**Study rationale**: ACEMS – Aspirin, Cooling and Exercise in Multiple Sclerosis: *The influence of aspirin and skin cooling on exercise capacity and postural sway in the heat in individuals with multiple sclerosis*

Physical activity results in an increase in metabolic heat load (active heat stress) causing an increase in core temperature. In those with multiple sclerosis (MS) there is a stronger link between increases in core temperature and fatigue compared to a healthy population (1-3). There are many benefits of exercise for individuals with MS (4) however they are deterred from exercise due to overheating, exhaustion and symptom worsening (“Uhthoff’s phenomenon”) (5). This in turn leads to lower exercise capacity (6), reduced postural control (7) and balance (8) and a concomitant increased risk of falling (9, 10).

Interventions to mitigate heat-related fatigue, increase exercise capacity and reduce postural sway and balance deficits in hot environmental conditions are necessary for the MS population. Some cooling strategies administered before and/or during heat exposure successfully mitigate the development of heat-related fatigue in people with MS (11). However, these methods, such as 30 min of lower body cold water immersion (12) or donning an ice vest (13), can prove impractical in the context of everyday life and incompatible with many jobs. This has led to researchers investigating other more practical methods of mitigating heat-related fatigue and increasing exercise capacity, such as cold water ingestion (14).

Preliminary findings suggest ingesting aspirin (acetylsalicylic acid - ASA), an antipyretic drug (lowering core temperature during a fever) prior to exercise, may also be a practical method to slow or reduce the rise in core temperature during exercise resulting in an improvement in exercise capacity in those with MS (15). However these findings are questionable as the mechanism of action of aspirin does not appear to play any particular role in active metabolic heat production. When a noxious stimulus is present in the body such as an infection or virus this results in an upregulation of cyclooxygenase (COX) and a large increase in prostaglandin E2 (PGE2). This increased PGE2 acts on the hypothalamus resulting in an increase in the body’s set point of core temperature which in turn leads to an increase in core temperature as the body aims to meet that new set point. The mechanism of action of aspirin is to inhibit COX resulting in lower production of PGE2. This mechanism is different from the increase in core temperature that naturally occurs as a result of an increase in metabolic heat production during physical activity. We aim to test the hypothesis that in individuals with MS, ingesting aspirin prior to exercise will not improve exercise capacity or reduce postural sway in the heat.

An increase in skin temperature has been associated with an increase in fatigue and a reduction in exercise capacity (16). Moreover, heat-related fatigue is determined by multiple physiological and psychological processes and not solely increases in core temperature (17). Cooling the skin has successfully been shown to improve exercise capacity in healthy populations (18) and improve functional capacity in MS populations (13) without differences in core temperature. As mentioned previously, these cooling strategies aren’t always practical. A practical way of cooling the skin could involve spraying cold water onto thermosensitive areas of the skin, such as the face, neck, back and arms. This cooling strategy might serve more practical compared to previous methods, however this strategy has not been scientifically tested. Hence, our second aim is to test the hypothesis that in individuals with MS, cooling the skin with a cold water spray during exercise will improve exercise capacity and reduce postural sway in the heat.

**References**

1. Krupp LB, Alvarez LA, LaRocca NG, Scheinberg LC. Fatigue in multiple sclerosis. *Archives of neurology*. 1988;45(4):435-7.

2. Nelson DA, McDowell F. The Effects of Induced Hyperthermia on Patients with Multiple Sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry*. 1959;22(2):113-6.

3. Simmons RD, Ponsonby A-L, Van Der Mei IA, Sheridan P. What affects your MS? Responses to an anonymous, Internet-based epidemiological survey. *Multiple Sclerosis Journal*. 2004;10(2):202-11.

4. Motl RW, Pilutti LA. The benefits of exercise training in multiple sclerosis. *Nat Rev Neurol*. 2012;8(9):487-97.

5. Uhthoff W. Studies on the occurring in multiple sclerosis stove eye disorders. *Arch Psychiat Nervenkr*. 1889;21:303.

6. Savci S, Inal-Ince D, Arikan H et al. Six-minute walk distance as a measure of functional exercise capacity in multiple sclerosis. *Disability and Rehabilitation*. 2005;27(22):1365-71.

7. Cattaneo D, Jonsdottir J. Sensory impairments in quiet standing in subjects with multiple sclerosis. *Multiple Sclerosis Journal*. 2009;15(1):59-67.

8. Soyuer F, Mirza M, Erkorkmaz Ü. Balance performance in three forms of multiple sclerosis. *Neurological Research*. 2006;28(5):555-62.

9. Matsuda PN, Shumway-Cook A, Bamer AM, Johnson SL, Amtmann D, Kraft GH. Falls in Multiple Sclerosis. *PM&R*. 2011;3(7):624-32.

10. Matsuda PN, Shumway-Cook A, Ciol MA, Bombardier CH, Kartin DA. Understanding Falls in Multiple Sclerosis: Association of Mobility Status, Concerns About Falling, and Accumulated Impairments. *Physical Therapy*. 2012;92(3):407-15.

11. Watson CW. Effect of Lowering of Body Temperature on the Symptoms and Signs of Multiple Sclerosis. *New England Journal of Medicine*. 1959;261(25):1253-9.

12. White A, Wilson T, Davis S, Petajan J. Effect of precooling on physical performance in multiple sclerosis. *Multiple Sclerosis Journal*. 2000;6(3):176-80.

13. Meyer-Heim A, Rothmaier M, Weder M, Kool J, Schenk P, Kesselring J. Advanced lightweight cooling-garment technology: functional improvements in thermosensitive patients with multiple sclerosis. *Multiple Sclerosis Journal*. 2007;13(2):232-7.

14. Chaseling GK, Filingeri D, Barnett M, Hoang P, Davis SL, Jay O. Cold-Water Ingestion Improves Exercise Tolerance of Heat-Sensitive People with MS. *Medicine and science in sports and exercise*. 2017.

15. Leavitt VM, Blanchard AR, Guo C-Y, Gelernt E, Sumowski JF, Stein J. Aspirin is an effective pretreatment for exercise in multiple sclerosis: A double-blind randomized controlled pilot trial. *Multiple Sclerosis Journal*. 2017:1352458517739138.

16. Sawka MN, Cheuvront SN, Kenefick RW. High skin temperature and hypohydration impair aerobic performance. *Experimental physiology*. 2012;97(3):327-32.

17. Cheung SS, Sleivert GG. Multiple triggers for hyperthermic fatigue and exhaustion. *Exercise and sport sciences reviews*. 2004;32(3):100-6.

18. Bongers CC, Thijssen DH, Veltmeijer MT, Hopman MT, Eijsvogels TM. Precooling and percooling (cooling during exercise) both improve performance in the heat: a meta-analytical review. *Br J Sports Med*. 2015;49(6):377-84.