

Exercise and Sleep in Community-Dwelling Older Adults

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Abstract Insomnia and other sleep complaints are highly prevalent in community-dwelling older adults yet often go under detected. Age-related physiological changes may affect sleep, but sleep disturbances and complaints should not be considered normal in this population. Various physiological, psychological, and social consequences have been associated with insomnia and sleep complaints. Treatment options are available so it is imperative to diagnose and treat these individuals to promote healthy aging. Exercise is known to have a wide variety of health benefits, but unfortunately most older adults engage in less exercise with advancing age. This paper describes age-related changes in sleep, clinical correlates of insomnia, consequences of untreated insomnia, and nonpharmacological treatments for insomnia in older adults, with a focus on the relationship between exercise and sleep in community-dwelling older adults with insomnia or sleep complaints. Possible mechanisms explaining the relationship between exercise and sleep are discussed. While the research to date shows promising evidence for exercise as a safe and effective treatment for insomnia and sleep complaints in community-dwelling older adults, future

research is needed before exercise can be a first-line treatment for insomnia and sleep complaints in this population.

Keywords Insomnia · Sleep disturbances · Older adults · Exercise

Introduction

Sleep disturbances are highly prevalent in older adults, with insomnia being the most common sleep disorder [1]. Insomnia is defined as “a chronic or acute sleep disorder characterized by a complaint of difficulty initiating, and/or maintaining sleep, and/or a subjective complaint of poor sleep quality that result in daytime impairment and subjective report of impairment” [2]. Exercise is thought to be a safe, efficacious, and cost-saving intervention to promote health and quality of life [3] and has been used in many studies as an intervention to improve insomnia or sleep complaints in community-dwelling older adults [4, 5, 6–8] and to improve sleep quality in community-dwelling sedentary older adults [9, 10, 11]. This review briefly describes the prevalence of insomnia, age-related changes in sleep architecture, consequences of untreated insomnia, as well as nonpharmacological treatments for insomnia in older adults and then focuses on synthesizing the association between exercise and insomnia or sleep complaints in community-dwelling older adults by reviewing recent literature (2008–2015) and exploring mechanisms by which exercise can improve sleep.

Prevalence of Insomnia

The prevalence of insomnia increases with age and varies depending on how it is defined, the rate of incidence,

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remission, and relapse. Epidemiological studies have reported a prevalence of 20–40 % for nighttime insomnia complaints and 10–20 % when daytime symptoms of fatigue or impaired concentration were included in the criteria for insomnia [12]. When more stringent diagnostic nosologies are applied, the prevalence decreased to about 2–5 % [13]. The incidence rate for insomnia symptoms ranged from 5 to 7.97 % per year in two studies of older adults [14, 15]. About 50 % of people with insomnia symptoms will go into remission in a 1-year follow-up [15, 16]. Unfortunately, less than 15 % of patients with insomnia receive treatment or consult a healthcare provider [17].

Age-Related Changes in Sleep

It is widely known that there are many measurable physiological age-related changes that affect sleep due to changes in sleep homeostasis and the circadian pacemaker, the suprachiasmatic nucleus (SCN), that influences circadian phase [1]. The degeneration of the SCN results in weaker and more disrupted circadian rhythms. Older adults also go to bed earlier and wake up earlier in relation to their endogenous melatonin secretion. Taken together, these findings suggest that aging is associated not only with phase advance of sleep and circadian rhythms but also with a decreased melatonin output [18].

Elements of sleep architecture change with age. Compared to people with a younger age, older adults are susceptible to decreased total sleep time, early morning awakenings, sleep fragmentation, and less proportion of slow wave sleep (SWS) [1]. In addition to the physiologic age-related changes in sleep architecture, sleep disturbances are much more common among people with poor health.

Another interesting aspect of sleep in older adults is the decoupling of objective changes in sleep and subjective perception of sleep; physiologic changes that occur with aging alone may not be responsible for poor sleep [19•, 20•, 21•]. In a cross-sectional analysis of 2006 the US Behaviors Risk Factor Surveillance System, investigators found that advancing age was not associated with increase in self-reported sleep disturbance, tiredness, or lack of energy, suggesting sleep problems in the elderly population are mediated by factors other than physiologic aging alone [20•]. Although the previous study could be subject to cross-sectional biases, results from a longitudinal study also suggest sleep disturbances in older adults are more dependent on physical, environmental, and comorbid health factors rather than on age-dependent sleep changes [21•]. Stranges and colleagues suggest sleep issues are strongly linked to poorer well-being and quality of life, as well as psychiatric comorbidities [19•]. As coexisting illnesses may cause or be exacerbated by sleep problems, it is evident that sleep disorders are a pressing issue in the older

adult. Normal physiological changes of aging may have an impact on sleep quality, but sleep problems should not be referred to as an expected change of aging.

Consequences of Untreated Insomnia

There are major consequences of untreated insomnia. Chronic or acute insomnia symptoms can lead to fatigue and daytime sleepiness; mood disturbances such as irritability, lethargy, anger, depression, and anxiety; somatic complaints such as joint pain, headaches, and muscle aches; impaired concentration and cognitive performance; decreased perception of quality of life; increased risk of cardiac, metabolic, and immune system problems; increased risk of psychiatric problems; and increased risk of accidents [22, 23]. Evidence from several studies supports an increased risk of depression in older adults with insomnia [24–29], with one study reporting that having insomnia symptoms was associated with a 23 % increased risk of developing depressive symptoms [24]. Insomnia in older adults has been shown to be associated with falls, mood and anxiety disorders, and cognitive impairments [4]. The risk ratio of developing heart disease from insomnia symptoms ranged from 1.47 to 3.90 in one meta-analysis, after controlling for age and cardiovascular risk factors [30]. Recent research also suggests that insomnia symptoms may lead to increase rates of prostate cancer [31]. Sleep quality can impact psychological and social parameters in older adults and inefficient sleep has been shown to predict physical decline in subjects over 75 [32].

Insomnia is associated with high levels of healthcare utilization and increased direct and indirect healthcare costs. Ozminkowski et al. (2007) estimated that over a 6-month period for US adults with insomnia, direct and indirect costs combined were \$1253.00 higher per person compared to matched controls. The cumulative costs of insomnia in Quebec, Canada, were estimated by Morin and colleagues to exceed six billions dollars annually in a population of around eight million people [33].

Nonpharmacological Treatment

There are various nonpharmacological treatment options such as improving sleep hygiene, stimulus control therapy, sleep restriction, relaxation training, and cognitive behavioral therapy for insomnia (CBT-I) and other sleep disturbances in older adults [34]. Sleep hygiene and CBT-I are the most commonly used approaches to treat insomnia, where CBT-I is usually initiated if addressing sleep hygiene alone is not effective. Sleep hygiene involves several interventions that promote a routine and stable sleep pattern in a nondisruptive environment. CBT-I consists of six to ten sessions with a therapist

that focus on maladaptive behaviors and cognitive beliefs that may perpetuate insomnia. There is limited evidence to suggest the effectiveness of sleep hygiene as a monotherapy [35]; however, the efficacy of CBT-I for older adults has been shown in many studies [36–38]. One randomized controlled trial showed improvements in global Pittsburgh Sleep Quality Index (PSQI) scores and PSQI sleep-efficiency sub-score in older adults randomized to a self-help and CBT-I treatment group compared to controls [39]. One meta-analysis reported no significant improvements in objective total sleep time (TST) after CBT-I immediately following treatment or at follow-up but significant improvements in subjective TST, suggesting that CBT-I may be effective at improving subjective sleep misperceptions without changing actual sleep length [40].

Exercise and Sleep

Participation in moderate exercise is known to reduce premature mortality and to protect against some influences of unhealthy lifestyles [41]. According to the Physical Activity Guidelines Advisor Committee in 2008, only about 10 % of the older adult population over the age of 65 meet the national physical activity guidelines needed to receive health benefits from exercise [11•]. Due to the health benefits associated with exercise, it is important to determine if older adults are able to participate in various physical activities. In this section, we aim to explore recent literature for the potential for exercise to serve as a nonpharmacological treatment for insomnia or sleep complaints in community-dwelling older adults. We will discuss the following: (1) What are plausible mechanisms for which exercise can improve sleep? (2) What types of exercise interventions have been used to improve sleep in older adults, and (3) Does exercise improve symptoms of insomnia and/or sleep quality in older adults?

Mechanisms Explaining Relationship Between Exercise and Sleep

Various mechanisms describing the relationship between exercise and sleep have been presented in the literature. Thermoregulation is one theory proposed to explain the relationship between exercise and sleep. It is postulated that increasing body temperature can activate heat loss and the associated sleep mechanisms [42]. Sleep onset is triggered by decline in body temperature which is mediated by increased blood flow to skin. Exercising causes an increase in core body temperature which can then facilitate the initiation of sleep due to the activation of heat dissipation mechanisms controlled by the hypothalamus [43]. Glotzbach and Heller argue that insomnia involves impairment in nocturnal temperature downregulation [43]. More experimental studies are needed that explore the

interactions among sleep, temperature, and exercise in elderly insomniacs.

Anxiety is thought to be a key player in insomnia. Therefore, another plausible mechanism by which exercise can improve insomnia symptoms is through the anxiolytic effects of exercise [44]. However, in a recent study with adult chronic insomniacs, presleep anxiety decreased after acute aerobic exercise but no correlation was observed between the reduction in anxiety and improvement in sleep [45].

The antidepressant effects of exercise may also play a role in the relationship between exercise and sleep. Multiple studies [4, 45, 46] have shown positive effects of aerobic exercise on sleep quality and correlations between reduction in depressive symptoms and improvement in sleep quality. A more recent study [47] described depression as a mediator/moderator of sleep improvement in adults and older adults [43]. The role of serotonin in insomnia is still controversial. It is thought that chronic insomnia may be associated with low serotonin levels, and rat studies suggest that exercise promotes feedback regulatory mechanisms that may increase serotonin [43].

A common belief is that sleep loss (accompanying insomnia) may increase vulnerability to disease and that one function of sleep is to promote illness recovery. Furthermore, exercise training has been shown to improve immune function. Therefore, another probable link between exercise and sleep is immunologic alterations [43]. A recent study of healthy older adult men found statistically significant decreases in time awake, rapid eye movement (REM) latency, interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), and the ratio of TNF- α /interleukin-10 (IL-10) and increases in IL-10 levels and self-reported quality of life following a 6-month moderate aerobic exercise training program [48•]. The data suggest that a 6-month exercise training program can improve sleep in healthy older adults via modification of cytokine profiles [48•]. Further research is warranted to determine if the cytokine profiles change in a similar manner in older adults with sleep disturbances.

Other mechanisms through which exercise may improve sleep are body restoration and energy conservation. Investigators suggest that high catabolic activity during wake (increased during exercise) will be favored by anabolic activity during sleep [42]. Additionally, greater energy expenditure during the day is thought to require greater rest in the evening. Youngstedt and colleagues report that exercise can affect sleep through its circadian shifting effects and increased adenosine [42]. It is widely known that circadian desynchronization can disrupt sleep. Approximately one third of older adults are in a chronic state of malsynchronization, and evidence suggests that exercise can elicit circadian phase shifting effects that are comparable to bright light [49]. Acute exercise can deplete peripheral glycogen stores, and it is claimed that adenosine release is provoked by depletion of central glycogen stores. Adenosine release is associated with sleep, so the thought here is that increasing adenosine release will promote sleep [49].

It is clear that various mechanisms describing the relationship between exercise and sleep have been explored. Further research into this relationship and the roles of thermoregulation, anxiolytic and antidepressant, body restoration, levels of serotonin and adenosine, as well as circadian shifting potentials of exercise is critical.

Types of Exercise

Various studies have utilized subjective and objective measures of sleep to determine efficacy of exercise interventions on community-dwelling older adults with sleep complaints or diagnosed insomnia. Five randomized controlled trials (RCTs) [4, 6, 8, 9, 10•] and three secondary data analyses [5•, 7, 11•] were included in this review (Table 1). Four studies involved moderate intensity aerobic and endurance exercise interventions [4, 5•, 6, 7]; three studies examined low-impact exercise interventions such as tai chi and yoga that involved mindful meditation and slow relaxing movements [9, 10•]; and one study examined leisure activity as exercise [11•].

Association Between Exercise and Sleep

Both short- and long-term experimental studies utilizing low-impact meditation and relaxation, aerobic, and leisure exercises have shown positive effects of exercise on subjective sleep quality in mild to moderately sleep-impaired older adults. The bidirectional relationship between sleep and exercise and also the intra-individual variability of sleep within one subject have been explored [37].

Positive outcomes of these studies are decreased stage 1 sleep, increase in stage 2 sleep, less wake after sleep onset (WASO), decreased sleep onset latency (SOL), increase in global PSQI sub-scores, improvement in intra-individual variability (IIV) SOL, and increase in sleep quality ratings, indicating that exercise may be beneficial in improving both objective sleep architecture as well as subjective sleep quality. In addition, there were improvements on subscales of the PSQI, such as sleep duration and sleep efficiency among the studies.

In details, one RCT study with moderate intensity exercise found decreased time spent in stage one sleep, increased time spent in stage two, and less awakenings measured by polysomnography following a 12-month program of moderate-intensity endurance training, compared to a control group who received health education only [6]. Seven of the eight studies found improvements in global PSQI scores and sleep onset latency in the exercise groups [4, 5•, 6, 8, 10•, 50], and one study found intra-individual variability improvements in time to fall asleep [7]. Another study reported a within-person association between exercise and general sleep quality rating (SQR) measured on a Likert scale [11•]. Sleep duration, total sleep time (TST), and sleep efficiency (SE) showed significant improvements following the exercise intervention in

four studies [4, 5•, 8, 10•]. One study looked into the bidirectional relationship between insomnia and exercise and reported that sleepiness negatively affected exercise duration and that TST moderated the daily relationship between TST and next-day exercise [5•]. Another study reported that age, WASO, and SQR were predictors of physical activity and that the location of the activity did not affect SOL, WASO, or SQR [11•].

One systematic literature review with meta-analysis [50] examining six trials sought to answer a similar question: Does an exercise training program improve sleep quality in middle-aged and older adults with sleep problems? There was a significant reduction in medication use and global PSQI scores in the exercise groups, but there were no statistical significant differences in sleep duration, efficiency, sleep disturbance, or daytime functioning [50]. One possible reason for the discrepancy between our results and the meta-analysis is that two studies were primarily comprised of middle-aged subjects, and one study did not enroll based on sleep disturbances. The other three studies in the meta-analysis were included in the present review.

In addition to the aforementioned studies conducted in community-dwelling older adults, Richards and colleagues conducted a series of studies to improve sleep in long-term care residents. Exercise, specifically strength training and walking, in combination with individualized social activities resulted in increased total nocturnal sleep in the long-term care residents [51, 52].

Implications and Future Directions

Exercise is not only a way to improve sleep but also a potential way to promote healthy aging. The studies evaluated in this paper show promising results for the use of exercise to improve sleep in older adults with insomnia and sleep complaints. Daytime sleepiness in older adults was associated with physical functional impairments and decreased exercise frequency [53]. Excessive daytime sleep and sleepiness are typical sedentary behaviors in older adults and have been linked to multiple adverse health outcomes, including disrupted nocturnal sleep, cardiovascular disease, type 2 diabetes mellitus, obesity, and mental disorders, musculoskeletal diseases, and neurodegenerative diseases [54–56]. Furthermore, sleep fragmentation has been showed to be associated with poorer physical function [57]. Promoting exercise may be an effective approach for older adults to improve sleep continuity, reduce daytime sedentary behaviors, enhance homeostatic and circadian processes of sleep, and improve other aspects of health.

Exercise and sleep can be mutually beneficial. A better night sleep may increase older adults' capacity to exercise, such as increasing motivation, duration, and frequency of exercise, and participating in physical activity may promote a better night sleep. In a large population-based study of older

Table 1 Description of studies included in this review

First author, year	Purpose	Study design	Sample/setting	Relevant data collected	Major findings	Authors' conclusion
King et al., 2008	To determine the 12-month effects of exercise on objective and subjective sleep quality in inactive older adults with mild to moderate sleep complaints	RCT assigned to a 12-month program of moderate-intensity endurance exercise or a health education control	Age 55 or older ($n=66$) Exercise ($n=36$) Mean age 61.86 ± 6.33 66.7 % female Control ($n=30$) Mean age 6.9 ± 7.19 66.7 % female	PSG, subjective measures of sleep quality, physical activity, and physical fitness	Exercisers spent less PSG time in stage 1 sleep ($p=0.03$), more time in stage 2 sleep ($p=0.04$), and had fewer awakenings during the first third of the sleep period ($p=0.03$) Reported improvements in PSQI sleep disturbance subscale ($p=0.009$), sleep diary-based minutes to fall asleep ($p=0.01$), and more rested in the morning ($p=0.02$) compared to controls	Improved some objective and subjective dimensions of sleep to modest degree Area understudied
Chen et al., 2008	To test the effects of 6 months of silver yoga exercises in promoting the mental health of older adults, especially their sleep quality, depression, and self-perception of health status	RCT assigned to a 6-month program of yoga three times per week or control group	Aged 60 or older ($n=128$) Mean age 69.20 ± 6.23 72.7 % female	PSQI	Significant improvements in PSQI global score in the yoga intervention group at 3 months ($p=0.003$) and 6 months ($p<0.001$) SOL did not improve after 3 months of the yoga training program ($p=0.717$) but did decrease after 6 months ($p<0.001$)	Improvements in sleep quality were seen in the yoga intervention group
Irwin et al., 2008	To determine the efficacy Tai Chi Chih to promote sleep quality in older adults with moderate sleep complaints	RCT assigned to 16 weeks of teaching followed by practice and assessment 9 weeks later (25 weeks total) or health education control	Age 55 and older ($n=112$) Mean age 69.9 ± 6.8 63.4 % female	PSQI	Baseline poor sleep quality (PSQI ≥ 5) improved in 63 % of intervention vs 32 % in control group (PSQI global score of <5 after 25 weeks ($p<0.05$)) Baseline poor sleep quality showed significant improvements in PSQI global score ($p<0.001$), and subscores, sleep quality, sleep efficiency, sleep duration, and sleep disturbance (all $p<0.05$)	Tai Chi Chih, slow-moving meditation, can be considered a useful nonpharmacologic approach to improve sleep quality in older adults with moderate complaints
Reid et al., 2010	To assess the efficacy of moderate aerobic physical activity with sleep hygiene education to improve sleep, mood, and	RCT comparing 16 weeks of aerobic physical activity plus sleep hygiene to nonphysical activity	Age 55 and older ($n=17$) Mean age 61.6 ± 4.3 94 % female	PSQI ESS CES-D SF-36	Physical activity group improved in sleep quality (global PSQI $p<0.0001$), sleep latency ($p=0.049$), sleep duration ($p=0.04$)	Aerobic physical activity and sleep hygiene education are effective to improve sleep quality, mood, and

Table 1 (continued)

First author, year	Purpose	Study design	Sample/setting	Relevant data collected	Major findings	Authors' conclusion
Buman et al., 2011	and quality of life in older adults with chronic insomnia	plus sleep hygiene control			daytime dysfunction ($p=0.027$), and sleep efficiency ($p=0.036$) on the PSQI subscales compared to controls Reductions in depressive symptoms ($p=0.044$), daytime sleepiness (0.02), and improvements in vitality ($p=0.017$) compared to baseline	quality of life in this population
	To determine whether physical exercise reduces intra-individual variability (IIV) in self-rated sleep outcomes among middle-aged and older adults with sleep complaints	Secondary analysis of RCT (12-month program of moderate-intensity endurance exercise or a health education control)	55 and older ($n=66$) Mean age 61.42 ± 6.72 67 % women	Daily sleep logs, PSQI, in-home PSG; IIV for SOL, time in bed, feeling rested in the morning, number of nighttime awakenings, wake after final awakening	SOL-based IIV was reduced in exercise group ($p=0.025$) IIV for time in bed, rested in the morning, WAFAs were not significantly different in either group	12 months of moderate-intensity exercise reduced night-to-night fluctuations in self-rated time to fall to sleep
Chen et al., 2012	To explore the effectiveness of a Baduanjin exercise program on sleep quality in Taiwanese elderly	RCT assigned to 12 weeks of Baduanjin exercise training or control group	60 and older ($n=55$) Mean age 71.75 ± 8.13 65.45 % female	PSQI Geriatric Depression Scale	Mean scores of sleep quality significantly improved in the exercise group over the control group in overall sleep quality ($p<0.001$) and in all subscales ($p=0.024$ to $p<0.001$)	Baduanjin, traditional Chinese exercise characterized by simple, slow, relaxing movement improved sleep quality in Taiwanese community-dwelling older adults
Baron et al., 2013	To evaluate the daily bidirectional relationships between exercise and sleep	Secondary data analysis; 16 weeks of aerobic exercise 30 min 3×/week	Females with insomnia ($n=11$) Mean age 61.2 ± 4.15	PSQI Sleep logs Actigraphy Exercise logs	TST, SE, and global PSQI improved ($p<0.05$); baseline sleepiness was negatively associated with exercise duration ($p<0.05$) Participants had shorter exercise duration following nights of longer SOL ($p<0.05$) TST moderated the daily relationship between TST and next-day exercise ($p<0.05$)	Sleep influences next-day exercise rather than exercise influencing sleep
Dzierzewski et al., 2014	To examine the chronic and acute relationships between exercise behavior and self-reported sleep in older adults	Secondary data analysis of clinical trial of lifestyle intervention; Assessments collected weekly at 18 weeks	Community-dwelling older adults ($n=79$) Mean age 63.58 ± 8.66 83.5 % female	Modified Leisure-Time Exercise Questionnaire (LTEQ) Self-reported SOL, WASO	Small positive between-person association between exercise and WASO, and within-person association between exercise and general sleep quality	More chronic levels of exercise were associated with lower self-reported WASO Increased prior day exercise was associated with high

Table 1 (continued)

First author, year	Purpose	Study design	Sample/setting	Relevant data collected	Major findings	Authors' conclusion
				Sleep quality rating (SQR) on a five-point scale	Education ($p=0.02$) between person predictor of SOL; age and physical activity ($p=0.03$, $p=0.01$) between person predictors of WASO; physical activity within person ($p=0.05$) predictor of SQR Age and WASO ($p=0.05$ and 0.008) between person predictors of physical activity; SQR ($p=0.001$) predictor of physical activity	subsequent nights of self-reported sleep quality Acute exercise-SQR relationship was reciprocal in nature Location in which the exercise was conducted did not impact the relationship between exercise and sleep

RCT randomized controlled trial, *PSQI*/Pittsburgh Sleep Quality Index, *ESS* Epworth Sleepiness Scale, *PSG* polysomnography, *CES-D* Center For Epidemiological Studies Depression Scale, *SF-36* Short Form 36, *SOL* sleep onset latency, *WAF4* wake after final awakening, *WASO* wake after sleep onset, *SMD* standard mean difference, *TST* total sleep time, *SE* sleep efficiency, *F1* fragmentation index, *SQR* sleep quality rating

adults in Japan, habitual physical activity was related to both a lower prevalence and incidence of insomnia, especially the symptom of difficulty in maintaining sleep [58•]. However, both physical exercise and sleep decline with age. Intervening on either the sleep or exercise component may improve overall health and quality of life in older adults.

Taking into account the results presented on both outcomes of these studies and also possible mechanisms to explain the relationship between sleep and exercise, certain questions arise. First, does the exercise need to be intense aerobic physical activity or is increasing leisure activity enough to improve the sleep quality of older adults in the community? Are there specific exercises that may be safe and effective to improve sleep in older adults with multiple chronic conditions? Could exercise be used as an adjunct to other therapies such as CBT-I? Does the quantity and quality of exercise (aerobic exercise, strength training/endurance, yoga/stretching, etc.), time of day (morning, evening, night), location (light exposure or not) confound, mediate, or moderate the relationship between exercise and sleep in older adults with insomnia? Does exercise decrease daytime sleep and improve nighttime sleep continuity? Does routine exercise lead to sustained benefits? Comparative effectiveness studies examining different types of exercise interventions in older adults with sleep complaints are warranted, as the studies in this review all compared an exercise intervention to a control group. In addition, further research is warranted to explore causal, directional, and mechanistic pathways between exercise and sleep.

Conclusion

Insomnia and sleep complaints are public health burdens that affect occupation, physical, and social performance. Treating insomnia and sleep complaints in older adults with multiple chronic conditions and various functional status and impairments is complex. Exercise is one potential safe and effective way to manage insomnia symptoms in community-dwelling older adults, but further research is needed. Future research should employ comparative effectiveness techniques to determine what treatment is the most effective, safe, and cost-effective.

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Compliance with Ethical Standards

Conflict of Interest Miranda Varrasse, Junxin Li, and Nalaka Gooneratne declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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