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Rozprawa doktorska

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Ocena związku stresu pre- i postnatalnego ze składem ciała i ryzykiem otyłości u dzieci w wieku szkolnym

Praca napisana pod kierunkiem

Prof. UAM dr. hab. Tomasza Hancia

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PhD Thesis

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Assessment of the relationship of pre- and postnatal stress with body composition and obesity risk

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Streszczenie

Wstęp: Otyłość jest chorobą uwarunkowaną wieloczynnikowo. W jej patogenezie znaczenie mają czynniki zarówno genetyczne jak i środowiskowe. Wśród czynników genetycznych wyróżnić można polimorfizmy genów FTO oraz MC4R, natomiast czynniki środowiskowe to m.in. czynniki rodzinne, okołourodzeniowe, związane ze stylem życia oraz doświadczanie niekorzystnych wydarzeń życiowych w życiu pre- i postnatalnym. Wzajemne interakcje wymienionych czynników i ich znaczenie w etiologii otyłości wymagają dalszych badań.

Cel badań: Celem badania była kompleksowa ocena związku stresu pre- i postnatalnego z ryzykiem rozwoju nadwagi i otyłości u dzieci oraz potencjalnych modyfikatorów składu i proporcji ciała u dzieci ze szczególnym uwzględnieniem znaczenia doświadczenia niekorzystnych wydarzeń życiowych i ich interakcji z polimorfizmami genów FTO (rs9939609) i MC4R (rs17782313).

Materiały i metody: W ramach badań wchodzących w skład pracy doktorskiej przebadano 530 dzieci uczęszczających do wybranych losowo 11 szkół podstawowych zlokalizowanych w Poznaniu i jego najbliższej okolicy. Grupa badana składała się z 254 dziewczynek i 276 chłopców. Badane dzieci były w wieku od 6 do 12 roku życia.

Doświadczenie stresu pre- i postnatalnego oceniono metodą ankietową. Rodzice lub opiekunowie dzieci odpowiadali na pytania o wystąpienie, u matek w czasie ciąży oraz u dzieci, określonych niekorzystnych wydarzeń życiowych o potencjale stresogennym. Kwestionariusz zawierał także pytania dotyczące statusu społeczno-ekonomicznego, czynników okołoporodowych i stylu życia dzieci. Dokonano pomiaru masy i wysokości ciała oraz oceniono skład ciała dzieci metodą bioimpedancji elektrycznej. Obliczono BMI (Body Mass Index), FMI (Fat Mass Index) i FFMI (Fat Free Mass Index). Niedowagę, nadwagę i otyłość rozpoznano na podstawie BMI wg kryteriów International Obesity Task Force (IOTF) i na podstawie zawartości tkanki tłuszczowej wg kryteriów McCarthy'ego. Oznaczono polimorfizmy genów FTO i MC4R. W tym celu pobrano próbki śliny od badanych dzieci. Wybrane polimorfizmy genotypowano metodą dyskryminacji alleli (SNP) z zastosowaniem sond TaqMan. Na podstawie deklarowanej masy i wysokości ciała rodziców obliczono ich BMI.

Wyniki: Nadwaga i otyłość rozpoznawane na podstawie zawartości tkanki tłuszczowej częściej występowały u chłopców niż u dziewcząt. Nie było różnic w częstości występowania nadwagi

i otyłości diagnozowanych na podstawie BMI u dzieci, które doświadczyły stresu prenatalnego w porównaniu z dziećmi, które nie doświadczyły stresu. Stres prenatalny był natomiast związany z nadwagą, ale nie z otyłością i niedowagą diagnozowanymi na podstawie zawartości tkanki tłuszczowej. Analizy post-hoc w grupie chłopców potwierdziły związek stresu prenatalnego i nadwagi, natomiast w grupie dziewczynek wyniki nie były istotne statystycznie. Otyłość występowała częściej u dzieci, które doświadczyły co najmniej jednego niekorzystnego wydarzenia w życiu postnatalnym. Szczegółowa analiza wykazała istotne związki otyłości z takimi niekorzystnymi doświadczeniami jak: bycie świadkiem przemocy, konflikty rodzinne, długotrwałe rozdzielenie z rodzicem oraz śmierć bliskiego członka rodziny. W badanej grupie obecność alleli ryzyka genu FTO (allel A) i genu MC4R (allel C) nie była związana z częstością występowania niedowagi, nadwagi i otyłości. W osobnych analizach z podziałem na płeć zaobserwowano natomiast, że w grupie dziewczynek otyłość diagnozowana na podstawie BMI była częstsza wśród heterozygot AT w porównaniu z homozygotami TT genu FTO. Podobnie standaryzowane BMI i FatM (zawartość tkanki tłuszczowej) były istotnie wyższe u heterozygot niż u homozygot TT genu FTO. W grupie dziewcząt homozygoty CC miały wyższy standaryzowany wskaźnik FatM niż u homozygot TT genu MC4R. Ponadto zaobserwowano efekty interakcji FTO z niekorzystnymi doświadczeniami z dzieciństwa w przypadku BMI oraz efekt interakcji MC4R z niekorzystnymi doświadczeniami z dzieciństwa w przypadku FMI i FatM. Modele regresji wskazały na znaczącą i dominującą nad czynnikiem stresu rolę czynników rodzicielskich związanych z wielkością masy ciała i wykształceniem oraz genetycznych w wyjaśnianiu zmienności składu i proporcji ciała dzieci. Wyższe wartości BMI dziecka były związane z wyższymi wartościami BMI ojca i młodszym wiekiem matki w chwili urodzenia dziecka. Wyższe wartości FMI były związane z wyższymi wartościami BMI ojca i większą masą ciała matki w czasie ciąży, niższym wykształceniem matki i obecnością allelu ryzyka FTO. Większa zawartość tkanki tłuszczowej wiązała się z niższym wykształceniem matki, młodszym wiekiem w chwili urodzenia dziecka, większym przyrostem masy ciała matki w ciąży, wyższym BMI ojca i obecnością allelu ryzyka genu FTO.

Wnioski: Nadwaga i otyłość rozpoznawane na podstawie tkanki tłuszczowej częściej występowały u chłopców niż u dziewcząt. Analiza związku stresu prenatalnego ze wskaźnikami antropometrycznymi dzieci wykazała, że chłopcy mogą być także bardziej podatni na rozwój nadmiernego otłuszczenia w konsekwencji doświadczenia stresu w okresie prenatalnym niż dziewczęta. Wystąpienie niekorzystnych doświadczeń o potencjale traumatyzującym w postnatalnej fazie rozwoju było również ważnym predyktorem otyłości, przy czym rodzaj

doświadczenia w istotny sposób różnicował poziom otłuszczenia ciała dzieci. W analizach jednoczynnikowych badane polimorfizmy FTO i MC4R były związane ze wskaźnikami proporcji i otłuszczenia ciała u dziewcząt, ale nie u chłopców. Regulacja poziomu tkanki tłuszczowej wydaje się więc pod większą kontrolą czynników genetycznych u dziewcząt, podczas gdy u chłopców zaobserwować można większy, modyfikujący wpływ stresu. Badanie wykazało ponadto dominujący wpływ czynników o dobrze udokumentowanym znaczeniu w etiologii otyłości na zmienność wartości wskaźników antropometrycznych. Polimorfizmy genów FTO i MC4R wchodziły natomiast z niekorzystnymi, stresogennymi doświadczeniami dziecięcymi w powiązane z BMI i wskaźnikami otłuszczenia liczne interakcje, co wskazuje na konieczność dalszych badań uwarunkowań otyłości dziecięcej z uwzględnieniem mechanizmów epigenetycznych.

Abstract

Introduction: Obesity is a multifactorial condition influenced by both genetic and environmental factors. In its pathogenesis, genetic factors such as FTO and MC4R gene polymorphisms play a role, while environmental factors include familial factors, perinatal factors, lifestyle-related factors, and experiencing adverse life events during the pre- and postnatal periods. The mutual interactions of the mentioned factors and their significance in the etiology of obesity require further research.

Research Objective: The aim of this study was to comprehensive evaluation of the association between pre- and postnatal stress and the risk of overweight and obesity in children, as well as potential modifiers of body composition and proportions in children, with particular emphasis on the significance of experiencing adverse life events and their interaction with FTO (rs9939609) and MC4R (rs17782313) gene polymorphisms.

Materials and Methods: As part of the research for the PhD thesis, 530 children attending 11 randomly selected primary schools in Poznań and its vicinity were examined. The study group consisted of 254 girls and 276 boys, ranging in age from 6 to 12 years. Pre- and postnatal stress experiences were assessed using a questionnaire method. Parents or guardians of the children answered questions about the occurrence of adverse life events with potential stress-inducing effects in mothers during pregnancy and in children. The questionnaire also included questions regarding socio-economic status, perinatal factors, and children's lifestyles. Body weight and height were measured, and children's body composition was assessed using the bioelectrical impedance method. BMI (Body Mass Index), FMI (Fat Mass Index), and FFMI (Fat-Free Mass Index) were calculated. Underweight, overweight, and obesity were determined based on BMI according to the International Obesity Task Force criteria and based on fat tissue content according to McCarthy's criteria. FTO and MC4R gene polymorphisms were determined by collecting saliva samples from the children. Genotyping of selected polymorphisms was performed using allele discrimination (SNP) with TaqMan probes. Parental BMI was calculated based on self-reported weight and height measurements.

Results: Overweight and obesity, diagnosed based on fat tissue content, were more common in boys than in girls. There were no differences in the frequency of overweight and obesity diagnosed based on BMI in children who experienced prenatal stress compared to children who did not experience stress. Prenatal stress was associated with overweight but not with obesity or underweight diagnosed based on fat tissue content. Post-hoc analyses in the boys' group

confirmed the relationship between prenatal stress and overweight, while in the girls' group, the results were not statistically significant. Detailed analysis revealed that obesity was more common in children who experienced at least one adverse life event in their postnatal life. Among the studied stressor types, significant associations with obesity were observed for witnessing violence, family conflicts, prolonged separation from a parent, and the death of a close family member. In the study group, the presence of risk alleles of the FTO (allel A) and MC4R (allel C) genes was not associated with the frequency of underweight, overweight, or obesity. In separate gender-specific analyses, it was observed that in the girls' group, obesity diagnosed based on BMI was more common among heterozygotes AT compared to homozygotes TT of the FTO gene. Similarly, BMI z scores and FatM z scores were significantly higher in heterozygotes compared to homozygotes for the FTO gene TT genotype. In the group of girls, CC homozygotes had a higher FatM z scores compared to MC4R gene TT homozygotes. Furthermore, interaction effects of FTO with adverse childhood experiences were observed for BMI, and interaction effects of MC4R with adverse childhood experiences were observed for FMI and FatM. Regression models indicated a significant and dominant role of parental factors related to body size and education, as well as genetic factors, in explaining the variability of children's body composition and proportions. Higher child BMI values were associated with higher paternal BMI and younger maternal age at the child's birth. Higher FMI values were associated with higher paternal BMI, greater maternal weight during pregnancy, lower maternal education, and the presence of the FTO risk allele. Higher fat tissue content (FatM) was associated with lower maternal education, younger maternal age at the child's birth, greater maternal weight gain during pregnancy, higher paternal BMI, and the presence of the FTO gene risk allele.

Conclusions: Overweight and obesity, diagnosed based on fat tissue content, were more common in boys than in girls. The analysis of the relationship between prenatal stress and children's anthropometric indicators revealed that boys may also be more susceptible to the development of excessive adiposity as a consequence of experiencing prenatal stress than girls. The occurrence of adverse experiences with traumatizing potential during the postnatal phase of development was also a significant predictor of obesity, with the type of experience significantly differing in the level of body adiposity among children. In single-factor analyses, the examined FTO and MC4R polymorphisms were associated with body composition and proportion indices in girls but not in boys. Therefore, the regulation of adipose tissue levels appears to be under greater genetic control in girls, while in boys, a larger modifying influence

of stress can be observed. The study also demonstrated a dominant influence on the variability of anthropometric indicators by factors with well-documented significance in the ethology of obesity. Gene polymorphisms of FTO and MC4R were found to be involved in various interactions with adverse, stress-inducing childhood experiences related to BMI and adiposity indicators, highlighting the need for further research into the determinants of childhood obesity, taking into account epigenetic mechanisms.

Wstęp

Wyniki największego reprezentatywnego badania OLAF przeprowadzonego w latach 2007-2009 wskazują, że wśród dzieci w Polsce w wieku od 7 do 12 lat nadwaga i otyłość według kryteriów IOTF występowały z częstością odpowiednio 18,4% oraz 3,6% u dziewcząt oraz 21,7% i 5,5% u chłopców [1]. Nadwaga lub otyłość to czynniki związane z występowaniem chorób takich jak cukrzyca typu 1 [2,3] i typu 2 [4], hipercholesterolemia [5,6], nadciśnienie tętnicze [5–7], miażdżyca [8], niealkoholowa stłuszczeniowa choroba wątroby [9] i zespół metaboliczny [10]. Otyłość współwystępuje często z zaburzeniami psychicznymi, jak depresja [11,12] lub zaburzeniami neurorozwojowymi, np. ADHD [13]. W przypadku dzieci z nadwagą istnieje także większe ryzyko jej utrzymania się do dorosłości [14,15]. Zapobieganie rozwojowi oraz leczenie otyłości jest więc jednym z najważniejszych wyzwań społecznych, a dalsze badania, których celem jest wyjaśnienie jej etiologii oraz wskazanie czynników ochronnych, mogących zapobiegać rozwojowi nadmiernego otłuszczenia, mają kluczowe znaczenie.

W najprostszym ujęciu nadwaga jest spowodowana przyjmowaniem większej ilości kalorii w stosunku do wydatku energetycznego, jednak allele niektórych genów mogą przyczynić się do zwiększenia ryzyka rozwoju otyłości i jej powikłań. Badania pokazują, że wśród polimorfizmów związanych z ryzykiem nadwagi i otyłości wyszczególnić możemy m.in. polimorfizm rs9939609 genu FTO oraz polimorfizm rs17782313 genu MC4R.

Gen FTO (Fat Mass and Obesity-Associated) zlokalizowany na chromosomie 16 (16q12.2) składa się z 9 egzonów obejmujących obszar ponad 400 kb [16]. Mechanizm działania genu FTO w regulacji równowagi energetycznej nie został jeszcze w pełni poznany. Gen koduje białko o nazwie FTO (α-ketoglutarate-dependent dioxygenase FTO). Białko FTO jest enzymem wykorzystującym α-ketoglutaran jako kofaktor oraz tlen do przeprowadzania reakcji chemicznych. Ten enzym jest obecny w wielu tkankach, szczególnie w podwzgórzu – obszarze mózgu kontrolującym apetyt i wydatkowanie energii [17]. Białko FTO działa jako demetylaza, usuwając grupy metylowe. Głównym znanym substratem dla enzymu FTO są reszty N6-metyloadenozyny w cząsteczkach RNA [18]. To działanie enzymatyczne ma wpływ na regulację ekspresji genów oraz inne procesy metaboliczne, które mogą oddziaływać na zdolność organizmu do kontrolowania masy ciała [19]. Poddany w niniejszej rozprawie doktorskiej badaniu polimorfizm genu FTO rs9939609 posiada dwa główne warianty alleli, które są oznaczane jako „A” i „T”. Nosiciele allelu A mają większe ryzyko wystąpienia otyłości

w porównaniu do nosicieli allelu T. Jedna z metaanaliz potwierdziła, że polimorfizm genu FTO rs9939609 jest związany z masą ciała i BMI oraz zawartością tkanki tłuszczowej nie tylko u osób dorosłych, ale również u dzieci [20]. Badania skupiające się na dzieciach i młodzieży w wieku 6-19 lat dowodzą, że obecność przynajmniej jednego allelu ryzyka genu FTO wiązała się z wyższym BMI i otyłością [21,22], i prawie dwukrotnie zwiększała ryzyko napadowego objadania się [21].

Gen MC4R (Melanocortin 4 Receptor) jest zlokalizowany na chromosomie 18 (18q21.32) i obejmuje obszar 1,714 kb [23]. Gen MC4R koduje receptor melanokortynowy 4 (MC4R), który jest białkiem transbłonowym odpowiedzialnym za łączenie się z ligandami, w tym z melanokortynami, i przekazywanie sygnałów sytości do wnętrza komórki [24]. Hormony obwodowe (leptyna - produkowana przez tkankę tłuszczową i insulina - wytwarzana w trzustce) łączą się z receptorami neuronów w jądrze łukowatym podwzgórza, co wzmaga przemianę proopiomelanokortyny (POMC) do α-melanokortyny (α-MSH) i β-melanokortyny (β-MSH), które oddziałują na receptor MC4R w jądrze przykomorowym przekazując sygnał sytości. Natomiast grelina wytwarzana w żołądku pobudza ekspresję neuropeptydu Y (NPY) i białka Agouti (AGRP) w neuronach jądra łukowatego. Mają one hamujący wpływ na receptor MC4R i przekazują sygnał głodu. Leptyna i insulina działają hamująco na ekspresję NPY i AGRP [25]. Receptor MC4R odgrywa kluczową rolę w regulacji łaknienia i kontrolowaniu masy ciała. Badany przeze mnie polimorfizm rs17782313 genu MC4R posiada dwa główne warianty alleli, które są oznaczane jako „C" lub „T". Osoby będące nosicielami allelu C są narażone na większe trudności w kontrolowaniu masy ciała i regulacji apetytu niż nosiciele allelu T. Wyniki badań w grupie dzieci wskazują, że polimorfizm rs17782312 może wiązać się z ryzykiem nadwagi i zwiększonego spożycia pokarmu u dzieci w wieku 6-12 lat. Obecność allelu C wiąże się z większą przyjemnością z jedzenia, mniejszym uczuciem sytości i większą skłonnością do jedzenia bez uczucia głodu, co może być czynnikiem przyczyniającym się do rozwoju otyłości u dzieci [26].

Wśród czynników środowiskowych zwiększających ryzyko rozwoju nadwagi wyróżnić możemy czynniki rodzinne, okołourodzeniowe, związane ze stylem życia oraz stresory prenatalne i doświadczanie niekorzystnych wydarzeń w dzieciństwie. Bardziej narażone na rozwój nadwagi lub otyłości są dzieci wychowywane przez samotnego rodzica [27], a także pochodzące z rodzin z niskim dochodem [28,29]. Duże znaczenie mają czynniki rodzicielskie takie jak BMI matki przed porodem [30], czy aktualny wskaźnik masy ciała rodziców [31,32]

oraz ich wykształcenie [33–35]. Czynniki okołoporodowe takie jak zbyt niska (<2500g) oraz zbyt wysoka (>4000g) urodzeniowa masa ciała związane są z występowaniem nadwagi, otyłości centralnej i zespołu metabolicznego u dzieci [36,37]. W badaniu obejmującym 12 krajów dowiedziono natomiast, że karmienie piersią może chronić przed otyłością i wysokim poziomem tkanki tłuszczowej u dzieci w wieku 9-11 lat [38], a urodzenie przez cesarskie cięcie jest związane z otyłością dziecięcą [39].

Wśród znanych czynników ryzyka rozwoju otyłości związanych ze stylem życia wyszczególnić można nieprawidłową dietę, brak aktywności fizycznej i siedzący tryb życia [40]. Zdrowa dieta, regularne posiłki [41,42], aktywność fizyczna [42] oraz ograniczony czas spędzany przed ekranem, to czynniki chroniące przed rozwojem nadwagi i otyłości u dzieci. Badania dowodzą, że spędzanie ponad 2 [43] lub ponad 4 godzin dziennie [44] przed ekranem wiąże się z większym prawdopodobieństwem nadwagi lub otyłości u dzieci. Kolejnym czynnikiem związanym ze stylem życia mającym wpływ na zdrowie dzieci jest długość snu. Dzieci śpiące mniej niż 5 godzin w ciągu nocy miały większe ryzyko nadwagi lub otyłości niż dzieci, które spały dłużej [33].

Wcześniejsze badania pokazują, że skłonności do rozwoju otyłości mogą być uwarunkowane czynnikami działającymi w życiu płodowym [45]. Zgodnie z hipotezą Barkera okres rozwoju płodowego to czas, w którym płód jest szczególnie wrażliwy na niekorzystne czynniki środowiskowe [46]. Mogą one mieć programujący wpływ na metabolizm płodu i oddziaływać na zmiany masy i proporcji ciała u dzieci [47]. Wyniki badań dowodzą, że wśród niekorzystnych czynników środowiskowych występujących w życiu płodowym, które mają istotny wpływ na późniejsze zdrowie dziecka, wyróżnić możemy m.in. palenie tytoniu [48,49], niedobór witaminy D3[50], spożywanie żywności przetworzonej, nadmiar nasyconych kwasów tłuszczowych i węglowodanów prostych [51] oraz spożywanie alkoholu przez matkę w okresie ciąży [52]. Jednak czynnikiem, który według mnie zasługuje na szczególną uwagę w kontekście badań nad otyłością są niekorzystne doświadczenia życiowe podczas ciąży [45]. Psychologiczny stres może być czynnikiem wpływającym istotnie na rozwój płodu. Pod wpływem stresu dochodzi do aktywacji osi podwzgórze-przysadka-nadnercza (HPA) oraz współczulnego układu nerwowego [53]. Spowodowany stresem podwyższony poziom kortyzolu we krwi matki może mieć negatywny wpływ na płód. W warunkach fizjologicznych płód jest chroniony przed nadmiernym stężeniem kortyzolu przez dehydrogenazę 11β-hydroksysteroidową (11BHSD2), która zapobiega przedostawaniu się 80–90% kortyzolu przez

barierę łożyskową. Jednak w sytuacji, gdy stres jest silny lub przewlekły, wydzielanie 11BHSD2 może zostać zablokowane i kortyzol w postaci aktywnej przedostaje się do krwi płodu [54], wpływając na funkcjonowanie osi HPA dziecka [55] oraz hormony regulujące mechanizmy głodu i sytości [56]. W konsekwencji zwiększa się wydzielanie leptyny i greliny. Wydzielanie leptyny prowadzi do uczucia sytości, ale jeśli jest ona wydzielana w nadmiarze, rozwija się oporność na leptynę i uczucie sytości po posiłku jest ograniczane lub całkowicie eliminowane [57]. Zwiększone wydzielanie greliny przy jednoczesnym zaburzeniu wydzielania leptyny prowadzi do zwiększonego spożycia pokarmu [58]. Ponadto podwyższony poziom glikokortykosteroidów zwiększa odkładanie się tłuszczu w adipocytach, głównie w tkance tłuszczowej trzewnej [59]. Ekspozycja na podwyższone stężenie kortyzolu w życiu płodowym może mieć negatywne skutki dla rozwijającego się organizmu i na stałe programować aktywność osi HPA. Jest to spowodowane epigenetycznymi zmianami związanymi z metylacją genów osi HPA [60,61]. Wysokie stężenie kortyzolu w płynie owodniowym jest związane z wyższym stężeniem kortyzolu w życiu postnatalnym niezależnie od wystąpienia stresora, ale również z jego zwiększoną produkcją w odpowiedzi na wystąpienie stresora [62]. Podwyższone stężenie kortyzolu w życiu płodowym zwiększa ryzyko nadciśnienia, cukrzycy typu 2 i zespołu metabolicznego w dorosłości [63]. Stres prenatalny jest również czynnikiem, który może odgrywać rolę w etiologii zaburzeń odżywiania, zarówno tych związanych z restrykcjami w przyjmowaniu pokarmów (zaburzenia związane z anoreksją) oraz z nadkonsumpcją pokarmu (napady objadania się) [64]. Większość badań skupia się jednak na wpływie stresu prenatalnego na zdrowie w dorosłości, a badania nad skutkami doświadczenia stresu prenatalnego i jego wpływu na zdrowie, w tym wielkość, proporcje i skład ciała w dzieciństwie dają niejednoznaczne wyniki.

Niekorzystne doświadczenia dziecięce (Adverse Childhood Experiences; ACE) również mogą odgrywać istotną rolę w zmianach masy i składu ciała u dzieci [64–68]. ACE to termin oznaczający negatywne, silnie stresujące doświadczania w dzieciństwie, mogące prowadzić do rozwoju traumy, mające często długotrwałe skutki na poziomie zdrowia fizycznego i psychicznego w późniejszym życiu. ACE mogą być związane m.in. z fizycznym lub emocjonalnym znęcaniem się nad dzieckiem, wykorzystaniem seksualnym, zaniedbaniem, rozwodem lub separacją rodziców, uzależnieniami w rodzinie, przemocą domową lub np. ze strony rówieśników. Pierwsze badania w tym obszarze zostały przeprowadzone w latach 90. XX wieku przez Vincenta Felittiego i Roberta Anda w Stanach Zjednoczonych [69]. Wyniki

badań pokazały, że doświadczenie różnego rodzaju traumatycznych wydarzeń w dzieciństwie jest częste i ma wpływ na późniejszy stan zdrowia badanych [70].

Większość wcześniejszych badań koncentrowała się na wpływie ACE na występowanie problemów zdrowotnych, w tym otyłości w wieku dorosłym [71]. Nadal nie ma jednoznacznych wniosków na temat ich wpływu na zmiany masy ciała już w dzieciństwie. We wcześniejszych badaniach wykazano, że niepożądane zdarzenia życiowe wiązały się zarówno z niedowagą, jak i otyłością [72–74]. Dotychczas przeprowadzone metaanalizy wskazują, że ACE są związane z otyłością dziecięcą [64–66], a płeć jest czynnikiem, który może istotnie modyfikować wyniki – dziewczęta są bardziej wrażliwe na skutki ACE niż chłopcy. Istotny wydaje się także rodzaj analizowanego stresora oraz czas od wystąpienia stresora, po którym może rozwinąć się nadwaga lub otyłość [64]. Liczba prac dotyczących wpływu ACE na skład ciała dzieci jest natomiast ograniczona. Badanie Derksa i wsp. [67] przeprowadzone wśród dzieci holenderskich pokazuje, że ACE nie mają istotnego wpływu na skład ciała, a główne znaczenie odgrywają czynniki socjoekonomiczne, jednak inne badanie przeprowadzone wśród dzieci w Wielkiej Brytanii dowodzi, że ACE są związane z większym BMI oraz FMI u dzieci w wieku 5-17 lat [68].

Wydaje się zasadne stwierdzenie, że u podłoża związku ACE z otyłością leżą interakcje biologicznej osi stresu ze zmianami na poziomie reakcji behawioralnych. Traumatyczne doświadczenia w dzieciństwie wpływają na oś HPA zwiększając stężenie kortyzolu [75], który odgrywa rolę w metabolizmie i odkładaniu tkanki tłuszczowej [76]. Kortyzol sprzyja różnicowaniu prekursorów komórek tłuszczowych do adipocytów i stymuluje lipogenezę w obecności insuliny [77]. Dysregulacja osi HPA prowadzi do zmiany w odpowiedzi hormonalnej na stresory, wpływa modyfikująco na apetyt, sprzyjając nieprawidłowym wyborom żywieniowym [78]. Doświadczenie stresorów może predysponować do obesogennych zmian u dzieci, takich jak pojawienie się zachowań impulsywnych [79], trudności ze snem [80], depresji [81]. Dodatkowo występowanie niekorzystnych wydarzeń, które dotyczą całej rodziny, utrudnia wspieranie zachowań prozdrowotnych przez innych członków rodziny, co może dodatkowo nasilać tendencje do rozwoju nadwagi i otyłości u dzieci.

Podsumowując, dotychczasowe badania sugerują istotną rolę stresu prenatalnego jako czynnika wpływającego na programowanie zmian fizjologicznych i metabolicznych. Te zmiany

mogą przyczynić się w przyszłości do nadmiernego przyrostu masy ciała, co może prowadzić do ryzyka wystąpienia otyłości. Co więcej, istnieją powiązania między traumatycznymi przeżyciami, narażeniem na długotrwałe stresory w dzieciństwie, a zwiększonym ryzykiem otyłości w dorosłym życiu. Dane, które zostały zebrane w niniejszej rozprawie doktorskiej mogą natomiast pomóc wyjaśnić, czy predyspozycje do rozwoju otyłości wynikające z narażenia na stresory są już obserwowalne w dzieciństwie. W swoich pracach uwzględniłam kompleksową ocenę narażenia na stresory, uwzględniając ocenę znaczenia zarówno stresorów prenatalnych jak i postnatalnych w kontekście skłonności do rozwoju nieprawidłowości masy i proporcji ciała dzieci.

Innym, wymagającym podkreślenia aspektem badań jest fakt, że dostępność danych dotyczących wpływu stresu na skład ciała u dzieci jest ograniczona. Tymczasem analiza parametrów składu ciała dzieci daje możliwość monitorowania subtelnych zmian w zawartości tkanki tłuszczowej oraz mięśniowej, które mogą poprzedzać rozwój otyłości. W związku z powyższym w analizach zaprezentowanych w pracach składających się na rozprawę doktorską uwzględniłam ocenę ryzyka rozwoju nadwagi i otyłości w oparciu zarówno o wskaźniki proporcji ciała, jak i składu ciała dzieci.

Jak wskazałam powyżej, istnieją czynniki genetyczne i środowiskowe o dobrze poznanym lub domniemanym udziale w etiologii otyłości. W badaniach nad związkiem stresu z otyłością ważnym wydaje się ich uwzględnianie jako potencjalnych modyfikatorów wyników analiz związku stres - otyłość. Dlatego w niniejszej pracy podjęłam się oceny związku stresu pre- i postnatalnego z masą, proporcjami i składem ciała z uwzględnieniem szerszego kontekstu tej relacji, biorącego pod uwagę m.in. wybrane czynniki genetyczne (polimorfizmy FTO i MC4R), rodzinne, socjoekonomiczne, okołourodzeniowe i te związane ze stylem życia dzieci.

Cele i hipotezy

Celem badania była ocena związku stresogennych doświadczeń pre- i postnatalnych z nadmierną masą ciała oraz poziomem otłuszczenia dzieci w wieku szkolnym.

Cele szczegółowe sformułowano w następujący sposób:

1. Ocena różnic w częstości występowania niedowagi, nadwagi i otyłości diagnozowanych na podstawie BMI oraz punktów odcięcia dla procentowej zawartości tkanki tłuszczowej u dzieci, które doświadczyły stresu pre- lub postnatalnego w porównaniu z dziećmi, które stresorów nie doświadczyły.
2. Wskazanie czynników modyfikujących związek stresogennych doświadczeń z nieprawidłowym składem i proporcjami ciała u dzieci.
3. Ocena znaczenia interakcji pomiędzy wybranymi polimorfizmami genów FTO i MC4R a doświadczeniem stresorów w warunkowaniu nieprawidłowej masy i otłuszczenia ciała dzieci.

Hipotezy:

1. Doświadczenie stresorów pre- i postnatalnych jest związane z wyższą zawartością tkanki tłuszczowej i częstszym występowaniem nadwagi i/lub otyłości u dzieci.
2. Skutki doświadczenia stresorów pre- i postnatalnych są odmienne u dziewcząt i chłopców.
3. Częstość nadwagi i/lub otyłości oraz nadmiernego otłuszczenia u dzieci są zależne od rodzaju doświadczonego stresora.
4. Obecność allelu A polimorfizmu rs9939609 genu FTO i allelu C polimorfizmu rs17782313 genu MC4R jest związana z częstszym występowaniem nadwagi i/lub otyłości u dzieci.
5. Występuje efekt interakcji pomiędzy czynnikami genetycznymi a stresorami postnatalnymi w procesie warunkowania nieprawidłowości proporcji i składu ciała u dzieci.

Wyniki przeprowadzonych przeze mnie analiz zostały zebrane w cykl trzech prac, z czego dwie opublikowano w czasopismach z listy „A" czasopism ministerialnych. Trzecia z prac podlega obecnie recenzji w czasopiśmie punktowanym. Analizy prowadzone były w oparciu o dane zgromadzone w ramach projektu finansowanego przez Narodowe Centrum Nauki, numer grantu 2016/21/B/NZ5/00492. Projekt realizowany był przez konsorcjum Uniwersytetu Medycznego im. Karola Marcinkowskiego w Poznaniu i Uniwersytetu im. Adama Mickiewicza w Poznaniu. Kierownikiem projektu była prof. dr hab. Monika Dmitrzak-Węglarz z Uniwersytetu Medycznego im. Karola Marcinkowskiego w Poznaniu. Koordynatorem projektu po stronie Uniwersytetu im. Adama Mickiewicza w Poznaniu był prof. UAM dr hab. Tomasz Hanć. Projekt realizowany był w latach 2017-2021. Na badania zgodę wydała Komisja Etyczna Uniwersytetu Medycznego im. Karola Marcinkowskiego (nr 542/14).

Prace nad dysertacją rozpoczęłam od przeglądowego artykułu dotyczącego związków stresu prenatalnego z masą, składem ciała oraz otyłością u dzieci. Artykuł ten stanowi ważny wstęp teoretyczny do analiz zaprezentowanych w pozostałych pracach. W kolejnym opublikowanym artykule opisałam wyniki swoich badań dotyczące związków stresu prenatalnego z ryzykiem rozwoju nadwagi/otyłości u dzieci. W dalszej pracy skupiłam się na kompleksowej ocenie uwarunkowań nieprawidłowego składu i proporcji ciała u dzieci, ze szczególnym uwzględnieniem znaczenia niekorzystnych doświadczeń dziecięcych i ich interakcji z polimorfizmami genów FTO i MC4R. Poniżej przedstawiam opis metod i najważniejsze wyniki z opublikowanych artykułów.

Materiały i metody

Metody zastosowane w przeglądzie systematycznym

Przegląd systematyczny zawiera publikacje, które ukazały się przed 15 marca 2020 roku. Do przeglądu badań wykorzystano 2 bazy danych: Scopus i Medline. Przegląd został oparty na systematycznym poszukiwaniu odpowiednich artykułów w bazach danych. Wykorzystano następujące kombinacje słów kluczowych:

/maternal lub mother/, /prenatal lub pregnant/, /stress lub distress/

oraz /BMI, body mass index lub overweight lub obesity lub body composition/.

Kryteria włączenia artykułu do przeglądu były następujące:

(1) badania przeprowadzone z udziałem ludzi;
(2) badania zawierające informacje dotyczące stresu doświadczonego przez kobiety w okresie ciąży (pod uwagę wzięto zarówno stres subiektywny jak i obiektywny);
(3) badania oceniające związek pomiędzy stresem prenatalnym a wskaźnikami nieprawidłowej masy i otłuszczenia ciała dzieci, takimi jak BMI, występowaniem niedowagi, nadwagi lub otyłości, obwodem talii i bioder, WHR (Waist to Hip Ratio – wskaźnik talia-biodra), WHtR (Waist to Height Ratio – wskaźnik talia-wysokość), oraz procentową zawartością tkanki tłuszczowej;
(4) badania, które oceniało wpływ stresu prenatalnego na zmiany parametrów składu ciała u potomstwa do 18 roku życia;
(5) pod uwagę brano wyłącznie badania ilościowe, nie uwzględniono metaanaliz oraz przeglądów badań;
(6) artykuł został opublikowany w języku angielskim.

Badania, które nie spełniały wyżej wymienionych warunków zostały wykluczone z przeglądu.

Po wpisaniu słów kluczowych do baz danych zostało wyszukanych 385 artykułów w Scopusie i 322 w Medline. Po usunięciu powtórzeń pozostało 468 artykułów do przeglądu. Na podstawie tytułu usuniętych zostało 388 artykułów, a na podstawie oceny pełnych tekstów kolejne 60. Ostatecznie 20 artykułów w pełni spełniło kryteria włączenia do przeglądu systematycznego (Publikacja 1, Ryc.1). Artykuły uwzględnione w przeglądzie systematycznym zostały opublikowane w latach 2007-2018.

Metody zastosowane w pracach badawczych

W ramach badań wchodzących w skład niniejszej pracy doktorskiej przebadano 530 dzieci uczęszczających do poznańskich szkół podstawowych. Proporcje chłopców i dziewczynek były porównywalne (52% chłopców, 48% dziewczynek). Badane dzieci były w wieku od 6 do 12 lat (średnia=8,99; odchylenie standardowe=1,32).

Pomiaru wysokości ciała dokonano stadiometrem Seca 213 (z dokładnością do 0,01 m), masy ciała (z dokładnością do 0,01 kg) oraz składu ciała metodą bioimpedancji elektrycznej

analizatorem składu ciała Tanita MC-780 MA. Podczas badania dzieci były ubrane w lekki strój sportowy. Pomiary antropometryczne przeprowadzono w godzinach od 8 do 14.00. W badaniu analizowane były surowe wartości wskaźników, takich jak FatM w kg. Obliczono BMI, FMI (Fat Mass Index - wskaźnik masy tłuszczowej) i FFMI (Fat Free Mass Index - wskaźnik masy beztłuszczowej) za pomocą wzorów:

$$BMI = \frac{masa\ ciała\ [kg]}{(wysokość\ ciała [m])^2},$$

$$FMI = \frac{masa\ tkanki\ \ tłuszczowej\ [kg]}{(wysokość\ ciała\ [m])^2},$$

$$FFMI = \frac{beztłuszczowa\ masa\ ciała\ [kg]}{(wysokość\ ciała\ [m])^2}.$$

BMI wystandaryzowano następnie na płeć i wiek na podstawie siatek centylowych WHO [82] za pomocą oprogramowania WHO AnthroPlus i przedstawiono jako wartości standaryzowane. FMI, FFMI i FatM były standaryzowane na wiek i płeć w próbie. Nadwagę, otyłość i niedowagę rozpoznano zgodnie z wytycznymi IOTF [83,84] oraz na podstawie punktów odcięcia dla zawartości tkanki tłuszczowej badanej metodą bioimpedancji [85]. Jako punkty odcięcia dla procentowej zawartości tkanki tłuszczowej stosuje się tu odpowiednio wartości: poniżej 2 centyla - niedowaga, od 2 centyla do 85 centyla - prawidłowe otłuszczenie, od 85 do 95 centyla - nadwaga i powyżej 95 centyla - otyłość.

Występowanie stresu prenatalnego oceniono metodą ankietową. Rodzice lub opiekunowie badanych dzieci byli pytani, czy w czasie ciąży wystąpiły u matek wybrane niekorzystne doświadczenia życiowe. Kwestionariusz zawierał pytania o:

1. trudną sytuację finansową;
2. problemy rodzinne;
3. chorobę lub śmierć członka rodziny;
4. obawę o możliwość wystąpienie nieprawidłowości ciąży;
5. inne stresory niewymienione w kwestionariuszu.

Występowanie niekorzystnych doświadczeń dziecięcych (ACE) oceniono metodą ankietową. ACE oceniano za pomocą pytań opracowanych w oparciu o kwestionariusz

Traumatic Events Screening Inventory - Parent Report Revised (TESI-PRR) [86]. Oryginalny kwestionariusz TESI-PRR składa się z 24 pytań obejmujących różnorodne potencjalne traumatyczne zdarzenia, w tym obecne i wcześniejsze urazy, hospitalizacje, przemoc domową, przemoc społeczną, katastrofy, wypadki, przemoc fizyczną i wykorzystanie seksualne. W badaniu wykorzystano uproszczoną listę 9 pytań dotyczących szerszych kategorii ACE obejmujących wydarzenia wymienione w TESI-PRR. Rodziców poproszono o wskazanie, czy:

1. życie lub zdrowie dziecka było zagrożone;
2. dziecko przeżyło zdarzenie, w którym życie lub zdrowie innej osoby było zagrożone;
3. dziecko doświadczyło przemocy fizycznej (np. bicie, popychanie, duszenie, potrząsanie, gryzienie, przypalanie, zmuszanie do jakiejkolwiek czynności seksualnej) lub psychicznej (np. wyśmiewanie, plotkowanie, krzyczenie, grożenie, odrzucenie przez kogoś bliskiego);
4. dziecko było świadkiem przemocy fizycznej lub znęcania się psychicznego;
5. dziecko doświadczyło śmierci kogoś bliskiego;
6. dziecko doświadczyło poważnych problemów rodzinnych (np. kłótnie, konflikty, bójki, rozstania, problemy alkoholowe lub innego typu uzależnienia, problemy emocjonalne lub psychiczne członków rodziny);
7. dziecko przez długi czas było oddzielone od rodziców;
8. dziecko miało poważne problemy w szkole, było zagrożone powtarzaniem klasy lub musiało powtarzać klasę;
9. dziecko doświadczyło innych stresorów, które nie zostały wymienione w kwestionariuszu.

Geny i polimorfizmy wybrano na podstawie ich wcześniej ustalonego związku z podatnością na nadwagę i otyłość (FTO rs9939609) oraz zaburzeniami kontroli łaknienia (MC4R rs17782313). DNA ekstrahowano ze śliny. Próbki śliny pobrano przy użyciu zestawu Oragene DNA® (OG-500) (DNA genotek TM, Ottawa, Kanada), zgodnie z instrukcjami producenta. Ekstrakcję DNA z próbek śliny przeprowadzono zgodnie z protokołem prepIT®L2P [87]. Wybrane polimorfizmy genotypowano przy użyciu metody dyskryminacji allelicznej polimorfizmu pojedynczego nukleotydu (SNP) systemem ABI 7900HT (Applied Biosystems). W reakcji Real-Time PCR zastosowano dostępne w handlu testy TaqMan Genotyping.

W badaniu kontrolowano płeć i wiek dzieci, czynniki społeczno-demograficzne, okołourodzeniowe i styl życia dzieci. Pytania dotyczące statusu społeczno-ekonomicznego zostały zawarte w kwestionariuszu dla rodziców. Wyróżniono trzy typy rodzin: oboje rodziców biologicznych, rodzic biologiczny z partnerem, rodzic samotnie wychowujący dziecko. Miejsce zamieszkania oceniono na podstawie liczby mieszkańców i podzielono na: wieś, małe i średnie miasto (10 000-100 000 mieszkańców), duże miasto (>100 000 mieszkańców) [88]. Sytuacja ekonomiczna była subiektywnie oceniana przez rodzica i kategoryzowana jako: zła, przeciętna, dobra. Przyrost masy ciała matki w czasie ciąży oceniano na podstawie opinii lekarza ginekologa i kategoryzowano jako: przekraczający normy lub nieprzekraczający normy [89]. Czas trwania ciąży podzielono na kategorie: <37 tygodni (poród przedwczesny), 37-42 tygodni (poród o czasie) i >42 tygodni (poród po terminie) [90]. Matki pytano, czy przed i w trakcie ciąży chorowały na: nadciśnienie tętnicze, cukrzycę, choroby tarczycy, choroby nerek, niewydolność serca (tak/nie). Rozróżniono ciążę pojedynczą lub bliźniaczą oraz poród naturalny lub przez cesarskie cięcie. Masę urodzeniową podzielono na 3 kategorie: <2500g (niska), 2500-4000g (prawidłowa), >4000g (wysoka) [91]. Zapytano również o to, czy dziecko było karmione piersią (tak/nie). Rodzice zadeklarowali swoją masę i wysokość ciała, na podstawie których obliczono BMI. BMI matki przed ciążą, aktualny BMI matki i BMI ojca zostały sklasyfikowane jako: niedowaga, prawidłowa masa ciała, nadwaga lub otyłość (zgodnie z wytycznymi WHO) [92]. Poziom wykształcenia rodziców klasyfikowano jako: podstawowe, zawodowe, średnie lub wyższe (licencjat lub magister). Kontrolowano posiadanie przez dziecko rodzeństwa (tak/nie). W przypadku stylu życia dzieci uwzględniono przeciętny czas snu, regularność posiłków, częstość aktywności fizycznej oraz czas spędzony przed ekranem. Długość snu skategoryzowano na ≥9h lub <9h [93], zachowania żywieniowe: co najmniej 3 regularne posiłki dziennie + przekąska lub nieregularne posiłki, aktywność fizyczną: 3 dni w tygodniu przez ≥3h lub mniej ćwiczeń w tygodniu, czas przed ekranem: ≤2h dziennie lub więcej [94].

Wyniki

Pierwsza publikacja pt.: „*The link between prenatal stress and indicators of fatness in children – literature review”*, która wchodzi w skład rozprawy doktorskiej jest przeglądem systematycznym badań dotyczących wpływu stresu prenatalnego na ryzyko zmian parametrów otłuszczenia ciała u dzieci. Spośród 20 artykułów włączonych do przeglądu systematycznego 19 to badania podłużne, a jedno to badanie przekrojowe [95]. Wszystkie badania dotyczyły zarówno dziewczynek jak i chłopców. Wielkość badanych grup wynosiła od 67 do 65212 osób. Podejście retrospektywne prezentowane było w 2 spośród 19 badań podłużnych (10%), resztę stanowiły badania prospektywne (90%).

Stres u matek badany był w czasie ciąży (19 artykułów, 95%) lub retrospektywnie (1 artykuł, 5%). W przypadku połowy analizowanych badań nie uwzględniono miesiąca ciąży, w którym kobieta doświadczyła stresu. Doświadczenie stresorów badane było w pierwszym trymestrze ciąży w 12 badaniach, w drugim trymestrze w 16 badaniach, w trzecim trymestrze w 15 badaniach. Wiek dzieci, u których przeprowadzane były pomiary antropometryczne, wynosił od 26 dni do 16 lat. Najczęściej badaną grupą wiekową były dzieci w wieku od 2 do 7 lat (n=15) i od 8 do 12 (n=6). Dzieci poniżej 2 lat (n=4) i powyżej 13 lat (n=4) były rzadziej badanymi grupami wiekowymi.

W przeglądzie literatury wzięto pod uwagę różne narzędzia do oceny stresu. Artykuły zostały podzielone pod względem wykorzystanych metod oceny stresu na subiektywne wskaźniki stresu (uwzględniono wszystkie badania, w których kobiety deklarowały występowanie psychologicznego stresu) i obiektywne (uwzględniono występowanie niekorzystnych doświadczeń życiowych w ciąży) oraz badania, w których oceniano stężenie kortyzolu.

W niektórych badaniach oceniano zarówno stres subiektywny jak i obiektywny. Stres subiektywny oceniany był częściej (70%, 14 artykułów). Stres obiektywny badany był w 50% artykułów (n=10), natomiast matczyne stężenie kortyzolu badane było w 20% artykułów (n=4).

We wszystkich artykułach zostały zbadane masa i wysokość ciała dzieci. Wskaźnik masy ciała został wzięty pod uwagę w 11 z 20 prac (55%). Inne wskaźniki otłuszczenia, które były analizowane, to całkowita zawartość tkanki tłuszczowej (n=4, 20%), oceniana za pomocą

bioimpedancji elektycznej (BIA), absorpcjometrii rentgenowskiej o podwójnej energii (DXA) oraz pomiarów fałdów skórnotłuszczowych, WHtR (n=3, 15%), masa ciała (n=1, 5%), obwód talii (n=1, 5%), FMI (n=1, 5%). Występowanie nadwagi (n=7, 35%), otyłości (n=4, 20%) i niedowagi (n=1, 5%) również były oceniane w analizowanych artykułach. W 11 badaniach (55%) zostało wskazane kryterium diagnostyczne nadwagi i otyłości. W 7 artykułach wykorzystano wytyczne IOTF, w 2 artykułach wykorzystano wytyczne Center of Disease Control (CDC), w 1 artykule wykorzystano normy Instytutu Medycyny oraz w 1 artykule przyjęto kryterium: niedowaga=BMI <-2 SD; nadwaga=BMI od 1 do 2 SD; otyłość=BMI >2SD.

Większość artykułów potwierdziła związek stresu prenatalnego z większymi wartościami wskaźników otłuszczenia u dzieci (n=13, 65%) niezależnie od narzędzi wykorzystanych do oceny stresu. W 3 artykułach (15%) stres w ciąży był związany z mniejszymi wartościami wskaźników otłuszczenia u dzieci. Brak statystycznie istotnych wyników zaobserwowano w 4 publikacjach (20%). Spośród 10 artykułów badających obiektywne stresory 7 badań potwierdziło związek stresu prenatalnego z podwyższonymi wartościami wskaźników otłuszczenia dzieci (70%), a 20% potwierdziło związek stresu prenatalnego z obniżeniem wskaźników otłuszczenia u dzieci. Natomiast w 10% badań nie zaobserwowano istotnych statystycznie wyników. Wszystkie 4 badania, w których oceniano poziom kortyzolu u matek w czasie ciąży potwierdziły związek stresu prenatalnego z podwyższonymi wskaźnikami otłuszczenia u dzieci w wieku szkolnym. Spośród 14 badań, w których zastosowano subiektywne wskaźniki stresu, 7 potwierdziło związek stresu z podwyższoną masą i wskaźnikami proporcji ciała (50%), a w 6 artykułach (43%) nie zaobserwowano żadnych istotnych zależności. W jednym badaniu stres prenatalny był związany z niższymi wartościami BMI. Wyniki przeglądu sugerują więc, że związek stresu prenatalnego z podwyższonymi wartościami wskaźników otłuszczenia ciała u dzieci jest bardziej wyraźny w przypadku oceny zobiektywizowanych wskaźników stresu w czasie ciąży, natomiast badania uwzględniające subiektywną ocenę stresu przez matki dają mniej jednoznaczne wyniki (Publikacja 1, Tabela 3).

Związek między stresem prenatalnym a wskaźnikami otłuszczenia był bardziej widoczny, gdy stres u matki wystąpił na początku lub pod koniec ciąży (1 lub 3 trymestr) dlatego możemy przypuszczać, że te okresy są kluczowe w kontekście przyszłego ryzyka nadwagi lub otyłości u dzieci. Wystąpienie stresora w pierwszym trymestrze ciąży daje

potencjalną możliwość, że stresor przez dłuższy czas oddziałuje na dziecko, prowadząc do programowania zmian w metabolizmie płodu, co może skutkować wystąpieniem zjawiska nadrabiania (catch-up growth), które jest czynnikiem ryzyka nadwagi i/lub otyłości [96]. Natomiast trzeci trymestr ciąży jest okresem kluczowym dla różnicowania adipocytów, dlatego wystąpienie stresora w tym okresie może mieć negatywne skutki związane z masą ciała dzieci w przyszłości [97,98] (Publikacja 1, Tabela 4).

Dzieci w wieku poniżej 2 lat badane były w 4 analizowanych artykułach. Wszystkie prace potwierdziły związek stresorów prenatalnych z podwyższeniem wskaźników otłuszczenia u dzieci. U dzieci w wieku 2-7 lat związek stresu prenatalnego ze wskaźnikami otłuszczenia badany był w 15 artykułach, z czego 8 (53%) potwierdziło związek między stresem a zwiększeniem wartości wskaźnika, 3 (20%) ze zmniejszeniem, a w 4 (26%) nie wykazano zależności. U dzieci w wieku 8-12 lat związek stresu prenatalnego ze wskaźnikami otłuszczenia badany był w 6 publikacjach, z czego 5 potwierdziło związek narażenia na stresor z podwyższeniem wskaźnika, a jedno badanie wskazywało na związek stresora z obniżeniem BMI. We wszystkich badaniach, w których parametry antropologiczne oceniane były u dzieci powyżej 13 roku życia dowiedziono istotnych związków między doświadczeniem stresorów a wyższym BMI, WHtR lub ryzykiem nadwagi.

Celem przeglądu była ocena związku pomiędzy stresem prenatalnym a ryzykiem nadwagi i otyłości u dzieci. Większość badań włączonych do przeglądu potwierdziła związek pomiędzy doświadczeniem stresu w życiu prenatalnym a masą ciała i proporcjami ciała u dzieci. Związek stresu prenatalnego ze zwiększeniem wskaźników otłuszczenia został potwierdzony w 65% analizowanych badań, natomiast w 15% badań włączonych do przeglądu opisano związek stresu prenatalnego ze zmniejszeniem wskaźników otłuszczenia. Wyniki przeglądu wskazują, że związek stresu prenatalnego z wyższymi wartościami wskaźników otłuszczenia jest bardziej wyraźny, kiedy badane są zobiektywizowane stresory, czas wystąpienia stresora to 1 lub 3 trymestr ciąży, a ryzyko rozwoju nieprawidłowości w masie lub składzie ciała jest wyższe u dzieci poniżej 2 lub powyżej 12 roku życia. Mając na uwadze wyniki przeglądu systematycznego w dalszej pracy badawczej skupiłam się w szczególności na ocenie zobiektywizowanych stresorów. Ponadto tylko w 4 z 20 artykułów wzięto pod uwagę zawartość tkanki tłuszczowej u dzieci, dlatego w dalszych badaniach oprócz oceny częstości występowania nadwagi i otyłości diagnozowanej na podstawie BMI skupiłam się na analizie parametrów składu ciała, zawartości tkanki tłuszczowej oraz beztłuszczowej, a także

wykorzystałam metodę diagnozy nadwagi opartą na procentowej zawartości tkanki tłuszczowej.

Jedyne uwzględnione w pracy badanie dotyczące związku stresu prenatalnego z częstością występowania niedowagi, nadwagi lub otyłości przeprowadzone w Polsce wykazało związek stresu prenatalnego z niedowagą. Co ważne, wyniki Żądzińskiej i wsp. [95] wykazały istotne różnice międzypłciowe, dlatego analizy w pracach badawczych wykonywałam zarówno w całej grupie, jak i z podziałem na płeć.

Drugi artykuł wchodzący w skład rozprawy doktorskiej nosi tytuł „The relations *between prenatal stress, overweight and obesity in children diagnosed according to BMI and percentage fat tissue*". W tym badaniu testowałam hipotezę mówiącą o tym, że dzieci matek, które doświadczyły stresu w czasie ciąży mają większe ryzyko otyłości. Jako wskaźniki ryzyka otyłości wykorzystałam BMI i procentową zawartość tkanki tłuszczowej mierzoną metodą bioimpedancji elektrycznej. Jako że przegląd literatury, który wykonałam wcześniej wskazywał na istnienie związku stresu prenatalnego z podwyższeniem wskaźników masy ciała i ryzyka nadwagi i/lub otyłości u dzieci, ważnym elementem niniejszej pracy było sprawdzenie, czy występują podobne związki, kiedy kryterium diagnostycznym jest procentowa zawartość tkanki tłuszczowej zamiast BMI. Co więcej, uwzględniłam możliwość odmiennej reakcji na stres u dziewcząt i chłopców.

W badanej grupie 21% (n=131) dzieci było narażonych na co najmniej jeden stresor w życiu prenatalnym, 9% (n=50) badanych dzieci doświadczyło dwóch stresorów, natomiast narażonych na trzy stresory było 3% (n=19) dzieci. Najczęściej doświadczanym rodzajem stresorów w czasie ciąży były problemy rodzinne (n=77, 14% z całej próby) oraz obawa przed możliwym wystąpieniem nieprawidłowości u dziecka (n=46, 9%) (Publikacja 2, Tabela 1).

Częstość występowania niedowagi, nadwagi i otyłości diagnozowana na podstawie IOTF nie różniła się między chłopcami i dziewczynkami (Publikacja 2, Tabela 2). Istotne różnice między płciami występowały natomiast, kiedy niedowaga, nadwaga i otyłość były rozpoznawane na podstawie zawartości tkanki tłuszczowej (χ^2=14,438; p=0,0024). Nadwaga i otyłość występowały częściej u chłopców (odpowiednio 21%, 22%) niż u dziewcząt (odpowiednio 11%, 18%). Analizy nie wskazują na istnienie istotnych różnic w częstości występowania niedowagi, nadwagi i otyłości diagnozowanej na podstawie BMI pomiędzy

dziećmi w wieku <9; 9-10 i >10 lat. Natomiast częstość występowania niedowagi, nadwagi i otyłości rozpoznawanej na podstawie zawartości tkanki tłuszczowej różniła się w grupach wiekowych (χ^2=18,851; p=0,004). Otyłość diagnozowana według punktów odcięcia dla procentowej zawartości tkanki tłuszczowej występowała częściej wśród dzieci poniżej 9 lat (23%) oraz między 9 a 10 rokiem życia (20%) niż u dzieci powyżej 10 roku życia (12%) (Publikacja 2, Tabela 3).

Poza stresem prenatalnym istnieje szereg czynników środowiskowych, których wpływ na masę ciała dzieci został potwierdzony we wcześniejszych badaniach. Przeprowadzona szczegółowa analiza związku między czynnikami społeczno-ekonomicznymi i rodzicielskimi a parametrami ciała u dzieci okazała się istotna również w badanej przez nas grupie. Zaobserwowaliśmy związek między BMI matki przed ciążą a masą ciała dziecka (χ^2=53,643; p<0,001). Dzieci matek z nadwagą przed ciążą częściej były otyłe (χ^2=22,520; p<0,001). Matki z otyłością przed ciążą częściej miały dzieci z nadwagą (χ^2=14,497; p=0,002). W badanej grupie wykształcenie matki (χ^2=31,038; p=0,002) oraz ojca (χ^2=22,673; p=0,006) były związane z masą ciała potomstwa. Wyższe wykształcenie matki wiązało się z niższym ryzykiem otyłości u dziecka (χ^2=26,92; p<0,001). Ojcowie z wyższym wykształceniem rzadziej mieli dzieci z nadwagą (χ^2=9,918; p=0,02) lub otyłością (χ^2=10,40; p=0,02) niż ojcowie z wykształceniem zawodowym. Otyłość u dzieci częstsza była przy trudnościach finansowych rodziny (χ^2=16,154; p=0,02) niż u dzieci rodziców bez takich trudności.

Analiza zawartości tkanki tłuszczowej wykazała, że dzieci matek doświadczających stresu w ciąży były bardziej narażone na nadwagę zdiagnozowaną wg kryteriów McCarty'ego (χ^2=4,273, p=0,038). Wykazano również, że dzieci matek otyłych przed ciążą częściej miały nadwagę (χ^2=8,095; p=0,044), a wyższe wykształcenie matki obniżało ryzyko otyłości u dziecka (χ^2=7,882; p=0,048). Niedowaga częstsza była u dzieci z masą urodzeniową < 2500 g (χ^2 = 12,271; p=0,002) niż u dzieci z masą 2500-4000 g (10%).

Podsumowując powyższe analizy, wykazały one związki między czynnikami społeczno-ekonomicznymi a zaburzeniami masy ciała u dzieci, podkreślając rolę BMI matki przed ciążą, wykształcenia rodziców oraz trudności finansowych. W obliczu istotności tych zależności w badanej grupie uwzględniłam powyższe czynniki jako zmienne kontrolne, żeby sprawdzić, czy niezależnie od ich występowania wpływ stresorów prenatalnych na masę ciała badanych dzieci pozostanie istotny statystycznie.

Analiza regresji logistycznej z jedną zmienną wyjaśniającą nie wykazała istotnego związku stresu prenatalnego (≥ 1 typ stresora vs. 0) z niedowagą (OR=0,94; 95% CI: 0,50–1,72), nadwagą (OR=1,01; 95% CI: 0,58–1,75) i otyłością (OR=0,94; 95% CI: 0,4–2,21) zdiagnozowanymi według IOTF. Model uwzględniający zmienne kontrolowane (wiek, płeć, miejsce zamieszkania, BMI matki przed ciążą, status ekonomiczny rodziny, wykształcenie rodziców, urodzeniowa masa ciała) również nie dostarczył dowodów na istotny związek stresu prenatalnego z niedowagą (OR=1,04; 95% CI:0,52–2,07), nadwagą (OR= 1,04; 95% CI: 0,58–1,84) i otyłością (OR=0,84; 95% CI: 0,30–2,29). W oddzielnych analizach dla chłopców i dziewczynek zależności między stresem prenatalnym a BMI również były nieistotne statystycznie (Publikacja 2, Tabela 6). Odmienne wyniki dała natomiast analiza z uwzględnieniem niedowagi, nadwagi i otyłości diagnozowanych na podstawie zawartości tkanki tłuszczowej. W modelu nieskorygowanym na inne zmienne stres prenatalny (≥ 1 typ stresora vs. 0) był związany z nadwagą (OR=1,65; 95% CI: 1,02–2,66). Wynik ten został potwierdzony w analizach skorygowanych na zmienne kontrolowane (OR=2,14; 95% CI: 1,25–3,66). Nie zaobserwowano związków stresu prenatalnego z niedowagą (OR=2,36; 95% CI: 0,15–38,27) lub otyłością (OR=1,21; 95% CI: 0,76–1,9) diagnozowanymi na podstawie tkanki tłuszczowej. Podobnie analizy skorygowane na zmienne kontrolowane dały wyniki nieistotne dla otyłości (OR=1,14; 95% CI: 0,68–1,91) rozpoznanej na podstawie zawartości tkanki tłuszczowej. Analizy w grupie chłopców uwzględniające zmienne kontrolowane potwierdziły związek stresu prenatalnego i nadwagi (OR=2,42, 95% CI: 1,20–4,89), natomiast w grupie dziewczynek wyniki nie były istotne statystycznie (Publikacja 2, Tabela 7).

Powyższe badanie miało na celu ocenę relacji między stresem prenatalnym a ryzykiem nadwagi i otyłości u dzieci. Testowałam hipotezę o większym ryzyku otyłości u dzieci, których matki doświadczyły stresu w ciąży. Badanie opierało się na dwóch sposobach oceny ryzyka otyłości: wskaźniku masy ciała (BMI) i procentowej zawartości tkanki tłuszczowej, co miało istotne znaczenie w interpretacji tych zależności. Analizy wykazały, że stres prenatalny może być związany z nadwagą, szczególnie w przypadku procentowej zawartości tkanki tłuszczowej, i że płeć dziecka może być ważnym modyfikatorem wykazanej zależności. Czynniki społeczno-ekonomiczne, takie jak wykształcenie rodziców i trudności finansowe, również miały istotny wpływ na masę ciała dzieci.

Kolejna część pracy doktorskiej to wyniki oryginalne, które aktualnie są w procesie recenzji w czasopiśmie Journal of Physiological Anthropology, a publikacja nosi tytuł „*FTO*

and MC4R Polymorphisms, and Selected Pre-, Peri- and Postnatal Factors as Determinants of Body Mass Index and Fatness in Children. A Thorough Analysis of the Associations".

Celem tej pracy była ocena związku między standaryzowanymi wartościami BMI, FMI, FFMI, FatM a ACE oraz polimorfizmami genów FTO rs9939609 oraz MC4R rs17782313 u dzieci w wieku 6-12 lat. W tym badaniu kompleksowej ocenie poddano również związki zmiennych takich jak status socjoekonomiczny, czynniki okołourodzeniowe, rodzicielskie oraz styl życia dzieci z badanymi parametrami składu ciała. Kontrolowanie tych zmiennych umożliwiło bardziej holistyczne spojrzenie na badane związki między ACE a parametrami składu ciała u dzieci. W niniejszej publikacji szczególnie ważnym aspektem analiz była ocena wpływu interakcji między niekorzystnymi, potencjalnie stresogennymi doświadczeniami w pierwszych latach życia dzieci i polimorfizmami genów FTO (rs9939609) oraz MC4R (rs17782313) na wskaźniki powiązane z otłuszczeniem organizmu.

Badane polimorfizmy genów zostały wybrane do analizy, ponieważ istnieją mocne dowody na ich związek z BMI i masą ciała u dzieci [20,26]. Warto jednak podkreślić, że dotychczas żadne badania nie wykazały związku między polimorfizmem genu FTO a spoczynkowym tempem metabolizmu [22]. Nadmierna masa ciała wynika z faktu, że dzieci z niekorzystnym allelem genu FTO spożywają posiłki o wyższej wartości energetycznej i wyższej zawartości tłuszczu [102]. Podobnie w przypadku genu MC4R, dzieci z obecnością allelu C odczuwają większą przyjemność z jedzenia przy mniejszym uczuciu sytości i mają tendencję do jedzenia, gdy nie są głodne, co może przyczyniać się do ich otyłości [26]. Tak więc sama obecność niekorzystnego allelu genu może nie determinować niekorzystnych zmian masy ciała. Jeśli jednak dodatkowo współwystępują z nimi czynniki środowiskowe (ACE), które mogą również wpływać na wybory żywieniowe [103], ryzyko nadmiernego otłuszczenia ciała może być większe.

Baza danych po usunięciu przypadków z brakującymi informacjami o parametrach składu ciała lub oznaczeniu polimorfizmów genów FTO i MC4R liczyła 456 dzieci. Pierwszym krokiem analizy danych było sprawdzenie różnic w częstości nadwagi i otyłości u dzieci w zależności od wystąpienia niekorzystnych doświadczeń dziecięcych. Dzieci, które doświadczyły co najmniej jednego typu ACE częściej miały niedowagę lub były otyłe niż dzieci, które nie doświadczyły żadnego (χ^2=12,53; p=0,01). Większa liczba doświadczonych typów ACE była związana z większą częstością otyłości rozpoznawanej zgodnie z kryteriami

IOTF (χ^2=17,27; p=0,04), ale nie z niedowagą lub nadwagą. Doświadczenie ACE nie wiązało się natomiast z niedowagą, nadwagą lub otyłością rozpoznawanymi na podstawie tkanki tłuszczowej (χ^2=2,85; p=0,42). Ważnym modyfikatorem związku ACE ze wskaźnikami otłuszczenia był typ stresora. Dzieci narażone na konflikty rodzinne częściej były otyłe niż dzieci, które nie doświadczyły tego stresora (χ^2=12,44; p=0,01). Dzieci będące świadkami przemocy częściej charakteryzowały się nadmierną tkanką tłuszczową (χ^2=12,63; p=0,01); dzieci, które doświadczyły śmierci bliskiej osoby, częściej miały rozpoznaną nadwagę na podstawie zawartości tkanki tłuszczowej (χ^2=8,50; p=0,04) a u dzieci z doświadczeniem długotrwałej rozłąki z rodzicami częściej stwierdzano niedowagę według kryteriów opartych na BMI (χ^2=8,44; p=0,04) lub otyłość według kryteriów opartych na zawartości tkanki tłuszczowej (χ^2=8,35; p=0,04). Rodzaje stresorów nie były jednak związane ze standaryzowanymi wskaźnikami składu ciała jako zmiennych ciągłych (Publikacja 3, Tabela 10).

Co ciekawe, nie stwierdzono różnic między występowaniem niedowagi, nadwagi i otyłości rozpoznanej według norm IOTF i McCarthy'ego u dzieci z allelem ryzyka FTO rs9939609 lub MC4R rs17782313 i dzieci bez alleli ryzyka. Nie było różnic w standaryzowanych BMI (F=0,98; p=0,38), FMI (F=2,26, p=0,11), FFMI (F=0,19; p=0,82) i FatM (F=2,63; p=0,07) pomiędzy homozygotami AA, heterozygotami AT i homozygotami TT genu FTO. Jednak dzieci, które były homozygotami CC, miały wyższy standaryzowany FMI (F=3,11; p=0,04) i FatM (F=4,09; p=0,02) niż dzieci bez allelu ryzyka (TT) genu MC4R (Publikacja 3, Tabela 2).

Następnym krokiem analiz była ocena częstości występowania nadwagi i otyłości w zależności od obecności alleli ryzyka genów FTO i MC4R w oddzielnych analizach ze względu na płeć. W grupie dziewczynek otyłość diagnozowana na podstawie BMI była częstsza wśród heterozygot AT w porównaniu do homozygot TT (χ^2 =14,14; p=0,03) genu FTO rs9939609. Podobnie standaryzowane BMI (F=3,17; p=0,04) i FatM (F=3,41; p=0,04) były istotnie wyższe u heterozygot niż u homozygot TT genu FTO. W grupie dziewcząt homozygoty CC miały wyższy standaryzowany wskaźnik FatM niż u homozygot TT genu MC4R (F=3,24; p=0,04). W grupie chłopców częstość występowania niedowagi, nadwagi i otyłości diagnozowane na podstawie BMI i tkanki tłuszczowej nie różniły się natomiast w zależności od wariantów genów FTO i MC4R. Wśród chłopców nie było różnic w standaryzowanych wartościach BMI, FMI, FFMI i FatM pomiędzy dziećmi będącymi homozygotami ryzyka, heterozygotami i

homozygotami bez allelu ryzyka poszczególnych badanych genotypów FTO i MC4R (Publikacja 3, Tabele 3-4).

W artkule opisałam również wpływ pozostałych zmiennych na występowanie nadwagi i otyłości (diagnozowanych na podstawie BMI oraz zawartości tkanki tłuszczowej) oraz ich związków ze standaryzowanymi wartościami BMI, FMI, FFMI oraz FatM. Poniżej prezentuję syntetyczny opis najważniejszych wyników dotyczących masy ciała rodziców, wykształcenia rodziców, stylu życia dzieci oraz czynników okołourodzeniowych.

Występowanie nadwagi lub otyłości u rodziców było związane z częstszym występowaniem nadwagi lub otyłości u dzieci oraz z wyższymi standaryzowanymi wartościami BMI i FMI. U dzieci matek z nadwagą przed ciążą częściej występowała nadwaga diagnozowana na podstawie BMI oraz otyłość diagnozowana na podstawie tkanki tłuszczowej (Publikacja 3, Tabela 6). Rodzice z wykształceniem zawodowym częściej mieli dzieci z nadwagą lub otyłością niż rodzice z wykształceniem wyższym. Ponadto dzieci rodziców z wykształceniem zawodowym mieli wyższe standaryzowane wartości BMI, FMI oraz FatM (Publikacja 3, Tabela 7). Spośród zmiennych związanych ze stylem życia istotne statystycznie zależności z występowaniem nadwagi stwierdzono w przypadku dzieci, które nie wykonywały regularnych ćwiczeń fizycznych. Natomiast wyższe wartości standaryzowanych BMI, FMI i FatM występowały u dzieci spędzających więcej niż 2 godziny dziennie przed ekranami (Publikacja 3, Tabela 8). Dzieci z masą urodzeniową powyżej 4000 g były bardziej narażone na nadwagę w dzieciństwie niż dzieci z masą urodzeniową 2500-4000 g (χ^2=16,25; p=0,01). Dzieci z rodzeństwem bliźniaczym, miały niższe standaryzowane wartości BMI (t=2,31; p=0,02) i FatM (t=1,97; p=0,049) niż dzieci urodzone z ciąży pojedynczej. Dzieci urodzone naturalnie miały niższe standaryzowane wartości FMI (t=2,64; p=0,01) niż dzieci urodzone przez cesarskie cięcie (t=2,06, p=0,04) (Publikacja 3, Tabela 9).

W następnym kroku analiz, w celu zidentyfikowania czynników najlepiej wyjaśniających standaryzowane parametry składu ciała dzieci (BMI, FMI, FFMI oraz FatM) wykonano regresję krokową postępującą. Modele regresji wielorakiej krokowej postępującej przygotowano dla każdej zmiennej zależnej (BMI, FMI, FFMI oraz FatM) uwzględniając następujące zmienne niezależne: doświadczenie ACE, doświadczenie stresu prenatalnego, polimorfizmy genów FTO i MC4R, typ rodziny, największa masa ciała w czasie ciąży, czas trwania ciąży, wiek matki w chwili urodzenia dziecka, BMI matki przed ciążą, aktualny BMI

matki, poziom wykształcenia matki, aktualny BMI ojca, poziom wykształcenia ojca, zachowania żywieniowe, aktywność fizyczna oraz długość snu dziecka. Zmienne włączano do momentu osiągnięcia najwyższej wartości R^2. Regresję wieloraką przeprowadzono w całej grupie oraz osobno w grupie chłopców i dziewczynek (Publikacja 3, Tabela 11).

Wyniki regresji wielorakiej wskazują, że czynnikami najsilniej związanymi z parametrami składu ciała były: BMI ojca, wykształcenie matki, najwyższa masa ciała matki w czasie ciąży oraz wiek matki w chwili urodzenia dziecka.

Doświadczenie stresu prenatalnego lub niekorzystnych wydarzeń dziecięcych było uwzględnione jako jedna ze zmiennych niezależnych w analizie regresji krokowej postępującej. We wszystkich modelach przewidujących wariancję standaryzowanych wartości BMI, FMI, FFMI oraz FatM osiągnięto istotność statystyczną. Jednak mimo tego, że zmienne dotyczące stresorów były uwzględnione w modelach przewidujących wariancję standaryzowanych zmiennych BMI, FMI oraz FatM w całej grupie badanej oraz w kontekście predykowania FMI, FFMI i FatM u dziewcząt oraz BMI i FFMI u chłopców, zmienne te nie były istotnie statystyczne powiązane z ocenianymi wskaźnikami otłuszczenia. Ich obecność w modelach świadczyć może jednak o tym, że mogły być one istotnie związane ze wskaźnikami antropometrycznymi poprzez interakcje z innymi zmiennymi niezależnymi, np. czynnikami genetycznymi. W związku z tym podjęłam się dalszych analiz, które miały na celu ocenę efektu interakcji pomiędzy doświadczeniem niekorzystnych wydarzeń dziecięcych a polimorfizmami genów FTO i MC4R i ich związków z parametrami składu ciała. Dalsza analiza skupiała się na poszukiwaniu interakcji jako potencjalnego klucza do pełniejszego zrozumienia związku niekorzystnych wydarzeń dziecięcych z parametrami składu ciała w kontekście genetycznych uwarunkowań.

Dwuczynnikowa analiza wariancji ujawniła wpływ licznych interakcji między polimorfizmami FTO i MC4R a typami ACE na standaryzowane wskaźniki BMI, FMI, FFMI i FatM (Publikacja 3, Tabela 14). Doświadczenie 3 lub więcej stresorów wiązało się z wyższym standaryzowanym BMI u homozygot AA w porównaniu z homozygotami TT polimorfizmu rs9939609 genu FTO oraz wyższym FMI i FatM u homozygot CC w porównaniu do homozygoty TT polimorfizmu rs17782813 genu MC4R. Rozdzielenie z rodzicami wiązało się z wyższymi standaryzowanymi wartościami BMI u homozygot AA w porównaniu z homozygotami TT polimorfizmu rs9939609 genu FTO oraz u homozygot CC w porównaniu z

homozygotami TT polimorfizmu rs17782813 genu MC4R. Analiza wykazała także większe standaryzowane wartości FMI i FatM u homozygot CC w porównaniu do homozygoty TT polimorfizmu rs17782813 genu MC4R. Problemy szkolne wiązały się z wyższymi standaryzowanymi wskaźnikami BMI i FMI u homozygot AA w porównaniu z homozygotami TT polimorfizmu rs9939609 genu FTO. Doświadczenie innych nieokreślonych stresorów wiązało się z wyższymi wskaźnikami standaryzowanych BMI i FMI u homozygot AA w porównaniu z homozygotami TT polimorfizmu rs9939609 genu FTO.

Niniejsze badanie potwierdziło związek niekorzystnych doświadczeń dziecięcych z ryzykiem otyłości oraz wykazało istotne, modyfikujące znaczenie typu ACE dla tej zależności. Związek stresu z ocenianymi wskaźnikami antropometrycznymi (zmienne ciągłe) okazał się natomiast nieistotny w analizie wieloczynnikowej uwzględniającej wpływ zmiennych kontrolowanych o dobrze udokumentowanym znaczeniu w etiologii otyłości. Co najważniejsze jednak, wyniki pracy wskazują na znaczenie interakcji między poddanymi ocenie czynnikami genetycznymi i niekorzystnymi doświadczeniami dziecięcymi. Niniejsze badanie sugeruje, że sama obecność alleli ryzyka może, ale nie musi być czynnikiem w istotny sposób determinującym rozwój nieprawidłowego otłuszczenia, ale ich współwystępowanie z niekorzystnymi, stresogennymi doświadczeniami dziecięcymi może ten efekt aktywować lub nasilać.

Podsumowanie i wnioski

1. Badania własne wykazały, że nadwaga i otyłość rozpoznawane na podstawie tkanki tłuszczowej częściej występowały u chłopców niż u dziewczynek. Nie było różnic w częstości występowania nadwagi i otyłości diagnozowanych na podstawie BMI. Metoda diagnozy nieprawidłowości poziomu tkanki tłuszczowej na podstawie zawartości tkanki tłuszczowej w organizmie dzieci wydaje się lepszą i bardziej czułą miarą skutków ubocznych stresu prenatalnego na organizm ludzki niż stosowanie norm opartych na BMI i uzasadnione może być jej częstsze stosowanie w przyszłych badaniach nad czynnikami ryzyka otyłości.

2. Stres prenatalny jest związany z nadwagą, ale nie z otyłością i niedowagą diagnozowanymi na podstawie zawartości tkanki tłuszczowej. Analizy w grupie

chłopców potwierdziły związek stresu prenatalnego i nadwagi, natomiast w grupie dziewczynek wyniki nie były istotne statystycznie.

3. Otyłość występuje częściej u dzieci, które doświadczyły co najmniej jednego niekorzystnego wydarzenia życiowego. Spośród badanych rodzajów stresorów istotne związki zaobserwowano pomiędzy zawartością tkanki tłuszczowej a byciem świadkiem przemocy, występowaniem otyłości a doświadczeniem konfliktów rodzinnych, występowaniem niedowagi lub otyłości i doświadczeniem separacji z rodzicem, występowaniem nadwagi diagnozowanej na podstawie zawartości tkanki tłuszczowej a śmiercią bliskiego członka rodziny. Rodzaj niekorzystnego doświadczenia jest więc ważnym czynnikiem modyfikującym rozwój otłuszczenia ciała. Mechanizmy leżące u podłoża tych zależności wymagają dalszych badań.

4. W badanej grupie obecność allelu A polimorfizmu rs9939609 genu FTO i allelu C polimorfizmu rs17782313 genu MC4R nie różnicowały częstości występowania niedowagi, nadwagi i otyłości. Jednak płeć okazała się ważną zmienną wpływającą na wyniki analiz związku polimorfizmów ze wskaźnikami otłuszczenia. U dziewcząt, w odróżnieniu od chłopców, stwierdzono istotne związki wskaźników otłuszczenia z badanymi polimorfizmami.

5. Polimorfizmy genów FTO i MC4R wchodzą w interakcje z wysokim obciążeniem stresem mierzonym liczbą typów (3+) niekorzystnych doświadczeń dziecięcych oraz z rodzajem stresora, kształtując poziom otłuszczenia dzieci.

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Prace wchodzące w skład rozprawy doktorskiej

Publikacja I

Ewa Bryl, Tomasz Hanć

“The link between prenatal stress and indicators of fatness in children - literature review”

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The link between prenatal stress and indicators of fatness in children – literature review

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With 1 figure and 4 tables

Abstract: *Background:* There are indications that the occurrence of metabolic diseases in children may be conditioned by factors experienced already in the utero. *Aim of the study:* The aim of this systematic review was to analyze the studies that examined the effects of stress experienced by a pregnant woman on the child's adiposity rates in postnatal life. *Methods:* The review includes 20 articles published before March 2020 in Scopus and Medline databases with the use of following keyword combinations: /maternal or mother/, /prenatal or pregnant/, /stress or distress/ and /BMI, body mass index or overweight or obesity or body composition/. *Results:* The results of the research were inconsistent. Nevertheless, most articles confirmed the positive association of prenatal stress with fatness indicators in children. The review raised a question of the role of the methods applied for stress measurement (objective vs. subjective indicators) and adiposity assessment, as well as the time of prenatal exposition to stress. *Conclusion:* Most studies have proved that prenatal stress is related to the children adiposity in postnatal life.

Keywords: prenatal stress; children; obesity

Introduction

According to the World Health Organization (WHO) in 2016 18% of children and adolescents aged 5–19 years suffered from overweight or obesity (World Health Organization, n.d.). The problem of obesity concerns 6% of girls and 8% of boys around the world. If untreated, excessive body mass can lead to an increased health risk such as a cardiovascular disease, cancer, diabetes (World Health Organization, n.d.) but also mental disorders (McClanahan et al. 2009). Therefore, the prevention and treatment of excessive body mass are one of the most important challenges of modern societies, and research aimed to explore obesity etiology and preventing factors is crucial.

Improper diet, lack of physical activity and sedentary lifestyle are common risk factors for obesity. The problem usually begins in childhood, and obese children often become obese adults (Eriksson et al. 2003; Freedman et al. 2007). However, results of previous studies (Entringer et al. 2010) suggest the predisposition to the development of obesity may already begin in utero. According to the Developmental Origins of Health and Disease (DOHaD) and to the Barker's hypothesis the fetal development period is the time when the fetus is particularly sensitive to adverse environmental factors, whose consequences may lead to e.g. overweight, obesity and metabolic diseases in adulthood (Barker 2004). Barker et al. (1989) were the first to prove the relationship between the environment in prenatal life and an increased risk of developing metabolic diseases in adulthood. It was observed that children with the lowest birth weight had a higher risk of developing in adulthood diseases such as hypertension (Barker et al. 1989; Strachan & Hart 1990), diabetes or hyperlipidemia (Barker et al. 1993). According to the most recent research, the unfavorable prenatal environmental factors which may lead to the development of excessive body weight in postnatal life are e.g. the mother's smoking (Rayfield & Plugge 2017; Cameron et al. 2018), inadequate diet during pregnancy, 25-hydroxyvitamin D deficiency (Boyle et al. 2017), eating processed food, saturated fats, simple sugars (Gillman et al. 2017) and alcohol consumption (Werts et al. 2014).

Another risk factor for overweight or obesity might be the occurrence of prenatal stress (Entringer et al. 2010; Burgueño et al. 2020). The studies showed that stress experienced by a pregnant woman affects the children's health. Apart from the abnormal body mass, children of the moth-

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ers who experienced stress during pregnancy, have a higher risk of heart diseases (Louey & Thornburg 2005; Bercovich et al. 2014), hypertension (Bercovich et al. 2014; Plana-Ripoll et al. 2016), diabetes (Barker et al. 1993; Li et al. 2012), insulin resistance (Bercovich et al. 2014), angina pectoris (Bercovich et al. 2014), higher low-density lipoprotein (LDL) levels (Bercovich et al. 2014; Wang et al. 2017) or wheezing (Guxens et al. 2014; Bacharier et al. 2019). Exposure to stress during pregnancy causes an increase in cortisol (Brennan et al. 2008) and cortisone levels (Molenaar et al. 2019), which can lead to endocrine changes and contribute to improper distribution of fat tissue mostly in the abdomen area in the child in postnatal life (Wolf 2002). Stress during pregnancy and increased exposure of a fetus to elevated cortisol levels in prenatal life can also adversely affect children's behaviour (Enlow et al. 2017), e.g. causing their lower orienting / regulatory capacity (Fuller 2018). There is evidence that children with lower regulatory skills may have poor control of their eating behaviour and thus have a greater probability of excessive body weight (Graziano 2010). Stress may also lead to epigenetic changes (Vidal et al. 2014) and increase the risk of eating disorders in later childhood (St-Hilaire et al. 2015). Compulsive overeating related to binge eating disorder or bulimia is commonly associated with overweight, obesity and excessive amount of fat tissue in adolescents (Puder & Munsch 2010; De Giuseppe et al. 2019).

Attempts to explain specifically how prenatal stress affects the development of abnormal body weight and high content of fat tissue seem to be crucial due to the rapid growth of overweight and obesity among young people. Although research indicates that stress can affect weight gain in children, the results of studies on the relationship between prenatal stress and postnatal obesity are inconsistent. This may be due to methodological difficulties related to the study and interpretation of the results of the stress assessment. Research differs in e.g. stress indicators and body measurements used as well as in time of exposure to stress and age of stress outcomes assessment. Therefore the aim of this review was to assess the association between prenatal maternal stress and indicators of fatness in offspring with careful attention paid to the methods applied, including the type of prenatal stress (subjective / objective), the trimester of pregnancy during which the mother was exposed to adverse factors, and the age of the child at which anthropometric measurements were taken.

The research hypothesis assumed that prenatal stress affects body mass parameters, anthropometric indicators such as BMI, WHR, WHtR and body fat, and increases the risk of overweight and obesity in children. We assumed that the strength of the association would depend on (1) the pregnancy period in which the mother experienced an adverse event, (2) the age at which the child's anthropometric indicators were tested, (3) the type of stress tested – whether subjective or objective.

Methods

The literature review included papers on relationship between prenatal stress and adiposity indicators in the offspring published before March 15th 2020 (Table 1). The Scopus and Medline databases were used to find the articles. The review is based on a systematic and comprehensive search of relevant articles using a combination of the following terms: /maternal or mother/, /prenatal or pregnant/, /stress or distress/ and /BMI, body mass index or overweight or obesity or body composition/. In order to be included the studies needed to: (1) be carried out on a human population; (2) include stress assessment in pregnant women, we took into account the mother's experience of either objective stressors or subjective experience of stress; (3) assess the relation between maternal stress and the offspring adiposity indicators, such as the presence of underweight, overweight and obesity, but also assessment of body weight, BMI, anthropometric indices (WHR, WHtR, waist and hip circumferences) and the percentage of body fat or (4) investigate the effect of prenatal stress on body composition parameters in offspring up to 18 years of age; (5) be a quantitative study, (6) be written in English. The review included all studies regardless of the country in which they were conducted and regardless of the number of participants included in the study. All studies that did not fulfill the above-mentioned conditions were excluded. We excluded studies that tested oxidative stress or nutritional stress. We also did not consider studies on depression or anxiety in a pregnant mother as stressors but included such studies in our review if depression or anxiety was part of a composite index of stress in pregnant women. We also did not review studies that looked at the influence of lifestyle factors like smoking and did not evaluate prenatal stress in any other way. We also excluded studies where there was no subjective or objective stress test, and only the concentration of glucocorticosteroids, which was associated with taking steroid drugs, was assessed. We considered several works from the same project if they provide at least partially different or supplementary information. The presented work was supported by the National Science Centre (NCN) in Poland (grant number OPUS 2016/21/B/NZ5/00492).

Characteristic of the studies

Based on the keywords, 385 and 322 articles were found in the Scopus, and Medline database respectively. After excluding duplicates (239) there were 468 articles left. As many as 388 articles were not included on the basis of the titles or abstracts since they did not meet the review inclusion criteria. Eighty articles were left for assessment of full texts. Only 20 articles fulfilled all the eligibility requirements. These 20 articles are all available studies on this topic, which at the same time meet all inclusion criteria for this systematic review.

The articles taken into consideration were published between 2007 and 2018. Five of the studies were carried out

Table 1. Basic information on articles analysed in the review.

Author, year, country	Name/Type of the study	Total sample	Moment of stress measurement in mothers	Mothers measurements	Age of children	Children measurements	Main results	Confounders
Dancause et al. 2015, Canada [34]	IowaFlood/ prospective longitudinal	106 mothers, 106 children	1st, 2nd, 3rd trimester	Objective hardship-Questionnaire about Storm (including 4 items Threat, Loss, Scope, Change, LES, Subjective Stress –IES-R	2.5, 4 y	Height, weight, BMI, triceps and subscapular skinfolds	Objective stress ($p = 0.03$) and subjective stress ($p = 0.04$) associated with a greater increase in total adiposity at the age of 4 y	Larger birth weight ($p = 0.03$), fewer fetal risk factors ($p = 0.01$), and larger maternal BMI ($p = 0.03$) predicted greater BMI Z-scores at 2.5. Fetal risk factors ($p = 0.04$) and maternal BMI ($p < 0.01$) predicted child BMI z- scores. Fewer fetal risk factors ($p = 0.01$), larger maternal BMI ($p < 0.01$), and more smoking during pregnancy ($p < 0.01$) predicted greater adiposity at 4. Breastfeeding duration, SES were not associated with children's weight. Covariates in models: maternal medical and obstetric history; smoking, alcohol consumption, SES (determined based on parental education and occupation status), fetal risk factor variable (combined medical and obstetric variable, which included history of diseases during pregnancy, breast-feeding patterns)
Kroska et al. 2018, USA [35]	IOWA Flood/ prospective longitudinal	103 mothers 103 children	1st, 2nd, 3rd trimester	Objective stress: Questionnaire about stress related to the flood Subjective stress: PDEQ, IES – R, PDI	2.5 y	Height, weight, BMI	Subjective stress associated with higher BMI ($r = 0.21$, $p < 0.05$)	Birth weight was associated with children BMI at 30 months. Gestational age, previous pregnancies, maternal age, SES were not associated. Moderated mediation results indicated that greater PNMS predicted greater BMI at age 30 months through effects on higher birth weight as a mediator, but only for participants with low social support. Covariates in models: number of previous pregnancies, age of mother at birth, timing of exposure in utero, offspring sex, offspring gestational weight, gestational age, social support

Table 1. continued.

Author, year, country	Name/Type of the study	Total sample	Moment of stress measurement in mothers	Mothers measurements	Age of children	Children measurements	Main results	Confounders
Stout et al. 2015, USA [36]	prospective longitudinal	246 mothers, 246 children	15, 19, 25, 30, 37 GW (2^{nd}-3^{rd} trimester)	Placental corticotropin realising hormone (pCRH), maternal cortisol level	3, 6 months, 1, 2 y	Height, weight, BMI, diagnose of underweight/ overweight/ obesity based on IOTF criteria	Higher pCRH in 30 GW associated with faster BMI growth from 6^{th} to 12^{th} and in 24^{th} month ($p < 0.046$).	Birth weight percentile was associated with BMIP at birth, 3, 6, and 12 months (range r: .19 to .25, all p-values < 0.05), but was not associated with BMIP at 24 months ($r = .12$, $p = 0.14$) BMIP profile groups did not differ by child (sex, child's duration of breastfeeding, gestational age at birth), maternal (parity, maternal prepregnancy BMI, maternal weight gain during pregnancy), or sociodemographic factors (race/ethnicity, age, cohabitation with baby's father, and household income) (all p-values > 0.10).
Watt et al. 2013, USA [37]	prospective longitudinal	153 mothers, 153 children	1^{st}, 3^{rd} trimester	Subjective stress: Cohen PSS	2, 6 months, 1 y	Height, weight, WHtR, waist circumference diagnose of underweight/	High stress level ($>=$ 1SD) associated with infant overweight ($p = 0.02$)	Alcohol consumption, smoking, maternal overweight, maternal health problems, breastfeeding, ethnicity, married/partner, no insurance were not associated with overweight. The only maternal dietary practices associated with infant weight are consumption of sugar sweetened beverages and consumption of sweets. Other maternal dietary practices (e.g. consumption of fast food, fruits and vegetables, fat) are not significantly related to infant overweight Covariates in models: food access, diet, cigarette and alcohol use, exercise, depression, social support, health conditions, demographics, and infant feeding practices, first language, marital status/ cohabitation, household size, insurance coverage, and pre-existing health conditions of diabetes, thyroid problem, overweight/ obesity, high cholesterol, high blood pressure, heart disease and/or depression
Entringer et al. 2017, USA [38]	prospective longitudinal	67 mothers, 67 children	1^{st}, 2^{nd}, 3^{rd} trimester	Maternal cortisol level	newborn (25.7 days), 6 months	Weight, length, total body fat (DEXA)	Maternal salivary cortisol in 3^{rd} trimester associated with higher %BF at 6 months ($p < 0.05$) and change in %BF from 0 to 6 months ($p < 0.01$)	Covariates in models: Maternal sociodemographic status (annual total household income), prepregnancy BMI, parity, presence of gestational diabetes, infant birth weight, gestational age at birth, infant sex, and infant feeding status

Table 1. continued.

Author, year, country	Name/Type of the study	Total sample	Moment of stress measurement in mothers	Mothers measurements	Age of children	Children measurements	Main results	Confounders
Hohwü et al. 2015, Denmark [39]	Aarhus Birth Cohort in Denmark, (ABC study)/ prospective longitudinal	2876 mothers, 2876 children	30 GW (3rd trimester)	Objective stress: questionnaire on life events experienced during pregnancy Subjective stress: Questionnaires on psychological distress	9–11 y	Height, weight, BMI – diagnose of overweight/ obesity based on IOTF criteria	Stress in pregnancy related to parting with a biological father associated with risk of overweight (OR 2.29) and obesity (OR 2.81)	Adjustment for the possible intermediate factors, birth weight and maternal smoking during pregnancy, did not produce substantial changes to the estimates for overweight and obesity, although OR for obesity became non-significant when adjusting for maternal smoking during pregnancy.
Hohwü et al. 2015, Denmark [40]	Aarhus Birth Cohort in Denmark, (ABC study)/ prospective longitudinal	655 mothers, 655 children	2nd, 3rd trimester	Maternal cortisol level	2–16 y (at least one measurement in one of three equal-sized age groups (2–6, 7-11, 12–16 y))	BMI – diagnose of overweight/ obesity based on IOTF criteria	Higher level of maternal cortisol (2nd trimester) associated with overweight in 2–6-year-olds and 12–16- year-olds; relative difference 19% (95% CI: 3; 37, $p = 0.02$) and 20% (95% CI: 3; 41, $p = 0.02$), respectively.	Birth weight and gestational week were associated with overweight in 2–16 years old children. Smoking cigarettes was associated with overweight in 7–16 years old children. Weight gain during pregnancy, educational level, maternal age, breastfeeding, parity were not associated. For all the three age groups (2–6, 7–11, 12–16 years), adjustment for the potential intermediate factor birth weight and maternal smoking during pregnancy did not change the results considerably compared with the adjusted estimates (0–4%) The relative differences were adjusted for gender, gestational age at delivery, maternal pre-pregnancy BMI, maternal weight gain during pregnancy, maternal educational level, age at child birth, parity, timing of cortisol sample, and breast feeding.
Ingstrup et al. 2012, Denmark [41]	retrospective longitudinal based on Danish National Birth Cohort (DNBC),	37764 mothers, 37764 children	30 GW – 3rd trimester	Subjective stress: GHQ	7 y	Height, weight, BMI, diagnose of underweight/ overweight/ obesity based on CDC criteria	Maternal stress not associated with childhood overweight in 7-year-olds (OR 1.06)	Lack of social support seemed to be slightly protective against childhood overweight (OR 0.93 (0.82; 1.04)) whereas children of mothers of low or medium socioeconomic status had an increased risk of overweight. Covariates were taken into account in models First adjusted model, were controlled for; age, parity, prepregnancy BMI, smoking during pregnancy, and SES. Second adjusted analysis, were also controlled for breastfeeding, gestational weight gain and recreational exercise of the mother.

Table 1. continued.

Author, year, country	Name/Type of the study	Total sample	Moment of stress measurement in mothers	Mothers measurements	Age of children	Children measurements	Main results	Confounders
Li et al. 2010, Denmark [42]	population based retrospective longitudinal	65212 mothers, 65212 children	1 year before pregnancy until childbirth	Objective stress: Stress assessed based on Danish Civil Registration System and Danish Birth System, stress factor – death of a close relative by the mother 1 year before pregnancy or during pregnancy until childbirth	7–13 y	Height, weight, BMI, diagnose of underweight/ overweight/ obesity based on IOTF criteria	Stress associated with higher rates of overweight at 10, 11, 12 and 13 y ($p < 0.001$); the highest risk of overweight observed when the death of relative occurred in the period from 6 to 0 month before pregnancy (OR 3.31, 95% CI 1.71–6.42 at age 12 y, and OR 2.31, 95% CI 1.08–4.97 at age 13 y)	The association was not significantly modified by gender, birth year, birth weight, gestational age, and maternal factors (age, education, income, and cohabitation status).
Liu et al. 2016, Canada [43]	Project Ice Storm/ prospective longitudinal	123 mothers, 123 children	1st, 2nd, 3rd trimester	Objective stress: Questionnaire about stress related to Ice Storm, Subjective stress: IES-R	5.5, 8.5, 11.5, 13.5, 15.5 y	Height, weight, BMI, waist circumference WHtR	Objective stress associated with higher BMI at the age of 5.5 y ($p = 0.02$) and at the age of 15.5 y ($p = 0.02$) and with higher WHtR at the age of 8.5 y ($p = 0.03$), 11.5 y ($p = 0.02$), 13.5 ($p = 0.01$), 15.5 y ($p = 0.04$); Subjective stress associated with higher WHtR at the age of 11.5 y ($p = 0.04$), 13.5 y ($p = 0.01$) and 15.5 y ($p = 0.04$)	Maternal age at birth, SES, smoking cigarettes number of children at birth were not associated with BMI and WHtR in 5.5–15.5 year old children. Control variables entered to the model: age of the child at assessment, sex of the child, and timing of ice storm exposure in utero,

Table 1. continued.

Author, year, country	Name/Type of the study	Total sample	Moment of stress measure-ment in mothers	Mothers measurements	Age of children	Children measurements	Main results	Confounders
Cao-Lei et al. 2015, Canada [44]	Project Ice Storm/ prospective longitudinal	66 mothers, 66 children	1st, 2nd, 3rd trimester	Objective stress: Questionnaire about stress related to Ice Storm, LES Subjective stress: IES-R, GHQ	13.5 y	Height, weight, waist circumference, BMI z-scores, WHtR	Objective ($p = 0.012$) and subjective stress ($p = 0.018$) associated with central adiposity; life events different from storm during pregnancy associated with central obesity ($p = 0.004$) and higher BMI ($p = 0.009$)	SES, obestric complications, birth weight, birth length, birth ponderal index were not associated with WHtR and BMI.
Dancause et al. 2012, Canada [45]	Quebeck Ice Storm/ prospective longitudinal	111 mothers 111 children	1st, 2nd, 3rd trimester	Objective stress: Questionnaire about stress related to ice storm, LES Subjective stress: IES-R	5.5 y	Height, weight, BMI, diagnose of underweight/ overweight/ obesity based on CDC criteria	Objective stress associ-ated with obesity risk (OR = 1.37, $p = 0.02$) and higher BMI ($p < 0.05$).	Birth weight predicted larger BMI. Shorter maternal height was associated with higher BMI in children. Maternal psychological functioning, SES, obstetric complications, birth weight, birth length, gestational age, maternal smoking were not associated with obesity. Maternal and family factors (psychological functioning, life events, obstetric complications, smoking, SES, and maternal height were allowed to enter during step 1, followed by child factors (birth weight, birth length, sex, and breastfeeding status) in step 2.
Guxens et al. 2013, The Netherlands [46]	Generation R Study/ prospective longitudinal	5283 mothers, 5283 children	3rd trimester	Subjective stress: BSI, "general functioning" subscale of the McMaster Family Assessment Device	3 months – 4 y	Height, Weight, BMI	Maternal stress not associated with overweight and obesity in children; family stress reported by mothers associated with higher child weight at the age of 6 months and higher BMI at 3 and 6 months	Birth weight was associated with childhood BMI group in 4 years old children. Gestational age, preterm birth, birth length were not. Models were adjusted for maternal age, body mass index, smoking during pregnancy, educational level, ethnicity, and parity; parental history of asthma or atopy and pet keeping; and children's sex, preterm birth, birth weight, breastfeeding, day care attendance, secondhand smoke at home, eczema, and lower respiratory tract infections.
van Dijk et al. 2012, Denmark [47]	ABCD Cohort Study/ Prospective longitudinal	2939 mothers, 2939 children	16 GW – 2nd trimester	Subjective stress: JCQ, Maternal cortisol level (gw≥16)	5 y	Height, weight, waist circumference BMI, WHtR, FMI (BIA)	Job strain not associated with higher BMI, WHtR or FMI; higher maternal cortisol associated with marginally higher FMI in girls, but marginally lover FMI in boys ($p < 0.01$)	Maternal characteristics considered potential confounders were age, prepregnancy BMI, educational level (years of education after primary school, as a measure of socio-economic status), parity, ethnicity, smoking and alcohol consumption during pregnancy Birth weight was standardized for sex, parity and gestational age.

Table 1. continued.

Author, year, country	Name/Type of the study	Total sample	Moment of stress measurement in mothers	Mothers measurements	Age of children	Children measurements	Main results	Confounders
van Dijk et al. 2010, The Netherlands [48]	ABCD Study/ prospective longitudinal	8266 mothers, 8266 children	1st trimester	Subjective stress: JCQ	5–7 y	Height, weight, BMI, waist circumference, WHtR, FMI (BIA)	Job strain associated with 0.4 difference in BMI (alpha = 0.05);	Maternal depression and anxiety, birth weight, gender, gestational age, parity, maternal age, educational level, SES, ethnicity, smoking and alcohol consumption, hypertension were taken into account.
Farewell et al. 2018, New Zealand [49]	The Growing Up in New Zealand (GUiNZ)/ prospective longitudinal	5839 mothers 5839 children	1st, 2nd, 3rd trimester	Objective stress: questionnaire on vulnerability operationalized on 9 objective risk factors, Subjective stress: Cohen PSS	2, 4.5 y	Height, weight, BMI, diagnose of underweight/ overweight/ obesity based on IOTF criteria	Objective stress associated with a 0.11 increase in BMI Z-score at the age of 2 ($p < 0.01$) and a 0.15 increase in BMI Z-score at 4,5 ($p < .01$); subjective stress not associated with children BMI at 2 and 4.5 y	Maternal age, education, household income, prepregnancy BMI, birth weight were associated with BMI at 24 and 54 months. Maternal race/ethnicity and parity were associated with BMI at 24 months and 54 month respectively. The following continuous and categorical variables were controlled for in the full models: maternal age at pregnancy, parity, ethnicity, education, total household income, maternal prepregnancy BMI. Child factors including birthweight z-score adjusted for gestational age and child gender were also included in the model.
Wu et al. 2018, Mexico [50]	Programming Research in Obesity Growth Environment and Social Stress (PROGRESS)/ prospective longitudinal	424 mothers, 424 children	2nd or 3rd trimester	Objective stress: ETV, CRISYS	4–6 y	Height, weight, BMI, waist circumference, BF (BIA)	Increased stress index (27.3) associated with a decrease in BMI Z-score (0.14 unit), BF (5.6%), %BF (3.5%), waist circumference (1.2%)	Major covariates include maternal prepregnancy BMI, parity, SES, birth weight, child sex, and child total energy intake and percent fat intake of total energy at 4–6 years of age.

Table 1. continued.

Author, year, country	Name/Type of the study	Total sample	Moment of stress measurement in mothers	Mothers measurements	Age of children	Children measurements	Main results	Confounders
Żądzińska & Rosset 2013, Poland [51]	cross-sectional	812 mothers, 812 children	7–10 years after childbirth	Objective stress: Questionnaire contains questions about trauma during pregnancy	7–10 y	Height, weight, BMI, diagnose of underweight/ overweight/ obesity based on IOTF criteria	Stress associated with a higher risk of body weight deficit in 7–10-year-olds (OR 2.77); Mothers' trauma associated with an increased risk of underweight in boys (OR 2.74) and with a decreased risk in girls (OR = 0.35)	Low birth weight significantly increased the risk of underweight only in boys (OR = 2.99) and mother's occupational activity decreased the risk of underweight only in girls (OR = 0.57). Maternal education, paternal education, parental education, number of children in family, passive smoking, maternal smoking during pregnancy, medicines during pregnancy, hospital admission, alcohol consumption by mother, occupational activity, first born child, caesarean section were not associated with body weight in children. The logistic regression models also included: parental education, number of children in the family, passive smoking, maternal smoking during pregnancy, medicines during pregnancy, hospital admissions, reported alcohol consumption by mother, first-born child, birth by Caesarean section
Rondo et al. 2013, Brazil [52]	longitudinal cohort study	409 mothers, 409 children	16 GW 20–26 GW 30–36 GW 1^{st}, 2^{nd}, 3^{rd} trimester	Subjective stress: PSS, GHQ	5–8 y	Height, weight, BMI	Stress associated with a decrease in children BMI (–0.09, (CI –0.18 to –0.6x10^3)) ($p = 0.04$)	BMI z-score for age was positively associated with maternal BMI and birthweight ($R^2 = 0.13$). Maternal age, maternal education, income, family size, maternal work, marital status, maternal BMI, length of breastfeeding, child gender, age, birthweight and gestational age were controlled.
Mizutani et al. 2007, Japan [53]	Project Enzan/ prospective longitudinal	1417 mothers, 1417 children	Most before 16 GW	Subjective stress: Questionnaire on lifestyle habits including stress during pregnancy	5 y	Height, weight, BMI, diagnose of underweight/ overweight/ obesity based on IOTF criteria	Maternal stress not associated with overweight (OR = 0.87) and obesity (OR = 1.09) in 5-year-olds	Maternal smoking habits were associated with overweight in the 5-year-old children [adjusted odds ratio (OR): 2.15; 95% confidence interval (CI): 1.12–4.11]. Maternal sleep duration of 8 h/d negatively affected childhood overweight (adjusted OR: 0.71; 95% CI: 0.49–1.04). Children whose mothers skipped breakfast were likely to become overweight (adjusted OR: 1.78; 95% CI: 1.14–2.77). There was no relationship between low-birth-weight infants and childhood obesity in our study.

Note: LES – Life Experiences Survey, IES–R – Impact of Event Scale – revised, BMI – Body Mass Index, PDEQ – The Peritraumatic Dissociative Experiences Questionnaire, PDI – The Peritraumatic Distress Inventory, GW – gestational week, IOTF – International Obesity Task Force, Cohen PSS – Cohen Perceived Stress Scale, WHtR – Waist to Hip Ratio, IOM – Institute of Medicine, DEXA – Dual-energy X-ray Absorptiometry, BF - Body fat mass, GHQ – General Health Questionnaire, CDC – Centre of Disease Control, BSI – Brief Symptom Inventory, JCQ – Job Content Questionnaire, ETV – Exposure to Violence, CRISYS – Crisis in Family system, FMI – Fat Mass Index, BIA – electrical bioimpedance, SES - socioeconomic status.

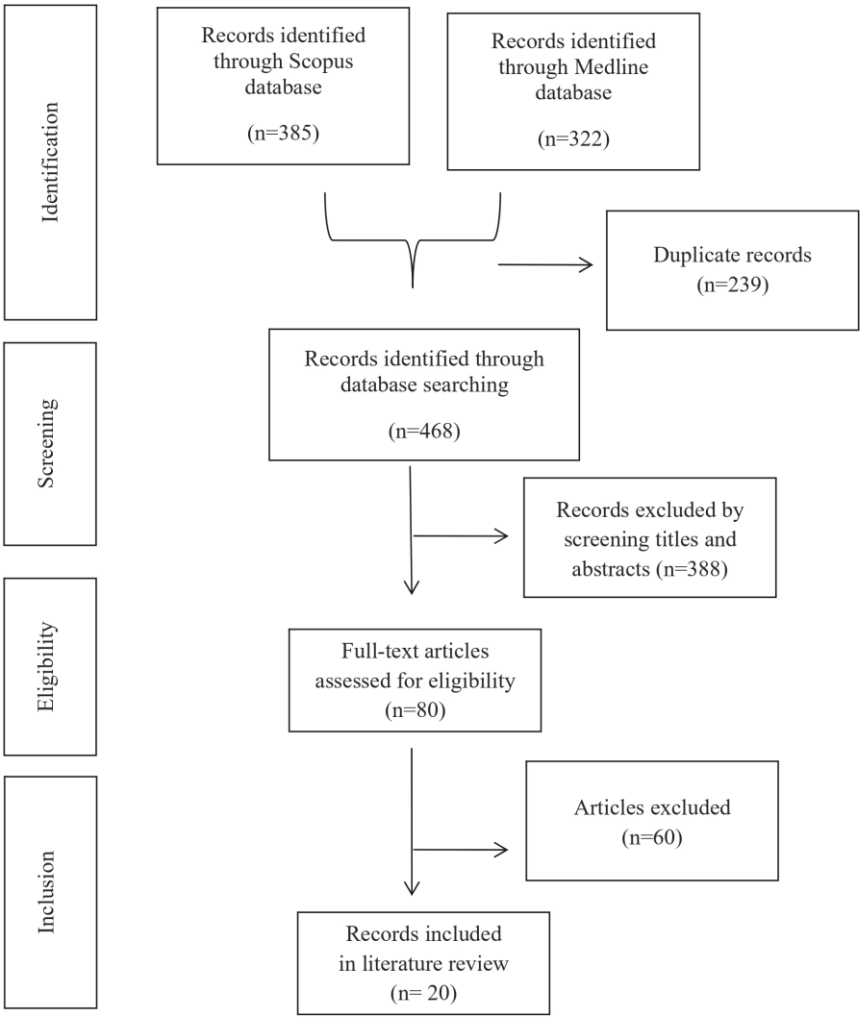

Fig 1. A selection of articles.

in the United States of America (Watt et al. 2013; Dancause et al. 2015; Stout et al. 2015; Entringer et al. 2017; Kroska et al. 2018), four in Denmark (Li et al. 2010; Ingstrup et al. 2012; Hohwü et al. 2015a; Hohwü et al. 2015b), three in Canada (Dancause et al. 2012; Cao-Lei et al. 2015; Liu et al. 2016) and three in The Netherlands (Guxens et al. 2013; van Dijk et al. 2010; van Dijk et al. 2012). Single studies were carried out in New Zealand (Farewell et al. 2018), Mexico (Wu et al. 2018), Poland (Żądzińska & Rosset 2013), Brazil (Rondó et al. 2013) and Japan (Mizutani et al. 2007). More than one article from the same project was qualified if the published articles differed in the age of examined children, the tools used to assess prenatal stress, adiposity indicators or statistical analyses.

Three different articles qualified for the Project Ice Storm because they varied in the methodology used. One of them

referred to obesity diagnosed on the basis of the Center for Disease and Prevention norms (Dancause et al. 2012), whereas in the other two BMI and WHtR were examined (Cao-Lei et al. 2015; Liu et al. 2016). However, they differed in the age of the children. One examined children aged 5.5–15.5 years, while the other one examined children aged 13.5 years and it included two additional questionnaires for testing mother's prenatal stress. The IOWA Flood Study presented two works. In the following articles data of children aged 2.5–4 years (Dancause et al. 2015) and 2.5 years (Kroska et al. 2018) were analysed. We decided to include both articles because of the differences in the assessment of stress and anthropometric measurements. Two articles were qualified from ABC Study as well. In the articles data on children aged 9–11 years (Hohwü et al. 2015b) and 2–16 years (Hohwü et al. 2015a) were analysed. Different methods of prenatal stress assessment were used in these studies. From ABCD Study two articles were also qualified. One of them described the analysis of children aged 5 years (van Dijk et al. 2010) and the other one children aged 5 to 7 (van Dijk et al. 2012). Both articles were qualified from this project because they differ in the questionnaires used to assess stress. In addition, one of them used cortisol assessment (van Dijk et al. 2010).

Results

Among 20 reviewed articles 19 presented longitudinal studies. The remaining one was cross-sectional (Żądzińska & Rosset 2013). All studies included both girls and boys. Sample size varied from 67 to 65212. Retrospective approach was presented in 2 out of 19 longitudinal studies (10%), the rest of which were prospective (90%).

The stress in mothers was most often measured during pregnancy (19 articles, 95%). In 1 paper (5%) mothers of children aged 7–13 years were asked about the stress they had experienced during pregnancy. In most studies stress was measured in women regardless of the month of their pregnancy during the study (n = 10, 50%). Women in the first, second and third trimester of pregnancy were a target study group respectively in 1 (5%), 2 (11%) and 2 (11%) of the analysed articles. Mothers in the first or second trimester were a target study group in 1 (5%) of articles. One of the papers focused exclusively on mothers in the first or third trimester (5%). In 3 studies (16%) stress was measured a few times in the second and third trimester. In total, stress in the 1st, 2nd and 3rd trimester was examined in 12 (65%), 16 (80%) and 15 articles (80%), respectively. The age of children at the time of anthropometric measurements ranged from 26 days to 16 years old. The most frequently studied age group were children from 2–7 years (n = 15, 75%) and from 8–12 years (n = 6, 30%). Children below 2 years (n = 4, 20%) and over 13 years were the least frequently examined group (n = 4, 20%).

The methods of stress assessment

The analyzed articles took into account a variety of stress-testing tools. In order to systematize and make comparisons, reviewed articles were divided into subgroups based on methods applied: the papers including subjective stress examination (here we classified all studies in which the psychological stress that mothers declared in the questionnaire was assessed), the articles with assessment of objective stressors (with adverse events in pregnancy assessment) and the studies with cortisol concentration measurements.

Some studies have examined both subjective experience of stress and objective stressors. Subjective stress was examined most frequently (70%, 14 articles). Objective stressors was studied in 50% of articles (n = 10), whereas maternal pregnancy cortisol concentration was tested in 20% of articles (n = 4).

Subjective stress was most often assessed using the Impact of Event Scale-Revised questionnaire (IES-R) (n = 5 out of 14 articles, 36%), Cohen 4-item Perceived Stress Scale (Cohen PSS) (n = 3, 21%), Job Content Questionnaire (JCQ) (n = 2, 14%), questions from GHQ60 (General Health Questionnaire-28) (n = 2, 14%) and questionnaires on psychological stress created for the purpose of particular study (n = 2, 14%). Other questionnaires such as The Peritraumatic Dissociative Experiences Questionnaire (PDEQ) (7%), The Peritraumatic Distress Inventory (PDI) (7%), Brief Symptom Inventory (BSI) (7%) were used in single studies. Objective stressors were most often assessed using questionnaires on natural disaster related events (n = 5 out of 10 articles, 50%). Other questionnaires that were used were Life Experiences Survey (LES) (n = 3, 30%) self-made questionnaires on traumatic life events (n = 3, 30%), Exposure to Violence (ETV) (n = 1, 10%), Crisis in Family System (CRISYS) (n = 1, 10%). Death of a close family member during pregnancy was the indicator of stress in one article (10%). Maternal cortisol concentration was studied in 3 articles (16%) and placental corticotrophin realizing hormone (pCRH) was measured in 1 article (5%).

Anthropometric measurements and indicators of fatness

In all of the studies the weight and height of children were measured. Body Mass Index (BMI) was taken into consideration in 11 out of 20 articles (55%). Other indicators of adiposity were total adiposity (n = 4, 20%), assessed via bioelectrical impedance analysis (BIA), dual-energy X-ray Absorptiometry (DEXA) or triceps and subscapular skinfolds, Waist to Hip Ratio (WHtR) index (n = 3, 15%), body mass (n = 1, 5%) and waist circumference (n = 1, 5%). Fat Mass Index (FMI) was calculated and analyzed in one article (n = 1, 5%). Prevalence of overweight (n = 7, 35%), obesity (n = 4, 20%) as well as underweight (n = 1, 5%), was also assessed in presented studies. In 11 studies (55%) a diagnostic criterion of overweight and obesity was reported.

Diagnosis of underweight, overweight and obesity was stated under the guidance of the International Obesity Task Force (IOTF) in 7 articles, the Center of Disease Control in 2 articles, the Institute of Medicine in 1 article and on the basis of BMI z-scores in 1 article (underweight: BMI z-score < –2; overweight: BMI z-score from 1 to 2; obesity: BMI z-score > 2).

The association of prenatal stress and fatness indicators in children

Generally, most articles (n = 13, 65%) confirmed the positive association of prenatal stress with fatness in children independently of stress assessment tools and adiposity indicators applied. In 3 articles (15%) stress during pregnancy was negatively associated with indicators of fatness in children. No significant relationships were presented in 4 papers (20%). Most of the studies in which BMI (n = 8, 73%), WHtR (n = 2, 67%), body weight (n = 1, 100%), overweight (n = 4, 57%) were analyzed, showed a positive relationship between these indicators and prenatal stress. The results of analyses of the relationship between stress and obesity (n = 2, 50%) were less clear. The association of prenatal stress and lower BMI, total adiposity, waist circumference and underweight was found respectively in 2 (18%), 1 (33%), 1 (100%) and 1 (100%) article. There were also some articles that didn't reveal a significant link between prenatal stress and BMI (n = 1, 9%), WHtR (n = 1 33%), obesity (n = 2, 50%), overweight (3, 43%). None of the studies that included FMI (n = 1, 100%) and central adiposity (n = 1, 100%) showed a significant relationship between these indicators and prenatal stress (Table 2).

Among the 10 studies that used objective stress indicators 7 confirmed the relationship of stress with an increase in any indicator of fatness (70%), and in 20% the relationship between prenatal objective stressors and decreased indicators of fatness were confirmed. In 10% no relationships were observed. Most studies in which BMI (n = 5, 62.5%), WHtR (n = 2, 100%), overweight (n = 2, 100%), and obesity (n = 1, 100%) were analyzed showed a positive relationship between these indicators and objective stress. The associations between prenatal objective stress and a decrease in indicator were confirmed in the case of BMI (n = 1, 12.5%), adiposity (n = 1, 50%) and waist circumference (n = 1, 100%). The only study including underweight diagnosis showed significant association of this indicator and prenatal stress (n = 1, 100%). No relationship between prenatal objective stress and BMI or central obesity was found in 2 (25%) and 1 (100%) article respectively (Table 3).

Among the 14 studies that used subjective stress indicators 7 confirmed the relationship of stress with an increase in body mass and proportion indexes (50%). In one study (7%) prenatal stress was related to a BMI decrease. In 6 articles (43%) no relationships were observed. A significant positive link was found between prenatal subjective stress and BMI, WHtR, overweight, adiposity and body weight in 3 (33%), 2 (67%), 1 (33%), 1 (100%) and 1 (100%) articles of those including specific indicators. The associations between prenatal subjective stress and decreased BMI were observed in one study (11% from all studies examined BMI). From the studies that included BMI, WHtR and overweight no relationships were found in 5 (56%), 1 (33%) and 2 (67%) articles, respectively. All studies that included obesity (n = 2), central adiposity (n = 1) and FMI (n = 1) gave insignificant results. Our review suggests that the results confirming the association of prenatal stress and increase fatness come from the studies focused on objective stressors measurements. The research including subjective stress measures gave more ambiguous outcomes.

Table 2. Significant and insignificant results of the analyses of relation between prenatal stress and indicators of body size, proportions, and fatness in children.

Anthropometric indicators	Number of articles (% of 20 articles reviewed)	Positive association* n (%)	Negative association* n (%)	Insignificant results* n (%)
BMI	11 (55%)	8 (73%)	2 (18%)	1 (9%)
WHtR	3 (15%)	2 (67%)	–	1 (33%)
Obesity	4 (20%)	2 (50%)	–	2 (50%)
Overweight	7 (35%)	4 (57%)	–	3 (43%)
Underweight	1 (5%)	1 (100%)	–	–
Adiposity	3 (15%)	2 (67%)	1 (33%)	–
Central adiposity	1 (5%)	–	–	1 (100%)
Waist circumference	1 (5%)	–	1 (100%)	–
Body weight	1 (5%)	1 (100%)	–	–
FMI	1 (5 %)	–	–	1 (100%)

Note: BMI – Body Mass Index, WHtR – waist to height ratio, FMI – Fat Mass Index, n – number of articles, * – n and % of all articles that include the indicator of fatness

In all of the studies that used maternal prenatal cortisol concentration a link between increased indicator of fatness and prenatal stress was confirmed. All the studies that analyzed BMI, obesity and total adiposity showed a positive relation of these indicators and prenatal cortisol concentration. However, in the case of FMI the results were gender-dependent. In the group of girls elevated maternal cortisol was associated with an increase, whereas in boys with a decrease of FMI (Table 3).

The results differed depending on the stage of pregnancy in which stress was assessed. In the studies that measured stress in the first trimester of pregnancy 9 out of 12 studies (75%) confirmed a positive association of prenatal stress with an indicator of fatness in children. A relationship between prenatal stress and lower BMI was found in 1 article (8%), while 2 papers showed no relationship (17%). In the studies that measured stress in the second trimester of pregnancy 8 out of 16 studies (50%) confirmed the positive association of indicator of fatness in children with prenatal stress. A negative relationship between prenatal stress and indicator of fatness was found in 3 articles (19%), while 5 remaining papers (31%) showed no association. In the studies that measured stress in the third trimester 11 out of 15 studies (74%) confirmed a positive association of fatness in children with prenatal stress. A negative relation between prenatal stress and fatness was showed in 2 articles (13%). No association was found in 2 papers (13%) (Table 4).

Children younger than 2 years were examined in 4 articles. All of them confirmed the relationship between prenatal stress and increased BMI, body weight, total adiposity, or an increased risk of obesity. Children aged 2–7 years and 8–12 years were examined in 15 and 6 articles respectively. Among children aged 2–7 years BMI was measured in 11 articles, 5 of which (45%) confirmed a relationship between stress and increased BMI, 2 (18%) with decreased BMI and 4 (36%) showed no relationship. Among children aged 2–7 years prenatal stress was associated with higher adiposity in 1 of the articles including this indicator (50%), higher risk

Table 3. Significant and insignificant results of the analyses of relation between prenatal stress and indicators of fatness in children by the type of stress assessment*.

Stress assessment (total number of articles)	Anthropometric indicators	Number and % of all articles that include objective OR subjective stressors' assessment	Positive association* n (%)	Negative association* n (%)	Insignificant results* n (%)
Objective stressors (n = 10)	BMI	8 (80%)	5 (62.5%)	1 (12.5%)	2 (25%)
	WHtR	2 (20%)	2 (100%)	–	–
	Obesity	2 (20%)	2 (100%)	–	–
	Overweight	2 (20%)	2 (100%)	–	–
	Underweight	1 (10%)	1 (100%)	–	–
	Adiposity	2 (20%)	1 (50%)	1 (50%)	–
	Central adiposity	1 (10%)	–	–	1 (100%)
	Waist circumference	1 (10%)	–	1 (100%)	–
Subjective experience (n = 14)	BMI	9 (64.3%)	3 (33%)	1 (11%)	5 (56%)
	WHtR	3 (22%)	2 (67%)	–	1 (33%)
	Obesity	2 (14%)	–	–	2 (100%)
	Overweight	3 (22%)	1 (33%)	–	2 (67%)
	Adiposity	1 (7.1%)	1 (100%)	–	–
	Central adiposity	1 (7.1%)	–	–	1 (100%)
	Body weight	1 (7.1%)	1 (100%)	–	–
	FMI	1 (7.1%)	–	–	1 (100%)
Maternal prenatal cortisol concentration (n = 4)	BMI	1 (25%)	1 (100%)	–	–
	Obesity	1 (25%)	1 (100%)	–	–
	Adiposity	1 (25%)	1(100%)	–	–
	FMI	1 (25%)	1 (100%) in girls group	1 (100%) in boys group	–

Note: BMI – Body Mass Index, WHtR – Waist to Hip Ratio, FMI – Fat Mass Index, n – number of articles, * – n and % of all articles that include the indicator of fatness

Table 4. The relation between prenatal stress and indicators of fatness in children depending on the trimester of pregnancy in which stress was examined.

Trimester	Number of articles* n (%)	Positive association* n (%)	Negative association* n (%)	Insignificant results* n (%)
I	12 (60%)	9 (75%)	1 (8%)	2 (17%)
II	16 (80%)	8 (50%)	3 (19%)	5 (31%)
III	15 (75%)	11 (74%)	2 (13%)	2 (13%)

Note: n – number of articles, * – n and % of all articles that include the trimester

of overweight in 1 (25%) and obesity also in 1 of the papers (50%). In this age group a link between stress and a decrease in fatness was found in 2 articles, 1 concerning adiposity and 1 waist circumference. No relationship was found between prenatal stress and higher WHtR (n = 1, 100%) and body weight (n = 1, 100%). Among children aged 8–12 years the BMI was measured in 3 articles, most of which confirmed a relationship between prenatal stress and increased BMI (n = 2, 67%), and 1 article showed the relationship with decreased BMI (33%). Among children aged 8–12 years all studies proved a positive association of prenatal stress with a risk of overweight (n = 3), obesity (n = 1), underweight (n = 1) and WHtR (n = 1). In the group of children over the age of 13 years all studies investigating the relationship between prenatal stress and BMI (n = 3), WHtR (n = 2) or overweight (n = 2) showed a positive relationship.

Controlling factors were taken into account in all the studies. In 14 articles (70%), separate analyses were performed between the body weight and modifying variables. In 17 articles (85%) the modifying variables were included in the model. The modifying variables that were included in the model most often were: birth weight (14, 82%), maternal smoking (12, 71%), parity (11, 65%), gender (11, 65%), parental education (9, 53%), maternal age (9, 53%), socioeconomic status (8, 47%), breastfeeding (8, 47%) gestational age (7, 41%), prepregnancy BMI (6, 35%), household income (4, 24%), ethnicity (4, 24%). Among the modifying variables that were included in separate analyses, the most common were: birth weight (11, 79%), smoking (7, 50%), socioeconomic status (6, 43%), parity (6, 43%), gestational age (5, 35%), maternal age (5, 35%), maternal BMI (4, 29%), breastfeeding (3, 21%), ethnicity (3, 21%), maternal education (3, 21%), birth length (3, 21%), weight gain (2, 14%), cohabitation status (2, 14%), household income (2, 14%), alcohol consumption (2, 14%), obstetric complication (2, 14%). Birth weight was significantly associated with the variables of body weight in 82% (9 out of 11), smoking in 43% (3 out of 7) of the articles analyzed, socioeconomic status and parity significantly influenced the variables in 33% (2 out of 6), maternal age in 80% (4 out of 5), gestational age in 20% (1 out of 5), maternal BMI 75% (3 out of 4) education, household income and ethnicity were related to body mass indices in 33% (1 out of 3), breastfeeding, birth length, weight gain, cohabitation status, alcohol consumption, maternal sleep habits, insurance status, cesarean section were not related to weight gain indices in children.

Discussion

The aim of the study was to assess the relationship between prenatal stress and risk of overweight and obesity in children. Most of the reviewed studies confirmed a positive relationship between prenatal stress and weight and body proportions in children. The risk of an increase in the levels of fatness indicators was confirmed in 65% and of a decrease in 15% of the articles. However, the results are vague not only because of the divergent confirmed relationships but also because in 20% of the analyzed studies no significant relationships were found at all.

The results of the review indicate that there are differences in the outcomes depending on the type of stress considered. The ambiguity of the results may derive from the specificity of each stressor. The study of objective stress concerns stressors to which no person can remain indifferent (King et al. 2012). Such stressors threaten the most basic needs, and it is difficult to prepare for them because they often come without any forecast (Madrid & Grant 2008). Moreover, they require adaptation to new conditions because under this type of stress not only the behaviour of an individual can change, but also some modifications in their environment may occur (Nagai et al. 2017; Mallett & Etzel 2018). Most of the works which took into account objective stress confirmed the relationship between this type of stress and increased values of fatness indexes (70%). In the case of subjective stress assessment, the relationship was not so clear because half of the studies confirmed the relationship of this type of stressor with an increase in body fat rates, while as many as 43% of the studies showed no relationship. Nevertheless, it is also worth noting that the reduction of fatness occurred almost three times more often after exposure to objective stress by a pregnant woman (20%) compared to the experience of subjective stress (7%). It is difficult to interpret this dependency since it is problematic to differentiate subjective stress from objective stress in general (Lazarus 1990).

The moment of exposure to stress during pregnancy was found to be important. The association of prenatal stress and fatness indicators was more visible when the mother's stress

occurred at the beginning or at the end of pregnancy (1st and 3rd trimester). Theoretically, it may seem that the earlier a stressor occurs during pregnancy (1st trimester), the longer it will affect the unborn child in prenatal life and enable the fetus to program changes in the metabolism for a longer time. This can lead to a catch-up growth and the development of overweight or obesity in postnatal life. The exposure to stress in the 3rd trimester may be significant since it is a critical period for the brain development because of the synapses formation (Rietman et al. 2016). Moreover, this period may be associated with an increase in the child's sensitivity to stress in the postnatal period. It can affect the child's stress coping strategy and lead to stress eating (St-Hilaire et al. 2015). Elevated cortisol levels associated with feeling of stress significantly increase the consumption of high-calorie food, potentially leading to overweight and obesity (Shearrer et al. 2016). Another critical development period is adipogenesis. It occurs in late fetal development and at the beginning of postnatal life (Kiess et al. 2008; Szabo 2019). That is why all the changes during these stages of life can program fetal metabolism and cause the development of overweight and obesity in later life (Entringer et al. 2010).

The results of the review show that depending on the age at which the child was examined, we receive different results. The results of the review indicate that prenatal stress may cause weight gain in children under 2 and in children over 10 years of age. However, when anthropometric indicators such as BMI, WHtR, waist circumference were assessed in children aged 2–10 years, the results were not conclusive. There were relationships between stress and overweight as well as underweight in children. A lower number of articles confirming the relationship of overweight or obesity in children aged 2–10 years can be explained by the fact that at this age physical activity is on a higher level than in older children (Corder et al. 2016) and there is a better parenting control over the children's food (Wojciechowska 2014). However, when it comes to children over 10 years, the results of our review and report of The National Center for Health Statistics (NCHS) are similar. The report revealed data on the youth aged 2–19 years showing that the older children were the more often obesity occurred (Hales et al. 2017). In the presented results obesity was most common in children over 12 years. Our review indicates that also the association of stress and excessive fatness is more visible in children over 10 years.

In the studies that showed the relationship between prenatal stress and weight loss in children, stress indicators were: exposure to violence during pregnancy, a family crisis, and other types of trauma. It is known that the violence experienced by a mother during pregnancy may contribute to very low birth weight of newborns, intrauterine growth retardation and preterm delivery (Bailey 2010). Violence in pregnancy creates a stressful, unpredictable and dangerous environment for a woman, which includes acute traumatic events, but also chronic exposure to adverse events (Maier & Seligman 2016). The violence to which a pregnant woman is exposed may be related to changes in stress-related behaviour, temperament and cause internalization and externalization behavior in children (Eriksson et al. 2003), which in later life may affect food-related behavior (Kaisari et al. 2017) and lead to overweight, obesity as well as underweight (Hanć & Cortese 2018). In our review, the mother's exposure to violence turned out to be related to underweight in children. This may be explained by the fact that violence against a pregnant woman most often occurs in low socioeconomic status population groups (Kaslow & Thompson 2008), which often goes along with incorrect changes in the diet of a pregnant mother (Darmon & Drewnowski 2008) and an improper diet in children (Dzielska et al. 2008).

While discussing the mechanisms linking prenatal stress with fatness in postnatal life, it should be noted that prenatal stress is a factor that can directly affect the fetus (Barker 2004). However, it can also lead to physiological programing effects which will become visible in the child's postnatal life (Szydełko et al. 2016). Under the influence of stress, the hypothalamic-pituitary-adrenal axis (HPA) and the sympathetic and parasympathetic nervous systems are activated (Geenen et al. 2006). Increased levels of cortisol in the mother's blood that occur under stress can have a negative effect on the fetus. Under physiological conditions, the fetus is protected from excess concentration of cortisol by 11β-Hydroxysteroid dehydrogenase (11BHSD2), which prevents 80–90% of cortisol from entering through the placenta barrier. However, in the situation where stress is severe or chronic 11BHSD2 may be blocked and cortisol in its active form gets into the blood of the fetus (Dahlerup et al. 2018), affecting the functioning of the child's HPA axis (Brennan et al. 2008) and the hormones regulating hunger and satiety mechanisms (Kłósek 2016). These changes increase the secretion of leptin and ghrelin. The secretion of leptin leads to satiety but if it is secreted in excess, leptin resistance develops and the feeling of satiety after a meal is restrained or completely eliminated (Korek & Krauss 2015). Increased ghrelin secretion with simultaneous leptin malfunction leads to an increased intake of food (Klok et al. 2007), which in turn leads to the development of obesity. In addition, elevated glucocorticosteroid levels increase fat deposition in adipocytes, mainly visceral fat (Wolf 2002).

The disturbance of glucocorticosteroid metabolism caused by chronic exposure to prenatal stress may be related to changes in glucocorticosteroids in a child in the postnatal life (Bertram & Hanson 2002; Fowden & Forhead 2004). Chronically elevated cortisol levels may also increase blood glucose levels in children (Khani & Tayek 2001). Prenatal stress was positively associated with insulin secretion (Dancause et al. 2013), and may lead to insulin resistance (Rizza et al. 1982; Nielsen et al. 2004). Insulin resistance may play a role in stimulating hunger signals by inhibiting the secretion of adiponectin (Yadav et al. 2013), which leads to the disappearance of its inhibitory effect on overeating

(Awofala et al. 2019)] increasing the risk of abnormal body weight (Nederkoorn et al. 2015).

The reason for more frequent occurrence of excessive body weight in children of mothers who were exposed to unfavorable life events during pregnancy may be the programming of the child's metabolism in a sparing mode, called 'thrifty phenotype' (Barker et al. 1993). Psychological stress may change the amount of food consumed by pregnant women (Lindsay et al. 2017). Psychological stress can be associated with reduced food intake (Wardle et al. 2000). The developing fetus of a mother who does not provide a proper amount of food adjusts her metabolism in order to conserve energy (Barker et al. 1993). After birth, when the environment is found to be rich in food, such babies are at an increased risk of faster weight gain (McLaughlin et al. 2020), which may predispose them to overweight and obesity (Monteiro & Victora 2005) or higher abdominal fat mass (Ong et al. 2000; Marcovecchio et al. 2020).

Another hypothesis that may clarify the relationship between prenatal stress and increased body weight in children is that a pregnant woman experiencing high stress, trauma, anxiety may change mentally after childbirth, which can affect her offspring. Stress in pregnancy may have an impact on an interaction with the child and the style of parenting, thus shaping the child's habits in later life (Braungart-Rieker et al. 2016; Grazuleviciene et al. 2017).

The strength of the study is the careful selection of studies that met all criteria for inclusion in the review. We paid attention to the prenatal stress effects on the development in childhood, the variability of stress and body size measurements, the moment of the occurrence of the stressor in the prenatal period and the moment of anthropometric examination in the offspring. We found that despite the differences in methods, most studies confirm the relationship between prenatal stress and the increase in adipose indicators in children. Although the methods used in studies modulated the results. Nevertheless, what we consider to be a strength of the review may, on the other hand, be understood as a weakness. The review includes only 20 articles, but these are all available articles that could be included, as only they met all the inclusion criteria for the study. It was possible to increase the number of works under review by adding articles about adults, but, for the clarity of the paper, we chose to focus only on the progressive phase of ontogenesis. However, the discussion was expanded to include data from the study of adults. The studies presented in the review vary in different ways, which is why it is difficult to compare all of their aspects. Although it is inevitable to present different stress factors for pregnant women, the review results would be clearer if the same validated questionnaires had been used in all studies and thus the presence of stress would be assessed in the same way. The use of a questionnaire designed especially for each survey makes it more complicated and specific to compare the outcomes. In addition, it is currently believed that the most objective indicator of the level of stress is the concentration of cortisol. Our review also showed this, because all the studies examining the effect of elevated glucocorticosteroids in pregnancy on the parameters of body weight in children turned out to be statistically significant. However, it was not a standard procedure in case of reviewed papers. Different methods of children's weight and body composition assessment were applied. Most research results were based on the analysis of measurements of height, weight, waist and hip circumferences. The inclusion of a body composition analysis may constitute an additional value giving the information on fat content and its distribution in the abdominal area. Another aspect which might appear to be problematic in case of the comparison of the research results is the fact that it is impossible to separate the stress effects from the other aspects of pregnant women's live. The size and fatness of children are also associated with socioeconomic conditions, the mother's body weight (Bellver & Mariani 2019) and her behaviour during pregnancy, e.g. smoking. Although in most studies they were checked, it is impossible to prove how much each of the factors influenced the children's weight and body composition. In our review, we took into account a wide age range of the examined children. It is difficult to draw conclusions on the entire offspring group, but we tried to make comparisons possible by dividing the children into age categories < 2 years, 2–7 years, 8–12 years and > 13 years.

Conclusions

Most of the reviewed studies showed that the stress in pregnancy is related to the children adiposity in postnatal life. However, the studies that measured objective stressors gave more consistent findings. It may suggest that a subjective perception of stressors doesn't always correspond with the strength of their influence at the biological level.

Adiposity rate in children was increased the most frequently among children affected by stress in the 1st or 3rd trimester of pregnancy, and the increase in fatness indicators was more evident in children under 2 and over 10 years of age. Nevertheless, the effects of the stressor in different stages of pregnancy and the age at which a child is most sensitive to adverse changes in anthropological parameters should be explored more in-depth in future research.

Although there are hypotheses on the mechanisms linking the prenatal stress and later body fatness, they need to be confirmed. The assessment of the impact of the interactions of prenatal stress and environmental factors, potentially associated with overweight and obesity in children, may also be an interesting direction for further studies.

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None.

Ethical standards
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Publikacja II

Ewa Bryl, Tomasz Hanć, Paula Szcześniewska, Agata Dutkiewicz, Monika Dmitrzak-Węglarz, Agnieszka Słopień, A.

"The relation between prenatal stress, overweight and obesity in children diagnosed according to BMI and percentage fat tissue"

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ORIGINAL ARTICLE

The relation between prenatal stress, overweight and obesity in children diagnosed according to BMI and percentage fat tissue

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Abstract

Background One of the environmental factors contributing to abnormal weight changes in children may be maternal exposure to adverse environmental factors during pregnancy, which in previous studies led to inconclusive results showing both overweight or obesity and underweight in children. The aim of the study was to assess the influence of prenatal stress on the BMI status and cut-off points for the percentage of fat content.

Methods The cohort study included 254 girls and 276 boys. Information on prenatal stress was collected retrospectively with a questionnaire on objective adverse events completed by a parent/guardian of a 6–12-year-old child. We examined the body weight of children and performed an electrical bioimpedance analysis of their body composition. We assessed the BMI status according to the International Obesity Task Force (IOTF) criterion and on the basis of body fat according to McCarthy criterion.

Results The results of our study show that the prenatal stress was related to increased risk of overweight (OR 2.14, 95% CI: 1.25–3.65) diagnosed on the basis of body fat cut-off points, but not when the BMI was a diagnostic criterion (OR 1.03, 95% CI: 0.58–1.83).

Conclusion The method of diagnosis based on the fat content appears to be an indicator of the occurrence of abnormalities in body composition due to prenatal stress more sensitive than that based on the BMI.

Level of evidence Level III evidence obtained from well-designed cohort or case–control analytic studies.

Keywords Prenatal stress · Overweight · BMI · Fat tissue · Children

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Purpose

Excessive body weight in children adversely affects their development and health. It is associated with the risk of developing type 1 [1, 2] and 2 diabetes [3], but also leads to an increase in total cholesterol [4, 5], triglycerides [5] and blood pressure [4–6] and increases the risk of atherosclerosis [7], non-alcoholic fatty liver disease [8] and metabolic syndrome [9]. Excessive body weight is also frequent comorbidity of the mental health problems such as depression [10, 11] and ADHD [12]. It is known that factors like too high energy supply, too little physical activity or a diet rich in simple sugars and saturated fatty acids increase the risk of overweight and obesity in children [13]. The results of some studies indicate that nutritional awareness is not significantly related to BMI, which means that the knowledge of the principles of proper nutrition is not sufficient in the effective prevention of overweight and obesity [14, 15]. The very knowledge of

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nutrition does not limit the scale of the phenomenon. It is quite the opposite; the trend is increasing. The prevalence of overweight and obesity in the world was 4% in 1975 and in 2016 the excessive weight was found to be 18% [16]. Thus, it is crucial for further studies to search the causes and factors modifying the development of overweight and obesity.

Previous research shows that not only postnatal life, but also the environment in intrauterine life affects the child's body weight [17, 18]. Adverse factors experienced by the mother during pregnancy may have a programming effect on the fetal metabolism, and affect changes in the body weight and proportions in the later life [19]. Prenatal stress deserves special attention in the context of obesity research. Unfavorable life experiences during pregnancy and psychological stress can be factors that significantly shape the development of the fetus. It is most detrimental to the developing fetus when the mother experiences extreme stress or when the stress she experiences is chronic. Exposure to these conditions may cause cortisol secretion released from the mother's body in response to stress, which may enter the bloodstream of the fetus [20]. Exposure to increased levels of cortisol in utero has a negative influence on the developing organism. Exposure to stress early in life shapes permanently the activity of the hypothalamic–pituitary–adrenocortical (HPA) axis and the brain. It is so because of epigenetic changes related to methylation of the HPA axis genes [21, 22]. Exposure to a higher concentration of cortisol in the amniotic fluid promotes an increased concentration of cortisol in the postnatal life, even before the onset of the stressor, and an altered response to stress [23]. Elevated cortisol in utero promotes the development of arterial hypertension, type 2 diabetes and metabolic syndrome in adulthood [24]. It is also possible that it affects the hormones that regulate the reading of hunger and satiety or it is associated with leptin resistance which may be involved in the pathogenesis of programming-induced obesity and metabolic disorders [25]. Prenatal stress is also a factor that might be associated with the occurrence of eating disorders, those related to both the restriction of food intake and overconsumption [26]. Most studies focus on the effects of prenatal stressors on adult health [27, 28]. Studies in the group of children do not provide fully unambiguous results showing how the mother's experience of an unfavorable life events during pregnancy affects the body weight of the offspring. Previous research has shown that stressors such as parting with the biological father during pregnancy [29] or difficulties caused by a snowstorm may be related to obesity [30, 31]. If prenatal stress is an important risk factor, preventive and therapeutic interventions to reduce stress during pregnancy could actually reduce the risk of obesity and its health complications in the offspring. Nevertheless, the results of previous studies are inconclusive and there are also studies that do not confirm the relationship [32, 33]. Thus, the problem requires further research.

The most commonly studied anthropometric indicator of excessive weight among children is Body Mass Index (BMI), which is used on a large scale because the examination is easy, quick, and requires no specialized equipment. However, BMI is not an ideal fatness indicator [34, 35]. While assessing body weight based on BMI, it is possible to overestimate the risk of excessive body weight in children who have high lean body mass [36, 37]. On the other hand, it is possible to underestimate the risk in children who, despite their relatively low body weight, have a high fat content dangerous to health [38]. The lack of unambiguous results regarding the relationship of prenatal stress with the occurrence of overweight and obesity may partly result from the use of BMI [29–33, 39–46] that is difficult to interpret in research, while the level of adipose tissue in this context has rarely been studied [47–50].

In this study, we have tested the hypothesis that children of mothers who experienced stress during pregnancy have an increased risk of obesity. As indicators we use BMI and the percentage of body fat measured with bioimpedance method.

Materials and methods

The study was conducted in 11 schools randomly selected from 128 primary schools in Poznań, Poland. The study was conducted between March 2017 and November 2019. The cohort study included 254 girls and 276 boys. At that time, 36,000 children attended schools in Poznań. The study was funded by the National Science Centre, Poland, grant number: 2016/21/B/NZ5/00492 and approved by the Institutional Bioethics Board of Poznan University of Medical Sciences (approval no. 542/14). The subjects and their legal guardians were fully informed about the research procedures and the legal guardians gave written consents to participate in the study. The data on prenatal maternal stress, body composition measurements as well as socioeconomic (SES) factors were collected for each child. Children from 6 to 12 years were examined.

Maternal psychological stress

The parents or guardians of a 6–12-year-old child were asked if there were any adverse stressful events during the pregnancy. The questionnaire included questions about the subjective perception of stress related to objectively occurring problems like 1. difficult financial situation, 2. family problems, 3. illness or death of a family member, 4. abnormalities occurring during pregnancy, 5. another type of stressors.

Anthropometric measurements in children

Body height was measured with the anthropometer Seca 213, with measurement accuracy of ± 1 mm. Body weight was measured with the use of TANITA MC-780 MA S multi frequency segmental body composition analyzer with measurement accuracy of 100 g. TANITA MC-780 MA S was also applied for body composition assessment. During the body weight measurements and body composition analyses, the examined children were in light clothes, did not wear outerwear, and before the examination they were asked to wear as little clothing as possible—no more than a T-shirt and trousers or a skirt. The children were barefoot, and the examiners checked the correct positioning of the feet on the electrodes and the correct grip of the electrodes. The children were measured between 8 a.m. and 2 p. m. in the nurse's offices in their schools by trained medical personnel. In our study, food consumption and exercise were not checked prior to the body composition analysis. However, as shown in previous studies, the effect of a meal on the analysis result was not clinically significant [51].

Body Mass Index (BMI, kg/m^2) was calculated as body weight (kg) divided by square height (m2). BMI was adjusted for sex and age on the basis of World Health Organization (WHO) growth charts [52] with the use of WHO AnthroPlus software and presented as z scores. Overweight, obesity and underweight were diagnosed under the guidance of the International Obesity Task Force (IOTF) [53, 54] and based on body fat cut-off points for the bioimpedance method [55]. The criteria were developed by experts from the International Obesity Task Force and are based on centile curves that passed through BMI cut-off points of 17, 25, and 30 kg/m^2 for underweight, overweight and obesity respectively at the age of 18. The McCarthy criteria are based on percentile curves where the cut-off points for underweight, overweight and obesity are set at the 2nd, 85th, and 95th percentiles for percent body fat.

Controlled factors

The following data related to the socio-demographic characteristics of the sample, maternal pre-pregnancy fatness and birth weight were checked in the study:

Economic status—assessment of meeting needs of the family (possible answers: low / rather low / not very low / quite high / high).

Place of residence (possible answers: village / city up to 1,000 inhabitants / city of 10–50 thousand inhabitants / city of 50–100 thousand inhabitants / city of 100–500 thousand inhabitants / city of over 500 thousand inhabitants).

Maternal and paternal education level (possible answers: basic / vocational / secondary / high).

BMI before pregnancy calculated according to the World Health Organization standards [16]; the mothers were divided into 4 groups based on their BMI (underweight with a BMI below 18.5 kg/m^2 / normal weight BMI 18.5–24.9 kg/m^2 / overweight BMI 25–29.9 kg/m^2 / obesity BMI over 30 kg/m^2).

Birth weight—we divided the children into 3 categories: < 2500 g, 2500–4000 g and > 4000 g.

The choice of control variables was preceded by the results of previous studies in which factors such as economic status [56], place of residence [57], parent's educational level [58], maternal BMI before pregnancy [59] and birth weight [60] had an impact on the risk of developing underweight, overweight or obesity in children.

Statistical analysis

To evaluate the prevalence of underweight, overweight and obesity diagnosed according to IOTF references and their association with sex, age, place of residence, meeting the financial needs of the family, maternal BMI before pregnancy and the mother's and father's education χ^2 test was used. The same procedure was performed to evaluate the prevalence of underweight, overweight and obesity diagnosed according to body fat cut-off points and their association with sex, age, place of residence, meeting the financial needs of the family, maternal BMI before pregnancy and the mother's and father's education.

The size and significance of the effects of prenatal stress (occurrence vs no) on underweight (1-underweight vs. 0-the rest), overweight (1-overweight vs. 0-the rest), obesity (1-obesity vs. 0-the rest) diagnosed according to BMI and diagnosed according to fat tissue content were assessed in logistic regression. Two sets of models were tested: the unadjusted one and the adjusted one for sex, age, socioeconomic variables (the parents' education level and parental subjective assessment of socioeconomic situation of the family) and pre-pregnancy maternal BMI. Regression models were also constructed separately for the boys and girls. All the tests were performed with the Statistica (Version 13.3) software and considered to be statistically significant at $p < 0.05$.

Results

The selection procedure

The sample included 553 children aged 6–12 (mean = 8.97, SD = 1.28) in comparable proportion of boys (52.23%) and girls (47.76%). The written consent for the research was submitted by 553 children. Incomplete information on prenatal stress was the reason for excluding 10 participants

and 13 others were excluded from the analysis because of incomplete information on bioimpedance analysis. Among the participants who were not included in the study, there were equal number of boys and girls. The final study group consisted of 530 children. Although in several cases the parents did not answer the questions about the size of place of residence ($n=25$, 4.71%), assessment of meeting financial needs ($n=21$, 3.96%), maternal pre-pregnancy BMI ($n=17$, 3.21%), the parents' level of education (mothers' education: $n=10$, 1.88% or fathers' education: ($n=29$, 5.47%), they were not excluded from the sample. The regression analysis of the models adjusted for the variables was limited to the cases with complete data ($n=459$, 86.60% of the sample). The basic characteristics of the sample are presented in Table 1.

Occurrence of stress in the study group

One hundred and fifty-eight (30%) out of 530 children were exposed to at least one type of the stressors in prenatal life. One type of prenatal stressors was experienced by 131 (21%), two types by 50 children (9%) and three types by 19 children (3%). The most frequently experienced type of stressors during pregnancy was family problems ($n=77$, 14%) and the fear of the possible occurrence of abnormalities in the child ($n=46$, 9%) (Table 1).

Sex and age differences in prenatal stress and body weight status

There were no differences between boys and girls in the occurrence of underweight, overweight and obesity diagnosed according to IOTF (Table 2). The significant differences between sexes were found when the body fat cut offs have been applied for the identification of individuals with underweight, normal weight, overweight and obesity ($\chi^2=14.438$, $p=0.0024$). Overweight (16%) and obesity (20%) were more common in the boys (21%, 22%) than the girls (11%, 18%). The analyses do not indicate the existence of significant differences in the occurrence of underweight, overweight and obesity diagnosed on the basis of BMI between particular age groups (< 9, 9–10 and > 10 years- old). The significant differences between age groups were found when the body fat cut offs have been applied for the identification of individuals with underweight, normal weight, overweight and obesity ($\chi^2=18.851$, $p=0.004$). Obesity diagnosed according to body fat cut-off points was more common among children under 9 years old (23%) and between 9 and 10 years old (20%) than children over 10 years old (12%, Table 3).

Associations of socioeconomic factors and mothers' pre-pregnancy weight with the prevalence of improper body mass

The analysis of the relation between socioeconomic factors and underweight, overweight or obesity diagnosed on the basis of BMI showed a significant relationship with the mother's BMI before pregnancy ($\chi^2=53.643$, $p<0.001$), the mother's education ($\chi^2=31.038$, $p=0.002$) and the father's education ($\chi^2=22.673$, 0.006). The children of the mothers overweight before pregnancy were more often obese (18%) than the children of the mothers with normal body weight before pregnancy (4%, $\chi^2=22.520$, $p<0.001$). The mothers who were obese before pregnancy had more often children who were overweight (50%) than the mothers with normal weight (14.32%, $\chi^2=14.497$, $p=0.002$). The children of the mothers with the higher education level were less often obese (2%) than the children of the mothers with vocational education level (17%, $\chi^2=26.92$, $p<0.001$). The fathers with higher education level were less likely to have children overweight (12%, $\chi^2=9.918$, $p=0.019$) or obese (2%, $\chi^2=10.40$, $p=0.015$) than the fathers with a vocational education level (29%, 9%). Obesity was observed more frequently (40%, $\chi^2=16.154$, $p=0.02$) in the children whose parents declared great difficulties in meeting the financial needs of their families than in the children of the parents who did not declare difficulties (5%). The place of residence was not significantly associated with the frequency of abnormalities in body weight categories (Table 4).

The analysis of the relation between socioeconomic factors and underweight, overweight and obesity diagnosed on the basis of body fat cut-off points showed a significant relationship with the mother's BMI before pregnancy, the mother's education and prenatal stress. Overweight (43%) was the most common in children of the mothers who were obese before pregnancy ($\chi^2=8.095$, $p=0.044$) (Table 5). The children of the mothers who had high education level were less likely obese (17%) than the mothers who had vocational education (31%, $\chi^2=7.882$, $p=0.048$). The children of the mothers who experienced stress during pregnancy were more often overweight (22%) than the children of the mothers who did not experience stress during pregnancy (14%, $\chi^2=4.273$, $p=0.038$).

Effects of birth weight on weight status

Underweight (32%) diagnosed on the basis of BMI was most common in children with birth weight less than 2500 g ($\chi^2=12{,}271$, $p=0.002$) than in children with birth weight between 2500–4000 g (10%) (Table 4). Birth weight was not associated with changes in body weight status diagnosed by body fat content (Table 5).

Table 1 Characteristics of the group

Variable	The information available for	Category	*N*	%
Age	530	< 9 years old	294	55
		9–10 years old	120	23
		> 10 years old	116	22
Sex	530	Girls	254	48
		Boys	276	52
Place of residence	505	Village	42	8
		City of up to 10 thousand residents	3	1
		City of 10 thousand up to 50 thousand residents	43	8
		City of 50 thousand up to 100 thousand residents	17	3
		City of 100 thousand up to 500 thousand residents	37	7
		City of over 500 thousand residents	363	69
Economic status – assessment of meeting needs	509	Low	5	1
		Rather low	14	3
		Not very low	90	17
		Quite high	235	44
		High	165	31
Maternal pre-pregnancy BMI	513	Underweight	51	10
		Normal weight	391	74
		Overweight	57	11
		Obesity	14	3
Mother's education level	520	Primary	5	1
		Vocational	52	10
		Secondary	121	23
		High	342	65
Father's education level	501	Primary	15	3
		Vocational	93	18
		Secondary	146	28
		High	247	47
The number of experienced prenatal stressors	530	1 type of stressors	131	21
		2 types of stressors	50	9
		3 types of prenatal stressors	19	3
Birth weight	526	< 2500 g	22	4
		2500–4000 g	433	78
		> 4000 g	71	13
The types of stressors	530	Financial problems	29	5
		Family problems	77	14
		Disease or death of a close relative	29	5
		Abnormalities during pregnancy	46	9
		Another	30	6
BMI status	530	Underweight	56	11
		Normal weight	366	69
		Overweight	80	15
		Obesity	28	5
Adiposity status	530	Underweight	2	0.4
		Normal weight	335	63.2
		Overweight	87	16.4
		Obesity	106	20

N number of individuals, %, percent, *BMI* Body Mass Index, BMI status diagnosis of the correctness of the body weight on the basis of BMI, adiposity status, diagnosis of the correctness of the body weight on the basis of fat tissue

Table 2 Prevalence of underweight, overweight and obesity diagnosed according to IOTF references in the group of children divided according to sex and age ($\chi 2$)

	Underweight		Normal weight		Overweight		Obesity		χ^2, p
	n	%	*N*	%	*n*	%	*n*	%	
Total	56	11	366	69	80	15	28	5	6.765, 0.08
Boys	21	8	195	71	47	17	13	5	
Girls	35	14	171	67	33	13	15	6	
< 9-year- olds)	35	12	205	70	39	13	15	5	2.967, 0.814
9–10-year- olds	11	9	80	67	22	18	7	6	
> 10-year- olds	10	9	81	70	19	16	6	5	

N number of individuals, %, percent, χ^2 chi-squared test result, *p* significance level

Table 3 Prevalence of underweight, overweight and obesity diagnosed according to body fat cut-off points in the group of children divided according to sex and age ($\chi 2$)

	Underweight		Normal weight		Overweight		Obesity		χ^2, *p*
	n	%	*n*	%	*n*	%	*N*	%	
Total (533)	2	0.3	335	63	87	16	106	20	
Boys (*n* = 278)	1	0.3	155	56	59	21	61	22	14.438, 0.002
Girls (*n* = 255)	1	0.0	180	71	28	11	45	18	
< 9-year- olds (*n* = 296)	0	0	170	58	56	19	68	23	18.851, 0.004
9–10-year- olds (*n* = 121)	0	0	83	69	13	11	24	20	
> 10-year- olds (*n* = 116)	2	2	82	71	18	16	14	12	

N number of individuals, %, percent, χ^2 chi-squared test result, *p* significance level

Effects of prenatal stress on weight status

The unadjusted logistic regression analysis did not reveal any associations of prenatal stress (≥ 1 type vs 0) with underweight (OR = 0.94, 95% CI: 0.50–1.72), overweight (OR = 1.01, 95% CI: 0.58–1.75) and obesity (OR = 0.94, 95% CI: 0.4–2.21) diagnosed according to IOTF. The analyses adjusted for other variables gave similarly non-significant results for underweight (OR = 1.04, 95% CI: 0.52–2.07), overweight (OR = 1.04, 95% CI: 0.58–1.84) and obesity (OR = 0.84, 95% CI: 0.30–2.29). In separate analyses of the group of the boys and the group of the girls the relations between prenatal stress and status BMI were also statistically non-significant (Table 6). However, the unadjusted logistic regression analysis revealed associations of prenatal stress (≥ 1 vs 0) with overweight (OR = 1.65, 95%CI: 1.02–2.66) diagnosed according to body fat cut-off points. This result was confirmed in the analyses adjusted for other variables (OR = 2.14, 95%CI: 1.25–3.66). The unadjusted logistic regression analysis did not reveal associations of prenatal stress and underweight (OR = 2,36, 95% CI: 0.15–38.27) or obesity (OR = 1.21, 95% CI: 0.76–1.9) diagnosed by body fat. The analyses adjusted for other variables gave non-significant results for obesity (OR = 1.14, 95% CI: 0.68–1.91) diagnosed by body fat cut-off points. A separate analysis in the group of boys, adjusted for other variables, confirmed the association of prenatal stress and overweight (OR = 2.42, 95% CI: 1.20–4.89) whereas, in a separate analysis for the girls the results were not statistically significant (Table 7).

Discussion

The use of BMI is the easiest, quickest and cheapest method of the assessment of overweight and obesity. Unfortunately, BMI is not an indicator that perfectly reflects changes in the body proportions. In adult studies obesity assessment based on BMI ≥ 30 kg/m^2 does not include even more than half of the people with excessive body fat [61]. The excess of adipose tissue contributes to the development of diseases such as diabetes [62], hypertension [62, 63] or cancers, e.g. colorectal cancer [64] and breast cancer [65]. To avoid underestimating the number of children with excessive fat tissue the use of standards based on body fat cut-off points for overweight seems to be the solution of diagnosing adiposity more accurately than with use of BMI [38]. We can assume that thanks to the use of standards based on body fat cut-off points for overweight we may be able to identify the children with abnormal body composition changes potentially dangerous to their health, which have not yet caused any important increase in the BMI. By applying these standards we may be able to avoid incorrect underdiagnosis of overweight and obesity in children [66] and intervene by introducing appropriate nutritional management sooner.

Table 4 Characteristics of socioeconomic environment of the studied groups of children and associations between these factors and the prevalence of underweight and overweight diagnosed according to IOTF ($\chi 2$)

	Underweight		Normal weight		Overweight		Obesity		χ^2, p
	n	%	*n*	%	*n*	%	*n*	%	
Place of residence									
Village	8	19.05	29	69.05	4	9.52	1	2.38	22.685, 0.091
City of up to 10 thousand residents	0	0	1	33.3	2	66.67	0	0	
City of 10 thousand up to 50 thousand residents	2	4.65	32	74.42	7	16.28	2	4.65	
City of 50 thousand up to 100 thousand residents	2	11.76	10	58.82	2	11.76	3	17.65	
City of 100 thousand up to 500 thousand residents	5	13.51	21	56.76	7	18.92	4	10.81	
City of over 500 thousand residents	37	10.19	259	71.35	51	14.05	16	4.41	
χ^2, p*	5.496, 0.358		6.69, 0.244		8.299, 0.140		9.118, 0.104		
Economic status – assessment of meeting needs									
Low	0	0	2	40	1	20	2	40	19.732, 0.072
Rather low	1	7.14	10	71.43	3	21.43	0	0	
Not very low	11	12.22	55	61.11	16	17.78	8	8.89	
Quite high	26	11.06	165	70.21	35	14.89	9	3.83	
High	18	10.91	119	72.12	20	12.12	8	4.85	
χ^2, p*	0.970, 0.914		5.531, 0.237		2.174, 0.707		16.154, 0.002		
Maternal pre-pregnancy BMI									
Underweight	14	27.45	29	56.86	8	15.69	0	0	53.643, < 0.001
Normal weight	39	9.97	281	71.87	56	14.32	15	3.84	
Overweight	2	3.51	39	68.42	6	10.53	10	17.54	
Obesity	1	7.14	5	35.71	7	50	1	7.14	
χ^2, p*	18.116, < 0.001		12.276, 0.006		14.497, 0.002		22,520, < 0.001		
Mother educational level									
Primary	0	0	3	60	1	20	1	20	31.038, < 0.001
Vocational	3	5.77	30	57.69	10	19.23	9	17.31	
Secondary	15	12.40	76	62.81	20	16.53	10	8.26	
High	36	10.53	250	73.10	49	14.33	7	2.05	
χ^2, p*	2,303, 0,511		8.157, 0.0428		1.088, 0.779		26.92, < 0.001		
Father educational level									
Primary	1	6.67	10	66.67	2	13.33	2	13.33	22.673, 0.006
Vocational	7	7.53	54	58.06	24	28.81	8	8.60	
Secondary	13	8.90	102	69.86	21	14.38	10	6.85	
High	30	12.15	182	73.68	30	12.15	5	2.02	
χ^2, p*	2.222, 0.527		7.837, 0.049		9.918, 0.019		10.40, 0.015		
Birth weight									

Table 4 (continued)

	Underweight		Normal weight		Overweight		Obesity		χ^2, p
	n	%	*n*	%	*n*	%	*n*	%	
< 2500 g	7	31.82	11	50.00	2	9.09	2	9.09	15.300, 0.02
2500–4000 g	45	10.39	304	70.21	63	14.55	21	4.85	
> 4000 g	4	5.63	48	67.61	15	21.13	4	5.63	
χ^2, p*	12.271, 0.002		4.074, 0.130		2.71, 0.256		0.816, 0.665		
Prenatal stress									
No	40	10.75	256	68.82	56	15.5	20	5.38	0.073, 0.994
Yes	16	10.13	110	69.62	24	15.19	8	5.06	
χ^2, p*	0.046, 0.830		0.033, 0.854		0.001, 0.968		0.022, 0.882		

N number of individuals, %, percent, χ^2 chi-squared test result, *p* significance level, *BMI* Body Mass Index

*$\chi 2$ tests results for each body weight category (underweight, normal weight, overweight and obesity) compared to the rest of the studied group

The results of previous work are inconsistent. Some of them confirmed the relationship between prenatal stress and overweight [46] or obesity [31], but others demonstrated the relationship between prenatal stress and underweight in children [67]. We did not find the relation of prenatal stress with underweight in our research, and the results of the analysis of the association of prenatal stress and adiposity depended on the overweight and obesity assessment method. However, the results of our study do show that the prenatal stress was related to increased risk of overweight (OR 2.14, 95% CI: 1.25–3.66) diagnosed on the basis of body fat cut-off points, but not when the BMI was a diagnostic criterion (OR 1.04, 95% CI: 0.58–1.84). These discrepancies are in line with the fact that BMI-based diagnosing of body weight status turns out to be underestimated in other studies. A Mexican study of 1061 girls and 1121 boys aged 3–17 years in which the bioimpedance method was performed and diagnosis of overweight and obesity was also made according to fat tissue, found a two-fold lower incidence of overweight in children when weight status was diagnosed on the basis of BMI compared to body fat [38]. The results were confirmed in a meta-analysis, in which the diagnosis of obesity based on BMI failed to show half of the people with an increased content of adipose tissue [66]. The above-mentioned studies show that the diagnosis of overweight on the basis of BMI often underestimates the number of people with abnormal body composition, and the results of our study give us the basis to conclude that prenatal stress can be considered a risk factor for the development of excessive body fat and subsequent obesity, even if the influence of stress on BMI is non-significant in children 6–12 years of age.

According to our knowledge, criteria for assessing underweight, overweight and obesity based on the cut-off points for percent body fat have not yet been used in any of the previous studies on prenatal stress. The most frequently used criterion was the IOTF [29, 31, 33, 39, 43, 45, 68] or CDC [41], both of which are based on BMI. If a study referred to a body composition, the percentage of adipose tissue [47, 50] or FMI [48, 49] were assessed. As in the case of our study, the results of studies focusing on the content of adipose tissue mostly indicate a relationship between prenatal stress and an increase in the amount of adipose tissue in children [47, 69]. Only one study showed that increased prenatal stress was associated with decrease in body fat in children [50].

Some inconsistent results of the previous research may also be caused by different methods of assessing prenatal stress. In most of the studies prenatal stress was examined during pregnancy and after a few years the anthropometric indicators in children were checked [31, 39, 48, 69]. However, there were also studies based on the survey filled in by the parents/caregivers retrospectively [33] which may have resulted in not remembering adverse life events that had

Table 5 Characteristics of socioeconomic environment of the studied group of children and associations between these factors and the prevalence of underweight and overweight diagnosed according to body fat cut-off points (χ2)

	Underweight		Normal weight		Overweight		Obesity		χ^2, p
	n	%	*n*	%	*n*	%	*N*	%	
Place of residence									
Village	0	0	25	59.52	5	11.90	12	28.57	21.644, 0.117
City of up to 10 thousand residents	0	0	1	33.33	1	33.33	1	33.33	
City of 10 thousand up to 50 thousand residents	0	0	32	74.42	5	11.63	6	13.95	
City of 50 thousand up to 100 thousand residents	1	5.88	9	52.94	2	11.76	5	29.41	
City of 100 thousand up to 500 thousand residents	0	0	21	56.76	7	18.92	9	24.32	
City of over 500 thousand residents	1	0.28	231	63.64	63	17.36	68	18.73	
χ^2, p*	13.602, 0.018		5.179, 0.394		2.634, 0.756		4.982, 0.418		
Economic status – assessment of meeting needs									
Low	0	0	3	60	0	0	2	40	10.018, 0.614
Rather low	0	0	10	71.43	1	7.14	3	21.43	
Not very low	1	1.11	52	57.78	18	20.00	19	21.11	
Quite high	1	0.43	162	68.94	32	13.62	42	17.02	
High	0	0	99	60	30	18.18	36	21.82	
χ^2, p*	1.918, 0.750		5.516, 0.238		4.434, 0.350		2.281, 0.560		
Maternal pre-pregnancy BMI									
Underweight	2	3.92	31	60.78	6	11.76	12	23.53	36.830,< 0.001
Normal weight	0	0	260	66.50	62	15.86	69	17.65	
Overweight	0	0	33	56.90	10	17.54	14	25.56	
Obesity	0	0	2	14.29	6	42.86	6	42.86	
$\chi 2$, p*	18.188, <0.001		17.088, 0.001		8.095, 0.044		7.115, 0.06		
Mother educational level									
Primary	0	0	3	60	1	20	1	20	10.815, 0.288
Vocational	0	0	27	51.92	9	17.31	16	30.77	
Secondary	1	0.83	76	62.81	14	11.57	30	24.79	
High	1	0.29	222	64.91	62	18.13	57	16.67	
χ^2, p*	0.912, 0.822		3.296, 0.348		2.855, 0.414		7.882, 0.048		
Father educational level									
Primary	0	0	10	66.67	1	6.67	4	26.67	7.344, 0.601
Vocational	0	0	55	59.14	15	16.13	23	24.73	
Secondary	0	0	90	61.64	22	15.07	34	23.29	
High	1	0.40	163	65.99	44	17.81	39	15.79	
χ^2, p*	1.030, 0.793		1.705, 0.635		1.592, 0.661		5.448, 0.141		
Birth weight									

Table 5 (continued)

	Underweight		Normal weight		Overweight		Obesity		χ^2, p
	n	%	*n*	%	*n*	%	*N*	%	
< 2500 g	0	0	17	77.27	2	9.09	3	13.64	2.657, 0.851
2500–4000 g	2	0.46	272	62.82	73	16.86	86	19.86	
> 4000 g	0	0	43	60.56	12	16.90	16	22.54	
χ^2, p*	0.431, 0.806		2.109, 0.348		0.923, 0.630		0.850, 0.654		
Prenatal stress									
No	1	0.27	247	66.40	53	14.25	71	19.09	6.49, 0.089
Yes	1	10.63	88	55.70	34	21.52	35	22.15	
χ^2, p*	0.391, 0.531		5.461, 0.019		4.273, 0.038		0.651, 0.419		

N number of individuals, % percent, χ^2 chi-squared test result, *p* significance level, *BMI* Body Mass Index

*χ^2 tests results for each body weight category (underweight, normal weight, overweight and obesity) compared to the rest of the studied group

Table 6 Logistic regression models for effects of prenatal stress on underweight, overweight and obesity diagnosed according to IOTF

Body weight abnormalities (based on IOTF criteria)												
	Total				Boys				Girls			
	OR	95% CI	Wald Chi2	*p*	OR	95% CI	Wald Chi2	*p*	OR	95% CI	Wald Chi2	*p*
Models for underweight determination												
1 Prenatal stress (1-yes, 0-no) unadjusted	0.94	0.50–1.72	0.045	0.830	0.89	0.33–2.39	0.052	0.818	0.99	0.37–2.61	< 0.001	0.984
2 Prenatal stress adjusted*	1.04	0.52–2.07	0.013	0.910	1.00	0.37–2.73	< 0.001	0.994	1.08	0.43–2.75	0.028	0.868
Models for overweight determination												
1 Prenatal stress (1-yes, 0-no) unadjusted	1.01	0.58–1.75	0.001	0.969	1.2	0.61–2.34	0.279	0.597	0.77	0.33–1.8	0.372	0.541
2 Prenatal stress adjusted*	1.04	0.58–1.84	0.014	0.904	1.63	0.74–3.59	1.478	0.224	0.73	0.28–1.89	0.424	0.515
Models for obesity determination												
1 Prenatal stress (1-yes, 0-no) unadjusted	0.94	0.4–2.21	0.021	0.884	0.39	0.08–1.83	1.420	0.232	1.71	0.58–5.01	0.967	0.325
2 Prenatal stress adjusted*	0.84	0.30–2.29	0.122	0.727	1.63	0.74–3.59	1.48	0.22	1.59	0.45–6.64	0.516	0.472

OR odds ratio, *CI* confidence intervals, *p* significance level

*Adjusted for age, sex, place of residence, maternal pre-pregnancy BMI, parental assessment of income, parental education, birth weight

Table 7 Logistic regression models for effects of prenatal stress on underweight, overweight and obesity diagnosed according to body fat cut-off points

Body fat abnormalities (McCarthy et al. criteria)												
		Total				Boys				Girls			
		OR	95% CI	Wald Chi^2	*p*	OR	95% CI	Wald Chi^2	*p*	OR	95% CI	Wald Chi^2	*p*
Models for underweight determination													
1	Prenatal stress (1-yes, 0-no) unadjusted	2.36	0.15–38.27	0.37	0.544								
Models for overweight determination													
1	Prenatal stress (1-yes, 0-no) unadjusted	1.65	1.02–2.66	4.22	0.04	1.59	0.873–2.919	2.33	0.126	1.71	0.756–387	1.68	0.195
2	Prenatal stress adjusted*	2.14	1.25–3.66	7.67	0.003	2.42	1.20–4.89	6.14	0.01	1.76	0.71–4.38	1.58	0.208
Models for obesity determination													
1	Prenatal stress (1-yes, 0-no) unadjusted	1.21	0.76–1.9	0.65	0.42	1.13	0.610–2.075	0.14	0.703	1.30	0.650–2.603	0.561	0.454
2	Prenatal stress adjusted*	1.14	0.68–1.91	0.24	0.627	1.03	0.49–2.18	0.008	0.931	1.31	0.605–2.827	0.47	0.492

OR odds ratio, *CI* confidence intervals, *p* significance level

*Adjusted for age, sex, place of residence, maternal pre-pregnancy BMI, parental assessment of income, parental education, birth weight

occurred in the past. Our study considered the adverse events experienced by the mother and their impact on changes in body weight status in children. The stress assessment concerned objectively occurring difficulties. Previous studies on objective stressors have largely examined the impact of very unfavorable phenomena such as a snowstorm [30, 31, 44], a bereavement [43] or flood [42, 69] and we do not fully know how the more common objective stressors affect changes in the children's body. In the literature, we also find references to the influence of subjectively perceived stressors on the body weight of children. [32, 41, 42, 45, 46]. However, by reviewing the research, we found that subjective stressors were more likely to give inconclusive results [70].

The results of the research indicate that there are sex-specific relationships in the studies evaluating the programming of the influence of prenatal maternal stress on the development of children [71]. The placenta differs in biological structure by gender, but there are also gender differences in the adaptation of the placenta to intrauterine conditions. Male fetuses invest in growth but adapt less to adverse environmental conditions than female fetuses [71]. These changes may be one of possible explanations for differences between the frequency of diagnosed overweight in the boys and girls in our study who experienced prenatal stress. In the group of boys whose mothers experienced adverse life events in pregnancy overweight was almost 2.5-fold more common than among the boys who were not exposed to prenatal stress. There are no statistically significant relationships in the group of girls. In most previous studies, no differences in BMI [69] or body composition [47] were found according to the gender of the child. However, in some previous studies, we saw gender-specific changes. Elevated maternal cortisol during pregnancy in one study was associated with higher FMI (fat mass index) in girls, but marginally lower in boys [49]. In contrast, another study shows that maternal trauma during pregnancy increased the risk of underweight in boys and decreased the risk of underweight in girls [33]. The result of our study in which boys exposed to prenatal stress were overweight more often may indicate that boys are more susceptible to the harmful effects of environmental factors such as stress. The results of other Polish studies confirm more frequent occurrence of overweight among boys [72]. The incidence of overweight in the group of boys higher than in the girls may be due to a different way of spending their free time. Boys tend to spend more time than girls on sedentary activities, e.g. playing computer games [73]. Additionally, it can be assumed that girls are more exposed to social pressure regarding a slim figure [74], which is why overweight and obesity occur in girls less frequently.

In our study overweight and obesity diagnosed on the basis of IOTF standards are less common in the children of the mothers and fathers with high education. Previous research shows that the level of parents' education is

related to the food consumed by their children [75]. The most favorable eating habits, the highest consumption of vegetables, fruit and dairy products and the lowest consumption of sweetened beverages and processed food are found in the children of parents with a better socioeconomic status, especially in terms of high education [76, 77]. The children of parents with low education more often ate foods with high content of sugar and fat than the children of parents with higher levels of education [78–80]. The mother's weight status before pregnancy also plays a role in developing a healthy body status in children. Results of our study show that the mothers who were overweight or obese before pregnancy had more often overweight or obese children, which is consistent with the results of other studies [81].

Conclusions

Prenatal stress is associated with an increased incidence of overweight diagnosed on the basis of body fat cut-off points. That method of diagnosing body fat level abnormalities in children seems to be a measure of the adverse effects of prenatal stress on the human body more sensitive than the use of standards based on BMI and may be recommended for future research on obesity risk factors. Further studies on the prenatal exposition to stress and body fat content as well as fat metabolism should be conducted.

Strength and limits

The advantage of our study is the use of two types of standards for the assessment of underweight, overweight and obesity. We used norms based on both BMI and based on the percentage of body fat. The use of body fat norms based on body fat appears to be a tool that will more accurately determine the actual number of children with abnormal body composition than BMI. To our knowledge, such a classification has not yet been used in any study dealing with the relationship between the body weight and prenatal stress. In addition, the analysis took into consideration the role of gender and socioeconomic status as modulators of the relationship between the prenatal stress and body weight. Despite the strengths of the study, there are also limitations that need to be considered. The study was a retrospective cohort which could lead the subjects to miss some events due to forgetfulness. We did not assess either the trimester in which the woman was exposed to stress, or the duration of the exposure to adverse factors. The adverse factors whose influence was assessed during pregnancy could also be factors that influenced the mother before pregnancy and the child in later stages of development. Another limitation of the study is the failure to collect data on the pubertal development of the children at the time of the study. Neither did we check the time of the children's last meal and physical activity prior to the body composition analysis.

What is already known on this subject?

The relationship between the prenatal stress and weight changes in children gives inconclusive results. Some studies have shown a relationship between prenatal stress and underweight, and others with overweight or obesity. More work is still needed to investigate this relationship.

What this study adds?

The study presents significant differences between the assessment of overweight and obesity based on two different diagnostic criteria.

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Declarations

Conflict of interest The authors declare no conflict of interest.

Ethical approval The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee Poznan University of Medical Sciences (approval no. 542/14).

Informed consent Informed consent was obtained from all subjects involved in the study.

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Publikacja III

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Ewa Bryl, Paula Szcześniewska, Agata Dutkiewicz, Monika Dmitrzak-Węglarz, Agnieszka Słopień, Tomasz Hanć

"FTO and MC4R Polymorphisms, and Selected Pre-, Peri- and Postnatal Factors as Determinants of Body Mass Index and Fatness in Children. A Thorough Analysis of the Associations"

"FTO and MC4R Polymorphisms, and Selected Pre-, Peri- and Postnatal Factors as Determinants of Body Mass Index and Fatness in Children. A Thorough Analysis of the Associations."

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Abstract

Background: Overweight and obesity among children have become significant global health concerns. Previous studies have highlighted the potential role of genetic factors, particularly polymorphisms in the FTO and MC4R genes, as well as environmental factors in the development of childhood obesity. This study aimed to investigate the relationships between genetic, socioeconomic and perinatal factors, adverse childhood events (ACEs), and lifestyle, and their impact on overweight, obesity and body composition parameters in children. Additionally, we explored potential interactions between genetic factors and ACEs.

Methods: 456 children aged 6-12 years participated in our study. Information on the socioeconomic status, perinatal factors, ACEs and lifestyle of the children was collected with a questionnaire completed by their parents/guardians. We examined the children's body weight and conducted an electrical bioimpedance analysis. Overweight and obesity were diagnosed based on the International Obesity Task Force and McCarthy criteria. We genotyped two selected polymorphisms in the FTO and MC4R genes using the TaqMan SNP allelic discrimination method.

Results: Higher BMI (Body Mass Index) z scores were related to higher paternal BMI and lower maternal age at the child's birth. Higher FMI (Fat Mass Index) z scores were associated with higher paternal BMI, increased gestational weight, lower maternal education and the presence of the FTO risk allele. Higher FatM (fat mass in kg) z scores were linked to lower maternal education, lower maternal age at the child's birth, higher maternal body weight gain, paternal BMI and the presence of the FTO risk allele. Moreover, interaction effects were observed on BMI z scores between ACE and FTO AA, and on FMI z scores and FatM z scored between ACE and MC4R CC.

Conclusions: The contribution of environmental factors is more strongly related to changes in body composition than genetic ones. Additionally, the presence of the risk allele combined with unfavourable environmental factors like ACEs leads to visible interaction effects, resulting in increased BMI z scores and FMI z scores in children.

Key words: body composition, children, BMI, FTO rs9939609, MC4R rs17782313, environmental factors, ACE

1. Introduction

The problem of overweight and obesity affects an increasing number of people, including children. According to the latest data from the World Health Organization (WHO), 39 million children under the age of 5 were overweight or obese [1]. Research is ongoing to identify factors influencing this phenomenon, which can be categorised as genetic and environmental ones. Genetic factors include gene polymorphisms that may be associated with a higher risk of developing overweight and obesity. The previous meta-analysis indicated that the polymorphism of the FTO rs9939609 gene is related to body weight, BMI (Body Mass Index) and body fat content not only in adults but also in children [2]. In a group of children and adolescents aged 6-19, the presence of at least one risk allele of the FTO gene was associated with higher BMI, BMI z scores and adiposity [3,4]. In the children, the presence of the unfavourable allele nearly doubled the risk of binge eating [3]. Similar findings emerged concerning the MC4R gene polymorphism. The results of studies carried out by Ho-Urriola et al. on a cohort of children also revealed that the MC4R rs17782313 polymorphism may be associated with the risk of overweight and increased food consumption in children aged 6-12 years. The presence of the C allele was associated with increased eating pleasure, reduced satiety and a greater tendency to eat without hunger, which may contribute to childhood obesity [5].

Family environment is a major factor for the children's health. Children raised by a single parent have a higher risk of experiencing overweight and obesity [6]. In children older than 7, the association between the family structure and the child's BMI increases and is mediated by household income levels [7]. Low income itself is a risk factor for higher BMI among children [8]. Various parental factors hold importance in shaping children's BMI and nutritional status. For instance, the mother's BMI both before and after the child's birth, the father's BMI, and the parents' level of education significantly contribute to this aspect [9,10]. A higher level of parental education, along with a greater income per family member, has been associated with more accurate children's BMI values [9,10]. In Serbia, for instance, mothers' educational attainment proved to be the most influential factor in determining the children's nutritional status [11]. Additionally, there is a positive correlation between parental BMI and the BMI of their children, indicating that higher parental BMI is linked to increased BMI in the children [12]. Specifically, a higher paternal BMI has been identified as a factor contributing to elevated body weight and body fat percentage in the children [13], while a higher maternal BMI before pregnancy increases the risk of overweight and obesity in the offspring [14]. The maternal age also exerts an impact on the children’s body weight. A study conducted by Potocka et al. found that younger maternal age was associated with higher BMI z scores and a higher percentage of energy intake in the children's diets [15].

Perinatal factors represent additional variables that can have implications for children's weight and body composition. Both a low (<2500g) and high (>4000g) birth weight have been associated with potential adverse effects on children's future health. A low birth weight may be associated with a higher risk of metabolic syndrome and central obesity [16]. On the other hand, a high birth weight may also contribute to a higher risk of overweight and abdominal obesity among children in Poland [17]. Another factor related to the child's health is breastfeeding. The results of a study conducted in 12 countries show that breastfeeding may protect from obesity

and excessive body fat levels in children aged 9-11 [18]. It is an important component of reducing BMI in children and lowering the risk of obesity [14]. The type of birth also matters. A recent meta-analysis indicates that a c-section (caesarean section) is associated with childhood obesity, yet not overweight [19].

In addition to genetic, socioeconomic and perinatal factors, lifestyle plays an important role in weight changes among children. A healthy diet, regular meals [20,21], physical activity [21] and limited screen time are protective factors against the development of overweight and obesity in children. Spending more than 2 hours [22] or more than 4 hours [23] in front of the screen was associated with greater likelihood of overweight/obesity. The length of sleep may also be related to the children's weight. In a study by Resiak et al., sleeping less than 5 hours was associated with a higher risk of overweight/obesity in the children [9]. The sleep length is positively affected by a bedtime routine, which is less often observed in households with many children and among the children of mothers with a low education [24], highlighting how all these factors relate.

Previous studies have shown that adverse life events in childhood (ACEs) may have a significant role in changes in the weight and body composition of children [25–29]. Most studies focused on the effect of ACEs on the occurrence of changes in body weight in adulthood [30]. However, there are still no clear conclusions about the impact of ACEs on changes in body weight in childhood. Meta-analyses have shown that ACEs are associated with both childhood obesity [25–27] and underweight [31,32]. Even less is known about the relationship between ACEs and body composition parameters. A study by Derks et al. conducted among Dutch children shows that ACEs do not have a significant effect on the body composition, and the most important factors are the socioeconomic conditions [28]. However, a study by Deng et al. finds that ACEs are associated with a greater increase in BMI and FMI (Fat Mass Index) in children aged 5-17 with significant gender differences [29].

The aim of our study was to investigate the potential associations between the BMI z scores, FMI z scores, FFMI (Fat Free Mass Index) z scores, FatM (Fat Mass in kg) z scores and the socioeconomic status, perinatal factors, parental factors, the children's lifestyle, ACEs and FTO rs9939609 and MC4R rs17782313 polymorphisms of Polish children aged 6-12 years. The study was exploratory.

In the context of previous research, the interactions between genes and the environment seem to be particularly interesting. One less explored aspect pertains to the interplay between unfavourable life experiences and polymorphisms of the FTO rs9939609 and MC4R rs17782313 genes and their impact on body composition parameters. The results of the Copenhagen General Population Study indicate a positive relationship between BMI and WHR (Waist to Hip Ratio) and distress in adults. However, while examining the same relationships using adiposity related genotypes (FTO rs9939609 and MC4R rs17782313) as instrumental variables inverse associations were observed [33].

2. Material and methods

The size of the study group was determined based on data published by the Statistics Poland [34], which indicated an approximate population of 36,000 primary school children in Poznan at the time of the research. To calculate the specified confidence level of 95%, a structure index of 18%, and an estimation error of 5%, a sample size of 225 or greater was calculated to ensure a robust representation. The study group consisted of 456 children with a comparable number of boys and girls (52.19 and 47.81%, respectively). The children were aged 6 to 12 (mean=8.99, SD=1.32). The study was conducted between March 2017 and November 2019 across 11 randomly selected state primary schools in Poznan. It was funded by the National Science Centre, Poland, grant number: 2016/21/B/NZ5/00492 and approved by the Institutional Bioethics Board of Poznan University of Medical Sciences (approval no. 542/14). Prior to

participation, the parents or legal guardians of the participants received written information about the study along with consent cards and questionnaires.

The collected material included information and measurements of 530 individuals (276 boys and 254 girls) aged 6-12 years (mean= 8.99 SD=1.32). After eliminating cases with missing information on body composition parameters or the FTO and MC4R gene polymorphisms determination, the final database included 456 children. The data on the socioeconomic status, ACEs and gene polymorphisms were collected for each child, however, there was a small rate of missing data for certain variables, such as family type (n=12, 2.63%), place of residence (n=27, 5.92%), parental subjective assessment of economic situation of the family (n=17, 3.73%), gaining weight during pregnancy (n=20, 4.39%), pregnancy duration (n=31, 6.80%), single/twin delivery (n=19, 4.17%), type of delivery (n=18, 3.95%), birthweight (n=13, 2.85%), breastfeeding (n=13, 2.85%), maternal BMI category before pregnancy (n=28, 6.14%), maternal current BMI category (n=23, 5.04%), maternal educational level (n=15, 3.29%), paternal current BMI category (n=27, 10.31%), paternal educational level (n=32, 7.02%), siblings (n=20, 4.39%), life threat (n=28, 6.14%), witness of life threat (n=28, 6.14%), violence victim (n=28, 6.14%), violence witness (n=30, 6.58%), death of someone close (n=28, 6.14%), family conflicts (n=29, 6.36%), separation from parents (n=30, 6.58%), school problems (n=3, 6.80%), other ACEs (n=33, 7.24%).

2.1.Anthropometric measurements

Each child was measured by qualified medical personnel. Body height was checked with a Seca 213 stadiometer (with an accuracy of 1 mm), and body weight (with an accuracy of 0.01 kg) and electrical bioimpedance with the Tanita MC-780 body composition analyser. During the body composition examination the children wearing light clothing (a blouse or shirt and skirt or trousers), with no outer clothing (a jacket or coat). They were barefoot and placed

appropriately on the electrodes while ensuring proper electrode positioning. The values of raw indicators, such as FatM in kg, were analyzed. Subsequently, BMI, FMI, and FFMI were calculated using the following equations:

$$BMI = \frac{body\ weight\ [kg]}{(body\ height[m])^2},\ FMI = \frac{body\ fat\ mass\ [kg]}{(body\ height[m])^2},\ FFMI = \frac{fat\ free\ body\ mass\ [kg]}{(body\ height[m])^2}.$$

The BMI was adjusted for sex and age on the basis of WHO growth charts [35] with the use of WHO AnthroPlus software and presented as z scores. FMI, FFMI and FatM were standardised by age and sex within the sample. The diagnosis of overweight, obesity, and underweight was determined following the guidelines of the International Obesity Task Force (IOTF) [36,37] and based on body fat cut-off points obtained using the bioimpedance method (McCarthy criteria) [38].

2.2.Socioeconomic and lifestyle factors

In the parental questionnaire, questions pertaining to the socioeconomic status enabled the classification of families into three types: both biological parents, a biological parent with a partner, or a single parent. The place of residence was determined based on the number of residents and categorised as a village (<10 000 residents), small and medium-sized town (10 000 – 100 000residents) or large city (>100 000 residents) [39]. The economic situation was assessed subjectively by the parent and categorised as: bad, average or good. The ‘bad economic situation’ group comprised the children whose parents reported facing serious difficulty or difficulty in meeting the family's needs, while the ‘average economic situation’ group included children whose parents reported some difficulty. The ‘good economic situation’ group consisted of the children whose parents indicated that meeting the family's needs was quite easy or easy. The maternal weight gain during pregnancy was assessed based on the gynaecologist’s opinion and categorised as: ‘exceeded’ or ‘non-exceeded’ in accordance with the guidelines from the Institute of Medicine. The recommended amount of weight gain

depends on the pre-pregnancy BMI (for women who had a BMI <18.5 before pregnancy, the recommended weight gain is 12.5-18 kg; for women with a pre-pregnancy BMI of 18.5-24.9 the recommended weight gain is 11.5-16; women with pre-pregnancy BMI 25-29.9 should aim for weight gain between 7-11.5, and women with pre-pregnancy BMI ≥30 should not exceed weight gain between the range of 5-7 kg) [40]. Pregnancy duration was divided into three categories:: <37 weeks (preterm birth), 37-42 weeks (term birth) and >42 weeks (post-term birth) [41]. The information on maternal health conditions before and during pregnancy, such as hypertension, diabetes, thyroid diseases, kidney diseases and heart failure was collected from parental responses (yes/no). We distinguished a single or twin pregnancy and a vaginal or c-section delivery. The birthweight was classified into 3 categories: <2500g, 2500-4000g, >4000g [42]. Additionally, information on breastfeeding (yes/no) was obtained.

The parents declared their weight and height, on the basis of which we calculated BMI. Maternal BMI before pregnancy, maternal current BMI and paternal current BMI were classified according to WHO guidelines as: underweight, proper weight, overweight or obesity [43]. The educational level of the parents was categorised as: primary (8 years of education), vocational (10 years), secondary (12 years) or university qualifications (bachelor's – 15 years or master's degree – 17 years). We asked about the presence of siblings in the household (yes/no). Regarding the children's lifestyle, sleep length was categorised as ≥9 hours or <9 hours [44], eating behaviours were classified as either at least 3 regular meals/day + a snack or irregular meals. Physical activity was divided into exercise 3 days/week for ≥3 hours or less [45], and screen time as ≤2 hours or more than 2 hours [46].

2.3.Measurements of adverse life events in childhood

Measurements of ACEs in the children were collected using a survey method. The parents or legal guardians received forms containing questions related to the occurrence of specific experiences in the child's life. The questionnaire was developed based on selected questions

from the Traumatic Events Screening Inventory (TESI) questionnaire, which originally consists of 24 questions. In order to simplify the form, we condensed the questionnaire to 9 questions concerning adverse events experienced by the children. The parents were asked to indicate whether:

1. The life or health of the child was threatened.

2. The child experienced an event in which the life or health of another person was endangered or someone died.

3. The child was assaulted physically (e.g. hitting, pushing, choking, shaking, biting, burning, forced into any type of sexual activity) or psychologically (e.g. mocking, gossiping, shouting, threatening, being rejected by someone close).

4. The child witnessed physical or psychological assault.

5. The child experienced the death of someone close.

6. The child experienced serious family problems (e.g. quarrels, conflicts, fighting, parting, alcohol problems or other addictions, emotional or mental problems of family members).

7. The child was separated from parents for an extended period.

8. The child encountered serious problems at school, such as being at the risk of failing or repeating a grade.

9. The child experienced other stressors that were not mentioned in the questionnaire.

2.4.Genetic tests (FTO rs993960, MC4R rs177823139)

Genes and polymorphisms were selected based on their previously established relationship with vulnerability to overweight and obesity (FTO rs9939609) and changes in food intake (MC4R rs17782313). Saliva samples were collected by qualified medical personnel and DNA was

extracted from the saliva following the designatedprotocol. The selected polymorphisms were genotyped using the Taq-Man single-nucleotide polymorphism (SNP) allelic discrimination method with the ABI 7900HT system (Applied Biosystems). The Real-Time PCR reaction employed commercially available TaqMan Genotyping assays for accurate results.

3. Statistical methods

All statistical analyses were performed using STATISTICA 13 software. The threshold of statistical significance was set at $p<0.05$. Analyses were conducted on tindividuals with complete information on the FTO and MC4R gene polymorphisms and body composition. For comparison analyses involving continuous dependent variables (BMI z scores, FMI z scores, FFMI z scores, and FatM z scores), we utilized the two-tailed t-test for independent groups. When comparing continuous dependent variables across more than two groups, we employed analysis of variance (ANOVA). To assess group differences in the ANOVA, Tukey's multiple comparisons test was performed. The chi-square test (χ^2) was applied for comparative analysis of categorical variables. In order to identify the most important variables associated with BMI z scores, FMI z scores, FFMI z scores and FatM z scores the forward stepwise multiple regression was applied. Two-way ANOVA was used to assess the effects of interaction between ACEs, FTO and MC4R gene polymorphisms on the BMI z scores, FMI z scores and FatM z scores. The analysis was applied for ACE as a categorized variable (0,1,2,3+) and for the types of ACEs (occurrence vs non-occurence). The size of effects was assessed with Cohen’s d.

4. Results

4.1.Differences according to the sex

There were no differences between the prevalence of underweight, overweight and obesity diagnosed according to IOTF between the boys and girls; however, there were differences when the diagnosis was based on body fat percentage. Obesity diagnosed according to body fat tissue

was slightly more common in the boys than in the girls (8.81% vs 5.95%, χ^2=11.70, p=0.01) (Table 1).

Table 1. Prevalence of underweight, overweight and obesity diagnosed according to IOTF (Body weight status) and according to McCarthy criteria (Body fat status) for both sexes

Variable		Body weight status					Body fat status			
	n	Underweight	Proper weight	Overweight	Obesity	n	Underweight	Proper weight	Overweight	Obesity
Sex	456					454				
Boys		17	169	41	11		1	148	48	40
		3.73%	37.06%	8.99%	2.41%		0.22%	32.60%	10.57%	8.81%
Girls		28	148	29	13		0	166	24	27
		6.14%	32.46%	6.36%	2.85%		0.00%	36.56%	5.29%	5.95%
	χ^2	5.44					**11.70**			
	p	0.14					**0.01**			

4.2.Gene polymorphisms

There were no differences between the occurrence of underweight, overweight and obesity diagnosed according to IOTF and McCarthy norms in children with the risk allele of FTO rs9939609 or MC4R rs17782313. No significant differences were observed in the BMI z scores (F=0.98, p=0.38), FMI z scores (F=2.26, p=0.11), FFMI z scores (F=0.19, p=0.82), and FatM z scores (F=2.63, p=0.07) between the children who were homozygotes AA, heterozygotes AT and homozygotes TT of the FTO gene. However, the children who were CC homozygotes had higher FMI z scores (F=3.11, p=0.04) and FatM z scores (F=4.09, p=0.02) than the children without the risk allele (TT) of the MC4R gene. There were no differences in the BMI z scores (F=2.72, p=0.07), and FFMI z scores (F=2.74, p=0.07). (Table 2).

Table 2. Prevalence of underweight, overweight and obesity diagnosed according to IOTF (Body weight status) and according to McCarthy criteria (Body fat status), and association between body composition parameters and genetic factors

variable		Body weight status					Body fat status					BMI z scores		FMI z scores		FFMI z scores		FatM z scores	
	n		Underweight	Proper weight	Overweight	Obesity	n	Underweight	Proper weight	Overweight	Obesity	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD
FTO	456						452												
AA		all	13	67	13	4		0	69	16	12	0.20	1.22	-0.18	0.86	0.05	0.85	-0.13	0.87
			2.85%	14.69%	2.85%	0.88%		0,00%	15.2%	3.52%	2.64%								
		girls	7	32	4	0		32	8	3	32								
			3.21%	14.68%	1.83%	0,00%		14.75%	3.69%	1.38%	14.75%								
		boys	6	35	9	4		0	37	8	9								
			2.52%	14.71%	3.78%	1.68%		0,00%	15.61%	3.38%	3.8%								
AT		all	15	146	32	15		1	139	32	34	0.40	1.24	0.02	1.05	0.08	0.90	0.11	1.11
			3.29%	32.02%	7.02%	3.29%		0.22%	30.62%	7.05%	7.49%								
		girls	6	69	15	10		71	11	17	71								
			2.75%	31.65%	6.88%	4.59%		32.72%	5.07%	7.83%	32.72%								
		boys	9	77	17	5		1	68	21	17								
			3.78%	32.35%	7.14%	2.1%		0.42%	28.69%	8.86%	7.17%								
TT		all	17	104	25	5		0	106	24	21	0.29	1.20	-0.15	0.83	0.12	0.92	-0.07	0.87
			3.73%	22.81%	5.48%	1.1%		0,00%	23.35%	5.29%	4.63%								
		girls	15	47	10	3		63	5	7	63								
			6.88%	21.56%	4.59%	1.38%		29.03%	2.3%	3.23%	29.03%								
		boys	2	57	15	2		0	43	19	14								
			0.84%	23.95%	6.3%	0.84%		0,00%	18.14%	8.02%	5.91%								
		χ^2	6.25					2.27				F	0.98		2.26		0.19		2.63	
		p	0.40					0.89				p	0.38		0.11		0.82		0.07	
MC4R	454						455												
CC			2	14	5	3		0	14	4	6	0.81	1.32	0.35	1.32	0.41	1.02	0.54	1.46
			0.44%	3.08%	1.1%	0.66%		0,00%	3.1%	0.88%	1.33%								
CT			13	95	23	9		0	96	22	22	0.38	1.19	-0.06	0.92	0.15	0.89	-0.02	0.92
			2.86%	20.93%	5.07%	1.98%		0,00%	21.24%	4.87%	4.87%								
TT			30	208	40	12		1	204	46	37	0.24	1.21	-0.13	0.90	0.02	0.88	-0.05	0.95
			6.61%	45.81%	8.81%	2.64%		0.22%	45.13%	10.18%	8.19%								
		χ^2	5.30					3.63				F	2.72		**3.11**		2.74		**4.09**	
		p	0.51					073				p	0.07		**0.04**		0.07		**0.02**	
															CCvsTT#				CC vs CT CCvs TT#	

$\bar{x}$ – mean, BMI – Body Mass Index, FMI – Fat Mass Index, FFMI – Fat Free Mass Index, FatM – Fat Mass in kg, # significant differences in the post hoc test

In the group of girls, obesity diagnosed on the basis of BMI was more frequent among AT heterozygotes compared to TT homozygotes (4.59% vs 1.38%, χ^2=14.14, p=0.03) of the FTO rs9939609 gene. BMI z scores (F=3.17, p=0.04) and FatM z scores (F=3.41, p=0.04) were higher in heterozygotes than in TT homozygotes of the FTO gene. Girls homozygous for the CC genotype had higher FatM z scores than those homozygous for the TT genotype of the MC4R gene (F=3.24, p=0.04) (Table 3).

In the group of boys, the incidence of underweight, overweight and obesity diagnosed on the basis of BMI and adipose tissue did not differ depending on the FTO and MC4R gene variant (Table 4). There were no differences in the BMI z scores, FMI z scores, FFMI z scores, and FatM z scores between risk homozygous, heterozygous, and homozygous children without the risk allele of the FTO and MC4R genes (Table 4).

Table 3. Prevalence of underweight, overweight and obesity diagnosed according to IOTF (Body weight status) and according to McCarthy criteria (Body fat status), and association between body composition parameters and genetic factors in girls

variable		Body mass status				Body fat status					BMI z scores		FMI z scores		FFMI z scores		FatM z scores	
	n	Underweight	Proper weight	Overweight	Obesity	n	Underweight	Proper weight	Overweight	Obesity	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD
FTO	218					217												
AA		7	32	4	0		32	8	3	32	0.09	0.96	-0.22	0.72	-0.02	0.63	-0.17	0.72
		3.21%	14.68%	1.83%	0,00%		14.75%	3.69%	1.38%	14.75%								
AT		6	69	15	10		71	11	17	71	0.44	1.17	0.11	1.06	0.08	0.75	0.18	1.11
		2.75%	31.65%	6.88%	4.59%		32.72%	5.07%	7.83%	32.72%								
TT		15	47	10	3		63	5	7	63	0.03	1.18	-0.24	0.83	0.07	0.95	-0.15	0.91
		6.88%	21.56%	4.59%	1.38%		29.03%	2.3%	3.23%	29.03%								
	χ^2	**14.14**					7.79				F	**3.17**		**3.75**		0.28		**3.41**
	p	**0.03**					0.10				p	**0.04**		**0.03**		0.76		**0.03**
												AT vs TT#		no differences#				AT vs TT#
MC4R	218					217												
CC		2	8	2	2		10	1	3	10	0.62	1.44	0.49	1.51	0.26	1.07	0.64	1.69
		0.92%	3.67%	0.92%	0.92%		4.61%	0.46%	1.38%	4.61%								
CT		10	50	7	5		55	9	8	55	0.26	1.16	-0.08	092	0.12	0.87	-0.05	0.92
		4.59%	22.94%	3.21%	2.29%		25.35%	4.15%	3.69%	25.35%								
TT		16	90	20	6		101	14	16	101	0.18	1.11	-0.13	0.86	0.002	0.73	-0.04	0.90
		7.34%	41.28%	9.17%	2.75%		46.54%	6.45%	7.37%	46.54%								
	χ^2	3.63					1.42				F	0.93		2.81		1.00		**3.24**
	p	0.73					0.84				p	0.40		0.06		0.40		**0.04**
																		CC vs TT#

$\bar{x}$ – mean, BMI – Body Mass Index, FMI – Fat Mass Index, FFMI – Fat Free Mass Index, FatM – Fat Mass in kg, # significant differences in the post hoc test

Table 4. Prevalence of underweight, overweight and obesity diagnosed according to IOTF (Body weight status) and according to McCarthy criteria (Body fat status), and association between body composition parameters and genetic factors in boys

variable		Body mass status				Body fat status					BMI z scores		FMI z scores		FFMI z scores		FatM z scores	
	n	Underweight	Proper weight	Overweight	Obesity	n	Underweight	Proper weight	Overweight	Obesity	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD
FTO	238					217												
AA		7	32	4	0		0	37	8	9	0.29	1.40	-0.14	0.96	0.10	0.99	-0.09	0.98
		3.21%	14.68%	1.83%	0,00%		0,00%	15.61%	3.38%	3.8%								
AT		6	69	15	10		1	68	21	17	0.37	1.31	-0.06	1.03	0.07	1.02	0.04	1.10
		2.75%	31.65%	6.88%	4.59%		0.42%	28.69%	8.86%	7.17%								
TT		15	47	10	3		0	43	19	14	054	1.18	-0.07	0.82	0.16	0.91	0.003	0.82
		6.88%	21.56%	4.59%	1.38%		0,00%	18.14%	8.02%	5.91%								
	χ^2	6.02					3.80				F	0.65		0.15		0.18		0.33
	p	0.42					0.70				p	0.52		0.86		0.84		0.72
MC4R	236					235												
CC		0	6	3	1		0	4	3	3	1.08	1.14	0.16	1.03	0.63	0.94	0.41	1.12
		0,00%	2.54%	1.27%	0.42%		0,00%	1.7%	1.28%	1.28%								
CT		3	45	16	4		0	41	13	14	0.51	1.22	-0.04	0.93	0.17	0.92	0.01	0.92
		1.27%	19.07%	6.78%	1.69%		0,00%	17.45%	5.53%	5.96%								
TT		14	118	20	6		1	103	32	21	0.29	1.30	-0.14	0.93	0.03	0.99	-0.05	0.99
		5.93%	50,00%	8.47%	2.54%		0.43%	43.83%	13.62%	8.94%								
	χ^2	8.36					4.85				F	2.23		0.66		2.05		1.07
	p	0.21					056				p	0.11		0.52		0.13		0.34

$\bar{x}$ – mean, BMI – Body Mass Index, FMI – Fat Mass Index, FFMI – Fat Free Mass Index, FatM – Fat Mass in kg

4.3.Socioeconomic factors

The type of family (χ^2=9.08, p=0.44), place of residence (χ^2=7.26, p=0.22), subjective assessment of economic status (χ^2= 4.52, p=0.61) were not associated with the prevalence of underweight, overweight and obesity. The type of family was not associated with the BMI z scores (F=0.20, p=0.90), FMI z scores (F=0.36, p=0.78), FFMI z scores (F=0.05, p=0.99) or FatM z scores (F=0.26, p=0.85). There were no differences in the BMI z scores (F=1.75, p=0.18), FMI z scores (F=1.28, p=0.28), FFMI z scores (F=0.55, p=0.56) or FatM z scores (F=1.37, p=0.25) depending on the place of residence. The parental subjective assessment of the economic situation of the family was not related to the BMI z scores (F=0.53, p=0.59), FMI z scores (F=0.31, p=0.73), FFMI z scores (F=0.90, p=0.41) or FatM z scores (F=0.37, p=0.69). (Table 5).

Table 5. Prevalence of underweight, overweight and obesity diagnosed according to IOTF (Body weight status) and according to McCarthy criteria (Body fat status), and association between body composition parameters and socioeconomic factors

Variable	Body weight status				Body fat status					BMI z scores		FMI z scores		FFMI z scores		FatM z scores	
n	Underweight	Proper weight	Overweight	Obesity	n	Underweight	Proper weight	Overweight	Obesity	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD
Type of family																	
444					442												
Both biological parents	31	260	54	16	0	252	58	49		0.30	1.17	-0.11	0.91	0.06	0.86	-0.03	0.94
	6.98%	58.56%	12.16%	3.60%	0.00%	57.01%	13.12%	11.09%									
Biological parents with partner	6	18	6	1	1	20	5	5		0.24	1.37	-0.05	0.89	0.06	0.92	-0.04	1.02
	1.35%	4.05%	1.35%	0.23%	0.23%	4.52%	1.13%	1.13%									
Single parent	7	32	7	5	0	33	8	10		0.42	1.40	0.03	1.04	0.11	0.98	0.10	1.05
	1.58%	7.21%	1.58%	1.13%	0.00%	7.47%	1.81%	2.26%									
χ^2	9.08				15.16				t	0.20		0.36		0.05		0.26	
p	0.44				0.09				p	0.90		0.78		0.99		0.85	
Place of residence																	
427					427												
Village	7	23	3	1	0	24	4	6		0.03	1.28	-0.20	0.86	-0.03	0.91	-0.15	0.90
	1.64%	5.39%	0.70%	0.23%	0.00%	5.62%	0.94%	1.41%									
Small and medium-sized town (0-100 000 residents)	5	35	11	5	1	35	7	11		0.52	1.44	0.09	1.21	0.17	0.86	0.17	1.28
	1.17%	8.20%	2.58%	1.17%	0,23%	8.20%	1.64%	2.58%									
Large city (>100 000 residents)	31	240	50	16	0	237	57	45		0.30	1.16	-0.10	0.88	0.06	0.88	-0.03	0.92
	7.26%	56.21%	11.71%	3.75%	0,00%	55.50%	13.35%	10.54%									
χ^2	8.26				9.79				F	1.75		1,28		0.58		1.37	
p	0.22				0.13				p	0.18		0,28		0.56		0.25	
Parental subjective assessment of economic situation																	
437					438												
Bad	1	10	4	1	0	13	1	2		0.49	1.35	-0.07	0.73	0.36	1.04	0.06	0.76
	0.23%	2.28%	0.91%	0.23%	0,00%	2.97%	0.23%	0.46%									
Average	10	46	12	6	0	48	15	11		0.41	1.33	-0.01	0.98	0.04	0.85	0.07	1.00
	2.28%	10.48%	2.73%	1.37%	0,00%	10.96%	3.42%	2.51%									
Good	34	248	51	16	1	242	54	51		0.28	1.20	-0.10	0.94	0.07	0.88	-0.03	0.98
	7.74%	56.49%	11.62%	3.64%	0.23%	55.25%	12.33%	11.64%									
χ^2	4.52				2.7				F	0.53		0.31		0.90		0.37	
p	0.61				0.85				p	0.59		0.73		0.41		0.69	

$\bar{x}$ – mean, BMI – Body Mass Index, FMI – Fat Mass Index, FFMI – Fat Free Mass Index, FatM – Fat Mass in kg

4.4. Parental body weight status

The children whose mothers had their body mass higher before pregnancy were diagnosed with overweight (IOTF) and obesity (McCarthy criteria) more often than the children whose mothers had a proper weight before pregnancy (54.55% vs 13.37%, χ^2=34.32, p<0.001; 36.36% vs 12.99%, χ^2=20.47, p=0.02, respectively). Maternal current BMI was associated with the body weight status in the children. The children of mothers who experienced obesity had higher risk of being overweight compared to the children of the mothers with a healthy weight (34.38% vs 11.45%, χ^2=34.92, p<0.001). The children whose mothers suffered from obesity before pregnancy had higher BMI z scores than the children of mothers who had underweight (1.35 vs -0.06) or had a proper body weight before pregnancy (1.35 vs 0.27, F=5.11, p<0.001). They also had higher FMI z scores than the children of mothers who had a proper weight before pregnancy (0.59 vs -0.14, F=3.28, p=0.02). The children of mothers who experienced obesity had higher BMI z scores (0.92 vs 0.17, F=6.23, p<0.001), FMI z scores (0.34 vs -0.18, F=4.48, p=0.004), FFMI z scores (0.43 vs -0.04, F=6.68, p<0.001) and FatM z scores (0.42 vs -0.12, F=4.83, p=0.002) than the children of the mothers with a proper body weight. The fathers with obesity were more likely to have children with obesity than the fathers with a proper body weight (13.92% vs 2.29%, χ^2=27.88, p<0.001). The children of fathers suffering from overweight or obesity had higher BMI z scores (F=13.44, p<0.001), FMI z scores (F=9.48, p<0.001), FFMI z scores (F=10.36, p<0.001) and FatM z scores (F=8.50, p<0.001) than the children whose fathers had a proper body weight (Table 6).

Table 6. Prevalence of underweight, overweight and obesity diagnosed according to IOTF (Body weight status) and according to McCarthy criteria (Body fat status), and association between body composition parameters and parental body weight status

Variable		Body weight status					Body fat status					BMI z scores		FMI z scores		FFMI z scores		FatM z scores	
	n	Underweight	Proper weight	Overweight	Obesity	n	Underweight	Proper weight	Overweight	Obesity		$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD
Maternal BMI before pregnancy		426				426													
Underweight		10	22	7	0		1	27	5	6		-0.06	1.38	-0.19	0.90	-0.19	0.91	-0.16	0.96
		2.35%	5.16%	1.64%	0,00%		0.23%	6.34%	1.17%	1.41%									
Proper weight		33	237	44	15		0	237	51	43		0.27	1.19	-0.14	0.89	0.07	0.87	-0.06	0.91
		7.75%	55.63%	10.33%	3.52%		0,00%	55.63%	11.97%	10.09%									
Overweight		1	35	6	5		0	31	8	6		0.59	1.04	0.11	1.06	0.16	0.82	0.17	1.15
		0.23%	8.22%	1.41%	1.17%		0,00%	7.28%	1.88%	1.41%									
Obesity		0	4	6	1		0	3	4	4		1.35	1.18	0.59	0.87	0.53	1.21	0.66	0.84
		0,00%	0.94%	1.41%	0.23%		0,00%	0.7%	0.94%	0.94%									
	χ^2	**34.32**					**20.47**				F	**5.11**		**3.28**		2.34		**3.07**	
	P	**<0.001**					**0.01**				p	**<0.001** underweight vs obesity, proper weight vs obesity#		**0.02** proper weight vs obesity#		0.07		**0.03** no differences#	
Maternal current BMI	431					432													
Underweight		4	6	4	0		0	10	2	2		0.03	1.51	-0.16	1.19	-0.03	0.90	-0.02	1.26
		0.93%	1.39%	0.93%	0,00%		0,00%	2.31%	0.46%	0.46%									
Proper weight		35	218	34	10		1	212	48	37		0.17	1.16	-0.18	0.85	-0.04	0.82	-0.12	0.86
		8.12%	50.58%	7.89%	2.32%		0.23%	49.07%	11.11%	8.56%									
Overweight		4	60	16	8		0	61	13	14		0.61	1.21	0.09	1.03	0.36	0.98	0.19	1.12
		0.93%	13.92%	3.71%	1.86%		0,00%	14.12%	3.01%	3.24%									
Obesity		1	16	11	4		0	18	7	7		0.92	1.26	0.34	1.03	0.43	0.96	0.42	1.10
		0.23%	3.71%	2.55%	0.93%		0,00%	4.17%	1.62%	1.62%									
	χ^2	**34.92**					4.35				F	**6,23**		**4.48**		**6.68**		**4,83**	
	P	**<0.001**					0.89				p	**<0,001** proper weight vs overweight, proper weight vs obesity#		**0.004** proper weight vs obesity#		**<0.001** proper weight vs overweight proper weight vs obesity#		**0.002** proper weight vs overweight, proper weight vs obesity#	
Paternal current BMI	408					408													
Proper weight		16	97	15	3		104	16	12	104		0.02	1.09	-0.30	0.83	-0.09	0.79	-0.21	0.89
		3.93%	23.83%	3.69%	0.74%		25.55%	3.93%	2.95%	25.55%									
Overweight		22	137	33	5		135	30	31	135		0.25	1.16	-0.14	0.77	0.04	0.87	-0.07	0.81
		5.41%	33.66%	8.11%	1.23%		33.17%	7.37%	7.62%	33.17%									
Obesity		1	52	15	11		47	19	13	47		0.99	1.13	0.35	1.15	0.51	0.79	0.43	1.17
		0.25%	12.78%	3.69%	2.7%		11.55%	4.67%	3.19%	11.55%									
	χ^2	**27.88**					0.34				F	**13.44**		**9.48**		**10.36**		**8.50**	
	P	**<0.001**					0.11				p	**<0.001** proper weight vs obesity, overweight vs obesity#		**<0.001** proper weight vs obesity, overweight vs obesity#		**<0.001** proper weight vs obesity, overweight vs obesity#		**<0.001** proper weight vs obesity, overweight vs obesity#	

$\bar{x}$ – mean, BMI – Body Mass Index, FMI – Fat Mass Index, FFMI – Fat Free Mass Index, FatM – Fat Mass in kg, # significant differences in the post hoc test

4.5. Parental education level

The mothers with a university education were more likely to have children with a healthy body weight compared to the mothers with a vocational education (74.01% vs 56.52%, χ=29.64, p<0.001). Conversely, the mothers with a vocational education had children with a higher prevalence of excessive body fat than those with a university education (28.26% vs 9.35%, χ^2=20.24, p=0.02). The children of mothers with a university education had lower BMI z scores (0.20 vs 0.78, F=3.37, p=0.02), FMI z scores (-0.23 vs 0.47, F=8.72, p<0.001) and FatM z scores (-0.15 vs 0.52, F=7.20, p<0.001) than the children of mothers with a vocational education. The fathers with a vocational education had children with overweight more often than the fathers with a university education (26.74%vs11.94%, χ^2=18.51, p=0.03). The children of fathers with a university education had lower BMI z scores (F=3.38, p=0.02), FMI z scores (F=5.21, p=0.002) and FatM z scores (F=4.60, p=0.004) than the children whose fathers had a vocational education (Table 7).

Table 7. Prevalence of underweight, overweight and obesity diagnosed according to IOTF (Body weight status) and according to McCarthy criteria (Body fat status), and association between body composition parameters and parental educational level

Variable	Body weight status					Body fat status					BMI z scores		FMI z scores		FFMI z scores		FatM z scores	
	n		Underweight	Proper weight	Overweight	Obesity	n	Underweight	Proper weight	Overweight	Obesity	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD
Maternal education level	439						439												
Primary			0	4	0	1		0	3	1	1	0.73	1.37	0.06	1.11	0.34	1.08	0.16	1.19
			0,00%	0.91%	0,00%	0.23%		0,00%	0.68%	0.23%	0.23%								
Vocational			3	26	9	8		0	25	8	13	0.78	1.49	0.47	1.36	0.33	0.94	0.52	1.41
			0.68%	5.92%	2.05%	1.82%		0,00%	5.69%	1.82%	2.96%								
Secondary			15	70	18	8		1	73	14	22	0.37	1.39	0.02	1.03	0.09	1.02	0.09	1.09
			3.42%	15.95%	4.1%	1.82%		0.23%	16.63%	3.19%	5.01%								
University			26	205	41	5		0	204	48	26	0.20	1.06	-0.23	0.73	0.03	0.81	-0.15	0.76
			5.92%	46.7%	9.34%	1.14%		0,00%	46.47%	10.93%	5.92%								
		χ^2	**29.64**					**20.24**				F	**3.37**		**8.72**		1.74		**7.20**	
		P	**0.001**					**0.02**				p	**0.02**		**<0.001**		0.16		**<0.001**	
													secondary vs higher#		secondary vs vocational, secondary vs higher#				Secondary vs vocational, secondary vs higher#	
Paternal education level	409						422												
Primary			11	7	2	1		0	7	1	3	0.53	1.39	0.18	1.19	0.18	1.26	0.20	1.18
			0.24%	1.65%	0.47%	0.24%		0,00%	1.66%	0.24%	0.71%								
Vocational			8	49	23	6		0	51	15	19	0.60	1.32	0.15	1.00	0.22	0.88	0.25	1.08
			1.89%	11.58%	5.44%	1.42%		0,00%	12.09%	3.55%	4.5%								
Secondary			11	88	17	9		0	88	18	19	0.40	1.24	-0.01	1.04	0.16	0.91	0.05	1.05
			2.6%	20.8%	4.02%	2.13%		0,00%	20.85%	4.27%	4.5%								
University			19	154	24	4		0	148	35	18	0.15	1.04	-0.26	0.71	-0.02	0.81	-0.17	0.74
			4.49%	36.41%	5.67%	0.95%		0,00%	35.07%	8.29%	4.27%								
		χ^2	**18.51**					11.95				F	**3.38**		**5.21**		2.11		**4.60**	
		P	**0.03**					0.22				p	**0.02**		**0.002**		0.10		**0.004**	
													secondary vs higher#		secondary vs higher#				secondary vs higher#	

$\bar{x}$ – mean, BMI – Body Mass Index, FMI – Fat Mass Index, FFMI – Fat Free Mass Index, FatM – Fat Mass in kg, # significant differences in the post hoc test

4.6.Lifestyle

Eating at least 3 meals and 1 snack per day was not associated with the prevalence of abnormal body weight, body fat status or body composition parameters ($p>0.05$). The children who exercised at least 3 hours 3 days per week had a proper body weight more frequently than the children who exercised less often (76.84% vs 67,41%, $\chi^2=8.08$, $p=0.04$). Spending time in front of the screen was not associated with the prevalence of an abnormal body weight or body fat status ($\chi^2=7.38$, $p=0.06$; $\chi^2=2.86$, $p=0.41$, respectively). The children who spent more than 2 hours in front of the screen had higher BMI z scores (0.42 vs 0.18, $t=2.03$, $p=0.04$), FMI z scores (0.01 vs -0.20, $t=2.44$, $p=0.02$), and FatM z scores (0.11 vs -0.16, $t=2.92$, $p=0.003$). Sleep length was not associated with underweight, overweight and obesity diagnosed according to IOTF and McCarthy norms ($\chi^2=0.37$, $p=0.94$; $\chi^2=0.41$, $p=0.93$, respectively) or body composition parameters ($p>0.05$) (Table 8).

Table 8. Prevalence of underweight, overweight and obesity diagnosed according to IOTF (Body weight status) and according to McCarthy criteria (Body fat status), and association between body composition parameters and lifestyle factors

Variable			Body weight status					Body fat status					BMI z scores		FMI z scores		FFMI z scores		FatM z scores	
	n		Underweight	Proper weight	Overweight	Obesity	n	Underweight	Proper weight	Overweight	Obesity		$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD
Eating behaviour	454						454													
Bad			24	167	44	16		1	165	44	40		0.39	1.25	-0.05	0.89	0.14	0.89	0.02	0.93
			5.29%	36.78%	9.69%	3.52%		0.22%	36.34%	9.69%	8.81%									
Good			21	148	26	8		0	149	28	27		0.23	1.18	-0.12	1.00	0.02	0.89	-0.03	1.05
			4.63%	32.6%	5.73%	1.76%		0,00%	32.82%	6.17%	5.95%									
		χ^2	3.61					3.27				t	1.40		0.79		1.40		0.59	
		P	0.31					0.35				p	0.16		0.43		0.16		0.55	
Physical activity	454																			
Bad			42	242	58	17		1	244	61	53		0.31	1.23	-0.08	0.93	0.05	0.88	-0.02	0.96
			9.25%	53.3%	12.78%	3.74%		0.22%	53.74%	13.44%	11.67%									
Good			3	73	12	7		0	70	11	14		0.37	1.21	-0.08	0.98	0.22	0.94	0.06	1.08
			0.66%	16.08%	2.64%	1.54%		0,00%	15.42%	2.42%	3.08%									
		χ^2	**8.08**					2.01				t	-0.46		0.08		-1.63		-0.66	
		P	**0.04**					0.57				p	0.64		0.94		0.10		0.51	
Screen time	454						454													
>2h			23	180	51	13		0	184	39	43		0.42	1.25	0.01	1.02	0.14	0.90	0.11	1.09
			5.07%	39.65%	11.23%	2.86%		0,00%	40.53%	8.59%	9.47%									
≤2h			22	135	19	11		1	130	33	24		0.18	1.17	-0.20	0.81	0.01	0.88	-0.16	0.79
			4.85%	29.74%	4.19%	2.42%		0.22%	28.63%	7.27%	5.29%									
		χ^2	7.38					2.86				t	2.03		2.44		1.57		2.92	
		P	0.06					0.41				p	0.04		0.02		0.12		0.003	
Sleep length	432						432													
<9h			35	267	59	19		1	265	61	53		0.34	1.21	-0.08	0.93	0.10	0.87	-0.01	0.97
			8.1%	61.81%	13.66%	4.4%		0.23%	61.34%	14.12%	12.27%									
≥9h			6	35	8	3		0	38	7	7		0.24	1.24	-0.13	0.89	0.01	0.99	0.01	0.99
			1.39%	8.1%	1.85%	0.69%		0,00%	8.8%	1.62%	1.62%									
		χ^2	0.37					0.41				t	0.52		0.37		0.68		-0.14	
		P	0.94					0.93				p	0.60		0.71		0.50		0.89	

$\bar{x}$ – mean, BMI – Body Mass Index, FMI – Fat Mass Index, FFMI – Fat Free Mass Index, FatM – Fat Mass in kg, ACE – Adverse Childhood Events

4.7.Perinatal factors

The children of mothers who had at least one disease (hypertension, diabetes, thyroid diseases, kidney diseases or heart failure) before pregnancy had obesity diagnosed according to body fat tissue less often (12.5% vs 21.19%, χ=8.66, p=0.03) than the children of mothers without the diseases. The children with a birthweight above 4000g had a higher risk of being overweight in childhood than the children with a birthweight 2500-4000g (23.33% vs 14.40%, χ^2=16.25, p=0.02). Birthweight had no association with the body fat status. The pregnancy duration was not associated with the BMI z scores (t=0.11, p=0.90), FMI z scores (t=0.24, p=0.79), FFMI z scores (t=0.10, p=0.90) or FatM z scores (t=0.42, p=0.66). Prenatal stress had no impact on the BMI z scores (t=-1.31, p=0.19), FMI z scores (t=-0.40, p=0.69), FFMI z scores (t=-0.89, p=0.38) or FatM z scores (t=-0.30, p=0.76). The children who had a twin had the BMI z scores (0.33 vs -0.31, t=2.31, p=0.02) and the FatM z scores (-0.01 vs -0.43, t=1.97, p=0.04) lower than the single born children. The type of delivery had an impact on the FMI z scores and FatM z scores. The children born vaginally had the FMI z scores (-0.02 vs -0.27, t-=2.64, p=0.01) lower than the children delivered by a c-section, but they had higher FatM z scores (0.04 vs -0.16, t=2.06, p=0.04). Breastfeeding was not related to the BMI z scores (t=-0.40, p=0.69), FMI z scores (t=-0.35, p=0.73), FFMI z scores (t=-0.80, p=0.43), or FatM z scores (t=-0.24, p=0.81). The children of the mothers with exceeded weight gain during pregnancy were more likely to suffer from obesity (12.2 vs 4.5, χ^2=12.79, p=0.01). Moreover, they had higher BMI z scores (0.82 vs 0.27, t=2.77, p=0.01), FMI z scores (0.33 vs -0.12, t=2.96, p<0.01), FFMI z scores (0.38 vs 0.05, t=2.29, p=0.02) and FatM z scores (0.53 vs -0.06, t=3.76, p<0.01). (Table 9).

Table 9. Prevalence of underweight, overweight and obesity diagnosed according to IOTF (Body weight status) and according to McCarthy criteria (Body fat status), and association between body composition parameters and perinatal factors.

Variable		Body weight status					Body fat status					BMI z scores		FMI z scores		FFMI z scores		FatM z scores	
	n		Underweight	Proper weight	Overweight	Obesity	n	Underweight	Proper weight	Overweight	Obesity		$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD
Pregnancy duration	425						423													
<37 week			1	19	6	4		0	40	9	9		0.35	1.14	-0.13	0.90	0.13	0.77	-0.08	0.87
			0.24%	4.47%	1.41%	0.94%		0,00%	9.46%	2.13%	2.13%									
37-42 week			40	276	59	19		1	250	56	56		0.34	1.23	-0.05	0.95	0.08	0.91	0.03	1.00
			9.41%	64.94%	13.88%	4.47%		0.24%	59.1%	13.24%	13.24%									
>42 week			0	1	0	0		0	0	2	0		0.74	0.59	0.20	0.20	0.01	0.76	0.36	0.03
			0,00%	0.24%	0,00%	0,00%		0,00%	0,00%	0.47%	0,00%									
		χ^2	6.15					10.84				F	0.11		0.24		0.10		0.42	
		p	0.41					0.09				p	0.90		0.79		0.90		0.66	
At least one disease during pregnancy	454						454													
No			27	223	46	13		0	217	53	38		0.31	1.14	-0.12	0.82	0.08	0.88	-0.06	0.85
			5.95%	49.12%	10.13%	2.86%		0,00%	47.8%	11.67%	8.37%									
Yes			18	92	24	11		1	97	19	29		0.36	1.39	0.02	1.15	0.10	0.92	0.13	1.22
			3.96%	20.26%	5.29%	2.42%		0.22%	21.37%	4.19%	6.39%									
		χ^2	4,74					7.24				t	-0.40		-1.54		-0.24		-1.93	
		p	0.19					0.06				p	0.69		0.12		0.81		0.05	
At least one disease before pregnancy	456						533													
No			33	241	48	16		0	237	57	42		0.30	1.19	-0.12	0.89	0.06	0.87	-0.05	0.92
			7.24%	52.85%	10.53%	3.51%		0,00%	52.2%	12.56%	9.25%									
Yes			12	76	22	8		1	77	15	25		0.40	1.31	0.04	1.06	0.14	0.97	0.16	1.14
			2.63%	16.67%	4.82%	1.75%		0.22%	16.96%	3.3%	5.51%									
		χ^2	2.43					**8.66**				t	-0.76		-1.52		-0.75		-2.00	
		p	0.49					**0.03**				p	0.45		0.13		0.45		0.05	
Prenatal stress	454						440													
No			35	229	47	17		1	237	44	47		0.28	1.22	-0.09	0.95	0.06	0.90	-0.01	1.00
			7.71%	50.44%	10.35%	3.74%		0.22%	52.2%	9.69%	10.35%									
Yes			10	86	23	7		0	77	28	20		0.44	1.23	-0.05	0.93	0.14	0.87	0.02	0.95
			2.2%	18.94%	5.07%	1.54%		0,00%	16.96%	6.17%	4.41%									
		X	1.65					6.64				t	-1.31		-0.40		-0.89		-0.30	
		p	0.64					0.08				p	0.19		0.69		0.38		0.76	
Type of pregnancy	437						435													
Single			39	294	65	19		1	288	68	58		0.33	1.20	-0.08	0.92	0.08	0.88	-0.01	0.95
			8.92%	67.28%	14.87%	4.35%		0.23%	66.21%	15.63%	13.33%									
Twin			5	12	1	2		0	17	1	2		-0.31	1.28	-0.46	0.82	-0.10	0.77	-0.43	0.72
			1.14%	2.75%	0.23%	0.46%		0,00%	3.91%	0.23%	0.46%									
		χ^2	7.53					2.49				t	**2.31**		1.82		0.89		**1.97**	
		p	0.06					0.48				p	**0.02**		0.07		0.37		**0.04**	
Type of delivery	434						434													
Vaginal			32	207	51	18		1	204	55	50		0.35	1.26	-0.02	0.99	0.10	0.93	0.04	1.02
			7.34%	47.48%	11.7%	4.13%		0.23%	46.79%	12.61%	11.47%									
C-section			11	98	16	3		0	99	16	11		0.21	1.07	-0.27	0.67	0.02	0.75	-0.16	0.73
			2.52%	22.48%	3.67%	0.69%		0,00%	22.71%	3.67%	2.52%									
		χ^2	4.70					7.41				t	1.11		**2.64**		0.83		**2.06**	
		p	0.20					0.06				p	0.27		**0.01**		0.41		**0.04**	
Birthweight <2500	441		6	10	2	2	441	0	16	2	2		-0.20	1.49	-0.32	0.95	0.01	1.05	-0.29	0.83

			1.36%	2.27%	0.45%	0.45%		0,00%	3.63%	0.45%	0.45%								
2500-4000			36	255	52	18		1	250	60	51		0.30	1.21	-0.08	0.92	0.06	0.89	-0.01	0.97
			8.16%	57.82%	11.79%	4.08%		0.23%	56.69%	13.61%	11.56%								
>4000			2	42	14	2		0	40	10	9		0.54	1.12	-0.09	0.92	0.24	0.82	0.07	0.95
			0.45%	9.52%	3.17%	0.45%		0,00%	9.07%	2.27%	2.04%								
		χ^2	**16.25**					3.38				t	2.85		0.64		1.18		1.06	
		p	**0.02**					0.97				p	0.06		0.53		0.31		0.35	
Breastfeeding	443						441													
Yes			40	283	60	20		1	282	64	54		0.30	1.22	-0.10	0.92	0.07	0.89	-0.02	0.96
			9.03%	63.88%	13.54%	4.51%		0.23%	63.95%	14.51%	12.24%									
No			4	26	8	2		0	25	8	7		0.38	1.20	-0.05	0.83	0.18	0.83	0.02	0.87
			0.9%	5.87%	1.81%	0.45%		0,00%	5.67%	1.81%	1.59%									
		χ^2	0.76					1.21				t	-0.40		-0.35		-0.80		-0.24	
		p	0.87					0.75				p	0.69		0.73		0.43		0.81	
Siblings	434						434													
Yes			33	238	47	16		1	238	51	43		0.27	1.18	-0.13	0.91	0.05	0.85	-0.05	0.93
			7.6%	54.84%	10.83%	3.69%		0.23%	54.84%	11.75%	9.91%									
No			11	66	19	4		0	68	17	16		0.35	1.25	-0.03	0.93	0.10	0.90	0.04	1.01
			2.53%	15.21%	4.38%	0.92%		0,00%	15.67%	3.92%	3.69%									
		χ^2	1.73					1.09				t	-0.60		-0.89		-0.57		-0.73	
		p	0.63					0.78				p	0.55		0.37		0.57		0.46	
Weight gain during pregnancy	434						434													
Exceeded			2	22	12	5		0	22	9	9		0.82	1.30	0.33	1.12	0.38	1.17	0.53	1.22
			0.46%	5.07%	2.76%	1.15%		0,00%	5.07%	2.07%	2.07%									
Non-exceeded			42	279	54	18		1	277	59	57		0.27	1.21	-0.12	0.91	0.05	0.85	-0.06	0.93
			9.68%	64.29%	12.44%	4.15%		0.23%	63.82%	13.59%	13.13%									
		χ^2	**12.79**					4.19				t	**2.77**		**2.96**		**2.29**		**3.76**	
		p	**0.01**					0.24				p	**0.01**		**<0.01**		**0.02**		**<0.001**	

$\bar{x}$ – mean, BMI – Body Mass Index, FMI – Fat Mass Index, FFMI – Fat Free Mass Index, FatM – Fat Mass in kg, ACE – Adverse Childhood Events

4.8.Adverse childhood experiences

The number of experienced events was associated with overweight diagnosed according to IOTF (χ^2=17.27, p=0.04). However, the experience of stressors was not associated with the body fat status (χ^2=13.0, p=0.16). The children who had been exposed to family conflicts had obesity more often than the children who had not experienced that stressor (9.46% vs 3.70%, χ^2=12.44, p=0.01). The children who had witnessed violence had excessive body fat more often than the children who had not experienced the stressor (18.18% vs 13.55%, χ^2=12.63, p=0.01). The children who had experienced death of someone close were diagnosed overweight according to body fat tissue more often than the children who had not experienced the stressor (22.67% vs 13.96%, χ^2=8.50, p=0.03). The children who had been separated from their parents were more often diagnosed underweight according to BMI (8.17% vs 19.30%, χ^2=8.44, p=0.04) and more often obese according to body fat tissue (12.81 vs 19.30%, χ^2=8.35, p=0.04) compared to the children who had not been separated from their parents. Various types of stressors were not associated with the body composition parameters (Table 10).

Table 10. Prevalence of underweight, overweight and obesity diagnosed according to IOTF (Body weight status) and according to McCarthy criteria (Body fat status), and association between body composition parameters and ACE

Variable		Body weight status					Body fat status					BMI z scores		FMI z scores		FFMI z scores		FatM z scores	
	n		Underweight	Proper weight	Overweight	Obesity	n	Underweight	Proper weight	Overweight	Obesity		$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD
ACE	454						454													
0			18	189	35	8		0	180	36	35		0.26	1.12	-0.14	0.88	0.04	0.84	-0.07	0.92
			3.96%	41.63%	7.71%	1.76%		0,00%	39.65%	7.93%	7.71%									
1			13	67	19	10		0	74	20	15		0.49	1.29	0.03	0.99	0.18	0.91	0.14	1.03
			2.86%	14.76%	4.19%	2.2%		0,00%	16.3%	4.41%	3.3%									
2			8	28	8	5		0	29	8	11		0.42	1.52	0.04	1.21	0.18	1.06	0.16	1.30
			1.76%	6.17%	1.76%	1.1%		0,00%	6.39%	1.76%	2.42%									
3+			6	31	8	1		1	31	8	6		0.14	1.27	-0.10	0.80	0.00	0.93	-0.10	0.83
			1.32%	6.83%	1.76%	0.22%		0.22%	6.83%	1.76%	1.32%									
		χ^2	**17,27**					13.00				F	1.33		1.14		0.97		1.80	
		p	**0.04**					0.16				p	0.27		0.33		0.41		0.15	
Life/health threat	426						426													
No			34	274	63	18		1	273	60	55		0.33	1.19	-0.08	0.92	0.07	0.86	0.00	0.96
			7.98%	64.32%	14.79%	4.23%		0.23%	64.08%	14.08%	12.91%									
Yes			7	24	4	2		0	27	6	4		0.09	1.35	-0.24	0.90	0.04	1.05	-0.15	0.95
			1.64%	5.63%	0.94%	0.47%		0,00%	6.34%	1.41%	0.94%									
		χ^2	4.45					0.42				t	1.15		1.00		0.21		0.92	
		p	0.22					0.95				p	0.25		0.32		0.83		0.36	
Life/health threat witness	426																			
No			41	270	62	19		1	279	60	53		0.29	1.22	-0.10	0.93	0.07	0.90	-0.02	0.97
			9.62%	63.38%	14.55%	4.46%		0.23%	65.49%	14.08%	12.44%									
Yes			0	28	5	1		0	21	6	6		0.53	0.89	-0.04	0.72	0.11	0.62	0.03	0.78
			0,00%	6.57%	1.17%	0.23%		0,00%	4.93%	1.41%	1.41%									
		χ^2	4.63					0.97				t	-1.12		-0.37		-0.23		-0.29	
		p	0.20					0.81				p	0.27		0.71		0.82		0.77	
Violence victim	426						426													
No			35	274	63	17		1	272	60	56		0.33	1.17	-0.09	0.91	0.07	0.85	-0.01	0.96
			8.22%	64.32%	14.79%	3.99%		0.23%	63.85%	14.08%	13.15%									
Yes			6	24	4	3		0	28	6	3		0.04	1.45	-0.18	0.97	0.07	1.16	-0.12	0.99
			1.41%	5.63%	0.94%	0.7%		0,00%	6.57%	1.41%	0.7%									
		χ^2	3.61					1.23				t	1.41		0.57		0.04		0.72	
		p	0.31					0.75				p	0.16		0.57		0.97		0.47	
Violence witness	424						424													
No			37	276	60	18		0	277	61	53		0.31	1.18	-0.11	0.90	0.07	0.88	-0.03	0.94
			8.73%	65.09%	14.15%	4.25%		0,00%	65.33%	14.39%	12.5%									
Yes			4	20	7	2		1	22	4	6		0.26	1.43	0.07	1.09	0.10	0.97	0.13	1.20
			0.94%	4.72%	1.65%	0.47%		0.24%	5.19%	0.94%	1.42%									
		χ^2	1.46					**12.63**				t	0.22		-1.08		-0.16		-0.92	
		P	0.69					**0.01**				p	083		0.28		0.87		0.36	
Disease/death of someone close	426						426													
No			35	247	52	16		0	253	49	49		0.29	1.18	-0.11	0.91	0.08	0.90	-0.03	0.95
			8.22%	57.98%	12.21%	3.76%		0,00%	59.39%	11.5%	11.5%									
Yes			6	51	15	4		1	47	17	10		0.39	1.29	-0.01	0.94	0.03	0.78	0.05	0.99
			1.41%	11.97%	3.52%	0.94%		0.23%	11.03%	3.99%	2.35%									
		χ^2	1.40					**8.50**				t	-0.65		-0.90		0.51		-0.62	
		P	0.70					**0.03**				p	0.52		0.37		0.61		0.54	

Family conflicts	425						425												
No			28	256	54	13		0	252	53	46		0.30	1.15	-0.12	0.89	0.05	0.85	-0.04	0.93
			6.59%	60.24%	12.71%	3.06%		0,00%	59.29%	12.47%	10.82%									
Yes			13	42	12	7		1	48	13	12		0.31	1.41	0.01	1.02	0.15	1.00	0.06	1.08
			3.06%	9.88%	2.82%	1.65%		0.24%	11.29%	3.06%	2.82%									
		χ^2	**12.44**					**5.83**				t	-0.09		-1.07		-0.82		-0.79	
		P	**0.01**					**0.12**				p	0.93		0.29		0.41		0.43	
Separation from parents																				
No			30	264	57	16		0	263	57	47		0.32	1.17	-0.10	0.88	0.09	0.87	-0.02	0.92
			7.08%	62.26%	13.44%	3.77%		0,00%	62.03%	13.44%	11.08%									
Yes			11	33	9	4		1	37	8	11									
			2.59%	7.78%	2.12%	0.94%		0.24%	8.73%	1.89%	2.59%		0.20	1.42	-0.03	1.14	-0.03	0.94	0.03	1.18
		χ^2	**8.44**					**8.35**				t	0.69		-0.55		0.99		-0.40	
		P	**0.04**					**0.04**				p	0.49		0.58		0.32		0.69	
School problems	423						423													
No			39	290	63	19		0	293	63	55		0.30	1.19	-0.10	0.92	0.06	0.87	-0.02	0.96
			9.22%	68.56%	14.89%	4.49%		0,00%	69.27%	14.89%	13,00%									
Yes			2	6	3	1		1	6	2	3		0.38	1.67	0.00	0.95	0.38	1.17	0.06	1.07
			0.47%	1.42%	0.71%	0.24%		0.24%	1.42%	0.47%	0.71%									
		χ^2	2.36					**36.16**				t	-0.22		-0.37		-1.23		-0.28	
		p	0.50					**<0.001**				p	0.83		0.71		0.22		0.78	
Other unspecified stressors	421						421													
No			38	284	61	19		1	286	62	53		0.30	1.19	-0.10	0.92	0.06	0.86	-0.02	0.96
			9.03%	67.46%	14.49%	4.51%		0.24%	67.93%	14.73%	12.59%									
Yes			3	10	5	1		0	12	3	4		0.41	1.60	0.03	0.95	0.26	1.26	0.14	0.97
			0.71%	2.38%	1.19%	0.24%		0,00%	2.85%	0.71%	0.95%									
		χ^2	3.04					1.04				t	-0.38		-0.60		-0.95		-0.72	
		P	0.39					0.79				p	0.71		0.55		0.34		0.47	

$\bar{x}$-mean, BMI – Body Mass Index, FMI – Fat Mass Index, FFMI – Fat Fress Mass Index, FatM – Fat Mass in kg, ACE – Adverse Childhood Events

4.9. Multiple regression models for body composition parameters

Multiple regression models were prepared for each dependent variable (BMI z scores, FMI z scores, FFMI z scores, and FatM z scores) including the following independent variables: the type of family, highest body weight during pregnancy, pregnancy duration, prenatal stress, mother's age at the child's birth, maternal BMI before pregnancy, maternal current BMI, maternal education level, paternal current BMI, paternal education level, ACE experience, eating behaviour, physical activity, screen time, sleep length, and polymorphisms of the FTO and MC4R genes. All thes variables were included in the stepwise multiple regression model. The variables were added until the highest value of R^2 was reached. Multiple regression was performed for the whole group and separately for boys and girls.

The variables that remained in the model for all groups, explaining 17.2% ($F=7.02$, $p<0.001$) of the variability in BMI z scores were paternal BMI, highest body weight during pregnancy, maternal age at the child's birth, paternal education level, prenatal stress, maternal BMI before pregnancy, eating behaviour and FTO and MC4R gene polymorphisms. Among these variables, paternal BMI, highest body weight in pregnancy and maternal age at the child's birth made the greatest contribution to the prediction of the dependent variable ($\Delta R^2=0.085$, $p<0.001$; $\Delta R^2=0.031$, $p=0.16$, $\Delta R^2=0.021$, $p=0.01$, respectively). Specifically, paternal BMI was positively associated with BMI z scores ($\beta=0.26$, $p<0.001$), while the mother's age at the child's birth was negatively associated with BMI z scores ($\beta=-0.13$, $p=0.01$) (Table 11).

Thirteen point eight percent (13.8%) of the variance in FMI z scores was explained by paternal BMI, maternal education, highest body weight during pregnancy, maternal age at the child's birth, FTO polymorphism, and experience of ACE. Among the variables, paternal BMI ($\beta=0.21$, $p<0.001$), maternal education ($\beta=0.18$, $p<0.001$), highest body weight in pregnancy ($\beta=0.16$,

p<0.001) and FTO polymorphism (β=0.10, p=0.04) were positively connected with FMI z scores. Paternal BMI, maternal education and highest body weight during pregnancy had the greatest contribution to predicting the variable (ΔR^2=0.056, p<0.001; ΔR^2=0.043, p<0.001, ΔR^2=0.025, p=<0.001, respectively) (Table 11).

The FFMI z scores were predicted by 6 variables: paternal BMI, maternal pre-pregnancy BMI, maternal age at the child's birth, eating behaviour, MC4R gene polymorphism, and paternal education. The model explained 12.5% of the variance in the dependent variable (p<0.001). Among the variables, paternal BMI, maternal pre-pregnancy BMI and maternal age at the child's birth had the greatest contributions (ΔR^2=0.075, p<0.001; ΔR^2=0.019, p=0.006, ΔR^2=0.018, p=0.01, respectively). Paternal BMI (β=0.25, p<0.001) and maternal pre-pregnancy BMI (β=0.14, p=0.006) were positively associated with the dependent variable, while the maternal age at the child's birth (β =-0.13, p=0.01) showed a negative association with FFMI z scores (Table 11).

The forward regression model for the FatM z scores included maternal education, highest body weight in pregnancy, paternal BMI, maternal age at the child's birth, FTO gene polymorphism, paternal education, experiences of ACE and eating behaviour, which explained 17.8% of the variance in FatM z scores. The FatM z scores were positively associated with maternal education (β=0.16, p=0.01), highest body weight in pregnancy (β=0.21, p<0.001), paternal BMI (β=0.17, p<0.001), and FTO polymorphism (β=0.11, p=0.03), while they were negatively associated with maternal age at the child's birth (β=-0.11, p=0.04). Maternal education, highest body weight in pregnancy and paternal BMI made the greatest contributions predicting the variable (ΔR^2=0.059, p=0.01, ΔR^2=0.054, p<0.001, ΔR^2=0.028, p<0.01, respectively) (Table 11).

Table 11. Regression analysis predicting BMI z scores, FMI z scores and FatM z scores in children

Variable	R2	β	F	p-value
Model 1: BMI z scores	0.172		7.02	<0.001
paternal BMI		0.26		<0.001
highest body weight in pregnancy		0.11		0.16
mother's age at the child's birth		-0.13		0.01
father's education (Reference: higher education)		0.08		0.11
prenatal stress at least one (Reference: 0)		0.07		0.17
maternal BMI before pregnancy		0.11		0.15
FTO (Reference: TT)		0.07		0.18
eating behaviour (Reference: good)		0.07		0.2
MC4R (Reference: TT)		0.05		0.31
Model 2: FMI z scores	0.138		10.24	<0.001
paternal BMI		0.21		<0.001
maternal education level (Reference: higher education)		0.18		<0.001
highest body weight in pregnancy		0.16		<0.001
mother's age at the child's birth		-0.10		0.06
FTO (Reference: TT)		0.10		0.04
ACE at least one (Reference: 0)		0.07		0.19
Model 3: FFMI z scores	0.125		8.09	<0.001
paternal BMI		0.25		<0.001
maternal pre-pregnancy BMI		0.14		0.006
mother's age at the child's birth		-0.13		0.01
eating behaviour (Reference: good)		0.08		0.15
MC4R (Reference: TT)		0.06		0.21
paternal education level (Reference: higher education)		0.05		0.30
Model 4: FatM z scores	0.178		9.17	<0.001
maternal education level (Reference: higher education)		0.16		0.01
highest body weight in pregnancy		0.21		<0.001
paternal BMI		0.17		<0.001
mother's age at the child's birth		-0.11		0.04
FTO (Reference: TT)		0.11		0.03
paternal education level (Reference: higher education)		0.06		0.28
ACE at least one (Reference: 0)		0.06		0.25
eating behaviour (Reference: good)		0.06		0.27

BMI – Body Mass Index, FMI – Fat Mass Index, FFMI – Fat Free Mass Index, FatM – Fat Mass in kg

In the group of girls, the variables that remained in the multiple regression model explaining 26% ($F=11.53$, $p<0.001$) of BMI variability in z scores were paternal BMI, highest body weight during pregnancy, FTO gene polymorphism, maternal education, and duration of pregnancy. Paternal BMI, highest body weight during pregnancy and FTO gene polymorphism had the greatest contribution to the prediction of the dependent variable (respectively: $\Delta R2=0.144$, $p<0.001$; $\Delta R2=0.07$, $p<0.001$, $\Delta R2=0.022$, $p=0.04$). These variables were positively correlated with BMI z scores (Table 12).

Twenty-nine percent (29%) of the variance in FMI scores in the girls' group was explained by paternal BMI, highest gestational weight, maternal education, FTO polymorphism, duration of pregnancy, MC4R polymorphism, current maternal BMI, prenatal stress experience and ACE. Father's BMI ($\beta=0.25$, $p<0.001$), highest gestational weight ($\beta=0.34$, $p<0.001$), maternal education ($\beta=0.26$, $p<0.001$) and FTO gene polymorphism ($\beta =0.15$, $p=0.03$) were positively associated with FMI z scores and had the greatest impact on the prediction of the dependent

variable (ΔR2=0.102, p<0.001; ΔR2=0.067, p<0.001, ΔR2=0.066, p=<0.001, ΔR2=0.002 p=0.03 respectively) (Table 12).

The girls' FFMI scores were predicted based on six variables: father's BMI, highest gestational weight, mother's age at birth, duration of pregnancy, prenatal stress experience and sleep duration. The model explained 14.7% of the variance of the dependent variable (p<0.001). Paternal BMI and highest body weight during pregnancy showed the strongest influence (ΔR2=0.096, p<0.001; ΔR2=0.024, p=0.04, respectively). Paternal BMI (β=0.27, p<0.001) and highest gestational weight (β=0.16, p=0.04) were positively associated with the dependent variable (Table 12).

The stepwise regression model for FatM z scores in the girls' group included highest gestational weight, paternal BMI, maternal education, FTO gene polymorphism, current maternal BMI, duration of pregnancy, experience of prenatal stress and ACE, which explained 28.9% of the variance in FatM z scores. FatM scores were positively associated with highest gestational weight (β=0.40, p<0.001), paternal BMI (β=0.23, p=0.001), maternal education (β=0.25, <0.001) and FTO gene polymorphism (β=0.14, p=0.04). The variables had the greatest impact on the prediction of the dependent variable (respectively, ΔR2=0.15, p<0.001, ΔR2=0.064, p=0.001, ΔR2=0.055, p<0.01, ΔR2=0.018, p=0.04) (tab. 12).

Table 12. Multiple forward regression results predicting BMI z scores, FMI z scores, FFMI z scores, and FatM z scores in girls

Variable	R2	β	F	p-value
Model 1: BMI z scores	0.260		11.53	<0.001
paternal BMI		0.329		<0.001
highest body weight in pregnancy		0.284		<0.001
FTO (ref. TT)		0.142		0.04
maternal education level (Reference: higher education)		0.131		0.05
pregnancy duration		-0.07		0.27
Model 2: FMI z scores	0.290		7.46	<0.001
paternal BMI		0.25		<0.001
highest body weight in pregnancy		0.34		<0.001
maternal education level (Reference: higher education)		0.26		<0.001
FTO (ref. TT)		0.15		0.03
pregnancy duration		-0.11		0.10
MC4R (ref. TT)		0.089		0.19
maternal current BMI		-0.09		0.38
prenatal stress (ref. 0)		-0.10		0.18
ACE at least one (ref. 0)		0.09		0.21
Model 3: FFMI z scores	0.147		4.68	<0.001
paternal BMI		0.27		<0.001
highest body weight in pregnancy		0.16		0.04
mother's age at the child's birth		-0.10		0.18
pregnancy duration		-0.07		0.31
prenatal stress (ref. 0)		-0.09		0.24
sleep duration		0.08		0.30
Model 4: FatM z scores	0.289		8.17	<0.001
highest body weight in pregnancy		0.40		<0.001
paternal BMI		0.23		0.001
maternal education level (Reference: higher education)		0.25		<0.001
FTO (ref. TT)		0.14		0.04
maternal current BMI		-0.13		0.19
pregnancy duration		-0.09		0.18
prenatal stress (ref. 0)		-0.12		0.10
ACE at least one (ref. 0)		0.11		0.13

The boys' BMI scores were predicted based on 7 variables: paternal BMI, maternal age at the child's birth, maternal BMI in pregnancy, experience of prenatal stress, eating habits, maternal education, and MC4R gene polymorphism. The model explained 14.6% of the variance in the dependent variable ($p<0.001$). Paternal BMI, maternal age at the child's birth, and maternal BMI before pregnancy had the greatest impact ($\Delta R2=0.053$, $p=0.002$; $\Delta R2=0.027$, $p=0.03$, $\Delta R2=0.022$, $p=0.02$, respectively). Paternal BMI ($\beta=0.08$, $p=0.002$) and maternal BMI before pregnancy ($\beta=0.07$, $p=0.02$) were positively associated with the dependent variable, while maternal age at the child's birth was negatively associated with the dependent variable ($\beta=-0.04$, $p=0.03$) (Table 13).

In the group of boys, the variables that remained in the multiple regression model explaining 8% ($F=5.04$, $p<0.002$) of the variability of FMI z scores were maternal education, maternal age at the child's birth, and paternal BMI ($\Delta R2=0.40$, $p=0.02$, $\Delta R2=0.019$, $p=0.04$, $\Delta R2=0.021$,

p=0.046, respectively). Paternal BMI (β=0.17, p=0.02) and maternal education (β=0.15, p=0.046) were positively associated with FMI z scores, while maternal age at the child's birth was negatively associated with FMI z scores (β= -0.15, p=0.04) (Table 13).

The stepwise regression model for FFMI z scores in the boys' group included paternal BMI, eating behavior, current maternal BMI, maternal age at the child's birth, prenatal stress experience, and paternal education, which explained 16.5% of the dependent variable's variance. FFMI z scores were positively related to paternal BMI (β=0.24, p<0.001), eating behaviour (β=0.16, p=0.02), and current maternal BMI (β=0.17, p=0.02). These variables had the greatest impact on the prediction of the explained variable (ΔR2=0.71, p<0.001, ΔR2=0.028, p=0.02, ΔR2=0.024, p=0.02, respectively) (Table 13).

Eight point five percent (8.5%) of the variance in FatM scores in the boys' group was explained by maternal education, paternal BMI, maternal age at the child's birth, and highest weight during pregnancy. Maternal education (β=0.16, p=0.04) and paternal BMI (β=0.15, p=0.04) were positively associated with FatM z scores, and maternal age at the child's birth was negatively associated with FatM z scores (β=-0.16, p=0.03) . Maternal education, paternal BMI and maternal age at the child's birth had the greatest impact on the prediction of the dependent variable (ΔR2=0.037, p=0.04; ΔR2=0.019, p=0.04, ΔR2=0.023, p=0.03, respectively) (Table 13).

Table 13. Multiple forward regression results predicting BMI z scores, FMI z scores, FFMI z scores and FatM z scores in boys

variable	R2	β	F	p-value
Model 1: BMI z scores	0.146		4.15	<0.001
paternal BMI		0.08		0.002
mother's age at the child's birth		-0.04		0.03
maternal BMI before pregnancy		0.07		0.02
prenatal stress (ref. 0)		0.34		0.09
eating behaviours (ref. good)		0.28		0.12
maternal educational level (ref. higher)		0.26		0.19
MC4R (ref. TT)		0.21		0.27
Model 2: FMI z scores	0.080		5.04	<0.002
maternal educational level (ref. higher)		0.17		0.02
mother's age at the child's birth		-0.15		0.04
paternal BMI		0.15		0.046
Model 3: FFMI z scores	0.165		5.69	<0.001
paternal BMI		0.24		0.001
eating behaviours (ref. good)		0.16		0.02
maternal current BMI		0.17		0.02
mother's age at the child's birth		-0.14		0.05
prenatal stress (ref. 0)		0.10		0.14
paternal educational level (ref. higher)		0.08		0.27
Model 4: FatM z scores	0.085		4.08	<0.001
maternal educational level (ref. higher)		0.16		0.04
paternal BMI		0.15		0.04
mother's age at the child's birth		-0.16		0.03
highest body weight in pregnancy		0.08		0.30

4.10. The effects of ACEs and genetic interactions on body composition parameters

The analysis revealed the effects of the interaction between the FTO and MC4R gene polymorphisms and ACE types on the BMI, FMI, FFMI and FatM z scores. The experience of 3 or more stressors was related to an increased BMI z scores (1.05 vs -0.24, Cohen's d= 1.05) (Table 14, Fig. 1) in the children with FTO AA compared to TT, and increased FMI and FatM z scores in the children with MC4R CC compared to TT (1.26 vs -0.33, Cohen's d=3.20; 0.56 vs -0.36, Cohen's d=2.54, respectively). (Table 14, Fig. 2,3). Separation from the parents was related to an increase in BMI z scores in the children with FTO AA compared to TT (0.73 vs -0.11, Cohen's d=0.62) (Table 14, Fig. 4) and MC4R CC compared to TT. It was also connected with an increase in FMI z scores (2.55 vs -0.23, Cohen's d=1.72) and FatM z scores (2.43 vs 0.27, Cohen's d=1.39) (Table 14, Fig. 5) in the children with MC4R CC compared to TT. Difficulties at school were related to increased BMI and FMI z scores in the children with FTO AA compared to TT (2.54 vs 0.80, Cohen's d=1.90; 1.47 vs -0.003, Cohen's d=2.33, respectively) (Table 14, Fig. 6,7). The experience of other unspecified stressors was related to

higher BMI and FMI z scores in the children with FTO AA compared to TT (1.59 vs -0.71, Cohen's d=1.43; 0.98 vs -0.59, Cohen's d=1.60, respectively) (Table 14, Fig. 8,9).

Table 14. Interactions between ACEs and polymorphisms of FTO and MC4R genes

	FTO		MC4R	
BMI z scores	F	p	F	p
ACE 0,1,2,3+	**2.59**	**0.02**	1.80	0.10
Life threatened	2.20	0.11	0.10	0.90
Life threatened witness	1.73	0.17	0.30	0.74
Violence victim	0.58	0.56	0.16	0.85
Violence witness	0.50	0.61	0.22	0.80
Death of someone close	1.65	0.19	0.10	0.91
Family conflicts	1.94	0.15	0.02	0.98
Separation from parent	**3.06**	**0.048**	**3.07**	**0.03**
School problems	**5.73**	**0.004**	1.33	0.27
Other unspecified stressors	**4.60**	**0.01**	0.14	0.87
ACE at least one	0.58	0.55	0.06	0.94
FMI z scores				
ACE 0,1,2,3+	1.65	0.13	**2.31**	**0.03**
Life threatened	1.32	0.26	0.08	0.92
Life threatened witness	1.96	0.14	0.73	0.48
Violence victim	0.44	0.65	0.11	0.90
Violence witness	0.27	0.76	0.07	0.93
Death of someone close	0.15	0.86	0.55	0.58
Family conflicts	1.55	0.21	0.55	0.58
Separation from parent	0.93	0.40	**8.34**	**<0.001**
School problems	**4.09**	**0.02**	0.81	0.44
Other unspecified stressors	**3.13**	**0.04**	1.02	0.36
ACE at least one	0.63	0.53	0.26	0.77
FFMI z scores				
ACE 0,1,2,3+	1.70	0.12	1.65	0.13
Life threatened	2.67	0.07	0.18	0.84
Life threatened witness	0.50	0.61	0.39	0.67
Violence victim	1.19	0.30	0.69	0.50
Violence witness	0.01	0.99	0.74	0.48
Death of someone close	2.33	0.10	0.60	0.55
Family conflicts	2.07	0.13	0.68	0.51
Separation from parent	**3.27**	**0.04**	2.16	0.11
School problems	**4.95**	**0.007**	1.91	0.15
Other unspecified stressors	**3.03**	**0.04**	0.54	0.58
ACE at least one	0.66	0.52	1.27	0.28
FatM z scores				
ACE 0,1,2,3+	0.80	0.57	**2.27**	**0.04**
Life threatened	0.98	0.38	0.13	0.88
Life threatened witness	0.62	0.54	0.27	0.77
Violence victim	0.41	0.67	0.007	0.99
Violence witness	0.22	0.81	0.13	0.88
Death of someone close	0.31	0.74	0.13	0.88
Family conflicts	1.34	0.26	0.11	0.90
Separation from parent	0.75	0.47	**9.73**	**<0.001**
School problems	2.28	0.10	0.34	0.71
Other unspecified stressors	1.99	0.14	0.22	0.80
ACE at least one	0.64	0.53	0.07	0.93

BMI – Body Mass Index, FMI – Fat Mass Index, FFMI – Fat Free Mass Index, FatM – Fat Mass in kg

Fig. 1. Effects of interaction between FTO polymorphism and ACEs on the BMI z scores

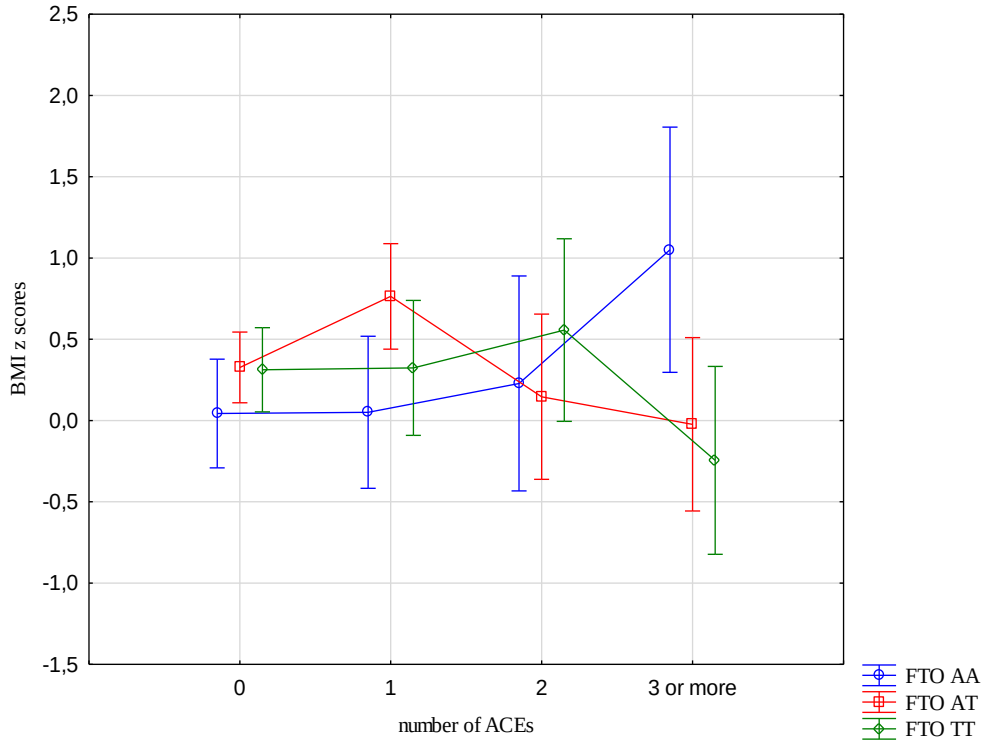


Fig. 2. Effects of interaction between MC4R polymorphism and ACEs on FMI z scores

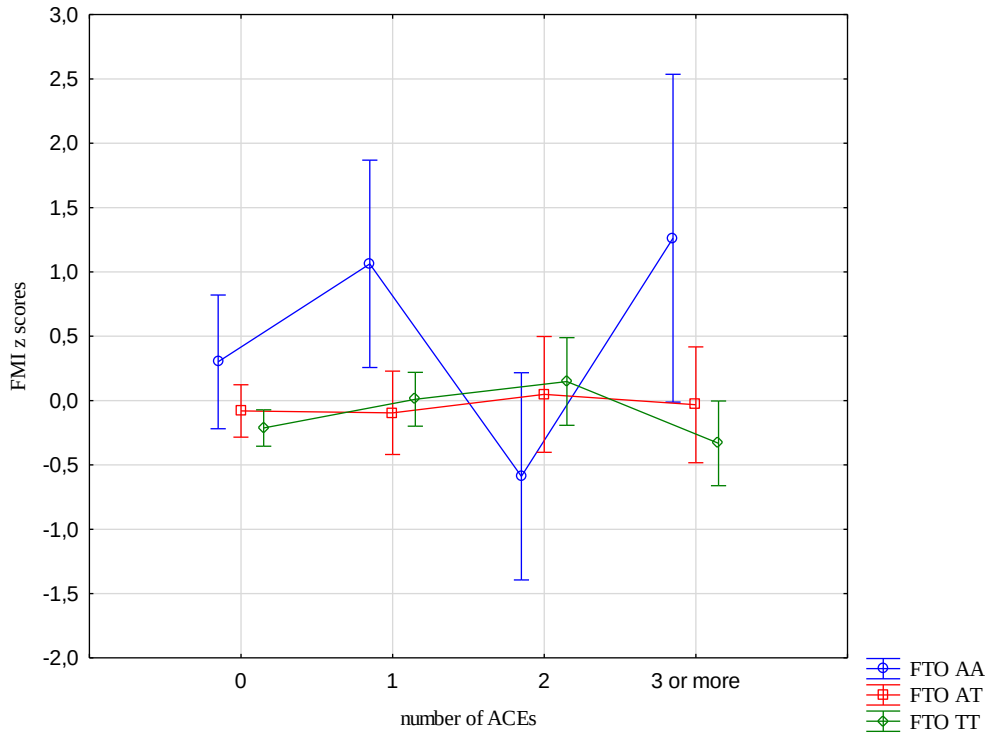


Fig. 3. Effects of interaction between MC4R polymorphism and ACEs on FatM z scores

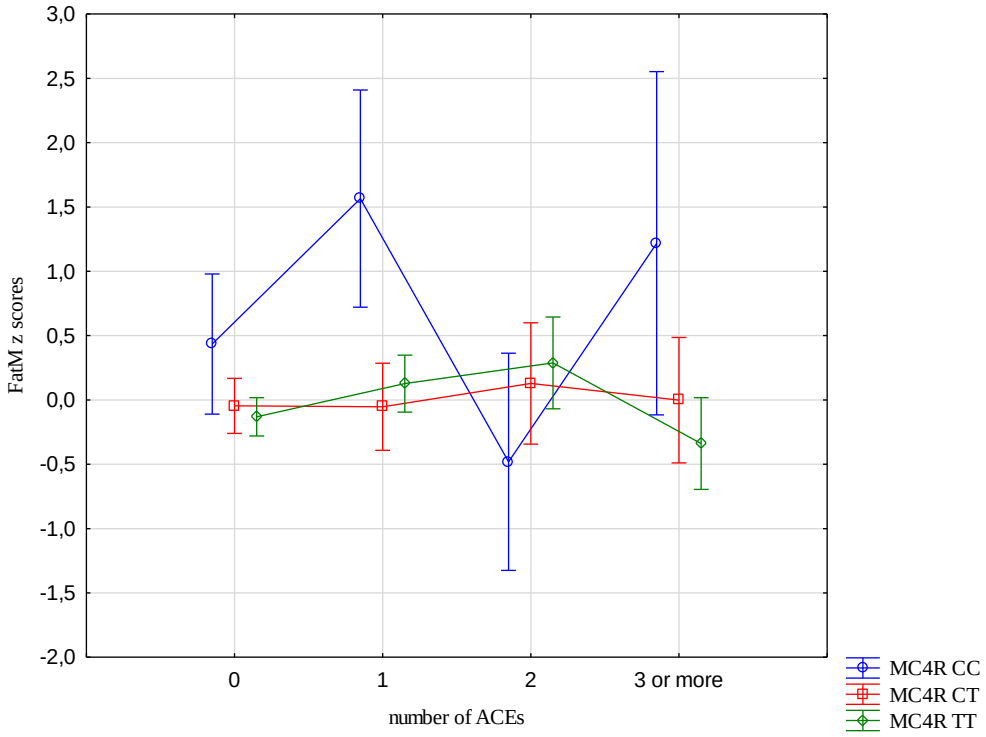


Fig. 4. Effects of interaction between FTO polymorphism and separation from parents on BMI z scores

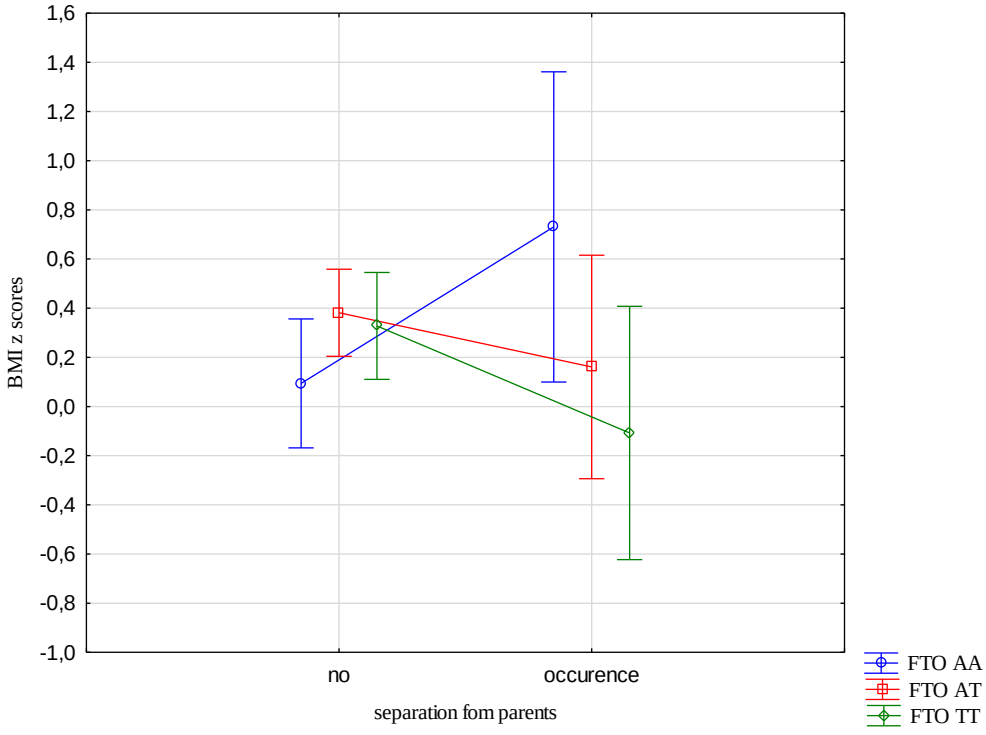


Fig. 5. Effects of interaction between MC4R polymorphism and separation from parents on FMI z scores

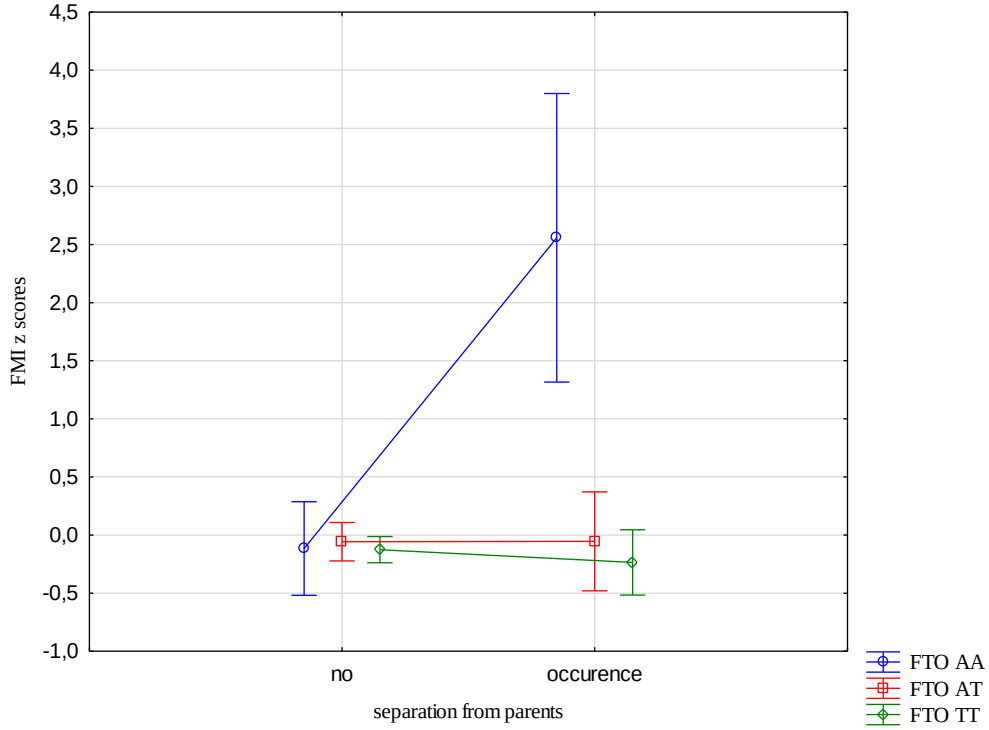


Fig. 6. Effects of interaction between FTO polymorphism and school problems on BMI z scores

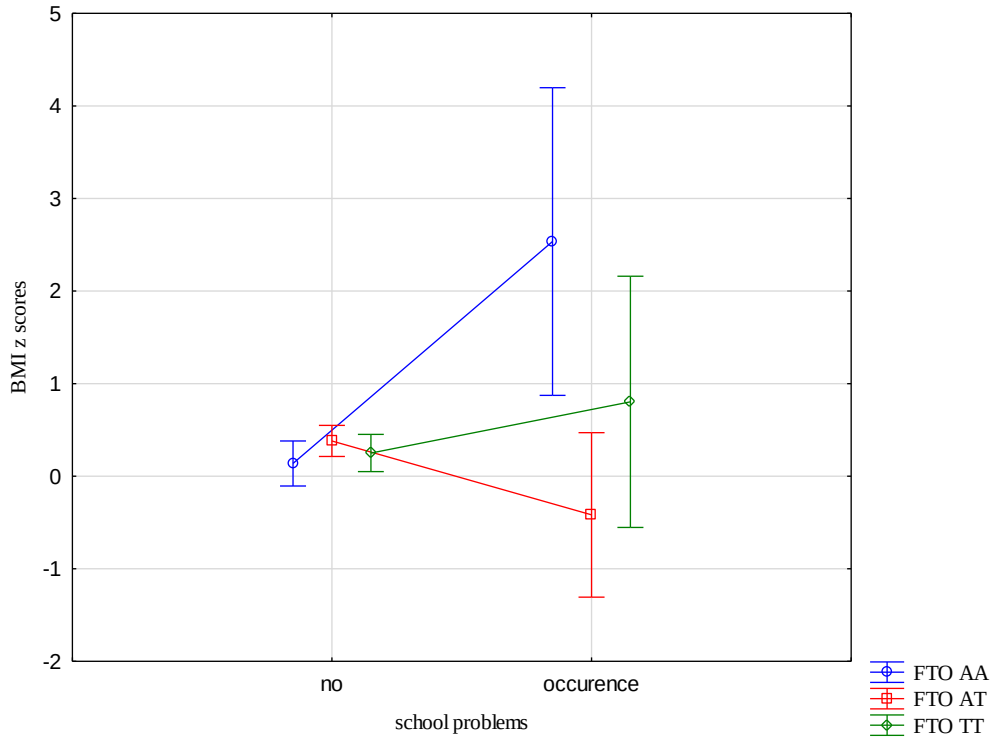


Fig. 7. Effects of interaction between FTO polymorphism and school problems on FMI z scores

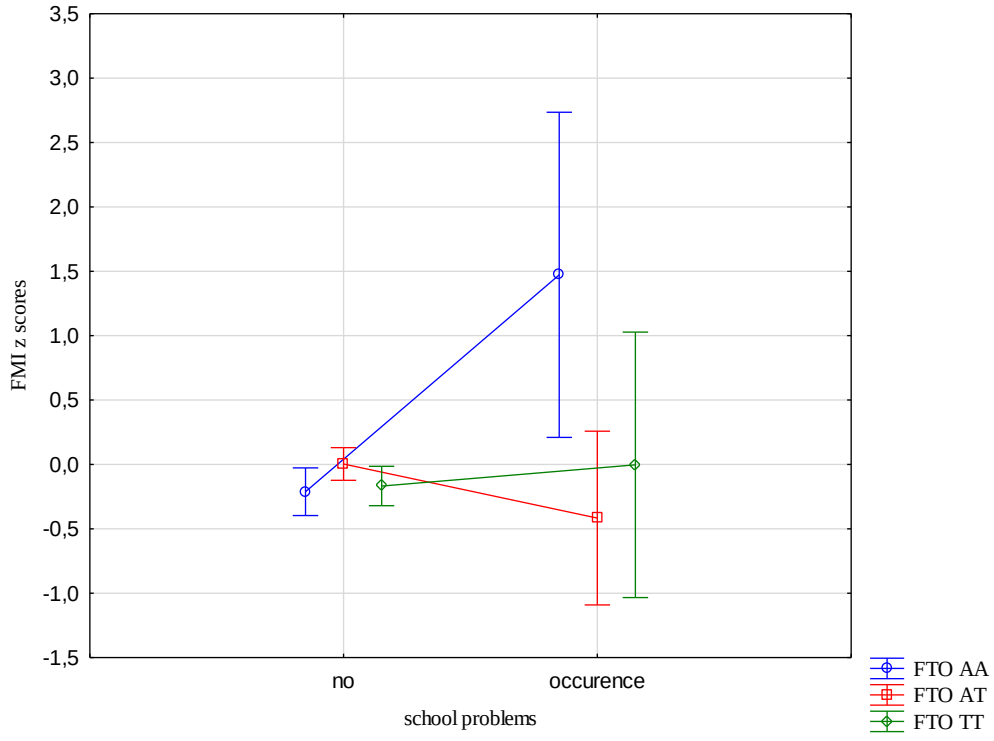


Fig. 8. Effects of interaction between FTO polymorphism and other stressful events on BMI z scores

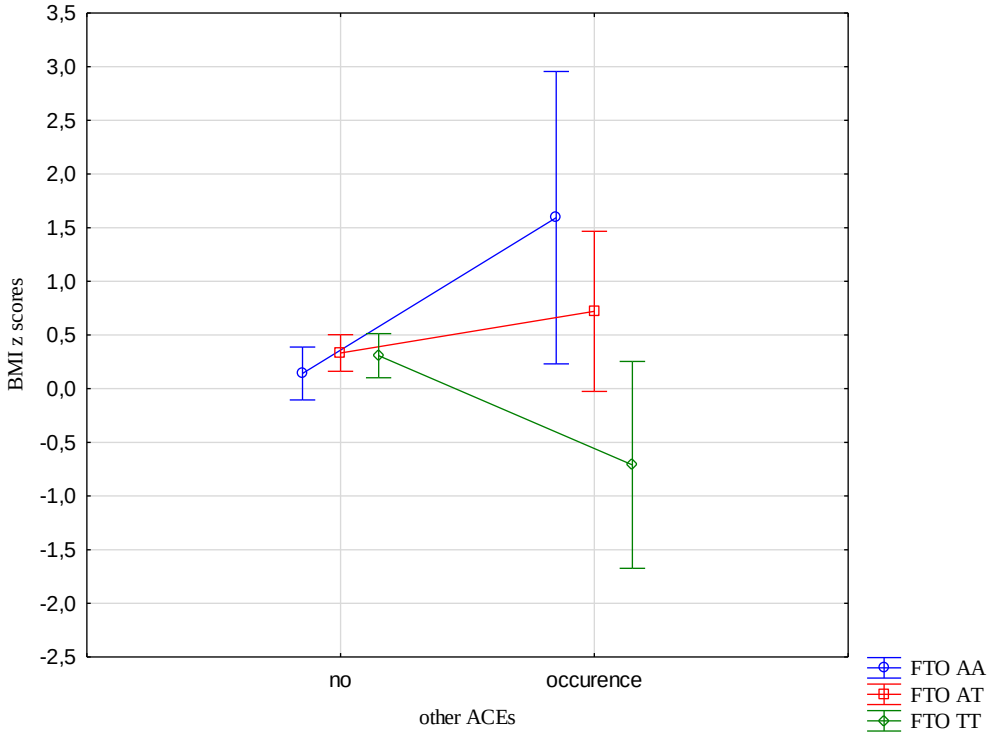
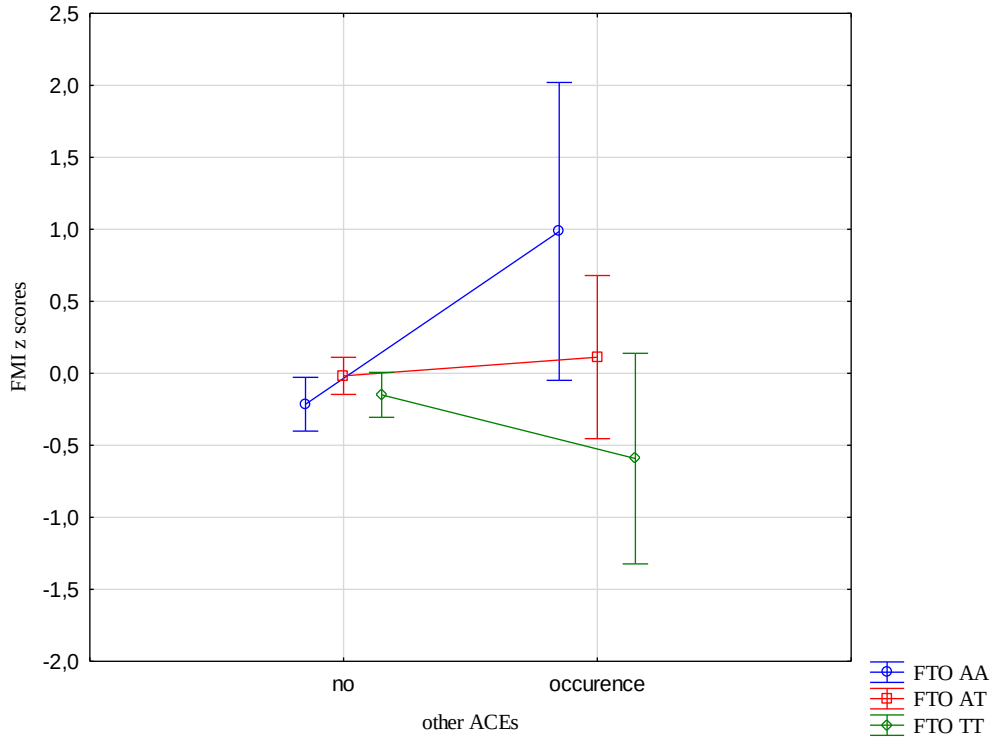


Fig. 9. Effects of interaction between FTO polymorphism and other stressful events on FMI z scores



5. Discussion

Overweight is influenced by both genetic and environmental factors. In our study we investigated the association of polymorphisms of the FTO rs9939609 and MC4R rs1778231 genes, which have been well-documented to be related to a higher prevalence of overweight and obesity [2,5].

The results of our study reveal that environmental factors have a significant influence on body composition changes in school-aged children, while genetic factors show less significance in the multiple regression model. This indicates that environmental factors play a more substantial role in shaping changes in body composition.

The study confirms that the most strongly influential factors on body composition parameters were the paternal BMI, maternal education, highest body weight in pregnancy and mother's age at the child's birth, although they explain a low variability of the dependent variable. The limited explanatory capacity of these variables needs further invastigation and additional research. It is

essential to acknowledge that beyond the factors explored in this study, numerous others may potentially influence body composition parameters. The available literature provides evidence that children of parents with overweight/obesity are more prone to developing obesity [47–50]. Other studies have indicated a stronger maternal intergenerational relationship with the child's body mass [47,48,51]. However, our findings demonstrate that the paternal BMI has the strongest influence on the child's body composition parameters. These results align with a meta-analysis that shows a connection between paternal BMI and the child's weight and/or body fat [13]. The higher the father's BMI, the greater the child's body weight and/or the higher the body fat percentage [52]. Our futher analysis reveals that paternal BMI in addition to BMI z scores significantly affects all other body composition parameters of the child, including FMI, FFMI, and FatM. A possible explanation for the influence of paternal BMI on the children's body composition could be the process of learning by imitation. Parents' weight is frequently related to their lifestyle, and it is well-documented that the dietary habits of individuals with a normal body weight differ from those who have overweight or obesity [53,54]. Children, being keen observers, often emulate the dietary choices [55] and leisure activities [56]. of their parents.

A high pregnancy weight is positively correlated with BMI z scores and FatM z scores. Previous research demonstrated that maternal gestational weight gain is associated with the child's obesity and high waist circumference [57]. Maternal overnutrition may affect the development of adipocytes and their capacity to regulate the appetite control system and energy metabolism later in life [58], which might lead to increased body fat in the offspring.

The mothers without a university education had children with higher FMI z scores and FatM z scores. There is an inverse relationship between the parents' level of education and obesity of their children, with the lowest level of education corresponding to the highest prevalence

of obesity in the children. The parents'education level has a significant impact on the child's body composition [28]. Education is also related to other components of socioeconomic status. Individuals with lower education tend to have lower income, which affects the quality of the food they choose, including the food served to their children [59]. Moreover, mothers with lower education levels are less likely to breastfeed their children [60], which is also a protective factor against the child's overweight and obesity later in life [61]. The socioeconomic conditions of parents are very important in shaping the children's eating habits since they influence the type of food available at home [62]. Studies indicate that the diet of children whose parents declared low socioeconomic status exhibita higher consumption of high-energy food with low nutritional value [63] and a higher consumption of sugary drinks [64] at a preschool age. The mother's impact on the child's nutritional preferences is already present in fetal life, as her diet during pregnancy and breastfeeding shapes the future nutritional preferences of her child [65,66].

The presence of risk alleles of the FTO and MC4R genes was included in the models describing the variability of the body composition parameters, but the relationships with MC4R were not statistically significant. However, we were interested in how genetic susceptibility and the coexistence of unfavourable environmental factors, such as ACEs would affect the body composition parameters. Experiencing three stressors while being homozygous for the risk allele was associated with higher BMI z scores for the FTO gene and higher FMI z scores and FatM z scores for the MC4R gene compared to the children who did not carry the risk allele. The results indicate interactions between genetic and environmental factors. The presence of risk alleles alone is not a factor for the occurrence of changes in children's weight and body composition, but it may become one depending on the environment. The results of our study indicate that the presence of 3 or more unfavourable life experiences could potentially serve as

a contributing factor. Upon separate examination of different types of stressors, such as separation from parents, problems at school and other unspecified types of stressors significant associations emerged.The children who were separated from their parents and also carried the risk homozygous alleles of the FTO and MC4R genes exhibited higher BMI z scores, FMI z scores, and FatM z scores. Similarly, those who were homozygous for the risk allele of the FTO gene and had serious problems in school showed higher BMI z scores, FMI z scores, and FFMI z scores. The occurrence of other unspecified stressful situations, combined with being homozygous for the risk allele of the FTO gene was also related to higher BMI z scores, FMI z scores and FFMI z scores. While considering only life stressors as the influencing factor no significant correlation was found with the body composition parameters in the children. The presence of the risk allele of the FTO gene did not demonstrate an important impact on the body composition parameters, whereas the presence of the risk allele of the MC4R gene was associated with increased FMI z scores and FFMI z scores. However, when the children were carriers of the risk allele as well as experienced ACEs, there was a statistically significant effect on all body composition parameters.

The gene polymorphisms investigated in our study were selected for analysis based on strong evidence supporting their association with BMI and body weight in children [2,5]. It is worth emphasizing, however, that no studies have so far demonstrated a direct association between the FTO gene polymorphism and a resting metabolic rate [4]. The development of excess body weight in children with the unfavourable allele of the FTO gene is attributed to their tendency to consume meals that are higher in energy and fat content [67]. Similarly for the MC4R gene, the presence of the C allele leads to increased eating pleasure, reduced satiety, and a tendency to eat when not hungry, which may contribute to obesity [5]. Thus the mere presence of an unfavourable allele of the gene does not singularly determine changes in the body weight.

However, if environmental factors, such as ACEs, which may also affect food choices [68] co-occure, the risk of changes in body composition parameters increases.

6. Conclusions

The results of our study indicate that within the multiple regression model, genetic factors exhibit a lower level of significance compared to the environment when elucidating alterations in body composition parameters among children. The presence of the risk allele does not determine a decisive influence on changes in body composition. However, together with the simultaneous occurrence of unfavourable environmental factors, such as ACEs a discernible interaction effect emerges, leading to an increase in BMI z scores and FMI z scores in children.

Strengths and weaknesses of the study

The strength of our study is the use of body weight normality variables, encompassing not only the weight itself and the BMI derived from it, but also indicators based on FMI and FFMI. Another significant aspect is the comprehensive consideration of numerous environmental, perinatal, ACE and lifestyle factors as well as the FTO and MC4R gene polymorphisms to examine their relationships with the body composition parameters. The influence of environmental factors on the risk of overweight and obesity in children has been extensively studied; however, research on ACEs and their association with body composition remains limited. To our knowledge, there have been only two previously published studies [28,29] that focused entirely on the relationship between ACEs and the body composition parameters, and their results were contradictory. Our study, therefore, represents an attempt to further explain this phenomenon. Another strength of the investigation is the examination of interactions between the genes and the environment and their mutual influence on the body composition parameters.

A weakness of the study is our reliance on information about the parents' weight and height derived solely from the questionnaires. This may be associated with an overestimation of height (especially in the case of men) and an underestimation of body weight (in women and individuals who are overweight or obese) [69]. We did not check food intake, physical activity and time of last urination prior to the body composition analysis. However, we would like to point out that other studies on this subject indicate that differences in body composition depending on external factors are not clinically significant [70]. Furthermore, limitations include the retrospective study of stressors, which increases the risk of memory error.

Ethics approval and consent to participate

The research was conducted in accordance with the principles outlined in The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans and approved by the Institutional Bioethics Board of Poznan University of Medical Sciences (approval no. 542/14). The subjects and their legal guardians were fully informed about the research procedures and they submitted a written consent to participate in the study.

Consent for publication

Not applicable

Availability of data and materials

Due to the sensitive nature of the data supporting the conclusions of the article, only selective access to data is offered on reasonable request to the principal investigator (MD-W)

Competing interests

The authors declare that they have no competing interests.

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Author Contributions: Conceptualization, TH, MD-W and AS; methodology, TH, MD-W and AS; investigation, EB, PS, TH, AD, MD-W; data curation, EB; writing – original draft preparation, EB, TH; project administration, TH; funding acquisition, TH, MD-W, AS All authors have read and agreed to the published version of the manuscript.

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