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ORIGINAL ARTICLE

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Association of muscular strength and targeted proteomics involved in brain health in children with overweight/obesity

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Muscular strength has been positively associated with better brain health indicators during childhood obesity. However, the molecular mechanisms underlying the positive impact of muscular strength in brain health are poorly understood. We aimed to study the association of muscular strength with neurology-related circulating proteins in plasma in children with overweight/obesity and to explore the role of cardiorespiratory fitness (CRF) as a confounder. The participants were 86 Caucasian children (10.1 ± 1.1 years old; 41% girls) from the ActiveBrains project. Muscular strength was measured by field and laboratory tests. CRF was assessed with an incremental treadmill test. Olink's technology was used to quantify 92 neurology-related proteins in plasma. Protein–protein interactions were computed using the STRING website. Muscular strength was positively associated with 12 proteins (BetaNGF, CDH6, CLEC10A, CLM1, FcRL2, HAGH, IL12, LAIR2, MSR1, SCARB2, SMOC2, and TNFRSF12A), and negatively associated with 12 proteins (CLEC1B, CTSC, CTSS, gal-8, GCP5, NAAA, NrCAM, NTRK2, PLXNB3, RSPO1, sFRP3, and THY1). After adjustment for CRF, muscular strength was positively associated with eight proteins (BetaNGF, CDH6, CLEC10A, FcRL2, LAIR2, MSR1, SCARB2, and TNFRSF12A) and negatively associated with two proteins (gal-8 and NrCAM). After applying FDR correction, only CLEC10A remained statistically significant. In conclusion, muscular strength was associated

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with blood circulating proteins involved in several biological processes, particularly anti-inflammatory response, lipid metabolism, beta amyloid clearance, and neuronal action potential propagation. More powered studies are warranted in pediatric populations to contrast or confirm our findings.

KEYWORDS

biomarkers, brain health, cardiorespiratory fitness, children, Muscular strength, proteomics

1 | INTRODUCTION

Children with overweight/obesity are at a high risk of developing type 2 diabetes, hypertension, cardiovascular and brain-related diseases later in life.[1–3] Particularly, childhood obesity has negatively been associated with brain health indicators such as hippocampal connectivity with frontal regions, reaction time to stimulus, white-matter microstructure fractional anisotropy, and white matter volumes.[4–7] The inflammatory state in obesity is reflected in elevated levels of circulating pro-inflammatory cytokines and their association with poor brain health.[8] Several health-related factors, such as physical fitness (e.g., cardiorespiratory fitness [CRF] or muscular strength), may attenuate the negative influence of obesity on brain health through shared and independent mechanisms.[9,10]

Traditionally, most of the previous evidence has focused on the role of CRF on physical[11,12] and brain health.[13] However, muscular strength is increasingly considered a relevant predictor of both physical and brain health.[6,14–18] Specifically, muscular strength is associated with a better white matter volume and microstructure, reduced disruption of white matter tracts and cortical thickness of gray matter in children with overweight/obesity.[4,5,7] Despite this, the molecular mechanisms and biological pathways underlying the positive impact of muscular strength in brain health are poorly understood. Analysis of blood biomarkers could provide a breadth understanding of dynamic changes in biological pathways through the concentrations of circulating proteins.[19,20]

Multiple investigations have found that regulation of certain neurological-related circulating proteins (i.e., brain-derived neurotrophic factor) are associated with CRF levels in animal models[21] and humans.[22] In recent years, high-throughput technologies let researchers simultaneously analyze hundreds/thousands of molecules in each biological sample.[23,24] In this regard, it was disclosed that higher CRF levels were associated with circulating levels of several proteins involved in the inflammatory response, cardiovascular disease, and brain health disorders in children with overweight/obesity.[25] However, to the best of our knowledge, the application of these technologies in the context of muscular strength and in relation to neurological-related circulating proteins in children is unexplored. Moreover, the potential confounder role of the main physical fitness component (CRF) in the association between muscular strength and the neurological-related circulating proteins remains unknown.

Therefore, the present study aims to further strengthen and develop the understanding of the potential molecular mechanisms that explain the link between muscular strength and brain health. Particularly, the specific aims of the present study are as follows: (i) to examine the association of muscular strength (i.e., bench press, leg press, standing long jump, and handgrip) with 92 neurology-related circulating proteins in children with overweight/obesity; and (ii) to explore whether CRF (i.e., VO_2peak) attenuates this relationship. Altogether, our hypothesis was that children with higher muscular levels have a better profile in neurology-related circulating blood levels of selected proteins.

2 | METHODS

2.1 | Participants

This cross-sectional study was conducted within the framework of the ActiveBrains project. For eligibility criteria, children require (1) to be between 8.0 and 11.9 years of age, (2) to be overweight or obese, categorized by international body mass index standards (World Obesity Federation), which corresponding specifically to >1SD according to sex and age,[26,27] (3) not to have any physical impairment or neurological disorder that restricts physical exercise, (4) not to take any medication that

influence central nervous system function, and (5) in the case of the girls, not having started the menstruation at baseline. Exclusion criteria were defined as follows: left-handedness (information acquired by the Edinburgh inventory), Attention-Deficit Hyper-activity Disorder (assesed by ADHD rating scale), and other self-reported psychiatric diagnoses.[10]

From a total of 109 participants, 86 Caucasian children (10.1 ± 1.1 years old; 41% girls) had valid baseline data (obtained between November 2014 and February 2016) on the compilation of variables included in the present analysis, except for data from muscular strength laboratory tests (leg and bench press) that were only available for 72 and 71 children, respectively. Description and characteristics of the trial were given to the parents or legal tutors, and written informed consent (following the Declaration of Helsinki) was provided to both the parents/tutor and the subject. University of Granada ethical committee approved The ActiveBrains trial (Reference: 848, February 2014).

2.2 | Physical fitness components

Muscular strength was evaluated in laboratory conditions ($n = 72$) and field testing ($n = 86$). Either laboratory (i.e., bench press and leg press) or field (i.e., handgrip and standing long jump) tests show valid and reliable sources for assessing muscular strength in children and adolescents.[28] In laboratory conditions, each participant's 1-repetition maximum was assessed when the participant was able to lift the full range of motion either in bench press or leg press testing. This maximum weight lifted was used in the analysis. In the field tests, the ALPHA battery of health-related physical fitness for children and adolescents was used to measure the muscular strength (handgrip test and standing long jump test). A complete description of the validity and reliability of the ALPHA battery has been reported elsewhere.[28] The handgrip strength test evaluated upper limb strength (TKK 5101 Grip D, Takei, Tokyo, Japan). The maximum score from two repetitions of each hand was obtained. The average from the best repetition of each hand was used. Lower limb strength was measured by the standing long jump. It was executed three times, and the longest jump was recorded in centimeters. Detailed information is available elsewhere.[29]

2.3 | Neurology targeted proteomics

Blood was obtained between 8 and 9 a.m. after an overnight fast (at least 12 h). Blood was collected in EDTA tubes by venipuncture and was centrifuged at 1000 × ***g*** for 10 min at 4°C. Isolated plasma was stored at −80°C. The 92 neurology-related proteins were quantified in plasma (1 μL) at the Olink laboratory in Uppsala, applying the PEA (Proximity Extension Assay) methodology. Details about PEA technology, assays performance, and validation data have been reported elsewhere and are available from the manufacturer's website (https://olink.com/). For the Olink target 92 Neurology protein assay, the protein MAPT was excluded from the statistical analysis because it was below the limit of detection in all plasma samples.

2.4 | VO_2peak

The assessment of CRF represented by VO_2peak was described elsewhere.[25] Briefly, VO_2peak was assessed using a metabolic cart (CPX Ultima CardiO_2, Medical Graphics) while performing a maximal incremental treadmill test (HP-Cosmos ergometer). The slope began at 6% with a 1% degree increment every minute until voluntary exhaustion, while the speed was steady during the incremental test (i.e., 4.8 km/h). CRF (i.e., VO_2peak) was expressed in relation to body weight (mL/kg/min).

2.5 | Confounders

Sex, peak height velocity (PHV), parental education level, body mass index (BMI) and CRF (i.e., VO_2peak) were used as potential confounders in the analyses, according to our previous study.[25] PHV was calculated to obtain the maturational status of the children using validated algorithms. Parental educational level was evaluated using a self-report questionnaire filled by the parents, and responses from both parents were pooled, as neither parent had a university degree; one parent had a university degree; and both parents had a university degree. Bodyweight and height were assessed using an electronic scale and a stadiometer (Seca Instruments, Germany, Ltd), and BMI was expressed in kg/m^2.

2.6 | Statistical analysis

R (version 4.2.0; R Foundation for Statistical Computing) was used for statistical analyses, and a threshold of $p < 0.05$ was assumed to be statistically significant. The characteristics of the study sample are shown as means and standard deviations or percentages. Multiple linear regression models were used to study the associations between obesity (i.e., BMI) and muscular strength variables (i.e., handgrip, standing long jump, bench press, and leg press) and circulating neurology-related

proteins. Multicollinearity analysis showed variance inflation factor values below 1.5, representing absence of multicollinearity in the model (see Figure S2 and File S3). Standardized β values from Model 1 were obtained after including sex, PHV, parental education, and BMI as covariates. Standardized β values from Model 2 were obtained after additionally adjusting by CRF. Because of the number of comparisons (4 muscular strength variables and 91 proteins), a false discovery rate (FDR) correction (Benjamini and Hochberg) was applied to the results of each muscular strength variable (i.e., 91 comparisons per predictor) using the "p.adjust" function in R.

2.7 | Protein–protein interaction network construction

STRING (Search Tool for the Retrieval of Interacting Genes/Proteins: http://string-db.org/) was used to analyze the functional connections and protein–protein interactions (PPI). PPI networks are essential components for understanding cellular processes at the systems level. Exploration of predicted interaction networks might suggest novel directions for future experimental investigations and provide predictions for efficient mapping of interactions. Required score (indicators of the confidence of the interaction, rank from 0 to 1) was set at low confidence (0.150) and FDR stringency to medium (5%). The number of nodes and edges of each protein was counted, and the PPI network of the proteins was constructed.

3 | RESULTS

The descriptive characteristics of the participants are summarized in Table 1. Of 86 participants, 59% were boys, and 41% were girls. Participants showed a BMI of 26.4 kg/m^2, being 36% of them overweight and 64% obese. Regarding the education university level of the parents, 64% did not have any and 36% had at least one of the parents with university education. In Model 1, BMI was positively associated with 14 proteins (ADAM23, CPM, GDF8, GFRalpha1, IL12, NCDase, NTRK2, SCARF2, SIGLEC1, SKR3, TNFRSF21, THY1, TNR, WFIKKN1) while it was inversely related to 1 protein (TMPRSS5) with standardized β values ranging from −0.327 to 0.415. In Model 2, BMI was positively associated with 12 proteins (CLEC10A, CPM, GDF8, GFRalpha1, IL12, NCDase, PDGFRalpha, ROBO2, SKR3, SMPD1, TNR, WFIKKN1) while it was negatively associated with 2 proteins (NBL1, TMPRSS5) with standardized β values ranging from −0.367 to 0.424 (all $p \leq 0.05$; File S4).

Figure 1 shows the associations of muscular strength variables (i.e., handgrip, standing long jump, bench press, and leg press) with the 91 circulating neurology-related proteins (for the full name of the proteins see File S1). Muscular strength tests showed moderate correlation between them (i.e., coefficients ranging from 0.44 to 0.63) (see Figure S1). In Model 1, muscular strength variables showed 15 negative associations with 12 proteins (CLEC1B, CTSC, CTSS, gal-8, GCP5, NAAA, NrCAM, NTRK2, PLXNB3, RSPO1, sFRP3, and THY1) with standardized β values ranging from −0.364 to −0.255 (all $p \leq 0.05$); while muscular strength variables revealed 14 positive associations with 12 proteins (BetaNGF, CDH6, CLEC10A, CLM1, FcRL2, HAGH, IL12, LAIR2, MSR1, SCARB2, SMOC2, and TNFRSF12A) with standardized β values ranging from 0.233 to 0.445 (all $p \leq 0.05$). In Model 2, upon the inclusion of CRF as a covariate (Figure 1; Model 2), muscular strength variables were inversely associated with two proteins (gal-8 and NrCAM) with standardized β values ranging from −0.311 to −0.301; while muscular strength variables produced nine positive associations with eight proteins (BetaNGF, CDH6, CLEC10A, FcRL2, LAIR2, MSR1, SCARB2, and TNFRSF12A) standardized β values ranging from 0.282 to 0.479 (all $p \leq 0.05$) (for linear regression models disclosure see File S2**)**. CLEC10A (C-type lectin domain family 10 member A) was the only protein that remained statistically significant after applying FDR correction (FDR <0.05) in both models.

Figure 2 shows the functional association networks using as input the circulating neurology-related proteins that were associated with muscular strength variables from Model 1 and Model 2 (non-corrected $p < 0.05$). Both networks are enriched in terms of PPI (PPI <0.01), and proteins in red from the network of Model 1 are involved in neuron processes (FDR <0.05; $\text{Max}_{r2} = 2.26$). In Model 2, no association between proteins was found in the network. The detailed information (e.g., molecular function, biological process, pathways, and tissue expression) of the 10 proteins associated with muscular strength variables independently of CRF is reported in Table 2.

4 | DISCUSSION

In this study, we examined the association between muscular strength and neurological-related circulating proteins, and whether CRF attenuates this relationship. Muscular strength is related to 24 out of 91 neurological proteins in children with overweight/obesity. Particularly, muscular strength shows positive associations with 12 proteins and negative associations with 12 proteins. Remarkably, neuronal action potential propagation was the most significantly enriched pathway in this model.

TABLE 1 Descriptive characteristics of the sample.

	All		Boys		Girls	
	N		*n*		*n*	
Physical characteristics	86		51		35	
Age (years)		10.08 ± 1.13		10.27 ± 1.12		9.79 ± 1.09
Weight (kg)		55.23 ± 11.24		55.60 ± 10.57		54.68 ± 12.29
Height (cm)		144.05 ± 8.64		144.65 ± 7.98		143.19 ± 9.59
Peak height velocity offset (years)[a]		−2.26 ± 0.97		−2.60 ± 0.80		−1.76 ± 0.99
Body mass index (kg/m^2)		26.37 ± 3.49		26.39 ± 3.56		26.35 ± 3.45
Cardiorespiratory fitness (mL/kg/min)[b]		37.59 ± 4.57		38.15 ± 4.61		36.78 ± 4.44
Body mass index category (%)	86		51		35	
Overweight		36.0		33.3		40.0
Obesity type I		51.2		51.0		51.4
Obesity type II/III		12.8		15.7		8.6
Parental education university level (%)	86		51		35	
None of the parents		64.0		68.6		57.1
One of the two parents		18.6		15.7		22.9
Both parents		17.4		15.7		20.0
Muscular strength measurements						
Handgrip (kg)	86	16.69 ± 4.20	51	17.11 ± 4.47	35	16.08 ± 3.74
Standing long jump (cm)	86	106.47 ± 18.28	51	107.92 ± 17.16	35	104.34 ± 19.86
Maximal repetition of bench press (kg)	71	21.46 ± 4.43	45	22.47 ± 4.55	26	19.73 ± 3.68
Maximal repetition of leg press (kg)	72	135.96 ± 26.81	45	137.02 ± 28.95	27	134.19 ± 23.22

Note: Values are mean ± SD or percentages.

[a]Peak height velocity offset was calculated as described for boys: −8.1 + (0.0070346 × (age × sitting height)) and girls: −7.7 + (0.0042232 × (age × height)).

[b]Cardiorespiratory fitness was assessed with an incremental treadmill test, and it was conducted with the use of a gas analyzer.

However, after controlling for CRF only 10 proteins (two downregulated and eight upregulated) remained related to muscular strength independently. Unfortunately, no enriched pathway was significant in this model. These proteins were involved in several biological process such as adaptive and innate immune response, cholesterol and lipoprotein transport, amyloid-beta clearance, angiogenesis, axon guidance, axonogenesis, among others. Notably, CLEC10A and FcRL2 are two neurological-related upregulated proteins, which are associated with at least two muscular strength indicators even after CRF adjustment, and one of them survived FDR correction (CLEC10A). Thus, several proteins involved in neuromuscular pathways were associated with muscular strength independent of CRF in children with overweight/obesity.

Interestingly, in our study, muscular strength (i.e., handgrip and bench press) was positively associated with CLEC10A in plasma, independent of CRF levels. CLEC10A, also known as macrophage galactose-type C-type lectin 1 (MGL1) or CD301, is a single-pass type II membrane protein with anti-inflammatory properties, involved in the regulation of immune responses. CLEC10A is associated with the enhancement of the adaptive and innate immune response of immune cells.[30] In previous studies with the present sample of overweight/obese children,[19,25] we found that CRF was also positively associated with circulating levels of CLEC10A[25]; however, a 20-week exercise intervention combining aerobic and strength training had no effects on CLEC10A levels.[19] Recent evidence has shown that, after an acute bout of bilateral arm resistance exercise with a previous program of 12 weeks unilateral arm resistance training, significant increases in M2 macrophages have been found in the skeletal muscle of the trained arm, correlating with anti-inflammatory and protective processes.[31] Importantly, M2 macrophages, involved in anti-inflammatory responses, manifest high

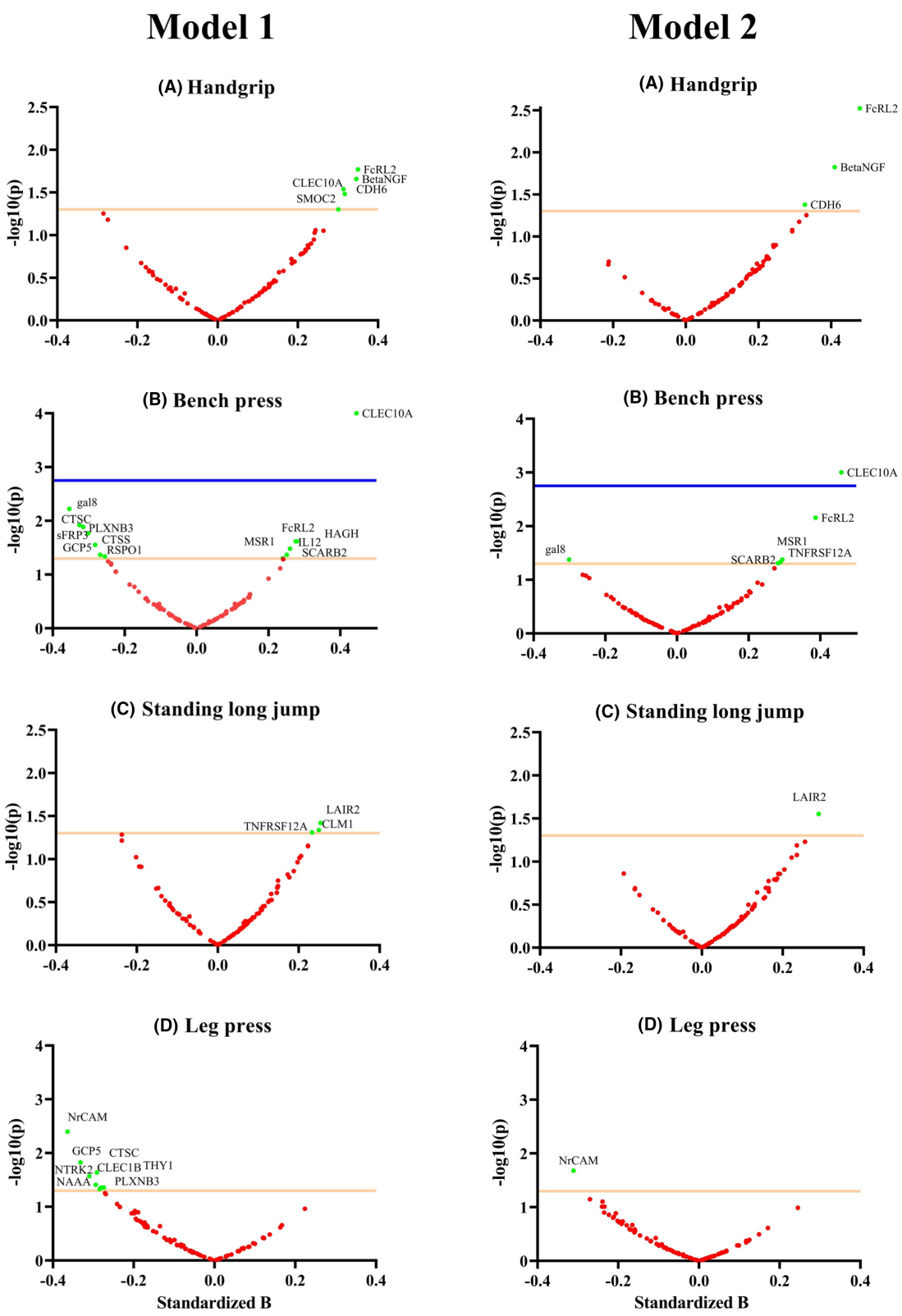

FIGURE 1 Volcano plots showing associations of muscular strength variables with proteins from the Olink neurological assay. Volcano plots show significative proteins ($p < 0.05$) in green and non-significative ($p > 0.05$) in red. The *x*-axis reflects the standardized B values from the linear regression models. The *y*-axis indicates statistical significance and the horizontal orange line showing the non-corrected $p < 0.05$ cut-point and the blue line showing the statistical significance cut-point after adjusting for multiple comparisons (False discovery rate of Benjamini [FDR] $p < 0.05$). Model 1 was adjusted by sex, peak height velocity, parental education, and body mass index. Model 2 was additionally adjusted by cardiorespiratory fitness.

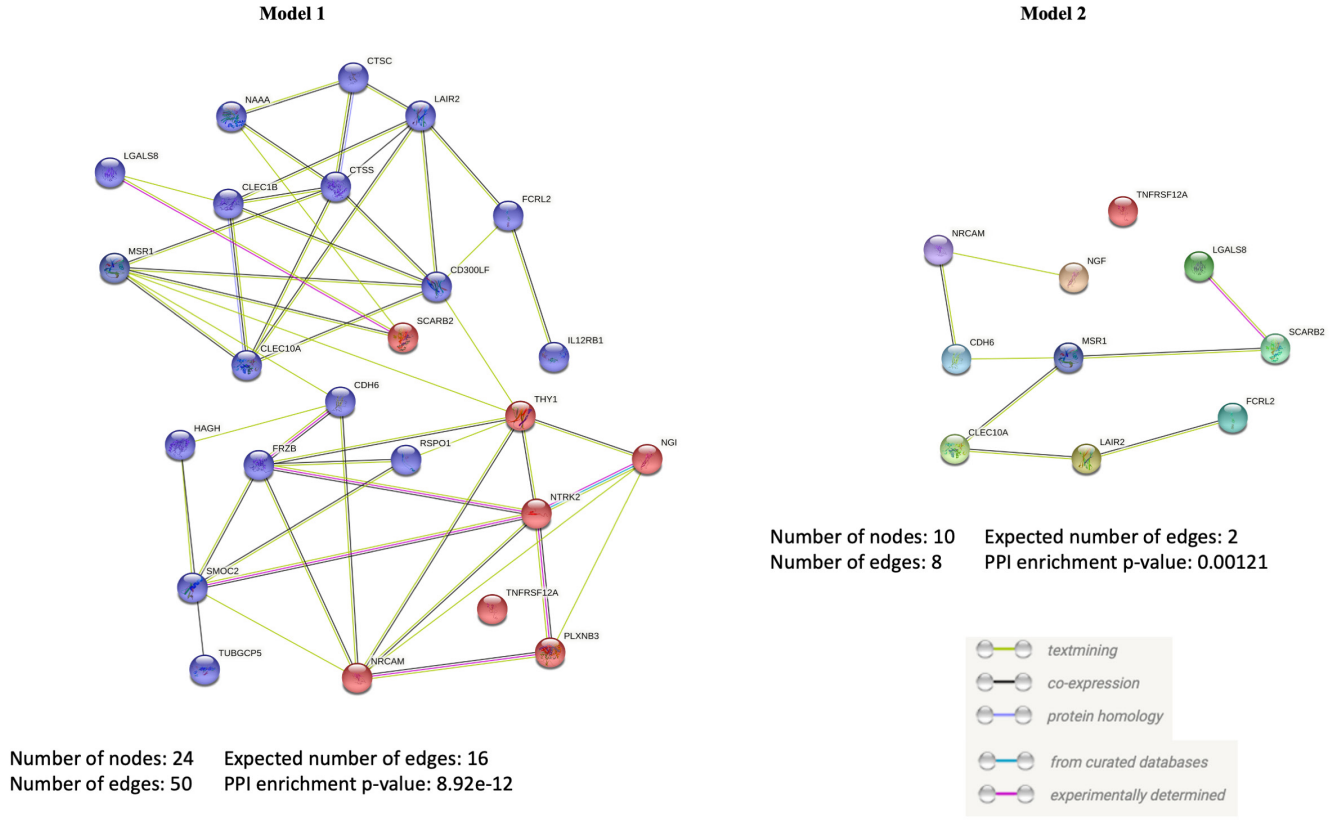

FIGURE 2 Functional association networks of muscular strength-related neurology proteins. The network from Model 1 consists of 24 nodes and 50 edges, whereas the network from Model 2 consists of 10 nodes and 8 edges. Protein–protein interactions (PPIs) describe how proteins interact together in protein complexes or functional modules. Lower PPIs enrichment p-values indicate a better functional association. The edges between nodes represent the interactions between proteins. The yellow line (*textmining*) indicates proteins jointly located in the same publication. The black line (*co-expression*) indicates proteins that are co-expressed in the same or in other species. The violet line (*protein homology*) indicates the sequence similarity between proteins. The pink line (*experimentally determined*) indicates proteins which are putative homologs in other species. The blue line (*from curated databases)* indicates proteins involved in the same biological, molecular, or metabolic pathways proofread. The legend describes topological statistics of the network: they are strongly enriched in terms of functional associations, as compared to a random network of similar size. Proteins in red from Model 1 are involved together in different biological processes (i.e., neuronal action potential propagation, regulation of axogenesis, regulation of neuron projection development and differentiation) while proteins in blue have no participation together in any biological process. In Model 2, no role is given to the protein color. Strength of these associations from Model 1 ranging from 1.05 to 2.26 (FDR <0.05). After adjusting with cardiorespiratory fitness (Model 2), none of these associations remained.

levels of CLEC10A,[32] which may partially explain present findings. Our study suggests that CLEC10A in plasma could be considered a novel anti-inflammatory biomarker related to higher muscular strength levels in children with overweight/obesity. However, the current study design precludes revealing the specific molecular mechanisms of how CLEC10A can affect brain health, future mechanistic studies and randomized controlled trials examining the effects of different types of exercise (i.e., aerobic vs strength training or concurrent training) on neurological-related circulating proteins are warranted.

Muscular strength (i.e., handgrip and bench press) was also positively associated with FcRL2 plasma levels. FcRL2 is a single-pass type I membrane protein with regulatory role in normal and neoplastic B-cell development, fundamental in immunity and inflammatory response.[33] In obesity, B cells regulate adipose tissue inflammation.[34] Remarkably, acute exercise is involved in B-cell mobilization and proliferation.[35] By the same token, a novel study with a 6-week exercise intervention induced positive changes in B-cell distribution in elderly women.[35] Thus, FcRL2 may serve as a positive regulator of memory B-cell response to recall antigens to encounter obesity problems.[34] An essential pathway by which systemic inflammation may cause neuronal damage is via communication across the blood–brain barrier (BBB).[36] Increased BBB permeability is witnessed in many neurological and psychiatric disorders (e.g., stroke, Alzheimer's disease, Parkinson's disease, and epilepsy). Thereby, disruption of the BBB integrity opens the gates to the central nervous

TABLE 2 Framework of significative proteins from Model 2.

Protein name	Protein features (UniprotKB entry, length and mass)	Cellular location	Molecular function	Biological process	Pathway	Tissue Protein expression (BioGPS)[a]
BetaNGF	P01138 241 26.959 Da	Located outside the cell membrane(s) and in the endosomal compartment bounded by the endosomal membrane. It is important for the development and maintenance of the sympathetic and sensory nervous systems. Activates cellular signaling cascades to regulate neuronal proliferation, differentiation and survival	Enables cysteine-type endopeptidase activator activity, involved in apoptotic process, death receptor agonist activity, growth factor activity, lipid binding, metallo-endopeptidase inhibitor activity and protein binding	Involved in activation of cysteine-type endopeptidase activity involved in apoptotic process, extrinsic apoptotic signaling pathway via death domain receptors, memory, modulation of chemical synaptic transmission and negative regulation of cell population proliferation	Apoptosis, MAPK signaling and neurotrophin signaling	Ciliary ganglion, subthalamic nucleus, Burkitt lymphoma, liver, skeletal muscle
CDH6	P55285 790 88.309 Da	Located in the cell membrane. Single pass type I membrane protein. Calcium-dependent cell adhesion protein. They preferentially interact with themselves in a homophilic manner in connecting cells; cadherins may thus contribute to the sorting of heterogeneous cell types	Enables cadherin and calcium ion binding	Involved in adherent's junction organization, calcium-dependent cell–cell adhesion via plasma membrane cell adhesion molecules, cell morphogenesis, cell adhesion, and Notch signaling	Cell junction organization and ERK signaling	Superior cervical ganglion, heart, skeletal muscle, trigeminal ganglion, and Burkitt lymphoma
CLEC10A	Q8IUN9 316 35.446 Da	Located in the cell membrane. Single pass type II membrane protein. Probable role in regulating adaptive and innate immune responses. Binds in a calcium-dependent manner to terminal galactose and N-acetylgalactosamine units, linked to serine or threonine. These sugar moieties are known as Tn-Ag and are expressed in a variety of carcinoma cells	Enables carbohydrate and protein binding	Involved in adaptive and innate immune response, biological process involved in interspecies interactions between organisms, endocytosis	Innate immune system	$CD14^+$ monocytes, $BDCA4^+$ dendritic cells, $CD33^+$ myeloid, lung and liver

(Continues)

TABLE 2 (Continued)

Protein name	Protein features (UniprotKB entry, length and mass)	Cellular location	Molecular function	Biological process	Pathway	Tissue Protein expression (BioGPS)[a]
FcRL2	Q96LA5 508 55.542 Da	Located in the cell membrane. Single pass type I membrane protein. May have a regulatory role in normal and neoplastic B-cell development	Enables protein binding, protein phosphatase binding, signaling adaptor activity and transmembrane signaling receptor activity	Involved in cell surface receptor and cell–cell signaling	B-cell regulation	$CD19^+$ B cells, tonsil, Burkitt lymphoma, lymphnode, and promyelocytic leukemia
gal-8	O00214 317 35.808 Da	Located in cell cytoplasm. Cytoplasmic vesicle. Acts as a sensor of membrane damage caused by infection and restricts the proliferation of infecting pathogens by targeting them for autophagy. Detects membrane rupture by binding beta-galactoside ligands located on the lumenal side of the endosome membrane; these ligands becoming exposed to the cytoplasm following rupture	Enables carbohydrate, integrin and protein binding	Involver in cellular response to virus, lymphatic endothelial cell migration and xenophagy	Autoimmune inflammation	Testis interstitial, testis germ cell, bronchial epithelial cells, testis Leydig cell and testis seminiferous tubule
LAIR2	Q6ISS4 152 16.280 Da	Protein located outside the cell membrane (secreted). Unknown function, it is thought that could help to modulate mucosal tolerance	Enables protein binding	Act as a decoy receptor by binding collagen with higher affinity than LAIR-1	Class I MHC mediated antigen processing and presentation and innate immune system	CD56+ Nkcells, appendix, placenta, medulla oblongata, and skeletal muscle
MSR1	P21757 451 49.762 Da	Protein also located in the cell membrane. Single pass type II membrane protein. Implicated in the pathologic deposition of cholesterol in arterial walls during atherogenesis. Two types of receptor subunits exist. These receptors mediate the endocytosis of a diverse group of macromolecules, including modified low-density lipoproteins	Enables amyloid-beta binding, cargo receptor activity, low-density lipoprotein particle and protein binding and scavenger receptor activity	Involved in amyloid-beta clearance, cellular response to organic cyclic compound, cholesterol and lipoprotein transport, negative regulation of gene expression and phagocytosis, engulfment	Phagosome	Lung, superior cervical ganglion, pineal night, appendix, and cardiac myocytes

TABLE 2 (Continued)

Protein name	Protein features (UniprotKB entry, length and mass)	Cellular location	Molecular function	Biological process	Pathway	Tissue Protein expression (BioGPS)[a]
NrCAM	Q92823 1304 143.890 Da	Located in the cell membrane, cell projection (axon) and nodes of Ranvier (secreted in all locations). It is required for normal responses to cell–cell contacts in brain and in the peripheral nervous system. Plays a role in neurite outgrowth in response to contacting binding. Plays a role in mediating cell–cell contacts between Schwann cells and axons. Plays a role in the formation and maintenance of the nodes of Ranvier on myelinated axons	Enables ankyrin binding, cell–cell adhesion mediator activity, protein binding and protein binding involved in heterotypic cell–cell adhesion	Involved in angiogenesis, axon guidance, axonal fasciculation, axonogenesis and brain development	CAMs	Occipital lobe, subthalamic nucleus, prefrontal cortex, Burkitt lymphoma and liver
SCARB2	Q14108 478 54.290 Da	Located in the lysosome membrane. Acts as a lysosomal receptor for GBA targeting and acts as a receptor for enterovirus 71	Enables cargo receptor activity, chaperone, enzyme, phosphatidylcholine, phosphatidylserine and cholesterol binding	Involved in aminophospholipid transport, gene expression, positive regulation of neuron projection development, protein targeting to lysosome and receptor-mediated endocytosis	Lysosome	Prostate, pineal day and night, prefrontal cortex and appendix
TNFRSF12A	Q9NP84 129 13.911 Da	Located in the cell membrane. Single pass type I membrane protein. Receptor for TWEAK. Weak inducer of apoptosis in some cell types. Promotes angiogenesis and the proliferation of endothelial cells. May modulate cellular adhesion to matrix proteins	Enables protein binding	Involved in angiogenesis, positive regulation apoptotic process, cell adhesion, and differentiation, positive regulation of extrinsic apoptotic signaling pathway and regulation of wound healing	Cytokine-cytokine receptor interaction	Bronchial epithelial cells, smooth muscle, colorectal adenocarcinoma, placenta and heart

Note: Data were gathered from different bioinformatics databases (Searching Tool for the Retrieval of Interacting Genes/Proteins [STRING], UniProtKB, NextProt, Genecards, Kyoto Encyclopedia of Genes and Genomes [KEGG] and Biology Gen Portal Services [BioGPS]).

Abbreviations: BetaNGF, beta-nerve growth factor; CAMs, cell adhesion molecules; CDH6, cadherin-6; CLEC10A, C-type lectin domain family 10 member A; ERK, extracellular signal-regulated kinase; FcRL2, Fc receptor-like protein 2; gal-8, galectin-8; GBA, glucosylceramidase; LAIR1, leukocyte-associated immunoglobulin-like receptor 1; LAIR2, leukocyte-associated immunoglobulin-like receptor 2; MAPK, mitogen-activated protein kinase; MHC, major histocompatibility complex; MSR1, macrophage scavenger receptor types I and II; NrCAM, neuronal cell adhesion molecule; SCARB2, lysosome membrane protein 2; TNFRSF12A, tumor necrosis factor receptor superfamily member 12A; TWEAK, TNF-related weak inducer of apoptosis.

[a]The five tissues with higher expression scores were reported, obtained from the BioGPS.

system setting, leading to disastrous consequences regarding brain health.[37] Our results suggests that CLEC10A and FcRL2 could have an anti-inflammatory role related to higher muscular strength levels and may be involved in the preservation of brain health.

Our functional association network enrichment analysis includes 24 nodes (i.e., Model 1), corresponding with 24 neurological proteins, 12 upregulated (i.e., BetaNGF, CDH6, CLEC10A, CLM1, FcRL2, HAGH, IL12, LAIR2, MSR1, SCARB2, SMOC2, and TNFRSF12A) and 12 downregulated (i.e., CLEC1B, CTSC, CTSS, gal-8, GCP5, NAAA, NrCAM, NTRK2, PLXNB3, RSPO1, sFRP3, and THY1) by muscular strength. Proteins associated with muscular strength are involved in different biological processes, including neuronal action potential propagation, regulation of axogenesis and regulation of neuron projection development and differentiation. The most significantly enriched pathway was neuronal action potential propagation (NrCAM and NTRK2 proteins). Neuronal action potentials may regulate myelination during development, a crucial process that enhances the speed of neural communication.[38] In this sense, human studies have shown that improved muscular strength induces changes in the myelin sheath,[39,40] and increases the levels of platelet-derived and fibroblast growth factors, closely linked to oligodendrocytes proliferation, fundamental in myelin sheath health.[41] Indeed, in a previous study with the present sample of children with overweight/obesity, we found that muscular strength could influence white matter volumes coupled with better academic performance.[4] However, when CRF was considered in the analysis, functional association network enrichment analysis includes 10 nodes, corresponding with 10 neurological proteins, eight upregulated (i.e., BetaNGF, CDH6, CLEC10A, FcRL2, LAIR2, MSR1, SCARB2, and TNFRSF12A) and two downregulated (i.e., gal-8 and NrCAM) by muscular strength; and no association between proteins was found in the network. Therefore, this suggests CRF may attenuate the negative relationships between muscular strength on neurological-related circulating proteins in children with overweight/obesity.

These findings, yet promising, must be viewed with some caution. First, considering the cross-sectional study design and exploratory approach, it is not possible to assume causality. Second, our relatively small sample ($n = 86$) implies less power, and therefore, additional proteins might be identify as relevant in future studies with larger sample sizes. Third, only one of the proteins persisted FDR correction (i.e., CLEC10A). Nonetheless, to the best of our knowledge, this is the first study performing proteomics analysis using PEA technology to investigate the relationship between muscular strength variables and novel neurological circulating proteins, and CRF as a confounder on these associations in children. Additional strengths include (i) VO_2 peak was measured using a gold standard method in an adapted protocol of treadmill for children with overweight/obesity, and (ii) muscular strength was assessed in both laboratory and field conditions with valid and reliable tests.

In conclusion, our results show that muscular strength is associated with proteins (βNGF, CDH6, CLEC10A, FcRL2, gal-8, LAIR2, MSR1, NrCAM, SCARB2, and TNFRSF12A) involved in neurology, neurobiology, inflammation, and immunity pathways. Further, PPI using STRING database detected enriched pathways in neuron development and function. Interestingly, CLEC10A remained statistically significant after FDR correction. Broadly translated our findings may indicate how muscular strength is related to brain health. Still, these findings need to be supported with exercise randomized control trials using larger sample sizes and addressing the effects of different types of exercise (i.e., aerobic vs. muscular training) on neurology-related circulating proteins in children with overweight/obesity.

5 | PERSPECTIVE

Muscular strength and CRF are the core markers of physical function connected with a better brain health in the pediatric population, which can be improved by resistance and aerobic training. In this work, Olink's PEA technology was used to discover association patterns between muscular strength and targeted protein biomarkers related to brain health. Indeed, we shown that muscular strength is associated independently of CRF negatively with 2 proteins (gal-8 and NrCAM) and positively with 8 proteins (BetaNGF, CDH6, CLEC10A, FcRL2, LAIR2, MSR1, SCARB2, and TNFRSF12A). Altogether, the blood proteomic profile spotted in our sample contributes to the understanding of molecular mechanisms and biological pathways (e.g., angiogenesis, beta-amyloid clearance, and immune response) through which muscular strength could improve brain health in childhood from a proteomic approach. In addition, our results suggest that CRF seems to attenuate the effect of downregulated levels of neurological-related proteins associated with muscular strength.

AUTHOR CONTRIBUTIONS

Marcos Olvera-Rojas had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Marcos Olvera-Rojas, Abel Plaza-Florido, Patricio Solis-Urra, Irene Esteban-Cornejo, and Francisco B. Ortega. Acquisition, analysis, or interpretation of data: Marcos Olvera-Rojas, Abel Plaza-Florido, Patricio Solis-Urra,

María Rodriguez-Ayllon, Irene Esteban-Cornejo, and Francisco B. Ortega. Drafting of the manuscript: Marcos Olvera-Rojas. Critical revision of the manuscript for important intellectual content: Abel Plaza-Florido, Patricio Solis-Urra, María Rodriguez-Ayllon, Angel Toval, Irene Esteban-Cornejo, and Francisco B. Ortega. Statistical analysis: Marcos Olvera-Rojas, Abel Plaza-Florido, Patricio Solis-Urra, and Francisco B. Ortega. Obtained funding: Irene Esteban-Cornejo and Francisco B. Ortega.

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CONFLICT OF INTEREST STATEMENT

The authors state that the research was conducted in the absence of any commercial or financial relationships that could be interpreted as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

We did not obtain children's parents consent to widely share the data nor was it included in the IRB protocol.

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SUPPORTING INFORMATION

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

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