Helsefak – Det helsevitenskapelige fakultet UiT

The beneficial health effects of voluntary exposure to cold water – a continuing subject of debate

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1 Preface

Wim Hof, a Dutch ice-water swimmer has for several decades intrigued medical experts by pushing physiological limits regarding cold exposure. He has also dedicated much of his time to introduce this activity to others through lectures and workshops. In part, because of my interest in medicine, I became interested in cold water swimming after reading about this physiologically intriguing person. For about three winter seasons, I have been actively participating in this activity. This stimulated me to start reading different articles, both in the popular and scientific literature, concerning possible health benefits of recreational cold water swimming. I have always found it strange that we were taught as children to avoid unnecessary exposure to cold, for example by going outdoors in the winter in light clothing, even for brief periods of time. It seems obvious to me that our body should be able to adapt to the cold, at least in part, if we are regularly exposed to it. We are, after all, descendants of people, who in prehistoric times, had to endure the extreme temperatures of the arctic climate. About two years ago, I read an article in *Fædrelandsvennen*, the regional newspaper of Agder county in Norway, regarding regular winter swimmers, where the newspaper contacted Professor Maja-Lisa Løchen, from the Faculty of Health Sciences at UiT, asking her about the health benefits associated with winter swimming. She cited a couple of articles with vague statements concerning the health benefits of cold water immersions and indirectly suggested that more research was needed. This led me to think of this as a possible subject for my master thesis. I wanted to do a laboratory study comparing experienced winter swimmers of Tromsø to a control group. Professor Emeritus James Mercer was suggested as one of the most qualified potential supervisors, and luckily he was interested in carrying out an experimental study on this topic and be the project leader of my master thesis. He proposed to conduct a comparative thermographic study comparing cold pain sensitivity and skin blood perfusion of the hands following a cold challenge between experienced and inexperienced winter swimmers. The main idea behind the planned study was to try and find evidence that regular cold water swimming improves peripheral circulation and reduces the temperature threshold for cold pain sensation. We arranged all the necessary preparations with an approved REK-application, willing winter swimming participants and the required equipment, but when the laboratory experiments were about to start, the covid-19 pandemic caused the cessation of this project. The research experiment was put on hold, but after some time it was clear that there would be no clinical research experiments that could be completed within the

time frame I had to complete my master thesis. Prof. Emeritus Mercer suggested to change the project and instead carry out a detailed literature search to try and ascertain whether there was any sound published scientific data to support the often contradictory views concerning the potential health benefits of this activity. This was the start of what has become an incredibly interesting and rewarding scientific experience.

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2 Abstract

This thesis is a review article based on a detailed multiple database literature survey of published literature in order to try and determine whether voluntary exposure to cold water immersion (CWI) has beneficial health effects. The literature research was deliberately restricted to only include studies in humans within a strict keyword-based framework. After a filtering process the number of studies regarded as being relevant was 92. While many of the studies demonstrated significant effects of CWI on various physiological and biochemical parameters, the question as to whether these changes are actually beneficial for health was difficult to objectively assess. Although some of the studies were based on established winter swimmers, many were performed on subjects with no previous winter swimming experience or in subjects not involving cold water swimming, for example cold water immersion as a post exercise treatment. In addition, clear conclusions from the majority of studies were hampered by the fact that they were carried out in small groups, often of one gender and with differences in exposure temperature and salt composition of the water. Although approached from different angles, CWI seems to have a positive effect on the reduction and/or transformation of body adipose tissue. This may have a protective effect against cardiovascular disease and potentially could have prophylactic effects on health. A further point that is unclear from the literature is as to whether winter swimmers as a group are naturally healthier and that the positive effects they report are not necessarily related to CWI itself but are more associated with the well described positive social aspects of winter swimming. In summary, there is increasing evidence that voluntary exposure to cold water has some beneficial health effects. However, until we have more conclusive studies, the topic will continue to be a subject of debate.

2.1 List of abbreviations

ACTH	Adrenocorticotropic hormone
ApoB	Apolipoprotein B
ApoA1	Apolipoprotein A1
at-pro-BNP	Aminoterminal pro- brain natriuretic peptide
AVA	Arteriovenous anastomosis
BAT	Brown adipose tissue
CD	Cluster of differentiation
CIVD	Cold induced vasodilation
CK	Creatine Kinase
CRP	C - reactive protein
CWI	Cold water immersion
DIRT	Dynamic infrared thermography
FSH	Follicle-stimulating hormone
GPX1	Glutathione peroxidase 1
HLA-DR	Human Leukocyte Antigen – DR isotype
hsTnI	High sensitivity troponin I
hsTnT	High sensitivity troponin T
Ig	Immunoglobulin
IISA	The International Ice Swimming Associations
IL	Interleukin
IWSA	The International Winter Swimming Association
LDS	Long distance swimming
LH	Luteinizing hormone
PON-1	Paraoxonase-1
PTH	Parathyroid hormone
RBM3	RNA binding protein 3
RNA	Ribonucleic acid
T3	Triiodothyronine
TSH	Thyroid-stimulating hormone
UCP1	Uncoupling protein 1
URTI	Upper respiratory tract infections
WAT	White adipose tissue

3 Introduction

Cold exposure in the form of cold water/ice bathing is a popular activity. There are many different forms of this activity and some have been clearly defined. For example, winter swimming is defined as the activity of swimming or immersion in cold water during the winter season (1). In colder countries, it may be synonymous with ice swimming, where the frozen ice layer has been removed to expose the water. The International Ice Swimming Associations (IISA) and the International Winter Swimming Association (IWSA) have similar competition guidelines (2, 3). These guidelines differentiate between swimming in ice water of -2 to +2°C, freezing water of +2.1 to 5°C and cold water of +5.1 to +9°C (2, 3).

Cold exposure in the form of ice bathing has been suggested to have many health benefits. For example, it has been claimed that it can boost the immune system, treat depression, enhance peripheral circulation, increase the libido, burn calories and reduce stress (4). Many of the proclaimed health benefits are based on subjective claims and anecdotal cases.

A few studies have been conducted which give some scientific insight on the health benefits of ice bathing and cold exposure. These studies suggest that regular cold exposure can be effective in treatment of chronic autoimmune inflammation (5), reduce hypercholesterolemia by brown adipose tissue activation (6) and have a positive effect on stress regulation (5). However, many of the health benefits claimed from regular cold exposure may not be causal and may, instead, be explained by other factors. Such factors include an active lifestyle, trained stress handling (meditation, breathing techniques, mindfulness), social interactions, aesthetic environmental surroundings, healthy food and healthy food intake patterns and a positive mindset.

While the details in the above introduction describe some of the proposed benefits of cold water bathing there is still much debate concerning this topic. From recent articles in the popular press, at least in Norway, there seems to be an upsurge of interest in cold water bathing in all age groups, although there are always special concerns with regard to the elderly (7). In light of this there is a clear need for evidence based scientific research documenting the potential health benefits. While there are a few published reviews on the subject (8), most of them have only concentrated on certain types of cold water exposure, for example extreme cold exposure.

The purpose of this review article is to make a thorough examination of the available published scientific documentation on recreational cold water bathing without any input from the large volume of articles in the popular press.

The review starts with an explanation of the literature search procedure and the narrowing down of the relevant publications. Based on the relevant selected articles, the physiological effects connected with regular cold water immersion (CWI) are discussed in detail.

4 Methods

As a starting point, contact was made with Senior Academic Librarian Eirik Reierth, Science and Health Library at UIT, the Arctic University of Norway, who was asked to assist in a detailed multiple database literature survey of the available published literature related to cold water immersion and its health benefits. Since it was decided to only focus on medically orientated research, the literature search was restricted to the databases medline, embase and pubmed. This required different advanced searches for each database.

At first a focus was made on MeSH (medical subject headings) -terms. The idea was to sort MeSH terms in categories related to either the medium, action, population or possible effects/results. The MeSH terms were discovered by using the function "explode" after typing in pre-established terms related to the thesis. This function suggested different MeSH-terms related to the established terms. The pre-established keywords were chosen from exploring claims from scientific articles found in the popular press and internet.

MEDLINE and EMBASE are both OVID databases and have the same display and search functions. This made it easier, as it was possible to use the same search in both databases. The initial strategy consisted of using a combination of MeSH terms related to the subject combined by the function OR, and later combined in groups by the function AND. But, after a number of failed attempts in MEDLINE and EMBASE, a different approach was necessary to get a more relevant result. This was achieved by the feature adjacency operator. Using the function ADJ with a number, it is possible to find research papers mentioning terms that are placed adjacent to each other, within the distance of the number of words or sentences typed next to "ADJ". It was decided to use the three main terms "cold", "water" and "swimming" in an advanced search consisting of this function; "cold water adj3 swimm*". Using the function

"*" the search included every term beginning with "swimm". This advanced search resulted in a total of 131 relevant research papers in MEDLINE and 204 relevant research papers in EMBASE.

In the database PUBMED the initial strategy was initiated. The MeSH terms were divided in groups related to either the medium, action, effects/results or population. The terms were combined with the function OR within each group and then the group clusters were combined using the function AND. The function OR adds the search results together into one search and the function AND finds research papers that include at least one MeSH from all four group clusters.
Group 1 consisted of MeSHs describing the medium; seawater, water, cold climate, cold temperature.
Group 2 consisted of MeSHs describing the action; immersion, swimming, physiological stress.
Group 3 consisted of keywords describing the results; Quality of life, health status, longevity, inflammation, brown adipose tissue, energy metabolism, body temperature regulation, acclimatization, neural conduction, synaptic transmission, blood circulation, immune system, oxidative stress, and oxidation reduction.
Group 4 consisted of MeSHs describing the population of interest; humans, females, males. The advanced search in PUBMED resulted in a total of 393 research papers.

In a further attempt to improve the selection of relevant publications, a small adjustment was tried by combining group 1 and group 2 with the function OR. However, instead of adding more relevance to the research this approach only succeeded in creating more unrelated publications, and was therefore not used.

Many of the published research articles concerned animals, which were included in the initial search, although most were later filtered out (see exclusion criteria below).

At this stage there were now a total of 727 results to analyse, where only studies with practical and clinical relevance were included. In order to focus on the health benefits of cold water immersion in humans it was necessary to employ the following exclusion criteria: - animal studies (with a few exceptions where it was felt they were relevant for humans), cold stress without water immersion, aggravations of medical conditions when exposed to

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seawater, accidental cold water immersions, water temperatures greater than 20°C, treatment of hyperthermia, therapy in general, studies investigating the effect of a medication on cold water immersion, research on people with conditions such as diabetes, Raynauds, cardiovascular disease, homozygous sickle cell disease, use of wet suits, cold weather altitude acclimatization, publications were there was only a title with an abstract or publications with only a title. Many of the publications only including the title were case studies, and many of these were in different languages; Russian, French, German, Italian, and Hebrew among others. After employing the exclusion criteria, the number of studies was narrowed down from 727 to 264.

Following a more thorough examination of these 264 studies, many more were regarded as being irrelevant due to factors such as double publication, non-regular cold water exposure, not-focusing on health benefits, research which are no longer valid and no available online research paper. Following this procedure we ended up with 92 relevant studies. What follows below is based on these final 92 selected articles. The main findings are described and categorised for convenience using different organ systems. Before these findings are described, a brief general introduction into human cold thermoregulation physiology is presented, with appropriate references to the 92 selected publications where appropriate.

5 Results

5.1 Physiological responses to cold

As in exercise and hypoxia, cold-water exposure is a physiological challenge to the body organ systems. The body has to adjust to the cool environment to maintain the temperature in the delicate organs of the core and brain. Body heat balance is maintained either by preventing heat loss, or by producing more heat.

5.1.1 Thermoregulation and skin blood perfusion

The vasomotor control of skin blood perfusion through vasoconstriction and vasodilation and its role in body thermoregulation is a well-established physiological mechanism. Heat is mainly distributed to the outer layer of the skin by blood flow. The warm blood from the core is transported to the dermis of the skin through a network of blood vessels which penetrates the subcutaneous tissue. A venous plexus in the subcutaneous skin layer plays an important

role in temperature regulation through its capacity of transporting large amounts of warm blood. The skin receives a continuous supply of blood from the core through the skin capillaries. While skin blood perfusion is important for tissue viability, the large changes in skin blood perfusion from full vasoconstriction to full vasodilation, especially in the acral parts of the body, are used for heat exchange between the skin surface and the environment. In the more exposed acral parts like the hands, feet, nose and ear helix, the blood from the subcutaneous arteries can be transmitted directly to the venous plexi through a network of small blood vessels called arteriovenous anastomosis, or AVAs. The AVAs are surrounded by smooth muscle that contracts and dilates to regulate the blood flow and therewith regulates the temperature in the respective skin areas they supply. These short circuit vessels are open in situations when the body needs to lose heat and are closed during heat conservation in the cold. The importance of AVA's in controlling heat loss from the hands can nicely be demonstrated with infrared thermography as shown in Figure 1 and also in the following publications (9-11).

In thermoneutral or warm environments (25-30°C) the skin, especially in the acral parts of the body, is overly perfused when compared with the nutritive needs of the skin tissue (12). The purpose of the extra blood flow is considered to be mainly connected to thermoregulation, by increased radiative and convective heat loss. The control of the blood flow is influenced by both neurogenic reflexes and local factors (13). Neural control of human skin circulation consists of both sympathetic adrenergic vasoconstrictor nerves and sympathetic vasodilator nerves. In thermoneutral environments this system is tonically active, altering slight changes in blood flow to maintain a constant body temperature. This automatic regulative effect is mainly controlled by cardiovascular homeostatic reflexes activated by carotid sinus pressure receptors and atrial volume receptors. Thermoregulatory hypothalamic neurons release norepinephrine with other cotransmitters and also local endothelium mediated factors provide adjustment in vasoconstriction in response changes in environmental temperature. This mechanism of narrowing the blood vessel reduces heat loss, skin temperature, blood flow and nerve conduction velocity (14).
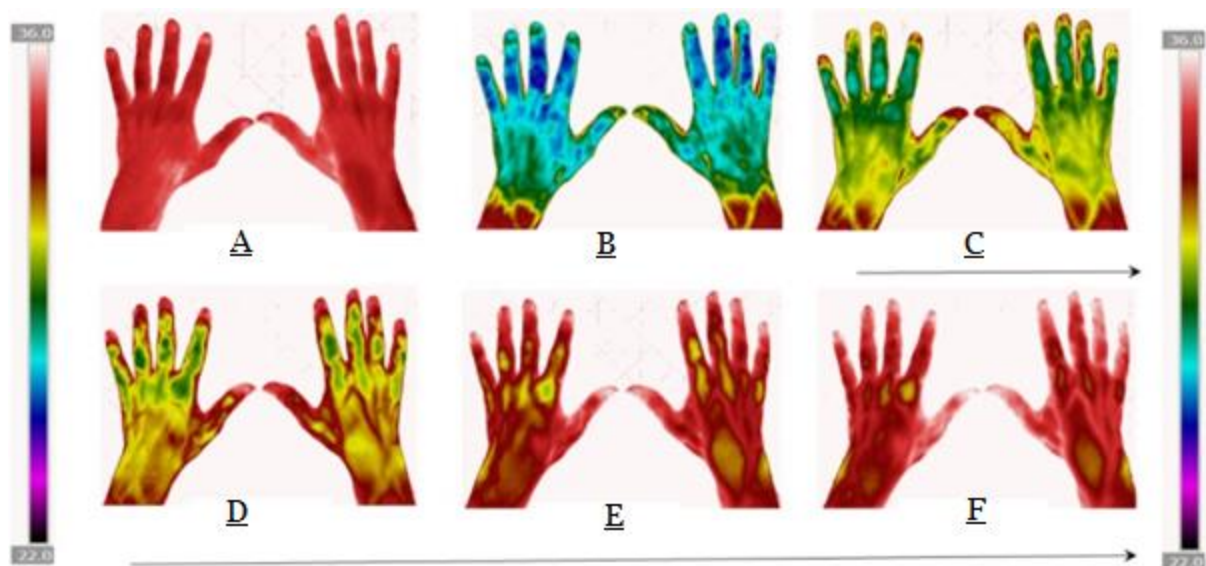
FIGURE 1: A series of thermographic images of the dorsal aspect of the hands in a healthy subject before (A), immediately after (B) and at 1 minute intervals during a 4 min recovery period (C-F) following a cold provocation test (1 min immersion of the lightly gloved hands in 20°C water for 1 min). Note that during the recovery period the rewarming process starts at the fingertips (opening of arteriovenous anastomosis located in the finger tips) and gradually spreads proximally. (private image James Mercer, UiT – the Arctic University of Norway)

Under normal conditions in the air the vasomotor response (vasodilation/vasoconstriction) is used to regulate body core temperature within the thermoneutral zone. Under these conditions the skin is fully vasoconstricted at the lower critical temperature (lower limit of the thermoneutral zone) (15).

The vasoconstriction of the peripheral microcirculation sets in at an estimated core temperature of 37.1°C when immersed in cold water and a temperature of 37.5°C when immersed in cold water post-exercise (16).

As body temperature falls below the lower critical temperature, the body is unable to prevent a further fall by vasomotor control alone. In order to prevent a further fall, it has to invoke its second heat defence system, namely increasing heat production by shivering (see below). The core temperature threshold for shivering was estimated to be 36.2°C pre-exercise and 36.5°C post-exercise, when immersed in cold water (16).

There are large individual variations in the physiological response to cold water exposure. This was nicely demonstrated in a recent study using dynamic infrared thermography (DIRT)

(17). In this study, Norheim et al were able to demonstrate the differences in rewarming ability in a cohort of 255 healthy Norwegian army conscripts exposed to a mild cold provocation test of the hand. While the majority passively were able to rewarm their hands to pre-test peripheral temperature within 4 minutes, 10% had a slowed rewarming ability. Figure 2 below is taken from (17).
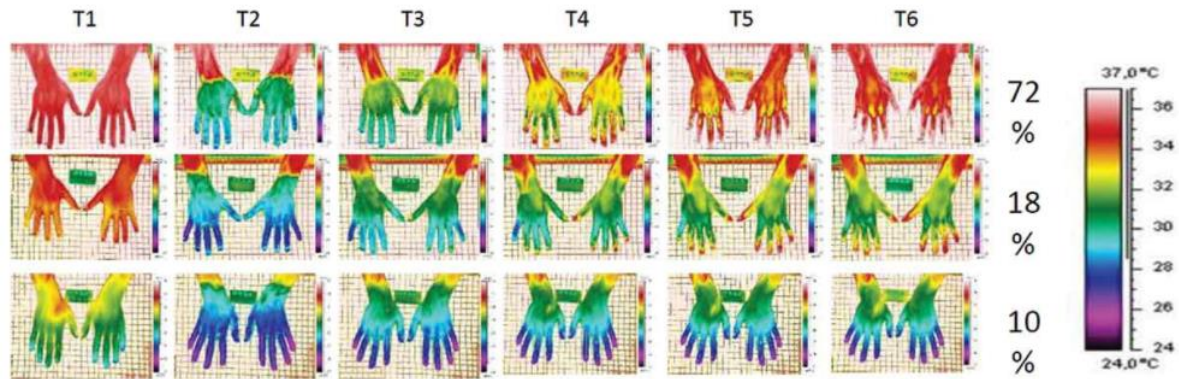

Figure 2: An example of the DIRT examinations in three individual recruits from the August cohort (a rapid rewarmer – top row; an intermediate rewarmer – middle row and a slow rewarmer – lower row). The distribution of these three different rewarming patterns are in percent (%) of the August cohort, n = 120. The thermographic images were obtained from six different time points: one before (T1) and one immediately after the cold challenge (T2) and thereafter at 1-min intervals during the 4-min spontaneous rewarming period (T3–T6). (from (17) (with permission))

As can be seen in Figure 2, the slower rewarmers tended to have lower pre-cooling average hand skin temperatures. This indicates that even among a group of largely heterogeneous healthy individuals, some individuals might have different physiological response to immersion in cold water.

5.1.2 Shivering and nonshivering thermogenesis

In addition to the production of body heat by normal basal metabolic processes, the body is, in addition to physical exercise, able to generate extra heat through the process of shivering and nonshivering thermogenesis.

Shivering is the process of continuous and asynchronous contraction of flexor and extensor skeletal muscles in the body. Peripheral and central thermal receptors stimulate the hypothalamic thermoregulatory control center, which mediates an effector response through supraspinal- and peripheral motorneurons. The increased muscle activity is highly energy

dependent and in consequence causes an elevated metabolic rate. The maximum amount of heat that the body can produce by shivering thermogenesis is about 5 times greater than basal metabolic heat production (18). Metabolic energy production, or cell respiration, is an exothermic reaction and is the chief generator of additional heat in cold environments (19).

While considerably more heat can be produced by physical activity than by shivering, shivering in a cold water immersion situation is more effective than exercise at producing heat because the individual remains still and less heat is lost to convection (20).

Brown adipose tissue (BAT) is capable of producing excess heat through the process of nonshivering thermogenesis. These adipocytes have, in contrast to white adipocytes, mitochondria. Through a chemical process involving loose coupling of oxidative phosphorylation the mitochondria in BAT are able to burn triglycerides and produce large quantities of heat which is released directly into the bloodstream. In response to cold stress BAT has increased blood flow, indicating a physiological response of heat generation rather than the insulative blood flow reduction related to white adipose tissue (WAT) (21). While brown fat deposits and the production of heat by non-shivering thermogenesis in humans are well established in the newborn, its role in thermoregulation in the adult has, for many years, been a subject of debate (22).

As actual brown fat deposits in adult humans are only a few grams, Muzik et al (23) showed that brown adipose tissue thermogenesis only accounts for metabolic energy consumption of <20kcal/day, equivalent to only 2 minutes moderate-intensity running. Browning of white fat is therefore necessary to show a physiological relevant effect on whole body metabolism (24).

5.1.3 Adipose tissue as a body thermal insulator

Fat thickness is an important insulator of heat during cold exposure. Hayward et al (25) performed an experiment comparing the importance of fat thickness to thermoregulatory reflexes in determining the ability to stabilize the body temperature in cold water. It was concluded that the importance varies in different parts of the body. The thorax was measured to be the main site for heat loss and that the subcutaneous fat accounted for half of the insulation. By contrast, the subcutaneous fat accounted for under a third of the insulation seen

in muscular limbs, and only about three percent of insulation in the hands and feet. Total body insulation by unit surface area was closely determined by mean subcutaneous fat thickness, regardless of fat distribution differences among genders. Also Glickman-Weiss et al (26) noted no differences in response to cold water immersions between men and women. Therefore no gender adjustments are necessary when body fatness and the body surface area to volume ratio are taken into account.

5.1.4 Gender, age and time of day responses to cold water immersion

When comparing gender specific cold water responses, Solianic et al (27) found that there was a significant difference in the thermoregulatory response between men and women. It was observed among participants exposed to cold stress by immersion in cold water that men tended to exhibit a greater metabolic response and shivering thermogenesis, whereas women had a greater insulative response. The cooling rate was similar in both genders.

As Solianic et al were investigating the differences of cold water immersion between the two genders, it was noted that although the experience of cold strain was similar in men and women, the neuroendocrine and immune responses were larger in men (27).

Another important predictor of how the physiology of our body is influenced by the cold is age, and hypothermia still remains one of the leading causes of death among older individuals (28). A study exploring the difference in thermoregulatory response between old and young individuals observed a higher mean skin temperature in old subjects compared to the younger subjects (29). This suggests a deficit of thermoregulation which may contribute to a loss in core temperature and development of hypothermia in older adult. On the other hand in a thermographic study comparing the response to local cooling of the hands and feet in young and elderly subjects, the elderly were found to have lower pre-cooling skin temperatures (9).

Body temperature in the humans has a well-established circadian rhythm, with core temperature varying with about 1°C throughout the day, reaching its lowest temperature at night (30). Although this raises the possibility that morning CWI may increase the risk of hypothermia because of lower initial core temperature, there seems to be no indications of circadian temperature rhythm affecting the thermoregulatory response to cold water immersion in terms of shivering and vasoconstriction (30).

5.1.5 Cold exposure

The hunting reaction/response is one of four possible responses to immersion of the hand in cold water (15). The peripheral blood vessels alternates between vasoconstriction and vasodilation in extremities immersed in cold water. The initial response is a vasoconstriction to reduce the heat loss, but this results also in reduced temperature of the extremities. After approximately 5-10 minutes of cold exposure, the blood vessels reverse the reaction by vasodilating, a process called cold induced vasodilation (CIVD). This process of CIVD is largely linked to the cold induced decrease of sympathetic activity around the sphincter muscle of the arteriovenous anastomosis. A new phase of vasoconstriction follows the vasodilation, after which the process repeats itself.

The other responses observed in the fingers after immersion in cold water are a continuous state of vasoconstriction, slow steady and continuous rewarming and a proportional control form in which the blood vessel diameter remains constant after an initial phase of vasoconstriction (15). However, of the vast majority of the vascular response to immersion of the finger in cold water, the hunting reaction is the most important.

While the genetic component influencing the strength of this response is largely unknown, individuals living or working in cold environments seem to have a more developed hunting reaction. Krog et al (31) and Leblanc et al measured that arctic fishermen and Norwegian Sami people had an increased hand blood flow in the cold (32). Nelms and Soper (33) noted a shorter time onset of CIVD in British acclimatized fish filleters. Although the genetic influence of physiological cold temperature response is unknown, it has been shown that Inuits have an increased ability of recovering to control temperature values after a cold water immersion of the hand, when compared to arctic Caucasian residents and especially when compared to individuals from a warmer climate (34). It is uncertain whether this is caused by a permanent genetic adaptation or an acclimatization to cold environments.

5.1.6 Cold water immersion

This thesis focuses on cold water immersions and excludes research regarding cold exposure and other mediums. One of the well-known and described differences regarding medium impact on heat loss from the skin relates to heat loss in air compared to water. This is related to the fact that heat conduction is superior to convection in terms of temperature exchange to

the environment (14). Heat conductance is about 3.34 times greater in water compared to air, depending largely on the skinfold thickness (35).

When immersed in cold water, the body experiences two antagonistic responses, namely the cold shock response and the diving response. The diving response is activated by the wetting and cooling of the face- and nostril receptors while breath holding, and causes a profound sinus bradycardia, peripheral vasoconstriction, inhibition of central respiratory neurons, and redirection of blood to vital organs and release of red blood cells stored in the spleen (36). The cold shock response is a series of reflexes triggered by cutaneous cold thermoreceptors and causes, by contrast, sympathetically mediated tachycardia, respiratory gasping, uncontrollable hyperventilation, peripheral vasoconstriction and hypertension (37). In a study by Shattock and Tipton, they proposed that this conflict of autonomic response could be a major contributor to the high incidence of cardiac arrhythmias among healthy individuals when immersed in cold water (38).

Without the antagonising autonomic responses to cold water immersions, the cold shock response can alone have a major impact on the body and alone be connected to an increased risk of drowning. The initial respiratory gasping and hyperventilation was linked in a study by Mantoni et al (39), to a decrease in cerebral blood flow velocity in the middle cerebral artery and was associated with disorientation and loss of consciousness among the participants.

5.2 Effects of regular cold water exposure on different organ systems

5.2.1 Respiratory and cardiovascular response

There are, as discussed above, some risk factors connected to the immersion in cold water. The cold shock response sets in and increases the respiration frequency, heart rate, blood pressure and decreases the cerebral blood perfusion. In a study, by Lesna et al (40), a group of cold-adapted winter swimmers were investigated and compared to a control group to determine the effect of cold adaptation on cardiovascular risk factors, thyroid hormones and the capacity of humans to reset the damaging effects of oxidative stress. The cold adapted group had a significant reduction in apolipoprotein B/apolipoprotein A1 (ApoB/ApoA1) ratio, plasma homocysteine levels, glutathione peroxidase 1 (GPX1) activity and oxidative stress markers. They also had an increase in triiodothyronine (T3) values, paraoxonase (PON)-1

activity and zinc concentration when compared to the control group. This study demonstrates that cold-adapted individuals show an improvement in cardiovascular risk factor markers. These findings imply a positive cardio-protective effect of regular cold water immersion.

Even though there is evidence of improved cardiovascular risk factors in cold adapted subjects, the act of cold water immersion still increases the workload of the heart and thus has a large stress impact on the heart. A group of Czech scientists (41) investigated the relationship between swimming in cold water and the cardiac markers high sensitivity troponin I (hsTnI), high sensitivity troponin T (hsTnT) and aminoterminal pro- brain natriuretic peptide (at-pro-BNP), during a winter swimming competition. Blood from elite winter swimmers were collected one day before, right after, two hours after and 24 hours after the cold water swim. They found a significant increase in plasma hsTnI concentration two hours after the cold water swim competition, while hsTnT and at-pro-BNP remained unchanged. Although the exercise in cold water caused a release of hsTnI, it is not clear if this is connected to an increased risk of developing acute coronary syndromes. Elevation of troponins is mainly an indication of damage to the cardiac muscle, most commonly caused by a mismatch between oxygen supply and demand (42), and high intensity exercise in thermoneutral environments is also known to cause elevation of troponins (43). Even when cold adapted show an improvement in cardiovascular risk factors (40), the findings in the study (43) could link cold adapted swimmers to an increased risk for coronary syndrome. More research is therefore necessary to conclude whether cold water swimming is linked to an increased risk of acute coronary syndrome among adapted cold water swimmers.

Another important factor to evaluate the cardiac impact of regular cold water swimming is the effect on blood pressure. If repeated cold water immersion causes elevation of blood pressure, this could be linked to several heart conditions, such as ventricular hypertrophy. A group of 28 regular winter swimmers underwent a study to investigate the cardiovascular responses to cold (44). Clinical examination and anamnesis was collected and revealed mostly healthy individuals, except one subject with hypertension (180/105mmHg) and three subjects with diastolic pressure of 95mmHg. A significant increased blood pressure was found while the subjects waited undressed in the cold winter air before immersion. Neither immersion nor swimming in the cold water caused further increase in blood pressure and the pressure returned to control values 4 min after the experience. Electro and vector cardiographic signs

remained unchanged, among the subjects. No signs of ventricular hypertrophy or of cardiovascular or cerebrovascular damage could be detected. Similar findings were also found when a group of healthy men were put through a cold acclimation program for five weeks (45). Blood pressure in the subjects increased significantly during the first cold water immersion, but had no significant changes after the cold acclimation program, indicating that an adaptive process has taken place.

With regards to the ventilator response of acute cold water exposure, both experienced and inexperienced cold water swimmers had a positive effect of acclimatizing to cold water immersion (46). Furthermore, it has been shown that skin cooling through cold water immersion caused a significant habituation in the respiratory response and lowered the cold-shock response (14).

5.2.2 Specific thermoregulative adaptations to regular exposure to cold air and/or -water exposure

While this thesis focuses mainly on cold water immersion, it is also relevant to also briefly mention how exposure to cold air impacts body physiology since some of the findings in these 2 different media are similar. Thermal stress due to exposure to cold air has a direct effect on progenitor cell plasticity (47). Cold adaptation induces BAT biogenesis in adipose tissue. The acute cold stress upregulates thermogenic gene expression through a complex process that requires both β-adrenergic-dependent phosphorylation of S265 and demethylation of H3K9me2 by JMJD1A (48). This stimulates the formation of BAT with enhanced glucose oxidation, which, as described in section "Shivering and nonshivering thermogenesis" above, is required to maintain energy/thermal homeostasis in cold environment. Some research suggests that the molecular mechanism of transition between acute and chronic adaptation to cold stress might prove to be a novel molecular target for the treatment of metabolic disorders, via promoting biogenesis of BAT (48). Although the "browning" of adipose tissue has a positive effect on long-term energy homeostasis and body-weight regulation, the thermogenic response needs to be maintained to keep these changes in the transition process of fat cells (49).

Adiponectin is a key protein produced by adipose tissue and plays an important role in protecting against insulin resistance, diabetes, atherosclerosis and other age-related diseases (50). Some research, looking at the plasma adiponectin levels in centenarians and their

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offspring, suggest that elevated plasma adiponectin levels may promote increased longevity (50). Cold exposure in air or water seems to increase the production of adiponectin in adipose tissue through the process of shivering and nonshivering thermogenesis (51).

Another study looked into the combination of moderate exercise and facial cooling that induced substantial fat loss in men, with an associated ketonuria, proteinuria, and increase of body mass (52). This was linked to several factors, such as small energy deficit, energy cost of synthesising new lean tissue, energy loss through the storage and excretion of ketone bodies, catecholamine-induced "futile" metabolic cycles with increased resting metabolism and a specific reaction to cold dehydration. The study still recognizes the limitations of implementing this as a clinical treatment of weight loss due to possible pathological reactions to cold and the less evident fat mobilisation seen in female patients undergoing winter swimming activities (52). Gender differences were also found when comparing skinfold thickness to regular cold water immersion. Skinfold thickness was found to increase in men (53) and decrease in women (54).

The effect of local cooling on skin temperature and blood flow in peripheral limbs were studied in a group of 64 men living in an Antarctic environment for 8 weeks (55). There was a significant fall in skin temperature and an increase in finger blood flow. It was hypothesised, based on these observations, that continuous cold exposure results in vasodilation to prevent cold injuries.

A study conducted by LeBlanc et al (32) demonstrated that local acclimatization can cause a local increase in the hunting response, increasing the CIVD reaction. They suggested that this may increase the dexterity of the limbs in a cold environment, but this may only be possible when the core temperature remains unchanged. If the core temperature decreases, as seen with whole body immersion in cold water, the acclimatization causes the opposite effect, with decreased CIVD reaction. Daanen (15) hypothesized that hypothermic acclimatization leads to reduced CIVD responses due to the reduced body core temperature and that insulative acclimatization has less impact on CIVD.

Cold acclimatization through the process of cold water immersion has been shown to alter the onset of metabolic responses to cold (53). The metabolic response to cold is delayed and subjective shivering attenuated. In the same study the shivering was found to be delayed

during cold water immersion by about 40 minutes in winter swimmers compared to the control group, suggesting the importance of non-shivering thermogenesis in early thermogenic response. Because of this induced potentiation of nonshivering heat production in cold water swimmers, it is hypothesised that cold water immersion increases the thermogenic capacity. This is largely influenced by catecholamine induced heat production. Cold acclimation causes increased noradrenaline-induced secretion of glucagon contributing to improved cold tolerance by non-shivering thermogenesis (56).

In winter swimmers cold thermogenesis is solely related to changes in rectal temperature, indicating the predominance of the central temperature input in activation of heat production mechanisms (57). The thermoregulatory threshold for induction of cold thermogenesis is lowered, but the apparent hypothalamic thermosensitivity remains the same as in non-cold-adapted subjects. These differences indicate an adaptation in the threshold for induction of cold thermogenesis by peripheral vasoconstriction (53, 58, 59).

Even though winter swimming is an exposure to an extreme stress environment, it is voluntarily practised by many people. It is heavily described as a joyful and positive leisure activity by experienced individuals. Research examining the thermal sensation and thermal comfort associated with regular winter swimming, indicates that thermal sensation and comfort become habituated after a few short lasting whole body immersions in cold water (54, 60). This is a temporarily change in the cold sensation and regulation lasting some weeks after cessation of cold water exposure (53, 57), meaning that winter swimmers undergo an acclimatization of thermal sensation and comfort, and not a permanent adaptation. Similar findings were especially apparent in a group of Korean-women-divers, called Ama. These women are exposed to regular cold water immersion from a young age, as they dive looking for pearls. In older cold water adapted Korean women the response to cold is heat loss reduction, rather than increased metabolic rate (61). They also show an increase in resting metabolism, which is speculated to be a shift from shivering to nonshivering thermogenesis (62). It was demonstrated that the acclimatization of these women divers slowly disappeared after they changed from diving with a thin cotton garment to an insulative diving suit (63).

As a side issue, an important aspect of assessing cold sensation is the level of discomfort. While CWI is pleasurable to some, it is discomforting to many, however cold pain sensation is difficult to assess both quantitatively and qualitatively (64).

5.2.3 Hormone system

Plasma adrenocorticotropic hormone (ACTH) and cortisol levels seem to decrease significantly after a short time of regular cold water exposure, probably due to acclimation or adaptation, suggesting that regular cold water exposure has little effect on stimulating the pituitary-adrenal cortex axis (5, 65). However, the plasma concentration of norepinephrine has a significant increase after each cold water exposure, even after long periods of regular cold water exposures. The increase in norepinephrine suggest that it might play a role in pain alleviation (5, 65), as well as improving the cold tolerance by non-shivering thermogenesis (66) and insulative peripheral vasoconstriction, as discussed earlier (53, 58, 59).

While the hormonal changes in regards to pain alleviation seem to be largely positive (5, 65), there is little data regarding the effects on other hormonal systems in the body. On the other hand, measurements of serum levels of growth hormone, prolactin, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in healthy females indicates an unaltered hormonal balance after regular cold water immersions (67, 68), although one study noted an increase in basal prolactin levels in late season winter swimming (68).

As discussed earlier, regular cold water swimming may have an impact on fat loss in men (52). The physiological reasons explaining this are not fully understood, although adiponectin secretion by nonshivering thermogenesis may contribute to this (50). If regular winter swimming leads to increased levels of plasma adiponectin, it would be expected to have a positive impact on insulin resistance, diabetes, atherosclerosis and other age-related diseases, which has been observed in several studies. Repeated cold water immersions during the winter months of both inexperienced and experienced subjects significantly increased insulin sensitivity and decreased insulin concentrations (68-70). It is difficult to predict the clinical implications of this finding, especially since the same study (70) noted a reduction in plasma leptin concentration in acute cold water immersions compared to pre-immersion. Although, in another study, this decline was shown to be reduced after regular cold water immersions (71).

When looking at the effect of regular cold water exposure on parathyroid- and thyroid hormones, a spike in parathyroid hormone (PTH) and thyroid-stimulating hormone (TSH) was reported after 15 min cold swim in cold-acclimatized individuals (72), as well as free T3 (40). In this study there were indications of a positive correlation between systemic PTH and nonshivering thermogenesis as shown by whole-body metabolic preference for lipids, as well as increased BAT volume and uncoupling protein 1 (UCP1) content. Increasing the UCP1 content ameliorates BAT function, as it is an important mitochondrial carrier in BAT (72). It is well established that BAT prefers metabolising lipids as triglycerides and that regular cold water exposure increases browning of fat. This finding might implicate that elevated PTH is involved in this browning of white adipose tissue.

5.2.4 Neural connectivity and thermal sensation

Little is known about the effect of regular cold water swimming on the nervous system in humans, although some studies concerning this have been made in animals. For example, a number of cold-shock proteins, including ribonucleic acid (RNA) binding protein (RBM3), are involved in the regeneration of synapses (reassembly of synapses) after cooling, for example after hibernation (73). Overexpression of RBM3 resulted in sustained synaptic protection in mice with neurodegenerative disease, as indicated from their findings in both prion disease infected mice and Alzheimers mutated mice (73). If this is applicable to regular cold water immersion in humans, this may enhance cold-shock pathways and potentially function as protective therapy in neurodegenerative disorders. Also in rats, the combination of mesenchymal stem cell transplantation and cold-water swimming was more effective in functional recovery following peripheral nerve injury than the mesenchymal stem cell transplantation alone (74). This may be connected to the capacity for synapse regeneration seen in the enhancement of cold-shock pathways (73).

5.2.5 Inflammation and stress

There is an expanding body of evidence linking inflammation with health and disease. It has been shown that centenarians have lower levels of inflammation than community-living elderly (85- to 99-year-old) (75). This study also showed that although centenarians and their offspring were able to maintain long telomeres, telomere length was not a predictor of successful ageing, whereas a low inflammation score was. Cold water immersion increases

the metabolic rate and spikes plasma concentrations of catecholamines (5, 65), which in turn affects the immune system. Regular CWI has, as mentioned above, (40), caused adaptations influencing oxidative stress markers giving some cardio-protective effect.

There are several studies which have investigated how the immune system responds to regular non-infectious stress stimuli after CWI. For example in one study (76) involving 6 weeks of regular 1 hour immersions in cold water (14°C), increases in plasma concentration of interleukin (IL)-6, total T lymphocytes (CD3), T helper cells (CD4), T suppressor cells (CD8), activated T and B lymphocytes (HLA-DR) were found. In the same study they found a decrease in the plasma concentration of alpha 1-antitrypsin. In another study, which compared habitual and inexperienced winter swimmers, the authors reported significantly higher concentrations of plasma IL-6, leukocytes, and monocytes in winter swimmers compared to inexperienced subjects. This indicates that adaptive mechanisms occur in habitual winter swimmers (77). As increased levels of the cytokine IL-10 are known to be anti-inflammatory (78), it would be interesting to see whether this cytokine is increased during CWI. However, no research on this was found.

There are indications of decreased plasma uric acid concentration, an important plasma antioxidant, following cold water exposure in regular winter swimmers (79). This is hypothesized to be caused by its consumption after formation of oxygen radicals, which is further supported by the measured increase in erythrocytic level of oxidized glutathione and the ratio of oxidized glutathione to total glutathione following cold exposure. However, the baseline concentration of activated glutathione is increased and the concentration of oxidized glutathione is decreased in the erythrocytes of winter swimmers as compared to those of non-winter swimmers. Similar findings were observed in other studies (80, 81). This is most likely connected to an adaptive response to repeated oxidative stress, or "body hardening", following cold stress, resulting in increased tolerance to stress, e.g. diseases (79, 82).

A clinical study of upper respiratory tract infections (URTI) in cold water swimmers compared to pool swimmers found no significant difference in the prevalence of these infections, although there was some evidence of less URTI in cold water swimmers compared to non-swimmers (83). Interestingly the same study showed that both cold- and pool

swimmers who had partners that were non swimmers, that the latter had significantly more URTIs than their swimming partners.

Although not strictly within the definitions of CWI as defined by IISA and IWSA (2, 3), the effect of long distance swimming (LDS) in open water temperatures ranging from 18 - 21°C on the immune system response has been investigated based on salivary and serum antibody concentration (84). It was found that at the end of six months of training, the average pre-exercise levels of serum immunoglobulin (Ig)-G, IgA, IgM and salivary IgA, decreased significantly. In the same study it was found that there was a significant suppression of pre-exercise serum and salivary antibody levels, although these changes did not affect the resistance of the swimmers to respiratory infections.

5.2.6 Psychology and mental health

Mental health is among the ten leading causes of disability in both developed and developing countries, and depression is the leading cause of years lost due to disability worldwide, projected to be ranked the number one global burden of disease within 2030 (85). One hypothesis proposes that a lifestyle without certain physiological stressors may cause inadequate functioning of the brain and lead to mental health problems, such as depression (86). The known cold water stress-induced increases in plasma noradrenaline, beta-endorphin and synaptic release of noradrenaline in the brain may therefore have a positive effect on mental health and brain development (86). In this study by Shevchuk, it was hypothesised that the strong afferent input to the brain from the stimulation of cold receptors in the skin during cold water immersion could result in an anti-depressive effect. The practical testing of the hypothesis indicated that regular cold water exposure could relieve depressive symptoms rather efficiently. However, the testing did not include a significant number of participants to make a firm conclusion. In a case study concerning a patient who wished to cease medication for a severe post-partum depressive disorder, regular cold water immersion had a remarkable positive effect (87).

The general implication regarding the positive mental health aspect of regular winter swimmers is mostly based on questionnaires. For example a questionnaires looking into the mental health of regular winter swimmers indicates relieved physical symptoms and positive mood, but no significant difference when compared to a control group (88). Another

questionnaire based study looked into general well-being and indicated a reduction of tension, fatigue, and an improvement in mood and memory, in winter swimmers (89). In addition the participants reported to be more energetic, active and brisk, compared to the control group. All swimmers in the study who suffered from rheumatism, fibromyalgia, or asthma reported that winter swimming relieved pain.

5.2.7 Exercise and cold water

Athletes competing in sports are exposed to physical stress, often multiple times each day, and especially during tournaments where they have to perform many times over a relatively short period of time. Cold water immersions could, according to some studies (90-92), play a role in preventing injuries and maintaining performance of athletes, when applied in the recovery period following a bout of exercise. A study by Leeder et al (90) compared competing professional athletes recovering with and without post exercise cold water immersion, and assessed recovery using markers of sprint performance, muscle function, muscle soreness and measured biochemical markers associated with damage (creatine kinase (CK)), inflammation (IL-6 and C-Reactive Protein (CRP)) and oxidative stress (lipid hydroperoxides and activity of lipid-soluble antioxidants). The cold water immersion group was associated with improved recovery time of sprint speed 24 hours post-exercise and an attenuated efflux of CK. The reduction in CK associated with reduced muscle damage may be due to reduced muscle blood flow (91). Similar findings were found in another study, and may explained a decreased muscle metabolic activity without affecting the tissue oxygenation necessary for normal muscle recovery (92).

6 Discussion

The main aim of this thesis was to carry out a detailed search of the scientific literature in order to try and determine whether voluntary exposure to cold water has beneficial health effects in humans. The literature research was deliberately restricted to only include studies within a strict keyword based framework. After a strict selection process the number of studies regarded as being relevant was narrowed down to 92. It has to be recognised that the exclusion criteria used to narrow down the number of relevant studies was based on a subjective evaluation and thus may have caused the exclusion of other relevant research,

although due to the selection process for the selected search criteria this is regarded as being unlikely.

While many of the studies demonstrated significant effects of CWI on various physiological and biochemical parameters, the question as to whether these are beneficial or not for health is difficult to assess. One of the problems is that some of the studies involves passive cold water immersion (45, 46, 49, 51, 53, 55, 56, 58-60, 66, 67, 71, 72, 76, 79, 90-92), while others deal with swimming in cold water (41, 44, 48, 52, 54, 57, 61-63, 68-70, 74, 77, 80-84, 87-89). In addition, many of the research studies are based on established winter swimmers (40, 62, 63, 66, 70, 72, 77, 79, 80, 82-84, 88, 89), most of the studies, investigating the beneficial effects of regular cold water immersion, were performed on subjects with no previous experience (45, 46, 49, 51, 53-55, 58-60, 64, 65, 67-69, 71, 76, 81, 86, 87). Also some research was based on subjects not involved in cold water swimming, for example as a post exercise treatment following sports activities (52, 90-92). However, as mentioned in the introduction, many of the health benefits claimed from regular cold exposure may not be causal and may, instead, be explained by other factors including an active lifestyle, trained stress handling, social interactions, as well as a positive mindset. In addition, clear conclusions from the majority of studies was hampered by the fact that they were carried out in small groups, often of one gender, and with differences in exposure temperature and salt composition of the water.

Although approached from different angles in different studies, one positive effect worth highlighting is the positive effects that cold water immersion have on the reduction and/or transformation of body adipose tissue (47-49, 52, 56, 72), These can be considered to be protective against diabetes (51, 69, 70) and cardiovascular disease (40, 51) and therefore potentially could have prophylactic effects on health. The reported positive findings regarding the effect of CWI on the immune system, especially concerning tolerance to stress (65, 66, 76, 77, 79-82) and respiratory infections (83, 84) are promising and new studies in this area would be of interest. It is also felt that detailed and well thought out questionnaires concerning individuals' experiences in relation to CWI, such as those reported in section 5.2.6. Psychology and mental health (88, 89), can provide very useful indicators for further research topics.

It is important to stress that while this thesis has gone into many aspects of the effects on health regarding CWI, including some health risks, the main focus was not especially related to the latter.

7 Conclusion

From the evidence described above it is clear that there is increasing evidence that voluntary exposure to cold water has some beneficial health effects. However, it is also clear that there is a need for new controlled research studies that are specifically focused on the topic. There are several specific areas regarding the potential preventive health effect of CWI that need further investigation. For example, its effect on the immune system (e.g. tolerance to stress and respiratory infections), potential prophylactic effects on the cardiovascular system and prophylaxis against insulin resistance and improved insulin sensitivity, are areas that are promising and warrant further investigation. In addition, the educational aspects in respect to both carrying out this activity in a responsible way and learning more about specific beneficial effects also need addressing. In conclusion, it would seem that the question proposed in the introduction to this study concerning the health benefits of CWI, based on the published scientific literature described above, has only been partly answered. Until we have more concrete scientific evidence the topic will continue to be a subject of debate.

8 References

1.	Wikipedia. Winter swimming. wikipediaorg. 2020.
2.	Association IIS. SWIMMING RULES AND REGULATIONS.
3.	Association IWS. Water classification. 2016.
4.	Hsaio A. 6 Amazing Health Benefits Of Cold Water Swimming. Lifehack.
5.	Leppaluoto J, Westerlund T, Huttunen P, Oksa J, Smolander J, Dugue B, et al. Effects of long-term whole-body cold exposures on plasma concentrations of ACTH, beta-endorphin, cortisol, catecholamines and cytokines in healthy females. Scand J Clin Lab Invest. 2008;68(2):145-53.
6.	Berbee JF, Boon MR, Khedoe PP, Bartelt A, Schlein C, Worthmann A, et al. Brown fat activation reduces hypercholesterolaemia and protects from atherosclerosis development. Nature communications. 2015;6:6356.
7.	Bøkenes L, Alexandersen TE, Østerud B, Tveita T, Mercer JB. Physiological and haematological responses to cold exposure in the elderly. Int J Circumpolar Health. 2000;59(3-4):216-21.
8.	Tipton MJ, Collier N, Massey H, Corbett J, Harper M. Cold water immersion: kill or cure? Experimental physiology. 2017;102(11):1335-55.

9.   Rasmussen L, Mercer J. A comparison of thermal responses in hands and feet of young and elderly subjects in response to local cooling as determined by infared imaging. Thermology International. 2004;14:71-6.

10.   Stikbakke E, editor An infrared thermographic and laser doppler flowmetric investigation of skin perfusion in the forearm and finger tip : following a short period of vascular stasis2010.

11.   Nielsen SB, Mercer J. Dynamic Thermography In Vascular Finger Disease A Methodological Study of Arteriovenous Anastomoses. Thermology International. 2010;20:93-9.

12.   Lossius K, Eriksen M, Walløe L. Fluctuations in blood flow to acral skin in humans: connection with heart rate and blood pressure variability. J Physiol. 1993;460:641-55.

13.   Miland ÅO, Mercer JB. Effect of a short period of abstinence from smoking on rewarming patterns of the hands following local cooling. European Journal of Applied Physiology. 2006;98(2):161-8.

14.   Hohenauer E, Deliens T, Clarys P, Clijsen R. Perfusion of the skin's microcirculation after cold-water immersion (10°C) and partial-body cryotherapy (-135°C). Skin research and technology : official journal of International Society for Bioengineering and the Skin (ISBS) [and] International Society for Digital Imaging of Skin (ISDIS) [and] International Society for Skin Imaging (ISSI). 2019;25(5):677-82.

15.   Daanen HA. Finger cold-induced vasodilation: a review. Eur J Appl Physiol. 2003;89(5):411-26.

16.   Kenny GP, Denis PM, Proulx CE, Giesbrecht GG. The effect of dynamic exercise on resting cold thermoregulatory responses measured during water immersion. European journal of applied physiology and occupational physiology. 1999;79(6):495-9.

17.   Norheim AJ, Borud E, Wilsgaard T, De Weerd L, Mercer JB. Variability in peripheral rewarming after cold stress among 255 healthy Norwegian army conscripts assessed by dynamic infrared thermography. International Journal of Circumpolar Health. 2018;77(1):1536250.

18.   Swift RW. The Effects of Low Environmental Temperature upon Metabolism: II. The Influence of Shivering, Subcutaneous Fat, and Skin Temperature on Heat Production. The Journal of Nutrition. 1932;5(3):227-49.

19.   Martin S, Cooper KE. Factors which affect shivering in man during cold water immersion. Pflügers Archiv. 1981;391(1):81-3.

20.   Haman F, Blondin DP. Shivering thermogenesis in humans: Origin, contribution and metabolic requirement. Temperature (Austin). 2017;4(3):217-26.

21.   Muzik O, Mangner TJ, Leonard WR, Kumar A, Granneman JG. Sympathetic Innervation of Cold-Activated Brown and White Fat in Lean Young Adults. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2017;58(5):799-806.

22.   Gilsanz V, Hu HH, Kajimura S. Relevance of brown adipose tissue in infancy and adolescence. Pediatric Research. 2013;73(1):3-9.

23.   Muzik O, Mangner TJ, Granneman JG. Assessment of oxidative metabolism in brown fat using PET imaging. Frontiers in endocrinology. 2012;3:15.

24.   Heinonen I, Laukkanen JA. Effects of heat and cold on health, with special reference to Finnish sauna bathing. American journal of physiology Regulatory, integrative and comparative physiology. 2018;314(5):R629-r38.

25.   Hayward MG, Keatinge WR. Roles of subcutaneous fat and thermoregulatory reflexes in determining ability to stabilize body temperature in water. J Physiol. 1981;320:229-51.

26.   Glickman-Weiss EL, Cheatham C, Caine N, Blegen M, Marcinkiewicz J, Mittleman KD. The influence of gender and menstrual phase on thermosensitivity during cold water immersion. Aviation, space, and environmental medicine. 2000;71(7):715-22.

27.   Solianik R, Skurvydas A, Vitkauskienė A, Brazaitis M. Gender-specific cold responses induce a similar body-cooling rate but different neuroendocrine and immune responses. Cryobiology. 2014;69(1):26-33.

28. Reingardiene D. [Hypothermia]. Medicina (Kaunas, Lithuania). 2003;39(1):90-7.

29. Potkanowicz ES, Caine-Bish N, Otterstetter R, Glickman EL. Age effects on thermal, metabolic, and perceptual responses to acute cold exposure. Aviation, space, and environmental medicine. 2003;74(11):1157-62.

30. Castellani JW, Young AJ, Kain JE, Sawka MN. Thermoregulatory responses to cold water at different times of day. Journal of applied physiology (Bethesda, Md : 1985). 1999;87(1):243-6.

31. Krog J, Folkow B, Fox RH, Andersen KL. Hand circulation in the cold of Lapps and North Norwegian fishermen. Journal of Applied Physiology. 1960;15(4):654-8.

32. LeBlanc J, Hildes JA, Héroux O. Tolerance of Gaspé fishermen to cold water. Journal of Applied Physiology. 1960;15(6):1031-4.

33. Nelms JD, Soper DJG. Cold vasodilatation and cold acclimatization in the hands of British fish filleters. Journal of Applied Physiology. 1962;17(3):444-8.

34. Livingstone SD, Grayson J, Reed LD, Gordon D. Effect of a local cold stress on peripheral temperatures of Inuit, Oriental, and Caucasian subjects. Canadian journal of physiology and pharmacology. 1978;56(5):877-81.

35. Smith RM, Hanna JM. Skinfolds and resting heat loss in cold air and water: temperature equivalence. J Appl Physiol. 1975;39(1):93-102.

36. Lindholm P, Lundgren CE. The physiology and pathophysiology of human breath-hold diving. Journal of applied physiology (Bethesda, Md : 1985). 2009;106(1):284-92.

37. Shattock MJ, Tipton MJ. 'Autonomic conflict': a different way to die during cold water immersion? J Physiol. 2012;590(14):3219-30.

38. Paton JF, Boscan P, Pickering AE, Nalivaiko E. The yin and yang of cardiac autonomic control: vago-sympathetic interactions revisited. Brain research Brain research reviews. 2005;49(3):555-65.

39. Mantoni T, Belhage B, Pedersen LM, Pott FC. Reduced cerebral perfusion on sudden immersion in ice water: a possible cause of drowning. Aviation, space, and environmental medicine. 2007;78(4):374-6.

40. Kralova Lesna I, Rychlikova J, Vavrova L, Vybiral S. Could human cold adaptation decrease the risk of cardiovascular disease? Journal of thermal biology. 2015;52:192-8.

41. Broz P, Rajdl D, Racek J, Zeman V, Novák J, Trefil L. Relationship between cold water swimming and increased cardiac markers: A pilot study. Klinicka Biochemie a Metabolismus. 2017;25:27-31.

42. Stark M KC, Sharma S. Troponin. StatPearls [Internet]. Updated 2020 Jul 10.

43. Baker P, Leckie T, Harrington D, Richardson A. Exercise-induced cardiac troponin elevation: An update on the evidence, mechanism and implications. Int J Cardiol Heart Vasc. 2019;22:181-6.

44. Zenner RJ, De Decker DE, Clement DL. Blood-pressure response to swimming in ice-cold water. Lancet (London, England). 1980;1(8160):120-1.

45. Muza SR, Young AJ, Sawka MN, Bogart JE, Pandolf KB. Respiratory and cardiovascular responses to cold stress following repeated cold water immersion. Undersea biomedical research. 1988;15(3):165-78.

46. Mantoni T, Rasmussen JH, Belhage B, Pott FC. Voluntary respiratory control and cerebral blood flow velocity upon ice-water immersion. Aviation, space, and environmental medicine. 2008;79(8):765-8.

47. Chen Y, Ikeda K, Yoneshiro T, Scaramozza A, Tajima K, Wang Q, et al. Thermal stress induces glycolytic beige fat formation via a myogenic state. Nature. 2019;565(7738):180-5.

48. Abe Y, Fujiwara Y, Takahashi H, Matsumura Y, Sawada T, Jiang S, et al. Histone demethylase JMJD1A coordinates acute and chronic adaptation to cold stress via thermogenic phospho-switch. Nature communications. 2018;9(1):1566.

49. Jankovic A, Golic I, Markelic M, Stancic A, Otasevic V, Buzadzic B, et al. Two key temporally distinguishable molecular and cellular components of white adipose tissue browning during cold acclimation. J Physiol. 2015;593(15):3267-80.

50. Atzmon G, Pollin TI, Crandall J, Tanner K, Schechter CB, Scherer PE, et al. Adiponectin levels and genotype: a potential regulator of life span in humans. J Gerontol A Biol Sci Med Sci. 2008;63(5):447-53.

51. Imbeault P, Dépault I, Haman F. Cold exposure increases adiponectin levels in men. Metabolism: clinical and experimental. 2009;58(4):552-9.

52. Shephard RJ. Adaptation to exercise in the cold. Sports medicine (Auckland, NZ). 1985;2(1):59-71.

53. Janský L, Janáková H, Uličný B, Šrámek P, Hošek V, Heller J, et al. Changes in thermal homeostasis in humans due to repeated cold water immersions. Pflügers Archiv. 1996;432(3):368-72.

54. Smolander J, Mikkelsson M, Oksa J, Westerlund T, Leppäluoto J, Huttunen P. Thermal sensation and comfort in women exposed repeatedly to whole-body cryotherapy and winter swimming in ice-cold water. Physiology & Behavior. 2004;82(4):691-5.

55. Naidu M, Sachdeva U. Effect of local cooling on skin temperature and blood flow of men in Antarctica. International journal of biometeorology. 1993;37(4):218-21.

56. Kuroshima A. [Regulation of thermoregulatory thermogenesis]. [Hokkaido igaku zasshi] The Hokkaido journal of medical science. 1995;70(1):1-8.

57. Vybíral S, Lesná I, Jansky L, Zeman V. Thermoregulation in winter swimmers and physiological significance of human catecholamine thermogenesis. Experimental physiology. 2000;85(3):321-6.

58. Janský L. [Physiologic basis of human adaptation to cold]. Ceskoslovenska fysiologie. 2003;52(3):107-17.

59. Elkington EJ. Finger blood flow in Antarctica. J Physiol. 1968;199(1):1-10.

60. Geurts CL, Sleivert GG, Cheung SS. Central and peripheral factors in thermal, neuromuscular, and perceptual adaptation of the hand to repeated cold exposures. Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme. 2006;31(2):110-7.

61. Park J, Kim S, Kim DH, Cha S, Lee JY. Whole-body cold tolerance in older Korean female divers "haenyeo" during cold air exposure: effects of repetitive cold exposure and aging. International journal of biometeorology. 2018;62(4):543-51.

62. Glickman EI, Caine-Bish N. Changes in Body Temperature and Basal Metabolic Rate of the Ama—A Commentary. Wilderness & Environmental Medicine. 2003;14(3):191-2.

63. Park YS, Rennie DW, Lee IS, Park YD, Paik KS, Kang DH, et al. Time course of deacclimatization to cold water immersion in Korean women divers. Journal of applied physiology: respiratory, environmental and exercise physiology. 1983;54(6):1708-16.

64. Lundgren P, Henriksson O, Kuklane K, Holmér I, Naredi P, Björnstig U. Validity and reliability of the Cold Discomfort Scale: a subjective judgement scale for the assessment of patient thermal state in a cold environment. Journal of clinical monitoring and computing. 2014;28(3):287-91.

65. Huttunen P, Rintamäki H, Hirvonen J. Effect of regular winter swimming on the activity of the sympathoadrenal system before and after a single cold water immersion. Int J Circumpolar Health. 2001;60(3):400-6.

66. Kauppinen K, Pajari-Backas M, Volin P, Vakkuri O. Some endocrine responses to sauna, shower and ice water immersion. Arctic medical research. 1989;48(3):131-9.

67. Smolander J, Leppäluoto J, Westerlund T, Oksa J, Dugue B, Mikkelsson M, et al. Effects of repeated whole-body cold exposures on serum concentrations of growth hormone, thyrotropin, prolactin and thyroid hormones in healthy women. Cryobiology. 2009;58(3):275-8.

68. Hermanussen M, Jensen F, Hirsch N, Friedel K, Kröger B, Lang R, et al. Acute and chronic effects of winter swimming on LH, FSH, prolactin, growth hormone, TSH, cortisol, serum glucose and insulin. Arctic medical research. 1995;54(1):45-51.

69. Gibas-Dorna M, Chęcińska Z, Korek E, Kupsz J, Sowińska A, Krauss H. Cold Water Swimming Beneficially Modulates Insulin Sensitivity in Middle-Aged Individuals. Journal of aging and physical activity. 2016;24(4):547-54.

70. Gibas-Dorna M, Checinska Z, Korek E, Kupsz J, Sowinska A, Wojciechowska M, et al. Variations in leptin and insulin levels within one swimming season in non-obese female cold water swimmers. Scand J Clin Lab Invest. 2016;76(6):486-91.

71. Zeyl A, Stocks JM, Taylor NA, Jenkins AB. Interactions between temperature and human leptin physiology in vivo and in vitro. Eur J Appl Physiol. 2004;92(4-5):571-8.

72. Kovaničová Z, Kurdiová T, Baláž M, Štefanička P, Varga L, Kulterer OC, et al. Cold Exposure Distinctively Modulates Parathyroid and Thyroid Hormones in Cold-Acclimatized and Non-Acclimatized Humans. Endocrinology. 2020;161(7).

73. Peretti D, Bastide A, Radford H, Verity N, Molloy C, Martin MG, et al. RBM3 mediates structural plasticity and protective effects of cooling in neurodegeneration. Nature. 2015;518(7538):236-9.

74. Yang CC, Wang J, Chen SC, Jan YM, Hsieh YL. Enhanced functional recovery from sciatic nerve crush injury through a combined treatment of cold-water swimming and mesenchymal stem cell transplantation. Neurological research. 2015;37(9):816-26.

75. Arai Y, Martin-Ruiz CM, Takayama M, Abe Y, Takebayashi T, Koyasu S, et al. Inflammation, But Not Telomere Length, Predicts Successful Ageing at Extreme Old Age: A Longitudinal Study of Semi-supercentenarians. EBioMedicine. 2015;2(10):1549-58.

76. Janský L, Pospísilová D, Honzová S, Ulicný B, Srámek P, Zeman V, et al. Immune system of cold-exposed and cold-adapted humans. European journal of applied physiology and occupational physiology. 1996;72(5-6):445-50.

77. Dugué B, Leppänen E. Adaptation related to cytokines in man: effects of regular swimming in ice-cold water. Clinical physiology (Oxford, England). 2000;20(2):114-21.

78. Kessler B, Rinchai D, Kewcharoenwong C, Nithichanon A, Biggart R, Hawrylowicz CM, et al. Interleukin 10 inhibits pro-inflammatory cytokine responses and killing of Burkholderia pseudomallei. Scientific Reports. 2017;7(1):42791.

79. Siems WG, van Kuijk FJ, Maass R, Brenke R. Uric acid and glutathione levels during short-term whole body cold exposure. Free radical biology & medicine. 1994;16(3):299-305.

80. Mila-Kierzenkowska C, Woźniak A, Boraczyński T, Szpinda M, Woźniak B, Jurecka A, et al. Thermal stress and oxidant–antioxidant balance in experienced and novice winter swimmers. Journal of thermal biology. 2012;37(8):595-601.

81. Lubkowska A, Dołęgowska B, Szyguła Z, Bryczkowska I, Stańczyk-Dunaj M, Sałata D, et al. Winter-swimming as a building-up body resistance factor inducing adaptive changes in the oxidant/antioxidant status. Scand J Clin Lab Invest. 2013;73(4):315-25.

82. Siems WG, Brenke R, Sommerburg O, Grune T. Improved antioxidative protection in winter swimmers. QJM : monthly journal of the Association of Physicians. 1999;92(4):193-8.

83. Collier N, Massey HC, Lomax M, Harper M, Tipton MJ. Cold water swimming and upper respiratory tract infections. Extreme Physiology & Medicine. 2015;4(1):A36.

84. Kormanovski A, Ibarra F, Padilla E, Rodriguez R. Resistance to respiratory illness and antibody response in open water swimmers during training and long distance swims. International Journal of Medicine and Medical Sciences. 2010;2:80-7.

85. Ms. Rachel Mayanjya DAA, Professor Sir Michael Marmot, Mr. Janne Taalas, Werner Haug, Dr. Wilfred Mlay, Mr. Sylvester Katontoka. Mental Health and Development. United Nations - Department of Economic and Social Affairs. Disability. 2010.

86. Shevchuk NA. Adapted cold shower as a potential treatment for depression. Medical hypotheses. 2008;70(5):995-1001.

87. van Tulleken C, Tipton M, Massey H, Harper CM. Open water swimming as a treatment for major depressive disorder. BMJ case reports. 2018;2018.

88. Lindeman S, Hirvonen J, Joukamaa M. Neurotic psychopathology and alexithymia among winter swimmers and controls--a prospective study. Int J Circumpolar Health. 2002;61(2):123-30.

89. Huttunen P, Kokko L, Ylijukuri V. Winter swimming improves general well-being. Int J Circumpolar Health. 2004;63(2):140-4.

90. Leeder JDC, Godfrey M, Gibbon D, Gaze D, Davison GW, Van Someren KA, et al. Cold water immersion improves recovery of sprint speed following a simulated tournament. European journal of sport science. 2019;19(9):1166-74.

91. Mawhinney C, Jones H, Joo CH, Low DA, Green DJ, Gregson W. Influence of cold-water immersion on limb and cutaneous blood flow after exercise. Medicine and science in sports and exercise. 2013;45(12):2277-85.

92. Ihsan M, Watson G, Lipski M, Abbiss CR. Influence of postexercise cooling on muscle oxygenation and blood volume changes. Medicine and science in sports and exercise. 2013;45(5):876-82.

			Studiedesign: Kasus-kontroll

			Grade - kvalitet LAV

Formål	Materiale og metode	Resultater	Diskusjon/kommentarer/sjekkliste
Utforske effekten av kuldeadaptasjon på kardiovaskulære risikofaktorer, tyroidhormoner og menneskers kapasitet til å reparere skadelige effekter av oksidativt stress	**Populasjon** 10 erfarne vintersvømmere og 16 kontrolldeltakere deltok i denne studien -kasus (definisjon/validert?) Blodprøver av deltakerne ble tatt for å måle verdier av diverse aktuelle blodprodukter. Man målte verdiene til deltakerne og sammenlignet resultetet fra isbaderne med kontrollgruppen	**Hovedfunn** **Hvor stor er effekten?** (adjusted odds ratio) Redusert ApoB/ApoA1 ratio, plasma homocystein, GPX1, CD og CAT hos isbadergruppen (p<0.05). Økt T3, PON1 og Zn aktivitet hos isbadergruppen (p<0.05)	Sjekkliste: • Er formålet klart formulert? Ja • Er kasus-kontroll design egnet for formålet? RCT hadde gitt en bedre studiedesign, men kasus-kontrollstudiet gir en god indikasjon på hypotesen • Er kasus rekruttert på en «god» måte? (Alle i en tidspieriode/grader av sykd.) (seleksjonsbias)* Ja • Diangosen validert? (Classific. bias) (prev/insi kasus?) Ja
Konklusjon Menneskelig kuldeadaptasjon kan påvirke markører for oksidativt stress, samt forbedre kardiovaskulære risikofaktorer	-kontroller («fri for sykdom») Ja Inklusjons-/eksklusjonskrit. Inkludert menn og kvinner med god erfaring innen vintersvømming, samt en kontrollgruppe menn og kvinner som ikke har hatt erfaring med denne aktiviteten	**Bifunn** Ikke aktuelt	• Er kontrollene rekrutterte på en «god» måte? Ja • Kan det utelukkes at kontrollgr. fri for aktuelle sykdom? (classific. Bias) Nei • Var kasus-kontrollgruppene hentet fra sammenlignbare befolkningsgrupper?* Ja • Non-responders/nekter å delta – frafalls analyser? Forskjeller kasus/kontroll-gruppe?* Nei
Land Praha, Tjekkia	**Hovedeksponering:** Regelmessig kuldeeksponering		• Er gruppene sammenlignbare i forhold til viktige bakgrunnsfaktorer?* Usikkert • Er main exposure validert? (Classific. Bias?) Nei
Ar data innsamling Mottatt 13. april 2015 Akseptert 22. juli 2015	**Viktige konfunderende faktorer** Ikke tatt stilling til		• Er gruppene «behandlet» likt – kan påvirke «exposure»? (deteksjonsbias?) Antas • Har forfatterne tatt hensyn til viktige konfunderende faktorer i design/analyse? Usikkert • Er eksponering for fare, skade, tiltak målt og gradert likt i begge gruppene? (Classific bias) Ja • Var den som målte eksponering/samlet inn data blinda mht hvem som var kasus/kontroll? (Classific bias) Nei • Tror du på resultatene? Ja • Kan resultatene overføres til praksis? Det gjenstår å se
	Statistiske metoder Statistisk inferens med hypotesetesting		• Støtter litteratruen resultatene? Annen litteratur gir lignende indikasjoner

Referanse: Leppaluoto J, Westerlund T, Huttunen P, Oksa J, Smolander J, Dugue B, et al. Effects of long-term whole-body cold exposures on plasma concentrations of ACTH, beta-endorphin, cortisol, catecholamines and cytokines in healthy females. Scand J Clin Lab Invest. 2008;68(2):145-53.	Studiedesign: Kasus-kontroll		
		Grade - kvalitet	Lav
Formål	**Materiale og metode**	**Resultater**	**Diskusjon/kommentarer/sjekkliste**
Denne studien ble designet for å utforske påvirkningen av langvarig regelmessig kaldtvannseksponering. To typer eksponering ble student: vintersvømming i iskaldt vann og kryoterapi i hele kroppen. Resultatet ble undersøkt på humorale faktorer som kan forklare smertelindring knyttet til eksponeringene. **Konklusjon** Hovedfunnet var den vedvarende kuldeinduserte stimuleringen av noradrenalin, som var bemerkelsesverdig lik mellom eksponeringene. Den økningen i noradrenalin kan ha en rolle i smertelindring ved helkropps kryoterapi og ved vintersvømming. **Land** Finland **År data innsamling** 2007	**Populasjon** En gruppe friske kvinner (n = 10) ble utsatt for vinterbad (vann 0–2 ° C) En gruppe friske kvinner (n = 10) til kryoterapi i hele kroppen (luft -110 ° C) -kasus (definisjon/validert?) I løpet av 12 uker, 3 ganger i uken, ble en gruppe friske kvinner (n = 10) utsatt for vinterbading (vann 0-2 ° C) i 20 sekunder og en annen gruppe (n = 10) for helkropps kryoterapi (luft -110 ° C) i 2 minutter i et spesielt kammer. Blodprøver ble trukket i uke 1, 2, 4, 8 og 12, på en dag da ingen kuldeeksponering oppstod (kontrollprøver) og på en dag med kuldeeksponering (kalde prøver) før eksponeringene (0 min), og deretter kl. 5 og 35 min. Inklusjons-/eksklusjonskrit. Friske kvinner inkludert. Eksklusjon av menn og individer med kroniske diagnoser **Hovedeksponering:** vinterbading (vann 0-2 ° C) i 20 sekunder og helkropps kryoterapi (luft -110 ° C) i 2 minutter i et spesielt kammer **Viktige konfunderende faktorer** Ikke aktuelt **Statistiske metoder** Statistisk inferens med hypotesetesting	**Hovedfunn** **Hvor stor er effekten?** (adjusted odds ratio) Signifikant lavere plasma ACTH og kortisol etter 35 min i uke 4–12 enn i uke 1, sannsynligvis på grunn av tilvenning, noe som antydet at verken vintersvømming eller helkropps kryoterapi stimulerte hypofyse-binyrebarkaksen. Plasmaadrenalin var uendret under begge eksperimentene, men noradrenalin viste signifikante økninger på 2-3 ganger utgangspunktet etter 12 uker med begge kaldeeksponeringene. **Bifunn** Plasma IL - 1 - beta, IL - 6 eller TNFα viste ingen endringer etter langvarig regelmessig kuldeeksponering.	**Sjekkliste:** - Er formålet klart formulert? Ja - Er kasus-kontroll design egnet for formålet? Ja - Er kasus rekruttert på en «god» måte? (Alle i en tidspieriode/grader av sykd.) (seleksjonsbias)* Ja - Diangosen validert? (Classific. bias) (prev/insi kasus?) Ja - Er kontrollene rekrutterte på en «god» måte? Ja - Kan det utelukkes at kontrollgr. fri for aktuelle sykdom? (classific. Bias) Nei - Var kasus-kontrollgruppene hentet fra sammenlignbare befolkningsgrupper?* Ja - Non-responders/nekter å delta – frafalls analyser? Forskjeller kasus/kontroll-gruppe?* Nei - Er gruppene sammenlignbare i forhold til viktige bakgrunnsfaktorer?* Ja - Er main exposure validert? (Classific. Bias?) Ja - Er gruppene «behandlet» likt – kan påvirke «exposure»? (deteksjonsbias?) Ja - Har forfatterne tatt hensyn til viktige konfunderende faktorer i design/analyse? Ja - Er eksponering for fare, skade, tiltak målt og gradert likt i begge gruppene? (Classific bias) Ja - Var den som målte eksponering/samlet inn data blinda mht hvem som var kasus/kontroll? (Classific bias) Usikkert - Tror du på resultatene? Ja - Kan resultatene overføres til praksis? Usikkert - Støtter litteratruen resultatene? Lignende studier med lignende funn

Referanse: Gibas-Dorna M, Checińska Z, Korek E, Kupsz J, Sowińska A, Krauss H. Cold Water Swimming Beneficially Modulates Insulin Sensitivity in Middle-Aged Individuals. Journal of aging and physical activity. 2016;24(4):547-54.			Studiedesign: RCT
			Grade - kvalitet **Høy**
Formål	**Materiale og metode**	**Resultater**	**Diskusjon/kommentarer/sjekkliste**
Formålet var å undersøke om kaldt vann svømming i seks sammenhengende måneder resulterer i adaptive endringer i kroppssammensetning og insulinfølsomhet **Konklusjon** Funn antyder at menn og kvinner har ulik respons på gjentatt eksponering for kulde i forhold til kroppssammensetning. Regelmessig svømming i kaldt vann kan forbedre insulinfølsomheten hos kuldeakklimatiserte magre svømmere. **Land** Poznan, Polen **År data innsamling** 2016	**Rekruttering deltakere** Tretti friske forsøkspersoner i alderen 50,2 ± 9,4 år ble utsatt for kaldtvannseksponering minst 2 ganger i uken i seks måneder. **Inklusjons-/eksklusjonskrit.** Friske deltakere uten kroniske lidelser, både menn og kvinner **Datagrunnlaget** Dataene som ligger til grunn for analysen er glukose- og insulinverdier innhentet fra blodprøver tatt før og etter kuldeeksponeringen i eksperimentet. Samt BMI, fettfri masse, muskelmasse, visceralt fettvevsnivå og prosent kroppsfett **Utfall (outcome) validering (for eks. diagnose)** Forbedret insulin-sensitivitet etter regelmessig isbading ila en vintersesong **Eksponeringsvariabler (validert/ikke validert)** **Viktige konfunderende faktorer** Validert **Statistiske metoder** Statistisk inferens med hypotesetesting	**Hovedfunn** Hvor stor er «intervensjons-effekten»? Incidence/RR/risk reduction/aRR CI Sammenlignet med kontrollpersoner var svømmere overvektige og hadde større prosent kroppsfett og betacellefunksjon. Kvinner hadde lavere BMI, fettfri masse, muskelmasse, visceralt fettvevsnivå og større prosent kroppsfett enn menn etter endt eksperiment. Det ble observert hos kvinner og hos magre personer økt insulinfølsomhet og redusert insulinsekresjon og resistans. **Bifunn – andre viktige endepunkter** Ikke aktuelt	**Sjekkliste:** • **Er formålet klart formulert?** Ja • **Hvem er inkludert/ekskludert?** (seleksjon/generaliserbarhet) Begge kjønn, flere ulike kroppsutgangspunkt. For det meste individer i overgangsalderen • **Var gruppene like ved starten?** (seleksjon?, har randomiseringen fungert?) Både eksponeringsgruppe og kontrollgruppe hadde like utgangspunkt • **Randomiseringsprosedyre?** Ja • **Ble deltakere/studiepersonell blindet mht gruppetilhørighet?** Ja • **Ble gruppene behandlet likt utover «intervensjonen»?** En gruppe utsatt for eksponering, mens kontrollgruppe ikke ble utsatt for eksponering • **Primære endepunktet – validert?** (Classification bias?) Ja • **Ble deltakernne gjort rede for på slutten av studien?** (attrition/follow-up bias) Ja

Studiedesign: RCT

Grade - kvalitet Høy

Formål	Materiale og metode	Resultater	Diskusjon/kommentarer/sjekkliste
Finne sammenhengen med kuldeeksponering og adiponektinsekresjon, sett i sammgitt med karbohydratinntak	**Rekruttering deltakere** 6 friske frivillige menn fordelt ved bruk av randomisert overkrysningsdesign **Inklusjons-/eksklusjonskrit.** Friske mannlige deltakere. Ekskludert damer og menn med kroniske lidelser **Datagrunnlaget** Dataene som ligger til grunn for analysen er blod-adiponektinverdier innhentet fra blodprøver tatt før og etter kuldeeksponeringen i eksperimentet **Utfall (outcome) validering (for eks. diagnose)** Kuldeeksponering fører til signifikant økning i adiponektinnivå **Eksponeringsvariabler (validert/ikke validert) Viktige konfunderende faktorer** Validert **Statistiske metoder** Statistisk inferens med hypotesetesting	**Hovedfunn** Hvor stor er «intervensjons-effekten»? Incidence/RR/risk reduction/aRR CI 1. studie: Ingen endring av adiponektinnivå ved inntak av 0.8 g/min glukosedrikk, mens man så 20% økning ved inntak av lavglukose-drikk (tilstand x tid interaksjon, P = .06). 2. studie: 70% endring av adiponektinnivå etter kuldeeksponering både med lav- og høykarbo-diett (effekt av tid, P < .05) **Bifunn – andre viktige endepunkter** Ikke aktuelt	Sjekkliste: • **Er formålet klart formulert?** Formålet er tydelig formulert i studiet • **Hvem er inkludert/ekskludert?** (seleksjon/generaliserbarhet) Tydelig seleksjonsgruppe, men ekskluderer damer og menn med kroniske lidelser. Ettersom studien utforsker sammenheng med karbohydrat-inntak og adiponektinutskillelse, kan det være problematisk at studien utelukker mennesker med ulike blodsukkerreguleringsegenskaper • **Var gruppene like ved starten?** (seleksjon?, har randomiseringen fungert?) 6 deltakere ble i 1. eksperiment eksponert for kulde i 120min etter inntak av drikk med enten høy eller lav glukosekonsentrasjon • **Randomiseringsprosedyre?** Randomisert med overkrysningsdesign • **Ble deltakere/studiepersonell blindet mht gruppetilhørighet?** Nei • **Ble gruppene behandlet likt utover «intervensjonen»?** Ja • **Primære endepunktet – validert?** (Classificatin bias?) Tiden mellom studie 1 og studie 2 kan ha påvirket det fysiologiske utgangspunktet for deltakerne spesielt med tanke på sekresjon av adiponektin • **Ble deltakerne gjort rede for på slutten av studien?** (attrition/follow-up bias) Ikke aktuelt • **Hva er resultatene? Presisjon?** Økning av adiponektin ved kuldeeksponering, som hemmes ved inntak av glukose • **Kan resultatene overføres til praksis?** Ja • **Ble alle utfallsmål vurdert?** Vurdert i forhold til standardnivåer adiponektin hos menn • **Er fordelene verdt ulemper/kostnader?** Ingen kjent risiko, dermed er fordelene verdt ulemper/kostnader • **Annen litteratur som styrker resultatene?** Nei **Hva diskuterer forfatterne som:** -styrke -svakhet Styrke er funn av økt utskillelse av adiponektin, men at dette er hemmet av inntak av glukose **Har resultatene plausible forklaringer?** Aktivering av sympatisk nervesystem av kuldeeksponering

Column 1 additional sections:

Konklusjon
Med en 120 min periode med kuldeeksponering følger en signifikant økning i adiponektin nivå hos friske menn. Denne økningen hemmes av inntak av glukose, men ikke av dietter med varierende karbohydrat-innhold

Land
Universitet i Ottawa, Ontario, Canada

År data innsamling
Akseptert: 4. november, 2008
Mottatt: 9. juli, 2008

Studiedesign: Kohortestudie

Grade - kvalitet Lav

Formål	Materiale og metode	Resultater	Diskusjon/kommentarer/sjekkliste
Utforske om menneskelig immunsystem kan aktiveres av ikke-infeksiøst stimulus, som kaldtvannsbading, og dermed forbedre den fysiologiske statusen til individet	**Populasjon:** Atletiske unge menn Kohorter: én kohorte **Hoved utfall:** Eksponert for 1 time kaldtvann 14 grader celcius 3 ganger i uken i 6 uker **Viktige konfunderende faktorer** Ikke aktuelt **Statistiske metoder** Statistisk inferens med hypotesetesting	**Hovedfunn** **Between exposes/unexposed:** Rate/proportion//ratio/rate difference How strong is the association (RR)? What the aboslute risk reduction (ARR)? CI (wide/narrow) Dose-response? Signifikant økning i konsentrasjonene av monocytter, lymfocytter med IL2-reseptorer (CD25) og i plasma tumornekrosefaktor alfa-innhold ble målt etter 6 ukers kaldtvannseksponering. Det ble også observert en økning i plasmakonsentrasjonen av noen akutt fase proteiner, slik som haptoglobin og hemopexin. Etter 6 uker med gjentatte nedsenkninger, målte man en trend i økt plasmakonsentrasjon av IL6 og mengden av totale T-lymfocytter (CD3), T-hjelperceller (CD4), T-suppressorceller (CD8), aktiverte T- og B-lymfocytter (HLA- DR), samt en reduksjon i plasmakonsentrasjonen av alfa 1-antitrypsin. **Bifunn** Konsentrasjoner av IL1 beta, neopterin, C-reaktivt protein, orosomucoid, ceruloplasmin, makroglobulin, immunglobuliner (IgG, IgM, IgA) og C3, C4 komponenter av komplementet, samt det totale antallet erytrocytter, leukocytter, granulocytter og nøytrofiler viste ingen signifikante endringer etter gjentatte nedsenkninger i kaldt vann.	**Sjekkliste:** · **Formålet klart formulert?** Tydelig formulert formål · **Er gruppene rekruttert fra samme populasjon/befolkningsgruppe? (seleksjons bias)** Atletiske unge menn · **Var de eksponerte individene representative for en definert befolkningsgruppe/populasjon?*** Ja · **Ble eksposisjon og utfall målt likt og pålitelig (validert) i de to gruppene? (Classification bias) **** Eksponert for vann med lik temperatur. Blodprøver tatt på samme tidspunkt hos deltakerne · **Er den som vurderte resultatene (endepunkt- ene) blindet for gruppetilhørighet?**** Ikke aktuelt ettersom lik gruppe med lik eksponering og gjennomført blodprøveanalyse · **Var studien prospektiv?** Ja · **Ble mange nok personer i kohorten fulgt opp? (Attrition bias/follow-up-bias)** Ja · **Er det utført frafallsanalyser? (Eval. attrition bias)** Ingen frafall · **Var oppfølgingstiden lang nok til å påvise positive og/eller negative utfall?** Ja · **Er det tatt hensyn til viktige konfunderende faktorer i design/ gjennomføring/analyser?** Ikke aktuelt i denne studien · **Tror du på resultatene?** -Bradford Hills criteria (time sequence, dose-response gradient, biological plausibility, consistency….) Resultatene virker plausible · **Kan resultatene overføres til den generelle befolkningen?** Ikke testet med kvinner eller individer med ulike tilstander som påvirker immunforsvaret · **Annen litteratur som styrker/svekker resultatene?** Lite litteratur på dette området, undertegnede kunne ikke finne dette · **Hva betyr resultatene for endring av praksis?** Kan gi en indikasjon for at man må bruke mer eksponeringsbasert immunforsvarsstyrkning
Konklusjon			
Det stressinduserte ikke-infeksiøse stimuliet kaldtvannsbading, førte til økt metabolsk aktivitet utløst av økt blodkonsentrasjon av katekolaminer, og dermed aktiverte immunsystemet i noe grad			
Land			
Praha, Tiekkia			
År data innsamling			
1996			