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The relationship between serum fatty acids and depressive symptoms in obese adolescents

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Abstract

Depression and obesity are highly prevalent and are considered inflammatory pathologies; in addition, they are also associated with dietary patterns including types of fatty acids (FA). Changes in the FA composition in the brain are determined by changes in the content and quality of dietary and serum FA. The aim of this study was to verify the relationships between serum-free FA, inflammatory processes and depressive symptoms in obese adolescents. This was a cross-sectional study that analysed a database composed of 138 post-pubertal adolescents. Data regarding the depressive symptoms, body composition, glucose metabolism, lipid profile, FA profile, leptin concentration, as well as adiponectin, IL-A, IL-6, IL-10, TNF-α, C-reactive protein and plasminogen activator inhibitor-1 levels of the subjects were collected. A total of 54·6 % of the adolescents presented with depressive symptoms, and there were positive correlations between depressive symptoms and serum saturated fatty acids (SFA) content, body fat, and inflammatory adipokines, such as leptin, IL-6, and the leptin/adiponectin ratio. Moreover, the content of *n*-3 polyunsaturated fatty acids (PUFA) was negatively correlated with depressive symptoms, suggesting that eicosatrienoic acid (C20:2n6) and dihomo-γ-linolenic acid (C20:3*n*-6) are independently associated with depressive symptom scores and can be critical predictors of poor mental health in humans. These results point to the relationship between SFA and depressive symptoms in obese adolescents. However, longitudinal studies are needed to confirm the causality between dietary SFA and depression in obese individuals.

Key words: **Fatty acids: Depression: Obesity**

Obesity is a highly prevalent disease and is currently one of the most severe public health problems worldwide[1,2]. Likewise, according to the WHO, epidemiological data indicate that the prevalence of obesity among European children and adolescents (5–19 years old) is increasing[3].

In a systematic review conducted by Riviera *et al.*[4], it has been reported that the prevalence of being overweight, including obesity, varied from 18·9 % to 36·9 % in school-aged children (5–11 years old) and from 16·6 % to 35·8 % in adolescents (12–19 years old) in various Latin American countries[4]. In Brazil, the Food and Nutrition Surveillance System has revealed that 18 % of adolescents are overweight, including 9·53 % who are obese and 3·98 % who are severely obese[5].

Obesity generates multiple co-morbidities, including insulin resistance, diabetes mellitus, cardiovascular diseases (CVD), and psychological illnesses such as depression and anxiety disorders[6]. Several previous studies have focused on the link between adolescent obesity and mental health, especially depression[7,8]. Obesity is associated with high levels of inflammatory mediators, resulting in adipose tissue hypertrophy,

Abbreviations: AA, arachidonic acid; DGLA, dihomo-γ-linolenic acid; FA, fatty acids.

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changes in the gut microbiota, increased intestinal permeability and sustained immune activation[9,10]. This chronic inflammatory state is associated with several psychiatric and neurological disorders, like depression[7,11].

Although the primary aim of the present study was not to evaluate the different brain FA, it must be mentioned that brain inflammation is called neuroinflammation, a process that is mediated especially by glial cells (i.e., astrocytes and microglia), which act like immune cells and express receptors to peripheral and central inflammatory triggers (i.e., gut microbiota-derived metabolites, cytokines, nutrients, etc.). These inflammatory triggers can cross the blood–brain barrier, which is more permeable during obesity and depression[11,12].

Furthermore, the relationship between obesity and depression is associated with several factors, including dietary-related factors. Some nutrients appear to trigger immune cell activation and promote inflammatory cytokine release, reinforcing the inflammatory state[12–14]. In addition, dietary FA intake can affect the inflammatory state. While SFA increase inflammatory mediators, PUFA can mitigate the inflammatory pathway[11,13].

It is important to note that the central nervous system has the highest concentration of lipids in the body after adipose tissue. The FA composition of the brain is highly variable; among PUFA, arachidonic acid (AA) and docosahexanoic acid (DHA) are present in high quantities[10,11]. Although brain lipogenesis can be considered as a relatively small contributor to FA levels, brain SFA, monounsaturated fatty acids (MUFA) and PUFA are mainly provided by the diet[11,15,16].

Dietary patterns with a high proportion of *n*-6 PUFA favour pro-inflammatory eicosanoid synthesis. In contrast, eicosapentaenoic acid (EPA) and DHA mitigate neuroinflammation. Moreover, PUFA improve serotonin neurotransmission[12,13].

In a systematic review and meta-analysis, Mannan *et al.*[17] have shown that obese adolescents have a 40 % increased risk of depression. Furthermore, Sánchez-Villegas *et al.*[18] have observed that a moderate intake of *n*-3 FA (approximately 0·5–1 g/d) is significantly associated with a lower prevalence of depression, concluding that a moderate but not a high intake of *n*-3 PUFA is associated with a lower likelihood of depression.

Therefore, considering the effect of FA on the inflammatory state, we aimed to verify the relationship between serum-free FA, the inflammatory process and symptoms of depression in obese adolescents.

Methods

Study design and subjects

This was a cross-sectional study originating from data collected from an obesity intervention programme during 2008–2012 that was developed by the Center for Studies in Psychobiology and Exercise (CEPE) with the Obesity Study Group (GEO) of the Federal University of São Paulo (UNIFESP). The details of this study have been described in detail in prior publications[19,20].

A group of post-pubescent obese adolescents was recruited by television, newspaper and radio advertisements to participate in an interdisciplinary intervention. The inclusion criteria to partake in the proposed therapy model were an age of 14–19 years, obesity according to the WHO criteria (body mass index [BMI] for age ≥ 97 percentile) and post-pubertal Tanner stage 5. Exclusion criteria included genetic, endocrine, CVD, metabolic or endocrine disease; previous nutritional supplementation and/or drug utilisation that altered metabolism during the last 6 months; musculoskeletal problems that limited the practice of physical exercise; and autoimmune diseases.

For the current investigation, 138 adolescents diagnosed with obesity (53 male and 85 female) were included. Data such as the depression score, body composition assessment, FA levels, and inflammatory profiles were collected from the subjects.

According to the Helsinki Declaration, this study was conducted and was approved by the Institutional Ethics Committee (CEP/UNIFESP 1464/2020). All volunteers and their parents signed the informed consent.

Medical screening

The subjects were medically screened, and their pubertal stage[21] and anthropometric parameters were assessed. An endocrinologist performed the clinical interviews to determine eligibility based on the inclusion and exclusion criteria (Fig. 1).

Anthropometric measurements and body composition

The body mass, height and waist circumference of the subjects were measured according to standard procedures. The volunteers were wearing light clothes and no shoes. The body mass was measured using a Filizola platform scale (Indústria Filizola S/A, São Paulo, SP, Brazil; model PL 180), with a capacity of 180 kg and an accuracy of 100 g. The height was assessed using a stadiometer with a precision of 0·1 cm (model ES 2030, Sanny). The BMI was calculated as the quotient of body mass (kg) and the height (m) squared. Plethysmography air displacement estimated the body composition (BOD POD version 1.69, Life Measurement Instruments)[22].

Serum analysis

Blood samples were collected after a 12-h overnight fast. The concentrations of glucose, insulin, triacylglycerol (TAG), total cholesterol, HDL-cholesterol, LDL-cholesterol and VLDL-cholesterol were determined by enzymatic colorimetric methods (CELM). Leptin, adiponectin, TNF-α, plasminogen activator inhibitor-1, C-reactive protein, IL-1, IL-6 and IL-10 were measured using a commercially available multiplex assay (EMD Millipore; HMHMAG-34K). The pro-inflammatory leptin/adiponectin ratio and the anti-inflammatory adiponectin/leptin ratio were calculated.

Serum-free fatty acids profile (%)

The serum-free FA composition was determined by GC using a Varian Model 3900 gas chromatograph coupled with flame ionisation detection and a CP-8410 autosampler. Methylation of each fraction was performed with acetyl chloride (5 % HCl in methanol), and the FA composition was determined as methyl esters. FA were identified by comparing the retention time using a known standard of fatty acid methyl esters. Fatty acid methyl esters were analysed on a capillary column (CP Wax 52 CB,

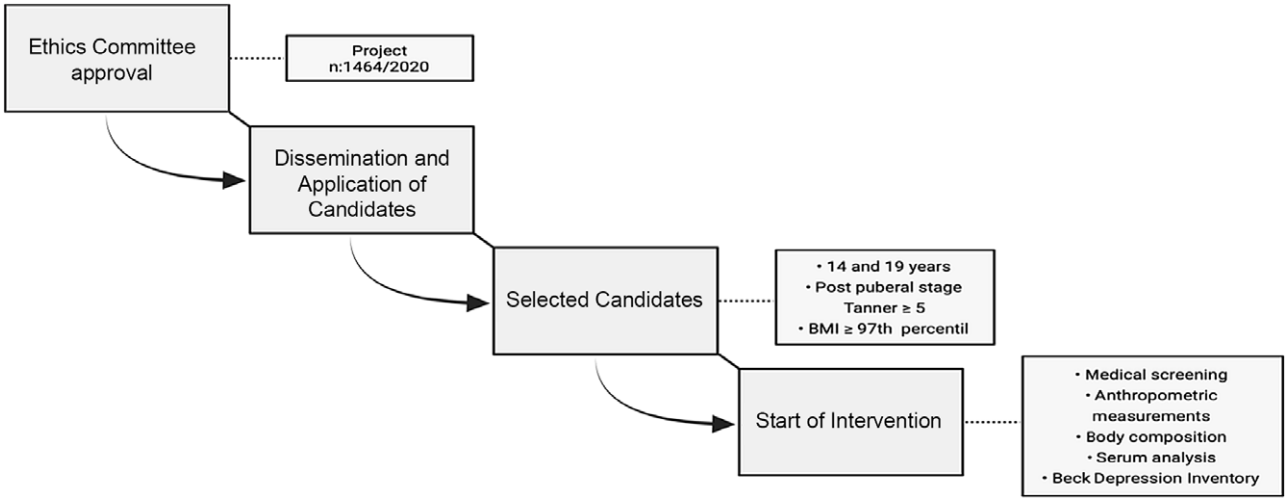

Fig. 1. Study protocol.

Varian; thickness: 0·25 µm, inside diameter: 0·25 mm and length: 30 m). Hydrogen was used as the carrier gas at a linear velocity of 22 cm/s. The temperature programme was 170°C for 1 min, followed by 2·5°C/min increases to 240°C, and a final hold time of 5 min. The injector and flame ionisation detection temperatures were 250°C and 260°C, respectively. Fatty acid methyl esters were identified by comparing the retention times of the samples with those of known standards (Supelco, 37 components; Sigma-Aldrich; Mixture, Me93, Larodan and Qualmix, PUFA fish M, Menhaden Oil, Larodan). The FA composition values were expressed as percentages of the total FA[23].

Beck Depression Inventory

The Beck Depressive Inventory (BDI) is a twenty-one-item self-reported questionnaire used to identify symptoms of depression. Each item comprises four statements typically associated with depressive symptomatology. The severity of depression was grouped according to the following degrees: no concern (0–11), mild (12–19), moderate (20–35) and severe (36–63)[24]. It has been translated into Portuguese and validated for the Brazilian population[25].

Statistical analysis

Descriptive statistics were used to assess the following sample characteristics: mean, standard deviation and percentage. The Student's *t* test and the Mann–Whitney test were used to compare the differences between boys and girls. Pearson's and Spearman's tests were performed for correlation analysis of parametric and non-parametric variables, respectively. A generalised linear model with Gaussian distribution and the identity link function for a better fit according to the Akaike information criterion was performed. The lowest value obtained by Akaike information criterion indicated that the assumption of normality of residues was met. The Akaike information criterion estimated the quality of each model compared with the other models proposed. The outcome variable was the BDI score, and exposure variables were IL-6, IL-10, C14:0, C16:0, C18:0, total MUFA and PUFA, C18:3n6, C20:2n6, C20:3n6, C22:4n6, *n*-3 PUFA, *n*-6 PUFA, and the *n*-6 PUFA/*n*-3 PUFA ratio. Moreover, sex and age were used as covariates and confounders. The order of insertion of the variables in the model considered the criterion of biological plausibility. All statistical analyses were performed using Jamovi, version 1.2.27. The significance level was set at $P < 0{\cdot}05$ for all analyses.

Results

A total of 138 obese adolescents were analysed in the present study. The body composition as well as the metabolic and inflammatory profiles are described in Table 1, separated by sex.

After comparison between boys and girls, it was observed that the boys presented with significantly greater body mass, height, fat-free mass, VLDL-cholesterol and TAG levels. On the other hand, the girls presented with higher body fat (%), HDL-cholesterol, leptin, C-reactive protein and IL-6 levels. No significant difference was observed in depressive symptom scores between boys and girls (Table 1).

According to the BDI, it was observed that 44·9 % ($n = 62$) of the subjects did not have symptoms of depression. However, 29·7 % ($n = 41$) presented with mild symptoms, 23·9 % ($n = 33$) presented with moderate symptoms and 1·4 % ($n = 2$) presented with severe symptoms of depression.

The serum-free FA profiles are listed in Table 2. Palmitic acid (C16:0) was the most abundant SFA observed. Meanwhile, oleic acid (C18:1n9) was the most abundant MUFA. Concerning PUFA, there was a higher concentration of total *n*-6 PUFA than total *n*-3 PUFA. In relation to free FA, girls presented higher amounts of C20:0, C20:3n3 and C21:5n3 and boys presented higher amounts of total MUFA and C18:1n9 (Table 2).

Correlation analysis

There was a positive correlation between depressive symptom scores and SFA content, including palmitic acid (C16:0), stearic acid (C18:0), lignoceric acid (C24:0) and total SFA (Table 3). In addition, the depressive symptom scores presented positive

Table 1. Body composition and metabolic and inflammatory profiles in obese adolescents, separated by sex

Variables	Total *n* 138		Male *n* 53		Female *n* 85	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	16·38	1·49	16·20	1·47	16·50	1·50
Body mass (kg)	100·93	16·57	108·53	16·11	96·19	15·11*
Height (m)	1·68	0·09	1·75	0·08	1·63	0·07*
BMI (kg/m^2)						
Median	34·49		35·38	4·60	36·08	4·91
Minimum–Maximum	28·19–48·51					
Body fat (%)	44·75	6·59	41·14	6·40	47·00	5·66*
Fat-free mass (%)	55·24	6·59	58·86	6·40	52·99	5·66*
Body fat (kg)	45·56	11·77	45·22	12·16	45·78	11·60
Fat-free mass (kg)	55·38	9·14	63·35	7,75	50·41	5·83*
Glycaemia (mg/dl)	91·20	6·55	92·58	6·23	90·34	6·63
Total cholesterol (mg/dl)	167·11	33·19	171·19	38·00	164·58	29·76
HDL-cholesterol (mg/dl)	45·20	9·31	40·92	8·10	47·87	9·05*
LDL-cholesterol (mg/dl)	102·02	28·66	107·38	32·51	98·74	25·67
	Median	Minimum–Maximum	Median	Minimum–Maximum	Median	Minimum–Maximum
VLDL-cholesterol (mg/dl)	17·50	7·00–54·00	21·00	7·00–54·00	16·00	7·0–41·00*
TAG (mg/dl)	87·00	35·00–271·00	103·50	35·00–271·00	79·00	35·00–206·00*
Adiponectin (ug/l)	9·93	0·26–97·18	8·61	1·87–42·71	11·17	0·26–97·18
Leptin (ng/ml)	34·23	1·24–124·38	25·11	1·24–124·38	41·10	12·67–100·00*
Leptin/Adiponectin ratio	2·28	0·15–31·11	2·20	0·15–31·11	2·76	0·19–26·06
Adiponectin/Leptin ratio	0·41	0·03–6·53	0·46	0·03–6,53	0·40	0·04–5·32
PAI-1 (ng/ml)	25·11	0·63–346·00	26·34	0·63–346·00	24·40	0·85–295·00
CRP (ng/ml)	0·25	0·02–3·39	0·18	0·02–3·39	0·29	0·02–2·24*
TNF-α (ng/ml)	7·84	2·33–300·00	8·71	4·15–136·82	6·96	2·33–300·00
IL-1 (ng/ml)	4·92	0·05–879·00	5·78	0·20–111·00	4·92	0·05–879·00
IL-6 (ng/ml)	0·76	0·01–169·32	0·40	0·01–111·41	1·23	0·04–169·32*
IL-10 (ng/ml)	0·47	0·01–42·90	0·64	0·04–18·39	0·36	0·01–42·90
Depression symptoms score						
Mean	14·05		13·26		14·54	
SD	8·02		8·25		7·87	

* Comparison between boys and girls; $P < 0·05$ for Student's *t* test and Mann–Whitney test.

Table 2. Serum-free fatty acid profile in obese adolescents, separated by sex

Fatty acids (% of total identified)	Total *n* 138		Boys *n* 53		Girls *n* 85	
	Mean	SD	Mean	SD	Mean	SD
Total SFA	29·49	3·73	29·65	3·87	29·35	3·66
C14:0						
Median	0·73		0·81		0·63	
Minimum–Maximum	0·14–4·45		0·22–3·31		0·15–4·45	
C16:0	19·13	3·46	19·58	3·79	18·84	3·23
C18:0	7·09	1·15	6·91	1·13	7·20	1·15
C20:0						
Median	0·15		0·12		0·17	
Minimum–Maximum	0·05–0·80		0·05–0·80		0·05–0·57*	
C24:0						
Median	0·48		0·44		0·57	
Minimum–Maximum	0·02–2·40		0·02–2·40		0·04–2·29	
Total MUFA	21·51	3·05	22·26	3·02	21·04	2·99*
C16:1n7	2·40	0·83	2·31	0·72	2·46	0·89
C18:1n9	15·27	3·69	16·11	4·13	14·75	3·32*
C18:1n7	1·51	0·41	1·52	0·42	1·51	0·41
Total PUFA	48·71	6·61	48·09	6·07	49·11	6·94
	Median	Minimum–Maximum	Median	Minimum–Maximum	Median	Minimum–Maximum
C18:4n3	0·31	0·02–11·61	0·31	0·02–11·61	0·33	0·03–5·24
C20:3n3	0·17	0·01–1·06	0·14	0·02–1·06	0·19	0·01–0·97*
C20:4n3	0·25	0·01–7·86	0·18	0·01–6·85	0·30	0·01–7·86
C20:5n3	0·92	0·06–101·00	0·86	0·10–8·74	0·92	0·06–101·00
	Mean	SD	Mean	SD	Mean	SD
C22:5n3	0·43	0·23	0·41	0·23	0·45	0·23
C22:6n3	0·62	0·36	0·59	0·30	0·64	0·40
C21:5n3						
Median	0·23		0·17		0·25	
Minimum–Maximum	0·01–3·06		0·01–2·98		0·01–3·06*	
C18:2n6c	27·04–37·48		22·69	10·06	24·92	8·64
C18:2n6t						
Median	2·03		2·66		27·56	
Minimum–Maximum	0·01–27·51		0·01–27·51		3·95–37·49	
C18:3n6						
Median	0·34		0·30		0·42	
Minimum–Maximum	0·02–3·11		0·07–0·91		0·02–3·11	
C20:2n6						
Median	0·40		0·42		0·34	
Minimum–Maximum	0·01–9·61		0·01–7·61		0·02–9·61	
C20:3n6	1·31	0·54	1·29	0·52	1·32	0·55
C20:4n6	5·60	1·87	5·34	1·65	5·77	1·99
C22:4n6						
Median	2·77		2·77		2·75	
Minimum–Maximum	0·03–10·13		0·03–10·13		0·07–9·61	
Total PUFA n3	6·16	3·29	5·88	3·17	6·33	3·36
Total PUFA n6	39·90	4·46	39·20	3·63	40·34	4·88
PUFAn6/PUFAn3 ratio	8·61	4·85	9·04	5·06	8·34	4·72

Comparison between boys and girls.
* $P < 0·05$ for Student's *t* test and Mann–Whitney test.

Table 3. Correlations between free fatty acids, depressive symptoms and inflammatory markers in obese adolescents

Depressive symptoms		
	r/rho	*P*
Fatty acids (%)		
C16:0	0·21	0·01
C18:0	0·19	0·02
C 24:0	0·37	< 0·001
C18:2n6c	0·30	< 0·001
C18:2n6t	-0·36	< 0·001
C20:4n3	0·28	0·00
C20:3n6	0·37	< 0·001
C20:4n6	0·24	0·01
C22:4n6	-0·33	< 0·001
Total SFA	0·19	0·02
Total n3 PUFA	-0·18	0·03
n6 PUFA/n3 PUFA ratio	0·23	0·01
Adipokines		
Leptin	0·23	0·01
Leptin/adiponectin ratio	0·36	< 0·001
TNF-α	0·24	0·03
Adiponectin	-0·39	< 0·001
Adiponectin/leptin ratio	-0·36	< 0·001
Fat mass		
Body fat (%)	0·24	0·00
Body fat (kg)	0·19	0·01

correlations with the body fat mass (% and kg), leptin and TNF-α levels, and leptin/adiponectin ratio as well as negative correlations with the adiponectin level and adiponectin/leptin ratio.

Regression analysis

Regression analysis with Gaussian distribution and the identity link function, whose Akaike information criterion is 360 874, explained a significant proportion of the BDI score variance ($R^2 = 0{\cdot}44$; $P < 0{\cdot}001$) (Table 4). According to the univariate regression, IL-6 ($\beta = 0{\cdot}05$; 95 % CI: 0·00, 0·103; $P < 0{\cdot}023$), C16:0 ($\beta = 0{\cdot}48$; 95 % CI: 0·10, 0·86; $P < 0{\cdot}014$), C18:0 ($\beta = 1{\cdot}38$; 95 % CI: 0·235, 2·53; $P < 0{\cdot}020$) and the *n*-6 PUFA/*n*-3 PUFA ratio ($\beta = 0{\cdot}37$; 95 % CI: 0·10, 0·64; $P < 0{\cdot}008$) were positively associated with a higher BDI score. In contrast, C22:4n6 ($\beta = -1{\cdot}02$; 95 % CI: −1·54, −0·49; $P < 0{\cdot}001$) and *n*-3 PUFA ($\beta = -0{\cdot}45$; 95 % CI: −0·85, 0·04; $P < 0{\cdot}030$) were negatively associated with the BDI score. However, in models 1 and 2, these associations disappeared. Moreover, according to univariate analysis ($\beta = 5{\cdot}53$; 95 % CI: 3·21, 7·85; $P < 0{\cdot}001$), C20:3n6 increased the BDI score with model 1 ($\beta = 10{\cdot}68$; 95 % CI: 2·86, 18·51; $P = 0{\cdot}011$) and model 2 ($\beta = 9{\cdot}53$; 95 % CI: 1·45, 17·60; $P = 0{\cdot}027$). Nevertheless, in model 1 ($\beta = 11{\cdot}22$; 95 % CI: 1·26, 21·18; $P = 0{\cdot}034$) and model 2 ($\beta = 11{\cdot}71$; 95 % CI: 1·92, 21·50; $P = 0{\cdot}025$), C20:2n6 also was positively associated with the BDI score.

Discussion

Our main results suggest that eicosatrienoic acid (C20:2n6) and dihomo-γ-linolenic acid (DGLA; C20:3n6) were independently associated with the depressive symptom scores and may be critical predictors of poor mental health in humans, since 54·6 % of the adolescents presented depressive symptoms. Moreover, obesity-related parameters and inflammatory biomarkers were positively correlated with depressive symptoms. The body fat mass and inflammatory adipokines, such as TNF-α, leptin and the leptin/adiponectin ratio, were positively correlated with depressive symptoms, while the adiponectin level and the adiponectin/leptin ratio were negatively correlated with depressive symptoms. Although our study did not present a difference between the depression score between females and males, it is important to highlight that girls had higher values of IL-6, CRP, fat mass and leptin, and these variables may be correlated with a higher risk of depression.

The FA C20:2n6 and DGLA are not essential, but they can be endogenously synthesised from linolenic acid (LA) in humans. Metabolically, DGLA is converted into AA, and prostaglandin E2 derived from AA and leukotriene B4 have pro-inflammatory properties[26]. Hence, excessive LA ingestion contributes to the development of obesity and a chronic inflammatory state via AA[27].

It should be noted that linoleic *n*-6 and linolenic *n*-3 FA are essential and compete for common metabolic enzymes: desaturases. Both have opposite effects on adipogenesis and especially on systemic inflammation, as the LA derivatives EPA and DHA are able to partially inhibit aspects of inflammation, including leucocyte chemotaxis, expression of adhesion molecules, leucocyte–endothelial cell interactions, production of eicosanoids such as prostaglandins and leukotrienes, and production of pro-inflammatory adipokines. Additionally, EPA contributes to eicosanoids, which often have a lower biological potency than compounds produced from AA[28,29].

Yari *et al.*[30] have investigated the effects of DGLA on depression and have discovered that higher serum DGLA concentrations may predict a lower risk of depression in elderly men, after adjustment for several potential confounders (hazard ratio: 0·53, CI 0·36, 0·79, $P = 0{\cdot}002$). The association between DGLA and depression was not dependent on inflammation ($P_{\text{interaction}} = 0{\cdot}618$). The authors suggest that more studies are required to address potential mechanisms.

Body composition- and inflammation-related results reinforce the link between obesity, inflammation and humour disorders. For example, MacGiollabhui *et al.*[14] investigated the influence of high levels of IL-6 and BMI on depressive symptoms in adolescents over 3 years and found that a higher BMI and elevated levels of IL-6 lead to increased depressive symptoms. However, although some studies have observed a relationship between IL-6, BMI and depressive symptoms, the association between these parameters and the BDI score was not verified in the current study. Milano *et al.*[12] justified the hypothesis that inflammation is the crosstalk between adiposity and depression and involves other neuroimmune pathways. High levels of inflammatory mediators can trigger microglia and astrocyte activation as well as negatively affect neurotransmission, leading to changes in depression-related factors.

In this study, total SFA, palmitic acid (C16:0), stearic (C18:0) and lignoceric acid (C24:0) were positively correlated with depressive symptoms. SFA have been shown to trigger

Table 4. Associations between independent variables and outcome (Beck Depression Inventory Score)

Variables	Univariate regression			Model 1			Model 2		
	Estimate	95 % CI	*P*	Estimate	95 % CI	*P*	Estimate	95 % CI	*P*
Fat mass (kg)	0·131	0·01, 0·244	0·023	0·13	–0·07–0·35	0·214	0·14	–0·07, 0·36	0·193
IL-6	0·05	0·00, 0·103	0·025	0·06	–0·1s7, 0·29	0·599	0·07	–0·16, 0·31	0·562
IL-10	0·05	–0·143, 0·263	0·566	0·05	–0·36, 0·47	0·800	0·03	–0·38, 0·46	0·861
C14:0	1·35	–1·18, 3·87	0·297	1·32	–2·43, 5·08	0·493	1·49	–2·40, 5·39	0·458
C16:0	0·48	0·10, 0·86	0·014	0·42	–1·26, 2·11	0·627	0·28	–1·44, 2·01	0·749
C18:0	1·38	0·235, 2·53	0·020	–2·32	–5·28, 0·63	0·132	–1·98	–4·9, 0·94	0·193
Total MUFA	0·30	–0·13, 0·74	0·181	–0·15	–1·66, 1·3	0·842	–0·09	–1·6, 1·4	0·903
C18:3n6	–1·06	–5·30, 3·18	0·626	–0·54	–5·5, 4·48	0·834	–0·48	–5·72, 4·7	0·857
C20:2n6	0·64	–0·29, 1·58	0·180	11·22	1·26, 21·18	0·034	11·71	1·92, 21·50	0·025
C20:3n6	5·53	3·21, 7·85	< 0·001	10·68	2·86, 18·51	0·011	9·53	1·45, 17·60	0·027
C20:4n6	1·01	0·30, 1·71	0·005	0·23	–1·55, 2·01	0·800	0·50	–1·30, 2·30	0·589
C22:4n6	–1·02	–1·54, –0·49	< 0·001	0·48	–1·62, 2·58	0·657	0·25	–1·8, 2·34	0·813
Total PUFA	–0·18	–0·382, 0·02	0·081	0·31	–1·23, 1·85	0·695	0·20	–1·35, 1·77	0·795
n-3 PUFA	–0·45	–0·85, –0·04	0·030	1·20	–0·95, 3·36	0·282	1·72	–0·48, 3·9	0·134
n-6 PUFA	0·18	–0·11, 0·48	0·236	–0·19	–1·56, 1·17	0·782	0·02	–1·34, 1·38	0·977
n6 PUFA/n3 PUFA ratio	0·37	0·10, 0·64	0·008	0·32	–0·79, 1·44	0·571	0·55	–0·58, 1·69	0·346
Sex	–1·28	–4·03, 1·47	0·365				2·47	–2·01, 6·9	0·288
Age	0·25	–0·64, 1·16	0·576				–1·29	–3·01, 0·43	0·150

periphery immune (i.e., leucocytes and neutrophils) and brain-related cells (i.e., astrocytes and microglia), thus increasing neuroinflammation and depressive symptoms[10,11,31,32].

Mendes *et al.*[33] have described an in-depth microglia-related mechanism on neuroinflammation in people living with obesity. The authors demonstrate that a Western dietary pattern, especially one rich in SFA, promotes several immune metabolic changes, including low-grade chronic systemic inflammation, thus favouring neuroinflammation. Furthermore, a high-fat diet promotes a positive energy balance and adipose tissue dysregulation, increasing a condition called metainflammation, which contributes to neuroinflammation in obese subjects (Fig. 2).

Neuroinflammation can trigger negative changes in neurotransmission, leading to depressive symptoms[34]. In contrast, PUFA can blunt peripheral and central inflammatory pathways[34,35]. For instance, *n*-3 FA can decrease inflammatory pathways by triggering anti-inflammatory responses after stimulating the GPR120 receptor. Furthermore, the *n*-3 PUFA-related effect on the cell membrane composition can explain, at least in part, the negative association with depressive symptoms[34,35].

On the other hand, serotonin is an important neurotransmitter that regulates mood, sleep, appetite, heart rate, body temperature, sensitivity and cognitive functions. In patients with depression, a decrease in the brain production of serotonin and an alteration in the function of the serotonin receptor have been reported. Serotonin production can be affected by several factors, such as stress and an unbalanced diet[36,37]. Indeed, serotonin is synthesised by serotonergic neurons of the central nervous system and enterochromaffin cells of the gastrointestinal tract in humans, thus demonstrating the relevance of a healthy gut cells and microbiota[37]. A diet rich in SFA and *trans*-FA can contribute to lipotoxicity and endotoxemia by the increase of lipopolysaccharide in the bloodstream[38], while the intake of MUFA and *n*-3 FA is associated with a reduction in the depression status[13,18,39].

On the other hand, the balanced relationship between *n*-6 FA and *n*-3 FA is essential for brain function and inflammatory processes. The WHO's recommendations indicate that dietary fat should provide 15–30 % of the daily energy intake, SFA should not contribute more than 10 % of the daily energy intake and ~6–10 % of the daily energy intake should come from *n*-3 and *n*-6 PUFA. Unfortunately, the use of the *n*-3 PUFA content and the *n*-6 PUFA/*n*-3 PUFA ratio to mitigate depression-related symptoms has not yet been established[11,28,40]. More recently, Liao *et al.*[41] have suggested that ≤ 1 g/d of *n*-3 PUFA (60 % EPA or more) may have beneficial effects on depression.

According to univariate analysis, our results demonstrated that the *n*-6 PUFA/*n*-3 PUFA ratio was positively associated with a higher BDI score. In contrast, C22:4n6 and *n*-3 FA were negatively associated with the BDI score. However, in models 1 and 2, these associations disappeared. Similar results have been described by Scola *et al.*[42], who observed higher AA:EPA ratios and AA:EPA + DHA ratios in patients with bipolar depression compared with those with bipolar disorder in euthymia or unipolar depression.

The content of *n*-6 PUFA correlated more significantly with depressive symptoms, thus demonstrating the importance of the balance between *n*-6 and *n*-3 PUFA. The positive effects of *n*-3 PUFA on depression-related parameters have been investigated extensively. However, the results have been inconsistent or conflicting according to the different study designs.

For instance, Zhang *et al.*[43], with data extracted from the US National Health and Nutrition Examination Survey, have suggested that a higher intake of *n*-6 PUFA and a lower intake of *n*-3 PUFA are associated with depressive symptoms. On the other hand, in a cross-sectional study of humans in Japan, Tsuboi *et al.*[44] have demonstrated a positive correlation between symptoms of depression and the percentage of serum palmitic acid, while these symptoms were negatively correlated with the AA content. Additionally, Thesing *et al.*[45] showed no relationship between serum *n*-6 FA and depression in humans. Therefore, the relationship between *n*-3 and *n*-6 FA on depression has not been fully elucidated, and further studies are required, including in adolescents.

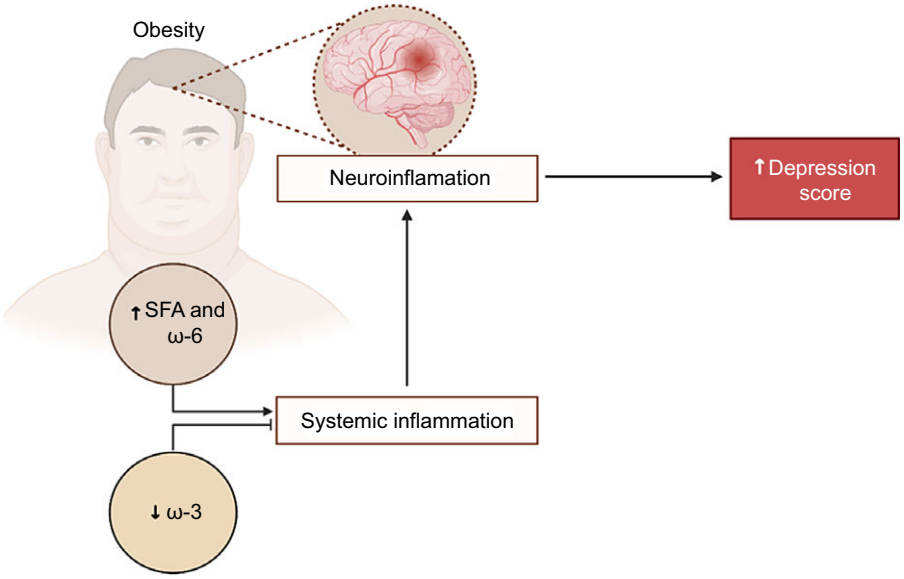

Fig. 2. Influence of AG on metainflammation and neuroinflammation in subjects with obesity. Created by Biorender.

Gabbay *et al.*[46] did not observe an effect of *n*-3 PUFA on depressive disorders in adolescents. In contrast, *n*-3 PUFA were negatively correlated with depressive symptoms in the current study. The anti-inflammatory actions of EPA and DHA include the composition of cell membrane phospholipids and NF-κB inhibition[28,32]. In the present study, the positive correlation observed between the total *n*-6 PUFA/*n*-3 PUFA ratio and depressive symptoms demonstrates the importance of a balanced diet, indicating that this ratio can be considered a mediating variable.

Sotoudeh *et al.*[13] have examined the association between depression and eating patterns through the intermediate role of PUFA in erythrocytes from 330 individuals. The authors concluded that elevated *n*-6 PUFA levels and decreased *n*-3 PUFA levels likely increase the risk of depression. Pottala *et al.*[39] also demonstrated an inverse association between *n*-3 PUFA levels and depressive symptoms in adolescents. Given that *n*-3 PUFA are constituents of cell membranes, including brain neurons, and modulate their synapse mechanisms, *n*-3 PUFA deficiency is related to dysfunction and impaired transmission of neurotransmitters such as serotonin, norepinephrine and dopamine, which can impact humour disorders[45,47]. A previous study has demonstrated that serum SFA and *trans*-FA are associated with the inflammatory process and that *n*-3 PUFA are associated with attenuation of inflammation in obese adolescents[20].

Some limitations of this study should be considered when interpreting the results. Although these data are consistent, data are only available from the baseline examination. A longitudinal study is necessary to confirm the relationship between DGLA and depression so that nutritional recommendations can be carried out more safely.

Conclusion

In conclusion, our results suggest that depressive symptoms are related to the inflammatory process, body fat and FA, especially SFA and *n*-6 PUFA, in obese adolescents. In addition, the inverse association between the total *n*-3 PUFA and the depressive symptom score is highlighted. However, longitudinal studies are needed to confirm causality between FA serum levels and depression in obese individuals and to fully elucidate the pathway that links *n*-3 PUFA levels with depression in obese patients in order to establish dietary and nutritional recommendations.

The controversial findings across studies could also be attributable to different types of diets and methodological issues, including differences in sample size, statistical adjustments for potential confounding factors, and daily consumption of *n*-3 and *n*-6 PUFA, thus demonstrating that the most important recommendation is the adequate consumption of FA.

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