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Comments

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AA and DHA are decreased in paediatric AD/HD and inattention is ameliorated by increased plasma DHA

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ABSTRACT

The purpose of this study was to assess long chain polyunsaturated fatty acid (LCPUFA) status in relation to socio-behavioral outcomes in children with Attention Deficit/Hyperactivity Disorder (AD/HD). In a case-control design, plasma phospholipid fatty acid content was assessed in children aged 5–12 years with AD/HD and in typically functioning children. Dietary intakes of LCPUFAs arachidonic acid (AA; 20:4n6) and docosahexaenoic acid (DHA; 22:6n3) were quantified using a four-day food record, polymorphisms were determined in *FADS1* and *FADS2*, and socio-behavioral outcomes were assessed using the Conners 3 Parent Rating Scales in a cross section of children with AD/HD. Compared to typically functioning children, plasma AA and DHA were 40% lower in children with AD/HD. Median intake of AA, but not DHA, was higher in children with AD/HD compared to typically functioning children. Polymorphisms in *FADS1* (rs174546) and *FADS2* (174575) were associated with higher plasma linoleic acid (LA; 18:2n6) level. Plasma DHA level was inversely associated with inattention score. Despite having an elevated intake of AA, children diagnosed with AD/HD have a reduction in plasma AA level which may be due in part to polymorphisms in the fatty acid desaturase (FADS) gene cluster or increased conversion to AA-derived metabolites. Increasing intake of DHA may ameliorate symptoms of inattention in AD/HD.

Introduction

AD/HD is the most prevalent neurodevelopmental disorder in paediatric populations [1,2,3,4]. Children with AD/HD present with chronic neuropsychological and cognitive deficits that severely impact social and academic functioning [1,2,5,6]. The disorder is associated with considerable psychological and financial burden [1,2,3,4]. Psychostimulants are the first line treatment indicated for AD/HD [3,4,7–9]. Medications do not address aetiological factors of the disorder and up to 40% of children do not respond favorably to pharmacological treatment [4,8,10].

Considered conditionally essential, deficiency in LCPUFA may be involved in the aetiology of AD/HD [11,12,13]. Twenty- and 22-carbon n-3 and n-6 fatty acids are vital for brain development and constitute 30 to 35% of total brain fatty acids [14]. DHA is necessary for optimal visual and cognitive development [2,15,16]. In addition to DHA, AA continues to accumulate in large amounts in the grey matter of the brain until five years of age [17]. Symptoms of essential fatty acid (EFA) deficiency predicted delay aversion and severity of AD/HD assessed by the Swanson, Nolan, and Pelham-IV questionnaire [18]. Furthermore, an increasing body of research suggests that deficiencies in LCPUFA in childhood may constitute a risk factor for developing psychopathology

Abbreviations: AA, arachidonic acid; AD/HD, Attention Deficit/Hyperactivity Disorder; ALA, alpha-linolenic acid; CRS-3, Connors 3 Rating Scales; DHA, docosahexaenoic acid; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders Fourth Edition; EFA, essential fatty acid; EPA, eicosapentaenoic acid; FADS, fatty acid desaturase; LA, linoleic acid; LCPUFA, long chain polyunsaturated fatty acid; SNPs, single nucleotide polymorphisms.

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later in life [19,20]. Children with hyperactivity exhibit lower levels of AA and DHA in serum phospholipids than non-hyperactive children [21]. It is not clear whether reduced dietary intake of LCPUFA is responsible for impaired LCPUFA status or for symptoms of AD/HD.

FADS converts precursor n-3 and n-6 fatty acids to long chain products. *FADS1* and *FADS2* encode delta-5 and delta-6 desaturase enzymes respectively [22,23] and regulate the conversion of LA and alpha-linolenic acid (ALA; 18:3n3) to AA and DHA. Carriers of minor alleles at specific loci in the FADS gene cluster exhibit reduced desaturase enzyme activity resulting in decreased levels of AA-and DHA--containing classes of phospholipids, phosphatidylcholine and phosphatidylethanolamine, and an apparent need to consume preformed LCPUFA [22,24,25]. Little is known about the conversion of fatty acid precursors LA and ALA to LCPUFA, or of LCPUFA to AA- and DHA-derived metabolites in the context of AD/HD. Accordingly, the present study was designed to examine if LCPUFA content in plasma phospholipids was related to LCPUFA intake, single nucleotide polymorphisms (SNPs) in the FADS gene cluster, and Connors 3 Rating Scales (CRS-3) in children diagnosed with AD/HD.

Materials and methods

Ethical approval

This study was conducted according to the guidelines in the Declaration of Helsinki and all procedures involving human subjects were approved by the Health Research Ethics Board (#5324) at the University of Alberta.

Recruitment

Children (n = 103) from Child and Adolescent Services Association and neurodevelopmental clinics in hospitals (Edmonton, Canada) diagnosed with AD/HD provided assent and parents provided informed consent to participate. The recruitment of a convenience sample of typically functioning children (control; n = 26) is described [26,27]. Children aged 5–12 years were diagnosed by a healthcare professional (Pediatrician, Psychiatrist or Psychologist) as having any sub-type of AD/HD, according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria [28]. Participants scoring a full scale IQ of 70 or greater on a standardised test conducted within the past year were included in the study. Children with other co-morbid conditions including Oppositional Defiant Disorder, Conduct Disorder, anxiety disorders, mood disorders or learning disorders were not excluded. Participants consuming a special diet, a supplement containing DHA, or diagnosed with Fetal Alcohol Syndrome or Autism were excluded from the study. Participants taking medication such as methylphenidate to treat AD/HD and/or other prescription medication were not excluded.

Fatty acid analysis

A blood sample was obtained from each child by a finger prick by a registered nurse. Blood samples were collected in heparinized tubes and put immediately on ice and transported for analysis. Isopropyl alcohol (70%) was added to sample tubes to preserve samples during transport to the laboratory for analysis. Plasma was separated by centrifugation and frozen until analysis. Plasma lipids were extracted using a modified Folch procedure [29] for subsequent fatty acid analyses. The phospholipid fraction was separated by thin layer chromatography [30]. For quantitation, a C17:0 standard was added, and fatty acid methylation was performed using 14% (w/v) BF_3/methanol. Fatty acids were separated by gas liquid chromatography (Vista 6010, Varian Instruments, Georgetown, Canada) on a fused silica BP20 capillary column (25 m × 0.25 mm internal diameter, Varian Instruments) [31].

LCPUFA intake

To determine whether LCPUFA status was related to diet, a four-day food intake record was completed. Parents were instructed to complete the diet record over four consecutive days, including one weekend day. Analysis of food intake records was conducted using Food Processor® Nutrition Analysis software (ESHA Research, Salem, United States).

Participant genotyping

To determine whether differences in LCPUFA status in children with AD/HD were due to SNPs in FADS gene locus, DNA was extracted from peripheral blood (n = 83) using a Gentra Puregene Blood Kit (QIAGEN, Germantown, United States) as per the manufacturer's protocol. Detailed methodology and primer sequences are described [25]. Alleles were respectively designated as major and minor (in brackets) for *FADS1* rs174537 (G; T), *FADS1* rs174546 (C; T), and *FADS2* rs174575 (C; G). Lewontin's D^I was used as an index for linkage disequilibrium.

Behavioral assessment

To determine whether LCPUFA status was associated with sociobehavioral outcomes, a subset of parents (n = 19) completed the short form of the CRS-3 [32] to assess co-morbid problems including inattention, hyperactivity, learning problems, executive function, aggression, peer relations, positive impression, and negative impression.

Statistical analysis

This observational research contains case control and cross sectional analyses (Fig. 1). Data was analyzed using SPSS 29.0 (SPSS Inc., Chicago, United States, 2007). Normality for parametric statistical testing

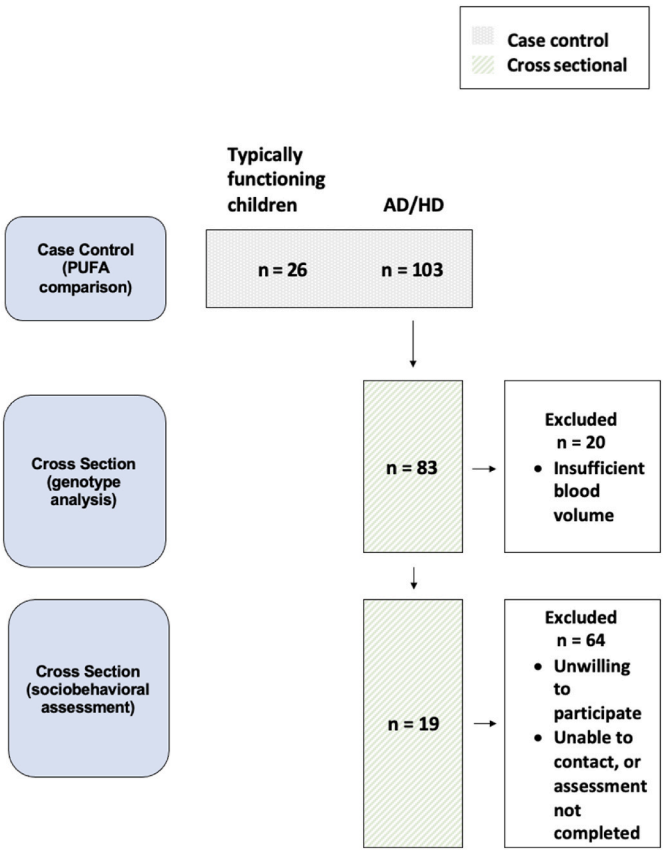

Fig. 1. Study flow diagram.

was assessed by Shapiro-Wilk test. T-test was used to compare demographics and to assess the differences in LCPUFA content (%w/w) among children with AD/HD and typically functioning children. Median LCPUFA intakes were compared using Kruskal-Wallis test in the case control analysis, and using a *t*-test in the cross sectional analysis within genotype. Pearson product correlations were computed and linear regression was used to assess the relation between the absolute concentration of fatty acids and socio-behavioral functioning outcomes from the CRS-3. Statistical significance was defined at alpha <0.05 and sample sizes were sufficient to achieve power >80% for the case control and genotype cross-sectional analyses. Multiple comparisons for the eight CRS-3 outcomes were accounted for using the Bonferroni correction and alpha <0.0063 was designated as statistically significant.

Results

Demographic data are summarized (Table 1) for the study participants. Age, weight, or height did not differ between study groups. Seventy-seven percent of diagnosed children were on medication for AD/HD.

Plasma phospholipid fatty acid content

Data were analyzed using parametric statistical methods since null hypothesis of Shapiro-Wilk test for normality was not rejected. Mean AA and DHA content in plasma were approximately one-half the level in children with AD/HD ($P < 0.01$) compared to levels found in typically functioning children (Table 2). The complete plasma phospholipid fatty acid profile is shown (Supplemental Table 1).

Dietary intake of LCPUFA

AA intake was significantly higher ($P < 0.05$) in children with AD/HD (median = 280 mg/day; range = 40–1140 mg/day) than typically functioning children (median = 50 mg/day; range = 3.2–356 mg/day). In children with AD/HD, AA intakes did not differ within *FADS1* rs174546 (319 ± 49.6 mg/day for CC vs. 298 ± 39.4 mg/day for T allele carrier) and *FADS2* rs174575 (352 ± 42.6 mg/day for CC vs. 241 ± 38.5 mg/day for G all carrier) genotypes. DHA intakes did not differ between children with AD/HD (median = 40 mg/day; range = 10–1290 mg/day) and typically functioning children (median = 14 mg/day; range = 0–403 mg/day), indicating that the ranks of the medians were similar between the groups. In children with AD/HD, DHA intakes did not differ within *FADS1* rs174546 (42.1 ± 74.7 mg/day for CC vs. 41.7 ± 57.3 mg/day for T allele carrier) and *FADS2* rs174575 (43.6 ± 70.0 mg/day for CC vs. 39.3 ± 59.6 mg/day for G all carrier) genotypes.

Fatty acid desaturase

FADS1 positions rs174546 and rs174537 were found to be in linkage disequilibrium ($D^I = 0.95$) consistent with previous findings in infants [25]. Thus, only the rs174546 position in *FADS1* was assessed with respect to LCPUFA content. There was no statistically significant relation between FADS genotype and plasma n-3 fatty acid levels or AA level (Table 3). Relative content (% w/w) of plasma LA was elevated by ~20% in carriers of a T allele in *FADS1* ($P = 0.04$) and carriers of a G allele in *FADS2* ($P = 0.03$) compared to carriers of two C alleles in rs174546 and rs174575. Plasma level of ALA was also elevated in T allele carriers compared to carriers of two C alleles in rs174546 *(FADS1)* but this finding was not statistically significant ($P = 0.05$; Table 3).

Table 1
Participant demographic.

	Control	AD/HD
Male, n	14	90
Female, n	12	13
Age, y	6.50 (± 0.8)	8.23 (± 1.9)
Weight, kg	24.0 (± 3.5)	30.7 (± 10.2)
Height, cm	122 (± 6.0)	130 (± 11.6)
Ethnicity, n		
Caucasian		88
Indigenous		11
Other		4
Not collected	26	

Table 2
Plasma phospholipid AA and DHA are lower in children with AD/HD.

Fatty Acid	Control (n = 26)		AD/HD (n = 103)		P-value
	Mean	SD	Mean	SD	
AA (20:4n-6)	12.88	1.99	6.97	2.92	<0.01
DHA (22:6n-3)	3.42	0.61	2.10	1.28	<0.01

Plasma phospholipid content (% w/w) of AA and DHA are significantly lower in children with AD/HD compared to typically functioning children (control). A *t*-test was used to compare means of plasma phospholipid LCPUFA between groups.
AA = arachidonic acid; AD/HD = Attention Deficit/Hyperactivity Disorder; DHA = docosahexaenoic acid; LCPUFA = long chain polyunsaturated fatty acid; SD = standard deviation.

Behavioral assessment

There was a significant ($P = 0.005$) association between plasma phospholipid DHA concentration and the inattention scale (Fig. 2). Elevated DHA was related to improvement in CRS-3 inattention scale, and there was no relation between plasma AA concentration and the inattention scale ($P = 0.21$). Other outcomes from the CRS-3 were not related to plasma phospholipid LCPUFA.

Discussion

The present study was designed to assess whether plasma LCPUFA level was related to LCPUFA intake, SNPs in the FADS gene locus, and socio-behavioral outcomes in AD/HD. Plasma AA was decreased in children with AD/HD compared to typically functioning children, despite higher dietary intake of AA. This observation suggests that the metabolism of AA to mediators implicated in neuroinflammatory processes may be increased in children with AD/HD. Although dietary intakes of DHA were similar, children with AD/HD had lower plasma DHA than typically functioning children. Finally, inattention was improved in children with AD/HD concurrent with an elevation in plasma DHA presenting a potential dietary strategy to impact socio-behavioral outcomes in AD/HD.

The current study supports the hypothesis that altered AA and DHA metabolism may be involved in the aetiology of AD/HD. As in this study, plasma n-3 LCPUFA was significantly lower in a cohort of children with AD/HD compared to a standard reference range for typically functioning adults [33]. In addition to erythrocyte eicosapentaenoic acid (EPA; 20:5n3) and DHA, AA was also lower in a cohort of children with AD/HD compared to typically functioning children [34]. In this study, higher intake of AA was not reflected in plasma phospholipid. This observation may suggest that FADS genotype and the elongation and desaturation of n-3 and n-6 series of fatty acids may be implicated in the aetiology of AD/HD. Alternatively, a study showing reduced red blood cell AA and DHA in children with autism also found that prostaglandin E2 was elevated compared to controls [35]. In combination with the present research, these studies suggest increased production of AA-derived metabolites in neurological development disorders. Future study might explore whether the elevated oxidative stress reported in some studies of AD/HD [36,37] may result from increased conversion of AA to pro-inflammatory mediators including prostaglandins and leukotrienes.

AA and DHA are generated from EFA precursors in several

Table 3
Plasma n-6 and n-3 phospholipid fatty acid levels among *FADS1* and *FADS2* in children with AD/HD.

Fatty Acid	*FADS1* rs174546				*FADS2* rs174575			
	CC [n = 38]		T carrier [n = 45]		CC [n = 52]		G carrier [n = 31]	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
LA (18:2n6)	15.99	6.68	18.80[Ł]	6.16	16.33	6.93	19.50[Ł]	5.29
ALA (18:3n3)	0.36	0.35	0.49	0.74	0.33	0.32	0.59	0.86
AA (20:4n6)	6.98	3.22	6.95	2.75	6.90	3.24	7.09	2.45
EPA (20:5n3)	0.31	0.32	0.36	0.47	0.37	0.42	0.28	0.39
DHA (22:6n3)	1.97	1.47	2.21	1.10	2.16	1.44	2.01	0.98

[Ł] The mean values for plasma phospholipid 18:2n6 differ ($P < 0.05$) within genotypes (CC vs. T carrier at rs174546, and CC vs. G carrier at rs174575) using a *t*-test for comparison.
AA = arachidonic acid; ALA = alpha-linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; LA = linoleic acid; SD = standard deviation.

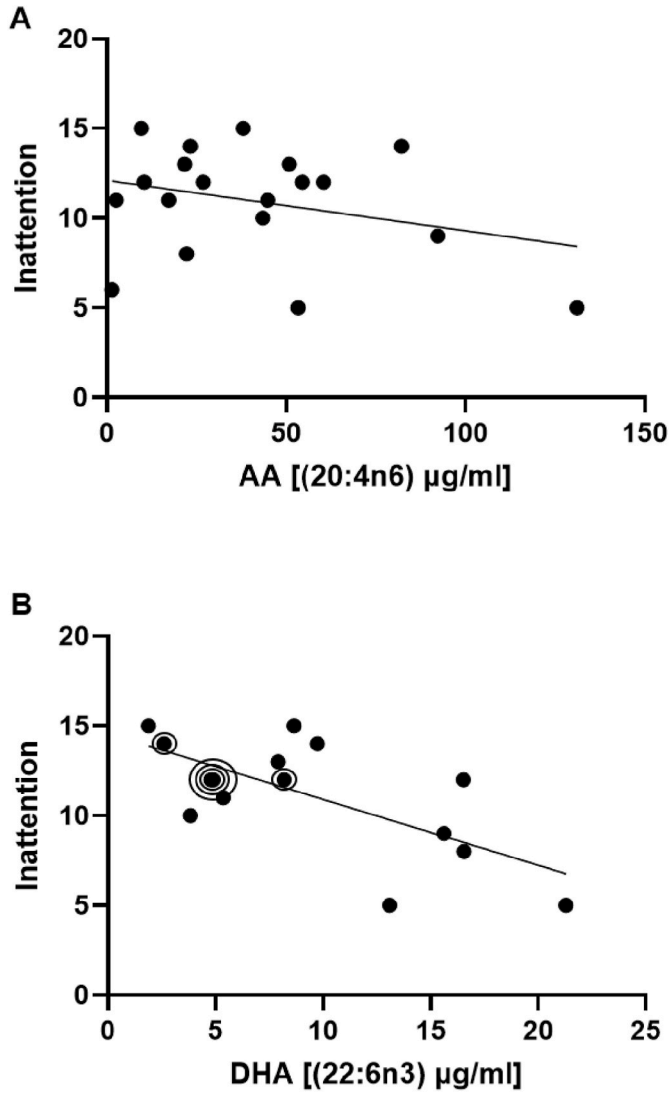

Fig. 2. Elevated DHA is related to inattention score from the CRS-3 Rating Scales. Inattention score was related to elevation in plasma phospholipid level of (B) DHA (n = 19, r = −0.82, β = −0.37; P = 0.005), but not (A) AA (n = 19, β = −0.03, r = −0.30; P = 0.21). Concentric circles around data points indicate similar data point values that are partially obscured by the regression line or dot resolution.

conversions using multiple elongase and desaturase enzymes. Minor alleles in the FADS gene cluster are associated with reduced desaturase activity especially when coupled with significantly low n-3 and n-6 fatty acid intakes. The increase in LA status in children with AD/HD in this study associated with slower desaturase activity is mechanistically suggestive of the reduction in AA status. Presence of these SNPs may constitute a risk for neurodevelopmental disorders such as AD/HD [22]. Future study warrants comparing the EFA-to-LCPUFA ratio of the n-3 and n-6 series of fatty acids between typically functioning children and those with AD/HD.

Results of clinical trials involving supplementation of LCPUFA have been mixed. Supplementation with therapeutic doses of n-3 fatty acids improves symptoms of AD/HD when assessed by parent and teacher standardized assessments [38,39,40]. Significant improvements were observed on Conners Parent Rating Scales of cognitive problems, anxiety/shyness, inattentiveness and hyperactivity/impulsiveness compared to a group of children receiving a placebo (olive oil). Improvement on the Conners AD/HD Index was observed in children receiving at least 186 mg EPA and 480 mg DHA per day [41]. In controlled supplementation studies, plasma n-3 LCPUFA status regularly reflects the intake n-3 fatty acids [42]. While supplementation with DHA appears to be effective, children with AD/HD supplemented only with EPA at 1.2 g daily had 1.6-fold increase in erythrocyte EPA, but no increase in DHA after 12 weeks [43].

Higher levels of n-6 and lower levels of n-3 fatty acid-derived metabolites may promote neuroinflammatory processes. This has been demonstrated in a study showing that the n-6/n-3 ratio was correlated with deficits in behavior rating scales in children with AD/HD [34]. As such, several studies suggest the importance of a balance of n-3 and n-6 intake. The amounts of AA than DHA in formula consumed by children predicted white matter volume in brain images at 9 years [44]. Furthermore, sustained attention, a rule-learning test requiring inhibition, and verbal IQ at ages 5–6 years were improved in children that consumed diets where AA to DHA ratio was greater than or equal to 1.0 [45]. Collectively, these studies suggest that impaired LCPUFA status is hallmark of neurodevelopmental trajectory, FADS genotype should be included as a potential modifier of outcomes in study designs, and supplementation strategies should consider how the amounts of AA and DHA consumed affect tissue levels of n-3 and n-6 fatty acids to ultimately improve symptoms of AD/HD.

Strengths and limitations

All children in the study were diagnosed with AD/HD by a healthcare professional in contrast to other studies that included children with symptoms of AD/HD but who were not diagnosed with the disorder [46,47,48]. Over three-quarters of study participants were taking medication to treat symptoms of AD/HD, suggesting a severely affected population. A four-day food record was adequate to determine dietary LCPUFA intake since it did not differ from a food frequency questionnaire [26]. LCPUFA content in plasma phospholipids is considered a reliable biomarker of LCPUFA status as this fraction contains a high proportion of the LCPUFA present in the blood [49,50]. The composition of plasma phospholipid fatty acids in this study was similar to reports from another cohort of children similar in age [51]. The CRS-3 measures

socio-behavioral functioning in children three to 17 years of age and was thus considered appropriate for this study population [32]. Children from both urban and rural areas of Alberta participated in the study, allowing for a representative sample. The Indigenous/Aboriginal population consisted of >10% of the affected study population and further study with diverse representation and genetic variability may allow for greater generalizability. No subgroup analysis was conducted on the basis of medication use or sex due to small sample size. The triene mead acid sometimes used to assess EFA deficiency was below the limit of detection. The composition of fatty acids was determined in the plasma fraction of phospholipids in this study, though long-term intake of PUFA may be better reflected in red blood cells. Due to the challenges in recruitment and retention with this specific study population, many studies with AD/HD patients have $n < 30$ [52,53,54] and this study was not powered for analysis of socio-behavioral outcomes in AD/HD in relation to LCPUFA status. Teachers of study participants did not complete the Conners 3 Teacher Rating Scale due to Summer vacation.

Conclusion

Attention is a main executive function needed to self-regulate responses for goal-directed behavior. Improvement in inattention leads to stronger ability to plan, organise, and self-direct behavior, thereby significantly increasing academic and social performance. Lower status of AA is likely due to increased formation of AA-derived metabolites or polymorphisms in FADS, and the inverse relation between plasma DHA level with inattention scores suggests that supplementation with DHA may be beneficial in improving attention. Improved DHA status may reduce the negative impact of AD/HD, leading to better academic and social prognoses for children with the disorder.

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CRediT authorship contribution statement

John J. Miklavcic: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing, All authors have approved the final version of the manuscript for submission. **Ellen Ivity:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing, All authors have approved the final version of the manuscript for submission. **Ian M. MacDonald:** Data curation, Resources, Software, Writing – review & editing, All authors have approved the final version of the manuscript for submission. **Liana Urichuk:** Conceptualization, Resources, Writing – review & editing, All authors have approved the final version of the manuscript for submission. **Vera C. Mazurak:** Conceptualization, Data curation, Resources, Validation, Writing – review & editing, All authors have approved the final version of the manuscript for submission. **Christina Rinaldi:** Conceptualization, Writing – review & editing, All authors have approved the final version of the manuscript for submission. **Michael T. Clandinin:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Software, Supervision, Validation, Writing – original draft, Writing – review & editing, All authors have approved the final version of the manuscript for submission.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hnm.2022.200183.

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