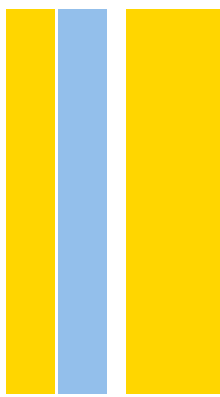


**MESTRADO**  
SAÚDE PÚBLICA

**Disordered eating, accumulated adiposity  
and cardiometabolic health:  
a longitudinal perspective throughout  
childhood, adolescence and young adulthood**  
Rita Bouça Soares Pereira

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**Disordered eating, accumulated adiposity and cardiometabolic health:  
a longitudinal perspective throughout childhood, adolescence and  
young adulthood**

Rita Bouça Soares Pereira

Dissertação de candidatura ao grau de Mestre em Saúde Pública apresentada  
à Faculdade de Medicina e Instituto de Ciências Biomédicas Abel Salazar da  
Universidade do Porto, Portugal

**Orientadora:** Professora Doutora Andreia Oliveira

**Coorientadora:** Professora Doutora Joana Araújo

**Afiliações:** EPIUnit - Instituto de Saúde Pública, Universidade do Porto, Rua das  
Taipas; Laboratório para a Investigação Integrativa e Translacional em Saúde  
Populacional (ITR), Universidade do Porto e Departamento de Saúde Pública e  
Ciências Forenses e Educação Médica, Faculdade de Medicina, Universidade  
do Porto

*Cada segundo de incertidumbre, cada momento de no saber  
Son la clave exacta de este tejido que llevo cargando bajo la piel.*

Natalia Lafourcade

Este trabalho foi elaborado no âmbito das coortes Geração XXI e EPITeen e desenvolvido no Departamento de Ciências da Saúde Pública e Forenses, e Educação Médica da Faculdade de Medicina da Universidade do Porto e no Instituto de Saúde Pública da Universidade do Porto. A sua realização só foi possível com a participação das crianças, adolescentes e famílias que aceitaram este desafio, às quais agradecemos a sua disponibilidade. A Coorte Geração XXI foi financiada pelo Programa Operacional de Saúde – Saúde XXI, Quadro Comunitário de Apoio III, pela Administração Regional de Saúde do Norte, pela Fundação Calouste Gulbenkian e pela Fundação para a Ciência e a Tecnologia. A coorte EPITeen foi financiada pela Fundação para a Ciência e a Tecnologia e pela Unidade de Investigação em Epidemiologia – Instituto de Saúde Pública da Universidade do Porto.

A presente dissertação é composta por uma introdução teórica, seguida por dois manuscritos, nos quais colaborei ativamente na formulação de hipóteses, análise de dados, interpretação de resultados, escrita e discussão científicas:

Artigo I: The association between the duration and degree of adiposity and appetitive behaviours profiles from childhood into early adolescence – results from the Generation XXI cohort

Artigo II: Disordered eating profiles and cardiometabolic health from early adolescence to early adulthood – findings from the EPITeen cohort

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## RESUMO

**Introdução:** Os comportamentos alimentares ocorrem num espectro, variando entre comportamentos saudáveis e comportamentos alterados. Os comportamentos alimentares alterados têm um grande impacto na saúde e bem-estar dos indivíduos, e englobam tanto uma componente cognitiva (como preocupações com o peso e insatisfação corporal), como uma componente comportamental (como a compulsão alimentar, a indução do vômito e comportamentos relacionados com o apetite). A teoria da suscetibilidade comportamental da obesidade sugere que os comportamentos relacionados com o apetite influenciam o risco de ganho de peso no atual ambiente obesogénico. Contudo, a ainda crescente evidência de estudos prospetivos parece indicar que, enquanto durante o início da infância os comportamentos alimentares relacionados com o apetite têm uma maior influência no peso, durante fases mais tardias da infância, o apetite poderá ser uma consequência mais evidente do peso e crescimento do corpo. Contudo, segundo o nosso melhor conhecimento, nenhum estudo até à data testou esta associação usando uma medida cumulativa de adiposidade durante a infância. Já na adolescência, um período particularmente vulnerável, as preocupações com a imagem corporal e o peso, bem como outras componentes dos comportamentos alimentares alterados, tornam-se altamente prevalentes, normalmente persistindo até à idade adulta. Os comportamentos alimentares alterados na adolescência e idade adulta têm sido associados a um posterior ganho de peso e obesidade - condições que podem ocorrer simultaneamente com outros fatores de risco cardiometabólico. No entanto, a evidência sobre o impacto dos comportamentos alimentares alterados na saúde cardiometabólica nesta fase de vida é escassa. Adicionalmente, uma abordagem *'person-centred'* parece ser um método pouco comum mas promissor na compreensão de como os comportamentos alimentares alterados se podem agregar e evoluir ao longo do tempo, contribuindo assim para identificar grupos de indivíduos em risco.

**Objetivos:** Estudar os comportamentos alimentares alterados, o seu desenvolvimento e consequências para a saúde, ao longo de diferentes fases de vida. Para dar resposta a este objetivo geral, foram realizados dois artigos distintos. O artigo I pretende avaliar a associação entre uma medida cumulativa do índice de massa corporal (IMC) (como um indicador de adiposidade), ao longo da infância até ao início da adolescência (4-13 anos), com perfis de comportamentos do apetite (7-13 anos); e adicionalmente explorar a associação do IMC em idades específicas

com perfis de comportamentos do apetite, independentemente da medida de IMC cumulativo. O artigo II pretende avaliar a associação entre perfis de comportamentos alimentares alterados desde o início da adolescência até ao início da idade adulta (13-21 anos) com o IMC e outras componentes cardiometabólicas associadas, aos 21 anos.

**Métodos:** O artigo I incluiu dados da Geração XXI (G21), uma coorte de nascimentos de base populacional recrutada no Porto, Portugal. As mães que deram à luz um nado-vivo, entre 2005/2006, e residentes na área de abrangência foram consideradas elegíveis. Um total de 8945 mães e 8647 recém-nascidos integraram o estudo. As reavaliações ocorreram posteriormente aos 4, 7, 10 e 13 anos, com uma proporção de participação de 86%, 80%, 74% e 54% (reavaliação interrompida devido à pandemia por COVID-19), respetivamente. A amostra final inclui 3339 participantes, utilizando-se dados de todas as avaliações. No artigo II, os participantes fazem parte do estudo EPITeen – Investigação Epidemiológica de Saúde de Adolescentes no Porto, uma coorte de base populacional de adolescentes nascidos em 1990 a frequentar escolas públicas e privadas no Porto, Portugal, em 2003/2004. A avaliação inicial ocorreu aos 13 anos, quando 77,5% dos 2786 participantes elegíveis consentiram participar (n=2159). As reavaliações ocorreram aos 17, 21, 24 e 27 anos. Aos 17 anos, 783 novos participantes integraram o estudo e 79,5% da avaliação *baseline* foram reavaliados; aos 21 anos, foi realizada a reavaliação de 70,6% dos indivíduos. A amostra final foi composta por 1619 participantes, utilizando-se dados das três primeiras avaliações (13, 17 e 21 anos). Na Geração XXI, os comportamentos alimentares alterados foram avaliados através do questionário validado *Children's Eating Behavior Questionnaire* (comportamentos de 'aproximação' e de 'afastamento' alimentar) aos 7, 10 e 13 anos, e os perfis de comportamento do apetite foram obtidos usando modelos de efeitos lineares mistos e, posteriormente, modelos de mistura Gaussiana. No EPITeen, os comportamentos alimentares alterados foram avaliados pelo *Eating Disorder Inventory* (subescalas 'Impulso para Emagrecer', 'Insatisfação Corporal' e 'Bulimia') aos 13, 17 e 21 anos e os perfis foram obtidos através de uma análise de classes latentes.

Em ambas as coortes, a avaliação antropométrica foi realizada por investigadores treinados, segundo os procedimentos padronizados. Até aos 17 anos, os valores de IMC e scores de desvio padrão de IMC (IMC z-score) foram calculados segundo a

referência e padrão de crescimento da Organização Mundial da Saúde (OMS). Aos 21 anos, foram considerados os pontos de corte para adultos da OMS.

No artigo I, a adiposidade cumulativa foi representada pelo grau e duração de IMC, calculando-se a área sob a curva do IMC ( $IMC_{AUC}$ ), que foi obtida a partir de uma interpolação de *spline* cúbica. Associações entre  $IMC_{AUC}$  e os perfis de comportamentos do apetite foram testadas por meio de regressões logísticas multinomiais, ajustadas para o sexo da criança, idade e escolaridade da mãe e tabagismo durante a gravidez.

No artigo II, os *outcomes* considerados foram o IMC e ter  $\geq 1$  componente de síndrome metabólico (SM): pressão arterial sistólica  $\geq 130$  e/ou diastólica  $\geq 85$  mmHg; colesterol de lipoproteína de baixa intensidade (HDL-c)  $< 40$  mg/dL, em homens, e  $< 50$  mg/dL em mulheres; triglicerídeos  $\geq 150$  mg/dL; glicose em jejum  $\geq 100$  mg/dL e perímetro da cintura  $\geq 94$  cm, em homens, e  $\geq 80$  cm em mulheres. A pressão arterial foi medida de acordo com as recomendações das Sociedades Americana e Internacional de Hipertensão. Os lípidos sanguíneos e a glicose foram medidas após jejum noturno. Modelos lineares generalizados e regressões logísticas binárias testaram as associações entre os perfis de comportamentos alimentares alterados e IMC e ter  $\geq 1$  componente de SM, respetivamente. As associações foram estratificadas por sexo e ajustadas para a escolaridade mais elevada dos pais, assim como para escolaridade, frequência de consumo de hortícolas e prática de desporto ou exercício dos participantes aos 21 anos.

**Resultados:** No artigo I foram obtidos seis perfis de comportamentos do apetite ao longo da infância até à adolescência: um perfil de 'apetite moderado' (25,6%); dois perfis de apetite extremos: o 'apetite ávido' (11,3%) e o 'menor apetite' (10,6%); e outros três: 'apetite pequeno, mas crescente' (7,8%), 'apetite pequeno a moderado' (27,9%) e 'apetite crescente' (16,8%). Em comparação com o 'apetite moderado', foi encontrada uma associação positiva entre o  $IMC_{AUC}$  e o perfil 'apetite ávido' (OR=1,47; IC 95%: 1,40-1,55), e negativa com os restantes perfis, nomeadamente o perfil de 'menor apetite' (OR=0,78; IC 95%: 0,73-0,83). Não foram encontradas associações significativas com o perfil de 'apetite crescente'. Independentemente da exposição cumulativa ao IMC ao longo da infância, ter excesso de peso/obesidade aos 7 anos aumentou em 113% as *odds* de pertencer a um perfil de 'apetite ávido' (OR=2,13; IC 95%: 1,42-3,21).

No artigo II foram identificados quatro perfis de comportamentos alimentares alterados ao longo da adolescência até ao início da idade adulta: dois perfis mais

extremos - perfil de comportamentos alimentares alterados 'mais altos' (18,6%) e 'mais baixos' (35,1%); e 'decrecentes' (18,7%) e 'crescentes' (27,6%). Cerca de um terço (32,3%) da amostra apresentou pelo menos um componente de SM e 1,3% apresentavam os critérios de diagnóstico de SM ( $\geq 3$  componentes). Em comparação com o perfil de níveis 'mais baixos', ambos os sexos (e particularmente o sexo masculino) com comportamentos alimentares alterados 'mais altos' e 'crescentes' apresentaram valores de IMC aumentados aos 21 anos. Indivíduos do sexo masculino que pertenciam aos perfis de níveis 'mais altos' (OR=4,50; IC 95%: 2,48-8,14) e 'crescentes' (OR=2,21; IC 95%: 1,50-3,26), apresentaram igualmente maiores *odds* de ter  $\geq 1$  componente de SM aos 21 anos. Por sua vez, o sexo feminino no perfil de níveis 'mais altos' de comportamentos alimentares alterados foi 116% mais provável de apresentar  $\geq 1$  componente de SM aos 21 anos (OR=2,16; IC 95%: 1,44-3,24).

**Conclusão:** Crianças com maior e menor exposição cumulativa a adiposidade ao longo da infância e início da adolescência foram mais propensas a apresentar um perfil de 'apetite ávido' (mais comportamentos de 'aproximação' alimentar) e o perfil de 'menor apetite' (mais comportamentos de 'afastamento' alimentar), respetivamente. Além disso, ter excesso de peso aos 7 anos poderá ser já indicativo de que a criança apresenta um perfil de 'apetite ávido'. Entre a adolescência e o início da idade adulta, os níveis de comportamentos alimentares alterados parecem evoluir de maneira diferente. Estar insatisfeito com a própria imagem corporal e desejar uma silhueta mais magra são duas dimensões comuns dos comportamentos alimentares alterados. Em ambos os sexos, mas particularmente no sexo masculino, os perfis com níveis 'mais altos' e 'crescentes' revelaram-se os mais preocupantes, já que mostraram associações positivas com o IMC e com a presença de  $\geq 1$  componente de SM aos 21 anos.

Estes dois artigos reforçam, por um lado, a importância de controlar o ganho de peso no início da infância de modo a evitar que as crianças desenvolvam um perfil de apetite obesogénico. Por outro lado, os resultados destacam o potencial impacto negativo dos comportamentos alimentares alterados, pela sua associação com o IMC aumentado e disfunção do funcionamento metabólico. Indivíduos (particularmente do sexo masculino) com níveis 'mais altos' ou 'crescentes' de comportamentos alimentares alterados podem apresentar maior risco de saúde cardiometabólica alterada aos 21 anos.

## ABSTRACT

**Background:** Eating behaviours occur on a spectrum, ranging from healthy to disordered. Disordered eating has great impact on individuals' health and well-being and comprises both cognitive components (such as weight concerns and body dissatisfaction), as well as behavioural components (such as binge eating, purging and appetitive behaviours). The behavioural susceptibility theory of obesity suggests that appetitive behaviours influence the risk of weight gain in the current obesogenic environment. Yet, growing prospective evidence indicates that while during infancy appetitive behaviours may have a greater influence on weight, during childhood, appetite may result as a more vivid consequence of body weight and growth. However, no study has, to our knowledge, tested associations using a cumulative measure of adiposity throughout childhood. In adolescence, a particularly vulnerable period, body image and weight concerns as well as other behavioural components of disordered eating become highly prevalent, commonly persisting into adulthood. Disordered eating in adolescence and young adulthood has been associated with future weight gain and obesity; conditions that can co-occur with other cardiometabolic risk factors. Yet, small is the evidence about the impact of disorder eating on cardiometabolic health outcomes at this life stage. In addition, a person-centred approach seems an infrequent, but promising method for capturing how disordered eating components can cluster and evolve across time, helping identify 'at risk' groups of individuals.

**Objective:** To study disordered eating, its development and health consequences, throughout different developmental stages of life. To accomplish this aim, two distinct papers were written. Paper I aims to test associations between a cumulative measure of BMI (as an indicator of adiposity), throughout childhood into early adolescence (4-13 years old (y)), and appetitive behaviours profiles (7-13y); and additionally to explore the association of BMI at specific ages with appetite profiles development, independently of the cumulative BMI. Paper II aims to test associations between disordered eating profiles from adolescence to young adulthood (13-21y) with both BMI and other related cardiometabolic features at 21y.

**Methods:** Paper I includes data from Generation XXI (G21), a population-based birth cohort assembled in Porto, Portugal. Mothers delivering a live-born child, between April 2005 and September 2006, and living in the catchment area were eligible for the study. A total of 8945 mothers and 8647 newborns enrolled the study. Participants were re-evaluated at 4y, 7y, 10y, and 13y, with a participation proportion of 86%,

80%, 74% and 54% (interrupted earlier due to COVID-19), respectively. The final sample was composed of 3339 participants using data from all the assessments. In paper II, participants are part of the EPITeen study – Epidemiological Health Investigation of Teenagers in Porto, a population-based cohort of adolescents born in 1990 attending public and private schools in Porto, Portugal, in 2003/2004. The baseline assessment occurred at 13y, when 77.5% of the 2786 eligible participants agreed to participate (n=2159). Re-evaluations occurred at 17y, 21y, 24y and 27y. At 17y, 783 new participants enrolled in the study and 79.5% from the baseline were re-evaluated and, at the 21y follow-up, 70.6% of individuals were reassessed. The final sample was composed of 1619 participants using data from the first three assessments (13, 17 and 21y).

In Generation XXI, disordered eating was assessed through the validated Children's Eating Behaviour Questionnaire (food approach and food avoidant appetitive behaviours) at 7y, 10y and 13y, and appetitive behaviours profiles were derived using linear mixed effect models followed by Gaussian mixture models. In EPITeen, disordered eating was assessed through the Eating Disorder Inventory ('Drive for Thinness', 'Body Dissatisfaction' and 'Bulimia' subscales) at 13y, 17y and 21y, and profiles were derived through a latent class analysis.

In both cohorts, anthropometric evaluation was done by trained researchers according to standardised procedures. Up to the age of 17, BMI values and BMI standard deviation scores (BMI z-scores) were calculated according to the World Health Organisation (WHO) growth standards and reference. At 21 y, the WHO cut-off points for adults were considered.

In paper I, the duration and degree of adiposity were summarized calculating the BMI area under the curve ( $BMI_{AUC}$ ), obtained from a cubic spline interpolation. Associations between  $BMI_{AUC}$  and appetitive behaviours profiles were tested using multinomial logistic regressions, adjusted for child's sex, mother's age, education and smoking during pregnancy.

In paper II, the outcomes considered were BMI and having  $\geq 1$  metabolic syndrome component (MetS): systolic  $\geq 130$  and/or diastolic BP  $\geq 85$ mmHg; high-density lipoprotein cholesterol (HDL-c)  $< 40$ mg/dL in men and  $< 50$ mg/dL in women; triglycerides  $\geq 150$ mg/dL; fasting glucose  $\geq 100$ mg/dL and waist circumference (WC)  $\geq 94$ cm in men and  $\geq 80$ cm in women. Blood pressure was measured according to the guidelines of the American and International Societies of Hypertension. Blood lipids and glucose were obtained after overnight fasting. Generalised linear models and

binary logistic regressions tested the associations between disordered eating profiles and BMI and having  $\geq 1$  component of MetS, respectively. Associations were stratified by sex and adjusted for the highest parental education; as well as for education, frequency of vegetables consumption and sports or exercise practice of the participants at 21y.

**Results:** In paper I, six different appetitive behaviours profiles were obtained throughout childhood into adolescence: a 'moderate appetite' (25.6%); two extreme profiles: the 'avid appetite' (11.3%) and the 'smallest appetite' (10.6%); and other three: 'small but increasing appetite' (7.8%), 'small to moderate appetite' (27.9%), and 'increasing appetite' (16.8%). In comparison to the 'moderate appetite', BMI<sub>AUC</sub> was positively associated with the 'avid appetite' (OR=1.47, 95%CI: 1.40-1.55), and negatively associated with the remaining profiles, particularly with 'smallest appetite' (OR=0.78, 95%CI: 0.73-0.83). The 'increasing appetite' profile yield no significant associations. Regardless of the cumulative exposure to BMI, having overweight/obesity at 7y increased 113% the odds of belonging to an 'avid appetite' profile (OR=2.13 95%CI: 1.42-3.21).

In paper II, four disordered eating profiles were identified throughout adolescence into young adulthood: two more extreme profiles - 'higher' (18.6%) and 'lower' (35.1%) disordered eating profiles; and the 'decreasing' (18.7%) and 'increasing' (27.6%) profiles. Around one third (32.3%) of the sample presented  $\geq 1$  MetS component and 1.3% met criteria for MetS diagnosis ( $\geq 3$  components). In comparison to the 'lower disordered eating' profile, both sexes (particularly males) with 'higher' and 'increasing' disordered eating presented increased BMI values at 21y. Males in the 'higher' (OR=4.50; 95%CI 2.48-8.14) and 'increasing' (OR=2.21; 95%CI 1.50-3.26) profiles also presented higher odds of having  $\geq 1$  MetS component at 21y. In its turn, females in the 'higher' profile were 116% more likely to present at  $\geq 1$  MetS component (OR=2.16; 95%CI 1.44-3.24).

**Conclusion:** Children with the highest and lowest cumulative exposure to adiposity throughout childhood and early adolescence were more likely to present the 'avid appetite' (overall high food approach behaviours) and the 'smallest appetite' profile (overall high food avoidant behaviours), respectively. Additionally, having excessive weight at 7y may be already indicative of being an avid eater. Between adolescence and young adulthood, disordered eating levels seem to evolve differently. Being dissatisfied with one's body image and desiring for a thinner silhouette are two common disordered eating dimensions. The 'higher disordered eating' and the

‘increasing disordered eating’ profiles revealed to be the most concerning ones, showing positive associations with BMI and having  $\geq 1$  MetS component at 21y for both sexes, but particularly among males.

These two papers reinforce, on the one hand, the importance of curbing weight gain in early childhood to protect children from the development of obesity-related appetite profiles. On the other, they raise awareness on the potential harm of disordered eating as a correlate of later increased BMI and disadvantaged metabolic functioning. Individuals (particularly males) with higher or increasing levels of disordered eating, may be at increased risk of altered cardiometabolic health at 21y.

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## **ABBREVIATION LIST**

ARFID - Avoidant restrictive food intake disorder rumination disorder  
BIC - Bayesian information criterion  
BDNF - Brain-derived neurotrophic factor  
BMI – Body mass index  
BMI z-scores – BMI standard deviation scores  
BMI<sub>AUC</sub> – BMI area under the curve  
CCK – Cholecystokinin  
CEBQ – Children’s Eating Behaviour Questionnaire  
COMT - Catechol-O-methyltransferase  
DEBQ - Dutch Eating Behaviour Questionnaire  
DSM-V - Diagnostic and Statistical Manual of Mental Disorders  
EAT - Eating Attitudes Test  
EDE -Q - Eating Disorder Examination Questionnaire  
EDI – Eating Disorder Inventory  
FTO - Fat mass and obesity related  
GBD - Global Burden of Diseases Study  
GLP-1 - Glucagon-like peptide 1  
HAES - Health at Every Size®  
HDL-c – High density lipoprotein cholesterol  
ICC – Intraclass correlation coefficient  
LDL-c - Low-density lipoprotein cholesterol  
MetS – Metabolic Syndrome  
Nw - Normal weight  
Ob - Obesity  
OSFED - Other specified feeding or eating disorders  
Ow - Overweight  
PYY - Peptide Y  
RMR - Resting metabolic rate  
TFEQ - Three Factor Eating Questionnaire  
Uw - Underweight  
WHO - World Health Organisation

# INTRODUCTION

## 1. The spectrum of eating behaviours

Eating behaviours arise from the interaction between an internal biological need along with an environmental exposure to factors such as food supply, economic conditions, culture, among others [1, 2]. Eating behaviours include what, how much, and timing to eat [3].

Ideally, we would eat according to our internal signals of hunger and satiety and the hedonic system would be paired with an efficient homeostatic system. Homeostatic processes mediate internal biological needs (i.e. need for energy) and the action of eating, prompted by feelings of hunger and inhibited by feelings of satiety [4]. Hedonic processes, in its turn, reflect food intake driven by reward and the desire for pleasurable taste food, usually generated by external food cues such as taste and smell, and food thoughts [5].

However, the controlling system of appetite seems to be asymmetrical, as it is more permissive to overconsumption without the establishment of a biological drive to undereat [1]. Historically, in the context of food scarcity and unpredictability of food intake, the efficient ability to store excess energy intake into body fat was a question of survival [6, 7]. Yet, in the current obesogenic food environment, hedonic or reward driven food intake may lead to overriding of homeostatic satiety signals and result in increased consumption, meal size and eating despite feelings of hunger [8, 9]. This is called an 'evolutionary mismatch', a concept that represents traits and characteristics that were once useful in a particular context but maladaptive in a different one. The rapid changes in evolution and in the environment are not always accompanied by a genetic adaption, turning those traits into potentially harmful [10].

Individuals can intentionally try to control and restrict their food consumption, engaging in behaviours to reduce or counteract their intake [1, 2]. Reasons for doing so can vary from, for instance, political reasons (such as a hunger strike) to health reasons and, most commonly, for aesthetic purposes [1, 11]. However, dietary restraint seems to be associated with overeating, weight gain and eating disorders; a hypothesis first postulated in the 1970s [12] and considered an established risk factor by 1990 [13]. Thus, both disinhibited eating or excessive appetite and food restriction or avoidance can be damaging and evolve into more serious health conditions [14, 15].

It is a challenge to establish what the 'normalcy' of eating behaviour is and what a healthy eating behaviour is. To encompass this variability, eating behaviours have been hypothesised to occur on a spectrum, ranging from healthy to disordered [16].

### **1.1. Disordered eating as a focus of research**

In the present dissertation, we will consider both cognitive and behavioural (including appetitive) features of disordered eating. Appetitive behaviours, also called appetitive traits in the literature, are persistent predispositions towards food, frequently grouped into two main categories: food approach and food avoidant behaviours, that reflect an overall greater and smaller appetite, respectively [17, 18]. These behaviours are commonly studied among infants and children [14]. Examples of food approach behaviours include being responsive to food cues and emotional overeating, whereas emotional undereating and being selective about which foods to eat are part of food avoidant behaviours [17].

Some appetitive behaviours can take part in a healthy development and growth. For instance, despite considerable individual differences, having low interest in food and being selective over the types of food chosen (fussiness) may dissolve with time: fussy eating seems to peak between 2 and 6 years and decreases afterwards [19, 20]. However, others may predispose to eating disorders. Some studies have shown an association between overeating throughout childhood and increased risk for binge eating and binge eating disorder in adolescence, as well as between persistent childhood fussy eating and undereating and increased risk for anorexia nervosa [21].

Although an agreement regarding nomenclature is still warranted [22, 23], appetitive behaviours can be considered part of problematic feeding behaviours [24, 25]. For purposes of congruency, however, and as some of the dimensions overlap, in the present dissertation we will consider appetitive behaviours under the broader concept of 'disordered eating'.

Disordered eating encompasses both cognitive and behavioural components. The cognitive component includes attitudes such as body dissatisfaction, weight concerns and overvaluation of shape and weight; whereas binge eating, emotional eating, dietary restriction and compensatory behaviours (to make up for food consumed or avoid weight gain) such as purging, use of laxatives, diuretics, fasting and excessive exercise, are part of the behavioural features [26].

When falling into specific criteria, disordered eating can evolve into an eating disorder, defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-

V) as a “*persistent disturbance of eating or eating related behaviour that results in the altered consumption or absorption of food and that significantly impairs physical health or psychosocial functioning*” [27].

The most commonly studied and more prevalent eating disorders are anorexia nervosa (restricting and binge eating/purging type), bulimia nervosa and binge-eating disorder, but other disorders exist, including avoidant restrictive food intake disorder (ARFID), rumination disorder and other specified feeding or eating disorders (OSFED). Briefly, anorexia nervosa is characterized by a restriction of energy intake below the body requirements and an intense fear of weight gain and distortion of body image perception. In the binge eating/purging type, individuals engage in these behaviours or other compensatory ones such as laxatives or diuretics to lose weight. Binge eating is characterized by consuming large amounts of food in a specific period of time with a lack of control over eating, until feeling uncomfortably full. The difference between binge eating disorder and bulimia nervosa is that, in the former, there are no compensatory behaviours to prevent weight gain [27].

In 2012, Brooks and colleagues [28] proposed an ‘Impulse-control spectrum model of eating disorders’ based on neuroimaging data (Figure 1). This model suggests that eating disorders can be understood as the responses to appetitive food stimuli that occur on a spectrum, where dominance of either ‘restraint and appetite control’ versus ‘binge eating and lack of appetite control’ can vary.

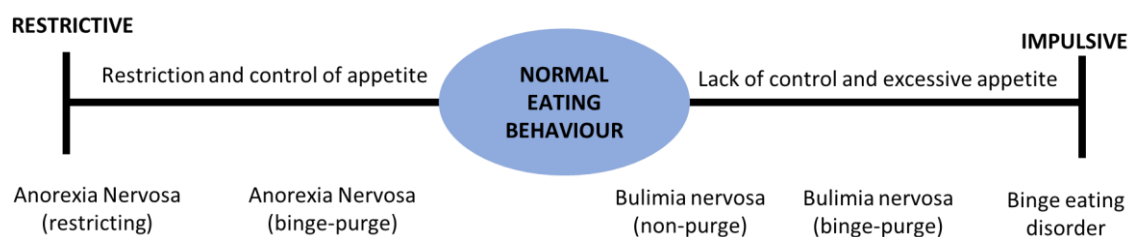


**Figure 1.** Impulse-control spectrum model of eating disorders. Adapted from Brooks (2012) [28].

## 2. The appetite control system

Appetite underlies eating behaviours [2], reflecting a complex set of processes that are behind our drive for food search, choice and, ultimately, responses to food and food consumption [29, 30]. The appetite control system is operationalized in the ‘appetite cascade’ [1] (Figure 2), which considers the events occurring before, during and after food ingestion; and reflects three levels of synchronous processes: 1) psychological events, such as hunger perception and hedonic sensations, which lead

to food intake; 2) physiologic events including nutrient absorption, use and storage and 3) brain processes that involve neurotransmitters and metabolic processes [31]. The regulation of this system occurs through the interaction of homeostatic and hedonic processes, shaping the motivation and the desire to eat certain foods [1, 32].

The hypothalamus is considered the “major homeostatic player” [33], responsible for receiving body nutrient status information and consequently driving or suppressing food intake [4, 34]. However, other areas in the brain are important for a better understanding of appetite and its relationship with food intake. The anterior insula, for instance, is part of the primary taste cortex, where food taste inputs arriving in the tongue are received [35]. The insula is also responsible for interoceptive awareness, including receiving information on gastric distention [36], body self-awareness, as well as with reward processing of external cues (contributing to the hedonic system) [37].

The taste inputs received at the primary taste cortex then reach different parts of the brain, from dopaminergic areas to other structures responsible for reward processing as well as for emotion processing (such as the striatum and the limbic system) [38]. The neurotransmitter dopamine is mainly responsible for motivation and reward seeking [39] which acts in conjunction with the neurotransmitter serotonin [40] – also involved in the regulation of the appetite and the eating system [30, 41]. Ultimately, the information reaches the frontal cortex [38]. The orbitofrontal cortex, particularly, is related to food intake regulation and when to cease consumption. While hunger initiates the meal, during and after ingestion, satiety signals are released to suppress hunger, controlling meal size, and ceasing ingestion (satiation); as well as further inhibiting eating until the next meal (satiety) [1, 42]. The orbitofrontal cortex has been further associated with food avoidant behaviours [43, 44]. Contrarily, food approach behaviours are the result of the interactions between the food stimulus and its emotional value, influencing the significance of the reward associated to that food stimuli and guiding future eating decisions [45, 46].

A more recent approach to appetite control adds that the processes that influence appetite can be tonic and episodic [42, 47]. Tonic processes are related to body composition and reflect energetic needs. Fat-free mass and the individuals' resting metabolic rate constitute excitatory signals, while fat mass and the action of leptin (the ‘satiety hormone’) work as inhibitory for the drive to eat [47]. Exception occurs in the case of high levels of adiposity and the occurrence of the leptin resistance phenomenon, where the leptin function is hampered [48]. Tonic signals are enduring,

stable in time and the main contributors to the drive to eat, leading to eating behaviour episodes – the episodic processes, which receive excitatory inputs from appetite hormones such as ghrelin (the ‘hunger hormone’), and are inhibited by the presence of nutrients and hormones in the gastrointestinal tract [49]. Yet, as previously briefly mentioned, this behavioural output of eating is shaped by a particular environment, within specific cultural, geographical and socioeconomic circumstances - determining what foods are eaten, how, where, with whom, with which frequency and for how long [50].

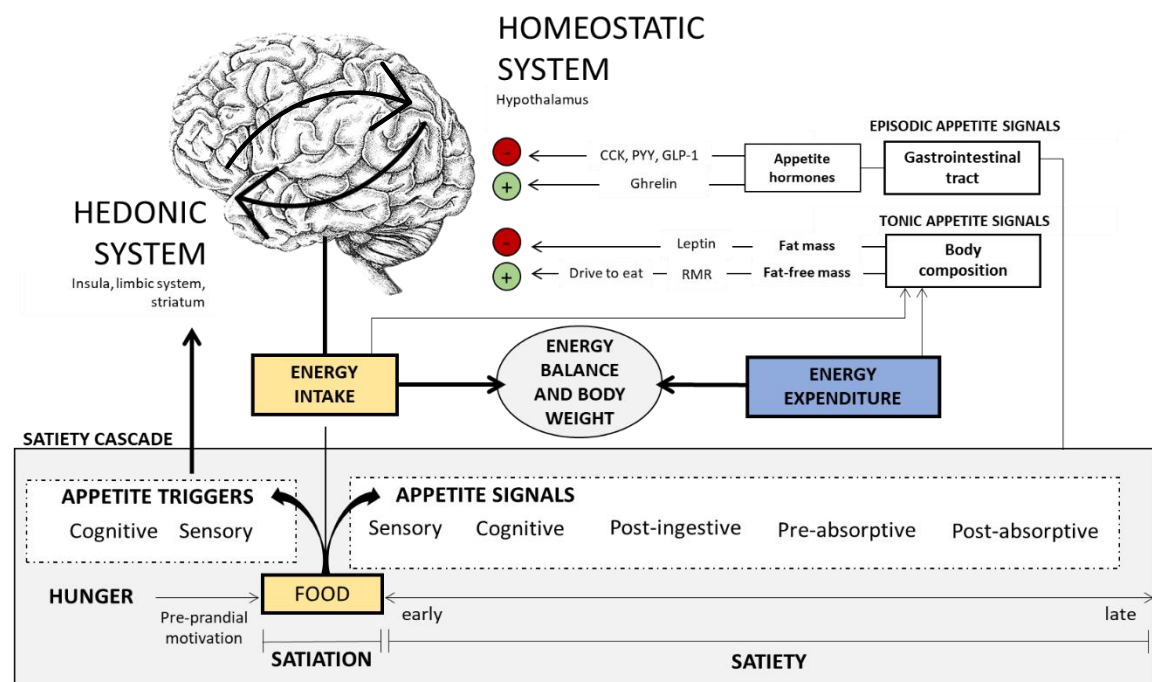


**Figure 2.** Appetite control systems using an energy balance framework, adapted from Blundell and Halford 1994, Blundell, Finlayson et al. 2015, Beaulieu and Blundell 2021 [1, 47, 50].

According to the ‘Satiety Cascade’, prior to eating, pre-prandial motivation drives and motivates the seeking of food. The sight and smell of food generate a response in the gastrointestinal tract, anticipating food ingestion (cephalic phase of appetite) [1, 51]. While eating, the brain receives information about the amount of food being ingested and the body’s nutrient status from the gastrointestinal tract (pre-absorptive phase). The post-absorptive phase follows digestion and absorption of nutrients, when metabolites resulting from food consumption reach the brain [1, 31]. In the hypothalamus, two types of neurons monitor energy status signals through the influence of insulin, ghrelin, and leptin: the orexigenic NPY/AgRP neurons and the anorexigenic POMC/CART neurons. Episodic signals arise from eating while tonic ones (enduring and stable) arise from body tissues and metabolism. Homeostatic and hedonic processes interact in the overall control of appetite and food intake. CCK: cholecystokinin, PYY: peptide Y, GLP-1 glucagon-like peptide 1, RMR: resting metabolic rate.

### 3. Development of disordered eating at the different life stages

#### 3.1. Infancy and childhood

Appetitive behaviours of infants and children have a strong genetic foundation. Evidence suggests moderate to strong heritability explaining appetitive behaviours

(i.e., the proportion of variance attributable to individual genetic differences); with studies commonly reporting a heritability higher than 50% [52-55]. Personality traits and temperament, which present a genetic basis, have also been associated with appetitive behaviours in children. Negative affectivity/neuroticism (related to anxiousness, mood instability, and dysregulated negative emotions) and low effortful control (a low ability for inhibitory control) have predicted higher food approach and food avoidant behaviours, whereas agreeableness (being altruistic, friendly and trusting) and consciousness (related to the child's control and regulation [56]) have predicted lower food approach and avoidant behaviours [57, 58].

The genetic susceptibility is, however, shaped by environmental factors that can modulate their expression (gene-environment interactions) [59] – which opens opportunity for preventing and acting on less desirable behaviours. While appetitive behaviours such as food responsiveness, enjoyment of food, satiety responsiveness, slowness in eating and food fussiness have a stronger genetic influence [52-55], emotional over and undereating may be more dependent on environmental cues [60].

Environmental exposures start in the uterus, with maternal nutrition as one of the first factors contributing to the development of the child's appetite [61]. During pregnancy, both over and undernutrition can impact appetite programming through changes in nutrient sensors, appetite-related hormones and the hypothalamic orexigenic and anorexigenic neurons functioning. The upregulation of appetite, along with an increased predisposition for adipogenesis, can contribute for later rapid growth and weight gain [61, 62]. Also, the foetus's exposure to the flavours coming via the amniotic fluid, from the mother's food consumption, can influence later food preference and acceptance, as well as the breast milk (that reflects the mother's diet) [63]. When fed directly from the breast instead of the bottle, the baby has a better control over the amount of milk consumed, contributing to appetite regulation, and respecting internal signals of satiety [64, 65].

During childhood, there is a decrease in appetite self-regulation which is not matched with the increase observed in self-regulation in other areas of development [19]. Appetite self-regulation results from a balance between regulatory processes (the ability of inhibitory control, also known as top-down processes) and reactive processes (both approach and avoidant behaviours, also known as bottom-up processes) [19, 66, 67]. Particularly, an increase in both bottom-up food approach

and avoidant behaviours along with a decrease in the responsiveness to internal cues of hunger and satiety processes is observed [19].

During middle childhood, from 6 to 12 years, the transition to adolescence is characterized by psychological and physical changes. This stage is marked by an increase in cognitive skills and autonomy, the onset of sexual attraction, social learning and integration and changes in food preferences [68, 69]. Also, after infancy, BMI decreases, reaching a minimum ('nadir') between 5.5 and 7 years, which is then followed by an increase throughout childhood called as adiposity rebound [70]. This increase is associated with changes in muscle and fat masses [69]. During this life stage, concerns about weight and appearance start emerging in both children (particularly girls) and parents, regarding their child's physical appearance [71-73]. Girls as young as 6 years may already be concerned about body image and desire a thinner silhouette [72] and, for instance, at 7 years of age, parents of girls in a Portuguese birth cohort (Generation XXI) showed to be more dissatisfied with their child's silhouette in comparison to parents of boys; desiring them to be thinner [73].

Parents and caregivers have a pivotal role in influencing their children's eating behaviours and relationship with food [74] and their bodies [75]. Not only do parents build the home food environment and serve as role models, as the adopted feeding practices seem to shape but also be influenced by the children's eating behaviour, temperament and appearance [76, 77]. For instance, parents of children who are fussier or eat small amounts of food may pressure them to eat, resulting in higher food avoidant behaviours [78-80], while parents of children with a higher body weight and a more avid appetite may try to restrict and control their food intake [74, 80]. Thus, parents adapt their feeding practices in response to their children's eating behaviours, but these behaviours are also reactive to parental feeding practices (bi-directional associations) [80].

### **3.2. Adolescence and young adulthood**

Concerns about appearance intensify during adolescence, where body image is developing and arises as part of the adolescent's self-concept [81]. Body dissatisfaction is a core disordered eating feature and may result from the imbalance between bottom-up and top-down processes in response to food stimuli. When received by the insula, this information leads to an altered processing of the self, body state and body image [33].

The contribution of genetics to the development of disordered eating has been suggested to increase considerably during puberty, explaining at least around 50% of individual variance [82, 83]. Hypothesised genetic markers involved in disordered eating and eating disorders are those related to serotonin, dopamine and the brain derived neurotrophic factor, as are the polymorphisms of 5HT2A (serotonin receptor), catechol-O-methyltransferase (COMT) that degrades dopamine, and the brain-derived neurotrophic factor (BDNF), related to regulation of food intake [26, 28].

Among girls, the influence of puberty status and timing, mediated by hormones effects such as estrogenic effects, seems considerable [84]. In this sense, adolescence is an important risky period for the onset of eating disorders [85, 86]. While Micali and colleagues (2013) found a peak age for diagnosis of anorexia nervosa between 10 to 14 years and of bulimia nervosa between 15 to 19 years old [87], Volpe and Tortella (2016) suggest that the onset for both pathologies is around 18 years of age [88]. Other important factors include personality traits such as perfectionism, neuroticism, and negative urgency (related to impulsivity) [26, 89].

Adolescence is also a period with an increased susceptibility to peer influence and internalizing body ideals imposed by the society [90]. In the presence of an underlying genetic susceptibility, the internalization of the thin-ideal and certain personality traits are important risk factors that, if paired with other sociocultural influences, can result in disordered eating [26, 89, 91]. Appearance and weight related comments or teasing, from both peers and parents/family members (that can act as perpetuators of sociocultural pressures) are associated with disordered eating [92-94]. These sociocultural pressures are portrayed and reinforced via social media, which commonly reflect the current accepted body ideal standards - often unrealistic - and instigate comparison, internalization of the thin ideal, self-objectification and unhealthy eating behaviours and related cognitions [95].

The problematic of social media influence is not, however, limited to adolescence and can extend into young adulthood [95, 96]. Young adulthood is the period between 18 and 25 years, and represents the transition between adolescence and adulthood, marked by important life changes: going to college and/or starting work, leaving parents' home, increasing independence and autonomy, sedentary habits and eating behaviours changes as well as developing one's identity [97-100].

Adverse experiences such as abuse and childhood trauma have also been considered as potential risk factor for later development of disordered eating and eating disorders [26]. Lastly, the learning experiences each individual has regarding

eating, dieting, thinness and the expectancies created around them (possibly due to pressure for thinness and teasing about appearance), may reinforce those behaviours [101].

Figure 3 summarises the different factors associated with disordered eating (both cognitions and behaviours, including appetitive ones) from early infancy to young adulthood.

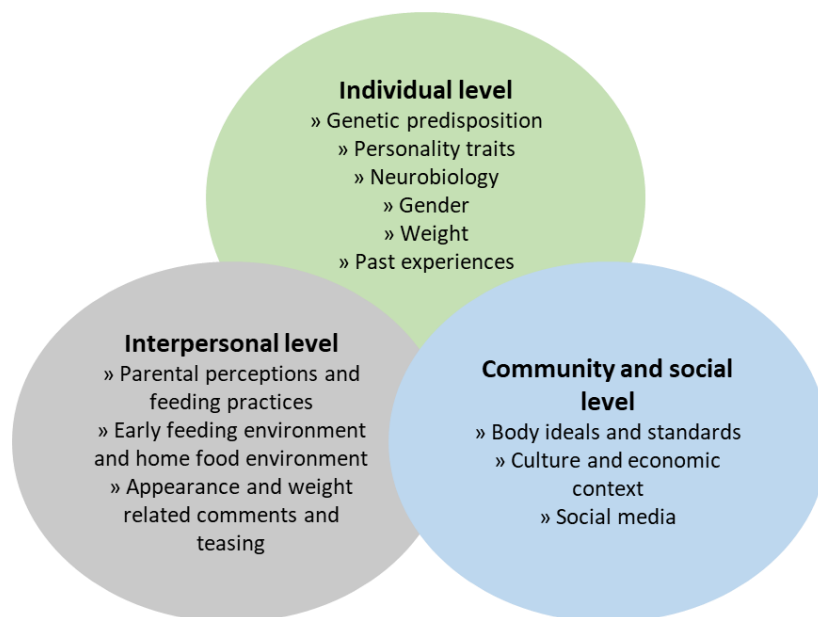


**Figure 3.** Factors associated with disordered eating at the different life stages.

## 4. Disordered eating and health

### 4.1. Disordered eating and weight

The behavioural susceptibility theory of obesity suggests that appetitive behaviours influence the risk of weight gain, thus aiming to explain why some people are more prone to obesity than others in the current obesogenic environment [102, 103]. This theory hypothesises that individuals with a genetic predisposition for an avid appetite may be more vulnerable to weight gain, in contrast to those who are wired for a smaller appetite [102, 103]. The fat mass and obesity related (FTO) gene, for instance, can be found in the hypothalamus – a central component of appetite regulation [104]. FTO seems to play a role in the development of obesity [105] and has been associated with satiety responsiveness in children [106, 107]. Yet, the variance in BMI explained by genetics, in particular the FTO gene, is relatively low (values ranging between 0.10-0.34) [108].

Cross-sectional evidence has been consistently suggesting associations between higher food approach and food avoidant behaviours and increased and decreased measures of adiposity (including BMI standard deviation scores (BMI z-scores) and percentiles, weight, and body composition measures), respectively, in infancy and childhood [14]. Yet, the relationship between appetite and weight is complex, and evidence on causality and on the actual direction of associations is still growing. So far, some longitudinal studies have explored associations between appetite and weight and other tested the possibility for bidirectionality. At 3 months of age, higher responsiveness to food cues or lower responsiveness to satiety cues were associated with accelerated growth up to 15 months [109] and, when assessed, bidirectional associations suggest a stronger influence of appetite on weight [110]. Other studies report that, from early to middle childhood, higher BMI z-scores have prospectively predicted higher emotional overeating, food responsiveness, enjoyment of food [111, 112] and desire to drink [112], as well as decreased satiety responsiveness [111, 112], slowness in eating and food fussiness [112]. Throughout middle childhood, increased BMI was related to higher food responsiveness and emotional overeating [113]. Overall, longitudinal evidence seems to indicate that, during infancy, appetitive behaviours may have a greater influence on the development of weight whereas, during childhood, appetite might be a consequence of body growth and change [14, 114].

Adding to influences on food approach and food avoidant behaviours, obesity may predispose to other disordered eating attitudes and behaviours which, by themselves, already have great impact on overall well-being as well as on physical, social and emotional functioning [15, 115-117]. Among children and adolescents, the impact extends to the school environment, social support and relationships with peers [116].

While increased body weight can contribute to disordered eating, in its turn, disordered eating seems to further contribute to weight gain. Features such as food, weight and body image concerns, peer and media pressure about eating, dieting and restrictive behaviours, unhealthy weight control behaviours, overeating and loss of control over eating, in middle childhood, predicted the onset of obesity during adolescence [118]. Throughout adolescence [119] and from adolescence to young adulthood [15, 120, 121], they increased risk for overweight and obesity.

Obesity is a well-recognized public health concern across the different life stages, with an increasing prevalence currently affecting 39 million children, 340

million adolescents and 650 million adults [122]. It is estimated that 55% of children with obesity will continue to have the disease in adolescence and that, 80% of adolescents with obesity will maintain it as adults [123]. In fact, there is considerable overlap between the risk factors and aetiology of obesity and both disordered eating and eating disorders, including genetic influences, the brain pathways associated with reward, weight related teasing and weight concerns, among others [124-126] – which represents a reinforced health burden. Disordered eating and eating disorders have also been considered important public health problems [116, 120, 126, 127]. Reported prevalence values of disordered eating attitudes and behaviours range from 10% [119, 15] to 58% [119] in females and from 3% [119] to 30% [119, 120] in males. In turn, eating disorders have a worldwide prevalence of 0.7% and represent 0.3% of all global disability-adjusted life years, with a possible underestimation of its prevalence [127].

#### **4.2. Disordered eating and other cardiometabolic health features**

Adding to body weight, part of the mentioned health burden is also attributed to cardiovascular complications [128]. In a more severe spectrum, anorexia nervosa presents a greater propensity for changes in heart rate and rhythm, haemodynamic and vascular abnormalities due to malnutrition [129]. In bulimia nervosa, purging, and the use of diuretics and laxatives can result in electrolyte unbalance, with cardiac arrhythmias as a possible cardiovascular outcome [130]. Moreover, in adults who had overweight/obesity and binge eating, an increased risk for hyperlipidaemia was observed seven years later [131]. In fact, binge eating disorder has been associated with increased risk for metabolic syndrome components in adults [132] - a cluster of cardiovascular risk factors including obesity, raised blood pressure, high fasting glucose and dyslipidaemia. Metabolic syndrome has become a global epidemic and, despite some uncertainty regarding its measurement, it is estimated to affect about one quarter of the overall world population [133].

Associations of disordered eating with altered cardiometabolic health start early in life. Appetitive behaviours such as food responsiveness, enjoyment of food and emotional overeating at 7 years were associated with increased cardiometabolic risk characterized by higher insulin resistance, waist circumference, systolic blood pressure and lower high density lipoprotein cholesterol (HDL-c) at 10 years of age; although associations were highly dependent on child's adiposity and weight [134]. Another study reported associations between disordered eating attitudes and

behaviours in middle childhood and the onset of high systolic and diastolic blood pressure in adolescence [118]. Lastly, among youth, loss-of-control over eating has been associated with various metabolic outcomes such as elevated systolic blood pressure and low-density lipoprotein cholesterol (LDL-c), independently of adiposity [135], metabolic markers of inflammation [136], as well as with insulin disturbances [137]. Concerningly, both disordered eating [15, 138, 139] and cardiometabolic risk [140] factors tend to persist beyond adolescence.

## **5. Methodological approaches to study disordered eating**

### **5.1. Psychometric tools**

Various questionnaires have been developed to assess appetitive behaviours and other symptoms related to disordered eating in population-based studies [141, 142]. The following section explores in more detail the questionnaires considered in the current dissertation: from childhood to early adolescence, the Children's Eating Behaviour Questionnaire (CEBQ) [18] and, from early adolescence to young adulthood, the Eating Disorder Inventory (EDI) [143]. These questionnaires fit the scientific purposes of two large population-based cohorts of children and adolescents from which data was used in this work.

#### Children's Eating Behaviour Questionnaire

The CEBQ was developed by Wardle and colleagues [18], in 2001, based on reported eating behaviours of children and adults, and parental interviews. CEBQ is a parent-reported questionnaire with eight subscales, each corresponding to an appetitive behaviour (Table 1), further grouped into food approach and food avoidant behaviours [17, 18]. Items are scored on a 5-point Likert scale, with the following answering options: 'never', 'rarely', 'sometimes', 'often' and 'always'. Only 5 items are reverse coded, considering their opposite phrasing. Higher scores represent higher levels of each behaviour. Since its development, CEBQ has been translated to different languages and validated in different samples, inclusively against behavioural measures [144], becoming a widely used measure of appetitive behaviours [14].

**Table 1.** Children's Eating Behaviour Questionnaire (CEBQ) subscales description [17, 18].

| CEBQ subscales                  | Description                                                                                                                            | Items | Example                                                                           |
|---------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|-------|-----------------------------------------------------------------------------------|
| <b>Food approach behaviours</b> |                                                                                                                                        |       |                                                                                   |
| Enjoyment of Food               | Displaying a general interest and desire towards food, translated into finding pleasure in food and constantly desiring to eat.        | 4     | <i>My child looks forward to mealtimes.</i>                                       |
| Food Responsiveness             | Eating in response to external food cues or stimuli - such as smell or food appearance - regardless of feelings of hunger or fullness. | 5     | <i>Even if my child is full up, she finds room to eat his/her favourite food.</i> |
| Emotional Overeating            | Increasing food intake in response to negative emotions (worry, anxiety, anger).                                                       | 4     | <i>My child eats more when annoyed.</i>                                           |
| Desire to Drink                 | A desire or craving to drink, which becomes particularly problematic if related to sugary drinks.                                      | 3     | <i>If given the chance, my child would always be having a drink.</i>              |
| <b>Food avoidant behaviours</b> |                                                                                                                                        |       |                                                                                   |
| Satiety Responsiveness          | Respecting satiety cues; feeling satiated.                                                                                             | 5     | <i>My child gets full up easily.</i>                                              |
| Slowness in Eating              | The speed of food intake during a meal.                                                                                                | 4     | <i>My child finishes his/her meal very quickly.</i>                               |
| Emotional Undereating           | Reducing food intake in response to negative emotions (anxiety, anger, fatigue).                                                       | 4     | <i>My child eats less when she is angry.</i>                                      |
| Food Fussiness                  | Being selective about the foods accepted to eat; unwillingness to try new foods and food rejection; lack of interest towards food.     | 6     | <i>My child is difficult to please with meals.</i>                                |

### Eating Disorder Inventory

The EDI [143] was initially developed in an adult population to assess characteristics that are relevant to eating disorders, namely to Anorexia Nervosa and Bulimia. The EDI is a self-reported instrument with a total of 63 items, answered on a Likert scale with six categories: 'always', 'usually', 'often', 'sometimes', 'rarely', and 'never'. These items are subdivided into eight subscales (Table 2), which are further grouped into 1) attitudes and/or behaviours related to eating and body shaping and 2) psychological associated characteristics. Each item can be scored up to a maximum of 3: the two most extreme answers ('always' or 'never', depending on the direction of the item), are given a score of 3; the two adjacent frequency options receive a score of 2 and, the following one, a score of 1. The 3 remaining options receive a score of 0. Higher scores correspond to increased disordered eating

symptomatology. In the present dissertation, only ‘Drive for thinness’, ‘Body dissatisfaction’ and ‘Bulimia’ subscales were considered, as they have previously shown the best psychometric characteristics [145] and are part of the core features of eating disorders. However, it is worth highlighting that this psychometric tool does not allow a clinical diagnosis of an eating disorder but can provide valuable information about the presence and severity of eating disorders symptomatology in a given population [143].

**Table 2.** Eating Disorder Inventory (EDI) subscales description [143].

| EDI subscales                        | Description                                                                               | Items | Example                                                                      |
|--------------------------------------|-------------------------------------------------------------------------------------------|-------|------------------------------------------------------------------------------|
| <b>Attitudes and behaviours</b>      |                                                                                           |       |                                                                              |
| Drive for thinness                   | Desire to lose weight and fear of gaining it; concerns with dieting.                      | 7     | <i>I exaggerate the importance of weigh.</i>                                 |
| Body dissatisfaction                 | Believing that some body parts – such as the hips, stomach, or thighs – are too large.    | 9     | <i>I think that my stomach is too big</i>                                    |
| Bulimia                              | Tendency to binge (uncontrollable episodes of eating) followed by self-induced vomiting.  | 7     | <i>I have gone on eating binges where I have felt that I could not stop.</i> |
| <b>Psychological characteristics</b> |                                                                                           |       |                                                                              |
| Ineffectiveness                      | Reflects feelings of inadequacy, insecurity, and worthlessness; negative self-concept.    | 10    | <i>I have a low opinion of myself.</i>                                       |
| Perfectionism                        | Having high personal performance expectations and high achievement standards.             | 6     | <i>Only outstanding performance is good enough in my family.</i>             |
| Interpersonal distrust               | Avoidance to form close relationships or be able to express emotions.                     | 7     | <i>I have trouble expressing my emotions to others.</i>                      |
| Interoceptive awareness              | Lack of ability to identify one’s emotions and sensations of hunger and satiety.          | 10    | <i>I get frightened when my feelings are too strong.</i>                     |
| Maturity fears                       | Feeling overwhelmed with adulthood demands and wishing to go back to preadolescent years. | 7     | <i>The happiest time in life is when you are a child.</i>                    |

Besides these, other questionnaires have been developed to assess appetitive behaviours and other disordered eating dimensions in population-based studies. Some commonly used are i) the ‘Dutch Eating Behaviour Questionnaire’ (DEBQ) [146] which assesses ‘Restrained eating’, ‘Emotional eating’ and ‘External eating’; ii) the ‘Three Factor Eating Questionnaire’ (TFEQ) [147], assessing Cognitive Restraint of Eating, Hunger and Disinhibition; iii) the ‘Eating Disorder Examination

Questionnaire' (EDE-Q) [148] which assesses 'Dietary Restrain' as well as 'Eating', 'Weight' and 'Shape' concern; and iv) the 'Eating Attitudes Test' (EAT) [149] with three categories: Dieting, Bulimia and Food Preoccupation, and Oral Control. Extensive research and testing were used to ensure the reliability and validity of these questionnaires, and they represent a very useful way of measuring disordered eating dimensions in large scale population-based studies [141].

## **5.2. Person-centred approaches to summarize the development of disordered eating**

Although an increase in appetite and decrease in satiety responsiveness is observed throughout childhood, research suggests that, once established, appetitive behaviours are relatively stable and track throughout time [21, 112, 150-152]. Other disordered eating dimensions, such as dieting, binge eating and compensatory behaviours also seem to track from adolescence to young adulthood [15, 138, 153]. Some studies, however, indicate a decrease in symptomatology severity at later stages of development (i.e., young and later adulthood) [15, 154]. Regarding disordered eating attitudes, 'Body dissatisfaction' and 'Drive for thinness' revealed to be stable throughout adolescence [155, 156]. From adolescence to young adulthood, studies indicate increases in body dissatisfaction [156, 157] or stability of symptoms such as feeling overweight and attributing importance to food [86].

The assessment of disordered eating development, particularly regarding appetitive behaviours, is commonly performed using a variable-centred approach, with an assessment of data at a populational level and without considering individual differences [158]. In contrast, person-centred approaches are based on the premise that individuals or groups of individuals present unique behaviour and psychological processes [159]. These approaches include methods such as latent class and latent profile analysis (for categorical and continuous data, respectively) as well as growth mixture models [158, 160].

The main advantage of person-centred approaches lies in their ability to capture intraindividual (within-person) and inter-individual (between-person) differences [161], thus allowing the identification of subgroups of individuals based on common characteristics, referred to as phenotypes or profiles [160]. Particularly, person-centred approaches can provide a deeper understanding of how disordered eating cognitions and behaviours cluster and evolve over time. Moreover, based on the

associations being explored, the identification of 'at risk' profiles may help guiding more targeted interventions [160, 162, 163].

## 6. Research gaps on disordered eating

So far, most studies using a person-centred approach have explored appetitive behaviours and other disordered eating attitudes or behaviours isolated [85, 86, 164-168] or in specific sample groups (e.g., pre-schoolers, girls, children with overweight) [85, 162, 169, 170]. Yet, these features often co-occur [86, 162], and profiles would provide a more comprehensive understanding of their development over time if various features were considered simultaneously.

Additionally, the association between adiposity and appetite in infancy and childhood requires further exploration, particularly if considering this direction of association, with the use of longitudinal data [14]. Studies testing this relationship have commonly used measures of BMI in specific time points [111-113] and fewer derived weight trajectories [171]. Yet, as a period of considerable body changes, no study has, to our knowledge, assessed a cumulative measure of adiposity throughout childhood - which would more comprehensively capture associations from a developmental and broader point of view. Lastly, despite biological plausibility for the association between disordered eating and cardiometabolic health, the focus of research has been to study cardiometabolic risk factors separately [118, 131, 135] instead of their clustering.

Considering the previous theoretical exposition, this dissertation is structured based on the following framework.

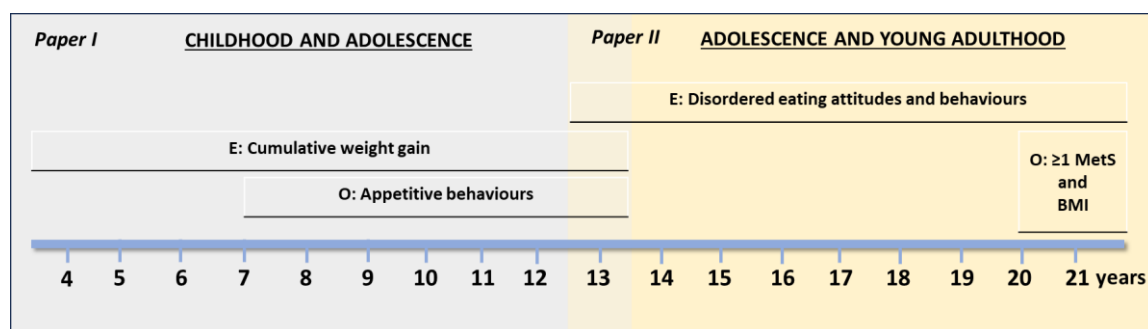


**Figure 4.** Dissertation framework. E: exposure, O: outcome, MetS: metabolic syndrome; BMI: body mass index

## OBJECTIVES

Focusing its core on disordered eating (attitudes and behaviours), their development and health consequences, this dissertation is composed of two papers that encompass different life stages (from 4 to 21 years of age).

The specific objectives are the following:

**Paper I:** i) To test associations between a cumulative measure of BMI throughout childhood into early adolescence (4-13 years) and appetitive behaviours profiles (7-13 years) and ii) To additionally explore the association of BMI at specific ages with appetitive profiles, independently of the cumulative BMI.

**Paper II:** To test associations between disordered eating profiles from adolescence to young adulthood (13-21 years) with both BMI and other related cardiometabolic features at 21 years.

## **PAPER I**

**The association between the duration and degree of adiposity and appetitive behaviours profiles from childhood into early adolescence – results from the Generation XXI cohort**

Rita Pereira<sup>1,2</sup>, Joana Araújo<sup>1,2,3</sup>, Alexandra Costa<sup>1,2</sup>, Milton Severo<sup>1,2,4</sup>,  
Andreia Oliveira<sup>1,2,3</sup>

(1) EPIUnit - Instituto de Saúde Pública, Universidade do Porto, Rua das Taipas, n° 135, 4050-600 Porto, Portugal

(2) Laboratório para a Investigação Integrativa e Translacional em Saúde Populacional (ITR), Universidade do Porto, Rua das Taipas, n° 135, 4050-600 Porto, Portugal

(3) Departamento de Saúde Pública e Ciências Forenses e Educação Médica, Faculdade de Medicina, Universidade do Porto, Alameda Prof. Hernâni Monteiro, 4200-319 Porto, Porto, Portugal

(4) Departamento de Ensino Pré-Graduado, Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto, Porto, Portugal

**Keywords:** Feeding behaviour, appetite, body weight, cohort studies, child, adolescent

**Corresponding author**

Andreia Oliveira, PhD.

Instituto de Saúde Pública, Universidade do Porto, Rua das Taipas 135, 4050-600 Porto, Portugal.

**Tel:** +351 222061820 **E-mail:** acmatos@ispup.up.pt

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**Author contributions:** RP was responsible for data analysis and interpretation, and for drafting the manuscript; JA and AC were responsible for data interpretation and critical revision of the manuscript for important intellectual content; MS was responsible for data analysis and interpretation; AO was co-responsible for the study concept and design; acquisition of data; data interpretation; critical revision for important intellectual content and final approval of the version to be published.

**Conflict of interest:** The authors declare no competing interests.

**Data Availability Statement:** The data from Generation XXI are not publicly available due to privacy or ethical restrictions. The data can be made available for research proposals on request to the Generation XXI Executive Committee (generationxxi@ispup.up.pt). Further information about Generation XXI can be obtained via the Generation XXI website [www.geracao21.com] or by emailing generationxxi@ispup.up.pt.

## Abstract

**Background:** Growing prospective evidence suggests that, during childhood, appetitive behaviours may be a consequence of body weight. However, an approach capturing a cumulative measure of adiposity and how it associates with the tracking and clustering of the various dimensions of appetite, over time, is lacking.

**Objective:** This study aims to i) capture a cumulative measure of adiposity throughout childhood into early adolescence (4-13 years old (y)) and associate it with derived appetitive behaviours profiles (7-13y), and ii) to additionally explore the association of BMI at specific ages with profiles, independently of the cumulative BMI.

**Methods:** Participants are from the Generation XXI birth cohort, assembled in Porto, Portugal. A final sample of 3339 participants was considered. Weight and height were measured at 4, 7, 10 and 13y follow-ups, and age- and sex-specific adjusted body mass index (BMI) standard deviation scores (BMI z-scores) were calculated according to the WHO criteria. For each participant, the duration and degree of BMI was summarized through the BMI area under the curve (BMI<sub>AUC</sub>), as an indicator accumulated adiposity. Appetitive behaviours were assessed at 7, 10 and 13y, through the Children's Eating Behaviour Questionnaire, previously validated. Individual appetitive behaviours trajectories were obtained using linear mixed effect models and profiles (representing individuals with similar trajectories) were derived by Gaussian mixture models. Associations between BMI<sub>AUC</sub> and appetitive behaviours profiles were tested using multinomial logistic regressions (odds ratio (OR)) and the respective 95% confidence intervals (CI), adjusted for child's sex, mother's age, education and smoking during pregnancy.

**Results:** The median exposure to BMI<sub>AUC</sub>, per month, was 17.4 kg/m<sup>2</sup>. Six appetitive behaviours profiles were obtained: 1. 'moderate appetite' (25.6%), 2. 'small but increasing appetite' (7.8%), 3. 'small to moderate appetite' (27.9%), 4. 'avid appetite' (11.3%), 5. 'increasing appetite' (16.8%) and 6. 'smallest appetite' (10.6%). In comparison to the 'moderate appetite', BMI<sub>AUC</sub> was positively associated with the 'avid appetite', and negatively associated with the remaining profiles (except for 'increasing appetite' which yield no significant associations). The strongest associations were observed for the 'smallest appetite' (OR=0.78, 95%CI: 0.73-0.83) and 'avid appetite' (OR=1.47, 95%CI: 1.40-1.55). Regardless of the cumulative exposure to BMI, having overweight/obesity at 7y increased 113% the odds of having

an 'avid appetite' profile throughout childhood and early adolescence (OR=2.13 95%CI: 1.42-3.21).

**Conclusion:** Children with the highest and the lowest cumulative exposure to adiposity throughout childhood and early adolescence were more likely to present the 'avid' and the 'smallest' appetite profiles, respectively. Additionally, having excessive weight at 7y may be already indicative of being an avid eater. These results reinforce the importance of curbing weight gain in early childhood to protect children from the development of obesity-related appetite profiles.

## Introduction

Appetite reflects a complex set of biological, psychological, and environmental processes that underlie our food consumption [1, 2]. Specific 'appetitive behaviours or traits' (i.e., persistent predispositions towards food) have been identified; namely food approach and avoidant behaviours which reflect an overall avid and small appetite, respectively [3, 4]. Adding to its genetic origin [5], appetite starts developing while in the uterus [6]. Maternal over or undernutrition during pregnancy may upregulate appetite as well as increase predisposition for adipogenesis - thus contributing to later rapid growth and weight gain [6, 7]. Existing research on appetitive behaviours has primarily focused on their associations with weight, aiming to understand why some children are more prone to develop overweight and obesity than others in the current obesogenic environment [3, 8-10].

Cross-sectional evidence is the most prevalent, indicating consistent associations between food approach and avoidant behaviours with increased and reduced adiposity, respectively [10]. The smaller but rising number of prospective studies suggest possible bidirectional influences between weight and appetite, with specific stronger pathways of association depending on the appetitive behaviours studied and the developmental stage considered [10, 11]. For instance, in the Gemini cohort, higher responsiveness to food cues or lower responsiveness to satiety cues at 3 months were associated with accelerated growth up to 15 months [12] and, when assessed, bidirectional associations were found with a stronger influence of appetite on weight [13]. In Generation XXI cohort, children born with low birth weight and in whom weight gain occurred mainly during infancy (first 2 years of life) had higher scores on food approach behaviours at 7y [14]. Other cohort studies further report that increased body mass index (BMI) standard deviation scores (BMI z-scores) at 4y [15] and 7y [16] predicted higher food approach and lower food avoidant behaviours at 10y; with bidirectionally only observed for emotional overeating [15] and eating slowly [16]. Still, the stronger path of association was from BMI z-score to the appetitive behaviour in subsequent ages.

Overall, it is possible that during infancy appetite has a greater influence on the development of weight whereas, during childhood, appetite may be a stronger consequence of acquired body growth and change [10, 11]. However, most studies use single time-point measurements of BMI [15-17], not assessing the duration and degree of exposure adiposity, which would reflect an accumulation of risk over time. Also, understanding how the various dimensions of appetite cluster and evolve over

time is lacking [18]. Few studies have adopted such approach, with most exploring each of the appetitive behaviours isolated [19-21], focusing only on children with overweight or obesity [22, 23] or pre-schoolers [24].

In the present study, we aim to i) capture a cumulative measure of BMI throughout childhood into early adolescence (4-13 years old (y)) and associate it with derived appetitive behaviours profiles (7-13y) and ii) additionally explore the association of BMI at specific ages with profiles, independently of the cumulative BMI.

## **Methods**

### **Study participants**

This study includes data from Generation XXI (G21), a population-based birth cohort assembled in Porto, Portugal. Mothers delivering a live-born child, with a gestational age above 24 weeks at any of the five-level III maternity units in the Porto Metropolitan Area, between April 2005 and September 2006, and living in the catchment area were eligible for the study. Mothers were invited 24 to 72 hours after delivery and 92% agreed to participate, resulting in the enrolment of 8945 mothers and 8647 newborns, as described elsewhere [25, 26]. Participants were re-evaluated at 4y (2009-2011), 7y (2012-2014), 10y (2015-2017) and 13y (2018-2020), with a participation of 86%, 80%, 74% and 54%, respectively. The last follow-up was interrupted in 2020 due to the COVID-19 pandemic, which explains the lower participation proportion observed.

For the present study, we considered singletons without malformations or feeding restrictions, with available anthropometric measures (height and weight) in at least two of the 4, 7, 10 and 13y follow-ups; and available appetitive behaviours data in at least two of the 7, 10 and 13y follow-ups. The final sample was composed of 3339 participants (Figure 1).

In comparison to the remaining cohort, mothers of the present study sample were older (mean (M) standard deviation (SD) = 30.3 (4.94) vs 28.1 (5.82),  $p$ -value<0.001) and with a higher number of completed schooling years (M (SD) = 11.6 (4.28) vs 9.7 (4.01),  $p$ -value<0.001). Also, included participants had higher weight at birth (M (SD) = 3205.1g (485.31) vs 3113.1g (566.13),  $p$ -value<0.001). Based on the Cohen's d effect size [27], these differences are moderate (0.40 and 0.44 for age and education, respectively) and small (0.17 for weight at birth). No differences were found regarding child's sex.

This study was approved by the University of Porto Medical School/ Hospital S. João Ethics Committee (27 April 2005), as well as by the Portuguese Data Protection Authority (Protocol code 5833, approved on 30 May 2011). The purpose and design of the study were explained and children's assent and consent from parents or legal representatives was obtained. All phases of the study complied with the Ethical Principles for Medical Research Involving Human Subjects expressed in the Declaration of Helsinki [28].

## **Data collection and handling**

### Anthropometric data

Anthropometric measures were collected at the 4, 7, 10 and 13y follow-ups. While in underwear and barefoot, child's height and weight were measured using a stadiometer to the nearest 0.1 cm and a digital scale to the nearest 0.1 kg, respectively. BMI was calculated by dividing weight (kg) by the height squared ( $m^2$ ) and age- and sex-specific adjusted BMI standard deviation (SD) scores (BMI z-scores) were derived according to the World Health Organization (WHO) Growth Standards [29] at 4y, and according to the WHO Growth Reference at 7, 10 and 13y [30].

At 4y, weight categories were defined as Underweight (Uw),  $< -2SD$ ; Normal weight (Nw), between  $\geq -2SD$  and  $\leq 2SD$ ; Overweight (Ow), between  $> 2SD$  and  $\leq 3SD$ ; and Obesity (Ob),  $>3SD$ . At the remaining follow-ups, weight was classified as Uw ( $< -2SD$ ), Nw ( $\geq -2SD$  and  $\leq 1SD$ ), Ow ( $>1$  and  $\leq 2SD$ ) and Ob ( $>2SD$ ). BMI z-scores categories were then grouped into Uw/Nw and Ow/Ob.

### Cumulative BMI - BMI<sub>AUC</sub>

As previously described [31], the BMI area under the curve (BMI<sub>AUC</sub>) was used as a cumulative measure of BMI, summarizing the duration and degree of adiposity for 108 months (corresponding to the time frame between the ages 4 and 13y). For this calculation, we considered children with available BMI data in at least two time-points. For each participant, a cubic spline interpolation was computed for those BMI data points, and the area under the curve was calculated using the composite trapezoid rule. The obtained BMI<sub>AUC</sub> value was divided by 108, such that BMI<sub>AUC</sub> can be interpreted as the average BMI per month. A higher BMI<sub>AUC</sub> value indicates a

higher exposure to accumulated adiposity. Statistical analysis was done on R studio®, with the package 'MESS' (Miscellaneous Esoteric Statistical Scripts).

### Appetitive behaviours

Appetitive behaviours were assessed using the Children's Eating Behaviour Questionnaire (CEBQ) [4] at 7, 10 and 13y. This is a parent-reported questionnaire with 35 items, developed by Wardle et al [4], which evaluates eight distinct types of appetitive behaviours. *Enjoyment of Food* (4 items), *Food Responsiveness* (5 items), *Emotional Overeating* (4 items) and *Desire to Drink* (3 items) fall into the group of Food Approach behaviours whereas *Satiety Responsiveness* (5 items), *Slowness in Eating* (4 items), *Emotional Undereating* (4 items) and *Food Fussiness* (6 items) are Food Avoidant behaviours [3, 4]. Items are scored on a 5-point Likert scale, with the answering options of *never* (1), *rarely* (2), *sometimes* (3), *often* (4) and *always* (5). Only 5 items are reverse coded considering their opposite phrasing. When <50% of items were missing (around 3% of the sample), there was an imputation of data using the average score of the remaining items of each subscale [32].

CEBQ has been previously validated in the present cohort [32] and has shown adequate internal consistency at 7y and 10y [16, 32]. Similarly, in the present study sample, Cronbach's  $\alpha$  coefficients varied between 0.76-0.85 at 7y, 0.77-0.89 at 10y and 0.76-0.89 at 13y, corroborating its good internal consistency.

### Appetitive behaviours profiles

The appetitive behaviours profiles analysis included participants with available CEBQ data in at least two out of the three follow-ups (7, 10 and 13y), resulting in a sample of 5139 children, of whom 70% had data in all the assessments. To derive appetitive behaviours profiles between ages 7 and 13, a person-centred approach was used. First, linear mixed effect models were run, fitted by the restricted maximum likelihood (REML) procedure [33]. These models allow for the estimation of within-subject and between-subject variability and account for both fixed and random effects. Age and its quadratic term were tested via fixed effects, with associations adjusted for sex. An interaction between sex and age in each CEBQ subscale was tested and no effects were found. Random effects were extracted from the previous model, allowing to derive appetitive behaviours individual trajectories over childhood and early adolescence (7, 10 and 13y), with each individual intercept and slope trajectory. The conditional and marginal coefficient of determination ( $R^2$ )

of the models were obtained, as well as the intraclass correlation coefficient (ICC) to assess the tracking of the appetitive behaviours over time (Table S1): almost perfect (ICC 0.81 – 1.00), substantial (ICC 0.61–0.80), moderate (ICC 0.41–0.60), fair (ICC 0.21–0.40), poor or slight tracking (ICC < 0.21) [34]. Then, gaussian mixture models fitted by the Expectation-Maximization (EM) algorithm were used to identify individuals with similar trajectories for the various appetitive behaviours [35]. The number of latent classes was selected based on the lowest Bayesian Information Criterion (BIC) value. Also, a sensitivity analysis was conducted using only cases with available CEBQ data at all the time points (n=3560) but as results were similar, the larger sample was considered. Statistical analysis was done on R studio®, with the packages ‘Nlme’ (Linear and Nonlinear Mixed Effects Models) - function ‘lme’, to extract the fixed and random effects; and the package ‘mclust’ – function ‘mclustBIC’, to derive and define the clusters.

### **Covariates**

Covariates were chosen based on previous literature [14, 16, 19, 32]. Maternal characteristics such as maternal age and education (completed years of schooling) at baseline, pre-pregnancy BMI (kg/m<sup>2</sup>), and smoking habits during pregnancy were obtained by face-to-face interviews conducted by trained researchers. Mother’s pre-pregnancy BMI (kg/m<sup>2</sup>) was classified according to the WHO cut-offs: Uw (BMI<18.5kg/m<sup>2</sup>), Nw (18.5 ≤ BMI < 25.0 kg/m<sup>2</sup>), Ow (25.0 ≤ BMI < 30.0 kg/m<sup>2</sup>) and Ob (BMI ≥30.0 kg/m<sup>2</sup>) [36] and further grouped into Uw/Nw and Ow/Ob. Smoking habits during pregnancy were categorized into ‘smoking during pregnancy’: ‘yes’ or ‘no’. Regarding child’s characteristics, we further considered sex, birth weight and gestational age – obtained from medical records at birth. Birth weight was categorized into ‘very low birth weight’ (<1500g), ‘low birth weight’ (≥1500g - <2500g), ‘normal birth weight’ (≥2500g - <4000g) and ‘high birth weight’ (≥4000g) and gestational age into ‘≥37 weeks’ and ‘<37 weeks’ [37].

### **Statistical analysis**

For the descriptive analysis, the distribution of the continuous variables was assessed through histograms and Q-Q plots; normal and non-normally distributed variables were described using the mean (M) and standard deviation (SD) and the median (Md) and interquartile range (IQR), respectively. Categorical data were reported as counts (n) and percentages (%). To test for differences between the

included and excluded participants, the Chi-squared test and the Student's t-test was conducted, and Cohen's d effect sizes were calculated. To test for differences between the appetitive behaviours profiles, One-way ANOVA with post-hoc analysis (Tukey's test), Kruskal Wallis test with post hoc analysis, and Pearson's Chi-square test were performed.

Associations between BMI<sub>AUC</sub> and appetitive behaviours profiles were assessed using multinomial logistic regression models and Odds Ratio (OR), and the respective 95% Confidence Intervals (CI) were obtained. The previously mentioned covariates were tested as potential confounders and included in the models based on the following criteria: being statistically significant in the model and/or having considerable scientific plausibility for inclusion. Models were then adjusted for child's sex, maternal education and age at baseline and smoking during pregnancy. The interaction between BMI<sub>AUC</sub>\*sex, BMI<sub>AUC</sub>\*mother's pre-pregnancy BMI in the tested associations was verified but no significant results were obtained. To test the association of BMI at specific ages with appetitive behaviours profiles, independently of the cumulative BMI (BMI<sub>AUC</sub>), BMI z-scores (using Uw/Nw as the reference category), at each age, were added to the adjusted model. The possibility of multicollinearity between predictors was tested using Pearson and Spearman r-correlation indices (for  $|r| > 0.80$ ) and through the calculation of tolerance and variance inflation factor ( $VIF > 5$ ) [38]. As the continuous format of the BMI z-scores at 4, 7, 10 and 13y presented a risk of multicollinearity with BMI<sub>AUC</sub>, the categorical format was considered after new testing for multicollinearity.

A two-sided significance of 5% was considered and statistical analysis was performed in IBM® SPSS® Statistics version 26.0 software (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp).

## Results

The characterization of the participants is presented in Table 1. The sample consisted of 51.3% boys. Mothers had a mean (SD) age of 30.3 (4.94) and 11.6 (4.28) completed years of schooling. Before pregnancy, most of the mothers had Nw (66.3%), while 21.5% and 9.0% had Ow and Ob, respectively. During pregnancy, 82% of the mothers did not smoke. The median exposure to BMI<sub>AUC</sub> (IQR) per month was 17.4 kg/m<sup>2</sup> (3.29). The highest proportion of children with Ow and Ob was at 10y (Ow=26.0%; Ob=15.5%) with an observed decrease at 13y (Ow=24.1%; Ob=9.1%).

### Appetitive behaviours and derivation of profiles

The ICC values presented in Table S1 suggest an overall stability of appetitive behaviours over time. Specifically, 'Enjoyment of Food' and 'Slowness in eating' (ICC=0.83), and 'Satiety Responsiveness' (ICC=0.81) exhibited almost perfect tracking, while the other behaviours showed substantial tracking, with ICC values ranging from 0.67 in 'Emotional Overeating' to 0.78 in 'Food Fussiness'. The low marginal  $R^2$  values obtained from the linear mixed model suggest that fixed effects (age and sex) account for a small proportion of the variance observed. Conversely, the high conditional  $R^2$  values indicate that random factors play a more significant role in explaining the variance. Thus, the observed differences may lie mainly between groups ('clusters') of children rather than within subjects.

The three best models identified 6 (BIC = 142748.1), 7 (BIC=142852.2) and 8 (BIC=142813.4) classes of appetitive behaviours profiles. Considering the lowest BIC value criterion, the 6 classes model was chosen. In the present study, each latent class was considered as a profile, representative of a pattern of evolution of appetitive behaviours, in which individuals were assigned according to the probability of the most likely latent class membership (median values ranging from 76% to 95%). Figure 2. presents the profiles (n=5139) organized by each of the individual appetitive behaviour over time (7, 10, 13y). Profile 1 (n=1495, 29.1%) was labelled as 'moderate appetite', as it contains the highest proportion of children and stands close to the average score of each appetitive behaviour. Profiles 4, the 'avid appetite' (n=606, 11.8%), and 6, the 'smallest appetite' (n=532, 10.4%), represent the extremes, as children consistently presented the highest scores on food approach and the lowest scores on food avoidant behaviours and vice-versa, respectively. In profile 2, the 'small but increasing appetite' (n=417, 8.1%), an increase in low food approach behaviours is observed, except for 'Desire to Drink' which, along with food avoidant behaviours, is high initially but decreases over time. Profile 3, the 'small to moderate appetite' (n=1343, 26.1%), represents children with the lowest scores on food approach behaviours and emotional undereating, while the other behaviours remain close to the average. Profile 5, the 'increasing appetite' (n=746, 14.5%), stands out for the increasing scores in food approach behaviours while food avoidant behaviours remain close to the average.

### Appetitive behaviours profiles characterization

In the current sample (n=3339), the majority of children belonged to the 'small to moderate appetite' (27.9%), followed by the 'moderate appetite' (25.6%), 'increasing appetite' (16.8%), 'avid appetite' (11.3%), 'smallest appetite' (10.6%) and 'small but increasing appetite' (7.8%). Mothers of children in the 'small to moderate appetite' profile and 'smallest appetite' were the oldest, while mothers in profile 4 were the youngest. The 'smallest appetite' and the 'increasing appetite' profile presented the mothers with the highest and the lowest number of years of complete schooling, respectively. The proportion of mothers with Ow/Ob before pregnancy was the highest in the 'avid appetite' and 'increasing appetite' profiles; and the lowest for the 'small but increasing appetite'. Regarding child's characteristics, the proportion of boys and girls was similar and evenly distributed across profiles. At all the follow-ups, the highest proportion of Ow/Ob was observed in the 'avid appetite' and the lowest in 'smallest appetite' profile'. A more detailed characterization of the appetitive behaviours profiles is presented in supplementary data (Table S2).

### BMI<sub>AUC</sub> and appetitive behaviours profiles

The cumulative exposure to adiposity, per month, was the highest for the 'avid appetite' profile, followed by 'increasing appetite', 'moderate appetite', 'small but increasing', 'small to moderate appetite', and the 'smallest appetite' (Table S2). In comparison to belonging to the 'moderate appetite' group (reference category), per increasing unit of BMI<sub>AUC</sub>, children had 47% higher odds of having an 'avid appetite' profile (OR=1.47, 95%CI: 1.40-1.55). Apart from the 'increasing appetite' profile, which yield no significant results, per increasing unit of BMI<sub>AUC</sub>, a decrease between 16 to 22% in the odds of belonging to the other profiles ('small but increasing', 'small to moderate appetite', and the 'smallest appetite') was observed. The magnitude of the negative association was the highest for the 'smallest appetite' profile (Table 2).

### BMI<sub>AUC</sub> Vs. BMI z-scores and appetitive behaviours profiles

The 'moderate appetite', 'small but increasing appetite' and 'increasing appetite' profiles showed the highest mean BMI z-score values at 10y, while in the 'small to moderate appetite', 'avid appetite' and 'smallest appetite', the highest BMI z-score occurred earlier, at 7y (Table S2). As in the main analysis (Table 2), when adding BMI z-scores categories, BMI<sub>AUC</sub> remained negatively associated with the profiles 'small but changing appetite', 'small to moderate appetite' and 'smallest

appetite' and positively associated with the 'avid appetite' one, at all the follow-ups (Table 3). Contrarily, the 'increasing appetite' profile gained significance at 7y, for which an increasing BMI<sub>AUC</sub> was associated with increased odds of having this profile. Regarding the BMI status of children at each assessment, in comparison to having Uw/Nw, children who had Ow/Ob at 7 and 10y respectively presented 113% and 68% higher odds of belonging to an 'avid appetite' profile, regardless of their cumulative adiposity measure (BMI<sub>AUC</sub>). In its turn, children with Ow/Ob at 7y, were 33% less likely of belonging to the 'increasing appetite' profile. At 13y, children with Ow/Ob presented 44% lower odds of having the 'smallest appetite' profile.

Overall, BMI<sub>AUC</sub> was more suggestive of the appetitive profile the child probably belongs to than the weight status at each time point.

## Discussion

The results of this study suggest an association between the cumulative exposure of BMI (as an indicator of adiposity), from 4 to 13y, and six different profiles of appetitive behaviours throughout childhood into early adolescence. Individuals with the highest cumulative exposure to adiposity were more likely to present the 'avid appetite' profile, whereas those with the lowest cumulative exposure to adiposity were more likely to belong to the 'smallest appetite' profile. Additionally, having excessive weight at 7y may be already indicative of being an avid eater in subsequent ages (from 7 to 13y).

The use of a person-centred approach, as we did in the current study, allows to identify groups of individuals with similar patterns of evolution. This type of analysis, covering important stages of development is not only innovative, but may also be a more comprehensive way of capturing children's appetite and more effectively target those with less desirable and more obesogenic appetitive behaviours profiles [18, 39]. From the few studies using this approach on CEBQ appetitive behaviours [19-24], only one considered more than one appetitive behaviour [24]. The mentioned study [24], in pre-schoolers (3-4y) from low-income backgrounds, identified three profiles: a 'high food approach', with the highest prevalence of obesity; a 'high food avoidant' where Uw/Nw was the most common group, and a 'moderate eating' with intermediary levels of all behaviours. Although presenting younger ages than the current study, and with only one-time point assessment, these profiles could somewhat correspond to the 'avid appetite', 'smallest appetite' and 'moderate

appetite' profiles we have identified. Also, the remaining profiles we obtained were less pronounced and less distinguishable between each other.

As expected, in our final sample ( $n=3339$ ), the proportion of Ow/Ob in all the follow-ups was the highest for the 'avid' and the lowest for the 'smallest appetite' profile. In accordance, the cumulative exposure to BMI during the considered period of childhood into early adolescence, per month, was also the highest and the lowest for these two profiles, respectively. Surprisingly, we found no significant associations between BMI<sub>AUC</sub> and the 'increasing appetite' profile which, following the 'avid appetite', was the one with the highest prevalence of Ow/Ob and presented increasing food approach behaviours along with stable to decreasing food avoidant behaviours over time. Associations with this profile were only significant and positive when adding BMI z-scores categories at 7y. The lack of association observed in the first scenario may be due to the close BMI<sub>AUC</sub> values observed for this profile and the 'moderate appetite' profile, considered as reference in the multinomial logistic regression models. Although 'moderate eating' was the most common profile in the original sample deriving them ( $n=5149$ ), it does not mean it is the healthiest or most desirable one. In fact, results of previous literature support that, overall, despite the considerable stability of behaviours [40-42] - as reinforced by the high ICC values obtained for each of the appetite behaviours in our dataset - there is a tendency for a decrease in appetite self-regulation, i.e., increase in food approach behaviours and a decrease in responsiveness to internal cues of satiety, over time [40]. The fixed effect results from the linear mixed models performed (Table S1) corroborate this fact: Enjoyment of Food, Food Responsiveness, Emotional Overeating (food approach behaviours) and Food Fussiness revealed a slightly increasing trend over time, whereas the remaining food avoidant behaviours declined.

Of note, although different possible confounders of associations were tested, the adjusted estimates between BMI<sub>AUC</sub> and appetitive behaviours profiles were very similar to the crude model (Table 2). Possibly, the fact that both exposure and outcome encompass a time window with different moments of assessment may have hampered finding the common confounding effects observed in literature when associations at specific ages are tested. Possible residual confounding could not be discarded.

When exploring the effect of BMI z-scores at each time point, independently of cumulative BMI, those who had Ow/Ob at 7y were less likely of belonging to the 'increasing appetite' profile. Although apparently contradictory, the latter may be

explained because the BMI z-scores children presented at early ages, at 4 and 7y in this profile, when compared to the reference, may not be sufficiently high to increase the odds of belonging to an 'increasing appetite' profile. This may also mean that in children with this type of appetitive profile, the accumulation of weight is delayed until later ages, in childhood. Contrarily, at 7 and 10y, regardless of the child's cumulative exposure to adiposity, having Ow/Ob at 7 or 10y may already be indicative of an avid appetite profile. Middle childhood (6-11/12y) is an important stage that bridges the transition between early childhood to adolescence and is characterized by various changes: increased cognitive skills, autonomy, brain and body growth, onset of sexual attraction, social learning and integration and changes in food preferences, among other [43, 44]. Regarding body growth, the beginning of adrenal androgens secretion ('adrenarche') seems to influence the shift in energy allocation from the brain to the body's preparation for puberty, by increasing muscle and fat mass [44]. In fact, after infancy, BMI decreases, reaching a minimum ('nadir') around the age of 6, which is then followed by an increase throughout childhood. This time point, after the nadir, where BMI rises is called the adiposity rebound [45]. An earlier timing of adiposity rebound (<5.5 y) has been associated with increased body fat mass and a higher risk of later obesity [45, 46]. Although we did not calculate the age at adiposity rebound, in the 'avid appetite' profile, at 4y, the mean BMI z-score was already correspondent to a nutritional status of overweight and the highest increase in BMI z-scores occurred from 4 to 7y, slightly decreasing but maintaining a high mean value at 10y. Thus, it seems plausible that having Ow/Ob at 7 and 10y would already be predictive of belonging to this profile.

There are different possible mechanisms through which weight may influence appetite. First, differences in inhibitory control and food cue responsiveness according to body weight categories have been reported. A meta-analysis including studies on children, adolescents, and adults concluded that individuals with normal weight reveal greater activity in the gustatory brain area, as well as a higher inhibitory control in response to food cues. Conversely, individuals with Ow/Ob present heightened activation of the visual cortex and reward-related brain areas in response to visual food cues, particularly if high-caloric foods, which can result in increased food consumption [47]. This increase in appetite via higher responsiveness to food cues, and consequent food consumption, likely mediates the continuous increase in body weight. Adding to the alarming childhood obesity prevalence [48], the previous becomes distinctly relevant considering the current permissive obesogenic food

environment that facilitates consumption and overriding of internal signals of hunger and satiety [49]. Additionally, the increase in general self-regulation, characteristic of childhood development, does not seem to match an increase in appetite self-regulation; instead, an increase in food approach and hedonic responses is observed along with a reduction in satiety responsiveness [40].

Second, BMI results from the sum of fat mass and fat-free mass. It was not the focus of the present study, but the association between body composition and appetite has been previously explored, mainly by the work of Professor John Blundell and his team. Results of their research suggest that, contrary to common belief, the drive to eat is mainly a result of the resting metabolic rate and the amount of fat-free mass an individual has [50]. Leptin (the so called 'satiety hormone') produced by the fat mass tissue would counterbalance this drive to eat due to its anorexigenic properties. Yet, for higher levels of this hormone, there is a process called leptin resistance that hampers its inhibitory effect [51]. At least in adults, these two facts could be part of the reason why individuals with *Ow/Ob* have a higher appetite: the increase in fat-free mass with increasing fat mass may result in a higher drive to eat which is not held on by leptin [52]. In children from Generation XXI, for instance, higher levels of leptin at 7y have already been associated with higher food responsiveness and emotional overeating at age 10 [53]. The association between body composition and appetitive behaviours has been previously explored. Some authors suggest that fat mass and related measures, such as central fat, prospectively impact the hedonic appetite control system (with increases in food approach behaviours) [15, 54, 55]. Yet, controversy lies regarding the direction of association for fat-free mass, for which there is both evidence suggesting that fat-free mass influences the homeostatic system (with decreases in food avoidant behaviours) [54] and that the stronger path of association is the opposite one [55].

This study has some limitations that deserve attention. There were losses to follow-up throughout assessments and missing data that resulted in a reduction of the final sample size. Yet, for a more representative understanding of appetitive behaviours profiles, we imputed missing data in CEBQ subscales and derived profiles from the whole cohort, considering children with available CEBQ information in at least two time points. Also, mothers in the considered sample were significantly older and more educated than the remaining cohort, and children heavier at birth, which may be indicative of selection bias. However, the magnitude of the difference was moderate for maternal variables and small for birth weight - the statistically

significant differences may be due to the large sample size and not due to systematic differences between participants [56]. Regarding assessment tools, CEBQ is a parent-reported questionnaire, susceptible to subjectivity, social desirability bias, and possible lack of awareness from parents/caregivers of their child's appetite. Still, this questionnaire has been originally validated against behavioural measures of eating [57] and has shown good psychometric properties in Generation XXI children [16, 32]. Also, appetitive behaviours in infancy and early childhood were not assessed and it is possible that, at these stages, the tendency for a more avid or smaller appetite has been already established, affecting weight in the time window we explored.

Regarding its strengths, this study is, to our knowledge, the first to i) use a cumulative measure of both the duration and degree of adiposity ( $BMI_{AUC}$ ) and associate it with appetitive behaviours and ii) derive profiles using concomitantly longitudinal data of eight behaviours from the most widely used questionnaire to report appetite-related eating behaviours, the CEBQ [10]. Other important topics relate to the inclusion of a large birth cohort data, encompassing information from a relevant period of development; the use of innovative analyses, including a person-centred approach and the calculation of  $BMI_{AUC}$  (able to capture fluctuations over time). However, it is important to note that despite presenting data from different assessments, no inference about causality can be extrapolated. The present analysis creates a "portrait" of a nine-year period exposure to adiposity and contributes to the disentanglement of the complexity of appetite dimensions, indicating how they can aggregate with each other and evolve over time.

Lastly, the BMI history of children throughout childhood until adolescence yield more significant associations with appetitive behaviours profiles than when weight status at each time point was considered. Thus, these findings suggest that cumulative exposure to adiposity may be a more representative indicator of the appetitive profile the child belongs to. In practical terms, however, the assessment of cumulative exposure to adiposity is not always straightforward. In contrast, identifying a particular age of concern regarding weight status, such as 7y, can be a more objective target. Additionally, the derivation of a 'moderate appetite' (characterized by increasing food approach behaviours and decreasing ability to respect internal cues of hunger and fullness) and the associations obtained for the 'avid appetite' profile reinforce the importance of curbing excessive weight gain in early childhood to protect from the development of obesity risk appetite profiles.

## Conclusion

This study identified six clusters of specific appetitive behaviours profiles among children/pre-adolescents, of which a 'moderate appetite', and two extremes: the 'avid appetite' and the 'smallest appetite' profiles. Children with the highest and lowest cumulative exposure to adiposity throughout childhood and early adolescence were more likely to present the 'avid appetite' (overall high food approach behaviours) and the 'smallest appetite' profile (overall high food avoidant behaviours), respectively, from 7 to 13y. Additionally, having Ow/Ob at an early age as 7y was already indicative of belonging to an avid appetite profile.

Future studies could extend the captured period for appetite behaviours and contribute to clarifying the specific role of fat mass and fat-free mass in the development of appetite trajectories over time.

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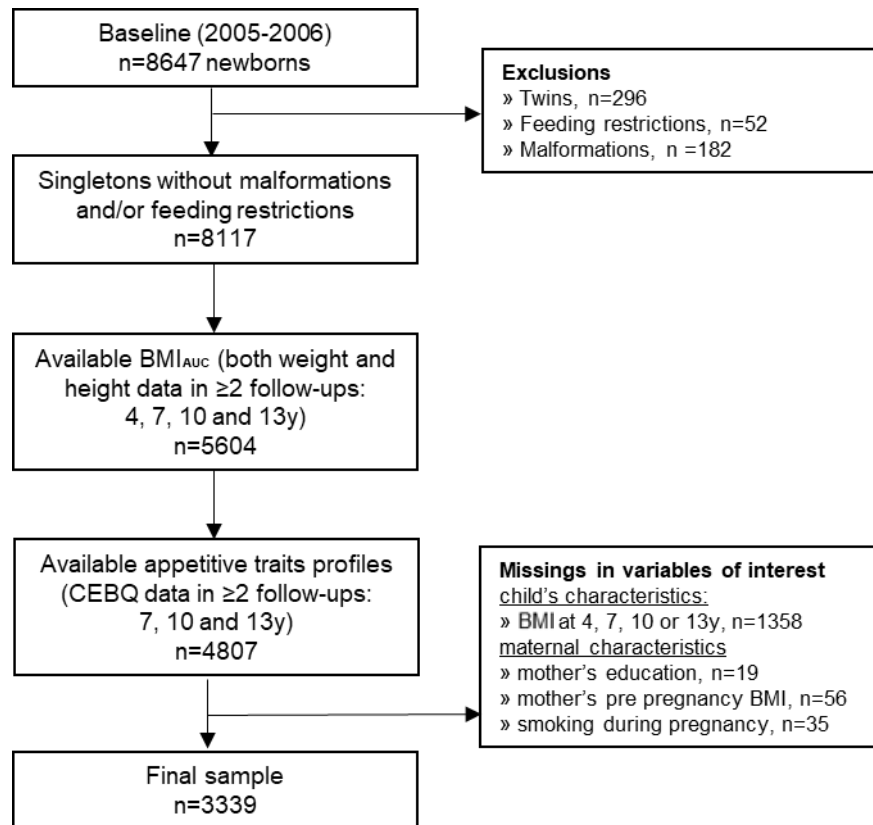


**Figure 1.** Flowchart of study participants.

CEBQ: Children's Eating Behaviour Questionnaire; BMI: Body Mass Index; BMI<sub>AUC</sub>: body mass index area under the curve

**Table 1.** Characterization of the Generation XXI participants included in the study (n=3339).

| Mother's characteristics at baseline   |             |             |             |             |
|----------------------------------------|-------------|-------------|-------------|-------------|
| Age (years), M (SD)                    | 30.3 (4.94) |             |             |             |
| Education (years of schooling), M (SD) | 11.6 (4.28) |             |             |             |
| Pre-pregnancy BMI, n (%)               |             |             |             |             |
| Underweight                            | 106 (3.2)   |             |             |             |
| Normal weight                          | 2214 (66.3) |             |             |             |
| Overweight                             | 718 (21.5)  |             |             |             |
| Obesity                                | 301 (9.0)   |             |             |             |
| Smoking during pregnancy, n (%)        |             |             |             |             |
| No                                     | 2739 (82.0) |             |             |             |
| Yes                                    | 600 (18.0)  |             |             |             |
| Child's characteristics                |             |             |             |             |
| Sex, n (%)                             |             |             |             |             |
| Girls                                  | 1625 (48.7) |             |             |             |
| Boys                                   | 1714 (51.3) |             |             |             |
| Anthropometrics                        |             |             |             |             |
| BMI <sub>AUC</sub> , Md (IQR)          | 17.4 (3.29) |             |             |             |
| BMI z-scores, n (%)                    | 4y          | 7y          | 10y         | 13y         |
| Underweight                            | 12 (0.4)    | 7 (0.2)     | 27 (0.8)    | 67 (2.0)    |
| Normal weight                          | 3017 (90.4) | 2172 (65.0) | 1928 (57.7) | 2161 (64.7) |
| Overweight                             | 231 (6.9)   | 726 (21.7)  | 868 (26.0)  | 806 (24.1)  |
| Obesity                                | 79 (2.4)    | 434 (13.0)  | 516 (15.5)  | 305 (9.1)   |
| Appetitive behaviours – CEBQ*, M (SD)  | 7y          | 10y         | 13y         |             |
| Enjoyment of food                      |             | 3.0 (0.79)  | 3.2 (0.78)  | 3.2 (0.78)  |
| Food Responsiveness                    |             | 2.0 (0.77)  | 2.2 (0.82)  | 2.2 (0.84)  |
| Emotional Overeating                   |             | 1.8 (0.62)  | 2.0 (0.67)  | 2.1 (0.74)  |
| Desire to drink                        |             | 2.2 (0.79)  | 2.1 (0.72)  | 2.0 (0.71)  |
| Satiety Responsiveness                 |             | 2.3 (0.68)  | 2.6 (0.66)  | 2.5 (0.64)  |
| Slowness in eating                     |             | 3.0 (0.87)  | 2.7 (0.86)  | 2.4 (0.82)  |
| Emotional Undereating                  |             | 2.5 (0.75)  | 2.4 (0.73)  | 2.3 (0.75)  |
| Food Fussiness                         |             | 3.0 (0.76)  | 3.0 (0.81)  | 2.9 (0.83)  |

M (SD): mean (standard deviation); Md (IQR): median (interquartile range); BMI: Body Mass Index; AUC: area under the curve; BMI z-scores categories at 4y: Underweight (< -2SD), Normal weight ( $\geq -2SD$  and  $\leq 2SD$ ), Overweight ( $>2SD$  and  $\leq 3SD$ ) and Obesity ( $>3SD$ ); BMI z-scores categories at 7, 10 and 13y: Underweight ( $\leq -2SD$ ), Normal-weight ( $> -2SD$  and  $< 1SD$ ), Overweight ( $\geq 1SD$  and  $< 2SD$ ) and Obesity ( $\geq 2SD$ ) [30]. BMI pre-pregnancy: Underweight ( $BMI < 18.5 \text{ kg/m}^2$ ), Normal weight ( $18.5 \leq BMI < 25.0 \text{ kg/m}^2$ ), Overweight ( $25.0 \leq BMI < 30.0 \text{ kg/m}^2$ ) and Obesity ( $BMI \geq 30.0 \text{ kg/m}^2$ ). CEBQ: Children's Eating Behaviour Questionnaire (n= 3211- 3285); \*possible range 1-5.

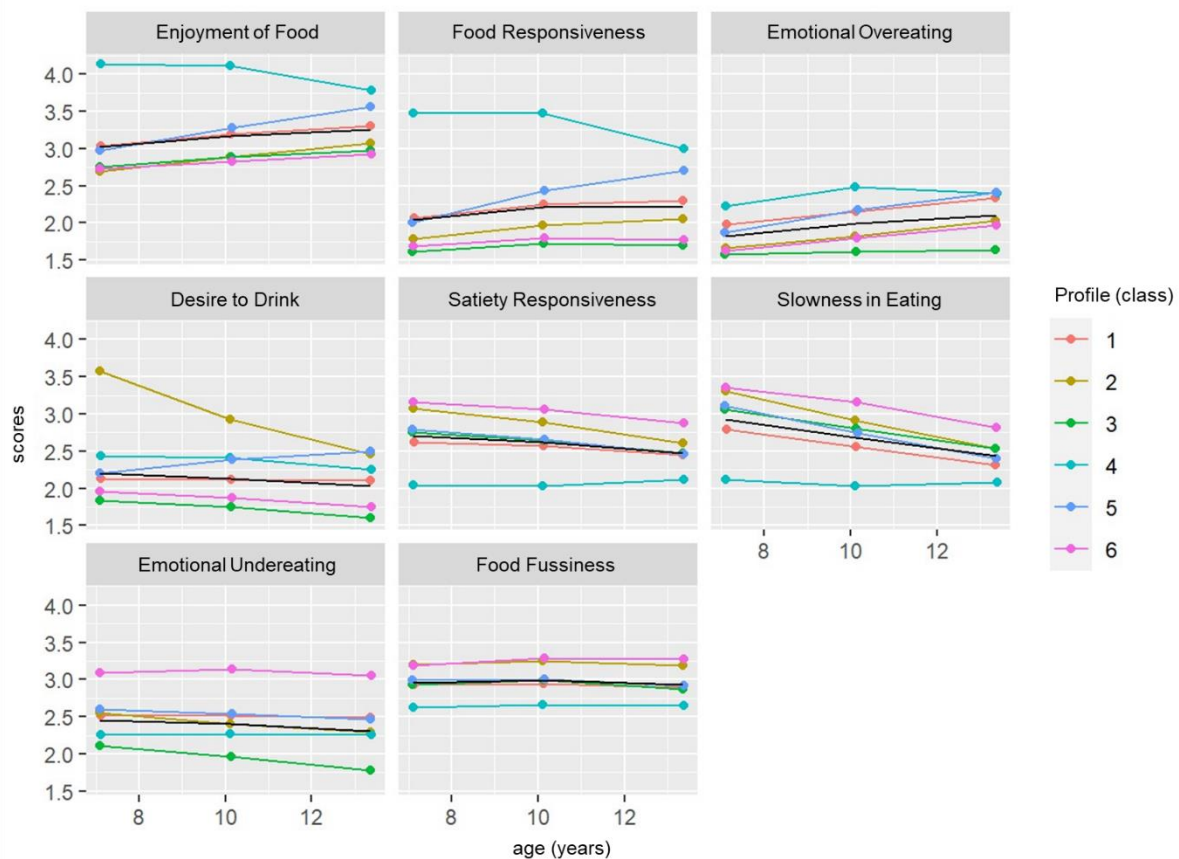


**Figure 2.** Appetitive behaviours profiles identified, described according to the evolution of each of the individual appetitive behaviour over time (7, 10, 13y) (n=5139).

Appetitive behaviours profiles: 1. 'Moderate appetite' (n=1495, 29.1%), 2. 'Small but increasing appetite' (n=417, 8.1%), 3. 'Small to moderate appetite' (n=1343, 26.1), 4. 'Avid appetite' (n=606, 11.8%), 5. 'Increasing appetite' n=746, 14.5%), 6. 'Smallest appetite' (n=532, 10.4%). The black line represents the average scores of each appetitive behaviour.

**Table 2.** Multinomial logistic regression between BMI<sub>AUC</sub> and appetitive behaviours profiles.

| Appetitive behaviours profiles | Model 0                 | Model 1                 |
|--------------------------------|-------------------------|-------------------------|
|                                | OR (95% CI)             |                         |
| Moderate appetite              | ref                     | ref                     |
| Small but increasing appetite  | <b>0.85 (0.80-0.91)</b> | <b>0.84 (0.79-0.90)</b> |
| Small to moderate appetite     | <b>0.83 (0.80-0.87)</b> | <b>0.83 (0.79-0.87)</b> |
| Avid appetite                  | <b>1.47 (1.40-1.55)</b> | <b>1.47 (1.40-1.55)</b> |
| Increasing appetite            | 1.03 (0.99-1.08)        | 1.02 (0.98-1.07)        |
| Smallest appetite              | <b>0.78 (0.73-0.83)</b> | <b>0.78 (0.73-0.83)</b> |

OR: odds ratio; CI: Confidence interval, Model 0: crude model, Model 1: adjusted for child's sex; mother's age, education and smoking during pregnancy; ref: reference class; **Bold**-type represents statistically significant associations (p<0.05).

**Table 3.** Adjusted multinomial logistic regression between BMI<sub>AUC</sub> Vs. BMI z-scores categories at each follow-up and appetitive behaviours profiles.

|                                      |                    | 4 years                 | 7 years                 | 10 years                | 13 years                |
|--------------------------------------|--------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Appetitive behaviours profiles       |                    | OR (95% CI)             |                         |                         |                         |
| Moderate appetite                    | BMI <sub>AUC</sub> | ref                     | ref                     | ref                     | ref                     |
|                                      | Ow/Ob              |                         |                         |                         |                         |
|                                      | Uw/Nw              | ref                     | ref                     | ref                     | ref                     |
| Small appetite but changing appetite | BMI <sub>AUC</sub> | <b>0.85 (0.79-0.92)</b> | <b>0.86 (0.78-0.95)</b> | <b>0.89 (0.80-0.99)</b> | <b>0.81 (0.74-0.88)</b> |
|                                      | Ow/Ob              | 0.82 (0.34-1.73)        | 0.90 (0.56-1.46)        | 0.73 (0.45-1.18)        | 1.37 (0.90-2.10)        |
|                                      | Uw/Nw              | ref                     | ref                     | ref                     | ref                     |
| Small to moderate appetite           | BMI <sub>AUC</sub> | <b>0.82 (0.78-0.86)</b> | <b>0.86 (0.80-0.92)</b> | <b>0.87 (0.81-0.94)</b> | <b>0.86 (0.81-0.91)</b> |
|                                      | Ow/Ob              | 1.11 (0.86-1.44)        | 0.83 (0.60-1.13)        | 0.76 (0.55-1.03)        | 0.79 (0.59-1.05)        |
|                                      | Uw/Nw              | Ref                     | ref                     | ref                     | ref                     |
| Avid appetite                        | BMI <sub>AUC</sub> | <b>1.44 (1.36-1.54)</b> | <b>1.35 (1.26-1.45)</b> | <b>1.41 (1.31-1.51)</b> | <b>1.43 (1.34-1.53)</b> |
|                                      | Ow/Ob              | 1.22 (0.78-1.91)        | <b>2.13 (1.42-3.21)</b> | <b>1.68 (1.10-2.58)</b> | 1.24 (0.86-1.79)        |
|                                      | Uw/Nw              |                         |                         |                         |                         |
| Increasing appetite                  | BMI <sub>AUC</sub> | 1.04 (0.96-1.01)        | <b>1.09 (1.01-1.16)</b> | 1.06 (0.99-1.14)        | 0.98 (0.92-1.04)        |
|                                      | Ow/Ob              | 0.76 (0.48-1.20)        | <b>0.67 (0.47-0.95)</b> | 0.80 (0.57-1.12)        | 1.33 (0.98-1.81)        |
|                                      | Uw/Nw              | ref                     | ref                     | ref                     | ref                     |
| Smallest appetite                    | BMI <sub>AUC</sub> | <b>0.77 (0.72-0.83)</b> | <b>0.77 (0.70-0.84)</b> | <b>0.84 (0.76-0.92)</b> | <b>0.84 (0.77-0.91)</b> |
|                                      | Ow/Ob              | 1.33 (0.68-2.62)        | 1.16 (0.75-1.81)        | 0.68 (0.44-1.06)        | <b>0.56 (0.37-0.85)</b> |
|                                      | Uw/Nw              | ref                     | ref                     | ref                     | ref                     |

OR: odds ratio; CI: Confidence interval; BMI: Body Mass Index; AUC: area under the curve; Uw/Nw: Underweight/Normal weight; Ow/Ob: Overweight/Obesity; BMI z-scores categories at 4y: Uw/Nw ( $\leq 2SD$ ) and Ow/Ob ( $>2SD$ ); BMI z-scores categories at 7, 10 and 13y: Uw/Nw ( $\leq 1SD$ ) and Ow/Ob ( $>1SD$ ); Associations adjusted for child's sex; mother's age, education and smoking during pregnancy; ref: reference class; **Bold**-type represents statistically significant associations ( $p < 0.05$ ).

## Supplementary materials

**Table S1.** Stability of each appetitive behaviour over time (from 7 to 13 years of age) and explained variance of fixed and random effects obtained from the linear mixed model.

| <b>Appetitive behaviour</b> | Time (y) <sup>1</sup><br>$\beta$ (95% CI) | Intraclass correlation<br>coefficient | Marginal R <sup>2*</sup> | Conditional R <sup>2**</sup> |
|-----------------------------|-------------------------------------------|---------------------------------------|--------------------------|------------------------------|
| Enjoyment of food           | <b>0.08 (0.07; 0.09)</b>                  | 0.83                                  | 0.01                     | 0.83                         |
| Food responsiveness         | <b>0.06 (0.05; 0.07)</b>                  | 0.75                                  | 0.01                     | 0.75                         |
| Emotional overeating        | <b>0.06 (0.05; 0.07)</b>                  | 0.66                                  | 0.02                     | 0.67                         |
| Desire to drink             | <b>-0.02 (-0.03; -0.01)</b>               | 0.75                                  | 0.01                     | 0.76                         |
| Satiety responsiveness      | <b>-0.02 (-0.03; -0.01)</b>               | 0.81                                  | 0.01                     | 0.81                         |
| Slowness in eating          | <b>0.03 (0.02; 0.04)</b>                  | 0.83                                  | 0.03                     | 0.84                         |
| Emotional undereating       | <b>-0.09 (-0.10; -0.07)</b>               | 0.68                                  | 0.00                     | 0.68                         |
| Food fussiness              | <b>-0.02 (-0.03; -0.01)</b>               | 0.78                                  | 0.00                     | 0.78                         |

y: years; <sup>1</sup>Estimates ( $\beta$ ) and 95% Confidence Intervals from multi-level model adjusted for child's sex; significant results in **bold-type** ( $p < 0.05$ ); R<sup>2</sup>: coefficient of determination; \*fixed effects from the linear mixed model; \*\*random effects from the linear mixed model.

**Table S2.** Characterization and comparison of the six appetitive behaviours profiles, in Generation XXI cohort (n=3339).

|                                             | Moderate appetite<br>(n= 856, 25.6%) | Small but increasing<br>appetite<br>(n= 259, 7.8%) | Small to<br>moderate<br>appetite<br>(n= 933, 27.9%) | Avid appetite<br>(n=376, 11.3%) | Increasing<br>appetite<br>(n=561, 16.8%) | Smallest appetite<br>(n=354, 10.6%) | p-value          |
|---------------------------------------------|--------------------------------------|----------------------------------------------------|-----------------------------------------------------|---------------------------------|------------------------------------------|-------------------------------------|------------------|
| <b>Mother's characteristics at baseline</b> |                                      |                                                    |                                                     |                                 |                                          |                                     |                  |
| Age (years), M (SD)                         | 30.30 (4.69) <sup>abc</sup>          | 29.72 (5.20) <sup>a</sup>                          | 30.98 (4.68) <sup>c</sup>                           | 29.49 (5.12) <sup>a</sup>       | 29.94 (5.44) <sup>ab</sup>               | 30.71 (4.76) <sup>bc</sup>          | <b>&lt;0.001</b> |
| Education (years of schooling), M (SD)      | 11.95 (4.20) <sup>b</sup>            | 10.88 (4.24) <sup>a</sup>                          | 11.65 (4.25) <sup>ab</sup>                          | 11.11 (4.00) <sup>a</sup>       | 11.04 (4.45) <sup>a</sup>                | 12.35 (4.40) <sup>b</sup>           | <b>&lt;0.001</b> |
| Pre-pregnancy BMI, n (%)                    |                                      |                                                    |                                                     |                                 |                                          |                                     |                  |
| Uw/Nw                                       | 602 (70.3) <sup>a,b,c</sup>          | 196 (75.7) <sup>c</sup>                            | 671 (71.9) <sup>a,b,c</sup>                         | 212 (56.4) <sup>d</sup>         | 378 (67.4) <sup>b</sup>                  | 261 (73.7) <sup>a,c</sup>           | <b>&lt;0.001</b> |
| Ow/Ob                                       | 254 (29.7) <sup>a,b,c</sup>          | 63 (24.3) <sup>c</sup>                             | 262 (28.1) <sup>a,b,c</sup>                         | 164 (43.6) <sup>d</sup>         | 183 (32.6) <sup>b</sup>                  | 93 (26.3) <sup>a,c</sup>            |                  |
| Smoking during pregnancy, n (%)             |                                      |                                                    |                                                     |                                 |                                          |                                     |                  |
| No                                          | 707 (82.6) <sup>a,b</sup>            | 199 (76.8) <sup>c</sup>                            | 790 (84.7) <sup>b,d</sup>                           | 288 (76.6) <sup>c</sup>         | 443 (79.0) <sup>a,c</sup>                | 312 (88.1) <sup>d</sup>             | <b>&lt;0.001</b> |
| Yes                                         | 149 (17.4) <sup>a,b</sup>            | 60 (23.2) <sup>c</sup>                             | 143 (15.3) <sup>b,d</sup>                           | 88 (23.4) <sup>c</sup>          | 118 (21.0) <sup>a,c</sup>                | 42 (11.9) <sup>d</sup>              |                  |
| <b>Child's characteristics</b>              |                                      |                                                    |                                                     |                                 |                                          |                                     |                  |
| Sex, n (%)                                  |                                      |                                                    |                                                     |                                 |                                          |                                     |                  |
| Girls                                       | 417 (48.7)                           | 121 (46.7)                                         | 460 (49.3)                                          | 199 (52.9)                      | 259 (46.2)                               | 169 (47.7)                          | 0.441            |
| Boys                                        | 439 (51.3)                           | 138 (53.3)                                         | 473 (50.7)                                          | 177 (47.1)                      | 302 (53.8)                               | 185 (52.3)                          |                  |
| Gestational age, n(%)                       |                                      |                                                    |                                                     |                                 |                                          |                                     |                  |
| ≥37 weeks                                   | 814 (95.1) <sup>a</sup>              | 240 (92.7) <sup>a,b,c</sup>                        | 850 (91.1) <sup>c</sup>                             | 351 (93.4) <sup>a,b,c</sup>     | 531 (94.7) <sup>a,b</sup>                | 326 (92.1) <sup>b,c</sup>           | <b>0.016</b>     |
| <37 weeks                                   | 42 (4.9) <sup>a</sup>                | 19 (7.3) <sup>a,b,c</sup>                          | 83 (8.9) <sup>c</sup>                               | 25 (6.6) <sup>a,b,c</sup>       | 30 (5.3) <sup>a,b</sup>                  | 28 (7.9) <sup>b,c</sup>             |                  |
| <b>Anthropometrics</b>                      |                                      |                                                    |                                                     |                                 |                                          |                                     |                  |
| Weight at birth                             |                                      |                                                    |                                                     |                                 |                                          |                                     |                  |
| Very low birth weight                       | 3 (0.4)                              | 2 (0.8)                                            | 5 (0.5)                                             | 3 (0.8)                         | 2 (0.4)                                  | 6 (1.7)                             | 0.248            |
| Low birth weight                            | 41 (4.8)                             | 17 (6.6)                                           | 62 (6.6)                                            | 17 (4.5)                        | 27 (4.8)                                 | 25 (7.1)                            |                  |
| Normal weight                               | 773 (90.3)                           | 234 (90.3)                                         | 832 (89.2)                                          | 339 (90.2)                      | 507 (90.4)                               | 307 (86.7)                          |                  |
| High birth weight                           | 39 (4.6)                             | 6 (2.3)                                            | 34 (3.6)                                            | 17 (4.5)                        | 25 (4.5)                                 | 16 (4.5)                            |                  |

|                               |                           |                           |                            |                           |                           |                           |                  |
|-------------------------------|---------------------------|---------------------------|----------------------------|---------------------------|---------------------------|---------------------------|------------------|
| BMI z-scores at 4y, M (SD)    | 0.62 (0.98) <sup>b</sup>  | 0.34 (0.92) <sup>a</sup>  | 0.33 (0.91) <sup>a</sup>   | 1.59 (1.15) <sup>c</sup>  | 0.60 (1.00) <sup>b</sup>  | 0.28 (0.93) <sup>a</sup>  | <b>&lt;0.001</b> |
| BMI z-scores at 4y, n (%)     |                           |                           |                            |                           |                           |                           |                  |
| Uw/Nw                         | 786 (91.8) <sup>a</sup>   | 249 (96.1) <sup>b</sup>   | 890 (95.4) <sup>b</sup>    | 246 (65.4) <sup>c</sup>   | 517 (92.2) <sup>a</sup>   | 341 (96.3) <sup>b</sup>   | <b>&lt;0.001</b> |
| Ow/Ob                         | 70 (8.2) <sup>a</sup>     | 10 (3.9) <sup>b</sup>     | 43 (4.6) <sup>b</sup>      | 130 (34.6) <sup>c</sup>   | 44 (7.8) <sup>a</sup>     | 13 (3.7) <sup>b</sup>     |                  |
| BMI z-scores at 7y, M (SD)    | 0.74 (1.06) <sup>b</sup>  | 0.34 (1.01) <sup>a</sup>  | 0.36 (0.97) <sup>a</sup>   | 1.94 (1.11) <sup>c</sup>  | 0.76 (1.11) <sup>b</sup>  | 0.29 (0.98) <sup>a</sup>  | <b>&lt;0.001</b> |
| BMI z-scores at 7y, n (%)     |                           |                           |                            |                           |                           |                           |                  |
| Uw/Nw                         | 540 (63.1) <sup>a</sup>   | 197 (76.1) <sup>b</sup>   | 730 (78.2) <sup>b</sup>    | 70 (18.6) <sup>c</sup>    | 361 (64.3) <sup>a</sup>   | 281 (79.4) <sup>b</sup>   | <b>&lt;0.001</b> |
| Ow/Ob                         | 316 (36.9) <sup>a</sup>   | 62 (23.9) <sup>b</sup>    | 203 (21.8) <sup>b</sup>    | 306 (81.4) <sup>c</sup>   | 200 (35.7) <sup>a</sup>   | 73 (20.6) <sup>b</sup>    |                  |
| BMI z-scores at 10y, M (SD)   | 0.78 (1.08) <sup>c</sup>  | 0.41 (1.11) <sup>b</sup>  | 0.34 (1.11) <sup>ab</sup>  | 1.84 (1.00) <sup>d</sup>  | 0.81 (1.19) <sup>c</sup>  | 0.19 (1.14) <sup>a</sup>  | <b>&lt;0.001</b> |
| BMI z-scores at 10y, n (%)    |                           |                           |                            |                           |                           |                           |                  |
| Uw/Nw                         | 470 (54.9) <sup>a</sup>   | 182 (70.3) <sup>b</sup>   | 671 (71.9) <sup>b</sup>    | 56 (14.9) <sup>c</sup>    | 303 (54.0) <sup>a</sup>   | 273 (77.1) <sup>b</sup>   | <b>&lt;0.001</b> |
| Ow/Ob                         | 386 (45.1) <sup>a</sup>   | 77 (29.7) <sup>b</sup>    | 262 (28.1) <sup>b</sup>    | 320 (85.1) <sup>c</sup>   | 258 (46.0) <sup>a</sup>   | 81 (22.9) <sup>b</sup>    |                  |
| BMI z-scores at 13y, M (SD)   | 0.52 (1.06) <sup>c</sup>  | 0.25 (1.15) <sup>b</sup>  | 0.14 (1.05) <sup>b</sup>   | 1.47 (0.98) <sup>d</sup>  | 0.63 (1.22) <sup>c</sup>  | -0.09 (1.04) <sup>a</sup> | <b>&lt;0.001</b> |
| BMI z-scores at 13y, n (%)    |                           |                           |                            |                           |                           |                           |                  |
| Uw/Nw                         | 560 (65.4) <sup>a</sup>   | 187 (72.2) <sup>b</sup>   | 742 (79.5) <sup>c</sup>    | 104 (27.7) <sup>d</sup>   | 331 (59.0) <sup>e</sup>   | 304 (85.9) <sup>f</sup>   | <b>&lt;0.001</b> |
| Ow/Ob                         | 296 (34.6) <sup>a</sup>   | 72 (27.8) <sup>b</sup>    | 191 (20.5) <sup>c</sup>    | 272 (72.3) <sup>d</sup>   | 230 (41.0) <sup>e</sup>   | 50 (14.1) <sup>f</sup>    |                  |
| BMI <sub>AUC</sub> , Md (IQR) | 17.71 (2.91) <sup>c</sup> | 16.95 (2.59) <sup>b</sup> | 16.74 (2.47) <sup>ab</sup> | 20.75 (3.98) <sup>d</sup> | 17.79 (3.33) <sup>c</sup> | 16.46 (2.35) <sup>a</sup> | <b>&lt;0.001</b> |

M (SD): mean (standard deviation); Md (IQR): median (interquartile range); BMI: Body Mass Index; Uw/Nw: Underweight/Normal weight; Ow/Ob: Overweight/Obesity; BMI z-scores categories at 4y: Uw/Nw ( $\leq 2SD$ ) and Ow/Ob ( $>2SD$ ); BMI z-scores categories at 7, 10 and 13y: Uw/Nw ( $\leq 1SD$ ) and Ow/Ob ( $>1SD$ ). **Bold-type** represents statistically significant associations ( $p<0.05$ ). Superscript letters are presented for variables in which significant differences were found among profiles; profiles with the same superscript letters indicate a non-significant difference, while profiles with different superscripts indicate significant differences between them ( $p<0.05$ ).

## **PAPER II**

## **Disordered eating profiles and cardiometabolic health from early adolescence to early adulthood – findings from the EPITeen cohort**

Rita Pereira<sup>1,2</sup>, Joana Araújo<sup>1,2,3</sup>, Milton Severo<sup>1,2,4</sup>, Elisabete Ramos<sup>1,2,3</sup>, Andreia Oliveira<sup>1,2,3</sup>

(1) EPIUnit - Instituto de Saúde Pública, Universidade do Porto, Rua das Taipas, n° 135, 4050-600 Porto, Portugal

(2) Laboratório para a Investigação Integrativa e Translacional em Saúde Populacional (ITR), Universidade do Porto, Rua das Taipas, n° 135, 4050-600 Porto, Portugal

(3) Departamento de Saúde Pública e Ciências Forenses e Educação Médica, Faculdade de Medicina, Universidade do Porto, Alameda Prof. Hernâni Monteiro, 4200-319 Porto, Porto, Portugal

(4) Departamento de Ensino Pré-Graduado, Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto, Porto, Portugal

**Keywords:** Feeding and eating disorders, Metabolic Syndrome, Body weight, Adolescent, Young adult

### **Corresponding author**

Andreia Oliveira, PhD.

Instituto de Saúde Pública, Universidade do Porto, Rua das Taipas 135, 4050-600 Porto, Portugal.

**Tel:** +351 222061820

**E-mail:** [acmatos@ispup.up.pt](mailto:acmatos@ispup.up.pt)

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**Author contributions:** RP was responsible for data analysis and interpretation, and for drafting the manuscript; JA was responsible for data interpretation and critical revision of the manuscript for important intellectual content; MS was responsible for data analysis and interpretation; ER was responsible for the study concept and design, acquisition of data and critical revision of the manuscript for important intellectual content; MS was responsible for data analysis and interpretation; AO was responsible for data interpretation, critical revision for important intellectual content and final approval of the version to be published.

**Conflict of interest:** The authors declare no competing interests.

**Data Availability Statement:** Data used in this study came from the EPITeen Cohort. The dataset analysed during the current study is available from the Cohort Coordination (ER, eliramos@med.up.pt).

## Abstract

**Background:** Disordered eating (i.e., body image and weight concerns, overeating, purging, dieting) is highly prevalent among adolescents. Yet, less is known about the clustering patterns of evolution of these symptoms or behaviours and their impact on cardiometabolic health outcomes.

**Objective:** We aimed to examine the association of disordered eating profiles, from adolescence to early adulthood, with body mass index (BMI) and related cardiometabolic features at 21 years old (y).

**Methods:** Participants are from the EPITeen study, a population-based cohort of adolescents born in 1990 and attending public and private schools of Porto in 2003/2004. Data from the 13, 17 and 21y follow-ups was considered and the final sample was composed of 1619 participants. 'Drive for Thinness', 'Body dissatisfaction' and 'Bulimia' were assessed through the self-reported 'Eating Disorder Inventory' (EDI) at each age. Due to zeros inflation, subscales were categorized into 'zero score', ' $\leq$  median' and '> median' and a latent class analysis derived the profiles. Outcomes were measured BMI and the 5 metabolic syndrome (MetS) components: systolic  $\geq 130$  and/or diastolic blood pressure  $\geq 85$ mmHg; high-density lipoprotein cholesterol (HDL-c)  $< 40$ mg/dL in men and  $< 50$ mg/dL in women; triglycerides  $\geq 150$ mg/dL; fasting glucose  $\geq 100$ mg/dL and waist circumference  $\geq 94$ cm in men and  $\geq 80$ cm in women. Generalised linear models (beta coefficients ( $\beta$ ) and their respective 95% confidence intervals (CI)) and binary logistic regressions (odds ratio (OR) and 95%CI) tested associations of disordered eating profiles with BMI and metabolic features ( $\geq 1$  MetS component), respectively. Associations were adjusted for the highest parental education; the participants' education at 21y, frequency of vegetables consumption and sports or exercise practice at 21y. A sex interaction in the studied associations were tested and the analysis stratified.

**Results:** Four disordered eating profiles (from 13 to 21y) were identified: 1. 'higher disordered eating' (18.6%), 2. 'increasing disordered eating' (27.6%), 3. 'decreasing disordered eating' (18.7%) and 4. 'lower disordered eating' (35.1%). The most prevalent MetS components at 21y were high waist circumference (14.7%) and low HDL-c (12.6%) and the least prevalent was fasting glucose (1.4%). Around one third (32.3%) of the sample presented  $\geq 1$  MetS component and 1.3% met criteria for MetS diagnosis ( $\geq 3$  components). In comparison to the 'lower disordered eating' profile, both sexes (but particularly males) with 'higher' and 'increasing' disordered eating

presented heightened BMI values at 21y. Males in profiles with higher (OR=4.50; 95%CI 2.48-8.14) and increasing (OR=2.21; 95%CI 1.50-3.26) disordered eating levels presented higher odds of having  $\geq 1$  MetS component at 21y. In its turn, females in the higher levels profile were 116% more likely to have  $\geq 1$  Mets feature (OR=2.16; 95%CI 1.44-3.24).

**Conclusions:** Between adolescence and young adulthood, disordered eating levels seem to evolve differently. Individuals (particularly males) with higher or increasing levels, may be at increased risk of altered cardiometabolic health at 21y. This study raises awareness on the potential harm of disordered eating as a correlate of later increased weight and disadvantaged metabolic functioning.

## Introduction

Disordered eating includes a complex range of manifestations from cognitive features, such as body dissatisfaction, weight concerns and overvaluation of shape and weight, to behavioural ones, including binge eating, food restriction, emotional eating and compensatory behaviours (as purging, use of laxatives and diuretics, excessive exercise) [1]. The occurrence of these manifestations is most common throughout adolescence, and particularly in girls. Studies among adolescents and young adults have found prevalence estimates of various measures of disordered eating, in females, ranging from around 10% [2, 3] to as high as 51% [4] and 58% [2] and, in males, between around 3% [2] to 26% [3] and 30% [2, 4]. When meeting specific diagnostic criteria, disordered eating can evolve into an eating disorder [2, 5] – a psychiatric pathology with one of the highest mortality rates among mental health disorders [6, 7].

The development of disordered eating results from a complex interplay between sociocultural, biological and psychological factors. Particularly, the internalization of the thin-ideal body image along with certain personality traits arise as two important risk factors that interact with underlying biological susceptibility for an eating disturbance [1, 8, 9].

Previous research has reported the impact and burden of disordered eating in overall well-being, physical and mental health [3, 10, 11]. The occurrence of disordered eating in adolescence has been associated with higher risk for overweight and obesity, as well as with increased body mass index (BMI) in subsequent years, both during adolescence [2, 12] and in young adulthood [3, 4, 13]. Moreover, obesity is further associated with the co-occurrence of other risk factors for cardiovascular disease and diabetes [14, 15], such as raised blood pressure, high fasting glucose and dyslipidaemia, that frequently cluster in the so called metabolic syndrome (MetS) [16]. However, few studies have explored associations with specific metabolic disturbances and their clustering. In adolescence, disordered eating has predicted future onset of high blood pressure [12] while other studies reported associations with altered blood pressure and blood lipids [17], metabolic markers of inflammation [18] and insulin disturbances [19]. In adults, binge eating and binge eating disorder have been associated with future increased risk for hyperlipidemia [20] and MetS components [21], respectively.

Given the concerning prevalence of MetS [22] and the tendency for disordered eating to persist beyond adolescence [3, 23, 24], it becomes relevant to understand

the evolution of eating disturbances over adolescence until adulthood. Previous studies assessing disordered eating evolution over this developmental period [25-28]. represented only females [26], one disordered eating symptom alone [27, 28] or assessed symptoms separately [25, 26]. However, disordered eating features are often interconnected and do not tend to occur isolated [25]. Thus, understanding their clustering patterns could provide valuable insights in identifying groups of individuals at higher risk of increased weight and cardiometabolic complications, so targeted interventions can be developed.

In this study, we aim to derive disordered eating profiles from adolescence (13 years old (y)) into young adulthood (21y) and to study their association with both BMI and related cardiometabolic features at 21y.

## **Methods**

### **Study participants**

Participants are part of the EPITeen study – Epidemiological Health Investigation of Teenagers in Porto, a population-based cohort of adolescents born in 1990 attending public and private schools in Porto, Portugal [29]. This longitudinal study started in 2003/2004 and comprised a total of five assessments, from 13y (baseline) to 27y. In the present study, we included participants from the 13, 17 and 21y follow-ups. At 13y, 77.5% of the 2786 eligible participants agreed to participate. At 17y, 783 new participants enrolled in the study and 1716 (79.5%) from the baseline were re-evaluated. At the 21y follow-up, 1764 individuals were reassessed. Inclusion criteria considered individuals with available disordered eating data in at least two follow-ups and complete BMI and MetS features data at 21y. A final sample of 1619 individuals was obtained (Figure 1).

In comparison to the included participants, the excluded individuals presented a similar median (Md) (interquartile range (IQR)) regarding the highest parental years of education (excluded= 12 (11) vs included =12 (9)). The effect size of this difference was moderate for Cohen's d effect size, with a value of 0.40 [30]. No significant differences were found regarding sex or BMI z-scores at 13y.

The Ethics Committee of the Hospital S João and the Ethics Committee of the Institute of Public Health from the University of Porto approved this project, and appropriate standard procedures were developed to guarantee data confidentiality and protection. Written informed consent was obtained from parents or legal guardians and adolescents at 13 and 17y and from participants at 21y. The study

complied with the Ethical Principles for Medical Research Involving Human Subjects expressed in the Declaration of Helsinki [31].

## **Data collection and treatment**

### **Exposure**

#### Disordered eating

Disordered eating was assessed using the Eating Disorder Inventory (EDI) [32]. This is a self-reported instrument with a total of 63 items, answered on a Likert scale with six categories: 'always', 'usually', 'often', 'sometimes', 'rarely', and 'never'. Items are further divided into eight subscales: three that measure attitudes and/or behaviours related to eating and body shape and five that represent psychological characteristics associated with disordered eating. Each item can be scored up to a maximum of 3: the two most extreme answers ('always' or 'never', depending on the direction of the item), are given a score of 3; the two adjacent frequency options receive a score of 2 and, the following option, a score of 1. The three remaining options receive a score of 0. Higher scores correspond to increased disordered eating symptomatology.

In 2001, a Portuguese version of the EDI was adapted and tested [33] and its psychometric characteristics were evaluated in adolescents [33, 34]. This EDI version was posteriorly applied in the EPITeen cohort, at the 13, 17 and 21y follow-ups. In this study, only 'Drive for thinness' (7 items), 'Bulimia' (7 items) and 'Body dissatisfaction' (9 items) subscales that measure attitudes and/or behaviours, will be considered. These were the subscales with the best psychometric characteristics at 13y [34]. In the current sample, Cronbach's  $\alpha$  values varied from 0.79-0.87 at 13y, 0.70-0.88 at 17y and from 0.67-0.89 at 21y, with the highest and lowest values corresponding to 'Body dissatisfaction' and 'Bulimia' subscales, respectively.

For descriptive purposes, other disordered eating related variables were included: the existence of a previous parental anorexia nervosa and/or bulimia medical diagnosis (yes/no); an own medical diagnosis of anorexia nervosa (yes/no) and bulimia (yes/no) until 21y, and the report of dieting in the last year, at 21y (yes/no). Body image dissatisfaction was assessed as the difference between perceived ideal and current body size, using the Stunkard silhouettes [34] (with nine numbered figures from 1 to 9, representing silhouettes of very thin to persons with obesity). The difference was then categorized into being satisfied with one's body

image (difference=0), desiring a smaller silhouette (difference < 0) and desiring a large body (difference > 0).

### Disordered eating profiles

To derive disordered eating profiles, a person-centred approach was employed [35]. We considered individuals with disordered eating data in at least two of the follow-ups (n=2855). To handle missing or incomplete data, we used the full information maximum likelihood method, which considers all the available data to estimate the model [36, 37].

As the EDI item scoring process attributes 'zero' to the lowest frequency answering options ('sometimes', 'rarely' and 'never'), a zero score inflation of results was observed, and the distribution of subscales showed to be positively skewed. To address this constraint, a 'zero score' category was created. Subsequently, without considering individuals in this category, the median score was obtained for each subscale, at each follow-up, and this median value was used as a cut-off to derive two more categories: ' $\leq$  median' and '> median'. Then, using the three categories ('zero score', ' $\leq$  median' and '> median'), a latent class analysis derived the clusters of individuals with similar patterns of EDI subscale scores from 13 to 21y. Individuals were assigned to each profile considering the highest probability of class membership. The best model and the number of chosen classes was selected based of the Bayesian information criterion (BIC). Visual inspection was performed to check if any of the profiles was associated specifically to either males or females, but no relevant differences were found. To assess the tracking of each disordered eating subscale over time, intraclass correlation coefficients (ICC) were calculated: almost perfect (ICC 0.81–1.00), substantial (ICC 0.61–0.80), moderate (ICC 0.41–0.60), fair (ICC 0.21–0.40), poor or slight tracking (ICC < 0.21) [38]. Fleiss' Kappa values were also computed to assess the stability of score categories, for each disordered eating subscale, at each of the follow-ups. The latent class models were obtained on R studio®, using Mplus package [41].

## **Outcome**

### Body mass index

At each follow-up, weight was measured in kilograms (kg), to the nearest 0.1 kg, using a digital scale and height was measured in centimetres (cm), to the nearest 0.1 cm. Standardized procedures were followed, and participants were in light indoor

clothes, without shoes. BMI was calculated as weight (kg) divided by squared height (meters). At 13 and 17y, sex and age adjusted standard deviations scores (BMI z-scores) were obtained following the World Health Organization (WHO) growth reference [42]. For descriptive purposes, BMI categories were considered as Underweight (Uw) ( $< -2SD$ ), Normal weight (Nw) ( $\geq -2SD$  and  $\leq 1SD$ ), Overweight (Ow) ( $>1$  and  $\leq 2SD$ ), and Obesity (Ob) ( $>2SD$ ). At 21y, The World Health Organization BMI cut-offs for adults were considered, classifying individuals as Uw (BMI  $<25\text{ kg/m}^2$ ), Nw ( $18.5 \leq \text{BMI} <25\text{ kg/m}^2$ ), Ow ( $25 \leq \text{BMI} <30\text{ kg/m}^2$ ) and Ob (BMI  $\geq 30\text{ kg/m}^2$ ) [43].

#### Other cardiometabolic health features

Blood pressure was measured following the American and International Societies of Hypertension guidelines [44], using the oscillometric method (OMRON Blood Pressure Monitor, M6 Comfort, OMRON Healthcare Co., Ltd., Kyoto, Japan). After resting for 10 minutes, two blood pressure measurements were taken with a rest of at least 5 minutes in between. If the difference between the first two measurements was  $\geq 5\text{ mmHg}$ , a third measurement was obtained. The average of the two closest measurements was considered for analysis. Waist circumference was measured to the nearest 0.1cm midway between the lower limit of the rib cage and the iliac crest, at the end of an expiration. Lastly, using an overnight fast intravenous blood sample from the antecubital vein, glucose, triglycerides, total cholesterol and high-density lipoprotein cholesterol (HDL-c) were measured with an Olympus AU5400 automated clinical chemistry analyser (Beckman-Coulter, Brea, CA, USA).

To characterize cardiometabolic health at 21y, the five components of MetS and their respective cut-offs were considered [16]: i) systolic blood pressure  $\geq 130\text{ mmHg}$  and/or diastolic blood pressure  $\geq 85\text{ mmHg}$ ; ii) HDL-c  $<40\text{mg/dL}$ , in men, and  $<50\text{mg/dL}$ , in women; iii) triglycerides  $\geq 150\text{mg/dL}$ ; iv) fasting glucose  $\geq 100\text{mg/dL}$  and v) waist circumference  $\geq 94\text{cm}$ , in men, and  $\geq 80\text{cm}$ , in women. Being on a drug treatment for elevated triglycerides, elevated glucose, high blood pressure and reduced HDL-c was additionally considered as an alternate indicator for high triglycerides, high fasting glucose, high blood pressure reduced HDL-c, respectively. For high blood pressure, being an individual with a history of hypertension was additionally an alternative indicator.

First, for each component, a categorical variable (yes/no) was obtained representing the prevalence of the condition. Second, a variable for having at least

one MetS ( $\geq 1$  Mets) component was created. Criteria for MetS diagnosis was met when an individual presented at least three out of the five components ( $\geq 3$  Mets) [16].

### **Covariates**

Data was gathered through self-administered questionnaires and face-to-face interviews. At baseline, maternal and paternal completed years of schooling were collected and a variable with the highest parental education was computed. Household income at 21y was categorized into <1000€, 1001-1500€, 1501-2000€ and >2000€. Regarding dietary habits, the intake of vegetables was considered as the number of times per week that vegetables or salads were eaten on the plate, and the intake of fruit as the usual number of pieces of fruit consumed per week. The practice of any kind of sports or physical exercise (yes/no) was also obtained.

### **Statistical analysis**

The distribution of variables was assessed through histograms and Q-Q plots. Continuous variables were summarized using the mean (M) and standard deviation (SD), and the median (Md) and interquartile range (IQR) based on their parametric and non-parametric distribution, respectively. Categorical variables were described as counts (n) and percentages (%). The comparison between included and excluded individuals was performed using the Mann–Whitney U test and by calculating Cohen d' effect sizes, as well as by performing the Student's T Test and the Chi-squared test. For the characterization and comparison of disordered eating profiles, the Chi-square test, One-way ANOVA and Kruskal Wallis tests with post hoc analysis, were employed.

To test associations between disordered eating profiles and BMI, generalised linear models were applied, and the respective  $\hat{\beta}$  regression coefficients and 95% confidence intervals (CI) were extracted. To test associations between disordered eating profiles and having  $\geq 1$  MetS component, binary logistic regressions were performed, and the respective odds ratios (OR) and 95% confidence intervals (95%CI) were obtained.

A set of covariates were tested as potential confounders based on previous literature [12, 45-49] and included in the models based on the following criteria: changing at least 10% of the coefficient when added, being statistically significant in the model and/or having considerable scientific plausibility for inclusion. Associations were then adjusted for the highest parental education years at baseline; and for the

participants' education at 21y, frequency of vegetables consumption and sports or exercise practice at 21y (model 1). The possibility of multicollinearity between predictors was ruled out after checking Pearson and Spearman r-correlation indices ( $|r| > 0.80$ ) [50]. A sex-interaction effect with the disordered eating profiles in the association with BMI and cardiometabolic health was tested and analyses were further stratified due to a significant interaction found for the outcome having  $\geq 1$  MetS feature.

A two-sided significance of 5% was considered and statistical analysis was performed in IBM® SPSS® Statistics version 26.0 software (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp).

## Results

The characterization of the total sample as well as stratified by sex is presented in Table 1. The sample presented a similar distribution by sex (51.1% were females). At baseline, parents had a median of 12 (IQR = 9.0) maximum completed schooling years while, at 21y, participants had 14 (IQR = 3.0) completed schooling years. The highest proportion of individuals (40%) had a monthly household income of more than 2000€ at 21y. Females consumed vegetables at a median of 7 times (IQR=7.0) per week whereas males consumed 4 (IQR=5.0). Regarding fruit, females and males consumed a median of 7 (IQR=8.0) and 6 (IQR=7) pieces per week, respectively. Sports and physical exercise practice was higher in males, with more than half reporting to do such practice.

In relation to disordered eating, almost one third of the females reported, at 21y, dieting in the last year, whereas in males the prevalence was much lower (16.3%). Six and 16 participants had been diagnosed with bulimia and anorexia nervosa before 21y, respectively. Lastly, from the sample with available data on parental disordered eating medical diagnosis (n=1614), around 1% presented parents with anorexia nervosa and/or bulimia.

### Disordered eating and profiles

According to the obtained BIC values (Figure 2.), the best model presents four classes (BIC=33787), meaning four disordered eating profiles. The Chi-square test of the model revealed a good fit ( $p\text{-value} > 0.999$ ), meaning that the observed data and the assumed model are consistent with each other and do not differ significantly. The frequency between observed and estimated response patterns was also

checked. The average latent class probabilities for the most likely latent class membership ranged from 66.8% (profile 2) to 80.7% (profile 1).

Regarding the stability of measures throughout assessments, 'Drive for thinness' and 'Body dissatisfaction' showed moderate tracking, whereas 'Bulimia' presented poor tracking. Fleiss' kappa values revealed minimal or no stability of the score categories (ranging from 0.03 to 0.37), at each follow-up, among profiles, suggesting that identified profiles differ from each other and each represents a unique cluster of disorder eating evolution levels from 13y to 21y (Table S1).

The four profiles (n=2855) are presented in Figure 3. Profile 1, named as 'higher disordered eating' (n=588, 20.6%), represents the overall highest scores of disordered eating across the three ages (13, 17 and 21y) due to the highest proportion of individuals in the '> median' score category for 'Body dissatisfaction' (76 to 90%) and 'Drive for thinness' (71 to 89%). In profile 2, the 'increasing body concerns but low 'Bulimia' (n=819, 28.7%), a consecutive increase in the '> median' category is observed in 'Body dissatisfaction' (36 to 53%) throughout follow-ups while, for 'Drive for thinness', the number of individuals with high scores remains stable at 13 and 17y but increases at 21y (24 to 36%). Regarding 'Bulimia', most of the individuals belonged to the 'zero-score' category (74 to 77%). From this moment on, we will name profile 2 as 'increasing disordered eating' in order to facilitate the paper readability. Profile 3, the 'decreasing disordered eating' (n=525, 18.4%), presents decreasing levels of all the disordered eating subscales throughout follow-ups, starting with around 40-45% of participants in the '> median' score category at 13y and reaching 6-14% at 21y. The last profile, considered as reference, was named 'lower disordered eating' (n=925, 32.4%) and contains the highest proportion of individuals without disordered eating or with low levels at all the follow-ups, particularly 'Bulimia', followed by 'Drive for thinness' and 'Body dissatisfaction'. Table S2, in supplementary data, presents the median values used as cut-off for each of the disordered eating subscales, at each follow-up, along with the descriptives of the categories.

Similar to the original sample deriving profiles, in the current sample (n=1619), the two most prevalent profiles were 'lower disordered eating' (n=568, n=35.1%), followed by 'increasing disordered eating' (n=447, 27.6%). The 'decreasing disordered eating' (n=303, 18.7%), and 'higher disordered eating' (n=301, 18.6%) presented a very similar prevalence. Table S3 presents the profiles characterization. The 'higher' and 'increasing' disordered eating profiles are mainly composed of

females (81.4% and 56.8%, respectively), while males belong mostly to the 'decreasing' (53.5%) and 'lower' disordered eating (65.3%) profiles. Also, individuals in the 'lower disordered eating' profile presented the parents with the highest number of completed schooling years. In all the follow-ups, the 'higher' and 'increasing' disordered eating profiles consistently presented the highest proportions of Ow/Ob. At all ages, the proportion of individuals desiring a thinner silhouette was notable in the 'higher' (76-90%) and 'increasing' (49-62%) disordered eating profiles. Conversely, the 'lower disordered eating' profile showed the highest proportion of individuals satisfied with their body image (51-62%). The prevalence of having reported dieting in the previous year, at 21y, was proportional to the severity of disorder eating level profile. Lastly, previous medical diagnosis of the eating disorders anorexia nervosa and bulimia and were also more frequent in profiles with 'higher' and 'increasing' disordered eating profiles.

#### BMI and other cardiometabolic health features at 21y

At 21y, males presented a Md (IQR) BMI of 23.0 kg/m<sup>2</sup> (25.50) and females of 21.6 kg/m<sup>2</sup> (4.05), with the highest prevalence of Ow and Ob being among males (Ow=24.3%; Ob=5.8%) (Table 2). Among females, the most common MetS components were high waist circumference (20.2%) and low HDL-c (13.6%) while in males, low HDL-c (11.5%) and high blood pressure (10.5%) were the most common. In both sexes, the majority of individuals presented none of the MetS components and 25.8% of females and 21.6% of males had at least one. Only 10 females and 10 males presented completed criteria for MetS ( $\geq 3$  components).

#### Associations between disordered eating profiles, BMI and other cardiometabolic health features

In the adjusted model (Table 3), in comparison to the 'lower disordered eating' profile, females in the 'higher' and 'increasing' profiles presented a mean of 3.90 (95% CI: 3.25-4.55) and 1.87 kg/m<sup>2</sup> (95%CI: 1.23-2.52) higher BMI values at 21y, respectively; while the increase among males was of 4.89 (95% CI: 3.98-5.80) and 2.69 (95% CI: 2.12-3.25) kg/m<sup>2</sup>, respectively. Regarding MetS components, females in the 'higher disordered eating' profile had 116% significantly higher odds of presenting  $\geq 1$  Mets component, whereas males in both the 'higher' and 'increasing' disordered eating profiles were 350% and 121% more likely of having  $\geq 1$  MetS

component, respectively. No significant associations for the 'decreasing levels' profile were found for neither of the sexes.

## **Discussion**

Findings from this study suggest the existence of distinct patterns of disordered eating profiles, from adolescence to young adulthood. While the majority of individuals belonged to the 'lower disordered eating' profile, a considerable proportion presented 'higher' and 'increasing' disordered eating levels (around 19% and 28%, respectively). As expected, these were the most important profiles in the association with BMI and other cardiometabolic indicators. Belonging to the 'higher' or 'increasing' disordered eating profiles, compared to those in the 'lower', was associated with higher BMI at age 21y, particularly in males. Regarding the MetS components, females in the 'higher disordered eating profile' showed higher odds of having  $\geq 1$  MetS component whereas, in males, this association was observed for both 'higher' and 'increasing' disordered eating profiles.

The 'high disordered eating' profile presented the highest levels of 'Body dissatisfaction' and 'Drive for thinness', while in the 'increasing' and 'decreasing' profiles, an upward and downward trend was observed, respectively. Body image is a mental representation of one's body, including perceptions, thoughts, and attitudes about our own body appearance [51, 52] and is connected to other cognitive dimensions such as preoccupation with weight, pursuit of thinness and fear of weight gain [32, 51]. Accordingly, the proportion of individuals dissatisfied with their bodies and desiring a thinner body in the 'higher disordered eating' profile was high and relatively stable across adolescence and young adulthood. Also, this profile primarily consisted of females, a result consistent with previous findings on studies assessing disordered eating from adolescence into young adulthood [24, 25, 53]. Adolescence arises as one important risk period for the onset of eating pathology [25, 26, 54], when individuals start worrying about their appearance and become more susceptible to internalizing the body ideals imposed by the society [55]. In fact, adolescents perception of their appearance is part of the development of their sense of self [56]. However, body image concerns may even start earlier for girls and boys, during childhood [57-59].

The least common observed disordered eating dimension in the derived profiles was 'Bulimia', that represents the tendency towards uncontrolled overeating (bingeing) that may be followed by purging [32]. A possible explanation is that the

cognitive dimensions of disordered eating (i.e., body dissatisfaction and weight concerns) may precede disordered eating behaviours [1]. As a non-clinical sample, it is possible that the disordered eating symptoms mainly occur on a cognitive level. Similarly, findings from a study in females suggest that the continued increase in overall disordered eating scores, from late adolescence to young adulthood, may be primarily driven by changes in cognitive concerns about weight and body image, rather than disordered eating behaviours, such as binge eating [26]. In the 'decreasing disordered eating' profile, however, bulimic behaviours were already present at 13y, and their decrease throughout assessments seems to accompany the concomitant observed decrease in 'Body dissatisfaction' and 'Drive for thinness'.

According to the dual pathway model for bulimia, originally developed by Stice in 1994, symptoms arise as a consequence of the sociocultural pressure and internalization of the thin ideal, leading to 'body dissatisfaction' which can result in restrained eating and affected regulation mechanisms [60]. In this reasoning, bulimic behaviours would occur as an effort to regulate a negative affective state [60, 61]. Yet, dieting may enhance attraction to food, thus making it challenging to maintain the restrictive behaviour and lead to periods of binge eating and overconsumption; ultimately promoting weight gain [62]. It is also important to mention that the assessment tool used, the EDI, only presents one item regarding purging - an important feature that distinguishes binge eating, where no compensatory behaviour is present, from bulimia [5]. Thus, the prevalence of this behaviour may be underestimated.

Various studies have assessed disordered eating evolution over time [8, 25-28, 63-65], although comparisons between them are not always straightforward. Methodologies vary widely in terms of the period assessed, the type disordered eating symptom, if considered separately or together, the inclusion of only females or both sexes and the stratification of analysis by sex. To the best of our knowledge, only one group of authors has examined disordered eating dimensions through the EDI but focused on a two-year period in adolescence and derived trajectories separately by sex. The mentioned study included 1115 high-school girls in Belgium and originated developmental disordered eating trajectory groups with the three subscales 'Body dissatisfaction', 'Drive for thinness' and 'Bulimia', simultaneously [53]. In girls, classes with 'very high', 'high', 'low' and 'very low' symptoms were observed while, for boys, only two classes arise: 'high' and 'low', suggesting that adolescent girls are more prone to body dissatisfaction and to desiring to be thinner

[53]. The prevalence and severity of disordered eating may differ among males and females, yet, the patterns of symptomatology evolution, or susceptibility to risk factors might be similar among sexes [25, 39, 40]. In fact, we observed a reasonable proportion of both sexes in the profiles, even the most extreme ones ('higher' and 'lower' disordered eating, composed mainly of females and males, respectively). These results suggest that, if derived per sex, profiles would not differ considerably between males and females. Regarding published studies on adolescence into young adulthood assessing both sexes together, one tracked eating disorders risk, defined as having at least two symptoms of the SCOFF questionnaire [25], and the other considered only body dissatisfaction, assessed from a body shape satisfaction scale [28]. Although they evaluated different disordered eating dimensions, both obtained two opposing and relatively stable classes, as we also observed in our findings: a 'higher' and 'lower' disordered eating group.

Regarding the assessed outcomes, consistent with literature, our 'higher' and 'increasing disordered eating' profiles were associated with increased BMI at 21y [2-4, 13, 66, 67], for both sexes, but particularly among males – as also previously observed [2, 13, 67]. However, having a higher body weight is also risk factor for engaging in disordered eating and, particularly, increase body dissatisfaction [53]. Individuals may feel they are more distant from the body image ideals standards, becoming a driver to change body appearance [60]. In fact, studies show that having OW or higher BMI at 7y predicted increased risk of fasting, purging, and binge eating at 11/12y and higher levels of overeating, weight and shape concerns as well as binge eating at 13y [68], respectively. To rule out the possible effect of reverse causality, we tested associations between disordered eating profiles and BMI adjusting for baseline BMI z-scores. The obtained associations in the main analysis for both sexes and for 'high' and 'increasing' disordered eating profiles remained in this new analysis (n=1166, considering participants without missing data at BMI z-scores at 13y). When further adjusting for BMI z-scores at 13y, only associations between the 'increasing disordered eating' profile and increased BMI at 21y, among females, lost significance; suggesting that overall increases in BMI were independent of baseline weight, except for females in this profile. Other studies in adolescence and young adulthood also found increases in BMI with disordered eating, regardless of their initial body weight status [4, 13].

The prevalence of MetS ( $\geq 3$  components) in the current sample was relatively smaller (1.3%) in comparison to what is commonly reported among young adults (5-

7%) [69] but is aligned with previous results in the same cohort at 27y [70]. The most prevalent MetS components at this life-stage seem to be low HDL-c followed by high blood pressure, high waist circumference, high triglycerides, and high fasting glucose [69]. In our sample, males followed this tendency, while high waist circumference and HDL-c were the most common in the whole sample. Also, our results indicate that males were more vulnerable to having  $\geq 1$  Mets component. Previous studies on adolescence and adulthood found associations between disordered eating components and specific metabolic disturbances (i.e., high blood pressure, altered blood lipids and insulin metabolism) [12, 17-20], but no study has explored associations using profiles of disordered eating, considering the clustering of MetS components, or stratifying the analysis by sex.

This study presents some limitations worth noting. The EDI is a self-reported tool, prone to bias and inaccurate report [32]. Yet, it has been previously validated in the current EPITeen cohort and the three subscales explored in this study presented adequate psychometric properties at 13y [34]. In the current sample, Cronbach's  $\alpha$  coefficients were  $\geq 0.70$  at all the follow-ups, supporting an adequate internal consistency. Also, the EDI does not address specific disordered eating dimensions, such as the drive for muscularity that, instead of the drive for thinness, may best represent the situation of male individuals [58, 71]. Participants' medical diagnoses of eating disorders were only observed in the profiles with 'higher' and 'increasing' disordered eating, namely anorexia nervosa and bulimia. Yet, it is important to highlight that diagnosis of other pathologies were not assessed, such as binge-eating disorder and other specified feeding or eating disorder (OSFED), which are more prevalent and seem to represent a great health burden [72].

Regarding strengths, this study is, as far as we know, the first study deriving disordered eating profiles from adolescence into early adulthood and their association with later BMI and risk for metabolic disturbances. First, the application of a person-centred approach through a latent class analysis, to identify and derive different disordered eating evolution profiles, allowed summarizing an important transitional period of development of an 8-year interval. Second, the availability of objective measures of weight and height as well as biochemical data to derive BMI and MetS features contributes to a higher quality and reliability of the results. Third, the use of data from a large cohort such as EPITeen permitted a sample of over 1500 participants, despite losses to follow-up. Regarding profiles, we used the full information maximum likelihood method that estimates parameters in the presence

of incomplete or missing data [36, 37]. Significant differences between included and excluded participants regarding parents' education were reported, but the magnitude of difference was moderate, and expected in population-based studies.

Lastly, the present study explores important public health concerns. On the one hand, the high proportion of profiles with high and increasing disordered eating levels. On the other, the prevalence of Ow/Ob observed among profiles with 'high' and 'increasing' levels and their associations with increased BMI. Disordered eating may arise as an attempt to change body weight and appearance but besides being hurtful, it is also counter-productive and can lead to further weight gain [13, 66]. Additionally, there is the fact that males may be at particular risk for later cardiometabolic disturbances and increased BMI, highlighting the relevance of detecting early signs of disordered eating among this gender. Men have historically been expected to hide their vulnerabilities [73]. Along with the stereotype that eating disorders is a "female" problem, which leads to higher stigma and shame, men also struggle to identify their symptoms, delaying help seeking, diagnosis and treatment [74, 75]. Disordered eating prevention strategies should be developed before symptoms are established in adolescence, with a shift in focus from weight to developing a better relationship with food, fostering body acceptance and a positive body image as well as controlling exposure to social media [76-78].

## **Conclusion**

We identified four distinct disordered eating profiles from adolescence to young adulthood. Being dissatisfied with one's body image and desiring for a thinner silhouette are two common disordered eating dimensions throughout this developmental stage. The 'higher disordered eating' and the 'increasing disordered eating' profiles revealed to be the most concerning ones, showing positive associations with BMI and MetS components at 21y for both sexes, but particularly among males. This study identifies groups at higher risk and raises awareness on the potential harm of disordered eating as a correlate of later increased weight and disadvantaged metabolic functioning.

Besides cognitive components such as 'Body dissatisfaction' and 'Drive for thinness', future studies could derive profiles with behavioural disordered eating dimensions such as restriction/dieting, compulsive exercise and binge eating and test associations with MetS components. The more comprehensive and specific the profiles are, the more precise the interventions can be developed.

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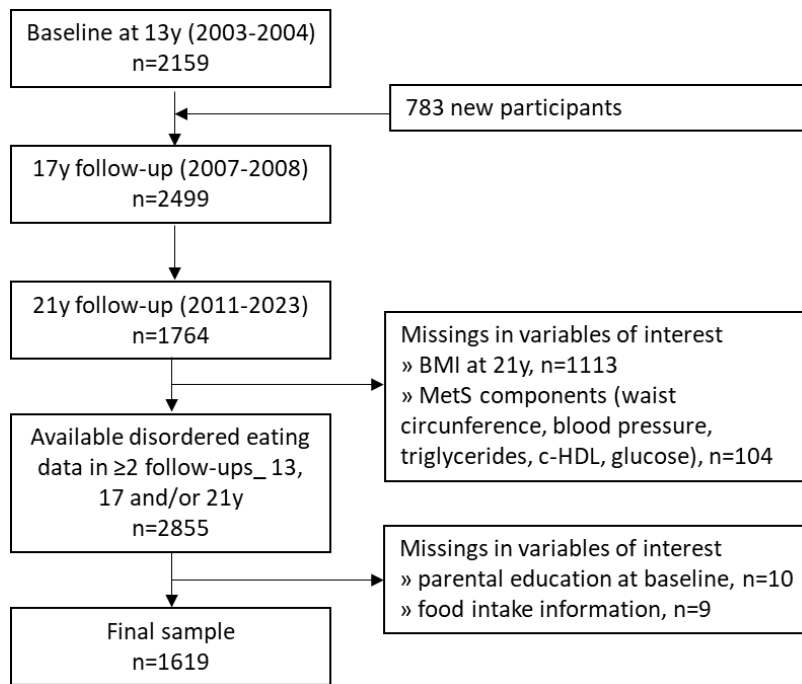


**Figure 1.** Flowchart of study participants.

y: years old; BMI: body mass index, MetS: metabolic syndrome; HLD-c: high-density lipoprotein cholesterol

**Table 1.** Characteristics of the EPITeen participants included in the study (n=1619), stratified by sex.

|                                                                     | <b>Total sample<br/>(n=1619)</b> | <b>Females<br/>(n=837)</b> | <b>Males<br/>(n=782)</b> |
|---------------------------------------------------------------------|----------------------------------|----------------------------|--------------------------|
| Parental highest education, Md (IQR)                                | 12 (9.0)                         | 11 (9.0)                   | 12 (9.0)                 |
| Participants' education at 21y, Md (IQR)                            | 14 (3.0)                         | 14 (3.0)                   | 13 (3.0)                 |
| Monthly household income at 21y, n (%) <sup>*</sup>                 |                                  |                            |                          |
| <1000 €                                                             | 314 (21.8)                       | 190 (26.1)                 | 124 (17.4)               |
| 1001-1500€                                                          | 320 (22.2)                       | 165 (22.7)                 | 155 (21.7)               |
| 1501-2000€                                                          | 237 (16.4)                       | 130 (17.9)                 | 107 (15.0)               |
| >2000€                                                              | 570 (39.6)                       | 243 (33.4)                 | 327 (45.9)               |
| Lifestyles at 21y                                                   |                                  |                            |                          |
| Vegetables intake (number of times/week), Md (IQR)                  | 5.0 (8.0)                        | 7.0 (7.0)                  | 4.0 (5.0)                |
| Fruit intake (number of pieces/week)                                | 7.0 (7.0)                        | 7.0 (8.0)                  | 6.0 (7.0)                |
| Practice of sports and exercise, n (%)                              |                                  |                            |                          |
| No                                                                  | 786 (48.5)                       | 505 (60.3)                 | 281 (35.9)               |
| Yes                                                                 | 833 (51.5)                       | 332 (39.7)                 | 501 (64.1)               |
| Disordered eating <sup>*</sup>                                      |                                  |                            |                          |
| Dieting during the last year, at 21y, n (%)                         |                                  |                            |                          |
| Never                                                               | 1233 (76.4)                      | 580 (69.5)                 | 653 (83.7)               |
| Yes                                                                 | 381 (23.6)                       | 254 (30.5)                 | 127 (16.3)               |
| Medical diagnosis of Anorexia Nervosa until 21y, n (%)              |                                  |                            |                          |
| No                                                                  | 1598 (99.1)                      | 818 (98.2)                 | 780 (99.9)               |
| Yes                                                                 | 16 (1.0)                         | 15 (1.8)                   | 1 (0.1)                  |
| Medical diagnosis of Bulimia until 21y, n (%)                       |                                  |                            |                          |
| No                                                                  | 1608 (99.6)                      | 827 (99.3)                 | 0 (0.0)                  |
| Yes                                                                 | 6 (0.4)                          | 6 (0.7)                    | 0 (0.0)                  |
| Parents medical diagnosis of Anorexia Nervosa and/or Bulimia, n (%) |                                  |                            |                          |
| No                                                                  | 1147 (98.9)                      | 612 (99.4)                 | 535 (98.3)               |
| Yes                                                                 | 13 (1.1)                         | 4 (0.6)                    | 9 (1.7)                  |

Md (IQR): median (interquartile range), <sup>\*</sup>Subsample with reduced available data: parental (n=1160) and participant's (n=1614) eating disorder information; household income at 21y (n=1441).

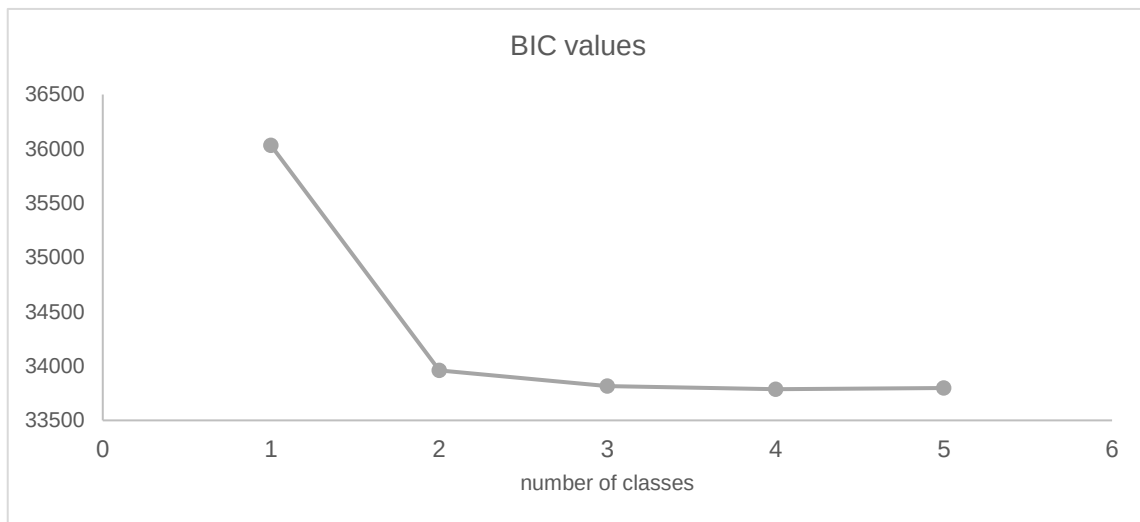


**Figure 2.** Identification of the final number of disordered eating profiles (classes), based on the Bayesian information criterion (BIC) values.

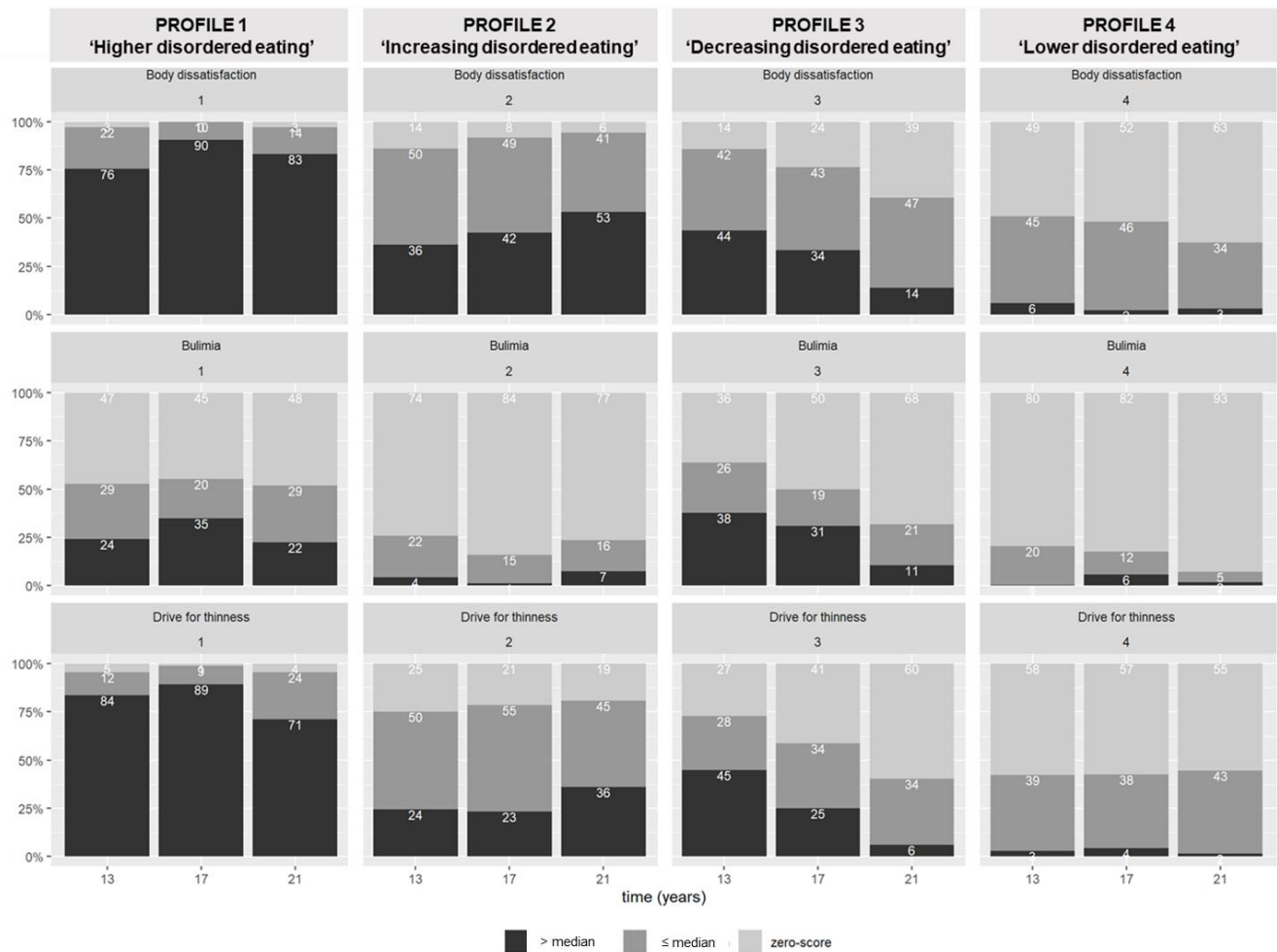


**Figure 3.** Disordered eating profiles identified by latent class analysis, using the three subscales of the Eating Disorder Inventory ('Body dissatisfaction', 'Bulimia', 'Drive for thinness', assessed at 13, 17 and 21 years old (EPITeen cohort, n=2855).

**Table 2.** Characterization of the EPITeen sample regarding body mass index and other indicators of cardiometabolic health at 21 years (n=1619).

|                                  | Total sample<br>(n=1619) | Women<br>(n=837) | Men<br>(n=782) |
|----------------------------------|--------------------------|------------------|----------------|
| BMI, Md (IQR)                    | 22.3 (4.40)              | 21.6 (4.05)      | 23.0 (25.50)   |
| BMI status, n (%)                |                          |                  |                |
| Underweight                      | 93 (5.7)                 | 59 (7.0)         | 34 (4.3)       |
| Normal weight                    | 1129 (69.7)              | 616 (73.6)       | 513 (65.6)     |
| Overweight                       | 309 (19.1)               | 119 (14.2)       | 190 (24.3)     |
| Obesity                          | 88 (5.4)                 | 43 (5.1)         | 45 (5.8)       |
| Waist circumference, Md (IQR)    | 76.0 (12.2)              | 71.9 (10.4)      | 80.1 (85.9)    |
| Systolic blood pressure, M (SD)  | 108.8 (11.9)             | 102.1 (8.8)      | 115.9 (10.6)   |
| Diastolic blood pressure, M (SD) | 68.7 (7.5)               | 68.0 (7.4)       | 69.5 (7.4)     |
| Total cholesterol, Md (IQR)      | 173.0 (43.0)             | 183.0 (46.0)     | 163.0 (183.0)  |
| HDL-c, Md (IQR)                  | 55.0 (17.0)              | 61.0 (16.0)      | 49.0 (55.0)    |
| LDL-c, Md (IQR)                  | 99.0 (34.0)              | 101.0 (36.0)     | 98.0 (115.0)   |
| Triglycerides, Md (SD)           | 76.0 (47.0)              | 83.0 (52.0)      | 70.0 (93.3)    |
| Fasting glucose, Md (SD)         | 83.0 (9.0)               | 81.0 (8.0)       | 85.0 (89.0)    |
| MetS components, n (%)           |                          |                  |                |
| High waist circumference         |                          |                  |                |
| No                               | 1381 (85.3)              | 668 (79.8)       | 713 (91.2)     |
| Yes                              | 238 (14.7)               | 169 (20.2)       | 69 (8.8)       |
| High blood pressure              |                          |                  |                |
| No                               | 1520 (93.9)              | 820 (98.0)       | 700 (89.5)     |
| Yes                              | 99 (6.1)                 | 17 (2.0)         | 82 (10.5)      |
| Low HDL-c                        |                          |                  |                |
| No                               | 1415 (87.4)              | 723 (86.4)       | 692 (88.5)     |
| Yes                              | 204 (12.6)               | 114 (13.6)       | 90 (11.5)      |
| High triglycerides               |                          |                  |                |
| No                               | 1495 (92.3)              | 748 (89.4)       | 747 (95.5)     |
| Yes                              | 124 (7.7)                | 89 (10.6)        | 35 (4.5)       |
| High fasting glucose             |                          |                  |                |
| No                               | 1597 (98.6)              | 830 (99.2)       | 767 (98.1)     |
| Yes                              | 22 (1.4)                 | 7 (0.8)          | 15 (1.9)       |
| Number of MetS components, n (%) |                          |                  |                |
| 0                                | 1095 (67.6)              | 536 (64.0)       | 559 (71.5)     |
| 1                                | 385 (23.8)               | 216 (25.8)       | 169 (21.6)     |
| 2                                | 117 (7.2)                | 75 (9.0)         | 42 (5.4)       |
| 3                                | 20 (1.2)                 | 10 (1.2)         | 10 (1.3)       |
| 4                                | 2 (0.1)                  | 0 (0.0)          | 2 (0.3)        |
| 5                                | 0 (0.0)                  | 0 (0.0)          | 0 (0.0)        |

M (SD): mean (standard deviation); Md (IQR): median (interquartile range); BMI: Body Mass Index; BMI categories: Underweight (BMI<18.5 kg/m<sup>2</sup>), Normal weight (18.5≤ BMI <25 kg/m<sup>2</sup>), Overweight (25≤ BMI <30 kg/m<sup>2</sup>) and Obesity (BMI≥30.0 kg/m<sup>2</sup>). HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; MetS: metabolic syndrome; High waist circumference: ≥94cm in men and ≥80cm in women. High blood pressure: systolic ≥130 and/or diastolic blood pressure ≥85mmHg; Low HDL-c: <40mg/dL in men and <50mg/dL in women; High triglycerides: ≥150mg/dL; High fasting glucose: ≥100mg/dL

**Table 3.** Generalized linear models and binary logistic regressions of disordered eating profiles with body mass index (as a continuous variable) and having  $\geq 1$  MetS component at 21 years, respectively, stratified by sex.

| Disordered eating profiles   | BMI <sup>a</sup>        |                         | $\geq 1$ MetS component <sup>b</sup> |                         |
|------------------------------|-------------------------|-------------------------|--------------------------------------|-------------------------|
|                              | Model 0                 | Model 1                 | Model 0                              | Model 1                 |
| Females (n=837)              | $\hat{\beta}$ (95% CI)  |                         | OR (95% CI)                          |                         |
| Higher disordered eating     | <b>3.93 (3.26-4.60)</b> | <b>3.90 (3.25-4.55)</b> | <b>2.21 (1.49-3.28)</b>              | <b>2.16 (1.44-3.24)</b> |
| Increasing disordered eating | <b>1.98 (1.32-2.65)</b> | <b>1.87 (1.23-2.52)</b> | 1.04 (0.69-1.55)                     | 0.97 (0.64-1.47)        |
| Decreasing disordered eating | 0.54 (-0.23-1.31)       | 0.47 (-0.28-1.22)       | 1.10 (0.69-1.75)                     | 1.04 (0.65-1.68)        |
| Lower disordered eating      | ref                     | ref                     | ref                                  | ref                     |
| Males (n=782)                |                         |                         |                                      |                         |
| Higher disordered eating     | <b>4.84 (3.93-5.74)</b> | <b>4.89 (3.98-5.80)</b> | <b>4.66 (2.60-8.34)</b>              | <b>4.50 (2.48-8.14)</b> |
| Increasing disordered eating | <b>2.75 (2.18-3.31)</b> | <b>2.69 (2.12-3.25)</b> | <b>2.39 (1.63-3.50)</b>              | <b>2.21 (1.50-3.26)</b> |
| Decreasing disordered eating | 0.18 (-0.42-0.77)       | 0.18 (-0.41-0.78)       | 1.19 (0.77-1.85)                     | 1.14 (0.73-1.78)        |
| Lower disordered eating      | ref                     | ref                     | ref                                  | ref                     |

BMI: Body Mass Index;  $\hat{\beta}$ : beta coefficient; OR: odds ratio; CI: confidence interval; ref: reference category; Model 0: crude associations; Model 1: associations adjusted for highest parental education at baseline; and for the participants' education at 21y, vegetables consumption and sports or exercise practice at 21y; associations tested through generalized linear models<sup>a</sup> and binary logistic regression<sup>b</sup>; **Bold**-type represents statistically significant associations ( $p < 0.05$ )

## Supplementary data

**Table S1.** Disordered eating subscales and stability measures.

|                      | Fleiss' Kappa | ICC (95%CI) |
|----------------------|---------------|-------------|
| Drive for thinness   |               |             |
| 13y                  | <b>0.24**</b> |             |
| 17y                  | <b>0.10**</b> | 0.45        |
| 21y                  | <b>0.37**</b> | (0.43-0.74) |
| Bulimia              |               |             |
| 13y                  | <b>0.18**</b> |             |
| 17y                  | 0.03          | 0.20        |
| 21y                  | <b>0.16**</b> | (0.18-0.23) |
| Body dissatisfaction |               |             |
| 13y                  | <b>0.27**</b> |             |
| 17y                  | <b>0.08**</b> | 0.52        |
| 21y                  | <b>0.35**</b> | (0.50-0.54) |

ICC: Intraclass correlation coefficient (reflects the stability of each subscale before deriving the profiles); 95%CI: 95% confidence intervals; y: years old; Fleiss' Kappa values reflect the stability of the subscales, at each follow-up, among the profiles; **Bold-type**: significant associations ( $p < 0.05$ ); \*\* $p$ -value  $< 0.001$

**Table S2.** Description of the disordered eating subscales score categories and the respective cut-offs among profiles (n=2855).

|                      | Median* | Higher disordered eating |              |              | Increasing disordered eating |              |              | Decreasing disordered eating |              |              | Lower disordered eating |              |              |
|----------------------|---------|--------------------------|--------------|--------------|------------------------------|--------------|--------------|------------------------------|--------------|--------------|-------------------------|--------------|--------------|
|                      |         | Zero score (%)           | ≤ Median (%) | > Median (%) | Zero score (%)               | ≤ Median (%) | > Median (%) | Zero score (%)               | ≤ Median (%) | > Median (%) | Zero score (%)          | ≤ Median (%) | > Median (%) |
| Drive for thinness   |         |                          |              |              |                              |              |              |                              |              |              |                         |              |              |
| 13y                  | 3.5     | 4.6                      | 11.8         | 83.7         | 25.0                         | 50.5         | 24.5         | 27.3                         | 28.0         | 44.8         | 57.8                    | 39.2         | 3.0          |
| 17y                  | 3.0     | 1.2                      | 9.4          | 89.4         | 21.4                         | 55.2         | 23.4         | 41.4                         | 33.7         | 24.9         | 57.5                    | 38.2         | 4.3          |
| 21y                  | 3.0     | 4.4                      | 24.5         | 71.1         | 19.3                         | 44.6         | 36.1         | 59.6                         | 34.4         | 6.0          | 55.4                    | 43.0         | 1.6          |
| Bulimia              |         |                          |              |              |                              |              |              |                              |              |              |                         |              |              |
| 13y                  | 3.0     | 47.4                     | 28.6         | 24.1         | 74.1                         | 21.7         | 4.2          | 36.2                         | 26.1         | 37.6         | 79.5                    | 20.1         | 0.4          |
| 17y                  | 2.8     | 44.7                     | 20.5         | 34.8         | 84.1                         | 14.6         | 1.2          | 50.3                         | 18.8         | 31.0         | 82.3                    | 12.1         | 5.6          |
| 21y                  | 2.0     | 48.2                     | 29.4         | 22.4         | 76.6                         | 16.1         | 7.4          | 68.2                         | 21.2         | 10.6         | 92.9                    | 5.4          | 1.7          |
| Body dissatisfaction |         |                          |              |              |                              |              |              |                              |              |              |                         |              |              |
| 13y                  | 6.0     | 2.8                      | 21.6         | 75.6         | 13.8                         | 49.9         | 36.3         | 14.3                         | 42.2         | 43.5         | 49.0                    | 45.2         | 5.8          |
| 17y                  | 6.0     | 0.0                      | 9.5          | 90.5         | 8.2                          | 49.4         | 42.4         | 23.6                         | 42.9         | 33.5         | 51.9                    | 46.0         | 2.2          |
| 21y                  | 5.0     | 2.9                      | 13.9         | 83.2         | 5.8                          | 41.0         | 53.2         | 39.3                         | 46.8         | 13.9         | 62.8                    | 34.3         | 3.0          |

\*The median corresponds to the cut-off value considered for deriving the below and above the median scores after excluding individuals with scores of zero; y: years old.

**Table S3.** Characterization of the disordered eating profiles according to family and participant's characteristics (n=1619).

|                                                     | Higher<br>disordered eating<br>(18.6%) | Increasing<br>disordered eating<br>(27.6%) | Decreasing<br>disordered eating<br>(18.7%) | Lower<br>disordered eating<br>(35.1%) | p-value          |
|-----------------------------------------------------|----------------------------------------|--------------------------------------------|--------------------------------------------|---------------------------------------|------------------|
| <b>Family characteristics</b>                       |                                        |                                            |                                            |                                       |                  |
| Parental highest education, Md (IQR)                | 11 (8.0) <sup>abc</sup>                | 11 (9.0) <sup>ad</sup>                     | 11 (9.0) <sup>bde</sup>                    | 12 (8.0) <sup>ce</sup>                | <b>0.010</b>     |
| Maternal BMI at baseline, Md (IQR)                  | 24 (6.3)                               | 24 (5.1)                                   | 23 (4.7)                                   | 23 (4.2)                              | 0.074            |
| <b>Participants' characteristics</b>                |                                        |                                            |                                            |                                       |                  |
| Sex, n (%)                                          |                                        |                                            |                                            |                                       |                  |
| Female                                              | 245 (81.4) <sup>a</sup>                | 254 (56.8) <sup>b</sup>                    | 141 (46.5) <sup>c</sup>                    | 197 (34.7) <sup>d</sup>               | <b>&lt;0.001</b> |
| Male                                                | 56 (18.6) <sup>a</sup>                 | 193 (43.2) <sup>b</sup>                    | 162 (53.5) <sup>c</sup>                    | 371 (65.3) <sup>d</sup>               |                  |
| Education at 21y, Md (IQR)                          | 14.00 (3.00)                           | 14.00 (3.00)                               | 14.00 (3.00)                               | 14.00 (3.00)                          | 0.501            |
| Monthly household income at 21y, n (%) <sup>*</sup> |                                        |                                            |                                            |                                       |                  |
| <1000 €                                             | 61 (24.1) <sup>a,b</sup>               | 84 (21.1) <sup>a,b</sup>                   | 74 (27.3) <sup>a</sup>                     | 95 (18.3) <sup>a</sup>                | <b>0.031</b>     |
| 1001-1500€                                          | 59 (23.3) <sup>a</sup>                 | 96 (24.1) <sup>a</sup>                     | 60 (22.1) <sup>a</sup>                     | 105 (20.3) <sup>a</sup>               |                  |
| 1501-2000€                                          | 43 (17.0) <sup>a</sup>                 | 70 (17.5) <sup>a</sup>                     | 44 (16.2) <sup>a</sup>                     | 80 (15.4) <sup>a</sup>                |                  |
| >2000€                                              | 90 (35.6) <sup>a</sup>                 | 149 (37.3) <sup>a</sup>                    | 93 (34.3) <sup>a</sup>                     | 238 (45.9) <sup>b</sup>               |                  |
| Anthropometrics                                     |                                        |                                            |                                            |                                       |                  |
| BMI z-scores at 13y, M (SD)                         | 1.10 (0.91) <sup>c</sup>               | 0.71 (1.00) <sup>b</sup>                   | 1.14 (1.02) <sup>a</sup>                   | 0.00 (0.89) <sup>a</sup>              | <b>&lt;0.001</b> |
| BMI z-scores at 13y, n (%)                          |                                        |                                            |                                            |                                       |                  |
| Uw/Nw                                               | 92 (44.2) <sup>a</sup>                 | 202 (62.9) <sup>b</sup>                    | 187 (83.5) <sup>c</sup>                    | 366 (88.6) <sup>c</sup>               | <b>&lt;0.001</b> |
| Ow/Ob                                               | 116 (55.8) <sup>a</sup>                | 119 (37.1) <sup>b</sup>                    | 37 (16.5) <sup>c</sup>                     | 47 (11.4) <sup>c</sup>                |                  |
| BMI z-scores at 17y, M (SD)                         | 0.84 (0.90) <sup>c</sup>               | 0.48 (0.97) <sup>b</sup>                   | 0.03 (0.86) <sup>a</sup>                   | -0.10 (0.78) <sup>a</sup>             | <b>&lt;0.001</b> |
| BMI z-scores at 17y, n (%)                          |                                        |                                            |                                            |                                       |                  |
| Uw/Nw                                               | 161 (57.9) <sup>a</sup>                | 297 (71.7) <sup>b</sup>                    | 248 (87.3) <sup>c</sup>                    | 504 (93.7) <sup>d</sup>               | <b>&lt;0.001</b> |
| Ow/Ob                                               | 117 (42.1) <sup>a</sup>                | 117 (28.3) <sup>b</sup>                    | 36 (12.7) <sup>c</sup>                     | 34 (6.3) <sup>d</sup>                 |                  |

|                                                         |                           |                           |                           |                           |                  |
|---------------------------------------------------------|---------------------------|---------------------------|---------------------------|---------------------------|------------------|
| BMI at 21y, Md (IQR)                                    | 24.60 (6.20) <sup>c</sup> | 23.10 (4.80) <sup>b</sup> | 21.20 (4.20) <sup>a</sup> | 21.60 (3.40) <sup>a</sup> | <b>&lt;0.001</b> |
| BMI at 21y, n (%)                                       |                           |                           |                           |                           |                  |
| Uw/Nw                                                   | 163 (54.2) <sup>a</sup>   | 307 (68.7) <sup>b</sup>   | 254 (83.8) <sup>c</sup>   | 498 (87.7) <sup>c</sup>   | <b>&lt;0.001</b> |
| Ow/Ob                                                   | 138 (45.8) <sup>a</sup>   | 140 (31.3) <sup>b</sup>   | 49 (16.2) <sup>c</sup>    | 70 (12.3) <sup>c</sup>    |                  |
| Body image satisfaction*, n (%)                         |                           |                           |                           |                           |                  |
| 13y                                                     |                           |                           |                           |                           |                  |
| Desire for a thinner silhouette                         | 148 (75.5) <sup>a</sup>   | 145 (48.7) <sup>b</sup>   | 70 (33.0) <sup>c</sup>    | 52 (13.5) <sup>d</sup>    | <b>&lt;0.001</b> |
| Satisfied with body image                               | 38 (19.4) <sup>a</sup>    | 110 (36.9) <sup>b</sup>   | 75 (35.4) <sup>b</sup>    | 197 (51.2) <sup>c</sup>   |                  |
| Desire for a larger body                                | 10 (5.1) <sup>a</sup>     | 43 (14.4) <sup>b</sup>    | 67 (31.6) <sup>c</sup>    | 136 (35.3) <sup>c</sup>   |                  |
| 17y                                                     |                           |                           |                           |                           |                  |
| Desire for a thinner silhouette                         | 153 (86.0) <sup>a</sup>   | 132 (48.7) <sup>b</sup>   | 50 (30.1) <sup>c</sup>    | 49 (14.0) <sup>d</sup>    | <b>&lt;0.001</b> |
| Satisfied with body image                               | 22 (12.4) <sup>a</sup>    | 93 (34.3) <sup>b</sup>    | 63 (38.0) <sup>c</sup>    | 217 (61.8) <sup>c</sup>   |                  |
| Desire for a larger body                                | 3 (1.7) <sup>a</sup>      | 46 (17.0) <sup>b</sup>    | 53 (31.9) <sup>c</sup>    | 85 (24.2) <sup>c</sup>    |                  |
| 21y                                                     |                           |                           |                           |                           |                  |
| Desire for a thinner silhouette                         | 257 (89.5) <sup>a</sup>   | 270 (62.2) <sup>b</sup>   | 81 (27.6) <sup>c</sup>    | 105 (19.3) <sup>d</sup>   | <b>&lt;0.001</b> |
| Satisfied with body image                               | 23 (8.0) <sup>a</sup>     | 114 (26.3) <sup>b</sup>   | 127 (43.3) <sup>c</sup>   | 307 (56.5) <sup>d</sup>   |                  |
| Desire for a larger body                                | 7 (2.4) <sup>a</sup>      | 50 (11.5) <sup>b</sup>    | 85 (29.0) <sup>c</sup>    | 131 (24.1) <sup>c</sup>   |                  |
| Dieting during the last year, at 21y*, n (%)            |                           |                           |                           |                           |                  |
| Never                                                   | 156 (51.8) <sup>a</sup>   | 297 (66.7) <sup>b</sup>   | 263 (87.1) <sup>c</sup>   | 517 (91.3) <sup>d</sup>   | <b>&lt;0.001</b> |
| Yes                                                     | 145 (48.2) <sup>a</sup>   | 148 (33.3) <sup>b</sup>   | 39 (12.9) <sup>c</sup>    | 49 (8.7) <sup>d</sup>     |                  |
| Medical diagnosis of Anorexia Nervosa until 21y*, n (%) |                           |                           |                           |                           |                  |
| No                                                      | 293 (98.8) <sup>a</sup>   | 441 (98.9) <sup>a,b</sup> | 300 (99.0) <sup>a,b</sup> | 564 (99.6) <sup>b</sup>   | 0.135            |
| Yes                                                     | 6 (2.0) <sup>a</sup>      | 5 (1.1) <sup>a,b</sup>    | 3 (1.0) <sup>a,b</sup>    | 2 (0.4) <sup>b</sup>      |                  |
| Medical diagnosis of Bulimia until 21y*, n (%)          |                           |                           |                           |                           |                  |
| No                                                      | 298 (98.7) <sup>a</sup>   | 444 (99.6) <sup>a,b</sup> | 303 (100.0) <sup>b</sup>  | 566 (100.0) <sup>b</sup>  | <b>0.013</b>     |
| Yes                                                     | 4 (1.3) <sup>a</sup>      | 2 (0.4) <sup>a,b</sup>    | 0 (0.0) <sup>b</sup>      | 0 (0.0) <sup>b</sup>      |                  |

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Parents' medical diagnosis of Anorexia Nervosa and/or

Bulimia\*, n (%)

|     |            |            |            |            |       |
|-----|------------|------------|------------|------------|-------|
| No  | 216 (99.1) | 318 (98.1) | 217 (99.1) | 396 (99.2) | 0.528 |
| Yes | 2 (0.9)    | 6 (1.9)    | 2 (0.9)    | 3 (0.8)    |       |

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M (SD): mean (standard deviation); Md (IQR): median (interquartile range); BMI: Body Mass Index; Uw/Nw: Underweight/Normal weight; Ow/Ob: Overweight/Obesity; BMI z-scores categories at 13 and 17y: Uw/Nw ( $\leq 1SD$ ) and Ow/Ob ( $> 1SD$ ); BMI categories at 21y: Uw/Nw ( $< 25.0 \text{ kg/m}^2$ ) and Ow/Ob ( $\geq 25.0 \text{ kg/m}^2$ ). \*Subsample with reduced available data: parental (n=1160) and participant's (n=1614) eating disorder information; Household income at 21y (n=1441), anthropometrics at 13y (n=1166) and 17y (n=1514); Body image satisfaction at 13y (n=1091), 17y (n=966) and 21y (n=1557). **Bold-type** represents statistically significant associations ( $p < 0.05$ ). Superscript letters are presented for variables in which significant differences were found among profiles; profiles with the same superscript letters indicate a non-significant difference, while profiles with different superscripts indicate significant differences between them ( $p < 0.05$ ).

## FINAL DISCUSSION AND MAIN CONCLUSIONS

The present dissertation explored various dimensions of disordered eating through different developmental life stages. In paper I, from childhood to early adolescence, we focused on the association between a cumulative measure of adiposity, assessed using BMI under the curve as an indicator of adiposity, and appetitive behaviours. As main findings, it should stand out the 'avid appetite' profile, representing overall high food approach behaviours - the profile to which children with the highest cumulative exposure to adiposity were more likely to belong to. Also, having overweight at 7y, independently of cumulative exposure to BMI throughout childhood, was already indicative of being an avid eater. In paper II, we studied the association of 'Drive for thinness' and 'Body dissatisfaction', as well as 'Bulimia' (disordered eating attitudes and behaviours, respectively) across adolescence and young adulthood with cardiometabolic health outcomes at 21y. The profiles with 'high' and 'increasing' disordered eating levels, mainly characterized by high levels of 'Drive for thinness' and 'Body dissatisfaction', were associated with increased BMI and higher odds of presenting  $\geq 1$  Mets component at 21y, particularly men. Overall, results identify potential groups of risk for the development of obesogenic and cardiometabolic disturbed profiles.

Despite all the efforts, obesity still represents an ongoing public health challenge, being considered a major determinant of disability and death in the WHO European Region [172]. It is estimated that one in three school-aged children have overweight or obesity [173] and evidence suggests that high weight will track over time [123]. Therefore, as a complex and multifactorial disease, a life course perspective may be an adequate approach for obesity research [174]; it presents an opportunity to study the dynamic development and health impact of various exposures, including obesity and eating behaviours, their determinants and outcomes, and to capture critical periods as well as the accumulation of risk over different life stages [175]. In this context, cohorts (particularly birth cohorts that can provide early life exposures) arise as unique portals for studying and accompanying the same individuals throughout time and collect data that allow a life course approach. In this dissertation, the use of longitudinal data from two large population-based cohorts - Generation XXI and EPITeen - were fundamental to answer the specific aims we had set. Findings from paper I suggest that a cumulative measure of adiposity, captured as the duration and degree of BMI across nine years of follow-up, was more indicative of the appetite

profile children belonged to, than to considered BMI at specific time points. In addition to the cumulative effect, as previously mentioned, having overweight at 7y was associated with belonging to an avid appetite profile - results that reinforce the importance of curbing weight gain in early childhood to protect children from the development of obesity-related appetite profiles across childhood.

Nevertheless, there seems to exist a conflicting nature in the public health messages to prevent overweight and obesity, as they may be contributing to the development of disordered eating and eating disorders [176, 177]. Evidence suggests the counterproductivity of dieting and weight control practices, which normally backfire and result in weight gain [119, 121, 153, 178, 179]. Most of the 12 studies included in a systematic review about the effects of anti-obesity public health messages on risk factors for disordered eating indicate that these messages were felt as stigmatizing and reinforced drive for thinness and the thin ideal [176]. Public health messages aiming to tackle obesity should displace their focus from weight loss and, instead, shift to an overall health and well-being approach [176]. Fortunately, this awareness is already raised in the latest WHO European Regional Obesity Report of 2022 [173], and topics such as weight stigma have been already been part of the agenda of the WHO Regional Office for Europe in 2017 [180] and on the World Obesity Day in 2018 [181], the latter claiming, among other facts, that *‘people with obesity can develop eating disorders’* and that *‘stigma is often perpetrated by friends and family’*.

Concerningly, one in every four children or adolescents is estimated to be subject of weight related comments and teasing [182], even individuals without overweight [183]. Weight related comments can affect one self-perception, attitudes and behaviours [184]. Thus, adding to peers, family members can either act as risk or protective factors in the prevention of disordered eating and body image dissatisfaction. It would be relevant to raise parents’ awareness on how they can adapt their speech and better communicate with their children and adolescents [92, 93]. In adolescents and young adults, social media literacy and body appreciation also appear to be protective risk factors for body image concerns and disordered eating behaviours – which are reinforced through comparison, internalization of the thin ideal and self-objectification [95].

It is interesting to trace back the history of the body image ideals and its close connection to the cultural and socioeconomic environment. The known Palaeolithic “Venus figurines”, representing pregnant women or women with obesity, have been

proposed to represent fertility, but also an adaptation to the harsh climate change of glaciers and very low temperatures. In this context, the ideal beauty in women was being over nourished, as a symbol of survival [185]. Contrarily, the thin ideal is characteristic of late-modern societies [186], with a progressive focus on 'slim' bodies since the 1950s [186, 187]. The rise of the thin ideal seems to be closely related to the fashion industry, with the industrialization of clothing manufacture after the Second World War, and the creation of the clothes sizing system [186, 188]. This clothing system had specific maximum sizes that did not include very large ones and also needed models that could advertise the clothes. As so, the thin ideal quickly became ingrained and continuously perpetuated in our daily lives' practices and behaviours [186].

Adding to the fashion industry, the food and beauty industries can benefit from people with unhealthy relationships with food and their bodies and could be important targets in disordered eating and eating disorders prevention [189, 190]. Particularly regarding the food industry, there are practices that can contribute to this disturbed relationship [189]. The current obesogenic food environment fosters overconsumption, particularly of ultraprocessed foods [191] - ready to eat, low cost, highly palatable foods rich in calories, fat, salt, sugar and additives, which have been suggested to have higher potential of being addictive and disturb appetite control processes [192, 193]. Thus, the food environment seems to go against the thin ideal and the stigmatization of the higher body weight, which may increase weight concerns and pressure for food intake restriction. To match the new consumers' needs regarding body image, food industry focused in delivering 'diet' foods, such as reduced-calorie and *light* products [189]. The marketing of such foods reinforces the culture of diet, the sociocultural body ideal discourse and may potentially promote disordered eating [194]. On the other hand, food labelling reports the composition and nutritional content of the product and allows consumers to have a more conscious choice [195]. However, the use of foods labels is dependent on the ability to interpret them and, in individuals with disordered eating, labels can contribute to their preoccupation around the calorie content of foods [189, 196].

In the last years, various movements have risen with some promising effects on fighting the diet culture, disordered eating and body shaming; as well as promote body acceptance. Examples include the media 'body-positivity' to combat images of unrealistic and unachievable body ideals on social media [197], the 'Health at Every Size®' (HAES) [198] which support a weight neutral approach to health, focusing on

wellness, or approaches to eating such as 'Intuitive eating' and 'Mindful eating', that aim to promote a positive relationship with both food and the body and encourage eating based on internal cues of hunger and fullness [199, 200].

Apart from associations between disordered eating and body weight, a visible characteristic, concerns are also placed regarding altered blood pressure, low HDL-c, high blood lipids or high fasting glucose, which are important cardiometabolic risk factors, but can often go unnoticed, particularly at young ages. In young adults, MetS is underdiagnosed, as individuals may not routinely do biochemical analysis [201, 202]. Those who are unaware of having MetS risk factors may remain without diagnosis until a major consequence occurs, such as diabetes type II or a cardiovascular disease [201]. It is estimated that since 2017, in some high-income countries, cardiovascular disease mortality has become stable or increased [203]. According to the Global Burden of Diseases Study (GBD) 2019, exposure to metabolic risk factors increased 1.4% per year, from 1990 to 2019 and 1.5% from 2010 to 2019. Among the risk factors, the most relevant are BMI and fasting plasma glucose, increasing at a concerning rate; and systolic blood pressure, which has become the global leading risk factor for disease burden [204].

Guidelines on the primary prevention of cardiovascular disease emphasise the important role of diet in the prevention of risk factors, and encourage a diet high in fruits, vegetables and whole grains; fish, legumes, and poultry as the preferred protein sources; and minimizing red meat, added sugars, sodium, trans and saturated fatty acids consumption [205]. However, prevention may have to go beyond diet quality and focus on a more behavioural and cognitive component in the relationship with food and eating. Although it may not be the first target or a direct cause, findings from paper II suggest the importance of preventing disordered eating in adolescence, as it is associated with higher BMI and with the presence of MetS components in young adulthood.

This dissertation presents strengths and limitations worth noting. The first strength is the use of data from two large population-based cohorts, as already mentioned, that enabled us to have considerable sample sizes despite losses to follow-up throughout assessments but, most importantly, to encompass data from childhood, adolescence and young adulthood. Both obesity and disordered eating are dynamic and evolve over time as part of an accumulation of risk, especially in specific critical periods of development such as childhood with adiposity rebound, and adolescence with puberty. Thus, the inclusion of Generation XXI, a birth cohort,

and EPITeen, a cohort that follows adolescents since 13y, allowed us to have a broader picture of the different life stages. These two cohorts are 15 years apart and, although they intend to represent a continuous, each has its own context and specificities, thus hampering comparisons between papers. Also, although this dissertation presents a longitudinal approach, inferences about causality should not be made. Proof of causality would require checking for other criteria and, in both papers, the time points used for assessment of the outcomes (from 7-13y in paper I and 21y in paper II) are considered in the measures of the exposures (from 4-13y in paper I and from 13-21y in paper II). Despite the risk of misreport and other biases in self-reported questionnaires, disordered eating was assessed using validated questionnaires, which previously presented good psychometric characteristics [112, 145, 206, 207]. Both CEBQ and EDI showed adequate internal consistency in the drafted papers, with Cronbach's  $\alpha$  coefficients varying between 0.76-0.89 and 0.67-0.89 in papers I and II, respectively.

The two papers add to previous knowledge and merge different but connected public health concerns: disordered eating, obesity and MetS in different ways: i) we explored adiposity and appetitive behaviours (as part of disordered eating), in the direction of association that recent prospective studies have been pointing out (in which weight contributes to the development of appetite [14, 111, 112, 114, 171], rather than the other way around); ii) we calculated a cumulative measure of the degree and duration of adiposity; the BMI<sub>AUC</sub> captures each child own BMI evolution over time rather than looking at only one specific time point; iii) when studying associations of eating disorders symptomatology with later cardiometabolic health, we included beyond BMI, the clustering of MetS components (the latter not so deeply studied in existing literature [118, 132, 135, 131]); iv) we performed a person-centred approach that considers each individual disordered eating evolution and identifies groups with similar evolution patterns. The combined use of robust methodologic approaches with quality data, including both self-reported and biochemical measures, contributes to the reliability of the obtained results.

On a final and personal note, the beauty of understanding eating behaviours is that they are part of us, not only because food is one of our basic survival needs, but also because our body tells a story by embodying our life experiences and cumulative exposures. As such, the ways in which we connect to food and eating is intrinsically related to our body, mind health and wellbeing. As a nutritionist and future public health professional, my perception is that there is an increasing interest in the

behavioural and psychological component of appetite and eating, and how to better approach eating behaviours and a disturbed relationship with food (particularly in the clinical context). However, there is still a long - but worth it - path to tackle obesity and disordered eating, that should start with parents and family, extend to schools and universities, healthcare facilities, and be supported on macro level. In Portugal, for instance, while fruitful efforts have been made to tackle the obesogenic environment [208], as far as I know, not much has been done on a governmental level to improve disordered eating and eating disorders. Societal and cultural pressures for specific body standards along with industry and economic interests can make this process harder. Yet, according to the 'Triggers-to-action Framework' [209], a regulatory action is instigated by several factors, including: a) evidence-based findings linking exposure to future impaired health (which exists regarding disordered eating and for which the findings of this dissertation contribute), and economic outcomes related to prevention (interventions promoting healthy nutrition, physical activity, and media use behaviours without producing weight stigma may additionally prevent against excess weight gain and has proven to be cost-effective [210]); b) practical considerations on how prevention can be translated into policies (for instance, in 2006, in Spain, the regional government banned the admission of adult models with a BMI  $<18 \text{ kg/m}^2$  [211]) and c) political will - it is time to bring disordered eating into the Portuguese political agenda [211, 212]. Meanwhile, being able to respect internal cues of hunger and satiety, fostering a healthy relationship with food and the body seems an important next step that can possibly help on weight and metabolic management.

Future studies could extend the captured period for disordered eating and include other behavioural dimensions such as restriction/dieting, compulsive exercise and binge eating. It would also be important to clarify the specific role of fat mass and fat-free mass in the development of appetite behaviours trajectories over time.

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