GRADUATE AND POSTDOCTORAL STUDIES

McGILL UNIVERSITY

FINAL ORAL EXAMINATION
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

OF

NEIL BRETT
SCHOOL OF HUMAN NUTRITION

AN INVESTIGATION OF THE EFFECT OF VITAMIN D INTAKE ON VITAMIN D STATUS AND FUNCTIONAL HEALTH OUTCOMES IN HEALTHY CHILDREN

July 27, 2017
9:15 AM

LOCATION: MS2-022 (Faculty Lounge),
McGill University, MacDonald Campus

COMMITTEE:
Dr. Arif Mustafa, Pro-Dean, Department of Animal Science
Dr. Timothy Johns, Departmental Chair, School of Human Nutrition
Dr. Hope Weiler, Supervisor, School of Human Nutrition
Dr. Jennifer Ronholm, Internal Member, Department of Food Science and Agricultural Chemistry
Dr. Grace Marquis, Internal Examiner, School of Human Nutrition
Dr. Genevieve Mailhot, External Examiner, Department of Nutrition, University of Montreal

Dr. Josephine Nalbantoglu, Dean of Graduate and Postdoctoral Studies
Members of the Faculty and Graduate Students
are invited to attend

ABSTRACT

Vitamin D is important to maintain calcium homeostasis and musculoskeletal health. Current vitamin D intake guidelines for young children were based on studies in adults and adolescents and thus may not be appropriate. The Estimated Average Requirement (EAR: 400 IU/d) and the Recommended Dietary Allowance (RDA: 600 IU/d) for vitamin D were set so that 50% and 97.5% respectively, of the healthy general population, would have vitamin D status (25-hydroxyvitamin D: 25(OH)D) of 40 nmol/L and 50 nmol/L respectively. These concentrations of 25(OH)D are designed to support bone health and calcium homeostasis. However, in North American young children, vitamin D food fortification studies have not been undertaken and the effect of vitamin D intakes on musculoskeletal health outcomes is unknown. Thus, the objectives of this thesis are: 1. determine the effect of 400 IU/d or 600 IU/d of vitamin D from fortified foods, on vitamin D status over 12 weeks (wk) in children 2-8 y; 2. A) determine if a similar effect on vitamin D status from 400 IU/d of vitamin D is seen over 6 months (mo); B) investigate the effect of this intake on musculoskeletal health; and 3. using a meta-analysis, investigate the effect of vitamin D interventions on vitamin D status in children 2-18 y.

Study 1 was a randomized placebo-controlled trial (RCT) where children consumed control or vitamin D fortified yogurt and cheese (to reach 400 IU/d or 600 IU/d) over 12 wk, with vitamin D status, anthropometry and dietary intakes measured. Study 2 was a 6 mo RCT of similar design, except there was only one intervention group (400 IU/d) and additional measures included other vitamin D metabolites, body composition and bone mineral (dual-energy x-ray absorptiometry), biomarkers of bone metabolism as well as 3-dimensional bone geometry and muscle (peripheral quantitative computed tomography). Study 3 was a meta-analysis of RCTs with vitamin D interventions in healthy children 2-18 y. The overall effect of interventions and subgroup analyses were investigated using PRISMA guidelines.

Results from study 1 (n=77) showed both interventions had significantly higher 25(OH)D concentration than control at 12 wk, but there were no differences (mean ± SD) between intervention groups (control: 55.8 ± 12.3; EAR: 64.1 ± 10.0; and RDA: 63.7 ± 12.4 nmol/L; $p < 0.05$). In both intervention groups, 96% of children maintained 25(OH)D ≥ 50 nmol/L. Study 2 (n=51) found differences in 25(OH)D between groups at 3 mo (control: 58.3 ± 15.3; intervention: 64.7 ± 12.2, $p < 0.05$), but not 6 mo (control: 56.6 ± 13.9; intervention: 58.4 ± 8.7, $p > 0.05$). Over the 6 mo, 85% of the intervention group maintained 25(OH)D ≥ 50 nmol/L. Lean mass accrual was greater in the intervention group ($p < 0.05$) whereas there were no differences between groups for bone health outcomes. Study 3 included 25 RCTs (n=5120 children) in the meta-analysis with a 25(OH)D weighted mean difference (23.2 nmol/L, 95% CI 20.6-25.8 nmol/L) with high heterogeneity among studies ($I^2 = 99.9\%$) that resulted in a 1.0 nmol/L increase for every 100 IU/d of vitamin D. The effect on vitamin D status was greater in subgroups with mean baseline

25(OH)D <30 nmol/L, using fortified foods and with baseline vitamin D intakes < 100 IU/d.

In conclusion, these results suggest consuming 400 IU/d of vitamin D exceeds the definition of the EAR but does not meet that of the RDA. In study 2, vitamin D may have been taken up by muscle and used to increase lean mass accrual. There was a strong effect of vitamin D interventions on 25(OH)D, however high heterogeneity remained in subgroup analyses. These studies will help to improve existing vitamin D recommendations for young children and food fortification guidelines.

CURRICULUM VITAE

UNIVERSITY EDUCATION

2014/9–2017/8 *Ph.D, Human Nutrition,* McGill University, Montreal, Canada. Dissertation: An investigation of the effect of vitamin D intake on vitamin D status and functional health outcomes in healthy children.

2013/9–2014/9 *M.Sc., Human Nutrition,* McGill University, Montreal, Canada (Fast-tracked to PhD).

2007/9–2012/12 *B.Sc., Nutrition and Food Science, Nutrition Major*, University of Alberta, Edmonton, Canada.

EMPLOYMENT

2016/4–2016/6 Course instructor: Contemporary Nutrition (NUTR-200), School of Human Nutrition, McGill University.

2017/1–2017/4 Teaching Assistantship, Applied Science Communication (NUTR-322). School of Human Nutrition, McGill University.

2016/9–2016/12 Teaching Assistantship, Nutrition and Health (NUTR-207). School of Human Nutrition, McGill University.

2015/9–2015/12 Teaching Assistantship, Nutrition and Health (NUTR-207). School of Human Nutrition, McGill University.

AWARDS

2017/6 New Investigator Award, International Conference on Children's Bone Health, Wurzburg, Germany.

2017/6 Graduate Research Enhancement and Travel Award, McGill University

2017/5 Winner of the Canadian Nutrition Society's Poster Competition, Montreal, QC.

2017/4 Winner of the American Society for Nutrition's Clinical Emerging Leader Oral Competition. Experimental Biology, Chicago, IL.

2017/4 Winner of the American Society for Nutrition's Emerging Leader Poster Competition, Maternal Perinatal and Pediatric Research Interest Group. Experimental Biology, Chicago, IL.

2017/04 Travel Award, McGill University Centre for Research in Reproduction and Development

2016/10 Finalist for the New Investigator Award, Canadian Musculoskeletal Conference, Toronto, ON.

2016-2017 Graduate Award Program, McGill University Institute of Health and Social Policy.

2016/05 Finalist in the Canadian Nutrition Society's Poster Competition, Gatineau, QC.

2016/04 Winner of the American Society for Nutrition's Emerging Leader Poster Competition, Maternal Perinatal and Pediatric Research

	Interest Group. Experimental Biology, San Diego, CA.
2016/04	Graduate Research Enhancement and Travel Award, McGill University.
2015/4	Finalist for the American Society for Nutrition Graduate Student Research Award, Boston, MA.
2015/4	Graduate Research Enhancement and Travel Award, McGill University.
2014/11	People's Choice Award, McGill University School of Human Nutrition 3 minute thesis competition.
2014–2017	Donald Mackenzie Munroe Fellowship, McGill University.
2014/9	Graduate Excellence Award, McGill University.
2014/4	Travel Award, Network for Oral and Bone Health Research.
2013/9	Graduate Excellence Award, McGill University.
2012/5	Undergraduate Student Research Award, Natural Sciences and Engineering Research Council.
2012/5	Undergraduate Research Initiative Stipend, University of Alberta.
2012/3	Winner of the Heroes for Health Competition, University of Alberta.
2009/4	Academic All Canadian, Canadian Interuniversity Sport.
2009/4	Jason Lang Scholarship, University of Alberta.
2007/9	Rutherford Scholarship, Government of Alberta.

PUBLICATIONS

Published:

Brett, N.R, Agellon, S, Lavery, P, Vanstone, C, Maguire, J.L, Rauch, F Weiler, H.A. Dietary vitamin D dose-response in healthy children 2 to 8 y of age: a 12-wk randomized controlled trial using fortified foods. Am J Clin Nutr 2016;103:144–52.

Morlock, G, **Brett, N.R**. Correct assignment of lipophilic dye mixtures? A case study for high-performance thin-layer chromatography-mass spectrometry and performance data for the TLC-MS Interface. Journal of Chromatography A, 2015. JCA-14-2292R1.

Under peer-review:

Parks, C.A, **Brett, N.R**, Agellon, S, Lavery, P, Vanstone, C, Maguire, J.L, Rauch, F Weiler, H.A. Omega-3 long-chain polyunsaturated fatty acids in red blood cell membranes are associated with dietary intakes of omega-3-rich fish in healthy children. Revision submitted to Prostaglandins Leukot Essent Fatty Acids, June 2017.

Brett, N.R, Gharibeh, N, Weiler H.A. The effect of vitamin D supplementation, food fortification or bolus injection on vitamin D status in children 2-18 years: a

meta-analysis. Submitted to JAMA Pediatr, May 2017.

Brett, N.R, Parks, C.A, Agellon, S, Lavery, P, Vanstone, C.A, Kaufmann, M, Jones, G, Maguire, J.L, Maguire, Rauch, F, Weiler, H.A. Vitamin D status and functional health outcomes in children 2-8 y: A 6-month vitamin D randomized controlled trial. Submitted to Am J Clin Nutr, May 2017.

In preparation:

Brett, N. R, Vanstone, C.A, Maguire, J. L, Rauch, F, Weiler H. A. Parents lack knowledge about milk and alternatives and their intake relates to intakes of their 2-8 y old children.

Brett, N. R, Agellon, S, Lavery, P, Vanstone, C.A, Goruk, S, Field, C. J, Weiler H. A. IL-6, TNFα and lymphocyte concentrations associate with vitamin D in children 2-8 y.

PRESENTATIONS

Oral Presentations

Brett, N.R, Vanstone, C.A, Weiler, H.A. Lean mass accretion increases during summer and positively associates with vitamin D status in healthy children 2-8 y. 8th International Conference on Children's Bone Health, Wurzburg, Germany, June 10-13, 2017.

Brett, N.R, Vanstone, C.A, Weiler, H.A. Bone mineral accretion is increased during winter and is positively related to lean mass accretion and calcium intake in healthy children 2-8 y. Experimental Biology, Chicago, Illinois, April 22-27, 2017.

Brett, N.R, Vanstone, C.A, Weiler, H.A. Lean mass accretion increases during summer and positively associates with vitamin D status in healthy children 2-8 y. Experimental Biology, Chicago, Illinois, April 22-27, 2017.

Brett N.R, Miller, F, Cohen, T.R, Agellon, S, Vanstone, C.A, Weiler, H.A. Irisin is proportionally lower in obese compared to healthy body mass index 6-9 y olds. Canadian Musculoskeletal Conference, Toronto, October 14-15, 2016.

Brett, N. R, Parks, C.A, Agellon, S, Lavery, P, Vanstone, C.A, Maguire, J.L, Rauch, F, Weiler, H.A. Lean mass accretion associates with vitamin D intake: A 6 month randomized controlled trial in 2-8 y olds using fortified food. Experimental Biology, San Diego, California, April 1-4, 2016.

Brett, N.R, Vanstone, C.A, Maguire, J.L, Rauch, F, Weiler, H.A. Parental knowledge, perceptions and consumption of milk and alternatives relates to intakes of young children 2-8 y of age. Experimental Biology, San Diego,

California, April 1-4, 2016.

Parks, C.A, **Brett, N.R**, Agellon, S, Lavery, P, Vanstone, C.A, Maguire, J.L, Rauch, F, Weiler, H.A. Erythrocyte omega-3 long chain polyunsaturated fatty acids are associated with lumbar spine but not whole body bone mineral density in healthy children. Experimental Biology, San Diego, California, April 1-4, 2016.

Brett, N.R, Agellon, S, Lavery, P, Vanstone, C.A, Maguire, J.L, Rauch, F, Weiler, H.A. Vitamin D status and functional health outcomes: A randomized vitamin D dose-response trial in 2-8 y olds. Experimental Biology, Boston, Massachusetts, March 28- April 1, 2015.

Brett, N.R, Agellon, S, Lavery, P, Vanstone, C.A, Maguire, J.L, Rauch, F, Weiler, H.A. Vitamin D dose-response in young children 2 to 8 y of age: a 12 wk randomized clinical trial to establish requirements in the absence of ultra-violet beta solar radiation. Research Feeding Industry Symposium, Montreal, September 17, 2014.

Brett, N.R, Agellon, S, Vanstone, C.A, Weiler, H.A. Vitamin D status positively associates with interleukin-6 and tumour necrosis factor alpha in healthy young children. Experimental Biology, San Diego, California, April 26-30, 2014.

Poster Presentations

Brett, N.R, Weiler, H.A. Vitamin D intake and status in children 2-18 years: a meta-analysis. 8th International Conference on Children's Bone Health, Wurzburg, Germany, June 10-13, 2017.

Brett, N.R, Vanstone, C.A, Weiler, H.A. Bone mineral accretion is increased during winter and is positively related to lean mass accretion and calcium intake in healthy children 2-8 y. 8th International Conference on Children's Bone Health, Wurzburg, Germany, June 10-13, 2017.

Brett, N.R, Weiler H.A. Vitamin D intake and status in children 2-18 years: a meta-analysis. Canadian Nutrition Society Annual Conference, Montreal, May 25-27, 2017.

Patel, S, Vanstone, C.A, **Brett, N.R**, Mullahoo, K, Glenn, L, Laliberte, A, Razaghi, M, Yuan, Y, Gharibeh, N, Wei, S, Weiler, H.A. Prenatal supplements are required to meet the Recommended Dietary Allowance for vitamin D but elevated intakes above the upper level for iron and folate in the majority of pregnant women. Canadian Nutrition Society Annual Conference, Montreal, May 25-27, 2017.

Brett, N.R, Vanstone, C.A, Weiler, H.A. The 6-month change in bone mineral density measured by a portable device has poor agreement with dual-energy x-

ray absorptiometry at the forearm in 2-8 y olds. Canadian Musculoskeletal Conference, Toronto, October 14-15, 2016.

Brett, N. R, Parsons, K.E. Vanstone, C.A, Weiler, H.A. Lean mass indices: An alternative to BMI for assessing growth outcomes in young children. American Society for Bone and Mineral Research Annual Meeting, Atlanta, Georgia, September 16-19, 2016.

Brett, N.R, Parsons, K.E. Vanstone, C.A, Weiler, H.A. Energy and protein intakes above recommendations inversely correlate with lean mass indices in 2-8 y olds. American Society for Bone and Mineral Research Annual Meeting, Atlanta, Georgia, September 16-19, 2016.

Brett, N.R, Parks, C.A, Agellon, S, Lavery, P, Vanstone, C.A, Maguire, J.L, Rauch, F, Weiler, H.A. Vitamin D status and markers of bone metabolism: a 6 month randomized vitamin D trial in healthy 2-8 y olds using fortified foods. Canadian Nutrition Society Annual Conference, Ottawa, May 5-7, 2016.

Parks, C.A, **Brett, N.R,** Agellon, S, Lavery, P, Vanstone, C.A, Maguire, J.L, Rauch, F, Weiler, H.A. Long-chain polyunsaturated fatty acids in erythrocyte membranes are associated with biomarkers of bone metabolism in healthy children. Canadian Nutrition Society Annual Conference, Ottawa, May 5-7, 2016.

Brett, N.R, Parks, C.A, Agellon, S, Lavery, P, Vanstone, C.A, Maguire, J.L, Rauch, F, Weiler, H.A. The effect of diet and seasonal ultraviolet beta radiation exposure on serum 25(OH)D in 2-8 y olds. 9th International Symposium on Nutritional Aspects of Osteoporosis, Montreal, June 17-20, 2015.

Brett, N.R, Agellon, S, Lavery, P, Vanstone, C.A, Maguire, J.L, Rauch, F, Weiler, H.A. Vitamin D status and functional health outcomes: A randomized vitamin D dose-response trial in 2-8 y olds. 2nd Annual Perform Centre Research Conference, Montreal, May 15, 2015.

Brett, N.R, Lavery, P, Vanstone, C.A, Maguire, J.L, Rauch, F, Weiler, H.A. Distal one-third forearm bone mineral density of healthy young children is more highly related to lumbar spine than whole body bone mineral density. McGill Biomedical Graduate Conference, Montreal, March 19, 2015.

Brett, N.R, Agellon, S, Lavery, P, Vanstone, C.A, Maguire, J.L, Rauch, F, Weiler, H.A. Milk product intake may not associate with body fat percentage or bone density in young children. Experimental Biology, Boston, Massachusetts, March 28-April 1, 2015.

Brett, N.R, Lavery, P, Vanstone, C.A, Maguire, J.L, Rauch, F, Weiler, H.A. Distal one-third forearm bone mineral density of healthy young children is more highly related to lumbar spine than whole body bone mineral density. American Society for Bone and Mineral Research Annual Meeting, Houston, Texas,

September 12-15, 2014.

Brett, N.R, Agellon, S, Lavery, P, Vanstone, C.A, Maguire, J.L, Rauch, F, Weiler, H.A. Vitamin D dose-response in young children 2 to 8 y of age: a 12 wk randomized clinical trial to establish requirements in the absence of ultra-violet beta solar radiation. American Society for Bone and Mineral Research Annual Meeting, Houston, Texas, September 12-15, 2014.