Healthy excursions outside the comfort zone

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Summary
Comfort and health may be related but are no synonyms. In the last years, we enhanced our knowledge regarding health effects of temperature exposure outside the human thermal comfort zone. Mild cold and warm environments increase metabolism, thereby targeting obesity by counterbalancing excess energy intake. Furthermore, we recently showed that mild cold influences glucose metabolism. Ten days of intermittent mild cold exposure in type 2 diabetes patients significantly increased insulin sensitivity, and thereby glucose handling capacity with more than 40\%. This is comparable to the best currently available pharmaceutical therapies. A new study in obese subjects confirms these findings. Does this mean that we have to suffer from discomfort in order to become healthy? Probably not. Firstly, prolonged temporal excursions outside the thermal comfort zone result in acclimatization and we show that both cold and heat acclimation go hand in hand with increased comfort ratings. Secondly, low or high temperatures in a dynamic thermal environment may be perceived as acceptable or pleasant and evoke alliesthesia. We advocate studying dynamic thermal conditions, link this to the adaptive comfort model, and monitor these conditions in actual living conditions. This information is needed to design both healthy, comfortable and energy-friendly indoor environments.

Keywords: Health, thermal comfort, indoor climate, obesity, diabetes, acclimation

1 Environmental temperature and health
The effects of environmental temperature on our health are difficult to study, since changes in health status are slow and may also have indirect causality with temperature. Important diseases or syndromes that may link to environmental temperature are obesity, diabetes, cardiovascular diseases, and eventually even cancer (Keith et al., 2006, Prospective Studies, 2009). When we started about ten years ago, we focused on the effects of mild cold on human energy metabolism, because of its mechanistic relation to obesity and the metabolic syndrome. In the next sections, we will elaborate on the recent findings on the relations between environmental temperature and some important diseases.

2 Obesity
The metabolic syndrome is one of the most widespread diseases worldwide and is characterized by obesity, accompanied by a high risk of developing type 2 diabetes and cardiovascular diseases (Singh et al., 2013). A positive human energy balance typifies obesity. Treatment is generally directed at weight loss or weight maintenance by affecting the energy balance. This can be achieved by dieting, by increasing physical activity or a combination of the two. Dieting affects the energy intake and physical activity may affect
the energy expenditure. However, long-term effects of such life style interventions are disappointing. An alternative way to affect the energy balance could be environmental temperature.

We hypothesise that environmental temperature relates to our body (energy) metabolism and thereby may affect our health status. Ideas were formulated earlier (van Marken Lichtenbelt and Kingma, 2013), but in the mean time, new data has been collected and insights have been deepened. Clearly, classical thermoregulation shows that both cold and warm environments can increase our energy expenditure. The latter has been described in the so-called Scholander model, which uses the concept of the thermoneutral zone ((Kingma and van Marken Lichtenbelt, 2015), and Kingma 2016 for an update on this model in these proceedings). In the past, the field of thermoregulation mainly focused on extreme temperatures, which may not be relevant to our daily circumstances. Despite some older studies (Dauncey, 1981, Kräuchi et al., 1999), investigations on mild temperature variations that may be encountered in daily practice originate from the last 10-15 years (van Marken Lichtenbelt et al., 2002, van Marken Lichtenbelt et al., 2001, Celi et al., 2010, Yoneshiro et al., 2013). Mild cold (i.e. cold conditions that do not evoke shivering) leads to non-shivering thermogenesis (NST), and brown fat (the ‘healthy’ fat) is activated (van Marken Lichtenbelt et al., 2009). Brown fat is different from white fat. White fat stores energy, while brown fat burns fatty acids and glucose when needed, for instance, during cold exposure. NST accounts for up to 30% of our resting metabolism (van Ooijen et al., 2004). However, NST is lower in obese persons and in elderly. Our research group showed that regular exposure to mild cold conditions may lead to an increased capacity of NST and brown fat in lean healthy young adults (Figure 1) (van der Lans et al., 2013), but also in obese subjects and elderly (Hanssen et al., 2016). Moreover, cold acclimation leads to a decrease of thermal discomfort in cold conditions (14-15 °C) (van der Lans et al., 2013, Hanssen et al., 2016).

A warm environment can also increase energy expenditure. Currently, we are studying the effect of mild heat acclimation on energy expenditure and other health related parameters. Preliminary results show that mild heat can affect human energy expenditure and that heat acclimation affects thermoregulatory behavior (Pallubinsky et al. 2016, these proceedings). The results indicate that higher indoor temperatures may be more easily accepted.

3 Diabetes
The effect of environmental temperatures on our energy metabolism is relatively straightforward. Studies on the effect of temperature on diabetes and insulin sensitivity are more complicated. Since we showed highly significant effects on energy metabolism even achieved by mild cold intervention, and because some studies hint towards an affect of low
environmental temperature on insulin sensitivity (Lee et al., 2014), we recently performed an experiment in patients with type 2 diabetes and cold acclimation. One of the primary outcome variables was insulin sensitivity. Insulin is one of the main regulators of blood glucose levels. High insulin sensitivity means that relatively small amounts of insulin are needed to metabolize glucose. Low insulin sensitivity or insulin resistance can ultimately turn into type 2 diabetes and can cause related health problems.

Results derived from our first experiment clearly showed that, in line with former studies in healthy volunteers, energy expenditure was affected by 10 days of cold acclimation (15°C, 6h per day). The most striking result, however, was that cold significantly, and to a high extent, affected insulin sensitivity (Hanssen et al., 2015). On average, insulin sensitivity increased by 43%, which is comparable to the best treatments strategies we know of, such as intense exercise programs. Interestingly, we showed that cold acclimation affected metabolic pathways in skeletal muscle (Figure 2). This tissue is known to be the main tissue with respect to the uptake of glucose. Parallel to the study in type 2 diabetic patients, we studied cold acclimation in healthy obese subjects and showed that cold acclimation lead to a cold-induced increase in energy expenditure too, affecting the same skeletal muscle metabolic pathways (Hanssen et al., 2016).

![Figure 2. Insulin sensitivity and skeletal muscle GLUT4 localization before and after cold acclimation. A: group mean ± s.e.m. (right) for glucose infusion rate (GIR), which is the measurement for insulin sensitivity. B and C: GLUT4 translocation in skeletal muscle before and after acclimation in diabetic (B) and obese (C) subjects, as made visible in D: Representative images of GLUT4 immuno-staining of skeletal muscle tissue sections from three individuals in the study. GLUT4 is the insulin-regulated glucose transporter in skeletal muscle fibers. The pictures show that there is more GLUT 4 on the membranes of the cells after cold acclimation.](image)

4 Cardiovascular and other diseases
Both obesity and diabetes are known to increase the risk of developing cardiovascular diseases. Therefore, thermal conditions may indirectly affect this risk, but it may also work more directly. Repeated exposure to hot or cold climates may elicit cardiovascular adaptations (Corbett et al., 2014). Clearly, changes in environmental temperature affect the heat strain on the body and a significant redistribution of the blood pool is accomplished, thereby affecting cardiac output and cardiac and vascular strain. Our hypothesis is, that through variation in environmental temperatures, the cardiovascular system is exercised, which may affect the resistance to heat and cold, but also the human immune system and resistance to flu or pneumonia. The latter, however, needs to be investigated in the near future. A first indication of the effect of mild cold acclimation on the immune system derives from our study inducing 10 days of intermittent cold exposure, that evoked considerable...
changes of immune cell markers expression in skeletal muscle of healthy lean subjects (example see Figure 3) (van der Lans et al., 2015). The physiological consequences and therapeutic relevance of these changes remain to be determined.

Figure 3. Expression of adaptive and innate immune markers in muscle biopsies before (PRE) and after (POST) 10 days of cold acclimation in healthy subjects. Immunofluorescence staining of CD68 in skeletal muscle cross sections. CD68 positive macrophages are stained in green, nuclei are stained in blue. Note the increase of green (CD68 macrophages, markers of the immune system) post acclimation.

5 Environmental temperatures, health and the built environment

The above made clear that, apart from healthy lifestyle factors as diet and physical exercise, temperature training might also be linked to health. Certainly, more studies are needed to confirm the results in different populations and to better determine time and intensity effects, as well as to study additional health related parameters. Moreover, we need to address long-term effects on health. Nevertheless, in the recent years, we have identified several important health-related parameters that are now known to be affected by temperature and can be studied in greater depth, such as the above mentioned parameters: energy expenditure, brown fat activity, insulin sensitivity, blood pressure and cardiac output.

We feel that enough physiological information on the effects of indoor temperature on health has been gathered to start putting this knowledge into practice. Therefore, the question rises: how can this knowledge be translated into the built environment?

Several aspects need to be taken into account. First of all, the proposed interventions must be acceptable. Secondly, an important aspect that should be taken into consideration is compliance with the intervention. Lifestyle intervention studies identified many reasons for the lack of compliance that may in part also affect temperature interventions: habits, discomfort, social conformation, and lack of tailored information. With respect to thermal (dis)comfort, the adaptive comfort model shows that variation in daily and seasonal temperatures can be offered without discomfort (Nicol and Humphreys, 1973, de Dear and Brager, 1998); ASHRAE’s adaptive comfort model; Annex 69). Moreover, we showed that independent of season, even elderly accept a daily variation of 7°C in a dynamic situation (Schellen et al., 2010). The temperatures used include those of which we now know that they do affect the body’s energy metabolism, glucose metabolism and potentially the cardiovascular system (see above). Secondly, low or high temperatures in a dynamic thermal environment may be perceived as acceptable or pleasant and support alliesthesia (de Dear, 2011). Another important facet is the building energy saving which could be achieved by implementing a dynamic temperature profile rather than a steady-state temperature.
We think dynamic (drifting) and locally varying temperatures can be implemented in practice. In fact, there already are quite a few modern buildings that make use of dynamic temperatures and different local indoor climate zones. In future, we need to set up monitoring studies under actual daily living conditions, preferably comparing different thermal strategy interventions. This can be accomplished by using living lab environments and even by studying effects in neighbourhoods. The latter can ideally be used for research involving long-term effects on health and wellbeing in combination with other lifestyle interventions.

References


