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The association between obesity severity and food reward in adolescents with obesity: A one-stage individual participant data meta-analysis

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Keywords: Obesity, morbid obesity, food preference, body composition, adolescent, reward

Abbreviations

BMI – Body Mass Index

CDC – Centers for Disease Control and Prevention

DXA – Dual-energy X-ray absorptiometry

FM – Fat Mass

FFM – Fat Free Mass

LFPQ – Leeds Food Preference Questionnaire

VAS - Visual Analogue Scale

IDP – Individual Participant Data

Clinical Trial Registrations:

NCT02925572: <https://classic.clinicaltrials.gov/ct2/show/NCT02925572>

NCT03807609: <https://classic.clinicaltrials.gov/ct2/show/NCT03807609>

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Abstract

Background: Food reward and cue reactivity have been linked prospectively to problematic eating behaviours and excess weight gain in adults and children. However, evidence to date in support of an association between degree of adiposity and food reward is tenuous. A non-linear relationship between reward sensitivity and obesity degree has been previously proposed, suggesting a peak is reached in mild obesity and decreases in more severe obesity in a quadratic fashion.

Objective: To investigate and characterise in detail the relationship between obesity severity, body composition, and explicit and implicit food reward in adolescents with obesity.

Methods: Data from seven clinical trials in adolescents with obesity were aggregated and analysed in an independent participant data meta-analysis. Linear and curvilinear relationships between degree of obesity and explicit and implicit reward for sweet and high-fat foods were tested in fasted and fed states with BMI-z as a continuous and discrete predictor using clinically recognised partitions.

Results: Although positive associations between obesity severity and preference for high fat (i.e., energy-dense) foods were observed when fasted, none reached significance in either analysis. Conversely, adiposity was reliably associated with lower reward for sweet, particularly when measured as implicit wanting ($p = .012$, $\eta p^2 = .06$), independent of metabolic state. However, this significant association was only observed in the linear model. Fat distribution was consistently associated with explicit and implicit preference for high fat foods.

Conclusions: A limited relationship was demonstrated between obesity severity and food reward in adolescents, although a lower preference for sweet could be a signal of severe obesity in a linear trend. Obesity is likely a heterogeneous condition associated with multiple potential phenotypes, which metrics of body composition may help define.

1. Background

Given the alarming rise in prevalence of paediatric obesity over recent years, the importance of this formative stage has been a salient focus for public health research [1].

30 Obesity severity in youth has been associated with a greater risk of obesity in adulthood along with salient comorbidities such as cardiovascular disease, certain types of cancer, and type 2 diabetes [2]. Importantly, the extant studies investigating these links may be underestimating the disease burden suffered by youth with severe obesity due to the general treatment of this cohort as a homogenous group [2]. Therefore, there is an increasing acknowledgement of
35 obesity as a heterogenous condition, which likely requires greater precision or personalisation when discerning aetiologies and appropriate clinical management strategies [3,4].

Consideration of all individuals with overweight/obesity as a homogenous group may also be inappropriate given the rise in more severe degrees of obesity, also referred to as morbid obesity, in recent decades, even in children

40 A potential aetiological pathway explored in youth is the role of hedonic appetite with concomitant impairments in executive function [5]. Hedonic, or reward-related, appetite is considered to be separable from the physiological drive for preserving energy and nutrient homeostasis under certain conditions, and is directly modulated by both intrinsic (i.e., the properties of a food) and extrinsic (i.e., environmental) cues [6,7]. For example, this could be
45 a food's palatability or mere exposure to food cues, respectively. Systematic reviews and meta-analyses have demonstrated that exposure and reactivity to palatable food cues, especially visual cues, positively predict food intake and weight gain in adolescents [8-11]. Moreover, impulsive dietary behaviours and adiposity in adolescents have been linked to adaptations in subcortical volume and functional connectivity within, and hyperactivation of,
50 brain regions implicated in reward processing such as the Striatum and Nucleus Accumbens [12-14]. Children with obesity or at risk for obesity also tend to differ in sensitivity to such

that they tend to rate the same food items associated with a definitive gustatory feature as less sweet or salty, for example, on average than their lean peers [15,16]. Therefore, heightened hedonic appetite has been considered a risk factor for obesity and weight gain in childhood and subsequently a credible target for preventative interventions [17].

Current evidence in support of the link between obesity and food reward may necessitate more nuance. A meta-analysis of 13 studies by Morys and colleagues [18] could not find a consistent association between weight status and greater visual food cue reactivity. However, age was found to significantly moderate this relationship such that differences in food cue reactivity between weight status groups was more pronounced in youth and decreased with age. The method to assess anthropometry may also contribute to mixed findings with methods ranging from self-report to advanced body composition assessment such as dual-energy X-ray absorptiometry (DXA). Likewise, a meta-analysis of 45 studies by Boswell and Kober [8] did not find either weight status or age to independently moderate the effect of food cue reactivity on food intake or weight gain, although an interaction between them was not investigated. In a study by Hofmann et al. [19] examining a sample of adolescents with a wide range of adiposity, weight status was only associated with higher liking and intake of energy dense food in a subgroup characterised by higher trait food craving. Dalton, Blundell, and Finlayson [20] demonstrated that young adults with obesity characterised as a binge eating phenotype expressed a higher implicit wanting for, and consumed more, high fat sweet food than their non-binge eating counterparts. It is also important to note that neural activity in reward-related brain regions may correlate more precisely with central or visceral obesity (i.e., waist circumference, android fat distribution) [21], or fat free mass (FFM) [22], rather than obesity as defined by body mass index (BMI) alone, thus warranting investigations of alternatives when as potential risk factors for reward-driven eating behaviours.

Related to neurocognitive profiles, a review by Horstmann and colleagues [23] suggests that adiposity may have a quadratic relationship with dopaminergic tone¹ (i.e., dopamine availability), which consequently has an inverse relationship with reward sensitivity. In their proposed model, dopaminergic tone initially decreases from lean to overweight, reaching a trough in mild obesity, then increases in more severe degrees of obesity. This elevation in more severe adiposity may be facilitated in part by the onset of leptin resistance, which in turn affects the rate of dopamine release in the limbic system. A recently submitted inpatient feeding study in young adults ranging from 20 to 44kg/m² in BMI has aimed to test the suitability of this quadratic model whilst utilising two different radiotracers for evaluating dopamine receptor binding potential, namely [¹⁸F]fallypride and [¹¹C]raclopride [24]. Whilst correlated, only when measured with the latter was BMI significantly and negatively associated with dopamine receptor binding potential, albeit in a linear manner. Moreover, associations with BMI and fat mass (FM) observed from these methods were significantly different, highlighting the role of methodology when interpreting mixed evidence from the literature. Relatedly, a recent meta-analysis by Pak and Nummenmaa [25] also found that the radiotracer method used significantly moderated the relationship between dopaminergic activity and obesity severity with a particular emphasis on contrasts in their interactions with dopamine availability. Whilst this emerging evidence is insightful for reconciling discrepancies in previously literature as it pertains to dopamine action and adiposity specifically, it is mainly pertinent to adults, and behavioural assessment of food reward sensitivity was not addressed. It may then be of interest to investigate how the degree of obesity is related to reward responses to food in youth specifically, given the relative paucity of evidence in this vulnerable population that are still developing key neural pathways involved in reward processing [26].

¹ Note that dopaminergic tone and binding potential are inversely related

In consideration of the challenges with recruiting large clinical samples of children and adolescents, which may be required to detect arguably modest effects associated with reward sensitivity, an individual participant data (IDP) meta-analysis was conducted to investigate the relationship between degree of obesity, body composition, and food reward in adolescents with obesity when in both fasted and postprandial states, which enabled an analysis of satiety in response to a meal. Consistent with the novel model proposed by Horstmann et al. [23], it was hypothesised that obesity severity would be negatively and curvilinearly associated with explicit and implicit reward for energy-dense and sweet foods in a fasted state (Hypothesis 1A), and physiological state would moderate this association such that differences between fasted and fed responses would be greatest in more severe obesity (1B). Additionally, we hypothesised that body composition metrics such as FM and FFM would have stronger associations with food reward than weight and BMI (Hypothesis 2).

2. Methods

2.1. Design and Participants

The relationship between degree of obesity and food reward was investigated by pooling and analysing primary data from seven distinct clinical intervention studies involving $N = 133$ adolescents with obesity conducted between 2016 and 2022. The primary data were derived from participants enrolled in short and long-term multidisciplinary interventions at baseline prior to any involvement in the clinical protocol. Importantly, all studies were conducted by the same research team and therefore were subject to the same protocols, methodology, setting, and time frame. A pooled analysis increased the available sample size and consequently broadened the heterogeneity in obesity degree and, relatedly, the statistical power to detect modest variations in food reward that may not be feasible for a single study to achieve. A detailed flow chart illustrating the study selection and analytic process can be found in the supplementary materials (**Figure 1**).

The pooled sample comprised of adolescents with obesity collected at two paediatric obesity centres in France (Children Medical Centre for Adolescents with Obesity, La Bourboule, France, and Paediatric Medical Centre, Romagnat, France). The following inclusion criteria were applied in all included studies: aged between 10 and 16 years; BMI > 95th percentile according to the international cut-off points [1]; Tanner stage between 3 and 5; for females, regular menstruations; not taking any medications, oral contraceptives, hormone replacement therapy, tobacco, or alcohol; not experiencing major orthopaedic problems; weight stable and no diet within the last 6 months; and no regular physical activity as defined by less than 10 metabolic equivalent of task hours/week and measured with the International Physical Activity Questionnaire [27].

2.2. Measures

2.2.1. Anthropometrics and Body Composition

Body weight to the nearest 0.1kg and height to the nearest 0.5cm was measured using a digital scale and a standard wall-mounted stadiometer, respectively, while wearing light clothes without footwear. BMI-z and BMI-percentile scores were calculated using the Centers for Disease Control (CDC) age- and sex-specific extended growth charts based on modified distributions that enable more precise tracking of severe levels of paediatric obesity [28,29]. Clinical classes of paediatric obesity were categorised according to guidelines suggested by the American Academy of Pediatrics as follows: Obesity defined as between 100% and 120% of the 95th BMI-percentile; Class 2 Obesity defined as between 120% and 140% of the 95th BMI-percentile; Class 3 Obesity defined as greater than 140% of the 95th BMI-percentile [30]. FM, including android and gynoid distributions, and FFM were assessed by DXA following a standardised procedure when the participant was in a fasted state (QDR4500A scanner, Hologic, Waltham, MA, USA).

2.2.2. *Lunch Test Meals*

All studies measured energy intake using a similar validated methodology with the same meal type (i.e., lunch) served with similar foods items within in a similar location, condition, and time frame (i.e., laboratory-based). Briefly, meal content was based on participants' food preferences and eating habits in accordance with a validation study conducted in a demographically and anthropometrically similar population [31]. Top rated foods as well as those disliked or not frequently consumed were excluded to avoid opportunistic, under-, and overconsumption. For all studies, the menu was typically composed of beef steaks, pasta, mustard, cheese, yoghurt, apple sauce, fruits, and bread. Although the methodological approach to meal composition were the same across studies, the meal sizes varied due to the provision of either fixed ($n = 2$) or ad libitum ($n = 5$) test meals in accordance with relevant study aims. For a more detailed description of the test meal methodology, see the study by Miguet and colleagues [32].

2.2.3. *Food Reward*

The French version of the Leeds Food Preference Questionnaire (LFPQ-fr) was used to assess adolescents' hedonic responses to foods. This questionnaire was developed and validated to measure two distinct components of food reward, namely liking (i.e., palatability) and wanting (relative motivation to eat) [33]. Participants were presented with images of 16 food images belonging to one of four discrete categories based on fat content and taste: i) savoury and high-fat; ii) savoury and low-fat; iii) sweet and high-fat; and iv) sweet and low-fat. The LFPQ-fr consists of two separate tasks designed to assess these reward-related constructs. The first task measures explicit liking and wanting for every image in the food matrix by requiring the user to answer the following: i) "How pleasant would it be to taste this food now?" (i.e., explicit liking) and ii) "How much do you want to eat this food now?" (i.e., explicit wanting) by 100-millimetre (mm) visual analogue scale (VAS). The second task utilises a forced choice

paradigm to assess implicit wanting and frequency of choice by requiring the user to rapidly and accurately select between two food images presented simultaneously and in quick succession. Reaction times were covertly recorded for every selection and standardised to calculate the implicit wanting score.

The primary outcomes of interest derived from this task were fat bias and sweet bias for each aforementioned food reward component. The fat bias score (relative preference for high fat foods) was calculated by subtracting mean ratings of low-fat foods from those of high fat and the sweet bias score (relative preference for sweet food) was obtained by subtracting mean ratings of all savoury foods from those of sweet. Therefore, positive scores indicate a preference for high-fat and sweet foods relative to low-fat and savoury foods, respectively [34]. The LFPQ-fr was developed and validated following a recommended procedure to appropriately adapt the task to culturally diverse populations, and has demonstrated high agreement in both fasted and fed states [35].

2.3. Procedure

The following procedure was similar across all studies. Participants had to complete a full medical examination and Tanner staging conducted by a paediatrician to confirm their eligibility, then their body composition was assessed by DXA. On the test day, adolescents were provided with a calibrated fixed breakfast of 500kcal in accordance with nutritional recommendations for their age and sex at 8:00am after an overnight fast [36]. As part of the control condition, participants were prohibited from engaging in any moderate-to-vigorous physical activity for the entire morning and asked to remain quietly and comfortably seated or in a semi-supine position from 11:00am to 11:30am. Afterwards, food reward was assessed using the LFPQ-fr task approximately 15 minutes prior provision of the afore described lunch test meal. The LFPQ-fr task was then completed again 15 minutes after their consumption of the lunch test meal. Informed consent was obtained from all participants as well as their legal

representatives prior to any study involvement. Data were extracted from clinical trials that received ethical approval from a local ethics committee (AU-1248; 2017-A00817-46; 2018-A02160-55; 2019-A00507-50; 2019-A00530-57; 2018-A02160-55; 2021-A02867-34), conducted in accordance with the principles outlined in the Declaration of Helsinki, and
205 prospectively registered (NCT02925572, NCT03807609, NCT03742622, NCT03967782, NCT03968458, NCT04739189, NCT05365685).

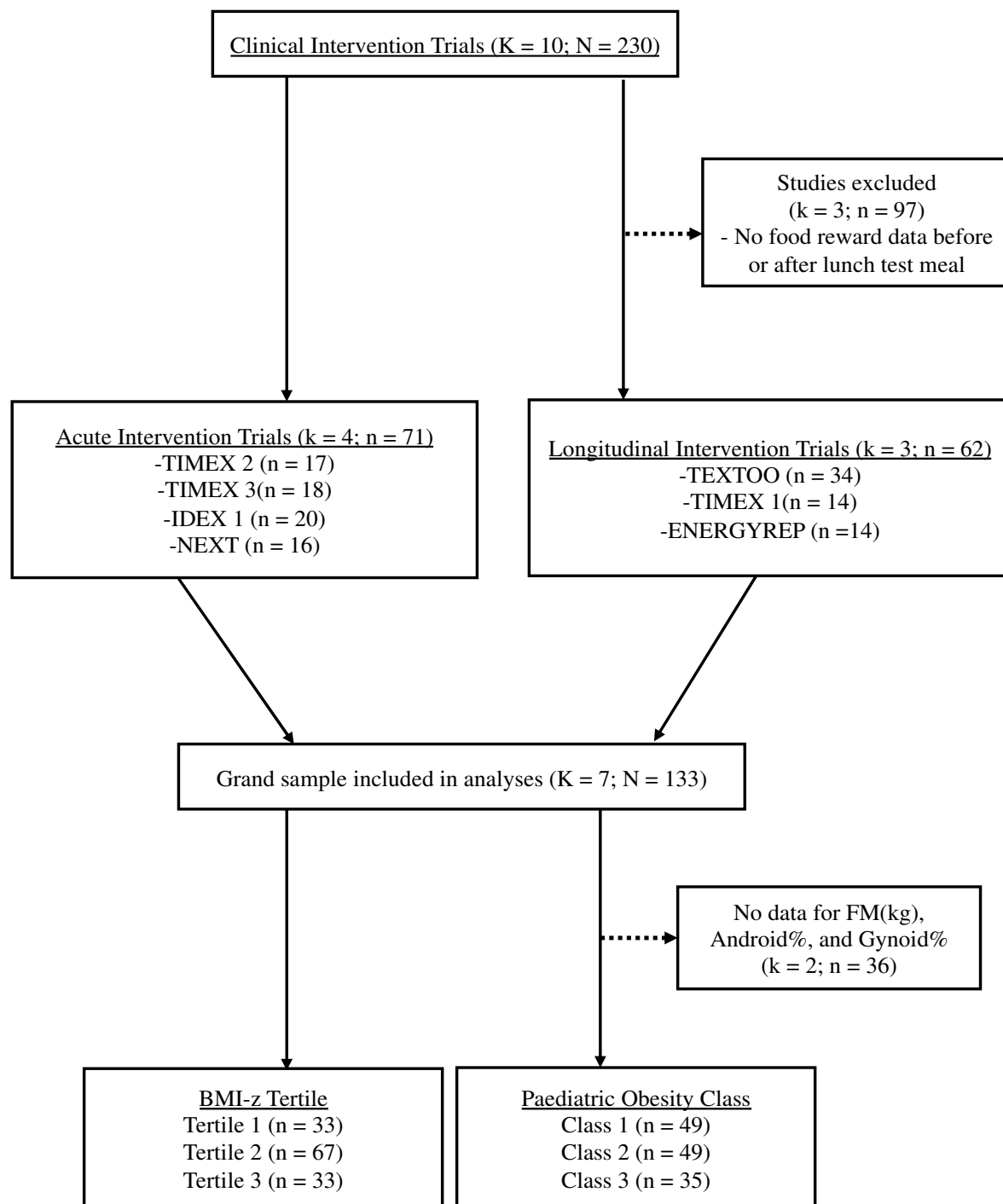


Figure 1. Flowchart illustrating the study selection process for the independent participant data meta-analyses. All studies from our laboratory with the appropriate data, population, and eligibility criteria were included in analyses and completed between 2016 and 2022. Data extracted from these studies were collected at baseline prior to commencement of any intervention. Categorical analyses were based on partitioning the grand sample into tertiles based on extended BMI-z scores [28] and paediatric obesity class based on extended BMI percentile scores updated in 2022 [30].

2.4. Statistical Analysis

This study utilised a one-stage approach to an IDP meta-analysis [37] of primary data extracted from seven studies in adolescents with obesity. Thus, all IDP was pooled in linear mixed effects models with ‘Study’ included as a random effect to account for participant clustering within studies. In line with recommendations from Legha and colleagues [38], a restricted maximum likelihood method of model estimation was applied with the Satterthwaite method of degrees of freedom estimation that better accounts for uncertainty of variance between studies and provides more conservative estimates of fixed effects. To comprehensively investigate the relationship between degree of obesity and food reward, models were constructed including BMI-z as a continuous and categorical predictor. For the latter, participants were split into tertiles by initially partitioning participants into quartiles by extended BMI-z score and combining the two middle quartiles, and the clinical obesity classes aforementioned. In the former analyses, curvilinear associations were also tested by including a quadratic term for BMI-z score.

Distinct models were tested with fasted and fed ratings of food reward by using baseline values alone and both pre- and post-meal scores, respectively. With regard to the latter, ‘State’ (fasted versus fed) was added as a fixed effect factor and ‘Subject’ as an additional random effect to account for the repeated measures within subject. All models were adjusted for sex and age. Significant main effects of obesity severity were probed using unstandardised regression coefficients and planned post hoc pairwise contrasts between partitions of the BMI-z term for fasted models and the ‘State’ by BMI-z interaction term in fed models in continuous and discrete analyses, respectively. Furthermore, FM (%) and FFM (kg) were entered into mixed effects models as sensitivity analyses to test whether the relationship between BMI-z score and food reward are moderated by key body composition metrics. Finally, exploratory partial correlations between food reward in fasted and fed states and key anthropometrics

without an alpha correction were extracted from linear mixed models, thus were adjusted for sex and age as fixed effects, and ‘Study’ as a random effect.

Checks for normal distribution of dependent variables and model-based residuals were undertaken using the Shapiro-Wilk test and visual inspection of histograms and QQ-plots.

245 Outliers beyond 3 *SDs* from the mean were winsorised. If necessary, log transformations of dependent variables were undertaken to ensure a normal distribution. Descriptive statistics were expressed as estimated marginal means and their standard errors or medians and interquartile ranges depending on statistical distribution. Along with descriptive and inferential statistics from the mixed models, tables included the intraclass correlation coefficient, indicating
250 between-study variance contributed to the model, and the marginal coefficient of determination (R^2), or the explanatory power of the fixed effects specifically, according to the method from Nakagawa and colleagues [39]. *P*-values were two-tailed and an alpha of 5% was used to determine statistical significance. Partial η^2 and Cohen’s *d* were used as estimates of effect size for omnibus fixed effects and pairwise contrasts, respectively, the latter being interpreted as a
255 negligible (0.2 or less), small (0.2 – 0.5), medium (0.5 – 0.8), or large effect (0.8 and greater) [40]. The Sidak method was applied to all pairwise comparisons to adjust for multiple tests. Analyses were conducted in the R environment [41].

3. Results

3.1. Participants

260 Pooled baseline data were available for $N = 133$ adolescents with obesity aged between 10 and 15 years ($Mdn = 13.00$, interquartile range [IQR] = 2.00, 74 female). The sample size of the included studies ranged from 14 to 34 participants ($Mdn = 17.00$, IQR = 4.00). The pooled sample had a median extended BMI-*z* score of 2.51 (IQR = 1.01) with 79% of participants having a BMI-*z* score of 2 or greater, a level considered to determine
265 paediatric obesity [42]. Nearly all participants ($N = 130$) had a BMI at or above the 95th

percentile based on sex- and age-specific growth reference curves ($Min = 93.26$), another clinical cutoff indicating paediatric obesity ($M = 98.77$, $SD = 1.48$), and approximately three-fourths of the sample were considered to have severe obesity with a BMI at 120% or greater of the 95th percentile. In the present sample, 35, 49 and 49 participants were defined as having class 1, class 2, and class 3 obesity, respectively. Apropos of body composition, participants had a median FM of 39.50% (IQR = 6.90), also indicative of severe obesity, and a median FFM of 51.27 kilograms (IQR = 19.80). Furthermore, participants had an approximately equal percentage of Android ($M = 40.87$, $SD = 5.03$) and Gynoid ($M = 39.52$, $SD = 4.79$) FM. Anthropometric and body composition information by BMI-z tertile and paediatric obesity class are detailed in **Tables S1 and S2**, respectively (see the supplementary materials).

3.2. Fasted Food Reward and Obesity Severity

Descriptive and inferential statistics of fasted food reward in analyses with BMI-z as a continuous predictor are summarized in **Table S3** and by extended BMI-z tertile and paediatric obesity class in **Tables S4 and S5**, respectively (see supplementary materials). Explicit and implicit reward for fat tended to be positively associated BMI-z score when designated as a continuous or discrete predictor (**Figure 2A; 2C**). However, mixed effects analyses did not yield any statistically significant effects of BMI-z score nor differences between BMI-z tertiles or paediatric obesity classes after alpha corrections. Moreover, the curvilinear relationships between fasted fat bias scores and BMI-z score were also non-significant.

However, there was only a statistically significant, negative association between BMI-z score and implicit wanting sweet bias, such that a higher BMI-z score was associated with a lower bias for sweet foods when measured implicitly ($B = -9.69$ FWA units $[-17.23, -2.15]$, $p = .012$, $\eta p^2 = .06$; **Figure 2B**). Importantly, the corresponding curvilinear association did not reach statistical significance, indicating that this relationship may be more appropriately characterised as linear ($B = -4.55$ FWA units $[-9.24, 0.13]$, $p = .056$, $\eta p^2 = .03$). Whilst negative associations were observed for all other explicit and implicit sweet biases, these did not reach statistical significance. Conversely, no discernable dose-response pattern was revealed in bias for sweet in categorical analyses, and no significant differences between salient obesity degree categories were detected (all $ps > .25$). Overall, curvilinear models did not explain a significantly greater proportion of variance than linear models. Additionally, it is worth noting that results for fasted food reward were not materially different whether obesity severity was demarcated based on either BMI-z tertile (**Figure S1**) or paediatric obesity class (**Figure 3**).

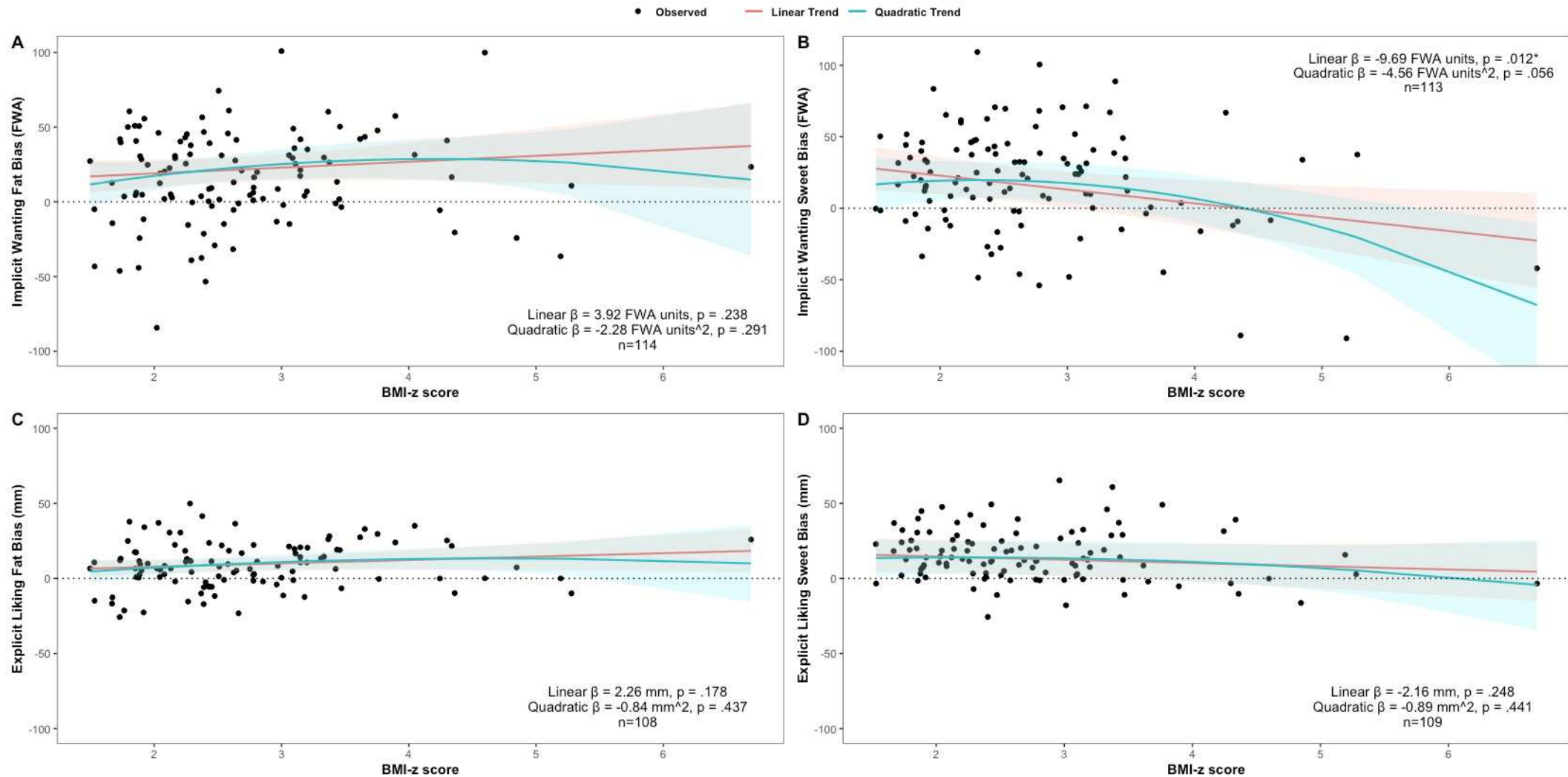


Fig. 2 Illustrations of fitted linear (red lines) and curvilinear (blue lines) associations between extended BMI-z score and Implicit Wanting Fat Bias (A), Implicit Wanting Sweet Bias (B), Explicit Liking Fat Bias (C), and Explicit Liking Sweet Bias (D) in a fasted state. Predicted values were derived from marginal (fixed) effects of the linear mixed models. Confidence bands indicate the 95% confidence interval. The dotted line represents a value of 0 indicating no preference. A positive value indicates preference for sweet (sweet bias) and high fat (fat bias) foods, and a negative value indicates preference for savoury (sweet bias) and low fat (fat bias) foods. Implicit wanting is expressed in frequency-weighted algorithmic (FWA) units and explicit liking in millimetres (mm), respectively.

*Significant at $p < .05$.

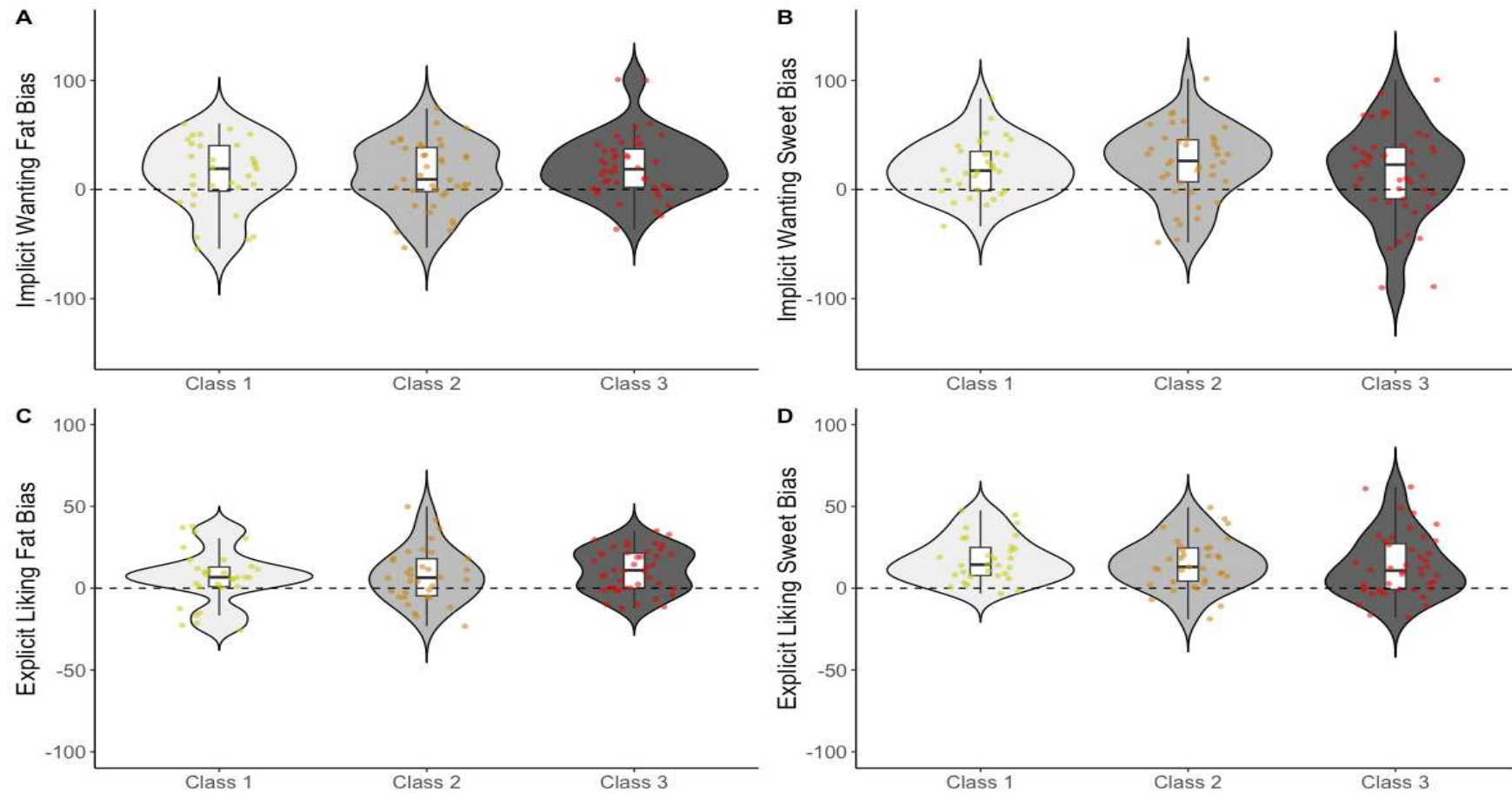


Fig. 3 Differences in Implicit Wanting Fat Bias (A) and Implicit Wanting Sweet Bias (B) in frequency-weighted algorithmic units, and Explicit Liking Fat Bias (C) and Explicit Wanting Sweet Bias (D) in millimetres between extended paediatric obesity classes when fasted. Paediatric obesity classes were based on the categorisations proposed by the American Academy of Pediatrics based on relative to the 95% BMI percentile [30]. Sample sizes for Class 1, Class 2 and Class 3 are $n = 35$, $n = 49$, and $n = 49$, respectively. The dotted line represents a value of 0 indicating no preference. A positive value indicates preference for sweet (sweet bias) and high fat (fat bias) foods, and a negative value indicates preference for savoury (sweet bias) and low fat (fat bias) foods.

3.3. Fed Food Reward and Obesity Severity

With regard to fat bias scores, there appeared to be divergent, albeit weak, trends depending on metabolic state such that BMI-z score was positively associated with explicit liking and implicit wanting fat bias scores when fasted, but negatively associated after a test meal. However, the state by BMI-z interactions terms did not reach statistical significance (**Figure 4A; 4C**). Indeed, metabolic state did not interact with any linear or curvilinear BMI-z terms to predict explicit or implicit bias for high fat foods (**Table S6**). In categorical analyses, it was observed that implicit wanting and choice frequency for high fat foods increased after meal consumption in the lowest obesity degree, but decreased in the other categories associated with more severe obesity on average (**Figure 5A**; also see **Tables S7 and S8** in the supplementary materials). Moreover, these trends were observed independent of repartition method (i.e., BMI-z tertiles or paediatric obesity class). However, differences between tertiles were not statistically significant after applying alpha corrections ($ps > .10$). By contrast, explicit preference for high fat uniformly decreased in all BMI-z tertiles after a meal as apparent from main effects of time in analyses of liking ($F(1, 105.89) = 4.81, p = .030, \eta p^2 = .04$; **Figure S2C**) and wanting ($F(1, 101.00) = 10.43, p = .002, \eta p^2 = .09$). Only the main time effect for explicit wanting was statistically significant in analyses with clinical obesity classes ($F(1, 100.25) = 8.34, p = .005, \eta p^2 = .08$), and no interactions with obesity degree were significant (all $ps > .20$).

Whilst no state by BMI-z interaction terms were significant for sweet bias scores as well, it is interesting to observe that, unlike trends observed for fat bias scores, similar trends were observed independent of metabolic state. Indeed, BMI-z remained significantly and negatively associated with implicit wanting for sweet foods in the linear model incorporating fed scores ($B = -9.90$ FWA units $[-18.07, -1.74], p = .018, \eta p^2 = .03$), but not the curvilinear model ($B = -4.38$ FWA units $[-9.54, 0.77], p = .095, \eta p^2 = .02$; **Figure 4B; 4D**). In line with

these trends, categorical analyses revealed that, whilst choice frequency for sweet foods invariably increased across BMI-z tertiles ($F(1, 110.63) = 4.93, p = .028, \eta p^2 = .04$), explicit wanting for sweet foods uniformly decreased post-meal ($F(1, 103.16) = 5.87, p = .017, \eta p^2 = .05$). A similar discordance in trends was observed between explicit liking and implicit wanting sweet bias, but the corresponding time effects were not statistically significant. Overall, these trends were also apparent in analyses of paediatric obesity classes specifically. As observed in analyses of continuous BMI-z, no significant state by obesity degree interactions were present in analyses of BMI-z tertiles and clinical obesity classes.

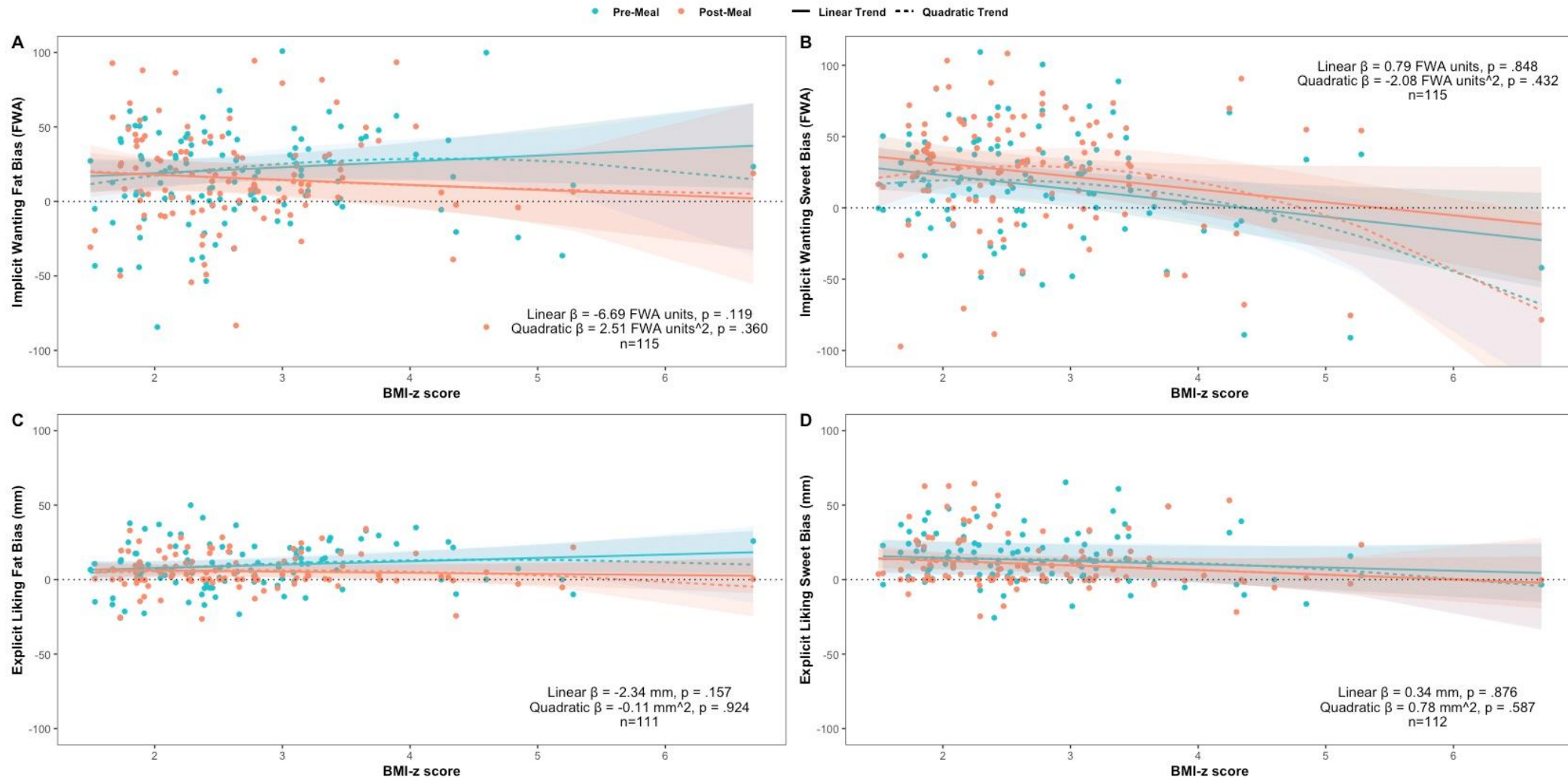


Fig. 4 Illustrations of fitted linear (solid lines) and curvilinear (dashed lines) associations between extended BMI-z score and Implicit Wanting Fat Bias (A), Implicit Wanting Sweet Bias (B), Explicit Liking Fat Bias (C), and Explicit Liking Sweet Bias (D) in fasted (blue lines) and fed (orange lines) states. Predicted values were derived from marginal (fixed) effects of the linear mixed models. Confidence bands for linear (darker) and curvilinear (lighter) trends indicate the 95% confidence interval. Regression coefficient estimates represent the BMIz*state interaction term. The dotted line represents a value of 0 indicating no preference. A positive value indicates preference for sweet (sweet bias) and high fat (fat bias) foods, and a negative value indicates preference for savoury (sweet bias) and low fat (fat bias) foods. Implicit wanting is expressed in frequency-weighted algorithmic (FWA) units and explicit liking in millimetres (mm), respectively.

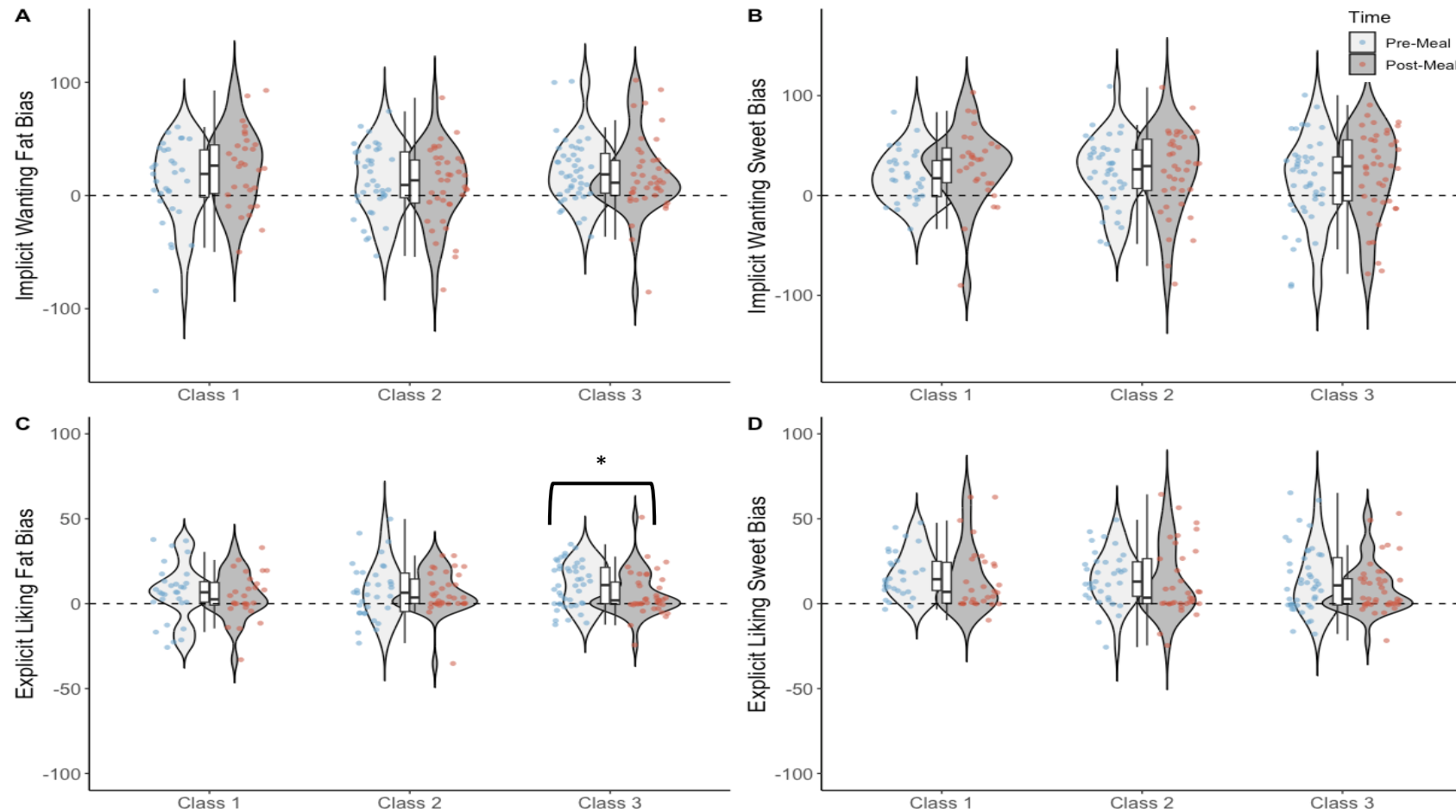


Fig. 5 Changes in differences in Implicit Wanting Fat Bias (A) and Implicit Wanting Sweet Bias (B) in frequency-weighted algorithmic units, and Explicit Liking Fat Bias (C) and Explicit Liking Sweet Bias (D) in millimetres by extended paediatric obesity classes after a test meal. Paediatric obesity classes were based on the categorisations proposed by the American Academy of Pediatrics based on relatively to the 95% BMI percentile [30]. Sample sizes for Class 1, Class 2 and Class 3 are $n = 35$, $n = 49$, and $n = 49$, respectively. The dotted line represents a value of 0 indicating no preference. A positive value indicates preference for sweet (sweet bias) and high fat (fat bias) foods, and a negative value indicates preference for savoury (sweet bias) and low fat (fat bias) foods. $*p < .05$.

3.4. Sensitivity Analyses: Fat Mass and Fat-free Mass

In sensitivity analyses with BMI-z included as a continuous predictor, the association of implicit wanting sweet bias when fasted and BMI-z was no longer statistically significant after the addition of FFM (kg) as a covariate. Rather, the independent association with FFM approached statistical significance ($B = 1.41$ FWA units $[-0.09, 2.90]$, $p = .065$, $\eta p^2 = .03$). Moreover, the FFM*BMI-z interaction term was statistically significant ($B = -0.52$ FWA units $[-1.00, -0.04]$, $p = .036$, $\eta p^2 = .04$), suggesting that the direction of the association between implicit wanting sweet bias and BMI-z was dependent on the level of FFM (i.e., becoming negative with higher FFM). Whilst this interaction did not maintain significance independent of metabolic state in the analysis of implicit wanting sweet bias ($B = -0.50$ FWA units $[-1.03, 0.03]$, $p = .064$, $\eta p^2 = .02$), an interaction independent of state was present in the model assessing choice frequency for sweet foods ($B = -0.16$ N $[-0.32, 0.00]$, $p = .047$, $\eta p^2 = .03$). FM and FFM did not significantly moderate any other associations between BMI-z and food reward.²

3.5. Exploratory Correlations: Body Composition and Food Reward

Heatmaps of partial correlations between key body composition and food reward metrics are displayed in **Figure 6**. With regard to food reward when fasted, percent Android FM was positively and significantly associated with both implicit wanting ($r(74) = .26$, 95% CI: .03, .45) and explicit liking fat bias ($r(68) = .34$, 95% CI: .11, .52), although percent Gynoid was only significantly associated with explicit liking fat bias ($r(68) = .30$, 95% CI: .07, .49). Interestingly, absolute (in kg) but not relative FM was also positively correlated with implicit wanting ($r(75) = .25$, 95% CI: .02, .44) and explicit liking ($r(69) = .24$, 95% CI: .00, .44) fat bias scores. Conversely, FFM (kg; $r(108) = -.20$, 95% CI: -.37, -.01), BMI ($r(108)$

² For sensitivity analyses involving models with BMI-z as a categorical predictor, see section S1 of the supplementary materials.

= -.22, 95% CI: -.38, -.03), and BMI-z ($r(108) = -.24$, 95% CI: -.40, -.05) was negatively associated with implicit wanting for sweet. No other notable associations with fasted reward measures were evident (see **Tables S9 and S10** for complete correlation matrices with fasted and fed food reward, respectively).

Contrary to results when fasted, a negative association was detected between percent FM and implicit wanting fat bias after a test meal ($r(105) = -.20$, 95% CI: -.37, -.01). This association was similarly reflected with absolute FM and percent Android FM, but these fell below the significance threshold. Interestingly, association of similar magnitude and direction were not observed in explicit liking fat bias scores. Although explicitly and implicitly assessed bias for sweet remained negatively associated with anthropometric characteristics when in a fed state, only the association between choice frequency sweet bias and BMI-z could be considered statistically significant ($r(108) = -.20$, 95% CI: -.37, -.01).

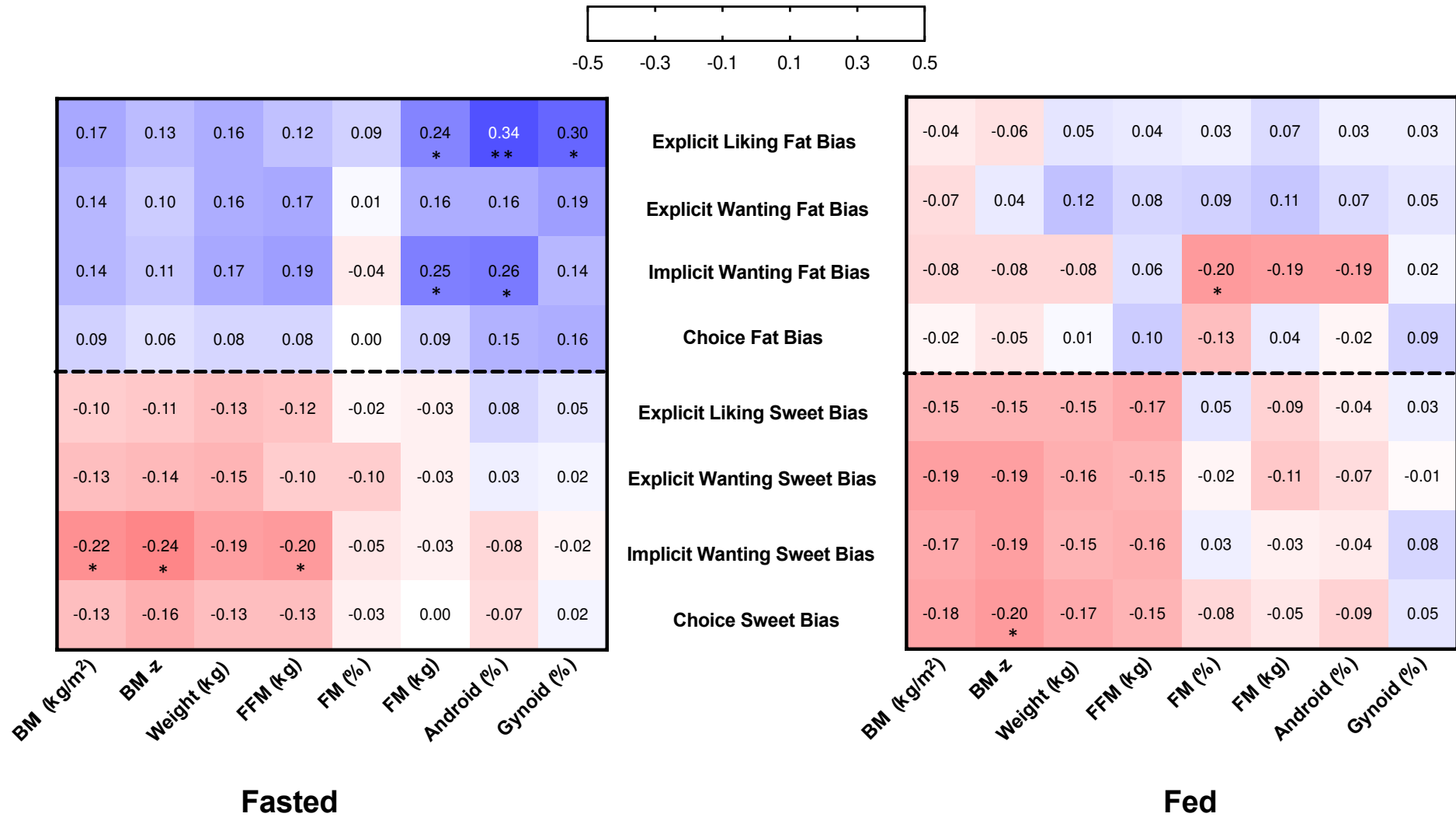


Fig. 6 Heatmaps of exploratory correlations between anthropometric measures and food reward in a fasted state (left) and after a lunch test meal (right). Partial correlations were extracted from linear mixed models, thus were adjusted for age and sex as fixed effects, and study as a random effect. The darker the colour, the stronger the relationship. Significance thresholds based on unadjusted familywise error rates for multiple comparisons. BMI = body mass index. FM = fat mass. FFM = fat free mass. Kg = kilograms. M = metres. * $p < .05$; ** $p < .01$.

4. Discussion

The primary aim of the present IDP meta-analysis was to examine several cohorts of adolescents with varying degrees of obesity severity on their explicit and implicit responsiveness to palatable, energy-rich food cues in fasted and fed metabolic states. The potential implications of this investigation are three-fold. First, the associations between hedonic appetite and different degrees of obesity severity in children could be simultaneously characterised. Second, if there was heterogeneous expression of food (cue) reactivity, this may be of importance for guiding more precise or nuanced strategies for the clinical management and prevention of obesity. Finally, the association between food reward and adiposity may be more robustly and comprehensively explored through alternative approaches to metabolically phenotyping individuals that extend beyond BMI, such as through salient body composition metrics (i.e., FM, FFM, visceral fat, fat distribution) [43]. In the present study, the expected negative associations with adiposity were only observed with sweet bias outcomes when fasted, particularly when measured as implicit wanting, in partial support of Hypothesis 1A. Contrary to Hypotheses 1B, metabolic state did not significantly moderate the relationship between food reward and obesity degree, with obesity degree significantly predicting implicit wanting for sweet foods independent of state. Overall, these findings provided tentative support for a linear and negative relationship between food reward and obesity severity when measured as implicit wanting for sweet foods. Rather, fat mass and its distribution may have a more prominent role in the strength of both explicit and implicit preference for high fat (i.e., energy-dense) foods (Hypothesis 2).

Methodological approaches to measuring reward-related cognition and appetite must be considered when interpreting these results. As in the present study, different approaches are typically taken to operationalise reward-based constructs such as liking and wanting in the literature, which limits a definitive synthesis of findings across studies [7]. Results from

analyses of fed food reward in this study may be relevant to the discussion of how to measure reward and under what contexts [44]. Specifically, the trends in preference for sweet after a test meal severity appeared to depend on whether food reward was measured implicitly or explicitly. Implicit wanting, but not explicit liking or wanting, for sweet food cues was negatively associated with adiposity. Moreover, stronger exploratory associations were mainly detected between adiposity and implicit, but not explicit, preference for sweet foods. Similarly, fasted preference for sweet appeared to be inversely related to FFM, but only when assessed implicitly. When considering these findings, it is important to note that previous studies have found behavioural and neural responses to food cues can be associated with weight independent of the expression of liking [45]. An exploratory study by Fearnbach and colleagues [22] found an association between food reward and FFM in children when utilising neuroimaging techniques to measure food cue sensitivity. Similarly, FFM moderated the association between sweet bias and obesity degree in the present study, but only when measured implicitly. It is also important to note that measures of explicit liking and implicit wanting, albeit related, may be associated with different effect sizes, thus a lack of detection in the former may be due to an insufficient sample size. Taken together, it is important for researchers and clinicians to account for the choice of pertinent reward-related construct and the corresponding measurement method when investigating associations between obesity and food reward in this population, and designing appropriate studies to do so.

Food cue reactivity, a construct putatively targeted in the present study, is a behavioural manifestation denoting food reward that may be associated with other salient traits or characteristics in addition to obesity. Indeed, other constructs, such as binge eating, disinhibited eating, or dietary restraint, have been measured by myriad questionnaires and other assessment tools with varying degrees of association with energy intake and BMI [46]. Thus, although the relationship between food reward and obesity severity appears to be

limited in this study, this does not necessarily preclude the potential usefulness of applying other dietary constructs or traits when phenotyping youth with, or at risk for, obesity. Indeed, certain dietary traits may mediate the relationship between food reward and obesity severity (or body composition), which was not tested in the present study. As demonstrated by previous studies, the complexity of obesity and its aetiologies becomes evident through mediation models that highlight interactions between obesity and dietary restraint [47,48], or trait binge eating [20], or trait food cravings [19] when attempting to predict food reward responses via behavioural metrics or neuroimaging techniques. Such a model is indicative of the hypothesis that certain predispositions, perhaps genetically or epigenetically derived, likely interact with a multitude of environmental factors to facilitate or impede a pathway to obesity development, and such interactions are likely dynamic over time rather than monotonic [49]. Such a multitude of variation in circumstances related to dietary behaviour represents substantial noise from which detect independent associations, thus more complex models are likely warranted when statistical power permits.

It is critical to acknowledge the lack of lean and overweight comparator cohorts when interpreting the present results. Indeed, all adolescents analysed in the present study were near or above both established clinical thresholds indicating obesity. Therefore, it is plausible to hypothesise that disparities in food reward responsivity may become more pronounced when comparing low (lean), moderate (overweight) and high (obesity) adiposity levels. Findings from the meta-analysis by Morys and colleagues [18] did detect differences in neural activity to food cue presentation between healthy weight children and those with obesity, and another recent study by Darcey et al. [24] found a negative and linear relationship between dopamine binding potential and BMI with the inclusion healthy- and over-weight participants. In the present study, the main effect of obesity degree independent of metabolic state in predicting implicit wanting for sweet foods partially supports such a linear model. Yet, it remains

unclear how the trends observed in the current study may have differed with comparator groups representing lower levels of adiposity, thus neither a linear nor a quadratic model can be conclusively supported when considering a complete spectrum of adiposity. Relatedly, whilst Horstmann and collaborators [23] provide a useful model by which to understand the adaptations of dopaminergic activity along the spectrum of obesity severity (i.e., none, mild, and severe), the aggregated evidence presented pertains specifically to adults, and the lack of adolescents without obesity in our analysis impede appropriate comparisons. Indeed, the salient differences in food cue reactivity between adults and children [e.g., 8,18] limit the extrapolation of such models to a young population undergoing significant neurobiological change [50]. Nevertheless, it is interesting to consider potential physiological mechanisms that may facilitate alterations in dopaminergic tone and reward-related behaviours in both youth and adults. Horstmann and colleagues [23] suggest that the onset of leptin and/or insulin resistance, which also occurs in youth, may facilitate changes in dopamine availability due to their modulatory effects on dopamine release in reward-related brain regions. Ultimately, the inclusion of healthy- and overweight cohorts would expand the present analysis to form a full spectrum of adiposity by which to detect potential linear or curvilinear associations with food reward.

Finally, it is worth pointing out the contrast in findings from analyses of sweet and fat biases in this study. Notable associations between the latter and body composition was limited to exploratory positive correlations with FM and its distribution. The present results, taken together, appear to challenge the conclusions by Cox and colleagues [15] that found a relationship between weight status and fat hedonics, but not sweet hedonics, in children. However, there was evidence to suggest a stronger preference for salty tastes in children with obesity relative to their lean peers, which could be consistent with the reduction in bias for sweet (i.e., elevated bias for savoury) as a function of adiposity observed presently, but the

absence of a lean cohort in the present study limits such a synthesis. Alternatively, Overberg et al. [16] observed the diminution of sensitivity to tastes, including sweet, in adolescents and children with obesity relative to their lean peers, which could be related to the effects on implicit wanting sweet bias observed here. In support of this hypothesis, previous work has demonstrated positive associations between sensitivity to sweetness and neural activation of hedonic hotspots in response to odours from, and preference for, sweet foods [51]. Therefore, at least in a paediatric population, predilection for sweet, rather than high fat, may represent a stronger reward-related signal that was detectable given the sample size of the present study, although both were found to be relatively modest. Conversely, an exploratory study by Hardikar and colleagues [52] observed that adults with obesity were more sensitive to sweet and salty tastes than lean adults. Whilst these results appear to contradict the Overberg et al. [16] study, this could further indicate that distinctions ought to be considered on the basis of age when examining relationships between reward and adiposity. Moreover, it is important to note that the present study does not challenge the existence of a relationship between adiposity and bias for high fat or energy-dense foods. Indeed, the positive associations between FM and explicit and implicit bias for high fat may provide tentative evidence to be further explored, and underscore the importance of including measures of body composition and adiposity beyond BMI. Therefore, it would be of great interest to reproduce the present analysis with a non-obese cohort to precisely track the evolution of different reward-related mechanisms along a full spectrum of adiposity in children.

4.1. Strengths and Limitations

One strength of the present analysis is the application of the current extended age- and sex-specific BMI growth charts recently released by the CDC [28] to calculate BMI-z scores and BMI percentiles, and repartitioning of the sample into tertiles and established clinical thresholds based on both. However, we observed no significant differences in results based on

approach to repartition method. Another strength was the homogeneity of methods used in the included studies that limited error variance from extraneous factors and thus improved the power to detect a potential effect. For example, all studies employed similar approaches to recruitment and experimental procedures, were conducted by the same investigators at a similar time of year, and all adolescents were in the initial clinical stage prior to treatment. This was borne out statistically by the relatively low intraclass correlations associated with the study factor in all analysis.

However, there were notable limitations. Primarily, studies included in this meta-analysis were derived from the same laboratory and not a systematic review of the literature. Therefore, the observations detailed in this study may not be representative of those from the wider literature. Another limitation apropos of the analyses of fed food reward was the provision of either fixed or *ad libitum* test meals across studies, which may have influenced the mean food volume consumed by participants in each study. Although this may be considered a potential confounder, our lab has recently shown that food reward may not be significantly influenced by the caloric volume of similarly composed meals when protein content is held constant [53]. With regard to outcomes related to fat distribution (i.e., Android/Gynoid), data was only available for five of the seven studies included in this analysis, which resulted in a much smaller percentage of available data relative to the entire sample. Thus, comparisons of analyses with these outcomes and other anthropometrics with more complete data (i.e., FM, FFM) should be treated with particular caution. Importantly, the studies included in the present analysis were not designed and powered *a priori* for this specific research question. Relatedly, the strength of associations observed may have been diminished due to the exclusive focus of adolescents with obesity, thus could signal a type 2 error. Finally, no type 1 error correction was applied to the correlation analyses, thus indications of statistical significance should be interpreted with caution. However, those

analyses were exploratory in nature and intended to provide an indication or description of potential relationships that may be investigated further in future research.

4.2. Conclusions

The present study utilised an IDP meta-analytic approach to a secondary analysis of seven individual trials involving adolescents with obesity, a challenging demographic to recruit for scientific investigations. The associations between obesity severity (i.e., mild to severe), body composition, and both explicit and implicit reward responsivity to high fat and sweet food cues were examined in distinct physiological states (i.e., fasted and fed). Overall, relationships between obesity severity and food reward in this demographic was modest in size and limited. Although the trends in food reward for high fat observed when fasted by obesity degree were in the expected direction, associations did not reach significance. Rather, FM, and the distribution thereof, may play a more significant role in the strength of bias for energy-dense or high fat foods, but conclusions should be drawn with caution due to the relatively smaller samples with availability of these data. Contrary to expectations, sweet bias was negatively associated with adiposity, and the linear relationship was modest, but significant for implicit wanting, suggesting that desensitisation of sweet tastes and a concomitant reduction in bias for them may be consequences of severe adiposity in youth. Moreover, FFM could have a role in determining this effect on sweet bias, but more suitably designed research is needed to clarify the nature of this role. Whilst bias for sweet appeared to better fit the model by Horstmann et al. [23], inclusions of a lean comparator cohort and other neuroimaging and tonic-oriented measures are needed to adequately test a quadratic model of reward and adiposity. Obesity may be more appropriately described as a heterogenous condition with varying aetiologies and contributing factors, an acknowledgement that could benefit clinical, personalised approach to treatment.

Statements and Declarations

Competing Interests

The authors declare that they have no conflict of interest.

Ethics Statement

The primary clinical trials that produced the data for the present study received Ethics approval by independent university review board and were conducted in accordance with the principles laid out by the 1964 Declaration of Helsinki and its later amendments. All parents or guardians provided their informed consent prior to their children being included in each study.

Author Contributions

HM and DT designed the analysis; DT, AF, MM, and JM conducted the research; DT provided essential reagents, or provided essential materials; HM and BP analysed the data; HM wrote the paper; GF and KB reviewed the paper and provided essential feedback; HM had primary responsibility for final content; All authors have read and approved the final manuscript.

Data Availability

Relevant data described in the manuscript will be made available upon reasonable request pending approval from relevant stakeholders.

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