J Musculoskelet Neuronal Interact 2020; 20(3):332-338

Journal of Musculoskeletal and Neuronal Interactions JMNI

Original Article

Exploring the brain-body composition relationship in Huntington's disease

Mitchell Turner[1,2], Alvaro Reyes[3], Danielle M. Bartlett[1,2], Scott Culpin[1,2], Nicolas H. Hart[1,2,4,5], Luca Hardt[6], Kirk Feindel[7,8,9], Govinda R. Poudel[10], Mel Ziman[1,9], Travis M. Cruickshank[1,2,11]

[1]School of Medical and Health Sciences, Edith Cowan University, Perth, Australia; [2]Exercise Medicine Research Institute, Edith Cowan University, Perth, Australia; [3]Facultad de Ciencias de la Rehabilitacion. Universidad Andrés Bello, Chile; [4]Institute for Health Research, University of Notre Dame Australia, Perth, Australia; [5]Western Australian Bone Research Collaboration, Perth, Australia; [6]Institute for Cardiovascular Research and Sports Medicine, German Sport University, Cologne, Germany; [7]Centre for Microscopy, Characterisation and Analysis, University of Western Australia, Australia; [8]School of Biological Sciences, University of Western Australia, Perth, Australia; [9]School of Biomedical Science, University of Western Australia, Perth, Australia; [10]Mary MacKillop Institute for Health Research, Australian Catholic University, Melbourne, Australia; [11]Perron Institute for Neurological and Translational Science, Perth, Australia

Abstract

Objective: Changes in body composition are a common feature of Huntington's disease (HD) and are associated with disease progression. However, whether these changes in body composition are associated with degeneration of the striatum is unknown. This study aimed to explore the associations between body composition metrics and striatal brain volume in individuals with premanifest HD and healthy controls. **Methods**: Twenty-one individuals with premanifest HD and 22 healthy controls participated in this cross-sectional study. Body composition metrics were measured via dual-energy X-ray absorptiometry. Structural magnetic resonance imaging of subcortical structures of the brain was performed to evaluate striatal volume. **Results**: There were no significant differences in body composition metrics between the premanifest HD and healthy controls group. Striatal volume was significantly reduced in individuals with premanifest HD compared to healthy controls. A significant association between bone mineral density (BMD) and right putamen volume was also observed in individuals with premanifest HD. **Conclusion**: These findings show striatal degeneration is evident during the premanifest stages of HD and associated with BMD. Additional longitudinal studies are nevertheless needed to confirm these findings.

Keywords: Bone mineral density, Caudate volume, Fat percentage, Putamen Volume, Striatum volume

Introduction

Body composition changes are a hallmark feature of Huntington's disease [HD][1]. Unintentional weight loss is considered a prominent and well-documented outcome in individuals affected by the disease[2,3]. Individuals with manifest and premanifest HD are observed to have reduced bone mineral density (BMD), fat mass and lean tissue mass[4].

Previous studies have documented a link between body mass index (BMI) values and the clinical progression of HD. In particular, relatively high BMI values have been found to be a robust predictor of disease progression, associated with a lower rate of functional, motor and cognition deterioration[2,5]. These findings indicate that body composition has a significant modulatory role on the clinical trajectory of HD. However, the relationship between body composition metrics and neuropathology, particularly striatal volume loss[6,7], is yet to be investigated.

The purpose of this exploratory study was to investigate, for the first time, associations between BMI and other body composition metrics, including lean tissue mass, fat mass and BMD and striatal pathology (caudate and putamen) in individuals with premanifest HD and healthy controls. Based on recent findings[2], we hypothesised that greater BMI, fat

The authors have no conflict of interest.

Corresponding author: Mr Mitchell Turner, MSc, Huntington's Disease Research Group, Exercise Medicine Research Institute, School of Medical and Health Sciences, Building 21, Room 223, Edith Cowan University, 270 Joondalup Drive, JOONDALUP, Perth, WA, Australia, 6027
E-mail: mitchel.turner@ecu.edu.au

Edited by: G. Lyritis
Accepted 14 April 2020

mass, lean tissue mass and BMD values would be associated with reduced striatal degeneration in individuals with premanifest HD.

Materials and methods

Study design

A cross-sectional design was used to examine the relationships between whole-body composition (whole-body lean, fat and bone mass) and striatal volume (left and right caudate and putamen) using Dual-energy X-ray Absorptiometry (DXA) and Magnetic Resonance Imaging (MRI), respectively. All aspects of the study were performed in accordance with the Declaration of Helsinki. This study was approved by Edith Cowan University Human Research Ethics Committee (ID: 13145). All participants provided written (via signature) and informed consent prior to enrolment and participation.

Participants

Forty-three participants (21 individuals with premanifest HD; 22 healthy age- and sex-matched controls) were recruited for the study. Individuals with premanifest HD were recruited from existing databases, HD clinics and media advertisements in Perth, Western Australia, clinically defined as cytosine-adenine-guanine (CAG) repeat length >39 and a diagnostic confidence score <2 on the Unified Huntington's Disease Rating Scale Total Motor Score (UHDRS-TMS)[8]. Participants were excluded if they had known cardiovascular, immunological, endocrine, metabolic or sleep disorders, recent or ongoing substance abuse, or concomitant neurological conditions. CAG age product (CAP) and disease burden score (DBS) data are measures of genetic burden and are presented for premanifest HD participants in Table 1. CAP score was calculated by multiplying the age at study entry by a scaling of the CAG repeat length as follows: CAPS=(Age × (CAG-33.66))/432.3326. CAP scores <1, 1 and >1 indicate a 5-year diagnosis probability of <0.5, 0.5 and >0.5, respectively[9]. DBS was calculated using the method described by Penney et al.[10]. One participant contributed incomplete data and was excluded from all analyses, resulting in 21 participants with premanifest HD and 22 healthy controls.

Study procedures

Anthropometry

Height was assessed using a wall-mounted stadiometer (Model 222, Seca, Hamburg, DE) to the nearest 0.1 centimetre (cm) in triplicate, with the average recorded. Weight was assessed using an electronic weight scale (AE Adams CPW Plus-200, Adam Equipment Inc., CT, USA) to the nearest 0.1 kilogram (kg). BMI was subsequently calculated for each participant as weight in kg, divided by height in metres squared (kg/m^2).

Dual-energy X-ray Absorptiometry (DXA)

Whole body lean tissue mass, lean mass index (LMI: lean tissue mass [kg]/(height [m])^2), fat mass, fat percentage, trunk fat mass, estimated visceral adipose tissue mass[11], fat mass index (FMI: fat mass [kg]/(height [m])^2) and BMD were assessed using DXA (Hologic Discovery A, Waltham, MA, USA). Standardised and reliable body positioning and scanning procedures were applied for all scans[12] whole body scan models separate the body into axial and appendicular regions, however there is a need for localised appendicular segmentation models to further examine regions of interest within the upper and lower extremities. Similarly, inconsistencies pertaining to patient positioning exist in the literature which influence measurement precision and analysis outcomes highlighting a need for standardised procedure. This paper provides standardised and reproducible: 1, shown to produce scan/re-scan coefficient of variations below 1% in our laboratory[12,13] whole body scan models separate the body into axial and appendicular regions, however there is a need for localised appendicular segmentation models to further examine regions of interest within the upper and lower extremities. Similarly, inconsistencies pertaining to patient positioning exist in the literature which influence measurement precision and analysis outcomes highlighting a need for standardised procedure. This paper provides standardised and reproducible: 1. Daily spine, step and radiographic uniformity calibrations were undertaken in accordance with manufacturer specifications.

Magnetic Resonance Imaging (MRI)

T_1-weighted structural images of the brain were acquired from each participant using a 3T MRI scanner (GE Healthcare Discovery MR750W, General Electric Company, NSW, Australia). Images were acquired with a 24-channel head coil using an IR-SPGR sequence (TA=9 m 59 s, TR=3 s, TE=3.1 ms, TI=400 ms, flip angle=11°, field of view=256 mm x 256 mm, image matrix=256 x 256, 1 mm^3 isotropic voxels). Acquired T_1-weighted MRI images were automatically processed with the longitudinal processing pipeline available in FreeSurfer[14]. The FreeSurfer pipeline creates an unbiased within-subject template using robust registration[14]. Other processing steps such as skull stripping, Talairach transforms, atlas registration, and spherical surface maps and parcellations, were then initialised with information from the within-subject template[14]. Volume of subcortical structures, including the caudate and putamen, were extracted and used in statistical analyses.

Statistical analysis

Participant demographics, clinical characteristics, body composition and striatal volume metrics are reported as mean and standard deviation unless otherwise stated. Normality assumptions were assessed using the Shapiro-Wilk test. Differences between individuals with premanifest HD and healthy controls were evaluated using independent t-tests.

Table 1. Comparison of baseline characteristics between premanifest HD and healthy control groups.

Variable	HD group (n=21)	HC group (n=22)	Difference [95% CI]	p-value
Demographic Characteristics				
Age (years)	41.90 (11.69)	45.21 (10.90)	-3.52 [-10.59; 3.54]	0.311
Male, n (%)	8 (38.1)	8 (34.8)	-	0.540
Clinical Characteristics				
CAGn	42.718 (2.88)	N/A	N/A	N/A
CAP score	0.89 (0.18)	N/A	N/A	N/A
DBS	300.062 (74.43)	N/A	N/A	N/A
UHDRS-TMS	4.93 (7.39)	N/A	N/A	N/A
DCL	0.43 (0.71)	N/A	N/A	N/A
TFC	13 (0)	N/A	N/A	N/A
Body Composition Measures				
BMI (kg/m^2)	27.02 (3.65)	26.10 (3.01)	0.91 [-1.14; 2.97]	0.186
BMD (g cm^2)	1.15 (0.11)	1.13 (0.10)	0.02 [-0.04; 0.08]	0.244
BMD T-score (SD)	-0.05 (1.02)	0.18 (1.14)	-0.23 [-1.20; 0.73]	0.690
BMD Z-score (SD)	0.41 (1.04)	0.15 (1.05)	0.25 [-0.51; 1.02]	0.250
Fat mass (g)	25042.64 (7289.16)	23661.17 (5546.43)	1381.47 [-2595.95; 5358.89]	0.243
Fat (%)	32.07 (7.34)	31.80 (6.18)	0.26 [-3.90; 4.44]	0.448
Trunk fat (g)	11868.22 (5047.93)	10289.26 (2782.57)	1578.96 [-915.82; 4073.74]	0.104
Est. VAT Mass (g)	474.09 (268.27)	371.17 (167.49)	102.22 [-34.82; 239.27]	0.069
Est. VAT Volume (cm^3)	473.60 (289.43)	402.09 (181.03)	71.51 [-76.41; 219.44]	0.167
FMI	8.84 (2.69)	8.35 (1.97)	0.49 [-0.95; 1.94]	0.248
LTM (g)	50772.71 (12270.92)	48759.23 (10300.05)	2013.48 [-4951.43; 8978.39]	0.281
LMI	17.5 (2.39)	17.03 (2.35)	0.46 [-0.99; 1.92]	0.260
Total mass (g)	78359.79 (16044.67)	74845.81 (12860.47)	3513.97 [-5420.61; 12448.55]	0.215
Neuroimaging Measures				
Caudate (L)	3009.59 (668.04)	3698.58 (555.93)	-688.98 [-1066.78; 311.18]	<0.001*
Caudate (R)	3117.45 (610.46)	3841.97 (586.12)	-724.51 [-1093.03; 356.00]	<0.001*
Putamen (L)	5324.96 (1270.40)	5842.08 (815.37)	-517.11 [-1171.42; 137.19]	0.059
Putamen (R)	5281.60 (1041.43)	5970.22 (715.85)	-688.61 [-1236.75; 140.47]	0.007**

*Note: HD, Huntington's disease; HC, healthy control; CAGn, number of cytosine-adenine-guanine repeats; CAP score: CAG-Age Product Scaled score; DBS, disease burden score; UHDRS-TMS, Unified Huntington's Disease Rating Scale-Total Motor Score; DCL, diagnostic confidence level; TFC, total functional capacity; BMI, body mass index; BMD, bone mineral density; Est. VAT Mass, estimated visceral adipose tissue mass; Est. VAT Volume, estimated visceral adipose tissue volume; FMI, fat mass index; LTM, lean tissue mass; LMI, lean mass index. * significant after correction for multiple comparisons, ** not significant after correction for multiple comparisons.*

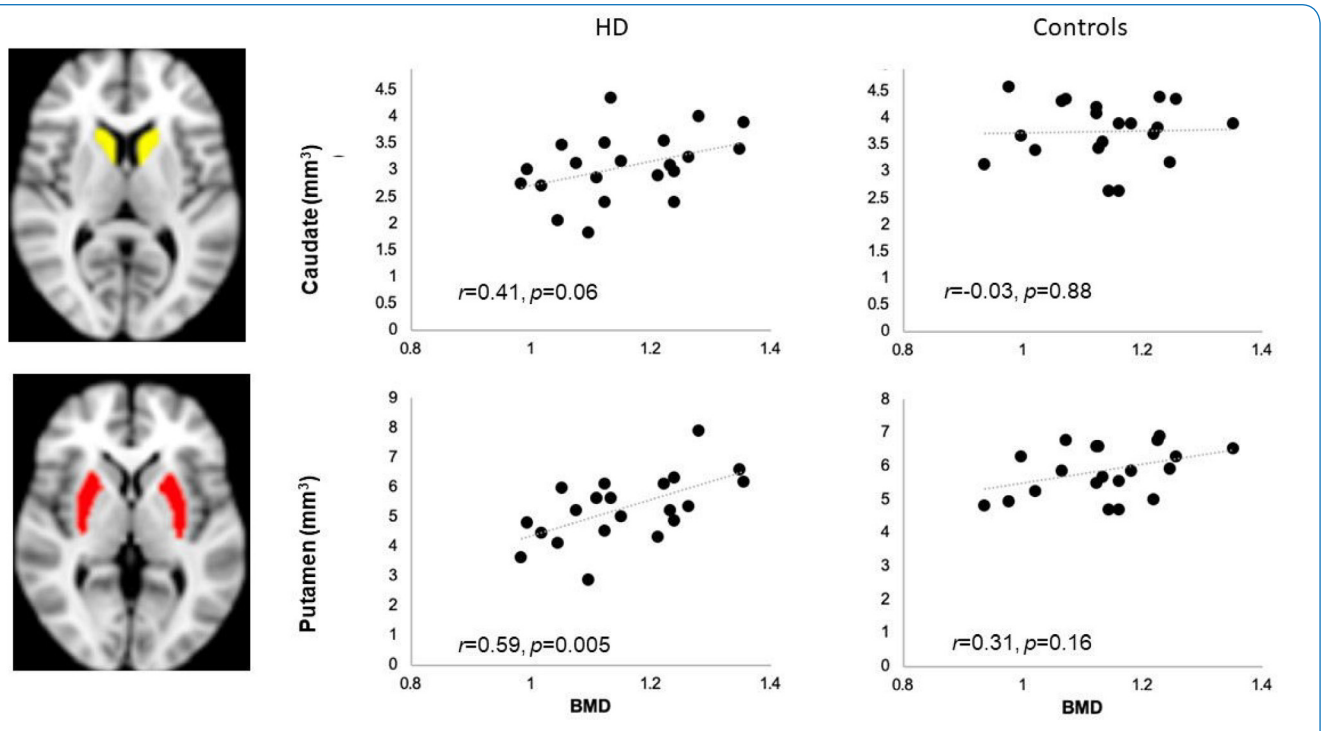

Figure 1. The association of bone mineral density (BMD) measured as g cm^{-2} with average caudate and putamen volume in 21 individuals with premanifest Huntington's disease (HD) and 22 healthy controls. The brain images highlight the specific areas of focus, including left and right caudate and putamen.

Associations between body composition and striatal volume were assessed using Pearson's correlation coefficients (r). Significance level was initially set at $p<0.05$ and then corrected for multiple comparisons using the Benjamini-Hochberg procedure. Data analysis was performed using STATA 15 (Stata Corp, 4905 Lakeway Dr, TX).

Results

Participant demographics and clinical characteristics

There were no significant differences for age or sex between individuals with premanifest HD and healthy controls (Table 1).

Body composition

Differences in body composition metrics between groups are presented in Table 1. No significant differences were observed for body composition metrics between the two groups.

Striatal volume

After correction for multiple comparisons significant differences in left caudate ($p<0.001$) and right caudate ($p<0.001$) volume were found between individuals with premanifest HD and healthy controls (Table 1).

Associations between body composition and striatal volume

After correction for multiple comparisons, a positive and significant association was observed between BMD and right putamen volume ($r=0.621$; $p=0.002$) in individuals with premanifest HD (Table 2). Non-significant associations were observed between BMD, right caudate ($r=0.483$; $p=0.026$) and left putamen ($r=0.530$; $p=0.013$). An inverse non-significant correlation was also observed between fat percentage and right putamen volume ($r=-0.446$; $p=0.042$). No associations were observed between whole body and trunk fat mass, lean tissue mass, estimated visceral adipose tissue mass and total mass and striatal volume in individuals with premanifest HD. There were no associations between body composition measures and striatal volume in healthy controls.

Discussion

Loss of weight, BMD and muscle mass are well-documented features of HD and have been linked to the clinical progression of HD[2,4,15]. It is not yet known whether alterations in body composition are associated with neuropathological changes, particularly striatal volume loss, in individuals with HD. Accordingly, we investigated associations between body

Table 2. Associations between striatal volume and BMI and body composition in HD and HC individuals.

		BMI	BMD	BMD T-score	BMD Z-score	Fat mass	Fat %	Trunk Fat	EST VAT MASS	EST VAT Volume	FMI	LTM	LMI	Total Mass
HC group														
Caudate (L)	r	0.063	-0.059	0.049	0.105	0.058	-0.100	0.102	0.028	0.028	-0.065	0.246	0.150	0.228
	P-value	0.779	0.791	0.861	0.693	0.797	0.656	0.650	0.899	0.900	0.773	0.267	0.504	0.306
Caudate (R)	r	0.048	0.004	0.107	0.144	0.018	-0.158	0.048	-0.060	-0.060	-0.110	0.254	0.163	0.220
	P-value	0.831	0.985	0.703	0.522	0.935	0.481	0.831	0.790	0.789	0.624	0.253	0.468	0.324
Putamen (L)	r	0.273	0.393	0.168	0.168	0.248	0.133	0.152	0.033	0.032	0.251	0.048	0.143	0.151
	P-value	0.218	0.070	0.547	0.453	0.264	0.552	0.498	0.883	0.884	0.258	0.831	0.523	0.500
Putamen (R)	r	0.130	0.200	0.147	-0.020	0.169	0.132	0.077	-0.020	-0.021	0.166	-0.023	0.033	0.055
	P-value	0.562	0.371	0.599	0.929	0.451	0.557	0.731	0.926	0.924	0.458	0.918	0.882	0.805
HD group														
Caudate (L)	r	0.094	0.333	0.114	0.340	0.169	0.012	0.134	0.156	0.158	0.092	0.128	0.022	0.185
	P-value	0.685	0.139	0.769	0.279	0.463	0.956	0.561	0.499	0.492	0.690	0.579	0.924	0.420
Caudate (R)	r	0.057	0.483	0.327	0.433	0.119	-0.102	0.146	0.231	0.226	-0.006	0.212	0.063	0.230
	P-value	0.805	0.026**	0.389	0.159	0.607	0.659	0.526	0.313	0.323	0.977	0.355	0.785	0.314
Putamen (L)	r	-0.092	0.530	0.491	0.509	-0.117	-0.326	-0.022	0.087	0.087	-0.234	0.243	0.084	0.149
	P-value	0.689	0.013**	0.179	0.090	0.612	0.148	0.921	0.706	0.707	0.305	0.286	0.714	0.518
Putamen (R)	r	-0.106	0.621	0.653	0.624	-0.198	-0.446	-0.067	0.117	0.130	-0.328	0.337	0.176	0.185
	P-value	0.647	0.002*	0.056	0.030**	0.389	0.042**	0.770	0.610	0.572	0.146	0.135	0.443	0.420

*HC, healthy control; HD, Huntington's disease; BMI, body mass index; BMD, bone mineral density; ESTVATMASS, estimated visceral adipose tissue mass; ESTVATVolume, estimated visceral adipose tissue volume; FMI, fat mass index; LTM, lean tissue mass; LMI, lean mass index; *significant after correction for multiple comparisons; **not significant after correction for multiple comparisons.*

composition metrics and striatal volume in individuals with premanifest HD relative to age- and sex- matched healthy controls. Contrary to our expectations, we found no evidence of differences in body composition variables between groups. However, a significant association between BMD and right putamen volume was observed.

Recent findings indicate that BMI is closely associated with the clinical trajectory of HD[2,5]. However, associations between BMI and other body composition parameters and neuropathology have not yet been investigated. Here, we investigated associations between body composition metrics and striatal pathology in individuals with HD. No significant associations were observed between BMI, fat mass or lean tissue mass and caudate and putamen volume. Significant associations were, however, observed between BMD and right putamen volume. To our knowledge, this is the first study to report an association between striatal pathology and bone mineral density in individuals with HD. While the nature of this relationship is not yet known, evidence from mouse models suggests that striatal pathology, particularly the loss of dopaminergic neurons, is associated with decreased osteogenic activity and bone mineral deposition[16]. Based on this preclinical data it is plausible that striatal degeneration mediates bone mineral density changes in individuals with HD. However, this is a tentative supposition, especially considering that no differences in body composition were observed between individuals with premanifest HD and healthy controls, which indicates a coincidental finding. It is likely that neuropathological changes, which arise early in the disease process, do not underlie changes in body composition. In accordance with this supposition, it is possible that lifestyle changes, including physical activity and

diet, as a result of the disease process may underpin body composition changes. This latter explanation nevertheless needs to be explored in future studies.

Consistent with previous observations, we found evidence of significant striatal degeneration. This finding was not surprising given the close proximity of participants to estimated clinical onset (within 5 years) as indicated by the high CAP score. The findings align with early evidence by Penney et al.[10], who noted a linear relationship between striatal damage and the product of age and the length of the CAG repeat.

Contrary to our hypothesis, we found no evidence of significant reductions in BMI, whole-body fat mass, whole-body BMD or whole-body lean tissue mass in premanifest HD individuals when compared to healthy controls. These results indicate that changes in body composition and whole-body BMD may only occur in the later stages of the disease. These results contrast previous findings, where reduced BMI, BMD and lean tissue mass has been reported in individuals with manifest and premanifest HD[1,4,15]. An explanation for the lack of whole-body BMD differences between groups may be that differences in bone structural parameters caused by chronic disease are more evident in load bearing bones of the lower-extremities compared to the bones of the upper-extremities[17]. Future research is needed to investigate the BMD differences in load bearing bone of the lower-extremities in individual with premanifest HD and healthy controls.

Several other explanations may account for the noted discrepancy in findings across studies, including differences in participant demographics, such as customary diet and habitual physical activity levels between studies, and/or difference models of DXA scanners (Lunar vs. Hologic) between the present and previous studies[1,18]. However, the variance between DXA scanners is unlikely a key factor, as previous studies have demonstrated high reproducibility of body composition values across different DXA scanners[19].

Several limitations need to be considered when interpreting our findings. The sample size in the present study was relatively small and may have limited our statistical power to detect between-group differences in body composition and bone mineral density. The study only investigated associations between body composition parameters and the integrity of striatal structures. It is possible that body composition parameters may have been associated with other neural structures, particularly as previous studies have noted links between greater cortical atrophy and higher BMI values and hypothalamic atrophy and bone loss in ApoE4 carriers and individuals with early Alzheimer's disease, respectively[20,21]. The study was also cross-sectional in nature, as such it is unknown whether the observed association between BMD and right putamen volume would persist over time. Finally, individuals in this study were sampled from Perth, Western Australia. It is possible that geographical differences may have affected body composition metrics. Longitudinal studies with larger sample sizes across various locations are needed to more robustly evaluate body composition changes and their relationship with disease progression in individuals with HD.

Despite these limitations, it is important to note that this is the first study to investigate associations between body composition metrics and striatal volume with the use of MRI and DXA in individuals with HD and healthy controls. Our findings nevertheless need to be confirmed and expanded on in larger observational trials. In particular, there is a fundamental need to evaluate the longitudinal trajectory of neuropathological and body composition changes and their respective relationships. There is also a need to evaluate whether changes in lifestyle throughout the disease are related to body composition changes.

Acknowledgements

The authors would like to thank the Huntington's disease and healthy control participants for their time and contribution to this study. We sincerely thank the patients, their families, the staff of Huntington's WA (Inc), Linda Hoult and Prof Brian Power.

Author contributions

Mitchell Turner: Conceptualised and ran the study, wrote the manuscript. Alvaro Reyes: Assisted with statistical analyses and analysis of data. Danielle Bartlett: Conceptualised and ran the study. Scott Culpin: Conceptualised and ran the study. Nicolas Hart: Contributed to the analysis and interpretation of data. Luca Hardt: Contributed to the analysis and interpretation of data. Kirk Feindel: Assisted with collection, analysis and interpretation of brain imaging data. Govinda Poudel: Analysed brain imaging data and contributed to the analysis and interpretation of data. Mel Ziman: Contributed to the analysis and interpretation of data. Travis Cruickshank: Conceptualised and ran the study, wrote the manuscript. All authors contributed to the writing and revision of the manuscript.

References

1. Goodman AOG, Barker RA. Body composition in premanifest Huntington's disease reveals lower bone density compared to controls. PLoS Curr 2011; 3:RRN1214.
2. van der Burg JMM, Gardiner SL, Ludolph AC, Landwehrmeyer GB, Roos RAC, Aziz NA. Body weight is a robust predictor of clinical progression in Huntington disease. Ann Neurol 2017;82(3):479-83.
3. Djoussé L, Knowlton B, Cupples LA, Marder K, Shoulson I, Myers RH. Weight loss in early stage of Huntington's disease. Neurology 2002 ;59(9):1325-30.
4. Costa de Miranda R, Di Lorenzo N, Andreoli A, Romano L, De Santis G Lou, Gualtieri P, et al. Body composition and bone mineral density in Huntington's disease. Nutrition 2019;59:145-9.
5. Myers RH, Sax DS, Koroshetz WJ, Mastromauro C, Cupples LA, Kiely DK, et al. Factors Associated With Slow Progression in Huntington's Disease. Arch Neurol 1991;48(8):800-4.
6. Poudel GR, Harding IH, Egan GF, Georgiou-Karistianis N. Network spread determines severity of degeneration and disconnection in Huntington's disease. Hum Brain Mapp 2019 ;40(14):4192-201.
7. Juan FDD, Julie CS, Govinda P, Andrew C, Phyllis C, Gary

FE, et al. Multimodal imaging biomarkers in premanifest and early Huntington's disease: 30-month IMAGE-HD data. Br J Psychiatry 2016;208(6):571-8.
8. Reilmann R, Leavitt BR, Ross CA. Diagnostic criteria for Huntington's disease based on natural history. Mov Disord 2014;29(11):1335-41.
9. Zhang Y, Long JD, Mills JA, Warner JH, Lu W, Paulsen JS. Indexing disease progression at study entry with individuals at-risk for Huntington disease. Am J Med Genet Part B Neuropsychiatr Genet 2011;156(7):751-63.
10. Penney JB, Vonsattel JP, MacDonald ME, Gusella JF, Myers RH. CAG repeat number governs the development rate of pathology in huntington's disease. Ann Neurol 1997;41(5):689-92.
11. Goldberg EK, Fung EB. Precision of the Hologic DXA in the Assessment of Visceral Adipose Tissue. J Clin Densitom 2019. pii: S1094-6950(19)30002-2.
12. Hart NH, Nimphius S, Spiteri T, Cochrane JL, Newton RU. Segmental Musculoskeletal Examinations using Dual-Energy X-Ray Absorptiometry (DXA): Positioning and Analysis Considerations. J Sports Sci Med 2015; 14(3):620-6.
13. Peiffer JJ, Galvão DA, Gibbs Z, Smith K, Turner D, Foster J, et al. Strength and Functional Characteristics of Men and Women 65 Years and Older. Rejuvenation Res 2010; 13(1):75-82.
14. Reuter M, Rosas HD, Fischl B. Highly accurate inverse consistent registration: A robust approach. Neuroimage 2010;53(4):1181-96.
15. Süssmuth SD, Müller VM, Geitner C, Landwehrmeyer GB, Iff S, Gemperli A, et al. Fat-free mass and its predictors in Huntington's disease. J Neurol 2015;262(6):1533-40.
16. Ali SJ, Ellur G, Khan MT, Sharan K. Bone loss in MPTP mouse model of Parkinson's disease is triggered by decreased osteoblastogenesis and increased osteoclastogenesis. Toxicol Appl Pharmacol 2019; 363:154-63.
17. Jenkins M, Hart NH, Nimphius S, Chivers P, Rantalainen T, Rothacker KM, et al. Characterisation of peripheral bone mineral density in youth at risk of secondary osteoporosis-a preliminary insight. J Musculoskelet Neuronal Interact 2020;20(1):27-52.
18. Shepherd JA, Fan B, Lu Y, Wu XP, Wacker WK, Ergun DL, et al. A multinational study to develop universal standardization of whole-body bone density and composition using GE Healthcare Lunar and Hologic DXA systems. J Bone Miner Res 2012;27(10):2208-16.
19. Tavares Ó, Duarte JP, Costa DC, Sousa-e-Silva P, Martinho D, Lus LGO, et al. Agreement between dual x-ray absorptiometers using pencil beam and fan beam: indicators of bone health and whole-body plus appendicular tissue composition in adult athletes. Rev Assoc Med Bras 2018;64(4):330-8.
20. Blautzik J, Kotz S, Brendel M, Sauerbeck J, Vettermann F, Winter Y, et al. Relationship between body mass index, ApoE4 Status, and PET-Based amyloid and neurodegeneration markers in amyloid-positive subjects with normal cognition or mild cognitive impairment. J Alzheimer's Dis 2018;65(3):781-91.
21. Loskutova N, Watts AS, Burns JM. The cause-effect relationship between bone loss and Alzheimer's disease using statistical modeling. Med Hypotheses 2019; 122:92-7.