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Effect of exercise on renal-relevant biomarkers in the general population: A systematic review and meta-analysis

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Complete List of Authors:	Liu, Qiaoling; University of Glasgow Celis-Morales, Carlos; University of Glasgow; University Católica del Maule Talca Mark, Patrick; University of Glasgow Welsh, Paul; University of Glasgow

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Effect of exercise on renal-relevant biomarkers in the general population: A systematic review and meta-analysis

Author names

Qiaoling Liu[1,*], Carlos Celis-Morales[1,2], Patrick Mark[1], Paul Welsh[1]

Affiliations

[1] School of Cardiovascular and Metabolic Health, University of Glasgow, The United Kingdom

[2]Human Performance Lab, Education, Physical Activity and Health Research Unit, University Católica del Maule, Talca, 3466706, Chile

Corresponding author

Qiaoling Liu

School of Cardiovascular and Metabolic Health, University of Glasgow,
Glasgow, G12 8TA
The United Kingdom

Email: q.liu.3@research.gla.ac.uk

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Abstract

Background: Physical activity (PA) has been generally recognized as a beneficial factor for health. Current research on PA's effect on the kidneys is inconsistent. The impact of change in PA on renal-relevant biomarkers in individuals without renal diseases remains unclear. This manuscript aims to investigate the association of changes in PA with renal-relevant biomarkers in the general population free of renal diseases.

Methods: We conducted a systematic search of four databases in March 2023 to identify studies reporting the association between the changes in PA and renal-relevant biomarkers in people without known renal diseases. The published results of renal-relevant biomarkers prior to and after changes in physical activity were pooled using random effects models. Bias was assessed by Egger regression; subgroup and sensitivity analysis were performed.

Results: Sixteen interventional studies with randomized or non-randomized designs involving 500 participants were identified. The median follow-up was 84 days. Ten studies were at high risk of bias. Studies with low quality were published prior to the year 2000. Changes in PA were found only to have a positive association with serum creatinine (SCr) (Hedge's g=0.69, 95%CI: 0.13, 1.24, I^2=81.37%) and not with plasma renin activity, urea, and urinary albumin-to-creatinine ratio. The positive association was only observed in people with obesity and those who exercise over 84 days.

Conclusions: Higher levels of PA are associated with increased SCr levels. It remains unclear if this association is related to impaired kidney function, as data on other kidney biomarkers did not support a certain link.

Keywords

Biomarkers, exercise, general population, kidney, meta-analysis.

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Strengths and limitations of this study:

- Comprehensive assessment of multiple renal biomarkers in renal-healthy population: The study examined several key renal biomarkers such as serum creatinine, urinary albumin-to-creatinine ratio, and plasma renin activity, providing a broader understanding of how changes in physical activity may affect kidney health.
- Limited by small study sizes and heterogeneity: Some of the included studies were small in size and with high attrition rates, which may introduce potential biases, especially in relation to the observed heterogeneity in outcomes.
- Implications for public health recommendations: The findings raise important questions about the long-term effects of physical activity on kidney function in healthy individuals, suggesting that while exercise is generally beneficial, its impact on renal health requires further investigation.

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Background

Cardiovascular disease (CVD) is a major public health concern worldwide, with high morbidity and mortality. According to the World Health Organization, an estimated 17.9 million people die from CVDs each year, accounting for 32% of all global deaths as of 2019 [1]. Also, CVDs pose a significant economic burden on the healthcare systems of developed and low- and middle-income countries [2 3]. A number of behavioural risk factors have been identified as contributing to CVD incidence, including tobacco use, unhealthy diets, and physical inactivity [4]. On the contrary, physical activity (PA) has been linked to the prevention of CVD, along with other chronic conditions such as chronic kidney disease (CKD) [5].

Despite the myriad of benefits of PA on cardiovascular health, its effect on kidney function is not well established. Impaired kidney function is a risk factor for cardiovascular disease [6], it is plausible that PA might also positively affect kidney function [7]. Serum creatinine-based estimated glomerular filtration rate is commonly used in clinical practice and creatinine is a product of muscle metabolism [8]. Therefore, any effect of PA on muscle metabolism may indirectly affect the measurement of kidney function. There is also evidence suggesting that extreme levels of PA may induce kidney damage via rhabdomyolysis or dehydration [9].

Evidence from randomised controlled trials suggests that PA is associated with multiple metrics of kidney function. However, evidence is controversial. PA is inversely associated with the risk of kidney function decline in people aged over 65, with an average estimated glomerular filtration rate (eGFR) of around 80 mL/min/1.73m^2 [10]. Yet, the same association was not observed in a younger general population (age 26-65 years) with a much higher average eGFR of 108 mL/min/1.73m^2 [11]. Regarding PA intensity, accelerometer-measured low- and moderate-intensity PA are positively associated with eGFR in a general Japanese population (age 35-79 years, average eGFR 92.6 mL/min/1.73m^2) across sexes and ages [12].

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PA has also been linked to urinary albumin excretion. As the dysfunction of the renal endothelial barrier and atherosclerosis contribute to the leakage of albumin into the urine, microalbuminuria has been suggested as an indicator of renal endothelial dysfunction [13 14]. The association between high PA levels and lower microalbuminuria has been observed consistently across blood pressure, heart rate, and diabetic/non-diabetic populations [15]. Novel biomarkers of renal impairment, such as liver-type fatty acid-binding protein, have also been found to be negatively impacted by habitual physical activities [16]. The degree of stress on the proximal tubule may be attenuated through physical activity, regardless of the renal functional reserve, suggesting PA's health benefits on the renal structure.

Although the effects of PA on the kidneys have been studied, many articles focus on the acute effect of physical activity, and they are not instructive on the effects of changing habitual PA. The study population is often restricted to patients with chronic kidney disease (CKD) / end-stage renal disease (ESRD) or those who undergo dialysis. These research findings may not be applicable to the general population without known renal diseases. A number of intervention studies discussed the effect of PA in combination with other treatments, like diet and pharmaceutical approaches; thus, it is difficult to measure PA’s direct effect. To date, there is a lack of systematic review of the literature which has been conducted on the effect of changes in physical activity on kidney health in populations without pre-existing kidney diseases. In this context, this study aimed to conduct a systematic review and meta-analysis to bridge the knowledge gap.

Methods

This review has been registered on PROSPERO (CRD42023407820). In this review, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement (PRISMA) [17] and the Cochrane Handbook for Systematic Reviews of Interventions [18].

One author (QL) performed systematic literature searches for longitudinal studies and clinical trials (randomized and non-randomized) in Embase, PubMed, MEDLINE, and Web of Science from

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database inception to March 12, 2023. Observational studies of longitudinal design and clinical trials (randomized/non-randomized) were initially selected for evaluation. Studies that met the following criteria were excluded: 1. Case-control studies; 2. Studies evaluating physical activity solely as a timepoint value; 3. Studies conducted in a population with pre-existing renal diseases, such as chronic kidney disease, dialysis, and renal transplantation; 4. Studies evaluating the impact of a single episode of physical activity, such as a sporting event; and 5. Non-English studies. The detailed search terms can be found in the Supplemental materials (Table S1).

Two authors (QL and PW) independently decided which studies should be included in this study, and any disagreements were resolved through a discussion with two other authors (CC and PM). To maximize the coverage of sources, one author (QL) checked the references of the selected articles and evaluated their relevance after reading the full text. Additively, one author (QL) performed manual searches on relevant studies.

Quality assessment

The quality of the selected studies was independently assessed by two reviewers using the Newcastle-Ottawa Scale (NOS), a tool commonly used in systematic reviews on physical activity [19]. A study was biased if the loss to follow-up was 20% or above [20]. The full score of NOS was nine.

To evaluate any methodological flaws in selected studies, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used [21]. Any disparities in judgment raised between the two reviewers were resolved through discussion with the help of a third author as needed.

Data synthesis

Using a predesigned table, information was extracted on the first author's family name, publication year, study type, study location, baseline characteristics of exercise groups, type of exercise, length/frequency/intensity of exercise, and outcomes. In case a study has both exercise and sedentary

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groups, only the information of the group which performed physical activity was included to align with our research theme.

For studies with multiple measurements, only the final measurement was used to calculate change, i.e., the measurement from the group with the longest exercise duration. In cases where a study reported outcomes for independent groups, such as sex-specific groups, each group was treated as a separate study, and the findings were listed individually. The median (interquartile range [IQR]) of reported data was converted to the mean (standard deviation [SD]) following established methods [22]. In case the standard error of the mean (SEM) was provided only, the SD was calculated from SEM multiplied by the square root of the number of study size.

As between-study heterogeneity was anticipated, we constructed random-effects models [23] to combine the mean (SD) of selected studies and applied the inverse variance weighting method. The Hedge's g expresses the difference of the means in units of the pooled standard deviation; it measures the effect size for the difference between the means. This study used it to synthesize effect sizes and obtain an overall estimate of the effect of physical activity. It incorporated a correction factor for small sample sizes, which is useful as many PA interventions were of small scales [24]. For interpretation, a value of 0.2, 0.5, and 0.8 was regarded as small, medium, and large effects [25]. Heterogeneity between studies was examined using the I^2 statistic and an I^2 above 50% means substantial heterogeneity [26 27]. Subgroup analyses and meta-regressions were conducted to investigate heterogeneity across age, obesity, and length of exercise. Due to insufficient data, some subgroup analyses and regressions were not performed for all outcomes. Funnel plots and Egger's test were performed to evaluate the risk of biased results [28]. Statistics analyses were performed using STATA 17 (StataCorp, USA). Data were visualized using Robvis [29].

Sensitivity analysis

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Leave-one-out analysis was performed to identify influential studies by conducting the meta-analysis multiple times while removing one of the included studies during each iteration. Results were presented as leave-one-out figures. A cumulative meta-analysis was also performed for each outcome according to publication year to identify secular trends.

Results

Identification of studies

After removing duplicated studies, 10294 potentially relevant studies were identified. Initial screening based on title and abstracts resulted in 155 studies retrieved for further evaluation. Following full-text assessment, 150 studies were excluded, leaving five studies. Additionally, 20 studies were identified through hand search and reading citations, of which nine were excluded, leaving 11 studies. In total, 16 studies were included in the study. All the included studies were intervention studies (Figure S1).

(Figure S1 is here)

Characteristics of the included studies

The identified 16 studies included 500 people. The sample size of the individual studies ranged from 4 to 162. The average age of participants was 50.1 years. Ten studies recruited people with essential hypertension [30-39], one study recruited people with type 2 diabetes mellitus [40], two studies recruited people with obesity [41 42], two studies recruited healthy people [43 44], and one study recruited patients with heart failure [45]. Participants in 12 studies were required to perform aerobic exercise only [30-39 44 45]; two studies involved aerobic exercise and its combinations with strength training [40 42], and two others involved resistance training only [41 43]. All the studies have a similar exercise frequency of 3-5 sessions per week, while the length of sessions varies according to the exercise intensity, with a median of 12 weeks. Seven studies have an attrition rate of 20% or above [30 31 33 38 39 41 42], with a maximum of 30.9% [33].

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Many included studies used maximum oxygen uptake (VO_{2max}) to measure the intensity of aerobic exercise, with a few studies using heart rate reserve [33], maximum heart rate [34 35 42], and lactate threshold [40]. For resistance and strength training, repetition maximum (RM) was used to measure the exercise intensity (Table 1).

(Table 1 is here)

Measurement of physical activities

Fourteen studies required participants to perform on-site physical activity under close supervision. The low-workload group in the study by Hagberg et al. [30] was supervised for the first month, and relied on self-reported forms for the remaining eight months. All the participants in the study by Passino et al. [45] had self-conducted exercises with their compliance to the instruction checked at the beginning and near the end of the study. All the studies have reported the arrangement of physical training.

Measurement of the outcomes

Serum creatinine (SCr), plasma renin activity (PRA), and urea were the most measured biomarkers in selected studies. Two studies reported eGFR [36 42], one study [42] reported urine albumin-to-creatinine ratio (UACR), and one study [31] was on angiotensin II (Ang II). Twelve of these studies measured fasting biomarkers, while three studies have not specified the fasting status [42 44 45]; one study explicitly measured biomarkers after participants have "a light breakfast" [39]. All the biomarkers were measured under resting conditions.

Potential bias and quality assessment

The Newcastle-Ottawa Scale was eight or above in 12 out of 16 studies. Most studies had a less representative intervention cohort, especially those published decades ago. Two studies scored six

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points, which were the lowest, were published in the 1980s [30 31]. Studies with better population representation were published after 2000. The follow-up period's adequacy was another major source of point deductions, with seven studies not receiving full marks due to a high attrition rate. Considering the nature of the intervention design and the objective evaluation of outcomes through laboratory testing, all studies received full marks for the selection of control groups and outcome assessment (Table 2).

(Table 2 is here)

Six studies with a randomized design have provided information on how the random sequence was generated [30 38 40 42 43 45]. Furthermore, it was impossible to blind participants in supervised situations due to the nature of the physical activity as an exposure. Objective laboratory testing was used to assess all outcomes, resulting in a low risk of detection bias. However, high attrition and selective reporting may have affected some studies. Some studies also have a higher risk of measurement error for exposure and outcome. Overall, the selected studies had a relatively high risk of bias (Figure 1, 2).

(Figure 1 is here)

(Figure 2 is here)

Changes in physical activity and serum creatinine

The meta-analysis included six study populations from four studies [33 41-43], including 197 participants with an average PA duration of 73 days. The pooled result showed a moderate positive effect of PA on SCr (Hedge's g=0.69, 95%CI: 0.13, 1.24). Substantial heterogeneity was detected among cohorts (I^2=81.37%). Regarding individual cohorts, all except one were positioned to the right of the reference line, showing a consistently positive effect (Figure 3a).

(Figure 3 is here)

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Stratifying by the status of obesity, only two groups of obese participants of a single study [42] have a statistically significant pooled effect (Hedge's =0.74, 95%CI: 0.29, 1.20). Stratified by the median of the length of exercises (12 weeks), only two cohorts from one study who have undergone exercises over 12 weeks have a significant pooled effect (Hedge's =0.74, 95%CI: 0.29, 1.20) (Figure S1a-b).

The funnel plot showed mild asymmetry, and Egger's test showed no small-study effects (P value=0.21). Sensitivity analysis showed a consistent result as that of the primary analysis; the removal of one cohort from Zaman [41] largely attenuated the pooled effect (Hedge's =0.38, 95%CI: 0.05, 0.72). Obesity was identified as the only important source of heterogeneity. Cumulative meta-analyses according to the year of publication showed significant evidence of secular trends for SCr (Figure S1c-e).

Changes in physical activity and eGFR

Three cohorts from two studies [36 42] included 50 people with an average exercise duration of 12 weeks were identified. No significant effect was found in the pooled result of the exercise on eGFR (Hedge's g=-0.30, 95%CI: -0.83, 0.24, I^2=48.57%) (Figure 3b).

Changes in physical activity and urinary albumin-to-creatinine ratio

Two cohorts from one study [42] included 38 people with an average exercise duration of three months were identified. No statistical significance was found in the pooled result of the exercise on UACR (Hedge's g=-0.15, 95%CI: -0.59, 0.29) (Figure 3c).

Changes in physical activity and plasma renin activity

Thirteen cohorts from eleven studies [30-32 34-39 44 45] included 184 people with an average exercise duration of 129 days in the meta-analysis. No association between PA and PRA was observed

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(Hedge's g=-0.12, 95%CI: -0.32, 0.09). Minor heterogeneity was found among cohorts (I^2=2.54%) (Figure 3d).

In stratified analyses, no associations were found by obesity status, exercise-length and age- groups. There was no statistically significant effect of exercise on PRA in people aged 60 and above, the upper 95% CI was close to zero (Hedge's =-0.54, 95%CI: -1.14, 0.06) (Figure S2a-c).

The funnel plot showed good symmetry. Egger's test showed no small-study effects (P value =0.39). Sensitivity analysis showed a consistently insignificant result as that of the primary analysis, with no influential single studies. Meta-regression showed no important source of heterogeneity. Cumulative meta-analysis showed no significant changes in research findings (Figure S2d-f).

Changes in physical activity and serum urea

Five cohorts from three studies [40 41 43] included 48 people with an average exercise duration of 73 days. No association was found between PA and urea (Hedge's g=-0.15, 95%CI: -0.50, 0.20). No heterogeneity was found among cohorts (I^2=0.00%) (Figure 3e). Data were consistent in subgroup analyses. (Figure S3a).

The funnel plot showed good symmetry, and Egger's test showed no small-study effects (P value =0.39). Sensitivity analysis showed a consistently insignificant result as that of the primary analysis, with no influential single studies. Meta-regression showed no important source of heterogeneity. Cumulative meta-analyses showed no significant changes in research findings (Figure S3b-d).

Changes in physical activity and other renal-related biomarkers

A study by Kiyonaga et al. [31] showed that after 20 weeks of mild aerobic exercise, the average level of Angiotensin II in eight patients with essential hypertension increased significantly from 58 to 91

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pg/ml. However, the increase in Angiotensin II was not observed after completing the first 10 weeks of training.

Discussion

In this systematic review and meta-analysis of 16 interventional studies involving 500 people without known kidney diseases, we evaluated the available data exploring the association of change in PA with kidney function. Change in PA was found only to have a positive association with SCr, not with eGFR. There was some limited evidence that participants with obesity and people who exercised over 12 weeks may have a larger increase in SCr as compared to their counterparts. Sensitivity analysis was in line with the primary analysis; mild publication bias and a secular trend were found. The general quality of studies was suboptimal to make robust conclusions, and the number and size of studies were generally small (ranging from 4 to 112 participants).

Due to the possibility of physical activity to induce muscle growth, which is the primary source of SCr, the role of body composition in the association between physical activity and SCr deserves discussion. Among three studies reporting on SCr and body composition, Szulinska et al.[42] reported a significant increase in lean body mass and SCr, and decrease in body fat% in a population receiving endurance and strength training for three months; Trabelsi et al.[43] reported no significant changes in body fat% but a significant increase in SCr in a population receiving one-month resistance training, while Sikiru et al.[33] reported no significant change in body fat% and a likely increase in SCr in a population receiving eight weeks of aerobic training. It is noteworthy that study populations of the above studies had markedly different body compositions, with the latter two having low baseline body fat% (11.9% and 13.5%, respectively), while the population in the first study had an average body fat% of over 33%. Additionally, Kinoshita et al.[36] reported no significant change in eGFR in 12 non-obese people after a ten-week aerobic exercise, which implied a possible insignificant change in SCr. Therefore, the impact of PA on SCr levels may be related to body composition.

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As an important chemical substance secreted by the kidney for regulating blood pressure, renin has long been a topic of interest. Among the biomarkers under discussion, renin is the most extensively researched, with the earliest studies dating back to the 1980s. However, nine of the eleven studies on renin were published in 1992 or earlier, with only two published after 2000. The studies involved a small number of participants, with most having between 10 and 20 individuals. Nevertheless, the cumulative meta-analysis based on publication year revealed a progressively narrowing 95% confidence interval with an upper limit approaching zero and a consistently negative effect size. In the research conducted by Matsuaki et al. [38]; despite the absence of a significant difference in baseline PRA between the low- (50% VO_{2max}) and the high-workload (75% VO_{2max}) group, both cohorts manifested a similar pattern characterized by two interlocking M shapes throughout six measurements conducted at baseline and week 1/2/4/7/10. The PRA pattern exhibited by the low-workload group between Week 1 and Week 10 was similar to that of the high-workload group between Week 0 and Week 7. The PRA change in the low-workload group was "delayed" by one week compared to the high-workload group. Specifically, the PRA in the low-workload group experienced a slight decline in the first week, followed by an increase in the second week, whereas the PRA in the high-workload group increased in the first week. The underlying mechanism of this finding remains elusive.

Kiyonaga et al. [31] reported a significant increase in Angiotensin II after 20 weeks of mild aerobic exercise in eight patients, yet no significant increase was observed by week 10. As renin secretion is the first step in the production of Angiotensin II, it can be speculated that an exercise lasting over 20 weeks may significantly impact renin (and thus Angiotensin II). Renin is rarely measured in clinical practice and is affected by many antihypertensive drugs. Although these findings are interesting, any effect of PA on renin is unlikely to translate to information used to inform clinical guidelines.

Urea is clinically measured to evaluate renal impairment. There was a lack of a significant association between exercise and urea levels. One possible explanation is that, considering the absence of renal disease in all study participants at baseline, the closely supervised, low to moderate-intensity exercise

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did not result in renal damage or alterations that exceeded the renal compensation, thus precluding significant observable variations in urea levels.

To the best of our knowledge, this is the first systematic review and meta-analysis to investigate the association between changes in physical activity and renal biomarkers in people without known renal diseases. The studies included underwent rigorous assessment based on strict criteria. We observed low heterogeneity among most of the biomarkers studied. Sensitivity analyses aligned with our primary findings.

It is unlikely that any rise in serum creatinine with PA represents an adverse effect of PA on kidney function, given the widespread benefits of PA on cardiovascular health. It is theoretically plausible that PA reduces glomerular perfusion and hence creatinine rises. This effect is seen in people taking both medications inhibiting the renin-angiotensin system [46] and sodium glucose transporter 2 inhibitors [47]. This transient rise in serum creatinine is associated with long-term cardiovascular and renal benefits with these agents. Studies of PA with long durations are required to determine if any change in creatinine with PA is associated with benefit or harm on cardiorenal health.

Although efforts have been made in this study, there are limitations readers should be aware of. Firstly, most studies had a very small sample size, with only a few exceptions. While this may be attributed to a general insufficiency of resources, such as funding and personnel. Secondly, over 50% of the studies were found to have considerable bias, primarily stemming from high attrition rates, negatively impacting the quality of these studies. Furthermore, some studies were conducted decades ago, which could introduce potential issues with measurement methods, accuracy, and lab standards. This underscores the pressing requirement for updated and standardized research.

In conclusion, by examining the changes in physical activity among individuals without diagnosed renal diseases, the findings of this study supported the positive association of physical activity with SCr. However, the association with kidney function specifically could not be confirmed by existing

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data on other kidney biomarkers. Given the global advocacy for increased physical activity by governments and medical professionals, and the clinical importance of kidney function, further research should be conducted in the general population to investigate the association of change in PA with kidney function.

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Declarations

Ethics approval

Not applicable, as this study retrieved and synthesised data from already published studies.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

Conceptualization, P.W., Q.L.; methodology, Q.L.; data curation, Q.L., P.W., C.C., P.M.; writing—original draft preparation, Q.L.; writing—review and editing, Q.L., P.W., C.C., P.M.; supervision, P.W., C.C., P.M. All authors have read and agreed to the published version of the manuscript.

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References

1. World Health Organization. Cardiovascular diseases (cvds) [Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) accessed April 24 2023.
2. Gheorghe A, Griffiths U, Murphy A, et al. The economic burden of cardiovascular disease and hypertension in low- and middle-income countries: a systematic review. *BMC Public Health* 2018;18(1):975. doi: 10.1186/s12889-018-5806-x
3. Tarride JE, Lim M, DesMeules M, et al. A review of the cost of cardiovascular disease. *Can J Cardiol* 2009;25(6):e195-202. doi: 10.1016/s0828-282x(09)70098-4 [published Online First: 2009/06/19]
4. Buttar HS, Li T, Ravi N. Prevention of cardiovascular diseases: Role of exercise, dietary interventions, obesity and smoking cessation. *Exp Clin Cardiol* 2005;10(4):229-49. [published Online First: 2005/01/01]
5. Guo C, Tam T, Bo Y, et al. Habitual physical activity, renal function and chronic kidney disease: a cohort study of nearly 200 000 adults. *British Journal of Sports Medicine* 2020;54(20):1225-30. doi: 10.1136/bjsports-2019-100989
6. Matsushita K, van der Velde M, Astor BC, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010;375(9731):2073-81. doi: 10.1016/s0140-6736(10)60674-5 [published Online First: 2010/05/21]
7. Park S, Lee S, Kim Y, et al. Causal effects of physical activity or sedentary behaviors on kidney function: an integrated population-scale observational analysis and Mendelian randomization study. *Nephrology Dialysis Transplantation* 2021;37(6):1059-68. doi: 10.1093/ndt/gfab153
8. Inker LA, Eneanya ND, Coresh J, et al. New Creatinine- and Cystatin C-Based Equations to Estimate GFR without Race. *N Engl J Med* 2021;385(19):1737-49. doi: 10.1056/NEJMoa2102953 [published Online First: 2021/09/24]
9. Rawson ES, Clarkson PM, Tarnopolsky MA. Perspectives on Exertional Rhabdomyolysis. *Sports Med* 2017;47(Suppl 1):33-49. doi: 10.1007/s40279-017-0689-z [published Online First: 2017/03/24]
10. Robinson-Cohen C, Katz R, Mozaffarian D, et al. Physical activity and rapid decline in kidney function among older adults. *Arch Intern Med* 2009;169(22):2116-23. doi: 10.1001/archinternmed.2009.438 [published Online First: 2009/12/17]
11. Herber-Gast G-CM, Hulsegge G, Hartman L, et al. Physical Activity Is not Associated with Estimated Glomerular Filtration Rate among Young and Middle-Aged Adults: Results from the Population-Based Longitudinal Doetinchem Study. *PLOS ONE* 2015;10(10):e0133864. doi: 10.1371/journal.pone.0133864
12. Sasaki S, Nakamura K, Ukawa S, et al. Association of accelerometer-measured physical activity with kidney function in a Japanese population: the DOSANCO Health Study. *BMC Nephrology* 2022;23(1):7. doi: 10.1186/s12882-021-02635-0
13. Deckert T, Feldt-Rasmussen B, Borch-Johnsen K, et al. Albuminuria reflects widespread vascular damage. The Steno hypothesis. *Diabetologia* 1989;32(4):219-26. doi: 10.1007/bf00285287 [published Online First: 1989/04/01]
14. Clausen P, Jensen JS, Jensen G, et al. Elevated urinary albumin excretion is associated with impaired arterial dilatory capacity in clinically healthy subjects. *Circulation* 2001;103(14):1869-74. doi: 10.1161/01.cir.103.14.1869 [published Online First: 2001/04/11]
15. Pöss J, Ukena C, Mahfoud F, et al. Physical activity is inversely associated with microalbuminuria in hypertensive patients at high cardiovascular risk: data from I-SEARCH. *Eur J Prev Cardiol* 2012;19(5):1066-73. doi: 10.1177/1741826711421301 [published Online First: 2011/09/09]

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Enseignement Superieur (ABES) .
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16. Kosaki K, Kamijo-Ikemori A, Sugaya T, et al. Effect of habitual exercise on urinary liver-type fatty acid-binding protein levels in middle-aged and older adults. *Scand J Med Sci Sports* 2018;28(1):152-60. doi: 10.1111/sms.12867 [published Online First: 2017/03/02]
17. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71
18. McKenzie JE, Brennan SE, Ryan RE, et al. Cochrane Handbook for Systematic Reviews of Interventions2019.
19. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [cited 2023 March 31]. Available from: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp accessed March 31 2023.
20. Fewtrell MS, Kennedy K, Singhal A, et al. How much loss to follow-up is acceptable in long-term randomised trials and prospective studies? *Archives of Disease in Childhood* 2008;93(6):458. doi: 10.1136/adc.2007.127316
21. Brozek JL, Akl EA, Alonso-Coello P, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. *Allergy* 2009;64(5):669-77. doi: 10.1111/j.1398-9995.2009.01973.x [published Online First: 2009/02/13]
22. Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Medical Research Methodology* 2014;14(1):135. doi: 10.1186/1471-2288-14-135
23. Borenstein M, Hedges LV, Higgins JP, et al. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods* 2010;1(2):97-111. doi: 10.1002/jrsm.12 [published Online First: 2010/04/01]
24. Hedges LV, Olkin I. Statistical methods for meta-analysis: Academic press 2014.
25. Cohen J. Statistical power analysis for the behavioral sciences: Academic press 2013.
26. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21(11):1539-58. doi: 10.1002/sim.1186 [published Online First: 2002/07/12]
27. Deeks JJ, Higgins JPT, Altman DG, et al. Analysing data and undertaking meta-analyses. Cochrane Handbook for Systematic Reviews of Interventions2019:241-84.
28. Sterne JAC, Sutton AJ, Ioannidis JPA, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;343:d4002. doi: 10.1136/bmj.d4002
29. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. *Research Synthesis Methods* 2020;n/a(n/a) doi: 10.1002/jrsm.1411
30. Hagberg JM, Montain SJ, Martin WH, et al. Effect of exercise training in 60- to 69-year-old persons with essential hypertension. *The American Journal of Cardiology* 1989;64(5):348-53. doi: https://doi.org/10.1016/0002-9149(89)90533-X
31. Kiyonaga A, Arakawa K, Tanaka H, et al. Blood pressure and hormonal responses to aerobic exercise. *Hypertension* 1985;7(1):125-31. doi: 10.1161/01.HYP.7.1.125
32. Urata H, Tanabe Y, Kiyonaga A, et al. Antihypertensive and volume-depleting effects of mild exercise on essential hypertension. *Hypertension* 1987;9(3):245-52. doi: 10.1161/01.hyp.9.3.245 [published Online First: 1987/03/01]
33. Sikiru L, Okoye GC. Therapeutic effect of continuous exercise training program on serum creatinine concentration in men with hypertension: a randomized controlled trial. *Ghana Med J* 2014;48(3):135-42. doi: 10.4314/gmj.v48i3.3 [published Online First: 2015/02/25]
34. Martinelli B, Barrile SR, Arca EA, et al. Effect of aerobic exercise on plasma renin in overweight patients with hypertension. *Arq Bras Cardiol* 2010;95(1):91-8. doi: 10.1590/s0066-782x2010005000066 [published Online First: 2010/06/22]

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Enseignement Superieur (ABES) .

35. Sullivan PA, Grosch C, Lawless D, et al. Short-term strenuous exercise training: effects on blood pressure and hormonal levels in mild hypertension. *Ir J Med Sci* 1992;161(12):666-9. doi: 10.1007/bf02942379 [published Online First: 1992/12/01]
36. Kinoshita A, Koga M, Matsusaki M, et al. Changes of dopamine and atrial natriuretic factor by mild exercise for hypertensives. *Clin Exp Hypertens A* 1991;13(6-7):1275-90. doi: 10.3109/10641969109042127 [published Online First: 1991/01/01]
37. Koga M, Ideishi M, Matsusaki M, et al. Mild exercise decreases plasma endogenous digitalislike substance in hypertensive individuals. *Hypertension* 1992;19(2_supplement):II231. doi: doi:10.1161/01.HYP.19.2_Suppl.II231
38. Matsusaki M, Ikeda M, Tashiro E, et al. Influence of workload on the antihypertensive effect of exercise. *Clin Exp Pharmacol Physiol* 1992;19(7):471-9. doi: 10.1111/j.1440-1681.1992.tb00492.x [published Online First: 1992/07/01]
39. Nelson L, Esler M, Jennings G, et al. EFFECT OF CHANGING LEVELS OF PHYSICAL ACTIVITY ON BLOOD-PRESSURE AND HAEMODYNAMICS IN ESSENTIAL HYPERTENSION. *The Lancet* 1986;328(8505):473-76. doi: https://doi.org/10.1016/S0140-6736(86)90354-5
40. de Oliveira VN, Bessa A, Jorge MLMP, et al. The effect of different training programs on antioxidant status, oxidative stress, and metabolic control in type 2 diabetes. *Applied Physiology, Nutrition and Metabolism* 2012;37(2):334-44. doi: https://dx.doi.org/10.1139/H2012-004
41. Zaman GS, Abohashrh M, Ahmad I, et al. The Impact of Body Resistance Training Exercise on Biomedical Profile at High Altitude: A Randomized Controlled Trial. *Biomed Res Int* 2021;2021:6684167. doi: 10.1155/2021/6684167 [published Online First: 2021/06/24]
42. Szulińska M, Skrypnik D, Ratajczak M, et al. Effects of Endurance and Endurance-strength Exercise on Renal Function in Abdominally Obese Women with Renal Hyperfiltration: A Prospective Randomized Trial. *Biomed Environ Sci* 2016;29(10):706-12. doi: 10.3967/bes2016.095 [published Online First: 2016/12/09]
43. Trabelsi K, Stannard SR, Maughan RJ, et al. Effect of resistance training during Ramadan on body composition and markers of renal function, metabolism, inflammation, and immunity in recreational bodybuilders. *Int J Sport Nutr Exerc Metab* 2012;22(4):267-75. doi: 10.1123/ijsnem.22.4.267 [published Online First: 2012/08/03]
44. Geyssant A, Geelen G, Denis C, et al. Plasma vasopressin, renin activity, and aldosterone: Effect of exercise and training. *European Journal of Applied Physiology and Occupational Physiology* 1981;46(1):21-30. doi: 10.1007/BF00422171
45. Passino C, Severino S, Poletti R, et al. Aerobic training decreases B-type natriuretic peptide expression and adrenergic activation in patients with heart failure. *J Am Coll Cardiol* 2006;47(9):1835-9. doi: 10.1016/j.jacc.2005.12.050 [published Online First: 2006/05/10]
46. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? *Arch Intern Med* 2000;160(5):685-93. doi: 10.1001/archinte.160.5.685 [published Online First: 2000/03/21]
47. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med* 2020;383(15):1436-46. doi: 10.1056/NEJMoa2024816 [published Online First: 2020/09/25]

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Tables

Table 1. General characteristics of the included studies

Author, year	Study type	Country	Exercise Group Characteristics	Baseline Size of Exercise Group	Attrition	Study Population Age	Type of Exercise	Exercise Frequency	Exercise Length	Exercise Intensity	Kidney-relevant outcome	Findings
de Oliveira *et al.*[40], 2012	RCT	Brazil	Patients with type 2 diabetes mellitus of a diabetes ambulatory clinic.	Aerobic training: 12 people Strength training: 12 people Combination training: 12 people	Aerobic training: 9.1% Strength training: 16.7% Combination training: 16.7%	Mean (SD), years: Aerobic training: 52.09 (8.71) Strength training: 54.10 (8.94) Combined training: 57.90 (9.82)	Aerobic training, strength training, and combined training	One hour/session, three sessions/week	12 Weeks	Not used VO2peak in aerobic and combined training due to unable to get accurate value, used lacate threshold. Strength training: 50% of 1 RM for the Week 1&2, 8-12 RM for Week 3&4.	Urea	Pre/Post Exercise, mean (SD), mg/dL Aerobic training: Urea 29.27 (5.93) / 28.18 (6.36) Strength training: Urea 31.00 (10.56) / 29.90 (8.82) Combined training: Urea 34.40 (9.91) / 35.20 (9.40)
Geyssant *et al.* [44], 1981	CT	France	Healthy male.	4 people	0%	Mean (SD), years: 36 (6.4)	Aerobic	One hour/session, four sessions/week	5 months	87% VO2max	PRA	Pre/Post Exercise, mean (SD), ng/l/mn PRA, 106.08 (48.48)/ 62.5 (49.9)
Hagberg *et al.* [30], 1989	RCT	United States of America	Patients with essential hypertension.	Low-intensity: 14 people Moderate-intensity: 10 people	Low-intensity: 21.4% Moderate-intensity: 0%	Mean (SD), years: all groups 64 (3)	Aerobic	Low-intensive: one hour/session, max three sessions/week Moderate-intensive: 45 to 60 minutes/session, 3 sessions/week for at least the last 4-5 months of training	9 months	Low-intensity: 50% VO2max Moderate-intensity: 70-85% VO2max	PRA	Pre/Post Exercise, mean (SD), ng/ml/hr Low-intensity: PRA 1.6 (1.1) / 0.7 (0.4) Moderate-intensity: PRA 2.0 (1.3) / 1.1 (0.9)
Kinoshita *et al.* [36], 1991	CT	Japan	Patients with essential hypertension.	12 people	0%	Mean (SD), years: 51.7 (2.3)	Aerobic	One hour/session, three sessions/week	10 weeks	50% VO2max	PRA, eGFR	Pre/Post Exercise, mean (SE), ng/ml/h PRA 1.3 (0.2) / 1.26 (0.4) Pre/Post Exercise, mean (SE), ml/min eGFR 99 (4.7) / 105 (5.2)

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Kiyonaga *et al.* [31], 1985	CT	Japan	Patients with essential hypertension.	12 people	At 10 weeks: 0% At 20 weeks: 25%	Mean (Range), years: 46 (34 to 56)	Aerobic	One hour/session, three sessions/week	20 weeks	Used lacate threshold, but claimed to have a 50% VO2max althouth data were not published.	PRA Ang II	Pre/Post Exercise, mean (SE), ng/ml/hr PRA 11 (4) / 13 (3) Pre/Post Exercise, mean (SE), pg/ml Ang II 58 (8) / 91 (12)
Koga *et al.* [37], 1992	CT	Japan	Female atients with essential hypertension	10 people	0%	Mean (SEM), years: 49 (2)	Aerobic	One hour/session, three sessions/week	10 weeks	50% VO2max	PRA	Pre/Post Exercise, mean (SE), ng/ml/h PRA 0.77 (0.19) / 0.4 (0.1)
Martinelli *et al.* [34], 2010	CT	Brazil	Overweight patients with hypertension.	20 people	0%	Mean (SD), years: 57 (7.1)	Aerobic	40 min/session, three sessions/week	16 weeks	60-80% HRmax	PRA	Pre/Post Exercise, median (IQR), ng/ml/h PRA 0.8 (0.45 - 2.0) / 1.45 (0.8 - 2.15)
Matsusaki *et al.* [38], 1992	CT	Japan	Patients with hypertension.	Low-workload: 16 people High-workload: 14 people	Low-workload: 0% High-workload: 28.6%	Mean (SEM), years: all groups 47.2 (1.5)	Aerobic	Low-workload: one hour/session, three sessions/week High-workload: 30-40 min/session, three sessions per week	10 weeks	Low-workload: 50% VO2max High-workload: 75% VO2max	PRA	Pre/Post Exercise, mean (SE), ng/ml/h Low-workload: PRA 0.82 (0.22) / 0.62 (0.27) High-workload: PRA 1.26 (0.15) / 1.47 (0.16)
Nelson *et al.* [39], 1986	CT	Australia	Patients with essential hypertension of a risk-evaluation clinic.	17 people	23.5%	Mean (Range) , years: 44 (25 to 62)	Aerobic	Three levels of activity for one month each successively. First month: normal sedentary, no training Second month: 45 min/session, three sessions/week Third month: 45 min/session, seven sessions/week	2 months (exclude the first sedentary month)	60-70% VO2max	PRA	Pre/Post Exercise, mean (SEM), ng/ml/h PRA 1.45 (0.51) / 1.46 (0.30)
Passino *et al.* [45], 2006	RCT	Italy	Patients with heart failure.	47 people	6.4%	Mean (SD), years: 60 (2)	Aerobic	Minimum 30 min/day, three days/week	9 months	Heart rate at 65% VO2max	PRA	Pre/Post Exercise, mean (SD), ng/ml/h PRA 3.04 (0.66) / 2.96 (0.62)

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Sikiru and Okoye [33], 2014	RCT	Nigeria	Patients with essential hypertension of a hypertensive clinic.	162 people	30.9%	Mean (SD), years: 58.63 (7.22)	Aerobic	45 min/session, three sessions/week for Week 1 and 2 One hour/session, three sessions/week, for Week 3-8	8 weeks	60-79% of HR reserve	SCr	Pre/Post Exercise, mean (SD), mg/dL SCr 0.81 (0.17) / 0.85 (0.39)
Sullivan *et al.* [35], 1992	CT	United States of America	Male patients with uncomplicated essential hypertension.	15 people	0%	Mean (SD), years: 42.3 (1.0)	Strenuous Aerobic	18 min/session, three sessions/week	6 weeks	90% HRmax	PRA	Pre/Post Exercise, mean (SE), ng/ml/h PRA 1.9 (0.3) / 1.94 (0.4)
Szulinska *et al.* [42], 2016	RCT	Poland	Women with obesity.	Endurance training: 22 people Endurance+strength training: 22 people	Endurance training: 4.5% Endurance+strength training: 22.7%	Mean (SD), years: Endurance 51.3 (8.3) Endurance+strength: 48.2 (11.2)	Endurance and Endurance+strength training	One hour/session, three sessions/week	3 months	Endurance group: 50-80% HRmax Endurance+strength group: 50-80% HRmax for endurance training, unclear intensity for strength exercise.	SCr eGFR UACR	Pre/Post Exercise, mean (SD) Endurance group SCr, mg/dL 0.76 (0.11) / 0.84 (0.11) eGFR-MDRD, 87.81 (18.43) / 77.90 (12.65) eGFR-CG, 129.47 (33.24) / 114.02 (24.98) UACR, mg/mmol cr 1.19 (2.32) / 1.28 (2.42) Endurance+strength group SCr, mg/dL 0.73 (0.10) / 0.81 (0.10) eGFR-MDRD, 93.58 (17.87) / 82.54 (12.01) eGFR-CG, 143.91 (36.69) / 124.65 (26.71) UACR, mg/mmol cr 0.76 (0.28) / 0.65 (0.28)
Trabelsi *et al.* [43], 2012	CT	Turnisa	Male recreational bodybuilders.	non-faster: 7 people	0%	Mean (SD), years: non-faster 26 (3)	Resistance	Four sessions/week	1 month	Four sets with a load of 10 RM for each exercise.	Urea SCr	Pre/Post Exercise, mean (SD), mmol/L Urea 4.51 (0.32) / 4.5 (0.26) Pre/Post Exercise, mean (SD), µmol/L

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												SCr 91.14 (4.45) / 94.29 (4.31)
Urata *et al.* [32], 1987	RCT	Japan	Patients with essential hypertension.	10 people	0%	Mean (SE), years: 51.4 (2.8)	Aerobic	One hour/session, three sessions/week	10 weeks	40-60% VO2max	PRA	Pre/Post Exercise, mean (SE), ng/mL/min PRA 1.24 (0.24) / 1.50 (0.39)
Zaman *et al.*[41], 2021	RCT	Saudi Arabia	Obese and non-obese male people.	Obese resistance training: 25 Non-obese resistance training: 25	Obese resistance training: 20% Non-obese resistance training: 20%	Range, years: 35 to 60	Resistance	50 min/session, three days/week	12 weeks	50-70% of 1 RM	Urea	Pre/Post Exercise, mean (SD), mg/dl Obese people Urea 33.33 (3.57) / 32.27 (2.54),

Ang II,angiotensin II; CT, clinical trial; eGFR, estimated glomerular filtration rate; HR, heart rate; PRA, plasma renin activity; RCT, randomized clinical trial; RM, repetition maximum; SCr, serum creatinine; SD, standard deviation;SE, standard error; UARC, urine albumin-to-creatinine ratio; VO2, maximum rate of oxygen.

Note: Conversion factors for units: serum creatinine in mg/dL to µmol/L, ×88.4; urea nitrogen in mg/dL to mmol/L, ×0.357.

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Table 2. Revised Newcastle-Ottawa quality assessment scale form

Author, Year	Selection				Comparability	Outcome			Total score
	Representativeness of the intervention cohort	Selection of the non-intervention cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
de Oliveira *et al.*[40], 2012	1	1	1	1	2	1	1	1	9
Geyssant *et al.* [44], 1981	0	1	1	1	2	1	1	1	8
Hagberg *et al.* [30], 1989	0	1	0	1	2	1	1	0	6
Kinoshita *et al.* [36], 1991	0	1	1	1	2	1	1	1	8
Kiyonaga *et al.* [31], 1985	0	1	0	1	2	1	1	0	6
Koga *et al.* [37], 1992	0	1	1	1	2	1	1	1	8
Martinelli *et al.* [34], 2010	0	1	1	1	2	1	1	1	8
Matsusaki *et al.* [38], 1992	0	1	1	1	2	1	1	0	7
Nelson *et al.* [39], 1986	0	1	1	1	2	1	1	0	7
Passino *et al.* [45], 2006	1	1	0	1	2	1	1	1	8
Sikiru and Okoye [33], 2014	1	1	1	1	2	1	1	0	8
Sullivan *et al.* [35], 1992	0	1	1	1	2	1	1	1	8
Szulinska *et al.* [42], 2016	1	1	1	1	2	1	1	0	8
Trabelsi *et al.* [43], 2012	0	1	1	1	2	1	1	1	8

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Urata *et al.* [32], 1987	0	1	1	1	2	1	1	1	8
Zaman *et al.*[41], 2021	1	1	1	1	2	1	1	0	8

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Figures

Figure 1. Summary of the risk of bias in GRADE framework

Figure 2. Study-specified risk of bias in GRADE framework

Figure 3. Meta-analysis on the associations of changes in physical activity with renal-relevant biomarkers (3a. Serum creatinine, 3b. eGFR, 3c. Urinary albumin-to-creatinine ratio, 3d. Plasma renin activity,3e. Urea)

Note for Figure 3:

Szulinska *et al*. [42], 2016a: Patients received endurance training.

Szulinska *et al.* [42], 2016b: Patients received both endurance and strength training.

Zaman *et al*. [41], 2021a: Patients with obesity

Zaman *et al.*[41], 2021b: Patients without obesity

Hagberg *et al.* [30], 1989a: Patients performed low-intensity physical activity.

Hagberg *et al*. [30], 1989b: Patients performed moderate-intensity physical activity.

Matsusaki *et al.* [38], 1992a: Patients performed low-workload physical activity.

Matsusaki *et al.*[38], 1992b: Patients performed high-workload physical activity.

de Oliveira *et al.* [40], 2012a: Patients performed aerobic training.

de Oliveira *et al.* [40], 2012b: Patients performed strength training.

de Oliveira *et al.* [40], 2012c: Patients performed aerobic and strength training.

Zaman *et al.* [41], 2021a: Patients with obesity.

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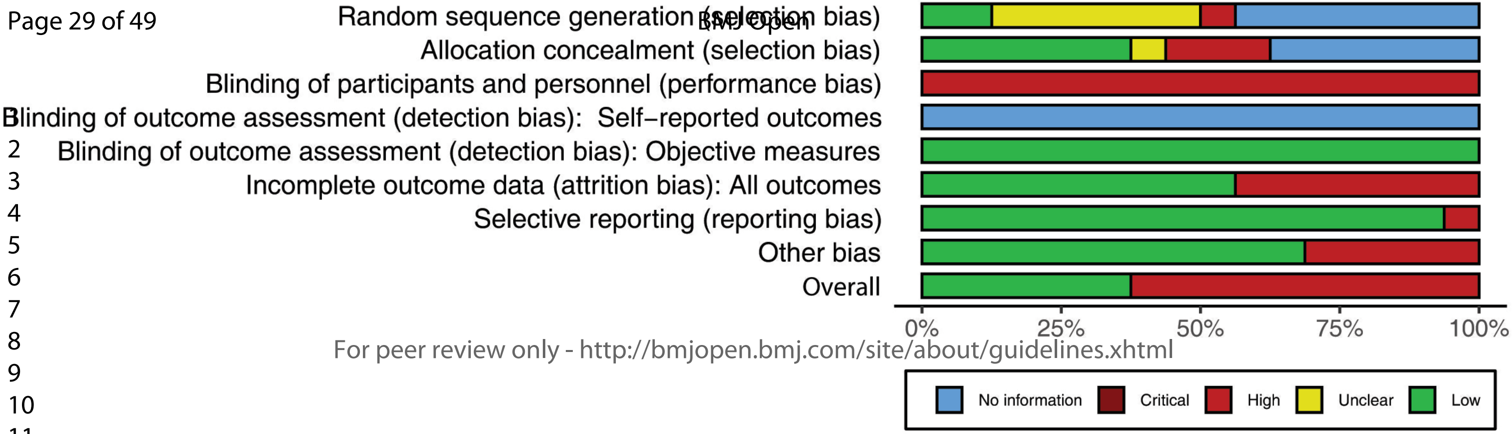

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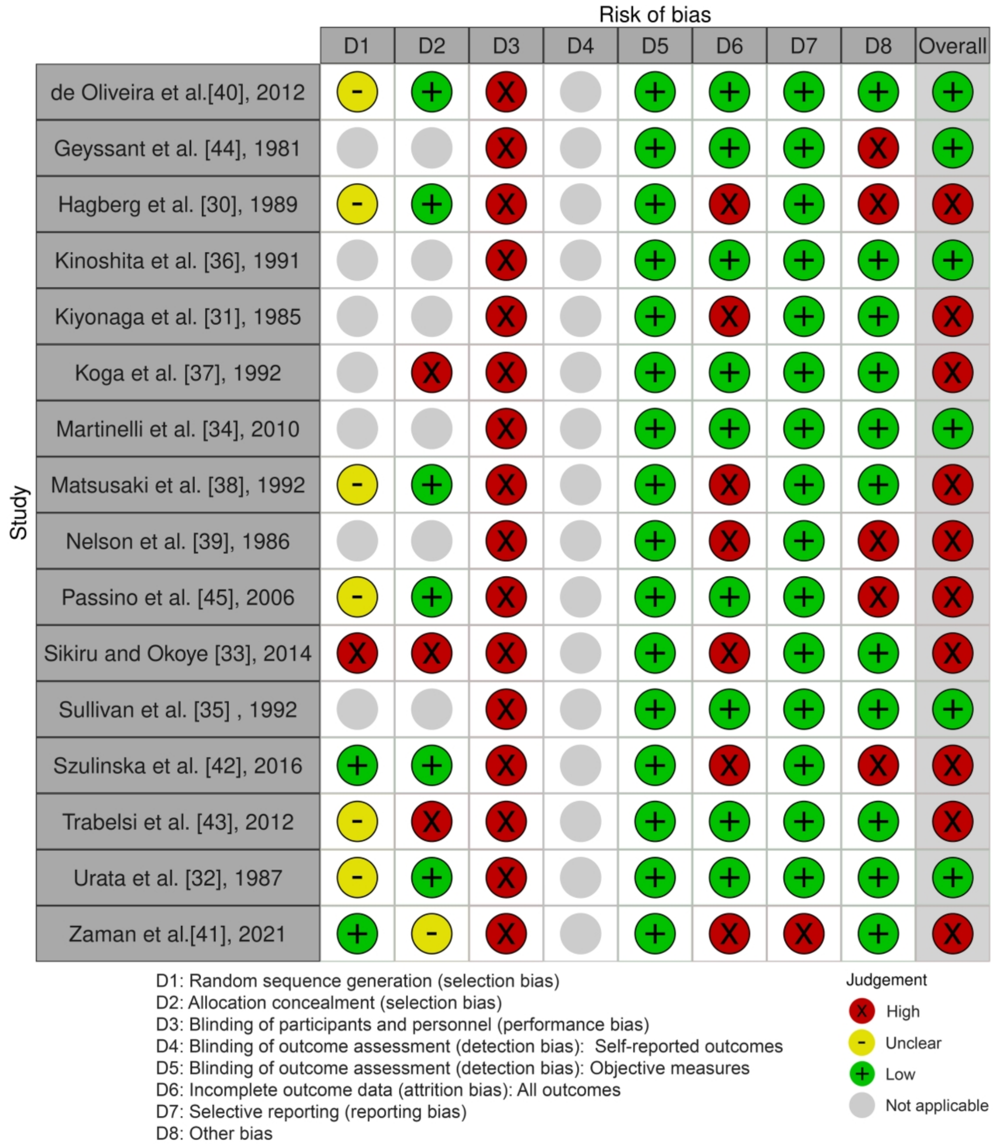

Figure 2. Study-specified risk of bias in GRADE framework

194x226mm (300 x 300 DPI)

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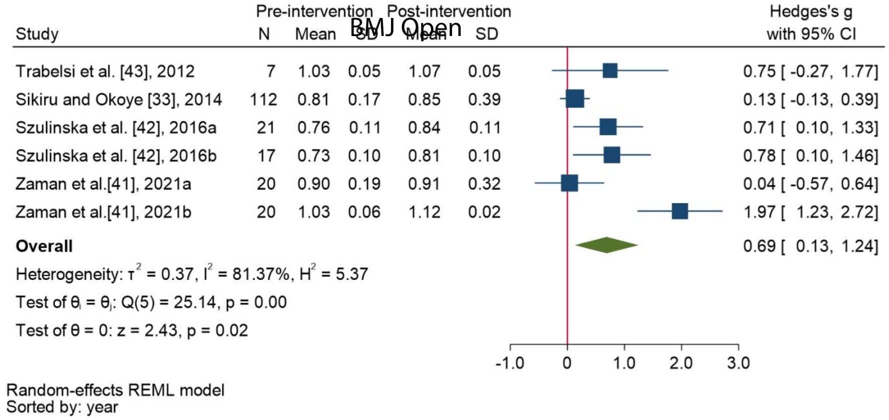
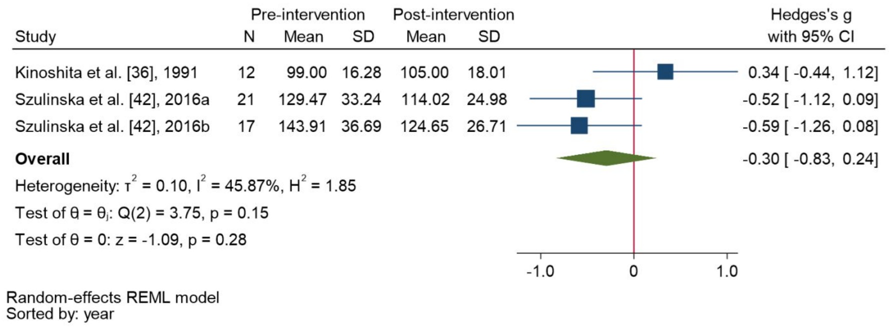
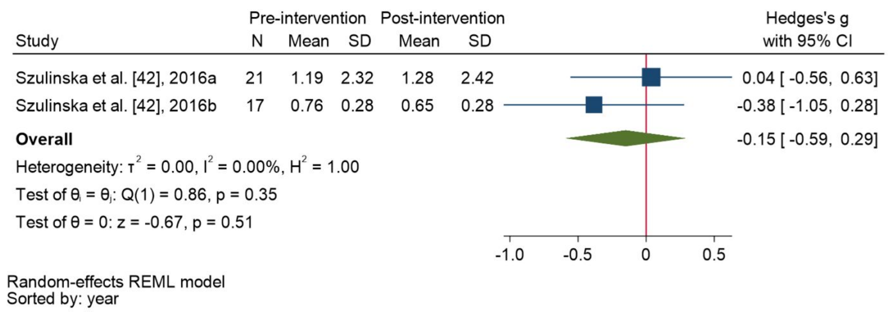
3a



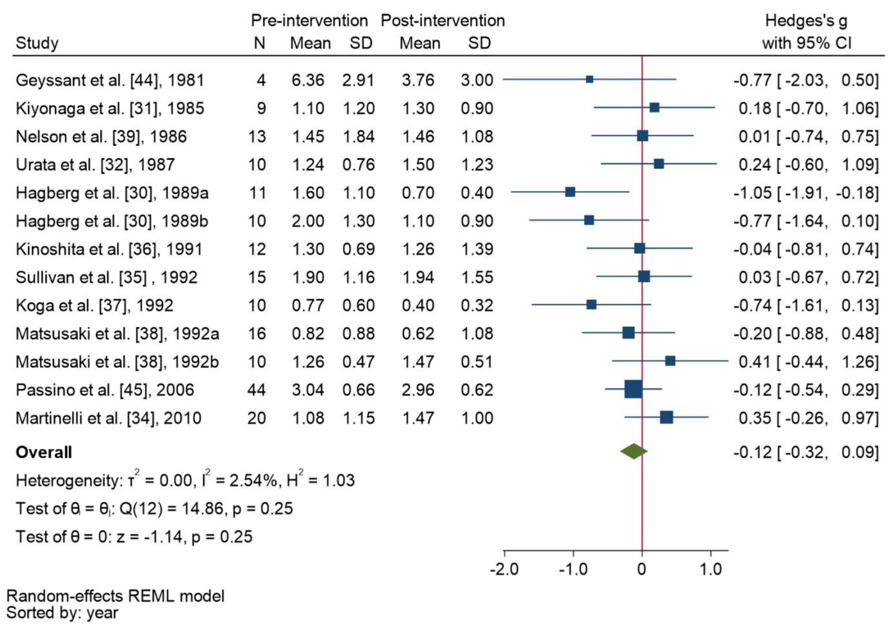
3b



3c



3d



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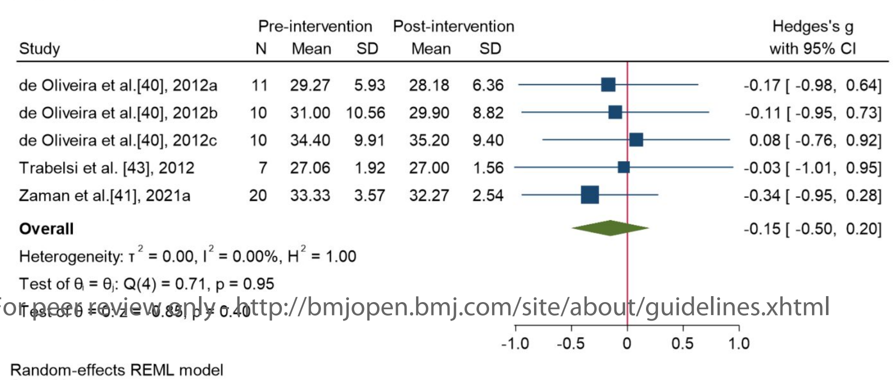

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Table S1 Search Terms

Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations , 1946 Year

Steps	Terms	Hits
1	exp physical activity/ or exp exercise test/	291234
2	exp physical education/ or exp physical fitness/ or exp cardiorespiratory fitness/	47746
3	(exercise* or sport* or walking* or cycling or swimming or running or jogging or sedentary or inactiv*).ti,ab.	974933
4	(physical* adj3 (activ* or inactiv* or treat* or exercis* or exertion*)).ti,ab.	189257
5	or/1-4	1150170
6	(controlled clinical trial).ti,ab.	18436
7	exp clinical trial/	960936
8	(randomized controlled trial).ti.	58191
9	(randomized or trial).ti.	353729
10	exp cohort studies/	2439066
11	(retrospective or prospective or longitudinal).ti.	346157
12	or/6-11	3359654
13	5 and 12	172209
14	(exp animal/ or nonhuman/) not exp human/	5086829
15	13 not 14	170034
16	(interven* or change* or traject* or shift* or switch* or alternat* or differen* or variat* or revamp*).ti,kw.	1810596
17	15 and 16	19570
18	(uremi* or uraemi* or albuminuria* or proteinuria* or urin* or albumin* or protein* or glomerular filtration rate* or ?GFR).ti,ab.	4047257
19	exp kidney/ or exp proteinuria/	400331
20	(kidney or renal or disease or insufficien* or failure* or nephro*).ti,ab.	5132016
21	or/18-20	8407973
22	(kidney or renal).mp. and (transplan* or graft*).ti.	94451
23	21 not 22	8319260
24	17 and 23	4571
25	(conference abstract or conference paper or conference review).pt.	0
26	24 not 25	4571
27	editorial/ or letter/ or case reports/ or comment/ or note/	4217780
28	26 not 27	4540

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Embase 1947-Present, updated daily

Steps	Terms	Hits
1	exp physical activity/ or exp exercise test/	623139
2	exp physical education/ or exp physical fitness/ or exp cardiorespiratory fitness/	65532
3	(exercise* or sport* or walking* or cycling or swimming or running or jogging or sedentary or inactiv*).ti,ab.	1279181
4	(physical* adj3 (activ* or inactiv* or treat* or exercis* or exertion*)).ti,ab.	260815
5	or/1-4	1707972
6	(controlled clinical trial).ti,ab.	24269
7	exp clinical trial/	1820578
8	(randomized controlled trial).ti.	71118
9	(randomized or trial).ti.	499542
10	exp cohort studies/	962599
11	(retrospective or prospective or longitudinal).ti.	484101
12	or/6-11	3118564
13	5 and 12	193380
14	(exp animal/ or nonhuman/) not exp human/	7826893
15	13 not 14	190775
16	(interven* or change* or traject* or shift* or switch* or alternat* or differen* or variat* or revamp*).ti,kw.	2269582
17	15 and 16	22019
18	(uremi* or uraemi* or albuminuria* or proteinuria* or urin* or albumin* or protein* or glomerular filtration rate* or ?GFR).ti,ab.	5179794
19	exp kidney/ or exp proteinuria/	643196
20	(kidney or renal or disease or insufficien* or failure* or nephro*).ti,ab.	7596748
21	or/18-20	1160591 6
22	(kidney or renal).mp. and (transplan* or graft*).ti.	156070
23	21 not 22	1145933 1
24	17 and 23	5916
25	(conference abstract or conference paper or conference review).pt.	5452713
26	24 not 25	4217
27	editorial/ or letter/ or case reports/ or comment/ or note/	2784877
28	26 not 27	4193

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Pubmed

Steps	Terms	Hits
1	"exercise"[mesh] OR "exercise test"[mesh]	291459
2	"Physical Education and Training"[mesh] OR "physical fitness"[mesh] OR "cardiorespiratory fitness"[mesh]	47747
3	(exercise*[tiab] OR sport*[tiab] OR walking*[tiab] OR "cycling"[tiab] OR "swimming"[tiab] OR "running"[tiab] OR "jogging"[tiab] OR "sedentary"[tiab] OR inactiv*[tiab])	991749
4	(physical*[tiab] AND (activ*[tiab] OR inactiv*[tiab] OR treat*[tiab] OR exercis*[tiab] OR exertion*[tiab]))	459726
5	#1 OR #2 OR #3 OR #4	1384590
6	("controlled clinical trial"[tiab])	18695
7	"clinical trial"[pt]	961591
8	("randomized controlled trial"[ti])	58192
9	("randomized"[ti] OR "trial"[ti])	353735
10	"cohort studies"[mesh]	2441995
11	("retrospective"[ti] OR "prospective"[ti] OR "longitudinal"[ti])	346215
12	#6 OR #7 OR #8 OR #9 OR #10 OR #11	3362395
13	#5 AND #12	210509
14	"animals"[mesh]	26116055
15	#13 NOT #14	8628
16	interven*[ti] OR change*[ti] OR traject*[ti] OR shift*[ti] OR switch*[ti] OR alternat*[ti] OR differen*[ti] OR variat*[ti] OR revamp*[ti]	1765363
17	#15 AND #16	1223
18	(uremi*[tiab] OR uraemi*[tiab] OR albuminuria*[tiab] OR proteinuria*[tiab] OR urin*[tiab] OR albumin*[tiab] OR protein*[tiab] OR glomerular filtration rate*[tiab] OR "eGFR"[tiab] OR "mGFR"[tiab])	4147077
19	"kidney"[mesh] OR "proteinuria"[mesh]	400520
20	("kidney"[tiab] OR "renal"[tiab] OR "disease"[tiab] OR insufficien*[tiab] OR failure*[tiab] OR nephro*[tiab])	5250858
21	#18 OR #19 OR #20	8585949
22	(("kidney"[tiab] OR "kidney"[mh]) OR ("renal"[tiab])) AND (transplan*[ti] OR graft*[ti])	87814
23	#21 NOT #22	8498135
24	#17 AND #23	295
25	"editorial"[pt] OR "letter"[pt] OR "comment"[pt]	2129064
26	#24 NOT #25	294

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Web of Science

Steps	Terms	Hits
1	TS=(physical activity OR exercise test OR physical fitness OR exercise OR sport OR sedentary OR inactive OR exertion)	2869900
2	TS=(controlled clinical trial OR clinical trail OR randomized controlled trial OR cohort study OR retrospective study OR prospective study OR longitudinal study)	4391262
3	#1 AND #2	230548
4	TS=(animal OR nonhuman OR non-human)	30545714
5	#3 NOT #4	118699
6	TS=(interven* or change* or traject* or shift* or switch* or alternat* or differen* or variat* or revamp*)	46832576
7	#5 AND #6	82111
8	TS=(uremi* or uraemi* or albumin* or proteinuria* or glomerular filtration rate* or eGFR or mGFR or kidney* or renal failure* or nephro*)	2677866
9	TS=(kidney or renal)	2378506
10	TS=(transplan* or graft*)	2270415
11	#9 AND #10	323241
12	#8 NOT #11	2405699
13	#7 AND #12	1320
14	TS=(editorial or letter or case report* or comment)	3433986
15	#13 NOT #14	1267

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Figure S1 PRISMA workflow

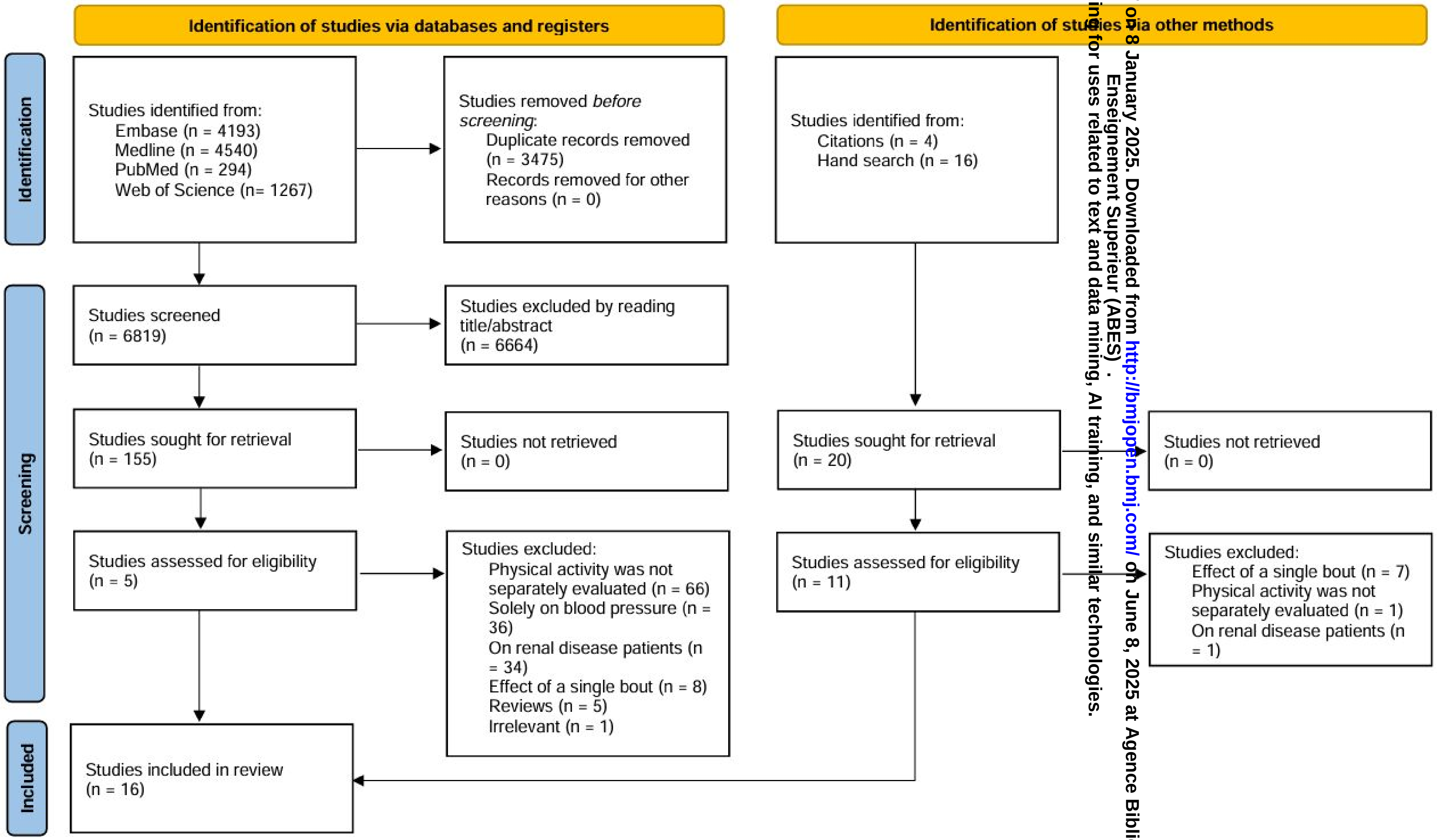

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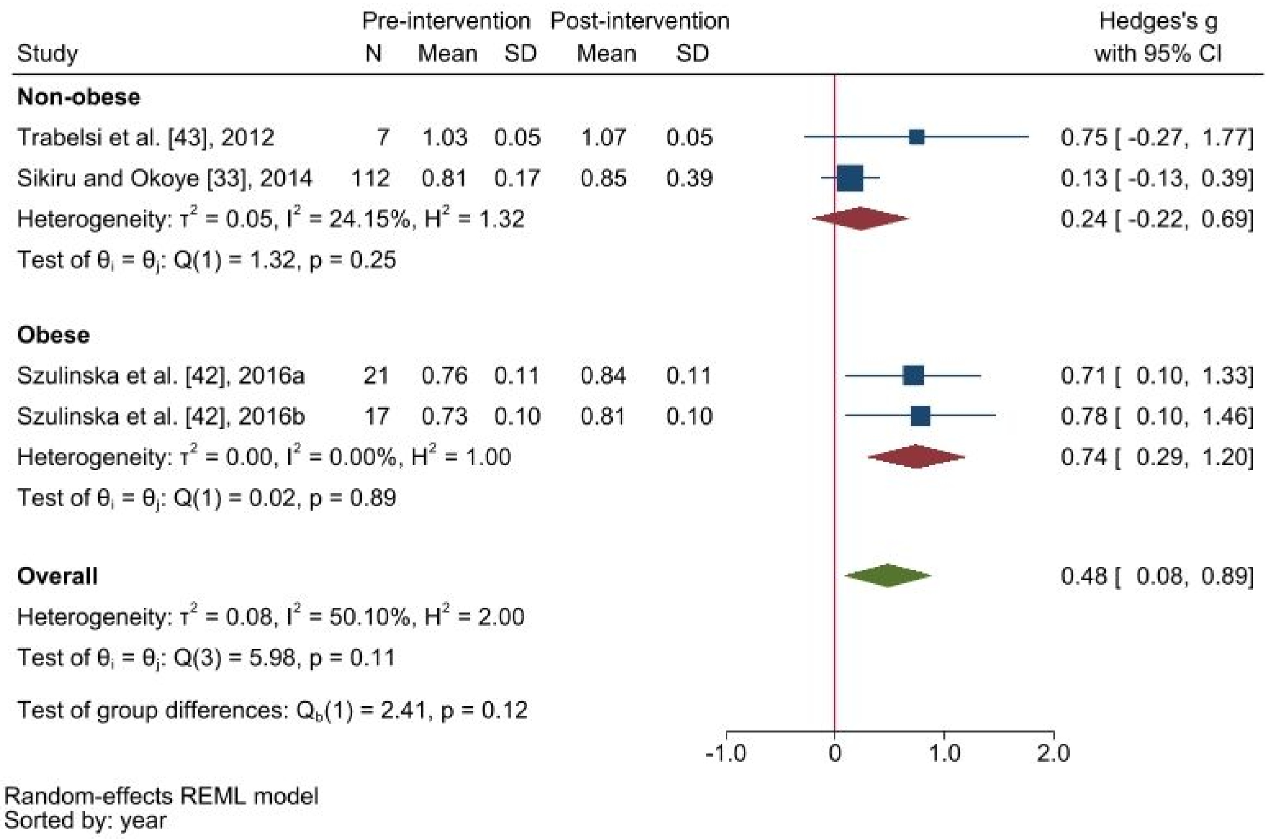
Figure S2a Obesity stratified meta-analysis on the association of changes in physical activity with serum creatinine.



Szulinska *et al.* [42], 2016a: Patients received endurance training.

Szulinska *et al.* [42], 2016b: Patients received both endurance and strength training.

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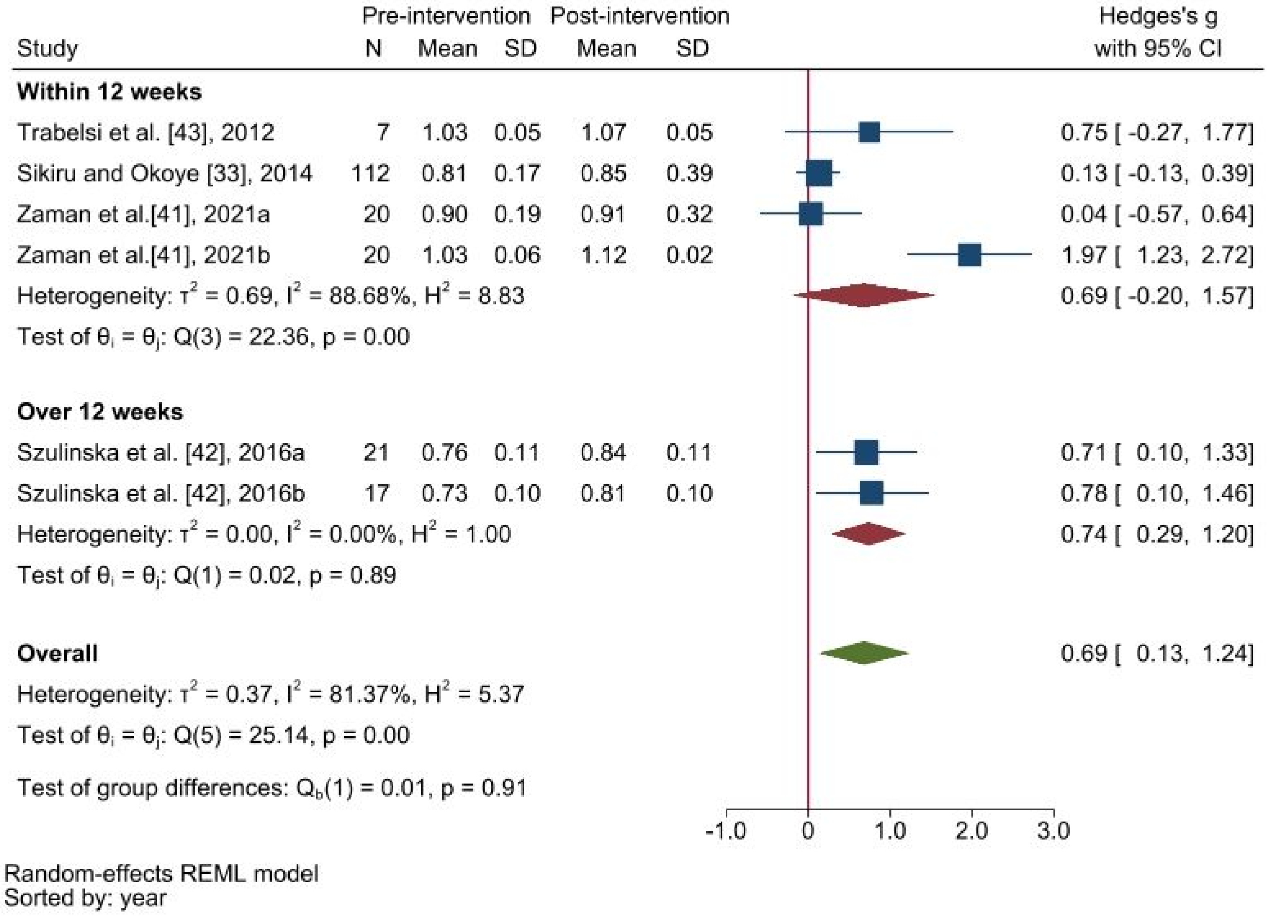
Figure S2b Exercise duration stratified meta-analysis on the association of changes in physical activity with serum creatinine.



Szulinska *et al.* [42], 2016a: Patients received endurance training.

Szulinska *et al.* [42], 2016b: Patients received both endurance and strength training.

Zaman *et al.* [41], 2021a: Patients with obesity

Zaman *et al*.[41], 2021b: Patients without obesity

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Figure S2c. Funnel plot of studies on the association of changes in physical activity with serum creatinine

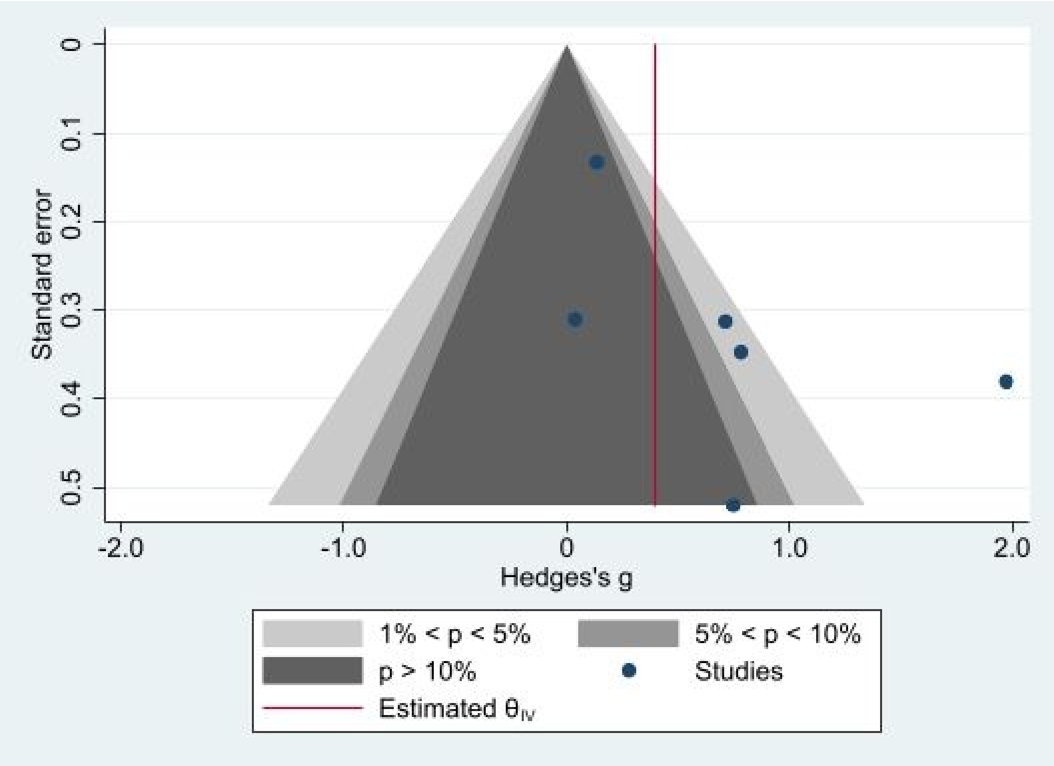
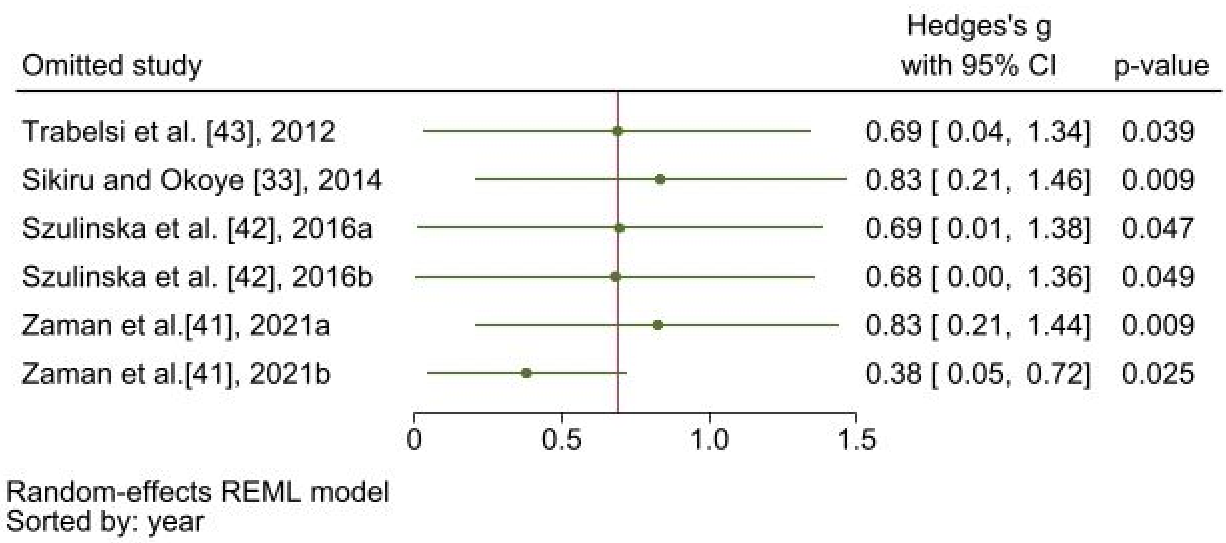


Figure S2d Leave-one-out figure of studies on the association of changes in physical activity with serum creatinine



Szulinska *et al.* [42], 2016a: Patients received endurance training.

Szulinska *et al.* [42], 2016b: Patients received both endurance and strength training.

Zaman *et al.* [41], 2021a: Patients with obesity

Zaman *et al.*[41], 2021b: Patients without obesity

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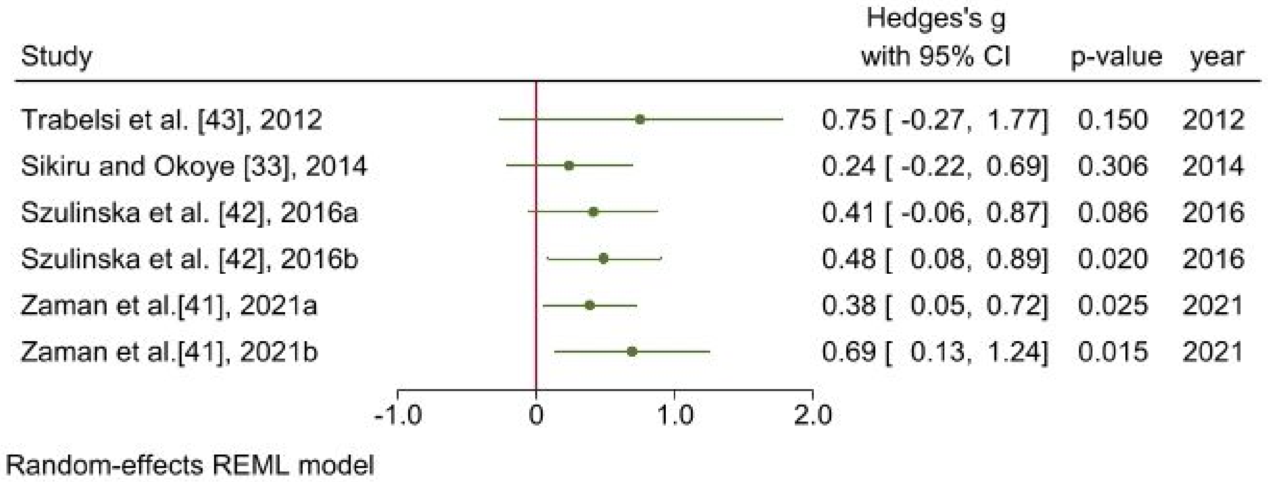
Figure S2e Cumulative meta-analysis of the association of changes in physical activity with serum creatinine



Szulinska *et al.* [42], 2016a: Patients received endurance training.

Szulinska *et al.* [42], 2016b: Patients received both endurance and strength training.

Zaman *et al.* [41], 2021a: Patients with obesity

Zaman *et al.*[41], 2021b: Patients without obesity

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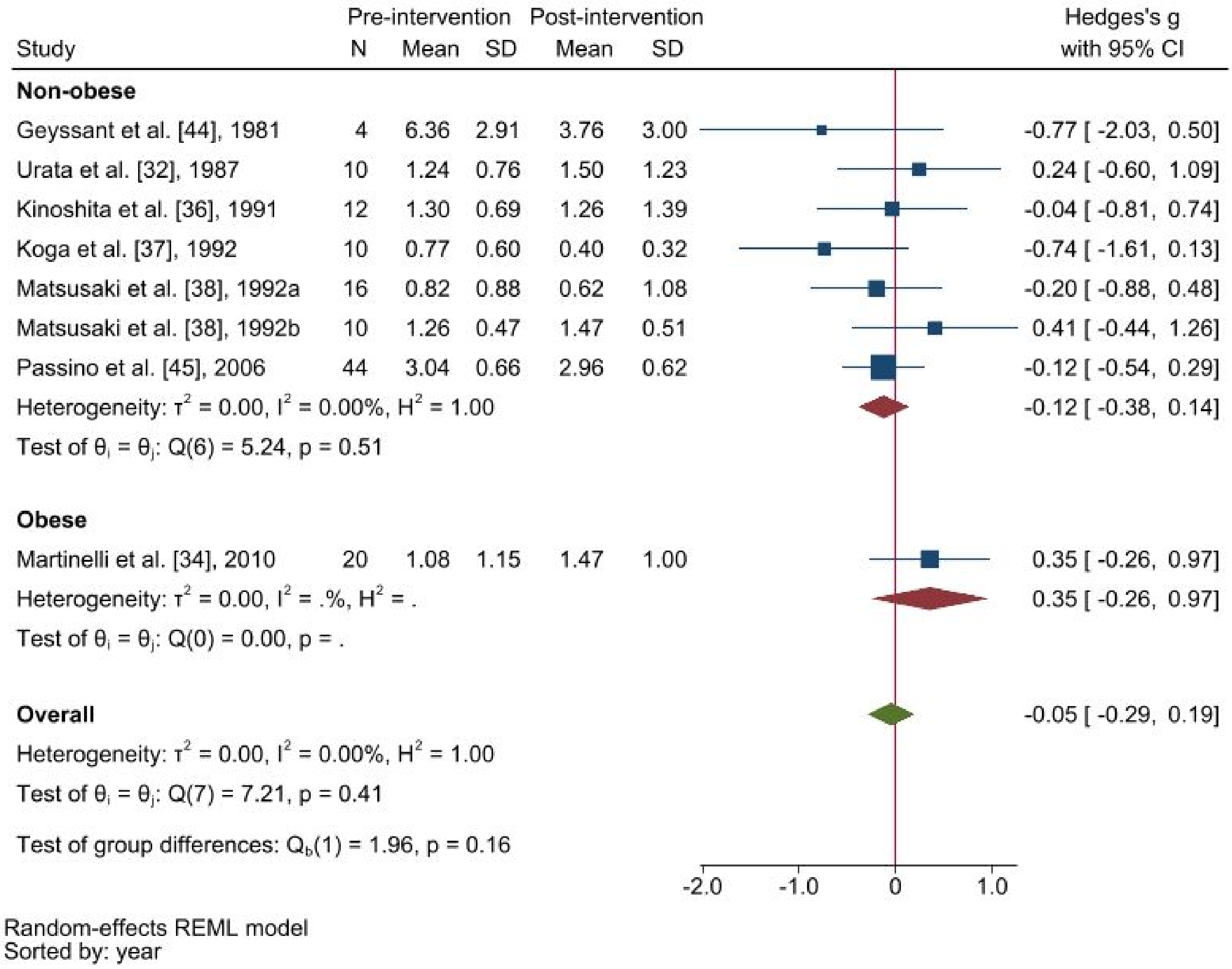
Figure S3a Obesity stratified meta-analysis on the association of changes in physical activity with plasma renin activity



Matsusaki *et al.*[38], 1992a: Patients performed low-workload physical activity.

Matsusaki *et al.*[38], 1992b: Patients performed high-workload physical activity.

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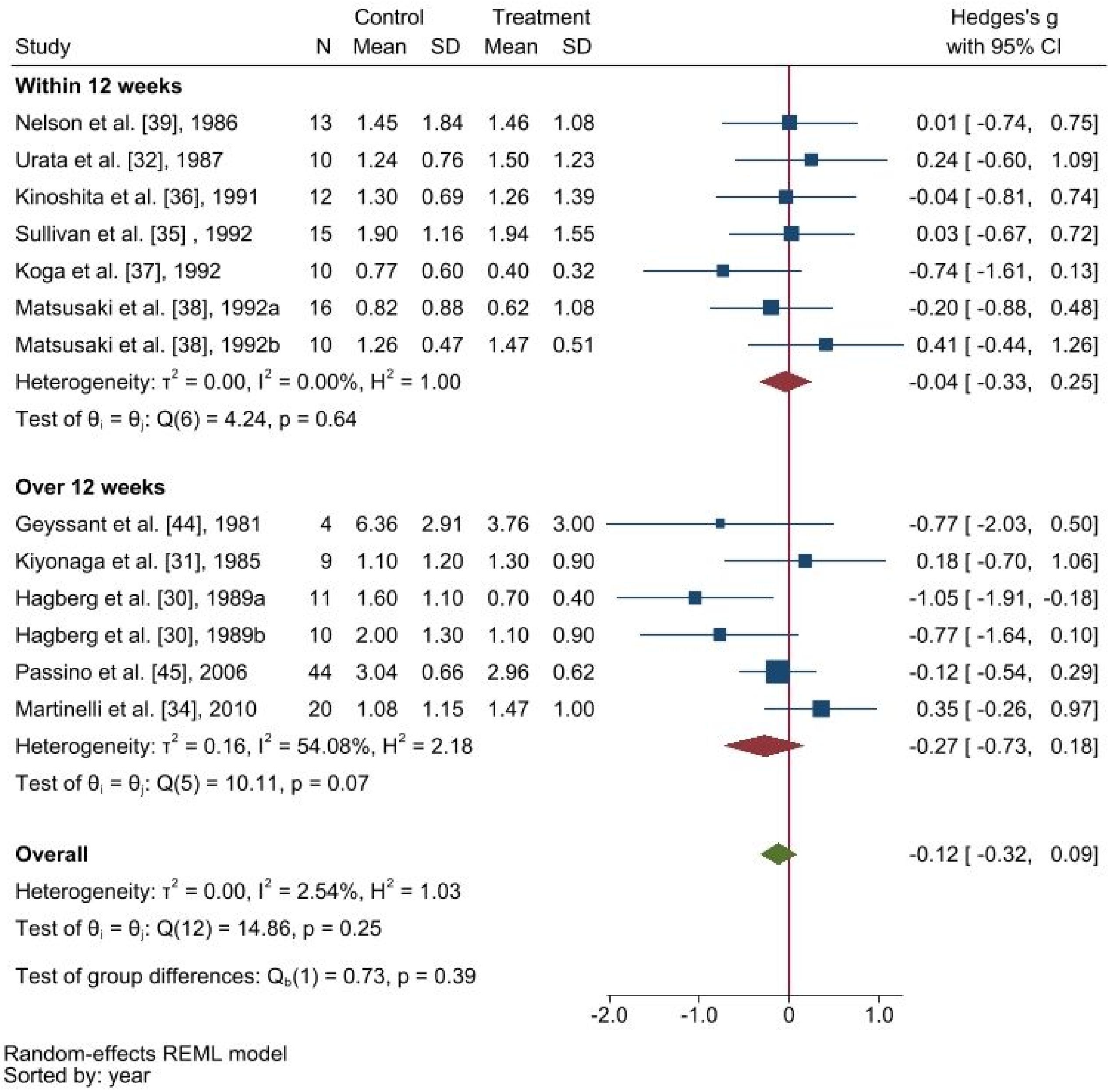
Figure S3b Exercise duration stratified meta-analysis on the association of changes in physical activity with plasma renin activity



Hagberg *et al.* [30], 1989a: Patients performed low-intensity physical activity.

Hagberg *et al.* [30], 1989b: Patients performed moderate-intensity physical activity.

Matsusaki *et al.*[38], 1992a: Patients performed low-workload physical activity.

Matsusaki *et al.*[38], 1992b: Patients performed high-workload physical activity.

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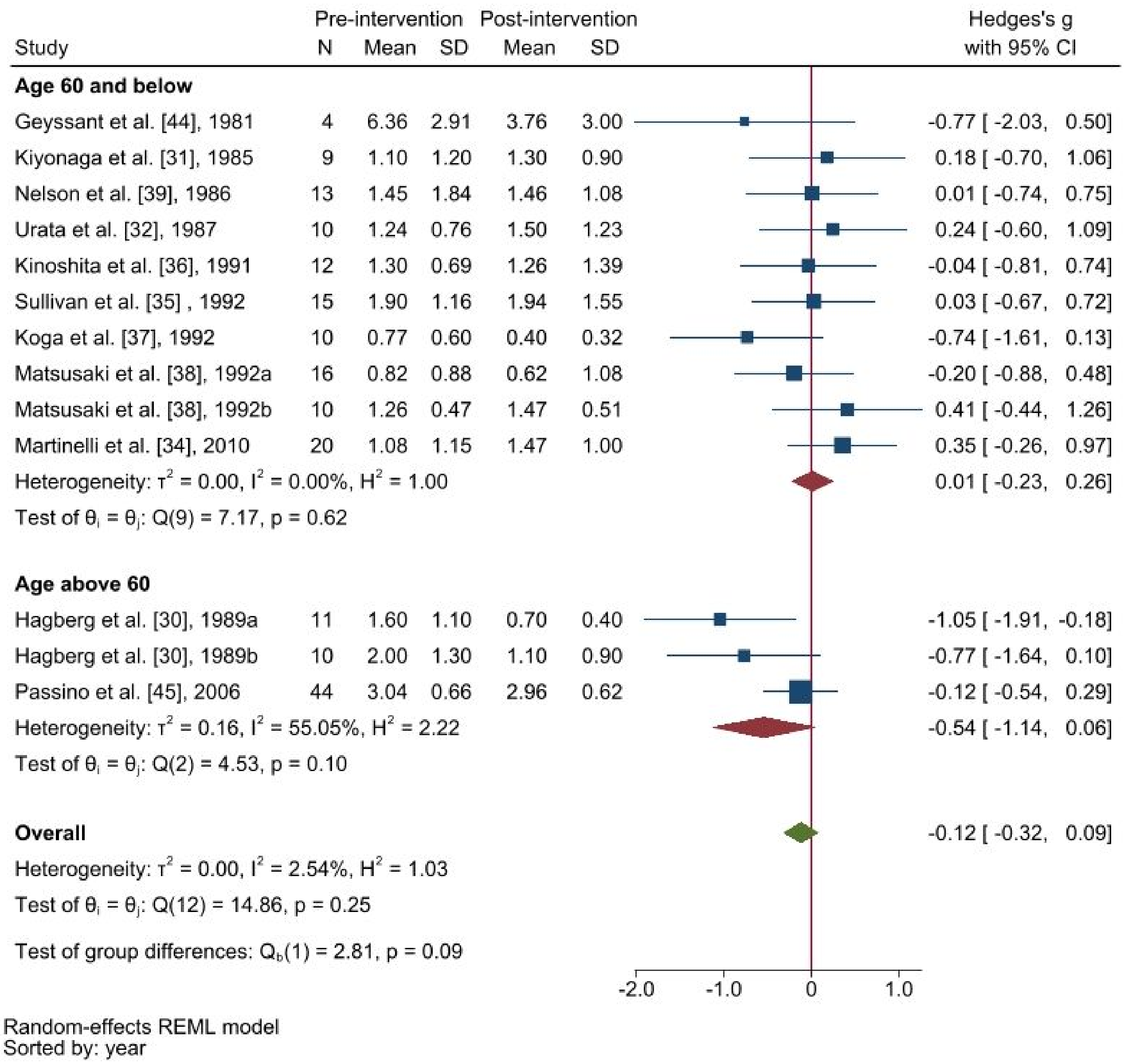
Figure S3c Age stratified meta-analysis on the association of changes in physical activity with plasma renin activity



Hagberg *et al.* [30], 1989a: Patients performed low-intensity physical activity.

Hagberg *et al.* [30], 1989b: Patients performed moderate-intensity physical activity.

Matsusaki *et al.*[38], 1992a: Patients performed low-workload physical activity.

Matsusaki *et al.*[38], 1992b: Patients performed high-workload physical activity.

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Figure S3d. Funnel plot of studies on the association of changes in physical activity plasma renin activity

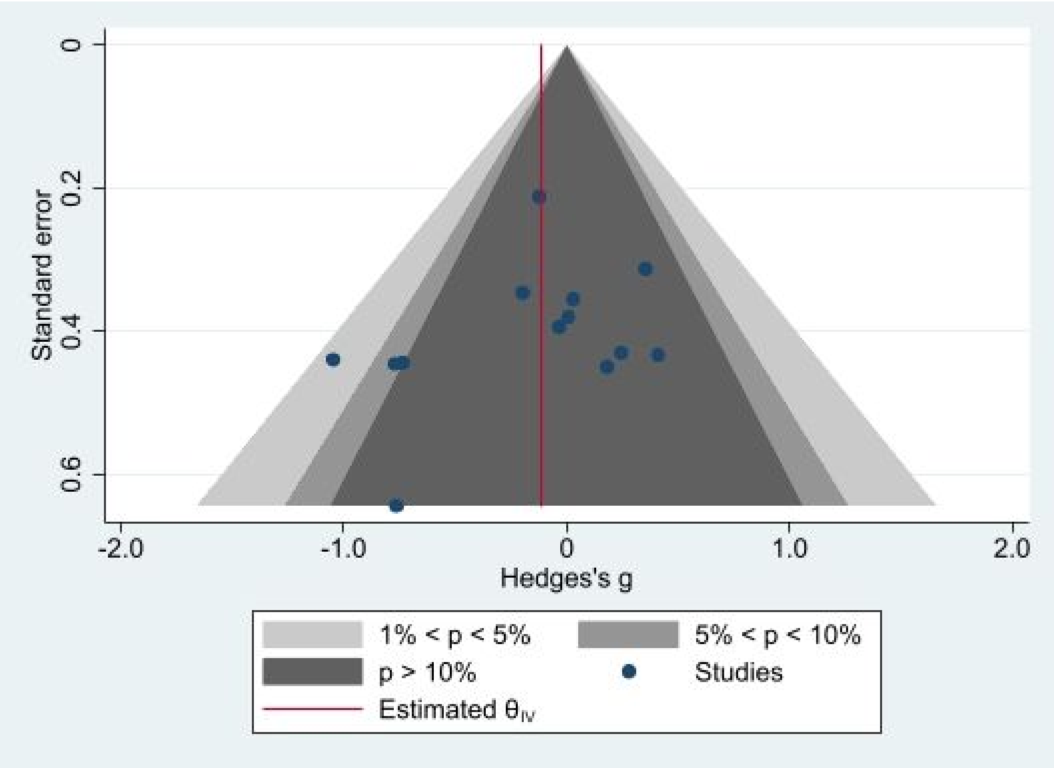

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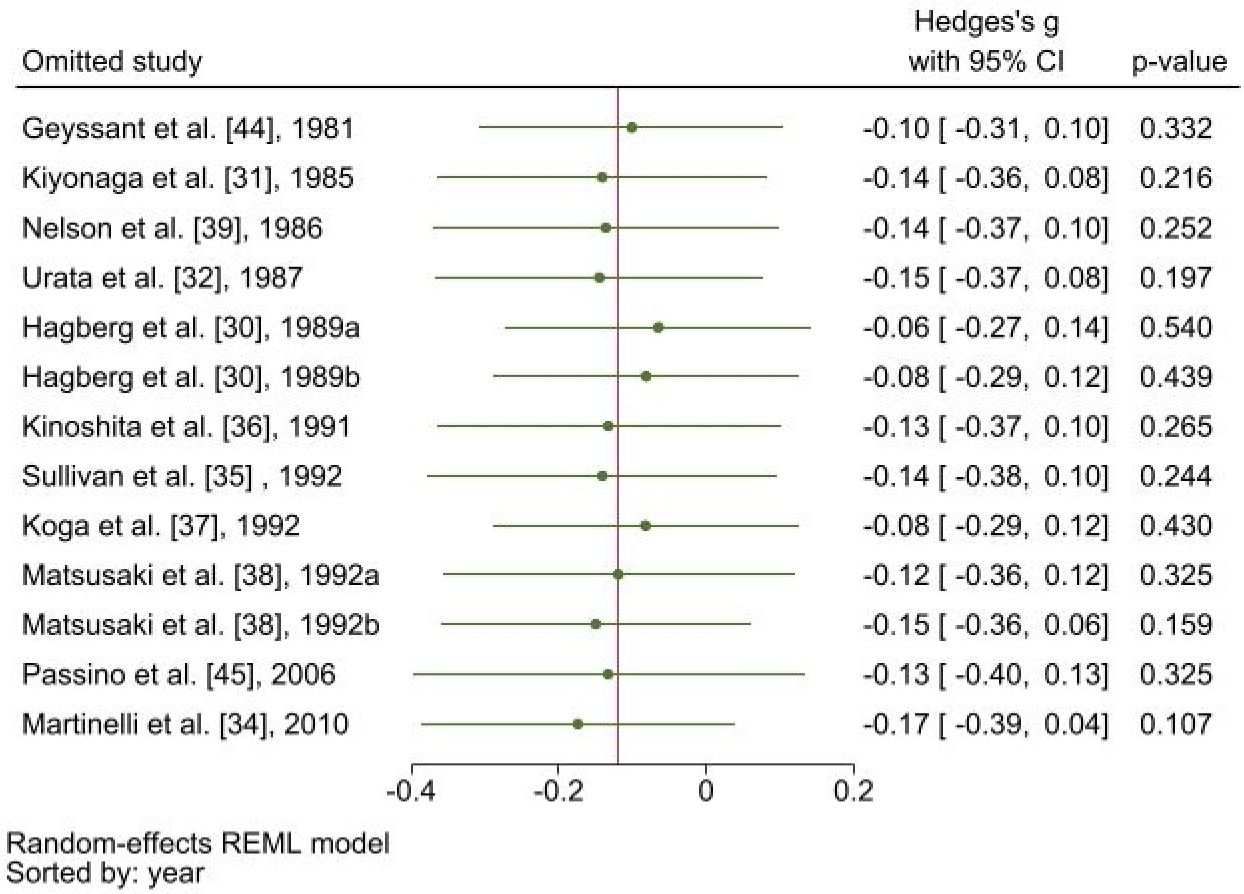
Figure S3e. Leave-one-out figure of studies on the association of changes in physical activity with plasma renin activity



Hagberg *et al.* [30], 1989a: Patients performed low-intensity physical activity.

Hagberg *et al.* [30], 1989b: Patients performed moderate-intensity physical activity.

Matsusaki *et al.*[38], 1992a: Patients performed low-workload physical activity.

Matsusaki *et al.*[38], 1992b: Patients performed high-workload physical activity.

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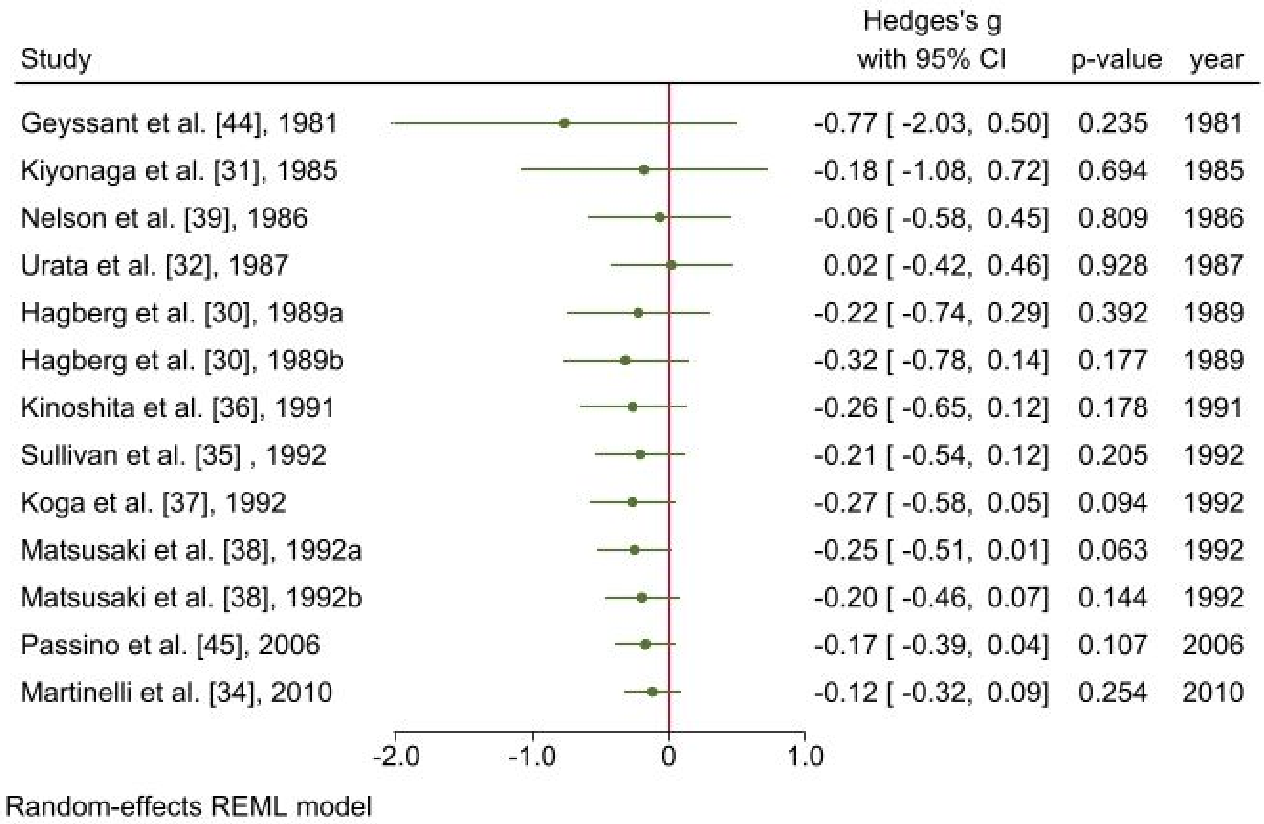
Figure S3f. Cumulative meta-analysis on the association of changes in physical activity with plasma renin activity



Hagberg *et al.* [30], 1989a: Patients performed low-intensity physical activity.

Hagberg *et al.* [30], 1989b: Patients performed moderate-intensity physical activity.

Matsusaki *et al.*[38], 1992a: Patients performed low-workload physical activity.

Matsusaki *et al.*[38], 1992b: Patients performed high-workload physical activity.

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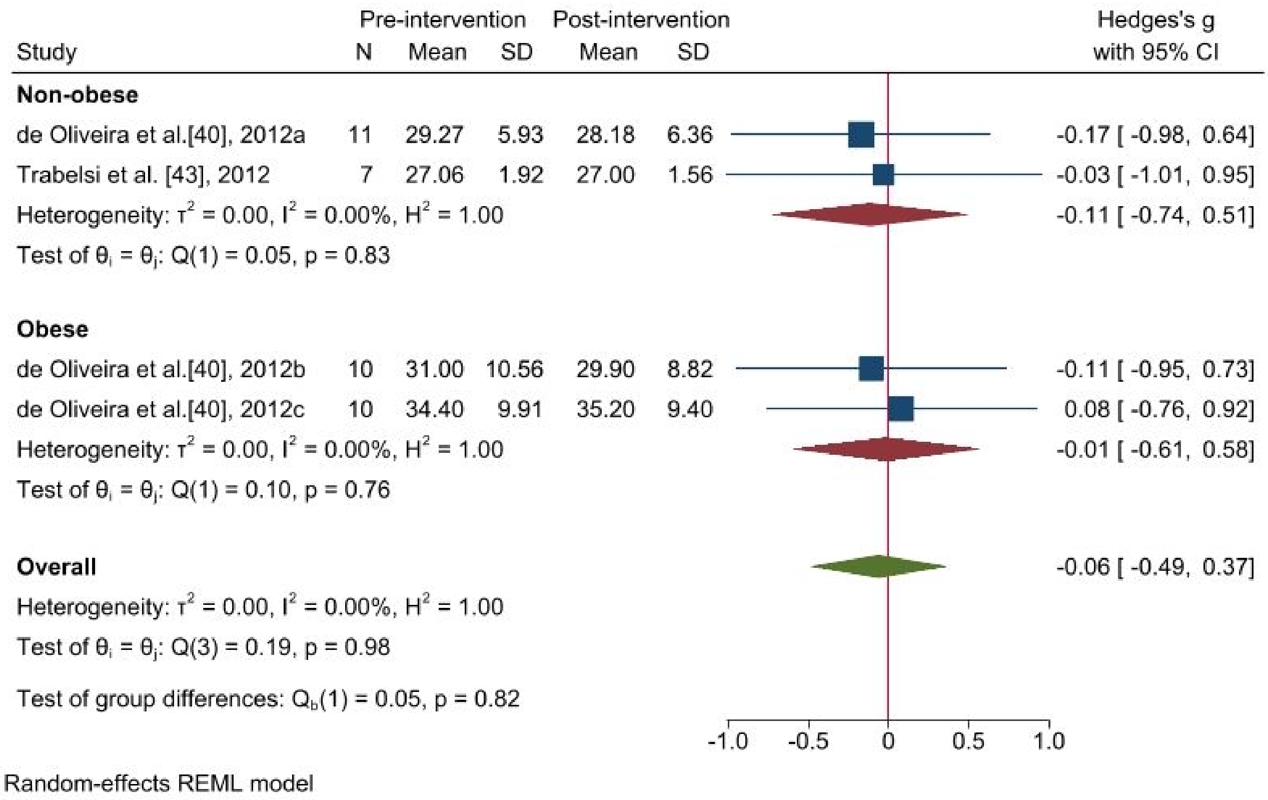
Figure S4a Obesity stratified meta-analysis on the association of changes in physical activity with urea



de Oliveira *et al.* [40], 2012a: Patients performed aerobic training.

de Oliveira *et al.* [40], 2012b: Patients performed strength training.

de Oliveira *et al.* [40], 2012c: Patients performed aerobic and strength training.

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Figure S4b Funnel plot of studies on the association of changes in physical activity with urea

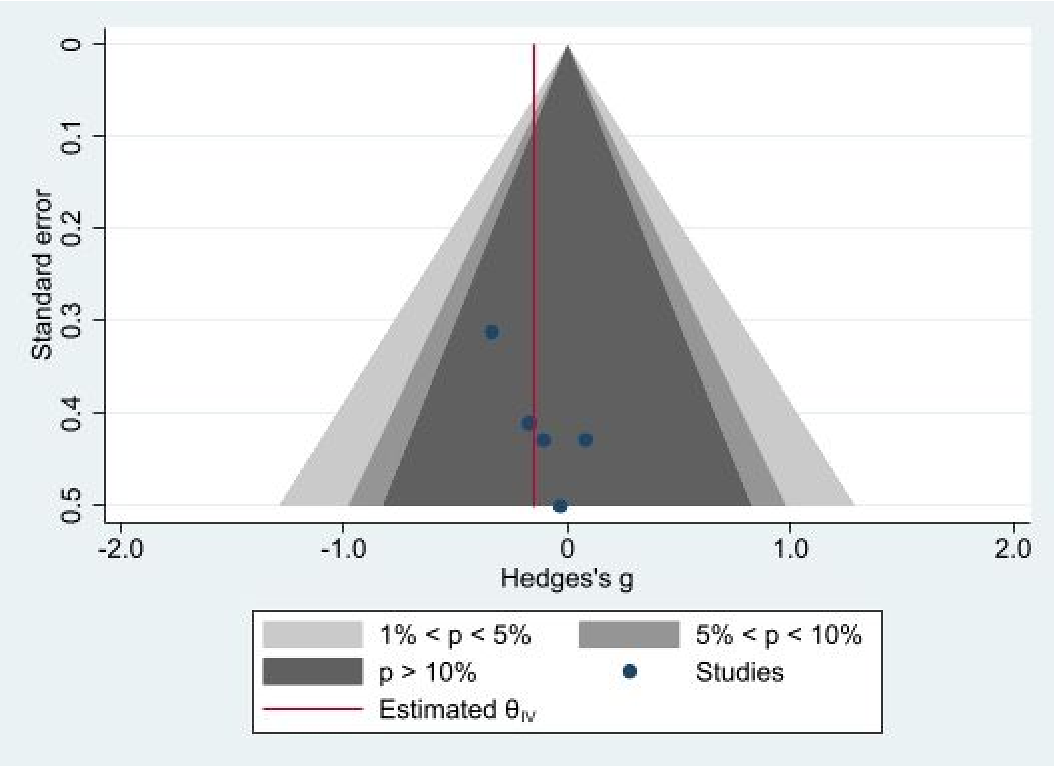
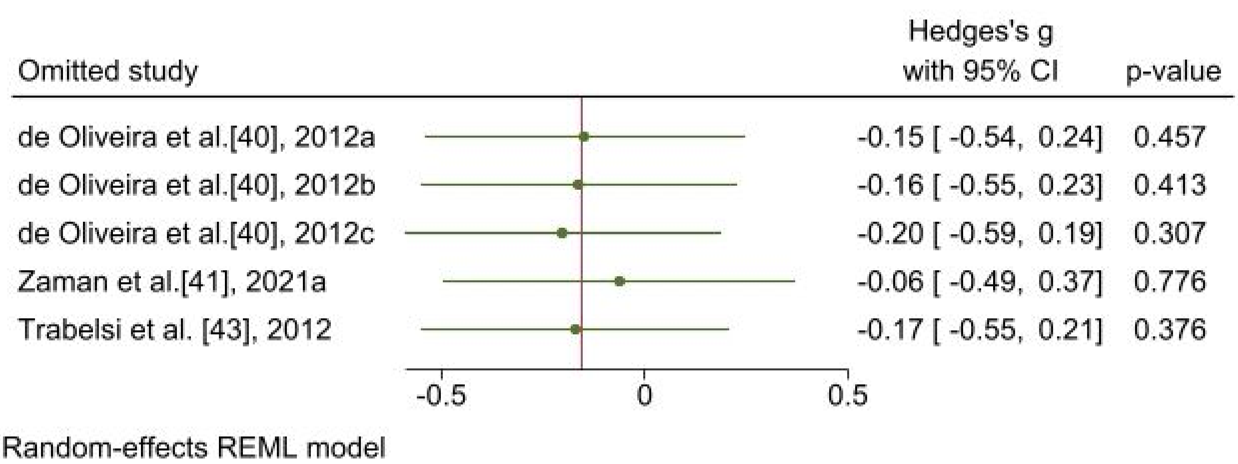


Figure S4c Leave-one-out figure of studies on the association of changes in physical activity with urea



de Oliveira *et al.* [40], 2012a: Patients performed aerobic training.

de Oliveira *et al.* [40], 2012b: Patients performed strength training.

de Oliveira *et al.* [40], 2012c: Patients performed aerobic and strength training.

Zaman *et al.* [41], 2021a: Patients with obesity

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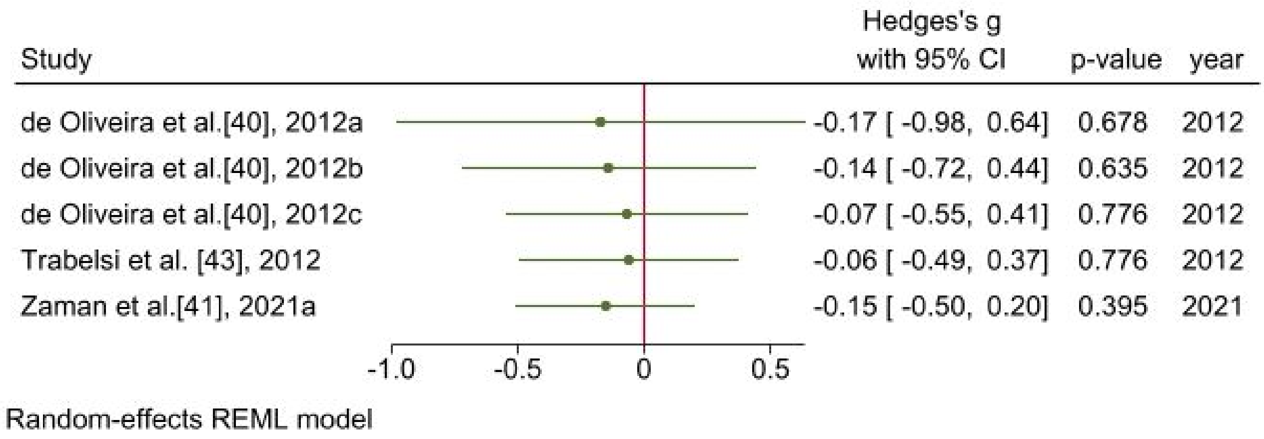
Figure S4d Cumulative meta-analysis on the association of changes in physical activity with urea



de Oliveira *et al.* [40], 2012a: Patients performed aerobic training.

de Oliveira *et al.* [40], 2012b: Patients performed strength training.

de Oliveira *et al.* [40], 2012c: Patients performed aerobic and strength training.

Zaman *et al.* [41], 2021a: Patients with obesity

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BMJ Open

Effect of exercise on kidney-relevant biomarkers in the general population: A systematic review and meta-analysis

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Date Submitted by the Author:	05-Nov-2024
Complete List of Authors:	Liu, Qiaoling; University of Glasgow, School of Cardiovascular and Metabolic Health Celis-Morales, Carlos; University of Glasgow, School of Cardiovascular and Metabolic Health; University Católica del Maule, Physical Activity and Health Research Unit Lees, Jennifer; University of Glasgow, School of Cardiovascular and Metabolic Health Mark, Patrick; University of Glasgow, School of Cardiovascular and Metabolic Health Welsh, Paul; University of Glasgow, School of Cardiovascular and Metabolic Health
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Epidemiology, Sports and exercise medicine
Keywords:	Exercise, Meta-Analysis, Behavior, Nephrology < INTERNAL MEDICINE, Physical Fitness

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Effect of exercise on kidney-relevant biomarkers in the general population: A systematic review and meta-analysis

Author names

Qiaoling Liu[1,*], Carlos Celis-Morales[1,2], Jennifer S. Lees[1], Patrick B. Mark[1], Paul Welsh[1]

Affiliations

[1] School of Cardiovascular and Metabolic Health, University of Glasgow, The United Kingdom

[2]Human Performance Lab, Education, Physical Activity and Health Research Unit, University Católica del Maule, Talca, 3466706, Chile

Corresponding author

Qiaoling Liu

School of Cardiovascular and Metabolic Health, University of Glasgow,
Glasgow, G12 8TA
The United Kingdom

Email: q.liu.3@research.gla.ac.uk

Word count for the main text: 4024

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Abstract

Objective Physical activity (PA) has been generally recognized as beneficial for health. The effect of change in PA on kidney biomarkers in healthy individuals without kidney disease remains unclear. This manuscript synthesized the evidence of the association of changes in PA with kidney biomarkers in the general population free from kidney disease.

Design Systematic review and meta-analysis.

Data sources Embase, PubMed, MEDLINE, and Web of Science databases searched from inception to March 12, 2023.

Eligibility criteria for selecting studies Studies of longitudinal or interventional design were initially selected. The following studies were excluded: 1. Case-control studies; 2. Studies where physical activity was measured at a single time point; 3. Populations with known kidney disease; 4. Studies evaluating the impact of a single episode/event of physical activity; and 5. Non-English language studies.

Data extraction and synthesis Two independent reviewers extracted data to a pre-designed table and assessed the risk of bias using the Cochrane Risk of Bias tool. Data were pooled using random effects model. Hedge's g was used to synthesize effect sizes and obtain an overall estimate. Heterogeneity between studies was measured using I^2. Funnel plots and Egger's test were performed to evaluate the risk of biased results.

Results: Sixteen interventional studies with randomized or non-randomized designs involving 500 participants were identified. The median follow-up was 84 days. Ten studies were at high risk of bias. Studies with low quality were published prior to the year 2000. Changes in PA were found only to have a positive association with serum creatinine (SCr) (Hedge's g=0.69, 95%CI: 0.13, 1.24, I^2=81.37%) and not with plasma renin activity, urea, or urine albumin-to-creatinine ratio. The positive association was only observed in people with obesity and those who exercised for more than 84 days.

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Conclusions: Higher levels of PA are associated with increased SCr levels in healthy people. It remains unclear if this association is related to impaired kidney function or gain in muscle mass, as data on other kidney biomarkers did not support a certain link.

Keywords

Biomarkers, exercise, general population, kidney, meta-analysis.

Strengths and limitations of this study:

- Different from existing studies that mainly focus on people with kidney diseases, this study focuses on populations without known kidney diseases, therefore extending the current knowledge.
- This study analyzed important kidney biomarkers, including serum creatinine, urine albumin-to-creatinine ratio, and plasma renin activity, providing a broader understanding of the possible effect of changes in physical activity on kidney health.
- Constrained by small sample sizes and heterogeneity, several included studies had limited population sizes and high attrition rates, which may lead to biases, particularly concerning the observed heterogeneity in outcomes.

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Background

Cardiovascular disease (CVD) is a major global health issue, causing approximately 17.9 million deaths annually, or 32% of all global fatalities as of 2019 [1]. CVD also imposes a significant economic burden on healthcare systems worldwide [2 3]. Physical inactivity has been recognized as a risk factor for CVD event [4 5] while performing physical activity (PA) is beneficial to the prevention of CVD, along with other chronic conditions such as chronic kidney disease (CKD) [6].

Despite the myriad of benefits of PA on cardiovascular health, its effect on kidney function is not well established. Impaired kidney function is a risk factor for cardiovascular disease [7], it is plausible that PA might also positively affect kidney function [8]. Serum creatinine-based estimated glomerular filtration rate is commonly used in clinical practice and creatinine is a product of muscle metabolism [9]. Therefore, any effect of PA on muscle metabolism may indirectly affect the measurement of kidney function. There is also evidence suggesting that extreme levels of PA may induce kidney damage via rhabdomyolysis or dehydration [10].

Evidence from randomised controlled trials suggests that PA is associated with multiple metrics of kidney function. However, the evidence is controversial. PA is inversely associated with the risk of kidney function decline in people aged over 65, with an average estimated glomerular filtration rate (eGFR) of around 80 mL/min/1.73m^2 [11]. Yet, the same association was not observed in a younger general population (age 26-65 years) with a much higher average eGFR of 108 mL/min/1.73m^2 [12]. Studies assessing PA intensity include data showing that accelerometer-measured low- and moderate-intensity PA are positively associated with eGFR in a general Japanese population (age 35-79 years, average eGFR 92.6 mL/min/1.73m^2) across sexes and ages [13].

PA has also been linked to urinary albumin excretion. As the dysfunction of the kidney endothelial barrier and atherosclerosis contribute to the leakage of albumin into the urine, microalbuminuria has been suggested as an indicator of kidney endothelial dysfunction [14]. The association between high PA levels and lower microalbuminuria has been observed consistently across variant populations [15].

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Novel biomarkers of kidney impairment, such as liver-type fatty acid-binding protein, have also been found to be negatively impacted by habitual physical activities [16]. The degree of stress on the proximal tubule may be attenuated through physical activity, regardless of the kidney functional reserve, suggesting PA's health benefits on the kidney structure.

Although the effects of PA on the kidneys have been studied, many articles focus on the acute effect of physical activity, and they are not instructive on the effects of changing habitual PA. The study population is often restricted to patients with chronic kidney disease (CKD) / end-stage kidney disease (ESKD) including those who undergo dialysis. These research findings may not be applicable to the general population without known kidney diseases. A number of intervention studies discussed the effect of PA in combination with other treatments, like diet and pharmaceutical approaches; thus, it is difficult to measure PA's direct effect. To date, there is a lack of systematic review of the literature which has been conducted on the effect of changes in physical activity on kidney health in populations without pre-existing kidney diseases. In this context, this study aimed to conduct a systematic review and meta-analysis to bridge the knowledge gap.

Methods

This review has been registered on PROSPERO (CRD42023407820). In this review, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement (PRISMA) [17] and the Cochrane Handbook for Systematic Reviews of Interventions [18]. We followed the Population, Intervention, Comparison, Outcomes and Study (PICOS) framework to develop our search strategy[19]. To be specific:

Population: Adults without known kidney diseases

Intervention: Physical activity

Comparator: Kidney-relevant biomarkers before physical activity

Outcome: Changes in kidney-relevant biomarkers after physical activity

Study Design: Cohort or interventional study

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The research theme is: "In adults without known kidney diseases, to what extent does physical activity affect the levels of kidney-relevant biomarkers compared to baseline levels?"

One author (QL) systematically searched Embase, PubMed, MEDLINE, and Web of Science databases from inception to March 12, 2023. The inclusion criteria were: 1. Cohort studies or interventional studies (randomized / non-randomized); 2. Studies in which the duration and/or intensity of physical activity was measured at least twice; 3. Studies in which the study population is based on the general population. It is expected that people with chronic kidney disease will form around 10% of the general population, so we additionally extracted baseline eGFR and Urine Albumin-to-Creatinine Ratio (UACR) (where available) as an indicator of the baseline level of kidney function in these studies. We also carefully examined the description of the study population in selected studies. Studies that met the following criteria were excluded: 1. Case-control studies; 2. Studies in which physical activity was measured at a single timepoint; 3. Studies conducted specifically in populations with pre-existing kidney diseases, such as chronic kidney disease, dialysis, and kidney transplantation.; 4. Studies evaluating the impact of a single episode of physical activity, such as a sporting event; and 5. Studies that were not published in English. The detailed search terms can be found in the Supplemental materials (Table S1).

Two authors (QL and PW) independently decided which studies should be included in this study, and any disagreements were resolved through a discussion with two other authors (CC and PBM). To maximize the coverage of sources, one author (QL) checked the references of the selected articles and evaluated their relevance after reading the full text. Additively, one author (QL) performed manual searches on relevant studies.

Study exposure

The study exposure was the change in physical activity. The change in physical activity was denoted as a categorical variable, i.e., from being sedentary to being active.

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Study outcome

The primary study outcome was the change in kidney-relevant biomarkers, including but not limited to serum creatinine, cystatin C, and UACR. This change was defined as the difference in a biomarker's level after the completion of a change in physical activity, for example, the difference in serum creatinine levels before and after a 12-week aerobic exercise programme. In addition, long-term kidney outcomes, such as the first diagnosis of chronic kidney disease and the presence of microalbuminuria, were also collected if relevant literature was identified.

Quality assessment

All the selected studies were interventional studies. The risk of bias for each selected study was assessed using the Cochrane Risk of Bias tool [20] by two reviewers independently. Seven domains of bias (sequence generation, allocation concealment, blinding of participants and personnel/outcome assessment, incomplete outcome data, selective reporting, and other biases) were assessed. The overall risk was categorized as low, high, critical, unclear, or no information. A study was biased if the loss to follow-up was 20% or above [21]. Any disparities in judgment raised between the two reviewers were resolved through discussion with the help of a third author as needed.

Data synthesis

Using a predesigned table, information was extracted on the first author's family name, publication year, study type, study location, baseline characteristics of exercise groups, type of exercise, length/frequency/intensity of exercise, and outcomes. In case a study has both exercise and sedentary groups, only the information of the group which performed physical activity was included to align with our research theme.

For studies with multiple measurements, we used the baseline and the final measurement to calculate the change. For example, if a kidney biomarker was measured at exercise week 0 (the baseline week), week 3, and week 6 (the final week), the change in the biomarker between week 0 and week 6 was

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used. In cases where subgroup findings were reported, those findings were extracted and compiled for meta-analysis subject to data availability. The median (interquartile range [IQR]) of reported data was converted to the mean (standard deviation [SD]) following established methods [22]. In case the standard error of the mean (SEM) was provided only, the SD was calculated from SEM multiplied by the square root of the number of study size.

As between-study heterogeneity was anticipated, we constructed random-effects models [23] to combine the mean (SD) of selected studies and applied the inverse variance weighting method. The Hedge's g expresses the difference of the means in units of the pooled standard deviation; it measures the effect size for the difference between the means. This study used it to synthesize effect sizes and obtain an overall estimate of the effect of physical activity. It incorporated a correction factor for small sample sizes, which is useful as many PA interventions were of small scales [24]. For interpretation, a value of 0.2, 0.5, and 0.8 was regarded as small, medium, and large effects [25]. Heterogeneity between studies was examined using the I^2 statistic and an I^2 above 50% means substantial heterogeneity [26,27]. Subgroup analyses and meta-regressions were conducted to investigate heterogeneity across age, obesity, and length of exercise. Due to insufficient data, some subgroup analyses and regressions were not performed for all outcomes. Funnel plots and Egger's test were performed to evaluate the risk of biased results [28]. Statistics analyses were performed using STATA 17 (StataCorp, USA). Data were visualized using Robvis (https://mcguinlu.shinyapps.io/robvis/) [29].

Sensitivity analysis

Leave-one-out analysis was performed to identify influential studies by conducting the meta-analysis multiple times while removing one of the included studies during each iteration. Results were presented as leave-one-out figures. A cumulative meta-analysis was also performed for each outcome according to publication year to identify secular trends.

Patient and Public Involvement

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It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Identification of studies

After removing duplicated studies, 10294 potentially relevant studies were identified. Initial screening based on title and abstracts resulted in 155 studies retrieved for further evaluation. Following full-text assessment, 150 studies were excluded, leaving five studies. Additionally, 20 studies were identified through hand search and reading citations, of which nine were excluded, leaving 11 studies. In total, 16 studies were included in the study. (Figure S1).

(Figure S1 is here)

Characteristics of the included studies

All the 16 included studies were of interventional design. The duration of intervention ranged between one month to nine months with a median duration of 2.8 months (11 weeks). The identified 16 studies have a total study population of 500 people (range 4 to 162 individuals). The average age of participants was 50.1 years. Ten studies recruited people with essential hypertension [30-39], one study recruited people with type 2 diabetes mellitus [40], two studies recruited people with obesity [41 42], two studies recruited healthy people [43 44], and one study recruited patients with heart failure [45]. Participants in 12 studies were required to perform aerobic exercise only [30-39 44 45]; two studies involved aerobic exercise and its combinations with strength training [40 42], and two others involved resistance training only [41 43]. All the studies have a similar exercise frequency of 3-5 sessions per week, while the length of sessions varies according to the exercise intensity, with a median of 12 weeks. Seven studies have an attrition rate of 20% or above [30 31 33 38 39 41 42], with a maximum of 30.9% [33].

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Eight studies used maximum oxygen uptake (VO_{2max}) to measure the intensity of aerobic exercise [30 32 36-39 44 45], with a few studies using heart rate reserve [33], maximum heart rate [34 35 42], and lactate threshold [31 40]. For resistance and strength training, repetition maximum (RM) was used to measure the exercise intensity (Table S2).

Measurement of physical activities

Fourteen studies required participants to perform on-site physical activity under close supervision. The low-workload group in the study by Hagberg et al. [30] was supervised for the first month, and relied on self-reported forms for the remaining eight months. All the participants in the study by Passino et al. [45] had self-conducted exercises with their compliance to the instructions checked at the beginning and near the end of the study. All the studies have reported the arrangement of physical training.

Measurement of the outcomes

Serum creatinine (SCr), plasma renin activity (PRA), and urea were the most measured biomarkers in selected studies. Two studies reported eGFR [36 42], one study [42] reported urine albumin-to-creatinine ratio (UACR), and one study [31] was on angiotensin II (Ang II). Twelve of these studies measured fasting biomarkers, while three studies have not specified the fasting status [42 44 45]; one study explicitly measured biomarkers after participants have "a light breakfast" [39]. All the biomarkers were measured under resting conditions.

Potential bias and quality assessment

Overall, the selected studies have medium to low quality. Ten out of sixteen studies were evaluated as having a high risk of bias. Most studies had a less representative cohort, especially those published decades ago as early as in the 1980s [30 31]. Studies with better population representation were published

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after 2000 [41 42]. The incomplete outcome data (attrition bias) was another major source of inferior quality, with seven studies having a high attrition rate of over 20% [30 31 33 38 39 41 42]. It was impossible to blind participants in supervised situations due to the nature of the physical activity as an exposure. Considering the nature of the intervention design and the objective evaluation of outcomes through laboratory testing, all studies have a high risk for blinding of participants and personnel (performance bias) and a low risk for blinding of outcome assessment (detection bias). Six studies with a randomized design have provided information on how the random sequence was generated [30 38 40 42 43 45]. Some studies also have a higher risk of measurement error for exposure and outcome (Table S3, Figure 1, 2).

(Figure 1 is here)

(Figure 2 is here)

Changes in physical activity and serum creatinine

The meta-analysis included six study populations from four studies [33 41-43], including 197 participants with an average PA duration of 73 days. The majority of findings have a mean Hedge's g on the right side of the reference line with a wide 95% CI. The pooled result showed a moderate positive effect of PA on SCr (Hedge's g=0.69, 95%CI: 0.13, 1.24). Substantial heterogeneity was detected among cohorts (I^2=81.37%). (Figure 3a).

(Figure 3 is here)

Stratifying by obesity, only two groups of participants with obesity from a single study [42] have a statistically significant pooled effect (Hedge's =0.74, 95%CI: 0.29, 1.20). Stratified by the median of the length of exercises (12 weeks), only two cohorts from one study who have undergone exercise over 12 weeks have a significant pooled effect (Hedge's =0.74, 95%CI: 0.29, 1.20) (Figure S2a-b).

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The funnel plot showed mild asymmetry, and Egger's test showed no small-study effects (P value=0.21). Sensitivity analysis showed a consistent result as that of the primary analysis; the removal of one cohort from Zaman [41] largely attenuated the pooled effect (Hedge's =0.38, 95%CI: 0.05, 0.72). Obesity was identified as the only important source of heterogeneity. Cumulative meta-analyses according to the year of publication showed significant evidence of secular trends for SCr (Figure S2c-e).

Changes in physical activity and eGFR

Three cohorts from two studies [36 42] included 50 people with an average exercise duration of 12 weeks were identified. No significant effect was found in the pooled result of the exercise on eGFR (Hedge's g=-0.30, 95%CI: -0.83, 0.24, I^2=48.57%) (Figure 3b).

Changes in physical activity and urine albumin-to-creatinine ratio

Two cohorts from one study [42] included 38 people with an average exercise duration of three months were identified. No statistical significance was found in the pooled result of the exercise on UACR (Hedge's g=-0.15, 95%CI: -0.59, 0.29) (Figure 3c).

Changes in physical activity and plasma renin activity

Thirteen cohorts from eleven studies [30-32 34-39 44 45] included 184 people with an average exercise duration of 129 days in the meta-analysis. No association between PA and PRA was observed (Hedge's g=-0.12, 95%CI: -0.32, 0.09). Minor heterogeneity was found among cohorts (I^2=2.54%) (Figure 3d).

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In stratified analyses, no associations were found by obesity status, exercise length, and age- groups. There was no statistically significant effect of exercise on PRA in people aged 60 and above, the upper 95% CI was close to zero (Hedge's =-0.54, 95%CI: -1.14, 0.06) (Figure S3a-c).

The funnel plot showed good symmetry. Egger's test showed no small-study effects (P value =0.39). Sensitivity analysis showed a consistently insignificant result as that of the primary analysis, with no influential single studies. Meta-regression showed no important source of heterogeneity. Cumulative meta-analysis showed no significant changes in research findings (Figure S3d-f).

Changes in physical activity and serum urea

Five cohorts from three studies [40 41 43] included 48 people with an average exercise duration of 73 days. No association was found between PA and urea (Hedge's g=-0.15, 95%CI: -0.50, 0.20). No heterogeneity was found among cohorts (I^2=0.00%) (Figure 3e). Data were consistent in subgroup analyses. (Figure S4a).

The funnel plot showed good symmetry, and Egger's test showed no small-study effects (P value =0.39). Sensitivity analysis showed a consistently insignificant result as that of the primary analysis, with no influential single studies. Meta-regression showed no important source of heterogeneity. Cumulative meta-analyses showed no significant changes in research findings (Figure S4b-d).

Changes in physical activity and other kidney-related biomarkers

A study by Kiyonaga et al. [31] showed that after 20 weeks of mild aerobic exercise, the average level of Angiotensin II in eight patients with essential hypertension increased significantly from 58 to 91 pg/ml. However, the increase in Angiotensin II was not observed after completing the first 10 weeks of training.

Discussion

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In this systematic review and meta-analysis of 16 interventional studies involving 500 people without known kidney diseases, we evaluated the available data exploring the association of change in PA with kidney function. Change in PA was found only to have a positive association with SCr, not with eGFR. There was some limited evidence that participants with obesity and people who exercised for more than 12 weeks may have a larger increase in SCr as compared to their counterparts. Sensitivity analysis was in line with the primary analysis; mild publication bias and a secular trend were found. The general quality of studies was suboptimal to make robust conclusions, and the number and size of studies were generally small (ranging from 4 to 112 participants).

Due to the possibility of physical activity to induce muscle growth, which is the primary source of SCr, the role of body composition in the association between physical activity and SCr deserves discussion. Among three studies reporting on SCr and body composition, Szulinska et al.[42] reported a significant increase in lean body mass and SCr, and a decrease in body fat% in a population receiving endurance and strength training for three months; Trabelsi et al.[43] reported no significant changes in body fat% but a significant increase in SCr in a population receiving one-month resistance training, while Sikiru et al.[33] reported no significant change in body fat% and a likely increase in SCr in a population receiving eight weeks of aerobic training. It is noteworthy that the study populations of the above studies had markedly different body compositions, with the latter two having low baseline body fat% (11.9% and 13.5%, respectively), while the population in the first study had an average body fat% of over 33%. Additionally, Kinoshita et al.[36] reported no significant change in eGFR in 12 non-obese people after a ten-week aerobic exercise, which implied a possible insignificant change in SCr. Therefore, the impact of PA on SCr levels may be related to body composition.

In the pooled result, there was no statistically significant association of exercise with UACR (Figure 3c). The pooled result came from two cohorts of one study with a small study population [42]. It should be noted that while urinary albumin and urinary creatinine both increased after endurance-strength training, their ratio did not change much, implying a balanced increase of albumin and creatinine. In

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people who only performed endurance training, no increases in albumin, creatinine, or UACR were found. Therefore, the increase in albumin and creatinine might be caused by increased muscle mass or post-activity proteinuria.

As an important hormone secreted by the kidney for regulating blood pressure, renin has long been a topic of interest. Among the biomarkers under discussion, renin is the most extensively researched, with the earliest studies dating back to the 1980s. However, nine of the eleven studies on renin were published in 1992 or earlier, with only two published after 2000. The studies involved a small number of participants, with most having between 10 and 20 individuals. Nevertheless, the cumulative meta-analysis based on publication year revealed a progressively narrowing 95% confidence interval with an upper limit approaching zero and a consistently negative effect size. In the research conducted by Matsuaki et al. [38]; despite the absence of a significant difference in baseline PRA between the low- (50% VO_{2max}) and the high-workload (75% VO_{2max}) group, both cohorts manifested a similar pattern characterized by two interlocking M shapes throughout six measurements conducted at baseline and week 1/2/4/7/10. The PRA pattern exhibited by the low-workload group between Week 1 and Week 10 was similar to that of the high-workload group between Week 0 and Week 7. The PRA change in the low-workload group was "delayed" by one week compared to the high-workload group. Specifically, the PRA in the low-workload group experienced a slight decline in the first week, followed by an increase in the second week, whereas the PRA in the high-workload group increased in the first week. The underlying mechanism of this finding remains elusive.

Kiyonaga et al. [31] reported a significant increase in Angiotensin II after 20 weeks of mild aerobic exercise in eight patients, yet no significant increase was observed by week 10. As renin secretion is the first step in the production of Angiotensin II, it can be speculated that an exercise lasting over 20 weeks may significantly impact renin (and thus Angiotensin II). Renin is rarely measured in clinical practice and is affected by many antihypertensive drugs. Although these findings are interesting, any effect of PA on renin is unlikely to translate into information used to inform clinical guidelines.

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Urea is clinically measured to evaluate kidney impairment although to a lesser degree than SCr. There was a lack of a significant association between exercise and urea levels. One possible explanation is that, considering the absence of kidney disease in all study participants at baseline, the closely supervised, low to moderate-intensity exercise did not result in kidney damage or alterations that exceeded the kidney compensation, thus precluding significant observable variations in urea levels.

To the best of our knowledge, this is the first systematic review and meta-analysis to investigate the association between changes in physical activity and kidney biomarkers in people without known kidney diseases. The studies included underwent rigorous assessment based on strict criteria. We observed low heterogeneity among most of the biomarkers studied. Sensitivity analyses aligned with our primary findings.

It is unlikely that any rise in serum creatinine with PA represents an adverse effect of PA on kidney function, given the widespread benefits of PA on cardiovascular health. It is theoretically plausible that PA reduces glomerular perfusion and hence creatinine rises. This effect is seen in people taking both medications inhibiting the renin-angiotensin system [46] and sodium-glucose transporter 2 inhibitors [47]. This transient rise in serum creatinine is associated with long-term cardiovascular and kidney benefits with these agents. Studies of PA with long durations are required to determine if any change in creatinine with PA is associated with benefit or harm on cardiorenal health.

Although efforts have been made in this study, there are several limitations. Firstly, most studies had a very small sample size, with only a few exceptions. This may, in part, be attributed to a general insufficiency of resources, such as funding and personnel. Secondly, over 50% of the studies were found to have considerable bias, primarily stemming from high attrition rates, negatively impacting the quality of these studies. Finally, some studies were conducted decades ago, which could introduce potential issues with measurement methods, accuracy, and lab standards. This underscores the pressing requirement for updated and standardized research.

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In conclusion, by examining the changes in physical activity among individuals without diagnosed kidney diseases, the findings of this study supported the positive association of physical activity with SCr. However, the association with kidney function specifically could not be confirmed by existing data on other kidney biomarkers. Given the global advocacy for increased physical activity by governments and medical professionals, and the clinical importance of kidney function, further research should be conducted in the general population to investigate the association of change in PA with kidney function.

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Declarations

Ethics approval

Not applicable, as this study retrieved and synthesised data from already published studies.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

Conceptualization, P.W., Q.L.; methodology, Q.L.; data curation, Q.L., P.W., C.C., P.B.M.; writing—original draft preparation, Q.L.; writing—review and editing, Q.L., P.W., C.C., J.S.L., P.B.M.; supervision, P.W., C.C., P.B.M; Critical revision for important intellectual content, P.W., C.C., J.S.L., P.B.M. All authors have read and agreed to the published version of the manuscript. Q.L. is the guarantor.

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References

1. World Health Organization. Cardiovascular diseases (cvds) [Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) accessed April 24 2023.
2. Gheorghe A, Griffiths U, Murphy A, et al. The economic burden of cardiovascular disease and hypertension in low- and middle-income countries: a systematic review. *BMC Public Health* 2018;18(1):975. doi: 10.1186/s12889-018-5806-x
3. Tajeu GS, Ruiz-Negrón N, Moran AE, et al. Cost of Cardiovascular Disease Event and Cardiovascular Disease Treatment-Related Complication Hospitalizations in the United States. *Circ Cardiovasc Qual Outcomes* 2024;17(3):e009999. doi: 10.1161/circoutcomes.123.009999 [published Online First: 2024/02/08]
4. Lavie CJ, Ozemek C, Carbone S, et al. Sedentary Behavior, Exercise, and Cardiovascular Health. *Circ Res* 2019;124(5):799-815. doi: 10.1161/circresaha.118.312669 [published Online First: 2019/03/01]
5. Bellettiere J, LaMonte MJ, Evenson KR, et al. Sedentary behavior and cardiovascular disease in older women: The Objective Physical Activity and Cardiovascular Health (OPACH) Study. *Circulation* 2019;139(8):1036-46. doi: 10.1161/circulationaha.118.035312 [published Online First: 2019/04/30]
6. Hayden CMT, Begue G, Gamboa JL, et al. Review of Exercise Interventions to Improve Clinical Outcomes in Nondialysis CKD. *Kidney International Reports* 2024;9(11):3097-115. doi: https://doi.org/10.1016/j.ekir.2024.07.032
7. Matsushita K, van der Velde M, Astor BC, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010;375(9731):2073-81. doi: 10.1016/s0140-6736(10)60674-5 [published Online First: 2010/05/21]
8. Park S, Lee S, Kim Y, et al. Causal effects of physical activity or sedentary behaviors on kidney function: an integrated population-scale observational analysis and Mendelian randomization study. *Nephrology Dialysis Transplantation* 2021;37(6):1059-68. doi: 10.1093/ndt/gfab153
9. Inker LA, Eneanya ND, Coresh J, et al. New Creatinine- and Cystatin C-Based Equations to Estimate GFR without Race. *N Engl J Med* 2021;385(19):1737-49. doi: 10.1056/NEJMoa2102953 [published Online First: 2021/09/24]
10. Rawson ES, Clarkson PM, Tarnopolsky MA. Perspectives on Exertional Rhabdomyolysis. *Sports Med* 2017;47(Suppl 1):33-49. doi: 10.1007/s40279-017-0689-z [published Online First: 2017/03/24]
11. Kim H, Ko MJ, Lim CY, et al. Association between physical activity and risk of renal function decline and mortality in community-dwelling older adults: a nationwide population-based cohort study. *BMC Geriatr* 2022;22(1):973. doi: 10.1186/s12877-022-03693-1 [published Online First: 2022/12/18]
12. Herber-Gast G-CM, Hulsegge G, Hartman L, et al. Physical Activity Is not Associated with Estimated Glomerular Filtration Rate among Young and Middle-Aged Adults: Results from the Population-Based Longitudinal Doetinchem Study. *PLOS ONE* 2015;10(10):e0133864. doi: 10.1371/journal.pone.0133864
13. Sasaki S, Nakamura K, Ukawa S, et al. Association of accelerometer-measured physical activity with kidney function in a Japanese population: the DOSANCO Health Study. *BMC Nephrology* 2022;23(1):7. doi: 10.1186/s12882-021-02635-0
14. Prasad RM, Bali A, Tikaria R. Microalbuminuria. StatPearls. Treasure Island (FL) ineligible companies. Disclosure: Atul Bali declares no relevant financial relationships with ineligible companies. Disclosure: Richa Tikaria declares no relevant financial relationships with ineligible companies.: StatPearls Publishing

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15. Vittori LN, Romasco J, Tarozzi A, et al. Urinary Markers and Chronic Effect of Physical Exercise. *Methods Mol Biol* 2021;2292:193-200. doi: 10.1007/978-1-0716-1354-2_17 [published Online First: 2021/03/03]
16. Kosaki K, Kamijo-Ikemori A, Sugaya T, et al. Effect of habitual exercise on urinary liver-type fatty acid-binding protein levels in middle-aged and older adults. *Scand J Med Sci Sports* 2018;28(1):152-60. doi: 10.1111/sms.12867 [published Online First: 2017/03/02]
17. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71
18. McKenzie JE, Brennan SE, Ryan RE, et al. Cochrane Handbook for Systematic Reviews of Interventions2019.
19. Thomas J, Kneale D, McKenzie JE, et al. Determining the scope of the review and the questions it will address. Cochrane Handbook for Systematic Reviews of Interventions2019:13-31.
20. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj* 2011;343:d5928. doi: 10.1136/bmj.d5928 [published Online First: 2011/10/20]
21. Fewtrell MS, Kennedy K, Singhal A, et al. How much loss to follow-up is acceptable in long-term randomised trials and prospective studies? *Archives of Disease in Childhood* 2008;93(6):458. doi: 10.1136/adc.2007.127316
22. Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Medical Research Methodology* 2014;14(1):135. doi: 10.1186/1471-2288-14-135
23. Borenstein M, Hedges LV, Higgins JP, et al. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods* 2010;1(2):97-111. doi: 10.1002/jrsm.12 [published Online First: 2010/04/01]
24. Hedges LV, Olkin I. Statistical methods for meta-analysis: Academic press 2014.
25. Cohen J. Statistical power analysis for the behavioral sciences: Academic press 2013.
26. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21(11):1539-58. doi: 10.1002/sim.1186 [published Online First: 2002/07/12]
27. Deeks JJ, Higgins JPT, Altman DG, et al. Analysing data and undertaking meta-analyses. Cochrane Handbook for Systematic Reviews of Interventions2019:241-84.
28. Sterne JAC, Sutton AJ, Ioannidis JPA, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;343:d4002. doi: 10.1136/bmj.d4002
29. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. *Research Synthesis Methods* 2020;n/a(n/a) doi: 10.1002/jrsm.1411
30. Hagberg JM, Montain SJ, Martin WH, et al. Effect of exercise training in 60- to 69-year-old persons with essential hypertension. *The American Journal of Cardiology* 1989;64(5):348-53. doi: https://doi.org/10.1016/0002-9149(89)90533-X
31. Kiyonaga A, Arakawa K, Tanaka H, et al. Blood pressure and hormonal responses to aerobic exercise. *Hypertension* 1985;7(1):125-31. doi: 10.1161/01.HYP.7.1.125
32. Urata H, Tanabe Y, Kiyonaga A, et al. Antihypertensive and volume-depleting effects of mild exercise on essential hypertension. *Hypertension* 1987;9(3):245-52. doi: 10.1161/01.hyp.9.3.245 [published Online First: 1987/03/01]
33. Sikiru L, Okoye GC. Therapeutic effect of continuous exercise training program on serum creatinine concentration in men with hypertension: a randomized controlled trial. *Ghana Med J* 2014;48(3):135-42. doi: 10.4314/gmj.v48i3.3 [published Online First: 2015/02/25]
34. Martinelli B, Barrile SR, Arca EA, et al. Effect of aerobic exercise on plasma renin in overweight patients with hypertension. *Arq Bras Cardiol* 2010;95(1):91-8. doi: 10.1590/s0066-782x2010005000066 [published Online First: 2010/06/22]

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Enseignement Superieur (ABES) .
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35. Sullivan PA, Grosch C, Lawless D, et al. Short-term strenuous exercise training: effects on blood pressure and hormonal levels in mild hypertension. *Ir J Med Sci* 1992;161(12):666-9. doi: 10.1007/bf02942379 [published Online First: 1992/12/01]
36. Kinoshita A, Koga M, Matsusaki M, et al. Changes of dopamine and atrial natriuretic factor by mild exercise for hypertensives. *Clin Exp Hypertens A* 1991;13(6-7):1275-90. doi: 10.3109/10641969109042127 [published Online First: 1991/01/01]
37. Koga M, Ideishi M, Matsusaki M, et al. Mild exercise decreases plasma endogenous digitalislike substance in hypertensive individuals. *Hypertension* 1992;19(2_supplement):II231. doi: doi:10.1161/01.HYP.19.2_Suppl.II231
38. Matsusaki M, Ikeda M, Tashiro E, et al. Influence of workload on the antihypertensive effect of exercise. *Clin Exp Pharmacol Physiol* 1992;19(7):471-9. doi: 10.1111/j.1440-1681.1992.tb00492.x [published Online First: 1992/07/01]
39. Nelson L, Esler M, Jennings G, et al. EFFECT OF CHANGING LEVELS OF PHYSICAL ACTIVITY ON BLOOD-PRESSURE AND HAEMODYNAMICS IN ESSENTIAL HYPERTENSION. *The Lancet* 1986;328(8505):473-76. doi: https://doi.org/10.1016/S0140-6736(86)90354-5
40. de Oliveira VN, Bessa A, Jorge MLMP, et al. The effect of different training programs on antioxidant status, oxidative stress, and metabolic control in type 2 diabetes. *Applied Physiology, Nutrition and Metabolism* 2012;37(2):334-44. doi: https://dx.doi.org/10.1139/H2012-004
41. Zaman GS, Abohashrh M, Ahmad I, et al. The Impact of Body Resistance Training Exercise on Biomedical Profile at High Altitude: A Randomized Controlled Trial. *Biomed Res Int* 2021;2021:6684167. doi: 10.1155/2021/6684167 [published Online First: 2021/06/24]
42. Szulińska M, Skrypnik D, Ratajczak M, et al. Effects of Endurance and Endurance-strength Exercise on Renal Function in Abdominally Obese Women with Renal Hyperfiltration: A Prospective Randomized Trial. *Biomed Environ Sci* 2016;29(10):706-12. doi: 10.3967/bes2016.095 [published Online First: 2016/12/09]
43. Trabelsi K, Stannard SR, Maughan RJ, et al. Effect of resistance training during Ramadan on body composition and markers of renal function, metabolism, inflammation, and immunity in recreational bodybuilders. *Int J Sport Nutr Exerc Metab* 2012;22(4):267-75. doi: 10.1123/ijsnem.22.4.267 [published Online First: 2012/08/03]
44. Geyssant A, Geelen G, Denis C, et al. Plasma vasopressin, renin activity, and aldosterone: Effect of exercise and training. *European Journal of Applied Physiology and Occupational Physiology* 1981;46(1):21-30. doi: 10.1007/BF00422171
45. Passino C, Severino S, Poletti R, et al. Aerobic training decreases B-type natriuretic peptide expression and adrenergic activation in patients with heart failure. *J Am Coll Cardiol* 2006;47(9):1835-9. doi: 10.1016/j.jacc.2005.12.050 [published Online First: 2006/05/10]
46. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? *Arch Intern Med* 2000;160(5):685-93. doi: 10.1001/archinte.160.5.685 [published Online First: 2000/03/21]
47. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med* 2020;383(15):1436-46. doi: 10.1056/NEJMoa2024816 [published Online First: 2020/09/25]

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Figures

Figure 1. Summary of the risk of bias by Cochrane Risk of Bias tool

Figure 2. Study-specified risk of bias by Cochrane Risk of Bias tool

Figure 3. Meta-analysis on the associations of changes in physical activity with kidney-relevant biomarkers (3a. Serum creatinine, 3b. eGFR, 3c. Urine albumin-to-creatinine ratio, 3d. Plasma renin activity,3e. Urea)

Note for Figure 3:

Szulinska *et al*. [42], 2016a: Patients received endurance training.

Szulinska *et al.* [42], 2016b: Patients received both endurance and strength training.

Zaman *et al*. [41], 2021a: Patients with obesity

Zaman *et al.*[41], 2021b: Patients without obesity

Hagberg *et al.* [30], 1989a: Patients performed low-intensity physical activity.

Hagberg *et al*. [30], 1989b: Patients performed moderate-intensity physical activity.

Matsusaki *et al.* [38], 1992a: Patients performed low-workload physical activity.

Matsusaki *et al.*[38], 1992b: Patients performed high-workload physical activity.

de Oliveira *et al.* [40], 2012a: Patients performed aerobic training.

de Oliveira *et al.* [40], 2012b: Patients performed strength training.

de Oliveira *et al.* [40], 2012c: Patients performed aerobic and strength training.

Zaman *et al.* [41], 2021a: Patients with obesity.

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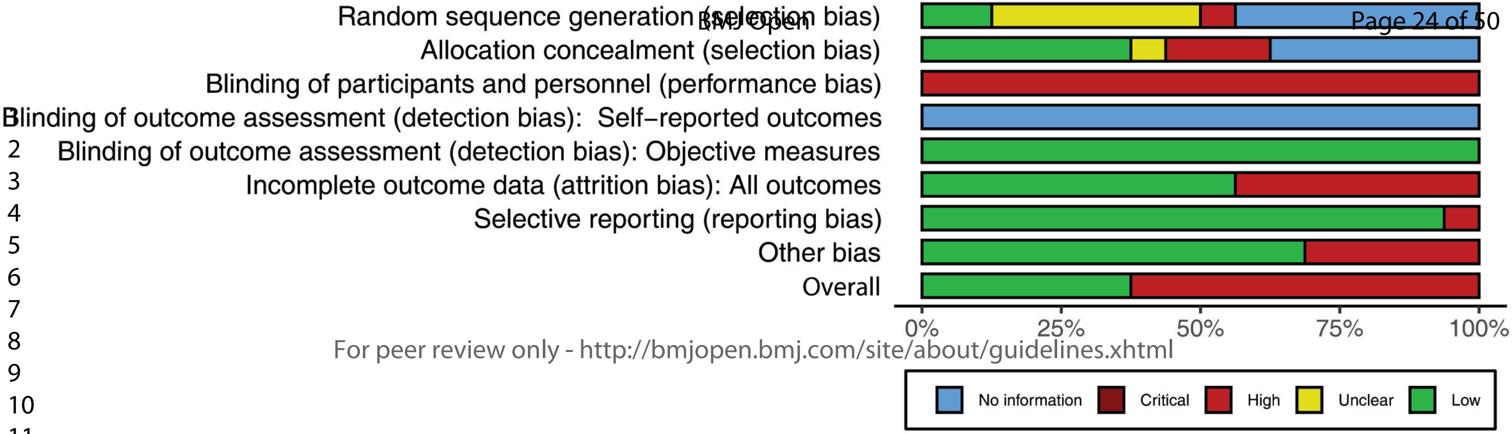
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias): Self−reported outcomes
Blinding of outcome assessment (detection bias): Objective measures
Incomplete outcome data (attrition bias): All outcomes
Selective reporting (reporting bias)
Other bias
Overall
0%
25%
50%
75%
100%
No information
Critical
High
Unclear
Low

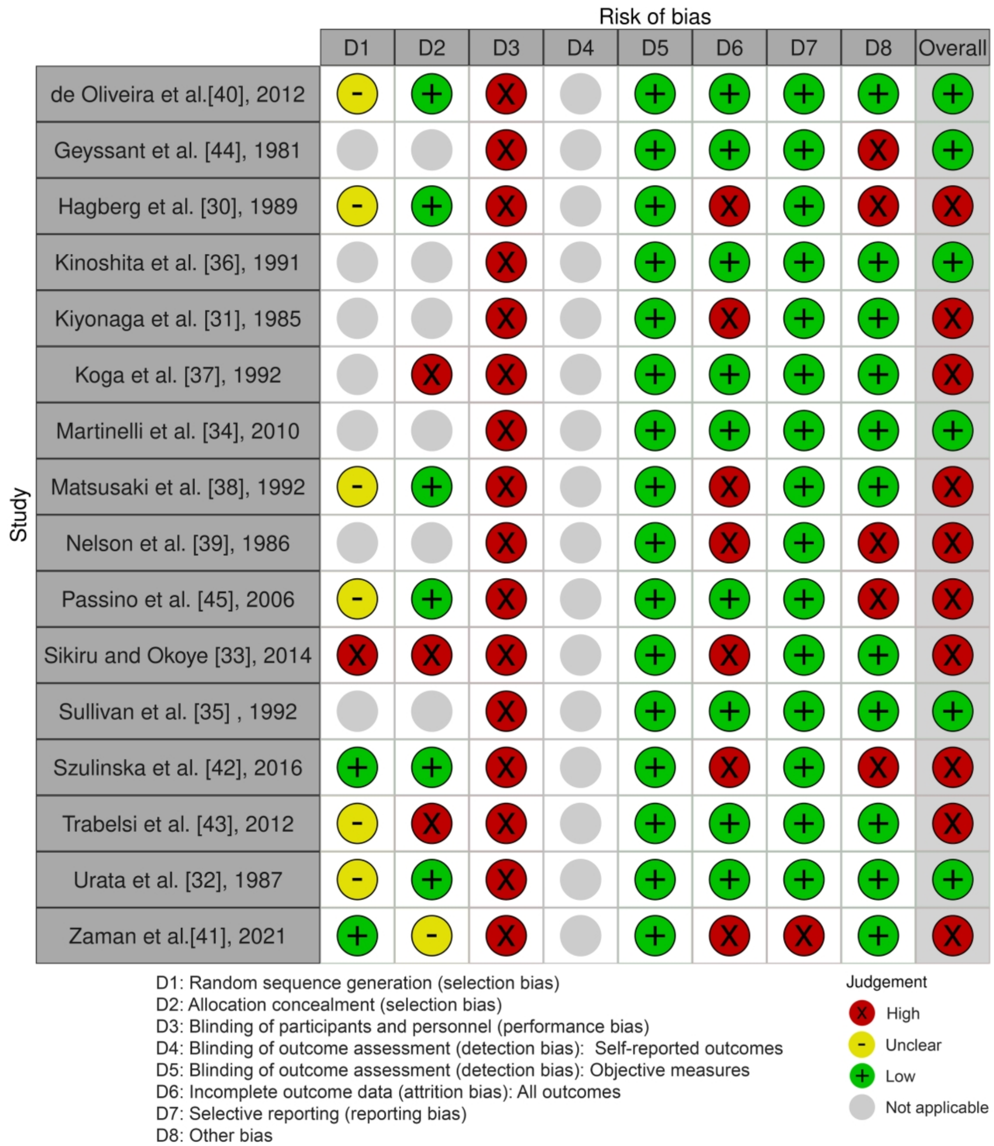

Figure 2. Study-specified risk of bias by Cochrane Risk of Bias tool

194x226mm (300 x 300 DPI)

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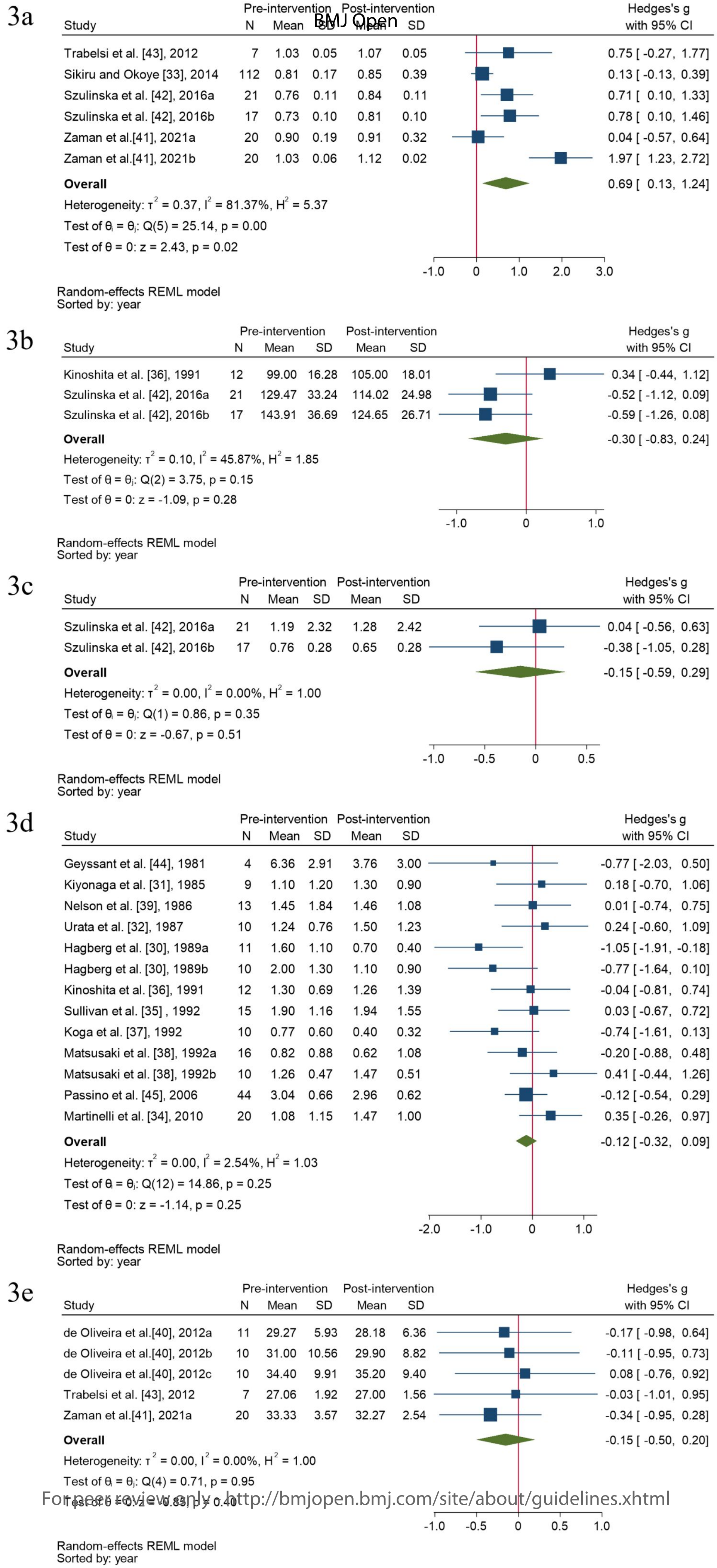

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Content

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Table S1 Search Terms

Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations , 1946 Year

Steps	Terms	Hits
1	exp physical activity/ or exp exercise test/	291234
2	exp physical education/ or exp physical fitness/ or exp cardiorespiratory fitness/	47746
3	(exercise* or sport* or walking* or cycling or swimming or running or jogging or sedentary or inactiv*).ti,ab.	974933
4	(physical* adj3 (activ* or inactiv* or treat* or exercis* or exertion*)).ti,ab.	189257
5	or/1-4	1150170
6	(controlled clinical trial).ti,ab.	18436
7	exp clinical trial/	960936
8	(randomized controlled trial).ti.	58191
9	(randomized or trial).ti.	353729
10	exp cohort studies/	2439066
11	(retrospective or prospective or longitudinal).ti.	346157
12	or/6-11	3359654
13	5 and 12	172209
14	(exp animal/ or nonhuman/) not exp human/	5086829
15	13 not 14	170034
16	(interven* or change* or traject* or shift* or switch* or alternat* or differen* or variat* or revamp*).ti,kw.	1810596
17	15 and 16	19570
18	(uremi* or uraemi* or albuminuria* or proteinuria* or urin* or albumin* or protein* or glomerular filtration rate* or ?GFR).ti,ab.	4047257
19	exp kidney/ or exp proteinuria/	400331
20	(kidney or renal or disease or insufficien* or failure* or nephro*).ti,ab.	5132016
21	or/18-20	8407973
22	(kidney or renal).mp. and (transplan* or graft*).ti.	94451
23	21 not 22	8319260
24	17 and 23	4571
25	(conference abstract or conference paper or conference review).pt.	0
26	24 not 25	4571
27	editorial/ or letter/ or case reports/ or comment/ or note/	4217780
28	26 not 27	4540

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Embase 1947-Present, updated daily

Steps	Terms	Hits
1	exp physical activity/ or exp exercise test/	623139
2	exp physical education/ or exp physical fitness/ or exp cardiorespiratory fitness/	65532
3	(exercise* or sport* or walking* or cycling or swimming or running or jogging or sedentary or inactiv*).ti,ab.	1279181
4	(physical* adj3 (activ* or inactiv* or treat* or exercis* or exertion*)).ti,ab.	260815
5	or/1-4	1707972
6	(controlled clinical trial).ti,ab.	24269
7	exp clinical trial/	1820578
8	(randomized controlled trial).ti.	71118
9	(randomized or trial).ti.	499542
10	exp cohort studies/	962599
11	(retrospective or prospective or longitudinal).ti.	484101
12	or/6-11	3118564
13	5 and 12	193380
14	(exp animal/ or nonhuman/) not exp human/	7826893
15	13 not 14	190775
16	(interven* or change* or traject* or shift* or switch* or alternat* or differen* or variat* or revamp*).ti,kw.	2269582
17	15 and 16	22019
18	(uremi* or uraemi* or albuminuria* or proteinuria* or urin* or albumin* or protein* or glomerular filtration rate* or ?GFR).ti,ab.	5179794
19	exp kidney/ or exp proteinuria/	643196
20	(kidney or renal or disease or insufficien* or failure* or nephro*).ti,ab.	7596748
21	or/18-20	11605916
22	(kidney or renal).mp. and (transplan* or graft*).ti.	156070
23	21 not 22	11459331
24	17 and 23	5916
25	(conference abstract or conference paper or conference review).pt.	5452713
26	24 not 25	4217
27	editorial/ or letter/ or case reports/ or comment/ or note/	2784877
28	26 not 27	4193

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Pubmed

Steps	Terms	Hits
1	"exercise"[mesh] OR "exercise test"[mesh]	291459
2	"Physical Education and Training"[mesh] OR "physical fitness"[mesh] OR "cardiorespiratory fitness"[mesh]	47747
3	(exercise*[tiab] OR sport*[tiab] OR walking*[tiab] OR "cycling"[tiab] OR "swimming"[tiab] OR "running"[tiab] OR "jogging"[tiab] OR "sedentary"[tiab] OR inactiv*[tiab])	991749
4	(physical*[tiab] AND (activ*[tiab] OR inactiv*[tiab] OR treat*[tiab] OR exercis*[tiab] OR exertion*[tiab]))	459726
5	#1 OR #2 OR #3 OR #4	1384590
6	("controlled clinical trial"[tiab])	18695
7	"clinical trial"[pt]	961591
8	("randomized controlled trial"[ti])	58192
9	("randomized"[ti] OR "trial"[ti])	353735
10	"cohort studies"[mesh]	2441995
11	("retrospective"[ti] OR "prospective"[ti] OR "longitudinal"[ti])	346215
12	#6 OR #7 OR #8 OR #9 OR #10 OR #11	3362395
13	#5 AND #12	210509
14	"animals"[mesh]	26116055
15	#13 NOT #14	8628
16	interven*[ti] OR change*[ti] OR traject*[ti] OR shift*[ti] OR switch*[ti] OR alternat*[ti] OR differen*[ti] OR variat*[ti] OR revamp*[ti]	1765363
17	#15 AND #16	1223
18	(uremi*[tiab] OR uraemi*[tiab] OR albuminuria*[tiab] OR proteinuria*[tiab] OR urin*[tiab] OR albumin*[tiab] OR protein*[tiab] OR glomerular filtration rate*[tiab] OR "eGFR"[tiab] OR "mGFR"[tiab])	4147077
19	"kidney"[mesh] OR "proteinuria"[mesh]	400520
20	("kidney"[tiab] OR "renal"[tiab] OR "disease"[tiab] OR insufficien*[tiab] OR failure*[tiab] OR nephro*[tiab])	5250858
21	#18 OR #19 OR #20	8585949
22	(("kidney"[tiab] OR "kidney"[mh]) OR ("renal"[tiab])) AND (transplan*[ti] OR graft*[ti])	87814
23	#21 NOT #22	8498135
24	#17 AND #23	295
25	"editorial"[pt] OR "letter"[pt] OR "comment"[pt]	2129064
26	#24 NOT #25	294

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Web of Science

Steps	Terms	Hits
1	TS=(physical activity OR exercise test OR physical fitness OR exercise OR sport OR sedentary OR inactive OR exertion)	2869900
2	TS=(controlled clinical trial OR clinical trail OR randomized controlled trial OR cohort study OR retrospective study OR prospective study OR longitudinal study)	4391262
3	#1 AND #2	230548
4	TS=(animal OR nonhuman OR non-human)	30545714
5	#3 NOT #4	118699
6	TS=(interven* or change* or traject* or shift* or switch* or alternat* or differen* or variat* or revamp*)	46832576
7	#5 AND #6	82111
8	TS=(uremi* or uraemi* or albumin* or proteinuria* or glomerular filtration rate* or eGFR or mGFR or kidney* or renal failure* or nephro*)	2677866
9	TS=(kidney or renal)	2378506
10	TS=(transplan* or graft*)	2270415
11	#9 AND #10	323241
12	#8 NOT #11	2405699
13	#7 AND #12	1320
14	TS=(editorial or letter or case report* or comment)	3433986
15	#13 NOT #14	1267

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Table S2 General characteristics of the included studies

Author, year	Study type	Country	Exercise Group Characteristics	Baseline Size of Exercise Group	Attrition	Study Population Age	Type of Exercise	Exercise Frequency	Exercise Length	Exercise Intensity	Kidney-relevant outcome	Findings
de Oliveira *et al.*[40], 2012	RCT	Brazil	Patients with type 2 diabetes mellitus of a diabetes ambulatory clinic.	Aerobic training: 12 people Strength training: 12 people Combination training: 12 people	Aerobic training: 9.1% Strength training: 16.7% Combination training: 16.7%	Mean (SD), years: Aerobic training: 52.09 (8.71) Strength training: 54.10 (8.94) Combined training: 57.90 (9.82)	Aerobic training, strength training, and combined training	One hour/session, three sessions/week	12 weeks	Not used VO2peak in aerobic and combined training due to unable to get accurate value, used lactate threshold. Strength training: 50% of 1 RM for the Week 1&2, 8-12 RM for Week 3&4.	Urea	Pre/Post Exercise, mean (SD), mg/dL Aerobic training: Urea 29.27 (5.93) / 28.18 (6.36) Strength training: Urea 31.00 (10.56) / 29.90 (8.82) Combined training: Urea 34.40 (9.91) / 35.20 (9.40)
Geyssant *et al.* [44], 1981	CT	France	Healthy male.	4 people	0%	Mean (SD), years: 36 (6.4)	Aerobic	One hour/session, four sessions/week	5 months	87% VO2max	PRA	Pre/Post Exercise, mean (SD), ng/l/mn PRA, 106.08 (48.48)/ 62.5 (49.9)
Hagberg *et al.* [30], 1989	RCT	United States of America	Patients with essential hypertension.	Low-intensity: 14 people Moderate-intensity: 10 people	Low-intensity: 21.4% Moderate-intensity: 0%	Mean (SD), years: all groups 64 (3)	Aerobic	Low-intensive: one hour/session, max three sessions/week Moderate-intensive: 45 to 60 minutes/session, 3 sessions/week for at least the last 4-5 months of training	9 months	Low-intensity: 50% VO2max Moderate-intensity: 70-85% VO2max	PRA	Pre/Post Exercise, mean (SD), ng/ml/hr Low-intensity: PRA 1.6 (1.1) / 0.7 (0.4) Moderate-intensity: PRA 2.0 (1.3) / 1.1 (0.9)
Kinoshita *et al.* [36], 1991	CT	Japan	Patients with essential hypertension.	12 people	0%	Mean (SD), years: 51.7 (2.3)	Aerobic	One hour/session, three sessions/week	10 weeks	50% VO2max	PRA, eGFR	Pre/Post Exercise, mean (SE), ng/ml/h PRA 1.3 (0.2) / 1.26 (0.4) Pre/Post Exercise, mean (SE), ml/min eGFR 99 (4.7) / 105 (5.2)

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Kiyonaga *et al.* [31], 1985	CT	Japan	Patients with essential hypertension.	12 people	At 10 weeks: 0% At 20 weeks: 25%	Mean (Range), years: 46 (34 to 56)	Aerobic	One hour/session, three sessions/week	20 weeks	Used lactate threshold, but claimed to have a 50% VO2max although data were not published.	PRA Ang II	Pre/Post Exercise, mean (SE), ng/ml/hr PRA 11 (4) / 13 (3) Pre/Post Exercise, mean (SE), pg/ml Ang II 58 (8) / 91 (12)
Koga *et al.* [37], 1992	CT	Japan	Female atients with essential hypertension	10 people	0%	Mean (SEM), years: 49 (2)	Aerobic	One hour/session, three sessions/week	10 weeks	50% VO2max	PRA	Pre/Post Exercise, mean (SE), ng/ml/h PRA 0.77 (0.19) / 0.4 (0.1)
Martinelli *et al.* [34], 2010	CT	Brazil	Overweight patients with hypertension.	20 people	0%	Mean (SD), years: 57 (7.1)	Aerobic	40 min/session, three sessions/week	16 weeks	60-80% HRmax	PRA	Pre/Post Exercise, median (IQR), ng/ml/h PRA 0.8 (0.45 - 2.0) / 1.45 (0.8 - 2.15)
Matsusaki *et al.* [38], 1992	CT	Japan	Patients with hypertension.	Low-workload: 16 people High-workload: 14 people	Low-workload: 0% High-workload: 28.6%	Mean (SEM), years all groups 47.2 (1.5)	Aerobic	Low-workload: one hour/session, three sessions/week High-workload: 30-40 min/session, three sessions per week	10 weeks	Low-workload: 50% VO2max High-workload: 75% VO2max	PRA	Pre/Post Exercise, mean (SE), ng/ml/h Low-workload: PRA 0.82 (0.22) / 0.62 (0.27) High-workload: PRA 1.26 (0.15) / 1.47 (0.16)
Nelson *et al.* [39], 1986	CT	Australia	Patients with essential hypertension of a risk-evaluation clinic.	17 people	23.5%	Mean (Range) years: 44 (25 to 62)	Aerobic	Three levels of activity for one month each successively. First month: normal sedentary, no training Second month: 45 min/session, three sessions/week Third month: 45 min/session, seven sessions/week	2 months (exclude the first sedentary month)	60-70% VO2max	PRA	Pre/Post Exercise, mean (SEM), ng/ml/h PRA 1.45 (0.51) / 1.46 (0.30)

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Passino *et al.* [45], 2006	RCT	Italy	Patients with heart failure.	47 people	6.4%	Mean (SD), years: 60 (2)	Aerobic	Minimum 30 min/day, three days/week	9 months	Heart rate at 65% VO2max	PRA	Pre/Post Exercise, mean (SD), ng/ml/h PRA 3.04 (0.66) / 2.96 (0.62)
Sikiru and Okoye [33], 2014	RCT	Nigeria	Patients with essential hypertension of a hypertensive clinic.	162 people	30.9%	Mean (SD), years: 58.63 (7.22)	Aerobic	45 min/session, three sessions/week for Week 1 and 2 One hour/session, three sessions/week, for Week 3-8	8 weeks	60-79% of HR reserve	SCr	Pre/Post Exercise, mean (SD), mg/dL SCr 0.81 (0.17) / 0.85 (0.39)
Sullivan *et al.* [35], 1992	CT	United States of America	Male patients with uncomplicated essential hypertension.	15 people	0%	Mean (SD), years: 42.3 (1.0)	Strenuous Aerobic	18 min/session, three sessions/week	6 weeks	90% HRmax	PRA	Pre/Post Exercise, mean (SE), ng/ml/h PRA 1.9 (0.3) / 1.94 (0.4)
Szulinska *et al.* [42], 2016	RCT	Poland	Women with obesity.	Endurance training: 22 people Endurance+strength training: 22 people	Endurance training: 4.5% Endurance+strength training: 22.7%	Mean (SD), years: Endurance 51 (8.3) Endurance+strength 48.2 (11.2)	Endurance and Endurance+strength training	One hour/session, three sessions/week	3 months	Endurance group: 50-80% HRmax Endurance+strength group: 50-80% HRmax for endurance training, unclear intensity for strength exercise.	SCr eGFR UACR	Pre/Post Exercise, mean (SD) Endurance group SCr, mg/dL 0.76 (0.11) / 0.84 (0.11) eGFR-MDRD, 87.81 (18.43) / 77.90 (12.65) eGFR-CG, 129.47 (33.24) / 114.02 (24.98) UACR, mg/mmol cr 1.19 (2.32) / 1.28 (2.42) Endurance+strength group SCr, mg/dL 0.73 (0.10) / 0.81 (0.10) eGFR-MDRD, 93.58 (17.87) / 82.54 (12.01) eGFR-CG, 143.91 (36.69) / 124.65 (26.71) UACR, mg/mmol

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												cr 0.76 (0.28) / 0.65 (0.28)
Trabelsi *et al.* [43], 2012	CT	Turnisa	Male recreational bodybuilders.	non-faster: 7 people	0%	Mean (SD), years: non-faster 26 (3)	Resistance	Four sessions/week	1 month	Four sets with a load of 10 RM for each exercise.	Urea SCr	Pre/Post Exercise, mean (SD), mmol/L Urea 4.51 (0.32) / 4.5 (0.26) Pre/Post Exercise, mean (SD), μmol/L SCr 91.14 (4.45) / 94.29 (4.31)
Urata *et al.* [32], 1987	RCT	Japan	Patients with essential hypertension.	10 people	0%	Mean (SE), years: 51.4 (2.8)	Aerobic	One hour/session, three sessions/week	10 weeks	40-60% VO2max	PRA	Pre/Post Exercise, mean (SE), ng/mL/min PRA 1.24 (0.24) / 1.50 (0.39)
Zaman *et al.*[41], 2021	RCT	Saudi Arabia	Obese and non-obese male people.	Obese resistance training: 25 Non-obese resistance training: 25	Obese resistance training: 20% Non-obese resistance training: 20%	Range, years: 35 to 60	Resistance	50 min/session, three days/week	12 weeks	50-70% of 1 RM	Urea	Pre/Post Exercise, mean (SD), mg/dl Obese people Urea 33.33 (3.57) / 32.27 (2.54),

Ang II,angiotensin II; CT, clinical trial; eGFR, estimated glomerular filtration rate; HR, heart rate; PRA, plasma renin activity; RCT, randomized clinical trial; RM, repetition maximum; SCr, serum creatinine; SD, standard deviation;SE, standard error; UARC, urine albumin-to-creatinine ratio; VO2, maximum rate of oxygen.

Note: Conversion factors for units: serum creatinine in mg/dL to μmol/L, ×88.4; urea nitrogen in mg/dL to mmol/L, ×0.357.

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Table S3 Cochrane Risk of Bias Assessment Form

Author, Year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias): Self-reported outcomes	Blinding of outcome assessment (detection bias): Objective measures	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Other bias	Overall
de Oliveira *et al.*[40], 2012	Unclear	Low	High	Not applicable	Low	Low	Low	Low	Low
Geyssant *et al.*[44], 1981	Not applicable	Not applicable	High	Not applicable	Low	Low	Low	Low	Low
Hagberg *et al.*[30], 1989	Unclear	Low	High	Not applicable	Low	High	Low	Low	High
Kinoshita *et al.*[36], 1991	Not applicable	Not applicable	High	Not applicable	Low	Low	Low	Low	Low
Kiyonaga *et al.*[31], 1985	Not applicable	Not applicable	High	Not applicable	Low	High	Low	Low	High
Koga *et al.*[37], 1992	Not applicable	High	High	Not applicable	Low	Low	Low	Low	High
Martinelli *et al.*[34], 2010	Not applicable	Not applicable	High	Not applicable	Low	Low	Low	Low	Low
Matsusaki *et al.*[38], 1992	Unclear	Low	High	Not applicable	Low	High	Low	Low	High
Nelson *et al.*[39], 1986	Not applicable	Not applicable	High	Not applicable	Low	High	Low	Low	High
Passino *et al.*[45], 2006	Unclear	Low	High	Not applicable	Low	Low	Low	Low	Low
Sikiru and Okoye[33], 2014	High	High	High	Not applicable	Low	High	Low	Low	High

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Sullivan *et al.*[35], 1992	Not applicable	Not applicable	High	Not applicable	Low	Low	Low	Low	Low
Szulinska *et al.*[42], 2016	Low	Low	High	Not applicable	Low	High	Low	Low	High
Trabelsi *et al.*[43], 2012	Unclear	High	High	Not applicable	Low	Low	Low	Low	High
Urata *et al.*[32], 1987	Unclear	Low	High	Not applicable	Low	Low	Low	Low	Low
Zaman *et al.*[41], 2021	Low	Unclear	High	Not applicable	Low	High	High	Low	High

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Figure S1 PRISMA workflow

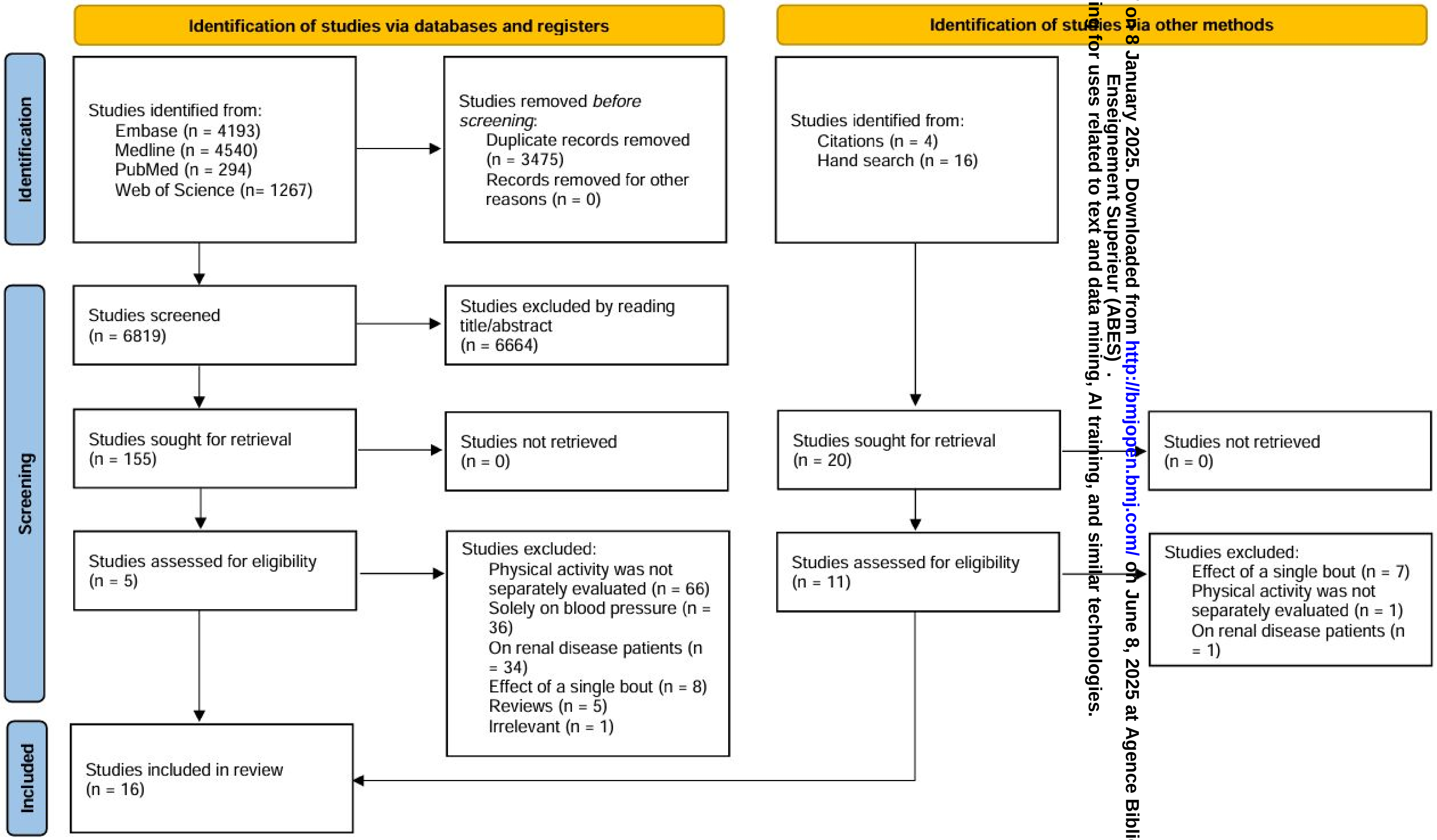

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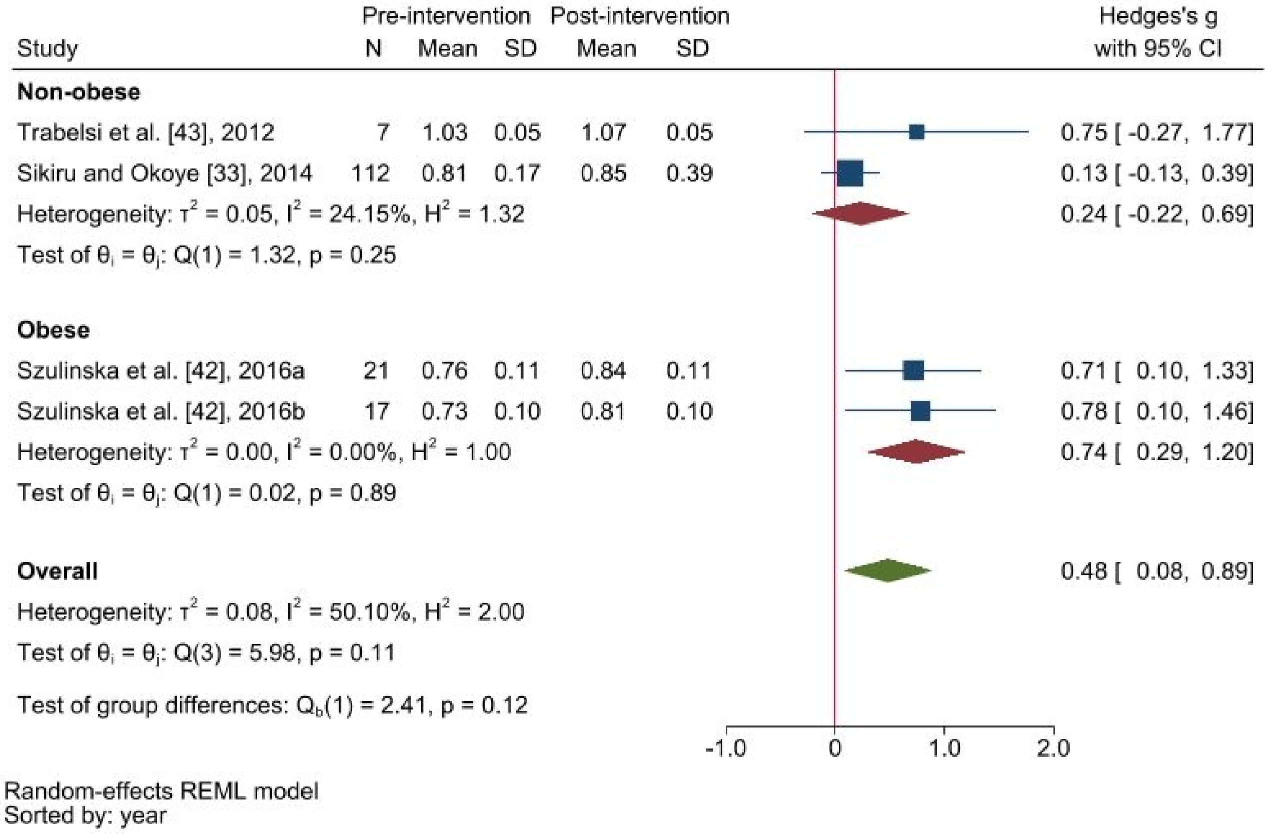
Figure S2a Obesity stratified meta-analysis on the association of changes in physical activity with serum creatinine.



Szulinska *et al.* [42], 2016a: Patients received endurance training.

Szulinska *et al.* [42], 2016b: Patients received both endurance and strength training.

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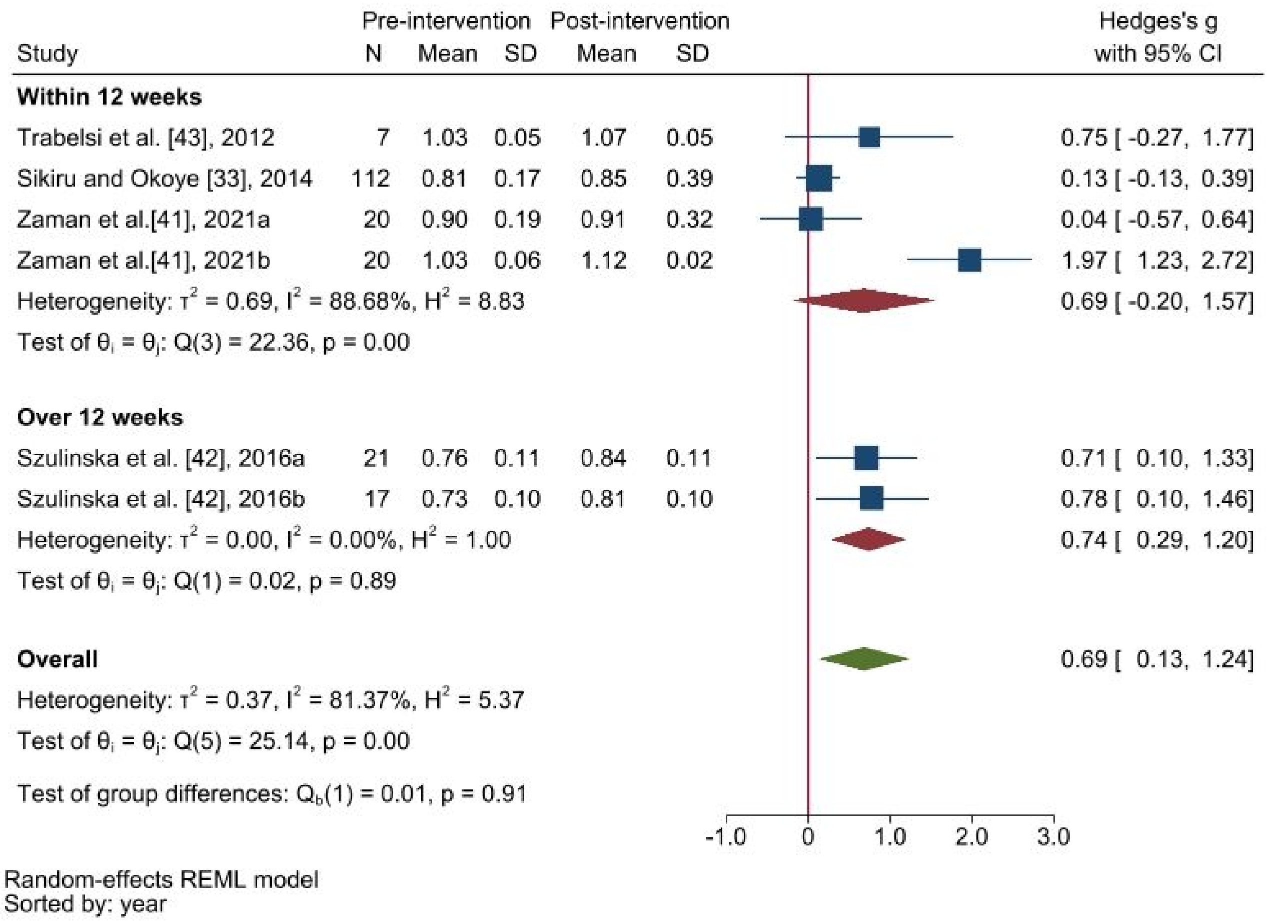
Figure S2b Exercise duration stratified meta-analysis on the association of changes in physical activity with serum creatinine.



Szulinska *et al.* [42], 2016a: Patients received endurance training.

Szulinska *et al.* [42], 2016b: Patients received both endurance and strength training.

Zaman *et al.* [41], 2021a: Patients with obesity

Zaman *et al*.[41], 2021b: Patients without obesity

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Figure S2c. Funnel plot of studies on the association of changes in physical activity with serum creatinine

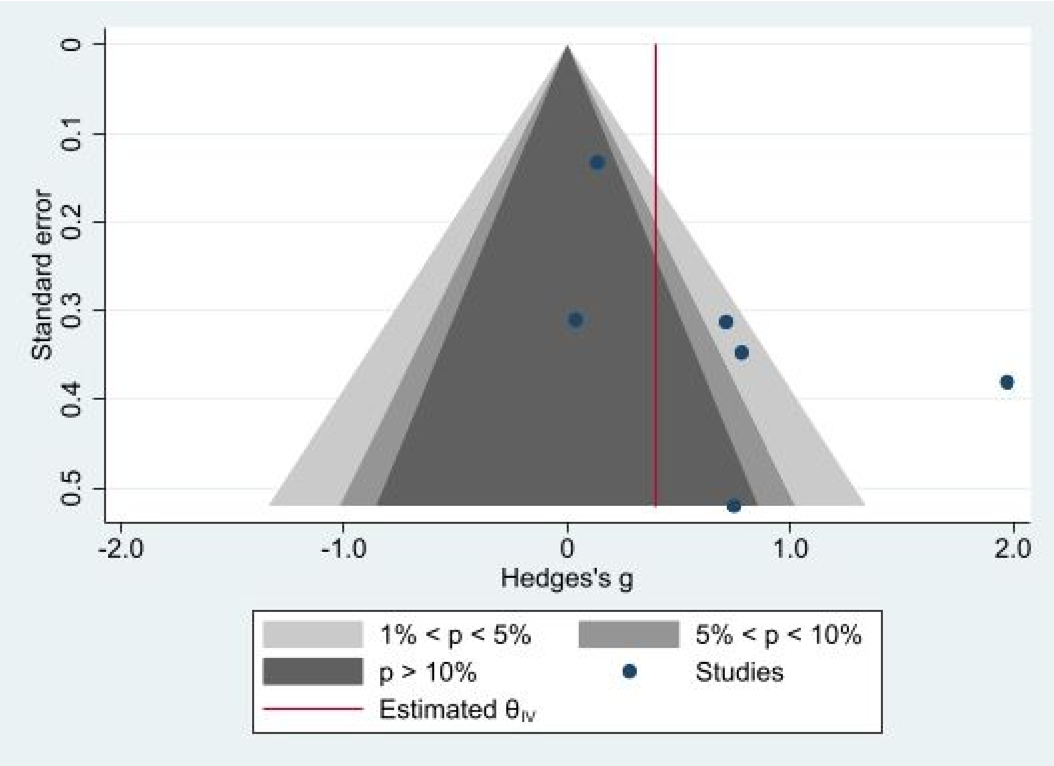
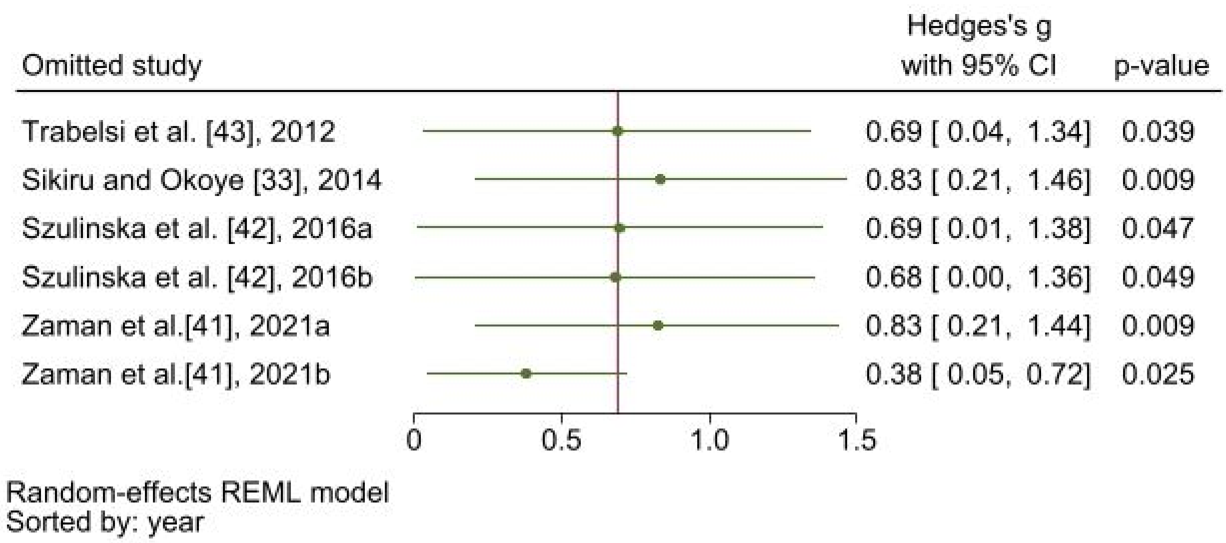


Figure S2d Leave-one-out figure of studies on the association of changes in physical activity with serum creatinine



Szulinska *et al.* [42], 2016a: Patients received endurance training.

Szulinska *et al.* [42], 2016b: Patients received both endurance and strength training.

Zaman *et al.* [41], 2021a: Patients with obesity

Zaman *et al.*[41], 2021b: Patients without obesity

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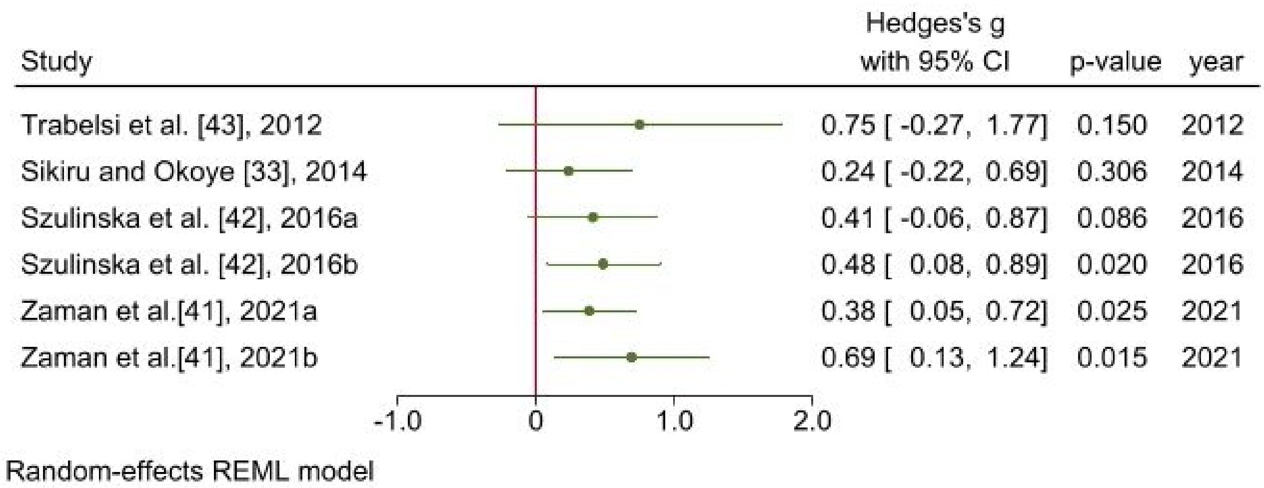
Figure S2e Cumulative meta-analysis of the association of changes in physical activity with serum creatinine



Szulinska *et al.* [42], 2016a: Patients received endurance training.

Szulinska *et al.* [42], 2016b: Patients received both endurance and strength training.

Zaman *et al.* [41], 2021a: Patients with obesity

Zaman *et al*.[41], 2021b: Patients without obesity

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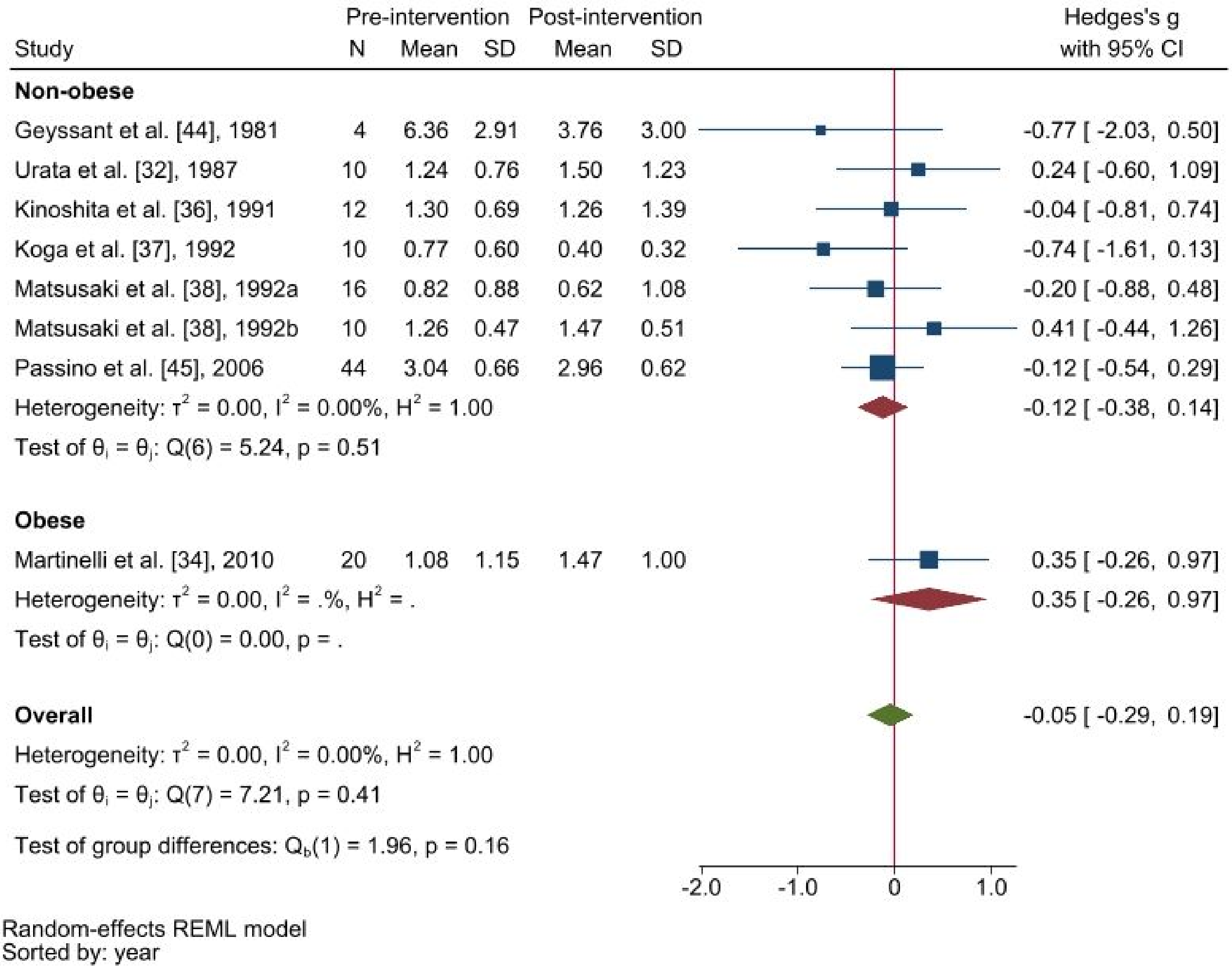
Figure S3a Obesity stratified meta-analysis on the association of changes in physical activity with plasma renin activity



Matsusaki *et al.*[38], 1992a: Patients performed low-workload physical activity.

Matsusaki *et al.*[38], 1992b: Patients performed high-workload physical activity.

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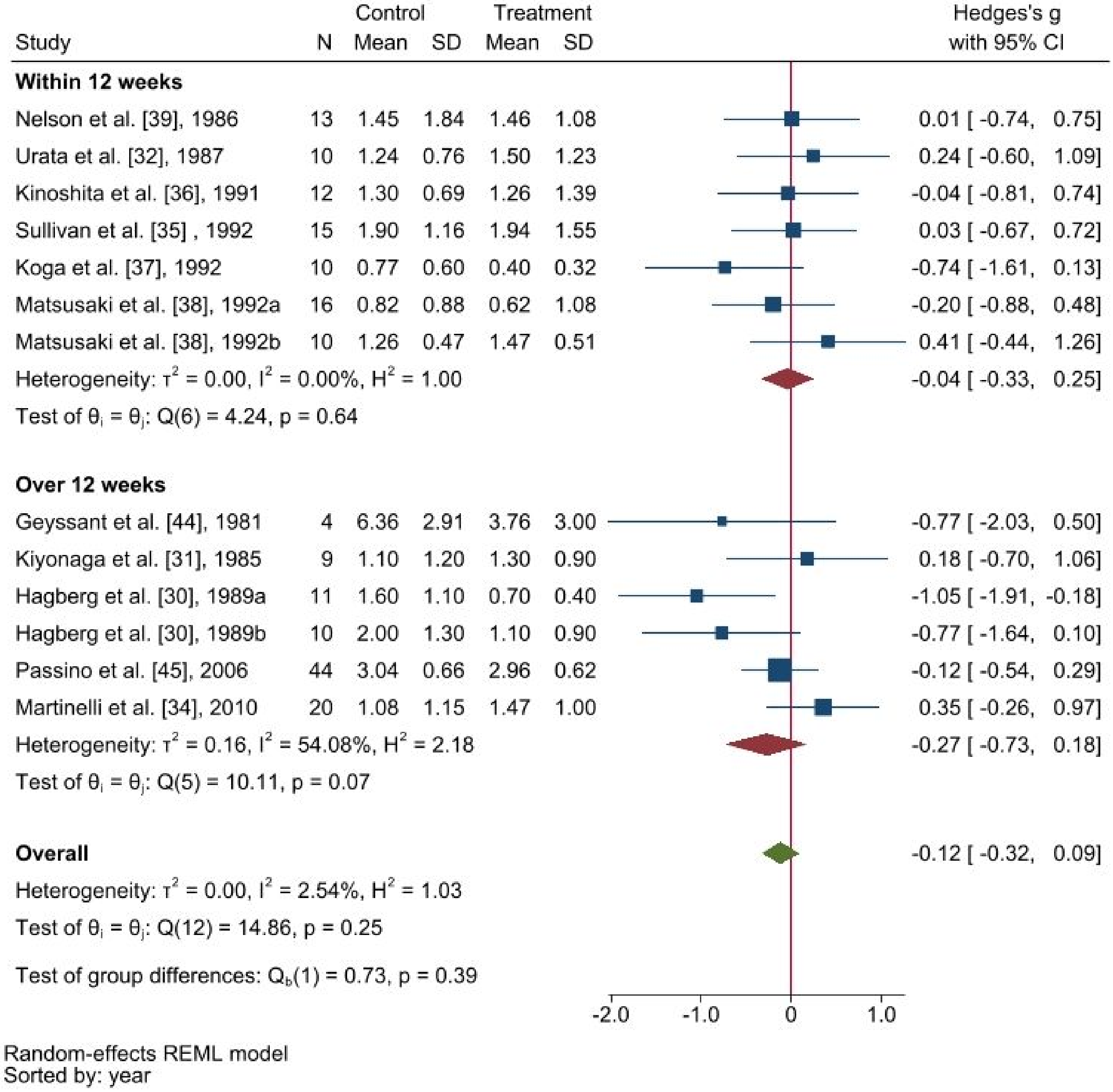
Figure S3b Exercise duration stratified meta-analysis on the association of changes in physical activity with plasma renin activity



Study	N	Control Mean	Control SD	Treatment Mean	Treatment SD	Hedges's g with 95% CI
Within 12 weeks						
Nelson et al. [39], 1986	13	1.45	1.84	1.46	1.08	0.01 [-0.74, 0.75]
Urata et al. [32], 1987	10	1.24	0.76	1.50	1.23	0.24 [-0.60, 1.09]
Kinoshita et al. [36], 1991	12	1.30	0.69	1.26	1.39	-0.04 [-0.81, 0.74]
Sullivan et al. [35] , 1992	15	1.90	1.16	1.94	1.55	0.03 [-0.67, 0.72]
Koga et al. [37], 1992	10	0.77	0.60	0.40	0.32	-0.74 [-1.61, 0.13]
Matsusaki et al. [38], 1992a	16	0.82	0.88	0.62	1.08	-0.20 [-0.88, 0.48]
Matsusaki et al. [38], 1992b	10	1.26	0.47	1.47	0.51	0.41 [-0.44, 1.26]
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$						-0.04 [-0.33, 0.25]
Test of $\theta_i = \theta_j$: Q(6) = 4.24, p = 0.64						
Over 12 weeks						
Geyssant et al. [44], 1981	4	6.36	2.91	3.76	3.00	-0.77 [-2.03, 0.50]
Kiyonaga et al. [31], 1985	9	1.10	1.20	1.30	0.90	0.18 [-0.70, 1.06]
Hagberg et al. [30], 1989a	11	1.60	1.10	0.70	0.40	-1.05 [-1.91, -0.18]
Hagberg et al. [30], 1989b	10	2.00	1.30	1.10	0.90	-0.77 [-1.64, 0.10]
Passino et al. [45], 2006	44	3.04	0.66	2.96	0.62	-0.12 [-0.54, 0.29]
Martinelli et al. [34], 2010	20	1.08	1.15	1.47	1.00	0.35 [-0.26, 0.97]
Heterogeneity: $\tau^2 = 0.16$, $I^2 = 54.08\%$, $H^2 = 2.18$						-0.27 [-0.73, 0.18]
Test of $\theta_i = \theta_j$: Q(5) = 10.11, p = 0.07						
Overall						-0.12 [-0.32, 0.09]
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 2.54\%$, $H^2 = 1.03$						
Test of $\theta_i = \theta_j$: Q(12) = 14.86, p = 0.25						
Test of group differences: $Q_b(1) = 0.73$, p = 0.39						

Hagberg *et al.* [30], 1989a: Patients performed low-intensity physical activity.

Hagberg *et al.* [30], 1989b: Patients performed moderate-intensity physical activity.

Matsusaki *et al.*[38], 1992a: Patients performed low-workload physical activity.

Matsusaki *et al.*[38], 1992b: Patients performed high-workload physical activity.

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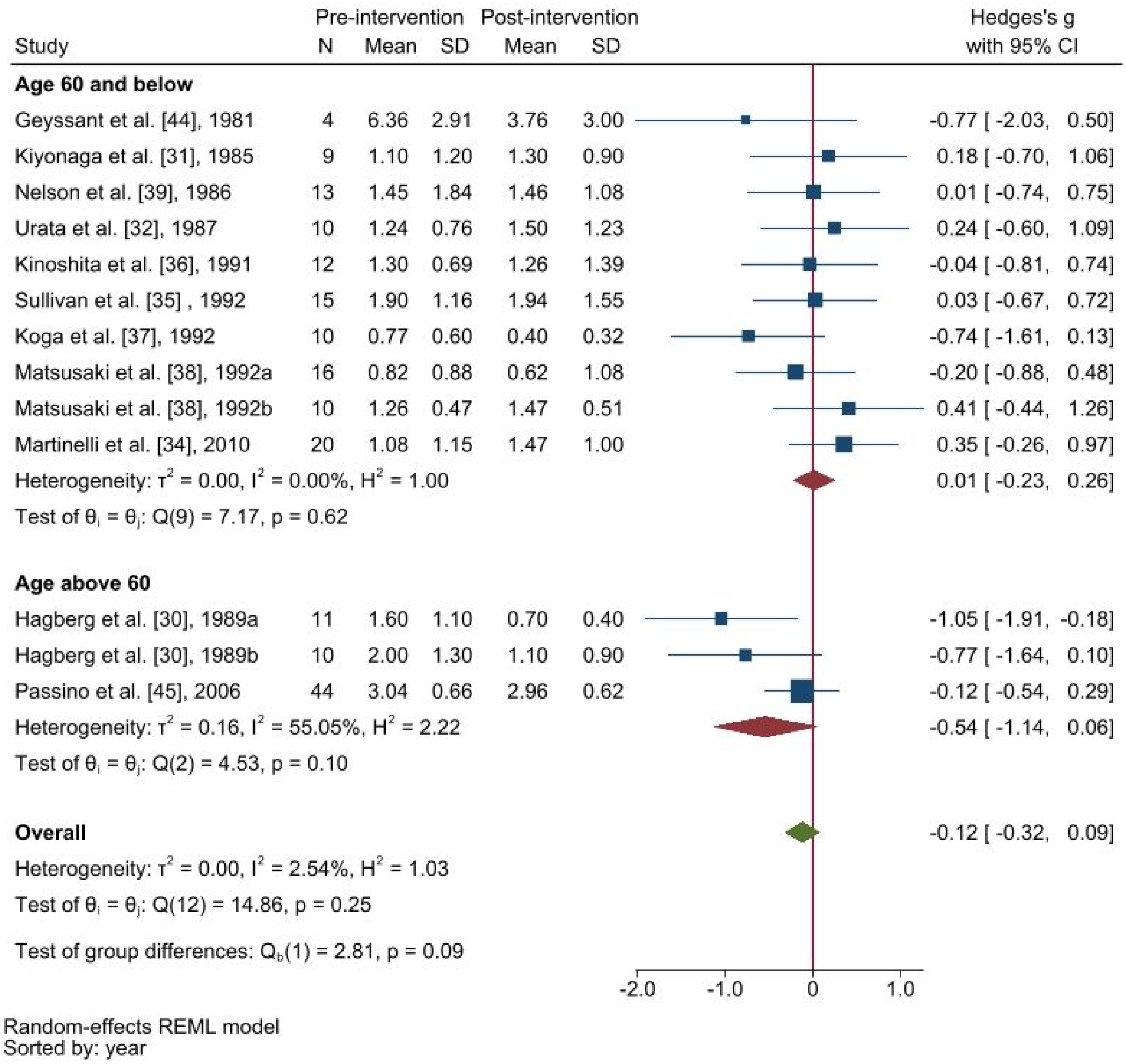
Figure S3c Age stratified meta-analysis on the association of changes in physical activity with plasma renin activity



Hagberg *et al.* [30], 1989a: Patients performed low-intensity physical activity.

Hagberg *et al.* [30], 1989b: Patients performed moderate-intensity physical activity.

Matsusaki *et al.*[38], 1992a: Patients performed low-workload physical activity.

Matsusaki *et al.*[38], 1992b: Patients performed high-workload physical activity.

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Figure S3d. Funnel plot of studies on the association of changes in physical activity plasma renin activity

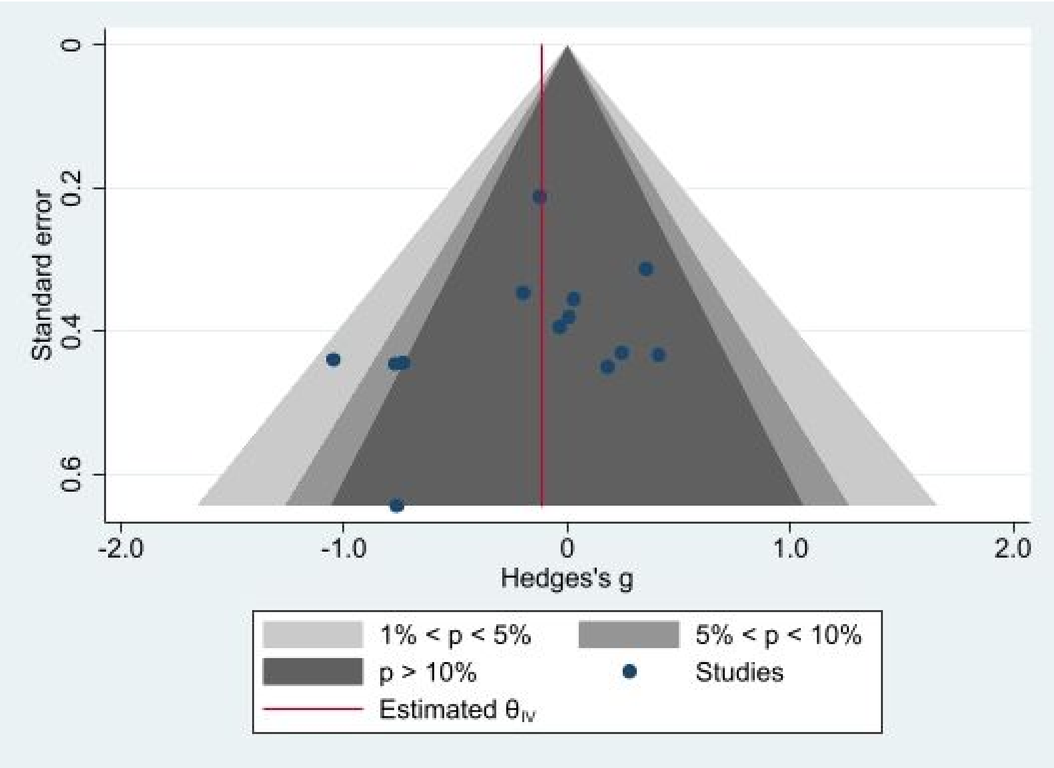

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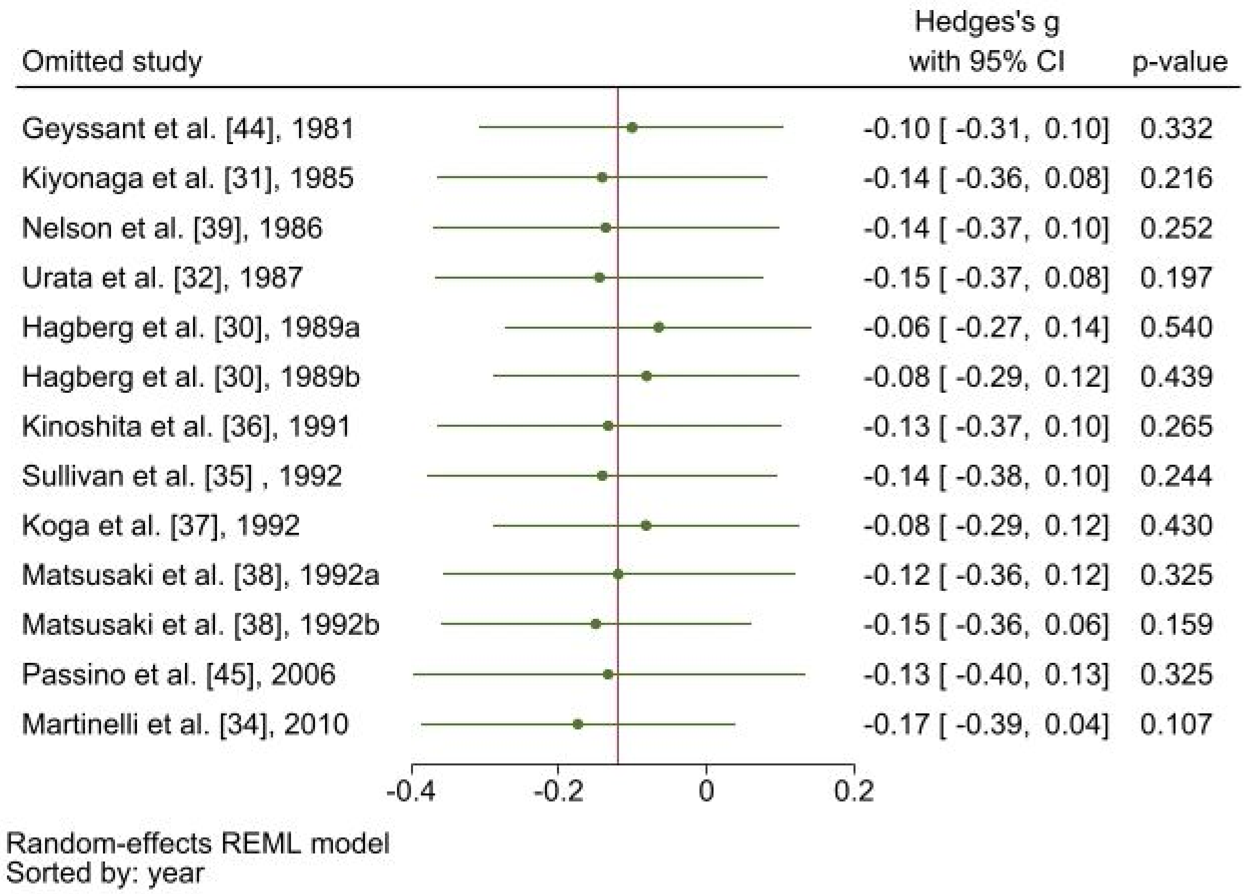
Figure S3e. Leave-one-out figure of studies on the association of changes in physical activity with plasma renin activity



Hagberg *et al.* [30], 1989a: Patients performed low-intensity physical activity.

Hagberg *et al.* [30], 1989b: Patients performed moderate-intensity physical activity.

Matsusaki *et al.*[38], 1992a: Patients performed low-workload physical activity.

Matsusaki *et al.*[38], 1992b: Patients performed high-workload physical activity.

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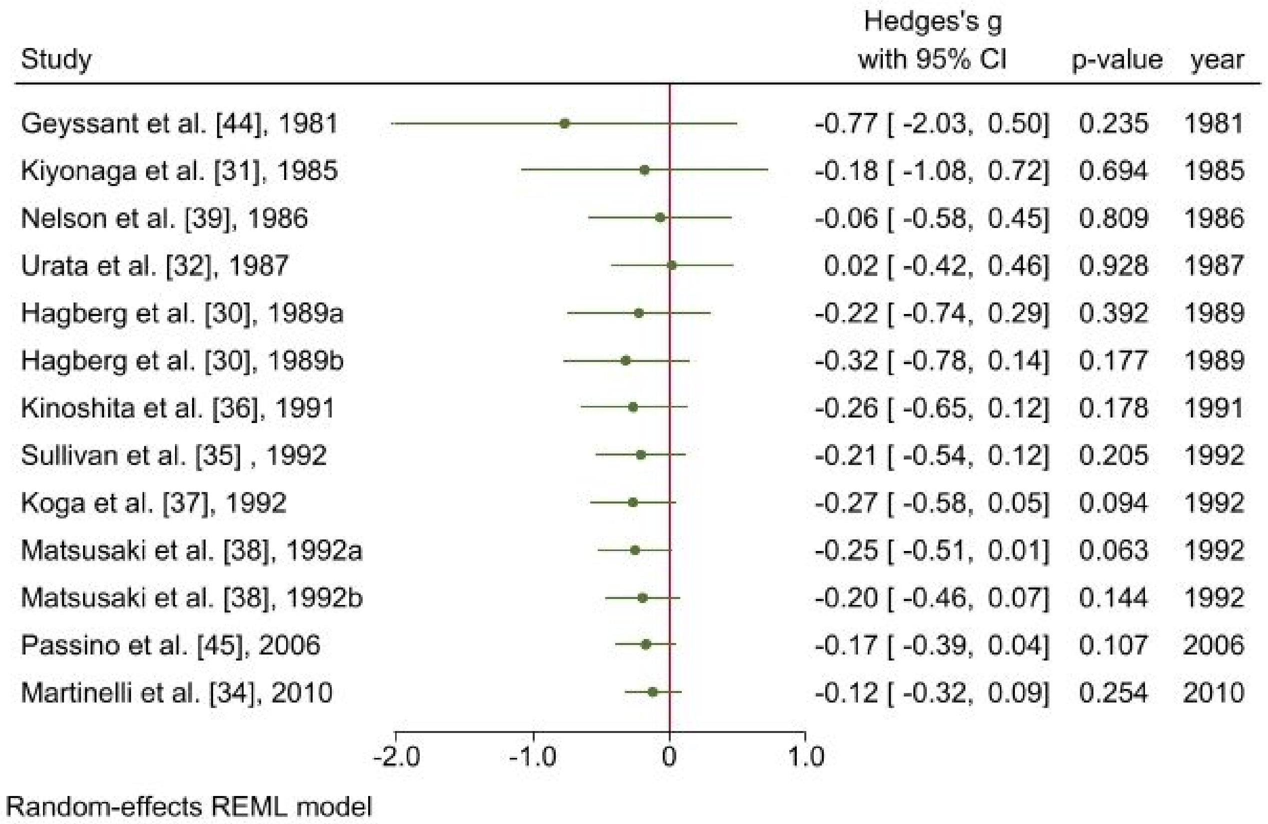
Figure S3f. Cumulative meta-analysis on the association of changes in physical activity with plasma renin activity



Hagberg *et al.* [30], 1989a: Patients performed low-intensity physical activity.

Hagberg *et al.* [30], 1989b: Patients performed moderate-intensity physical activity.

Matsusaki *et al.*[38], 1992a: Patients performed low-workload physical activity.

Matsusaki *et al.*[38], 1992b: Patients performed high-workload physical activity.

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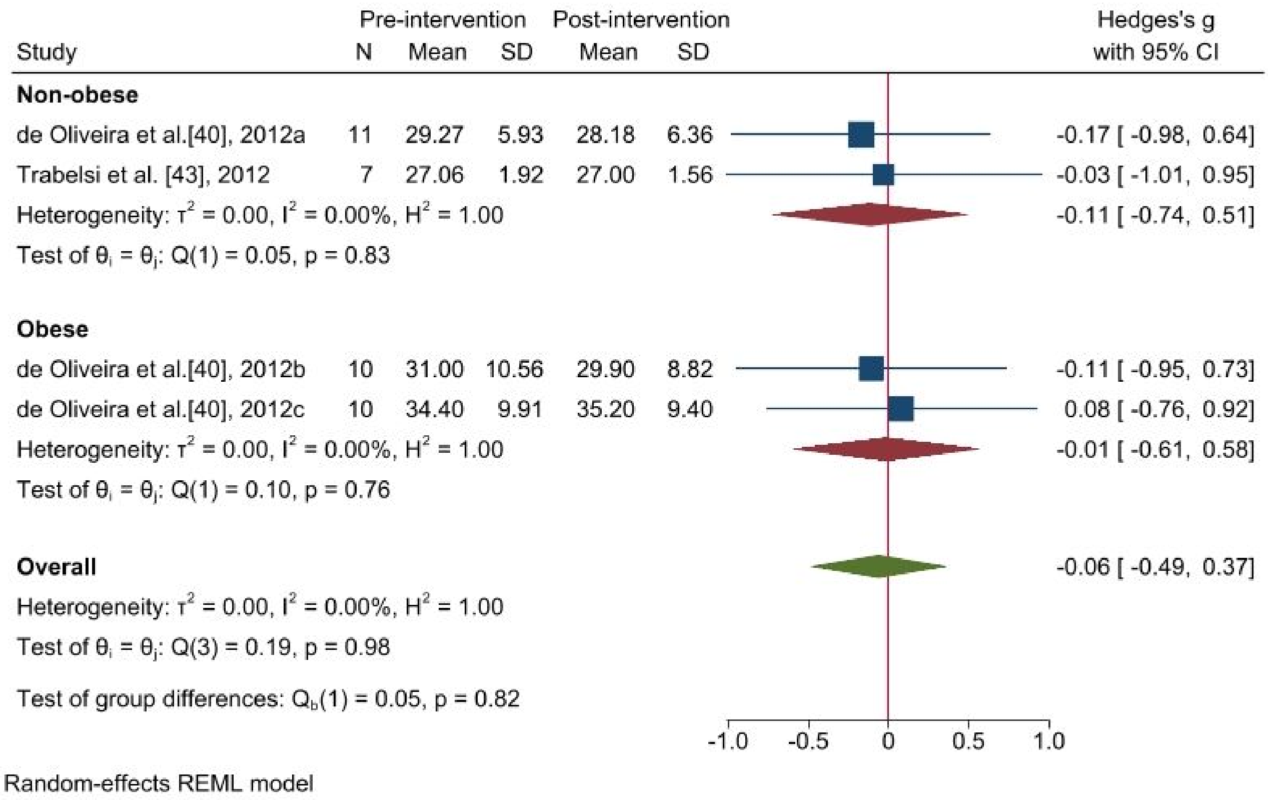
Figure S4a Obesity stratified meta-analysis on the association of changes in physical activity with urea



de Oliveira *et al.* [40], 2012a: Patients performed aerobic training.

de Oliveira *et al.* [40], 2012b: Patients performed strength training.

de Oliveira *et al.* [40], 2012c: Patients performed aerobic and strength training.

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Figure S4b Funnel plot of studies on the association of changes in physical activity with urea

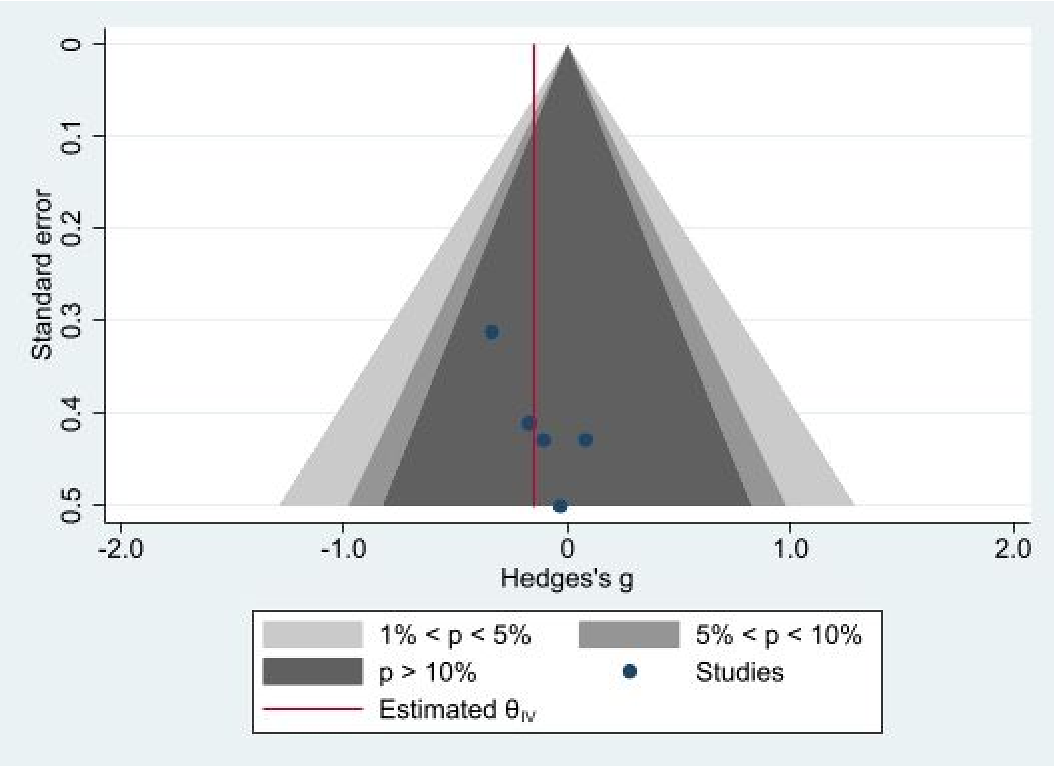
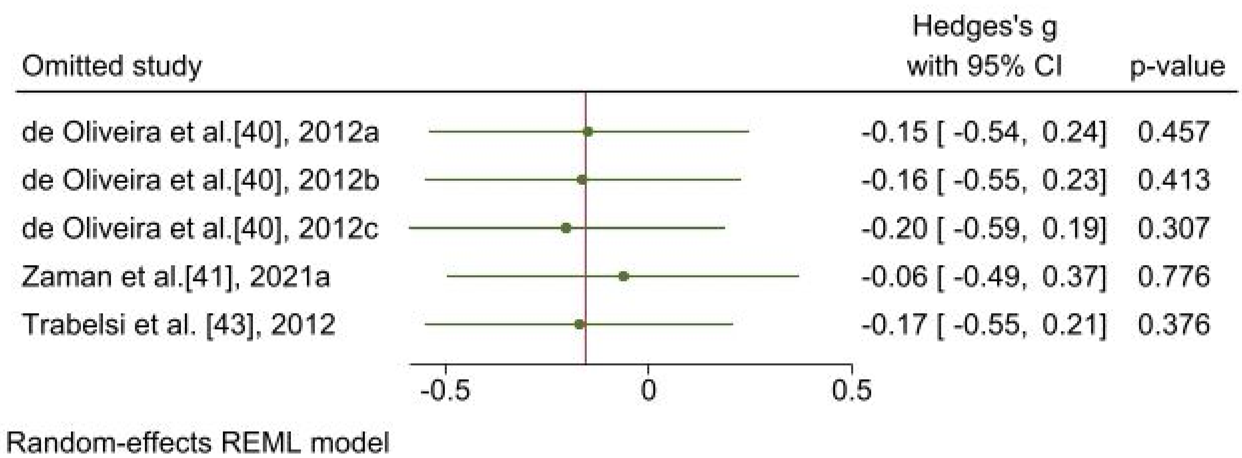


Figure S4c Leave-one-out figure of studies on the association of changes in physical activity with urea



de Oliveira *et al.* [40], 2012a: Patients performed aerobic training.

de Oliveira *et al.* [40], 2012b: Patients performed strength training.

de Oliveira *et al.* [40], 2012c: Patients performed aerobic and strength training.

Zaman *et al.* [41], 2021a: Patients with obesity

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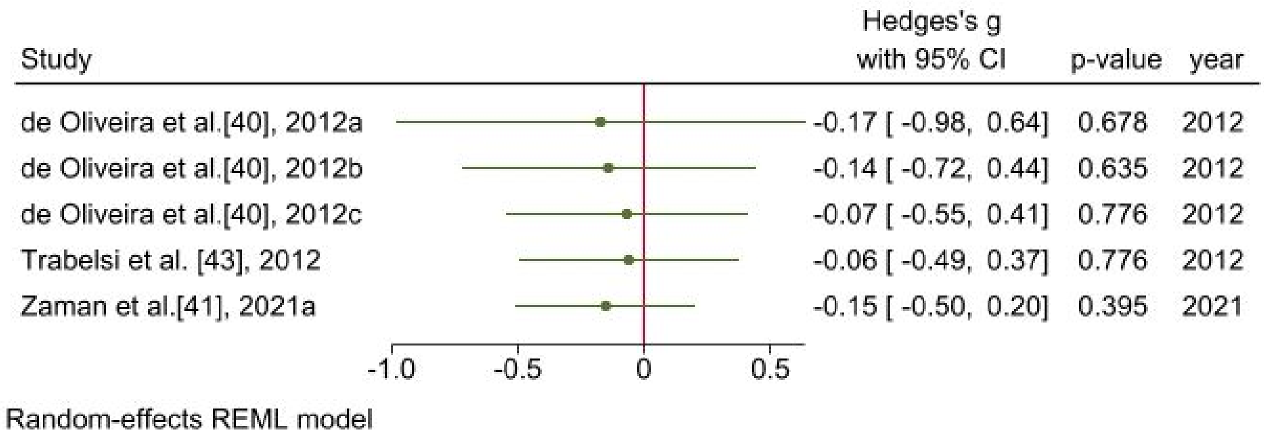
Figure S4d Cumulative meta-analysis on the association of changes in physical activity with urea



de Oliveira *et al.* [40], 2012a: Patients performed aerobic training.

de Oliveira *et al.* [40], 2012b: Patients performed strength training.

de Oliveira *et al.* [40], 2012c: Patients performed aerobic and strength training.

Zaman *et al.* [41], 2021a: Patients with obesity

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