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Cold extremities and difficulties initiating sleep: evidence of co-morbidity from a random sample of a Swiss urban population

KURT KRÄUCHI[1], PAOLA FONTANA GASIO[1], STEPHANIE VOLLENWEIDER[1], MARIELLA VON ARB[1], BARBARA DUBLER[2], SELIM ORGÜL[2], JOSEF FLAMMER[2] and ELISABETH ZEMP STUTZ[3]

[1]Thermophysiological Chronobiology, Centre for Chronobiology, Psychiatric University Clinics, Wilhelm Klein Strasse 27, [2]University Eye Clinic, Mittlere Strasse 91 and [3]Institute of Social & Preventive Medicine, University of Basel, Steinengraben 49, 4000 Basel, Switzerland

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SUMMARY Difficulties initiating sleep (DIS) can frequently occur in psychiatric disorders but also in the general population. The primary vasospastic syndrome is a functional disorder of vascular regulation in otherwise healthy subjects complaining of thermal discomfort from cold extremities (TDCE). Laboratory studies have shown a close relationship between long sleep onset latency and increased distal vasoconstriction in healthy young subjects. Considering these findings, the aims of the Basel Survey were to assess the prevalence rates for DIS and TDCE and to determine whether both symptoms can be associated in the general population. In a random population sample of Basel-Stadt, 2800 subjects (age: 20–40 years) were requested to complete a questionnaire on sleep behavior and TDCE (response rate: 72.3% in women, $n = 1001$; 60.0% in men, $n = 809$). Values of DIS and TDCE were based on questionnaire-derived scores. In addition, TDCE was externally validated in a separate group of subjects ($n = 256$) by finger skin temperature measurements—high TDCE values were significantly associated with low finger skin temperature. A total of 31.1% of women and 6.9% of men complain of TDCE. In contrast, prevalence rates of DIS were only slightly higher in women in comparison to men (9.3% versus 6.7%, $P < 0.1$). Irrespective of gender, each seventh subject complaining of TDCE had concomitant DIS and the relative risk in these subjects was approximately doubled. Therefore, a thermophysiological approach to DIS may be relevant for its differential diagnosis and its treatment.

KEYWORDS cold hands and feet, difficulties initiating sleep, epidemiology, thermal discomfort, thermoregulation, vasospastic syndrome

INTRODUCTION

All species, irrespective of exhibiting nocturnal or diurnal in habit, usually sleep or rest during the circadian trough of their core body temperature (CBT) rhythm (Zepelin, 2000). There is substantial evidence indicating that sleep in humans typically occurs on the declining portion of the CBT curve when its rate of change, and body heat loss, are maximal (Campbell and Broughton, 1994; Kräuchi *et al*., 2000), thus indicating a close link between sleep induction and body heat loss. Distal vasodilatation and hence heat redistribution from the core to the shell appear to represent the main determining component of a well-orchestrated down-regulation of CBT in the evening (Aschoff, 1983; Kräuchi *et al*., 2000). Prior to lights off, distal vasodilatation is associated with sleepiness and the rapid onset of sleep (Brown, 1979; Magnusson, 1943; Kräuchi *et al*., 1999, 2000; Fronczek *et al*., 2006).

The circadian down regulation of CBT is under control of the autonomic nervous system, which in turn is under control of the circadian clock, localized in the suprachiasmatic nuclei of the hypothalamus (Moore and Danchenko, 2002). CBT is primarily under homeostatic control and is secondarily

Correspondence: Kurt Kräuchi, Thermophysiological Chronobiology, Centre for Chronobiology, Psychiatric University Clinics, Wilhelm Klein Strasse 27, 4025 Basel, Switzerland. Tel.: +41613255508; fax: +41613255577; e-mail: kurt.kraeuchi@upkbs.ch

modulated by the circadian clock through daily oscillation in the thermoregulatoy 'set-point' (Aschoff, 1983). In order to achieve homeostasis, physiological, and behavioral thermoregulatory responses are, therefore, activated (Mekjavic and Eiken, 2006; Cline *et al*., 2004). Considering all the thermoregulatory responses, thermal sensation and thermal comfort, seem to be the easiest to investigate in humans, simply by asking subjects if they feel uncomfortable coldness or heat. Since thermal comfort requires a thermoregulatory system in equilibrium, the recognition of thermal discomfort may be an indication of a deviation of the subjects' thermoregulatory 'set point'.

There are individuals who refer thermal discomfort of high degree in their daily life. Unusual cold thermal discomfort has been more often observed in women than in men and is highly prevalent in Japan where it is called hi-e-sho, meaning 'cold syndrome' or 'vasospastic syndrome' (VS) (Nagashima *et al*., 2002; Flammer *et al*., 2001). The primary VS has been described as a functional disorder of vascular regulation in otherwise healthy subjects, whose main symptom is thermal discomfort from cold extremities (TDCE) (hands and feet) (Flammer *et al*., 2001). In addition, these subjects may exhibit a tendency of low blood pressure, migraine, and tinnitus. The VS can represent a similar, though weaker, form of Raynaud's phenomenon (Belch, 1997; Cooke and Marshall, 2005). While the classical symptom of Raynaud's phenomenon comprises the triphasic color changes of the digits of the hands and feet from white to blue to red, this is not habitually encountered in VS. The latter is mostly harmless and does not require treatment. Nevertheless, there is evidence that this syndrome may predispose individuals to some diseases, which include normal-tension glaucoma, myocardial, and cerebral infarction (Flammer *et al*., 2001). Unfortunately epidemiological data in the general population for VS are rather sparse. Prevalence rates for Raynaud's phenomenon are relatively high, ranging between 5 and 10%, depending on survey methodology and definition utilized, being considerably higher in women than in men (see below) (Belch, 1997; Cooke and Marshall, 2005; Voulgari *et al*., 2000). Therefore, it can be expected that the prevalence rate of VS is even higher.

Recently, the relationship between VS and prolonged sleep onset latency (SOL) has been studied in two subjects groups (Pache *et al*., 2001). Accordingly, subjects with VS, which comprises a heterogeneous group of glaucoma patients and of healthy subjects, reported a significantly prolonged SOL at onset of night-time sleep than controls (Pache *et al*., 2001). Thus, VS seems to be in fact associated with difficulties initiating sleep (DIS). DIS belongs to the DSM-IV diagnosis for insomnia together with disrupted sleep and non-restorative sleep (American Psychiatric Association, 1994). Insomnia is a frequent symptom in the general population of western European countries. Estimated prevalence rates suggest that about 30% of the general population have insomnia symptoms (Hajak, 2001; Leger *et al*., 2000; Ohayon, 1996; Ohayon and Zulley, 2001; Ohayon and Partinen, 2002). DIS occurs in about 10% of the general population, in women slightly more often than in men (Ohayon and Partinen, 2002; Pallesen *et al*., 2001), with higher prevalence rates and gender differences in higher age categories. In Switzerland, the few epidemiological sleep studies reported similar results (Schmitt *et al*., 2000; Borbély, 1984; Haldemann *et al*., 1996). Although the concept of 'hyperarousal' in insomniacs has attained general consensus, a physiological correlate of insomnia has not been yet established.

It can be assumed that the different symptoms of insomnia (e.g. sleep onset disturbances, sleep maintenance) have numerous causes with different physiological correlates (Fischer, 1967). Considering the aforementioned thermoregulatory concepts, we propose that DIS may be related to vasoconstricted distal skin regions before habitual bedtimes. The main aims of this study were, firstly, to provide a prevalence rate of TDCE and DIS of women and men in a random sample of a Swiss urban population, and, secondly, to test whether TDCE and DIS are significantly associated. Additionally, in a separate sample, TDCE-related questions were externally validated with objective finger skin temperature measurements.

METHODS

Epidemiological study

A random sample of 2800 men and women aged 20–40 years was selected from the population register of Basel-Stadt, Switzerland. The study was approved by the ethical committee of the canton Basel-Stadt and Baselland (EKBB). A postal questionnaire on sleep behavior and TDCE was sent to all subjects. The study was carried out between February and May 2004. Two questions referring to the leading symptoms of VS were used for the definition of TDCE: (1) During the past month, how intensively did you suffer from cold hands? (2) During the past month, how intensively did you suffer from cold feet? Answer categories: 0 = 'not at all', 1 = 'a little', 2 = 'quite', 3 = 'extraordinary'. For categorical analyses TDCE was rated as relevant when the answer to question 1 or 2 was 'quite' or 'extraordinary'. Additionally, for a dimensional analysis a score of the two questions was calculated and redefined in four increasing TDCE levels as follows: score 0 = 'not at all'; 1–2 = 'a little'; 3–4 = 'quite'; 5–6 = 'extraordinary'. Two questions referring to the leading symptoms of DIS have been used: (1) During the past month, how often was your SOL longer than 30 min? Answer categories: 'never', 'seldom', '1–2 times per week', '≥3 times per week'. 2. During the past month, was it a problem for you to fall asleep? Answer categories: 'not at all', 'a little', 'quite', 'extraordinary'. For categorical analyses, DIS was categorized as relevant when the answer to question 1 was ≥'1–3 times per week' and the answer of question 2 was 'quite' or 'extraordinary'. In addition, SOL was inquired by the question: During the past month, how long (in minutes) has it usually taken to fall asleep? Log transformed SOL [log(SOL)] was utilized for dimensional analysis to obtain normally distributed values.

Furthermore, two questions referring to the thermoregulatory behavior were asked: (1) During the past month, did you apply a 'warm bath/shower' or 'bedsocks/warm water bottle' shortly before bedtime? Answer categories: 'never', 'seldom', '1–2 times per week', '≥3 times per week'. 2. During the past month, did you wear warmer clothes than others? Answer categories: 'yes' or 'no'. The detailed analysis of sleep habits (sleep times etc.) and thermophysiology-related behaviors will be addressed in a separate paper.

Validation study

In a separate sample, we externally validated the two questions on TDCE with objective finger skin temperature measurements (TASCO infrared thermometer THI-500, Osaka, Japan). Data were collected from participants of diverse other studies carried out in the University Eye Clinic Basel, using the same questionnaire in addition to the right middle finger skin temperature measurement on the nail fold (n = 165 women and n = 91 men; age median: 45 years, range: 18–84). Finger skin temperature was measured in the early afternoon (1 p.m. to 4 p.m.) until a constant value was reached (measurement duration: < 1 min; sitting position for 15 min before start of the measurement; room temperature: 22–26 °C; normal room light conditions, 100–200 lux on eye level; measurements equally distributed over all seasons). With respect to the relationship between TDCE and finger skin temperature, no significant influence of gender and age was found (data not shown).

Statistical Analyses

Statistical analysis was performed using StatView 5.0.1 (SAS Institute Inc., Cary, NC, USA) and Statistica 7.0 (StatSoft, Inc., Tulsa, OK, USA). In general, non-parametric statistical tests were used. Statistical analysis was initiated with categorical (dichotomic) analysis. Prevalence rates of DIS and TDCE and gender differences were calculated by chi-square statistics. Odd's ratio (OR) for the association between DIS and TDCE was calculated for women and men separately. Dimensional analyses of log(SOL) at different TDCE-levels (not at all, a little, quite, extraordinary) were performed for each gender separately by the Kruskal–Wallis test corrected for ties. Mann–Whitney *U*-test was used to identify differences between women and men and differences between TDCE-levels followed by alpha-correction for multiple comparisons (Curran-Everett, 2000). In order to test a monotonic increase or decrease of the dependent variable (SOL or finger skin temperature) Spearman's rank correlations were calculated.

RESULTS

Epidemiological study

A total of n = 1001 women (= 72.3% response rate reached in two waves) and n = 809 men (= 60.0% response rate reached in three waves) returned a completed questionnaire. No significant differences in the results were found between the three waves. Since women were overrepresented in the study population (55% women versus 45% men) compared to the population of Basel-Stadt (51% versus 49%), results are presented separately for women and men. The distribution of age, BMI, and smoker/non-smoker ratio within the gender groups did not differ statistically from the distribution in the population of Basel-Stadt (comparisons carried out with data of the annual statistical report of Kanton Basel-Stadt 2004; data not shown) indicating a representative sample in these respects.

Analyses of categorized data showed a pronounced gender difference in the prevalence of TDCE: 31.13% (95%CI: 28.26–34.00) in women versus only 6.93% (95%CI: 5.18–8.68) in men [OR of women versus men = 6.07 (95%CI: 4.49–8.22); $P < 0.0001$]. However, DIS showed only a tendency to a higher prevalence in women than men: 9.29% (95%CI: 7.49–11.09) versus 6.68% (95%CI: 4.96–8.40) [OR of women versus men = 1.43 (95%CI: 1.00–2.03); $P < 0.1$]. A highly significant association was found between TDCE and DIS. In subjects reporting TDCE, 16.07% (95%CI: 12.00–20.16) of women and 14.29% (95%CI: 5.12–23.45) of men also complained of DIS. The detailed cell distribution for women was: (+TDCE, +DIS) : (+TDCE,−DIS) : (−TDCE, +DIS) : (−TDCE,−DIS) = 50:261:43:645; and for men = 8:48:46 : 706. TDCE and DIS were significantly associated, in both women [OR = 2.87 (95%CI: 1.86–4.43)] and men [OR: 2.56 (95%CI: 1.14–5.73)], whereas the association of TDCE and DIS did not differ between women and men (OR, Not Significant). Thus, irrespective of gender, each seventh subject complaining of TDCE also had DIS. The relative risk (RR) for DIS in these subjects was approximately doubled (RR in women: 1.866, 95%CI: 1.51–2.31 versus RR in men: 2.33, 95%CI: 1.16–4.66).

Dimensional data analyses revealed a significant association between TDCE and SOL (Fig. 1) (women: Kruskal–Wallis test H(df = 3) = 35.84, $P < 0.0001$; men: H(df = 3) = 26.43 $P < 0.0001$). Spearman's rank correlation analysis showed a significant monotonic interrelation between TDCE and log(SOL) in women and men (both $P < 0.0001$). A significantly different distribution between women and men was found with higher levels of TDCE (see numbers above and below box-plots; G^2 = 266, $P < 0.0001$). However, no gender difference was found in log(SOL) (Mann–Whitney *U*-tests at all TDCE-levels, NS).

The analysis of two questions on thermoregulatory behavior revealed a significant association with TDCE (most prominent in women) (see Table 1). About half of women with (+) TDCE reported to wear warmer clothes than others and applied warm remedies before and during sleep, compared to only about 25–30% of women without (−) TDCE. In men, the differences were in the same direction, however, less pronounced than in women. The second question of thermoregulatory behavior regarding sleep did not obtain statistical significance.

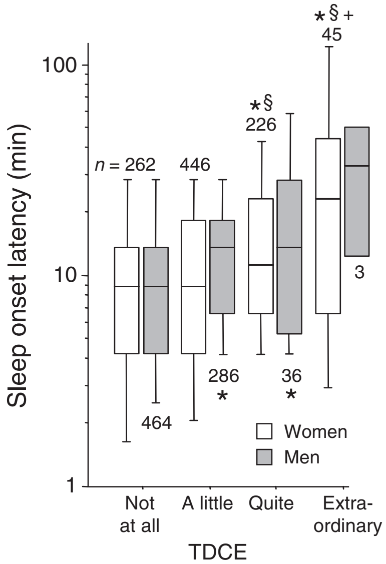

Figure 1. Relationship between SOL (log min-scale) and thermal discomfort from cold extremities (TDCE) shown for each gender separately. Post-hocs were calculated by Mann–Whitney *U*-tests followed by Curran–Everett procedure for alpha-correction. Results are presented as boxplots (10, 25, 50, 75, and 90 percentiles; for statistical details see text). Significant differences ($P < 0.05$) were found between: *, 'not at all' and all other TDCE levels; §, 'a little' and 'quite' or 'extraordinary' TDCE levels: +, 'quite' and 'extraordinary' TDCE levels. Numbers below and above the boxplots indicate number of men (below) and women (above), respectively.

Table 1 Thermoregulatory behaviors in women and men in relation to thermal discomfort from cold extremities (TDCE)

	Women		*Men*	
	+TDCE	*−TDCE*	*+TDCE*	*−TDCE*
'Warmer clothes than others'				
Yes	150 (48%)	169 (25%)	19 (34%)	82 (11%)
No	160 (52%)	515 (75%)	37 (66%)	670 (89%)
Chi square-statistics	$P < 0.0001$		$P < 0.0001$	
'Warm bath/shower before sleep; bedsocks, warm water bottle'				
≥1/week	150 (49%)	195 (29%)	10 (18%)	120 (16%)
Never/seldom	158 (51%)	487 (71%)	46 (82%)	623 (84%)
Chi square-statistics:	$P < 0.0001$		$P = 0.884$	

Validation Study

The external validation study in 165 women and 91 men, regarding the two questions concerning TDCE with objective finger skin temperature measurements, revealed a significant relationship between TDCE levels and finger skin temperature (Kruskal–Wallis test $H(df = 3) = 25.63$, $P < 0.0001$) (Fig. 2). Spearman's rank correlation analysis showed a significant monotonic interrelation between TDCE and finger skin temperature ($P < 0.0001$): the higher the degree of TDCE, the lower the skin temperature measurements.

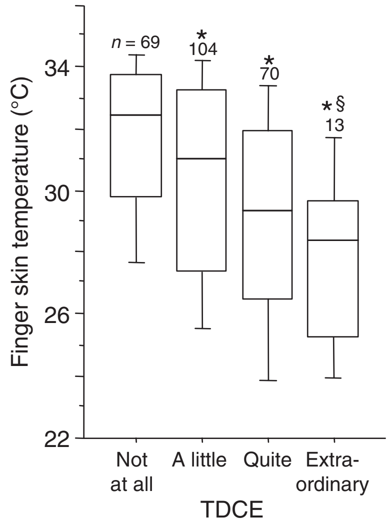

Figure 2. Relationship between measured finger skin temperature and thermal discomfort from cold extremities (TDCE). Results are presented as boxplots (10, 25, 50, 75, and 90 percentiles; for statistical details see text). Post-hocs were calculated by Mann–Whitney *U*-tests followed by Curran–Everett procedure for alpha-correction. Significant differences ($P < 0.05$) were found between: *, 'not at all' and all other TDCE levels; §, 'a little' and 'extraordinary' TDCE levels. Numbers above the boxplots indicate number of subjects.

Furthermore, 37% of the sample had TDCE and 11.5% DIS. Although this rather small sample is non-representative with respect to gender and age, it disclosed a similar significant association between TDCE and DIS [OR = 2.26 (95%CI: 1.03–4.94)], as we found in the epidemiological study (see above).

DISCUSSION

Categorical and dimensional data analyses reveal that TDCE and DIS are significantly interrelated phenomenon in a general urban population.

Nearly every third woman between 20 and 40 years exhibits TDCE—men suffering 4.5 times less frequently of TDCE. This finding confirms clinical reports in many uncontrolled studies (Flammer *et al.*, 2001). Recent studies aiming to determine the prevalence of Raynaud's phenomenon showed conflicting results, depending on the diagnostic criteria, the survey technique (sampling design, interview, and examination procedures), and the characteristics of studied populations in various geographical regions and seasons. It can be assumed that the reported prevalence of TDCE may also depend on these factors. Nevertheless, a significant gender difference was found for the prevalence of Raynaud's phenomenon across 18 different studies, with higher prevalence rates in women (ranging from 1.8 to 21.2%) than in men (ranging from 0.85 to 16.0%) (Voulgari *et al.*, 2000; Cooke and Marshall, 2005). Furthermore, the prevalence of Raynaud's phenomenon is clearly lower, nearly four times less (median prevalence observed in 18 studies: 8%) (Voulgari *et al.*, 2000; Cooke and Marshall, 2005) than the prevalence of TDCE in our study (31%).

Why do women complain 4.5 times more about cold hands and feet than men? Not only women report complaints about cold extremities, they do, in fact, exhibit cooler distal skin regions than men (Cankar *et al*., 2000; Nagashima *et al*., 2002; Karjalainen, 2007). However, their local thermal discomfort was found to be similar for the same local skin temperature levels as in men (Cankar *et al*., 2000; Nagashima *et al*., 2002; Karjalainen, 2007). As a consequence, women experience thermal discomfort before men in most of the colder conditions (Candas and Dufour, 2007). Moreover, such a thermophysiological explanation does not preclude socio- and psychological causes for thermal discomfort. Indeed, women with both TDCE and DIS turn their experienced anger more often inwards than control women (Von Arb *et al*., 2007). This could represent a causal reason for an increase in sympathetic/vagal balance, as found by heart rate variability analyses (Anders *et al*., 2008), and hence for the increase in distal vasoconstriction (Gompper *et al*., 2007; Vollenweider *et al*., 2008). Furthermore, one can hypothesize that such a pathway from increased sympathetic/vagal balance to increased distal vasoconstriction to TDCE and to DIS belongs to a self-sustaining vicious circle of DIS. In turn, DIS could also lead to an increase in the sympathetic/vagal balance.

In comparison to TDCE, DIS revealed a smaller prevalence rate, being only slightly higher in women than in men (9.29% versus 6.68%). This finding underlines that women do differentially estimate different kinds of complaints, which is in accordance with many other reports with the same age-range of subjects (e.g. Lack and Thorn, 1992; Ohayon, 1996). Significant gender differences in DIS seem to appear in older age groups above 40 years. However, as for TDCE, the same diagnostic criteria and survey technique are seldom used.

The main finding of the present study is the significant association between TDCE and DIS in a random sample of a general urban population in Switzerland. The association was found with categorized and with dimensional data analysis, indicating a robust finding. Subjects with high TDCE (ratings of quite or extraordinary suffering-degree of cold hands and feet) showed a doubling of prevalence, and of RR, for DIS. This result confirms results of studies carried out under very stringent controlled laboratory conditions with a constant routine protocol (Kräuchi *et al*., 1999, 2000), minimizing the so-called masking effects (see below). It has been shown that SOL significantly depends on thermophysiological heat loss before lights off (Kräuchi *et al*., 1999, 2000). Vasodilatation of distal skin regions and body heat loss as measured by low distal–proximal skin temperature gradient around 90 min before lights off is a good predictor for a rapid onset of sleep (Kräuchi *et al*., 1999, 2000).

Under real life situations, skin and CBTs may be masked by many factors, such as intake of large meals and drinks, physical activity, changes in body position and, lights off. However, these masking effects usually support the endogenous down regulation of CBT occurring in the evening after onset of melatonin secretion (e.g. lying down, relaxation). In fact, even in a 1-week ambulatory study under uncontrolled real life conditions women having both VS and DIS exhibited lower distal skin temperatures than controls throughout day, and most importantly in the evening before bedtimes (Gompper *et al*., 2007). In a recent published study, we showed that under very controlled conditions of a constant routine protocol women with both VS and DIS exhibit a circadian phase delay of the thermoregulatory system by approximately 1 h in relation to their similar sleep–wake cycles, in comparison to controls (Vollenweider *et al*., 2008). These findings suggest that women with VS and DIS are thermophysiologically unprepared for sleep.

In order to obtain an indicator for distal skin temperatures under ambulatory conditions, questions on TDCE were chosen in the present community survey. The validity of this indirect measure is shown in Fig. 2, with a significant relationship between TDCE and finger skin temperature. Subjects with quite or extraordinary TDCE have a median finger skin temperature below 30 °C, which corresponds to the cut-off value recently found in finger temperature for overall cool-discomfort (Wang *et al*., 2007). In order to investigate the relationship between objectively measured skin temperature and thermal comfort skin temperatures of the upper-extremities were manipulated in the cited study. A useful warm/cold boundary of 30 °C was found in finger temperature, for both steady state and transient conditions (Wang *et al*., 2007). While TDCE was often reported when finger temperature was below 30 °C, there was no TDCE when finger temperature was above 30 °C (Wang *et al*., 2007).

In the present study, questions on TDCE were asked for a time interval over the past month. However, skin temperature measurements were carried out afterwards. Nevertheless, the ratings of TDCE seem to be in fact a good correlate of finger skin temperature and of the general thermophysiological body state (Cline *et al*., 2004). In a further separate analysis, we could show that both thermal discomfort from cold hands and cold feet are correlated with cool finger skin temperature (data not shown).

Changes in vasoconstriction and vasodilatation occur in order to redistribute heat inside the body without high metabolic costs (e.g. sweating and shivering). Such a redistribution of heat in the body is the first counteraction of the thermoregulatory system to keep the CBT constant (Cline *et al*., 2004). Furthermore, behavioral temperature regulation occurs almost constantly (e.g. clothing adjustment). These voluntary actions originate from thermal stimuli, which are perceived at the periphery by thermoreceptors integrated at the central level and lead to action and reactions. In the present survey, we found a significant association of TDCE with behavioral thermoregulation in both women and men. However, only women exhibited a significant thermoregulatory behavior with respect to sleep—men use less often thermophysiological remedies before sleep to cure their cold extremities. This finding suggests that TDCE can indeed be a strong problem in the evening prior to lights off, at least in women. Whether men apply other methods to warm up their cold feet remains to be established. Moreover, a further analysis did not reveal an influence of the thermoregulatory behavior on DIS—subjects with or without thermoregulatory behavior showed similar values of DIS (separate Mann–Whitney *U*-tests for each gender, data not shown). This indicates that the thermoregulatory behavior is not sufficient for a complete remission of TCE and DIS. However, based on the fact that many subjects with TCE regularly use such thermophysiological remedies in the evening, there is a likelihood that they partially profit from this type of therapy.

Taken together, our epidemiological study provides evidence that about 30% of women between age 20 and 40 years experience high TDCE. This thermophysiological state of body heat conservation (i.e. cold hands and feet) is significantly associated with prolonged SOL in the general population. Each seventh person with TDCE suffers from DIS, but only each 16th person without TDCE suffers from DIS. Future studies will demonstrate if any thermophysiological and/or chronobiological intervention can be successful in subjects with DIS and TDCE. Warming up the extremities before habitual bedtimes, phase advancing the circadian system by morning light and phase delaying of the sleep–wake cycle are currently under investigation.

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