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Childhood Obesity with Resting State Functional Connectivity and Premature Pubarche with Neuroimaging Methods: A Systematic Review

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Abstract: Childhood obesity is a global health problem, the prevalence of which has rapidly increased in recent years, which is the result of the interaction between a complex set of factors and leads to serious medical consequences. rs-fMRI(resting-state functional magnetic resonance imaging) analysis techniques may be useful in elucidating the pathophysiology of obesity the progression of the disease and the changes in the brain functional structure caused by the disease state associated with high body mass index. Pubarche is a physiological condition that refers to the onset of hair growth in the pubic and axillary areas under the influence of sex hormones and develops due to the increase in adrenal hormones. Childhood obesity causes early puberty and a significant portion of children with premature puberty are individuals with obesity. Studies on childhood obesity using different rs-fMRI analysis techniques were analyzed in detail in the literature to examine the contributions and innovations of these studies. In addition, premature pubarche has been systematically analyzed in studies using different neuroimaging methods. Due to the limited number of neuroimaging studies on premature pubarche and the lack of examination of its relationship with obesity and brain functionality, it presents itself as an issue that requires study.

Keywords: Childhood obesity, premature pubarche, neuroimaging, fMRI

Dinlenme Durumu Fonksiyonel Bağlantısı ile Çocukluk Çağı Obezitesi ve Nörogörüntüleme Yöntemleri ile Prematür Pubarş: Sistematik Bir İnceleme

Özet: Çocukluk çağı obezitesi, son yıllarda görülme sıklığı hızla artan, karmaşık faktörlerin etkileşimi sonucu ortaya çıkan ve ciddi tıbbi sonuçlara yol açan küresel bir sağlık sorunudur. rs-fMRG(dinlenme durumu fonksiyonel manyetik rezonans görüntüleme) analiz teknikleri, obezitenin patofizyolojisini, hastalığın seyrini ve yüksek vücut kitle indeksi ile ilişkili hastalık durumunun beyin fonksiyonel yapısında neden olduğu değişiklikleri aydınlatmada faydalı olabilir. Pubarş, seks hormonlarının etkisi altında kasık ve koltuk altı bölgelerinde kıllanmanın başlamasını ifade eden ve adrenal hormonların artmasına bağlı olarak gelişen fizyolojik bir durumdur. Çocukluk çağı obezitesi erken ergenliğe neden olur ve erken ergenliğe giren çocukların önemli bir kısmı obeziteye sahip bireylerdir. Literatürde farklı rs-fMRG analiz teknikleri kullanılarak çocukluk çağı obezitesi üzerine yapılan çalışmalar detaylı bir şekilde analiz edilerek bu çalışmaların katkıları ve yenilikleri incelenmiştir. Ayrıca farklı nörogörüntüleme yöntemlerinin kullanıldığı çalışmalarda prematüre pubarş sistematik olarak analiz edilmiştir. Prematüre pubarş ile ilgili nörogörüntüleme çalışmalarının sınırlı olması, obezite ve beyin işlevselliği ile ilişkisinin incelenmemesi nedeniyle üzerinde çalışılması gereken bir konu olarak karşımıza çıkmaktadır.

Anahtar Kelimeler: Çocukluk çağı obezitesi, prematür pubarş, nörogörüntüleme, fMRG

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1. INTRODUCTION

The prevalence of childhood overweight and obesity is a global health problem that has increased rapidly in recent years. Studies estimate that almost 60% of children aged 2-19 will

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suffer from obesity in adulthood [1]. The childhood obesity rate is 18.5% in the United States [2]. Although the rate of overweight and obesity has stabilized in Europe, the study stated that severe obesity is a problem seen in many European countries, especially in boys. One in 20 boys in Southern Europe and one in 25 boys in Eastern Europe have severe obesity [3]. The prevalence of obesity in England was stated as 9.5% in children aged 4-5 and 20.1% in children aged 10-11 in 2017-2018 [4]. In a study conducted in Turkey, the obesity prevalence of school-age children and adolescents between the ages of 6-19 was found to be 7.3% [5]. In the 2022 report of the World Obesity Federation, Turkey was predicted to have an estimated prevalence of 19% in children aged 5-19 in 2030, ranking first in Europe [6]. When the 2023 report is examined, it is estimated that a total of 21 million children and adolescents between the ages of 5-19 in Europe will be affected by obesity [7]. Figure 1 shows the obesity prevalence expectations of children aged 5-19 in different regions in the future, according to the 2023 report of the World Obesity Federation.

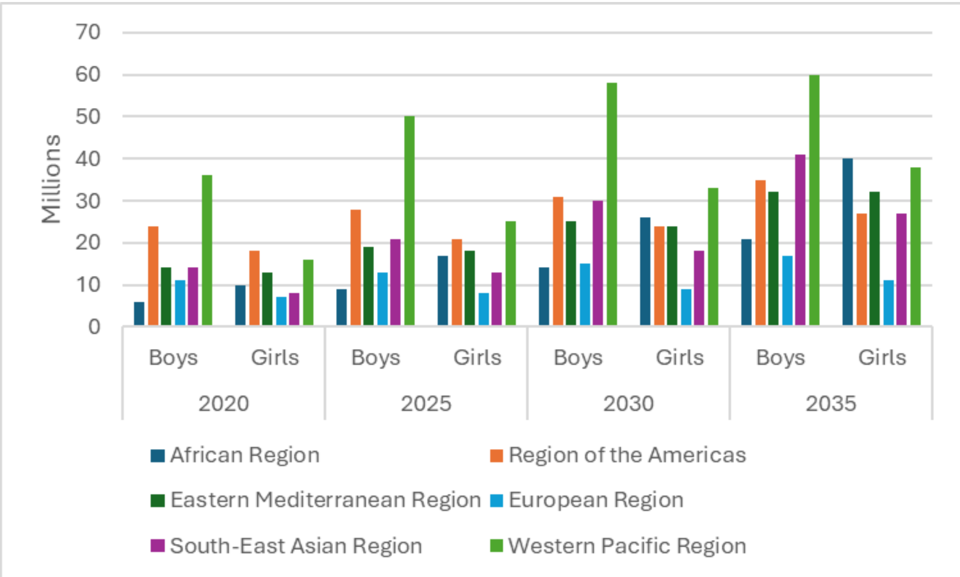

Figure 1. Prevalence expectation of girls and boys obese children and adolescents (5-19 years old) in different regions according to the 2023 report of the World Obesity Federation [7].

Childhood obesity is a health problem that is the result of the interaction between a complex set of factors (environment, family, genetics, society, ecological influences, etc.) and leads to serious medical consequences [8]. With the increasing prevalence of childhood obesity, diseases that only occur in adulthood (diabetes, hypertension, non-alcoholic fatty liver disease, obstructive sleep apnea, cardiovascular and cerebrovascular risks, cancer, etc.) have begun to be seen frequently at early ages [9]. Assessment of weight status during infancy and childhood is important because of the effects of overweight and obesity on child development, health, and well-being. It is very important to detect this serious health problem in childhood, examine its effects, and start treatment immediately.

It is known that obesity can have effects not only on physical health but also on emotional and mental health. The effects of obesity can be seen at hormonal, neurological, and cognitive levels. This condition is associated with increased mood disorders, anxiety levels, and addiction problems. It may also contribute to neurocognitive deficits, negatively impacting an individual's cognitive abilities. Studies have shown that being overweight or obese in childhood is associated with psychological problems such as depression [10], anxiety, low self-confidence and self-esteem, eating disorders, and ADHD [11,12,13]. The fact that obesity causes a wide range of health problems and that these problems are not limited to physical health but also affect mental and emotional health shows that this issue is a comprehensive health problem and draws attention to the importance of further research on the causes and consequences of obesity. While obesity is usually detected most simply by calculating body mass index (BMI), various endocrinological tests at high BMI values obtain information about its level and etiology. In addition, neuroimaging studies conducted on individuals with obesity provide important information about the neurobiological mechanisms underlying this health problem. Studies have shown that obesity causes changes in the brain at both structural and connectivity levels [14,15].

It can be said that the structural changes caused by obesity in the brain are associated with altered cortical morphometry, decreased gray/white matter volume and impaired white matter integrity [16]. Over the past two decades, neuroimaging methods, particularly functional magnetic resonance imaging (fMRI), structural imaging (sMRI), and diffusion tensor imaging (DTI), have become popular and rapidly advancing tools for investigating the neurobiology of diseases [16].

In studies where childhood obesity was investigated with fMRI, it was found to affect brain connectivity. Research has linked childhood obesity to resting-state functional connectivity in various brain networks, including visual, somatosensory, dorsal attention, ventral attention, limbic, frontoparietal, and default mode networks [17,18]. Considering the far-reaching consequences of childhood obesity on both physical and cognitive health, it is clear that addressing this issue requires a multifaceted approach.

Functional magnetic resonance imaging (fMRI) is increasingly used today as a safe and non-invasive tool to examine conditions that affect the brain and its functional functioning. In functional magnetic resonance imaging, brain function is examined using task-based paradigms (task-based) that require subjects to perform cognitive tasks or in the absence of a task or stimulus (resting-state) [19].

In addition to task-based studies to examine the effect of obesity on brain functions, rs-fMRI (resting-state functional magnetic resonance imaging) analysis techniques may be useful in elucidating the pathophysiology of obesity, the progression of the disease, and the changes in the brain functional structure caused by the disease state associated with high body mass index [20]. Therefore, a systematic review of the scope of findings will help determine the relevance of functional connectivity in the resting state brain in overweight or obese individuals.

Although there are studies on obese individuals causing functional connectivity changes in the resting brain, the extent of these changes, which brain regions are more affected, and the etiology of the disorder remains unclear in literature. One of the focuses of this review is to examine the connectivity differences caused by childhood obesity in the brain.

Adolescence, as the transition phase between childhood and adulthood, is the turning point of many important physical, cognitive, and psychosocial developmental events [21]. It is an important period of development, including hormonal changes, brain reorganization, and maturation [22]. In studies conducted worldwide in the last 50 years, it has been reported that the age at which early puberty occurs has a continuous downward trend [23]. It has been shown that early adolescence can lead to psychological and social problems in children, increasing the likelihood of depression, aggression, behavioral problems, social withdrawal, sleep problems, obsessive behavior, and psychological stress, which has negative effects on quality of life [24].

Regarding the etiology of obesity and its relationship with premature adrenarche, it is one of the issues that need to be investigated in a complex and multifaceted manner. Overweight/obesity causes various changes in the endocrine system, and these changes may affect sexual maturity by increasing the activation of endocrine system pathways such as the hypothalamic-pituitary-gonadal axis. These hormonal changes may cause an early onset of sexual maturation in childhood. High dehydroepiandrosterone sulfate (DHEAS) levels in early adrenarche contribute to accelerated growth and bone maturation, which may further contribute to obesity [25].

Pubarche is a physiological condition that refers to the onset of hair growth in the pubic and axillary areas under the influence of sex hormones and develops due to the increase in adrenal hormones. Other changes seen with the effect of adrenal hormones are acne on the face, increased oiliness in the skin and hair, and adult-type body odor [26]. If this physiological condition begins to occur before the age of 8 in girls and before the age of 9 in boys, the definition of "premature pubarche" is used. Premature pubarche is more common in girls than in boys [27] and in a study conducted in Turkey, the prevalence of premature pubarche in girls aged 4-8 was found to be 4.3% [28]. The most common cause of premature pubarche is premature adrenarche (PA). During adrenarche, zona reticularis of the adrenal glands develops, resulting in increased levels of the adrenal hormones DHEA (dehydroepiandrosterone), its sulfate DHEA-S, and testosterone [29]. Studies have evaluated the effects of increased DHEA and DHEA-S on mental health and have shown that it is associated with psychiatric disorders such as conduct disorder, oppositional defiant disorder, and anxiety disorders in children [30,31].

It is thought that children with increased body mass index may be associated with PA and early puberty and that these children will be at risk for conditions such as obesity, hypertension, insulin resistance, and polycystic ovary syndrome in girls later in life [32,33]. It is reported in the literature that childhood obesity causes early puberty and that a significant portion of children with premature puberty are individuals with obesity [28]. In their study, Corvalan et al. showed that obesity was directly related to DHEA-S levels in 7-year-old children with normal birth weight [34]. In the literature, the rate of overweight or obesity in Australian children diagnosed with premature pubarche was found to be 65%, while this rate was reported to be 60% in Caucasian girls [35,36]. Charkaluk et al. documented that only 32.5% of French female patients diagnosed with premature pubarche were obese [37]. In a study conducted in Turkey, it was stated that 55% of patients presenting with premature pubarche were overweight or obese [38]. However, although DHEA-S height is not found in all patients followed for obesity, many studies have shown that obesity has a positive correlation with DHEA-S height [38]. Due to the close relationship between premature adrenarche and obesity, another focus of this review is to examine the findings related to premature pubarche using neuroimaging methods in literature.

In this study, studies on childhood obesity using different rs-fMRI analysis techniques were analyzed in detail in the literature to examine the contributions and innovations of these studies. In addition, in literature, premature pubarche, one of the first stages of adolescence, has been systematically analyzed in studies using different neuroimaging methods.

2. METHOD

For the main results, we used the databases PubMed, Google Scholar, ScienceDirect, and Web of Science to find relevant articles published until August 2024. Various keywords and their combinations were used to identify appropriate obesity-related topics. (childhood obesity, pediatric obesity, Child Obesity, childhood overweight, body mass index, rs-fMRI, functional connectivity). Different keywords and their combinations were used to identify appropriate titles related to premature pubarche (premature pubarche, premature adrenarche, Neuroimaging, MRI, fMRI, Diffusion weighted imaging). We present recent advances in studies examining the impact of overweight/obesity in childhood with rs-fMRI (2019-2024) and a review of peer-reviewed neuroimaging studies (2019-2024) on premature pubarche. While the review included studies in children and young adults (under 20 years of age), no other demographic restrictions were imposed.

Relevant articles were identified using a comprehensive search strategy for all publications related to childhood obesity and rs-fMRI in Table 1. Following our search strategy, citations of the included studies were examined and other works of the authors of the included studies were also searched to identify other relevant publications.

Table 1. All publications related to childhood obesity and rs-fMRI.

Authors	Year	Sample	Region Examined
Zhang et al. [39]	2015	<18 years (n=39)	Whole Brain
Sun et al. [40]	2018	9-17 years (n=69)	Reward network regions
Kahathuduwa et al. [41]	2019	<18 years (n=81)	Default Mode Network and Central Executive Network
Singh ve et al. [42]	2019	9-17 years (n=42)	Anterior Cingulate Cortex and Hippocampus
Nakamura et al. [43]	2020	14.1-19.9 years (n=20)	Caudat and Reward network regions
Shearrer et al. [44]	2020	n=510	Whole Brain
Esteban-Cornejo et al. [45]	2021	8-11 years (n=99)	Hippocampus
Adise et al. [46]	2021	9-10 years	Reward Network Regions
Assari and Boyce [47]	2021	9-11 years	Putamen ve Salience Network
Pujol et al. [48]	2021	8-12 years (n=230)	Reward Network Regions
Logan et al. [49]	2022	7-11 years (n=121)	Whole Brain

Snyder et al. [50]	2022	12-17 years (n=21)	Default Mode Network
Solis- Urra et al. [18]	2023	8-11 years (n=96)	Hippocampus
Kaltenhauser et al. [51]	2023	9-10 years (n=4576)	Reward Network Regions
Zhang ve et al. [52]	2023	9-11years (n=11.878)	Default Mode Network
Brooks ve et al. [53]	2023	8-11 years (n=4922)	Whole Brain
Huang et al. [54]	2023	7-8 years	Caudat
Chen et al.[55]	2024	8-12 years(n=130)	Hippocampus

In Table 2, relevant articles were identified using a comprehensive search strategy for all publications related to premature pubarche and neuroimaging methods. Similarly, to identify other relevant publications following our search strategy, citations of the included studies were examined and other works of the authors of the included studies were also searched.

Table 2. Publications on premature pubarche and neuroimaging methods.

Authors	Year	Age (Sample)	Method	Region Examined
Whittle et al. [56]	2015	8-9 years (n=1239)	Task Based fMRI	Amygdala, hippocampus, cingulate cortex, insula, dorsolateral prefrontal cortex and striatum.
Klauser et al. [57]	2015	8,5/9,5 years (n=85)	Structural MRI	Whole Brain
Murray et al. [58]	2016	Mean 9,5 (n=95)	Structural MRI	Hypophysis
Barendse et al. [33]	2018	Mean 9,53 (n=83)	Task Based fMRI	Amygdala
Barendse et al. [59]	2018	Mean 9,56 (n=87)	Diffusion-weighted imaging	Whole brain
Barendse et al. [60]	2020	Mean 9.5 (n=64)	Task Based fMRI	Amygdala
Cole et al. [61]	2023	Mean 8.6 (n=92)	Structural MRI	Right superior frontal gyrus, anterior cingulate cortex, and right amygdala

Part of this review includes published peer-reviewed neuroimaging studies investigating differences between individuals with childhood obesity using different resting-state magnetic resonance imaging techniques. Task-based fMRI studies were excluded from the study. The main aim of all included studies was to investigate resting-state functional connectivity changes in children with overweight/obesity. To fully understand the impact of childhood obesity, studies examining changes in functional connectivity in adults were not included. Apart from age criteria, no demographic restrictions such as gender, culture, health status, or education were used in the study selection. The studies selected for review were published between 2015 and 2023. Functional connectivity studies in the under 18 age group using different rs-fMRI analysis methods such as ALFF (Amplitude of low frequency fluctuations), ReHo (Regional Homogeneity) ICA (Independent Component Analysis), SCA (Seed-based Correlation Analysis), and Graph Theory were included in this review.

When Table 1 is examined in detail, studies on childhood obesity with resting state fMRI analysis can be seen in the literature between 2015 and 2024. From the table, we see that rs-fMRG studies are concentrated in the DMN (default mode network), CEN (executive control network) and reward networks (amygdala, insula and nucleus accumbens), which are associated with obesity. Figure 2 shows some of the brain regions examined in rs-fMRI studies conducted with obese/overweight children in the literature.

When Table 2 is examined, studies on premature pubarche using various neuroimaging techniques can be seen in the literature between 2015 and 2024. While scanning the literature in our study, the most common cause of premature pubarche was included in studies on premature adrenarche. However, since gonadarchy, the other stage of adolescence is associated with the activation of the hypothalamic- hypophysis -gonadal axis, relevant studies were not included. There is a consensus in the literature that amygdala connectivity affects the timing of puberty. Amygdala function peaks during adolescence. For this reason, it has been observed that the main focus in studies on premature pubarche is amygdala analysis.

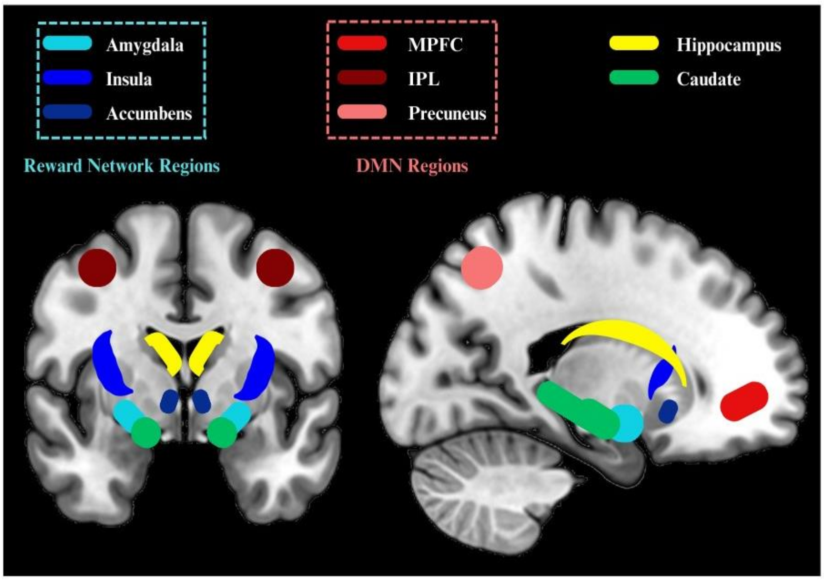

Figure 2. Brain regions examined in literature in rs-fMRI studies conducted with obese/overweight children. While the brain regions expressed in blue and their shades represent the Reward network regions, the brain regions expressed in red and their shades represent the default mode network.

3. CONCLUSION AND DISCUSSION

This review article presents a comprehensive review of recently published rs-fMRI studies on childhood obesity and neuroimaging studies on premature pubarche associated with obesity. After screening the title, abstract, and full text of relevant articles, 18 studies with childhood obesity and 7 studies with premature pubarche met all inclusion criteria. In Table 1 and Table 2, many systematic reviews of the studies conducted in the last 8 years are shown in general.

When the literature is examined, the relationship between childhood obesity and resting state activity appears complex. Assari and Boyce found a significant interaction suggesting that the association with children's BMI was moderated by race [47]. The study stated that BMI is associated with the connection of the dorsal attention network, ventral attention network, default mode network, auditory network, visual network and somatosensory networks. Adise et al. One of the focuses of his studies is to investigate whether overweight/obesity in children is associated with functional changes in the brain's reward system [46]. Pujol et al., Kaltenhauser et al. Participants with obesity have been shown to show increased activation in regions related to reward processing [48,51]. Both structural and functional neuroimaging of the caudate have been associated with obesity in children and adolescents [54].

Nakamura et al. they stated that caudate-lateral prefrontal cortex functional connectivity may have a preventive effect on weight gain in adolescents [43]. Pujol et al. in their study, they found that the reward system was dysfunctional in overweight children. Higher BMI has been associated with poor connectivity between cortical and subcortical elements of the reward system [48].

There is evidence for the role of hypothalamic dysfunction in the pathogenesis of obesity [62]. As seen in Table 1, there are studies examining only the hypothalamus. Solis-Urra et al. showed that early life factors are associated with hippocampal connectivity in children with overweight/obesity [18]. Chen et al. focused on examining changes in functional connectivity and effective connectivity in the hippocampus in overweight/obese children [55]. Esteban-Cornejo et al. stated that physical fitness components (i.e., cardiorespiratory, motor, and muscular fitness) in children with overweight/obesity would be associated with functional connectivity between hippocampal subregions and frontal regions [45].

Studies on the DMN, which plays a central role in the resting state and is associated with cognitive functions such as our inner thoughts, self-awareness, and social relationships, attract attention. Kahathuduwa et al. in their study investigating high rates of obesity in autism, they found that children with overweight/obesity showed hyperconnectivity between the anterior and posterior DMN [41]. Snyder et al. they stated that no significant brain activation differences were recorded in their study examining intra-network resting state functional connectivity in the DMN between children with obesity (with or without diabetes) and lean controls [50].

There are few studies examining childhood overweight/obesity in the whole brain with rs-fMRI. Brooks et al. They aimed to investigate the negative effects of excessive BMI on the brain during neurodevelopmentally sensitive periods. As a result of their study, they found differences in default mode, dorsal attention, salience, limbic, and reward networks between young people with obesity and those with normal body mass index [53].

When literature is examined in general, the results of the studies suggest that there is abnormal communication between more than one brain area at rest in patients with childhood obesity. The most significant difference was found to be in the reward network regions. Few studies have focused on examining neuroimaging biomarkers of childhood obesity with artificial intelligence. Although there are studies in the literature that use machine learning and rs-fMRI to identify neuroimaging biomarkers of obesity, these studies have generally focused on the adult age group [63]. In childhood obesity, Chen et al. investigated whether hippocampus connectivity can predict a child's future eating behaviors and BMI with linear support vector regression, a machine learning method [55]. However, more research is needed in this area due to the limited literature.

There appear to be few resting-state functional magnetic resonance imaging studies on childhood overweight/obesity. Considering the rates of childhood overweight/obesity and associated comorbidities and the prevalence of the disease, it seems that more studies are needed.

When the literature is examined, it is noteworthy that the number of neuroimaging studies on premature pubarche/adrenarche is low. When we examine structural MRI studies, it can be said that premature adrenarche causes volume changes in different regions of the brain. Klauser et al. while premature adrenarche was associated with reduced white matter volume in the frontal lobe of the brain [57], Murray et al. have associated higher DHES levels with larger hypophysis gland volume [58]. Cole et al. found that DHEA-S had an effect on gray matter volume in the right superior frontal gyrus, anterior cingulate cortex, and right amygdala [61]. When task-based fMRI studies are examined, it is seen that the analyses focus on the amygdala. Whittle et al. They hypothesized that early exposure to DHEA would have an impact on brain function and psychopathology. In the study where gender differences were examined, while there were differences in the middle cingulate cortex in both genders, differences (decrease in brain activity) were found in some cortical and subcortical regions in girls [56]. Barendse et al. in studies examining the amygdala connection in different years, stated that adrenarche hormones (DHEA, DHEA-S, testosterone) affect the functional connection of the amygdala and that the timing of adrenarche is related to the functional connection of the amygdala [33]. Barendse et al. in their study using diffusion-weighted MRI, associated high DHEA levels with high fractional anisotropy [59]. Due to the lack of neuroimaging studies in literature, more research should be done on this subject. In particular, priority may be given to neuroimaging methods that have not been studied in literature.

fMRI studies show a relationship between obesity and abnormal brain function [16]. Although there are inconsistent results in the literature regarding the relationship between childhood obesity and the timing of puberty in boys, childhood obesity has been associated with the earlier onset of puberty in girls [64,65]. While its relationship with overweight/obesity and premature pubarche/adrenarche in childhood has been examined in very few neuroimaging studies, no examination with fMRI studies could be found according to our literature search [66]. Since neuroimaging studies on premature pubarche/adrenarche are limited and its relationship with obesity has not been examined together with brain functionality, it presents itself as an issue that requires particular attention and study. Situations in which obesity and accompanying disorders such as premature pubarche/adrenarche develop separately and together need to be further investigated. The prevalence of obesity in children with premature pubarche and its estimated future prevalence should be taken into consideration, and the effect of obesity should not be ignored in future studies. Considering the lack and necessity of studies on this subject, the effect of premature pubarche/adrenarche on brain functions should be studied with different neuroimaging techniques in the presence and absence of obesity disease.

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