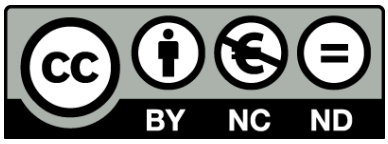
UNIVERSITAT DE BARCELONA

The Neurocognitive Phenotype of Excess Weight in Adolescents and Young Adults: Biological, Genetic, and Psychosocial Factors

Anna Prunell Castañé



The Neurocognitive Phenotype of Excess Weight in Adolescents and Young Adults: Biological, Genetic, and Psychosocial Factors

Doctoral thesis presented by

Anna Prunell Castañé

to apply for the degree of doctor from the University of Barcelona

Supervised by

Dr. María Ángeles Jurado Luque

Departament de Psicologia Clínica i Psicobiologia, Facultat de Psicologia, Universitat de Barcelona.
Institut de Neurociències, Universitat de Barcelona.

Dr. Maite Garolera Freixa

Unitat de Neuropsicologia, Consorci Sanitari de Terrassa.
Departament de Ciències Bàsiques, Facultat de Medicina i Ciències de la Salut, Universitat Internacional de Catalunya.

Doctoral Program in Medicine and Translational Research
School of Medicine and Health Sciences
University of Barcelona
June 2024

Acknowledgements

To my thesis supervisors, Dr. María Ángeles Jurado and Dr. Maite Garolera, for opening your doors and letting me in. María Ángeles, you have given me the most generous platform anyone could wish for. A platform where, both personally and professionally, I have had the chance to be surrounded by freedom: freedom to be wrong, to learn, to grow, to fight, to be sad, to pause, to celebrate. I hope that, over time, this place can be honored, perhaps with the smell of coffee, a phone call, or with new ideas for a paper. I will always and forever treasure it. Thank you. Maite, I really appreciate all the enthusiasm, advice, and support you have given me throughout these years. Thank you.

To Isabel, for being a key piece in my progress, for your intelligence and patience.

To Jonatan, for always helping in the distance.

To Veronica, for giving me the chance to learn from you and your group.

To Frauke, for sharing your talent with me.

To Montse, for such a precious and colorful friendship.

To Adrià, for being a fantastic company.

To Juanca, for being there and bringing joy to my life.

To Meghedi, for making my stay in Leipzig feel like a second home.

To my dad, for always being proud of me. This is for you.

To my mom, for all the love.

To Gemma, for being an amazing sister.

To Kirki, the sweetest cat this life could ever bring to me.

To Iván, my husband, for everything. Life with you feels like this beautiful soundtrack I can't stop listening to.

To every knockdown that turned out to be a comeback,

To the songs that made my journey better,

To this very moment,

Thank you.

The studies included in this thesis were financially supported by a PhD fellowship from the Spanish Ministry of Science, Innovation and Universities (PRE2019-087430), which included funding for a visiting research fellowship. Additional financial support was received from the Spanish Ministry of Economy and Competitiveness (PSI2017-86536-C2-1-R and PSI2017-86536-C2-2-R), funded by MCIN/AEI/ https://doi.org/10.13039/501100011033 and the European Regional Development Fund (ERDF). Financial support from the Departament d'Innovació, Universitats i Empresa, Generalitat de Catalunya (2021SGR0801), and the Institut de Neurociències de la Universitat de Barcelona through Maria de Maeztu funding was also received.

TABLE OF CONTENT

ABBREVIATIONS

ACEs	adverse childhood experiences
AL	allostatic load
AxD	axial diffusivity
BMI	body mass index
CPT-II	Conners' Continuous Performance Test II
CRP	C-reactive protein
DTI	diffusion tensor imaging
EF	executive functions
FA	fractional anisotropy
FTO	fat mass and obesity-related gene
GM	gray matter
GPS	genome-wide polygenic score
GWAS	genome-wide association studies
HDL	high-density lipoprotein cholesterol
HPA	hypothalamic-pituitary-adrenal
IL-6	interleukin 6
LDL	low-density lipoprotein cholesterol
MD	mean diffusivity
MRI	magnetic resonance imaging
NAcc	nucleus accumbens
NW	normal weight
OB	obesity
OFC	orbitofrontal cortex
OW	overweight
PFC	prefrontal cortex
RD	radial diffusivity
SES	socioeconomic status
TFEQ-R18	Three-Factor Eating Questionnaire R-18
TNFα	tumor necrosis factor alpha
WC	waist circumference
WCST	Wisconsin Card Sorting Test
WM	white matter

LIST OF FIGURES

LIST OF TABLES

FOREWORD

Thesis in compendium of publications format. The thesis consists of six objectives and three articles:

Prunell-Castañé A, Beyer F, Witte V, Sánchez Garre C, Hernán I, Caldú X, Jurado MÁ, Garolera M. From the reward network to whole-brain metrics: structural connectivity in adolescents and young adults according to body mass index and genetic risk of obesity. Int J Obes. 2024;48(4):567–74. IF (2022): 4.9, Q2 in Endocrinology and Metabolism.

Prunell-Castañé A, Jurado MÁ, Ottino-González J, Prats-Soteras X, Sánchez Garre C, Cano Marco N, Gómez-Pablos PS, García-García I, Garolera M. Beyond BMI: cardiometabolic measures as predictors of impulsivity and white matter changes in adolescents. Brain Struct Funct. 2023;228(3):751–60. IF (2022): 3.1, Q1 in Anatomy.

Prunell-Castañé A, Garolera M, Ottino-González J, Jurado MÁ. Allostatic load, adverse childhood experiences, executive functions, and BMI status in adolescents and young adults. Am J Hum Biol. 2024;e24089. IF (2022): 2.9, Q1 in Anthropology and Q2 in Biology.

RESUM

Títol: El fenotip neurocognitiu de l'excés de pes en adolescents i adults joves: factors biològics, genètics i psicosocials

Introducció: L'excés de pes és una condició de salut complexa que s'associa amb el desenvolupament de (multi)morbiditat. El fet que els adolescents amb excés de pes tinguin cinc vegades més risc de mantenir aquesta condició en l'edat adulta posa de manifest la necessitat d'estudiar quins factors afavoreixen la seva aparició i cronicitat. El fenotip neurocognitiu de l'excés de pes es podria referir a aquelles característiques psicològiques i cerebrals que representen una vulnerabilitat per adoptar comportaments que promouen l'excés de pes. Estudiar els correlats d'aquest fenotip neurocognitiu ajudaria a identificar individus amb risc de desenvolupar excés de pes i proposar intervencions específiques.

Hipòtesis: Aquesta tesi aborda l'excés de pes més enllà de l'adipositat i se centra en factors biològics, genètics i psicosocials per estudiar el fenotip neurocognitiu de l'excés de pes en adolescents i adults joves. Així, aquesta tesi presenta tres hipòtesis. En primer lloc, l'excés de pes i l'al·lel A del gen associat a la massa grassa i l'obesitat rs99396309 podrien estar associats amb una connectivitat estructural més baixa a la xarxa de recompensa. En segon lloc, els factors cardiometabòlics habitualment presents en l'excés de pes podrien estar associats a una major impulsivitat i alteracions en la microestructura de la substància blanca. En tercer lloc, l'estrès, ja sigui precedit per l'exposició a experiències adverses en la infància o subseguit per la càrrega alostàtica, podria estar associat a un pitjor funcionament executiu.

Objectius: En el primer estudi es va investigar els patrons de connectivitat estructural de la xarxa de recompensa segons l'índex de massa corporal i el risc genètic d'obesitat avaluat per l'al·lel A del gen associat a la massa grassa i l'obesitat rs99396309. En el segon estudi es va avaluar l'associació entre factors cardiometabòlics, la impulsivitat i els canvis microestructurals en els tractes de substància blanca normalment associats amb l'excés de pes i la impulsivitat. En el tercer estudi es va estudiar si les funcions executives eren vulnerables a l'estrès fisiològic (càrrega alostàtica) i psicològic (experiències adverses en la infància).

Mètodes: Al llarg de tres estudis originals, vam incloure adolescents i adults joves (de 10 a 21 anys) amb i sense excés de pes. Es van sotmetre a una avaluació mèdica (antropometria, pressió arterial, extracció de sang, genètica) i neuropsicològica (funcions executives,

impulsivitat, exposició a experiències adverses en la infància), i a l'adquisició d'una ressonància magnètica cerebral. L'índex de càrrega alostàtica es va estimar amb biomarcadors que representen l'estrès fisiològic. Les anàlisis de neuroimatge es van basar en imatges per tensor de difusió, tant per avaluar la microestructura de la substància blanca com la connectivitat estructural.

Resultats principals: En el primer estudi vam trobar una connectivitat estructural més baixa de la xarxa de recompensa en participants amb categories d'índex de massa corporal més altes, però no en aquells portadors de l'al·lel A del gen associat a la massa grassa i l'obesitat rs99396309. En una anàlisi exploratòria vam observar que la connectivitat estructural global estava positivament associada amb l'índex de massa corporal. En el segon estudi vam observar una relació inversa entre l'hemoglobina glicada i l'anisotropia fraccional al cíngol. A més, vam evidenciar que nivells més alts de triglicèrids estaven associats amb més errors de comissió al *Conners' Continuous Performance Test (CPT-II)* i que la glucosa i la pressió arterial diastòlica es van associar amb puntuacions més altes a la subescala d'ingesta emocional del *Three-Factor Eating Questionnaire R-18*. En el tercer estudi, vam trobar que una exposició més elevada a experiències adverses en la infància, però no la càrrega alostàtica, estava associada amb un pitjor funcionament executiu.

Conclusions: En adolescents i adults joves, els mecanismes pels quals l'excés de pes afecta la connectivitat estructural cerebral van més enllà del risc genètic d'obesitat. A més, factors cardiometabòlics de diferent naturalesa s'associen amb una impulsivitat més alta i una anisotropia fraccional més baixa en els tractes de substància blanca normalment relacionats amb l'excés de pes i la impulsivitat, cosa que suggereix que fins i tot a nivells preclínics, els factors cardiometabòlics són potencials biomarcadors del fenotip neurocognitiu de l'excés de pes. Finalment, l'estrès psicològic mesurat per l'exposició a experiències adverses en la infància, però no l'estrès fisiològic estimat per un índex de càrrega alostàtica, s'associa amb un pitjor funcionament executiu.

SUMMARY

Title: The neurocognitive phenotype of excess weight in adolescents and young adults: biological, genetic, and psychosocial factors

Introduction: Excess weight is a complex health condition that is associated with the development of (multi)morbidity. The fact that adolescents with excess weight have a five-fold increased risk of maintaining this condition as adults highlights the need to study which factors favor its emergence and chronicity. The neurocognitive phenotype of excess weight could be referred to as the psychological and brain characteristics that represent a vulnerability to engage in behaviors that promote excess weight. Studying the correlates of this neurocognitive phenotype would help identify individuals at risk of developing excess weight and to propose specific interventions.

Hypotheses: This thesis approaches excess weight beyond adiposity and targets biological, genetic, and psychosocial factors to study the neurocognitive phenotype of excess weight in adolescents and young adults. Consequently, the hypotheses of this thesis are threefold. First, excess weight and the A allele of the fat mass and obesity-related gene rs9939609 may be associated with lower structural connectivity in the reward network. Second, cardiometabolic factors usually present in excess weight may be associated with increased impulsivity and alterations in white matter microstructure. Third, stress, either led or followed by exposure to adverse childhood experiences or allostatic load, may be associated with poorer executive functioning.

Objectives: In the first study, we aimed to investigate the structural connectivity patterns in the reward network according to body mass index and the genetic risk of obesity assessed by the A allele of the fat mass and obesity-related gene rs99396309. In the second study, we evaluated the association between cardiometabolic factors and both impulsivity and microstructural changes in white matter tracts typically associated with excess weight and impulsivity. In the third study, we examined whether executive functioning was vulnerable to physiological (allostatic load) and psychological stress (adverse childhood experiences).

Methods: Along three original studies we included adolescents and young adults (aged 10-21) with and without excess weight. They underwent a medical (i.e., anthropometry, blood pressure, blood draw, genetics) and neuropsychological (i.e., executive functions, impulsivity, exposure to adverse childhood experiences) evaluation, and a brain magnetic resonance

acquisition. The allostatic load index was estimated using biomarkers representing physiological stress. Neuroimaging analyses were based on diffusion tensor imaging to evaluate white matter microstructure and structural connectivity.

Main results: In the first study, we found lower structural connectivity in the reward network in participants with higher body mass index categories, but not in those carriers of the A allele of the fat mass and obesity-related gene rs99396309. In an exploratory analysis we found that whole-brain structural connectivity was positively associated with body mass index. In our second study, we observed an inverse relationship between glycated hemoglobin and fractional anisotropy in the cingulum. We also reported that higher triglyceride levels were associated with higher commission errors in Conners' Continuous Performance Test (CPT-II), and that glucose and diastolic blood pressure were associated with higher scores on the emotional eating subscale of the Three-Factor Eating Questionnaire R-18 8 (TFEQ-R18). In the third study, we found that higher exposure to adverse childhood experiences, but not to allostatic load, was associated with worse executive functioning.

Conclusions: In adolescents and young adults, the mechanisms by which excess weight affects brain structural connectivity go beyond the genetic risk of obesity. Moreover, cardiometabolic factors of different nature are associated with higher impulsivity and lower fractional anisotropy in white matter tracts typically related to both excess weight and impulsivity, suggesting that even at preclinical levels, cardiometabolic factors are potential biomarkers for the neurocognitive phenotype of excess weight. Finally, psychological stress, measured by exposure to adverse childhood experiences but not physiological stress estimated by an allostatic load index, is associated with poorer executive functioning.

Chapter 1. Introduction

Excess Weight: Public Health, Determinants, and Pathophysiology

1.1. Excess weight as a public health concern

Excess weight is a health condition defined as the excessive accumulation of body fat. The most commonly used anthropometric measure to classify excess weight is the body mass index (BMI), calculated as the body weight in kilograms divided by the square of the body height in meters (kg/m2). Within this thesis, the term **excess weight** will be used to group both **overweight** (OW) **and obesity** (OB) conditions. A BMI of 25 kg/m^2 or higher would be indicative of OW, while a BMI of 30 kg/m^2 or higher would be indicative of OB. In children (aged less than 10 years) and adolescents (aged 10-19), excess weight status is determined by applying age and sex-specific centile curves equivalent to adults' BMI (2). Table 1 displays the excess weight cut-off points according to age. Although BMI is widely used, it is an indirect and limited measure of adiposity. BMI does not differentiate between body lean mass and body fat mass, nor does it capture the location of body fat accumulation. On the other hand, waist circumference (WC) measures abdominal adiposity and can thus detect higher-risk phenotypes of OB. However, there is no consensus on how WC should be measured (i.e., by using the midpoint between the lower border of the last rib and the iliac crest, or by using the superior border of the iliac crest), and absolute differences between these two measurements have been reported in females, even in samples including children and adolescents (3). Other sensitive but also subject to error methods to measure adiposity are bioelectric impedance and skinfold thickness, among others (4). Overall, the precise characterization of excess weight requires the use of multiple measurements.

Table 1. Excess weight definition by age.

	Excess weight	
	Overweight	**Obesity**
Children and adolescents	≥ 85th BMI Pc <95th for age and sex	BMI Pc ≥ 95^{h} for age and sex
Adults	BMI ≥ 25 kg/m^2 and < 30kg/m^2	BMI ≥ 30 kg/m^2

Adapted from Hampl (5). Abbreviations: BMI: body mass index; Pc: percentile.

Despite the World Health Organization targets, no country has reported a decline in OB prevalence. In 2020, 38% of the global population had excess weight, and current predictions suggest that the global prevalence of excess weight will increase to 51% by 2035. Obesity

alone is also expected to increase worldwide from 14% in 2020 to 24% by 2035. The prevalence of OB is particularly concerning in children and adolescents. Globally, although the prevalence in adults is higher in women, it is predicted that 18% of girls and 20% of boys will be living with OB by 2035. In Europe, these estimates are 14% for girls and 21% for boys. In Spain, projections indicate a 2.5% annual increase in childhood OB from 2020 to 2035 (6). Importantly, pediatric OB is not limited to the developmental period in which it occurs. Obesity throughout childhood and adolescence is associated with a 5-fold increased risk of OB in adulthood (7). Moreover, OB is not an isolated health condition. Its presence is a risk factor for other diseases and their co-occurrences. In children and adolescents, OB is linked to a higher risk of hypertension, dyslipidemia, fatty liver disease, impaired glucose tolerance, metabolic syndrome, and type 2 diabetes mellitus, among others (8). This morbidity also protracts into adulthood and, in adults, a large observational multicohort study reported that the OB condition was related to a 50% risk increase in developing 21 non-overlapping diseases compared to those with normal weight (NW). Moreover, the degree of OB was associated with complex multimorbidity (i.e., ≥4 co-occurring diseases) in a dose-response relationship (9).

Given the high prevalence of excess weight in our society, understanding the determinants of this health condition might help implement preventive strategies to diminish its current impact.

1.2. Excess weight determinants

Excess weight is usually the product of energy imbalance, where energy intake exceeds expenditure and the surplus of energy is stored (10). However, excess weight is not only the result of specific nutritional and lifestyle-related habits; it is a complex and multifactorial health condition that can also be modulated by genetic and environmental factors.

1.2.1. Genetic factors

From a genetic perspective, OB can be classified into two categories: monogenic and polygenic. Monogenic OB is an infrequent condition characterized by an early onset of severe OB and involves chromosomal deletions or single-gene defects. On the other hand, polygenic OB – otherwise known as common OB – is the product of the small effect of hundreds of polymorphisms and the environment. Gene discovery for both monogenic and

polygenic OB was initially restricted to candidate gene studies, based on their susceptibility to the phenotype of interest, and genome-wide linkage studies, which tested whether certain chromosomal regions co-segregate with a specific phenotype across individuals from the same pedigree (11).

Over time, gene discovery methods rapidly advanced, and the study of genetic variants across the whole genome became possible, although most were – and still are – performed in European populations, not accurately representing other ancestries. In 2007, the first genome-wide association study (GWAS) for OB identified a cluster of variants in the first intron of the fat mass and OB-related gene *(**FTO**)* locus that were associated with BMI. Multiple GWAS later, more than 750 loci have been associated with BMI, including variants in brain-derived neurotrophic factor and melanocortin 4 receptor (11), both of which are highly expressed in the hypothalamus and are associated with food intake and energy homeostasis (12,13). However, *FTO* is the locus with the largest effect (0.35 kg/m^2 per risk allele), which can start as early as 3 years old and increase progressively to reach its peak in the twenties. However, the underlying biological mechanisms by which *FTO* affects body weight have not been fully elucidated. In humans, the literature suggests that variations in *FTO* may modulate food intake by influencing the brain regions that affect appetite and reward processing. Still, the presence of the *FTO* risk allele is not deterministic. Even polygenic score studies that estimate susceptibility to OB by summarizing the effect of multiple variants observed in a GWAS report a discrete explained variance (11,14).

Thus, if genes only explain a small fraction of phenotypic variations, it is possible that OB-associated variants interact with the environment to modify OB risk. Concerning lifestyle habits, which are subject to socioeconomic status (SES), evidence suggests that moderate-to-vigorous physical activity may attenuate the effect of *FTO* on OB development. On the other hand, eating-related habits, such as the consumption of high-fat, high-sugar foods, may accentuate OB risk (15). Therefore, in common OB, although genetics may play an important role in OB development and maintenance, adherence to healthy habits may act as a protective factor.

1.2.2. Environmental factors and adverse childhood experiences

Given that no human exists out of a concrete context, environmental factors are crucial builders of an individual's reality.

The **obesogenic environment** can be defined as "the sum of influences that the surroundings, opportunities, or conditions of life have on promoting OB in individuals or populations" (16). These influences may be due to the increased availability of palatable foods, or from neuromarketing strategies that condition food intake in the absence of metabolic need or amplify hedonic hunger in the presence of metabolic depletion (17). One of the key neural substrates of incentive salience may be the mesolimbic dopamine system, including the ventral tegmental area, nucleus accumbens (NAcc), prefrontal cortex (PFC), and hippocampus (17). Beyond how modern times have changed access to certain types of food and implemented aggressive food marketing campaigns, **SES** also shapes adherence to healthy habits. SES is an increasing field of interest in neuroscience, and although there is no consensus on its definition, the most commonly used measures are parental education, income, occupational status, and neighborhood quality (18). Research on the importance of social inequalities in health is mostly based on high-income countries, underrepresenting impoverished countries and populations (19). With that in mind, a meta-analysis concluded that individuals with a lower life SES had a higher mean BMI than those with a more privileged SES and that there was an association between lower SES and OB among women, but not among men (20).

In children, multiple socioeconomic factors may interact to influence the development of excess weight, such as food insecurity, which leads to affordable high-energy dense foods with limited nutritional value, or neighborhoods with high crime rates that are not safe to engage in physical activity (19). Moreover, significant SES and brain system interactions have been reported, in which more deprivation imposes distinctive effects on brain health. Structurally, reductions in gray matter (GM) volumes in the prefrontal, insular, frontal opercular, lateral parietal, and lateral temporal regions, as well as subcortical areas including the cerebellum, striatum, and thalamus, have been described in lower SES, with a special stronger association in the striatum (21). Despite this, low SES should not be pathologized, categorizing it as a property of the brain rather than a situation that needs to be politically and socially addressed (22).

Adverse childhood experiences (ACEs), defined as potential traumatic events that destabilize children's lives, are a form of victimization – usually more prevalent in vulnerable SES (23) – that have long-lasting consequences on mental and physical health. Adolescents exposed to ACEs are more likely to develop mental health conditions such as depression, anxiety, behavioral problems, attention-deficit/hyperactivity disorder, or substance use disorder (24). On the physical dimension, ACEs have been associated with higher BMI

measures as early as 6 years of age (25). Consistently, ACEs increase the odds of adult OB, cardiovascular disease, and diabetes, among others (26). Possible factors that may mediate the relationship between ACEs and excess weight are lack of social support, engagement in unhealthy habits, changes in the stress response – including the possible disruption of the hypothalamic-pituitary-adrenal (HPA) axis and the chronic role of weight stigma –, and mental health issues (27)

Overall, excess weight development and maintenance are modulated by multiple factors – from genetic to environmental – that interact with each other and condition the adherence to health-related habits.

1.3. Excess weight pathophysiology

A sustained positive energy balance initiates pathophysiological changes that can ultimately lead to disease. Taking adipose tissue expansion as the starting point, other processes, such as inflammation, insulin resistance, dyslipidemia, and stress responses, are also involved.

1.3.1. Adipose tissue

The surplus energy is stored in adipocytes, which are known as adipose tissue cells. Although adipose tissue was initially considered as an energy reservoir depot, it was subsequently redefined as an endocrine organ (28). Adipose tissue can be classified into two types: brown adipose tissue and white adipose tissue, which exhibit functional differences. Brown adipose tissue is present in small proportions, mainly in the shoulders and ribs, and it has thermoregulatory properties. In contrast, white adipose tissue is present throughout the body at both the subcutaneous and visceral levels, and is the main source of energy storage and regulation (29).

When there is a positive energy balance, insulin drives lipid storage in white adipocytes by stimulating fatty acid uptake and converting the heightened levels of glucose, via de novo lipogenesis, into lipids, which are also stored in the adipose tissue (29). If this situation is sustained over time, white adipocytes will eventually expand to accommodate the need for increased lipid storage, either by number (i.e., hyperplasia) or size (i.e., hypertrophy) (30). However, white adipocyte expansion has a limit and, when reached, its vascular supply becomes insufficient, angiogenesis is inhibited, fibrosis is accelerated, macrophages infiltrate and polarize to an inflammatory profile, and inflammatory cytokines are locally produced

(e.g., tumor necrosis factor alpha (TNFα), interleukin 6 (IL-6)) (29), leading to subsequent chronic low-grade systemic inflammation (28). In addition, visceral adipose tissue is considered to be more active than subcutaneous tissue, displaying higher levels of lipolysis, macrophage infiltration, and cytokine production, and thus is associated with a less favorable metabolic profile (29). In addition, when the storage capacity of adipose tissue is exceeded, the remaining circulating lipids accumulate in other organs (i.e., the liver, muscle, heart, and pancreas), a phenomenon known as ectopic fat accumulation, which promotes systemic insulin resistance and inflammation (30).

1.3.2. Chronic low-grade systemic inflammation

Inflammation is an immune physiological reaction to harmful stimuli intended to restore homeostasis. When an acute insult occurs, inflammatory, cellular, and molecular mediators interact to heal the affected tissue. If successful, harmful stimuli are eliminated, inflammatory responses dissipate, and tissue repair is initiated (31). However, under excess weight conditions, an inflammatory response of a different nature is generated. The trigger is not an infection or trauma but metabolic in nature, leading to chronic low-grade systemic inflammation. It is hypothesized that the chronicity of the inflammatory state observed in excess weight might be related to the metabolic origin of inflammation. It is possible that a metabolic trigger does not initiate inflammatory responses that are strong enough to resolve noxious stimuli, or that there is an evolutionary defect in responding to such metabolic signals. Nevertheless, the presence of chronic low-grade systemic inflammation is one of the hallmarks of excess weight and has multiple implications (32). Table 2 summarizes the main biomarkers involved in the inflammatory process.

Table 2. Biomarkers involved in chronic low-grade systemic inflammation.

Cytokines	Adipokines	Acute-phase proteins
↑ TNFα	↑ Leptin	↑ Fibrinogen
↑ IL-6	↓ Adiponectin	↑ CRP

Abbreviations. CPR: C reactive protein, IL-6: interleukin 6, TNFα: tumor necrosis factor alpha.

Local inflammatory responses that are initiated within the dysregulated adipose tissue involve the presence of proinflammatory factors – at the expense of protective anti-inflammatory

adipokines, such as **adiponectin** – that not only contribute to local inflammation but also induce systemic inflammation (33). Proinflammatory cytokines, such as **TNFα** and **IL-6,** decrease insulin sensitivity and glucose uptake, and induce lipolysis (32). IL-6 also acts in the hypothalamus to regulate satiety and energy expenditure (34), influences the secretion of other cytokines from adipocytes (35), and stimulates hepatocytes to synthesize and secrete **fibrinogen** and C-reactive protein (**CRP**), which are markers of systemic inflammation (34). **Leptin**, an adipokine that also acts in the hypothalamus, promotes lipolysis by stimulating neuroadipose junctions and promotes an inflammatory state by directly interacting with immune cells. (29)

Systemic inflammation has been associated with metabolic and cardiovascular pathologies, as well as cognitive decline, possibly due to metabolic and endothelial dysfunction, and neuroinflammation, respectively (34). Regarding neuroinflammation, when the blood-brain barrier is persistently challenged, such as in low-grade chronic systemic inflammation, its permeability changes, and pro-inflammatory molecules can enter the brain and interact with microglia, the brain-resident macrophages. Microglia then induce the secretion of more inflammatory cytokines, particularly in brain regions with higher microglial density, such as the hypothalamus, hippocampus, cerebral cortex, and striatum (36).

1.3.3. Cardiometabolic and cardiovascular alterations

Although excess weight itself has been described as an independent predictor of cardiovascular risk, the initial consequences of adipose tissue dysregulation – such as alterations in lipid metabolism and insulin resistance – can act as intermediate risk factors that promote cardiovascular and metabolic events (37). Table 3 provides a list of biomarkers whose dysregulation may lead to cardiometabolic diseases.

Table 3. Biomarkers associated with cardiometabolic diseases.

Dyslipidemia	Hypertension	Diabetes
↑ Total cholesterol	↑ Systolic blood pressure	↑ Glucose
↓ HDL	↑ Diastolic blood pressure	↑ Glycated hemoglobin
↑ LDL		
↑ Triglycerides		

Abbreviations. HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol.

Alterations in lipid metabolism can lead to dyslipidemia, characterized by increased levels of low-density lipoprotein cholesterol (**LDL**), **triglycerides** and **total cholesterol**, and decreased levels of high-density lipoprotein cholesterol (**HDL**). Dyslipidemia is one of the features of metabolic syndrome, and it is also related to atherosclerosis through the accumulation of LDL particles. Moreover, the presence of endothelial dysfunction – the inability of the endothelium to vasodilate correctly – is considered an early marker of atherosclerosis and one of the possible mechanisms leading to hypertension (i.e., high **systolic** and **diastolic blood pressure**) (38). On the other hand, peripheral insulin resistance can dysregulate hepatic and pancreatic mechanisms that support **glucose** homeostasis. In the liver, decreased insulin sensitivity prevents the regulation of glucose production, contributing to hyperglycemia. In the pancreas, the overproduction of insulin to remove excess circulating glucose levels results in the apoptosis of pancreatic β cells, a common feature of diabetes mellitus (32). Diabetes mellitus can be diagnosed using plasma glucose and **glycated hemoglobin** concentrations (39).

These intermediate risk factors lead to the development of metabolic and cardiovascular diseases such as diabetes, coronary heart disease, and ischemic stroke (37). However, engagement in healthy lifestyle habits can improve metabolic profiles. Specifically, physical activity has been associated with improvement in glucose tolerance and HDL-LDL ratio, as well as with decreases in triglyceride concentration and platelet aggregation (38).

1.3.4. Stress and allostatic load

Stress responses are adaptive and allow the organism to maintain stability through challenging contexts and to recover homeostasis. However, when facing long-term stress, the primary neuroendocrine responses (i.e., catecholamines from the sympathetic adrenal-medullary axis or glucocorticoids from the HPA axis) that prepare the organism for a fight-or-flight response become chronically over-activated. This over-activation, in conjunction with cytokine engagement (e.g., IL-6, TNFα), dysregulates other interconnected systems that, by trying to compensate for the chronic effects of neuroendocrine mediators (e.g., **cortisol**), initiate secondary preclinical variations. This preclinical state is known as allostatic load (**AL**) and affects the metabolic (e.g., glycated hemoglobin, HDL, LDL, and triglycerides), cardiovascular (e.g., systolic and diastolic blood pressure), and immune systems (e.g., fibrinogen and CRP). If sustained over time, what was initially a dysregulation eventually

becomes a disease, a final stage known as allostatic overload (40). Figure 1 illustrates the progression of AL.

When excess weight is added to this cascade of events, some mediators may become even more affected. Cardiometabolic and cardiovascular dysregulations already present in excess weight can increase the cumulative effects of AL (41). Moreover, low-grade inflammation can increase HPA axis activity and cortisol production (42). This increase in cortisol levels has different implications. First, cortisol also contributes to hepatic glucose production (43). Second, cortisol promotes eating by enhancing reward pathways (i.e., dopamine release) and leptin resistance in the brain, as well as promoting abdominal fat deposition, leading to a vicious cycle of excess weight and stress responses (44).

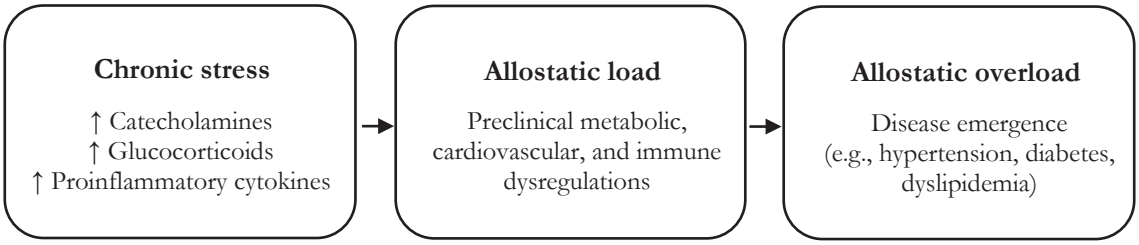


Figure 1. Allostatic load diagram. Original figure created specifically for this doctoral thesis.

Overall, the medical consequences of excess weight are not the result of a single physiological alteration but rather of the interconnected dysregulation of multiple systems, which confers a challenge for its correct management. Disentangling how these dysregulations may affect neurocognitive traits that ultimately favor excess weight development and maintenance requires the implementation of neuropsychological and neuroimaging protocols.

Brain Characterization Using Magnetic Resonance Neuroimaging

1.4. A brief history of human white matter

Throughout human history, the study of the brain has been an ongoing question. While the prevalent doctrine in antiquity was that the ventricular system acted as a recipient for mental functions, a scientific revolution started in 1543, when Andreas Vesalius differentiated human GM and white matter (WM) for the first time. The anatomical and functional

understanding of the brain advanced, and almost 100 years later, it was proved that WM was formed by fibers. Subsequently, numerous advances happened, such as the description of WM tracts, their classification (i.e., projection, association, or commissural fibers) and organization, and the acknowledgement of the communication between brain regions. However, the architecture of the WM fibers was still unknown. The discovery by Santiago Ramón y Cajal of neurons as an independent entity of the nervous system was crucial to enable a finer examination of fiber bundles. Studies focusing on myelination and the description of the pathological correlates of WM disturbance continued, and an *in vivo* study of the cerebral anatomy became a reality using magnetic resonance imaging (MRI) techniques (45). The first brain MRI of a living human being was performed in 1978 (46). In the 1990s, the possibility of using the diffusion tensor in MRI, known as diffusion tensor imaging (DTI), was introduced. This diffusion tensor model allowed the indirect measurement of the diffusion of water molecules in the brain and to infer the architecture of its surroundings (47).

1.5. Diffusion tensor imaging

MRI techniques allow the study of the brain from different perspectives. Structural MRI provides information on the macrostructural features of the brain, such as volume, area, surface, length, or thickness. The GM can be assessed using either voxel- or surface-based approaches. Voxel-based morphometry, using probabilistic segmentation, labels each brain voxel as GM, WM, or cerebrospinal fluid and returns an estimated measure of tissue volume (48). Surface-based morphometry, by identifying the borders between tissue types, has the ability to measure GM volume, cortical thickness, surface area, gyrification, and folding patterns (49). Microstructural features, which assess the properties of tissue components, are usually studied using DTI, a type of diffusion MRI.

DTI describes diffusion in each voxel by modeling it as a mathematical tensor that can be decomposed into eigenvectors representing the direction of diffusion and eigenvalues representing the magnitude of diffusion. Diffusion can be either isotropic, where water molecules disperse equally in all directions, or anisotropic, where molecules follow a certain direction owing to structural limits (i.e., WM axons). Tract-based spatial statistics is one of the most common methods for quantitatively assessing diffusion. This method produces different measures, including fractional anisotropy (**FA**), mean diffusivity (**MD**), axial diffusivity (AxD), and radial diffusivity (RD), which provide an indirect estimation of

microstructural status. FA is the most used metric to study WM microstructure. FA – ranging from 0 meaning isotropic to 1 meaning anisotropic – indicates how coherent the movement of the water is along the fiber with higher values suggesting well-myelinated and undamaged tracts. MD is the average of all eigenvalues ($\lambda_1, \lambda_2, \lambda_3$) and reflects the overall magnitude of diffusion, where lower values are indicative of heightened myelination (50). AxD is a measure of diffusivity along the primary axis (λ_1), which reflects axonal integrity, and RD is a measure of the amount of diffusivity perpendicular to the primary axis of diffusion, calculated by averaging λ_2 and λ_3, and reflects myelin integrity (47). Figure 2 provides a graphical representation of the diffusion tensor ellipsoid.

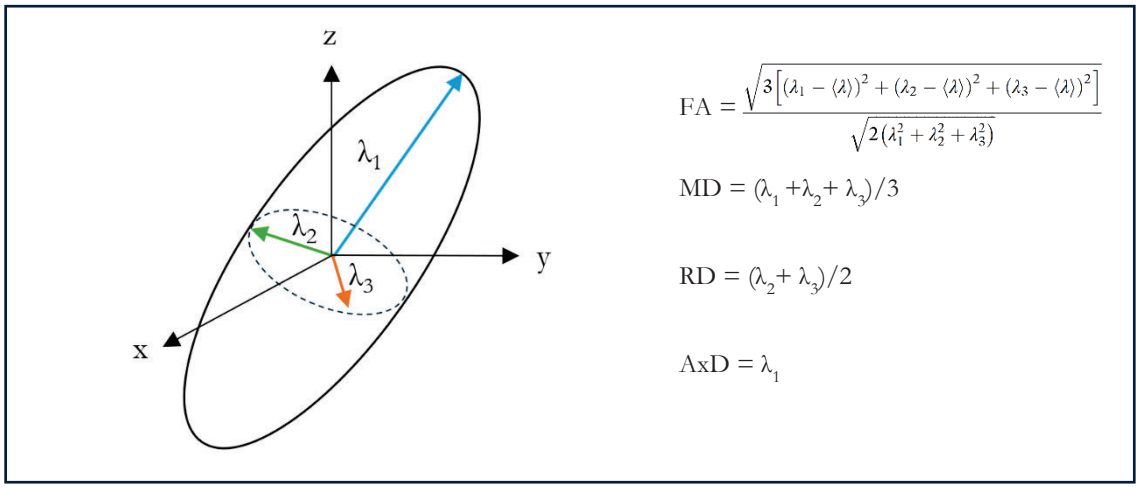


Figure 2. Diffusion tensor ellipsoid representing anisotropic diffusion. Adapted from García-Martín and López-Larrubia (51). Abbreviations. AxD: axial diffusivity, FA: fractional anisotropy, MD: mean diffusivity, RD: radial diffusivity.

Structural connectivity

The architecture of WM fibers and their connections with cortical and subcortical regions – the structural connectome – can be studied using tractography and graph metrics. Deterministic tractography reconstructs WM pathways by inferring the orientation of the principal eigenvector of the tensor model in each voxel, whereas probabilistic tractography models multiple diffusion orientations per voxel based on their probability distribution (47). Either way, tractography visually reconstructs the inferred WM fiber connections between GM areas using DTI (52). Graph theory suggests that structural brain networks can be represented as graphs composed of nodes (i.e., brain regions usually defined by brain parcellation methods) connected by edges (i.e., axonal projections). The connectivity of these

edges can be assessed quantitatively (e.g., number of streamlines between regions) or qualitatively (e.g., mean value of a diffusion metric across voxels included in the streamlines) (52). Moreover, the organization of a brain network can be analyzed globally by means of connectivity strength, which describes the overall strength of the connections between brain regions, or locally by means of a clustering coefficient, which measures the probability of neighboring nodes in the network being interconnected (53).

1.6. Normative brain development

Human brain development is a dynamic and adaptive process that begins in the third gestational week and extends at least through late adolescence, facilitating the emergence of new neural organizations (54). Brain development occurs at different rates across brain regions, and beyond the complexity of developing in a posterior-to-anterior fashion, the temporal sequence of maturation is mostly led by the function served rather than its location. Thus, GM maturation begins in brain regions that underlie basic sensory (i.e., primary visual, sensory, olfactory, and gustatory areas) and motor (i.e., precentral gyrus) functions, followed by the development of regions that assist complex processing, spatial orientation, and attention (i.e., inferior-posterior temporal and inferior parietal areas). Regions implicated in executive functioning (i.e., PFC) and multimodal integration (i.e., superior temporal areas) are the last to develop (55), with full maturation of the PFC in the mid-twenties indicating complete brain development (56). Consistently, WM somatosensory pathways mature first, whereas frontotemporal tracts show a protracted maturational trajectory (55).

Throughout development, the global GM volume strongly increases from mid-gestation onwards, peaking before the onset of puberty – at 5.9 years – and following a progressive reduction (57) that reflects synaptic pruning (54). Cortical thickness peaks early at 1.7 years, but its maximum velocity development peaks even earlier, during mid-gestation (57). Subcortically, GM volume is characterized by an intermediate growth pattern, peaking in adolescence and mid-puberty at 14.4 years (57). Concerning WM trajectories, WM volume increases quickly from mid-gestation to early childhood, peaking in adulthood at 28.7 years, with a subsequent rapid decline after the fifties (57). Microstructurally, FA exponentially increases in the first three years of life and continues to increase until age 25 in a more discrete

manner, while the reverse pattern is observed for MD (58). In addition, the increased structural connectivity present during development, which follows an inverted U-shaped trajectory and peaks approximately in the third decade, is supported by the parallel nonlinear trajectories of WM integrity. The most prominent changes in brain connections occur in the prefrontal and temporal cortices, facilitating higher-order cognitive functions during development (59). Figure 3 provides a visual representation of the age at peak of the different brain development trajectories.

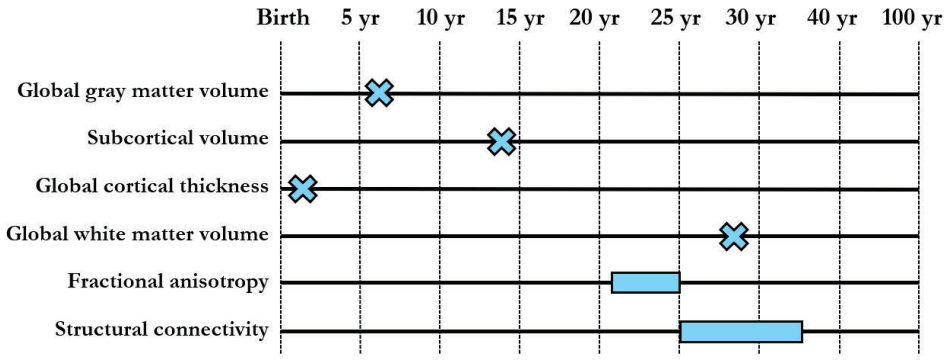


Figure 3. Age at peak of normative neurodevelopmental trajectories. Adapted from Bethlehem (57), Lebel (58), and Zaho (59). Crosses and rectangles represent the peak value (57) and peak range (58,59) of each brain category, respectively. Abbreviations. Yr: years.

Moreover, developmental brain trajectories might not only be a function of age, but also of sex and puberty. At the macrostructural level, more advanced pubertal stages and higher testosterone and estradiol levels are associated with GM volume reductions, even though their effects may differ depending on sex (60). WM maturation starts earlier in girls than in boys and is positively associated with more advanced pubertal maturation, either defined using physical measurements (i.e., Tanner scale) or hormonal markers (i.e., gonadal hormones). However, boys develop larger WM volumetric increments than girls do (61).

To summarize, while trajectories of brain development are variable between brain tissues, there is consistency between WM, GM, and structural connectivity patterns to first develop core sensory and motor regions, followed by more protract development in frontal and temporal areas. In addition, biological sex and hormonal changes during puberty may influence these trajectories. Determining how excess weight might uniquely impact the

developing brain can help elucidate the neural mechanisms that promote and maintain such condition in adolescent populations.

1.7. Normative development of executive functions

Normative brain developmental trajectories are synchronized with the development of neurocognitive skills. The protract maturation of the PFC parallels the continuous advances seen in **executive functions** (EF) throughout childhood and adolescence, although EF also rely on other interconnected brain areas (e.g., the anterior cingulate and parietal cortices, hippocampus, or amygdala) that support their correct functioning (62). EF can be defined as top-down mental processes that allow goal-oriented behavior. Therefore, EF are essential for maintaining one's health and cognitive, social, and psychological development, as well as academic and personal achievement (63). Within this set of skills, according to Diamond's framework (63), three core EF can be distinguished: inhibitory control, working memory, and cognitive flexibility. Table 4 provides a description of each domain. From these core EF, higher-order EF are built, including problem-solving, reasoning, and planning (63). EF can be further distinguished by using the hot and cold principle, where EF that are required in emotionally charged situations would be hot EF, whereas those required in more affectively neutral contexts would be cold EF (64).

Table 4. Description of core executive functions.

Inhibitory control	Ability to control one's attention, behavior, thoughts, or emotions to ignore a strong internal predisposition or external distractors, and instead do what's more appropriate.
Working memory	Involves holding information in mind, either verbal or visual-spatial, and mentally working with it.
Cognitive flexibility	Allows the adjustment to changing environments or demands by inhibiting previous perspectives and loading into working memory a new perspective.

Adapted from Diamond 2013 (63)

The development of EF is gradual. Even in the immaturity of a newborn, primitive reflexes are shown in their interaction with the environment. In the first months of life, early evidence of inhibitory control, working memory, and cognitive flexibility is shown in infants' looking

behavior, which extends to reaching behavior by the second half of the first year of life. From 3 to 5 years of age, children show dramatic improvements in inhibitory control and cognitive flexibility, as well as working memory by 5 years of age. Nevertheless, their executive skills are error-prone and require refinement (64,65).

During middle childhood, improvement in EF is more evident. Inhibitory control, which is disproportionately difficult for young children, shifts from reactive to proactive and becomes less sensitive to interference. Working memory boosts, and children can engage in complex span and spatial tasks that require the manipulation of multiple elements. Cognitive flexibility also improves, and the cost of switching declines progressively (64).

EF skills continue to mature and stabilize throughout adolescence, following nonlinear trajectories. Significant age-related changes in EF accuracy (i.e., increases in correct responses) and latency (i.e., decreases in response speed) are observed from 10 to 15 years of age. More discrete changes occur from age 15 to 18, and very little improvement is seen after age 18, suggesting a potential closure of adolescent EF development between 18 and 20 years of age, which some studies extend into the mid-twenties (66).

1.8. Adolescent behavior: impulsivity, reward, and stress responses

Adolescence is a vulnerable developmental period characterized by dramatic biological, behavioral, emotional, and social changes. The onset of puberty determines its beginning, and from an evolutionary perspective, the full acquisition of independence skills marks the transition to adulthood. Adolescence is characterized by suboptimal decisions that are generally the product of impulsive and reward-seeking behaviors (56). These tendencies seem to underlie the normative maturation of the adolescent brain, and do not necessarily represent psychopathology. Individual differences in neural responses to rewards may explain the predisposition of some adolescents to engage in risky behaviors (56).

Impulsive and reward-seeking behaviors follow distinct developmental trajectories. **Impulsivity**, which can be conceptualized as a multidimensional construct that involves urgency, lack of perseverance and premeditation, and sensation seeking (67), steadily diminishes with age across childhood and adolescence. The protracted and linear development of the PFC sustains the ongoing acquisition of inhibitory control competence, which is paired with progressive reduction of impulsivity. However, **reward**-seeking and risky behaviors appear to increase during adolescence. It has been proposed that this is due to a developmental mismatch between the early maturation of subcortical structures that

influence affect and reward, as opposed to the delayed maturation of the PFC, which is involved in cognitive control. The delayed functional connectivity between prefrontal and limbic subcortical regions observed in adolescents could explain the lack of top-down control of reward processing (56,68). In addition, puberty itself may intensify sensitivity to reward (69).

Adolescence is characterized by increased **stress** and heightened stress reactivity (70). Stress can be defined as a "negative emotional experience accompanied by predictable biochemical, physiological, and behavioral changes that are directed toward adaptation either by manipulating the situation to alter the stressor or by accommodating to its effects" (71). During this time of development, the HPA axis is remarkably sensitive to social challenges and the PFC is richer in cortisol receptors, making adolescents more susceptible to the consequences of stress. The nature of stressors varies among adolescents. Some are only subjected to adolescent-specific daily stressors, such as academic, peer, or romantic pressures, whereas others face additional exposure to adverse and victimizing experiences (70) that further dysregulate the HPA axis (72).

1.9. A neural, cognitive, and behavioral approach to adolescent eating behavior

Eating behavior is the product of the interaction between multiple homeostatic and non-homeostatic systems. **Homeostatic** regulation of eating behavior relies on information about the energy status provided by physiological signals (e.g., ghrelin, insulin, and leptin) to the hypothalamus. Under conditions of negative energy balance, neuropeptide Y, agouti-related protein, and gamma-aminobutyric acid neurons located in the arcuate nucleus of the hypothalamus are activated and stimulate food intake. Satiety perception is posteriorly determined by peptide secretion from the gastrointestinal tract (e.g., glucagon-like peptide 1 and cholecystokinin) and by neural signaling of gastric distension via the vagus nerve to the hindbrain. Moreover, leptin favors brain responsiveness to satiety signals and stimulates hypothalamic proopiomelanocortin neurons, which inhibit food intake (73).

These homeostatic processes do not operate alone. Eating behavior is also guided by **reward** and **cognitive control** systems, among others. Several brain regions are involved in reward processes. Although the anterior cingulate cortex, orbitofrontal cortex (OFC), ventral striatum, ventral pallidum, and midbrain dopamine neurons could be considered key structures, connections to and projections from these areas to others (e.g., hippocampus, hypothalamus, and amygdala) are also important (74). However, in this thesis, the reward

network is defined – following Marqués-Iturria et al. (75) approach – as lateral and medial OFC, NAcc, caudate nucleus, and putamen. The reward network is influenced by signals that inform about the energy status, which are used to adjust the rewarding value of food, defined as the momentary value of a specific food to a person. Thus, hunger states would increase food reward to facilitate meal initiation, and satiety states would decrease food reward to facilitate meal termination. However, the rewarding aspect of food can go beyond nutritional purposes (73). It is hypothesized that either hypo- or hyperactivation of the reward network can lead to food ingestion in the absence of an energy deficit, favoring excess weight states. Dopamine deficiency in the reward network may decrease the reward sensitivity to food consumption and induce overeating as a compensatory mechanism. Likewise, elevated reward responsivity to food cues may lead to overeating (76).

On the other hand, cognitive control, which mainly depends on the PFC, is central to successful regulation of eating behavior. Working memory supports long-term goal achievement (e.g., healthy eating) by maintaining goal-relevant information and redirecting attention away from the tempting stimuli. Inhibitory control limits impulsive responses that may impede goal accomplishment (e.g., eating highly palatable foods), and cognitive flexibility facilitates health-related goals by pursuing a more adaptive method to accomplish them (e.g., avoiding unrealistic or too restrictive dieting) (77). Although all EF are involved in eating behavior, it has been theorized that deficits in inhibitory control can increase sensitivity to food reward and impulsivity traits, leading to food overconsumption and excess weight (76).

Throughout adolescence, the interaction between multiple systems that regulate eating behavior is conditioned by ongoing developmental processes. Rapid physical growth and elevated metabolic activity increase food intake. Moreover, the conjunction of changes in caloric needs, increased reward sensitivity, and the development of PFC and cognitive control abilities (e.g., inhibitory and impulsivity control) can easily lead to overconsumption of highly palatable and nutritionally deprived foods. Simultaneously, repetitive exposure to unhealthy food increases the vulnerability of developing brain systems involved in self-regulation by inducing structural and functional changes in the PFC and altering the mesocorticolimbic system (78). Additionally, the increased exposure to stress seen in adolescents may promote dopamine release and thus food reward responsivity (44). Finally, environmental factors (e.g., food insecurity and food availability) also determine the quality of food choices.

1.10. Brain characteristics of the excess weight phenotype

Excess weight involves increases in adiposity, the onset of cardiometabolic changes, and higher AL states, among others. Research has suggested that these factors are associated with varying degrees of structural, microstructural, and connectivity changes in the brain. Different frameworks have been proposed to outline the directionality of this relationship; however, there is still no consensus. Brain changes have been described as predictors and outcomes of excess weight. Some studies suggest that individual differences in regions that support cognitive control, such as the PFC and particularly the dorsolateral PFC, may predict susceptibility to overeating. Others point to pathophysiological changes associated with excess weight as disruptors of brain health. Even some researchers have proposed a potential reciprocal relationship between the brain and excess weight (79). This thesis follows the premise that brain changes may be a consequence of the excess weight phenotype. A description of these brain outcomes across different age ranges (children younger than 10 years, adolescents: 10-19, young adults: 20-39, middle-aged adults: 40-64, and old adults aged 65 years or older) continues below.

1.10.1. Structural brain changes

Excess weight is associated with structural changes in the brain. This relationship has been primarily studied in adult populations, and there is less evidence in younger populations, particularly adolescents. Table 5 highlights how brain regions that undergo structural changes in excess weight states are also involved in impulsivity (e.g., basal ganglia, frontal gyri, insula, anterior cingulate cortex, OFC (80)), reward (e.g., lateral and medial OFC, NAcc, caudate nucleus, putamen (75)), and executive functioning (e.g., PFC including the OFC, anterior cingulate cortex, parietal cortex, cerebellum (81)).

1.10.2. Microstructural brain changes

Excess weight and its related physiological characteristics are also related to WM microstructural changes, which have been reported in association fibers connecting cortical areas within the same hemisphere, commissural fibers connecting the two hemispheres, and in projection and thalamic fibers connecting cortical and subcortical structures. Again, this relationship has been underexplored in youth, especially in adolescents. Table 6 provides

information about how WM tracts affected in excess weight states are intrinsically related to neuropsychological processes that could potentially maintain or increase the excess weight condition, such as impulsivity (e.g., superior longitudinal fasciculus, forceps major, corticospinal tract (82)), reward (e.g., corpus callosum, uncinate fasciculus, cingulum (83)), and executive functioning (e.g., superior longitudinal fasciculus, corpus callosum, forceps major, anterior corona radiata, fornix, cingulum (84)).

1.10.3. Structural connectivity changes

Excess weight can affect the structural connectome. Although multiple brain networks may support eating behaviors, the reward network is particularly relevant for the excess weight phenotype. Higher **adiposity** measures have been related to lower structural connectivity of the reward network in samples comprising adolescents, young adults, and middle-aged adults (75,85). Studies assessing brain signatures of the excess weight phenotype beyond the reward network found, in young adults with OW (compared to their NW peers), an increased structural connectivity between the reward network and regions of executive control, emotional arousal, and somatosensory networks. Moreover, decreased connectivity was found between the ventromedial PFC and anterior insula, and between the thalamus and executive control network regions (86). Another study of young adult females with OB reported lower connectivity in WM tracts connecting the insula, amygdala, PFC, OFC, and striatum, as well as higher connectivity between the amygdala and anterior cingulate cortex (87). Regarding eating patterns, in healthy adolescents and young adults aged 17-25, those with higher scores on a food addiction scale presented lower structural connectivity between brain regions related to reward, cognitive control, and interoceptive processes (i.e., the insula and anterior cingulate cortex, insula and caudate, and ventromedial PFC and putamen) than those with lower food addiction scores (88). In addition, in healthy adults aged 50 years or older, a higher adherence to the Mediterranean diet was associated with higher structural connectivity between the left amygdala, left lingual, olfactory, and middle occipital gyri, and left calcarine areas, suggesting their possible implication in the integration of sensory and tase stimuli, and thus in food intake (89).

The extent to which **cardiometabolic** factors and **AL** affect structural connectivity is underexplored. Adults aged 50-70 with type 2 diabetes showed lower structural connectivity in the bilateral lingual gyrus than healthy controls (90). In another study comprising young and middle-aged adults with schizophrenia and healthy controls, higher AL scores were

associated with lower structural connectivity between the hippocampus and hypothalamus, regardless of the diagnosis (91). Overall, despite initial efforts made to disentangle the impact of the excess weight phenotype on the structural connectome, evidence is limited and mainly focused on adults.

Table 5. Structural brain changes associated with adiposity, cardiometabolic factors, and allostatic load.

Article	Sample characteristics		MRI measure	Excess weight feature	Results
Adiposity					
Kaltenhauser 2023 (92)	N (% females)	4576 (48.3)	CTh	BMI z-score, WC	Baseline: negative association (BMI z-score and WC) in both hemispheres. Strongest association in the R rostral middle frontal cortex. Longitudinal (2-year follow-up): higher baseline BMI z-score associated with decelerated interval development of the L rostral middle frontal cortex.
	Age range	9-10			
	Weight status (n)	191 $_{UW}$, 3046 $_{NW}$, 683 $_{OW}$, 656 $_{OB}$			
Laurent 2018 (93)	N (% females)	3190 (49)	CTh	BMI	Negative association in the L-R rostral middle frontal gyri, L-R lateral OFC, L-R superior frontal gyri, L-R entorhinal, L-R pars triangularis, L superior temporal lobe, L-R temporal lobes, L inferior temporal lobe, R medial OFC, R frontal pole, R fusiform gyrus.
	Age range	9-10			
	Weight status (n)	2270 $_{UW/NW}$, 429 $_{OW}$, 491 $_{OB}$			
Ronan 2020 (94)	N (% females)	3297 (49.9)	CTh	BMI z-score	Negative association in the L-R lateral OFC, L-R inferior frontal gyri (pars orbitalis and pars triangularis), L-R rostral middle frontal cortices, L-R superior frontal cortices, L entorhinal cortex, R medial OFC, R temporal lobe.
	Age range	9-11			
	Weight status (n)	127 $_{UW}$, 2197 $_{NW}$, 472 $_{OW}$, 501 $_{OB}$			
Steegers 2021 (95)	N (% females)	3160 (50.3)	CTh	BMI standard deviation score	Positive association in the R superior parietal, R inferior temporal, R pericalcarine and L superior parietal gyrus, L-R superior temporal, L-R occipital, L-R postcentral, and L-R lingual gyri.
	Age range	9-11			
	Weight status (n)	168 $_{UW}$, 2464 $_{NW/OW}$, 528 $_{OB}$			

Table 5. Continued.

Article	Sample characteristics		MRI measure	Excess weight feature	Results
Adiposity					
García-García 2019 (96)	Meta-analysis		GM volume	BMI, BMI group	Negative association in the medial PFC (ventral subdivision), cerebellum, temporal pole, precentral gyrus, and inferior parietal cortex.
	N (% females)	5882 (54)			
	Age range	18-92			
	Weight status (n)	N/A $_{NW}$, N/A $_{OW/OB}$			
Pflanz 2022 (97)	N (% females)	15634 (N/A)	Total brain, GM, and WM volumes	WHR, BMI, body fat	(Whole-brain and ROI-based analysis: caudate, putamen, pallidum, thalamus, amygdala, Nacc, hippocampus) Total brain volume: negative association with body fat. GM volume: negative association with body fat and WHR. GM volume ROIs: negative associations with WHR/BMI in the L-R thalamus, L-R caudate, L-R pallidum, and L-R Nacc. WM volume: no significant associations.
	Age range	50-69			
	Weight status (n)	N/A $_{NW}$, N/A $_{OW}$, N/A $_{OB}$			
Cardiometabolic factors					
Silva 2021 (98)	N (% females)	3098 (50.3)	Total brain, GM, and WM volumes	Blood pressure, insulin, glucose, total cholesterol, HDL, triglycerides	Total brain volume: no associations. GM volume: negative association with diastolic blood pressure and positive association with triglycerides. WM volume: no associations.
	Mean age (SD)	9.8 (0.3)			
	Weight status (n)	201 $_{UW}$, 2355 $_{NW}$, 536 $_{OW/OB}$			
Ross 2015 (99)	N (% females)	130 (58.5)	CTh, GM volume	Insulin resistance	(ROI-based analysis: OFC, anterior cingulate cortex) CT: negative association in the OFC. GM volume: no significant associations.
	Age range	15-21			
	Weight status (n)	51 $_{NW}$, 79 $_{OB}$			

Table 5. Continued

Article	Sample characteristics		MRI measure	Excess weight feature	Results
Cardiometabolic factors					
Gabay 2022 (100)	N (% females)	125 (58.4)	CTh, GM volume	Insulin resistance	(ROI-based analysis: OFC, anterior cingulate cortex, insula) CT: negative association in the insula and medial OFC only in females. GM volume: negative association in the anterior cingulate cortex only in females.
	Age range	16-21			
	Weight status (n)	N/A $_{NW}$, N/A $_{OB}$			
Shang 2022 (101)	N (% females)	36647 (53.4)	Total brain and GM volumes	57 major diseases (n = 10 cardio-metabolic/ vascular)	Total brain volume: negative association mainly with hypertension, dyslipidemia, coronary heart disease and diabetes. GM volume: negative association mainly with hypertension, dyslipidemia, and diabetes.
	Age range	44-81			
	BMI	N/A			
Beyer 2019 (102)	N (% females)	748 (44.4)	GM volume	Metabolic profile (BMI, WHR, glycated hemoglobin, total cholesterol, LDL, CRP, IL-6, adiponectin, leptin)	Negative association between metabolic profile (manly driven by BMI, WHR, glycated hemoglobin, CRP, and leptin) and GM volumes in the frontal, temporal and occipital lobes, thalamus, L-R insular cortices, L amygdala-hippocampus, L cerebellum, R temporal pole, R planum polare and R postcentral gyrus.
	Age range	60-79			
	Mean BMI (SD) BMI range	27.7 (4.1) 16.8 - 42.3			
Allostatic load					
Ottino-González 2017 (103)	N (% females)	63 (57.1)	CTh	AL (15 biomarkers)	Negative relationship (only for OW/OB) in the L pars triangularis, L superior frontal gyrus, L supramarginal gyrus, L inferior parietal cortex, L Precuneus, R precentral gyrus, R precuneus, R transversal temporal gyrus, R inferior parietal cortex, R lateral OFC.
	Age range	21-40			
	Weight status (n)	29 $_{NW}$, 34 $_{OW/OB}$			

Table 5. Continued.

Article	Sample characteristics		MRI measure	Excess weight feature	Results
Allostatic load					
Ottino-González 2018 (104)	N (% females)	52 (57.7)	GM volume	AL (15 biomarkers)	Negative relationship (only for OW/OB) in the L precentral gyrus, L lateral occipital gyrus, and R pars opercularis.
	Age range	21-40			
	Weight status (n)	21 $_{NW}$, 31 $_{OW/OB}$			
Booth 2015 (105)	N (% females)	633 (47.3)	Total brain, GM, and WM volumes	AL (10 biomarkers)	Total brain volume: negative association. GM volume: no association. WM volume: negative association.
	Mean age (SD)	72.49 (0.72)			
	Mean BMI (SD)	27.8 (4.38)			

Abbreviations: AL: allostatic load, BMI: body mass index, CRP: c-reactive protein, CTh: cortical thickness, GM: gray matter, L: left, MRI: magnetic resonance imaging, N/A: not available, NAcc: nucleus accumbens, NW: normal weight, OB: obesity, OFC: orbitofrontal cortex, OW: overweight, PFC: prefrontal cortex, R: right, ROI: region of interest, UW: underweight, WC: waist circumference, WHR: waist-to-hip ratio, WM: white matter.

Table 6. Microstructural brain changes associated with adiposity, cardiometabolic factors, and allostatic load.

Article	Sample characteristics		MRI measure	Excess weight feature	Results
Adiposity					
Kaltenhauser 2023 (92)	N (% females)	4576 (48.3)	FA, MD	BMI z-score, WC	Baseline FA: global negative association with BMI z-score and WC, and locally in the corpus callosum, forceps major and minor, fornix, and superior longitudinal fasciculi. Baseline MD: no global association with BMI z-score or WC. Locally, negative association between WC and the corpus callosum and forceps minor. Longitudinal (2-year follow-up): higher baseline BMI z-score was associated with lower FA increments in the inferior fronto-occipital fasciculi, anterior thalamic radiations, striatal inferior cortices, corpus callosum, forceps minor, R inferior longitudinal fasciculus, and superior longitudinal fasciculus.
	Age range	9-10			
	Weight status (n)	191 UW, 3046 NW, 683 OW, 656 OB			
Silva 2021 (98)	N (% females)	3098 (50.3)	FA, MD	BMI standard deviation score, body fat	Global FA: negative association with BMI standard deviation score and body fat. Global MD: negative association with BMI standard deviation score and body fat.
	Mean age (SD)	9.8 (0.3)			
	Weight status (n)	201 UW, 2355 NW, 536 OW/OB			
Daoust 2021 (106)	Meta-analysis		FA	OB (defined either by BMI, BMI group, WC, WHR, or body fat)	Negative association in the R genu of the corpus callosum.
	N (% females)	4453 (55)			
	Age range	18-92			
	Weight status (n)	N/A NW, N/A OW/OB			
Cardiometabolic factors					
Nouwen 2017 (107)	N (% females)	33 (78.8): 20 healthy, 13 diabetes	FA, MD	Diabetes	FA: negative association in the L corticospinal tract, corpus callosum, L fornix, L thalamic radiation, L retrolenticular internal capsule, inferior fronto-occipital fasciculi, R anterior corona radiata, L uncinate, L callosal body, cingulum, and L anterior external capsule. MD: no associations.
	Age range	12-18			
	Mean BMIz (SD)	0.23 (0.96) healthy 2.2 (1.55) diabetes			

Table 6. Continued.

Article	Sample characteristics		MRI measure	Excess weight feature	Results
Cardiometabolic factors					
Repple 2021 (108)	N (% females)	737 (54.5)	FA	Glycated hemoglobin	Negative association in the genu of the corpus callosum, L-R longitudinal superior fasciculi, L-R internal and external capsules, L-R uncinate fasciculus, corticospinal tract, and cerebellar peduncles.
	Mean age (SD)	28.8 (3.69)			
	Mean BMI (SD)	27.09 (5.89)			
Cox 2019 (109)	N (% females)	9722 (52.5)	FA, MD	Smoking, hypertension, diabetes, pulse pressure, high cholesterol, BMI and WHR	(ROI-based analysis: acoustic radiation, anterior thalamic, cingulum gyrus, and parahippocampal, corticospinal, forceps major and minor, inferior fronto-occipital, inferior longitudinal, middle cerebellar peduncle, medial lemniscus, posterior thalamic, superior longitudinal, superior thalamic, and uncinate.) Global FA and MD: negative and positive associations, respectively, with smoking, hypertension, pulse pressure, and diabetes across thalamic and association fibers, and forceps minor. For BMI and WHR, these associations were more consistent across projection bundles. High cholesterol was not associated with FA or MD.
	Age range	44-79			
	Mean BMI (SD)	26.08 (5.36)			
Jing 2022 (110)	N (% females)	2218 (54.1): 509 healthy, 1205 prediabetes, 504 diabetes	FA, MD	Prediabetes, diabetes	Prediabetes (vs. controls): FA: reductions in restricted WM tracts (L-R anterior corona radiata, R superior longitudinal fasciculus, posterior corona radiata, anterior limb of internal capsule. MD: increments in the R external capsule, L-R anterior corona radiata, anterior limb of internal capsule, superior longitudinal fasciculi, and superior corona radiata. Diabetes (vs controls): decrease of FA and increase in MD in widespread WM tracts.
	Age range	50-75			
	Mean BMI (SD)	23.2 (2.7) healthy, 24 (3) prediabetes, 24.7 (3.2) diabetes			
Zsoldos 2018 (111)	N (% females)	349 (19.5)	FA, MD	Metabolic syndrome	FA: no association. MD: no association.
	Age range	60-83			
	BMI	N/A			

Table 6. Continued.

Article	Sample characteristics		MRI measure	Excess weight feature	Results
Allostatic load					
Ottino-González 2018 (104)	N (% females)	52 (57.7)	FA, MD	AL (15 biomarkers)	FA: Negative relationship (only for OW/OB) in the inferior fronto-occipital fasciculi and R anterior corona radiata. MD: no association.
	Age range	21-40			
	Weight status (n)	21 $_{NW}$, 31 $_{OW/OB}$			
Ritchie 2017 (112)	N (% females)	731	FA, MD	AL (8 biomarkers)	(Longitudinal approach, 3-year follow-up. ROI-based analysis: L-R anterior thalamic radiation, L-R arcuate fasciculi, genu and splenium of the corpus callosum, L-R cingulum, L-R inferior longitudinal fasciculi, L-R uncinate fasciculi). FA: negative association at baseline, no association at follow-up. MD: no association at baseline, positive association at follow-up.
	Mean age (SD)	Baseline: 68 (0.72) Follow-up: 76.38 (0.65)			
	BMI	N/A			
Zsoldos 2018 (111)	N (% females)	349 (19.5)	FA, MD	AL (9 biomarkers)	FA: no association. MD: no association.
	Age range	60-83			
	BMI	N/A			

Abbreviations: AL: allostatic load, BMI: body mass index, FA: fractional anisotropy, L: left, MD: mean diffusivity, MRI: magnetic resonance imaging, N/A: not available, NAcc: nucleus accumbens, NW: normal weight, OB: obesity, OW: overweight, R: right, ROI: region of interest, UW: underweight, WC: waist circumference, WHR: waist-to-hip ratio, WM: white matter.

1.11. Psychological characteristics of the excess weight phenotype

Excess weight has been widely associated with changes in several psychological domains. From EF to impulsivity, reward, and stress responses, among others, the literature suggests that individuals with excess weight perform poorly or have increased vulnerability in these domains, with most of the evidence centered on EF. While excess weight has usually been studied under the umbrella of adiposity, the impact of cardiometabolic changes and AL states on psychological traits is emerging as a new area of interest.

1.11.1. Executive functions

While the excess weight phenotype (i.e., adiposity, cardiometabolic features, and AL) has been previously associated with multiple cognitive functions (113,114), EF are of special relevance for eating behaviors and excess weight development and maintenance (77).

Excess weight, defined by measures of **adiposity**, has been widely associated with changes in working memory, cognitive flexibility, and inhibitory control across all age groups, as reported in meta-analyses and reviews (115–117). Theoretically, the low-inflammatory processes and cardiometabolic dysregulations associated with increased adiposity could potentially induce structural and functional brain changes in the PFC, resulting in poorer EF performance, which has been found to be more pronounced in higher BMI categories (117). Longitudinal studies showing an improvement in EF after bariatric surgery or weight loss programs may provide initial evidence of the direction of the relationship between excess weight and EF (115,116). However, it has also been hypothesized that EF may serve as predictors of excess weight, where ineffective cognitive control at baseline, especially inhibitory control, would favor overeating. This view has been supported by longitudinal studies in which better EF predicted greater weight loss after bariatric surgery or weight-reduction programs (115,116). Although no single theoretical model prevails, and both are supported by empirical data, this thesis is based on the hypothesis that excess weight may lead to EF impairments.

Cardiometabolic changes, another feature of the excess weight phenotype, are associated with differences in EF. A large cross-sectional study of young adults showed a negative association between glycated hemoglobin and working memory (108). Moreover, a meta-analysis of individuals aged 13-40 reported that, compared to healthy controls, those with type 1 diabetes performed poorly across all EF domains (118). Another meta-analysis that assessed differences in EF (i.e., working memory and cognitive flexibility) in adults aged 50

years or older showed that those with type 2 diabetes had deficits in cognitive flexibility, but not in working memory (119). Moreover, in a study of adolescents, the association between multiple metabolic factors (i.e., insulin resistance, low HDL, high systolic blood pressure, triglycerides, and WC) and inhibitory control was tested. Their results suggested that higher triglyceride and lower HDL levels were associated with poorer inhibitory performance (120). Consistently, in another study of adults aged 40 years or older, those with metabolic syndrome exhibited poorer EF performance, although the number of altered metabolic syndrome components did not show an additive effect on EF (121). In contrast, a large longitudinal study (10-year follow-up) of middle-aged women with metabolic syndrome did not show reductions in working memory performance (122).

Evidence on how **AL** impacts EF is primarily from adult samples. A meta-analysis of adults aged 18 years or older concluded that there was a significant association between higher AL and poorer EF (113).

1.11.2. Impulsivity, reward, and stress

Adiposity measures that reflect excess weight have been linked to impulsivity, reward, and stress. A large meta-analysis evidenced that higher impulsivity levels, assessed by either questionnaires or behavioral tasks, were associated with higher BMI categories (123). Another review highlighted that temporal discounting (i.e., the preference for small immediate rewards over larger delayed rewards) was associated with OB in most studies (124). In addition, a large study of adults aged 18 years or older showed that the prevalence of OB increased as the number and severity of ACEs increased too (125).

Although the effect of **cardiometabolic** factors on impulsivity traits is usually studied in samples with mental health conditions (e.g., bipolar disorder, depression, schizophrenia, addiction, and self-harm tendencies), there is initial evidence of this relationship in healthy participants. In a large study of participants aged 14-92, impulsivity traits were associated with higher triglyceride and lower HDL levels (126). In contrast, a study of middle-aged twins found no association between lipid profile measures (i.e., total cholesterol, HDL, LDL, and triglycerides) and self-control (127). Regarding reward and stress features, a study of female young adults evidenced that in those with lower total cholesterol levels, there was a preference for immediate rewards despite being subjected to higher losses over time (128). Another study of adults aged 18-49 indicated that work stress was associated with metabolic syndrome, especially in young males (129). Consistently, a large study of adults aged 18 years

or older showed that individuals exposed to higher numbers and severity of ACEs had a higher risk of diabetes and cardiovascular disease (125).

The impact of **AL** on impulsivity and reward responses has yet to be determined. Regarding stress, a study of adults aged 27-65 showed that AL was associated with increased self-reported chronic stress and burnout symptoms (130). A systematic review also reported that exposure to ACEs was associated with elevated AL levels (131).

1.12. A comprehensive model of excess weight development and maintenance in adolescents.

Excess weight is a health condition that goes far beyond the act of overeating. Throughout this thesis, several factors that condition excess weight development or promote its maintenance have been presented, recognizing their multiple interactions, and emphasizing the developmental period in which they occur. Given that excess weight at young ages is associated with increased morbidity, it is particularly important to understand this condition holistically to provide appropriate medical and (neuro)psychological interventions. Figure 4 shows the proposed comprehensive model of excess weight development and maintenance in adolescents.

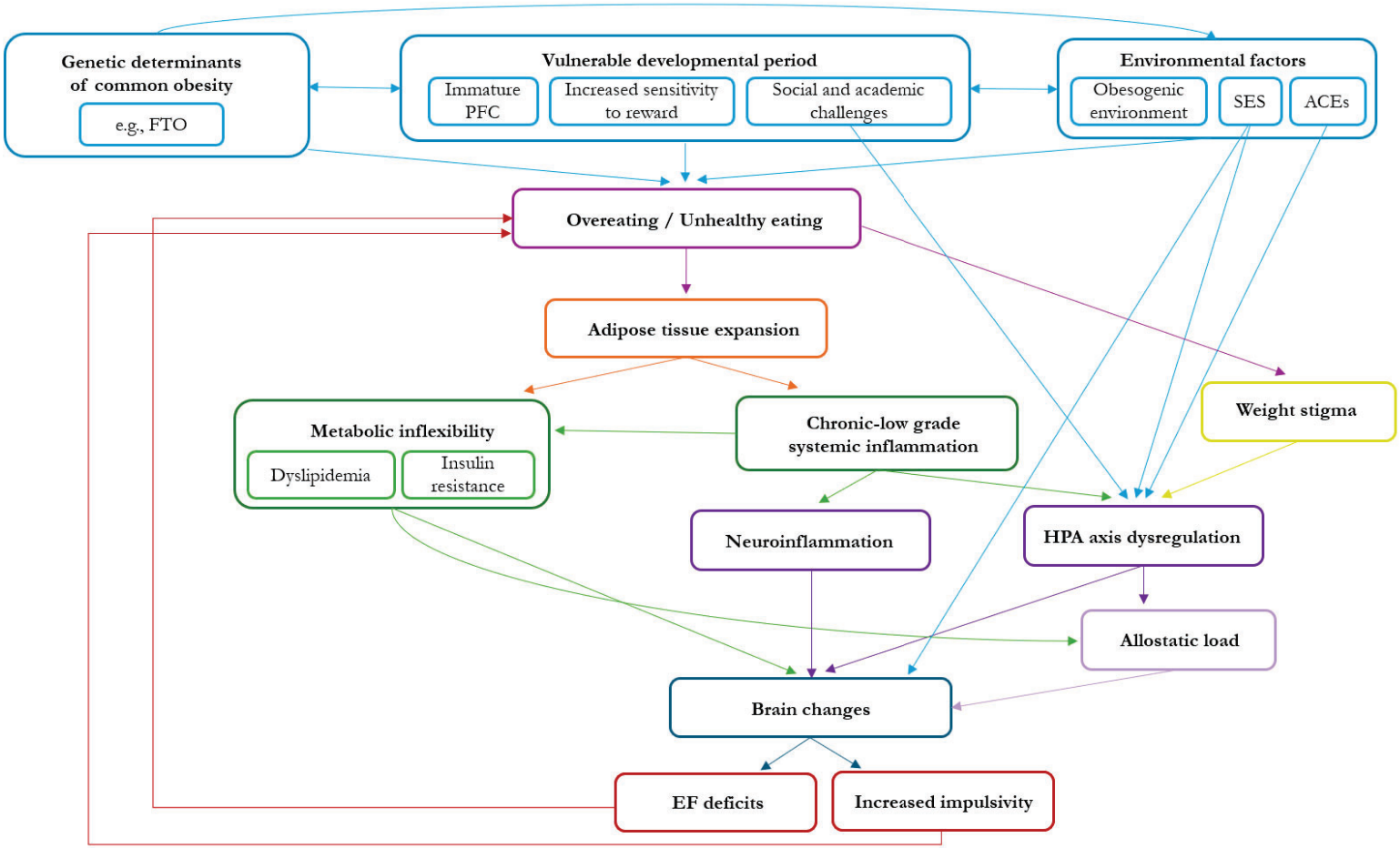


Figure 4. Proposed comprehensive model of excess weight development and maintenance in adolescents. Abbreviations. ACEs: adverse childhood experiences, EF: executive functions, FTO: mass and obesity-related gene; HPA: hypothalamic-pituitary-adrenal, PFC: prefrontal cortex, SES: socioeconomic status. Original figure created specifically for this doctoral thesis.

Chapter 2. Hypotheses and Objectives

HYPOTHESES

This thesis frames excess weight as a multifactorial condition and acknowledges its complexity by proposing a comprehensive model in which genetic, developmental, environmental, biological, neurological, and psychological elements interact, ultimately promoting the development and maintenance of excess weight during adolescence. Targeting different aspects of this model, and to disentangle potential biomarkers that may help better predict the neurocognitive changes associated with the excess weight phenotype, the present thesis proposes the following hypotheses:

1. Excess weight and the A allele of the fat mass and obesity-related gene rs9939609 may be associated with lower structural connectivity in the reward network.

2. Cardiometabolic factors usually present in excess weight may be associated with increased impulsivity and alterations in white matter microstructure.

3. Stress, either led or followed by exposure to adverse childhood experiences or allostatic load, respectively, may be associated with poorer executive functioning.

OBJECTIVES

1. To investigate the structural connectivity patterns of the reward network in adolescents and young adults.
   1.1. To determine the structural connectivity differences in the reward network according to body mass index.
   1.2. To determine the structural connectivity differences in the reward network in carriers versus non-carriers of the A allele of the fat mass and obesity-related gene rs99396309.

2. To evaluate the association between cardiometabolic factors, white matter microstructure, and impulsivity in adolescents with and without excess weight.
   2.1. To assess the relationship between cardiometabolic factors and microstructural changes in white matter tracts typically associated with both excess weight and impulsivity.
   2.2. To assess the relationship between cardiometabolic risk factors and impulsivity.

3. To establish whether executive functioning is vulnerable to physiological and psychological stress in adolescents and young adults with and without excess weight.
   3.1. To test the association between executive functioning and allostatic load.
   3.2. To test the association between executive functioning and adverse childhood experiences.

Chapter 3. Materials and Methods

Study 1

International Journal of Obesity www.nature.com/ijo

ARTICLE

Pediatrics

From the reward network to whole-brain metrics: structural connectivity in adolescents and young adults according to body mass index and genetic risk of obesity

Anna Prunell-Castañé[1,2,3], Frauke Beyer[4,5], Veronica Witte[4,5], Consuelo Sánchez Garre[6], Imma Hernán[7], Xavier Caldú[1,2,3], María Ángeles Jurado[1,2,3]✉ and Maite Garolera[8,9]

BACKGROUND: Obesity is a multifactorial condition. Genetic variants, such as the fat mass and obesity related gene (FTO) polymorphism, may increase the vulnerability of developing obesity by disrupting dopamine signaling within the reward network. Yet, the association of obesity, genetic risk of obesity, and structural connectivity of the reward network in adolescents and young adults remains unexplored. We investigate, in adolescents and young adults, the structural connectivity differences in the reward network and at the whole-brain level according to body mass index (BMI) and the FTO rs9939609 polymorphism.
METHODS: One hundred thirty-two adolescents and young adults (age range: [10, 21] years, BMI z-score range: [−1.76, 2.69]) were included. Genetic risk of obesity was determined by the presence of the FTO A allele. Whole-brain and reward network structural connectivity were analyzed using graph metrics. Hierarchical linear regression was applied to test the association between BMI-z, genetic risk of obesity, and structural connectivity.
RESULTS: Higher BMI-z was associated with higher ($B = 0.76$, 95% CI = [0.30, 1.21], $P = 0.0015$) and lower ($B = -0.003$, 95% CI = [−0.006, −0.00005], $P = 0.048$) connectivity strength for fractional anisotropy at the whole-brain level and of the reward network, respectively. The FTO polymorphism was not associated with structural connectivity nor with BMI-z.
CONCLUSIONS: We provide evidence that, in healthy adolescents and young adults, higher BMI-z is associated with higher connectivity at the whole-brain level and lower connectivity of the reward network. We did not find the FTO polymorphism to correlate with structural connectivity. Future longitudinal studies with larger sample sizes are needed to assess how genetic determinants of obesity change brain structural connectivity and behavior.

International Journal of Obesity; https://doi.org/10.1038/s41366-023-01451-w

INTRODUCTION

Obesity is a complex condition caused by a combination of biological, social, psychological, and environmental factors [1]. Genetic variants, with heritability estimates of 40–70%, may underlie the inter-individual variation in the susceptibility to the obesogenic environment. The fat mass and obesity related gene (FTO), the first gene to emerge from body mass index (BMI) genome-wide association studies, has been consistently associated with obesity. The most representative single nucleotide polymorphism in the first intron of the FTO gene is rs9939609 [2]. The effect of the FTO on BMI is relatively large (0.35 kg/m^2 per A allele), although the underlying biological mechanisms have not yet been fully elucidated [3].

In humans, variations in the FTO gene may exert an effect on BMI by modulating food intake rather than energy expenditure [4]. Polymorphisms in the FTO may regulate the activity of dopaminergic neurons in the reward circuit, thus affecting reward sensitivity within the reward network [5]. The reward network comprises interconnected cortical and subcortical structures (lateral and medial orbitofrontal cortices, nucleus accumbens, caudate nucleus and putamen) that are involved in reward processing, learning, motivation and self-regulation [6]. Evidence suggests that a disruption in this network may increase food cravings and preference for high-calorie food, as well as impair reward learning and impulse control, thus changing feeding behavior and producing weight gain [7].

[1]Departament de Psicologia Clínica i Psicobiologia, Facultat de Psicologia, Universitat de Barcelona, Passeig de la Vall d'Hebron, 171, 08035 Barcelona, Spain. [2]Institut de Neurociències, Universitat de Barcelona, Barcelona, Spain. [3]Institut de Recerca Sant Joan de Déu, Esplugues de Llobregat, Spain. [4]Clinic for Cognitive Neurology, University of Leipzig Medical Center, Leipzig, Germany. [5]Department of Neurology, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany. [6]Pediatric Endocrinology Unit, Hospital de Terrassa, Consorci Sanitari de Terrassa, Terrassa, Barcelona, Spain. [7]Molecular Genetics Unit, Consorci Sanitari de Terrassa, Terrassa, Spain. [8]Brain, Cognition and Behavior: Clinical Research, Consorci Sanitari de Terrassa, Terrassa, Barcelona, Spain. [9]Neuropsychology Unit, Hospital de Terrassa, Consorci Sanitari de Terrassa, Terrassa, Barcelona, Spain. ✉email: majurado@ub.edu

Received: 24 August 2023 Revised: 5 December 2023 Accepted: 12 December 2023
Published online: 25 December 2023

Various neuroimaging approaches have been used to assess the structural and functional neurobiology of obesity. A compromised (lower) structural connectivity within the reward network has been associated with obesity [6, 8, 9]. However, other studies showed contradictory results, describing both higher and lower structural connectivity between the ventral striatum and the frontal cortex [10, 11]. Gray matter volume of the reward network has also been studied in the context of obesity. In a recent meta-analysis, greater volumes of the nucleus accumbens were associated with higher BMI in adolescents, whereas the opposite result was found in adults [12].

Importantly, not only is weight status associated with the reward network, but also having a genetic risk of developing obesity. A functional neuroimaging study suggested a positive and additive relationship between obesity genetic factors and striatal activation [13]. Similarly, another study [14] revealed disrupted structural connectivity in the nucleus accumbens and the thalamus in homozygous participants for the FTO A allele, while another study found increased structural connectivity between the ventral tegmental area/substantia nigra and the nucleus accumbens in FTO A allele carriers [7].

While other studies have investigated the relationship between FTO polymorphisms and brain structural connectivity in children and adults with diverse BMI values [7, 9, 14, 15], to our knowledge, the associations of structural connectivity with BMI and genetic risk of obesity in adolescents and young adults remain unexplored. Since changes in the reward network connectivity might stem from adverse effects of obesity (i.e., metabolic burden) or arise from predisposing factors (i.e., genetics), in this study we investigate, in a sample of adolescents and young adults, the structural connectivity differences in the reward network according to (i) BMI and (ii) being carrier of the FTO rs9939609 A allele. Based on previous literature, we hypothesized that (i) higher BMI and (ii) the presence of the FTO rs9939609 A allele may be related to lower connectivity in the reward network. Using an exploratory approach, we also investigated the same hypotheses at the whole-brain level.

METHODS

Participants selection and procedure

Potential participants from public primary care centers of the Consorci Sanitari de Terrassa were randomly contacted by telephone and invited to take part in the study. If they agreed, they underwent a telephonic screening interview to assess the adequacy of their participation. Inclusion criterion was being aged between 10 and 21 years [16]. Exclusion criteria were: (i) underweight, (ii) psychiatric, neurological, developmental (e.g., attention-deficit/hyperactivity disorder, autism spectrum disorder), cardiometabolic (e.g., diabetes, metabolic syndrome, hypo/hyperthyroidism), or systemic (e.g., cancer, lupus) diagnosis, and (iii) global cognitive impairment or bulimia-like behaviors. Additionally, the medical doctor explored with the participants their medical history to ensure the suitability of their inclusion.

The first day, 144 potential candidates were cited to undergo a medical evaluation and a blood sample extraction at the Hospital de Terrassa – Consorci Sanitari de Terrassa ($n = 89$), or to undergo an at-home medical visit and blood sample extraction (after SARS-Cov-2 breakdown, $n = 55$). Pubertal stage was determined according to the Tanner scale of sexual maturity. The second day, we further assessed exclusion criteria with specific questionnaires: a scalar score <7 in the Weschler Adults Intelligence Scale-III/Weschler Intelligence Scale for Children-IV vocabulary subtest determined global cognitive impairment, and meeting criteria for bulimia nervosa at the Mini International Neuropsychiatric Interview for Bulimia or a score ≥20 in the Bulimia Inventory Test of Edinburgh determined bulimia-like behaviors. Three participants were excluded for presenting bulimia-like behaviors ($n = 2$ assessed with the Bulimia Inventory Test of Edinburgh and $n = 1$ with the Mini International Neuropsychiatric Interview for Bulimia). Bulimia was not assessed using the same questionnaire for all participants due to a change in the protocol. Anxiety and depression symptoms were also assessed using the Hospital Anxiety and Depression Scale. Recruitment and data collection were carried out between 2010 and 2022. Some of the participants in the present study were already included in previous works [17, 18].

Participants without claustrophobia or metal protheses also underwent a brain magnetic resonance imaging (MRI) acquisition on a 3T MAGNETON (Siemens, Germany) at the Centre de Diagnòstic per la Imatge Clínica at the Hospital Clínic de Barcelona. One participant was excluded during the MRI acquisition due to the detection of a low-grade glioma and was immediately referred to neurology and oncology services. Eight more participants were excluded after the neuroimaging quality control (see imaging preprocessing and connectome reconstruction section). This led to a final sample size of 132 adolescents and young adults, of which two had missing genetic data.

This study was approved by the Ethics Committee for Clinical Research of the Consorci Sanitari de Terrassa, and Institutional Ethics Committee of the University of Barcelona (Institutional Review Board IRB00003099, assurance number FWA00004225). The research was conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from all participants, or their legal guardian in underage participants, prior to entry in the study.

Anthropometric measurement

Anthropometric measures were obtained by a trained nurse from participants in light clothing without shoes. Height was measured with two different devices ($n = 81$: Holtan Limited Harpenden Stadiometer, and $n = 51$: Längenmessstab 5003-Soehnle Professional). Weight was also measured with two different devices ($n = 81$: Seca 704 s, and $n = 51$: Tanita InnerScan-V). T-tests were performed and no differences in height and weight measurements were observed ($P > 0.05$). BMI was calculated as kilograms/meters^2 (kg/m^2), and then transformed into BMI z-score using the R package *cdcanthro*. Since BMI-z values can be calculated for participants up to 20 years, for those participants aged 20 and 21, their BMI z-score was calculated as if they were 19 years and 11 months [19]. For descriptive purposes, we classified participants as normal-weight or overweight/obesity using the BMI cut-offs from Cole and Lobstein [20] for underage participants, and the 25 kg/m^2 BMI cut-off from the World Health Organization [21] for participants aged 18–21.

Genotyping

Peripheral blood samples were obtained from 130 participants and genomic DNA was extracted automatically using the MagNaPure Compact Instrument (Roche Applied Science, Barcelona, Spain). The FTO polymorphism rs9939609 was genotyped in 70 participants using polymerase chain reaction and Sanger Sequencing (primers and conditions available on request). On the other 60 patients, rs9939609 was genotyped using the Flex Six GT Integrated Fluidic Circuit and SNP Type assays according to the manufacturer's protocol using the genotyping platform Fluidigm Juno System and Biomark HD (Fluidigm Corp, South San Francisco, CA, USA). The risk allele of this variant is the A allele. The genotype counts in our sample were $n_{TT} = 39$, $n_{AT} = 68$, $n_{AA} = 23$ (minor allele frequency = 0.44, test for Hardy–Weinberg equilibrium $Chi^2 = 0.33$, $df = 1$, $P = 0.56$). Two participants had missing genetic data. Participants were mostly White and Spaniard ($n = 124$). Six participants had American Latino ancestry, and for two participants race or ethnicity was not reported. For the analysis, we grouped together carriers of at least one risk allele (A) vs. non-carriers, and we controlled for the batch effect by adding a covariate indicating which laboratory genotyped the FTO polymorphism.

MRI data acquisition

MRI acquisition was performed using a 3 T Siemens Magnetom Trio ($n = 72$) and a 3 T Siemens Magnetom Prisma ($n = 60$). T1-weighted images were acquired with the following parameters for the Trio scanner: inversion time = 900 ms, repetition time = 2300 ms, echo time = 2.98 ms; flip angle = 9°, band width = 240 Hz/Px, field of view = 256 × 256 × 240 mm^3, voxel size = 1 × 1 × 1 mm^3, slices = 240, total scan time = 7:48 min; and with these parameters for the Prisma scanner: inversion time = 1000 ms, repetition time = 2400 ms, echo time = 2.22 ms; flip angle = 8°, band width = 220 Hz/Px, field of view = 256 × 240 × 167 mm^3, voxel size = 0.8 × 0.8 × 0.8 mm^3, slices = 208, total scan time = 6:38 min.

Diffusion-weighted images (DWI) were acquired with the following parameters for the Trio scanner: repetition time = 7700 ms, echo time = 89 ms, field of view = 244 × 244 × 120 mm^3, diffusion directions = 30, slice thickness = 2 mm, number of slices = 60, max b value = 1000 s/mm^2, total

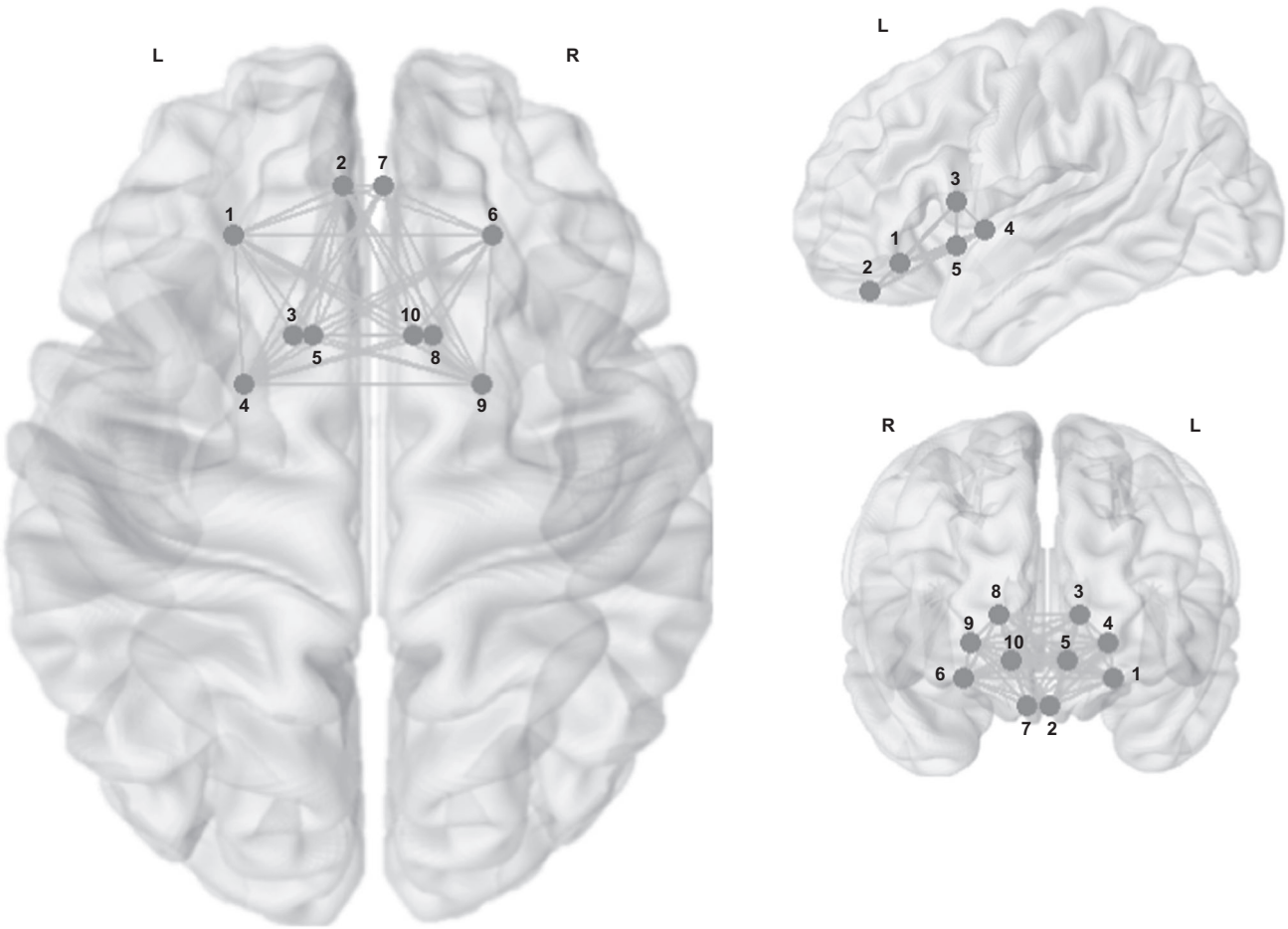


Fig. 1 Reconstruction of the reward network using R's package *brainconn*. Dots refer to hubs of the lateral (1,6) and medial orbitofrontal cortex (2,7), caudate nucleus (3,8), putamen (4,9), and nucleus accumbens (5,10). Lines indicate structural connections.

scan time = 4:23 min; and these parameters for the Prisma scanner: repetition time = 3230 ms, echo time = 89.2 ms, field of view = 210 × 210 × 138 mm^3, diffusion directions = 99, slice thickness = 1.5 mm, number of slices = 92, max *b* value = 3000 s/mm^2, total scan time = 5:41 min.

Imaging preprocessing and connectome reconstruction

DWI data were denoised using MRtrix's tool *dwidenoised* [22] and corrected for distortions ($n = 40$ Brainsuite registration-based distortion correction [23], $n = 92$ FSL *topup* [24]) and eddy-current and head motion [25], while performing outlier detection and replacement [26]. Quality control was performed using *eddyqc* (FSL) output [27]. Two participants were excluded for having large ventricles and 6 participants were excluded for excessive (>3 SD) head motion. The final sample size included 132 participants.

DWI were resampled to 2 mm isotropic resolution and rotated to align with the anterior commissure – posterior commissure line. The diffusion data were reconstructed using generalized q-sampling imaging [28] with a diffusion sampling length ratio of 2. Deterministic whole-brain fiber tracking was implemented in DSI Studio using a modified fiber assignment by continuous tracking algorithm [29]. For each subject, 1.000.000 streamlines with a length between 30–300 mm were initiated. Fiber tracking was performed with randomized angular threshold, step size and anisotropy threshold values. Fractional anisotropy (FA) was calculated for each reconstructed streamline.

Brain parcellation was performed using DSI Studio's built-in Freesurfer Desikan-Killiany Cortical and Subcortical atlases, with 80 regions of interest that were transformed to each participant's native space. For every participant, structural weighted and undirected connectivity matrices were constructed by using 80 cortical and subcortical regions as nodes, and connectivity weights between the regions as edges. Two types of connectivity weights were evaluated: the total number of connecting streamlines touching two regions and the mean FA across voxels included in these streamlines.

Reward network analyses

The reward network was reconstructed based on ten bilateral regions (Fig. 1): lateral and medial orbitofrontal cortex, nucleus accumbens, caudate nucleus and putamen [6]. Again, such regions were defined as nodes, and the number of streamlines (NOS) and average FA between regions as edges. We calculated graph metrics using the Brain Connectivity Toolbox (Matlab) implemented in DSI Studio. The organization of the reward network was analyzed by means of connectivity strength (CS), that describes the overall strength of connections between regions both quantitatively (NOS) and qualitatively (FA), and clustering coefficient (CC), that measures local organization as the average probability of neighboring nodes in the network to be interconnected. The resulting network metrics (NOS CS, NOS CC, FA CS, FA CC) were normalized by the whole brain connectivity metrics [6, 9] and harmonized between-scanners and protocols using ComBat (see Supplementary Fig. S1), a batch-effect correction tool that removes the unwanted variation by site and preserves biological variability [30].

Data treatment and statistical analysis

Prior to conducting the analyses, we registered our analysis plan in Open Science Framework: https://osf.io/nfyha. Data manipulation and statistical procedures were performed in R statistical package v.4.0.5 and RStudio v.2022.02.3. Mann–Whitney U and Chi-square tests were used to analyze between-group differences in sample demographic characteristics. Assumptions of linear regression were visually checked for all models using R's *check_model* in package *performance*. If the assumptions were not met, we log-transformed the variables.

Main analysis. We performed hierarchical linear regression analyses to assess the relationship between reward network (REW) metrics (NOS CS, NOS CC, FA CS, FA CC) and different predictors, which were entered in the models by steps. We used F-tests and associated *P* values from ANOVA to compare the models.

Table 1. Demographic characteristics of the BMI and FTO groups.

	BMI groups							FTO groups						
	NW ($n = 62$)			OW/OB ($n = 70$)			Test	P	TT ($n = 39$)			AT/AA ($n = 91$)			Test	P
	Mean (sd)	Min	Max	Mean (sd)	Min	Max			Mean (sd)	Min	Max	Mean (sd)	Min	Max		
Age (years old)	15.6 (2.63)	10	21	15.2 (2.68)	10	21	2381[a]	0.34	15.7 (2.65)	11	21	15.3 (2.69)	10	21	1935[a]	0.42
Prepubescents (*n*)	4			2			0.32[b]	0.57	3			3			0.41[b]	0.52
Sex (*n* females)	32			32			0.25[b]	0.61	21			43			0.25[b]	0.62
BMI z-score	−0.1 (0.62)	−1.76	0.89	1.79 (0.4)	0.95	2.69	0[a]	<0.001	0.85 (1.11)	−0.98	2.61	0.96 (1.04)	−1.76	2.69	1648[a]	0.52
Anxiety	5.92 (3.17)	0	13	5.24 (3.26)	0	14	2436[a]	0.22	5.31 (3.15)	0	13	5.75 (3.25)	0	14	1614[a]	0.41
Depression	2.71 (2.24)	0	12	3.04 (2.53)	0	9	2037[a]	0.54	3.13 (2.55)	0	12	2.82 (2.34)	0	9	1893[a]	0.54
Estimated intelligence	11.2 (2.44)	7	19	11 (2.47)	7	19	2269[a]	0.65	10.9 (2.51)	7	17	11.2 (2.44)	7	19	1719[a]	0.78
FTO A Carrier (*n*)	43			48			0.04[b]	0.85	–			–			–	–

BMI body mass index, *Estimated intelligence* calculated using the Weschler Adults Intelligence Scale-III/Weschler Intelligence Scale for Children-IV vocabulary subtest, *FTO* fat mass and obesity related gene, *NW* normal-weight, *OW/OB* overweight/obesity.
[a]Mann–Whitney U test
[b]Chi Squared Test.

To assess the first hypothesis – whether higher BMI may be related to lower connectivity in the reward network –, we tested the null model 1a: REW metric ~ age + sex + estimated intracranial volume (eTIV) vs. the full model 1b: REW metric ~ age + sex + eTIV + BMI-z). For the second hypothesis – whether the FTO rs9939609 A allele is related to lower connectivity in the reward network – we used the same approach (null model 2a: REW metric ~ age + sex + eTIV + batch effect; full model 2b: REW metric ~age + sex + eTIV + batch effect + FTO). Additionally, we investigated whether the FTO locus explained variance in BMI-z (null model 3a: BMI-z ~age + sex + batch effect; full model 3b: BMI-z ~age + sex + batch effect + FTO). Unstandardized betas were reported. To assess whether the results were consistent despite possible confounders, we repeated the analyses of hypotheses (1) and (2) controlling for pubertal stage (prepubescent or pubertal), and the anxiety and depression scores of the Hospital Anxiety and Depression Scale. We based the inference of whether the effect was still present on the uncorrected *p* values of the model comparison. A sensitivity analysis without controlling for eTIV can be found in Supplementary Material.

Exploratory analysis. We further performed an exploratory analysis that was not included in the registration of the study. Hypotheses (1) and (2) were explored at the whole-brain level using the same predictors and structure described above (model 4a: whole-brain metric ~age + sex + eTIV; model 4b: whole-brain metric ~age + sex + eTIV + BMI-z; model 5a: whole-brain metric ~age + sex + eTIV + batch effect; model 5b: whole-brain metric ~age + sex + eTIV + batch effect + FTO), as well as repeating the analyses controlling for possible confounders. A sensitivity analysis without controlling for eTIV can be found in Supplementary Material.

Multiple comparison correction: Using R studio, we applied a false discovery rate (FDR) correction to 17 models: REW metrics and BMI-z (4 models), REW metrics and FTO (4 models), whole-brain metrics and BMI-z (4 models), whole-brain metrics and FTO (4 models), and BMI-z and FTO (1 model). Significance was set at FDR-corrected *p*-value < 0.05. When testing if the results were consistent after controlling for possible confounders (anxiety, depression, pubertal stage), we reported the results at an uncorrected level.

RESULTS

Descriptive characteristics of the sample according to BMI ($n = 132$) and FTO status ($n = 130$) are detailed in Table 1. A histogram of age distribution is provided in Supplementary Fig. S2.

Main analysis: reward network results

When testing if the variables of interest (BMI-z or FTO A allele carrier) explained variance in the graph metrics of the reward network, we did not find significant results (FDR > 0.05; Supplementary Table S1). After controlling for possible confounders, we observed that higher BMI-z was associated with lower FA CS (beta = −0.003, F = 3.97, uncorrected $P = 0.048$, Table 2). That is, with a lower white matter integrity among the white matter tracts that interconnect the reward network brain regions (lateral and medial orbitofrontal cortex, nucleus accumbens, caudate nucleus and putamen). Additionally, we investigated whether the FTO polymorphism explained variance in BMI-z, and found no significant results (beta = 0.11, F = 0.0026, FDR > 0.05).

Exploratory analysis: whole-brain results

Furthermore, we investigated differences in the whole-brain structural connectivity according to BMI-z and genetic risk of obesity. We observed that higher BMI-z was associated with higher FA CS (beta = 0.77, F = 11.34, FDR = 0.017, Supplementary Table S2). After controlling for confounders (Table 3), this relationship was still significant (beta = 0.76, F = 10.49, uncorrected $P = 0.0015$). No significant associations were found regarding whole-brain structural connectivity and FTO variants.

DISCUSSION

In this pre-registered study of adolescents and young adults, we examined the relationship between the structural connectivity of

Table 2. Results from the hierarchical multiple regression analysis of BMI-z, FTO and reward network structural connectivity after controlling for confounders.

REW metric	Model	Multiple regression		Model comparison		Variable of interest			
		Adj R^2	*P* model	F	$P_{uncorrected}$		*b*	95% CI	*P*
CC NOS (log)	1c	0.007	0.27	–	–	BMI-z	–	–	–
	1d	−0.002	0.45	0.62	0.61		–	–	–
	1e	−0.009	0.57	0.03	0.86		0.004	(−0.04, 0.05)	0.87
	2c	0.006	0.32	–	–	FTO	–	–	–
	2d	−0.0004	0.44	0.74	0.53		–	–	–
	2e	−0.0003	0.44	1	0.32		−0.06	(−0.17, 0.06)	0.32
CS NOS	1c	−0.013	0.74	–	–	BMI-z	–	–	–
	1d	−0.023	0.81	0.58	0.63		–	–	–
	1e	−0.03	0.85	0.29	0.59		−0.01	(−0.05, 0.03)	0.59
	2c	−0.02	0.81	–	–	FTO	–	–	–
	2d	−0.03	0.83	0.65	0.58		–	–	–
	2e	−0.03	0.85	0.56	0.45		−0.037	(−0.13, 0.06)	0.45
CC FA	1c	0.06	0.012	–	–	BMI-z	–	–	–
	1d	0.06	0.026	1.2	0.31		–	–	–
	1e	0.07	0.026	1.64	0.2		−0.01	(−0.03, 0.005)	0.2
	2c	0.05	0.025	–	–	FTO	–	–	–
	2d	0.06	0.037	1.31	0.27		–	–	–
	2e	0.06	0.04	1.2	0.27		0.02	(−0.02, 0.06)	0.27
CS FA	1c	−0.005	0.52	–	–	BMI-z	–	–	–
	1d	−0.0009	0.44	1.23	0.3		–	–	–
	1e	0.02	0.2	3.97	0.048		−0.003	(−0.006, −0.00005)	0.048
	2c	−0.01	0.62	–	–	FTO	–	–	–
	2d	−0.003	0.47	1.32	0.27		–	–	–
	2e	0.003	0.48	0.99	0.32		0.004	(−0.004, 0.01)	0.32

Model 1c: REW metric ~age + sex + eTIV; model 1d: REW metric ~age + sex + eTIV + prepubescent + anxiety + depression; model 1e: REW metric ~age + sex + eTIV + prepubescent + anxiety + depression + BMI-z; model 2c: REW metric ~age + sex + eTIV + batch effect; model 2d: REW metric ~age + sex + eTIV + batch effect + prepubescent + anxiety + depression; model 2e: REW metric ~age + sex + eTIV + batch effect + prepubescent + anxiety + depression + FTO. Unstandardized betas were reported.

BMI-z body mass index z-score, *CC* clustering coefficient, *CS* connectivity strength, *eTIV* estimated total intracranial volume, *FA* fractional anisotropy, *FTO* fat mass and obesity related gene (A-allele carrier vs. non carrier), *NOS* number of streamlines, *REW* reward network.

the reward network, BMI-z, and the genetic risk of obesity. Here, a higher BMI-z was significantly associated with lower structural connectivity of the reward network. Specifically, a higher BMI-z was associated with lower FA CS. Interestingly, when exploring the direction of the results at the whole-brain level, we found that a higher BMI-z was significantly related to higher FA CS. Regarding the FTO polymorphism, we did not observe genetic associations with measures of structural connectivity neither in the reward network nor at the whole-brain level. Moreover, the FTO polymorphism was not associated with BMI-z differences.

BMI-z and FTO

In our sample, although the FTO polymorphism was not significantly associated with BMI-z, the association was in the expected direction. This is contrary to the results of a meta-analysis [31] that assessed, in children and adolescents of diverse ethnicities, the effect of the FTO risk alleles on obesity. We hypothesize that such unexpected results might be explained by both methodological considerations and the presence of confounders. First, it is possible that we could not detect the effect due to the relatively small sample size and low power. Furthermore, our approach for the FTO analysis (carriers of the risk allele vs. non carriers; instead of differentiating between homozygous and heterozygous genotypes) might also have influenced the results. Additionally, it is worth considering that other factors such as developmental stage, socioeconomic status, and epigenetics might modify the effects of the FTO polymorphism on BMI in this group. Regarding developmental status, a previous study suggested that the influence of a genome-wide polygenic score of obesity on BMI trajectories was more pronounced as development advanced and adulthood was reached [32]. Thus, the genetic effect of FTO might be age-dependent [33], and the impact of FTO on BMI in our sample might be blurred due to the wide age range of our participants (10 to 21 years old), probably via the endocrinological and physiological changes present during midpuberty that might temporarily diminish the association between BMI-z and FTO [34]. There is also evidence of the interaction between socioeconomic status and FTO, and how a higher socioeconomic status exerts a protective effect regarding obesity in both children [35] and adults [36]. Although the socioeconomic status was an intended question of our protocol, 65% of the sample did not provide information about their monthly family income. Thereby, this variable was not included in the analyses. However, we stress the importance of including social determinants in genetic studies. Additionally, lifestyle variables (e.g., diet, physical activity, sleeping patterns, and alcohol intake) and environmental exposure to endocrine disruptors (e.g., bisphenol A or organophosphate

Table 3. Results from the hierarchical multiple regression analysis of BMI-z, FTO and whole-brain structural connectivity after controlling for confounders.

Whole-brain metric	Model	Multiple regression		Model comparison		Variable of interest			
		Adj R^2	*P* model	*F*	$P_{uncorrected}$		*b*	95% CI	*P*
CC NOS	4c	0.001	0.37	–	–	BMI-z	–	–	–
	4d	−0.003	0.47	0.82	0.49		–	–	–
	4e	0.001	0.42	1.58	0.21		0.0002	(−0.0001, 0.0006)	0.21
	5c	0.21	0.0000009	–	–	FTO	–	–	–
	5d	0.19	0.00002	0.12	0.95		–	–	–
	5e	0.2	0.00002	2.05	0.15		0.0006	(−0.0002, 0.001)	0.15
CS NOS	4c	−0.01	0.7	–	–	BMI-z	–	–	–
	4d	−0.02	0.8	0.55	0.65		–	–	–
	4e	−0.009	0.57	2.73	0.1		0.038	(−0.007, 0.08)	0.1
	5c	−0.018	0.8	–	–	FTO	–	–	–
	5d	−0.03	0.85	0.56	0.64		–	–	–
	5e	−0.02	0.67	2.39	0.12		0.09	(−0.02, 0.2)	0.12
CC FA	4c	0.014	0.19	–	–	BMI-z	–	–	–
	4d	0.016	0.24	1.1	0.35		–	–	–
	4e	0.036	0.12	3.61	0.06		0.004	(−0.0001, 0.009)	0.06
	5c	0.006	0.31	–	–	FTO	–	–	–
	5d	0.01	0.29	1.26	0.29		–	–	–
	5e	0.005	0.38	0.03	0.85		0.001	(−0.01, 0.01)	0.85
CS FA	4c	0.1	0.0006	–	–	BMI-z	–	–	–
	4d	0.11	0.002	1.22	0.31		–	–	–
	4e	0.17	0.00007	10.49	0.0015		0.76	(0.30, 1.21)	0.0015
	5c	0.1	0.002	–	–	FTO	–	–	–
	5d	0.1	0.004	1.3	0.28		–	–	–
	5e	0.1	0.007	0.27	0.6		0.3	(−0.84, 1.44)	0.6

Model 4c: whole-brain metric ~age + sex + eTIV; model 4d: whole-brain metric ~age + sex + eTIV + prepubescent + anxiety + depression; model 4e: whole-brain metric ~age + sex + eTIV + prepubescent + anxiety + depression + BMI-z; model 5c: whole-brain metric ~age + sex + eTIV + batch effect; model 5d: whole-brain metric ~age + sex + eTIV + batch effect + prepubescent + anxiety + depression; model 5e: whole-brain metric ~ age + sex + eTIV + batch effect + prepubescent + anxiety + depression + FTO. Unstandardized betas were reported.
BMI-z body mass index z-score, *CC* clustering coefficient, *CS* connectivity strength, *eTIV* estimated total intracranial volume, *FA* fractional anisotropy, *FTO* fat mass and obesity related gene (A-allele carrier vs. non carrier), *NOS* number of streamlines, *REW* reward network.

pesticides) are known to contribute to obesity via alterations in DNA methylation, histone modification, and non-coding RNAs [37]. Thus, and although we did not include these variables in our study, epigenetics might explain BMI variance and should be considered in future studies.

BMI and structural connectivity

Our results suggested a divergence in the structural connectivity patterns in adolescents and young adults with higher BMI-z. In the reward network, and consistent with other studies [6, 9, 38], BMI-z was associated with lower structural connectivity, whereas the opposite relationship was found at the whole-brain level, similar to the results reported by Augustijn et al. [39]. While these findings (at an uncorrected level) in the reward network agreed with our hypothesis, the finding of higher global FA CS related to higher BMI-z values was unexpected. We presume that the contrary findings in our study may evidence that the obesity-related alterations of white matter integrity are not widespread across the brain, but that distinct brain regions may not be affected equally by BMI. Specifically, we hypothesize that lower FA CS values in the reward network may explain the alterations in the reward processing of food seen in obesity states [40]. However, in supplementary analyses, we found that higher BMI was not significantly related to the reward network FA CS when using raw (not normalized) values. This might indicate that the relationship was to some extent driven by the positive association of BMI and whole brain FA CS (Supplementary Section A and Supplementary Figure 3). Moreover, it is possible that differences in brain development due to age and sex may moderate the relationship between FA CS and BMI [41, 42]. Longitudinal sex-stratified approaches are required to assess how the obese physiological state affects structural connectivity during development. Importantly, since our sample size was small and our results regarding the reward network were significant at an uncorrected level, they should be considered preliminary. Validating these results in an independent cohort (e.g., ABCD dataset) is advised to confirm our findings. Additionally, it would be interesting to assess if body fat percentage – which highly correlates with BMI but may be a more specific measure of adiposity and probably more relevant in the context of adolescence – has a stronger relationship with structural connectivity in the reward network and at the whole-brain level.

FTO and structural connectivity

In our study, and consistent with the results of Beyer et al. [9], we did not find an association between the FTO polymorphism and structural connectivity. Few studies have assessed the effect of the FTO gene on brain structure and function. One study found that

high-risk FTO genotype carriers had greater activation by high energy dense food in the ventral tegmental area/substantia nigra, amygdala, and ventral striatum, suggesting that allelic variations in FTO may disturb satiety processing [43]. Another study found that the FTO risk allele was associated with lower nucleus accumbens volumes, indicating possible impairment of dopaminergic projections in the reward network [44]. Overall, it is still unclear whether FTO really exerts its obesity risk via reward network structures. We suggest that using polygenic risk scores in larger sample sizes might elucidate with greater predictive power the relationship between the FTO gene and the reward network structural connectivity.

Adolescence and reward system neurodevelopment

The dopamine system undergoes significant changes across development. Dopamine-rich regions, such as frontal and striatal regions, undergo maturational processes during adolescence. At the functional level, the reward system becomes hyper-responsive to reward and incentives, and rewarding events may result in a larger dopamine release that can contribute to a cycle of reward-seeking behavior [45]. The asynchrony between a heightened bottom-up reward-related drives and a not fully matured top-down cognitive control may underpin the adolescents' sub-optimal decision-making regarding risk and health behaviors (e.g., substance use or overconsumption of palatable foods) [46, 47]. Structurally, the reported increases in white matter volumes during adolescence are accompanied by progressive increases in white matter integrity – such as FA –, that may reflect the continuous axonal myelination that undergoes during this developmental window [48]. However, both higher BMI categories and high fat diets may affect early myelinization, either via disruption of essential fatty acid production or oligodendrocytes impairment [49]. Thus, it is possible that individual differences in white mater maturation [50] condition the effect of biological insults, such as having overweight/obesity.

Strengths and limitations

Strengths of our study include a high-resolution MRI protocol and the application of ComBat harmonization. Further, we pre-registered our hypotheses and thereby increase transparency and reliability of human neuroimaging. Limitations include that we could not assess potential mediating factors (see the registered analysis plan to check the conditions in which the mediation analyses would have been performed: https://osf.io/nfyha). Second, the sample size used might have been under-powered to detect the effect of the FTO polymorphism on brain connectivity. Third, lifestyle factors [51, 52] and cardiometabolic or inflammatory variables that could help to better define our sample were not included in our study. Fourth, we preregistered using normalized graph metrics of the reward network, but this made it difficult to understand whether reward vs. whole-brain changes drove the effect. Future studies should study those independently or use other metrics to adjust for whole-brain effects.

CONCLUSIONS

We provide evidence that, in healthy adolescents and young adults, higher BMI-z is associated with higher connectivity at the whole-brain level. Using an uncorrected threshold, we show that higher BMI-z is associated with lower structural connectivity of the reward network. Such findings may be indicative of specific anatomical alterations associated with obesity in adolescents and young adults. We did not find the FTO polymorphism to correlate with structural connectivity, suggesting that the genetic contribution of this variant to white matter microstructure patterns is small and not a plausible mechanism through which obesity risk is conferred. Future longitudinal studies with larger sample sizes are needed to assess how genetic determinants of obesity may change brain structural connectivity and its behavioral implications.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Safaei M, Sundararajan EA, Driss M, Boulila W, Shapi'i A. A systematic literature review on obesity: Understanding the causes & consequences of obesity and reviewing various machine learning approaches used to predict obesity. Comput Biol Med. 2021;136:1–17.
2. Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, et al. A Common Variant in the FTO Gene Is Associated with Body Mass Index and Predisposes to Childhood and Adult Obesity. Science. 2007;316:889–94.
3. Loos RJF, Yeo GSH. The genetics of obesity: from discovery to biology. Nat Rev Genet. 2022;23:120–33.
4. Speakman JR. The "Fat Mass and Obesity Related" (FTO) gene: Mechanisms of Impact on Obesity and Energy Balance. Curr Obes Rep. 2015;4:73–91.
5. Hess ME, Hess S, Meyer KD, Verhagen LAW, Koch L, Brönneke HS, et al. The fat mass and obesity associated gene (Fto) regulates activity of the dopaminergic midbrain circuitry. Nat Neurosci. 2013;16:1042–8.
6. Marqués-Iturria I, Scholtens LH, Garolera M, Pueyo R, García-García I, González-Tartiere P, et al. Affected connectivity organization of the reward system structure in obesity. Neuroimage. 2015;111:100–6.
7. Edwin Thanarajah S, Hanssen R, Melzer C, Tittgemeyer M. Increased meso-striatal connectivity mediates trait impulsivity in FTO variant carriers. Front Endocrinol. 2023;14:1130203.
8. Adise S, Allgaier N, Laurent J, Hahn S, Chaarani B, Owens M, et al. Multimodal brain predictors of current weight and weight gain in children enrolled in the ABCD study ®. Dev Cogn Neurosci. 2021;49:1–14.
9. Beyer F, Zhang R, Scholz M, Wirkner K, Loeffler M, Stumvoll M, et al. Higher BMI, but not obesity-related genetic polymorphisms, correlates with lower structural connectivity of the reward network in a population-based study. Int J Obes. 2021;45:491–501.
10. Gupta A, Mayer EA, Sanmiguel CP, Van Horn JD, Woodworth D, Ellingson BM, et al. Patterns of brain structural connectivity differentiate normal weight from overweight subjects. NeuroImage Clin. 2015;7:506–17.
11. Riederer JW, Shott ME, Deguzman M, Pryor TL, Frank GKW. Understanding neuronal architecture in obesity through analysis of white matter connection strength. Front Hum Neurosci. 2016;10:271.
12. García-García I, Morys F, Dagher A. Nucleus accumbens volume is related to obesity measures in an age-dependent fashion. J Neuroendocrinol. 2020;32:1–12.
13. Lancaster TM, Ihssen I, Brindley LM, Linden DE. Preliminary evidence for genetic overlap between body mass index and striatal reward response. Transl Psychiatry. 2018;8:1–9.
14. Olivo G, Latini F, Wiemerslage L, Larsson EM, Schiöth HB. Disruption of accumbens and thalamic white matter connectivity revealed by diffusion tensor tractography in young men with genetic risk for obesity. Front Hum Neurosci. 2018;12:1–10.
15. Lugo-Candelas C, Pang Y, Lee S, Cha J, Hong S, Ranzenhofer L, et al. Differences in brain structure and function in children with the FTO obesity-risk allele. Obes Sci Pract. 2020;6:409–24.
16. Sawyer SM, Azzopardi PS, Wickremarathne D, Patton GC. The age of adolescence. Lancet Child Adolesc Heal. 2018;2:223–8.
17. Prats-Soteras X, Jurado MA, Ottino-González J, García-García I, Segura B, Caldú X, et al. Inflammatory agents partially explain associations between cortical thickness, surface area, and body mass in adolescents and young adulthood. Int J Obes. 2020;44:1487–96.
18. Prunell-Castañé A, Jurado MÁ, Ottino-González J, Prats-Soteras X, Sánchez Garre C, Cano Marco N, et al. Beyond BMI: cardiometabolic measures as predictors of impulsivity and white matter changes in adolescents. Brain Struct Funct. 2023;228:751–60.
19. Must A, Anderson SE. Body mass index in children and adolescents: Considerations for population-based applications. Int J Obes. 2006;30:590–4.
20. Cole TJ, Lobstein T. Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. Pediatr Obes. 2012;7:284–94.
21. Organization WH. World Health Organization. Obesity and overweight. Available from: https://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight
22. Veraart J, Novikov DS, Christiaens D, Ades-aron B, Sijbers J, Fieremans E. Denoising of diffusion MRI using random matrix theory. Neuroimage. 2016;142:394–406.

23. Bhushan C, Haldar JP, Joshi AA, Leahy RM. Correcting susceptibility-induced distortion in diffusion-weighted mri using constrained nonrigid registration. Signal Inf Process Assoc Annu Summit Conf APSIPA Asia Pac. 2012.
24. Andersson JLR, Skare S, Ashburner J. How to correct susceptibility distortions in spin-echo echo-planar images: application to diffusion tensor imaging. Neuroimage. 2003;20:870–88.
25. Andersson JLR, Sotiropoulos SN. An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. Neuroimage. 2016;125:1063–78.
26. Andersson JLR, Graham MS, Zsoldos E, Sotiropoulos SN. Incorporating outlier detection and replacement into a non-parametric framework for movement and distortion correction of diffusion MR images. Neuroimage. 2016;141:556–72.
27. Bastiani M, Cottaar M, Fitzgibbon SP, Suri S, Alfaro-Almagro F, Sotiropoulos SN, et al. Automated quality control for within and between studies diffusion MRI data using a non-parametric framework for movement and distortion correction. Neuroimage. 2019;184:801–12.
28. Yeh FC, Wedeen VJ, Tseng WYI. Generalized q-sampling imaging. IEEE Trans Med Imaging. 2010;29:1626–35.
29. Yeh FC, Verstynen TD, Wang Y, Fernández-Miranda JC, Tseng WYI. Deterministic diffusion fiber tracking improved by quantitative anisotropy. PLoS One. 2013;8:1–16.
30. Fortin JP, Parker D, Tunç B, Watanabe T, Elliott MA, Ruparel K, et al. Harmonization of multi-site diffusion tensor imaging data. Neuroimage. 2017;161:149–70.
31. da Silva TER, Andrade NL, de Oliveira Cunha D, Leão-Cordeiro JAB, Vilanova-Costa CAST, Silva AMTC. The FTO rs9939609 polymorphism and obesity risk in teens: Evidence-based meta-analysis. Obes Res Clin Pract. 2018;12:432–7.
32. Khera AV, Chaffin M, Wade KH, Zahid S, Brancale J, Xia R, et al. Polygenic prediction of weight and obesity trajectories from birth to adulthood. Cell. 2019;177:587–96.
33. Ganeff IMM, Bos MM, Van Heemst D, Noordam R. BMI-associated gene variants in FTO and cardiometabolic and brain disease: obesity or pleiotropy? Physiol Genomics. 2019;51:311–22.
34. Rutters F, Nieuwenhuizen AG, Bouwman F, Mariman E, Westerterp-plantenga MS. Associations between a single nucleotide polymorphism of the FTO Gene (rs9939609) and obesity-related characteristics over time during puberty in a Dutch children cohort. J Clin Endocrinol Metab. 2011;96:939–42.
35. Foraita R, Günther F, Gwozdz W, Reisch LA, Russo P, Lauria F, et al. Does the FTO gene interact with the socioeconomic status on the obesity development among young European children? Results from the IDEFICS study. Int J Obes. 2015;39:1–6.
36. Rask-Andersen M, Karlsson T, Ek WE, Johansson Å. Gene-environment interaction study for BMI reveals interactions between genetic factors and physical activity, alcohol consumption and socioeconomic status. PLoS Genet. 2017;13:1–20.
37. Mahmoud AM. An overview of epigenetics in obesity: the role of lifestyle and therapeutic interventions. Int J Mol Sci. 2022;23:1341.
38. Tan Z, Hu Y, Ji G, Li G, Ding Y, Zhang W, et al. Alterations in functional and structural connectivity of basal ganglia network in patients with obesity. Brain Topogr. 2022;35:453–63.
39. Augustijn MJCM, Di Biase MA, Zalesky A, Van Acker L, De Guchtenaere A, D'Hondt E, et al. Structural connectivity and weight loss in children with obesity: a study of the "connectobese.". Int J Obes. 2019;43:2309–21.
40. Meng X, Huang D, Ao H, Wang X, Gao X. Food cue recruits increased reward processing and decreased inhibitory control processing in the obese/overweight: an activation likelihood estimation meta-analysis of fMRI studies. Obes Res Clin Pract. 2020;14:127–35.
41. Carbine KA, Duraccio KM, Hedges-Muncy A, Barnett KA, Kirwan CB, Jensen CD. White matter integrity disparities between normal-weight and overweight/obese adolescents: an automated fiber quantification tractography study. Brain Imaging Behav. 2020;14:308–19.
42. Ma J, Mcglade EC, Id RSH, Lyoo IK, Renshaw F, Yurgelun-todd DA. Overweight/Obesity-related microstructural alterations of the fimbria-fornix in the ABCD study: the role of aerobic physical activity. PLoS One. 2023;18:1–16.
43. Melhorn SJ, Askren MK, Chung WK, Kratz M, Bosch TA, Tyagi V, et al. FTO genotype impacts food intake and corticolimbic activation. Am J Clin Nutr. 2018;107:145–54.
44. De Groot C, Felius A, Trompet S, De Craen AJM, Blauw GJ, Van Buchem MA, et al. Association of the fat mass and obesity-associated gene risk allele, rs9939609A, and reward-related brain structures. Obesity. 2015;23:2118–22.
45. Galvan A. Adolescent development of the reward system. Front Hum Neurosci. 2010;4:1–9.
46. Reichelt AC. Adolescent maturational transitions in the prefrontal cortex and dopamine signaling as a risk factor for the development of obesity and high fat/high sugar diet induced cognitive deficits. Front Behav Neurosci. 2016;10:1–17.
47. Geier CF. Adolescent cognitive control and reward processing: implications for risk taking and substance use. Horm Behav. 2013;64:333–42.
48. Blakemore SJ. Imaging brain development: the adolescent brain. Neuroimage. 2012;61:397–406.
49. Sadler JR, Thapaliya G, Ranganath K, Gabay A, Chen L, Smith KR, et al. Paediatric obesity and metabolic syndrome associations with cognition and the brain in youth: Current evidence and future directions. Pediatr Obes. 2023;18:1–27.
50. Stiles J, Jernigan TL. The basics of brain development. Neuropsychol Rev. 2010;20:327–48.
51. Loos RJF, Yeo GSH. The bigger picture of FTO - the first GWAS-identified obesity gene. Nat Rev Endocrinol. 2014;10:51–61.
52. Jiang Y, Mei H, Lin Q, Wang J, Liu S, Wang G, et al. Interaction effects of FTO rs9939609 polymorphism and lifestyle factors on obesity indices in early adolescence. Obes Res Clin Pract. 2019;13:352–7.

ACKNOWLEDGEMENTS

The authors thank Isabel García-García and Jonatan Ottino-González their support. The authors also thank all the participants that made this project possible. We acknowledge the Centres de Recerca de Catalunya (CERCA) Program/Generalitat de Catalunya, the Institute of Neurosciences, the Institute of Biomedical Research August Pi i Sunyer (IDIBAPS), the Consorci Sanitari de Terrassa, and the Hospital de Terrassa. We acknowledge the following funding sources, which were not involved in the study conceptualization, interpretation or writing: APC received a Ph.D. scholarship from the Spanish Ministry of Science, Innovation and Universities (PRE2019-087430). MAJ and MG received Grants from the Spanish Ministry of Economy, Industry and Competitiveness (PSI2017- 86536-C2-1-R and PSI2017-86536-C2-2-R, respectively), funded by MCIN/AEI/https://doi.org/10.13039/501100011033 and the European Regional Development Fund (ERDF). MAJ, MG, XC and APC have additionally received funding from the Departament d'Innovació, Universitats i Empresa, Generalitat de Catalunya (2021SGR0801).

AUTHOR CONTRIBUTIONS

APC, MAJ, MG, FB, and VW contributed to study design and conception. APC, IH, CSG, XC participated in data acquisition. APC performed the analyses. APC, MAJ, and FB contributed to results interpretation. APC wrote the original manuscript. All authors critically reviewed the manuscript, approved its final version for publishing, and agreed to be accountable for all aspects of such work.

COMPETING INTERESTS

The authors declare no competing interest.

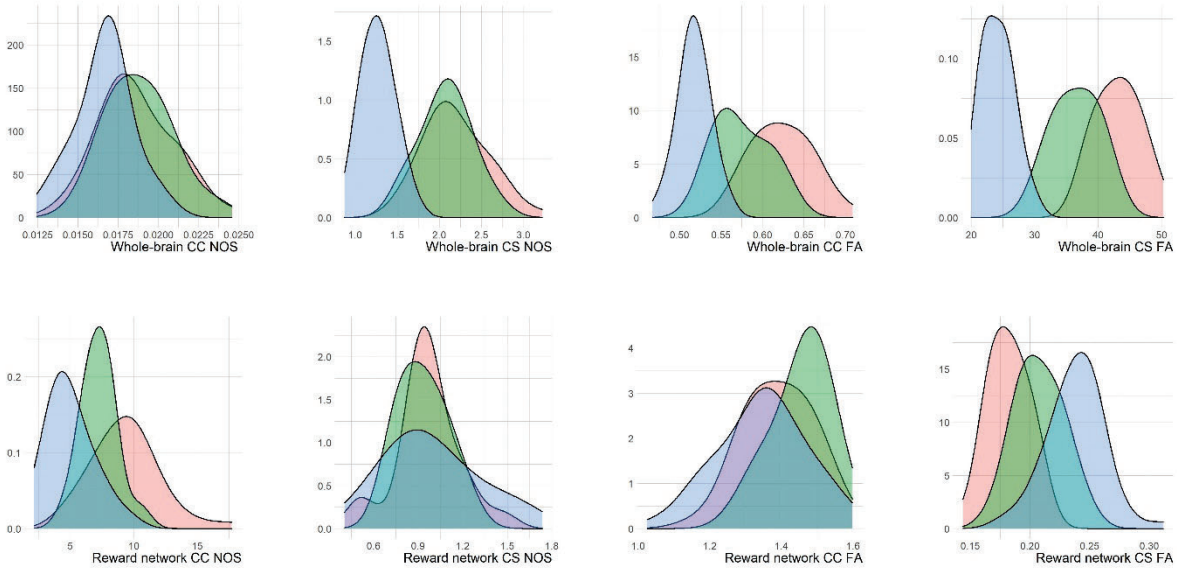
ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41366-023-01451-w.

Correspondence and requests for materials should be addressed to María Ángeles Jurado.

Supplementary Material Study 1

Not harmonized



Harmonized

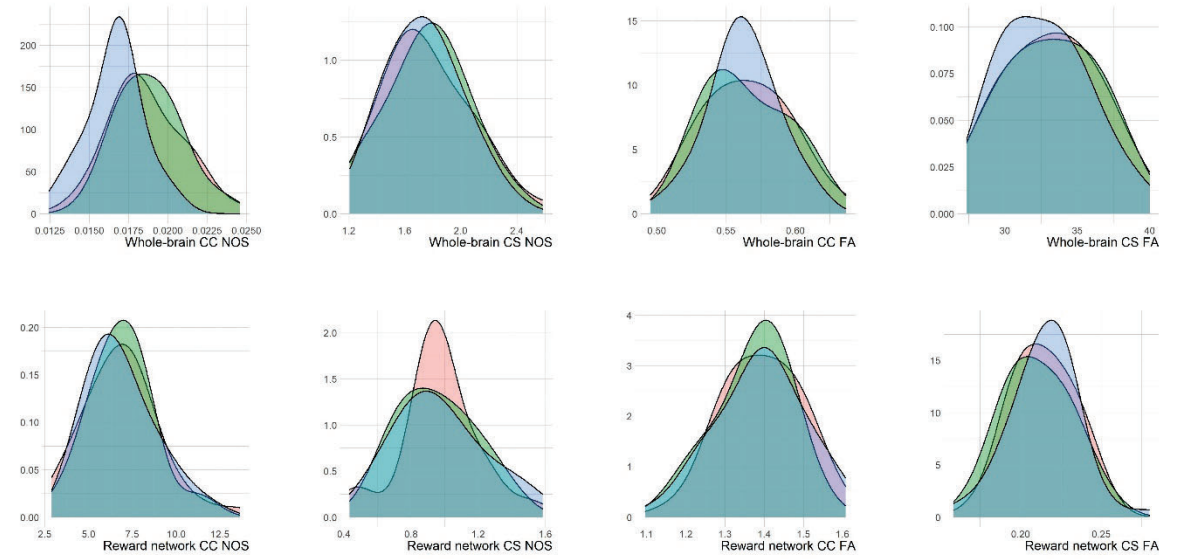


Figure S1. Graph metrics (NOS CS, NOS CC, FA CS, FA CC) with and without ComBat harmonization application. Each color represents a different neuroimaging protocol acquisition. Abbreviations: CC: clustering coefficient; CS: connectivity strength; FA: fractional anisotropy; NOS: number of streamlines.

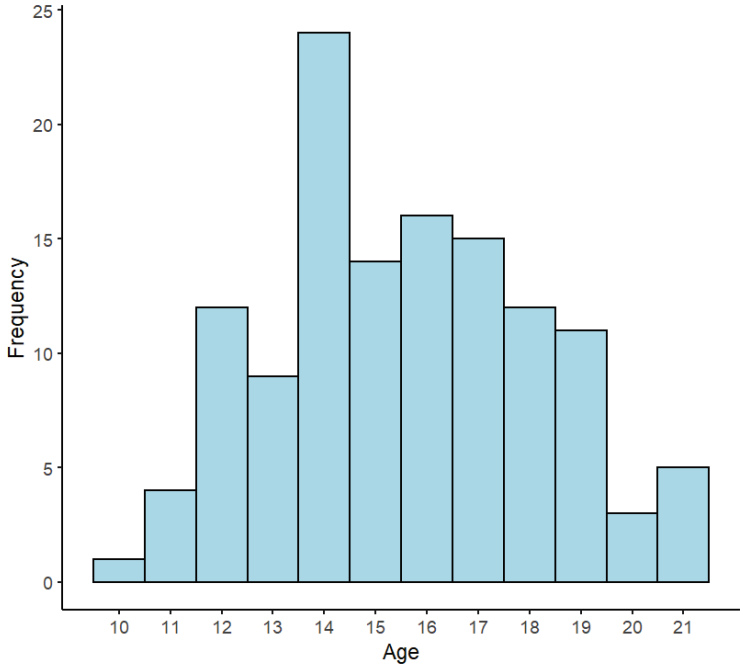


Figure S2. Histogram of age distribution.

A) Testing the effect of BMIz on whole-brain CS FA and reward network CS FA

We performed an exploratory analysis and regressed both whole-brain and reward network FA CS on BMIz (BMz ~ whole-brain CS FA + reward network CS FA). We used the raw values for reward network FA CS because the normalized reward network FA CS depends on whole brain FA CS. We found that whole-brain FA CS was positively associated with BMIz (beta = 0.11, 95% CI = (0.05, 0.17), P = 0.0009), whereas the coefficient for the reward network FA CS was negative but not significant (beta = -0.14, 95% CI = (-0.52, 0.33), P = 0.44).

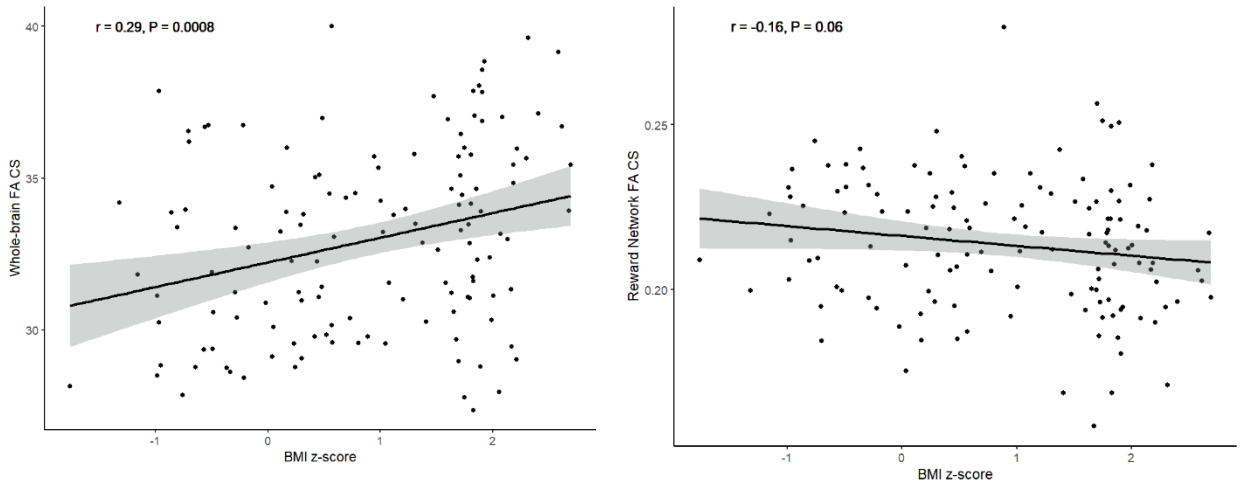


Figure S3. Association between BMI-z and whole-brain FA CS (left), and BMI-z and reward network FA CS (right). FA CS is defined as the sum of FA values that connect the nodes either for the whole-brain cortical and subcortical structures (n = 80), or the nodes of the reward network (n = 10). Abbreviations: BMI-z: body mass index z-score, FA: fractional anisotropy, CS: connectivity strength.

Table S1. Results from the hierarchical multiple regression analysis of BMI-z, FTO and reward network structural connectivity

REW metric	Model	Multiple regression		Model comparison		Variable of interest			
		Adj R^2	*P* model	F	FDR		*b*	95% CI	*P*
CC NOS (log)	1a	0.007	0.27	----	----		----	----	----
	1b	0.0001	0.41	0.09	0.93	BMI-z	0.007	(-0.04, 0.05)	0.76
	2a	0.006	0.32	----	----		----	----	----
	2b	0.008	0.31	1.28	0.4	FTO	-0.06	(-0.18, 0.05)	0.26
CS NOS	1a	-0.01	0.74	----	----		----	----	----
	1b	-0.02	0.84	0.13	0.93	BMI-z	-0.007	(-0.05, 0.03)	0.71
	2a	-0.02	0.81	----	----		----	----	----
	2b	-0.02	0.81	0.66	0.59	FTO	-0.04	(-0.13, 0.06)	0.42
CC FA	1a	0.06	0.01	----	----		----	----	----
	1b	0.06	0.02	1.39	0.4	BMI-z	-0.009	(-0.02, 0.006)	0.24
	2a	0.05	0.02	----	----		----	----	----
	2b	0.06	0.02	1.78	0.4	FTO	0.02	(-0.01, 0.06)	0.18
CS FA	1a	-0.005	0.52	----	----		----	----	----
	1b	0.01	0.2	3.76	0.31	BMI-z	-0.003	(-0.006, 0.00003)	0.05
	2a	-0.01	0.62	----	----		----	----	----
	2b	-0.006	0.52	1.59	0.4	FTO	0.005	(-0.003, 0.01)	0.21

Model 1a: REW metric ~ age + sex + eTIV; model 1b: REW metric ~ age + sex + eTIV + BMI-z; model 2a: REW metric ~ age + sex + eTIV + batch effect; model 2b: REW metric ~ age + sex + eTIV + batch effect + FTO. Unstandardized betas were reported.

Abbreviations: BMI-z: body mass index z-score; CC: clustering coefficient; CS: connectivity strength; eTIV: estimated total intracranial volume; FA: fractional anisotropy; FTO: fat mass and obesity related gene (A-allele carrier vs. non carrier); NOS: number of streamlines; REW: reward network

Table S2. Results from the hierarchical multiple regression analysis of BMI-z, FTO and whole-brain structural connectivity

Whole-brain metrics	Model	Multiple regression		Model comparison		Variable of interest			
		Adj R^2	*P* model	F	FDR		*b*	95% CI	*P*
CC NOS	4a	0.001	0.37	----	----		----	----	----
	4b	0.004	0.34	1.45	0.4	BMI-z	0.0002	(-0.0001, 0.0006)	0.23
	5a	0.2	$9.49x10^{-7}$	----	----		----	----	----
	5b	0.21	$1.23x10^{-6}$	2.1	0.4	FTO	0.0006	(-0.0002, 0.001)	0.15
CS NOS	4a	-0.01	0.7	----	----		----	----	----
	4b	0.001	0.39	2.75	0.4	BMI-z	0.038	(-0.007, 0.08)	0.1
	5a	-0.02	0.8	----	----		----	----	----
	5b	-0.01	0.6	2	0.4	FTO	0.078	(-0.03, 0.19)	0.16
CC FA	4a	0.01	0.19	----	----		----	----	----
	4b	0.04	0.06	4.29	0.31	BMI-z	0.004	(0.0002, 0.009)	0.04
	5a	0.006	0.31	----	----		----	----	----
	5b	-0.001	0.44	0.02	0.94	FTO	-0.0008	(-0.01, 0.01)	0.88
CS FA	4a	0.1	0.0006	----	----		----	----	----
	4b	0.17	0.00001	11.34	**0.017**	BMI-z	0.77	(0.32, 1.22)	0.001
	5a	0.1	0.002	----	----		----	----	----
	5b	0.09	0.004	0.04	0.94	FTO	0.11	(-1.01, 1.24)	0.84

Model 4a: whole-brain metric ~ age + sex + eTIV; model 4b: whole-brain metric ~ age + sex + eTIV + BMI-z; model 5a: whole-brain metric ~ age + sex + eTIV + batch effect; model 5b: whole-brain metric ~ age + sex + eTIV + batch effect + FTO. Unstandardized betas were reported.

Abbreviations: BMI-z: body mass index z-score; CC: clustering coefficient; CS: connectivity strength; eTIV: estimated total intracranial volume; FA: fractional anisotropy; FTO: fat mass and obesity related gene (A-allele carrier vs. non carrier); NOS: number of streamlines; REW: reward network.

Sensitivity analysis

Table S3. Results from the hierarchical multiple regression analysis of BMI-z, FTO and reward network structural connectivity *without* controlling for estimated total intracranial volume.

REW metric	Model	Multiple regression		Model comparison		Variable of interest			
		Adj R^2	*P* model	F	*P* uncorrected		*b*	95% CI	*P*
CC NOS (log)	1c	0.01	0.14	----	----		----	----	----
	1d	0.007	0.27	0.07	0.79	BMI-z	0.006	(-0.04, 0.05)	0.79
	2c	0.01	0.19	----	----		----	----	----
	2d	0.01	0.2	1.25	0.26	FTO	-0.06	(-0.17, 0.05)	0.26
CS NOS	1c	-0.008	0.62	----	----		----	----	----
	1d	-0.01	0.76	0.2	0.65	BMI-z	-0.009	(-0.05, 0.03)	0.65
	2c	-0.01	0.7	----	----		----	----	----
	2d	-0.01	0.73	0.57	0.45	FTO	-0.04	(-0.13, 0.06)	0.45
CC FA	1c	0.07	0.004	----	----		----	----	----
	1d	0.07	0.007	1.35	0.25	BMI-z	-0.009	(-0.02, 0.006)	0.25
	2c	0.06	0.01	----	----		----	----	----
	2d	0.07	0.01	1.68	0.20	FTO	0.02	(-0.01, 0.06)	0.2
CS FA	1c	0.002	0.33	----	----		----	----	----
	1d	0.02	0.11	3.85	0.052	BMI-z	-0.003	(-0.006, -0.000004)	0.05
	2c	-0.003	0.45	----	----		----	----	----
	2d	0.002	0.38	1.55	0.21	FTO	0.005	(-0.003, 0.01)	0.22

Model 1c: REW metric ~ age + sex; model 1d: REW metric ~ age + sex + BMI-z; model 2c: REW metric ~ age + sex + batch effect; model 2d: REW metric ~ age + sex + batch effect + FTO. Unstandardized betas were reported.

Abbreviations: BMI-z: body mass index z-score; CC: clustering coefficient; CS: connectivity strength; FA: fractional anisotropy; FTO: fat mass and obesity related gene (A-allele carrier vs. non carrier); NOS: number of streamlines; REW: reward network.

Table S4. Results from the hierarchical multiple regression analysis of BMI-z, FTO and whole-brain structural connectivity *without* controlling for estimated total intracranial volume.

Whole-brain metrics	Model	Multiple regression		Model comparison		Variable of interest			
		Adj R^2	*P* model	F	*P* uncorrected		*b*	95% CI	*P*
CC NOS	4a	-0.009	0.67	----	----		----	----	----
	4b	-0.001	0.42	2.03	0.16	BMI-z	0.0002	(-0.0001, 0.0006)	0.16
	5a	0.21	4.34×10^{-7}	----	----		----	----	----
	5b	0.22	5.21×10^{-7}	2.51	0.11	FTO	0.0006	(-0.0001, 0.001)	0.12
CS NOS	4a	-0.005	0.52	----	----		----	----	----
	4b	0.009	0.24	2.88	0.09	BMI-z	0.04	(-0.006, 0.08)	0.09
	5a	-0.01	0.65	----	----		----	----	----
	5b	-0.003	0.46	1.95	0.16	FTO	0.08	(-0.03, 0.18)	0.16
CC FA	4a	0.01	0.16	----	----		----	----	----
	4b	0.04	0.04	4.95	0.03	BMI-z	0.005	(0.0005, 0.009)	0.03
	5a	0.008	0.26	----	----		----	----	----
	5b	0.0005	0.4	0.07	0.78	FTO	-0.001	(-0.01, 0.009)	0.78
CS FA	4a	0.08	0.001	----	----		----	----	----
	4b	0.17	0.00001	13.31	0.0004	BMI-z	0.83	(0.38, 1.28)	0.0004
	5a	0.08	0.003	----	----		----	----	----
	5b	0.07	0.008	0.002	0.96	FTO	-0.03	(-1.15, 1.1)	0.96

Model 4a: whole-brain metric ~ age + sex; model 4b: whole-brain metric ~ age + sex + BMI-z; model 5a: whole-brain metric ~ age + sex + batch effect; model 5b: whole-brain metric ~ age + sex + batch effect + FTO. Unstandardized betas were reported.

Abbreviations: BMI-z: body mass index z-score; CC: clustering coefficient; CS: connectivity strength; FA: fractional anisotropy; FTO: fat mass and obesity related gene (A-allele carrier vs. non carrier); NOS: number of streamlines; REW: reward network.

Table S5. Results from the hierarchical multiple regression analysis of BMI-z, FTO and reward network structural connectivity *without* controlling for estimated total intracranial volume *but controlling* for other confounders (pubertal stage and anxiety and depression scores).

REW metric	Model	Multiple regression		Model comparison		Variable of interest			
		Adj R^2	*P* model	F	$P_{uncorrected}$		*b*	95% CI	*P*
CC NOS (log)	1c	0.01	0.14	----	----		----	----	----
	1d	0.006	0.33	0.63	0.6	BMI-z	----	----	----
	1e	-0.001	0.45	0.03	0.85		0.004	(-0.04, 0.05)	0.85
	2c	0.01	0.19	----	----		----	----	----
	2d	0.008	0.33	0.75	0.53	FTO	----	----	----
	2e	0.008	0.34	1.03	0.31		-0.06	(-0.17, 0.05)	0.31
CS NOS	1c	-0.008	0.62	----	----		----	----	----
	1d	-0.01	0.71	0.66	0.58	BMI-z	----	----	----
	1e	-0.02	0.77	0.34	0.56		-0.01	(-0.05, 0.03)	0.56
	2c	-0.01	0.7	----	----		----	----	----
	2d	-0.02	0.74	0.69	0.56	FTO	----	----	----
	2e	-0.02	0.78	0.51	0.48		-0.03	(-0.13, 0.06)	0.48
CC FA	1c	0.06	0.005	----	----		----	----	----
	1d	0.07	0.01	1.19	0.32	BMI-z	----	----	----
	1e	0.07	0.01	1.51	0.22		-0.01	(-0.02, 0.006)	0.22
	2c	0.06	0.01	----	----		----	----	----
	2d	0.07	0.02	1.28	0.28	FTO	----	----	----
	2e	0.07	0.03	1.07	0.3		0.02	(-0.02, 0.06)	0.3
CS FA	1c	0.002	0.33	----	----		----	----	----
	1d	0.008	0.32	1.26	0.29	BMI-z	----	----	----
	1e	0.03	0.13	3.92	0.05		-0.003	(-0.006, -0.00003)	0.05
	2c	-0.003	0.45	----	----		----	----	----
	2d	0.004	0.37	1.3	0.27	FTO	----	----	----
	2e	0.004	0.39	0.9	0.34		0.004	(-0.004, 0.01)	0.34

Model 1c: REW metric ~ age + sex; model 1d: REW metric ~ age + sex + prepubescent + anxiety + depression; model 1e: REW metric ~ age + sex + prepubescent + anxiety + depression + BMI-z; model 2c: REW metric ~ age + sex + batch effect; model 2d: REW metric ~ age + sex + batch effect + prepubescent + anxiety + depression; model 2e: REW metric ~ age + sex + batch effect + prepubescent + anxiety + depression + FTO. Unstandardized betas were reported.

Abbreviations: BMI-z: body mass index z-score; CC: clustering coefficient; CS: connectivity strength; FA: fractional anisotropy; FTO: fat mass and obesity related gene (A-allele carrier vs. non carrier); NOS: number of streamlines; REW: reward network.

Table S6. Results from the hierarchical multiple regression analysis of BMI-z, FTO and whole-brain structural connectivity *without* controlling for estimated total intracranial volume *but controlling* for other confounders (pubertal stage and anxiety and depression scores).

Whole-brain metric	Model	Multiple regression		Model comparison		Variable of interest			
		Adj R^2	*P* model	F	*P* uncorrected		*b*	95% CI	*P*
CC NOS	4c	-0.009	0.67	----	----		----	----	----
	4d	-0.005	0.50	1.2	0.31	BMI-z	----	----	----
	4e	0.003	0.38	1.99	0.16		0.0003	(-0.0001, 0.0006)	0.16
	5c	0.21	$4.34x10^{-7}$	----	----		----	----	----
	5d	0.19	0.00001	0.06	0.98	FTO	----	----	----
	5e	0.2	0.00001	2.50	0.12		0.0006	(-0.0001, 0.001)	0.12
CS NOS	4c	-0.005	0.52	----	----		----	----	----
	4d	-0.01	0.69	0.59	0.62	BMI-z	----	----	----
	4e	-0.002	0.45	2.7	0.1		0.04	(-0.007, 0.08)	0.1
	5c	-0.01	0.65	----	----		----	----	----
	5d	-0.02	0.77	0.56	0.64	FTO	----	----	----
	5e	-0.01	0.57	2.43	0.12		0.09	(-0.02, 0.2)	0.12
CC FA	4c	0.01	0.16	----	----		----	----	----
	4d	0.01	0.22	1.17	0.32	BMI-z	----	----	----
	4e	0.04	0.08	4.14	0.04		0.004	(0.0002, 0.009)	0.04
	5c	0.008	0.26	----	----		----	----	----
	5d	0.02	0.24	1.34	0.26	FTO	----	----	----
	5e	0.008	0.34	0.006	0.94		0.0004	(-0.01, 0.01)	0.94
CS FA	4c	0.08	0.001	----	----		----	----	----
	4d	0.09	0.004	1.54	0.21	BMI-z	----	----	----
	4e	0.16	0.00007	12.15	0.0007		0.81	(0.35, 1.26)	0.0007
	5c	0.08	0.003	----	----		----	----	----
	5d	0.09	0.005	1.53	0.21	FTO	----	----	----
	5e	0.09	0.01	0.09	0.76		0.17	(-0.96, 1.31)	0.76

Model 4c: whole-brain metric ~ age + sex; model 4d: whole-brain metric ~ age + sex + prepubescent + anxiety + depression; model 4e: whole-brain metric ~ age + sex + prepubescent + anxiety + depression + BMI-z; model 5c: whole-brain metric ~ age + sex + batch effect; model 5d: whole-brain metric ~ age + sex + batch effect + prepubescent + anxiety + depression; model 5e: whole-brain metric ~ age + sex + batch effect + prepubescent + anxiety + depression + FTO. Unstandardized betas were reported. Abbreviations: BMI-z: body mass index z-score; CC: clustering coefficient; CS: connectivity strength; FA: fractional anisotropy; FTO: fat mass and obesity related gene (A-allele carrier vs. non carrier); NOS: number of streamlines; REW: reward network

Study 2

Brain Structure and Function (2023) 228:751–760
https://doi.org/10.1007/s00429-023-02615-0

ORIGINAL ARTICLE

Beyond BMI: cardiometabolic measures as predictors of impulsivity and white matter changes in adolescents

Anna Prunell-Castañé[1,2,3] · María Ángeles Jurado[1,2,3] · Jonatan Ottino-González[4] · Xavier Prats-Soteras[1,2] · Consuelo Sánchez Garre[5] · Neus Cano Marco[6] · Paloma Salas Gómez-Pablos[7] · Isabel García-García[1,2] · Maite Garolera[6,8]

Received: 14 October 2022 / Accepted: 25 January 2023 / Published online: 13 February 2023

Abstract

Obesity is characterized by cardiometabolic and neurocognitive changes. However, how these two factors relate to each other in this population is unknown. We tested the association that cardiometabolic measures may have with impulse behaviors and white matter microstructure in adolescents with and without an excess weight. One hundred and eight adolescents (43 normal-weight and 65 overweight/obesity; 11–19 years old) were medically and psychologically (Temperament Character Inventory Revised, Three-Factor Eating Questionnaire-R18, Conners' Continuous Performance Test-II, Stroop Color and Word Test, Wisconsin Card Sorting Test, Kirby Delay Discounting Task) evaluated. A subsample of participants ($n = 56$) underwent a brain magnetic resonance imaging acquisition. In adolescents, higher triglycerides and having a body mass index indicative of overweight/obesity predicted a more impulsive performance in Conners' Continuous Performance Test-II (higher commission errors). In addition, higher glucose and diastolic blood pressure values predicted increments in the Three-Factor Eating Questionnaire-R18 emotional eating scale. Neuroanatomically, cingulum fractional anisotropy showed a negative relationship with glycated hemoglobin. The evaluation of the neurocognitive differences associated with obesity, usually based on body mass index, should be complemented with cardiometabolic measures.

Keywords Impulsivity · Adolescence · Obesity · White matter · Cardiometabolic

Abbreviations

BMI	Body mass index
CPT-II	Conners' Continuous Performance Test-II
DBP	Diastolic blood pressure
DDT	Kirby Delay Discounting Task
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
FDR	False discovery rate
HDL-c	High-density lipoprotein cholesterol
IFOF	Inferior fronto-occipital fasciculus
LDL-c	Low-density lipoprotein cholesterol
MD	Mean diffusivity
MRI	Magnetic resonance imaging
ROI	Region of interest
TCI-R	Temperament Character Inventory Revised
TFEQ-R18	Three-Factor Eating Questionnaire-R18
WCST	Wisconsin Card Sorting Test
WM	White matter

✉ María Ángeles Jurado
majurado@ub.edu

1 Departament de Psicologia Clínica i Psicobiologia, Facultat de Psicologia, Universitat de Barcelona, Passeig de la Vall d'Hebron, 171, 08035 Barcelona, Spain

2 Institut de Neurociències, Universitat de Barcelona, Barcelona, Spain

3 Institut de Recerca Sant Joan de Déu, Barcelona, Spain

4 Department of Endocrinology, Children's Hospital Los Angeles, Los Angeles, USA

5 Pediatric Endocrinology Unit, Hospital de Terrassa, Consorci Sanitari de Terrassa, Barcelona, Spain

6 Brain, Cognition and Behavior: Clinical Research, Consorci Sanitari de Terrassa, Barcelona, Spain

7 Catlab, Consorci Sanitari de Terrassa, Barcelona, Spain

8 Neuropsychology Unit, Hospital de Terrassa, Consorci Sanitari de Terrassa, Barcelona, Spain

Introduction

Overweight and obesity represent a major public health concern. Since 1975, the prevalence of excess weight among children and adolescents has more than quadrupled.

Psychological, biological, and sociocultural factors can contribute to the development of overweight/obesity (World Health Organization 2020). Impulsivity is a multidimensional construct that can correlate with the expression of excess weight, since it may lead to a rapid and unplanned reaction towards food. Impulsivity involves urgency, lack of perseverance and premeditation, and sensation seeking (Mobbs et al. 2010). Importantly, it is a broad concept that has diverse traits and manifestations. A systematic review (Liang et al. 2014) highlighted that, although the literature had mixed results, most studies found more pronounced impulsive behaviors in children and adolescents with overweight/obesity.

Overweight/obesity is also associated with neuroanatomic changes. White matter (WM) differences in this population have been studied with diffusion tensor imaging (DTI). DTI research evidenced WM alterations related to excess weight. Two common measures of WM microstructure are fractional anisotropy (FA) and mean diffusivity (MD). Lower FA and higher MD may reflect disturbances in WM microstructure. In adults, many studies found a negative association between body mass index (BMI) and FA in several WM tracts (Verstynen et al. 2012; Xu et al. 2013; Papageorgiou et al. 2017; Rodrigue et al. 2019). A positive association between BMI and MD was also described (Xu et al. 2013); although another study did not find associations between BMI and MD (Papageorgiou et al. 2017). In children and adolescents, there are mixed results regarding BMI and WM microstructure. There was described a positive (Ou et al. 2015), negative (Alarcón et al. 2016), and no relationship (Alosco et al. 2014) between BMI and FA. Concerning BMI and MD, no significant relationship was found in two studies (Ou et al. 2015; Alarcón et al. 2016), while another observed higher MD values in participants with excess weight (Carbine et al. 2019).

Moreover, not only BMI is related to WM microstructure. Obesity is usually accompanied by cardiometabolic changes that might have a potential impact on neural integrity. How WM integrity is negatively related to cardiometabolic measures has been studied under a broader approach: metabolic syndrome. Metabolic syndrome has been related to WM microstructure (Segura et al. 2009) and macrostructure (Morys et al. 2021), and in adolescents (Yau et al. 2012) and adults (Segura et al. 2009). Studies evaluating the independent effect that each cardiometabolic variable may have on WM are sparse and focused on adults (Verstynen et al. 2013; Lou et al. 2014; Cox et al. 2019; Johnson et al. 2019).

While BMI is a commonly used indirect measure of overweight/obesity, it is an incomplete diagnostic tool (Barlow 2007).

Thus, to favor an integrative assessment of overweight/obesity, we complemented BMI with cardiometabolic variables. Despite the emerging interest in the study of cardiometabolic profile as a possible biomarker of impulsivity—especially focused on mental health (Conklin and Stanford 2008; Kavoor et al. 2017; Messaoud et al. 2017)—, the relationship of cardiometabolic measures with impulsivity and neuroanatomical differences in adolescents with overweight/obesity remains unknown.

The present study evaluates, in adolescents with normal weight and overweight/obesity, the association of cardiometabolic risk factors with (1) impulsive behaviors and (2) WM microstructure. We hypothesize that greater cardiometabolic risk factors might be related to (1) more impulsive behaviors, and (2) to WM microstructure differences. Specifically, we expect to find lower FA and higher MD values in association with greater cardiometabolic risk.

Materials and methods

Participants

We recruited 108 adolescents (mean age = 15 ± 2.02 years old) from public primary care centers. From this sample, 53 participants were already included in a previous work regarding inflammation and grey matter (Prats-Soteras et al. 2020). Inclusion criteria involved being from 11 to 19 years old and having a BMI indicative of normal weight, overweight or obesity. Participants were classified into two groups: normal-weight ($n = 43$) and overweight/obesity ($n = 65$). For that purpose, Cole and Lobstein centile curves (Cole and Lobstein 2012), that provide age and sex-specific cut-off points from 2 to 17 years old, were used to classify underage participants. In participants aged 18 and 19, according to the World Health Organization's classification (World Health Organization 2020), those with a BMI between ≥ 18.5 and < 25 kg/m^2 were classified as normal-weight, and those with BMI ≥ 25 kg/m^2 were classified as overweight/obesity.

Exclusion criteria were (1) being prepubescent and (2) having a psychiatric, neurological, developmental, or systemic diagnosis. Participants did not take any chronic medication. Participants aged 18 and 19 were excluded if they met metabolic syndrome criteria (Alberti et al. 2009). For underage participants, and given the lack of general consensus to define pediatric metabolic syndrome (Yau et al. 2012), we used the cut-off points available from the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (De Jesus 2011) as exclusion criteria. Finally, participants showing global cognitive impairment (i.e., scalar score < 7 in the Weschler Adults Intelligence Scale-III/Weschler Intelligence Scale for Children-IV vocabulary subtest (WAIS-III/WISC-IV)), significant anxiety and depression symptoms (i.e., anxiety or depression symptoms total score ≥ 11 in the

Hospital Anxiety and Depression Scale), and binge eating behaviors (i.e., score ≥ 20 in the Bulimia Inventory Test of Edinburgh) were also excluded.

This study was approved by the Institutional Ethics Committee. The research was conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from all participants, or their respective legal guardian in underage participants, prior to entry into the study.

Procedure

Participants were randomly contacted by phone and briefly interviewed about general health aspects. The first day, potential candidates were cited to undergo a complete medical evaluation and a fasting blood sample extraction in the Pediatric Endocrinology Unit at a Public Hospital. Subjects not presenting any medical comorbidity were neuropsychologically evaluated in the next days. Participants without claustrophobia or metal prothesis also underwent a brain magnetic resonance imaging (MRI) acquisition on a 3T MAGNETON Trio (Siemens, Germany) at a Public Hospital.

Measures

Anthropometric and cardiometabolic measures

All anthropometric measurements were taken by a trained nurse from participants in light clothing without shoes: waist circumference, height (Holtan Limited Harpenden Stadiometer), weight (Seca 704 s) and BMI (kg/m^2), which was transformed into BMI *z*-score. Pubertal stage was determined according to the Tanner scale of sexual maturity. Cardiometabolic measures included total cholesterol, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), triglycerides, glucose and glycated hemoglobin. Diastolic (DBP) and systolic blood pressure were manually determined twice (Riester Big Ben Round), and the mean of both determinations was used for posterior analyses. A description of cardiometabolic measures can be found in Supplementary Material-1a.

Impulsivity measures

The neuropsychological evaluation included: Temperament Character Inventory Revised (TCI-R), Three-Factor Eating Questionnaire-R18 (TFEQ-R18), Conners' Continuous Performance Test II (CPT-II), Stroop Color and Word Test, Wisconsin Card Sorting Test (WCST) and Kirby Delay Discounting Task (DDT). We used the following scores to characterize impulsivity: higher scores in the TCI-R novelty seeking subscale, TFEQ-R18 uncontrolled and emotional eating scales, CPT-II commissions errors, WCST perseverative errors and DDT geometric mean; and lower scores in Stroop Interference score. A description of the neuropsychological assessment can be found in Supplementary Material-1b.

Image acquisition and diffusion-tensor imaging processing

DTI is a neuroimaging analysis technique that quantifies the directionality of water molecules in the brain (Basser et al. 1994). A common measure used in DTI studies is FA, which reflects the orientation dependence of water movement, and hence gives information about WM microstructure. FA measurement ranges from 0 to 1. Higher FA values may suggest well myelinated and undamaged tracts constraining the directional diffusion of water to be parallel, whereas lower FA values may reflect disturbed WM microstructure (Kullmann et al. 2015). Since FA is unspecific to the source driving the changes in WM microstructure, we tested a complementary diffusivity scalar. MD is the average of all eigenvalues with higher values meaning exacerbated cell permeability and thus WM impairments.

Fifty-six participants (25 normal-weight and 31 overweight/obesity) underwent an MRI. The parameters used to acquire the diffusion-weighted images are detailed in Supplementary Material-1c. Image processing was performed in FMRIB Software Library (FSL) v.6.0.4 and BrainSuite v.18a1. Estimated total intracranial volume was obtained for each participant using Freesurfer v.6.0 recon-all pipeline. An explanation of the imaging processing procedure can be found in Supplementary Material-1d.

Two approaches were considered in the DTI analysis: region of interest (ROI) and whole brain. Using the JHU ICBM-DTI-81 White-Matter Labels Atlas and JHU White Matter Tractography Atlas, five ROIs previously implicated in obesity and impulsivity were defined: cingulum, corona radiata, corpus callosum, inferior fronto-occipital fasciculus (IFOF) and internal capsule (Verstynen et al. 2012; Yau et al. 2012, 2014; Kullmann et al. 2015; Ou et al. 2015; Uhlmann et al. 2016; Jeong et al. 2017; Jiang et al. 2017; Papageorgiou et al. 2017; Bessette and Stevens 2019; Reich et al. 2019; Rodrigue et al. 2019; Carbine et al. 2019; Schreiner et al. 2020; Huang et al. 2020; Owens et al. 2020; Morys et al. 2021). FA and MD values of every ROI were averaged per individual and WM tract.

To explore additional relationships between the cardiometabolic profile and WM microstructure, whole-brain contrasts were implemented in FSL randomise with 10,000 iterations and a Threshold-Free Cluster Enhancement approach (Smith et al. 2006). Age, sex, BMI *z*-score and estimated total intracranial volume were modeled as nuisance variables. Due to the exploratory nature of these tests, a Bonferroni correction was applied. This method is more restrictive

than the False Discovery Rate (FDR) correction used in the ROI analysis. Thus, for whole-brain analysis, statistical significance was set at $P < 0.0015$ (8 cardiometabolic variables × 2 WM measures × 2 contrasts).

Data treatment and statistical analyses

Data manipulation and statistical procedures were performed in R statistical package v.4.0.5 and RStudio v.1.2.5033. Normality was determined with Shapiro–Wilk tests. Positively and non-normally distributed variables were transformed into their logarithmic form prior to any analyses. Briefly, we performed three different types of analyses: (a) Mean/median differences between BMI groups in all variables, (b) multiple regression: impulsivity or DTI measures ~ cardiometabolic variables + covariates, and (c) median differences of impulsivity measures between high/low cardiometabolic groups. Analysis (a) was performed to describe between-group differences. Analysis (b) was performed with all variables of interest, regardless of whether they were or not significantly different between groups in analysis (a). Analysis (c) was performed with only those variables that were significant in analysis (b).

Specifically, (a) independent sample *T*-tests, Mann–Whitney *U* tests and Chi-square tests were used to analyze between-group differences. Effect sizes were calculated using R packages *effsize* and *rcompanion*. Missing values for every variable were reported in Tables 1 and 2. We repeated these analyses for the subsample of participants that underwent an MRI acquisition (Supplementary Material, Tables S1 and S2). (b) Multiple regression analyses were performed to determine which cardiometabolic variables were the strongest predictors of impulsivity measures (covariates: age, sex, BMI *z*-score and intelligence quotient estimation (WAIS-III/WISC-IV vocabulary subtest)) and FA/MD differences (covariates: age, sex, BMI *z*-score and estimated total intracranial volume) in 5 WM tracts. Variance inflation factor (VIF) was used to assess multicollinearity within the predictors. To avoid a misestimation of the regression coefficients, total cholesterol was removed for having a VIF > 10. Confidence intervals at 95% for the regression coefficients were calculated as follows: $[\beta i - 1.96 \times SE(\beta i), \beta i + 1.96 \times SE(\beta i)]$. Multiple testing was controlled by FDR for 17 models (i.e., 7 impulsivity, 5 ROI-FA and 5 ROI-MD models). Only those with FDR < 0.05 were considered significant. (c) To provide a better visualization of the relationship between cardiometabolic measures with impulsivity, and only for those cardiometabolic regressors that were statistically significant in the multiple regression analysis, we defined two groups: participants with lower (≤ percentile 50th measure of interest) and higher (> percentile 50th measure of interest) cardiometabolic values. Then, the Mann–Whitney *U* test was used to analyze between-group differences in impulsivity test medians, and their ratio was calculated.

Results

Groups were not significantly different for sex, age, bulimia, anxiety, and depression symptoms ($P > 0.05$). As expected, the overweight/obesity group had a higher BMI *z*-score and waist circumference (mean = 1.95 and 95.08, respectively; $P < 0.01$) than their peers with normal weight (mean = −0.06 and 69.85, respectively). Significant between-group differences were also found in the lipid profile: the overweight/obesity group had lower HDL-c values ($P < 0.01$) and higher triglycerides ($P < 0.01$) than the normal-weight group. Neither LDL-c ($P = 0.7$) nor total cholesterol ($P = 0.2$) were significantly different. Differences in demographic, anthropometric and cardiometabolic measures are detailed in Table 1. Regarding impulsivity measures, participants belonging to the overweight/obesity group performed higher commission errors in the CPT-II test ($P < 0.01$). No significant differences between groups were found in the other impulsivity measures ($P > 0.05$). Table 1 provides a summary of impulsivity measures for both groups.

Cardiometabolic and impulsivity measures

After FDR correction, two out of the seven impulsivity models remained statistically significant: CPT-II commission errors [R^2 adj = 0.24; R^2 adj 95% CI = (0.11, 0.36), FDR = 0.0016] and TFEQ-R18 emotional eating [R^2 adj = 0.18; R^2 adj 95% CI = (0.06, 0.29); FDR = 0.012] models. The CPT-II model showed that for a 1% increase in triglycerides there was an increment of 0.04 commission errors in CPT-II ($P = 0.018$), and that for each unit of BMI *z*-score there was an increment of 2.1 commission errors ($P = 0.004$). Also, the TFEQ-R18 emotional eating model indicated that for each unit of glucose (mmol/L) and DBP (mmHg) there was an increment of 1.11 ($P = 0.016$) and 0.06 ($P = 0.02$) in this scale score, respectively. Table 2 provides a summary of the significant models. Correlations between cardiometabolic and impulsivity measures are included in Supplementary Material (Table S3).

Additionally, we tested for differences between participants with lower (values ≤ percentile 50th) and higher (values > percentile 50th) cardiometabolic values and impulsivity (Fig. 1). Participants from the higher triglycerides group (26% normal-weight, 74% overweight/obesity) committed 19% more CPT-II commission errors than those within the lower triglycerides group (53.7% normal-weight, 46.3% overweight/obesity): median = 25 and 21, respectively; $P = 0.006$. Also, participants from the higher DBP group (15.7% normal-weight, 84.3%

Table 1 Demographic, anthropometric, cardiometabolic and impulsivity measures in the normal-weight (NW) and overweight/obesity (OW/OB) groups

	NW ($n=43$)			OW/OB ($n=65$)			Test statistic	Effect size	P
	Mean (SD)	Range	NA	Mean (SD)	Range	NA			
Demographic measures									
Females (n)	23	–	–	30	–	–	$x^2=0.3^a$		0.58
Age (years old)	15.28 (2.08)	12–19	–	14.83 (1.99)	11–19	–	$W=1539^b$	$r=0.09^N$	0.37
Anthropometric measures									
BMI z-score	−0.06 (0.59)	−1.3 to 0.9	–	1.95 (0.38)	0.8–2.69	–	$W=2.5^b$	$r=0.84^L$	<0.01*
WC (cm)	69.85 (7.2)	59–90	–	95.08 (10.24)	70–117	1	$W=75.5^b$	$r=0.79^L$	<0.01*
Cardiometabolic measures									
SBP (mmHg)	107.78 (12.3)	82.5–132	–	116.69 (9.84)	96–135	–	$W=813.5^b$	$r=0.35^M$	<0.01*
DBP (mmHg)	60.32 (7.95)	45–82.5	–	67.95 (8.92)	50–85	–	$W=727.5^b$	$r=0.41^M$	<0.01*
Glucose (mmol/L)	4.32 (0.4)	3.12–4.91	–	4.52 (0.41)	3.62–5.39	–	$W=1043^b$	$r=0.21^S$	0.03*
HbA1c (%)	5.06 (0.24)	4.4–5.5	–	5.19 (0.28)	4.5–5.7	1	$t=-2.48^c$	$d=-0.49^S$	0.015*
TC (mmol/L)	4.06 (0.6)	2.9–5.95	–	3.9 (0.62)	2.67–5.58	–	$t=1.3^c$	$d=0.25^S$	0.2
HDL-c (mmol/L)	1.53 (0.32)	1.05–2.35	–	1.22 (0.25)	0.67–1.76	–	$t=5.69^c$	$d=1.12^L$	<0.01*
LDL-c (mmol/L)	2.21 (0.49)	1.3–3.5	–	2.25 (0.54)	1.3–3.5	–	$t=-0.38^c$	$d=-0.07^N$	0.7
TG (mmol/L)	0.65 (0.25)	0.34–1.63	–	0.96 (0.44)	0.35–2.02	–	$t=-4.51^c$	$d=-0.82^L$	<0.01*
Estimated intelligence quotient									
WAIS-III/WISC-IV vocabulary	11.07 (2.43)	8–19	–	10.31 (2.17)	7–17	–	$t=1.7$	$d=0.33^S$	0.09
Impulsivity measures									
TFEQ-R18 Emotional eating	4.58 (2.01)	3–11	–	4.86 (1.83)	3–9	–	$W=1235^b$	$r=0.1^S$	0.29
TFEQ-R18 Uncontrolled eating	16.37 (5.13)	3–29	–	17.03 (5.22)	9–30	–	$W=1306^b$	$r=0.060^N$	0.57
TCI-R Novelty seeking total score	104.49 (11.25)	82–129	6	103.44 (11.69)	79–130	15	$t=0.42^c$	$d=0.09^N$	0.67
CPT-II Commission errors	19.5 (6.39)	3–30	1	23.45 (7.13)	5–35	–	$t=-2.9^c$	$d=-0.58^M$	<0.01*
Stroop Interference score	3.49 (5.7)	−9.19 to 20.37	–	2.77 (6.86)	−16.91 to 21.24	–	$t=0.57^c$	$d=0.11^N$	0.56
WCST Perseverative errors	16.48 (11.92)	4–51	1	18.66 (12.63)	5–65	–	$t=-1.27^c$	$d=-0.18^N$	0.2
DDT Geometric mean	0.01 (0.01)	0.0001–0.047	2	0.01 (0.02)	0.0001–0.117	11	$W=1240^b$	$r=0.1^S$	0.32

BMI: body mass index; WC: waist circumference; SBP: systolic blood pressure, DBP: diastolic blood pressure; HbA1c: glycated hemoglobin; TC: total cholesterol; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; TG: triglycerides, WAIS-III: Weschler Adults Intelligence Scale-III; WISC-IV: Weschler Intelligence Scale for Children-IV; TFEQ-R18: Three-Factor Eating Questionnaire-R18; TCI-R: Temperament Character Inventory Revised; CPT-II: Conner's Continuous Performance Test-II; Stroop: Stroop Color and Word Test; WCST: Wisconsin Card Sorting Test; DDT: Kirby Delay Discounting Task

Test statistics: [a]Chi Squared Test; [b]Mann–Whitney U test; [c]t-test

Effect size interpretation: [N]negligible; [S]small; [M]medium; [L]large

*Significant differences between groups

overweight-obesity) scored 25% higher in the TFEQ-R18 emotional eating scale than those within the lower DBP group (61.4% normal-weight, 38.6% overweight/obesity): median = 5 and 4, respectively; $P=0.04$. The rest of the regressors did not show significant statistical differences between higher and lower values.

Cardiometabolic and neuroanatomical measures

Global FA and MD were not significantly different between groups ($P>0.05$). In the ROI-based analysis, and regarding FA, the cingulum was significantly predicted by cardiometabolic variables [R^2 adj = 0.31; R^2 adj 95% CI = (0.15, 0.46); FDR = 0.015] (Table 3; Fig. 2; Supplementary Fig. S1). Specifically, glycated hemoglobin

Table 2 Multiple regression coefficients of the TFEQ-R18 emotional eating and CPT-II commission errors models

	TFEQ-R18—emotional eating			CPT-II—commission errors		
	b	95% CI	*P*	*b*	95% CI	*P*
Sex (female)	1.15	(0.45, 1.85)	0.002*	−1.6	(−4.14, 0.94)	0.22
Age (years old)	0.18	(−0.006, 0.36)	0.06	−0.92	(−1.59, −0.25)	0.009*
BMI *z*-score	0.07	(−0.31, 0.45)	0.7	2.1	(0.71, 3.48)	0.004*
Estimated IQ (WAIS-III/ WISC-IV vocabulary)	−0.07	(−0.23, 0.09)	0.37	−0.11	(−0.68, 0.45)	0.71
HDL (mmol/L)	0.33	(−0.96, 1.63)	0.62	−0.18	(−4.88, 4.53)	0.94
LDL-c (mmol/L)	−0.41	(−1.08, 0.26)	0.23	−0.26	(−2.68, 2.16)	0.83
TG (mmol/L) (Log)	−0.07	(−0.99, 0.85)	0.88	4.09	(0.74, 7.43)	0.018*
Hb1Ac (%)	−0.64	(−1.94, 0.66)	0.33	0.8	(−3.91, 5.51)	0.74
Glucose (mmol/L)	1.11	(0.26, 1.96)	0.016*	−1.56	(−4.66, 1.54)	0.32
DBP (mmHg)	0.06	(0.007, 0.11)	0.02*	−0.17	(−0.36, 0.02)	0.08
SBP (mmHg)	−0.03	(−0.07, 0.01)	0.23	−0.05	(−0.2, 0.1)	0.48

BMI: body mass index; IQ: intelligence quotient; WAIS-III: Weschler Adults Intelligence Scale-III; WISC-IV: Weschler Intelligence Scale for Children-IV; TFEQ-R18: Three-Factor Eating Questionnaire-R18; CPT-II: Conner's Continuous Performance Test-II; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; TG: triglycerides; HbA1c: glycated hemoglobin; DBP: diastolic blood pressure; SBP: systolic blood pressure

*Significant associations (*P* values < 0.05) for the CPT and TFEQ-R18 emotional eating regression models with FDR < 0.05

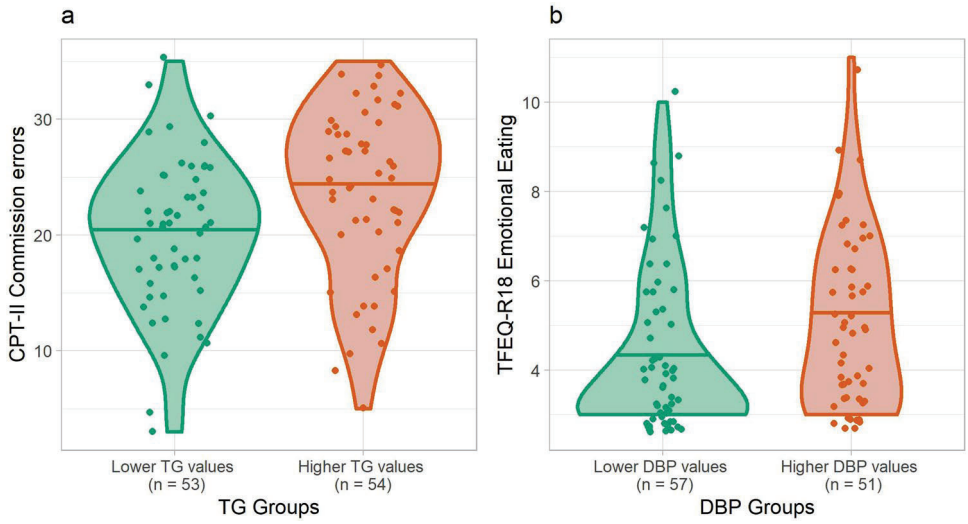


Fig. 1 **a** Boxplot of CPT-II commission errors test (raw scores). **b** Boxplot of the TFEQ-R18 emotional eating scale (raw scores). Participants with lower TG and DBP (values ≤ median) are grouped as 'Lower TG or lower DBP values', whereas those with higher TG and DBP (values > median) are grouped as 'Higher TG or higher DBP values'. Participants are not stratified by normal-weight and overweight/obesity groups. Abbreviations: CPT-II: Conners' Continuous Performance Test-II; TFEQ-R18: Three-Factor Eating Questionnaire-R18; TG: triglycerides; DBP: diastolic blood pressure

and BMI *z*-score were negatively associated with FA ($b = -0.01$, $P = 0.012$; and $b = -0.002$, $P = 0.0495$, respectively). Another WM tract, the IFOF, was significantly associated with glycated hemoglobin ($b = -0.003$, $P = 0.01$), although the model did not overcome FDR correction (FDR = 0.059). Regarding MD, no significant associations were found. Correlations between cardiometabolic and neuroanatomical measures are included in Supplementary Material (Table S4). To second-assess the results obtained in the ROI-based analysis, we did a whole-brain analysis. After applying Bonferroni adjusted threshold for 32 tests ($P < 0.0015$), no significant associations were found.

Table 3 Multiple regression coefficients of the significant white matter tract

	FA cingulum		
	b	95% CI	*P*
Sex (female)	9.56e−04	(−5.4e−03, 7.3e−03)	0.77
Age (years old)	1.84e−03	(5.45e−04, 3.1e−03)	0.008*
BMI *z*-score	−2.35e−03	(−4.6e−03, −7e−05)	0.0495*
HDL (mmol/L)	−6.53e−03	(−1.6e−02, 2.7e−03)	0.17
LDL-c (mmol/L)	4.13e−03	(−4.1e−04, 8.7e−03)	0.08
TG (mmol/L) (Log)	5.99e−04	(−5.5e−03, 6.7e−03)	0.85
Hb1Ac (%)	−1.05e−02	(−1.8e−02, −2.6e−03)	0.012*
Glucose (mmol/L)	3.92e−04	(−5.6e−03, 6.3e−03)	0.9
DBP (mmHg)	2.22e−04	(−1.9e−04, 6.3e−04)	0.3
SBP (mmHg)	−1.3e−04	(−4.7e−04, 2.1e−04)	0.45
Total ICV (mm^3)	1.83e−10	(4e−10, 1e−11)	0.04*

FA: fractional anisotropy; BMI: body mass index; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; TG: triglycerides; HbA1c: glycated hemoglobin; DBP: diastolic blood pressure; SBP: systolic blood pressure; Total ICV: estimated total intracranial volume

*Significant associations (P values < 0.05) for the WM tract regression model with FDR < 0.05

Discussion

We examined the relationship of cardiometabolic measures with impulsive behaviors and WM differences in adolescents with normal-weight and overweight/obesity. First, we explored the relationship that cardiometabolic measures might have with impulsivity. We found that triglycerides were associated with a more impulsive performance in the CPT-II test (higher commission errors), and that glucose and DBP were associated with higher scores on the TFEQ-R18 emotional eating scale. Second, we assessed whether cardiometabolic variables were related to WM microstructure in five ROIs. We found that FA values in the cingulum were negatively associated with glycated hemoglobin.

Impulsivity

The most common ways to evaluate impulsivity are through rating scales and performance-based tests. Rating scales measure self-reported features of impulsive behavior over time, whereas performance-based tests provide an objective

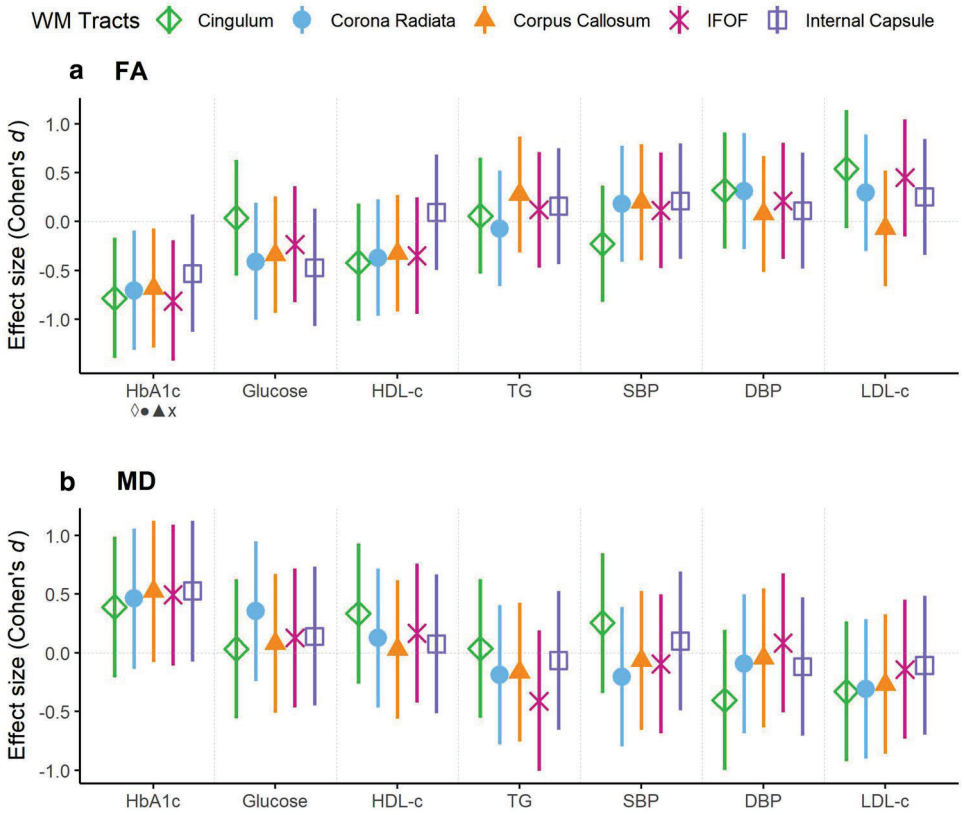


Fig. 2 **a** Fractional anisotropy (FA), **b** mean diffusivity (MD) effect sizes—Cohen's *d*—with 95% confidence intervals of lipid and cardiometabolic traits on the cingulum, corona radiata, corpus callosum, inferior fronto-occipital fasciculus (IFOF) and internal capsule. Significant effect sizes are labeled in the *X* axis with rhombus, circle, triangle, cross and square symbols for cingulum, corona radiata, corpus callosum, IFOF and internal capsule, respectively. After FDR correction, only the FA cingulum model remained significant. Abbreviations: DBP: diastolic blood pressure; HbA1c: glycated hemoglobin; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; SBP: systolic blood pressure; TG: triglycerides

assessment of behaviors related to impulsive actions (Emery and Levine 2017). Impulsivity has been conceptualized as a broad trait composed of different phenotypes that manifest in a similar manner (Sharma et al. 2014). Within our sample, higher triglycerides were related to greater commission errors in the CPT-II test, which is also the only impulsivity measure (Shaked et al. 2020) significantly different between groups in the *t*-tests. Performance-based tests can never assess an isolated cognitive domain. It is possible that, compared to other tests, the CPT-II evaluates more directly impulsivity because it leads to more automatic responses and the capacity of inhibition becomes fundamental.

To date, there is a lacking consensus about the relationship between impulsivity and cardiometabolic measures. A study in a large healthy sample (Sutin et al. 2010) evaluated the relationship of personality traits (NEO Personality Inventory) with lipid profile. They found that impulsivity was positively associated with triglycerides, while self-discipline and deliberation were negatively associated with triglycerides and positively with HDL-c. Excitement-seeking was not significantly associated with lipid profile. Conversely, another study (Peterfalvi et al. 2019) did not find any relationship between the lipid profile (total cholesterol, HDL-c, LDL-c, triglycerides) and any CPT-II parameter in adults with major depression disorder, whereas lower HDL-c values did predict poorer shifting (WCST) abilities in this population. Although, as mentioned, there is a disparity in the literature, our results agree with previous studies that reported associations between cardiometabolic risk factors and impulsivity (Pozzi et al. 2003; Sutin et al. 2010). However, more research in clinical and healthy populations is needed to assess the nature of this relationship.

In addition, higher glucose and DBP values were related to higher scores on the TFEQ-R18 emotional eating scale. Emotional eating leads to the consumption of highly palatable and energy-dense foods—comfort foods—as a mechanism to cope with negative emotions. Given this, we hypothesize that such an eating pattern is accompanied by immediate glucose spikes and, at a mid/long term, with higher basal glucose levels. Also, negative emotions as a form of stress may be related to higher blood pressure. Particularly, the obesogenic environment and the easy access to palatable foods may be a key factor in this eating pattern, and future research studying its possible mediator effect may help to target specific public health actions.

Overall, our results support our first hypothesis. In our data, cardiometabolic risk factors are associated with impulsivity. Importantly, this association was found with cardiometabolic variables of different nature: blood pressure, glucose, and triglycerides.

White matter microstructure

The present study provides new evidence regarding WM microstructure and cardiometabolic measures in adolescents with and without excess weight. Our results suggested an inverse association between glycated hemoglobin and FA values in the cingulum; a WM tract that has been previously related to obesity (Verstynen et al. 2012; Kullmann et al. 2015; Papageorgiou et al. 2017; Carbine et al. 2019). This finding is consistent with a recent study in healthy adults (Repple et al. 2021) that demonstrated that non-pathological variations in glycated hemoglobin are related to WM microstructure. Regarding our second hypothesis, we expected to find more cardiometabolic components associated with WM microstructure. It is possible that glycated hemoglobin, even at levels much below the prediabetes, works as an early indicator of cardiometabolic risk (Veeranna et al. 2011), whereas more morbid levels may be required for the other cardiometabolic components to show an association with WM microstructure. Also, and since our research targets adolescence—a period where individuals undergo several developmental processes, including WM maturation (Barnea-Goraly et al. 2005)—future longitudinal studies are necessary to see if our findings are related to brain maturation and myelination processes that occur in adolescence.

Limitations and future directions

This study has some limitations that should be acknowledged: (1) given our cross-sectional design, we could not assess causality in our results, (2) the smaller sample size used for the neuroimaging analyses limited their statistical power, and (3) the diffusion-weighted images were acquired with only 30 directions. Future studies including larger sample sizes and a longitudinal approach are needed to confirm whether our findings are consistent in different age spectrums and persist over time.

Conclusions

Our findings show that, in adolescents, triglycerides and having a BMI indicative of overweight/obesity predict a more impulsive performance in the CPT-II test (higher commission errors). In addition, glucose and DBP predict increments in the TFEQ-R18 emotional eating scale. Neuroanatomically, the cingulum FA shows a negative association with glycated hemoglobin and BMI. Our study provides a comprehensive overview of the relationship between cardiometabolic risk factors typically related to overweight/obesity and neurocognitive variables; and invites us to look beyond the BMI when evaluating possible behavioral, cognitive, and

neuroanatomical differences associated with overweight/obesity.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00429-023-02615-0.

Acknowledgements The authors thank Nuria Miró, Mónica González-Juanmartín and Gemma Monté Rubio their support. The authors also thank all the participants that made this project possible. We acknowledge the Centres de Recerca de Catalunya (CERCA) Program/Generalitat de Catalunya, the Institute of Neurosciences, the Institute of Biomedical Research August Pi i Sunyer (IDIBAPS), the Consorci Sanitari de Terrassa and the Hospital de Terrassa. We also acknowledge the Spanish Ministry of Science, Innovation and Universities, the Spanish Ministry of Economy, Industry and Competitiveness, the European Regional Development Fund and the Departament d'Innovació, Universitats i Empresa (Generalitat de Catalunya).

Author contributions APC, MAJ, IGG, and MG contributed to the study design and conception. JOG, XPS, CSG, PSG, and NCM participated in data acquisition. APC performed the analyses. APC, MAJ, and IGG contributed to the results interpretation. APC wrote the original manuscript. MAJ, JOG, IGG, and MG critically edited it. MAJ and MG provided funding for the study. All authors approved its final version for publishing and agreed to be accountable for all aspects of such work.

Funding Open Access funding provided thanks to the CRUE-CSIC agreement with Springer Nature. APC received a Ph.D. scholarship from the Spanish Ministry of Science, Innovation and Universities (PRE2019-087430). MAJ and MG received Grants from the Spanish Ministry of Economy, Industry and Competitiveness (PSI2017-86536-C2-1-R and PSI2017-86536-C2-2-R, respectively), funded by MCIN/AEI/https://doi.org/10.13039/501100011033 and the European Regional Development Fund (ERDF). MAJ has additionally received funding from the Departament d'Innovació, Universitats i Empresa, Generalitat de Catalunya (2017SGR748).

Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare that the research was conducted in the absence of any commercial financial or non-financial relationships that could be construed as a potential conflict of interest.

Consent to participate Written informed consent was obtained from all participants, or their respective legal guardian in the case of underage participants, prior to entry into the study.

Ethics approval This study has been approved by the University of Barcelona's (CBUB) Institutional Ethics Committee, Institutional Review Board (IRB 00003099, assurance number: FWA 00004225; http://www.ub.edu/recerca/comissiobioetica.htm). The research has been conducted in accordance with the Helsinki Declaration.

References

Alarcón G, Ray S, Nagel BJ (2016) Lower working memory performance in overweight and obese adolescents is mediated by white matter microstructure. J Int Neuropsychol Soc 22:281–292. https://doi.org/10.1017/S1355617715001265

Alberti KGMM, Eckel RH, Grundy SM et al (2009) Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; National heart, lung, and blood institute; American heart association; World heart federation; International. Circulation 120:1640–1645. https://doi.org/10.1161/CIRCULATIONAHA.109.192644

Alosco ML, Stanek KM, Galioto R et al (2014) Body mass index and brain structure in healthy children and adolescents. Int J Neurosci 124:49–55. https://doi.org/10.3109/00207454.2013.817408

Barlow SE (2007) Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. Pediatrics. https://doi.org/10.1542/peds.2007-2329C

Barnea-Goraly N, Menon V, Eckert M et al (2005) White matter development during childhood and adolescence: a cross-sectional diffusion tensor imaging study. Cereb Cortex 15:1848–1854. https://doi.org/10.1093/cercor/bhi062

Basser PJ, Mattiello J, Lebihan D (1994) MR diffusion tensor spectroscopy and imaging. Biophys J 66:259–267

Bessette KL, Stevens MC (2019) Neurocognitive pathways in attention-deficit/hyperactivity disorder and white matter microstructure. Biol Psychiatry Cogn Neurosci Neuroimaging 4:233–242. https://doi.org/10.1016/j.bpsc.2018.09.007

Carbine KA, Duraccio KM, Hedges-Muncy A et al (2019) White matter integrity disparities between normal-weight and overweight/obese adolescents: an automated fiber quantification tractography study. Brain Imaging Behav. https://doi.org/10.1007/s11682-019-00036-4

Cole TJ, Lobstein T (2012) Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. Pediatr Obes 7:284–294. https://doi.org/10.1111/j.2047-6310.2012.00064.x

Conklin SM, Stanford MS (2008) Premeditated aggression is associated with serum cholesterol in abstinent drug and alcohol dependent men. Psychiatry Res 157:283–287. https://doi.org/10.1016/j.psychres.2007.02.006

Cox SR, Lyall DM, Ritchie SJ et al (2019) Associations between vascular risk factors and brain MRI indices in UK Biobank. Eur Heart J 40:2290–2299. https://doi.org/10.1093/eurheartj/ehz100

De Jesus JM (2011) Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics 128:213–256. https://doi.org/10.1542/peds.2009-2107C

Emery RL, Levine MD (2017) Questionnaire and behavioral task measures of impulsivity are differentially associated with body mass index: a comprehensive meta-analysis. Psychol Bull 143:868–902. https://doi.org/10.1037/bul0000105

Huang S, Yang W, Luo J et al (2020) White matter abnormalities based on TBSS and its correlation with impulsivity behavior of methamphetamine addicts. Front Psychiatry 11:1–9. https://doi.org/10.3389/fpsyt.2020.00452

Jeong BS, Han DH, Kim SM et al (2017) 'White matter connectivity and Internet gaming disorder' and broader considerations in the field. Addict Biol 22:44–46. https://doi.org/10.1111/adb.12265
Jiang W, Shi F, Liu H et al (2017) Reduced white matter integrity in antisocial personality disorder: a diffusion tensor imaging study. Sci Rep 7:1–11. https://doi.org/10.1038/srep43002
Johnson NF, Gold BT, Ross D et al (2019) Non-fasting high-density lipoprotein is associated with white matter microstructure in healthy older adults. Front Aging Neurosci 11:1–9. https://doi.org/10.3389/fnagi.2019.00100
Kavoor AR, Mitra S, Kumar S et al (2017) Lipids, aggression, suicidality and impulsivity in drug-naïve/drug-free patients of schizophrenia. Asian J Psychiatr 27:129–136. https://doi.org/10.1016/j.ajp.2017.03.002
Kullmann S, Schweizer F, Veit R et al (2015) Compromised white matter integrity in obesity. Obes Rev 16:273–281. https://doi.org/10.1111/obr.12248
Liang J, Matheson BE, Kaye WH, Boutelle KN (2014) Neurocognitive correlates of obesity and obesity-related behaviors in children and adolescents. Int J Obes 38:494–506. https://doi.org/10.1038/ijo.2013.142
Lou B, Chen M, Luo X, Dai Y (2014) Reduced right frontal fractional anisotropy correlated with early elevated plasma LDL levels in obese young adults. PLoS ONE 9:1–9. https://doi.org/10.1371/journal.pone.0108180
Messaoud A, Mensi R, Mrad A et al (2017) Is low total cholesterol levels associated with suicide attempt in depressive patients? Ann Gen Psychiatry. https://doi.org/10.1186/s12991-017-0144-4
Mobbs O, Crépin C, Thiéry C et al (2010) Obesity and the four facets of impulsivity. Patient Educ Couns 79:372–377. https://doi.org/10.1016/j.pec.2010.03.003
Morys F, Dadar M, Dagher A (2021) Association between mid-life obesity, its metabolic consequences, cerebrovascular disease and cognitive decline Filip. J Clin Endocrinol Metab 106:e4260–e4274. https://doi.org/10.1210/clinem/dgab135
Ou X, Andres A, Pivik RTT et al (2015) Brain gray and white matter differences in healthy normal weight and obese children. J Magn Reson Imaging 42:1205–1213. https://doi.org/10.1002/jmri.24912
Owens MM, Hyatt CS, Gray JC et al (2020) Neuroanatomical correlates of impulsive traits in children aged 9 to 10. J Abnorm Psychol 129:831–844. https://doi.org/10.1037/abn0000627
Papageorgiou I, Astrakas LG, Xydis V et al (2017) Abnormalities of brain neural circuits related to obesity: a diffusion tensor imaging study. Magn Reson Imaging 37:116–121. https://doi.org/10.1016/j.mri.2016.11.018
Peterfalvi A, Németh N, Herczeg R et al (2019) Examining the influence of early life stress on serum lipid profiles and cognitive functioning in depressed patients. Front Psychol 10:1–16. https://doi.org/10.3389/fpsyg.2019.01798
Pozzi F, Troisi A, Cerilli M et al (2003) Serum cholesterol and impulsivity in a large sample of healthy young men. Psychiatry Res 120:239–245. https://doi.org/10.1016/S0165-1781Ž03.00192-6
Prats-Soteras X, Jurado MA, Ottino-González J et al (2020) Inflammatory agents partially explain associations between cortical thickness, surface area, and body mass in adolescents and young adulthood. Int J Obes 44:1487–1496. https://doi.org/10.1038/s41366-020-0582-y
Reich R, Gilbert A, Clari R et al (2019) A preliminary investigation of impulsivity, aggression and white matter in patients with bipolar disorder and a suicide attempt history. J Affect Disord 247:88–96. https://doi.org/10.1016/j.jad.2019.01.001
Repple J, Karliczek G, Meinert S et al (2021) Variation of HbA1c affects cognition and white matter microstructure in healthy, young adults. Mol Psychiatry 26:1399–1408. https://doi.org/10.1038/s41380-019-0504-3
Rodrigue AL, Knowles EEM, Mollon J et al (2019) Evidence for genetic correlation between human cerebral white matter microstructure and inflammation. Hum Brain Mapp 40:4180–4191. https://doi.org/10.1002/hbm.24694
Schreiner MW, Mueller BA, Klimes-Dougan B et al (2020) White matter microstructure in adolescents and young adults with non-suicidal self-injury. Front Psychiatry 10:1–10. https://doi.org/10.3389/fpsyt.2019.01019
Segura B, Jurado M, Freixenet N et al (2009) Microstructural white matter changes in metabolic syndrome: a diffusion tensor imaging study. Neurology 73:438–444. https://doi.org/10.1212/WNL.0b013e3181d2b837
Shaked D, Faulkner LMD, Tolle K et al (2020) Reliability and validity of the conners' continuous performance test. Appl Neuropsychol 27:478–487. https://doi.org/10.1080/23279095.2019.1570199
Sharma L, Markon KE, Clark LA (2014) Toward a theory of distinct types of "impulsive" behaviors: a meta-analysis of self-report and behavioral measures. Psychol Bull 140:374–408. https://doi.org/10.1037/a0034418
Smith SM, Jenkinson M, Johansen-Berg H et al (2006) Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 31:1487–1505. https://doi.org/10.1016/j.neuroimage.2006.02.024
Sutin AR, Terracciano A, Deiana B et al (2010) Cholesterol, triglycerides, and the five-factor model of personality. Biol Psychol 84:186–191. https://doi.org/10.1016/j.biopsycho.2010.01.012
Uhlmann A, Fouche JP, Lederer K et al (2016) White matter microstructure and impulsivity in methamphetamine dependence with and without a history of psychosis. Hum Brain Mapp 37:2055–2067. https://doi.org/10.1002/hbm.23159
Veeranna V, Ramesh K, Zalawadiya SK et al (2011) Glycosylated hemoglobin and prevalent metabolic syndrome in nondiabetic multiethnic US adults. Metab Syndr Relat Disord 9:361–367. https://doi.org/10.1089/met.2011.0032
Verstynen T, Weinstein A, Schneider W et al (2012) Increased body mass index is associated with a global and distributed decrease in white matter microstructural integrity. Psychosom Med 74:682–690. https://doi.org/10.1097/PSY.0b013e318261909c
Verstynen TD, Weinstein AM, Schneider WW et al (2013) Competing physiological pathways link individual differences in weight and abdominal adiposity to white matter microstructure. Neuroimage 79:129–137. https://doi.org/10.1016/j.neuroimage.2013.04.075
World Health Organization (2020) Obesity and overweight. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
Xu J, Li Y, Lin H et al (2013) Body mass index correlates negatively with white matter integrity in the fornix and corpus callosum: a diffusion tensor imaging study. Hum Brain Mapp 34:1044–1052. https://doi.org/10.1002/hbm.21491
Yau PL, Castro MG, Tagani A et al (2012) Obesity and metabolic syndrome and functional and structural brain impairments in adolescence. Pediatrics. https://doi.org/10.1542/peds.2012-0324
Yau PL, Minsung K, Tirsi A, Convit A (2014) Retinal vessel alterations and cerebral white matter microstructural damage in obese adolescents with metabolic syndrome. JAMA Pediatr 168:e142815. https://doi.org/10.1001/jamapediatrics.2014.2815

Supplementary Material Study 2

1a. Biological roles of the cardiometabolic measures

Cholesterol is (i) a key component of cell membranes, (ii) needed to produce hormones (including sex hormones) and vitamin D, and (iii) needed to produce bile acids to digest food. When the level of cholesterol is above the normal range, it can combine with other substances and build up plaques in the arteries. If this situation persists, a condition known as atherosclerosis is likely to appear, which increases the cardiovascular risk. *LDL-cholesterol* contributes to plaque formation, and *HDL-cholesterol* collects excessive blood cholesterol levels and transports them to the liver for excretion. *Triglyceride*s are fundamentally involved in energy storage. Excessive levels of triglycerides contribute to atherosclerosis development. *Glucose i*s the body's main source of energy. When eating, glucose levels spike, and the pancreas produces insulin to regulate blood glucose levels. If glucose levels are persistently high, the risk of insulin resistance and diabetes increases. The excess of blood glucose is attached to hemoglobin –*glycated hemoglobin* –, which is one of the diabetes diagnostic biomarkers. *Blood pressure* allows blood circulation. When the levels of blood pressure are high, cardiovascular risk increases (Wishart et al. 2022).

1b. Description of impulsivity measures

Temperament Character Inventory Revised (TCI-R) (Gutierrez and Bayón 2004) is a 240 questions self-administered questionnaire designed for the evaluation of the seven dimensions of personality: novelty seeking, harm avoidance, reward dependence, persistence, self-directedness, cooperativeness and self-transcendence. Novelty seeking subscale comprises a punctuation range from 35 to 175, where higher scores indicate greater impulsivity traits.

Three-Factor Eating Questionnaire-R18 (TFEQ-R18) (Stunkard and Messick 1985) examines cognitive and behavioral components of eating. It is an 18 self-report questionnaire that targets three eating behaviors: uncontrolled eating, emotional eating and cognitive restraint eating. Impulsiveness is assessed through emotional eating (tendency to eat in response to negative emotions) and uncontrolled eating (tendency to overeat while experiencing feelings of being out of control). Uncontrolled eating comprises a punctuation range from 9 to 36, and emotional eating from 3 to 12. In both cases, higher scores indicate greater impulsivity traits (Aoun et al. 2019)

The Conners' Continuous Performance Test-II (CPT-II) (Conners 2004) is a computerized task that assesses inattention and the response inhibition component of executive function. Participants are required, with a previous short training, to press a computer key after every letter except the *X*. Commission errors are computed as the number of responses given to the non-target letter. Higher commission errors are indicative of greater impulsivity.

The Stroop Color and Word Test (Golden 1995) assesses the ability to inhibit cognitive interference. The Stroop test consists of three sheets with 20 words distributed in five columns each. Participants have forty-five seconds to read aloud and as fast as possible each sheet. The word-sheet (W) requires the participant to read a list of black-inked color names (i.e., red, green, blue). In the color-sheet (C), the subject is required to name the color (i.e., red, green or blue) of non-readable stimuli (i.e., "XXXX"). The incongruent-sheet (I) requires the participant to name the color of the word, which differs from the written name (i.e., "blue" in red-ink). The interference score is calculated with the formula: I – [(W x C)/W + C)]. Lower interference values denote less ability to suppress automatic responses, and thus greater impulsivity.

The Wisconsin Card Sorting Test (WCST) (Heaton 1999) is a computerized task that measures cognitive flexibility. Participants are asked to match 64 cards based on a principle (i.e., color, shape or number of elements) that is not explained to them and needs to be learned from the feedback as to whether their responses are correct or incorrect. After ten consecutive hits, the matching rule changes without announcement. Perseverative errors are computed as the number of incorrect responses that would have been correct for the preceding matching rule. Higher perseverative errors scores mirror impulsivity traits and cognitive rigidity, or the inability to switch from the original mindset to an alternative one.

The Kirby Delay Discounting Task (DDT) (Kirby 1996) is a task that measures impulsive decision-making, evaluating the preference for smaller and immediate rewards over larger and delayed rewards. Participants are asked to answer 27 questions that require them to choose between small ($25-35), medium ($50-60) and large ($75-85) delayed rewards. For example, '*Would you prefer $33 today or $80 in 14 days*?'. The discount rate *k* is estimated within each range (small, medium, large), and the geometric mean of the three rates is calculated for each participant. Higher k values indicate the preference for small immediate rewards, which correspond to higher levels of impulsivity.

1c. Parameters used to acquire the diffusion weighted images

The diffusion-weighted images (DWI) were acquired with the following parameters: repetition time = 7,700 ms, echo time = 89 ms, acquisition matrix = 122 × 122, 2 mm isotropic voxel, field of view = 244 × 244 mm2, diffusion directions = 30, slice thickness = 2 mm, number of slices = 60, b-values = 0 and 1,000 s/mm2, IPAT factor = 2 and total scan time = 4:23 minutes. A T1-weighted MPRAGE 3D sequence was also acquired for registration, EPI distortion correction, and cortical grey matter morphometry analysis using the following parameters: TR = 2300 ms, TE = 2.98 ms, inversion time = 900 ms, 240 slices, FOV = 256 × 256 mm2, 1 mm isotropic voxel.

1d. Explanation of the DTI imaging processing procedure

All DWI sequences were visually inspected to detect artifacts, skull-stripped and corrected for head motion and eddy currents. Parallel skull stripping and bias-filed correction (FAST) were applied to the T1-weighted images. EPI distortions of DWI images were solved by using a constrained non-rigid registration to each participants' T1-weighted image (Bhushan et al. 2012), which is a default step from the BS diffusion pipeline (http://brainsuite.org/processing/diffusion/). Gradient rotation after this registration was also performed to optimize tensor fitting in subsequent steps. The diffusion tensor was fitted to each voxel to generate the FA maps with a linear weighted least squares model to appropriate scale data variances (Jones et al. 2013). FA maps were non-linearly registered onto the most representative participant's FA map to prevent anatomical misalignments (Bach et al. 2014). To limit the presence of spurious tracts, the mean FA skeleton was generated based on each participants' FA values with a threshold > 0.25. MD was also projected onto the mean FA skeleton for complementary analysis.

Programs used for neuroimaging and statistical analyses

- FMRIB Software Library (FSL) v.6.0.4: https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL
- BrainSuite v.18a1: http://brainsuite.org/
- Freesurfer v.6.0 recon-all pipeline: https://surfer.nmr.mgh.harvard.edu/fswiki/recon-all
- R statistical package v.4.0.5: https://www.r-project.org
- RStudio v.1.2.5033: https:// www.rstudio.com

References

Aoun C, Nassar L, Soumi S, et al (2019) The Cognitive, Behavioral, and Emotional Aspects of Eating Habits and Association With Impulsivity, Chronotype, Anxiety, and Depression: A Cross-Sectional Study. Front Behav Neurosci 13:. https://doi.org/10.3389/fnbeh.2019.00204

Bach M, Laun FB, Leemans A, et al (2014) Methodological considerations on tract-based spatial statistics (TBSS). Neuroimage 100:358–369. https://doi.org/10.1016/j.neuroimage.2014.06.021

Bhushan C, Haldar JP, Joshi AA, Leahy RM (2012) Correcting Susceptibility-Induced Distortion in Diffusion-Weighted MRI using Constrained Nonrigid Registration. Signal Inf Process Assoc Annu Summit Conf APSIPA Asia Pac

Conners KC (2004) Conners' CPT-II continuous performance test II. MHS Multi Heath Syst. Inc.

Golden CJ (1995) STROOP, test de colores y palabras. TEA Ediciones

Gutierrez JA, Bayón C (2004) Inventario del temperamento y el carácter-revisado (TCI-R). Baremación y datos normativos en una muestra de población general. Actas españolas Psiquiatr 8:8–15

Heaton RK (1999) Wisconsin Card Sorting Test: Computer Version 4-Research Edition. Psychol. Assess. Resour.

Jones DK, Knösche TR, Turner R (2013) White matter integrity, fiber count, and other fallacies: The do's and don'ts of diffusion MRI. Neuroimage 73:239–254. https://doi.org/10.1016/j.neuroimage.2012.06.081

Kirby KMN (1996) Delay-discounting probabilistic rewards: Rates decrease as amounts increase. Psychon Bull Rev 100–104

Stunkard AJ, Messick S (1985) The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger. J Psychosom Res 29:71–83

Wishart DS, Guo AC, Oler E, et al (2022) HMDB 5.0: The Human Metabolome Database for 2022. Nucleic Acids Res 50:D622–D631. https://doi.org/10.1093/nar/gkab1062

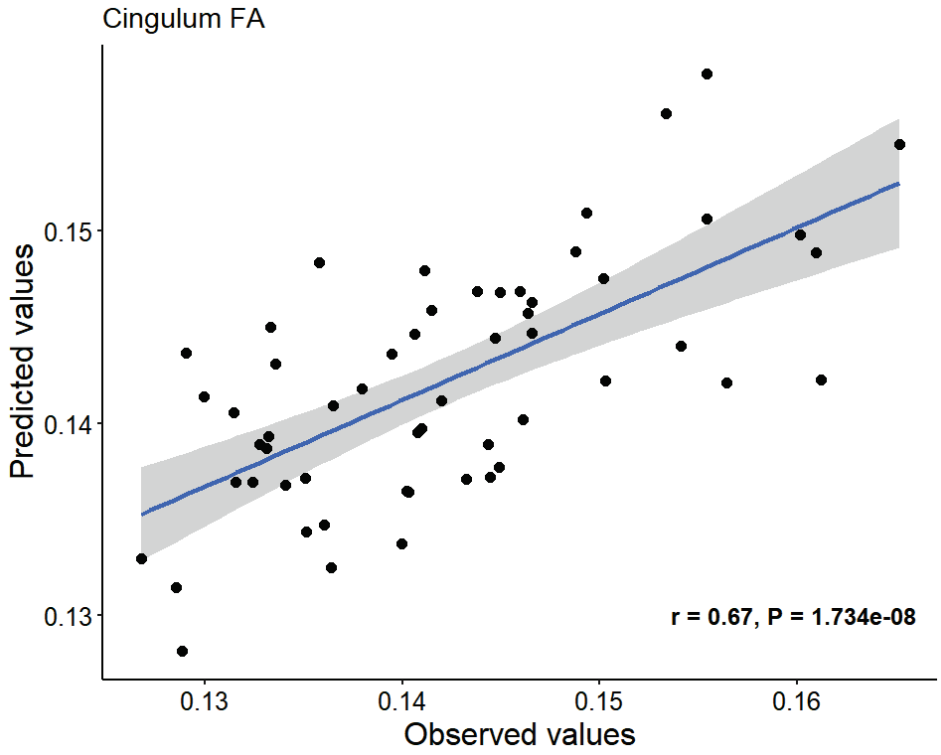


Fig. S1 Scatterplot of the observed vs predicted cingulum FA values of the multiple regression model. All the independent variables included in the full model were used to predict cingulum FA values (sex + age + BMIz + HDL + HDL + TG(log) + Hb1Ac + glucose + DBP + SBP + Total ICV)

Table S1. Demographic, anthropometric, cardiometabolic and measures in normal-weight (NW) and overweight/obesity (OW/OB) groups of the participants that underwent an MRI acquisition.

	NW (n = 25)			OW/OB (n = 31)			Test statistic	Effect size	*P* value
	Mean (SD)	**Range**	**NA**	**Mean (SD)**	**Range**	**NA**			
Females (n)	12			13			x2 = 0,03[a]		0,85
Age (years old)	14,88 (2,05)	12 – 19	-	15,42 (2,11)	12 – 19	-	T = -0,96[b]	*d* = -0,26[S]	0,34
BMI z-score	-0,13 (0,58)	-1,28 – 0,9	-	1,94 (0,34)	1,06 – 2,69	-	T = -16,82[b]	*d* =-4,52[L]	<0,01*
WC (cm)	69,6 (6,88)	59 – 89,5	-	98,15 (10,67)	78 – 117	1	T = -11,5[b]	*d* = -3,11[L]	<0,01*
SBP (mmHg)	107,7 (11,59)	85 – 125	-	115,34 (11,33)	96 – 135	-	W = 248[c]	r = 0,3[M]	0,02*
DBP (mmHg)	61,6 (8,65)	50 – 82,5	-	67,81 (9,77)	50 – 83,5	-	T = -2,48[b]	*d* = -0,67[M]	0,02*
Glucose (mmol/L)	4,26 (0,43)	3,12 – 4,79	-	4,52 (0,38)	3,62 – 5,3	-	T = -2,39[b]	*d* = -0,64[M]	0,02*
HbA1c (%)	5,05 (0,25)	4,4 – 5,5	-	5,1 (0,3)	4,5 – 5,7	-	T = -0,6[b]	*d* = -0,16[N]	0,55
TC (mmol/L)	4 (0,6)	2,9 – 5,08	-	3,98 (0,63)	2,67 – 5,11	-	T = 0,15[b]	*d* = 0,04[N]	0,88
HDL-c (mmol/L)	1,46 (0,3)	1,05 – 2,35	-	1,19 (0,24)	0,67 – 1,67	-	T = 3,75[b]	*d* = 1[L]	<0,01*
LDL-c (mmol/L)	2,24 (0,48)	1,3 – 3,1	-	2,31 (0,51)	1,4 – 3,3	-	T = -0,64[b]	*d* = -0,17[N]	0,53
TG (mmol/L)	0,69 (0,3)	0,34 – 1,63	-	1,04 (0,5)	0,35 – 1,98	-	T = -2,86[b]	*d* = -0,82[L]	<0,01*

Abbreviations. BMI: Body Mass Index; WC: waist circumference; SBP: systolic blood pressure, DBP: diastolic blood pressure; HbA1c: glycated hemoglobin; TC: total cholesterol; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; TG: triglycerides.

Test statistics: [a] Chi Squared Test; [b] *t*-test; [c] Mann-Whitney U Test
Effect size interpretation: [N] negligible; [S] small; [M] medium; [L] large
*Significant differences between groups

Table S2. Impulsivity measures in the normal-weight (NW) and overweight/obesity (OW/OB) groups of the participants that underwent an MRI acquisition.

Impulsivity measures	NW (n = 25)			OW/OB (n = 31)			Test statistic	Effect size	P
	Mean (SD)	Range	NA	Mean (SD)	Range	NA			
TFEQ-R18									
Emotional eating	4,68 (2,08)	3 – 11	-	4,9 (1,94)	3 – 9	-	W = 357[a]	r = 0,07[N]	0,61
Uncontrolled eating	17,4 (5,3)	9 – 29	-	18,22 (5,29)	9 – 30	-	T = -0,58[b]	d = -0,15[N]	0,56
TCI-R									
Novelty seeking total score	103,92 (8,99)	83 – 129	1	100,8 (7,84)	87 – 113	6	T = 1,26[b]	d = 0,36[S]	0,21
CPT-II									
Commission errors	19,6 (6,37)	3 – 28	-	23,19 (6,91)	5 – 35	-	W = 261[a]	r = 0,28[S]	0,04*
Stroop									
Interference score	3,24 (4,14)	-6,58 – 11,48	-	2,1 (5,29)	-7,92 – 12,59	-	T = 0,89[b]	d = 0,24[S]	0,4
WCST									
Perseverative errors	15,12 (9,95)	4 – 47	-	20,48 (14,8)	6 – 65	-	T = -1,69[b]	d = -0,42[S]	0,1
DDT									
Geometric mean	0,01 (0,008)	0,0004 – 0,02	1	0,02 (0,03)	0,0001 – 0,12	6	W = 318[a]	r = 0,05[N]	0,73

Abbreviations. TFEQ-R18: Three-Factor Eating Questionnaire-R18; TCI-R: Temperament Character Inventory Revised; CPT-II: Conner's Continuous Performance Test-II; Stroop: Stroop Color and Word Test; WCST: Wisconsin Card Sorting Test; DDT: Kirby Delay Discounting Task.

Test statistics: [a] Chi Squared Test; [b] *t*-test
Effect size interpretation: [N] negligible; [S] small; [M] medium; [L] large
*Significant differences between groups

Table S3. Bivariate correlations between cardiometabolic and impulsivity measures (n = 108).

		Cardiometabolic measures										Impulsivity measures							
		BMI-z	WC	SBP	DBP	HbA1c	Glucose	TC	HDL-c	LDL-c	TG (log)	Vocabulary_ss	Stroop_INT	CPT_CE	TFEQ_UE	TEFQ_EE	TCI_NS	DDT_Geomean	WCST_PE (log)
Cardiometabolic measures	Age	-0,08	0,18	0,23*	0,3**	-0,08	-0,18	-0,02	0,07	-0,11	0,08	0,29**	0,03	-0,35***	0	0,19*	0,06	0,24*	-0,14
	BMI-z		0,86***	0,38***	0,4***	0,23*	0,25**	-0,12	-0,49***	0,04	0,39***	-0,16	-0,11	0,32***	0,05	0,08	-0,1	0,08	0,1
	WC			0,44***	0,44***	0,15	0,24*	-0,06	-0,5***	0,09	0,45***	-0,05	0,02	0,2*	0,12	0,16	-0,09	0,19	0,09
	SBP				0,68***	0,02	0,13	0,13	-0,22*	0,19	0,37***	0,04	-0,06	-0,08	0,02	0,02	-0,12	0,01	0,08
	DBP					0,08	0,12	0,05	-0,18	0,06	0,4***	0,08	-0,09	-0,14	0,1	0,25**	-0,17	0,01	0,12
	HbA1c						0,17	-0,16	-0,25**	-0,04	0,06	-0,2*	-0,04	0,11	-0,01	-0,03	0,08	0,02	0,1
	Glucose							0	-0,16	0,05	0,14	0,01	-0,08	0,05	0,27**	0,15	0,11	0,05	-0,03
	TC								0,45***	0,88***	0,15	0,16	0,19	-0,03	-0,2*	-0,11	-0,05	-0,07	0,13
	HDL-c									0,07	-0,46***	0,19*	0,09	-0,24*	-0,16	0	-0,02	-0,2*	-0,05
	LDL-c										0,13	0,05	0,17	0,02	-0,18	-0,14	-0,02	0	0,15
	TG (log)											0,03	-0,05	0,25**	0,1	0,01	-0,06	0,18	0,04
Impulsivity measures	Vocabulary_ss												0,17	-0,17	-0,15	-0,05	0,09	0,05	-0,03
	Stroop_INT													-0,08	-0,03	0,04	0,21	-0,05	0,02
	CPT_CE														0,03	-0,23	-0,02	0,02	0,15
	TFEQ_UE															0,47	0,07	0,03	0,11
	TEFQ_EE																0	-0,02	0,06
	TCI_NS																	0,01	-0,03
	DDT_Geomean																		0

Abbreviations. BMI-z: Body Mass Index z-score; WC: Waist Circumference; SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure; HbA1c: Glycated Hemoglobin; TC: Total Cholesterol; HDL-c: High-Density Lipoprotein cholesterol; LDL-c: Low-Density Lipoprotein cholesterol; TG: Triglycerides; Vocabulary_ss: WAIS-III/WISC Vocabulary subtest scalar score; Stroop_INT: Stroop Color and Word Test_Interference score; TFEQ_UE: Three-Factor Eating Questionnaire-R18_Uncontrolled Eating; TFEQ_EE: Three-Factor Eating Questionnaire-R18_Emotional Eating; TCI_NS: Temperament Character Inventory Revised_Novelty seeking subscale; CPT_CE: Conner's Continuous Performance Test-II_Commission errors; WCST_PE: Wisconsin Card Sorting Test_Perseverative errors; DDT_Geomean: Kirby Delay Discounting Task_Geometric mean.

Significant correlations
P<0.05* P<0.01** P<0.001***

Table S4. Bivariate correlations between cardiometabolic, FA and MD measures (n = 56).

		Cardiometabolic measures										FA					MD				
		BMI-z	WC	SBP	DBP	HbA1c	Glucose	TC	HDL-c	LDL-c	TG (log)	CR	CINGULUM	IFOF	CC	INT CAPSULE	CR	CINGULUM	IFOF	CC	INT CAPSULE
Cardiometabolic measures	AGE	0,2	0,45***	0,48***	0,5***	0,08	-0,12	-0,13	-0,21	-0,11	0,27*	0,07	0,42**	0,28*	-0,06	0,37**	-0,25	-0,4**	-0,3*	-0,18	-0,3*
	BMI-z		0,88***	0,34**	0,35**	0,07	0,34**	-0,06	-0,51***	0,08	0,38**	-0,05	-0,03	0	-0,12	0,03	0,05	-0,15	0,03	0,04	-0,08
	WC			0,46***	0,48***	0,05	0,38**	-0,01	-0,5***	0,11	0,43***	-0,02	0,1	0,12	-0,15	0,16	-0,08	-0,22	-0,08	-0,03	-0,13
	SBP				0,79***	-0,08	0,26	0,17	-0,18	0,15	0,45***	0,26	0,31*	0,34*	0,12	0,42**	-0,3*	-0,26	-0,24	-0,19	-0,22
	DBP					-0,01	0,23	0,15	-0,19	0,1	0,57***	0,25	0,34**	0,33*	0,11	0,35**	-0,27*	-0,37**	-0,22	-0,19	-0,22
	HbA1c						0,2	-0,1	-0,07	-0,11	0,06	-0,38**	-0,29*	-0,37**	-0,34**	-0,28*	0,27*	0,13	0,21	0,26	0,24
	Glucose							0,01	-0,22	0,05	0,19	-0,17	-0,09	-0,15	-0,18	-0,2	0,19	0,06	0,15	0,12	0,11
	TC								0,4**	0,9***	0,28*	0,13	0,12	0,18	0,04	0,19	-0,2	-0,03	-0,08	-0,16	-0,04
	HDL-c									0,08	-0,48***	-0,07	-0,15	-0,14	-0,09	0,01	0,04	0,22	0,14	0,01	0,09
	LDL-c										0,24	0,16	0,16	0,21	0,03	0,15	-0,19	-0,09	-0,09	-0,16	-0,04
	TG (log)											0,12	0,22	0,25	0,14	0,21	-0,23	-0,23	-0,27*	-0,15	-0,14
FA	CR												0,49***	0,78***	0,66***	0,75***	-0,78***	-0,46***	-0,67***	-0,72***	-0,68***
	CINGULUM													0,7***	0,41**	0,73***	-0,49***	-0,83***	-0,52***	-0,48***	-0,63***
	IFOF														0,7***	0,79***	-0,78***	-0,59***	-0,76***	-0,69***	-0,68***
	CC															0,49***	-0,51***	-0,32*	-0,49***	-0,55***	-0,43**
	INT CAPSULE																-0,75***	-0,7***	-0,67***	-0,64***	-0,8***
MD	CR																	0,54***	0,87***	0,89***	0,82***
	CINGULUM																		0,6***	0,58***	0,76***
	IFOF																			0,81***	0,77***
	CC																				0,84***
	INT CAPSULE																				

Abbreviations. BMI-z: Body Mass Index z-score; WC: Waist Circumference; SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure; HbA1c: Glycated Hemoglobin; TC: Total Cholesterol; HDL-c: High-Density Lipoprotein cholesterol; LDL-c: Low-Density Lipoprotein cholesterol; TG: Triglycerides; CC: Corpous callosum; CR: Corona radiata; INT CAPSULE: Internal capsule; IFOF: inferior fronto-occipital fasciculus.

Significant correlations
P<0.05* P<0.01** P<0.001***

Study 3

Received: 28 February 2024 | Revised: 3 April 2024 | Accepted: 15 April 2024

DOI: 10.1002/ajhb.24089

ORIGINAL ARTICLE

American Journal of Human Biology WILEY

Allostatic load, adverse childhood experiences, executive functions, and BMI status in adolescents and young adults

Anna Prunell-Castañé[1,2,3] | **Maite Garolera**[4,5] | **Jonatan Ottino-González**[6] | **María Ángeles Jurado**[1,2,3]

[1]Departament de Psicologia Clínica i Psicobiologia, Facultat de Psicologia, Universitat de Barcelona, Barcelona, Spain

[2]Institut de Neurociències, Universitat de Barcelona, Barcelona, Spain

[3]Institut de Recerca Sant Joan de Déu, Esplugues de Llobregat, Barcelona, Spain

[4]Brain, Cognition and Behavior: Clinical Research, Hospital de Terrassa, Barcelona, Spain

[5]Neuropsychology Unit, Hospital de Terrassa, Barcelona, Spain

[6]Department of Endocrinology, Children's Hospital Los Angeles, Los Angeles, California, USA

Correspondence

Maite Garolera, Neuropsychology Unit. Brain, Cognition, and Behavior: Clinical Research, Hospital de Terrassa, Ctra. Torrebonica s/n, 08227 Terrassa, Barcelona, Spain.
Email: mgarolera@cst.cat

María Ángeles Jurado, Institut de Neurociències, Departament de Psicologia clínica i Psicobiologia, Facultat de Psicologia, Universitat de Barcelona, Passeig de la Vall d'Hebron 171, 08035 Barcelona, Spain.
Email: majurado@ub.edu

Funding information

Ministerio de Economía y Competitividad; Ministerio de Ciencia, Innovación y Universidades; Departament d'Innovació, Universitats i Empresa, Generalitat de Catalunya

Abstract

Objectives: Chronic stress induces preclinical changes in the metabolic, cardiovascular, and immune systems. This phenomenon, known as allostatic load (AL), can impair executive functions (EF), which may be even more affected in individuals with excess weight due to their characteristic inflammatory state and cardiometabolic changes. Adverse childhood experiences (ACEs) contribute to AL and may influence executive functioning presumably via alterations within the hypothalamic–pituitary axis, including epigenetic modifications. We assess the relationship between AL and EF in youth with and without excess weight, and the effect ACEs on executive functioning.

Methods: One hundred eighty-two adolescents and young adults (85 with normal weight and 97 with overweight/obesity; 10–21 years) were recruited. The estimated AL index included the following: systolic and diastolic blood pressure, glycated hemoglobin, high- and low-density lipoprotein cholesterol, triglycerides, high-sensitivity C-reactive protein, fibrinogen, and cortisol. ACEs were measured using the Juvenile Victimization Questionnaire. The neuropsychological evaluation included the assessment of inhibition, working memory, and cognitive flexibility processes.

Results: AL was not significantly associated with executive functioning, and this relationship did not depend on body-weight status. ACEs, available for 57 of 182 participants, were significantly associated with poorer executive functioning.

Conclusions: Our study shows that AL is not associated with executive functioning in adolescents and young adults. Since the current sample was young, we hypothesize that a longer exposure to AL might be required for its negative effects to surface. Nevertheless, exposure to early adversity seems to be associated with poorer executive functioning in youth.

1 | INTRODUCTION

Stress involves allostasis, a complex process where the organism initiates physiological multisystemic adaptations to overcome a challenging scenario and return to a new stable state. When the brain interprets a situation as a threat, primary mediators in the form of neuroendocrine responses prepare the organism for a fight-or-flight response. Such adaptations are necessary to maintain stability through adversity but, when facing long-term stress, secondary outcomes take place as preclinical variations in metabolic, cardiovascular, and immune systems. This preclinical state is known as allostatic load (AL) and, if sustained over time, tertiary outcomes—clinical disorders—can arise (Juster et al., 2010).

Throughout adolescence, there is an increased sensitivity to stress and a change in the biological responses to stress, making this period particularly vulnerable to its effects (Whelan et al., 2021). For example, the prefrontal cortex (PFC) is richer in cortisol receptors during this time of development, making it more susceptible to the neurocognitive consequences of stress (Tottenham & Galván, 2016). The PFC includes brain regions that support executive functions (EF), namely inhibition, cognitive flexibility, and working memory, key functions that collectively facilitate the achievement of goals (Diamond, 2013). Cognitive dysfunction is known to be one of the tertiary outcomes of AL (Juster et al., 2010), and a recent meta-analysis in adults suggested that higher AL values were associated with poorer EF (D'Amico et al., 2020).

Chronic stress can be triggered by multiple reasons but here we focus on excess weight and early life adversity. Excess weight has been broadly related to states of low-grade chronic inflammation and cardiometabolic alterations that can not only initiate or add up to the effects of AL (Suvarna et al., 2020) but also hinder executive functioning (Farruggia & Small, 2019). Similarly, the accumulation of adverse childhood experiences (ACEs) across childhood can trigger adaptative multisystemic responses that may in turn have long-lasting effects on cognition among children (Guinosso et al., 2016) and adults (Hawkins et al., 2021). Moreover, the nature of the ACEs has also been described as a possible contributor to cognitive dysfunction (McLaughlin et al., 2014).

To the best of our knowledge, although previous works have explored the association between AL and EF in adult populations (D'Amico et al., 2020), none have focused on adolescents and young adults. Moreover, given that the literature suggests a relationship between body mass index (BMI) and AL in pediatric and adult samples (Cedillo et al., 2019; Suvarna et al., 2020), we explore whether the association between AL and EF might be different according to the BMI group. This has already been done in adult samples (Ottino-González et al., 2019), but not in adolescents. On the other hand, ACEs are strongly associated with psychopathology, and psychopathology affects cognitive functioning. Therefore, studying the extent to which ACEs affect EF in a sample without mental health diagnoses may help to disentangle this relationship without the influence of such an important confounder.

Thus, the present study fills a gap in the literature by evaluating, in adolescents and young adults, the relationship between (i) AL and EF, and (ii) AL and EF according to BMI. Additionally, we assessed how (iii) ACEs—from infancy to adolescence—as a form of chronic stress may affect EF. We hypothesized that (i) a higher AL index will be related to lower EF, (ii) and that this relationship will be stronger in participants with overweight/obesity. Also, we hypothesize that (iii) higher ACEs will be associated with poorer EF.

2 | MATERIALS AND METHODS

Recruitment and data collection took place between 2010 and 2022 and included three different protocols. Potential candidates ($n = 205$) underwent a medical evaluation and a blood draw either in person at the Hospital de Terrassa-Consorci Sanitari de Terrassa or at home due to the SARS-CoV-2 outbreak. The pubertal stage was determined in this visit according to the Tanner scale of sexual maturity. A neuropsychological evaluation, either in-person or online, was completed in a second visit. The inclusion criterion was being aged between 10 and 21 years old. Exclusion criteria were having (i) underweight, (ii) high sensitivity C-reactive protein (hs-CRP) >10 mg/L as a likely indicator of acute infection (Pearson et al., 2003), (iii) psychiatric, neurological, developmental, cardiometabolic, or systemic diagnosis, (iv) global cognitive impairment, or (v) bulimia-like behaviors. Exclusion criteria application led to a final sample size of 182. Most participants self-identified as White and Spaniard ($n = 170$). Ten participants self-identified as Latino, and two participants did not report their race or ethnicity. The socioeconomic status, assessed by monthly family income, was only available for 96 participants. From the sample used in this study, some participants were already included in previous works (Prunell-Castañé, Beyer, et al., 2023; Prunell-Castañé, Jurado, et al., 2023).

This study was approved by the Institutional Ethics Committee of the University of Barcelona (Institutional Review Board IRB00003099, assurance number FWA00004225). The research was conducted by the

Helsinki Declaration. Written informed consent was obtained from all participants, or their legal guardians in underage participants before they entered into the study.

2.1 | Anthropometric measurement

Participants wore light clothing and no shoes for height and weight measurments. BMI was calculated as kilogram per square meter and transformed into BMI *z*-scores (BMIz) after CDC growth charts with the R package *cdcanthro*. Since BMIz can be calculated for participants up to 20 years, the BMIz for participants aged 20 and 21 years was calculated as if they were 19 years and 11 months (Must & Anderson, 2006). We classified participants as normal weight or overweight/obesity using the BMI cutoffs from Cole and Lobstein (2012) for underage participants, and the 25 kg/m^2 BMI cutoff from the World Health Organization (2021) for participants aged 18–21 years.

2.2 | AL index

The AL index included nine biomarkers representing cardiovascular (systolic blood pressure and diastolic blood pressure), metabolic (glycated hemoglobin, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and triglycerides), immune (hs-CRP and fibrinogen), and neuroendocrine (cortisol) systems. Supplementary material S1 provides information on how the concentrations of hs-CRP, fibrinogen, and cortisol were determined. Anthropometric measures are usually included in the calculation of AL (Whelan et al., 2021). However, we aimed to assess differences in AL between BMI groups. Therefore, including anthropometric measurements in the AL index would be a circular analysis, since they strongly correlate with BMI. Given this, we did not consider anthropometric measurements in the AL calculation but rather included other biomarkers that broadly represent the metabolic system.

We used two different methods to calculate the AL index. Although the high-risk percentile is the most used in the literature, we additionally calculated the AL as a composite *z*-score, as it uses the full continuum of data (Carbone et al., 2022). For both methods, a prorated AL index was computed in participants with missing values. Supplementary material provides a more thorough explanation of both methods.

- In the first method, the AL index was the sum of all nine biomarkers' dichotomous scores, that is, each participant surpassing the biomarker's high-risk percentile scored 1 on that biomarker (i.e., ≥75th or ≤25th in the case of HDL cholesterol). The sum of all biomarkers constituted the AL index (range 0–9), with higher scores meaning higher AL. Cutoff scores were based on the normal weight group ($n = 85$) to prevent setting the thresholds too high by including participants with overweight/obesity, as these are more likely to have higher values in all biomarkers (Ottino-González et al., 2017). Additionally, we set different cutoffs for males and females (Kerr et al., 2020), and for the time of blood draw (morning or afternoon) in biomarkers that presented statistical differences ($p < .05$). Table 1 shows the cutoff points for all biomarkers.
- In the second method, all biomarkers were *z*-scaled and added into a composite with greater scores meaning higher AL. The HDL *z*-score was reverse-scored so that higher values reflected greater alteration. Additionally, we adjusted the AL composite score to sex and blood draw daytime. To do so, we used the standardized residuals of the linear regression: AL composite score ∼ sex + blood draw daytime.

2.3 | Neuropsychological assessment

The neuropsychological assessment included in-person and online evaluation of EF and ACEs. A more detailed description of these assessments can be found in Supplementary Material. Working memory was assessed using the Letter–Number Sequencing scalar score of the WAIS-III/WISC-IV (Wechsler, 2002, 2007). Inhibition was evaluated using the Stroop color and word test interference score (Golden, 1995). Cognitive flexibility was assessed using the perseverative raw errors from the computerized version of the Wisconsin Card Sorting Test (Heaton, 1999). We additionally calculated a composite to assess EF globally. Higher scores in working memory, inhibition, and EF composite, and lower scores in cognitive flexibility indicated better performance.

Furthermore, the Juvenile Victimization Questionnaire (Pereda et al., 2014) was used to assess ACEs exposure among participants. It is a self-reported questionnaire translated into Spanish and validated in the Spanish population that focuses on six types of victimization from infancy to adolescence: conventional crimes, caregiver victimization, peer and sibling victimization, sexual victimization, witnessing and indirect victimization, and electronic victimization. Higher scores were indicative of higher victimization. Only participants of the third protocol ($n = 57$) received this questionnaire.

TABLE 1 Allostatic load cutoff points for the high-risk percentile calculation method.

	Females			Males		
	Both	Morning	Afternoon	Both	Morning	Afternoon
Diastolic blood pressure (mmHg)	-	65.75	75.5	72.75	-	-
Systolic blood pressure (mmHg)	112.5	-	-	124.5	-	-
Glycated hemoglobin (%)	-	5.17	5.4	-	5.3	5.37
HDL (mmol/L)	1.42	-	-	1.3	-	-
LDL (mmol/L)	2.6	-	-	-	2.5	2.05
Triglycerides (mmol/L)	0.865	-	-	0.95	-	-
hs-CRP (mg/L)	0.775	-	-	0.9	-	-
Cortisol (nmol/L)	-	642.82	213.5	-	470.7	250
Fibrinogen (g/L)	3.72	-	-	-	3.25	3.83

Abbreviations: HDL: high-density lipoprotein cholesterol; hs-CRP: high-sensitivity C-reactive protein; LDL: low-density lipoprotein cholesterol.

2.4 | Statistical analysis

The analytical plan of this paper was preregistered in Open Science Framework (osf.io/37t2e). Data manipulation and statistical procedures were performed in R (v.4.0.5) and RStudio (v.2022.02.3). Independent sample *T*-tests, Mann–Whitney *U* tests, and Chi-squared tests were used to analyze between-group differences in sample characteristics. We assessed potential differences in cognitive variables in participants who underwent the neuropsychological assessment in-person versus online, as well as the interaction of confounding variables such as age, sex, and BMI group with the modality of evaluation (see Table S1). Regarding ACEs, we compared the estimated prevalence of juvenile victimization in Spain with our data. The following methods were used for both AL index calculations (sum of the high-risk percentile of the sample distribution and composite mean z-score):

- Semi-partial correlations in the entire sample ($n = 182$) were conducted between AL and EF (*ppcor* package, v.1.1). We controlled EF for age, sex, BMI*z*, and estimated intelligence (WAIS-III/WISC-IV Vocabulary subtest scalar score). Then, to further assess the effect of BMI on the relationship among AL and EF, we repeated the analysis stratifying our data into two BMI groups (normal weight and overweight/obesity) while still adjusting EF for age, sex and estimated intelligence. The resulting *p*-values from multiple tests were adjusted with a false discovery rate (FDR). FDR-corrected *p*-values <0.05 were considered significant. For the group-specific correlations, we assessed whether the correlation coefficients were different between BMI groups (*cocor* package, v.1.1.4).
- Using a subsample of $n = 57$, multiple regression determined how ACEs predicted EF. Age, sex, BMIz, and estimated intelligence were included as nuisance covariates. Multiple testing was controlled by FDR correction. Mediation analysis, as specified in the preregistered analytical plan, could not be performed due to the lack of association between ACEs (X) and AL (mediator).

We examined descriptive characteristic differences between the whole sample and the subsample. Additionally, we performed a sensitivity analysis excluding prepubescent participants.

3 | RESULTS

3.1 | AL index, EF, and BMI

Groups did not differ for sex, age, anxiety/depression symptoms, or monthly family income ($p > .05$). As expected, the overweight/obesity group had higher AL index (Figure 1). Also, the overweight/obesity group performed worse in the overall assessment of EF. Table 2 provides descriptive characteristics for BMI groups.

Using both AL indexes and after FDR correction, semi-partial correlations did not reveal a significant association between AL and any EF, including its composite, either for the whole sample or at the BMI group-specific level. At an uncorrected level, the semi-partial correlation between cognitive flexibility and the AL composite score was significant for the overweight/obesity group ($sr = 0.21$, $p = .04$). Semi-partial correlation coefficients were also not different between groups (Table 3).

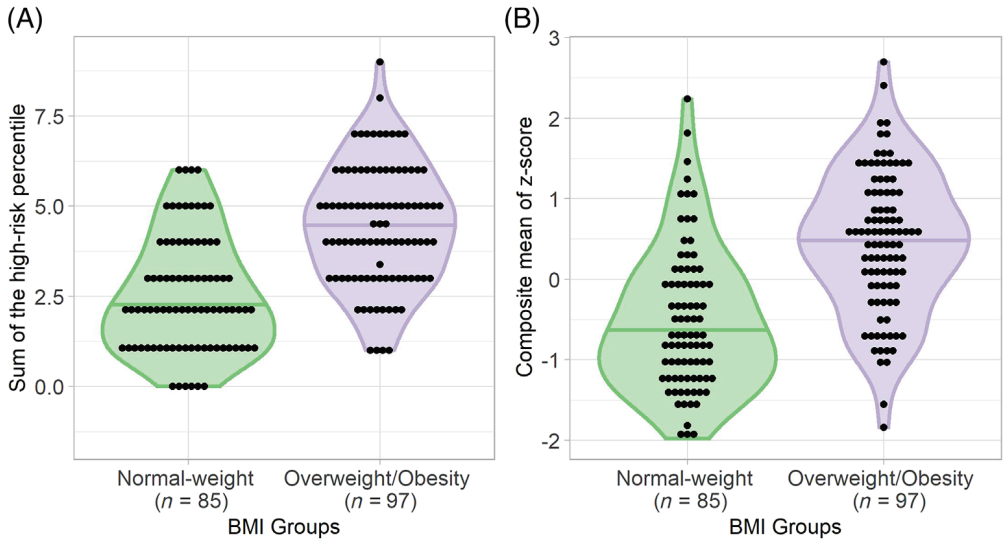


FIGURE 1 Allostatic load (AL) indexes (A: AL composite mean of *z*-score, B: AL high-risk percentile sum) comparison between body mass index (BMI) groups.

TABLE 2 Sample descriptive characteristics.

	NW ($n = 85$)		OW/OB ($n = 97$)			
	Mean (SD)	**Range**	**Mean (SD)**	**Range**	**Test statistic**	***p* value**
Age (years)	15.8 (2.92)	10, 21	15.06 (2.43)	10, 21	$W = 4674$	0.12
Sex (*n* females, %)	43 (50.6%)	-	46 (47.42%)	-	$\chi^2 = 0.07$	0.78
Prepubescents (*n*, %)	6 (7%)	-	4 (4.12%)	-	$\chi^2 = 0.29$	0.59
Monthly family income (€)						
300–899 (*n*, %)	4 (4.7%)	-	3 (3.1%)	-	$\chi^2 = 1.79$	0.77
900–1499 (*n*, %)	9 (10.59%)	-	9 (9.28%)	-		
1500–2099 (*n*, %)	16 (18.82%)	-	10 (10.31%)	-		
2100–2699 (*n*, %)	8 (9.41%)	-	11 (11.34%)	-		
≥2700 (*n*, %)	14 (16.48%)	-	12 (12.36%)	-		
N.A. (*n*, %)	34 (40%)	-	52 (53.61%)	-		
BMI *z*-score	−0.07 (0.62)	−1.76, 0.82	1.81 (0.42)	0.95, 3.02	$W = 0$	<0.001
AL index high-risk percentile	2.47 (1.6)	0, 6	4.43 (1.67)	1, 9	$W = 1690$	<0.001
AL index composite score	−0.53 (0.88)	−1.97, 2.24	0.46 (0.87)	−1.84, 2.7	$W = 1704$	<0.001
HADS anxiety	4.83 (2.55)	0, 10	4.54 (2.72)	0, 10	$W = 4390$	0.45
HADS depression	1.98 (1.75)	0, 6	2.49 (2.27)	0, 9	$W = 3688$	0.21
Estimated intelligence	11.26 (2.32)	7, 19	10.82 (2.37)	7, 19	$W = 4546$	0.23
Working memory	11.63 (2.42)	5, 17	10.94 (2.7)	5, 18	$T = 1.83$	0.07
Cognitive Flexibility	14.87 (10.91)	4, 51	16.05 (12.01)	4, 65	$W = 3797$	0.43
Inhibition	4.75 (6.54)	−9.7, 23.5	3.77 (7.06)	−16.9, 22.75	$W = 4340$	0.54
EF composite	0.09 (0.66)	−2.02, 1.88	−0.08 (0.66)	−1.87, 1.43	$W = 4939$	0.02

Note: We provide mean (SD) and range for numerical variables, and n counts (%) for categorical variables (sex, prepubescents, monthly family income). Estimated intelligence was assessed by the Weschler Adults Intelligence Scale-III/Weschler Intelligence Scale for Children-IV (WAIS-III/WISC-IV) vocabulary subtest scalar score. Working memory was assessed using the Letter-Number Sequencing scalar score of the WAIS-III/WISC-IV. Cognitive flexibility was assessed by the Wisconsin Card Sorting Test perseverative raw errors. Inhibition was assessed by the Stroop Test Interference score.
Abbreviations: AL, allostatic load; BMI, body mass index; EF, executive functions; HADS, hospital anxiety and depression scale; NA, not available; NW, normal weight; OW/OB, overweight/obesity.

TABLE 3 Spearman's semi-partial correlation estimates between executive functions and allostatic load (AL) index using two AL index calculations.

		AL high-risk percentile		AL composite mean of z-score	
		Spearman semi-partial correlation estimate (sr)	sr comparison between BMI groups	Spearman semi-partial correlation estimate (sr)	sr comparison between BMI groups
Working memory	Whole sample	−0.03	-	0.001	-
	NW group	0.03	$Z = 0.49$ $p = 0.62$	−0.005	$Z = -0.16$ $p = 0.87$
	OW/OB group	−0.04		0.02	
Cognitive Flexibility	Whole sample	0.07	-	0.1	-
	NW group	0.04	$Z = -0.71$ $p = 0.47$	0.08	$Z = -0.86$ $p = 0.39$
	OW/OB group	0.14		0.21*	
Inhibition	Whole sample	−0.004	-	0.01	-
	NW group	−0.02	$Z = -0.45$ $p = 0.65$	−0.004	$Z = -0.34$ $p = 0.74$
	OW/OB group	0.05		0.05	
EF Composite	Whole sample	−0.07	-	−0.08	-
	NW group	−0.007	$Z = 0.88$ $p = 0.38$	−0.04	$Z = 0.69$ $p = 0.48$
	OW/OB group	−0.14		−0.15	

Note: All FDR-corrected p-values of the *sr* estimates were >0.05.

Abbreviations: AL, allostatic load; BMI, body mass index; EF, executive functions; NW, normal weight; OW/OB, overweight/obesity.

*Significant at an uncorrected level ($p = 0.04$).

Sensitivity analyses without prepubescent participants provided similar results (Table S2).

3.2 | ACEs and EF

The descriptive characteristics of the subsample ($n = 57$, Table S3) were not statistically different from the whole sample ($n = 182$). There were no differences in the prevalence of ACEs between the study by Pereda et al. (2014) and our study (Table S4).

Multiple regression analyses (Table 4) indicated that higher ACEs were associated with worse performance in cognitive flexibility ($b = 0.07$, $p_{\text{b-value}} = 0.0009$, Adj $R^2 = 0.26$, $\text{FDR}_{\text{model}} = 0.003$) and the overall EF ($b = -0.09$, $\text{P}_{\text{b-value}} = 0.0005$, Adj $R^2 = 0.2$, $\text{FDR}_{\text{model}} = 0.01$). Although higher ACEs were associated with poorer inhibitory control ($b = -0.66$, $p_{\text{b-value}} = 0.02$), the model only reached significance at a trend level (Adj $\text{R}^2 = 0.1$, $\text{FDR}_{\text{model}} = 0.09$). Working memory was not associated with ACEs. Moreover, age was significantly associated with cognitive flexibility, inhibitory control, and overall EF ($p_{\text{b-values}} < 0.05$). Sensitivity analyses without prepubescent participants ($n = 50$) provided similar results (Table S5).

4 | DISCUSSION

In this preregistered study, we evaluated the relationship between EF and AL in adolescents and young adults, and how this relationship might differ according to BMI status. Furthermore, we studied the effect of ACEs on EF. Importantly, our approach included two different calculations of the AL index. As highlighted in a recent review (Carbone et al., 2022), the sum of the high-risk percentiles of the sample distribution is the most commonly used method in the literature, whereas composite mean z-scores permits using the full continuum of data. Here, regardless of the method chosen, adolescents and young adults with overweight/obesity exhibited greater levels of AL. This is not an unexpected result, as BMI or

TABLE 4 Multiple regression coefficients for the working memory, cognitive flexibility, inhibition, and executive functions composite models.

	Predictors							
Variable of interest		**ACEs**	**Sex**	**BMIz**	**Age**	**Intelligence**	**Adj R^2**	**FDR**
Working memory	*b*	−0.22	−0.72	−0.34	0.19	0.05	0.002	0.41
	95% CI	−0.44, 0.006	−2.32, 0.92	−1.11, 0.43	−0.12, 0.5	−0.27, 0.38		
	p	0.06	0.38	0.38	0.22	0.75		
Cognitive flexibility	*b*	0.07	−0.05	−0.11	−0.12	0.01	0.26	0.003
	95% CI	0.03, 0.11	−0.35, 0.24	−0.25, 0.03	−0.17, −0.06	−0.05, 0.07		
	p	0.0009	0.72	0.11	0.00008	0.72		
Inhibition	*b*	−0.66	1.53	−0.23	0.86	0.12	0.1	0.09
	95% CI	−1.18, −0.13	−2.34, 5.4	−2.05, 1.58	0.12, 1.59	−0.64, 0.88		
	p	0.02	0.43	0.8	0.02	0.75		
EF composite	*b*	−0.09	−0.02	−0.01	0.11	0.01	0.2	0.01
	95% CI	−0.14, −0.04	−0.37, 0.34	−0.18, 0.15	0.04, 0.18	−0.06, 0.08		
	p	0.0005	0.92	0.85	0.002	0.76		

Note: Working memory was assessed using the Letter-Number Sequencing scalar score of the Weschler Adults Intelligence Scale-III/Weschler Intelligence Scale for Children-IV (WAIS-III/WISC-IV). Inhibition was assessed with the Stroop Test Interference score. Cognitive flexibility was assessed using the Wisconsin Card Sorting Test perseverative raw errors, which was transformed into its logarithmic form. Adverse childhood experiences were assessed with the Juvenile Victimization Questionnaire. Estimated intelligence was assessed with the Vocabulary scalar score of the WAIS-III/WISC-IV. Unstandardized betas were reported.

Abbreviations: ACEs: adverse childhood experiences; AL: allostatic load; BMIz: body mass index *z*-score; EF: executive functions; FDR: false discovery rate; Intelligence: estimated intelligence.

other measures of adiposity are almost universally included in estimated AL indices. Also, adolescents and young adults with overweight/obesity performed worse in EF. However, the relationship between AL and EF was not significant either for the whole sample (irrespective of BMI) or when assessing BMI groups separately. Interestingly, we found that higher exposure to ACEs was associated with poorer EF.

4.1 | Executive functioning, AL, and BMI

Cognition is known to be sensitive to physiological dysregulations (Juster et al., 2010), such as AL or obesity. Concerning AL, a meta-analysis—with samples formed mostly by senior participants—reported that poorer EF were related to a higher AL (D'Amico et al., 2020). Consistently, a recent study with adults (Beydoun et al., 2023) described an association between worse EF and higher AL. Interestingly, and despite all the evidence for the existing relationship between EF and AL in adults, we did not find significant results in adolescents and young adults. Given that the AL model suggests that the physiological burden and disease states of chronic stress exposure accumulate over time, we speculate that adolescents and young adults may not have had sufficient exposure to the effects of AL. Notably, we found an association at the trend level between poorer cognitive flexibility and higher AL composite scores, but only in participants with overweight/obesity. Previous research has reported a relationship between AL and BMI in children and adolescents (Calcaterra et al., 2019), and concluded that there is a cumulative physiological dysregulation in higher BMI categories. Furthermore, a recent study suggested that BMI might be one of the earliest signs of increased AL in adolescents (King et al., 2019). Thus, it is conceivable that excess weight, which has also been consistently associated with poorer EF regardless of age (Yang et al., 2018), could potentiate physiological stress status (i.e., low-grade inflammation and cardiometabolic changes) and favor its consequences.

4.2 | ACEs and executive functioning

Exposure to ACEs can cause health consequences not only within the vulnerable developmental window they occur but also into adulthood (Finlay et al., 2022). Here, we found that ACEs were associated with worse EF in adolescents and young adults, as reported elsewhere (Johnson et al., 2021; Li et al., 2013; Lund et al., 2020).

Theoretically, exposure to ACEs could generate epigenetic modifications (Juster et al., 2016) and alterations in the activity of the hypothalamic–pituitary–adrenal axis (responsible for mobilizing the primary mediators of AL), subsequently inducing changes in the PFC and in the development of EF (Lund et al., 2020). Additionally, the timing, duration, type, and severity of the ACEs might influence the emergence of cognitive dysregulations (De Bellis & Zisk, 2014). In our study, the results of the multiple regression analysis showed that age was positively associated with EF, which is consistent with the ongoing maturation of the PFC observed during adolescence (Tervo-Clemmens et al., 2023). However, these age-related increases in cognitive performance may not be sufficient to compensate for the detrimental effects of ACEs, whose exposure also increases with age (see Figure S1). Moreover, individuals who have survived more severe forms of ACEs might display greater cognitive changes. Individual characteristics, such as resilience and vulnerability, might also shape psychological responses to ACEs. A recent study with adults (D'Amico et al., 2022) reported that AL mediated the relationship between ACEs and cognitive function. Given that we could not perform mediation analysis, future studies should replicate these results in adolescent and young adult samples.

4.3 | Strengths and limitations

Strengths of our study include its preregistration, using two methods to calculate the AL index to ensure that the results were not driven by a specific calculation method, and controlling for sex differences in the AL index calculation. Moreover, other than overweight/obesity, our sample did not have any medical condition (tertiary outcome) that could increase the AL index, or blur whether such condition predated or emerged from allostatic overload. The present study also has limitations. The retrospective and self-report recall of ACEs might diminish their accuracy. The tests chosen for neuropsychological assessment may not be sensitive enough to detect differences in young and predominantly healthy samples. Socioeconomic status, which is associated with EF (Lawson et al., 2018), was not included as a confounding variable due to a large proportion of missing values. Also, 95% of the sample identified themselves as White, a race that does not experience certain adverse events such as racism and is less likely to suffer from poverty. These two dimensions—poverty and racism—are known to be related to higher AL (Miller et al., 2021; Thomas Tobin & Hargrove, 2022). Given this, future studies with a more diverse sample size are needed to confirm our results and to evaluate potential differences in the relationship between AL and EF in adolescents and young adults according to weight status and psychosocial risk exposure.

5 | CONCLUSIONS

We provide evidence that, in adolescents and young adults, overweight/obesity is associated with higher levels of AL and worse executive functioning. However, we did not find AL to be related to EF either for the whole sample or when assessing BMI groups separately. We hypothesize that the AL burden might affect cognition only if sustained over time. Still, we found that exposure to ACEs was associated with poorer executive functioning. This could be taken to suggest that exposure to early chronic psychological stress is related to dysregulations that might detriment cognitive functions.

AUTHOR CONTRIBUTIONS

Anna Prunell-Castañé: Investigation, Conceptualization, Formal analysis, Writing—Original Draft; **Maite Garolera**: Conceptualization, Writing—review & editing, Funding acquisition; **Jonatan Ottino-González**: Investigation, Writing—review & editing; **María Ángeles Jurado**: Conceptualization, Writing—review & editing, Funding acquisition.

ACKNOWLEDGMENTS

The authors thank Neus Cano Marco for her support. The authors also thank all the participants that made this project possible. We acknowledge the Institute of Neurosciences, the Consorci Sanitari de Terrassa, and the Hospital de Terrassa. We also acknowledge the following funding sources, which were not involved in the study conceptualization, interpretation, or writing: APC received a Ph.D. scholarship from the Spanish Ministry of Science, Innovation, and Universities (PRE2019-087430). MAJ and MG received Grants from the Spanish Ministry of Economy, Industry, and Competitiveness (PSI2017- 86536-C2-1-R and PSI2017-86536-C2-2-R, respectively), funded by MCIN/AEI/ https://doi.org/10.13039/501100011033 and the European Regional Development Fund (ERDF). MAJ, MG, and APC have additionally received funding from the Departament d'Innovació, Universitats i Empresa, Generalitat de Catalunya (2021SGR0801).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Anna Prunell-Castañé https://orcid.org/0000-0001-8565-0966
Maite Garolera https://orcid.org/0000-0001-7443-8249
Jonatan Ottino-González https://orcid.org/0000-0003-2910-9926
María Ángeles Jurado https://orcid.org/0000-0002-9403-1670

REFERENCES

Beydoun, H. A., Beydoun, M. A., Maldonado, A. I., Fanelli-Kuczmarski, M. T., Weiss, J., Evans, M. K., & Zonderman, A. B. (2023). Allostatic load and cognitive function among urban adults in the healthy aging in neighborhoods of diversity across the life span study. *Journal of Alzheimer's Disease*, *92*(2), 425–443. https://doi.org/10.3233/JAD-220888

Calcaterra, V., Vinci, F., Casari, G., Pelizzo, G., de Silvestri, A., De Amici, M., Albertini, R., Regalbuto, C., Montalbano, C., Larizza, D., & Cena, H. (2019). Evaluation of allostatic load as a marker of chronic stress in children and the importance of excess weight. *Frontiers in Pediatrics*, *7*, 1–5. https://doi.org/10.3389/fped.2019.00335

Carbone, J. T., Clift, J., & Alexander, N. (2022). Measuring allostatic load: Approaches and limitations to algorithm creation. *Journal of Psychosomatic Research*, *163*, 111050. https://doi.org/10.1016/j.jpsychores.2022.111050

Cedillo, Y. E., Murillo, A. L., & Fernández, J. R. (2019). The association between allostatic load and anthropometric measurements among a multiethnic cohort of children. *Pediatric Obesity*, *14*(6), 1–8. https://doi.org/10.1111/ijpo.12501

Cole, T. J., & Lobstein, T. (2012). Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. *Pediatric Obesity*, *7*, 284–294. https://doi.org/10.1111/j.2047-6310.2012.00064.x

D'Amico, D., Amestoy, M. E., & Fiocco, A. J. (2020). The association between allostatic load and cognitive function: A systematic and meta-analytic review. *Psychoneuroendocrinology*, *121*, 104849. https://doi.org/10.1016/j.psyneuen.2020.104849

D'Amico, D., Amestoy, M. E., & Fiocco, A. J. (2022). The mediating role of allostatic load in the relationship between early life adversity and cognitive function across the adult lifespan. *Psychoneuroendocrinology*, *141*, 105761.

De Bellis, M. D., & Zisk, A. (2014). The biological effects of childhood trauma. *Child and Adolescent Psychiatric Clinics of North America*, *23*(2), 185–222. https://doi.org/10.1016/j.chc.2014.01.002

Diamond, A. (2013). Executive functions. *Annual Review of Psychology*, *64*, 135–168. https://doi.org/10.1146/annurev-psych-113011-143750

Farruggia, M. C., & Small, D. M. (2019). Effects of adiposity and metabolic dysfunction on cognition: A review. *Physiology and Behavior*, *208*, 112578.

Finlay, S., Roth, C., Zimsen, T., Bridson, T. L., Sarnyai, Z., & McDermott, B. (2022). Adverse childhood experiences and allostatic load: A systematic review. *Neuroscience and Biobehavioral Reviews*, *136*, 104605. https://doi.org/10.1016/j.neubiorev.2022.104605

Golden, C. J. (1995). *STROOP, test de colores y palabras*. TEA Ediciones.

Guinosso, S. A., Johnson, S. B., & Riley, A. W. (2016). Multiple adverse experiences and child cognitive development. *Pediatric Research*, *79*(1–2), 220–226. https://doi.org/10.1038/pr.2015.195

Hawkins, M. A. W., Layman, H. M., Ganson, K. T., Tabler, J., Ciciolla, L., Tsotsoros, C. E., & Nagata, J. M. (2021). Adverse childhood events and cognitive function among young adults: Prospective results from the national longitudinal study of adolescent to adult health. *Child Abuse and Neglect*, *115*, 105008. https://doi.org/10.1016/j.chiabu.2021.105008

Heaton, R. K. (1999). *Wisconsin card sorting test: Computer version 4* (Research ed.). Psychological Assessment Resources.

Johnson, D., Policelli, J., Li, M., Dharamsi, A., Hu, Q., Sheridan, M. A., McLaughlin, K. A., & Wade, M. (2021). Associations of early-life threat and deprivation with executive functioning in childhood and adolescence: A systematic review and meta-analysis. *JAMA Pediatrics*, *175*(11), 1–10. https://doi.org/10.1001/jamapediatrics.2021.2511

Juster, R. P., McEwen, B. S., & Lupien, S. J. (2010). Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neuroscience and Biobehavioral Reviews*, *35*(1), 2–16. https://doi.org/10.1016/j.neubiorev.2009.10.002

Juster, R. P., Russell, J. J., Almeida, D., & Picard, M. (2016). Allostatic load and comorbidities: A mitochondrial, epigenetic, and evolutionary perspective. *Development and Psychopathology*, *28*(4), 1117–1146. https://doi.org/10.1017/S0954579416000730

Kerr, P., Kheloui, S., Rossi, M., Désilets, M., & Juster, R. P. (2020). Allostatic load and women's brain health: A systematic review. *Frontiers in Neuroendocrinology*, *59*, 100858. https://doi.org/10.1016/j.yfrne.2020.100858

King, A. L., Garnier-Villarreal, M., Simanek, A. M., & Johnson, N. L. (2019). Testing allostatic load factor structures among adolescents: A structural equation modeling approach. *American Journal of Human Biology*, *31*(4), 1–11. https://doi.org/10.1002/ajhb.23242

Lawson, G. M., Hook, C. J., & Farah, M. J. (2018). A meta-analysis of the relationship between socioeconomic status and executive function performance among children. *Developmental Science*, *21*, e12529. https://doi.org/10.1111/desc.12529

Li, Y., Dong, F., Cao, F., Cui, N., Li, J., & Long, Z. (2013). Polyvictimization and executive functions in junior college students. *Scandinavian Journal of Psychology*, *54*(6), 485–492. https://doi.org/10.1111/sjop.12083

Lund, J. I., Toombs, E., Radford, A., Boles, K., & Mushquash, C. (2020). Adverse childhood experiences and executive function difficulties in children: A systematic review. *Child Abuse and Neglect*, *106*, 104485. https://doi.org/10.1016/j.chiabu.2020.104485

McLaughlin, K. A., Sheridan, M. A., & Lambert, H. K. (2014). Childhood adversity and neural development: Deprivation and threat as distinct dimensions of early experience. *Neuroscience and Biobehavioral Reviews*, *47*, 578–591. https://doi.org/10.1016/j.neubiorev.2014.10.012

Miller, H. N., LaFave, S., Marineau, L., Stephens, J., & Thorpe, R. J. (2021). The impact of discrimination on allostatic load in adults: An integrative review of literature. *Journal of Psychosomatic Research*, *146*, 110434. https://doi.org/10.1016/j.jpsychores.2021.110434

Must, A., & Anderson, S. E. (2006). Body mass index in children and adolescents: Considerations for population-based applications. *International Journal of Obesity*, *30*(4), 590–594. https://doi.org/10.1038/sj.ijo.0803300

Ottino-González, J., Jurado, M. A., García-García, I., Caldú, X., Prats-Soteras, X., Tor, E., Sender-Palacios, M. J., & Garolera, M. (2019). Allostatic load and executive functions in overweight adults. *Psychoneuroendocrinology*, *106*, 165–170. https://doi.org/10.1016/j.psyneuen.2019.04.009

Ottino-González, J., Jurado, M. A., García-García, I., Segura, B., Marqués-Iturria, I., Sender-Palacios, M. J., Tor, E., Prats-Soteras, X., Caldú, X., Junqué, C., & Garolera, M. (2017). Allostatic load is linked to cortical thickness changes depending on body-weight status. *Frontiers in Human Neuroscience*, *11*, 1–11. https://doi.org/10.3389/fnhum.2017.00639

Pearson, T. A., Mensah, G. A., Alexander, R. W., Anderson, J. L., Cannon, R. O., Criqui, M., Fadl, Y. Y., Fortmann, S. P., Hong, Y., Myers, G. L., Rifai, N., SmithJr, S. C., Taubert, K., Tracy, R. P., & Vinicor, F. (2003). Markers of inflammation and cardiovascular disease: Application to clinical and public health practice: A statement for healthcare professionals from the centers for disease control and prevention and the American Heart Association. *Circulation*, *107*(3), 499–511. https://doi.org/10.1161/01.CIR.0000052939.59093.45

Pereda, N., Guilera, G., & Abad, J. (2014). Victimization and polyvictimization of Spanish children and youth: Results from a community sample. *Child Abuse and Neglect*, *38*(4), 640–649. https://doi.org/10.1016/j.chiabu.2014.01.019

Prunell-Castañé, A., Beyer, F., Witte, V., Sánchez Garre, C., Hernán, I., Caldú, X., Jurado, M. Á., & Garolera, M. (2023). From the reward network to whole-brain metrics: Structural connectivity in adolescents and young adults according to body mass index and genetic risk of obesity. *International Journal of Obesity*, *48*, 567–574. https://doi.org/10.1038/s41366-023-01451-w

Prunell-Castañé, A., Jurado, M. Á., Ottino-González, J., Prats-Soteras, X., Sánchez Garre, C., Cano Marco, N., Gómez-Pablos, P. S., García-García, I., & Garolera, M. (2023). Beyond BMI: Cardiometabolic measures as predictors of impulsivity and white matter changes in adolescents. *Brain Structure and Function*, *228*(3), 751–760. https://doi.org/10.1007/s00429-023-02615-0

Suvarna, B., Suvarna, A., Phillips, R., Juster, R. P., McDermott, B., & Sarnyai, Z. (2020). Health risk behaviours and allostatic load: A systematic review. *Neuroscience and Biobehavioral Reviews*, *108*, 694–711. https://doi.org/10.1016/j.neubiorev.2019.12.020

Tervo-Clemmens, B., Calabro, F. J., Parr, A. C., Fedor, J., Foran, W., & Luna, B. (2023). A canonical trajectory of executive function maturation from adolescence to adulthood. *Nature Communications*, *14*(1), 1–17. https://doi.org/10.1038/s41467-023-42540-8

Thomas Tobin, C. S., & Hargrove, T. W. (2022). Race, lifetime SES, and allostatic load among older adults. *Journals of Gerontology: Series A Biological Sciences and Medical Sciences*, *77*(2), 347–356. https://doi.org/10.1093/gerona/glab160

Tottenham, N., & Galván, A. (2016). Stress and the adolescent brain: Amygdala-prefrontal cortex circuitry and ventral striatum as developmental targets. *Neuroscience and Biobehavioral Reviews*, *70*, 217–227. https://doi.org/10.1016/j.neubiorev.2016.07.030

Wechsler, D. (2002). *WAIS III. Escala de Inteligencia de Wechsler para Adultos III*. TEA.

Wechsler, D. (2007). *WISC-IV: Escala de Inteligencia de Wechsler para Niños-IV* (2nd ed.). TEA.

Whelan, E., O'Shea, J., Hunt, E., & Dockray, S. (2021). Evaluating measures of allostatic load in adolescents: A systematic review. *Psychoneuroendocrinology*, *131*, 105324. https://doi.org/10.1016/j.psyneuen.2021.105324

World Health Organization. (2021). Obesity and overweight. Retrieved from. https://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight

Yang, Y., Shields, G. S., Guo, C., & Liu, Y. (2018). Executive function performance in obesity and overweight individuals: A meta-analysis and review. *Neuroscience and Biobehavioral Reviews*, *84*(2), 225–244. https://doi.org/10.1016/j.neubiorev.2017.11.020

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Prunell-Castañé, A., Garolera, M., Ottino-González, J., & Jurado, María Ángeles (2024). Allostatic load, adverse childhood experiences, executive functions, and BMI status in adolescents and young adults. *American Journal of Human Biology*, e24089. https://doi.org/10.1002/ajhb.24089

Supplementary Material Study 3

1. Determination of hs-CRP, fibrinogen, and cortisol concentrations.

Concentrations of hs-CRP, fibrinogen, and cortisol were determined at CatLab (https://www.catlab.cat/en/about-us) through nephelometry (Beckman Coulter Immage 800), PT-derived fibrinogen assay, and electrochemiluminescence (Elecsys Cortisol II), respectively. Three participants did not have the hs-CRP measured and instead had the CRP. We did not exclude these participants from the study (their CRP values were <1mg/L), but, when calculating the AL index, these three CRP values were considered missing. Fibrinogen values (g/L) of 71 participants were quantified with STA-Neoplastin-Plus reactive (STA-Rack) (mean = 3.36, SD = 0.58, range = 2.23 – 5.19), while for the rest of the sample, Recombiplastin 2 G reactive (ACLTOP 700) was used (mean = 3.83, SD = 0.58, range = 2.49 – 6.21). The inter-assay coefficients for STA-Rack and ACLTOP 700 were 6.52% and 3.18%, respectively, and the intra-assay coefficient of variability for ACLTOP 700 was 0.75%. We cannot provide the intra-assay coefficient of STA-Rack because these data are not available.

2. Allostatic load index calculations

For both methods, a prorated AL index was conducted in participants with missing values. The variables with missing values were the following: glycated hemoglobin n = 3, hs-CPR n = 3, cortisol n = 2, and fibrinogen n = 1.

Sum of the high-risk percentile of the sample distribution. The AL index was the sum of all 9 biomarkers' dichotomous scores, with higher scores meaning higher allostatic overload (range 0-9). For every participant, we gave a score of "1" to those biomarkers that were in the high-risk percentile (i.e., ≥75th or ≤25th in the case of HDL-cholesterol), or a "0" to those biomarkers that didn't exceed their cut-off point. Since in our sample we had a large proportion of participants with overweight/obesity, the calculation of the high-risk percentiles was based on the control group (normal weight, n = 85). That is because, although participants with overweight/obesity did not meet diagnostic criteria for cardiometabolic diseases when they were included in the study, they were more likely to have higher values in almost all biomarkers. Additionally, and since there are well-known sex differences in the AL, we set different cut-off points for males (n = 42) and females (n = 43). Given that some participants underwent the sample blood extraction in the morning (n = 28 males, n = 34 females), while others in the afternoon (n = 14 males, n = 9 females), we further set different cut-off points for each daytime in those biomarkers that presented statistical differences ($p < 0.05$). If a participant had missing values, we applied a cross-

multiplication to calculate the proportion of risk biomarkers they would have if all biomarkers were available (e.g., the AL index included 9 biomarkers). If a participant had only available 8 biomarkers and 2 of them were at the high-risk percentile, we calculated the AL index as follows: (9*2)/8 = 2.25).

Composite mean of z-score: All biomarkers were z-scaled and added into a composite with greater scores meaning higher AL (i.e., (Z systolic blood pressure + Z diastolic blood pressure + Z glycated hemoglobin + Z HDL-Cholesterol + Z LDL-Cholesterol + Z triglycerides + Z hs-CRP + Z fibrinogen + Z cortisol)/9). The HDL z-score was reversed so that higher values reflected greater physiological dysregulation. If a participant had missing values, the allostatic index composite was calculated according to the number of available biomarkers (e.g., if a participant had only available 8 out of 9 biomarkers, the composite was calculated as follows: $((Z_1 + Z_2 + Z_3 + Z_4 + Z_5 + Z_6 + Z_7 + Z_8) /8)$. Additionally, we adjusted the AL mean z-score to sex and blood sample extraction daytime. To do so, we used the standardized residuals of AL mean z-score ~ sex + blood extraction daytime.

3. Neuropsychological evaluation

Bulimia-like behaviors: assessed by the Mini International Neuropsychiatric Interview for Bulimia or a score ≥20 in the Bulimia Inventory Test of Edinburgh.

Global cognitive impairment: assessed by a scalar score <7 in the Weschler Adults Intelligence Scale-III/Weschler Intelligence Scale for Children-IV (WAIS-III/WISC-IV) vocabulary subtest.

Working memory was assessed using the Letter-Number Sequencing scalar score of the WAIS-III/WISC-IV. In this task, after listening to a sequence of numbers and letters, participants had to repeat aloud the numbers ordered (from 1 to 10), and then the letters in alphabetical order. A higher scalar score represented better performance in working memory.

Inhibition was evaluated using the Stroop Color and Word Test interference score. In the Stroop test, participants were required to read as fast as possible. In the word-sheet condition (W), they had to read aloud a list of black-inked color names (i.e., red, green, or blue). In the color-sheet condition (C) they were required to name the color (i.e., red, green, or blue) of non-readable stimuli (i.e., "XXXX"). In the incongruent-sheet condition(I), they were required to name the color of the word, which differed from the written name (i.e., "blue" in red ink). The interference score was calculated with the formula: I – [(W x C)/W + C)]. Higher interference values indicated more ability to inhibit automatic responses.

Cognitive flexibility was assessed using the perseverative raw errors from the computerized version of the Wisconsin Card Sorting Test (WCST). In the WCST, participants were asked to match 64 cards based on a principle (i.e., color, shape, or number of elements) that was not explained to them and needed to be learned from the feedback as to whether their responses were correct or incorrect. After ten consecutive hits, the matching rule changed without announcement. Perseverative errors were computed as the number of incorrect responses that would have been correct for the preceding matching rule. Higher perseverative errors reflected worse cognitive flexibility. One participant had a missing value in the WCST. Although in the preregistration we specified that cognitive flexibility would be assessed using both the WCST and the Trail Making Test (TMT), we found statistically significant differences between participants that completed the TMT in person vs. online that could not be explained by confounding variables such as age, sex, or BMI. Thus, we excluded the TMT from the analyses.

EF composite: we additionally calculated a composite to assess EF globally. The composite was calculated as follows: (Z scalar score Letters-Numbers Sequencing + Z Stroop test interference score + Z WCST perseverative errors)/3). The WCST scores were reversed so that higher values reflected better performance. One participant had a missing value in the WCST. In this case, we calculated a prorated EF composite (i.e., Z scalar score Letters-Numbers Sequencing + Z Stroop test interference score/2).

Table S1. Cognitive variables differences according to the method of evaluation (in-person vs. online).

		In-person (n = 135)	Online (n = 47)	Test Statistic	P value
Demographic and anthropometric measures					
Age (years)		15.57 (2.65)	14.94 (2.78)	W = 3475	0.33
Sex (n females, %)		70 (51.85%)	19 (40.42%)	Chi^2 = 1.39	0.24
Overweight/Obesity (n, %)		73 (74.04)	24 (51.06%)	Chi^2 = 0.03	0.85
Neuropsychological evaluation					
Estimated intelligence	WAIS-III/WISC-IV Vocabulary subtest scalar score	11 (2.4)	11.11 (2.24)	W = 3083	0.77
Inhibition	Stroop interference	3.69 (6.71)	5.77 (6.7)	T = -1.78	0.08
Cognitive flexibility	WCST perseverative errors	17.71 (12.17)	9.22 (5.85)	W = 4801	< 0.001
	TMT part B - part A	41.9 (21.75)	53.23 (28.65)	W = 2258	< 0.001
Working memory	WAIS-III/WISC-IV Letter-Number Sequencing scalar score	11.3 (2.56)	11.17 (2.7)	T = 0.28	0.78

We provide mean (sd) for numerical variables, and n counts (%) for categorical variables (sex, overweight/obesity).

Abbreviations: CPT-II: Conners' Continuous Performance Test-II; Stroop: Stroop Color and Word Test; TMT: Trail Making; WAIS-III/WISC-IV: Weschler Adults Intelligence Scale-III/Weschler Intelligence Scale for Children-IV; WCST: Wisconsin Card Sorting Test.

The differences seen in the perseverative errors of the WCST according to the method of evaluation were explained by age (significant interaction between method of evaluation and age (beta = -3.8; 95% CI = -6.6, -0.99; P = 0.008)

Table S2. Spearman's semi-partial correlation estimates between executive functions and allostatic load (AL) index using two AL index calculations (n = 172, prepubescent participants excluded).

		AL high-risk percentile		AL composite mean of z-score	
		Spearman semi-partial correlation estimate (*sr*)	***sr* comparison between BMI groups**	**Spearman semi-partial correlation estimate (*sr*)**	***sr* comparison between BMI groups**
Working memory	**Whole sample**	-0.03	------	-0.01	------
	NW group	0.03	Z = 0.49	-0.01	Z = -0.12
	OW/OB group	-0.05	P = 0.62	0.006	P = 0.9
Cognitive Flexibility	**Whole sample**	0.07	------	0.09	------
	NW group	0.05	Z = -0.4	0.09	Z = -0.63
	OW/OB group	0.11	P = 0.69	0.18*	P = 0.53
Inhibition	**Whole sample**	0.001	------	0.02	------
	NW group	-0.04	Z = -0.64	-0.02	Z = -0.54
	OW/OB group	0.06	P = 0.52	0.07	P = 0.59
EF Composite	**Whole sample**	-0.07	------	-0.08	------
	NW group	-0.03	Z = 0.56	-0.06	Z = 0.47
	OW/OB group	-0.12	P = 0.57	-0.14	P = 0.64

All FDR-corrected p-values of the *sr* estimates were >0.05.
*Significant at a trend level (P = 0.08)

Abbreviations: AL: allostatic load; BMI: body mass index; EF: executive functions; NW: normal weight; OW/OB: overweight/obesity

Table S3. Subsample descriptive characteristics.

	NW (n = 31)		OW/OB (n = 26)		Test statistic	P value
	Mean (SD)	**Range**	**Mean (SD)**	**Range**		
Age (years)	15.03 (2.98)	10, 20	14.61 (2.48)	10, 19	T = 0.57	0.57
Sex (n females, %)	13 (42%)	-----	11 (42.3%)	-----	$Chi^2 < 0.001$	1
Prepubescents (n, %)	6 (19.3%)	-----	1 (3.8%)	-----	$Chi^2 = 1.88$	0.17
Monthly family income (€)						
300 – 899 (n| %)	2 (6.4%)	-----	1 (3.8%)	-----		
900 – 1499 (n, %)	4 (12.9%)	-----	4 (15.4%)	-----		
1500 – 2099 (n, %)	6 (19.3%)	-----	2 (7.7%)	-----	$Chi^2 = 3.96$	0.41
2100 – 2699 (n, %)	3 (9.7%)	-----	7 (27%)	-----		
≥ 2700 (n, %)	11 (35.5%)	-----	9 (34.6%)	-----		
N.A. (n, %)	5 (16.2%)	-----	3 (11.5%)	-----		
BMI z-score	-0.04 (0.67)	-1.76, 0.80	1.63 (0.42)	0.95, 2.58	W = 0	< 0.001
AL index high-risk percentile	2.52 (1.52)	0, 5	3.88 (1.53)	1, 7	W = 218	0.003
AL index composite score	-0.45 (0.88)	-1.98, 1.82	0.33 (0.76)	-1.84, 1.58	T = -3.56	< 0.001
HADS anxiety	5.32 (2.57)	1, 10	4.92 (2.56)	0, 10	T = 0.58	0.56
HADS depression	2.39 (1.91)	0, 5	3.54 (2.97)	0, 9	W = 325	0.21
Estimated intelligence	11.42 (2.39)	7, 18	11.31 (2.69)	7, 19	T = 0.16	0.87
Working memory	11.29 (2.71)	6, 17	10.73 (3)	6, 18	T = 0.73	0.47
Cognitive Flexibility	12.19 (9.4)	4, 43	9.88 (6.14)	4, 25	W = 463	0.33
Inhibition	4.62 (6.72)	-9.70, 23.5	3.8 (7.16)	-16.9, 22.75	T = 0.78	0.43
EF Composite	0.1 (0.68)	-2.02, 1.88	-0.07 (0.66)	-1.87, 1.43	T = 1.66	0.1
Adverse childhood experiences	4.25 (4.3)	0, 17	3.65 (3.11)	0, 12	W = 407	0.95

We provide mean(sd) and range for numerical variables, and n counts (%) for categorical variables (sex, prepubescents, monthly family income).

Abbreviations: AL: allostatic load; BMI: body mass index; EF: executive functions; HADS: hospital anxiety and depression scale; NA: not available; NW: normal weight; OW/OB: overweight/obesity. Estimated intelligence was assessed by the Weschler Adults Intelligence Scale-III/Weschler Intelligence Scale for Children-IV (WAIS-III/WISC-IV) vocabulary subtest scalar score. Working memory was assessed using the Letter-Number Sequencing scalar score of the WAIS-III/WISC-IV. Cognitive flexibility was assessed by the Wisconsin Card Sorting Test perseverative raw errors. Inhibition was assessed by the Stroop Test Interference score. Adverse childhood experiences were assessed with the Juvenile Victimization Questionnaire.

Table S4. Comparison of the prevalence of juvenile victimization in Spain with our data.

	Pereda et al., 2014 (n = 1107)				Present study (n = 57)				
	n YES	**% YES**	**n NO**	**% NO**	**n YES**	**% YES**	**n NO**	**% NO**	**P value**
Conventional crimes	681	61.5	426	38.5	38	66.66	19	33.34	>0,05
Caregiver victimization	280	25.3	827	74.7	19	33.33	38	66.67	>0,05
Peer and sibling victimization	540	48.8	567	51.2	30	52.63	27	47.37	>0,05
Sexual victimization	96	8.7	1011	91.3	6	10.52	51	89.48	>0,05
Witnessing and indirect victimization	541	48.9	566	51.1	30	52.63	27	47.37	>0,05
Electronic victimization	139	12.6	968	87.4	12	21.05	45	78.95	>0,05

Reference

Pereda N, Guilera G, Abad J. Victimization and polyvictimization of Spanish children and youth: Results from a community sample. Child Abus Negl. 2014;38(4):640–9.

Table S5. Multiple regression coefficients for the working memory, inhibition, cognitive flexibility, and executive functions composite models (n = 50, prepubescent participants excluded).

Variable of interest		Predictors					Adj R^2	FDR
		ACEs	**Sex**	**BMIz**	**Age**	**Intelligence**		
Working memory	*b*	-0.24	-0.96	-0.37	0.08	0.03	-0.001	0.41
	95% CI	-0.47, -0.001	-2.7, 0.83	-1.2, 0.48	-0.27, 0.45	-0.31, 0.37		
	P	0.05	0.29	0.38	0.64	0.88		
Cognitive flexibility	*b*	0.07	0.001	-0.11	-0.1	0.02	0.22	0.01
	95% CI	0.03, 0.12	-0.32, 0.32	-0.26, 0.04	-0.16, -0.03	-0.04, 0.08		
	P	0.001	0.99	0.16	0.004	0.54		
Inhibition	*b*	-0.62	2.08	0.03	1.05	0.1	0.1	0.11
	95% CI	-1.19, -0.05	-2.25, 6.41	-2.03, 2.08	0.17, 1.93	-0.73, 0.93		
	P	0.03	0.34	0.98	0.02	0.81		
EF composite	*b*	-0.09	-0.04	-0.008	0.09	0.002	0.17	0.02
	95% CI	-0.14, -0.04	-0.45, 0.35	-0.19, 0.18	0.02, 0.17	-0.07, 0.08		
	P	0.0008	0.82	0.93	0.02	0.95		

Working memory was assessed using the Letter-Number Sequencing scalar score of the Weschler Adults Intelligence Scale-III/Weschler Intelligence Scale for Children-IV (WAIS-III/WISC-IV). Inhibition was assessed with the Stroop Test Interference score. Cognitive flexibility was assessed using the Wisconsin Card Sorting Test perseverative raw errors, which was transformed into its logarithmic form. Adverse childhood experiences were assessed with the Juvenile Victimization Questionnaire. Estimated intelligence was assessed with the Vocabulary scalar score of the WAIS-III/WISC-IV. Unstandardized betas were reported.

Abbreviations: ACEs: adverse childhood experiences; AL: allostatic load; BMIz: body mass index z-score; EF: executive functions; FDR: false discovery rate; Intelligence: estimated intelligence.

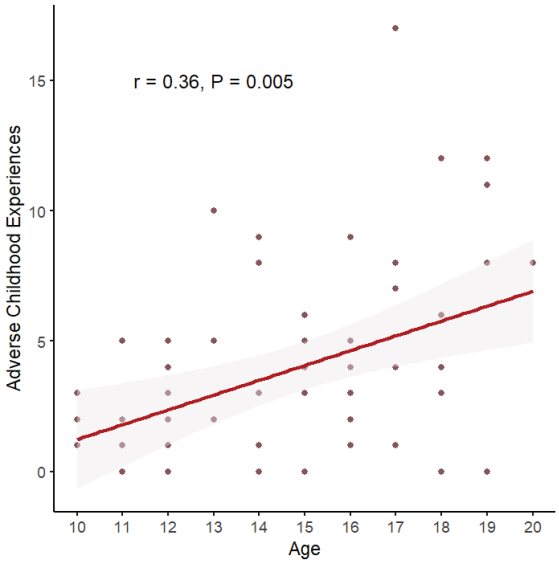


Figure S1. Scatter plot of the correlation between Adverse Childhood Experiences and age.

Chapter 4. Discussion

The present thesis focused on identifying biomarkers associated with neurocognitive changes in adolescents and young adults with excess weight. In three studies, we explored the relationship between genetic (i.e. FTO), biological (i.e., adiposity, cardiometabolic factors, allostatic load), and psychosocial (i.e., ACEs) elements with changes in structural connectivity, WM microstructure, impulsivity, and executive functioning. Overall, despite some results, higher biological and psychosocial burdens were associated with neurocognitive changes.

Structural connectivity in excess weight states

The first objective of this thesis was to determine the structural connectivity differences in the reward network according to BMI in adolescents and young adults. As hypothesized, we found lower structural connectivity of the reward network – when normalized by whole-brain connectivity metrics – in participants with higher BMI categories. When assessing whether the raw connectivity metrics of the reward network were also associated with BMI, significance was not achieved, possibly suggesting that our findings were driven to some extent by whole-brain connectivity metrics. In an exploratory analysis, we observed a positive association between whole-brain structural connectivity and BMI.

Brain regions are interconnected in such complex and well-organized networks that any disruption severe enough to a node has the potential to result in redistribution of network traffic. Initially, as a compensatory mechanism, damage to one node results in increased connectivity in another node. If the affected node recovers from the disruptor, normal connectivity is restored. However, if more nodes begin to be affected, and consequently other nodes become persistently overloaded, structural and functional damage will occur, impairing connectivity (132). This framework could be applied to excess weight, in which either higher BMI categories or more years of exposure would represent more severe disruptors. Following this idea, despite our results being only significant when normalized by whole-brain metrics, initial disruption of the reward network in excess weight – possibly via neuroinflammation and metabolic inflexibility – would initiate compensatory mechanisms (i.e., increases in brain connectivity) that would ultimately fail in OB states (i.e., decreases in brain connectivity). This was also described in a study of adults aged 50-70, which showed that, although both global connectivity density and strength weakened as diabetes progressed (from healthy controls to prediabetes to diabetes), compensatory mechanisms also emerged. In prediabetes, connectivity first decreased in frontal regions,

which extended to subcortical areas with the onset of diabetes. Interestingly, these subcortical regions displayed *stronger* connections in prediabetes, suggesting an attempt to counteract the increasing disruption in brain connectivity as the disease advanced (133). Given the approach of our first study, in which the reward network was targeted as the primary analysis and whole-brain connectivity was an exploratory one, we could not evaluate which brain regions initiated the hypothesized compensatory mechanisms. Furthermore, studying brain features in young samples represents a challenge, as developmental changes in microstructural properties inevitably result in changes in connectome architecture. Throughout adolescence, increases in axonal diameter and myelination or synaptic pruning translate into increases in structural connectivity to facilitate a topology that progressively improves higher-order cognitive functioning (59). It is therefore reasonable to question the extent to which, in individuals undergoing developmental processes, brain differences reflect the phenotype of interest (i.e., excess weight), normative brain trajectories, or both.

The influence of age and development on brain structure in excess weight was clearly evidenced in a meta-analysis testing the relationship between NAcc volume and OB measures, where positive and negative relationships were found in younger and older individuals, respectively (134). Thus, it is possible that in our study, both normative brain trajectories and the emergence of compensatory mechanisms explained the increased whole-brain connectivity observed in excess weight states. This positive association between BMI and structural connectivity was also evidenced in a recent study of adults, in which multiple adiposity measures were associated with increased connectivity between brain regions involved in reward processing, appetite regulation, and cognitive control (135). These results lead to two other interpretations. On one hand, increments in brain connectivity, particularly in brain regions of special importance for the excess weight phenotype, may increase susceptibility to weight gain. On the other hand, structural connectivity between brain regions of different networks, rather than the connectivity within a network, may better characterize the brain correlates of the excess weight phenotype and its behavioral implications.

Structural connectivity according to genetic risk of obesity (FTO)

The second objective of this thesis was to determine the structural connectivity differences in the reward network in adolescent and young adult carriers versus non-carriers of the FTO rs99396309 A allele. Contrary to our hypothesis, we did not find any significant connectivity

differences in individuals with a genetic risk of OB. Although the literature suggests that FTO may modulate weight status by affecting brain regions associated with food intake and reward (11), it is probable that this relationship is influenced by other variables.

The functional relevance of FTO is extensive, from its implications for behavioral encoding in the brain to its effects on neurodevelopmental pathways. FTO can modulate both the activity of dopamine receptors in meso-striatal regions and the expression of numerous genes involved in cell proliferation, migration, and neuronal development, among others (136). In humans, the role of FTO in brain development has been demonstrated in loss-of-function studies, in which FTO inactivation resulted in microcephaly, functional brain deficits, and structural changes (137). Consequently, the involvement of FTO in neurodevelopment may partially explain the mixed results in the literature regarding FTO-associated brain differences. Studies of children with a genetic risk of OB, as determined by FTO, reported volumetric increases in cortical and subcortical regions (138–140), while the opposite pattern was found in old adults (141,142). In young and middle-aged adults, increases, decreases, and no significant differences in structural connectivity have been reported in reward structures (85,143). Despite the evidence being limited and at times inconsistent, we can extract a trend from these studies, in which the relationship between FTO and brain metrics is positive in children and progressively turns negative as adulthood is reached.

These early FTO-related increases in volume and connectivity between brain regions, particularly within the dopaminergic system, may also represent increased susceptibility to weight gain. Following this idea, as excess weight is developed over time and physiological burden arises, the relationship between FTO and brain metrics would become negative. Interestingly, this scenario is paired with the effect of the genetic risk of OB on BMI. A genome-wide polygenic score (GPS) study of OB showed that the GPS predicted only minimal differences in birth weight, which progressively increased in subsequent years and diverged widely by adulthood (144).

In our study, there were no significant differences (positive or negative) in the structural connectivity of the reward network in adolescent and young adult carriers of the FTO rs99396309 A allele. Although the age range of our participants (from 10 to 21 years) had the potential to display the differential effect of FTO on brain metrics across development, methodological considerations, such as sample size, may have affected the results. Moreover, while our approach focused on the reward network, the effect of FTO on brain structure has been reported in other brain regions, such as the cerebellum, right fusiform cortex, and

frontal and occipital lobes (138,141). Additionally, FTO variants have been associated with attention deficit hyperactivity disorder, Alzheimer's disease, and major depressive disorder (137), suggesting their involvement in brain changes beyond reward structures. Therefore, ROI selection may have influenced our findings. Importantly, although our objective was to evaluate the direct influence of FTO on the reward network, it may also exert its effect by interacting with dopamine-related variants such as the Taq1A polymorphism near the D2 dopamine receptor (145,146). While FTO is considered the locus with the largest impact on BMI, a single variant is far from having the predictive power that polygenic risk scores, ideally GPS, may have. Given the polygenic nature of common OB, studying its inherited susceptibility using the whole genome has the potential to identify individuals at risk before the onset of the condition, providing a window to intervene and avoid future consequences.

White matter microstructure and cardiometabolic factors

The third objective of this thesis was to assess the relationship between cardiometabolic factors and the microstructure of WM tracts associated with both excess weight and impulsivity (i.e., cingulum, corona radiata, corpus callosum, inferior fronto-occipital fasciculus, and internal capsule) in adolescents. As hypothesized, we found an inverse relationship between glycated hemoglobin and FA in the cingulum. Nevertheless, no other cardiometabolic biomarkers (glucose, diastolic blood pressure, systolic blood pressure, HDL, LDL, and triglycerides) were related to WM microstructure.

The literature suggests that cardiometabolic factors are associated with changes in the brain. An extensive review revealed a clear relationship between hyperglycemia, central OB, and hypertension and brain alterations (i.e., structural, microstructural, functional features, and presence of small vessel disease), while the role of dyslipidemia was less consistent (147). Although our sample included adolescents without a clinical diagnosis of cardiometabolic disease, our results suggested that variations in glycated hemoglobin were associated with WM microstructure. Glycated hemoglobin has already been described as a possible early biomarker of metabolic syndrome, even at preclinical levels (148). A recent study on healthy adults also demonstrated that a glycated hemoglobin level below the threshold for prediabetes diagnosis (<5.7%) was associated with lower FA in multiple WM tracts (108). In our study, although only the cingulum remained significant after correction for multiple testing, FA of the corpus callosum, corona radiata, and inferior fronto-occipital fasciculus was also associated with glycated hemoglobin.

Even though the brain requires a constant glucose supply, which is guaranteed by specific transcellular glucose transporters, the uptake of glucose also depends on its extracellular concentration. Acute or sustained hyperglycemia inevitably over increases glucose entry into the brain, which can cause neural damage. The neurotoxicity caused by uncontrolled hyperglycemia may explain why structural brain deficits have been reported in children with type 1 diabetes shortly after diagnosis (149). Contrary to our expectations, we did not find glucose to be associated with WM microstructure. Since circulating levels of glucose only indicate the current glycemic state, it is possible that glycated hemoglobin, as an indicator of plasma glucose control over the last three months (150), may be a more representative marker of cumulative hyperglycemic insults in the brain. In addition, given that our sample included adolescents, it is possible that higher exposure to hyperglycemia, as assessed by glycated hemoglobin, may have disrupted the development of brain myelination (151), which would explain the decrease in FA observed in our study.

Interestingly, we did not find an association between other cardiometabolic factors and WM microstructure. A systematic review highlighted that metabolic syndrome was associated with reductions in FA across studies including wide age ranges (i.e., from childhood to old adulthood) (152). While the effect of glycated hemoglobin on WM microstructure is gradual, and even small changes in preclinical levels show an influence on FA (108), other cardiometabolic markers may require further dysregulation to have an effect on WM microstructure. Excluding participants with cardiometabolic disease may have prevented us from exploring the whole continuum of the relationship between cardiometabolic factors and WM microstructure. Moreover, the trajectories of cardiometabolic factors across developmental stages are affected by the onset of puberty (153). Both linear and non-linear reductions and increments in cardiometabolic factors have been reported throughout adolescence (154). Hence, our results may have been affected by these dynamic changes in the cardiometabolic profile that occur during puberty.

Impulsivity and cardiometabolic factors

The fourth objective of this thesis was to evaluate the relationship between impulsivity and cardiometabolic factors among adolescents. As hypothesized, we found that higher triglyceride levels were associated with higher commission errors in the Conners' Continuous Performance Test (CPT-II) and that glucose and diastolic blood pressure were associated

with higher scores on the emotional eating subscale of the Three-Factor Eating Questionnaire R-18 (TFEQ-R18).

Over the years, impulsivity has gained attention as a correlate for excess weight. A large meta-analysis showed a significant yet small effect size in the relationship between impulsivity and BMI (123). The variability in the direction and magnitude seen across studies may be explained by the lack of consensus on the operationalization of impulsivity. This has promoted the development of multiple models and measures that, instead of having convergent validity, appear to measure distinct impulsive traits. Thus, the association between impulsivity and excess weight may depend on the measure of impulsivity selected for the specific domain of impulsivity being evaluated (123). In this sense, a proper characterization of impulsivity in excess weight would help to identify individuals at greater risk of developing or maintaining this condition, define specific neural correlates of the different constructs of impulsivity, and evaluate the effectiveness of specific neuropsychological interventions (155).

In our study, we assessed behavioral task measures of impulsivity using the Stroop Test interference score, Wisconsin Card Sorting Test (WCST) perseverative errors, CPT-II commission errors, and Kirby Delayed Discounting Task geometric mean. These tasks are aligned with four higher-order factors of performance-based impulsivity: inattention, set-shifting, inhibition, and impulsive decision-making, respectively (123). However, it is worth noting that behavioral tasks often lack specificity and measure multiple processes, making it difficult to disentangle what cognitive factors influence the performance (123). We also used the novelty-seeking subscale of the Temperament Character Inventory Revised and the uncontrolled and emotional eating subscales of the TFEQ-R18 as questionnaire measures of impulsivity. While the novelty seeking subscale is aligned with the extraversion/positive emotionality higher-order factor of impulsive personality traits (123), there is a lack of agreement about the impulsive nature of uncontrolled and emotional eating. However, some studies have reported small-to-moderate correlations between these two subscales and impulsivity questionnaires (156,157).

Although the effect of impulsivity on excess weight (as defined by BMI) has been a topic of interest for years, the extent to which cardiometabolic factors are also associated with impulsivity in samples with excess weight is understudied. This approach has been explored particularly in samples with mental health conditions, in which alterations in glucose levels and lipid profile (HDL, LDL, triglycerides) have been associated with more suicidal ideation,

suicide attempts (158,159), and aggression (160), among other conditions also related to impulsivity. However, some inconsistencies have also been reported (161). The neurobiological mechanisms by which cardiometabolic factors are associated with impulsive phenotypes are still to be fully elucidated. Nevertheless, several frameworks have been proposed to explain this relationship. On the one hand, reductions in cholesterol may influence the microviscosity of serotonin receptors, affecting serotonin activity and contributing to impulsive behaviors. On the other hand, pro-inflammatory states characterized by increased cytokine production may lead to increases in lipid profile, affecting melatonin release and increasing impulsivity (159). Alterations in glucose metabolism have also been associated with suicidal tendencies, although there is no evidence that this relationship is causal nor is its direction clear (162).

Focusing on our results, it is possible that the association we found between higher triglycerides and more commission errors in the CPT-II was mediated by inflammatory biomarkers. Also, finding that higher glucose and diastolic blood pressure levels were associated with higher scores on the emotional eating subscale of the TFEQ-R18 may reflect the natural consequences of consuming highly palatable, sugary, and energy-dense foods. Moreover, as mentioned above, the dynamic trajectories of the cardiometabolic profile observed throughout adolescence may have influenced our results (154).

Executive functioning and allostatic load

The fifth objective of this thesis was to evaluate the association between EF and AL in adolescents and young adults, and to assess whether this relationship differed according to BMI status. Contrary to our hypothesis, we found no association between AL and EF in the whole sample. However, AL correlated with cognitive flexibility (assessed by perseverative errors of the WCST), but only in individuals with excess weight at the nominal level.

While the estimation of AL in early studies was based on the same 10 biomarkers (163), later studies have proposed alternative AL indices (164). Across the literature, not only is there variability as to which biomarkers should or should not be included in the AL index, but also regarding which algorithm should be applied (164). Moreover, AL at different ages can only be considered to have the same interpretation if two assumptions are met: i) the same biomarkers contribute to AL, and ii) the magnitude of these contributions is equal. It is possible that a group of biomarkers that are sensitive and clinically significant across all ages fails to construct an invariant AL index, as their intercorrelations and cumulative meaning

may change over time (165). This was evidenced by a recent study in which the same factor structure of AL was not observed across children, adolescents, and young adults (165). Moreover, and given that AL refers to the accumulation of the 'wear and tear' of the body, and this implicitly requires time, findings of AL in children and adolescents may be more likely indicative of stress severity rather than chronicity. It may also suggest that during vulnerable periods, such as adolescence, physiological systems are more sensitive to being disrupted (166). Thus, our proposed estimation of AL (i.e., systolic blood pressure, diastolic blood pressure, glycated hemoglobin, HDL, LDL, triglycerides, high sensitivity CRP, fibrinogen, and cortisol) and the age range of our participants (i.e., 10–21 years) may have conditioned both our results and their comparability with other studies.

In the context of acute stress, it has been theorized that stress can affect executive functioning by biasing cognition to process information directly related to the stressor, shifting cognition from top-down control processes to bottom-up automatic responses, or through the upregulation of cortisol and other biological factors (167). An extensive meta-analysis evaluated the effect of acute stress on three core EF, and their results suggested that stress impaired working memory and cognitive flexibility but did not influence inhibitory control. In our study, while we did not assess acute stress but instead used an estimated AL index that represented the physiological stain of chronic stress, we found that only cognitive flexibility was associated with AL in participants with excess weight, which is consistent with the results of the meta-analysis. We hypothesize that since cognitive flexibility is a complex EF that requires the coordinated use of working memory and inhibitory control to manage and integrate multiple streams of information (63), it may be more vulnerable to the effects of stress. Furthermore, the fact that this relationship was only significant in individuals with excess weight suggests that the definition of AL could include both the cumulative effects of stressful situations and the physiological consequences of unhealthy lifestyles, such as sedentarism or diets based on high-fat and high-sugar foods (168). In children and adolescents, both excess weight and malnutrition have been associated with higher AL, highlighting that unhealthy lifestyles contribute to physiological dysregulation and development of illnesses (168).

Importantly, although AL represents the wear and tear of the body, the biomarkers used do not provide information on the underlying causes. This emphasizes the importance of using an integrated approach that includes both biomarkers and clinimetric criteria to identify AL states (169).

Executive functioning and adverse childhood experiences

The sixth objective of this thesis was to assess the relationship between EF and ACEs in adolescents and young adults. As hypothesized, higher exposure to ACEs was associated with worse performance in cognitive flexibility (perseverative errors of the WCST) and the overall EF composite (including the perseverative errors of the WCST, Stroop interference, and letter–number sequencing of the Weschler Adults Intelligence Scale-III/Weschler Intelligence Scale for Children-IV).

When adversity occurs during sensitive developmental periods (i.e., ACEs), neuroplastic processes that disrupt normative brain structure and function can occur. Different types of ACEs are considered to leave a mark on specific parts of the brain, although a common substrate has been described (i.e., anterior cingulate cortex, PFC, amygdala, hippocampus, striatum, and thalamus) (Figure 5) (170). Since the PFC is one of the last brain structures to fully develop and is also particularly dense in glucocorticoid receptors, it may be more vulnerable to the effects of chronic stress associated with ACEs exposure (72). Consistent with our results, two meta-analyses including children, adolescents and young adults evidenced that ACEs were associated with lower inhibitory control, cognitive flexibility, and working memory (171,172). While our approach was based on the deficit model, in which children exposed to highly adverse environments are at risk of cognitive and behavioral impairments, it is worth noting that exposure to ACEs can also lead to successful adaptation and the development of resilience. In this case, cognitive capacities, despite adversity, would be either enhanced or maintained (173). However, it should not be overlooked that the development of resilience may require the repeated activation of allostatic systems, which can induce AL over time (174).

Interestingly, while we found a negative association between ACEs and EF in our study, the results of one of the covariates (i.e., age) provided further insight into the interpretation, as it was positively associated with better EF performance. While this is consistent with the ongoing maturation of the PFC observed throughout adolescence (66), it seems that these age-related increases in cognitive capacity may not be sufficient to compensate for the detrimental effects of ACEs, whose exposure also increases with age. This highlights the importance of the timing of trauma, as well as the duration, type, and severity, as they can modulate the HPA axis differently depending on the stage of development. Earlier and repetitive exposure to more severe types of ACEs would result in greater dysregulation and thus lead to a more pronounced EF impairment (175).

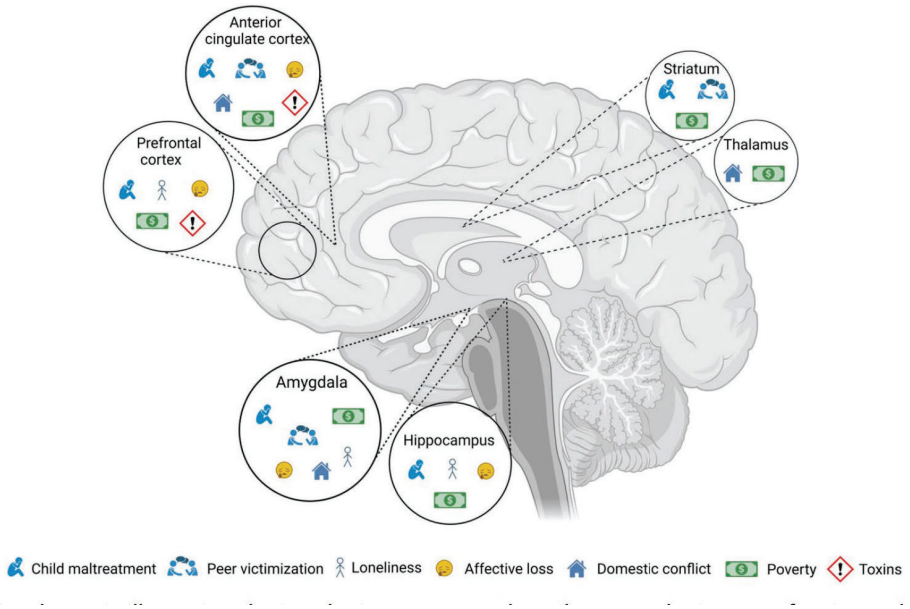


Figure 5. Schematic illustration of the impact of various adversities on selected brain regions. Reproduced from Vaidya (170) under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

The relevance of including confounders when studying the cognitive effects of ACEs was demonstrated by a longitudinal study. Their findings indicated that childhood victimization predicted impaired cognitive functioning in young adulthood and midlife. Strikingly, these significant bivariate associations were attenuated after controlling for child and maternal intelligence quotient, and family SES (176). This challenges the conventional causal interpretation of the relationship between ACEs and cognition, and suggests that preexisting cognitive vulnerabilities (i.e., low intelligence quotient) and socioeconomic disadvantage may explain the cognitive deficits described in those victimized (176). Other possibilities have also been proposed, such as the mediating role of AL in the relationship between ACEs and cognitive functions (177).

Final remarks

Excess weight does not have a unique phenotype and is not the product of a single habit. While usually directly associated with overeating or unhealthy eating, there are multiple factors that interfere in between. Starting with the basics, and despite the lack of significant results in our first study, genetic variants such as FTO may modulate food intake by disrupting brain regions that affect appetite and reward processing (e.g., the reward network)

(11). Additionally, environmental factors such as exposure to childhood adversity may affect EF (171). This was confirmed in our third study, in which a higher number of ACEs was associated with poorer overall executive functioning. Of course, although it was not the focus of this thesis, there are many other socioeconomic and sociocultural factors that can also favor the development of excess weight via brain and cognitive changes, or directly by malnutrition in those without access to healthy food. Importantly, both genetic and environmental vulnerabilities, especially during adolescence, occur without choice. Thus, the paradigm 'calories in, calories out' does not integrate the complexity of excess weight.

With the progressive increase in adiposity above healthy ranges and the onset of excess weight, several neurocognitive changes can emerge (106,117). While most of the literature is focused on BMI, an indirect and non-specific measure of adiposity, we have broadened this perspective by including cardiometabolic factors, which are usually dysregulated in excess weight. Our first study indicated that BMI was associated with lower structural connectivity in the reward network. Our second study showed that glycated hemoglobin was associated with lower FA in the cingulum, triglycerides were associated with higher impulsivity performance, and glucose and systolic blood pressure were associated with higher impulsive traits. AL, which could be considered the physiological result of both the exposure to vulnerable situations and excess weight (168), can also impair EF (113), although this was not evidenced in our third study.

By integrating biological, genetic, and psychosocial factors in the evaluation of the excess weight phenotype, vulnerabilities at both the population and individual levels can be approached and interventions can be proposed. Reductionist perspectives on excess weight not only prevent the correct management of this condition but also promote stigmatizing environments. Adolescence is by itself a challenging developmental period in which the foundations for adulthood are built. Thus, addressing any risk factors that may lead to morbidity in later years, such as excess weight, is of paramount importance to guarantee positive health outcomes.

Strengths, limitations, and future research

The present thesis tried to bring inside into one of the most vulnerable developmental periods: adolescence. Excess weight is a health condition that increases the odds of developing cardiometabolic and cardiovascular events, and longitudinal studies have shown

that adolescents with excess weight have an increased risk of maintaining this condition as adults (7).

One of the main **strengths** of the present thesis is that we characterized adolescents from multiple perspectives (i.e., biological, genetic, and psychosocial) to avoid a reductive approach when studying the neurocognitive characteristics of the excess weight phenotype. Moreover, by applying strict exclusion criteria, we ensured that excess weight was the only health condition our participants could have. This allowed the study of excess weight without the interaction of important confounders, from neuropsychiatric conditions to cardiometabolic comorbidities, among others.

Specific **limitations** from each study can be found in the section "Methods and Results" section. Here, general limitations of the present thesis are mentioned. All our studies had a cross-sectional design, which prevented us from establishing causation. In addition, the sample sizes used were small, thus our studies were possibly underpowered. Despite the incorporation of ACEs exposure as a psychosocial variable in the third study, SES was not included in our three studies due to a large proportion of missing values. SES is a transversal determinant of health and, as such, has the potential to mediate the relationships tested in this thesis (18). Moreover, two of the three studies in this thesis were based on DTI, a neuroimaging technique that is influenced by both biological and methodological factors. On the one hand, the tensor model is not able to correctly characterize diffusion regions of complex fiber architectures, such as crossing fibers, which can yield lower anisotropy metrics because there is no dominant diffusion direction. On the other hand, the role of the analytical approach is of paramount importance. Different results can be obtained using the same dataset because each approach utilizes different assumptions and image processing strategies (47). Therefore, our results should be interpreted with due caution.

The findings obtained in this thesis indicate the need for **further research**. In the first study, while we assessed the independent effect of FTO on the structural connectivity of the reward network, the possible interaction between FTO and dopamine-related variants should also be evaluated in adolescents and different age groups. In addition, OB-related GPS studies are encouraged to assess with greater predictive power how inherited susceptibility to excess weight may change over the lifespan, and thus determine the best window to implement interventions (144). Moreover, it would be of particular interest to study brain characteristics (i.e., structural, microstructural, and connectivity) in individuals that, despite an unfavorable GPS maintain a NW status, or despite a favorable GPS develop OB (144).

In the second study, since puberty influences cardiometabolic trajectories, the use of specific reference values that consider both linear and non-linear reductions and increments in cardiometabolic factors throughout adolescence would help standardize them and provide a more accurate interpretation and reliable comparison between studies (154). Moreover, since excess weight is associated with both impulsivity and cardiometabolic alterations and, at the same time, these two characteristics are associated with one another, studying their independent and shared neural correlates would open a window to new interventions in the excess weight context. For example, identifying the healthy range of cardiometabolic values associated with more restrained impulsivity traits and brain integrity.

As for the third study, complementing the use of AL indices with clinimetric criteria would provide context to this set of biological parameters. The Psychosocial Index, a questionnaire that includes 55 items covering 6 domains (i.e., sociodemographic and clinical data, stress, psychological distress, abnormal illness behavior, well-being, and quality of life), is the first step in the clinimetric assessment of AL (169). This questionnaire has already provided a sensitive assessment of AL in various studies, highlighting its potential to increase the number of people screened (169). The detection of adolescents with past and present vulnerable backgrounds using both biological and psychosocial measurements (e.g., the AL index, Psychosocial Index, or ACEs questionnaire) would help identify those with an increased risk of developing or maintaining toxic levels of stress, which have been associated with a broad range of health conditions, including excess weight.

Chapter 5. Conclusions

The main conclusions of the three studies included in the present thesis, which focused on adolescents and young adults with and without excess weight, are as follows:

1. A higher body mass index, but not the genetic risk of obesity assessed by the A allele of the fat mass and obesity-related gene rs99396309, is associated with lower structural connectivity in the reward network and increased whole-brain structural connectivity. The mechanisms by which excess weight affects brain structural connectivity go beyond genetic risk and are probably modulated by developmental processes.

2. Cardiometabolic factors of different nature are associated with higher impulsivity and lower fractional anisotropy in white matter tracts typically related to both excess weight and impulsivity. Cardiometabolic factors, even at preclinical levels, are potential biomarkers for the neurocognitive phenotype of excess weight.

3. Psychological stress, measured by exposure to adverse childhood experiences, but not physiological stress estimated by an allostatic load index, is associated with poorer executive functioning.

References

1. World Health Organization. Obesity and Overweight [Internet]. 2020. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

2. Cole TJ, Lobstein T. Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. Pediatr Obes. 2012;7(4):284–94.

3. Ross R, Neeland IJ, Yamashita S, Shai I, Seidell J, Magni P, et al. Waist circumference as a vital sign in clinical practice: a Consensus Statement from the IAS and ICCR Working Group on Visceral Obesity. Nat Rev Endocrinol. 2020;16(3):177–89.

4. Nuttall FQ. Body mass index: Obesity, BMI, and health: A critical review. Nutr Today. 2015;50(3):117–28.

5. Hampl SE, Hassink SG, Skinner AC, Armstrong SC, Barlow SE, Bolling CF, et al. Clinical Practice Guideline for the Evaluation and Treatment of Children and Adolescents With Obesity. Pediatrics. 2023;151(2):e2022060640.

6. Global Obesity Observatory. World Obesity Atlas [Internet]. 2023. Available from: https://data.worldobesity.org/publications/?cat=19

7. Simmonds M, Llewellyn A, Owen CG, Woolacott N. Predicting adult obesity from childhood obesity: A systematic review and meta-analysis. Obes Rev. 2016;17(2):95–107.

8. Lister NB, Baur LA, Felix JF, Hill AJ, Marcus C, Reinehr T, et al. Child and adolescent obesity. Nat Rev Dis Prim. 2023;9(24):1–19.

9. Kivimäki M, Strandberg T, Pentti J, Nyberg ST, Frank P, Jokela M, et al. Body-mass index and risk of obesity-related complex multimorbidity: an observational multicohort study. Lancet Diabetes Endocrinol. 2022;10(4):253–63.

10. Hill JO, Wyatt HR, Peters JC. Energy balance and obesity. Circulation. 2012;126(1):126–32.

11. Loos RJF, Yeo GSH. The genetics of obesity: from discovery to biology. Nat Rev Genet. 2022;23(2):120–33.

12. Doulla M, McIntyre AD, Hegele RA, Callego PH. A novel MC4R mutation associated with childhood-onset obesity: A case report. Paediatr Child Health (Oxford). 2014;19(10):515–8.

13. Lebrun B, Bariohay B, Moyse E, Jean A. Brain-derived neurotrophic factor (BDNF) and food intake regulation: A minireview. Auton Neurosci Basic Clin. 2006;126–127:30–8.

14. Loos RJF, Yeo GSH. The bigger picture of FTO - The first GWAS-identified obesity gene. Nat Rev Endocrinol. 2014;10(1):51–61.

15. Albuquerque D, Nóbrega C, Manco L, Padez C. The contribution of genetics and environment to obesity. Br Med Bull. 2017;123(1):159–73.

16. Swinburn B, Egger G, Raza F. Dissecting obesogenic environments: The development and application of a framework for identifying and prioritizing environmental interventions for obesity. Prev Med (Baltim). 1999;29(6):563–70.

17. Berthoud HR. The neurobiology of food intake in an obesogenic environment. Proc Nutr Soc. 2012;71(4):478–87.

18. Farah MJ. The Neuroscience of Socioeconomic Status: Correlates, Causes, and Consequences. Neuron. 2017;96(1):56–71.

19. Vazquez CE, Cubbin C. Socioeconomic Status and Childhood Obesity: a Review of Literature from the Past Decade to Inform Intervention Research. Curr Obes Rep. 2020;9:562–70.

20. Newton S, Braithwaite D, Akinyemiju TF. Socio-economic status over the life course and obesity: Systematic review and meta-analysis. PLoS One. 2017;12(5):1–15.

21. Kweon H, Aydogan G, Dagher A, Bzdok D, Ruff CC, Nave G, et al. Human brain anatomy reflects separable genetic and environmental components of socioeconomic status. Sci Adv. 2022;8(20):1–10.

22. Farah MJ. Socioeconomic status and the brain: Prospects for neuroscience-informed policy. Nat Rev Neurosci. 2018;19:428–38.

23. Walsh D, McCartney G, Smith M, Armour G. Relationship between childhood socioeconomic position and adverse childhood experiences (ACEs): A systematic review. J Epidemiol Community Health. 2019;73(12):1087–93.

24. Bomysoad RN, Francis LA. Adverse Childhood Experiences and Mental Health Conditions Among Adolescents. J Adolesc Heal. 2020;67(6):868–70.

25. Elsenburg LK, van Wijk KJE, Liefbroer AC, Smidt N. Accumulation of adverse childhood events and overweight in children: A systematic review and meta-analysis. Obesity. 2017;25(5):820–32.

26. Hughes K, Bellis MA, Hardcastle KA, Sethi D, Butchart A, Mikton C, et al. The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. Lancet Public Heal. 2017;2(8):e356–66.

27. Wiss DA, Brewerton TD. Adverse Childhood Experiences and Adult Obesity: A Systematic Review of Plausible Mechanisms and Meta-Analysis of Cross-Sectional Studies. Physiol Behav. 2020;223:1–11.

28. Choe SS, Huh JY, Hwang IJ, Kim JI, Kim JB. Adipose tissue remodeling: Its role in energy metabolism and metabolic disorders. Front Endocrinol (Lausanne). 2016;7:1–16.

29. Sakers A, De Siqueira MK, Seale P, Villanueva CJ. Adipose-tissue plasticity in health and disease. Cell. 2022;185(3):419–46.

30. Longo M, Zatterale F, Naderi J, Parrillo L, Formisano P, Raciti GA, et al. Adipose tissue dysfunction as determinant of obesity-associated metabolic complications. Int J Mol Sci. 2019;20(9):2358.

31. Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, et al. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget. 2018;9(6):7204–18.

32. Gregor MF, Hotamisligil GS. Inflammatory mechanisms in obesity. Annu Rev Immunol. 2011;29:415–45.

33. Kawai T, Autieri M V., Scalia R. Adipose tissue inflammation and metabolic dysfunction in obesity. Am J Physiol - Cell Physiol. 2021;320(3):C375–91.

34. Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y. Obesity & inflammation: The linking mechanism & the complications. Arch Med Sci. 2017;13(4):851–63.

35. Eder K, Baffy N, Falus A, Fulop AK. The major inflammatory mediator interleukin-6 and obesity. Inflamm Res. 2009;58(11):727–36.

36. Salas-Venegas V, Flores-Torres RP, Rodríguez-Cortés YM, Rodríguez-Retana D, Ramírez-Carreto RJ, Concepción-Carrillo LE, et al. The Obese Brain: Mechanisms of Systemic and Local Inflammation, and Interventions to Reverse the Cognitive Deficit. Front Integr Neurosci. 2022;16:1–19.

37. Bastien M, Poirier P, Lemieux I, Després JP. Overview of epidemiology and contribution of obesity to cardiovascular disease. Prog Cardiovasc Dis. 2014;56(4):369–81.

38. Gaal LF Van, Mertens IL, DeBlock CE. Mechanisms linking obesity with cardiovascular disease. Nature. 2006;444:875–80.

39. Ortiz-Martínez M, González-González M, Martagón AJ, Hlavinka V, Willson RC, Rito-Palomares M. Recent Developments in Biomarkers for Diagnosis and Screening of Type 2 Diabetes Mellitus. Curr Diab Rep. 2022;22(3):95–115.

40. Juster RP, McEwen BS, Lupien SJ. Allostatic load biomarkers of chronic stress and impact on health and cognition. Neurosci Biobehav Rev. 2010;35(1):2–16.

41. Suvarna B, Suvarna A, Phillips R, Juster RP, McDermott B, Sarnyai Z. Health risk behaviours and allostatic load: A systematic review. Neurosci Biobehav Rev. 2020;108:694–711.

42. van der Valk ES, Savas M, van Rossum EFC. Stress and Obesity: Are There More Susceptible Individuals? Curr Obes Rep. 2018;7(2):193–203.

43. Xiao Y, Liu D, Cline MA, Gilbert ER. Chronic stress, epigenetics, and adipose tissue metabolism in the obese state. Nutr Metab. 2020;17(1):1–16.

44. Tomiyama AJ. Stress and Obesity. Annu Rev Psychol. 2019;70:703–18.

45. Schmahmann JD, Pandya DN. White Matter Pathways in Early Neuroscience. In: Fiber Pathways of the Brain. 2006. p. 7–38.

46. Viard A, Eustache F, Segobin S. History of Magnetic Resonance Imaging: A Trip Down Memory Lane. Neuroscience. 2021;474:3–13.

47. Hecke W Van, Emsell L, Sunaert S. Diffusion Tensor Imaging. A Practical Handbook. New York: Springer; 2016.

48. Ashburner J, Friston KJ. Voxel-based morphometry - The methods. Neuroimage. 2000;11:805–21.

49. Mills KL, Tamnes CK. Methods and considerations for longitudinal structural brain imaging analysis across development. Dev Cogn Neurosci. 2014;9:172–90.

50. Kullmann S, Schweizer F, Veit R, Fritsche A, Preissl H. Compromised white matter integrity in obesity. Obes Rev. 2015;16(4):273–81.

51. García-Martín ML, López-Larrubia P. Preclinical MRI: Methods and Protocols. 2018.

52. Yeh CH, Jones DK, Liang X, Descoteaux M, Connelly A. Mapping Structural Connectivity Using Diffusion MRI: Challenges and Opportunities. J Magn Reson Imaging. 2021;53(6):1666–82.

53. Bullmore E, Sporns O. Complex brain networks: Graph theoretical analysis of structural and functional systems. Nat Rev Neurosci. 2009;10(3):186–98.

54. Stiles J, Jernigan TL. The basics of brain development. Neuropsychol Rev. 2010;20(4):327–48.

55. Gerván P, Soltész P, Filep O, Berencsi A, Kovács I. Posterior-anterior brain maturation reflected in perceptual, motor and cognitive performance. Front Psychol. 2017;8:1–10.

56. Casey BJ, Getz S, Galvan A. The adolescent brain. Dev Rev. 2008;28(1):62–77.

57. Bethlehem RAI, Seidlitz J, White SR, Vogel JW, Anderson KM, Adamson C, et al. Brain charts for the human lifespan. Nature. 2022;604:525–33.

58. Lebel C, Deoni S. The development of brain white matter microstructure. Neuroimage. 2018;182:207–18.

59. Zhao T, Cao M, Niu H, Zuo XN, Evans A, He Y, et al. Age-related changes in the topological organization of the white matter structural connectome across the human lifespan. Hum Brain Mapp. 2015;36(10):3777–92.

60. Vijayakumar N, Op de Macks Z, Shirtcliff EA, Pfeifer JH. Puberty and the human brain: Insights into adolescent development. Neurosci Biobehav Rev. 2018;92:417–36.

61. Piekarski DJ, Colich NL, Ho TC. The effects of puberty and sex on adolescent white matter development: A systematic review. Dev Cogn Neurosci. 2023;60:1–27.

62. Cristofori I, Cohen-Zimerman S, Grafman J. Executive functions. In: Handbook of Clinical Neurology. Elsevier B.V.; 2019. p. 197–219.

63. Diamond A. Executive functions. Annu Rev Psychol. 2013;64:135–68.

64. Diamond A. Executive functions. In: Handbook of Clinical Neurology. Elsevier B.V.; 2020. p. 225–40.

65. De Luca CR, Leventer RJ. Developmental trajectories of executive functions across the lifespan. In: Executive functions and the frontal lobes: A lifesp Taylor & Francis; 2008. p. 23–56.

66. Tervo-Clemmens B, Calabro FJ, Parr AC, Fedor J, Foran W, Luna B. A canonical trajectory of executive function maturation from adolescence to adulthood. Nat Commun. 2023;14(1):1–17.

67. Whiteside SP, Lynam DR. The five factor model and impulsivity: Using a structural model of personality to understand impulsivity. Pers Individ Dif. 2001;30(4):669–89.

68. Mills KL, Goddings AL, Clasen LS, Giedd JN, Blakemore SJ. The developmental mismatch in structural brain maturation during adolescence. Dev Neurosci. 2014;36:147–60.

69. Forbes EE, Dahl RE. Pubertal development and behavior: Hormonal activation of social and motivational tendencies. Brain Cogn. 2010;72(1):66–72.

70. Tottenham N, Galván A. Stress and the adolescent brain: Amygdala-prefrontal cortex circuitry and ventral striatum as developmental targets. Neurosci Biobehav Rev. 2016;70:217–27.

71. Baum A. Stress, intrusive imagery, and chronic distress. Health Psychol. 1990;9(6):653–75.

72. Lund JI, Toombs E, Radford A, Boles K, Mushquash C. Adverse childhood experiences and executive function difficulties in children: A systematic review. Child Abus Negl. 2020;106:1–19.

73. Morton GJ, Meek TH, Schwartz MW. Neurobiology of food intake in health and disease. Nat Rev Neurosci. 2014;15(6):367–78.

74. Haber SN. Anatomy and connectivity of the reward circuit. In: Decision Neuroscience: An Integrative Perspective. Elsevier Inc.; 2017. p. 3–19.

75. Marqués-Iturria I, Scholtens LH, Garolera M, Pueyo R, García-García I, González-Tartiere P, et al. Affected connectivity organization of the reward system structure in obesity. Neuroimage. 2015;111:100–6.

76. Stice E, Yokum S. Neural Vulnerability Factors That Predict Future Weight Gain. Curr Obes Rep. 2021;10(4):435–43.

77. Dohle S, Diel K, Hofmann W. Executive functions and the self-regulation of eating behavior: A review. Appetite. 2018;124:4–9.

78. Lowe CJ, Morton JB, Reichelt AC. Adolescent obesity and dietary decision making—a brain-health perspective. Lancet Child Adolesc Heal. 2020;4(5):388–96.

79. Lowe CJ, Reichelt AC, Hall PA. The Prefrontal Cortex and Obesity: A Health Neuroscience Perspective. Trends Cogn Sci. 2019;23(4):349–61.

80. Whelan R, Conrod PJ, Poline JB, Lourdusamy A, Banaschewski T, Barker GJ, et al. Adolescent impulsivity phenotypes characterized by distinct brain networks. Nat Neurosci. 2012;15:920–5.

81. Nowrangi MA, Lyketsos C, Rao V, Munro CA. Systematic review of neuroimaging correlates of executive functioning: Converging evidence from different clinical populations. J Neuropsychiatry Clin Neurosci. 2014;26(2):114–25.

82. Alfano V, Longarzo M, Aiello M, Soricelli A, Cavaliere C. Cerebral microstructural abnormalities in impulsivity: a magnetic resonance study. Brain Imaging Behav. 2021;15(1):346–54.

83. Park HRP, Verhelst H, Quak M, Jeurissen B, Krebs RM. Associations between different white matter properties and reward-based performance modulation. Brain Struct Funct. 2021;226(4):1007–21.

84. Goddings AL, Roalf D, Lebel C, Tamnes CK. Development of white matter microstructure and executive functions during childhood and adolescence: a review of diffusion MRI studies. Dev Cogn Neurosci. 2021;51:1–12.

85. Beyer F, Zhang R, Scholz M, Wirkner K, Loeffler M, Stumvoll M, et al. Higher BMI, but not obesity-related genetic polymorphisms, correlates with lower structural connectivity of the reward network in a population-based study. Int J Obes. 2021;45:491–501.

86. Gupta A, Mayer EA, Sanmiguel CP, Van Horn JD, Woodworth D, Ellingson BM, et al. Patterns of brain structural connectivity differentiate normal weight from overweight subjects. NeuroImage Clin. 2015;7:506–17.

87. Riederer JW, Shott ME, Deguzman M, Pryor TL, Frank GKW. Understanding neuronal architecture in obesity through analysis of white matter connection strength. Front Hum Neurosci. 2016;10:1–8.

88. Peng-Li D, Sørensen TA, Li Y, He Q. Systematically lower structural brain connectivity in individuals with elevated food addiction symptoms. Appetite. 2020;155:1–10.

89. Rodrigues B, Coelho A, Portugal-Nunes C, Magalhães R, Moreira PS, Castanho TC, et al. Higher Adherence to the Mediterranean Diet Is Associated With Preserved White Matter Integrity and Altered Structural Connectivity. Front Neurosci. 2020;14:1–12.

90. Cui Y, Tang TY, Lu CQ, Lu T, Wang YC, Teng GJ, et al. Disturbed Interhemispheric Functional and Structural Connectivity in Type 2 Diabetes. J Magn Reson Imaging. 2022;55(2):424–34.

91. Savransky A, Chiappelli J, Rowland LM, Wisner K, Shukla DK, Kochunov P, et al. Fornix Structural Connectivity and Allostatic Load: Empirical Evidence from Schizophrenia Patients and Healthy Controls. Psychosom Med. 2017;79(7):770–6.

92. Kaltenhauser S, Weber CF, Lin H, Mozayan A, Malhotra A, Constable RT, et al. Association of Body Mass Index and Waist Circumference with Imaging Metrics of Brain Integrity and Functional Connectivity in Children Aged 9 to 10 Years in the US, 2016-2018. JAMA Netw Open. 2023;6(5):1–14.

93. Laurent JS, Watts R, Adise S, Allgaier N, Chaarani B, Garavan H, et al. Associations among Body Mass Index, Cortical Thickness, and Executive Function in Children. JAMA Pediatr. 2020;174(2):170–7.

94. Ronan L, Alexander-Bloch A, Fletcher PC. Childhood Obesity, Cortical Structure, and Executive Function in Healthy Children. Cereb Cortex. 2020;30(4):2519–28.

95. Steegers C, Blok E, Lamballais S, Jaddoe V, Bernardoni F, Vernooij M, et al. The association between body mass index and brain morphology in children: a population-based study. Brain Struct Funct. 2021;226(3):787–800.

96. García-García I, Michaud A, Dadar M, Zeighami Y, Neseliler S, Collins DL, et al. Neuroanatomical differences in obesity: meta-analytic findings and their validation in an independent dataset. Int J Obes. 2019;43(5):943–51.

97. Pflanz CP, Tozer DJ, Harshfield EL, Tay J, Farooqi S, Markus HS. Central obesity is selectively associated with cerebral gray matter atrophy in 15,634 subjects in the UK Biobank. Int J Obes. 2022;46(5):1059–67.

98. Silva CCV, Jaddoe VWV, Muetzel RL, Santos S, El Marroun H. Body fat, cardiovascular risk factors and brain structure in school-age children. Int J Obes. 2021;45(11):2425–31.

99. Ross N, Yau PL, Convit A. Obesity, fitness, and brain integrity in adolescence. Appetite. 2015;93:44–50.

100. Gabay A, London S, Yates KF, Convit A. Does obesity-associated insulin resistance affect brain structure and function of adolescents differentially by sex? Psychiatry Res - Neuroimaging. 2022;319:1–9.

101. Shang X, Zhang X, Huang Y, Zhu Z, Zhang X, Liu J, et al. Association of a wide range of individual chronic diseases and their multimorbidity with brain volumes in the UK Biobank: A cross-sectional study. eClinicalMedicine. 2022;47:1–16.

102. Beyer F, Masouleh SK, Kratzsch J, Schroeter ML, Röhr S, Riedel-Heller SG, et al. A metabolic obesity profile is associated with decreased gray matter volume in cognitively healthy older adults. Front Aging Neurosci. 2019;11:1–14.

103. Ottino-González J, Jurado MA, García-García I, Segura B, Marqués-Iturria I, Sender-Palacios MJ, et al. Allostatic load is linked to cortical thickness changes depending on body-weight status. Front Hum Neurosci. 2017;11:1–11.

104. Ottino-González J, Jurado MA, García-García I, Segura B, Marqués-Iturria I, Sender-Palacios MJ, et al. Allostatic load and disordered white matter microstructure in overweight adults. Sci Rep. 2018;8(1):1–12.

105. Booth T, Royle NA, Corley J, Gow AJ, Valdés Hernández M del C, Muñoz Maniega S, et al. Association of allostatic load with brain structure and cognitive ability in later life. Neurobiol Aging. 2015;36(3):1390–9.

106. Daoust J, Schaffer J, Zeighami Y, Dagher A, García-García I, Michaud A. White matter integrity differences in obesity: A meta-analysis of diffusion tensor imaging studies. Neurosci Biobehav Rev. 2021;129:133–41.

107. Nouwen A, Chambers A, Chechlacz M, Higgs S, Blissett J, Barrett TG, et al. Microstructural abnormalities in white and gray matter in obese adolescents with and without type 2 diabetes. NeuroImage Clin. 2017;16:43–51.

108. Repple J, Karliczek G, Meinert S, Förster K, Grotegerd D, Goltermann J, et al. Variation of HbA1c affects cognition and white matter microstructure in healthy, young adults. Mol Psychiatry. 2021;26(4):1399–408.

109. Cox SR, Lyall DM, Ritchie SJ, Bastin ME, Harris MA, Buchanan CR, et al. Associations between vascular risk factors and brain MRI indices in UK Biobank. Eur Heart J. 2019;40(28):2290–9.

110. Jing J, Zhou Y, Pan Y, Cai X, Zhu W, Zhang Z, et al. Reduced white matter microstructural integrity in prediabetes and diabetes: A population-based study. eBioMedicine. 2022;82:1–13.

111. Zsoldos E, Filippini N, Mahmood A, Mackay CE, Singh-Manoux A, Kivimäki M, et al. Allostatic load as a predictor of grey matter volume and white matter integrity in old age: The Whitehall II MRI study. Sci Rep. 2018;8(1):1–11.

112. Ritchie SJ, Tucker-Drob EM, Cox SR, Dickie DA, del C. Valdés Hernández M, Corley J, et al. Risk and protective factors for structural brain ageing in the eighth decade of life. Brain Struct Funct. 2017;222(8):3477–90.

113. D'Amico D, Amestoy ME, Fiocco AJ. The association between allostatic load and cognitive function: A systematic and meta-analytic review. Psychoneuroendocrinology. 2020;121:104849.

114. Mina T, Yew YW, Ng HK, Sadhu N, Wansaicheong G, Dalan R, et al. Adiposity impacts cognitive function in Asian populations: an epidemiological and Mendelian Randomization study. Lancet Reg Heal - West Pacific. 2023;33:100710.

115. Favieri F, Forte G, Casagrande M. The executive functions in overweight and obesity: A systematic review of neuropsychological cross-sectional and longitudinal studies. Front Psychol. 2019;10:1–27.

116. Mamrot P, Hanć T. The association of the executive functions with overweight and obesity indicators in children and adolescents: A literature review. Neurosci Biobehav Rev. 2019;107:59–68.

117. Yang Y, Shields GS, Guo C, Liu Y. Executive function performance in obesity and overweight individuals: A meta-analysis and review. Neurosci Biobehav Rev. 2018;84(2):225–44.

118. Broadley MM, White MJ, Andrew B. A Systematic Review and Meta-analysis of Executive Function Performance in Type 1 Diabetes Mellitus. Psychosom Med. 2017;79(6):684–96.

119. Sadanand S, Balachandar R, Bharath S. Memory and executive functions in persons with type 2 diabetes: a meta-analysis. Diabetes Metab Res Rev. 2016;32(30):13–23.

120. Bugge A, Möller S, Westfall DR, Tarp J, Gejl AK, Wedderkopp N, et al. Associations between waist circumference, metabolic risk and executive function in adolescents: A cross-sectional mediation analysis. PLoS One. 2018;13(6):1–13.

121. Falkowski J, Atchison T, Debutte-Smith M, Weiner MF, O'Bryant S. Executive functioning and the metabolic syndrome: A project FRONTIER study. Arch Clin Neuropsychol. 2014;29(1):47–53.

122. Kazlauskaite R, Janssen I, Wilson RS, Appelhans BM, Evans DA, Arvanitakis Z, et al. Is midlife metabolic syndrome associated with cognitive function change? The study of women's health across the nation. J Clin Endocrinol Metab. 2020;105(4):E1093–105.

123. Emery RL, Levine MD. Questionnaire and behavioral task measures of impulsivity are differentially associated with body mass index: A comprehensive meta-analysis. Front Physiol. 2017;143(8):868–902.

124. Bickel WK, Freitas-Lemos R, Tomlinson DC, Craft WH, Keith DR, Athamneh LN, et al. Temporal discounting as a candidate behavioral marker of obesity. Neurosci Biobehav Rev [Internet]. 2021;129(March):307–29. Available from: https://doi.org/10.1016/j.neubiorev.2021.07.035

125. Salas J, van den Berk-Clark C, Skiöld-Hanlin S, Schneider FD, Scherrer JF. Adverse childhood experiences, depression, and cardiometabolic disease in a nationally representative sample. J Psychosom Res. 2019;127:109842.

126. Sutin AR, Terracciano A, Deiana B, Uda M, Schlessinger D, Lakatta EG, et al. Cholesterol, triglycerides, and the Five-Factor Model of personality. Biol Psychol. 2010;84(2):186–91.

127. Schwartz JA, Rowland MW, Beaver KM. A genetically informed test of cholesterol levels and self-control, depressive Symptoms, antisocial behavior, and neuroticism. J Affect Disord. 2014;164:139–47.

128. Gendle MH, Flashburg AG, Higgins KL, Oristian KM. Low Total Cholesterol Levels and Performance on the Iowa Gambling Task. J North Carolina Acad Sci. 2015;131(2):19–24.

129. Schmidt B, Bosch JA, Jarczok MN, Herr RM, Loerbroks A, Van Vianen AEM, et al. Effort-reward imbalance is associated with the metabolic syndrome - Findings from the Mannheim Industrial Cohort Study (MICS). Int J Cardiol. 2015;178:24–8.

130. Juster RP, Sindi S, Marin MF, Perna A, Hashemi A, Pruessner JC, et al. A clinical allostatic load index is associated with burnout symptoms and hypocortisolemic profiles in healthy workers. Psychoneuroendocrinology. 2011;36(6):797–805.

131. Finlay S, Roth C, Zimsen T, Bridson TL, Sarnyai Z, McDermott B. Adverse childhood experiences and allostatic load: A systematic review. Neurosci Biobehav Rev. 2022;136:104605.

132. Stam CJ. Hub overload and failure as a final common pathway in neurological brain network disorders. Netw Neurosci. 2024;8(1):1–23.

133. Zhou Y, Jing J, Zhang Z, Pan Y, Cai X, Zhu W, et al. Disrupted pattern of rich-club organization in structural brain network from prediabetes to diabetes: A population-based study. Hum Brain Mapp. 2024;45:e26598.

134. García-García I, Morys F, Dagher A. Nucleus accumbens volume is related to obesity measures in an age-dependent fashion. J Neuroendocrinol. 2020;32(12):1–12.

135. Okudzhava L, Schulz S, Fischi-Gomez E, Girard G, Machann J, Koch PJ, et al. White adipose tissue distribution and amount are associated with increased white matter connectivity. Hum Brain Mapp. 2024;45(5):1–11.

136. Edwin Thanarajah S, Hanssen R, Melzer C, Tittgemeyer M. Increased meso-striatal connectivity mediates trait impulsivity in FTO variant carriers. Front Endocrinol (Lausanne). 2023;14:1130203.

137. Annapoorna PK, Iyer H, Parnaik T, Narasimhan H, Bhattacharya A, Kumar A. FTO: An Emerging Molecular Player in Neuropsychiatric Diseases. Neuroscience. 2019;418:15–24.

138. Lugo-Candelas C, Pang Y, Lee S, Cha J, Hong S, Ranzenhofer L, et al. Differences in brain structure and function in children with the FTO obesity-risk allele. Obes Sci Pract. 2020;6(4):409–24.

139. Rapuano KM, Zieselman AL, Kelley WM, Sargent JD, Heatherton TF, Gilbert-Diamond D. Genetic risk for obesity predicts nucleus accumbens size and responsivity to real-world food cues. Proc Natl Acad Sci U S A. 2017;114(1):160–5.

140. Thapaliya G, Kundu P, Jansen E, Naymik MA, Lee R, Bruchhage MMK, et al. FTO variation and early frontostriatal brain development in children. Obesity. 2024;32(1):156–65.

141. Ho AJ, Stein JL, Hua X, Lee S, Hibar DP, Leow AD, et al. A commonly carried allele of the obesity-related FTO gene is associated with reduced brain volume in the healthy elderly. Proc Natl Acad Sci U S A. 2010;107(18):8404–9.

142. De Groot C, Felius A, Trompet S, De Craen AJM, Blauw GJ, Van Buchem MA, et al. Association of the fat mass and obesity-associated gene risk allele, rs9939609A, and reward-related brain structures. Obesity. 2015;23:2118–22.

143. Olivo G, Latini F, Wiemerslage L, Larsson EM, Schiöth HB. Disruption of accumbens and thalamic white matter connectivity revealed by diffusion tensor tractography in young men with genetic risk for obesity. Front Hum Neurosci. 2018;12(75):1–10.

144. Khera A V., Chaffin M, Wade KH, Zahid S, Brancale J, Xia R, et al. Polygenic Prediction of Weight and Obesity Trajectories from Birth to Adulthood. Cell. 2019;177(3):587–96.

145. Hess ME, Hess S, Meyer KD, Verhagen LAW, Koch L, Brönneke HS, et al. The fat mass and obesity associated gene (Fto) regulates activity of the dopaminergic midbrain circuitry. Nat Neurosci. 2013;16(8):1042–8.

146. Sevgi M, Rigoux L, Kühn AB, Mauer J, Schilbach L, Hess ME, et al. An obesity-predisposing variant of the FTO gene regulates D2R-dependent reward learning. J Neurosci. 2015;35(36):12584–92.

147. Vergoossen LWM, Jansen JFA, Backes WH, Schram MT. Cardiometabolic determinants of early and advanced brain alterations: Insights from conventional and novel MRI techniques. Neurosci Biobehav Rev. 2020;115:308–20.

148. Veeranna V, Ramesh K, Zalawadiya SK, Niraj A, Pradhan J, Jacob S, et al. Glycosylated hemoglobin and prevalent metabolic syndrome in nondiabetic multiethnic U.S. adults. Metab Syndr Relat Disord. 2011;9(5):361–7.

149. Cacciatore M, Grasso EA, Tripodi R, Chiarelli F. Impact of glucose metabolism on the developing brain. Front Endocrinol (Lausanne). 2022;13:1047545.

150. Nathan DM, Turgeon H, Regan S. Relationship between glycated haemoglobin levels and mean glucose levels over time. Diabetologia. 2007;50(11):2239–44.

151. Barnea-Goraly N, Raman M, Mazaika P, Marzelli M, Hershey T, Weinzimer SA, et al. Alterations in white matter structure in young children with type 1 diabetes. Diabetes Care. 2014;37(2):332–40.

152. Alfaro FJ, Gavrieli A, Saade-Lemus P, Lioutas VA, Upadhyay J, Novak V. White matter microstructure and cognitive decline in metabolic syndrome: a review of diffusion tensor imaging. Metabolism. 2018;78:52–68.

153. Steinberger J, Daniels SR, Hagberg N, Isasi CR, Kelly AS, Lloyd-Jones D, et al. Cardiovascular Health Promotion in Children: Challenges and Opportunities for 2020 and Beyond: A Scientific Statement from the American Heart Association. Circulation. 2016;134(12):e236–55.

154. Stavnsbo M, Resaland GK, Anderssen SA, Steene-Johannessen J, Domazet SL, Skrede T, et al. Reference values for cardiometabolic risk scores in children and adolescents: Suggesting a common standard. Atherosclerosis. 2018;278:299–306.

155. Mattavelli G, Gorrino I, Tornaghi D, Canessa N. Cognitive and motor impulsivity in the healthy brain, and implications for eating disorders and obesity: A coordinate-based meta-analysis and systematic review. Cortex. 2024;171:90–112.

156. Aoun C, Nassar L, Soumi S, El Osta N, Papazian T, Rabbaa Khabbaz L. The Cognitive, Behavioral, and Emotional Aspects of Eating Habits and Association With Impulsivity, Chronotype, Anxiety, and Depression: A Cross-Sectional Study. Front Behav Neurosci. 2019;13(204).

157. Lattimore P, Fisher N, Malinowski P. A cross-sectional investigation of trait disinhibition and its association with mindfulness and impulsivity. Appetite. 2011;56(2):241–8.

158. Koponen H, Kautiainen H, Leppänen E, Mäntyselkä P, Vanhala M. Association between suicidal behaviour and impaired glucose metabolism in depressive disorders. BMC Psychiatry. 2015;15(1):1–8.

159. Qing G, Deng W, Zhou Y, Zheng L, Wang Y, Wei B. The association between non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR) and kidney stones: a cross-sectional study. Lipids Health Dis. 2024;23(1):1–10.

160. Herceg D, Mimica N, Herceg M, Puljić K. Aggression in Women with Schizophrenia Is Associated with Lower HDL Cholesterol Levels. Int J Mol Sci. 2022;23(19).

161. Hjell G, Mørch-Johnsen L, Holst R, Tesli N, Bell C, Lunding SH, et al. Disentangling the relationship between cholesterol, aggression, and impulsivity in severe mental disorders. Brain Behav. 2020;10(9):1–13.

162. Dong R, Haque A, Wu HE, Placide J, Yu L, Zhang X. Sex differences in the association between suicide attempts and glucose disturbances in first-episode and drug naive patients with major depressive disorder. J Affect Disord. 2021;292:559–64.

163. Seeman TE, Singer BH, Rowe JW, Horwitz RI, Mcewen BS. Price of Adaptation—Allostatic Load and Its Health Consequences. MacArthur Studies of Successful Aging. Arch Intern Med. 1997;157(19):2259–68.

164. Carbone JT, Clift J, Alexander N. Measuring allostatic load: Approaches and limitations to algorithm creation. J Psychosom Res. 2022;163:111050.

165. Holochwost SJ, Volpe V V., Collins AN, Propper CB, Mills-Koonce WR, Brown ED, et al. Allostatic Load in Childhood, Adolescence, and Young Adulthood: Are Assumptions of Measurement Invariance Warranted? Psychosom Med. 2024;86(3):169–80.

166. Whelan E, O'Shea J, Hunt E, Dockray S. Evaluating measures of allostatic load in adolescents: A systematic review. Psychoneuroendocrinology. 2021;131:105324.

167. Shields GS, Sazma MA, Yonelinas AP. The effects of acute stress on core executive functions: A meta-analysis and comparison with cortisol. Neurosci Biobehav Rev. 2016;68:651–68.

168. Lucente M, Guidi J. Allostatic Load in Children and Adolescents: A Systematic Review. Psychother Psychosom. 2023;92(5):295–303.

169. Fava GA, Sonino N, Lucente M, Guidi J. Allostatic Load in Clinical Practice. Clin Psychol Sci. 2023;11(2):345–56.

170. Vaidya N, Marquand AF, Nees F, Siehl S, environMENTAL and IMAGEN consortium, Schumann G. The impact of psychosocial adversity on brain and behaviour: an overview of existing knowledge and directions for future research. Mol Psychiatry. 2024;1–23.

171. Op den Kelder R, Van den Akker AL, Geurts HM, Lindauer RJL, Overbeek G. Executive functions in trauma-exposed youth: a meta-analysis. Eur J Psychotraumatol. 2018;9(1).

172. Johnson D, Policelli J, Li M, Dharamsi A, Hu Q, Sheridan MA, et al. Associations of Early-Life Threat and Deprivation with Executive Functioning in Childhood and Adolescence: A Systematic Review and Meta-analysis. JAMA Pediatr. 2021;175(11):1–10.

173. Ellis BJ, Bianchi JM, Griskevicius V, Frankenhuis WE. Beyond Risk and Protective Factors: An Adaptation-Based Approach to Resilience. Perspect Psychol Sci. 2017;12(4):561–87.

174. Trudel-Fitzgerald C, Ouellet-Morin I. The cost of resilience: How allostatic load may jeopardize health through repeated demands for (successful) adaptation. Psychoneuroendocrinology. 2022;144.

175. De Bellis MD, Zisk A. The Biological Effects of Childhood Trauma. Child Adolesc Psychiatr Clin N Am. 2014;23(2):185–222.

176. Danese A, Moffitt TE, Arseneault L, Bleiberg BA, Dinardo PB, Gandelman SB, et al. The origins of cognitive deficits in victimized children: Implications for neuroscientists and clinicians. Am J Psychiatry. 2017;174(4):349–61.

177. D'Amico D, Amestoy ME, Fiocco AJ. The mediating role of allostatic load in the relationship between early life adversity and cognitive function across the adult lifespan. Psychoneuroendocrinology. 2022;141.