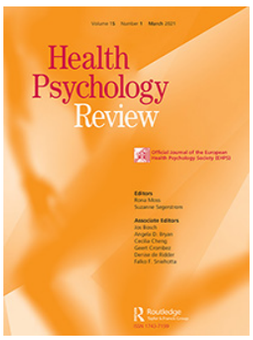
Meditation interventions efficiently reduce cortisol levels of at-risk samples



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Adam Koncz, Zsolt Demetrovics & Zsofia K. Takacs

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Meditation interventions efficiently reduce cortisol levels of at-risk samples: a meta-analysis*

Adam Koncz [a], Zsolt Demetrovics [b] and Zsofia K. Takacs [c]

[a]Doctoral School of Psychology, ELTE Eötvös Loránd University, MTA-ELTE Lendület Adaptation Research Group, Budapest, Hungary; [b]Institute of Psychology, ELTE Eötvös Loránd University, Budapest, Hungary; [c]Institute of Education, ELTE Eötvös Loránd University; MTA-ELTE Lendület Adaptation Research Group, Budapest, Hungary

ABSTRACT

Previous meta-analytic results showed beneficial effects of meditation interventions for cortisol levels. In the present meta-analysis we tested whether effects are larger for those who might be in need of such stress reduction programs due to a risk for elevated cortisol levels as compared to no-risk samples. We included RCTs that measured change in cortisol levels. Based on 10 studies using blood samples meditation interventions had a significant, medium effect from pre-to post-test compared to the control group. Upon closer inspection, this effect was only present for at-risk samples, that is, patients with a somatic illness. In the 21 studies using saliva samples the effect was small and not significant, but there was a marginally significant effect for groups living in stressful life situations. This pattern may suggest that that meditation interventions are most beneficial for at-risk populations. These interventions might provide people with strategies of stress management that can contribute to well-being. Preliminary results suggest that benefits of meditation interventions might not fade with time.

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meditation; cortisol; meta-analysis; at-risk samples; stress management; long-term effect

Cortisol is a stress hormone that is released by the activity of the hypothalamic–pituitary–adrenal (HPA) axis. In addition to a circadian rhythm – after an increase around waking it has a steady decrease during the day – it shows elevated concentration in reaction to stress. In case of chronic stress, cortisol shows high concentrations after awakening (Schulz et al., 1998). Higher perceived levels of stress are related to elevated daily cortisol secretion, which in turn is associated with a wide array of health complaints (Lovell et al., 2011). Chronic stress can have a negative effect on the immune and cardiovascular systems and some processes of the metabolism (McEwen, 2004). There are several mental disorders (e.g., depression or anxiety disorders) and somatic illnesses (Barič ević et al., 2006; Chiodini et al., 2007) or life situations (Chida & Steptoe, 2009) that are characterized by elevated cortisol levels. For instance, elevated hair cortisol levels were measured in depression (Dettenborn et al., 2012) and patients with an anxiety disorder show higher cortisol levels in hair (Steudte et al., 2011) and saliva samples (Mantella et al., 2008). Regarding somatic illnesses, type II diabetes is associated with elevated blood serum cortisol (Chiodini et al., 2007), while Tsilchorozidou et al. (2003) showed higher daily cortisol production from urine cortisol metabolites in polycystic ovarium syndrome (PCOS) patients. It is known that stressful life situations (e.g., low socioeconomic status) are associated with higher salivary cortisol levels (Cohen et al., 2006). Thus, taking into

CONTACT Zsofia K. Takacs takacs.zsofia@ppk.elte.hu
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consideration the health risks and the number of conditions that are linked to elevated cortisol levels, investigating the efficacy of interventions that might help reducing elevated cortisol levels is of high importance. Furthermore, it is important to assess whether benefits are sustained over time (Slopen et al., 2014).

Meditation is a widely spreading stress reduction technique. In fact, in a previous meta-analysis Goyal et al. (2014) found that mindfulness meditation has moderate beneficial effects on symptoms of anxiety ($d = 0.38$) and depression ($d = 0.30$), but no convincing evidence on stress in clinical populations. Meditation, however, is not a clearly defined concept and it has several different schools. Mindfulness is one of the most widespread approaches. The goal of mindfulness meditation is to focus on the sensations and feelings of the present moment and pay attention non-judgmentally (Kabat-Zinn & Hanh, 2009). Meditation is often used in combination with other practices. For instance, Integrative Body-Mind Training (IMBT) uses mindfulness training elements and also body relaxation and mental imagery (Tang, 2011). Mindfulness-Based Stress Reduction (MBSR) and Mindfulness-Based Cognitive Therapy (MBCT) combine mindfulness meditation practices with elements of cognitive behavioral therapy or some other psychoeducational elements (Fjorback et al., 2011). The most commonly used components in mindfulness-based programs are breath awareness, psycho-education and group discussions (Zenner et al., 2014).

Five categories of meditation techniques are mentioned by Simkin and Black (2014). During focused attention trainings (FA) meditators are concentrating on explicit objects to avoid the mind wander. The widely used mindfulness-based programs like MBSR and MBCT belong here. The aim of open monitoring (OM) techniques is not to concentrating on explicit objects, rather the practitioner is trying to be a monitoring state. Meditative techniques in this category are Sahaja type meditations. The third category is transcendental meditation (TM). In this technique, instead of focusing on something or being aware of the moment, the meditator repeats a mantra. The goal of this action is to subside the thoughts and mental processes. Mind–body approaches (M-B) can involve components from the previous three techniques. And finally, body–mind programs (B-M) use movement series thus these are body-centered but can also incorporate elements from the first three types. Body–mind programs include movements like dance therapy or yoga, etc.

In a meta-analysis MBSR compared to wait-list controls was found to be effective in reducing self-reported stress (Cohen's d for MBSR group was 0.74, while it was – 0.21 for the control group), however, results are not conclusive whether these benefits remain more than 3 months later (Chiesa & Serretti, 2009). In a systematic review, Fjorback et al. (2011) found that only the minority of the studies include follow-up assessments after more than a year. Moreover, self-reported assessment of stress is more prone to bias, while objective biomarkers such as cortisol levels might be more suitable for a firm test of the effects of meditation on stress (Matousek et al., 2010). Sanada et al. (2016) conducted a meta-analysis of the available randomized controlled trials (RCTs) of mindfulness-based programs on salivary cortisol levels in non-clinical adult populations and revealed a significant, moderate-sized benefit of almost half a standard deviation ($g = .41$, $p = .025$). Pascoe et al. (2017) synthesized the results of the RCTs regarding the effects of any types of meditation compared to an active control group on blood cortisol data and also found a significant, medium effect ($Z = -2.92$, $p < .01$). However, there is a call for investigating the long-term effects of meditation (Chiesa & Serretti, 2009; Fjorback et al., 2011).

According to Creswell and Lindsay (2014) mindfulness has positive effects on health outcomes via improving stress management (mindfulness stress buffering hypothesis). The authors proposed that mindfulness affects both top-down and bottom-up stress processes in the brain including increased activation in regulatory areas like the prefrontal cortex and decreased stress reactivity in, for instance, the amygdala. Based on the stress buffering account, Creswell and Lindsay (2014) predicted that mindfulness-based interventions should have the largest effect for at-risk populations: highly stressed people or populations with diseases that are susceptible to stress such as mental disorders and somatic illnesses like inflammatory diseases or diabetes.

Based on these previous considerations, the main aim of the present study was to assess whether meditation is more effective in samples who are in most need of stress reduction: samples with

elevated cortisol levels, that is, clinical samples and participants in stressful life situations as compared to healthy subjects with supposedly lower cortisol levels. Secondly, we investigated whether the benefits of meditation are sustained over time by focusing on the latest follow-up assessments. Additionally, we extended the previous results in several ways: (i) we included all kinds of meditative interventions as we expected similar benefits of mindfulness-based as other schools of meditation such as zen or transcendental meditation, (ii) we also included any cortisol sampling procedure, not only saliva or blood, but also urine samples because there is a high correlation between cortisol concentration measured from blood and saliva samples (Obayashi, 2013), and urine (Contreras et al., 1986). Besides the aforementioned, hair cortisol is also included because it reflects the changes in cortisol secretion as well (Wright et al., 2015), (iii) we did not restrict our search to active control conditions, and finally, (iv) we did not restrict our search according to participants' age or clinical status as we aimed to test whether meditative interventions have different efficacy at different ages and in samples who are at risk for elevated cortisol levels.

In line with previous results (Pascoe et al., 2017; Sanada et al., 2016), it was hypothesized that meditation interventions decrease cortisol levels because of their stress-reducing effects (Goyal et al., 2014). However, while Goyal et al. (2014) found an effect of mindfulness-based programs (e.g., MBSR, MBCT, Zen meditation, etc.), they did not find one of mantra meditation (e.g., Transcendental meditation). The evidence in the included studies regarding mantra meditation was low or insufficient. On the other hand, in a literature review Walton et al. (2002) state that transcendental meditation does reduce stress. Furthermore, we expected a larger effect for samples that are at risk for elevated cortisol levels (based on the mindfulness stress buffering account of Creswell and Lindsay 2014). Finally, regarding the long-term effects of these programs, we expected smaller effects with more and more time after the end of the intervention. For instance, Hsiao et al. (2016) found a larger effect right after the intervention as compared to follow-up measures at 3, 6 and 12 months.

Methods

Operational definitions

Meditation in the present study was defined as a contemplative activity during which subjects focus their attention on the object of the meditation instead of letting their minds wonder, regardless of what the object of meditation is: for instance, breathing, sensations in the body, a mantra, sounds or one's thoughts. Accordingly, all schools of meditative practices (e.g., mindfulness, transcendental or zen meditation) were included (similar to Goyal et al., 2014; Pascoe et al., 2017).

We aimed to assess the effect specifically for subjects who are at a risk for elevated cortisol levels. In the primary studies the effect of meditation was assessed regarding a variety of at-risk samples, for example, participants with a somatic illness (e.g., cancer, Bränström et al., 2013), polycystic ovary syndrome (Stefanaki et al., 2015), cardiovascular disease (Robert McComb et al., 2004), type 2 diabetes (Jung et al., 2015), or samples with a mental illness (e.g., depression (Gex-Fabry et al., 2012), or post-traumatic stress disorder (Kim et al., 2013)) in addition to clinically indicated samples such as participants showing depressive symptoms (Prakhinkit et al., 2014). Furthermore, participants living in stressful life circumstances were also considered as at-risk groups (e.g., cancer survivors (Carlson et al., 2013), dementia caregivers (Oken et al., 2010), or low socioeconomic status (Sibinga et al., 2013)). See Table 1 for an overview of the risk factors in the primary studies in addition to references confirming that these conditions are associated with elevated cortisol levels.

Search strategy

We conducted a systematic search in the databases of Web of Science (Core collection), EBSCO (PsychInfo, PsychArticles, MEDLINE) and PubMed for journal articles and in the ProQuest database for dissertations and theses with a detailed search string (Appendix 1) up to November 15, 2018, to locate all

Table 1. Risk factors for elevated cortisol levels in the primary studies.

Risk factor	Reference
Cancer diagnosis	Andersen et al., 1989
Chronic pain (e.g., fibromyalgia)	Van Uum et al., 2008
Depression	Dettenborn et al., 2012
Generalized anxiety disorder	Mantella et al., 2008
Glaucoma	Schwartz et al., 1987
History of cardiovascular disease	Manenschijn et al., 2013
Inflammatory gastrointestinal diseases (e.g., colitis ulcerosa, Cohn's disease)	Baričević et al., 2006
Low socioeconomic status (Low-SES)	Cohen et al., 2006
Polycystic ovary syndrome (PCOS)	Tsilchorozidou et al., 2003
Posttraumatic stress disorder (PTSD)	Steudte et al., 2011
Stressful life situations (Caregiving of patients with dementia can lead to depression over time Wright et al., 1999)	Chida & Steptoe, 2009
Type 2 diabetes	Chiodini et al., 2007

randomized controlled trials that used meditation as an intervention and cortisol measures before and after the intervention to calculate the change in cortisol levels as an outcome (see the PRISMA diagram in Figure 1). All searching and screening procedures were done independently by

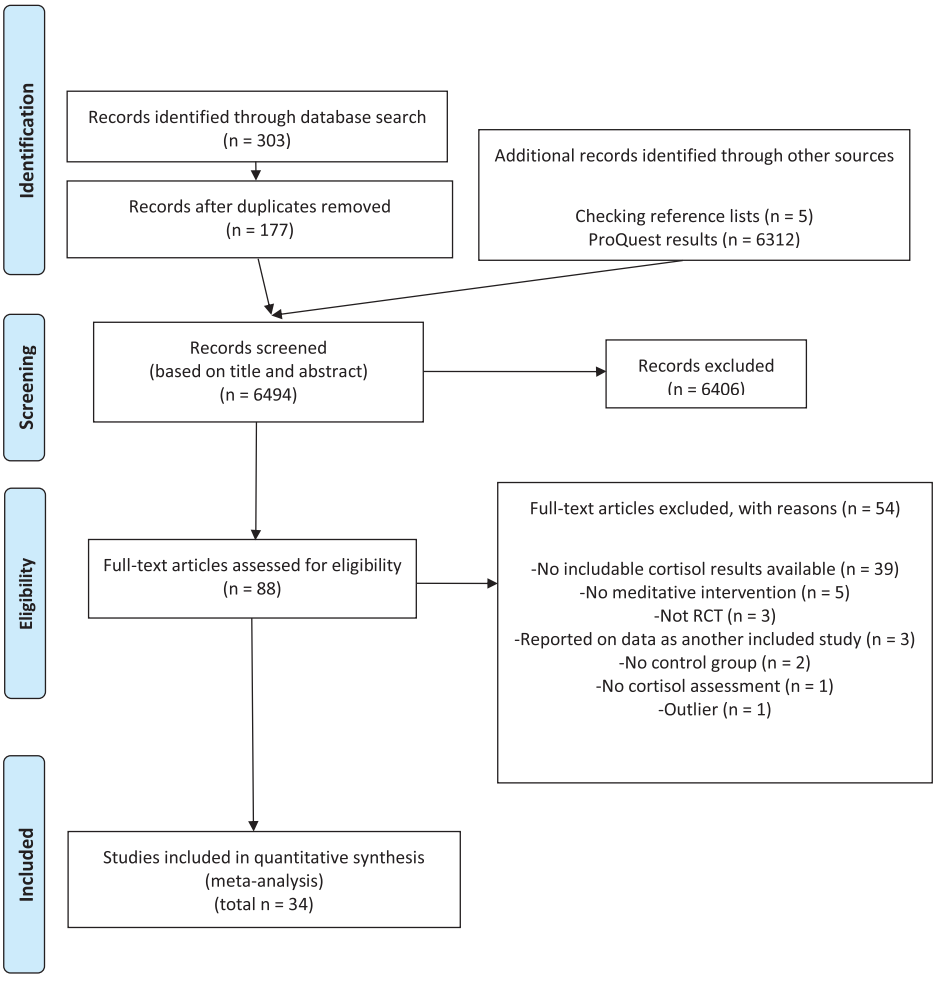


Figure 1. PRISMA Flow diagram.

the first author and a research assistant. As a secondary search, the reference lists of the included articles and other review studies were checked to find all relevant articles by the coders of the study.

Inclusion criteria

(1) The intervention condition had to include meditation as the main component of the intervention (e.g., the intervention was a meditation-based program like MBSR or MBCR). The study was excluded if meditation was only a small part of the program (e.g., Dialectical Behavior Therapy is a type of cognitive–behavioral program for treating mental disorders that also uses mindfulness elements during acceptance procedures (Dimeff & Linehan, 2001), however, the basis of the program is not mindfulness.)
(2) There had to be a passive or an active control condition without meditation to which the meditation condition could be contrasted.
(3) The study had to have a randomized controlled design.
(4) There had to be an outcome measure regarding participants' cortisol levels on pre- and post-test/follow-up: either a single measure, the average of multiple measure(s), the diurnal mean or the area under curve respect to the ground (AUCg) during the day. Alternatively, the first sample taken before a stress test was also included as long as it was taken at approximately the same time of the day on the post-test/follow-up as on the pre-test.
(5) The study had to be written in English.

We had no restrictions regarding the age or clinical status of the participants in the primary studies.

Coding procedure

The following informations were coded: (a) bibliographic information, (b) sample characteristics (e.g., at-risk for elevated cortisol levels or not), (c) characteristics of the meditation intervention (e.g., length of the intervention), (d) characteristics of the control condition (e.g., active or passive), (e) cortisol sampling, and (f) effect size information (sample sizes, and means and standard deviations of cortisol measures in the meditation and the control groups on pre- and post-test/follow-up), (g) the number of days between the end of the intervention and the post-test/follow-up cortisol sampling, (h) type of meditation, (i) intervention components, (j) risk of bias. If the necessary information to calculate the effect size (for example, if a study reported only diurnal slope but not the means of cortisol levels at each time point (e.g., Bränström et al., 2013)) or to estimate the number of days between the end of the intervention and the cortisol sampling was not available, we contacted the authors by e-mail.

In order to test the long-term effects of meditation intervention programs, we conducted a meta-regression analysis in which we used the elapsed time after the intervention until the cortisol measurement to test whether the effects of the interventions fade with time. In case of hair samples (because it is a retrospective analysis with about one cm of hair sample reflecting the total cortisol production from the last month) we calculated the 'mean' of the sampling time (for example in case of a hair sample from one month after the intervention we coded 15 days). If the hair sample was collected within one month from the end of the program (e.g., Nery et al., 2018; Younge et al., 2015) we excluded the study because the sample thus contained cortisol from the time of the intervention and cannot be regarded as a post-test.

To test the effect of the length of the intervention we coded the whole length, but we made an exception for one study (Vandana et al., 2011) in which subjects partook in an eight-month-long intervention. Measures were taken after 48 hours, two months and eight months from the start of the program. In this case, instead of using the measure taken at the end of the intervention (after 8 months), we chose to include the intermittent measure taken two months after the beginning

of the intervention because two months of intervention was more similar in length to the interventions used in the other studies.

Additionally, we coded risk of bias in the included randomized controlled trials using the Cochrane Collaboration's risk of bias tool 2.0 (Sterne et al., 2019). This criteria tool measures with specific questions on five domains such as the randomization process, assignment to intervention, missingness of data, the measurement and selective reporting. Based on the five domains' results, coders decide the overall risk level of the study.

All included studies were coded by two independent coders. The coders were the first author, the research assistant who was involved in the searching and screening process along with other university students. Disagreements were settled in discussion, and if the coders could not make a decision, the first and the last authors were included in the discussion. The Krippendorff's alpha values of inter-rater reliability (Krippendorff, 1980) were calculated with the KALPHA macro for SPSS (Hayes & Krippendorff, 2007). Based on these values inter-rater reliability was always acceptable, ranging from 0.99 (total time of the intervention) to 1.00 (gender distribution).

Meta-analytic procedure

In this meta-analysis we synthetized the evidence regarding the effects of meditation on change in cortisol levels from pre-test to post-test/follow-up assessment. Additionally, we used a meta-regression analysis to test the effect of time between the end of the intervention and the cortisol assessment to investigate whether effects fade with time. The dependent variable in the present study was the standardized mean difference between the meditation and the control group in the change in cortisol from pre- to post-test/follow-up. We utilized the standardized mean difference as an effect size because different sampling strategies were used in the primary studies: a single measurement (Jung et al., 2015), the diurnal mean calculated from more measures (Cash et al., 2015) or the area under the curve respect to the ground (AUCg). If different cortisol indices were reported in a study, we preferred the AUCg measure first, followed by the mean of multiple measures instead of a single measurement. We used the effect size estimate Hedges' *g*, which is similar to Cohen's *d* but corrects for small sample sizes (Borenstein et al., 2009). Effect sizes are considered low around 0.20, medium around 0.50 and large around 0.80 (Cohen, 1988) as an agreement in behavioral sciences (Stoové & Andersen, 2003). Only one study (Malarkey et al., 2013) reported the correlation between the pre- and post-test scores so we standardized the effect sizes by the post-test standard deviations. Data were entered and analyzed in the Comprehensive Meta-Analysis Software 3.3 (Borenstein et al., 2014). If more post-test/follow-up measurements were available in a study, we included all of those and the program calculated the mean of the effect sizes before including the study in the grand average over the different studies. However, for testing the sustained effects in a meta-regression, we only included the results of the cortisol sample that was taken at the latest from the end of the intervention program. In case results were reported for more than one control condition in a study we included both contrasts. For instance, Prakhinkit et al. (2014) used a sedentary control and a traditional walking exercise as control conditions. Again, the software takes the average of the two effect sizes in one study as these are not independent from each other before calculating a grand average.

Positive effect size indicates the advantage of the meditation intervention for cortisol levels as compared to the control condition, that is, either a larger decrease or a smaller increase from pre- to post-test. Effect sizes were inspected for outliers (exceeding a standardized residual of +/−3.29). As the primary studies employed different samples, meditation interventions, control conditions and cortisol sampling approaches, average effect sizes and corresponding 95% confidence intervals were calculated based on the random-effects model, which allows for between-study variances (Borenstein et al., 2009).

Publication bias means that due to having more difficulty publishing non-significant results, significant findings might be overrepresented in meta-analyses (Borenstein et al., 2009). We used the

funnel plot method (Egger et al., 1997) to assess the possibility of publication bias, which plots the inverse of the standard errors (precision) against the effect sizes of the individual studies. An asymmetrical plot suggests that studies with non-significant results might be missing. In case of asymmetry, Duval and Tweedie's trim and fill method (Duval & Tweedie, 2000) can be applied to adjust the average effect size. Rosenthal's fail-safe N method (Rosenthal, 1979) estimates the confidence of the results by calculating the number of studies with non-significant results that would be needed to turn the average effect non-significant. As a rule of thumb, the average effect size is robust if the number is larger than $5k$ +10 (where k is the number of the studies included). Additionally, we used the weight function model (Vevea & Hedges, 1995) that gives a corrected effect size as a result of the adjusted model. This adjusted estimate corrects the effect with pre-specified weights of p-value intervals. Heterogeneity of the average effect size was calculated by the Q-statistics and I^2. Significant heterogeneity means that the variability between effect sizes cannot be attributed to sampling error alone (Borenstein et al., 2009). When the Q-value shows a heterogenous effect it is sensible to conduct moderator analyses in order to explain the variance. The I^2 (Higgins & Thompson, 2002) shows what part of the total variation is caused by the heterogeneity between studies in percentage. As a rule of thumb of interpreting I^2 values under 40% is considered low, between 40–60% moderate, and 60–90% substantial (Schünemann, 2013). Moderator analyses were conducted to (1) test the difference between at-risk and no-risk samples, (2) test the effects of time (the number of days between the end of the intervention and the cortisol sampling on post-test/follow-up), and (3) to check potential sources of bias such as differences in the interventions, the control conditions and the cortisol sampling procedure. In case of categorical variables, we applied subgroup analyses, while for numerical variables regression analyses were conducted. Statistical power calculations were based on recommendations of Hedges and Pigott (2004). If there was not sufficient statistical power, only descriptive results were reported regarding the moderator variables (see Kassai et al., 2019 for a similar procedure). For more details on the statistical power analyses see Appendix 2. Each of the above-mentioned analyses was performed separately for each sample source.

Results

Effect of meditation on blood cortisol

We synthetized the results of 10 studies including data of 395 participants' using blood samples. For the characteristics of the studies see Table 2. Four of these studies utilized a focused attention (FA) type meditation program and were based on mindfulness, three of them used transcendental meditation, two applied body–mind and one mind–body program. In all the studies one blood sample was taken. Only one study did not provide more information (Jung et al., 2015), while nine studies (90%) sampled cortisol in the morning. Five mentioned that sampling was done after fasting. The classic fail-safe N method showed that 67 non-significant studies would turn the average effect non-significant. Thus, according to Rosenthal's criterion, the average effect was robust. The funnel plot was symmetrical so there were no signs of publication bias. Risk of bias in the included studies was 'some concerns' in case of eight studies, while in case of one study it was low and in another it was high (see Table 2 and Appendix 3). Meditation interventions had a medium effect on the change in cortisol levels ($g = 0.62$, $k = 10$, $SE = 0.21$, 95% CI = [0.22, 1.02], $p = .003$). The effect was heterogeneous (Q (9) = 28.99, $p = .001$), $I^2 = 68.95$, 95% CI = [0, 92]. The weight function model produced a bigger effect estimate ($g = 1.20$, 95% CI = [0.47, 1.91]) and the likelihood of this model was −1.66 and for the original model it was 0.70. The likelihood ratio test was significant ($p = .03$) indicating that the adjusted model could be better. Additionally, we tested the overall effect excluding one study at a high risk for bias (Robert McComb et al., 2004). The effect remained medium-sized and significant ($g = 0.62$, $k = 9$, SE = 0.23, 95% CI = [0.18, 1.07], $p = .006$). This effect was also heterogeneous (Q (7) = 28.98, $p < .001$), $I^2 = 72.40$, 95% CI = [3, 94].

Table 2. Characteristics of the studies included in the meta-analysis.

Study name	Participants (age in years and gender distribution if available)	Risk for elevated cortisol levels	Intervention (sample size), (type of meditation)	Control condition (sample size)	Total intervention time	Cortisol measurements	Time from the end of the intervention until cortisol sampling	Risk of bias
Bergen-Cico et al., 2014	age: $M = 48$, $SD = 16$, range: no data; gender: 90% male	Risk (diagnosed: PTSD)	Primary Care brief Mindfulness Program (PCbMP); ($n = 9$), (FA/MBI)	Passive: Primary Care Treatment as Usual (PC-TAU); ($n = 21$)	6 h (4 sessions through 4 weeks)	Five saliva samples each day at specified times for 2 consecutive days (AUCg)	–	Some concerns
Bowden et al., 2012	age: $M = 34$, range: 18–50; gender: 36% male	No risk	Mindfulness procedure; ($n = 12$), (FA/MBI)	Active: Brain Wave Vibration (BWV); ($n = 12$)	12.5 h (10 through 5 weeks)	Two saliva samples between 11 am and 3 p.m.	–	Some concerns
Bowden et al., 2012	age: M = 34, range: 18–50; gender: 36% male	No risk	Mindfulness procedure; ($n = 12$), (FA/MBI)	Active: Iyengar Yoga; ($n = 9$)	12.5 h (10 through 5 weeks)	Two saliva samples between 11 am and 3 p.m.	–	Some concerns
Bränström et al., 2013	age: $M = 51.80$, $SD = 9.86$; range: no data; gender: 1% male	Risk (diagnosed: cancer)	Mindfulness Based Stress Reduction (MBSR); ($n_{(3\ month)} = 29$, $n_{(6\ month)} = 30$), (FA/MBI)	Passive: Wait-List Control; ($n_{(3\ month)} = 37$, $n_{(6\ month)} = 38$)	16 h (8 sessions through 8 weeks)	One saliva sample immediately after awakening (a.m.)	Sampling after 3 and 6 months (90 and 180 days)	Some concerns
Carlson et al., 2013	age: $M = 54.66$, $SD = 9.71$ (intervention), $M = 53.62$, $SD = 10.11$ (control); range: no data; gender: 0% male	Risk (distressed and diagnosed: breast cancer survivor (stage I–III))	Mindfulness-based cancer recovery (MBCR); ($n = 66$), (FA/MBI)	Active: Supportive-expressive group therapy (SET); ($n = 68$)	18 h (8 sessions through 8 weeks + one 6-hour workshop)	Four saliva samples at awakening, noon, 5 p.m. and bedtime through 3 days to calculate diurnal mean	Sampling within two weeks after the intervention (14 days)	Low
Carlson et al., 2013	age: $M = 54.66$, $SD = 9.71$ (intervention), $M = 56.27$, $SD = 1.89$ (control); range: no data; gender: 0% male	Risk (distressed and diagnosed: breast cancer survivor (stage I–III))	Mindfulness-based cancer recovery (MBCR); ($n = 66$), (FA/MBI)	Active: 1-day stress management seminar (SMS); ($n = 34$)	18 h (8 sessions through 8 weeks + one 6-hour workshop)	Four saliva samples at awakening, noon, 5 p.m. and bedtime through 3 days to calculate diurnal mean	Sampling within two weeks after the intervention (14 days)	Low
Cash et al., 2015	age: $M = 48.03$, $SD = 10.09$, range: 23–74; gender: 0% male	Risk (diagnosed: fibromyalgia)	Mindfulness based stress reduction; ($n = 41$), (FA/MBI)	Passive: Wait-list control; ($n = 27$)	20 h (8 sessions through 8 weeks)	Six saliva samples at waking, 45-minutes post-waking (+45 m), 12:00, 16:00, 20:00 h and bedtime through 2 consecutive days to calculate diurnal mean	–	Some concerns

(*Continued*)

Table 2.
Continued.

Study name	Participants (age in years and gender distribution if available)	Risk for elevated cortisol levels	Intervention (sample size), (type of meditation)	Control condition (sample size)	Total intervention time	Cortisol measurements	Time from the end of the intervention until cortisol sampling	Risk of bias
Cash et al., 2015	age: $M = 48.03$, $SD = 10.09$, range: 23–74; gender: 0% male	Risk (diagnosed: fibromyalgia)	Mindfulness based stress reduction; ($n = 41$), (FA/MBI)	Passive: Wait-list control; ($n = 27$)	26 h (8 sessions through 8 weeks + half day meditation retreat (6 h))	Six saliva samples at waking, 45-minutes post-waking (+45 m), 12:00, 16:00, 20:00 h, and bedtime through 2 consecutive days to calculate diurnal mean	two months after the intervention (60 days)	Some concerns
Chhatre et al., 2013	age: $M = 49.7$, $SD = 7.1$ (intervention); $M = 50.0$ $SD = 4.4$ (control), range: over 18; gender: 19% male	Risk (diagnosed: HIV infection)	Transcendental meditation; ($n = 11$), (TM)	Active: Healthy eating education program (HE); ($n = 9$)	18 h (9 sessions through 24 weeks with decreasing frequency)	One blood sample between 9:00 and 10:00; (a.m.)	–	Some concerns
Fan et al., 2013	age: $M = 20.87$, $SD = 0.26$, range: no data; gender: 47% male	No risk	Integrative body–mind training (IMBT); ($n = 17$), (B-M)	Active: Relaxation training (RT); ($n = 17$)	8.3 h (20 sessions through 4 weeks)	One saliva sample after a rest phase before the Mental arithmetic task between 14:00-18:00; (p.m.)	Within five days (5 days)	Some concerns
Flook et al., 2013	age: $M = 43.06$, $SD = 9.87$, range: 25–56; gender: 11% male	No risk	Modified Mindfulness-Based Stress Reduction (mMBSR) adapted for teachers; ($n = 10$), (FA/MBI)	Passive: Wait-List control; ($n = 8$)	26 h (8 sessions through 8 weeks + a day-long immersion (6 hr.))	One saliva sample 30 min after waking on three consecutive working days; (a.m.)	Within one or two week (10.5 days)	Some concerns
Frisvold, 2009	age: $M = 48.3$, $SD = 5.0$ (intervention), $M = 48.4$, $SD = 6.2$ (control), range: 39–57; gender: 0% male	Risk (highly stressed)	Mindfulness Based Stress Reduction (MBSR); ($n = 20$), (FA/MBI)	Active: Midlife health education; ($n = 18$)	26 h (8 sessions through 8 weeks + full day retreat of silent meditation)	One blood sample at 7:00 after 12 h fasting; (a.m.)	16th week after starting the 8-week program (56 days)	Some concerns
Gagrani et al., 2018	age: $M = 57.28$, $SD = 9.37$, range: no data; gender: 65% male	Risk (diagnosed: primary open angle glaucoma (POAG))	Meditation daily; ($n = 30$), (FA/MBI)	Passive: Wait-List control (Standard medical treatment); ($n = 30$)	31.5 h (41 sessions through 6 weeks)	One blood sample at 8:00; (a.m.)	24 h (1 d)	Some concerns

Gainey et al., 2016	age: $M = 58$, $SD = 10.39$ (intervention), $M = 63$, $SD = 6.63$ (control), range: 50–75; gender: 17% male	Risk (diagnosed: Type 2 diabetes)	Buddhism-based walking meditation; ($n = 12$), (B-M)	Active: Traditional walking; ($n = 11$)	30 h (36 sessions through 12 weeks)	One blood sample after 8 h of overnight fasting; (a.m.)	–	Some concerns
Gex-Fabry et al., 2012	age: *Mdn*: 46, range: 24–66; gender: 29% male	Risk: (diagnosed: History of recurrent major depressive disorder)	Mindfulness-based cognitive therapy (MBCT) plus treatment as usual (TAU); ($n = 22$), (FA/MBI)	Passive: Treatment as usual (TAU) for depression relapse prophylaxis; ($n = 22$)	16 h (8 sessions through 8 weeks)	Seven saliva samples at awakening, 15, 30, 45 and 60 min post-awakening, 3 am and 8 p.m. to calculate AUCg	–	Seome concerns
Goldberg et al., 2014	age: $M = 42.2$, $SD = 11.4$, range: 25–65; gender: 44% male	Risk (smoking in the first half of the intervention (smoking cessation program))	Mindfulness training for smokers (MTS); ($n = 10$), (FA/MBI)	Active: Cognitive-behavioral therapy (CBT); ($n = 8$)	20 h (8 sessions through 7 week)	1 cm hair samples 1 month after quit attempt	One month after the end of the intervention (hair), (we used 15 days)	Some concerns
Gotink et al., 2017	age: $M = 43.2$, $SD = 14.1$ (intervention); $M = 43.2$, $SD = 13.7$ (control), range: 18–65; gender: 54% male	No risk (structural heart disease)	Online mindfulness training; ($n = 107$), (FA/MBI)	Passive: Usual care alone (UC); ($n = 98$)	6 h (12 sessions through 12 weeks)	Hair sample from scalp	8.5 months after the end of the intervention (hair) (we used 255 days)	Some concerns
Hsiao et al., 2016	age: $M = 52.5$, $SD = 8.4$ (intervention), $M = 47.9$, $SD = 6.1$ (control), range: 18–65; gender: 0% male	Risk (breast cancer survivors)	Couples support group with mindfulness (CSG); ($n = 10$), (M-B)	Active: Individual support program (ISP); ($n = 10$)	16 h (8 sessions through 8 weeks)	Six saliva samples during the day (at wake up, 30 and 45 min after waking up, at 12:00 17:00 21:00) to calculate diurnal mean	–	Some concerns
Hsiao et al., 2016	age: $M = 52.5$, $SD = 8.4$ (intervention), $M = 47.9$, $SD = 6.1$ (control); range: 18–65, gender: 0% male	Risk (breast cancer survivors)	Couples support group with mindfulness (CSG); ($n = 10$), (M-B)	Active: Individual support program (ISP); ($n = 10$)	16 h (8 sessions through 8 weeks)	Six saliva samples during the day (at wake up, 30 and 45 min after waking up, at 12:00 17:00 21:00) to calculate diurnal mean	Three, six and 12 months after the end of the intervention (90, 180 and 365 days)	Some concerns
Jedel et al., 2014	age: $M = 46.04$, $SD = 12.80$	Risk (diagnosed: (Inactive) Ulcerative Colitis)	Mindfulness Based Stress Reduction	Active: Attention control; ($n = 13$)		Urine samples through a 24-hour	12 months (365 days)	Some concerns

(*Continued*)

Table 2.
Continued.

Study name	Participants (age in years and gender distribution if available)	Risk for elevated cortisol levels	Intervention (sample size), (type of meditation)	Control condition (sample size)	Total intervention time	Cortisol measurements	Time from the end of the intervention until cortisol sampling	Risk of bias
	(intervention), *M*= 39.68, *SD* = 11.06 (control), range: 18–70; gender: 44% male		(MBSR); (*n* = 16), (FA/MBI)		20 h (8 sessions through 8 weeks)	period to calculate 24-Hour cortisol in µg		
Jensen et al., 2011	age: *M* = no data, range 20–36; gender: 38% male	No risk	Mindfulness-Based Stress Reduction (MBSR); (*n* = 14), (FA/MBI)	Active: Non-mindfulness Stress Reduction (NMSR); (*n* = 13)	27 h (8 sessions through 8 weeks + 7 h retreat)	Five saliva samples: first upon awakening, and Samples 2–5every 15 min for the subsequent hour to calculate AUCg; (a.m.)	–	Some concerns
Jensen et al., 2011	age: *M* = No data, range 20–36; gender: 38% male	No risk	Mindfulness-Based Stress Reduction (MBSR); (*n* = 14), (FA/MBI)	Passive: Inactive controls (incentive and No incentive analysed together = collapsed inactive controls (CICO)); (*n* = 14)	27 h (8 sessions through 8 weeks + 7 h retreat)	Five saliva samples: first upon awakening, and Samples 2–5every 15 min for the subsequent hour to calculate AUCg; (a.m.)	–	Some concerns
Jung et al., 2015	age: *M* = 66.27, *SD* = 8.36 range: no data; gender: 48% male	Risk (diagnosed: type 2 diabetes mellitus)	Korean mindfulness-based stress reduction (K-MBSR) + PE; (*n* = 21), (FA/MBI)	Passive: Patient education only (PE); (*n* = 17)	20 h (16 sessions through 8 weeks)	One blood sample (no more information)	–	Some concerns
Jung et al., 2015	age: *M* = 66.27, SD = 8.36 range: no data; gender: 48% male	Risk (diagnosed: type 2 diabetes mellitus)	Korean mindfulness-based stress reduction (K-MBSR) + PE; (*n* = 21), (FA/MBI)	Active: Walking exercise program + PE; (*n* = 18)	20 h (16 sessions through 8 weeks)	One blood sample (no more information)	–	Some concerns
Kim et al., 2013	age: *M* = 47.6, *SD* = 7.7 (intervention), M = 45.0, SD = 10.0 (control) range: no data; gender: 5% male	Risk: (participants with subclinical features of PTSD)	Mind-body intervention (MBX); (*n* = 11), (M-B)	Passive: Control; (*n* = 11)	16 h (16 sessions through 8 weeks)	One blood sample around 8:00; (a.m.)	–	Some concerns
Lipschitz et al., 2013	age: *M* = 50.8, *SD* = 9.10 (intervention), *M* = 51.6, *SD* = 10.7 (control), range: 18–75; gender: 21% male	Risk (cancer survivor)	Mindfulness meditation (MM) (*n* = 20), (FA / MBI)	Active: Sleep Hygiene Education (SHE); (*n* = 18)	No data (3 sessions through 3 weeks)	Four saliva samples (Post-awake, Noon, Afternoon (5 p.m.), Evening (10 p.m.)) to calculate diurnal mean	Minimum of one week following the final session (7 days)	Some concerns

Lipschitz et al., 2013	age: $M = 50.8$, $SD = 9.10$ (intervention), $M = 55.4$, $SD = 9.6$ (control), range: 18–75 gender: 27% male	Risk (cancer survivor)	Mindfulness meditation (MM) ($n = 20$), (FA / MBI)	Active: Mind-Body Bridging (MBB); ($n = 19$)	No data (3 sessions through 3 weeks)	Four saliva samples (Post-awake, Noon, Afternoon (5 p.m.), Evening (10 p.m.)) to calculate diurnal mean	Minimum of one week following the final session (7 days)	Some concerns
Marshall et al., 2018	age: $M = 56.38$, $SD = 14.57$, range: 38-73; gender: 63% male	No risk (but: diagnosed: aphasia after stroke)	Mindfulness meditation ($n = 5$), (FA / MBI)	Active: Mind wandering ($n = 3$)	0.75 h (3 sessions through 3 days)	One saliva sample in the afternoon; (p.m.)	1 day after the 3th session (1 day)	Some concerns
MacLean et al., 1997	age: $M = 25$, range: 18-32; gender: 100% male	No risk	Transcendental Meditation ™ program; ($n = 16$), (TM)	Active: Stress education control (SEC); ($n = 13$)	65.3 h (124 sessions through 16 weeks)	One blood sample between 8:30-9:30 after 12 hr. fasting before a TSST; (a.m.)	-	Some concerns
Malarkey et al., 2013	age: $M = 51$, $SD = 7.67$ (intervention), $M = 49$, $SD = 7.72$ (control), range: no data; gender: 13% male	Risk (elevated CRP levels or/and have risk for cardiovascular disease, or depression hypertension hyperlipidemia, gastroesophageal reflux disease (GERD), osteoarthritis, diabetes)	Low dose Mindfulness-Based Intervention (MBI-ld); ($n = 84$), (FA/MBI)	Active: Education Control; ($n = 86$)	10 h (8 sessions through 8 weeks + 2 h retreat)	Four saliva samples 20 min post rising, noon, 5 pm, and bedtime on three days (days 2, 8 and 14 of a 2-week period)	In a two-week period after the intervention (14 days)	Some concerns
Nyklíček et al., 2013	age: $M = 46.1$, $SD = 10.6$, range: no data; gender: 29% male	Risk (elevated stress levels)	Mindfulness-Based Stress Reduction; ($n = 32$), (FA/MBI)	Passive: Wait-list control; ($n = 30$)	20 h (8 sessions through 8 weeks)	One saliva sample after a resting period before a computerized stress session in the afternoon; (p.m.)	-	Some concerns
Oken et al., 2010	age: $M = 62.50$, $SD = 11.61$, (intervention), $M = 67.09$, $SD = 8.36$ (control), range: 45–85; gender: 19% male	Risk (dementia caregivers)	An adapted meditation intervention based on MBSR and MBCT; ($n = 10$), (FA / MBI)	Active: A program adapted from Powerful Tools for Caregivers (PTC): 'Education'; ($n = 11$)	9 h (6 sessions through 7 weeks)	Three saliva samples within 5 min after awakening, 30 min later before eating, bedtime, (10–11 *p*m) to calculate diurnal mean	Within three weeks after the last class (21 days)	Some concerns
Oken et al., 2010	age: $M = 62.50$, $SD = 11.61$, (intervention), $M =$	Risk (dementia caregivers)	An adapted meditation intervention based	Passive: Respite-only; ($n = 10$)	9 h (6 sessions through 7 weeks)	Three saliva samples within 5 min after awakening, 30 min	Within three weeks after the	Some concerns

(*Continued*)

Table 2.
Continued.

Study name	Participants (age in years and gender distribution if available)	Risk for elevated cortisol levels	Intervention (sample size), (type of meditation)	Control condition (sample size)	Total intervention time	Cortisol measurements	Time from the end of the intervention until cortisol sampling	Risk of bias
	63.80, *SD* = 7.93 (control), range: 45–85; gender: 19% male		on MBSR and MBCT; (*n* = 10), (FA / MBI)			later before eating, bedtime, (10–11 *pm*) to calculate diurnal mean	last class (21 days)	
Prakhinkit et al., 2014	age: *M* = 74, *SD* = 6.36 (intervention); *M* = 74.8, *SD* = 6.13, (control) range: 60–90; gender: 0% male	Risk (mild-to-moderate depressive symptoms)	Buddhism-based walking meditation (BWM), (*n* = 14), (B-M)	Active: Traditional walking exercise (TWE); (*n* = 13)	15 h (36 sessions through 12 weeks)	One blood sample after 8 h overnight fasting; (a.m.)	-	Some concerns
Prakhinkit et al., 2014	age: *M* = 74, *SD* = 6.36; (intervention), *M* = 81.0, *SD* = 6.14 (control), range: 60–90; gender: 0% male	Risk (mild-to-moderate depressive symptoms)	Buddhism-based walking meditation (BWM), (*n* = 14), (B-M)	Passive: Sedentary control; (*n* = 13)	15 h (36 sessions through 12 weeks)	One blood sample after 8 h overnight fasting; (a.m.)	-	Some concerns
Robert McComb et al., 2004	age: *M* = 60, *SD* = 6.3, range: no data; gender: 0% male	Risk (history of heart disease)	Mindfulness-Based Stress Reduction; (*n* = 9), (FA / MBI)	Passive: Wait-list control; (n = 9)	16 h (8 sessions through weeks)	One blood sample in the morning after 12 h. fasting (a.m.)	-	High
Roeser et al., 2013	age: *M* = 50, *SD* = no data, range 28–59 (intervention), M = 46 SD = no data, range: = 29–63 (control); gender: 10% male	No risk	Mindfulness Training Program (*n* = 26), (FA / MBI)	Passive: Waitlist-control (n = 32)	36 h (11 sessions through 8 week)	Three saliva samples at awakening, 30 min after awakening, and at bedtime	-	Some concerns
Roeser et al., 2013	age: *M* = 50, *SD* = no data, range 28–59 (intervention), *M* = 46 *SD* = no data, range: = 29–63 (control); gender: 10% male	No risk	Mindfulness Training Program (*n* = 26), (FA / MBI)	Passive: Waitlist-control (n = 32)	36 h (11 sessions through 8 week)		Three months follow up (90 days)	Some concerns
Schonert-Reichl et al., 2015	age: *M* = 10.24, *SD* = 0.53, range: 9.00–11.16; gender: 46% male	No risk	MindUP program (a mindfulness-based education social and emotional learning (SEL) program); (*n* = 48), (FA / MBI)	Active: Regular social responsibility program; (*n* = 51)	9 h (12 sessions through 12 weeks)	Three saliva samples at 9:00 a.m. 11:30 a.m. and 2:30 p.m. to calculate daily mean	Within one week after the intervention (7 days)	Some concerns

Sibinga et al., 2013	age: $M = 12.5$, $SD =$ no data, range: 11–14; gender: 100% male	Risk (low income)	Mindfulness-Based Stress Reduction; ($n = 22$), (FA / MBI)	Active: Health education (Healthy Topics – HT); ($n = 11$)	10 h (12 sessions through 12 weeks)	Three saliva samples at awakening, 60 min post-awakening and bedtime, to calculate AUCg	Within two weeks after the intervention (14 days)	Some concerns
Turan et al., 2015	age: $M = 40.61$, $SD = 10.28$, range: 25–60; gender: 0% male	No risk	Meditation and emotional skills training; ($n = 35$), (FA / MBI)	Passive: No treatment control; ($n = 35$)	42 h (4 all-day and 4 evening sessions through 8 weeks)	One saliva sample following a 20 min resting phase before a TSST	On the concluding occasion (0 days)	Some concerns
Turan et al., 2015	age: $M = 40.61$, $SD = 10.28$, range: 25–60; gender: 0% male	No risk	Meditation and emotional skills training; ($n = 35$), (FA / MBI)	Passive: No treatment control; ($n = 35$)	42 h (4 all-day and 4 evening sessions through 8 weeks)	One saliva sample following a 20 min resting phase before a TSST	Five months after the intervention (150 days)	Some concerns
Van Dam, 2013	age: $M = 40.0$, $SD = 13.3$ (intervention), $M = 36.9$, $SD = 14.2$ (control) range: 28–65; gender: 32% male	Risk (community sample with undiagnosed, but significant, symptoms of anxiety, depression, and stress)	Mindfulness meditation training (MMT); ($n = 21$), (FA / MBI)	Passive: Wait-list control (NT); ($n = 11$)	26 h (8 sessions through 8 weeks + 6-hour retreat)	One saliva sample before a TSST	One and a half months after the intervention (45 days)	Some concerns
Vandana et al., 2011	age: $M =$ no data, range: 18–21; gender: 19% male	No risk	Integrated Amrita Meditation (IAM); ($n = 30$), (TM)	Active: Progressive Muscle Relaxation (PMR); ($n = 31$)	14.93 h (32 sessions through 8 weeks)	One blood sample at 8:00; (a.m.)	One day	Some concerns
Vandana et al., 2011	age: $M =$ no data, range: 18–21; gender: 18% male	No risk	Integrated Amrita Meditation (IAM); ($n = 30$), (TM)	Passive: No treatment control; ($n = 28$)	14.93 h (32 sessions through 8 weeks)	One blood sample at 8:00; (a.m.)	One day	Low
Zhang & Emory, 2015	age: $M = 25.3$, $SD = 4.6$, range: 18–45; gender: 0% male	Risk (pregnant)	Mindful Motherhood; ($n = 12$), (FA/MBI)	Passive: Treatment as usual (TxAU); ($n = 14$)	(8 sessions through 4 weeks)	One saliva sample between 8:30 a.m. and 12:00 p.m. before an audio clip of a baby's cry (a 'stress' reactivity test)	–	Some concerns

There was also a significant medium-sized effect for at-risk samples and a large but non-significant effect for no-risk samples. Without the high-risk bias study, there was a similar, marginally significant effect for at-risk samples ($g = 0.50$, $k = 7$, SE = 0.26, 95% CI = [−0.004, 1.007], $p = .052$) and it was heterogeneous (Q (6) = 21.06, $p = .002$), $I^2 = 71.51$, 95% CI = [0, 93].

We investigated the efficacy of meditation interventions for different at-risk samples. Three studies included participants with a mental problem and showed no effects of the interventions. Five studies included participants with a somatic illness. In these studies the effect was large and significant. Furthermore, we checked the effect of methodological differences between the primary studies. To test the effect of the type of control group we excluded three studies (Jung et al., 2015; Prakhinkit et al., 2014; Vandana et al., 2011) that used both an active and a passive control condition. In contrast to active control groups, there was a large, marginally significant effect of meditation intervention, while compared to passive controls, the effect size was medium-sized and non-significant. We did not have enough statistical power to compare these subgroups. One study did not report information about the time of sampling (Jung et al., 2015), while the others took samples before noon (for more details and the results of subgroup analyses see Table 3 and Figure 2 and 3).

We had sufficient statistical power to run meta-regression analyses (Table 4). Intervention duration had a significant positive effect on the effect size after excluding one outlier (MacLean et al., 1997) suggesting that longer meditation interventions had larger effects on participants' blood cortisol levels. It seems that interventions longer than 1200 minutes seem to be most effective (see Figure 4). The other interesting finding is that these programs are more effective for men (see Figure 5). We were unable to test the effect of the elapsed time after the intervention until the post-test cortisol sampling because only three studies reported on this information. There was no effect of age (see Table 4).

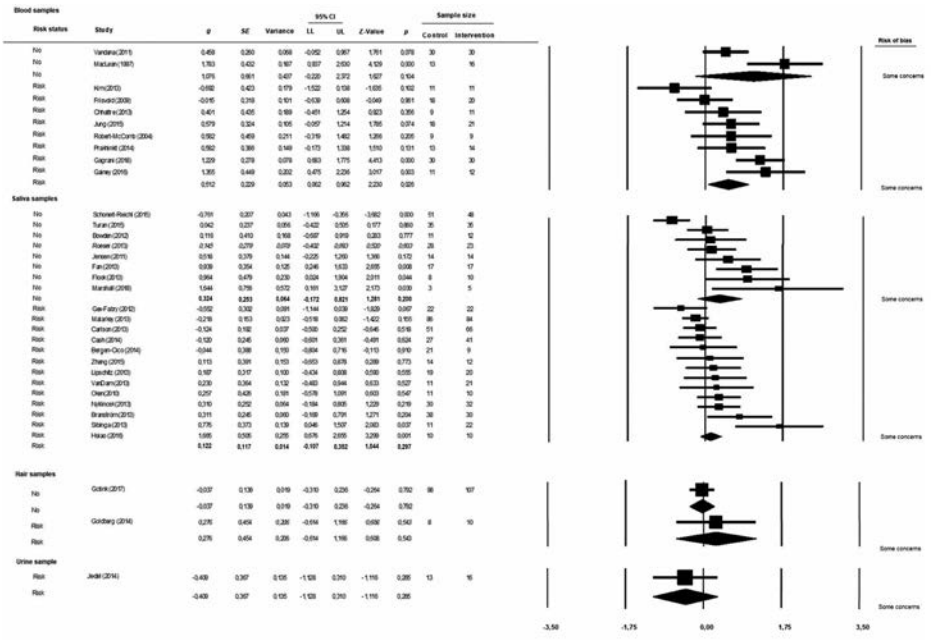
Effect of meditation on salivary cortisol

There was one outlying study (Stefanaki et al., 2015) based on standardized residuals. After excluding that study, we synthesized the results of 21 trials including data of 1163 participants. For the characteristics of the studies see Table 2. Nineteen of these studies utilized a meditation program based on mindfulness and used focused attention (FA) type meditation, while one used mind–body (M-B) (Hsiao et al., 2016) and the other study a body–mind (B-M) intervention (Fan et al., 2013). Only five studies (24%) took saliva samples on more days: one of them sampled one per day, while two sampled four and another two on five occasions during the

Table 3. Effects of meditation interventions on change of blood cortisol in the different subgroup moderator analyses for methodological differences in the primary studies.

					95% CI			*Q statistic*			*I^2 statistic*		
												95% CI	
Moderator	*g*	*k*	*n*	*SE*	LL	UL	*p*	*Q*	*df (Q)*	*p*	*I^2*	LL	UL
Risk status													
No risk	1.08	2	118	0.66	−0.22	2.37	.104	6.92	1	.009	86%	0%	99%
At-risk	0.51	8	277	0.23	0.06	0.96	.026	21.06	7	.004	67%	0%	93%
Type of problem in case of at-risk samples													
Mental	−0.02	3	100	0.34	−0.69	0.64	.945	4.96	2	.08	60%	0%	97%
Somatic	0.87	5	177	0.19	0.49	1.24	<.001	5.18	4	.26	23%	0%	87%
Stressful life situation	-	-	-	-	-	-	-	-	-	-	-	-	-
Control condition													
Active	0.85	4	110	0.44	−0.002	1.70	.051	13.94	3	.003	78.48	0%	97%
Passive	0.40	3	100	0.59	−0.76	1.56	.500	14.39	2	.001	86.10	0%	98%
Sampling time													
A.M.	0.63	9	339	0.23	0.17	1.08	.007	28.97	8	<.001	72.39	0%	93%
P.M.	-	-	-	-	-	-	-	-	-	-	-	-	-

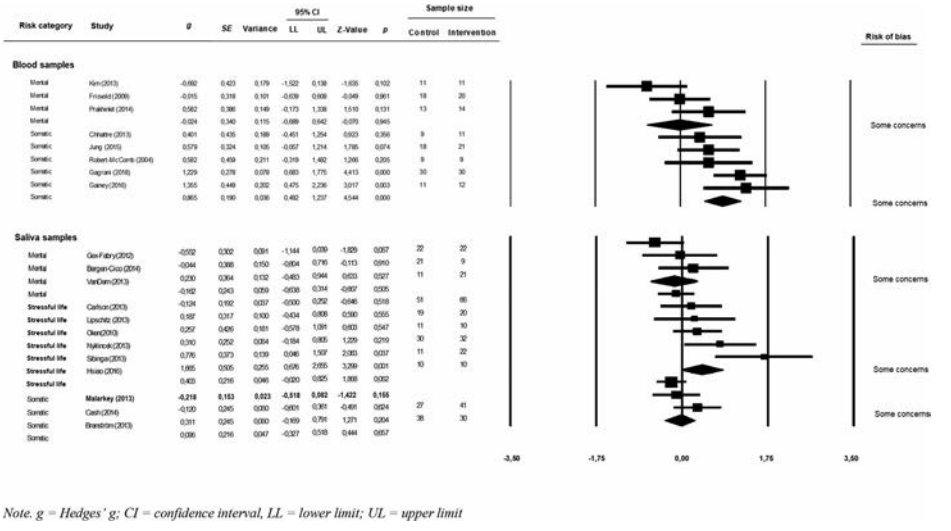
Note: g = Hedges' g; CI = confidence interval, LL = lower limit; UL = upper limit.



Note. g = Hedges' g; CI = confidence interval, LL = lower limit; UL = upper limit

Figure 2. Forest plot for all included studies.

day. Sixteen studies (76%) sampled on only one day and half of them sampled on three or more occasions per day, in seven studies samples were taken on only one occasion per day, while one study sampled twice on the sampling day. From all the included studies, only three synchronized all sampling times to waking times. The classic fail-safe N method showed that 11 non-significant studies would turn the average effect non-significant. Thus, according to Rosenthal's criterion, the average effect was not robust. The Duval and Tweedie's trim and fill method showed eight trimmed studies and the adjusted effect size was $g = -0.10$ and non-significant (95% CI = [−0.33; −0.13]). Risk



Note. g = Hedges' g; CI = confidence interval, LL = lower limit; UL = upper limit

Figure 3. Forest plot for subgroups in at-risk categories.

Table 4. Results of meta-regression analyses for methodological differences in the primary studies that used blood cortisol sampling.

				95%CI		
Regression	Coefficient	*k*	*SE*	LL	UL	*p*
Gender distribution	0.0114	10	0.0049	0.0018	0.0209	.020
Mean age	−0.0022	10	0.0133	−0.0284	0.0239	.867
Total intervention time	0.0010	9	0.0004	0.0003	0.0018	.009
Elapsed time after intervention	–	–	–	–	–	–

Note: CI = confidence interval, LL = lower limit; UL = upper limit.

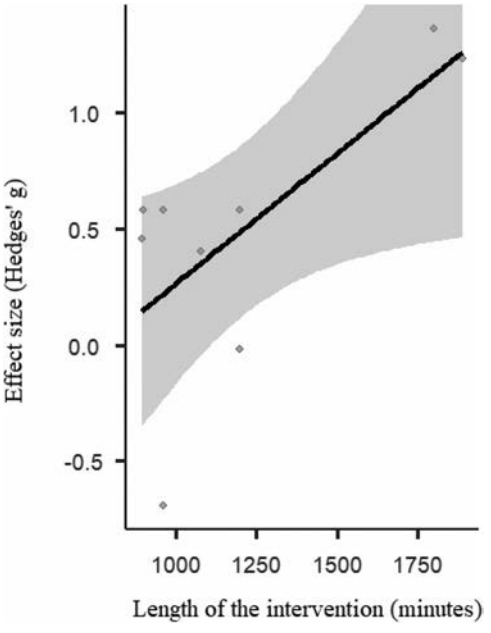


Figure 4. Effect of the length of the intervention in blood samples.

of bias analyses in these studies indicated some concerns and only one study's risk was low (see Table 2 and Appendix 3). Meditation had a small and marginally significant effect on change in cortisol levels in salivary samples ($g = 0.18$, $k = 21$, $SE = 0.11$, 95% CI = [−0.04, 0.40], $p = .102$). The effect was heterogeneous (Q (20) = 56.77, $p < .001$, $I^2 = 64.77$, 95% CI = [11, 86]). Estimating the effect with the weight function model resulted in a negative effect ($g = -0.10$, 95% CI = [−0.28, 0.08]) and the likelihood of this model was −1.73 and −2.50 for the original model. The likelihood ratio test was non-significant ($p = .21$) indicating that the original model is as good as the adjusted one. After excluding the two studies that reported on the results of participants under 18 years (Schonert-Reichl et al., 2015; Sibinga et al., 2013) the effect was similar in size and marginally significant ($g = 0.20$, $k = 19$, $SE = 0.10$, 95% CI = [−0.002, 0.398], $p = .052$). Again, this was a heterogeneous effect (Q (18) = 37.02, $p = .005$) $I^2 = 51.38$, 95% CI = [0, 83].

Furthermore, we assessed the moderator of the samples' risk status. For both at-risk and no-risk samples the effect was small and not significant. We had insufficient statistical power to contrast the above mentioned average effect sizes. We also investigated the efficacy of meditation interventions for different at-risk samples. For the results of subgroup analyses see Table 5 and Figure 3. Three studies reported on participants with a diagnosis or symptoms of a mental illness and three on somatic problems. On average, there was no significant effect of meditation either for the samples

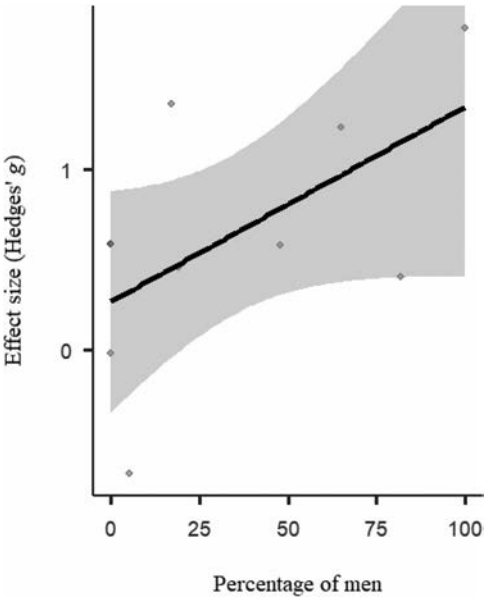


Figure 5. Effect of gender distribution in blood samples.

with a mental disorder or in the studies including participants with somatic issues. In the six studies that tested samples in stressful life situation a marginally significant, medium effect appeared. The statistical power was not enough to compare the above-mentioned categories. One study with a sample at a risk for elevated cortisol levels including pregnant women (Zhang & Emory, 2015) could not be categorized into the above-mentioned categories.

To check the methodological differences between the primary studies we, again, ran subgroup analyses (see Table 5). For testing the effect of the type of control group, we excluded those studies that

Table 5. The effect in change of salivary cortisol. Results of subgroup moderator analyses for methodological differences in the primary studies.

					95% CI			*Q statistic*			I^2 *statistic*		
												95% CI	
Moderator	*g*	*k*	*n*	*SE*	LL	UL	*p*	*Q*	*df(Q)*	*p*	I^2	LL	UL
Risk status													
No risk	0.32	8	354	0.25	−0.17	0.82	.200	31.46	7	<.001	78%	13%	94%
At-risk	0.12	13	809	0.12	−0.11	0.35	.297	25.31	12	.013	53%	0%	87%
Type of problem in case of at-risk samples													
Mental	−0.16	3	106	0.24	−0.64	0.31	.505	2.91	2	.233	31%	0%	94%
Somatic	−0.05	3	306	0.16	−0.36	0.26	.765	3.40	2	.184	41%	0%	94%
Stressful life situation	0.40	6	371	0.22	−0.02	0.83	.062	13.75	5	.017	64%	0%	93%
Control condition													
Active	0.22	8	614	0.23	−0.22	0.66	.323	38.17	7	<.001	82%	33%	94%
Passive	0.13	11	477	0.12	−0.09	0.36	.246	14.64	10	.146	32%	0%	83%
Sampling time													
A.M.	0.40	4	153	0.17	0.06	0.73	.020	2.15	3	.541	0%	0%	74%
P.M.	0.74	3	104	0.33	0.10	1.39	.024	4.14	2	.126	52%	0%	96%
A.M. and P.M.	0.01	12	804	0.14	−0.27	0.29	.951	33.37	11	<.001	67%	0%	90%
Sampling procedure													
One sample/day	0.39	8	320	0.14	0.12	0.66	.005	9.57	7	.215	27%	0%	85%
More samples	0.04	13	843	0.14	−0.23	0.32	.756	36.09	12	.001	67%	0%	90%

Note: *g* = Hedges' g; CI = confidence interval, LL = lower limit; UL = upper limit.

used both an active and a passive control condition (Jensen et al., 2011; Oken et al., 2010). There were no significant effects of meditation compared either to active or passive control groups and we had insufficient statistical power to contrast them. In case of those four studies that reported the time of sampling, studies in which they collected samples before noon showed a small and significant effect, and in those three studies that sampled in the afternoon the effect was large and also significant. Those 12 studies that sampled both AM and PM showed an effect that was near to zero and non-significant (see Table 5). There was no sufficient statistical power for contrasting. Two studies did not report this information (Turan et al., 2015; Van Dam, 2013). Additionally, we tested the effect of the number of cortisol samples that were collected in the primary studies. In case of the 13 studies that collected multiple samples, 12 of them collected them both AM and PM (the same group as mentioned above), while in one study (Jensen et al., 2011) they collected samples before noon. There was no significant effect in those studies that collected multiple samples. In those studies that collected only one sample during a day (three sampled AM, three sampled PM and two did not give any information) (Turan et al., 2015; Van Dam, 2013) the effect was medium-sized and significant (see Table 5). There was not enough statistical power to contrast them.

We had enough statistical power for all the meta-regression analyses (Table 6). There were no effects of gender distribution, the age of the participants or the total time of the intervention. In case of the elapsed time after the intervention we excluded one study (Hsiao et al., 2016) because it was an outlier in this regard (the latest sampling was after one year). The effect was non-significant (see Table 6 and Figure 6).

Comparison of results from blood and saliva samples

As the results show, a significant main effect of meditation interventions was found in the studies that utilized blood samples. More specifically, these interventions had a large effect on samples with a somatic illness. In contrast, studies assessing saliva cortisol showed no significant main effect of meditation interventions except for the subset of studies that sampled people living in stressful life situations. Thus, a plausible explanation for the differential main effects of meditation interventions on blood and saliva cortisol is that 80% of the studies focusing on blood cortisol included at-risk samples and, more specifically, half of the studies included participants with a somatic illness (for whom a large effect was found). On the other hand, only 62% of the studies focusing on saliva samples included at-risk participants, more specifically, 14% of the studies recruited participants with a somatic illness and 29% included samples living in stressful life situations (for whom a moderate-sized effect was found). In sum, the overall large effect found on blood samples might be explained by the fact that the proportion of studies with at-risk samples (and more specifically, patients with a somatic illness) was larger for these studies as compared to trials utilizing saliva samples to assess cortisol levels.

Another possible explanation is that 90% of the blood samples were taken before noon, in which studies the effect was medium-sized and significant. In contrast, studies that took saliva samples before noon also showed a medium-sized and significant effect. However, half of these studies included at-risk samples. If we look at those studies that collected saliva samples both before and afternoon, there was no effect. Nine of these studies (75%) focused on at-risk samples. A puzzling

Table 6. Results of meta-regression analyses for methodological differences in the primary studies that use salivary cortisol.

				95%CI		
Regression	Coefficient	*k*	*SE*	LL	UL	*p*
Gender distribution	0.0024	21	0.0042	−0.0059	0.0107	0.572
Mean age	0.0023	21	0.0081	−0.0136	0.0182	0.775
Total intervention time	0.0000	19	0.0002	−0.0004	0.0004	0.981
Elapsed time after intervention	0.0001	15	0.0023	−0.0043	0.0045	0.962

Note: CI = confidence interval, LL =lower limit; UL = upper limit.

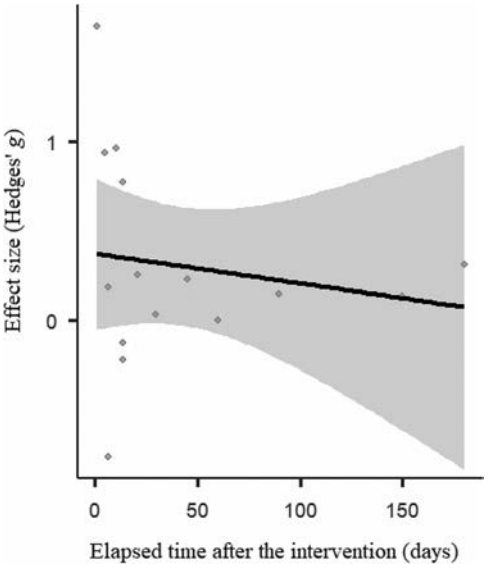


Figure 6. Effect of the elapsed time after the intervention in saliva samples.

finding is that saliva samples taken in the afternoon showed a large and significant effect. In sum, although no clear pattern emerges, the timing of cortisol sampling could have an effect on the results.

Effect of meditation on hair cortisol

Only two included studies reported results based on hair cortisol. Mindfulness-based and focused attention (FA) interventions were used in both studies. The average effect size of the two studies including a total of 223 participants showed no effect ($g = -0.01$, $k = 2$, $SE = 0.13$, 95% CI = [−0.27, 0.25], $p = .94$), which was a homogeneous result (Q (1) = 0.43, $p = .510$, $I^2 = 0.00$). Gotink et al. (2017) reported results of participants with no risk (structural heart disease) and found a null effect ($g = -0.04$, $k = 1$, $SE = 0.14$, 95% CI = [−0.31, 0.24], $p = .79$) compared to a passive control condition. The overall risk of bias in this study indicated some concerns. Goldberg et al. (2014) reported results of at-risk participants as they were in the middle of smoking cessation. In this study there was a small and non-significant effect of the intervention ($g = 0.28$, $k = 1$, $SE = 0.45$, 95% CI = [−0.61, 1.16], $p = .54$) compared to an active control condition. There were some concerns regarding the risk of bias in this study.

Effect of meditation on urine cortisol

One study assessed the effects of a meditation intervention on urine cortisol of 29 participants (Jedel et al., 2014). In this study there was a non-significant, medium-sized negative effect ($g = -0.41$, $k = 1$, $SE = 0.36$, 95% CI = [−0.13, 0.31], $p = .27$) of the Mindfulness-Based Stress Reduction program compared to an active control condition in an at-risk sample of inactive ulcerative colitis patients. The risk of bias showed some concerns in this study.

Discussion

The present meta-analysis provides a synthesis of all available evidence regarding the efficacy of meditation interventions on the change in participants' cortisol levels in different sampling

sources. Effects were tested not only on the short-, but also on the long-term. Additionally, we assessed whether participants at a risk for elevated cortisol levels (e.g., due to mental and somatic illnesses or a stressful life situation) benefit more from these interventions as compared to no-risk samples. We extended previous results by an exhaustive review of the available evidence: we included studies with any sources of cortisol sampling (saliva, blood, urine or hair), any types of meditation interventions, any control conditions (active or passive) and any samples of participants. Still, it should be noted that most of the included studies utilized a meditation program based on mindfulness. Risk of bias was also evaluated.

In 10 randomized controlled trials including data of 395 participants, there was a significant, medium-sized effect of meditation interventions on changes in cortisol levels in blood samples ($g = 0.62$), however, there were some concerns about the risk of bias in the included studies. The publication bias indicators did not suggest any problems so the effect seems to be robust. This finding is in line with the result of Pascoe et al. (2017) who found a medium-sized effect of meditation interventions on blood cortisol.

There was a significant, medium-sized benefit of meditation interventions for at-risk samples and a non-significant but large effect for no-risk participants when considering blood samples. More specifically, meditation interventions showed a large, significant effect on cortisol for samples with a somatic illness and no effect for samples with mental problems. Thus, partially in line with our expectations and the mindfulness stress buffering account of Creswell and Lindsay (2014) who predicted more benefits of mindfulness interventions for at-risk samples (people experiencing a large amount of stress or having an illness that is susceptible to stress), upon closer inspection we only found a significant effect for samples with a somatic illness. It should be noted that there were only two no-risk samples in the studies focusing on blood cortisol and we did not have enough statistical power to statistically contrast effects for the different samples. Thus, these results should be considered preliminary.

When assessing results on salivary cortisol, there was no main effect of meditation interventions or any effects for at-risk or no-risk samples either. However, there was a moderate-sized benefit of these programs for samples living in stressful life situations such as low-income family members, dementia caregivers, cancer survivors or cancer patients. Additionally, when we focused on adult participants only, there was a marginally significant, small effect for no-risk samples. It should be noted that we found signs of a possible publication bias and the average effect size was not robust. Moreover, the risk of bias in the primary studies was categorized as 'some concerns' with one exception, thus the results should be regarded cautiously. The reason for this categorization in most cases was a lack of a statistical analysis plan reported.

In sum, we found differential main effects of meditation interventions on blood and saliva samples, however, we suspect that it is due to the larger ratio of studies with at-risk samples and, more specifically, patients with a somatic illness in the studies focusing on blood samples. This is also conceivable as access to blood samples is more likely in studies including hospitalized samples as compared to studies utilizing saliva samples. Upon closer inspection, both sets of studies seem to show, in line with our hypothesis, that meditation interventions are especially beneficial for samples at a risk for elevated cortisol levels.

A puzzling finding is that meditation interventions showed no effects, based on the available three studies on blood cortisol and three studies on salivary cortisol for participants with a diagnosis or symptoms of a mental disorder. This contrasts previous results showing the benefits of meditation for symptoms of depression and anxiety (Goyal et al., 2014). Further research is warranted.

In contrast to previous reviews, we intended to conduct meta-regression analyses to test the sustained effect of meditation interventions on follow-up assessments. We could only test this variable on saliva samples. Surprisingly, when focusing on the results of the cortisol sampling furthest in time from the end of the intervention, we did not find any significant effect of the time between the end of the intervention and the sampling on the effect size on salivary cortisol. This is a very preliminary result, but it seems to suggest that effects do not disappear with time. We have no information

regarding whether participants sustained a meditation practice after the intervention, but it is also plausible that a few weeks long meditation program could provide participants with strategies of stress management that are used on the long-run, even without a lasting meditation practice. At the same time, we would like to emphasize that only a very limited number of studies provided information on more than three-month follow-up assessment. Further studies including repeated assessments over longer periods of time are needed.

An interesting finding of the present study was the significant effect of the length of the interventions on the effect size in case of blood samples suggesting that longer meditation programs were more effective in stress reduction. This result has important practical implications. Interventions longer than 20 hours seem to be most effective as shown in Figure 6.

Finally, in contrast with Sanada et al. (2016) results regarding salivary cortisol, a puzzling finding of the present study is a marginally significant effect of gender ratio in the studies assessing blood cortisol. We found that meditation interventions might be more effective for men.

Recommendations for future research

Based on our results and the state of the available scientific evidence, further research is clearly needed. As our results show, the available information regarding the effect of meditation programs on cortisol levels of people with mental problems is very limited. Further RCTs should focus on homogeneous samples with diagnosed mental disorders in order to get a clear picture on the effectiveness of these techniques for such populations. Although Goyal et al. (2014) found that mindfulness has beneficial effects on symptoms of anxiety and depression, it is not clear yet whether this effect can also be confirmed by cortisol results. Furthermore, with substantially more studies focusing on homogeneous samples with mental disorders future meta-analyses will be able to invesitage for which disorders meditation interventions might be beneficial. In contrast, it seems that meditation can be beneficial in case of somatic problems (based on blood cortisol results) and for people in stressful life situations (based on salivary cortisol results). However, these categories were still very heterogeneous. Further RCTs with a variety of somatic disorders and stressful life situations will enable more specific suggestions.

Another gap in the literature is that most of the evidence come from adult samples. In fact, we only found two studies assessing the effects of a meditation intervention on children's cortisol levels (Schonert-Reichl et al., 2015; Sibinga et al., 2013). It is not clear yet if these techniques could be effective in reducing children's cortisol levels because the available results are contradictory. Further RCTs should be conducted with children. Measurement of cortisol levels from saliva, hair and urine are non-invasive procedures that can be easily implemented with children.

An interesting result of the present study is that meditation interventions might be more effective for males than for females. Further studies should directly contrast the efficacy of programs for the two genders and investigate the possible reasons for this difference.

Finally, the field should be more rigorous regarding the design of RCTs and limit the moderate level risk of bias found in the present meta-analysis. While most of the included studies performed well on the first four domains of the Cochrane Collaboration's risk of bias tool 2.0 (Sterne et al., 2019), almost none of them mentioned that there was a pre-specified analysis plan. Further researches should pre-specify and report a detailed statistical analysis plan.

Recommendations for clinical practice

In contrast to Goyal et al. (2014) findings that symptoms of anxiety and depression can be effectively decreased with mindfulness, we could not confirm this with results on cortisol in the present meta-analysis. However, we found that meditative programs can be used for people in life situations where with a risk for elevated cortisol levels such as caregivers of dementia patients, or in case of people with somatic illnesses (e.g., colitis ulcerosa or Cohn's disease). Additionally, longer programs were

found more effective and it is recommended that meditative interventions should last at least 20 hours in order to reach the desired effect (e.g., Jung et al., 2015 or Frisvold, 2009) (see Figure 4).

Recommendations for future meta-analyses

In our meta-analysis we extended previous review results by investigating whether meditation-based programs are equally effective for different populations. With substantially more available primary studies, future meta-analyses will be able to further specify the efficacy of such interventions for different at-risk groups such as people diagnosed with an anxiety disorder.

Limitations

There was a small number of randomized controlled trials of meditation interventions that provided information on changes in cortisol levels that we could include and they used different sample sources (e.g., blood, saliva, urine and hair samples) or sampling schedules (one or more sampling occasion per day, sampling on one or more consecutive days). Unfortunately, only two studies reported on hair and one reported on urine cortisol results, thus this part of the present meta-analysis remains descriptive and preliminary. Accordingly, statistical power in the present meta-analysis was low for all subgroup analyses, however, we had sufficient power to conduct the meta-regression analyses. Furthermore, most studies used a meditation intervention based on mindfulness and thus other schools of meditation are highly underrepresented. Additionally, interventions in the primary studies were complex and not described in details making it difficult to determine what exactly happened during the sessions.

We assessed whether effects were larger for samples at a risk for elevated cortisol levels. We reported results for samples with a somatic illness, participants with a diagnosis or symptoms of a mental disorder and subjects living in stressful life situations – conditions that have been shown to be associated with higher cortisol levels. Still, these are highly heterogeneous groups. Without more studies to be included in a meta-analysis like the present one, however, we cannot make more fine-grained analyses. It is important to point out that although we only included randomized controlled trials, the risk of bias in these studies was mostly categorized as 'some concerns'.

Finally, the measurement of cortisol also varied substantially in the primary studies. In case of saliva samples, studies tended to report on less reliable cortisol estimates such as a single sample or a daily average as opposed to indicators such as the AUCg. Furthermore, the risk status of the sample and the source of cortisol sampling seem to be confounded thus it is difficult to make definite conclusions.

Conclusion

Meditation interventions were shown to have a significant medium effect on changing cortisol levels assessed from blood samples, which is in line with the conclusions of a previous meta-analysis. More specifically, significant effects were found for samples at a risk for elevated cortisol levels such as patients with a somatic illness and people living in stressful life situations. Preliminary results seem to show that the beneficial effects of meditation programs might not fade with time. Finally, longer meditation programs were found to be more effective.

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ORCID

Adam Koncz http://orcid.org/0000-0003-1114-5734
Zsolt Demetrovics http://orcid.org/0000-0001-5604-7551
Zsofia K. Takacs http://orcid.org/0000-0003-0190-0628

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Appendices

Appendix 1

The search string utilized in title and abstract to allocate all relevant publications:

(cortisol OR adrenocortic* OR glucocortic* OR hydrocortisone) AND (meditat* OR mindful*) AND (experiment* OR "randomized controlled" OR "randomized control" OR "randomised control" OR RCT).

Appendix 2

Table A1. Results of statistical power analyses of subgroup analyses.

Comparison	Statistical power (Blood cortisol)	Statistical power (Salivary cortisol)
Risk status		
No Risk – At risk	–	18%
At risk		
Mental – Somatic	10%	14%
Mental – Stressful life situation	–	12%
Somatic – Stressful life situation	–	16%
Control condition		
Active – Passive	6%	17%
Sampling time		
AM- PM	–	10%
AM- Both	–	20%
PM- Both	–	18%
Sampling procedure		
One sample/day – More samples	–	25%

Table A2. Results of statistical power analyses of meta regression analyses.

Regression	Statistical power (Blood cortisol)	Statistical power (Salivary cortisol)
Gender distribution	100%	100%
Mean age	100%	100%
Total intervention time	100%	100%
Elapsed time after intervention	–	100%

Appendix 3

Table A3. Risk of bias in the included studies in each domain.

	Levels of risk of bias					
Study	Randomization process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall risk
Bergen-Cico et al., 2009	Low	Low	Low	Low	Some concerns	Some concerns
Bowden et al., 2013	Low	Low	Low	Low	Some concerns	Some concerns
Branström et al., 2013	Low	Low	Low	Low	Some concerns	Some concerns
Carlson et al., 2015	Low	Low	Low	Low	Low	Low
Cash et al., 2013	Low	Low	Low	Low	Some concerns	Some concerns
Chhattre et al., 2009	Low	Low	Low	Low	Some concerns	Some concerns
Fan et al., 2011	Low	Some concerns	Low	Low	Some concerns	Some concerns
Flook et al., 2009	Some concerns	Low	Low	Low	Some concerns	Some concerns
Frisvold 2018	Low	Low	Low	Low	Some concerns	Some concerns
	Low	Low	Low	Low	Some concerns	

(*Continued*)

Table A3. Continued.

Study	Levels of risk of bias					Overall risk
	Randomization process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	
Gagrani et al., 2016						Some concerns
Gainey et al., 2012	Some concerns	Low	Low	Low	Some concerns	Some concerns
Gex-Fabry et al., 2014	Low	Some concerns	Low	Low	Some concerns	Some concerns
Goldberg et al., 2017	Some concerns	Low	Low	Low	Some concerns	Some concerns
Gotink et al., 2014	Low	Low	Low	Low	Some concerns	Some concerns
Hsiao et al., 2014	Low	Low	Low	Low	Some concerns	Some concerns
Jedel et al., 2011	Low	Low	Low	Low	Some concerns	Some concerns
Jensen et al., 2015	Low	Low	Low	Low	Some concerns	Some concerns
Jung et al., 2009	Low	Some concerns	Low	Low	Some concerns	Some concerns
Kim et al., 1980	Low	Low	Low	Low	Some concerns	Some concerns
Lipschitz et al., 2011	No	Low	Low	Low	Some concerns	Some concerns
Marshall et al., 2010	Some concerns	Low	Low	Low	Some concerns	Some concerns
MacLean et al., 2013	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Malarkey et al., 2013	Low	Low	Low	Low	Some concerns	Some concerns
Nyklíček et al., 2013	Low	Low	Low	Low	Some concerns	Some concerns
Oken et al., 2017	Low	Some concerns	Low	Low	Some concerns	Some concerns
Prakhinkit et al., 2004	Low	Some concerns	Low	Low	Some concerns	Some concerns
Robert-McComb et al., 2013	High	Low	Low	Low	Some concerns	High
Roeser et al., 1979	Some concerns	Low	Low	Low	Some concerns	Some concerns
Schonert-Reichl et al., 1998	Low	Some concerns	Low	Low	Low	Some concerns
Sibinga et al., 2014	Low	Low	Low	Low	Some concerns	Some concerns
Turan et al., 2013	Some concerns	Low	Low	Low	Some concerns	Some concerns
Van Dam, 2008	Low	Low	Low	Low	Some concerns	Some concerns
Vandana et al., 1995	Low	Low	Low	Low	Low	Low
Zhang and Emory, 2015	Some concerns	Low	Low	Low	Some concerns	Some concerns