#### 1 Review

# A biopsychosocial model of sex differences in children's eating behaviors

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11 Abstract: The prevalence of obesity and eating disorders varies by sex, but the extent to which sex 12 influences eating behaviors, especially in childhood, has received less attention. The purpose of this 13 paper is to review the literature on sex differences in eating behavior in children and present new 14 findings supporting the role of sex in child appetitive traits and neural responses to food cues. In 15 children, the literature shows sex differences in basic taste response, food acceptance, eating self-16 regulation, and appetitive traits. New analyses demonstrate that sex interacts with child weight 17 status to differentially influence appetitive traits and neural responses to food cues. Further, 18 neuroimaging results suggest that obesity in female children is positively related to brain reactivity 19 to higher-energy-dense food cues in regions involved with learning, memory, and object 20 recognition, while the opposite was found in males. In addition to differences in how the brain 21 processes information about food, other factors that may contribute to sex differences include 22 parental feeding practices, societal emphasis on dieting, and peer influences. Future studies are 23 needed to confirm these findings, as they may have implications for the development of effective 24 intervention programs to improve dietary behaviors and prevent obesity.

25 Keywords: sex differences; eating behavior; food intake; biopsychosocial; children; brain imaging

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### 27 Introduction:

28 Sex and gender are important characteristics that contribute to individual variability in the 29 development of disordered eating and obesity, but the extent to which they impact eating behaviors 30 in children is less clear. It has been suggested that sex differences in eating behavior arise in 31 adolescence because of the physiological changes and sociocultural pressures experienced during this 32 developmental period. Prior to adolescence, sex-based influences on eating behavior have been 33 thought to be minimal. However, there are both biological (e.g., sexual dimorphic patterns of in utero 34 neural development, sex chromosome effects) and psychosocial (e.g., parental feeding practices, 35 societal body ideals) factors that may affect the way children eat prior to puberty. Despite these 36 potential influences, this period of development has received little attention in the literature. Because 37 of the sex differences that occur in the prevalence of both disordered eating <sup>1-3</sup> and obesity <sup>4,5</sup>, there is 38 a need to understand the role of sex in the development of behaviors involved with the etiology of 39 these diseases prior to puberty. To call attention to this gap in the literature, this paper will review 40 the extant literature and present new data demonstrating that sex differences in eating behavior arise 41 prior to puberty and have effects on children's appetitive traits and neural responses to food cues.

The National Academy of Sciences has outlined rationale for when sex differences should be studied <sup>6</sup>. Several of their criteria apply to eating and weight disorders and therefore are relevant to the current paper. The first criterion is if there are known sex differences in the prevalence or incidence of a disease. Globally, the prevalence of obesity is higher in females than males across all

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46 income groups 4 and eating disorders occur nearly 8 times more frequently in females than males 1-3. 47 These striking statistics provide support for studying the role of sex in eating behaviors because they 48 are integral to the development of these conditions. Another criterion outlined in this report is if there 49 are known sex differences in disease severity, progression, or outcome. In the case of obesity, there 50 are well-described differences in body composition, with adult males carrying fat around the 51 abdomen and chest (i.e., visceral adipose tissue), which is associated with higher metabolic risk, while 52 pre-menopausal adult females are metabolically protected by accumulating fat in the lower 53 extremities <sup>7,8</sup>. In addition, males tend to have more fat free mass than females. These differences are 54 present throughout development and become more robust at puberty<sup>9</sup>. Furthermore, symptomology 55 associated with binge eating (i.e., frequency, level of distress) is more severe in females relative to 56 males on average. A final criterion suggested in the report is if sex influences the success or outcome 57 of interventions <sup>6</sup>. In both children <sup>10</sup> and adults <sup>11</sup>, males tend to be more responsive to weight loss 58 interventions than females. With the potential promise of personalized medicine for treatment of 59 complex diseases like obesity, understanding how sex influences response to treatment could 60 highlight novel therapies that could specifically be targeted to males or females.

61 Before reviewing the literature, it is important to note that much of the research in this area has 62 not distinguished between the constructs of "sex" and "gender". Sex refers to the biological 63 classification of male or female according to chromosomes and reproductive organs. Gender, on the 64 other hand, refers to one's self-representation, which is influenced by sociological and cultural factors 65 <sup>12</sup>. Often one's biological sex matches with self-assigned gender, but this is not always the case. The 66 multitude of factors influencing both sex and gender have made the study of individual differences 67 between males and females complicated. Because we are applying a biopsychosocial framework to 68 describing sex-effects on eating behavior, we will include discussion of biological factors more likely 69 to influence sex and social and psychological factors more likely to influence gender. However, as 70 most prior studies do not clarify whether they distinguished between the two constructs when 71 collecting participant data, it is not possible to make clear distinctions about how the terminology is 72 used when referring to these studies. In order to avoid switching between "sex" and "gender" 73 throughout the paper, we will use the term "sex" as a combined term that includes not only biological, 74 but also social and psychological influences.

75 The goal of this paper is to review the literature and present new analyses supporting differential 76 eating behavior characteristics among male and female children. We will also review potential 77 mechanisms that drive these differences using a biopsychosocial framework to guide the discussion. 78 "Eating behavior" will be used as an umbrella term that encompasses children's oral sensory 79 responses, food acceptance, food intake patterns, eating self-regulation, appetitive traits, and meal-80 specific microstructural patterns (e.g., bite rate, eating speed). Additionally, to avoid the inclusion of 81 effects on eating behavior that could be influenced by the physiological and hormonal events related 82 to puberty, to the extent possible, the literature search will focus on children age 11 years and under, 83 although it is recognized that this may not fully eliminate pubertal influences. Due to the paucity of 84 evidence in some sections, however, we have included a few studies that report on an age range 85 beyond 11 years, although we recognize that the results may be driven by pubertal development. 86 Within the age group of children discussed, infants will be defined as < 1 year, toddlers will be 87 defined as age 1-2 years, preschool children will be defined as 3-5 years, and middle childhood will 88 include ages 6-11 years.

#### 89 1. Evidence of sex differences on eating behavior in children

90 The first section of the paper will review evidence for sex differences in childhood eating 91 behaviors. Based on our general use of the term "eating behavior," this section will be divided into 92 studies that have examined sex differences in oral sensory responses to taste and flavor, food 93 acceptance, food intake, eating self-regulation, appetitive traits, and meal-specific microstructure.

94 1.1. Sex differences in oral taste responses:

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95 Taste is a primary driver of food intake <sup>13</sup>, therefore, understanding the role of sex in perception 96 and liking of the basic tastes (i.e., bitter, umami, salt, sweet, sour) may have implications for the 97 development of targeted interventions to improve childhood nutrition. Some studies have found that 98 males and females differ in their response to the basic tastes as early as infancy. For example, human 99 newborn females have shown increased acceptance of sweetened formulas compared to males 14, 100 suggesting that differences in taste-guided behaviors may occur early in development. Despite these 101 observations, other studies in newborns have found no sex differences in response to basic tastes, 102 including sweet <sup>15-17</sup>. Sex differences may arise, however, as children grow older because female 103 children and adolescents tend to have lower thresholds for sucrose than males <sup>18-20</sup>. Heightened taste 104 sensations in females may persist across development as female adults are more likely to be classified 105 as "supertasters" of the bitter thiourea compound 6-*n*-propylthiouracil (PROP). This is potentially 106 due to greater density of fungiform taste papillae in females compared to males <sup>21</sup>. However, sex 107 differences in taste anatomy <sup>22</sup> and ability to taste PROP <sup>23</sup> have not been reported in children. Other 108 studies have found that females (ages 6-18 years) are better at identifying taste qualities than males, 109 although no differences were reported in taste intensity ratings <sup>24</sup>. Males tend to like sweeter 110 concentrations of sucrose and lactose than females <sup>19,25</sup>, possibly because females have demonstrated 111 greater taste sensitivity than males across development. Together, these studies suggest the 112 possibility of innate sex differences in the response to basic taste stimuli that may influence hedonic 113 ratings.

114 In addition to sex differences in response to the basic tastes, there may also be differences in how 115 taste perception relates to more complex behaviors like food acceptance and intake. For example, 116 female preschool children who were non-tasters of PROP had higher liking of full-fat milk and 117 reported greater parentally reported intake of discretionary fats (i.e., salad dressings, toppings, and 118 spreads) than males <sup>23</sup>. Similarly, while male non-taster children reported greater intake of soy-119 containing foods than males who were tasters, the relationship was opposite in females <sup>26</sup>. Because 120 there is no difference in taste anatomy (i.e., fungiform papillae)<sup>22</sup> or bitter taste sensitivity reported 121 in children, the observed sex differences in the relationship between PROP status and diet suggest 122 that environmental influences on feeding (e.g., parental feeding practices) might drive these reported 123 sex differences. This will be discussed in more detail in the second part of the paper.

#### 124 1.2. Sex differences in food acceptance/preference:

125 The impact of sex on liking and perception of basic tastes suggests there may also be sex 126 differences in food acceptance (i.e., hedonic response measured independently of another 127 food/beverage) or preference (i.e., hedonic ranking of a food/beverage compared to other options)<sup>27,</sup> 128 <sup>28</sup>. Cooke and colleagues <sup>29</sup> found that females (ages 4-7 years old) liked a greater number of foods 129 than male children. With regards to specific foods or food groups, studies including children from 130 various countries have consistently shown that females rate liking of fruits 29-32 and vegetables 29-35 131 higher than males, while male children report higher liking for meat, fish, poultry, and high-fat foods 132 compared to females <sup>29-31, 36</sup>. Furthermore, male children in middle childhood have higher acceptance 133 of fatty and sugary foods <sup>29</sup> and foods and beverages characterized as "unhealthy" (e.g., sweet snacks, 134 savory snacks, sugar sweetened beverages) compared to female children <sup>31</sup>. Additionally, as children 135 grow older, females tend to increase liking for vegetables <sup>33</sup> while males tend to increase liking for 136 meat products <sup>29</sup>.

137 While the aforementioned studies demonstrate sex differences in food acceptance in middle 138 childhood, studies in toddlers and preschool-aged children have shown no differences 37 38. However, 139 it is not clear if null findings are in part due to a lack of sensitivity in the methods available to measure 140 liking in preschool children (i.e., hedonic facial scales, parental report). In summary, these results 141 demonstrate that females in middle childhood typically like or prefer foods that are often regarded 142 as lower in energy, but nutrient dense, such as fruits and vegetables, whereas males tend to like 143 meats, meat products, and foods high in fat and sugar. The sensory and/or nutritional characteristics 144 of the foods that drive these sex-effects are not known.

#### 145 1.3. Sex differences in food intake:

146 As liking and preference are primary determinants of what children eat <sup>39,40</sup>, it is likely that sex 147 also influences children's dietary intake. This is especially apparent for fruits and vegetables <sup>39</sup>. In 148 children as young as 2 years, intake of vegetables 41-44, fruits 35, 42, 43, 45 and fruits and vegetables 149 combined <sup>42,46-48</sup> is higher among females than males. Female children have similarly reported greater 150 intake of foods classified as "healthy" and lower intake of "unhealthy" foods when compared to 151 males <sup>43</sup>. Since these studies used self- and parentally-reported measures of food intake, there is 152 potential for response bias as fruit and vegetable intake is a socially desirable behavior. However, 153 studies that have used more objective assessment methods in schools have also observed that female 154 students are more likely to consume from a salad bar than males 49, 50. The alignment with 155 observational data strengthens the findings from questionnaires, suggesting that female children 156 tend to consume more fruits and vegetables than males.

157 In addition to fruits and vegetables, self-reported intake of other foods and food groups also 158 varies by sex. In cohorts of European children, males report consuming more sugar and sweets 47, 51, 159 breakfast cereals, full-fat milk, meats/meat products, and baked beans while females consumed more 160 oily fish, eggs, and cheese 47. In the United States, male children tend to have higher intake of most 161 food groups, as well as higher overall energy intake 48,52, although overall variety of foods consumed 162 tends to be higher in females <sup>53</sup>. This finding supports the previously discussed observations that 163 found females also liked a greater number of foods than male children <sup>29</sup>. Although these studies 164 provide support for the notion that sex differences in eating behavior arise in childhood, not all 165 studies agree <sup>38, 54</sup>. Inconsistencies across studies could be due to variability in how dietary intake is 166 measured (e.g., 24-hour recall, food frequency, direct observation), who is reporting dietary intake 167 (e.g., parent vs. child), and the age and cognitive abilities of the child being studied <sup>55</sup>. There is a need 168 to conduct more observational studies where food intake is directly measured to confirm sex-effects 169 on reported intake in children.

#### 170 1.4. Evidence of sex-effects on eating self-regulation in children:

171 Self-regulation is a multi-dimensional construct referring to one's ability to manage thoughts, 172 actions, and emotions in favor of reaching a desired goal 56, 57. Poor self-regulation early in life has 173 been associated with negative health outcomes in adulthood 58, including obesity 59,60. Sex differences 174 in self-regulation, assessed by the delay of gratification task, were first reported by Mischel and 175 Underwood <sup>61</sup> who found that female preschool children could wait longer to receive a tasty treat 176 (i.e., a marshmallow) than male children. A more recent meta-analyses that included both children 177 and adults also confirms females show better delay of gratification for food than males <sup>62</sup>. The early 178 emergence of sex differences in self-regulation suggests that observed differences in children's eating 179 behaviors may in part be related to differences in the ability to adhere to dietary goals more broadly.

180 Related to the broader concept of self-regulation is eating-related self-regulation, or the ability 181 to begin and end an eating event in response to internal cues of hunger and fullness <sup>63</sup>. While the 182 extent to which these two constructs are related has been debated, it has been suggested that eating 183 self-regulation is a domain-specific manifestation of broader self-regulatory capacity <sup>64</sup>. Based on this 184 apparent relationship, we might expect to see better eating self-regulation in female relative to male 185 children. However, in studies that have assessed eating self-regulation using the compensation 186 protocol, this has generally not been the case 67, 68, 70, 71. Compensation or preloading trials are typically 187 done using a crossover design where children consume appetizers or 'preloads' on two separate 188 visits. These preloads are matched for taste, sensory characteristics, and often volume, but are 189 covertly manipulated to vary in energy density (kcal per weight or volume of food or beverage) 190 and/or macronutrient content. Participants are compelled to finish the preload and are served an ad 191 libitum meal some time later (often 25-30 minutes with children) to measure consumption. Children 192 who have "good" energy compensation can adjust their intake at the subsequent meal based on the 193 energy content of the preload <sup>65, 66</sup>. Poorer compensation ability has been associated with higher 194 weight status in children 67-69, suggesting that performance on this measure may generalize to eating 195 regulation more broadly. Several studies that have used this protocol in preschool children found

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that males have better energy compensation than females <sup>67, 68, 70, 71</sup>, which is consistent with studies in adults <sup>72, 73</sup>. Notably, other studies in preschool children do not report sex differences <sup>74, 75</sup> <sup>76</sup> and the individual variability in this measure is poorly understood. Of note, all the studies that have found that males compensate better than females have used beverages as a preload, raising the possibility that sex differences in energy compensation are specific to the ability to regulate calories in liquid rather than solid form.

202 The notion that sex differences around eating self-regulation are specific to beverages is further 203 supported by studies that have tested the effect of varying the energy density of a beverage served 204 within a meal. Whereas the traditional preloading study measures "satiety" by testing the extent to 205 which a preload or snack delays hunger at the following meal, serving a beverage within a meal 206 captures "satiation" by determining the effect of varying energy content on total meal intake. Kling 207 and colleagues <sup>77</sup> tested the effect of varying the energy density (ED) of milk on satiation by 208 conducting a crossover study where either lower- (1% fat) or higher- (3.25% fat) ED milk was served 209 to children with a typical preschool meal served in a childcare setting. When the higher-ED milk was 210 served, males decreased their intake of the other meal items, whereas females did not. Thus, 211 compared to males, females were less accurate at adjusting their intake to account for additional 212 energy consumed from the higher-ED milk. These sex differences were independent of possible 213 confounders, including the type of milk children consumed at home, child age and body size, milk 214 liking and preference ratings, children's appetitive traits, and parent feeding practices. The consistent 215 pattern of sex differences observed in both satiety and satiation studies challenges the notion that 216 compensatory responses are solely due to the delay between the preload and subsequent meal that 217 allows for the release of sensory and nutrient signals that influence fullness. Other possible 218 explanations of these sex differences are differences in the response to food sensory properties <sup>23</sup>, 219 social expectations placed on males and females 78, or sex-effects on meal time behaviors 79. 220 Additionally, subtle differences in children's body composition present prior to puberty 9 could also 221 promote males' advantage at energy compensation as fat free mass is the primary determinant of 222 metabolic rate and, hence, energy needs. However, these speculations require further investigation 223 to confirm.

#### 224 1.5. Sex differences in child appetitive traits and Eating in the Absence of Hunger:

225 Several studies have investigated whether there are sex differences among other appetitive traits 226 assessed by the Children's Eating Behavior Questionnaire (CEBQ) 80. The CEBQ is a 35-item parental 227 report instrument that assesses child appetitive traits which can be grouped into those related to food 228 avoidance (i.e., slowness in eating, satiety responsiveness, emotional undereating, and food 229 fussiness) and those related to food approach (i.e., enjoyment of food, food responsiveness, desire to 230 drink, and emotional overeating)<sup>80</sup>. Higher scores on food approach related subscales and lower 231 scores on food avoidant related subscales have been positively associated with weight status in 232 children 81-83. Several prior studies have examined whether subscales of the CEBQ vary by sex. A 233 cohort in middle childhood from Thailand found that males had greater enjoyment of food than 234 females<sup>84</sup>, however the opposite was found in a cohort of 6- to 7-year-old Dutch children (i.e., females 235 higher than males) <sup>85</sup>. When looking more broadly across appetitive traits, male children showed 236 greater desire to drink <sup>84</sup>, emotional overeating <sup>85</sup>, and food responsiveness <sup>86</sup>. In contrast, females 237 showed greater avoidance behaviors (e.g., slowness of eating, satiety responsiveness) 87 81.

238 In order to better understand whether appetitive traits differ by sex, age, and adiposity, we 239 examined CEBQ scores from 11 data sets collected from studies conducted at the Children's Eating 240 Behavior Laboratory at The Pennsylvania State University from 2012 - 2018. A total of 263 (M=133; 241 50.6%) 3- to 12-year-old children had complete parent-reported anthropomorphic and CEBQ data as 242 well as measured child anthropometrics. Males and females did not differ by age (t(260)=0.553, 243 P=0.581, d=0.07), body mass index (BMI)-for-age percentile (BMI%; t(260)=-0.859, P=0.391; d=0.11), 244 race (Fisher's P=0.276), ethnicity (Fisher's P=0.999), maternal education (t(260)=0.551, P=0.58, d=0.07;), 245 or CEBQ subscales (P values ranging from 0.073 – 0.681; see Supplementary Materials (SM) Table S1). 246 Although maternal education did not differ by child sex, it was used as a proxy for socioeconomic

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status as maternal education has been shown to be more highly associated with adiposity than

income <sup>88</sup>. Child weight status was assessed by measuring height and weight on a digital scale (Tanita,

Arlington Heights, IL) and stadiometer (SECA, Chino, CA) and children were categorized as either

having healthy weight (BMI-for-age <  $85^{\text{th}}$  percentile) or overweight/obesity (BMI-for-age >  $85^{\text{th}}$ 

251 percentile). [Table 1]

**Table 1.** Demographic Characteristics.

	CEBQ		fMRI	
	Males	Females	Males	Females
	(n=133)	(n=130)	(n=20)	(n=25)
Age (yrs)	7.40 (2.28)	7.56 (2.10)	8.75(0.99)	9.06(1.34)
BMI percentile	61.53 (29.06)	58.50 (28.20)	52.50(27.12)	53.57(30.93)
Maternal Ed. (yrs)	16.19 (2.63)	16.35 (2.71)	16.91(2.49)	16.88(1.90)
Weight Status (n)				
Obese/Overweight	43	27	3	6
Healthy Weight	90	103	19	19
Ethnicity (n)				
Not Hispanic/Latinx	94	84	20	25
Hispanic/Latinx	4	4	1	0
Not Reported	35	35	1	0
Race (n)				
Black/African American	6	2	2	0
White	119	112	19	25
Other	7	4	1	0
Not Reported	1	2	0	0
SES (n)				
>\$100,000	16	19	7	5
\$51,000-\$100,000	30	29	11	15
<= \$50,000	18	18	3	5
Not Reported	69	64	1	0

Means (SD) reported for Age, BMI percentile, and Maternal Education. Weight Status categories
defined by BMI percentile: Obese/Overweight ≥ 85th percentile; Healthy Weight < 85th percentile.</li>
BMI: body-mass index; CEBQ: Child Eating Behaviors Questionnaire Sample; fMRI: functional
Magnetic Resonance Imaging Sample.

Food approach and avoidance, as measured with CEBQ, were examined separately using the same hierarchical model steps—1: child age and maternal education; 2: a quadratic age term; 3: child sex and adiposity; 4: a sex X age interaction; and 5: a sex X adiposity interaction (Table 2). The change in model fit, R<sup>2</sup>, was tested at each step to determine whether the model explained significantly more variance with the added terms. Once the best model was identified, exploratory analyses examined the component subscales that contribute to the food avoidance and approach scores to determine whether the effect seen was consistent across subscales or driven by an individual subscale.

264 Individual differences in CEBQ avoidance and approach behaviors were best fit by different 265 models. Child sex was not a significant predictor of avoidance for any of the models where it was 266 included. In contrast, food approach was best modeled by including the interaction between child 267 sex and weight status (Table 2). The interaction between sex and weight status was significant such 268 that the association between having overweight or obesity and greater food approach was stronger 269 for females than males. This suggests that weight status may be more predictive of food approach 270 behaviors in females than in males. Exploratory analyses of approach subscales indicated that this 271 finding was primarily driven by the food responsiveness subscale which showed a suggested sex by 272 weight status interaction ( $\beta$ (SE) = -0.36 (0.20), p = 0.073). The interactions between weight status and 273 other CEBQ approach subscales were not significant (P values ranging from 0.155-0.255). Overall, 274 these results suggest that in female children, food responsiveness could be a better predictor of 275 weight status than other CEBQ approach subscales, and therefore may be a target for intervention 276 studies in this population.

Although the ability to reliably assess appetitive traits quickly via parent-report is valuable to the study of eating behaviors in children, it is equally important to identify how laboratory

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- 279 assessments of overconsumption relate to sex in children. Eating in the absence of hunger (EAH) is a 280 standard paradigm to assess hedonic eating <sup>89-91</sup> and has been shown to be stable through childhood 281 <sup>92</sup> and a phenotype for childhood obesity <sup>93</sup>. Studies in preschoolers <sup>74</sup> <sup>93</sup> and middle childhood <sup>94</sup> have 282 found greater eating in the absence of hunger in males compared to females. However, in 5- to 18-283 year-old Hispanic children from the United States, sex differences did not persist after adjusting for 284 energy needs <sup>95</sup>. Similar to reported findings on food approach, individual differences in eating in the 285 absence of hunger were associated with weight status 69, 94, 96, 97, parental dieting characteristics, and 286 feeding practices <sup>90,96</sup> in females but not males. Together, these findings suggest that eating in the
- absence of hunger and food approach traits are associated with individual differences (e.g., weight
- status, parental feeding practices) in females, but not in males. [Table 2]
- 289

Table 2. Hierarchical Regression for Approach and Avoidance Scales of the Child Eating Behavior Questionnaire	egression	tor Ap	proac	h and A	voidai	nce Scal	es of the	e Child	Eating B	ehavior	Questr	onnaire			
							A	Approach	h						
		1			7			ю			4			ы	
	B	SE	β	В	SE	β	В	SE	β	В	SE	β	В	SE	β
Maternal Education	-0.005 0	0.01 -	-0.027	-0.005	0.01	-0.028	-0.005	0.01	-0.025	-0.005	0.01	-0.025	-0.003	0.01	-0.015
Age	0.008 0.01		0.034	-0.003	0.09	-0.015	0.0003	0.09	-0.001	0.001	0.02	0.003	-0.002	0.01	-0.008
Age <sup>2</sup>				0.001	0.01	0.050	I	I	ł	I	I	I	I	ł	I
Weight Status							0.288	0.07	0.572***	0.288	0.07 0	0.07 0.571***	0.455	0.11 <b>0</b> .	0.110.902***
Sex							-0.119	0.06	-0.237†	-0.107	0.22	-0.002	-0.046	0.07	-0.091
Sex X Age										-0.002	0.03	-0.007	ł	ł	ł
Sex X Weight Status													-0.286	0.14	-0.567*
$\mathbb{R}^2$		•	0.002			0.002			0.071			0.071			0.086
AΔ R <sup>2</sup> F-statistic						$^{1}0.017$		Ħ.	19.591***			30.003			34.212*
·								Avoid							
Maternal Education	0.017 0.01		0.094	0.016	0.01	0.093	0.017	0.01	0.094	0.017	0.01	0.097	0.017	0.01	0.093
Age	-0.029 0	0.01 -0.137*		-0.072	0.08	-0.339	-0.027	0.01	-0.126*	-0.035	0.02	-0.165	-0.026	0.01	-0.125*
Age <sup>2</sup>				0.003	0.01	0.205	l	I	ł	I	l	I	I	ł	ł
Weight Status							-0.073	0.07	-0.156	-0.071	0.07	0.151	-0.087	0.10	-0.184
Sex							0.068	0.06	0.143	-0.049	0.21	0.143	I	ł	ł
Sex X Age										0.015	0.03	0.072	0.062	0.07	0.131
Sex X Weight Status													0.023	0.13	0.049
$\mathbb{R}^2$		•	0.029			0.030			0.038			0.039			0.038
$^{\rm A}\Delta$ R <sup>2</sup> F-statistic						$^{1}0.303$			11.137			10.871			10.765
Unstandardized coefficient (B) and standard errors are presented along with the standardized $eta$ for steps 1-5.	cient (B) a	nd staı	ndard	errors a	re pre	sented a	long wi	th the s	standardi	ized $\beta$ fo	or steps	1-5.			
A: superscript number	: indicates step model was compared to	step m	odel v	vas com	ıpared	to									

Table 2. Hierarchical Regression for Approach and Avoidance Scales of the Child Eating Behavior Ouestionnaire

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 $\dagger$  p<0.10, \*p<0.05, \*\*p<0.01, \*\*\*p<0.001

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#### 292 Meal-related microstructure:

293 Microstructural components of a meal include bite rate, eating rate, and bite size <sup>98</sup>. Of these 294 characteristics, eating rate has been most consistently associated with weight status in adults <sup>99</sup> and 295 children <sup>100</sup>, and is therefore a target for interventions to treat obesity <sup>101</sup>. Observational coding of 296 meal-time behaviors in the GUSTO cohort from Singapore showed that male children have faster 297 eating rate (g/min), larger bite size (g/bite), and shorter oral exposure (min) than female children 102. 298 Similar findings have been reported in adolescents <sup>103, 104</sup>. While the research in this area is limited, 299 the observation of sex differences in eating speed and oral processing time prior to puberty has 300 implications for the development of personalized interventions to reduce overeating in males and 301 females.

While there is a lack of studies that have included sex as a primary determinant of eating behaviors, the reviewed findings are suggestive of male-female differences in basic taste response, food liking and intake, eating self-regulation, appetitive traits, and meal-related microstructure. Since these differences could impact the success of dietary and behavioral interventions <sup>10</sup>, additional research focused on investigating sex differences in pre-pubertal children is needed to confirm these finding as well as identify mechanisms driving these early-life differences.

#### 308 2. Biopsychosocial contributions to sex differences

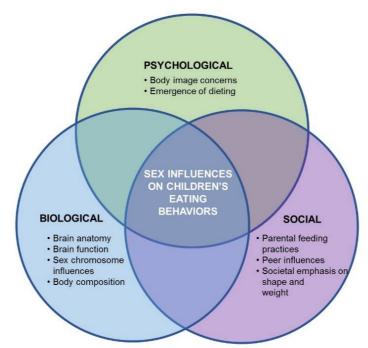
309 The second part of the paper will explore possible mechanisms for the observed sex differences

310 in children's eating behaviors. The scope of the discussion has been limited to potential biological

311 influences (i.e., neural responses to food cues), psychological influences (i.e., body image and weight

312 concerns), and social influences (i.e., parental feeding styles and practices). Additional potential

313 influences are presented in Figure 1, but will not be explored at length in this paper.



**Figure 1.** Biopsychosocial model of sex effects on children's eating behaviors. Potential biological influences could come from differences in brain anatomy or brain function that arise early in development, effects due to sex chromosomes, or differences in body composition that can influence food intake regulation. Psychological influences include body image concerns and the emergence of dieting, typically observed more frequently in females than males. Social influences include differences in parental feeding practices directed at males and females, peer influences, and societal pressures emphasis on "thinness" in females and "bigness" in males.

314

#### 315 2.1. Neural differences in the response to food cues.

316 One potential contribution to explain differences in eating behavior between male and female

317 children is variation in neural processing of food cues. Food cues elicit responses in brain regions

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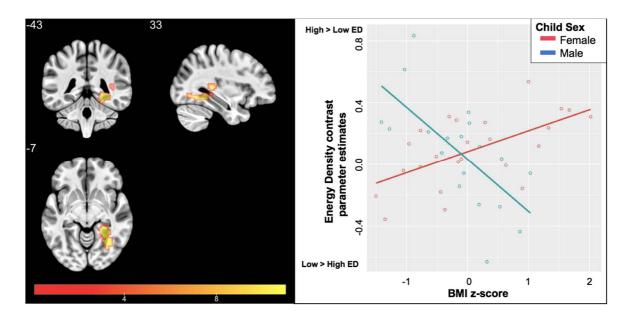
318 implicated in executive function, subjective valuation (e.g., orbitofrontal cortex), and visual 319 processing (e.g., fusiform gyrus) <sup>105</sup> that are correlated with eating behaviors <sup>106, 107</sup>. Several studies 320 have observed sex differences in neural response to food cues. For example, in adult samples that 321 have used functional magnetic resonance imaging (fMRI) to asses food cue reactivity, females show 322 greater activation than males in a number of brain regions associated with executive function (i.e., 323 dorsolateral and ventromedial prefrontal cortex)<sup>108, 109</sup>, visual processing <sup>110</sup>(e.g., fusiform gyrus), taste 324 and interoceptive processing<sup>110</sup>(e.g., insula), and reward (e.g., caudate) <sup>111</sup>. To date, only one study 325 has reported sex differences in children, although the findings contradicted those from adults. Luo 326 and colleagues <sup>112</sup> found that compared to females, 7-11 year-old males had greater activation to food 327 relative to non-food images in the right posterior hippocampus and temporal occipital fusiform 328 cortex, regions implicated in memory and visual processing. To date, the developmental trajectory of 329 neural response to food cues remains unclear, making it difficult to interpret the inconsistent patterns 330 of sex differences between adult and child samples.

To further investigate and potentially confirm the findings of Luo and colleagues <sup>112</sup>, we conducted a secondary data analysis in a similar age group (age 7-11 years; see demographic characteristics in Table 1) to determine whether male and female children differed in their neural processing of food images that varied in energy density and portion size. Males (N=22) and females (N=25) did not differ by age (t(45)=0.89, P=0.378, d=0.260), BMI-for-age % (t(45)=0.125, P=0.901, d=0.036), race (Fisher's p=0.095), ethnicity (Fisher's p=0.456), or maternal years of education (t(45)=-0.045, P=0.964, d=0.013).

338 On the day of the MRI, children arrived after a 2-hour fast and were scanned during a usual 339 meal-time. Before and after the scan, children rated fullness level on a validated, pictorial visual 340 analogue scale <sup>113</sup>. Children were imaged at 3T (MAGNETOM Trio) with a T1-weighted structural 341 (MPRAGE) sequence and a T2\*-sensitive gradient echo pulse sequence (see supplementary materials 342 (SM) for image acquisition parameters). Food images were presented using MATLAB Version 8<sup>114</sup> 343 and viewed through a mirror mounted on the head coil using a magnet-compatible projector. The 344 protocol for task design and image development has been reported elsewhere 107, 115. In brief, children 345 viewed a total of 180 images (120 food, 30 furniture, 30 scrambled images) presented in block design. 346 The food cues differed in portion size (large, small) and energy density (high-ED, low-ED). High-ED 347 foods were > 1.5 kcal/gram and included French fries, chicken nuggets, cookies, and pizza. Low-ED 348 foods were < 1.5 kcal/gram and included grilled chicken, carrots, broccoli, and apples. Data were 349 preprocessed and analyzed using Analysis of Functional NeuroImages (AFNI) <sup>116</sup> using standard 350 preprocessing steps (See SM for details). Four participants (3 Male, 1 Female) were excluded due to 351 excessive motion (defined as fewer than 4/6 usable runs; see SM for motion and outlier criteria). For 352 each subject, a general linear model was constructed including 6 parameters of interest (i.e., one for 353 each image condition) and 12 parameters of no-interest to control for motion (see SM). Group 354 analyses were then conducted using energy density contrasts (high-ED - low-ED) derived from 355 parameter estimates for each portion size condition separately, as well as a composite (i.e., across 356 both portion sizes). Multiple comparisons were controlled by using Monte-Carlo simulations ( $^{117}P <$ 357 0.001; k=29) using AFNI's 3dClustSim to achieve a final P < 0.05.

358 As there was no main effect of portion size, or a portion size X sex interaction on neural response 359 to high- or low-ED cues (see SM), the remaining group analyses focused on the ED contrast collapsed 360 across portion size. An analysis of covariance (ANCOVA; 3dMVM,<sup>118</sup>) showed a significant sex X BMI 361 z-score interaction in right superior temporal gyrus, extending to both parahippocampal and 362 fusiform gyri F(1,39)=29.21; peak: x=-37.5, y=37.5, z=7.5; k-173; Figure 2A). Post-hoc correlations 363 confirmed a significant positive association between BMI z-score and BOLD response to higher 364 (compared to lower) ED food images in females (R=0.598; P=0.002), while in males this relationship 365 was negative (R=-0.667; P =0.002) [Figure 2B]. There was no evidence for a main effect of BMI z-score 366 or sex. Although pre- and post-scan fullness differed in males and females, the same pattern of results 367 was seen when controlling for fullness ratings and when analyses included ED contrasts for each 368 portion size (see SM). [Figures 2A, 2B]

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#### 369

370Figure 2. Left: Statistical parametric map (F-statistic) of the interaction between BMIz and child sex371on neural responses to high-ED compared to Low-ED food cues. Cluster extends from the right372superior temporal gyrus into the parahippocampal and fusiform gyri. Right: Extracted energy density373contrast (high-ED – low-ED) parameter estimates, illustrating increased activation to high-ED374compared to low-ED food cues for girls with BMIz greater than the 50th percentile and increased375activation to high-ED compared to low-ED food cues for boys with BMIz greater below the 50th percentile.

Although preliminary, these results suggest that increased weight status in female children is
positively related to brain activation to higher-ED food cues in regions typically associated with
learning, memory (i.e., parahippocampal gyrus) and visual object recognition (i.e., fusiform gyrus),
while in male children the opposite pattern was observed. Future studies are needed to confirm these
findings and determine their long-term implications.

#### 382 2.2. Body image and weight concerns.

383 From a young age, individual differences in eating behaviors may be, in part, driven by sex 384 differences in perceived ideal and preferred body size. Sex differences in dieting and body image 385 concerns have been consistently documented in children as young as 8 years <sup>119</sup>; however, differences 386 in younger children are less consistent <sup>119-121</sup>. Compared to males, school-aged females report higher 387 levels of weight-related behaviors and concerns, including desire to lose weight <sup>122</sup>, dieting behavior 388 <sup>120</sup>, level of worry about weight <sup>120</sup>, <sup>123-125</sup>, thoughts about which foods might promote weight gain <sup>120</sup>, 389 <sup>123, 125</sup>, and feelings of guilt over eating too much <sup>123</sup>. Females also tend to be more dissatisfied with 390 their bodies 121, 122, 124, 126, 127 and have lower self-esteems 127-129. By 8 years of age, females have greater 391 body dissatisfaction than males <sup>119, 121-124, 129, 130</sup> and this tends to increase during middle childhood <sup>129</sup>. 392 Overall, greater emphasis on the maintenance of an ideal body weight in females than males may 393 encourage sex differences in eating behaviors that are adopted to achieve "the perfect figure".

#### 394 2.3. Parental feeding styles and practices.

395 The greater emphasis on "thinness" as a cultural ideal in females likely encourages sex 396 differences in parental feeding practices and attitudes directed at children. In general, parents are 397 more concerned about weight status in female children than they are in males <sup>122, 131</sup>; thus, they are 398 more likely to assume an active role in training, redirecting, and encouraging healthful eating 399 behaviors in female children <sup>122, 131</sup>. Several studies have also found that male children are encouraged 400 to eat more than female children <sup>132, 133</sup>, while females are more likely to seek parental praise and 401 approval for meal-time behaviors <sup>132</sup>. In response to maternal concerns, female children are more 402 likely than male children to change eating behaviors <sup>130,134</sup>. These observations could help to partially

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403 explain sex differences in food acceptance and intake, whereby female children show more nutritious
 404 food intake patterns than males <sup>43</sup>. Greater need for external attentions, like praise, among females
 405 could mean that they are less attentive to internal signals of hunger and fullness when compared to
 406 males, which may increase their risk for disordered eating behaviors.

407 The influence of controlling feeding practices, like restriction and pressure-to-eat, have also been 408 found to vary depending on the sex of the child. Greater laboratory 90, 135 and parentally-reported 409 restriction 68, 136, 137 have been associated with higher weight status in primarily Caucasian females, 410 but not males. In addition, Arredondo and colleagues 138 have found in Latino families that greater 411 parental control over feeding is associated with increased reported intake of "unhealthy" foods (e.g., 412 sodas, sugar sweetened beverages, chips, sweetened cereals) in females, but not males. In general, 413 mothers tend to use greater feeding control with female than male children<sup>139</sup>. Increased use of 414 parental control, specifically within the domain of feeding, may weaken females' ability to eat in 415 response to internal satiety signals, which may ultimately increase weight gain and risk for obesity. 416 Notably, these patterns have not been consistently observed across studies. Studies in both preschool 417 children<sup>140</sup> and a Dutch sample in middle childhood<sup>141</sup> found that controlling feeding practices were 418 associated with greater eating in the absence of hunger <sup>140</sup> and external and emotional eating <sup>141</sup> in 419 males, but not females. Overall, the influence of child age, ethnicity, and socioeconomic status, as 420 well as parental factors including education, weight status, and general parenting style have not been 421 clarified and require additional investigation.

#### 422 2.4. Peer and social influences.

423 In addition to parental influences that may serve to engender children with different eating 424 behaviors, societal ideals include expectations about what and how males and females should eat. A 425 feminine identify is characterized by eating smaller portions, consuming less meat, and preferring 426 healthier options to maintain appearance, while a masculine eating identify is characterized by 427 feeling full, with a focus on physical performance <sup>142, 143</sup>. Within these ideals, female children are seen 428 as a more effective at modeling healthy behaviors than males <sup>144, 145</sup>. Furthermore, females are also 429 more likely to respond to modeled eating behaviors including vegetable acceptance 144 and fruit and 430 vegetable intake<sup>146</sup>. The higher success of modeling and dietary interventions among females 431 suggests a greater awareness of social expectations related to eating <sup>147</sup>. Moreover, greater self-control 432 among females <sup>59,78</sup> may help facilitate greater uptake of these behaviors.

#### 433 3. Conclusions and recommendations for future research

434 In this paper, we reviewed evidence of sex differences in children's eating behaviors and 435 presented new data showing that sex and weight status interact to differentially influence appetitive 436 traits and neural response to food images in males and females. In the reviewed literature, we 437 identified differences in basic taste response and acuity, food acceptance, food intake, appetitive 438 traits, and eating rate between male and female children. In addition, new analyses showed that child 439 weight status interacts with sex to influence appetitive traits such that food approach behaviors (i.e., 440 food responsiveness) are stronger predictors of increased weight status in females than in males. 441 Similarly, in a separate cohort of 7- to 11-year-olds, we found that sex and weight status interact to 442 influence children's neural responses to food images that vary in energy density. In females, greater 443 activation to higher energy food cues in brain regions implicated in learning, memory, and object 444 recognition was positively related to weight status, while the opposite pattern was observed in males. 445 Although we cannot fully discount the possibility that some of the observed differences are driven 446 by physiological changes that occur with puberty, the focus on children under 11 years of age likely 447 reduces these influences. The evidence presented underscores the need to study the etiology and 448 implications of sex differences in children's eating behaviors.

449 Despite inconsistencies across the literature, a few consistent themes are apparent. First, sex 450 differences in children's eating behaviors were more often found in school-aged children. Few 451 consistent differences in eating behaviors were identified among infants and toddlers. It is possible 452 that differences are present in younger children, but unable to be measured due to methodological

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453 limitations. Perhaps more likely, however, is that these patterns arise during childhood due to 454 differential parenting practices and social influences directed at males and females. Second, female 455 children tend to report liking and eating more foods that are lower in energy density and higher in 456 critical nutrients (i.e., fruits and vegetables) than males. Due to the lack of clear biological differences 457 in taste anatomy, these differences are also likely to be influenced by parent, peer, and societal factors. 458 Importantly, the self-report nature of most of this literature highlights the need to confirm these 459 findings with more objective measures of eating behavior. Third, sex differences in appetitive traits, 460 EAH, and parental feeding attitudes are influenced by complex interactions with child weight status. 461 In general, parents are more concerned about excess weight in female compared to male children. As 462 a result, they likely feed children differently depending not only on the sex of the child, but also their 463 perception that the child is at risk for developing overweight. It is likely that parental characteristics, 464 like dieting history, cognitive restraint, socioeconomic status, and weight status influence the 465 relationship between child sex and eating behaviors, highlighting the need to conduct larger studies 466 that are sufficiently powered to query three-way interactions (e.g., child sex X child weight status X 467 parent weight history).

468 Caution is recommended when interpreting the findings discussed, both from the literature and 469 the new analyses presented. First, the majority of studies that have reported sex differences were not 470 designed to detect sex as a primary determinant of outcomes; thus, it is not possible to rule out chance 471 findings. Second, among the studies that did not report differences, sex was often controlled for as a 472 covariate, but results for main outcomes were not stratified and reported by sex. This makes it 473 difficult to determine whether primary eating behavior outcomes differed in males and females and 474 limits the ability to conduct meta-analyses across studies. Third, determining the underlying 475 mechanisms for sex differences in eating behavior is complicated by the lack of clarity in how sex and 476 gender are defined in the literature. A concern moving forward is that researchers will overgeneralize 477 findings by developing separate intervention approaches for males and females without considering 478 that sex and gender are non-binary, multidimensional constructs. To avoid this type of 479 overgeneralization, we caution against using sex or gender as the basis to group participants prior to 480 assigning treatments. Instead, sex and gender should be measured and considered like other 481 individual subject characteristics, and used to provide information to help phenotype risk groups.

482 When planning and reporting on future studies, it is important that researchers clearly define 483 the constructs of sex and gender, in terms of how they are measured and reported. In addition, in 484 studies that statistically control for sex as a covariate, it would be helpful for researchers to report 485 applicable estimates, coefficients, and p-values for covariates, either in the manuscript or in 486 supplementary data. This would facilitate the ability to conduct systematic reviews on this topic. 487 Moreover, research in children, especially infants and preschool children, should utilize objective and 488 observational measures of children's eating behaviors and intake when possible to limit the influence 489 of parental beliefs and perceptions along with probable response bias for questionnaires. Lastly, in 490 regards to intervention efforts for obesity, sex or gender should be considered when determining 491 target behaviors as well as evaluating the impact of the intervention on primary and secondary 492 outcomes. Together, these recommendations will help advance our understanding of the role that sex 493 and gender play in the development of weight and eating disorders.

494 In conclusion, children exhibit sex differences in basic taste response and acuity, food 495 acceptance, food intake, appetitive traits, and eating rate that are unlikely to be driven solely by 496 puberty. In addition, new analyses show that child weight status interacts with sex to influence 497 appetitive traits and the neural response to food cues. Generally, female children are more responsive 498 to socially driven expectations about how and what they should eat, while male children may be less 499 attentive to these cues. The reported differences between males and females have implications for 500 intervention. Females' inclination to more readily adopt modelled eating behaviors could diminish 501 responsiveness to internal cues of hunger and fullness, but may result in greater adherence to dietary 502 goals and interventions. On the other hand, males may be less at risk for overriding internal cues, but 503 may not respond as readily to typical intervention techniques. These potential implications

- 504 underscore the importance of understanding the mechanisms underlying sex differences in order to 505 prevent development of maladaptive eating behaviors.
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