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Yoga and immune system functioning: a systematic review of randomized controlled trials

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Abstract Yoga is an ancient mind–body practice that is increasingly recognized to have health benefits in a variety of clinical and non-clinical conditions. This systematic review summarizes the findings of randomized controlled trials examining the effects of yoga on immune system functioning which is imperative to justify its application in the clinic. Fifteen RCTs were eligible for the review. Even though the existing evidence is not entirely consistent, a general pattern emerged suggesting that yoga can down-regulate pro-inflammatory markers. In particular, the qualitative evaluation of RCTs revealed decreases in IL-1beta, as well as indications for reductions in IL-6 and TNF-alpha. These results imply that yoga may be implemented as a complementary intervention for populations at risk or already suffering from diseases with an inflammatory component. Beyond this, yoga practice may exert further beneficial effects by enhancing cell-mediated and mucosal immunity. It is hypothesized that longer time spans of yoga practice are required to achieve consistent effects especially on circulating inflammatory markers. Overall, this field of investigation is still young, hence the current body of evidence is small and for most immune parameters, more research is required to draw distinct conclusions.

Keywords Yoga · Immune · Inflammation · Systematic review · Randomized controlled trials · Mind–body-therapy

Introduction

Yoga is an integrated mind–body practice, originating about 5000 years BC in ancient India. Since then, it has been employed to promote health and well-being across various conditions. The word ‘yoga’ is derived from Sanskrit and may be translated as ‘union’ or ‘conjunction’ (Feuerstein, 2011), entailing the idea of uniting body, mind, and spirit (Feuerstein, 2011). Though yoga is in the western world predominantly used as a recreational practice, it is increasingly gaining attention as a clinical intervention. In fact, yoga did not primarily evolve as a system of physical exercises, but also as a healing system (Desikachar et al., 2005). This healing system is based on the assumptions that a human being is a unique, holistic, and interconnected entity; that yoga can empower a person to become active in his or her own healing; and that a person’s state of mind is central to this healing process (Desikachar et al., 2005).

This ancient idea that the mind and physiological processes, including both healing and disease, are centrally intertwined has nowadays become scientifically substantiated. It is broadly accepted that psychological stress or

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other adverse mental conditions can impact on several physiological systems, amongst these also the immune system (Irwin, 2008). Both acute and chronic stressors can, mediated through effector pathways such as the sympathetic nervous system and the HPA-axis, entail a dysregulation of different immune parameters such as inflammatory pathways and thereby lead to disease (Irwin, 2008; Purdy, 2013; Steptoe et al., 2007). In turn, so-called mind–body therapies (MBTs), which aim at inducing relaxation and reducing stress, can through the selfsame effector pathways exert beneficial effects on the immune system and thus potentially prevent or alleviate a variety of diseases (Morgan et al., 2014; Purdy, 2013). Although its exact mechanisms of action are not yet entirely clarified, yoga is, similar to other MBTs, supposed to modulate the central stress response and to regulate autonomic balance (Riley & Park, 2015). Thereby it may equally impact immune functioning in beneficial ways (Purdy, 2013). This might, for example, entail a modulation of a chronic inflammatory state or a bolstering of impaired immune function in conditions such as HIV infection or situations of acute life stress. In fact, yoga is already employed as a complementary intervention in a variety of clinical conditions, yet its potential benefits often still lack rigorous empirical verification (Bayley-Veloso & Salmon, 2016).

In the last years, concurrent with an expansion of research on MBTs in general, empirical research on the effects of yoga on immune functioning has been increasing. To our knowledge, no study has however systematically reviewed existing randomized controlled trials (RCTs) that investigated the effects of yoga on the immune system. Narrative reviews and meta-analyses that have been conducted in this field have summarized the effects of different MBTs on immune functioning (Bower & Irwin, 2016; Morgan et al., 2014) and the impacts of yoga on various aspects of health (Field, 2011, 2016). Presenting a comprehensive picture of the existing evidence regarding the effects of yoga on immune functioning is essential to make justified recommendations for future research in this field as well as concerning evidence-based applications of yoga as a clinical intervention.

Methods

A systematic review of RCTs examining the effects of yoga on immune system functioning was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for conducting systematic reviews (Moher et al., 2009). The review was registered in the international prospective register of systematic reviews PROSPERO (CRD42017071064).

Search process

An electronic search was performed in the Pubmed, Web of Science, and PsycINFO databases. Used keywords were 'yoga' in combination with 'immune system', 'immune function', 'cytokines', 'inflammation', 'telomeres', and 'infection', as well as the wildcard 'immun*'. The search was limited to articles being published after the year 1970 in English. In the PsychINFO database which also includes books, these were excluded from the search a priori. No further limitations were set to the search. The literature search was conducted in duplicate form by the second and first author on June 10th 2017 and June 11th 2017, respectively.

Inclusion criteria

Eligible studies were RCTs published in full text form employing a yoga intervention and investigating its effects on at least one immunological parameter. For inclusion, studies were required to administer a yoga intervention primarily based on yoga postures (asanas), while no specific limitations were set regarding yoga style, length of individual sessions, overall duration, and frequency of the intervention. Studies that merely administered related or derived practices such as yogic meditation and yogic breathing were excluded. Studies that combined yoga with another main intervention were excluded as well, as their intervention effects cannot be specifically attributed to yoga. No limitation was set with regard to study participants, as the effects of yoga on the immune system can be studied across a range of clinical and non-clinical conditions. The immune outcomes that were focused on in this review included different cytokines and other circulating inflammatory markers such as CRP and endothelial microparticles, as well as immune cell counts, antibody responses, and markers of gene expression in immune cells. In order to limit the focus of the review, adipocytokines and markers of oxidative stress were not considered as outcome parameters.

Study selection

In order to identify eligible publication, the titles and abstracts of the publications resulting from the search were screened individually by the first and second author, applying the aforementioned inclusion criteria. Discrepancies were discussed until consensus was reached, and papers meeting the inclusion criteria were retrieved and analyzed in full text.

Data extraction and synthesis

The first and second author individually conducted the data extraction. An extraction sheet was developed to compile the following data items from eligible publications: sample size and characteristics; employed yoga intervention, including yoga style, length of individual sessions, frequency, and duration of the intervention; type of control condition; type and timing of outcome assessment; and reported immune-outcomes. A descriptive synthesis of results was conducted for each immune parameter.

Beyond this, in order to estimate the magnitude of effects observed in the evaluated studies, effect size calculations were performed. Were no effect sizes were reported, the standardized mean-difference Cohen's d was calculated which is the most widely employed measure for the assessment of magnitudes of effects (McGough & Faraone, 2009). To calculate Cohen's d from pre- and post-intervention means and the respective standard deviations (SD), a web-based effect size calculator was used (http://cebcp.org/practical-meta-analysis-effect-size-calculator/) which employs the formula given by Lipsey and Wilson (2015). When studies gave medians and interquartile range or minimum and maximum values, means and SD were estimated from these values and the sample size, as described by Wan et al. (2014). One study reported effect sizes in terms of Spearman rank-order correlation (r). When data was not sufficiently reported to conduct the calculations, the authors of the respective studies were contacted. Effect size calculations were performed individually by the first and third author and in case of discrepancies a third round of calculations was run. As recommended by Cohen (1992), effect sizes of 0.2 were considered as small, 0.5 as medium, and 0.8 as large. For r a value of 0.1 was considered small, 0.3 as medium, and 0.5 as large (Cohen, 1992).

Risk of bias assessment in individual studies

Risk of bias assessment was performed individually by the first and second author, based on the Cochrane Collaboration's tool for assessing risk of bias in randomised trials (Higgins, 2008; Higgins et al., 2011). Accordingly, the risk of bias assessment conducted for this review included the following domains: selection bias (random sequence generation, allocation concealment), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other bias. An assessment of performance bias was not applicable to this review, as the nature of the intervention does not allow blinding of participants and personnel. All domains were scored as a) low risk of bias, b) unclear, or c) high risk of bias. Discrepancies were discussed and in case of disagreement the third author was consulted to reach consensus. As suggested by the Cochrane Collaboration, risk of bias was summarized for each study as a) low if risk of bias was low for all assessed domains, b) unclear if risk of bias was unclear for one or more of the assessed domains, c) high if there was a high risk of bias for one or more of the assessed domains (Higgins, 2008).

Results

Literature search

As depicted in Fig. 1, the search in the three databases yielded 521 results of which 225 titles remained after removal of duplicates. Of these, 205 publications were excluded because they did not meet the inclusion criteria while 20 full text articles were read. Five papers were excluded after full-text examination for different reasons: In two papers it was unclear whether the administered yoga intervention included asanas (Rao et al., 2008a, b), two papers appeared to report on the same data as another, already included publication (Pullen et al., 2008; Pullen, 2009), and another paper reported on a non-RCT study (Qu et al., 2013). Finally, 15 papers were eligible and included in the review. The eligible studies, their characteristics and immune-related findings with effect sizes in brackets behind the respective outcome are shown in Table 1.

Characteristics of the included studies

Sample size and characteristics

The sample sizes of the studies varied widely, ranging from one study examining only eleven persons in one group (Harkess et al., 2016) to sample sizes of $n = 121$ per condition (Agnihotri et al., 2014). The mean sample size of the examined studies was $n = 70$ and the average number of participants per condition was $n = 34$. In total, 1053 participants were included in the qualitative synthesis of this review.

The studies' samples included a variety of clinical and non-clinical populations (see Table 1). Eight studies included clinical populations, i.e. breast cancer patients (Bower et al., 2014; Kiecolt-Glaser et al., 2014; Long Parma et al., 2015), patients with HIV infection (Cade et al., 2010; Naoroibam et al., 2016), heart failure (Pullen et al., 2010), asthma (Agnihotri et al., 2014), and inflammatory bowel disease (IBD) (Sharma et al., 2015). Five studies investigated healthy subjects, including young adolescents (Chen et al., 2016; Gopal et al., 2011; Lim & Cheong, 2015), older adults (Vogler et al., 2011), and women at 16 weeks gestation (Chen et al., 2017). Two

RCTs studied participants at risk of increased inflammation, one of these examined industrial workers (Rajbhoj et al., 2015) and the other middle-aged men and women experiencing psychological distress (Harkess et al., 2016).

Women were generally overrepresented in the samples of the reviewed studies. Seven of the included studies investigated samples consisting of 100% women (Bower et al., 2014; Chen et al., 2016, 2017; Gopal et al., 2011; Harkess et al., 2016; Kiecolt-Glaser et al., 2014; Long Parma et al., 2015), while only one study examined exclusively men (Rajbhoj et al., 2015).

Intervention and control characteristics

The length of individual sessions, the frequency, and the overall duration of the yoga interventions employed in the included studies were relatively heterogeneous. The individual sessions of the yoga interventions varied in length from 30 min (Agnihotri et al., 2014) to 90 min (e.g. Bower et al., 2014). The frequency of yoga sessions ranged from once a week (Lim & Cheong, 2015) to daily practice (Gopal et al., 2011). The overall duration of the yoga interventions varied from 1 month (Naoroibam et al., 2016) to 6 months (Agnihotri et al., 2014; Long Parma et al., 2015), while most studies employed yoga programs of 8–12 weeks duration. Some studies recommended home practice in addition to guided yoga sessions (e.g. Lim & Cheong, 2015; Vogler et al., 2011) or included a given time of monitored home practice after a shorter period of daily guided interventions (Sharma et al., 2015).

Seven RCTs specified the type of yoga that was administered (Bower et al., 2014; Cade et al., 2010; Chen et al., 2016; Kiecolt-Glaser et al., 2014; Long Parma et al., 2015; Pullen et al., 2010; Vogler et al., 2011). All of these studies employed a Hatha yoga program. Two studies further specified the style, indicating Ashtanga Vinyasa yoga (Cade et al., 2010) or Iyengar yoga (Vogler et al., 2011) which are subtypes of Hatha yoga. Eight studies gave a detailed description of the yogic techniques included in the intervention, thus providing, for example, tables listing each asana or other exercise (Agnihotri et al., 2014; Bower et al., 2014; Kiecolt-Glaser et al., 2014; Lim

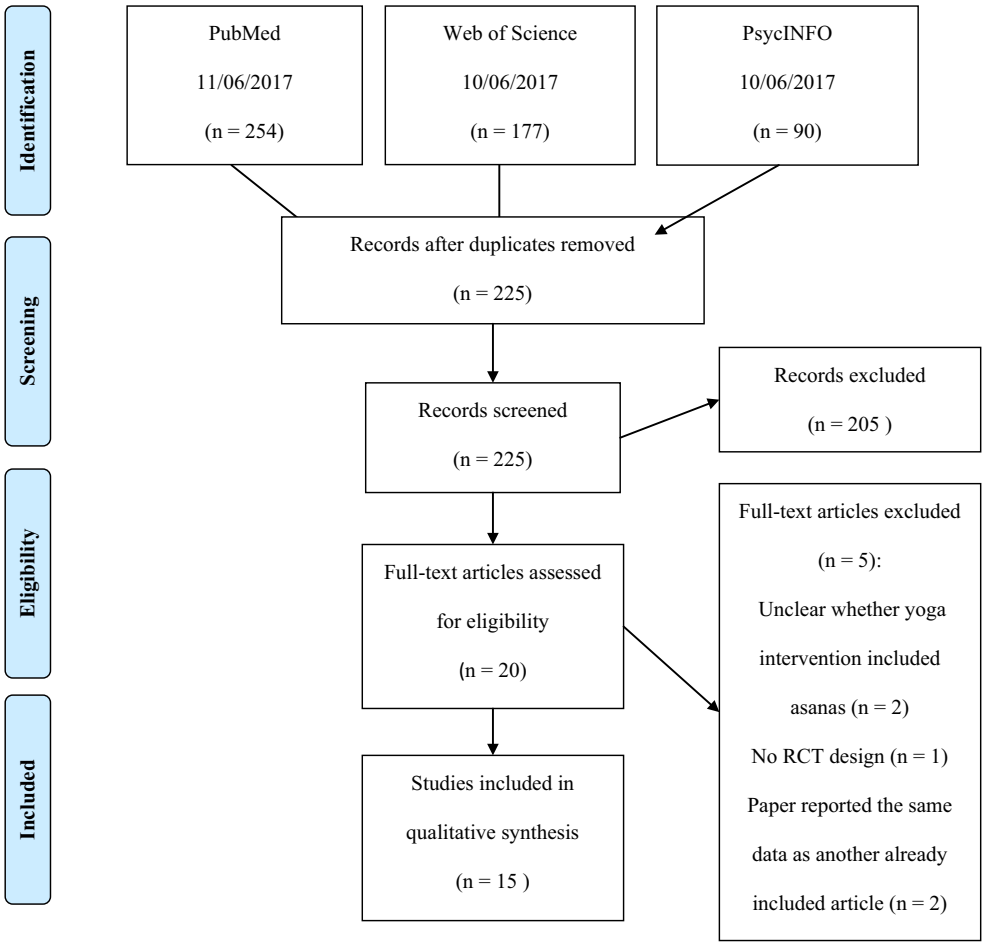

Fig. 1 PRISMA flow diagram showing the study selection process

Table 1 Characteristics and findings of the included RCTs

Author	Sample size	Sample characteristics	Intervention type	Length and frequency of sessions and duration of overall intervention	Control condition	Type and timing of outcome assessment	Immune-related findings (If not specified otherwise, Cohen's d is indicated in brackets behind the respective parameter)
Agnihotri et al. (2014)	Yoga group n = 121; control group n = 120	Patients with mild to moderate asthma; 43% female; mean age 37.86 (range 12–60) years	Yoga practice including asanas, pranayama, and meditation	30 min/session; 5 times/week; 6 months	Standard medical care	Blood samples at baseline and post-intervention	Significant decrease in eosinophils (0.422) in yoga group compared to controls; no significant between-group difference in total leukocyte count (− 0.314), polymorphs (0.096), monocytes (0.186), and lymphocytes (0.015)[a]
Bower et al. (2014)	Yoga group n = 14, 13 at follow up; control group n = 15	Breast cancer survivors experiencing cancer-related fatigue; 100% female; mean age 54 ± 5.4 years	Hatha yoga practice (Iyengar) including asanas, controlled breathing, and relaxation	90 min/session; 2 times/week; 12 weeks	Health education control; 120 min/session; once/week; 12 weeks	Blood samples at baseline, post-intervention, and 3 months follow-up	Significantly reduced activity of NF-kappaB, increased activity of anti-inflammatory glucocorticoid receptor, and reduced activity of CREB family transcription factors in yoga group compared to controls; sTNF-rII levels remained stable in yoga group but significantly increased in controls (0.892); no significant between-group difference in CRP (0.351), IL-1ra (0.304) and IL-6 (0.127)
Cade et al. (2010)	Yoga group n = 29; control group n = 21	HIV-infected individuals with mild to moderate CVD risk; 26% female; mean age 45 years (range 18–70)	Ashtanga Vinyasa Yoga practice including asanas, pranayama, and restorative relaxation	60 min/session; 2–3 times/week; 20 weeks; home practice recommended once/week	Standard medical care	Fasting blood samples at baseline and post-intervention	No significant between-group difference in CD4 + cell count (0.009)
Chen et al. (2016)	Yoga group n = 15; control group n = 15	Healthy individuals, 100% female; age 18–25 years (mean age not reported)	Hatha yoga practice including pranayama, asanas, and meditation	60 min/session; 2 times/week; 8 weeks	No intervention	Fasting blood samples at baseline and post-intervention	Significant reduction in circulating CD31+/CD42b− EMPs in yoga group compared to controls; significant reduction in unstimulated and TLR2 receptor agonist stimulated levels of IL-6, TNF-alpha and IL-1beta in ex vivo cultured blood in yoga group compared to controls; significant reduction in LPS stimulated TNF-alpha but no effect on LPS stimulated IL-6 and IL-1beta in ex vivo cultured blood; no significant between-group difference in circulating IL-8 (− 0.215), TNF-alpha (− 0.077), and CD62E + EMPs

Table 1 continued

Author	Sample size	Sample characteristics	Intervention type	Length and frequency of sessions and duration of overall intervention	Control condition	Type and timing of outcome assessment	Immune-related findings (If not specified otherwise, Cohen's d is indicated in brackets behind the respective parameter)
Chen et al. (2017)	Yoga group n = 48; control group n = 46	Healthy women at 16 weeks gestation; 100% female; mean age 33.0 ± 3.8 years (range 24–43)	Yoga practice including asanas, deep breathing, guided imagery, and deep relaxation	70 min/session; 2 times/week; 20 weeks	Routine prenatal care	Saliva samples before and after yoga at 16, 20, 24, 28, 32, and 36 weeks' gestation	Significantly higher IgA levels at all time points in yoga group compared to controls
Gopal et al. (2011)	Yoga group n = 30; control group n = 30	Healthy students assessed at enrollment and during examination period; 100% female; age 17–20 years (mean age not reported)	Yoga practice including pranayama and meditation	35 min/session; daily; 12 weeks	No intervention	Blood samples at baseline and post-intervention	Decrease in IFN-gamma during examination stress significantly less pronounced in yoga group compared to controls (0.257); no significant between-group difference in IL-4 (0.045)
Harkess et al. (2016)	Yoga group n = 11; control group n = 15	Healthy individuals reporting psychological distress; 100% female; mean age 41.21 ± 4.18 years	Yoga practice, described in other, not yet published study	60 min/session; 2 times/week; 8 weeks	Waitlist control	Blood samples at baseline, post-intervention, and 1 month follow-up	No significant between-group differences post-intervention for CRP (− 0.591), IL-6 (r = 0.35) and TNF-alpha (r = 0.05) or at follow-up for CRP (− 0.607)
Kiecolt-Glaser et al. (2014)	Yoga group n = 96; control group n = 90	Breast cancer survivors; 100% female; mean age 51.6 ± 9.2 years	Hatha yoga practice including asanas, pranayama, and restorative relaxation	90 min/session; 2 times/week; 12 weeks; home practice recommended and recorded in weekly logs	Waitlist control	Fasting blood samples at baseline, post-intervention, and 3 months follow-up	Significant reduction of LPS stimulated production of IL-6 (0.276) TNF-alpha (0.306) and IL-1beta (0.377) at 3 months follow-up in yoga group compared to controls, no significant between-group differences immediately post-intervention (0.173, 0.199, 0.236)
Lim and Cheong (2015)	Yoga group n = 12; control group n = 13	Healthy students inexperienced in yoga; 56% female; mean age 21.5 years (range 19–25)	Yoga practice including asanas, pranayama, and meditation	90 min/session, once/week; 12 weeks; home practice recommended 40 min/day	Supervised physical exercise (e.g. cycling, treadmill running, …)	Fasting blood samples at baseline and post-intervention	Significant increase in IL-12 and INF-gamma in yoga group compared to controls; no significant between-group difference in TNF-alpha
Long Parma et al. (2015)	Yoga group n = 20; control group 1 n = 26; control group 2 n = 26	Breast cancer survivors; 100% female; mean age 56.2 ± 7.9 years	Hatha yoga practice; details not further specified	60 min/session; 3 times/week; 6 months	1.comprehensive, individualized exercise program (aerobic, resistance, and flexibility training); 2. participants performed exercises of their choice	Blood samples at baseline and post-intervention	No significant difference between yoga and both control groups for IL-6 (0.095 and 0.211), IL-8 (− 0.379 and − 0.377), TNF-alpha (0.513 and − 0.526), and CRP (− 0.035 and 0.017)
Naoroibam et al. (2016)	Yoga group n = 22; control group n = 22	HIV-infected individuals; 42% female; mean age 36.14 years	Yoga practice including asanas, pranayama, relaxation, and meditation	60 min/session, 6 times/week; 1 month	Standard medical care	Blood samples at baseline and post-intervention	Significant increase in CD4 + cell count in yoga group compared to controls (0.461)

Table 1 continued

Author	Sample size	Sample characteristics	Intervention type	Length and frequency of sessions and duration of overall intervention	Control condition	Type and timing of outcome assessment	Immune-related findings (If not specified otherwise, Cohen's d is indicated in brackets behind the respective parameter)
Pullen et al. (2010)	Yoga group n = 18; control group n = 16	Heart failure patients; 42% females; mean age 54.23 years (range 31–76)	Hatha yoga practice including asanas, pranayama, and meditation	60 min/session; 2 times/week; 16 sessions over 8–10 weeks; home practice recommended at least once/ week	Standard medical care	Fasting blood samples at baseline and post-intervention	Significant decrease in IL-6 (1.769) and CRP (1.143) in yoga group compared to controls
Rajbhoj et al. (2015)	Yoga group n = 19; control group n = 18	Industrial workers with increased risk of chronic inflammation; 100% male; mean age 40.45 years (range 30–58)	Yoga practice including asanas, pranayama, and meditation	45 min/session; 6 times/week; 12 weeks	Waitlist control	Fasting blood sample at baseline and post-intervention	Significant decrease in IL-1beta (0.661) and significant increase in IL-10 (0.793) in yoga group compared to controls
Sharma et al. (2015)	Yoga group n = 44; control group n = 43	Patients with inflammatory bowel disease; sex and age not reported (inclusion criterion 16–60 years)	Yoga practice including asanas, pranayama, and meditation	60 min/session; daily for one week; continued by 60 min daily monitored home practice for 7 weeks	Standard pharmacological treatment	Blood samples at baseline and post-intervention	No significant between-group difference in sIL-2r (0.003)
Vogler et al. (2011)	Yoga group n = 19; control group n = 19	Physically inactive older adults; 84% female; mean age 73.21 ± 8.38 years	Iyengar yoga practice including asanas and relaxation	90 min/session, 2times/week, 8 weeks; home practice recommended at least 15–20 min 3 times/week	Waitlist control	Saliva samples at baseline and post-intervention	No significant between-group difference in IgA

Sample size indicates the sample size analyzed. Concerning participants' age, the weighted average of the groups was calculated if mean age of all participants was not given. If an indication of the effect size is missing behind the respective parameter, no sufficient data was available to perform calculations

[a]The original paper also reports a significant effect for lymphocytes but this appears to be tested within the yoga group. Yet, the decrease in the control group was of the same magnitude and also significant

& Cheong, 2015; Naoroibam et al., 2016; Rajbhoj et al., 2015; Sharma et al., 2015; Vogler et al., 2011). Four studies provided a general description of the yoga intervention, mentioning types of exercises such as standing postures or sitting postures, yet without specifying individual exercises (Cade et al., 2010; Chen et al., 2016, 2017; Pullen et al., 2010). One study did not further describe the techniques employed in the yoga intervention (Long Parma et al., 2015), and one study referred to another, yet unpublished paper for a more detailed description of the yoga intervention (Harkess et al., 2016).

Active control conditions to account for unspecific effects of yoga practice such as time, attention, and group effects were administered in three RCTs (Bower et al., 2014; Lim & Cheong, 2015; Long Parma et al., 2015). Of these, one study employed a health education intervention (Bower et al., 2014) and two studies administered different types of physical exercise as a control condition (Lim & Cheong, 2015; Long Parma et al., 2015). In the remaining studies, the control groups did not receive an active intervention besides standard medical treatment in case clinical populations were investigated.

Type and timing of outcome assessment

All studies except two (Chen et al., 2017; Vogler et al., 2011) collected blood samples for the biochemical assessment of circulating and stimulated immune parameters, immune cells, or genomic markers. The two remaining studies analyzed immunoglobulin levels in saliva samples. In the majority of studies, specimen were collected immediately pre- and post-intervention, while only three studies included follow-up assessments after 1 month (Harkess et al., 2016) or 3 months (Bower et al., 2014;

Kiecolt-Glaser et al., 2014). One study collected saliva samples before and after yoga sessions every 4 weeks during the course of the 20 week study period (Chen et al., 2017).

Risk of bias assessment

Risk of bias assessment revealed that an adequate method of random sequence generation was employed in ten of the investigated studies, while in five studies, this aspect was judged as unclear (Cade et al., 2010; Gopal et al., 2011; Harkess et al., 2016; Pullen et al., 2010; Vogler et al., 2011). Only two of the RCTs reported on allocation concealment (Bower et al., 2014; Sharma et al., 2015). Blinding of outcome assessment was employed in four studies (Bower et al., 2014; Harkess et al., 2016; Kiecolt-Glaser et al., 2014; Pullen et al., 2010). In all other included studies, this aspect remained unclear, while only one study clearly stated that there was no blinding of outcome assessment (Chen et al., 2017). Risk of attrition bias related to incomplete outcome data was low in six studies (Cade et al., 2010; Chen et al., 2016, 2017; Long Parma et al., 2015; Rajbhoj et al., 2015; Sharma et al., 2015) while in the remaining publications, this aspect was unclear. Risk of reporting bias was unclear in all studies except one, which had a low risk of bias (Chen et al., 2016). Risk of other bias could be identified in none of the studies. Summarizing the overall risk of bias for each study resulted in an unclear risk of bias for all included RCTs. The results of the risk of bias assessment are shown in Table 2.

Immune outcomes

Cytokines and other circulating immune markers

Ten of the included studies evaluated levels of cytokines and other circulating immune parameters, including IL-1-beta, IL-4, IL-6, IL-8, IL-10, IL-12, soluble IL-2 receptor (sIL-2r), TNF-alpha and soluble TNF-receptor II (sTNF-rII), CRP, IFN-gamma, and circulating endothelial microparticles (EMPs). Two studies included an assessment of stimulated levels of IL-6, TNF-alpha, and IL-1beta from whole blood culture (Chen et al., 2016; Kiecolt-Glaser et al., 2014). For reasons of clarity, the ensuing description of results is structured into pro- and anti-inflammatory cytokines, cytokines being primarily involved in cell-mediated immunity, and other circulating immune parameters.

Pro-inflammatory cytokines IL-6 was measured in six RCTs. Three of these found no significant differences in IL-6 levels between yoga and control group in breast cancer survivors (Bower et al., 2014; Long Parma et al., 2015) and healthy individuals (Harkess et al., 2016). One RCT documented a significant reduction of IL-6 levels in the yoga group compared to controls in heart failure patients (Pullen et al., 2010). Kiecolt-Glaser et al. (2014) observed no significant between-group difference in LPS-stimulated IL-6 levels in breast cancer survivors immediately post-intervention, yet found a significant reduction compared to control group at 3 months follow-up. These authors moreover report increasing yoga practice leading to a more pronounced decrease in IL-6, pointing towards a potential dose–response effect. Another RCT reported significantly reduced IL-6 secretion after yoga practice in healthy individuals, and significantly reduced secretion of IL-6 when cultured blood was challenged with a TLR2 agonist, yet no difference when challenged with LPS as a TLR4 agonist (Chen et al., 2016).

IL-1beta was assessed in three RCTs. Rajbhoj et al. (2015), investigating industrial workers at increased risk of chronic inflammation, observed a significant decrease of IL-1beta levels in the yoga group compared to the control group. Kiecolt-Glaser et al. (2014) reported, similar to their findings for IL-6, a significant decrease in LPS-stimulated IL-1beta levels in the yoga group at 3 months follow-up yet not immediately post-intervention, as well as an indication of a potential dose–response effect similar to that for IL-6. The findings of Chen et al. (2016) for IL-1beta equally paralleled their results for IL-6 with significantly reduced IL-1beta secretion in the yoga group and reduced secretion when cultured blood was stimulated with a TLR2 agonist, yet no difference when challenged with LPS.

TNF-alpha levels were assessed in five studies. Additionally, one RCT evaluated sTNF-rII, which is an indicator of TNF-alpha activity as it is released from cell surfaces after engagement by TNF-alpha (Bower et al., 2014). Three of these RCTs reported no significant between-group differences in TNF-alpha levels after yoga practice in healthy students (Harkess et al., 2016; Lim & Cheong, 2015) and breast cancer survivors (Long Parma et al., 2015). Kiecolt-Glaser et al. (2014) found no significant between-group difference in LPS-stimulated TNF-alpha levels in breast cancer survivors immediately post-intervention, yet, similar as for IL-beta and IL-6, a significant reduction in the yoga group compared to controls at 3 months follow-up. Chen et al. (2016) reported no significant effects on circulating TNF-alpha levels but a significant reduction in the yoga group compared to controls in TNF-alpha secretion in the whole blood culture, as well as when cultured blood was challenged with both a TLR2 agonist and LPS. The RCT investigating levels of sTNF-rII found a significant between-group difference with increases in the control group but stable levels in the yoga

Table 2 Risk of bias in the included studies

	Random sequence generation	Allocation concealment	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Overall risk of bias
Agnihotri et al. (2014)	+	?	?	?	?	+	?
Bower et al. (2014)	+	+	+	?	?	+	?
Cade et al. (2010)	?	?	?	+	?	+	?
(Chen et al. 2016)	+	?	?	+	+	+	?
Chen et al. (2017)	+	?	–	+	?	+	?
Gopal et al. (2011)	?	?	?	?	?	+	?
Harkess et al. (2016)	?	?	+	?	?	+	?
Kiecolt-Glaser et al. (2014)	+	?	+	?	?	+	?
Lim and Cheong (2015)	+	?	?	?	?	+	?
Long Parma et al. (2015)	+	?	?	+	?	+	?
Naoroibam et al. (2016)	+	?	?	?	?	+	?
Pullen et al. (2010)	?	?	+	?	?	+	?
Rajbhoj et al. (2015)	+	?	?	+	?	+	?
Sharma et al. (2015)	+	+	?	+	?	+	?
Vogler et al. (2011)	?	?	?	?	?	+	?

+ indicates low risk of bias, ? indicates unclear risk of bias, − indicates high risk of bias concerning the respective item

group, indicating that yoga has a buffering effect on abnormal TNF-alpha activity in breast cancer survivors (Bower et al., 2014).

Levels of IL-8 were assessed by two RCTs, neither of which found a significant between-group difference after yoga practice in healthy individuals (Chen et al., 2016) or breast cancer survivors (Long Parma et al., 2015).

Anti-inflammatory cytokines The anti-inflammatory cytokines IL-4 and IL-10 were assessed by one RCT each. Yoga practice was found to have no significant effect on IL-4 levels in healthy students during examination stress (Gopal et al., 2011). Rajbhoj et al. (2015) observed that after a yoga intervention, the above reported decrease in IL1-beta was accompanied by significantly increased levels of IL-10 in industrial workers with an elevated risk of sustained inflammation (Rajbhoj et al., 2015).

Cytokines primarily involved in cell-mediated immunity IFN-gamma was assessed in two RCTs. One of these reported a significantly smaller decrease in IFN-gamma levels in healthy students during examination stress in the yoga group compared to the control group (Gopal et al., 2011), indicating a buffering effect of the yoga intervention. Another RCT, also examining healthy students, reported a significant increase in IFN-gamma levels in the yoga group compared to controls (Lim & Cheong, 2015).

Besides IFN-gamma, Lim and Cheong (2015) also investigated IL-12. Similar to their finding for IFN-gamma, these authors reported a significant increase in IL-12 levels after yoga practice in healthy individuals, compared to controls (Lim & Cheong, 2015). Another individual study evaluated levels of sIL-2r which regulates processes of tolerance and immunity, yet found no significant between-group difference in this marker in IBD patients after yoga practice (Sharma et al., 2015).

Other circulating immune parameters Levels of CRP were evaluated in four studies. Three RCTs found no significant between-group differences in CRP levels after a yoga intervention in breast cancer patients or healthy individuals (Bower et al., 2014; Harkess et al., 2016; Long Parma et al., 2015). Meanwhile, Pullen et al. (2010) reported significant reductions in CRP in the yoga group compared to controls in heart failure patients with pronounced risk of inflammation, paralleling the decrease in IL-6 observed in the same study.

Chen et al. (2016) assessed levels of circulating EMPs. The study reported a significant decrease in CD31 +/ CD42b − EMPs in healthy individuals after yoga intervention compared to controls, yet no significant between-group difference in CD62E + EMPs (Chen et al., 2016).

Immune cell counts and receptors

Three RCTs assessed the effect of yoga on cells of both the innate and the adaptive immune system. One study examining asthma patients found a significant decrease in eosinophils in the yoga group compared to controls (Agnihotri et al., 2014). No significant between-group differences were found for total leukocyte count, polymorphs, lymphocytes, and monocytes (Agnihotri et al., 2014). Two RCTs examined CD4 + cell counts in HIV infected individuals. One of these studies reported no significant between-group difference (Cade et al., 2010), while one study observed a significant increase in CD4 + cell count in the yoga group compared to controls (Naoroibam et al., 2016).

Antibody response

Two RCTs included measures of immunoglobulins. One of these reported no significant between-group difference in IgA levels in older adults (Vogler et al., 2011), while one study reported a significant increase in IgA levels after yoga practice compared to controls in pregnant women (Chen et al., 2017).

Markers of gene expression

One RCT examined the effects of yoga on immune-related gene expression (Bower et al., 2014). It was found that the pro-inflammatory transcription factor NK-kappaB as well as the activity of CREB family transcription factors were significantly reduced in the yoga group compares to controls (Bower et al., 2014). Further, transcription of genes exhibiting a glucocorticoid receptor (GR) response element was significantly increased.

Discussion

Synthesis of findings

This systematic review is the first to summarize the findings of existing RCTs examining the effects of yoga on immune system functioning. Overall, the review revealed that this field of investigation is still young (all eligible papers were published after 2010) and thus lacking an extensive body of studies. Moreover, the existing RCTs are subject to some limitations which restrict their informative value to a certain extent. Regarding several immune parameters, the effects of yoga practice have, until today, only been examined by very few studies. This lack of replication necessitates further research and only allows drawing preliminary and tentative conclusions. Furthermore, as depicted in Table 1, the magnitudes of effects observed in the studies were (if calculable) mostly small to medium, and in how far the observed effects have clinical relevance and are associated with improved health outcomes remains to be determined. Nevertheless, the reviewed studies provide interesting and potentially relevant indications regarding the effects of yoga practice on immune functioning and suggest several directions for further investigation.

Effects of yoga practice on markers of inflammation

An overall pattern that can be identified regarding the effects of yoga on immune functioning is the downregulation of pro-inflammatory markers. With regard to cytokines and other circulating inflammatory parameters, the most conclusive finding is that yoga practice decreases levels of the pro-inflammatory cytokine IL-1beta, in both healthy individuals and in a clinical population. Though effect sizes were only small to medium, this effect was unequivocally indicated by all studies that investigated this parameter.

Regarding the effects of yoga on IL-6, the evidence is less consistent. Half of the studies investigating this parameter indicated that yoga practice decreases IL-6 levels, with no directly opposing results. Effect sizes of these studies were mostly small to medium, yet Pullen et al. (2010) found a very large effect ($d = 1.769$), further supporting that yoga can reduce IL-6 levels.

Concerning TNF-alpha, the existing studies report mixed results, currently impeding distinct conclusions. Yet, there are indications that yoga can decrease levels of this inflammatory marker as well, and similar as for IL-6, no directly opposing results were found. While the magnitudes of effects observed in these studies were again mainly small or medium, Bower et al. (2014) observed a large effect ($d = 0.892$) for lower sTNF-rII levels in the yoga group, underlining the potential of yoga to reduce levels of TNF-alpha.

Regarding CRP, only one out of four studies observed a significant reduction. However, the magnitude of the decrease in CRP observed by Pullen et al. (2010) was large ($d = 1.143$), indicating the importance of further investigating if yoga can reduce also this inflammatory parameter.

While the findings concerning reductions in CRP, TNF-alpha, and IL-6 are thus not all as conclusive as those for IL-1beta, an association between yoga practice and decreases in these markers would be concordant with reductions in IL-1beta. All of these biomarkers are central mediators of the inflammatory response, thus being vital for an adequate immune function. Yet, a dysregulation or chronic elevation of any of these parameters can have adverse impacts: IL-1beta plays a role in the pathogenesis of inflammatory diseases such as rheumatoid arthritis, diabetes type 2, or gout (Dinarello, 2011). Similarly, IL-6 is implicated in several clinical conditions such as cardiovascular disease, diabetes, obesity, and cancer (Hunter & Jones, 2015; Yadav et al., 2012). Elevated levels of TNF-alpha are equally related to a variety of diseases and chronic inflammatory processes, and can be implicated in delayed wound healing (Ashcroft et al., 2012; Popa et al., 2007). Meanwhile, CRP is recognized to be a biomarker as well as a mediator of inflammatory diseases such as artherosclerosis and coronary heart disease (Shrivastava et al., 2015).

Beyond this, other individual studies further substantiate the notion that yoga practice can downregulate inflammatory processes. An isolated study reported that yoga practice increased levels of the anti-inflammatory cytokine IL-10, with a rather large effect size ($d = 0.793$). Moreover, another RCT reported that yoga practice reduced levels of CD31 +/CD42b- EMPs, though no effect on CD62E + EMPs. EMPs promote vascular inflammation, and are observed to be elevated in several vascular and inflammatory diseases (Mezentsev et al., 2005).

The RCT that examined genomic effects of yoga suggests that yoga practice can mediate anti-inflammatory effects also on a transcriptional level (Bower et al., 2014). Here, yoga reduced activity of NF-kappaB which mediates inflammatory processes and is implicated in several chronic inflammatory diseases (Lawrence, 2009). The authors further report that yoga increased transcription of genes with a GR response element, which signifies higher GR activity. Glucocorticoids and other corticosteroids acting via the GR are recognized to suppress pro-inflammatory genes and to activate transcription of anti-inflammatory genes (Barnes, 2006). Bower et al. (2014) equally observed reduced activity of CREB family transcription factors after a yoga intervention. According to these authors, this can signify reduced sympathetic nervous system signalling through β-adrenergic receptors which normally activate NF-kappaB and upregulate the transcription of proinflammatory cytokine genes.

In sum, even though the available evidence regarding several parameters is scarce and often not entirely consistent, and the magnitudes of effect were mostly small to medium, the existing RCTs generally indicate anti-inflammatory effects of yoga practice. In particular, yoga seems to downregulate pro-inflammatory cytokines. Moreover, it may also counteract inflammatory processes on a transcriptional level. Interestingly, though not all of the investigated studies did find reductions in pro-inflammatory parameters, no study reported increases in a pro-inflammatory marker or decreases in an anti-inflammatory one, suggesting that yoga practice does not have adverse effects in this regard.

If future research confirms that yoga practice has beneficial regulatory effects in conditions of abnormal or chronic inflammation, this would warrant its implementation in the prevention and treatment of diseases with an inflammatory component. Inflammatory parameters are recognized to be implicated in a wide variety of diseases, including physical conditions such as asthma, rheumatoid arthritis, cardiovascular disease, obesity, and diabetes as well as psychological conditions such as depression (Slavich, 2015). Therefore, yoga practice may be beneficial for populations at risk and could be implemented as a complementary therapy for those already affected by diseases with an inflammatory component. Indeed, those studies that examined such populations, namely heart failure patients and industrial workers with an increased risk of chronic inflammation, consistently observed decreases in pro-inflammatory markers.

Yet, other factors besides the investigated population, such as the duration of the yoga intervention may equally influence the effects of yoga practice on inflammatory markers. Potentially, in populations with a high risk of increased inflammation such as the heart failure patients investigated by Pullen et al. (2010), shorter interventions of only 8 weeks duration might be sufficient to reduce inflammatory processes while in other populations effects might take longer to emerge. Kiecolt-Glaser et al. (2014), for example, observed that inflammatory markers were not reduced in breast cancer survivors directly after the yoga intervention, yet they found significant decreases at 3 months follow-up. These results indicate that yoga practice might take longer than only 8–12 weeks, as administered in most RCTs, to exert consistent effects on inflammatory markers in many populations.

Interestingly, two case–control studies that compared subjects practicing yoga for at least 2 or at least 5 years to subjects inexperienced in yoga reported significantly lower levels of TNF-alpha, CRP, and IL-6 in the long-term practitioners (Kiecolt-Glaser et al., 2010; Vijayaraghava et al., 2015). These studies thus support the hypothesis that only very sustained yoga practice may lead to consistent decreases in circulating inflammatory markers.

Cell-mediated and mucosal immunity

Besides reducing inflammation, yoga may exert beneficial effects on other parameters of the innate and adaptive immune systems, including cell-mediated and mucosal immunity. The reviewed studies indicate that yoga practice can, in healthy individuals, increase levels of IFN-gamma, which is a central regulator of cell-mediated immunity, having antiviral, immune-regulatory, and anti-tumor properties (Schoenborn & Wilson, 2007). This conclusion is supported by the finding that yoga practice elevated levels of IL-12 which stimulates the production of IFN-gamma, thereby further promoting cell-mediated immunity (Del Vecchio et al., 2007). These studies indicate that yoga may potentially provide improved protection against intracellular pathogens and tumor development. Moreover, the study by Gopal et al. (2011) which found that yoga practice buffered decreased IFN-gamma levels during examination stress suggests that yoga might be particularly beneficial in situations of acute stress where the immune system is at risk of being suppressed. As IFN-gamma is also involved in autoimmune diseases (Pollard et al., 2013), it remains to be clarified how yoga practice affects individuals with potentially abnormal IFN-gamma activity.

A few other studies further suggest that yoga practice may have beneficial effects on cell-mediated immunity. Evidence from one RCT indicates that yoga practice can reduce eosinophil counts in asthma patients. As these cells play a crucial role in the pathogenesis of asthma, their reduction through yoga practice could help to alleviate asthmatic disease (Abbas et al., 2016; Agnihotri et al., 2014). Besides this, although one study found no effects of yoga practice on CD4 + cells in HIV infected individuals, another RCT suggests that yoga practice can increase CD4 + cell count in this population. In the pathogenesis of AIDS, the decline of CD4 + cell count is a characteristic feature. Therefore, if further research confirms that yoga practice can elevate CD4 + cell count, this would imply its feasibility as a complementary therapy for HIV infected individuals or other diseases marked by a decline in CD4 + cells.

Beyond this, the increases in IgA in pregnant women after yoga observed by of Chen et al. (2017) suggest that yoga might improve protection against invading pathogens and thus infections, as this antibody isotype is central to mediating mucosal immunity (Abbas et al., 2016).

Considered together, these studies indicate that yoga may exert beneficial effects on cell-mediated or mucosal immunity. Hence, it may hold potential for the treatment of diseases such as AIDS or for enhancing immune function in general, counteracting, for example, suppressions of immune function in stressful situations. However, also the effects observed in these studies were rather small to medium or not calculable due to lack of data. In general, the paucity of evidence concerning these effects does not allow drawing distinct conclusions and necessitates further research in this field.

Situation of the results within previous research on the effects of MBTs on the immune system

Yoga is frequently compared to other MBTs such as mindfulness meditation, Tai Chi, or Qigong, as these practices are assumed to function through similar mechanisms such as inducing relaxation and regulating autonomic balance. Hence, it may prove valuable to situate the results of this review within previous research in this area. Indeed, the general pattern of reducing inflammation that emerged in the present review appears to be a common effect of several MBTs, as shown by other reviews and meta-analyses in this field (Black & Slavich, 2016; Bower & Irwin, 2016; Buric et al., 2017; Morgan et al., 2014).

A meta-analysis investigating the effects of MBTs on different immune parameters concluded that MBTs reduce inflammation, mainly evidenced through reductions in CRP (Morgan et al., 2014). Yet, similar to our review, this study found inconsistent evidence regarding the effects of MBTs on different other circulating markers of inflammation. Bower et al. (2016), in a descriptive review, made equally mixed findings regarding reductions in circulating inflammatory markers, yet they reported highly consistent and robust evidence that MBTs decrease genomic markers of inflammation. Another recent systematic review that examined the effects of different MBTs on gene expression equally reported that MBTs downregulate pro-inflammatory genes (Buric et al., 2017).

Attempting to unite the consistent results regarding downregulation of inflammation on a genomic level with the inconsistent findings concerning circulating markers of inflammation, Bower et al. (2016) as well as Buric et al. (2017) suggested that MBTs may have rather rapid effects on gene expression, while effects on circulating markers of inflammation might take longer to develop. This proposition is in line with our hypothesis that yoga needs to be practiced for a sustained time span in order to show consistent effects on circulating inflammatory markers across different populations. However, whether genomic effects of yoga may emerge after shorter periods of practice cannot yet be conclusively determined as only one study investigated such parameters.

Concerning other immune markers besides inflammation, another systematic review concluded that mindfulness meditation can reduce CD4 + cell counts in HIV infected individuals (Black & Slavich, 2016). This observation supports the finding of the Naoroibam et al. (2016) study included in our review that reported similar effects for yoga

practice. The review by Black and Slavich (2016) moreover indicates that mindfulness meditation can counteract cellular aging through enhancing telomerase activity. So far, no RCT has studied the effects of yoga on markers of cellular aging. Yet, some studies using case–control or single arm exploratory designs already indicate increased telomere length and telomerase activity due to yoga practice (Krishna et al., 2015; Kumar et al., 2015; Tolahunase et al., 2017).

While yoga hence seems to have basically similar effects on the immune system as different MBTs, it may nevertheless have some advantages compared to other MBTs as well as to exercise-based interventions. Yoga has shown to lead to larger increases in psychological well-being compared to other MBTs such as sitting meditation (Sauer-Zavala et al., 2013), and to equal or superior effects on various health-related outcomes compared to other exercise-based interventions (Ross & Thomas, 2010). Yoga practice may be particularly beneficial as it combines the positive effects of physical activity with those of mindfulness, thus further investigating the benefits of yoga-based interventions is of particular relevance.

Limitations and suggestions for further research

This review is subject to some limitations at the level of the investigated literature as well as at the level of the review itself. It is apparent that the existing body of research on the effects of yoga on the immune system is currently small and should be expanded, especially by methodologically rigorous studies. In all included RCTS, risk of bias was unclear, thus future studies should ensure to include more detailed descriptions of their study design.

Beyond this, most of the reviewed studies had rather small sample sizes and did not include estimates of statistical power to determine the required sample size. Seven of the reviewed studies included only female participants, limiting the generalizability of findings. Though these studies' results do not seem to differ fundamentally from those including both sexes or only male participants, future RCTs should nevertheless try to have a balanced sex distribution and/or compare the effects of yoga on men and women. Furthermore, the existing studies examined a wide range of clinical as well as non-clinical populations, hampering a comparison of findings. However, this can also be a considered a strength as it increases generalizability of the findings and can indicate for whom yoga may be especially beneficial.

Another limitation of the existing research is the heterogeneity of employed yoga interventions and their dosage. In line with this, future studies should ensure including detailed descriptions of the employed type of yoga and the specific sequences that were used. Providing adequate descriptions and ideally randomizing the employed yoga style, the intensity of practice, the employed sequences, as well as session length, frequency, and duration of practice is of particular importance. For study replication and to examine potentially underlying mechanisms, knowledge of the exact yoga practice used is crucial. Another element of heterogeneity is the inclusion of home practice in some studies but not in others. The inclusion of home practice offers the advantage that yoga interventions can become more intensive without having to spend resources on further guided sessions, and it may facilitate integration and continuation of practice in daily life. However, a disadvantage is that there is little control on both the frequency and quality of the home practice. Future studies using home practice should carefully document the actual practice frequency, for example by using diaries, and virtual teachers could be used to demonstrate the right postures and sequences. Beyond this, only three RCTs employed active control conditions while the others did not account for unspecific effects of the yoga intervention such as social support or teacher-student relationship, another aspect that should be considered in future studies.

In addition, several studies employed yoga interventions of a relatively short duration, which might not suffice to induce consistent changes especially in circulating inflammatory markers, and only three of the reviewed studies included a follow-up assessment of immune parameters. In light of the suggestion that yoga might show lasting effects on circulating inflammatory markers only when practiced for years, it would be highly relevant to further examine the effects of such sustained yoga practice. As this might be difficult to achieve in RCTs, well-designed case–control studies with large sample sizes might prove valuable in this regard.

We have suggested that yoga practice may be beneficial in diseases with an inflammatory component, as well as in conditions such as AIDS. Yet, research directly linking changes in immune parameters due to yoga to disease outcomes currently appears to be lacking, thus, future studies should aim at investigating these associations.

Related to this, most of the included studies focused on reporting their outcomes in terms of statistical significance while indications of the magnitude of the observed effects were mostly missing. Several studies did not provide sufficient data to calculate effect sizes for all included outcomes, and most authors did not reply when being contacted for more data. Given the limited clinical relevance of statements about the statistical significance of findings, it would be recommendable for future studies to include calculations of effect sizes or at least provide sufficient data to do so.

A limitation at the level of the review itself is that only studies using an RCT design were considered. While several studies examining the effects of yoga on the immune

system using a different design are available, combining all those studies in one review would have been difficult as the various designs are often hardly comparable with each other. Beyond this, due to the heterogeneity of the included RCTs, we have only descriptively summarized and analyzed the results and conducted no meta-analysis. Last, this review has only briefly mentioned some of the major mechanisms that are supposed to mediate the effects of yoga on the immune system, namely inducing a relaxation response and regulating autonomic balance. Yet, in the literature, a multitude of such mechanisms is discussed in much more detail and the pathways through which yoga functions are far from being understood.

Conclusion

The current evidence suggests that yoga can downregulate pro-inflammatory parameters and may thus hold potential for the complementary treatment and prevention of inflammation-associated diseases. Yet, regarding several parameters, the existing evidence is inconsistent or too scarce, necessitating examination through further studies. Specifically, it remains to be established whether consistent effects of yoga on circulating pro-inflammatory markers emerge after longer periods of practice. In addition, potentially beneficial effects of yoga on other aspects of immune functioning such as cell-mediated immunity need to be examined further. In general, this field of investigation would benefit from more methodologically rigorous studies in line with the specific recommendations for future research that have been made. As yoga has several advantages to other, for example pharmacological therapies, such as its higher potential to be integrated into everyday life, its non-invasive character, and the absence of negative side effects, more research in this field is of great significance.

Compliance with ethical standards

Conflict of interests R. I. Falkenberg, C. Eising, and M. L. Peters declare that they have no conflict of interest.

Human and animal rights and Informed consent This article does not contain any studies with human participants or animals performed by any of the authors.

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