individuals with obesity and binge eating showed significantly more self-reported delay discounting and inattention than those with obesity but without binge eating. However, due to the pilot nature of the study, larger studies are warranted. Therefore, the hypothesis of “cool/hot” dysfunctioning in ADHD/obesity requires further investigation, extending current research mainly focused on “cool” executive functions.

***4.4. Stress as a risk factor of obesity in individuals with ADHD***

Adverse life events (Friedman et al., 2015), family dysfunctions (Tabak et al., 2012), family instability (Crosnoe, 2012) and posttraumatic stress disorder (PTSD) increase the risk of obesity later in life (Perkonigg et al., 2009). For instance, a study has found that girls with a high level of cumulative social risk (maternal depression, maternal alcohol use, housing and food insecurity, paternal incarceration and paternal violence against the mother) at the age of 1 or 3 years (Suglia et al., 2012), were more likely to be obese at the age of 5. Earlier work has shown that ADHD significantly increases the risk of adverse, stressful life events (Bernardi et al., 2012). ADHD is associated with low self-esteem, poor peer relations, social exclusion, school failure and generally more stressful relationship with parents (Hanć and Brzezińska, 2009). Additionally, high levels of impulsivity, high sensitivity to reward, novelty-seeking and the tendency to take risks and engage in potentially dangerous behaviors and situations are traits of ADHD that may result in stressful situations. People with ADHD generally experience more adverse events in life, have a higher level of subjectively perceived stress and are more likely to suffer from PTSD (Bernardi et al., 2012). Thus, stress may be another important factor that mediates the relation between ADHD and obesity. So far, however, limited research has tested this hypothesis. A study by Pauli-Pott et al. (2017) concluded that the relationship between ADHD symptoms and excessive body weight in boys aged 6-7 is completely accounted for by psychosocial cumulative risks associated with the family environment. Psychosocial risk included low socioeconomic status, low education of parents, poor housing, mental illness of parents, parental separation, and unwanted pregnancy and early parenthood. A relationship of at least some of these factors with increased weight of children might be explained by the phenomenon of stress. However, further research on this issue is needed, taking into account the stressful individual events or long-term situations that could be a consequence of the symptoms of ADHD, such as academic failure, problematic relationships with peers and parents, and increased health risk (e.g., children with ADHD have an increased risk of unintentional physical injuries). In addition, available data do not ultimately explain the mechanism by which stress contributes to obesity in children with ADHD. Available studies arise, however, quite plausible hypotheses. Chronic stress can impact body weight through hormonal mechanisms. Persisting high levels of cortisol cause an increase in appetite (increased intake of high-caloric and high-fat food) and the accumulation of body fat (Hewagalamulage et al., 2016). From an evolutionary perspective, overeating can be understood as an adaptation to unpredictable environmental conditions, in which the body should accumulate energy whenever possible. On the other hand, adverse events can affect the life style of an individual. For example, social rejection in adolescents may result in fewer opportunities to participate in structured games and activities, lower physical activity, more sedentary ways of spending time (watching TV and playing computer games) and unhealthy methods of mood regulation, e.g. through food, drinking alcohol. Regardless of the presumed mechanism, the cumulative effects of stress translate into a positive energy balance, which leads to obesity. Although highly plausible, these mechanisms need further empirical testing.

***4.5 Factors associated with positive energy balance***

For the positive energy balance to occur, the amount of accumulated energy must be higher than the amount of energy expended. This can be a result of overeating but also of decreased physical activity and sedentary lifestyle. So far, a number of studies have specifically focused on the analysis of the relationship of these factors with obesity in people with ADHD. Their results are not conclusive and vary according to the age group considered. One study showed that high level of symptoms of hyperactivity and inattention in children aged 4-6 was related to lower body fat, increased physical activity and generally lower level of sedentary behaviors (Ebenegger et al., 2012). Nevertheless, ADHD was significantly related also with a significantly greater amount of time spent watching television and eating unhealthy behaviors (snacking in front of the TV). Therefore, it seems that, initially, during the preschool age, hyperactivity leads to a negative energy balance, but already in this young age behaviors that in the future may contribute to the development of obesity are also present. Several studies have confirmed this hypothesis. ADHD has been associated with a longer exposure time to television or TV game time (Erhart et al., 2012; Kim et al., 2011; van Egmond-Frohlich et al., 2012), poorer motor performance (de Nascimento et al., 2013) and a low level of physical activity (Cook et al., 2015; de Nascimento et al., 2013; Erhart et al., 2012; Kim et al., 2011) in children and adolescents. Of note, the presence of ADHD in childhood has been reported as an important predictor of both obesity and reduced physical activity in adolescence (Khalife et al., 2014). But a direct link of obesity with low physical activity in children with ADHD has been confirmed only in two studies (Cook et al., 2015; Kim et al., 2011).

On the other hand, several studies have shown that ADHD is associated with dysfunctional eating patterns, which can lead to the development of obesity. For example, unstable eating patterns, including skipping breakfast, eating in the evening and at night, and short sleep were factors increasing the risk of obesity in patients with ADHD (Vogel et al., 2015). There is also some evidence that children and adolescents with ADHD eat and drink more during the day and their meals are more caloric than their peers’ food (Ptacek et al., 2014; van Egmond-Frohlich et al., 2012), they are significantly more likely to eat snacks (Hartmann et al., 2012) and junk food (Kim et al., 2014), have increased focus on eating, fear of losing control over eating (Erhart et al., 2012) and significantly more bulimic behaviors (Kim et al., 2014; Tong et al., 2017). Overeating in these patients is related to eating in response to negative mood and social cues rather than hunger (Pott et al., 2013), and with immediate and impulsive eating (Wilhelm et al., 2011). The majority of the studies indicated that disrupted patterns of eating are related to ADHD. This is consistent with the above mentioned mechanism focusing on ADHD - adverse events - stress – overeating, but it could also be more directly the expression of hot executive dysfunctions. Food, especially highly processed and caloric, may be an important source of stimulation and constitute a form of immediate reward. Nevertheless, some studies (e.g., Mousavi et al., 2015) showed that even though children with ADHD had a higher BMI compared to healthy peers, they had a similar level of food energy content and the content of macro and micronutrient in food during a three-day observation. Therefore, future studies linking abnormal eating patterns and physical activity to executive dysfunction in individuals with ADHD may advance our knowledge of the mechanisms underlying the association between ADHD and obesity.

***4.6 The sleep disorders hypothesis***

Sleep rhythms and biological clock disruptions are often reported in children with ADHD (Cortese et al., 2009). Previous research focused on sleep showed that excessive daytime sleepiness was more frequent in individuals with ADHD comparing to the control group (Marcotte et al., 1998; Owens et al., 2000) and the prevalence of comorbid sleep disorder or sleep disturbance among youth with ADHD is around 25-50% (Corkum et al., 1998). Children and adolescents with ADHD have been reported with significantly more daytime sleepiness than controls during daytime (Golan et al., 2004; Lecendreux et al., 2000). These findings are in line with ‘the hypoarousal theory’ of ADHD (Weinberg and Brumback, 1990), according to which people with ADHD might be more sleepier than control group and hyperactivity/impulsivity could be a strategy to stay alert. Short or disturbed sleep at night may be the factor that cause fatigue during the day, decreased level of physical activity and excessive daytime sleepiness (Fliers et al., 2013). Of note, sleep deprivation reduces leptin and raises ghrelin level (Carter et al., 2011). The consequence of circadian rhythm disruption is skipping breakfast and lunch, which is often observed in adults with ADHD (Kooij, 2013). In turns, postponing or skipping meals may trigger binge eating later in the day. Furthermore, it has been reported that, due to disrupted insulin response, the glucose level do not drop sufficiently after late evening meals (Kooij, 2013; Qin et al., 2003). These physiological changes, together with fatigue, low level of physical activity and also excessive daytime sleepiness, may cause excessive weight gain, overweight and obesity (Vgontzas et al., 2006). Therefore, it has been proposed that short sleep disruption (Lundahl and Nelson, 2016) and/or excessive daytime sleepiness (Cortese et al., 2008; Cortese and Morcillo, 2010) could contribute to explaining the association between ADHD and obesity. Nevertheless, so far only two studies were focused on testing ‘the sleep disorders hypothesis’, providing mixed findings. Whilst Fliers (2013) did not find any significant association between short sleep duration at night and overweight in children and adolescents with ADHD, whilst Vogel et al (2015) concluded that short sleep on free days mediated the relationship between ADHD symptoms and BMI in adults. Further investigation is needed to examine this hypothesis, as well as other possible characteristics of sleep disruption in relation to the link between ADHD and obesity.

**5. Synthesis and conclusions**

Two recent meta-analyses overall confirmed a significant association between ADHD and obesity, albeit with partially different results. Nevertheless, the mechanisms underpinning the relationship between ADHD and obesity are far from being clear. So far, the majority of the studies aimed to explain this link have focused on physical activity and eating patterns as possible and most direct causes of weight gain. However, these aspects do not seem to fully explain the link and need to be integrated in a broader bio-psychosocial model. Based on empirical evidence reported in the previous sections, we elaborated a comprehensive model (see Fig. 1). We propose that ADHD and obesity might have a common neurocognitive phenotype, characterized by deficits in hot executive functions, associated with impulsivity and difficulties in postponing gratification. These features may be determined partly by multiple genes, as demonstrated by preliminary evidence pointing to genetic alterations common to both ADHD and obesity. An important element in the model is represented by possible fetal programming related to epigenetic mechanisms occurring in the prenatal stage, that could contribute to disruption of executive function development. Possible programming factors are environmental agents as maternal stress, maternal smoking and drinking alcohol during pregnancy (Odent, 2010). Deficits in hot executive functions may increase the risk of obesity via disordered eating patterns, increased amount of food and calorific value of meals. In addition, people with low impulse control and difficulties in postponing gratification may have a greater tendency to engage in a highly stimulating and rewarding but sedentary activities, like playing computer games and watching TV. In turns, overeating and sedentary behaviors lead ultimately to a positive energy balance and, consequently, to obesity. There is also evidence that disrupted sleep patterns may play an important role. Short sleep, excessive daytime sleepiness and disruptions of biological clock seem to be connected with binge eating and altered glucose regulation. Deficits in executive functions could also expose a person with ADHD to more stressors than their healthy peers and stress may be associated with obesity via physiological and behavioral mechanisms leading to overeating. Reduced physical activity and sedentary behaviors may also be the consequence of stressful life events, such as e.g. social rejection. In this way, the relationships between the biological, environmental and lifestyle level may underpin the co-occurrence of ADHD and obesity.

Overall, the empirical evidence that we retrieved on the mechanisms underlying the association between ADHD and obesity focuses especially on the possible common genetic causes and on the role of psychosocial factors.

Physiological/metabolic alterations have been overall scarcely investigated so far. path. Of note, none of the studies that we retrieved has evaluated the physiological mechanisms leading to obesity (e.g. hormonal disorders, improper neurobiological regulation of appetite). Research exploring the genetic basis for the coexistence of ADHD and obesity and epigenetic mechanisms seem also promising, with particular emphasis on stress, both pre- and postnatal. Moreover, future search should address prenatal environment factors that could contribute to the link between ADHD and obesity, especially related to mother’s lifestyle, e.g., cigarette smoking and drinking alcohol, eating habits but also exposure to pollutants.

Based on reviewed literature we conclude that simple explanations of the link between ADHD and obesity seem not plausible. Rather, a complex bio-psycho-social model, including both cognitive-behavioral and physiological path, may advance future research on this topic which is highly relevant from a scientific, clinical, and public health standpoint.

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