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Søgaard, Karen; Sjøgaard, Gisela

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Physical Activity as Cause and Cure of Muscular Pain: Evidence of Underlying Mechanisms

Karen Søgaard and Gisela Sjøgaard

Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense M, Denmark

SØGAARD, K. and G. SJØGAARD. Physical activity as cause and cure of muscular pain: evidence of underlying mechanisms. *Exerc. Sport Sci. Rev.*, Vol. 45, No. 3, pp. 136–145, 2017. *Work-related physical activity (PA), in terms of peak loads and sustained and/or repetitive contractions, presents risk factors for the development of muscular pain and disorders. However, PA as a training tailored to the employee's work exposure, health, and physical capacity offers prevention and rehabilitation. We suggest the concept of "Intelligent Physical Exercise Training" relying on evidence-based sports science training principles.* **Key Words:** occupational physical activity, leisure time physical activity, muscular pain, productivity, sickness absence, public health

Key Points

- Physical activity (PA) includes the domains of leisure, occupation, and sleep, each having different profiles of intensity, duration, and repetitiveness of muscular activity and, therefore, different effects on musculoskeletal health.
- Occupational PA often involves static load, repetitive movements, and high peak forces, all of which — if occurring for prolonged duration — are risk factors documented to compromise musculoskeletal health and to causally relate to muscle pain development.
- Physical exercise training can be planned to obtain health-enhancing effects and can be targeted toward maintaining and improving muscular strength, endurance, and resilience. Recent studies also show effects in pain reduction.
- An individual's daily PA profile is the accumulated impact from all the domains of PA and should be balanced to counteract lifestyle diseases, including musculoskeletal disorders.
- The workplace offers an arena for exercise training that is beneficial for health. Future research must focus on how organizational, motivational, and financial aspects can be addressed across a range of workplaces to promote implementation and improve adherence to attain significant effects.



Editor's note: Go online to view the Video Abstract in the Supplemental Digital Content: see <http://links.lww.com/ESSR/A35>.

INTRODUCTION

This article deals with the contrasting effects of physical activity (PA), which can cause muscular pain but also can reduce muscular pain, maintain function, and prevent lifestyle diseases. PA has been considered health enhancing for decades, with health authorities advising that PA should be part of daily life throughout the whole lifespan. Extensive changes in working environments have increased time spent on sedentary work and have a major impact on the accumulated PA profile and the related lifestyle diseases (19). Muscular inactivity has been estimated to cause more than 1 million deaths annually in European countries (26). This has even led experts to advise changes in classic ergonomic recommendations to focus on ways to increase the load and strain embedded in modern work activities (81).

The focus on inactivity as a health risk factor is not new. More than 300 yr ago, Ramazzini suggested that,

"...those who sit at their work and are therefore called 'chair workers', should be advised to take physical exercise, at any rate on holidays. Let them make the best use they can of some one day, and so to some extent counteract the harm done by many days of sedentary life." (28).

However, claiming inactivity as an independent risk factor for poor health has led to an oversimplified disregard for the potentially detrimental effects of some forms of PA.

Address for correspondence: Karen Søgaard, Ph.D., Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, Campusvej 55, DK-5230 Odense M, Denmark (E-mail: ksogaard@health.sdu.dk).

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Although there is no doubt in the increased risk of overall low PA level for sedentary “chair workers,” there also is a concurrent risk of overloading, which Ramazzini also was aware of:

“The incessant driving of the pen over paper causes intense fatigue of the hand and the whole arm because of the continuous ... strain on the muscles and tendons.” (28)

In comparison with the increased focus in recent decades on cardiovascular mortality and longevity associated with sedentary jobs, much less attention has been paid to the equally important issue of musculoskeletal disorders (MSD), pain, and impaired function that has a major impact on prospects for living independently and with high quality of life (20).

Good muscle function is fundamental for living a physically active and independent life. Muscle activity is not only beneficial for maintaining the muscles’ own capacity but also for maintaining the function of other organs and tissues. Muscle is the main energy consumer posing a demand on the other body systems to provide the adequate energy delivery by regulating blood flow. Therefore, improving the capacity of the cardiovascular system is in general achieved by activating a large muscle mass dynamically at a high intensity. A significant increase in whole body energy turnover is additionally a key feature in prevention of obesity, metabolic syndrome, and diabetes. Therefore, a compromised muscular function that impairs an active lifestyle with leisure time PA (LTPA) also may potentially increase the risk of common lifestyle diseases. It should be noted that the activity of only small muscle groups — as in light office work — will not sufficiently impact the cardiovascular system to attain a health effect.

PA is a broad term normally defined as any bodily movement produced by skeletal muscles that requires energy expenditure. It can involve playing, working, active transportation, household tasks, and exercise training. These tasks can be described

in Newtonian equations, and if the efficiency is known, the summarized force produced over time can be converted into total energy consumption (88). This means that individual PA can be classified from high to low. However, as illustrated in Figure 1, PA takes place in different domains of daily life such as work, leisure, and sleep. Each domain contains subcategories of PA that present distinct profiles. Transport and domestic duties take place in the leisure time domain and occupational tasks in the work domain. Other subcategories of exercise training, sport, and rehabilitation may take place in both work and leisure domains. The sleep domain almost holds no PA and, therefore, adds to total inactivity, but it plays an important and often overlooked role in recovery. Over a lifespan, although the work domain counts for by far the largest share of the total energy expenditure during working days because of the large proportion of waking hours spent at work, this is seldom at a level that can promote fitness. In contrast, sport and recreation count for only a minor share but nevertheless are the most important factors in prevention of lifestyle diseases (14,67,68).

International recommendations for health-promoting PA do not distinguish between occupational PA (OPA) and LTPA (30) as regards the effect of PA. This is in line with classical studies from cohorts a century ago, which found similar positive effects of PA in terms of OPA and LTPA, for instance the famous studies of London bus drivers (59) and the Harvard alumni study (63).

This is, however, in direct contrast to studies from recent cohorts undertaken this century, which have indicated distinct differences in health effects between LTPA and OPA. The expected beneficial effect of LTPA was found as a decreased risk of cardiovascular disease among women and a decreased risk of cardiovascular death among men (1,39). In contrast, high OPA was associated with a substantially increased risk. This interactive effect is further supported by a study of sickness absence also showing negative effects of OPA and positive effects of LTPA (37). Similar effects also may be relevant for MSD, because the risk of repetitive, work-related strain injury has been found to be significantly reduced through high levels of LTPA (68).

It seems clear, then, that today, the profiles of these two major domains of OPA and LTPA differ. LTPA is, in general, performed at the participants’ own discretion and may include training aimed at specific health-enhancing effects in relation to intensity, duration, or type of contraction. However, exaggeration of intensity or duration, as in elite sports, for example, may well lead to injuries. The level, intensity, and duration of OPA are determined primarily by the demands of productivity, the purpose of the tasks, and the time allowed for certain productivity. Such PA may well be health enhancing but only if maintained at moderation, as was already recognized as early as 1757 by the notorious royal physician, J.F. Struensee (82).

The physical demands on muscle may be characterized by combinations of intensity and duration, which result in peak loads, static muscle activity, movements repeated for prolonged periods of time, or constrained postures. These are all well-known risk factors in work-related MSD [(65) (4,92) (47)]. From the perspective of muscular health, it is, therefore, imperative to focus on the underlying variation in intensity, duration, repetition, and adequate restitution time for the different subdomains and specified on body regions.

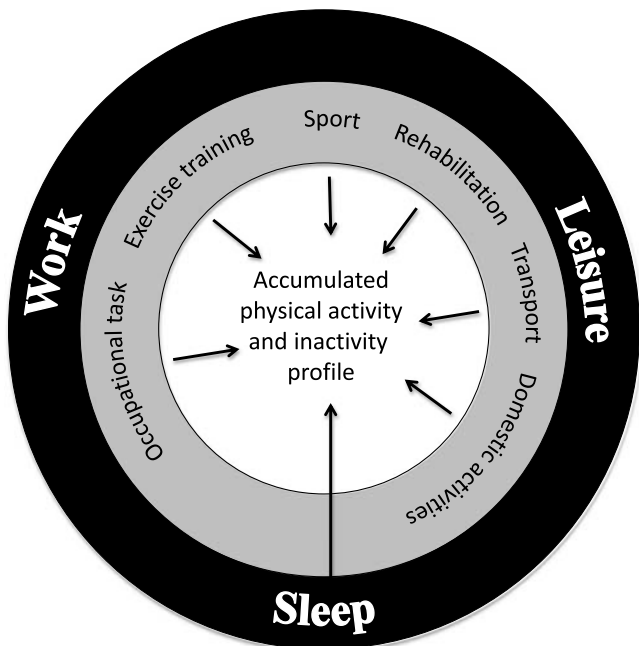


Figure 1. The daily profile of physical activity (PA) consists of the three domains of work, leisure time, and sleep alongside their subdivisions, each with its positive or negative contributions to effects on musculoskeletal health.

Epidemiological studies have shown distinctly different effects of OPA and LTPA, but the individual worker in daily life does not choose between the impact of physical exercise training and the occupational demands. Rather, daily life is an interplay between OPA and LTPA and evidence-based tailored physical exercise training, which, as Ramazzini suggested, can interrupt work and counteract the mechanisms evoking muscle pain. From the perspective of muscular health, it may be too simple to focus on decreasing inactivity or increasing PA in general. The challenge is rather to provide specific and intensive evidence-based training programs targeting the relevant body parts for the purpose of balancing those PA profiles that cause and cure muscular pain. This is shown in Figure 2 together with the beneficial side effects (73,75) potentially preventing lifestyle diseases and improving health as well as function.

Novel Hypothesis

We propose the concept of “Intelligent Physical Exercise Training” (IPET), which aims to match and counterbalance the deteriorating impact of physical work demands including physical inactivity. IPET is derived from evidence-based sports science training principles, tailored to the individual employee’s work exposure, health, and physical capacity. This approach involves adjusting the profile of physical exercise training to match the impact of workload, including prolonged inactivity and overload, as well as the individual’s physical capacity and function. Furthermore, both the localization and degree of muscular pain and relevant motivational factors should be considered. The workplace setting is where most of the working age population spends most of its waking hours on work days. As pointed out by the World Health Organization, the workplace also offers an optimal setting in terms of accessibility, infrastructure, and social context for embedding PA into daily life

routines and thereby increasing the chance for sustained muscular health effect (57).

PA AS CAUSE OF PAIN DEVELOPMENT AND MSD

MSD is a broad term covering any nonspecific disorder characterized by pain or decreased function and described as musculoskeletal trouble, ache, pain, or discomfort having a muscular, nervous, or arthritic origin. MSD often is self-reported but can be classified into diagnoses on the basis of symptoms found in clinical examination. There is no total overlap between self-reported pain, functional impairment, and diagnostic criteria. However, e.g., among computer users, most (60%) of the self-reported neck/shoulder pain could be specified into clinical diagnoses, myalgia being the most frequent (45,46).

MSD is highly prevalent and poses serious consequences for the individual as the most important cause of functional impairment. From a global perspective, MSD is the largest contributor, accounting for 31% of all years lived with disability (14). In Denmark, MSD has serious financial implications, because it increases fivefold the use of health care and is the most frequent reason for sickness absence and early retirement from work. The average Danish citizen lives 7 yr with decreased quality of life because of MSD and, importantly, since 1990, there has been a steady increase of 40% in the proportion of citizens with MSD (27).

A U-shaped relation exists between physical loading and the relative risk of disorders in muscle (88), which mirrors the relation between physical loading and viability (72). A physical exercise training program optimizes the dose of muscle activation in relation to a specific training effect. In contrast, inactivity and lack of strain infer a risk of tissue atrophy and degeneration, whereas excessive amounts of activity in terms of repetitions or intensities involve a risk of tissue damage mechanically or

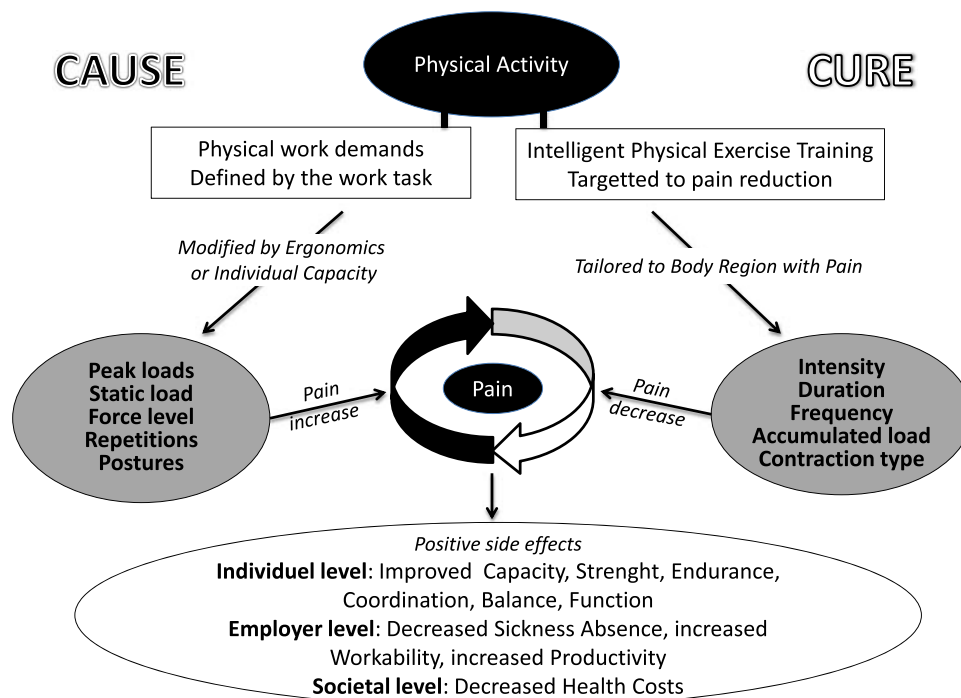


Figure 2. The model shows the counterbalancing effect of physical activity in terms of work and Intelligent Physical Exercise Training (IPET) on pain status and the additional side effects of IPET.

metabolically causing muscle pain and MSD. In defining an optimal physical exercise training program for an employee, it is of the utmost importance to identify risk factors for muscular pain. An appropriate physical exercise training program not only enforces and maintains optimal muscular function but also may serve as treatment for pain reduction (74).

MSD is multifactorial but, whatever its cause, it may interfere with functioning and therefore decrease work ability and productivity. However, among the working age population, a part of the MSD is work related. This health-impairing effect of OPA on body region-specific MSD has been extensively documented over the years (25,65,90). In manual handling, the most commonly affected body regions are the hands, arms, and shoulder/neck. In jobs involving standing, walking, and lifting, the main areas affected are the lower back, hip, and knee (25,65).

There has been a global increase in sedentary jobs and a decrease in physically demanding jobs, but nevertheless, there has been a steady raise in MSD prevalence since early 1980s (21).

From the perspective of muscular health, a sedentary work task may present with an inhomogeneous activity demand on body regions. Although the large leg and body core muscles suffer from a lack of activity, heavy relative demands may be present for the small upper extremity muscles. Therefore, a job that from a cardiovascular perspective is inactive may from a muscular point of view present a risk of overload and exertion in specific body regions such as the small forearm and finger muscles.

The global increase in sedentary computer jobs and use of handheld digital devices also increase the need to maintain strenuous postures with static sustained contractions in the neck, shoulder, and wrist muscles and repetitive movements of the wrist and finger extensor muscles (93). Such tasks demand continuous low levels of muscle activity and are associated with high prevalence of pain in the neck, shoulders, and forearms (45). Despite these well-documented ergonomic risk factors, evidence is sparse regarding significant effects of ergonomic interventions on MSD (13,50,91). The underlying risk factor in these tasks may be the long duration of sustained activation of specific motor units (MU) in the muscle, thereby eliciting muscular pain (76,78).

Muscle Activation Pattern in Simulated Work Tasks

In a number of studies, we have quantified work demands and the related muscle activity in job tasks associated with a high risk of pain development. Work demand at a whole muscle level may be misleading, particularly at low force levels, due to the large degree of spatial inhomogeneity in activity within a specific muscle or muscle group. In accordance with the size principle, work tasks with low force demands will only activate the low threshold subpopulation of MU whereas the high threshold MUs will remain inactive until the central drive increases to above their threshold (36).

Studies with intramuscular electrodes, such as needle or fine wire, have shown continuous activation patterns in the same part of the MU pool during contractions that simulate repetitive job tasks. Recruitment was independent of contraction mode, and in some cases, the exact same MU could be identified in fast and slow, concentric and eccentric contractions (83,85). It has been proposed in the pain-adaptation model that the muscular pain as a protective mechanism locally may inhibit muscle activation (56). However, using a hypertonic saline model to induce pain did not indicate a pain-related inhibition of recruitment when keeping the work tasks constant (11). Muscle fatigue can be indicated by an increased drive to sustain the same target force, due to the decline in the force-generating properties of the active MU (86). However, even this condition did not seem to inhibit activation to protect the fatigued MU from sustained prolonged activity (42,62).

In addition, activity patterns have been studied in functional free-finger movements during stereotyped tasks, including double-clicking on an instrumented computer mouse. Index finger movement during double-clicking almost approached maximal frequency of finger tapping (79). Such high demands for rate of force development may impose a high and localized strain on the muscle fibers. Interestingly, a temporal inhomogeneity in activity pattern of some MUs — involving close motor unit action potentials, so called doublets, with less than 20 ms between potentials — seemed to be an integrated part of the activation pattern. This was seen even in the MU activation pattern of the contralateral finger extensor muscle despite no change in movement and muscle length (89). A follow-up study of the

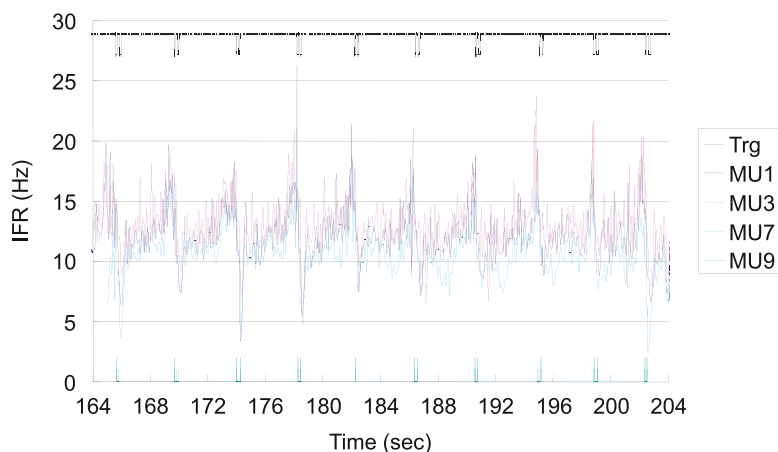


Figure 3. The motor units (MU) activity pattern in the right trapezius muscle for one subject performing 10 double-clicks on a computer mouse with the right index finger. The double-clicks are shown as bars in the upper trace. Three MU are continuously active with an instantaneous firing rate (IFR) modulation related to the timing of the double-click. The bottom of the figure shows the activity of one MU consistently only showing activity during the double-click and mostly with double discharges indicated by the high bars. [Adapted from (87). Copyright © 2014 the authors.]

MU activity pattern in the remote trapezius muscles during double-clicking with the index finger showed a MU activity pattern in both the ipsi- and contralateral trapezius muscle, closely following the fast dynamic movements of the unilateral finger performing the double-clicking (87). Most surprising was again the amount of recorded doublets. These consistently were evoked when the concurrently active MU reached peak firing rates of approximately 20 Hz during each double-click (Fig. 3). It is known from stimulation experiments that doublets can potentiate the force development per action potential and facilitate a rapid increase in force (15,94). This may be an elegant motor control compensation to bypass the slow contractile properties normally assumed for a low-threshold MU. However, doublets cause a large release of Ca^{2+} from sarcoplasmic reticulum into the cytosol of the muscle fiber, thereby elevating cytosolic calcium concentrations, compromising intracellular homeostasis, and eventually impairing action potential transients. This process may promote breakdown of the muscle cell membrane, and a leaky sarcolemma may cause muscle metabolites to stimulate the nociceptive free nerve endings in the interstitial space (78).

In summary, repetitive work elicits recruitment of low threshold MU and activation of contralateral as well as stabilizing muscles, following the fluctuation in the dynamically contracting finger extensor. High kinematic demands were associated with doublets of MU firings as a consistent part of a voluntary recruitment pattern in the agonist, contralateral, and stabilizing muscles. We found during these work tasks no indication of protective inhibition of activity by either pain or fatigue.

Biomarkers Indicating Pathomechanisms

Perception of muscular pain is elicited by the excitation of afferent nerve fibers, terminating as free nerve endings with nociceptive properties in the interstitial space of the muscle. These nociceptors are abundant and respond to chemical substances released in excess from overloaded or damaged muscle fibers. However, the actual concentration of pain-eliciting substances is not a direct indicator of pain intensity, because this depends on the nociceptor threshold. Peripheral sensitization, whereby a lower stimulus than normal activates nociceptors, may cause a chronic perception of pain that over time also may lead to central sensitization (58).

The inhomogeneous MU activation described previously during low-force sustained or repetitive contractions may create a localized increase in intramuscular pressure, which in turn may impede blood flow specifically to the locations of continuously active MUs belonging to the low threshold part of the motor neuron pool. This mismatch between use and delivery of oxygen with blood flow may disturb the aerobic energy turnover and result in more anaerobic processes. Use of near-infrared spectroscopy technique during a 40-min standardized work task actually confirmed that oxygen availability initially showed a steep decrease and stayed low in the myalgic muscle, whereas during the same work task the oxygen availability in the healthy muscle gradually returned to baseline values. Furthermore, in this same 40-min low force repetitive work task, microdialysis revealed a local increase in the interstitial level of lactate and pyruvate both in healthy and myalgic muscles (54,69,70,77). The myalgic trapezius muscle, however, despite

similar blood flow as in the healthy muscle showed higher levels of these indicators of anaerobic metabolism, even in the baseline resting condition. In addition to the differences in metabolically related substances, elevated concentrations of algescic substances were identified. The myalgic muscles in three different study populations showed higher levels of glutamate and serotonin than the normal muscle (54,70,77). These substance concentrations correlate with pain intensity and are associated with muscle cell damage and necrosis (55). The findings of an elevated level of serotonin in the myalgic muscle are supported by a recent review on biochemical biomarkers (31).

Taken together, myalgic muscles present adverse functional, metabolic, and morphological characteristics compared with healthy muscles both at rest and during a standardized repetitive task (71). This indicates a peripheral origin of the muscle pain that may be a subsequent phenomenon to the disturbed energy turnover in the continuously active MU and the doublet phenomenon. In addition, peripheral or central sensitization may add to the pain experience.

PA AS CURE FOR MUSCULAR PAIN AND HEALTH ENHANCEMENT

For many years, prevention of work-related MSD has focused on ergonomic optimization in terms of reducing muscular strain by lowering the high force levels, minimizing the static levels, and overall increasing variation in force demands. However, the similarity of muscle activity in work tasks allows only limited variation (78). Furthermore, the effect of task variation is limited due to a large amount of coactivation in both manual handling and precision work.

A review supports that ergonomic improvements or the use of tools such as biofeedback have limited effect on musculoskeletal health or even provide clear evidence of a lack of effect (38).

Even optimal ergonomics may not eliminate the risk of muscular pain, and opportunities for changing the work tasks to include activities reaching health-enhancing levels of intensity are limited. Sports science has provided evidence for effective training principles for optimizing performance. Training is a general term for a systematic planned effort over time to improve performance within a chosen dimension and includes also cognitive behavioral training and computer skill training, besides training within a large variety of disciplines. Similarly, an exercise may aim to improve any type of skill within a training program and may refer to just a single exercise bout. Therefore, to avoid misunderstanding, we have chosen to focus on physical exercise training. Physical exercise training in sports targets strength, aerobic power, and coordination and shows efficacy on improved performance associated with changes in physical capacity. As has been pointed out in a recent review (31), much less is known about a possible pain-reducing effect of physical exercise training and the morphological and biochemical mechanisms underlying a reduction in pain.

In a carefully planned randomized controlled trial (RCT) involving subjects with trapezius myalgia compared with matched healthy control subjects, we were able to show a number of differential beneficial effects of two types of exercise training: strength training and aerobic training (8). Strength training was applied specifically to the neck and shoulder muscles. This initially acutely increased pain in the myalgic muscle after an exercise session, but over a 10-wk training period, a significant

decrease was found. It also increased maximal muscle activation, strength, muscle cross-sectional area (specifically of type II fibers), and the number of satellite cells — the muscles' own stem cells (5,84). Aerobic training was performed with the leg muscles without involvement of the myalgic trapezius but nevertheless showed an acutely increased blood flow in the passive trapezius muscle during an exercise session (5,6). The aerobic exercise training caused a transient decrease in pain after each exercise session. Furthermore, during a standardized repetitive work task, an improved blood flow and oxygenation as well as a reduced work-related pain were found after the 10-wk training period compared with baseline (84).

In addition, the aerobic training decreased both peripheral and central pain sensitivity (61). Other beneficial effects were found to include a number of health-related factors such as lowered blood pressure. Direct measures at the muscle level using biopsy and microdialysis techniques showed an increase in metabolic capacity (84), demonstrated even at the gene level (80). Morphological recovery also was documented using advanced immunohistochemical stainings, for example, satellite cells (54) — and neuronal nitric oxide synthase (43). Overall, the largest functional and morphological improvements were seen in the trapezius muscle after strength training, whereas the largest aerobic metabolic improvements were seen after the dynamic leg training. Therefore, rather different mechanisms may underlie the pain reductions seen with these different training schedules (74). As a follow-up on these positive results in trapezius myalgia, a number of workplace RCT interventions have been conducted, mostly offering participation for all employees at a specific workplace and tailoring the PA intervention content to the occupational exposure.

The Concept of IPET for Workplaces With a Variety of Occupational Exposures

To provide an effective intervention content, the challenge is to carefully match the OPA profile determined by the work demands with training tailored to conquer pain in the designated body regions at risk of pain development (38,74). The RCT studies involved job groups with a wide range of exposure profiles with a variety of risk factors for MSD. In all studies, the intervention content was based on sports science principles, tailored to work exposures for a job sector level, to employees' health, and finally, to physical capacity, which also accounts for the employees' LTPA. In some studies, this has been assessed at a group level, in others on an individual level, and as an overall framework, it subsequently has been described using the term Intelligent Physical Exercise Training or IPET (71,74).

Exercises were performed for approximately 1-h a week at the workplace and in general supervised to monitor and encourage adherence. In contrast to OPA, IPET often involved dynamic activities performed with large muscle groups that increased muscular, metabolic, and cardiovascular load. Different modes of activities were combined and high intensity tasks interspersed with breaks for recovery. Because the 1-hr training was offered during work hours, the exercise prescription was optimized so that this short period of exercise provided the greatest possible outcome for enhancing health.

An overview of the workplace RCT studies conducted in our group is given in the Table, summarizing the extent of positive effects of the RCTs for the individual and the workplace. The

most consistent finding was the decrease in neck/shoulder pain among office workers (2,3,5,7,12,22–24,32,64), dentists (29), musicians (10), and industrial technicians [(40,41) (95)]. This effect was present with both strength and aerobic training and was not dependent on how the 1 hr of exercise training was distributed over the work days (22). Positive effects were seen even after spending only 6 min of elastic band training a day (29). Interestingly, the RCT that implemented the IPET concept in its most elaborate form also showed marked effects both on productivity and on sickness absence (44). However, it may be more important that, despite the training sessions being performed during working hours, no reduction was seen in productivity in any of the studies. In the physically demanding jobs of health care workers (9,16,18,66), cleaners (48,51), and construction workers (33), a consistent increase in aerobic power was shown, and in one study a decreased sickness absence (9). Two studies of health care workers were multifactorial interventions. One, combining physical exercise training with ergonomics and cognitive behavioral training, resulted in a decrease in low back pain intensity and days with pain (66). The other, combining tailored physical training with dietary advice and cognitive behavioral training, found an increase in productivity with increased muscle strength (16,17). Among cleaners, one study found a reduction in chronic neck-shoulder pain (49), whereas another study with an aerobic intervention in the long term not only increased aerobic power but also decreased low back and neck-shoulder pain (52). Finally, two studies found positive effects on neck pain among F16 and helicopter pilots, but only for those who complied with the specific strength training program (53,60).

Taken together, the RCT studies provide evidence that the detrimental effect of OPA can be counteracted by the pain-alleviating effect of a carefully planned exercise training such as IPET introduced in the workplace. We additionally have shown that IPET proves to be more than medicine, due to number of positive side effects that have been documented (71). On the individual level, IPET benefits the worker in terms of decreasing health risk indicators and improving physical capacity and functions, as well as perceived health (71). The employer also benefits from allowing the employees' work time for IPET training through decreased sickness absence and improved or maintained productivity and work ability (17,66). From a public health perspective, IPET decreases health costs due to beneficial effects that counter major lifestyle diseases. The workplace setting allows a focus on subpopulations with similar occupational physical workload and those most in need of initiatives to maintain the individual's ordinary daily physical functions and ability to live an active, independent, and health-sustaining life.

CARE OR CURSE

In our opinion, maintaining muscular health across the span of a working life should not be considered just an individual obligation but as a societal responsibility. Therefore, it is important that daily life environments provide time and opportunities for IPET, specifically in job sectors where occupational risk factors cannot always be eliminated. IPET should not become a curse leaving to the individual workers' own responsibility to maintain work ability. Equally important, it should never substitute for good ergonomics and the adjustment of work demands to individual capacity. Accordingly, implementation of IPET should be integrated in an overall occupational

TABLE. Overview of positive results found in 17 RCT studies conducted at the workplace comprising more than 3500 workers with different job exposure

	Job Type	Intervention Category	Muscle Pain Reduction	Other Health Benefits	Workplace Benefits
Blangsted <i>et al.</i> , 2008; Pedersen <i>et al.</i> , 2009	N = 549 Office workers	Strength training and aerobic training	Neck-shoulder and low back	Shoulder strength, $\dot{V}O_{2max}$, $\dot{V}O_{2min}^{-1}\cdot kg^{-1}$, BP, and % body fat	
Andersen <i>et al.</i> , 2012; Gram <i>et al.</i> , 2014; Dalager <i>et al.</i> , 2015	N = 573 Office workers	Strength training	Neck-shoulder	Neck-shoulder strength, neck-shoulder endurance, and headache	
Sjøgaard <i>et al.</i> , 2014; Justesen, 2015; Dalager <i>et al.</i> , 2016; Dalager <i>et al.</i> , 2017	N = 391 Office workers	Aerobic training, strength training, and health ambassadors	Neck-shoulder ^a	$\dot{V}O_{2max}$, $\dot{V}O_{2min}^{-1}\cdot kg^{-1}$, BP, and resting heart rate	Productivity, work ability, and sickness absence
Andersen <i>et al.</i> , 2014a ^b	N = 47 Computer users	Functional training	Neck-shoulder	Neck-shoulder strength	
Andersen <i>et al.</i> , 2008; Andersen <i>et al.</i> , 2014b ^b	N = 48 Computer intensive work	Strength training and aerobic training	Neck-shoulder	Neck-shoulder strength	
Fredslund <i>et al.</i> , 2014 ^b	N = 110 Dental teams	Strength training	Neck-shoulder		Work ability
Zebis <i>et al.</i> , 2011; Pedersen <i>et al.</i> , 2013	N = 537 Industrial workers	Strength training	Neck-shoulder, upper back, low back, and forearm		
Jay <i>et al.</i> , 2015; Jay <i>et al.</i> , 2016 ^b	N = 112 Laboratory technicians	Strength training, functional training, and CBT + mindfulness	Neck-shoulder, upper back, and low back		Work-related fear avoidance
Andersen <i>et al.</i> , 2017	N = 23 Musicians	Strength training and aerobic training	Neck-shoulder ^c	$\dot{V}O_{2max}$	Better performance on instrument
Jorgensen <i>et al.</i> , 2011a; Jorgensen <i>et al.</i> , 2011b	N = 294 Cleaners	Functional training	Neck-shoulder	Core muscle strength and balance	
Korshoj <i>et al.</i> , 2016; Korshoj <i>et al.</i> , 2017	N = 116 Cleaners	Aerobic training	Neck-shoulder and low back	$\dot{V}O_{2max}$, resting heart rate, % heart rate reserve, % body fat, weight, and waist circumference	
Christensen <i>et al.</i> , 2012; Christensen <i>et al.</i> , 2015	N = 144 Health care workers	Aerobic training, CBT, and dietary advice	Neck-shoulder ^c	$\dot{V}O_{2min}^{-1}\cdot kg^{-1}$, BP, body weight, % body fat, BMI, and waist circumference	Productivity and sickness presenteeism
Andersen <i>et al.</i> , 2016	N = 60 Health care workers	Strength training and aerobic training	Neck-shoulder ^c and low back ^c	Kinesiophobia	Sickness absence
Rasmussen <i>et al.</i> , 2015	N = 594 Health care workers	Strength training, aerobic training, CBT, and ergonomics	Low back	Kinesiophobia, perceived work exertion, and self-reported strength, aerobic power, and overall capacity	
Gram <i>et al.</i> , 2012	N = 67 Construction workers	Aerobic training and strength training		$\dot{V}O_{2max}$ and $\dot{V}O_{2min}^{-1}\cdot kg^{-1}$	
Murray, 2016	N = 69 Military helicopter pilots	Strength training	Neck ^a	Neck extension strength and shoulder elevation strength	
Lange <i>et al.</i> , 2013	N = 55 F16 fighter pilots	Strength training	Neck		

^aPer protocol analysis.^bOnly offered to workers with pain.^cWithin group effect.

BMI, body mass index; BP, blood pressure; CBT, cognitive behavioral training; RCT, randomized controlled trial.

health perspective, and IPET should become part of the employer's responsibility for the employee.

The workplace represents an arena with the infrastructure, social network, and support for tailored physical exercise training. The workplace that provides time and instruction for evidence-based exercise training may benefit from a higher productivity and lower sickness absence and brand the company by caring for the workers' health and sustained work ability. The workplace may ensure that employers are committed to the PA program for the long term and can ensure that workplace environments and policies build activity into employees' routines.

FUTURE PERSPECTIVES

Integrative approaches are critical to advancing the understanding of pathophysiology of work-related muscular pain in MSD and its prevention and rehabilitation by exercise training. Strict RCT study designs at workplaces embedding advanced

methods to evaluate the specific effect of training on biochemical and metabolic mechanisms are urgently needed. Such studies are still sparse, but they are crucial in providing evidence for the pain-relieving effect of specific physical exercise training modes that effectively counterbalance the work-related MSD. Advanced new analytical methods for muscle biopsy, microdialysate, and blood samples are now available — such as omic techniques — and provide new opportunities for identifying complex spectra of proteins in the painful versus healthy muscle and the training-induced changes (34,35). It is still not known whether the effect of physical exercise training is mediated by the muscle becoming stronger and more resilient, by lowering the relative load of a given task, by interrupting a stereotyped MU recruitment or whether the muscle contraction *per se* has a positive effect on thresholds for nociceptors or for central pain perception, possibly mediated by myogenic activity, blood borne stem cells, cytokines, or the like. Interventions representing different modes of exercise training systematically should be

explored because they show a range of effects in enhancing health and in preventing or relieving pain.

The effect of IPET depends crucially on the workers' compliance in the program. Therefore, it is important to explore and document optimal motivational factors that may commit both employer and employees to the IPET program in the long term. Future interdisciplinary intervention studies should investigate how to integrate organizational and motivational aspects into a workplace environment to boost training compliance. IPET may be delivered with a variety of modes of exercises aiming at progress and variation in the training exercise sessions. The vision is to create activities that are in themselves fun, motivating, include individual preferences, promote wellness, and as a side effect are also health enhancing. If, apart from its health benefits, IPET is enjoyable for the employees, this may facilitate lifelong maintenance. This calls for a highly participatory approach that brings into play individual preferences, barriers, and current levels of PA. We need evidence for efficient ways to integrate these aspects into the future development of the IPET concept.

Research is required providing clear evidence of the benefits for the company. It is imperative to promote the implementation of IPET in the workplace and to encourage companies to acknowledge the financial incentives in allowing time and space for IPET. Cost-benefit analysis should go beyond sickness absence and include work ability and productivity in terms of both quantity and quality with a focus on the broader outcomes for the workplace. As evidence emerges in existing and future RCT studies on the positive effects of IPET, we need to shift the research focus toward improved implementation, involving both the motivational factors, the economical consequences for the workplace, and the benefits for public health.

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