Physical activity influences cortisol and dehydroepiandrosterone (sulphate) levels in older adults: a systematic review and meta-analysis.

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PHYSICAL ACTIVITY INFLUENCES CORTISOL AND DHEA(S)

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Abstract

Age-related changes affect the ratio between two steroid hormones of the hypothalamic-pituitary-adrenal (HPA) axis, cortisol and dehydroepiandrosterone (sulphate) (DHEA(S)). Physical activity (PA) may buffer the effects of chronic stress and counteract the ageing decline of DHEA(S). Therefore, a systematic review was conducted to understand how PA influences physiological markers of cortisol and/or DHEA(S) and whether there was a difference in observational associations or experimental effects in older adults aged 65 years and above. A narrative synthesis was performed on nine observational studies, and meta-analyses were performed on 22 randomised controlled trials. There was low to moderate-quality evidence that regular PA beneficially reduces cortisol and increases DHEA(S) levels. Subgroup analyses showed no clinically important differences between males and females, different exercise modalities or health states. The findings cautiously suggest that regular PA of older adults' own choice as they find enjoyable could be recommended to improve cortisol and/or DHEA(S) levels.

Keywords: exercise, physical fitness, healthy ageing, chronic stress, aged 65 and over

Background

In the past century, lifespan has increased significantly (Roser, Ortiz-Ospina, & Ritchie, 2013). Although humans live longer, data suggests these additional years are often not spent in good health (Crimmins & Beltrán-Sánchez, 2011; Crimmins, 2004). The increasing long-term multimorbidity of the population poses an enormous burden of capacity on the healthcare system (Barnett et al., 2012). Therefore, research is increasingly needed to conceptualize what governs healthy ageing. A lot of progress has been made in evidencing how physical activity (PA) contributes to good health (Macera, Cavanaugh, & Bellettiere, 2017; Peterson et al., 2009). For example, a recent study states that being sufficiently active at an older age greatly decreases the odds of disability (Dos Santos & Gobbo, 2021). Despite this progress, research remains to be conducted to fully understand the mechanisms of how PA can improve health span, which is essentially defined as maintaining wellness throughout old age (Aronson, 2020).

In ageing, hormonal balances and endocrine pathways become increasingly challenged (van den Beld et al., 2018). There is evidence for age-related alterations to the hypothalamic-pituitary-adrenal (HPA) axis, driving imbalances in the adrenal hormones, cortisol and dehydroepiandrosterone sulphate (DHEAS) (Ferrari et al., 2001). One of the main stress hormones, cortisol, is key for establishing an adequate response to stress (Ockenfels et al., 1995), however when cortisol levels are chronically elevated, its effects will have negative implications on health (Juster, McEwen, & Lupien, 2010). On the other hand, DHEA, a steroid hormone also produced in the adrenals, often measured in its active sulphated form DHEAS, appears to counterbalance many of the negative effects of cortisol (Buoso et al., 2011; Pluchino et al., 2015), thereby implicating the importance of cortisol:DHEA(S) ratio in ageing (Butcher et al., 2005; Phillips, Burns, & Lord, 2007). Several age-related changes can be noted in these two hormones: older adults display an increased daily cortisol output

(Heaney, Phillips, & Carroll, 2012a; Karlamangla, Friedman, Seeman, Stawksi, & Almeida, 2013; Nater, Hoppmann, & Scott, 2013; Van Cauter, Leproult, & Kupfer, 1996), a blunted cortisol awakening response (CAR) (Kudielka, Buske-Kirschbaum, Hellhammer, & Kirschbaum, 2004) and a flatter diurnal profile (Deuschle et al., 1997; Heaney, Phillips, & Carroll, 2012b; Kumari et al., 2010). In contrast, studies reported a steady decline in levels of the hormone DHEA(S) with age (Heaney et al., 2012a; Orentreich, Brind, Rizer, & Vogelman, 1984) and a flatter diurnal profile in both older males and females compared to younger adults (Al-Turk & Al-Dujaili, 2016). Not surprisingly, the cortisol:DHEA ratio increases with age (Phillips et al., 2007). High cortisol:DHEA(S) ratios are associated with immune impairment (Butcher et al., 2005), dementia (Ferrari et al., 2001), metabolic syndrome (Phillips et al., 2010b), and mortality (Phillips et al., 2010a). As stated above, research has shown changes in endocrine pathways in ageing. However, important questions regarding the role of these hormones and the cortisol:DHEA(S) ratio in healthy ageing remain unanswered, such as how they relate to PA to maintain health.

Several previous studies suggest the cortisol:DHEA ratio is an important marker of healthy ageing with an increased cortisol:DHEA ratio relating to poorer physical function (Heaney et al., 2012a), low social support, and higher depression, anxiety and chronic stress (Heaney, Phillips, & Carroll, 2010). Further, Heaney et al. noted that older adults reporting more severe recent stressful events, but low PA show a higher cortisol:DHEA ratio than those reporting fewer stressful experiences (Heaney, Carroll, & Phillips, 2014). Moreover, they found evidence that the observed association between stress severity and cortisol:DHEA was driven by lower DHEA levels in those experiencing more severe stress rather than high levels of cortisol. They argued that regular PA may potentially buffer against negative influence of stressful life events on the cortisol:DHEA ratio. This agrees with the conclusions of a more recent study (Moraes, Deslandes, Maciel-Pinheiro, Corrêa, & Laks, 2016) and adds to the

consensus that PA may buffer the effects of chronic stress (Rimmele et al., 2009; Unger, Johnson, & Marks, 1997; Zschucke, Renneberg, Dimeo, Wüstenberg, & Ströhle, 2015) and decrease stress reactivity (Rimmele et al., 2007). Similar results are found in experimental studies, where it was shown that exercise programmes can produce psychological and physiological changes (Klaperski, von Dawans, Heinrichs, & Fuchs, 2014; Kraemer, Ratamess, Hymer, Nindl, & Fragala, 2020; Kraemer & Ratamess, 2005). Despite increasing interest on how PA impacts the endocrinology of stress and healthy ageing over the last few decades (for most recent reviews on this topic, see (Anderson & Wideman, 2017; Daskalopoulou et al., 2017; Duclos & Tabarin, 2016; Fragala et al., 2011; Sellami et al., 2019)), the association between PA and cortisol and DHEA(S) levels have not yet been systematically reviewed in older adults.

This review focused on broader physical activity (incorporating exercise) on hormone responses rather than the impact of acute exercise bouts or exercise only for several reasons. First, physical activity goes beyond the regular planned activities that we know as exercise to also incorporate unplanned movement that can contribute to physical health, such as active travel, moving about in the workplace and during chores etc. as part of an active lifestyle and these types of bodily movement all contribute to overall health and have therefore formed the significant evidence base behind global and national physical activity guidelines (Bull et al., 2020). For example, both exercise and physical activity improve stress and prevent or improve several physical and mental health problems such as depression, cardiovascular, immunological and metabolic diseases (Hill et al., 2008; Penedo & Dahn, 2005; Ströhle et al., 2007). In older adults, an active lifestyle is associated with a higher quality of life (Koltyn, 2001), and there is consensus that PA in older adults yields salutary psychological and physical effects. This includes moderate-intensity aerobic activity, muscle-strengthening activity, reducing sedentary behaviour, and risk management (Nelson et al., 2007). More

specifically, Heaney et al (2014) found that habitual PA buffers the adverse effects of stress in older men and women by opposing the stress-associated increases in the ratio between cortisol and DHEA (Heaney et al., 2014). The evidence further shows that higher physical fitness is associated with lower daily cortisol output (Lucertini et al., 2015). In addition, a physically active life yields positive effects on the brain structures, promoting better control of the HPA-axis and greater resilience to stress (McEwen & Morrison, 2013). Second, while there is indeed a whole-body adaptation through acute exercise challenges (Hawley, Hargreaves, Joyner, & Zierath, 2014), which not all physical activity might be sufficient to induce, there is also an important behavioural health perspective to active lifestyles that should not be overlooked. This systematic review was conducted to inform future research where implementing the research into clinical practice is considered important. Exercise programs are proven to be feasible and effective for multiple health outcomes. However, many people do not continue exercising after the end of a program. Therefore, investigating population associations between longer-term PA as part of an active lifestyle (as well as exercise interventions) and more favourable cortisol levels might yield engaging and pragmatic clinical guidance for long-term health. Third, for healthy ageing, one needs to adapt and effectively respond to the dynamic challenges of daily life. Allostasis is a dynamic concept where the brain is considered to have a role in feedback regulation to adapt to these challenges and where health is conceived as a whole-body adaptation to contexts (Schulkin, 2003; Sterling, 2004). Allostatic load has been proposed as a cumulative measure of dysregulation across multiple systems, such as the neuroendocrine system, autonomic nervous system, and immune system (McEwen & Stellar, 1993). The glucocorticoid cascade hypothesis of ageing is a prime example of allostatic load since it recognizes a feed-forward mechanism that gradually wears down a fundamental brain structure, the hippocampus. At the same time, the gradually dysregulated HPA axis promotes pathophysiology in tissues and organs throughout the body

(McEwen, 2003). In this model, PA is identified as an important allostatic load covariate in older adults (Karlamangla, Singer, McEwen, Rowe, & Seeman, 2002; Kubzansky, Kawachi, & Sparrow, 1999; Seeman, Singer, Rowe, Horwitz, & McEwen, 1997). As a result, in light of the health impact and practice applications of PA, and the allostatic load model, it is important to investigate further the associations between PA as well as exercise and more favourable endocrine profiles in older adults.

Therefore, the main aim of this systematic review was to explore the existing literature on how PA influences physiological markers of cortisol and/or DHEA(S) in older adults aged 65 years and above. The main objectives were to investigate: (1) whether there is observational evidence to suggest regular PA is associated with lower cortisol and/or higher DHEA(S) levels and which factors contribute most to these levels; (2) the average effect of physical exercise interventions of at least 12 weeks duration on reducing cortisol and/or increasing DHEA(S) levels in older adults. The sub-objectives were to determine different effects between males and females, different exercise types (e.g., aerobic, resistance, mixed-types or mind-body) or intensities (low-moderate, moderate-high), and in a healthy population versus those with a specific disease and; and the influence of differences between cortisol or DHEA(S) sample timing, and the number of samples throughout the day. These objectives and sub-objectives were set to reveal current knowledge gaps, provide future directions to develop a better understanding of the intervention effects of PA programmes on endocrine health in older adults, and contribute to the development of better clinical guidance.

Methods

Protocol

The conduct and analysis of this SR is mainly based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (Page et al., 2021), complemented with

guidance from the Cochrane Handbook (Higgins et al., 2021). The published protocol for the review is available at PROSPERO https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021236934, registration number CRD42021236934. For transparent reporting of the review, the PRISMA checklist 2020 was used (Appendix 1).

Study eligibility criteria

The selection process used for inclusion of studies in the review was as follows: (1) Original sources of peer reviewed evidence to date with both experimental and observational designs, in the English language, except for letters and conference abstracts. To this end, it was considered that observational studies would be used to report population-based data that would usefully supplement and extend the data drawn from RCTs. (2) Studies irrespective of publication status, unless exclusion is explicitly justified. (3) Articles addressing the pre-defined Population, Intervention, Comparison and Outcome (PICO) criteria (Richardson, Wilson, Nishikawa, & Hayward, 1995). The PICO criteria were:

Population: community-dwelling free living older adults, 65 years or older and older individuals in supporting housing or care homes. Eligible studies were also included if they involved only a subset of relevant participants but had separate analyses on them. Intervention: Experimental or observational studies looking at PA, daily living activities, or exercise programs maintained long enough for possible habit formation (≥ 12 weeks). interventions which included PA and/or exercise protocols equal to, or longer than, 12 weeks. Comparison: Controls having an inactive/sedentary lifestyle, or receiving no intervention or usual care. Outcome: Cortisol and/or DHEA(S), objectively measured in saliva, blood, hair or urine samples.

Search strategies

The searches were run on 01/03/2021 and re-run just prior to the final analyses on 02/09/2021. The following electronic bibliographic databases were searched: PubMed, PEDro, PsycINFO, OvidSP, the Cochrane Library (the Cochrane Central Register of Controlled Trials (CENTRAL)), CINAHL and Web of Science (no data limits were chosen). The search strategy included only terms relating to or describing the PICO criteria of interest and were adapted for use for each specific bibliographic database. Grey literature searches were conducted searching online databases (ClinicalTrials.gov) and using the Google Scholar search engine according to the recommendations of Haddaway (Haddaway, Collins, Coughlin, & Kirk, 2015). The exact search strategy used with suitable search terms for each database is available in Appendix 2. Finally, to identify most prominent papers in this field, the tool "connected papers" (https://www.connectedpapers.com/) was used. Reference lists of key papers, and already included papers, were searched and cross-referenced by hand to supplement initial keyword searches.

Data collection and management

Search results were collected in Sciwheel (sciwheel.com) and the extracted titles and abstracts of papers were screened using Rayyan (rayyan.qcri.org) (Ouzzani, Hammady, Fedorowicz, & Elmagarmid, 2016). Two reviewers (LDN & EO) independently performed a first-stage screening of titles and abstracts to determine whether each study met the eligibility criteria. Any study identified by either reviewer was included for further screening. A second-stage screening of the selected full-text articles was again performed by the two independent reviewers. Further, a third-stage screening consisted of a pilot data extraction screening of the retrieved full-text articles. Disagreements in the screening process were resolved by consensus. Reasons for exclusion of studies excluded at the pilot data extraction screening were documented. Finally, a flowchart showing the screening and selection process was made.

Study authors were contacted to obtain missing data if needed (n = 5). Data extraction was conducted in Excel, where two independent reviewers collected the following: study ID, design, PICO characteristics, general findings, and statistics relevant to the research question. Retrieved data from observational studies were extracted separately from intervention studies. Assembling and grouping data elements was done using RevMan 5 software (The Cochrane Collaboration, 2020). Any transformations of the reported data can be found in Appendix 3.

Assessment of risk of bias

Two reviewers (LDN and EO) independently assessed the risk of bias using the Joanna Briggs Institute (JBI) tool (https://joannabriggs.org/critical-appraisal-tools) (Vardell & Malloy, 2013) for observational studies and the Cochrane Risk of Bias (RoB) 2.0 Tool (Higgins et al., 2011; Ma et al., 2020) for intervention studies. The certainty of all evidence was assessed using the GRADE approach (Guyatt et al., 2008) for the cortisol and DHEA(S) outcomes. For randomized controlled trials, a starting rating of 'High quality' evidence was downgraded by one level if serious concerns (or by two levels for very serious concerns) became apparent in terms of risk of bias, inconsistency, indirectness, imprecision or publication bias. For studies with observational features, a starting rating of 'Low quality' was downgraded, as proposed by GRADE guidelines (Schünemann, Brożek, Guyatt, & Oxman, 2013). A funnel plot (Egger's test) (Egger, Smith, Schneider, & Minder, 1997) was performed for the included RCTs to visualize possible reporting bias. There were insufficient observational studies to allow construction of such a plot.

Data synthesis

When included study data were found similar enough in terms of methodological and clinical characteristics to ensure meaningful conclusions from a statistically pooled result, meta-analyses were performed.

Observational studies were considered not similar enough to combine data using meta-analysis, so narrative analyses were conducted. All studies were given equal weight. Effect directions for both outcomes were assessed, and p-values reported for the sign test based on existing guidance (Boon & Thomson, 2021). The p-value from a sign test represents the probability of observing the given number of positive and negative results if the null hypothesis were true. To calculate the p-value of each outcome domain, GraphPad was used (https://www.graphpad.com/quickcalcs/binomial1/). Differences in relative sizes of the studies were accounted for visually, not statistically (Borenstein, Hedges, Higgins, & Rothstein, 2009).

Intervention studies were deemed similar enough to allow pooling of data using meta-analysis. The data were analysed based on mean, standard deviation (SD) and number of participants assessed for both the intervention and comparison groups, and used to calculate the standardized mean differences (SMD) and 95% Confidence Intervals (CI) using the generic inverse variance method in RevMan5 (The Cochrane Collaboration, 2020). Assuming a true effect was not the same in all studies, or that studies were performed in different populations, random-effects models were used to analyse data. These analyses were visualised by forest plots. The degree of heterogeneity was thus assessed through Chi-squared (Chi^2) statistics. Heterogeneity was quantified and interpreted using the I-squared (I^2) statistic (Higgins et al., 2011). There were no deviations from the protocol in this final paper.

Subgroup analysis and investigation of heterogeneity

Where substantial heterogeneity was present, it was addressed by exploring possible reasons and conducting subgroup analyses as suggested by the Cochrane Handbook (Higgins et al., 2020). Studies were grouped based on the category that best explains heterogeneity and makes most clinical and/or methodological sense to the reader, as *a priori* defined in the protocol. To be consistent across the review, forest plots of the DHEA(S) outcomes low in

heterogeneity were visualised with the same subgroups as the studies of cortisol. Meta-analytic scores of subgroups are presented with the overall effects for both outcomes, although there was still substantial statistical heterogeneity across the subgroups for cortisol.

Sensitivity analysis

To assess robustness of results, several analyses were performed. The effect of intervention duration was compared (12 weeks vs. >12 weeks), also aspects of trial size, quality assessment, patient characteristics and measurement of outcomes were considered. Finally, analyses were performed with and without outliers studies, excluding these sequentially one by one to see if this changed the overall results.

Results

Results of the search

A total of 4834 records were identified through database searches, and an additional 18 through reference list searches (see PRISMA diagram Figure 1). After removing duplicates, 3069 titles and abstracts were screened for eligibility, 147 abstracts were obtained for further review and 31 articles met the inclusion criteria. Reasons for exclusion are outlined in Figure 1. One ongoing trial was found NCT03794050, but was paused due to SARS-CoV-2 pandemic, and therefore excluded. A table with characteristics of excluded studies during the pilot data extraction can be found in Appendix 5.

Description of included studies

Observational studies were synthesized separate from obtained RCTs and study characteristics were sorted by outcome (Tables 1 and 2).

Study and participant characteristics

Included observational studies were all cross-sectional designs (n= 9), involving a total of 729 participants (38% female) (Abbasi et al., 1998; Bonnefoy et al., 1998, 2002; de Gonzalo-Calvo et al., 2012; Heaney et al., 2014; Lucertini et al., 2015; Moraes et al., 2016; Pauly et al., 2019; Ravaglia et al., 2001). All studies, except one (Moraes et al., 2016), were conducted in high-income countries; all participants were Caucasians. The included RCT's (22) involved 1346 participants (79% female) (Banitalebi, Faramarzi, Bagheri, & Kazemi, 2018; Borst, Vincent, Lowenthal, & Braith, 2002; Campo et al., 2013; Furtado et al., 2016, 2020; Furtado et al., 2021; Ha & Son, 2018; Hersey et al., 1994; Ho et al., 2020; Im, Bang, & Seo, 2019; Kim, Park, & Lim, 2018; Lu et al., 2020; Mura et al., 2014; Prakhinkit, Suppapitiporn, Tanaka, & Suksom, 2014; Rieping et al., 2019; Sin, Ibarra, Tae, & Murphy, 2015; Son, Pekas, & Park, 2020; Tada, 2018; Tsang et al., 2013; Venturelli et al., 2016; Vrinceanu et al., 2019; Yamada, Nishiguchi, Fukutani, Aoyama, & Arai, 2015), conducted in 10 countries. Studies were published between 1994 and 2021, however, most studies were published last five to 10 years (n= 25).

Observational studies included mostly generally healthy older adults (n= 8), and subgroup analyses in studies were performed by fitness level (n= 4), gender (n= 2), age (n= 1), stress exposure (n= 1) or DHEA level (n= 1). Intervention studies with a cortisol outcome investigated generally healthy older adults (n= 8), or individuals with mood disorders (n=3), cognitive impairment (n=3) or other (n= 3, cancer survivors, metabolic syndrome or frailty). Intervention studies with a DHEA(S) outcome investigated generally healthy older adults (n= 5), frail or pre-frail older adults (n= 1).

Cortisol or DHEA(S) measurement

Cortisol and/or DHEA(S) samples of both cross-sectional studies and RCTs were taken either from saliva (n= 19) or blood serum (n= 15). None used urine or hair samples. Identified studies that focused on the diurnal cortisol slope, took three to six samples during

the day (Heaney et al., 2014; Ho et al., 2020; Lu et al., 2020; Lucertini et al., 2015; Pauly et al., 2019; Venturelli et al., 2016). Cortisol Awakening Response (CAR) was analysed three studies (Campo et al., 2015; Heaney et al., 2014; Vrinceanu et al., 2019). All other studies performed a one-time measurement, almost exclusively in the morning, in a fasted state.

Risk of bias in studies

Across all studies a low to moderate risk of bias was identified (Figures 2 and 3). In the cross-sectional studies, the fifth question in the JBI checklist asks if confounding factors are identified in each study. The review team recognised many confounding factors are at play in a one-time point endocrinology measurement, certainly when trying to define life stressors, however, many studies did account for at least some confounders. Further, most studies measured PA with reliable and valid questionnaires, these are not robust activity measurements compared to e.g., accelerometery, however, the review team judged that the exposure of all studies was measured in a valid and reliable way in studies that reported clear and standardised (*a priori*-defined) PA measurement tools. Traffic light plots summarising these decisions are shown in Appendix 7.

Reporting biases

The funnel plot showed slight asymmetry due to missing studies in areas of 'no intervention effect' (Figure 4). While reporting bias is thus considered, this asymmetry could be due to chance as the analysis contains few studies with a relatively small number of participants (Sterne et al., 2011). The funnel plot is grouped by intensity solely for consistency, and it should be acknowledged there are too few studies to interpret the findings by each subgroup. Other sources of bias, such as selection bias, performance and detection bias and attrition bias were considered (Appendix 7).

Results of syntheses and certainty of evidence

Observational studies

Cortisol. There was very low-quality evidence suggesting regular PA is associated with lower cortisol in both older males and females compared to being more sedentary (n = 333 with 53% male, p value for sign test = .063 in males, all the studies reported a negative effect direction; and p value for sign test = 0.38 in females, four studies reported a negative effect direction, with one unclear result) (Figure 5 and Table 3). GRADE guidelines state that grading the evidence of non-RCTs starts at 'low quality'. It was deemed that inconsistency and/or indirectness did not appear to be an issue with this outcome nor was there any publication bias detected. However, based on quality assessments, studies were downgraded (-1) because some imprecision exists, following the GRADE 'rule of thumb' that information is likely to be insufficient when rating continuous outcomes, when the total number of participants is less than 400 (Schünemann et al., 2013).

DHEA(S). There was low quality evidence to suggest that being physically active in daily life is associated with higher DHEA(S) levels compared to being more sedentary. (n = 545 with 59% male, p value for sign test = 0.02 in males, with seven out of seven reporting a positive effect direction, and p value for sign test = 0.45 in females, with five out of seven studies reporting a positive effect direction) (Figure 5 and Table 3). The same GRADE factors were considered, but none of these features appeared to be an issue for this outcome, so the overall quality of evidence was not downgraded.

Cortisol:DHEA(S) ratio. Only one study was found where higher PA levels were associated with a lower cortisol:DHEA(S) ratio (p = .05), mainly driven by significantly higher average DHEA(S) levels in people who regularly engaged in PA (p = .009) compared to those who did not (Heaney et al., 2014).

RCTs

Cortisol. There was moderate quality evidence that exercise interventions in older adults for at least 12 weeks probably reduces cortisol levels compared to no intervention (SMD = -0.61, [-0.90, -0.33], 17 studies, 736 participants) (Figure 6 and Table 3). The overall quality was graded as moderate because of substantial statistical heterogeneity (I^2 = 69%) when pooling the studies. The heterogeneity was explained; thus the overall grade of evidence was downgraded by only one level due to issues of inconsistency. After pre-specified sub-group comparisons and through sensitivity analyses, three studies with the highest effect sizes were found to explain all heterogeneity (Tada et al., 2018, Kim et al., 2018, Venturelli et al., 2016) (SMD = -1.83 [-2.26, -1.40], three studies, 121 participants). When including these studies, the overall finding in favour of the interventions was relatively strong but with substantial variability. When these three studies were removed from the meta-analysis, the heterogeneity was substantially reduced. Excluding these three articles from the equation still resulted in high quality evidence that exercise interventions of at least 12 weeks reduce cortisol levels slightly compared to controls in older adults (SMD = -0.35 [-0.51, -0.18], 15 studies, 615 participants).

DHEA(S). There was moderate quality evidence that exercise interventions in older adults for at least 12 weeks improved DHEA(S) levels slightly compared to no intervention (SMD = 0.39 [0.10, 0.68], six studies, 203 participants) (Figure 7 and Table 3). The studies were considered homogeneous (I^2=0). The quality of the evidence was rated as moderate due to some imprecision may exist because of the number of participants (n= 203) is lower than the general GRADE 'rule of thumb' of n ≥ 400 to be sufficient.

Cortisol:DHEA(S) ratio. No RCTs reported the impact of exercise interventions on the cortisol: DHEA(S) ratio.

Sub-grouping intervention studies

Cortisol. To further explore heterogeneity in the cortisol outcome, subgroup analyses were conducted by gender, intervention types, intensity, duration, and participants' health status showed no clinically important differences (Table 4). An overview of the intervention specifics and adherence is shown for both outcomes combined in the TiDieR checklist (Appendix 6). Intervention intensity was rated as low-moderate intensity (20-75% VO_{2max}) or moderate-high intensity (>75% VO_{2max}) as stated by the American College of Sports Medicine (ASCM) (American College of Sports Medicine, 2013). The forest plots of all relevant sub-groups can be found in Appendix 4.

DHEA(S). Subgrouping of this outcome was explored narratively as there was no heterogeneity in the pooled data. To sum, there were no important differences detected between sub-groups. Of the six studies, interventions were as follows: aerobic training (n= 1), resistance training (n= 2), combined interventions (n= 2) and mind-body interventions (n= 1). Further, most of the studies were of low-moderate intensity (n= 4). Durations were 12 weeks (n= 3) or between 24 and 28 weeks (n= 3). Four studies were conducted in generally healthy older adults, whereas one study was in frail older adults.

Discussion

This review used a rigorous systematic approach to assess the impact of PA on cortisol and DHEA(S) levels in older adults. Findings from the narrative synthesis of observational studies suggested that there may be an association between regular PA in daily life and lower total cortisol output compared to being more sedentary. Further, analyses of the DHEA(S) outcomes showed that active older adults may have higher DHEA(S) levels, compared to older adults that did not regularly engage in PA. As such, this cautiously confirms the hypothesis that there is low quality evidence that regular PA in daily life is associated with a lower cortisol:DHEA(S) ratio, although only one study directly looked at this ratio as an outcome. Results obtained by the meta-analysis of RCTs evidenced with moderate quality

evidence that PA interventions of 12 weeks or longer may reduce cortisol and increase DHEA(S) levels compared to control conditions in older adults (≥65 years).

Overall completeness and applicability of evidence

The aim of this review was twofold. First to systematically review the existing literature to date on how PA influences physiological markers of cortisol and/or DHEA(S) in older adults, which is the first systematic review on this topic using rigorous methods. The second aim was to examine whether there was a difference in observational associations or experimental effects. These two aims were addressed by including nine cross sectional studies to assess whether there is evidence to suggest that regular PA is associated with lower cortisol and/or higher DHEA(S) levels, and the 22 RCTs included in a meta-analysis to measure the average effect of physical exercise intervention on these outcomes. The overall certainty of evidence was deemed low to very low for observational studies, using the GRADE approach (Schünemann et al., 2013). More studies with observational features with consistent methodologies could improve the precision and consistency across studies, which were the main concern for both outcomes. In contrast, grading the intervention studies revealed moderate certainty of evidence.

There was substantial heterogeneity when combining the studies statistically for cortisol, however, after sensitivity analysis, three studies (Kim et al., 2018; Tada, 2018; Venturelli et al., 2016) were found to account for all heterogeneity. Removing these did not change the clinical importance of the prior intervention effects. Further, subgroups had too few participants to draw firm conclusions. Therefore, the findings regarding subgroup analyses should be considered tentative. More studies differentiating between intervention type, duration or intensity, or differentiating between health states, such as older adults with mood disorders or frail older adults, could possibly determine clinically important differences and increase the quality of evidence in the proposed subgroups.

It should also be noted that the included RCTs did not comment in detail on whether variation in response in the intervention groups might reflect a lack of physiological response to exercise among some participants as opposed to being attributable to intervention factors such as duration. Physiological exercise responses are driven by differences in genetics as well as epigenetic changes and gene transcription mechanisms (Hawley et al., 2014). Consequently, it would be important to measure these factors alongside hormone levels where possible in future exercise/physical activity interventions as they drive exercise effects on hormones via such mechanisms as changing receptor number or sensitivity (Hackney & Hackney, 2005).

Observational studies were all cross-sectional, mostly including generally healthy older adults in high income countries, highlighting a clear research gap in population-based assessments, whether longitudinally or cross-sectionally, exploring associations between PA levels and cortisol and/or DHEA(S) levels in an older population with varying health status, in low to middle income countries.

Included studies where cortisol was the outcome investigated generally healthy older adults (n = 8), those with mood disorders (n = 3), cognitive impairment (n = 3) or other (n = 3, cancer survivors, metabolic syndrome or frailty). This revealed that little research has been conducted on objective stress measures and their association with PA (≥12 weeks) in people with existing disease states. More specifically, no RCTs were identified on reducing cortisol through long term resistance or aerobic training in older adults with mood disorders. This is important to note as chronic stress and inadequate cortisol regulation are key drivers of non-communicable diseases (Joseph & Golden, 2017; McEwen & Stellar, 1993) and is often seen in older populations experiencing depressive episodes (Murri et al., 2014). Included studies with DHEA(S) as the outcome also investigated generally healthy older adults (n = 5) or frail

or pre-frail older adults (n = 1). Thus, quality research is lacking measuring the effects of exercise interventions on DHEA(S) in people with specific disease states and/or frailty.

Contrary to expectations, the associations from observational studies between PA and a decrease in total cortisol output were small. This is in contrast with the present meta-analytic findings, which are in line with other reviews suggesting a regulatory role of PA on stress and cortisol levels (Anderson & Wideman, 2017; Corazza et al., 2013; Fragala et al., 2011; Sellami et al., 2019). Other PA intervention studies also report a cortisol lowering response in generally healthy older adults (Chaturvedi, Nayak, Nayak, & Rao, 2016; Ibáñez et al., 2008; Ponzio et al., 2015), however, other quality intervention studies found conflicting results, showing no effects, or even higher cortisol levels after an exercise intervention (Banitalebi et al., 2018; Borst et al., 2002; Häkkinen, Pakarinen, Kraemer, Newton, & Alen, 2000; Hayes et al., 2013; Izquierdo et al., 2001; Kraemer et al., 1999; Sillanpää et al., 2010). These studies generally used strength and resistance training protocols, which may acutely increase the activation of adrenal glands and stimulate cortisol production (Ahn & Kim, 2018). Yet, no important differences in effect sizes were found in the present meta-analysis when exploring subgroup differences by intervention type (aerobic vs. resistance vs. combined vs mind-body). Overall, there is more quality research required to confidently understand the effect of different exercise types.

The findings of this review show low-quality evidence that regular PA at older age is associated with increased DHEA(S) levels . There is indeed consensus that DHEA(S) decreases with age for both active and sedentary people (Heaney et al., 2014; Orentreich, Brind, Vogelman, Andres, & Baldwin, 1992) and that regular moderate PA is associated with higher levels of DHEA(S) in older adults (Abbasi et al., 1998; Aldred, Rohalu, Edwards, & Burns, 2009; Bonnefoy et al., 1998; Ravaglia et al., 2001; Tissandier, Péres, Fiet, & Piette, 2001). In addition, the present meta-analytic findings showed exercise interventions of at least

12 weeks probably improves DHEA(S) levels slightly compared to no intervention in older adults. Similar results (Sato et al., 2014) and no changes (Häkkinen et al., 2000; Häkkinen et al., 2002) were found in non-controlled resistance training interventions of at least 12 weeks. Further, DHEA can be maintained at a high level by long-term training in older adults (de Gonzalo-Calvo et al., 2012).

Gender

Observational studies included 38% women (out of 729 participants), whereas interventional studies included 79% women (out of 1314 participants). As eight studies included females only, findings were meta-analysed, evidencing exercise interventions may reduce cortisol levels slightly in older females, compared to controls. Laughlin & Barret-Connor (2000) found, however, that the cortisol:DHEA(S) ratio increased in ageing for both genders, levels of DHEA(S) remained lower, and cortisol and the cortisol:DHEA(S) ratio was higher in women than in men throughout the 50-89 years of age range (Laughlin & Barrett-Connor, 2000). These results are in line with a cross-sectional study in a group of healthy older Tunisians investigating the gender-specific age-related alterations in cortisol and DHEAS, stating the cortisol:DHEAS ratio increases with age, with larger increases in women (Chehab, Ouertani, Chaieb, Haouala, & Mahdouani, 2007). This echoes the findings of studies on gender effects in ageing on cortisol (Zhao et al., 2003) and DHEA(S) (Berr, Lafont, Debuire, Dartigues, & Baulieu, 1996; Mazat et al., 2001; Zumoff, Strain, Miller, & Rosner, 1995).

Exercise intensity, type, duration and adherence

Exercise can act as a stimulus to the HPA axis, increasing cortisol levels. This is due to the intensity and the duration of exercise (McMurray & Hackney, 2000). Essentially, physical exercise programs seek to produce favourable physiological adaptation effects,

contributing to improved regulatory capacity, increased receptor number in the target tissue, and improved receptor sensitivity (Hackney & Hackney, 2005). There is more research needed to clearly elucidate exactly how different exercises impact the endocrine regulatory axes. For this reason, an important research question of this systematic review was to differentiate between different exercise intensities, types and duration. PA (incorporating planned exercise) may contribute to influencing hormonal profiles in the longer term, and therefore this review included PA interventions and observational data. To this end, there were no important subgroup differences found between intensity types. However, there is an overarching consensus that the HPA-axis is most impacted when training intensity is higher than 60% of VO_{2max} (Caiozzo et al., 1982; Hill et al., 2008). This is evidenced by studies pointing out that this intensity increases the rate of glandular secretions and elevations of cortisol are not due to decreases in metabolic clearance rate (Hill et al., 2008; VanBruggen, Hackney, McMurray, & Ondrak, 2011). Other factors that are also shown to influence hormonal release with exercise are aerobiosis, strength modalities, timing of the day, meal ingestion and participant characteristics (such as previous training and gender) (Hackney & Viru, 1999; Hackney, 2006; Leal-Cerro et al., 2003; Luger et al., 1987; Strüder et al., 1998; Traustadóttir, Bosch, & Matt, 2003). However, not all older adults may be able to exercise at this intensity but would still see some physical and mental health benefits from adopting an active lifestyle (Bull et al., 2020) and possible longer-term benefits on endocrine function. Hence, this review also incorporated PA interventions and observational data.

The included RCTs overall reported good adherence rates, and there was no detected difference in adherence between exercise types or intensities (Appendix 6). It is important to note that in one study, although physical wellbeing was maintained after the completion of the programme, the therapeutic effects on depression were not sustained in the follow-up period (Tsang et al., 2013). This highlights the need for long-term adherence to an exercise

programme. An exercise duration of 12 weeks could be long enough for participants to form a sustained habit change (Lally, van Jaarsveld, Potts, & Wardle, 2010). This is important, as the largest body of evidence points to the fact that sustained regular exercise is needed to maintain any gained health benefits (Garber et al., 2011). In addition, there is literature suggesting that the affective response to exercise is also important (Wegner et al., 2020). This is clinically important if we want people to engage and maintain in regular exercise for both their mental and physical health. Further, most exercise adherence is seen near the ventilation threshold (65% VO_{2max}) (Ekkekakis, Parfitt, & Petruzzello, 2011). However, studies highlight that pleasure and adherence are highest when the intensity (including during HIT) is self-selected, rather than imposed (Ekkekakis et al., 2011; Parfitt, Rose, & Burgess, 2006). To sum up, it seems to be important for people to choose the exercise programme they enjoy most, in whichever modality or intensity they will adhere to, to optimize endocrinological responses and healthy ageing.

Subgrouping for duration revealed no important effectiveness differences, suggesting an exercise intervention of 12 weeks yields the same effects compared to longer interventions (14-28weeks). This could help guide researchers when deciding on the duration of future exercise interventions (for time/cost efficacy). In clinical practice, however, it should be noted that it is uncertain whether beneficial effects of interventions are maintained for long periods of time (only one study measured this: (Tsang, Mok, Yeung, & Chan, 2003)). This is similar to the consensus that PA of any kind needs to be maintained to sustain health benefits.

Health status

When subgrouping by health status for the cortisol outcome, the meta-analysis showed exercise interventions may decrease cortisol levels slightly compared to controls in different disease states. This is consistent with findings of other intervention studies showing somewhat reduced cortisol in adults with different health conditions, such as breast cancer

patients (Ho, Fong, Cheung, Yip, & Luk, 2016) or females with Multiple Sclerosis (Najafi & Moghadasi, 2017). However, other research groups found no change in cortisol after exercise in older adults with rheumatoid arthritis (Häkkinen et al., 2005) or fibromyalgia (Valkeinen et al., 2005).

For DHEA(S), only one study was conducted in frail older adults. This RCT found an increase in DHEA(S) levels after a multimodal chair-based programme (Furtado et al., 2020), in accordance with a prior intervention study in older adults (Heaney, Carroll, & Phillips, 2013). Furtado et al. further highlight the importance of maintaining exercise to keep DHEA levels elevated into older age, as suggested by an earlier review about chronic exercise in older adults (Corazza et al., 2013).

Cortisol and DHEA(S) sampling

Most of the studies (n= 16) measured cortisol in saliva, while others (n= 6) measured serum cortisol. Cortisol salivary measures are accurate, non-invasive and rapidly sampled tests to measure the response to physical stress, making it increasingly used in research (Gatti & De Palo, 2011). Further, research seem to favour saliva measures over serum measures for the clinical assessment of adrenocortical function (Aardal-Eriksson, Karlberg, & Holm, 1998; Gozansky, Lynn, Laudenslager, & Kohrt, 2005; Vining, McGinley, Maksvytis, & Ho, 1983). In contrast, more DHEA(S) samples were taken from blood (n= 10) vs. saliva (n= 3), although salivary DHEA has the same feasibility advantages as salivary cortisol, and it is shown DHEA(S) concentrations in saliva are highly correlated with those in serum (Ahn, Lee, Choi, Kwon, & Chun, 2007; Whetzel & Klein, 2010).

Number of samples for accurate measurement

The majority of included studies took cortisol and DHEA(S) samples at one point in time, mostly in the morning. Where samples were taken on multiple days (e.g., pre- post-

tests), measurements were at the same time on different days to decrease within subject's diurnal variations. Indeed, often diurnal secretory activity is reliably determined by a single sample in the morning to assess within-subject variations over a certain period in an older population (Kraemer et al., 2006), however, this has limited prognostic value due to intra-individual differences (Coste, Strauch, Letrait, & Bertagna, 1994; Pruessner et al., 1997). This, together with the known diurnal rhythmicity of these hormones (Adam & Kumari, 2009; Stalder et al., 2016), the flattening of the diurnal profile with ageing (Deuschle et al., 1997; Van Cauter et al., 1996) and an increased day-to-day variation in older adults (Ice, Katz-Stein, Himes, & Kane, 2004), means that there is a need for protocols with multiple measurements targeting the overall diurnal pattern (Segerstrom, Boggero, Smith, & Sephton, 2014). This further highlights a need for measurement consistency in research, in order to compare different study findings (Dickerson & Kemeny, 2004; Ryan, Booth, Spathis, Mollart, & Clow, 2016). An accepted sampling design for cortisol involves e.g., measurements immediately after awakening, 30-min post awakening, noon, in the late afternoon, and immediately prior to bed (Hellhammer et al., 2007). This is similar to the measurement methods of the identified cross-sectional studies (Heaney et al., 2014; Lucertini et al., 2015; Pauly et al., 2019) and RCTs (Ho et al., 2020; Lu et al., 2020; Venturelli et al., 2016). Further guidance for conducting field research on cortisol is given in another article (Saxbe, 2008) and for an overview of the definitions of different cortisol indices, read the review of Khoury et al. (Khoury et al., 2015).

Strengths and limitations

This systematic review used rigorous methods throughout the whole process to prevent possible bias by carefully following several established guidelines on systematic reviewing, both for narrative- as well as for meta-analyses (see Methods). Further, the selection of studies, critical appraisal and data extraction was conducted by two independent

researchers (LDN and EO), while the data analysis and interpretation were carefully followed by the whole research team (AW, GR, JC). Further, relevant findings were compared with previous findings in an objective way, by considering the "five C's" (Cite, Compare, Contrast, Critique and Connect) (Kennedy, 2016) of most prominent trials revealed during the review process.

Several limitations are considered in the conduct of this review process. First, although the sign test is a useful tool to interpret the overall pattern of effect direction, it raises several issues, as acknowledged by the authors who updated the effect direction plot for better research guidance (Boon & Thomson, 2021). Thus, the power of the sign test used in the narrative analysis of observational studies is limited due to the small number of included studies. Also, there are well-recognized caveats about the limitation of p-values and significance testing in judging associations(Sterne & Smith, 2001; Wasserstein, Schirm, & Lazar, 2019), and with vote counting. Therefore, claims made regarding effectiveness of regular PA in the cross-sectional studies were modest. Second, there was substantial heterogeneity in the cortisol outcome, complicating a meaningful summary. However, it was deemed appropriate to combine studies and the heterogeneity was properly explored by conducting *a priori* defined subgroup analyses and explained after sensitivity analysis. Third, established pitfalls about claims of subgrouping were considered (Burke, Sussman, Kent, & Hayward, 2015), therefore, subgroupings were performed to allow for better interpretation, rather than to let the conclusions of the discussed subgroup influence clinical guidance.

Conclusion

This systematic review suggests that engagement in regular PA beneficially impacts cortisol and DHEA(S) levels. The evidence fell into two categories: First, a narrative synthesis of nine cross-sectional studies in older adults showed small associations between regular PA in daily life and lower total cortisol output. However, there was low quality

evidence that being physically active in daily life at older age is associated with increased DHEA(S) levels. Second, meta-analysis of 17 RCTs showed that exercise interventions probably reduce cortisol levels compared to no intervention. In addition, meta-analytic findings of six RCTs showed exercise training of at least 12 weeks probably improves DHEA(S) levels slightly compared to no intervention in older adults

Implications for practice

The general picture emerging from the analysis is that regular PA in older adults is associated with improved cortisol and or DHEA(S) levels and that physical exercise interventions of at least 12 weeks of any modality can beneficially improve these levels. The low to moderate certainty of this effect does not extend to different subgroups of health status or low-income countries. Considering the present findings in the light of previous literature about adherence to PA and habit formation, it is recommended that practitioners advise older adults to choose any kind of activity they enjoy doing, will do regularly, and maintain over a long period of time.

Implications for research

Further research is required to assess the associations between regular PA and hormonal balances including data from low-to-middle-income countries, varying in socio-economic status and ethnicity, in line with a recent review (Daskalopoulou et al., 2017). As feasibility and safety is established in older adults for all discussed exercise modalities and health states, studies should continue to explore exercise intervention effects on cortisol and/or DHEA(S), and the ratio in older adults, differentiating between different health states (e.g., metabolic syndrome, different mood states, cognitive decline, frailty) or different exercise modalities (types or intensities) in well-controlled clinical trials. With this, a

systematic review could be repeated to increase the precision of understanding of intervention effects in different health states for different exercise modalities.

Saliva samples are accurate, non-invasive and rapidly taken, so future studies could certainly use this measurement approach. Further, multiple measurements to make assumptions about the diurnal slope of cortisol are best practice, however, the number of sampling times is clearly a cost/accuracy trade-off. These measures should be complemented with a more comprehensive assessment quality of life outcomes (e.g., questionnaires about well-being, anxiety, stress perception, feelings of loneliness), as this will provide more in-depth insights on different variables contributing to how PA and hormonal parameters influence the general health of older adults. These recommendations are based on the literature base found through systematic review processes until September 2021.

Competing interests

The author confirms that there are no relevant financial or non-financial competing interests to report.

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Table 1

Characteristics of included cross-sectional studies

Study	Country	Population			PA measurement	Outcome		Relevant findings
		Sample size n (%male)	Mean age (SD) in years	Main group – subgroups		Cortisol (times - measure)	DHEA(S) (times - measure)	
Lucertini et al., 2015	Italy, Marche Region	22 (100%)	67.4 (1.5)	Generally healthy – high vs low fitness	Time/week: categorical questionnaire	Saliva sample (6x – diurnal slope)	-	High fitness levels = lower cortisol*
Pauly et al., 2019	Canada	162 (50%)	71 (6)	Generally healthy, community-dwelling – high and low daily steps	Counts: accelerometery	Saliva sample (4x – diurnal slope)	-	High daily steps were correlated with lower cortisol*
Bonnefoy et al., 2002	France, Lyon	50 (50%)	71 (4)	Generally healthy – men vs women	Energy expenditure: Questionnaire d'Activité Physique Saint-Etienne (QAPSE)	Blood sample (1x – morning)	Blood sample (1x – morning)	In women, higher PA = higher DHEAS*
Heaney et al., 2014	UK, Birmingham	36 (50%)	72.6 (5.5)	Generally healthy, community-dwelling – high stress vs low stress group	Time/week: categorical questionnaire	Saliva sample (6x – diurnal slope)	Saliva sample (6x – diurnal slope)	Higher PA = higher DHEA, and therefore lower cortisol:DHEA ratio*

Study	Country	Population			PA measurement	Outcome		Relevant findings
		Sample size n (%male)	Mean age (SD) in years	Main group – subgroups		Cortisol (times - measure)	DHEA(S) (times - measure)	
Moraes et al., 2016	Brazil	63 (13%)	71.5 (12)	Mood disorders – depressed vs healthy	Energy expenditure: International Physical activity questionnaire (IPAQ)	Saliva sample (1x – afternoon)	Saliva sample (1x – afternoon)	Depressed patients = lower levels of cortisol than healthy controls
Abbasi et al., 1998	US, Wisconsin	262 (55%)	69.9 (4.5)	Generally healthy, community-dwelling – men vs women and quartiles of serum DHEAS	Time/week: 7-day activity recall method	-	Blood sample (1x – morning)	Higher PA = higher DHEAS, in men*
Bonnefoy et al., 1998	France	60 (43%)	70 (4)	Generally healthy, community-dwelling – men vs women and high vs low active	Energy expenditure: QAPSE	-	Blood sample (1x – morning)	Lower habitual PA = lower levels of DHEAS*
de Gonzalo-Calvo et al., 2012	Spain, Oviedo	26 (100%)	75.5 (5)	Generally healthy, community-dwelling – long term trained vs sedentary	Time/week: checklist about regular physical activity	-	Blood sample (1x – morning)	Trained group = higher DHEA levels*
Ravaglia et al., 2001	Italy, Bologna	96 (100%)	67.8 (2.2)	Generally healthy – middle-aged vs older adults	Energy expenditure: checklist about regular physical activity	-	Blood sample (1x – morning)	Physically active men = higher DHEAS levels*

Note. *: marks significance in study

Table 2

Characteristics of included intervention studies

Study	Population				Intervention			Outcome		Relevant findings
	Sample size n (%male)	Mean age (range) (years)	Setting	Health status	Type	Duration	Control group	Cortisol (times - measure)	DHEA(S) (times - measure)	
Banitalebi et al., 2018	40 (0%)	M=67.35	Outpatient	Generally healthy	Resistance /endurance	12 weeks 3x per week (70 mins per session)	Aerobic vs resistance vs no exercise	Blood sample (1x morning)	-	Exercise = no change in cortisol levels
Borst et al., 2002	62 (45%)	60-85 (M= 68.1)	Centre for exercise and science, University of Florida, Gainesville	Generally healthy	Resistance	24 weeks 3x per week	No exercise program	Blood sample (1x time)	-	Resistance group = elevations in cortisol*
Campo et al., 2013	63 (0%)	65.9 (55-84)	Free living	Cancer survivors	Tai Chi - mind body	12 weeks 3x per week (60mins/session)	Health education	Saliva sample (5x for diurnal slope)	-	Tai chi group = lower cortisol levels*

Study	Population				Intervention			Outcome		Relevant findings
	Sample size n (%male)	Mean age (range) (years)	Setting	Health status	Type	Duration	Control group	Cortisol (times - measure)	DHEA(S) (times - measure)	
Furtado et al., 2016	35 (0%)	M= 83.81	Social and health care support centres	Generally healthy	Chair based yoga	14 weeks 2-3x per week	No exercise	Saliva sample (1x morning)	-	Yoga group = unchanged levels, control group = increased cortisol levels*
Furtado et al., 2021	32 (0%)	82.4 (4.6)	Social and healthcare centres	Generally healthy/ pre-frail	Combined chair-based	14 weeks 2-3x per week (60mins/session)	No exercise	Saliva Sample (1x morning)	-	Exercise group = no changes, control group = increased cortisol*
Ho et al., 2020	204 (18%)	M=79	Outpatient psycho-geriatrics/ older adult community centre	Cognitive impairment	Dance movement therapy (DMT) /exercise	12 weeks 2x per week (1hr/session)	Regular care	Saliva sample (5x morning)	-	DMT group = Improved diurnal cortisol slope*

Study	Population				Intervention			Outcome		Relevant findings
	Sample size n (%male)	Mean age (range) (years)	Setting	Health status	Type	Duration	Control group	Cortisol (times - measure)	DHEA(S) (times - measure)	
Kim et al., 2018	20 (0%)	66.4	Free living/ house wives	Metabolic - Obese	Aerobic/resistance	12 weeks 3x per week (90-120mins/session)	No exercise program	Saliva sample (1x morning)	-	Exercise groups = decrease in cortisol*
Lu et al., 2020	30 (52%)	60+	Nursing homes	Mood disorder	Qigong	12 weeks 2x per week (60mins/session)	Cognitive training	Saliva sample (5x for diurnal slope)	-	Qigong group = decrease in cortisol levels*
Mura et al., 2014	42 (62%)	65+	Community dwelling	Generally healthy	Aerobic /anaerobic	12 weeks	Gymnastic group	Blood sample (1x morning)	-	Both groups = cortisol rise*
Prakhinkit et al., 2014	45 (0%)	60-90 years	University hospital/ welfare centre	Mood disorder	Buddhism walking meditation/aerobic	12 weeks 3x per week (20-30mins/session)	No exercise program	Blood sample (1x morning)	-	Buddhism walking meditation group = cortisol decreased*

Study	Population				Intervention			Outcome		Relevant findings
	Sample size n (%male)	Mean age (range) (years)	Setting	Health status	Type	Duration	Control group	Cortisol (times - measure)	DHEA(S) (times - measure)	
Rieping et al., 2019	47 (0%)	80	Care home	Generally healthy	Chair based aerobic/ elastic band	14 weeks 3x per week (45 mins/ session)	No exercise program	Saliva sample (1x morning)	-	No cortisol level changes
Sin et al.,2015	70 (44%)	60-87	Korean community senior centre	Generally healthy	Walking	12 weeks	Walk on their own and no pedometer	Blood sample (1x morning)	-	No cortisol level changes
Tada, 2018	61 (31%)	70.9 (60-87)	Community-dwelling	Generally healthy	Resistance	24 weeks 2x per week (20mins/session)	No exercise program	Saliva sample (1x morning)	-	Exercise group = decrease in cortisol levels*
Tsang et al., 2013	38 (31%)	65+	Psychogeriatric day clinics/ day care centres/ care homes	Generally healthy vs Depression	qigong	12 weeks 3x per week (45mins/session)	No exercise program	Saliva sample (1x morning)	-	Exercise groups = decreasing trend in cortisol

Study	Population				Intervention			Outcome		Relevant findings
	Sample size n (%male)	Mean age (range) (years)	Setting	Health status	Type	Duration	Control group	Cortisol (times - measure)	DHEA(S) (times - measure)	
Venturelli et al., 2016	80 (25%)	65-75	Nursing homes	Cognitive impairment – Alzheimer's disease	Aerobic exercise	12 weeks 5x per week (60mins/session)	No exercise program	Saliva sample (5x for diurnal slope)	-	Exercise group = cortisol levels reduced*
Vrinceanu et al., 2019	40 (25%)	67.45 (60-86)	Geriatric institution/ gym	Generally healthy	Dance/aerobic	12 weeks 3x per week (60mins/session)	Waiting list	Saliva sample (3x morning)	-	Exercise group = decrease in cortisol level*
Furtado et al., 2020	60 (0%)	M= 81	Institutionalized older adults	Frail or pre-frail	Chair Based Exercise (CBE) /resistance	28 weeks 3x per week (45mins/session)	No exercise program	Saliva sample (1x morning)	Saliva sample (1x morning)	CBE group = DHEA increased, control group = DHEA decreased *
Ha et al., 2018	20 (0%)	70-80	Living in Korea	Generally healthy	Aerobic /anaerobic /resistance	12 weeks 3x per week (60mins/session)	No exercise program	-	Blood sample (1x time)	Exercise group = increase in DHEAS*

Study	Population				Intervention			Outcome		Relevant findings
	Sample size n (%male)	Mean age (range) (years)	Setting	Health status	Type	Duration	Control group	Cortisol (times - measure)	DHEA(S) (times - measure)	
Hersey et al., 1994	52 (45%)	M= 72 (70-79)	Living in Gainesville	Generally healthy	Endurance/ resistance exercise	24 weeks 3x per week (35-45 mins/ session)	No exercise program	-	Blood sample (1x morning)	No change in DHEA levels
Im et al., 2019	25 (0%)	M= 70	Fitness centre	Post-menopausal	Yoga and dance	12 weeks 3x per week (60mins/session)	No exercise program	-	Blood sample (1x morning)	Exercise group = decrease in DHEAS*
Son et al., 2020	20 (0%)	M= 67.7	Multi-health community centre	Generally healthy	Resistance	12 weeks 3x per week (60mins/session)	Sedentary activities	-	Blood sample (1x morning)	Exercise group = increase in DHEAS*
Yamada et al., 2015	227 (37%)	65+	Community dwelling	Generally healthy	Walking	24 weeks	Walking & nutrition & inactive control	-	Blood sample (1x morning)	walking/ nutrition group = DHEAS increased *

Note. *: marks significance in study

Table 3

GRADE table

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Certainty (overall score)[1]	Participants	Effect	
Average effect of physical activity intervention in older adults, compared to controls *Outcome: cortisol*								N (%male)	SMD [95% CI]	I^2
17	RCT	+	-	+	+	undetected	⨁⨁⨁◯	759 (23%)	-63 [-0.90, -0.36]	69%
Outcome: DHEA(S)										
6	RCT	+	+	+	-	undetected	⨁⨁⨁◯	203 (14%)	0.44 [0.20, 0.68]	0%

Evidence of effect of regular physical activity compared to sedentary *Outcome: cortisol*									Effect direction	P-value (sign test)	
										M	F
5	Cross-sectional	+	+	+	-	undetected	⨁◯◯◯	333 (53%)	-	.0625	.3750
Outcome: DHEA(S)											
7	Cross-sectional	+	+	+	+	undetected	⨁⨁◯◯	545 (59%)	+	.0156	.4531

Note. SMD= Standardised Mean Difference, CI= Confidence Interval, I^2= I-square statistic, M= Male, F= Female

[1]4 ⊕⊕⊕⊕ High = This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different** is low.

3 ⊕⊕⊕◯ Moderate = This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different** is moderate.

2⊕⊕◯◯ Low = This research provides some indication of the likely effect. However, the likelihood that it will be substantially different** is high.

1 ⊕◯◯◯ Very low = This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different** is very high.

** Substantially different = a large enough difference that it might affect a decision

Cross-sectional studies start out with ⊕⊕◯◯, conform to the GRADE guidelines.

Based on: Cochrane Consumers and Communication La Trobe University; Ryan, Rebecca; Hill, Sophie (2018): How to GRADE. La Trobe. Journal contribution. https://doi.org/10.26181/5b57d95632a2c

Table 4

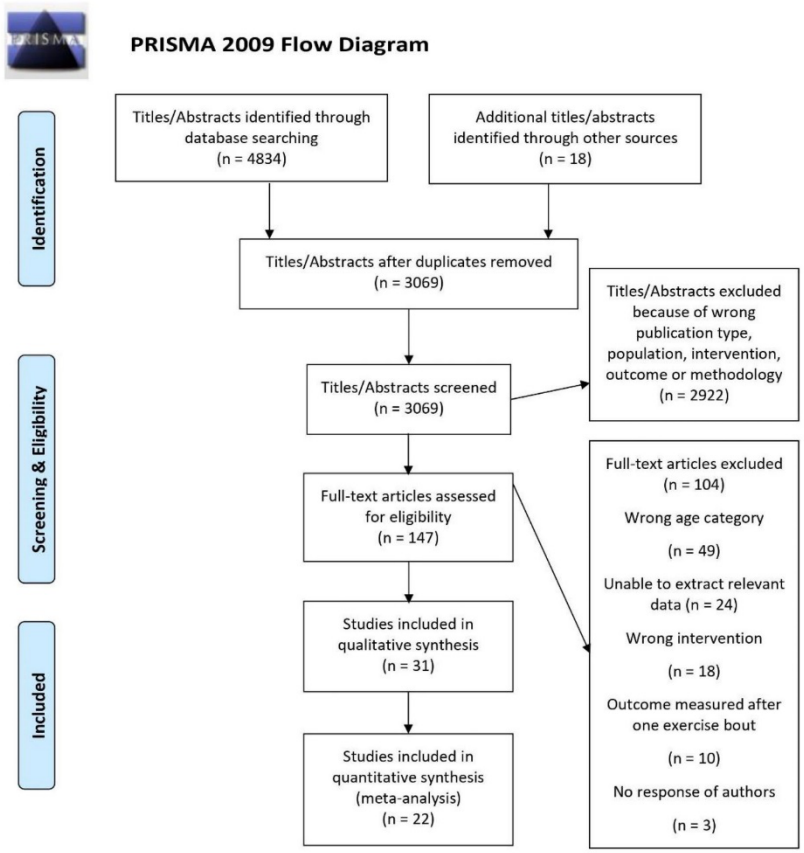
Standardized Mean Differences (SMD) and 95% Confidence intervals (CI) of meta-analytic findings of the cortisol outcome subgroups

	SMD [95% CI]	N studies	N participants
Gender			
Males and females	-0.61, [-0.90, -0.33]	17	736
Females only	-0.52 [-0.79, -0.25]	8	290
Intervention types			
Aerobic exercise	-0.54 [-1,05, -0.03]	6	319
Resistance training	-0.91 [-1.95, 0.14]	3	141
Combined protocol	-0.67 [-1.20, -0.14]	4	127
Mind body exercise	-0.47 [-0.79, -0.14]	4	149
Intervention intensity			
Low-moderate	-0.65 [-0.96, -0.33]	15	656
Moderate-high	-0.41 [-1.01, 0.20]	2	80
Intervention duration			
12 weeks	-0.58 [-0.89, -0.27]	12	531
14-28 weeks	-0.67 [-1.32, -0.01]	5	205
Health status			
Generally healthy participants	-0.59 [-1.02, -0.16]	9	385
Participants with mood disorders	-0.36 [-0.79, 0.06]	3	87
Participants with other health issues	-0.86 [-1.46, -0.26]	6	264

Note. SMD: Standardized Mean Difference, CI: Confidence interval.

Figure 1

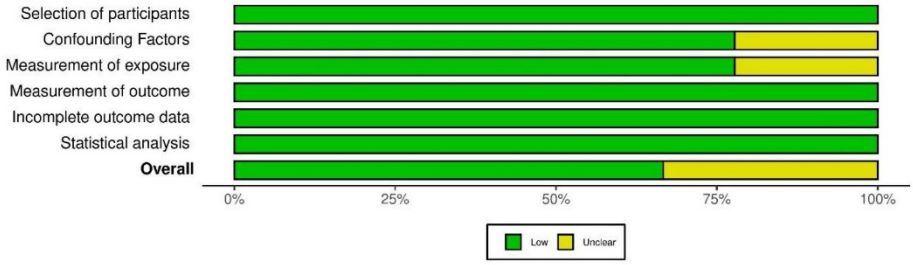
PRISMA flow diagram of the systematic review



Note. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Figure 2

Critical appraisal of cross-sectional studies, appraised by the JBI-tool



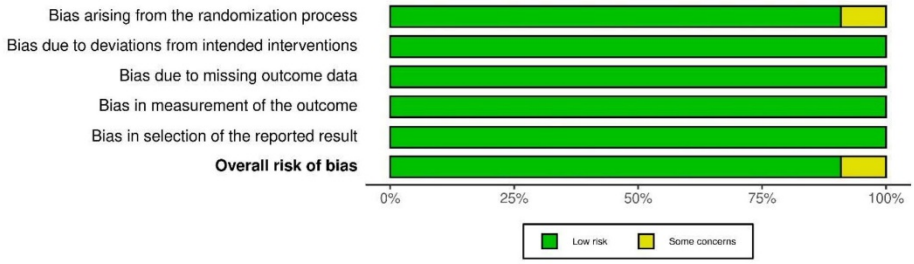
Note. Green: low risk of bias, yellow: unclear information about given topics, yet included in further analysis. From: robvis tool, https://mcguinlu.shinyapps.io/robvis/.

1

2

Figure 3

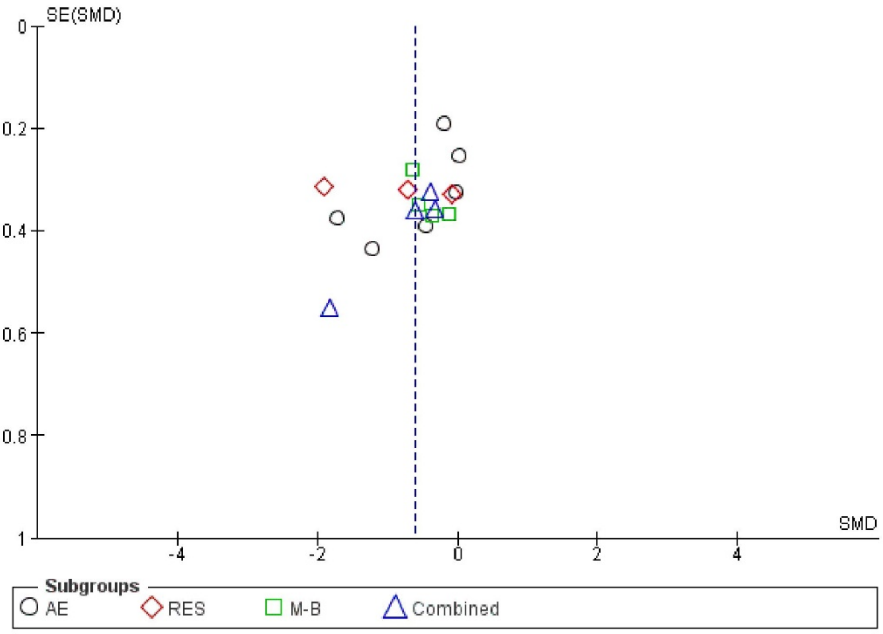
Critical appraisal of RCTs, appraised by the Cochrane RoB tool



Note. Green: low risk of bias, yellow: some concerns about given topics, yet included in further analysis. From: robvis tool, https://mcguinlu.shinyapps.io/robvis/.

Figure 4

Egger's test by Funnel plot



Note. AE = aerobic exercise, RES = resistance training, M-B = mind-body exercise, Combined = intervention including aerobic and resistance training elements.

1

2

Figure 5

Effect direction plot summarizing direction of cortisol and DHEA(S) hormone level impacts from cross-sectional studies.

Study	Cortisol male	Cortisol female	DHEA male	DHEA female
Lucertini F. et al., 2015	▼	◄►		
Pauly T. et al., 2019	▼	▼		
Bonnefoy M. et al., 2002	▼	▼	▲	▲
Heaney J. et al., 2014	▼	▼	▲	▲
Moraes H. et al., 2016	▼	▼	▲	▲
Abbasi A. et al., 1998			▲	▲
Bonnefoy M. et al., 1998			▲	▲
de Gonzalo-Calvo D. et al., 2012			▲	◄►
Ravaglia G. et al., 2001			▲	◄►

Note. Effect direction: upward arrow ▲= increase in endocrine outcome , downward arrow ▼= decrease in endocrine outcome, sideways arrow ◄►= no change/mixed effects/conflicting findings. Sample size: Final sample size (individuals) in intervention group Large arrow ▲ >300; medium arrow ▲ 50-300; small arrow ▲ <50. Study quality: denoted by row colour: green = low risk of bias; amber = some concerns; red = high risk of bias.

Figure 6

Forest plot for cortisol

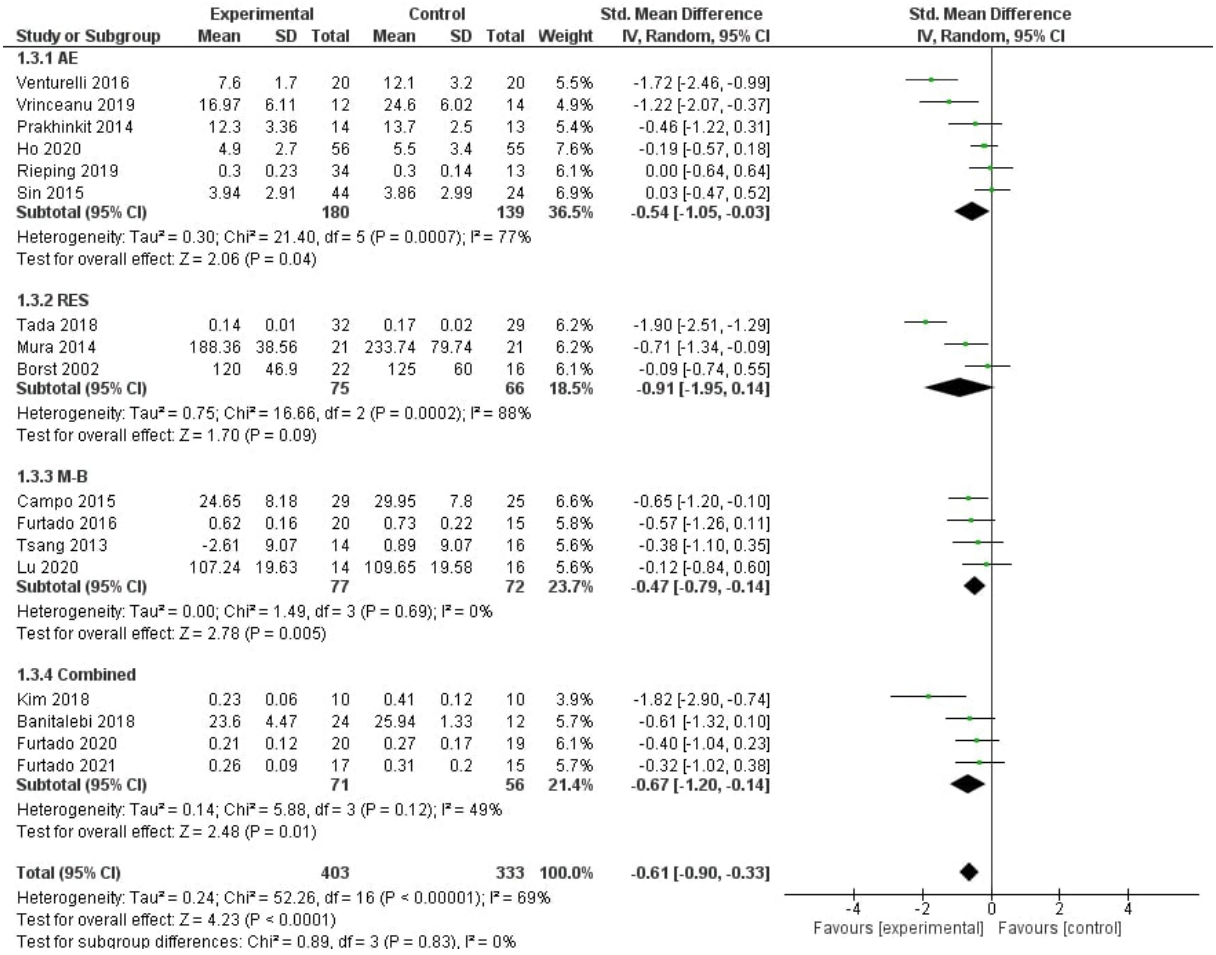


Figure 7

Forest plot for DHEA(S)