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# Saudi Consensus on the Usage of Sodium-Glucose Cotransporter-2 Inhibitors on the Management of Chronic Kidney Diseases

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## Abstract

According to recent epidemiological data, chronic kidney diseases (CKDs) affect approximately 10% of the global population. Like many countries, CKD is a significant public health issue in Saudi Arabia. The prevalence of CKD in Saudi Arabia is estimated to be around 4.5% of the adult population, with a higher prevalence in older age groups. Sodium-glucose cotransporter-2 inhibitors (SGLT2is) are a class of oral medications used to treat type 2 diabetes mellitus (T2DM). In addition to their glucose-lowering effects, SGLT2i have been shown to have beneficial effects on kidney function in patients with or without T2DM. Therefore, a Saudi task force gathered to develop an explicit, evidence-based consensus on SGLT2i use in CKD Saudi patients. A panel of 14 experts made up a task force. An initial concept proposal was obtained. The proposal was divided into several topics discussed on 24 May 2023. A literature review was carried out. The literature search was completed on 3rd

June 2023. A drafted report was distributed to the entire panel. Approval of the recommendations required consensus, defined as a majority approval (*i.e.* above 75%). The recommendations were revised to accommodate any differences of opinion until a consensus was reached. Recommendations were finally formulated on 21st June 2023. Subsequently, the panel reviewed and discussed the supporting rationale of the revised recommendations. This article presents these practical recommendations.

## Keywords

Chronic Kidney Disease, Sodium-Glucose Cotransporter-2 Inhibitors, Adverse Effects, Monitoring, Canagliflozin, Dapagliflozin, Empagliflozin

## 1. Introduction

### 1.1. Chronic Kidney Disease and Its Prevalence

Chronic kidney disease (CKD) is a common and serious health problem characterized by the gradual loss of kidney function over time [1]. According to recent epidemiological data, CKD affects approximately 10% of the global population, with an estimated 800 million people worldwide living with the condition [2]. CKD is more common in older adults and is often associated with other chronic conditions such as diabetes (DM) and hypertension. A comprehensive systematic review and meta-analysis of 100 studies comprising almost seven million patients reported a global prevalence of 13.4% for CKD stages 1 - 5 and 10.6% for CKD stages 3 - 5. The prevalences of the individual CKD stages were 3.5% (stage 1), 3.9% (stage 2), 7.6% (stage 3), 0.4% (stage 4), and 0.1% (stage 5), respectively [3].

Like many countries, CKD is a significant public health issue in Saudi Arabia [1]. The prevalence of CKD in Saudi Arabia is estimated to be around 4.5% of the adult population, with a higher prevalence in older age groups. The study also found that DM and hypertension were the most common risk factors for CKD, with rates of both conditions increasing in recent years [4].

More efforts are needed to prevent and manage the tremendous burden of CKD. Therefore, efforts to prevent and manage CKD in Saudi Arabia and around the world include early detection and treatment of risk factors such as DM and hypertension, lifestyle modifications such as healthy diet habits and regular exercise, and medication management to slow the progression of CKD [1] [5].

### 1.2. Brief Overview of SGLT2 Inhibitors

Sodium-glucose cotransporter-2 inhibitors (SGLT2is) are a class of oral medications used to treat type 2 diabetes mellitus (T2DM). They work by inhibiting glucose reabsorption in the kidneys, increasing urinary glucose excretion, and lowering blood glucose levels. By promoting glucose excretion, SGLT2is lead to

modest weight loss and lower blood pressure. The first SGLT2i, canagliflozin, was approved by the US Food and Drug Administration (FDA) in 2013. Since then, several other SGLT2is have been approved, including dapagliflozin, empagliflozin, ertugliflozin, and sotagliflozin. These medications are typically taken once daily, usually in the morning, and can be used alone or in combination with other antidiabetic medications such as metformin or insulin [6] [7] [8].

In addition to their glucose-lowering effects, SGLT2is have been shown to have beneficial effects on cardiovascular (CV) outcomes and kidney function in patients with T2DM and established cardiovascular disease (CVD) or CKD [6] [7]. These benefits have led to the use of SGLT2is in patients at high risk for CVD or kidney complications.

While generally well-tolerated, SGLT2is can cause adverse effects such as genital mycotic infections, urinary tract infections, and an increased risk of diabetic ketoacidosis in certain populations [8]. As with any medication, the benefits and risks of SGLT2is should be weighed carefully before initiating therapy.

Therefore, a Saudi task force, including nephrologists, endocrinologists, diabetologists, and internal medicine experts, gathered to develop an explicit, evidence-based consensus on SGLT2is use in Saudi patients with CKD, when to use this class, why, and how to monitor its impact on the progression of CKD? This article has the recommendations of this expert panel.

## 2. Methods

Fourteen experts, including nephrologists, endocrinologists, diabetologists, and internal medicine experts from 14 centers with more than 15 years of experience, made up the task force. An initial concept proposal included the definition of CKD, population, scope, and prevalence in Saudi Arabia. The proposal was divided into several topics discussed in two meetings. The meetings panel approved that the consensus will include diagnosis, management, monitoring of CKD and special populations, and finally, among the entire Saudi population. An expert writer searched the literature based on their search strategies, and they determined their databases. The included literature; guidelines, RCTs, consensus, and systematic reviews, were screened for relevance, quality and evidence. A draft report was written and distributed electronically to the expert panel. Approval of the recommendations required consensus, defined as a majority approval. The recommendations were revised to accommodate any differences of opinion until a consensus was reached. Recommendations were finally formulated. Subsequently, the panel reviewed and discussed the revised recommendations and tried to develop a consensus statement to be valid for the Saudi society and health care professionals (HCPs).

## 3. SGLT2 Inhibitors, a Multi-Indications Class

### SGLT2 Inhibitors for Indications Other than DM

The success of SGLT2is in DM and the ongoing research in other indications

paved the way for their utilization as a multi-indication therapy. SGLT2is have been shown to have several benefits beyond glycemic control, including cardiovascular [9] [10] [11] and renal benefits [7] [12] and reduction in heart failure hospitalizations [13] [14] [15] [16]. These benefits have led to the use of SGLT2 inhibitors in patients with T2DM and high CV or renal risk and CKD patients apart from DM.

Both the dapagliflozin and prevention of adverse outcomes in heart failure (DAPA-HF trial) and the empagliflozin outcome trial in patients with chronic heart failure and a reduced ejection fraction (EMPEROR-reduced study) proved SGLT2is benefits for patients with heart failure with reduced ejection fraction (HFrEF). In the DAPA-HF and EMPEROR-Reduced trials, SGLT2is reduced the composite of CV death or HF hospitalization by approximately 25%, compared to placebo. The benefit in reduction of hospitalization was 30% greater than standard of care in both trials. The risk of CV death was significantly lower (18%) with dapagliflozin, as was the risk of all-cause mortality (17%). Although no significant CV mortality benefit was observed with empagliflozin in a meta-analysis of DAPA-HF and EMPEROR-Reduced trials, SGLT2is therapy was associated with reducing all-cause mortality and CV death. The benefits in both trials were seen irrespective of baseline DM status [17]. Therefore, the 2022 AHA/ACC/HFSA guideline suggests that SGLT2 inhibitors may be beneficial in patients with HFrEF and some patients with HFpEF [18].

After their success in patients with HFrEF, SGLT2 inhibitors have emerged as a promising class of medications for treating heart failure with mildly reduced EF, preserved ejection fraction (HFpEF) and CKD as the mechanism of action of SGLT2is is beneficial in patients with HF or CKD, who often have comorbidities such as DM and hypertension [16] [19].

## 4. SGLT2 Inhibitors and CKD

### 4.1. Current Options for CKD Management and Their Limitations

The available options for CKD management include lifestyle interventions (healthy diet, exercise, weight management, and quitting smoking), control of hypertension and blood glucose, and lipid-lowering therapies. These measures can help prevent the onset or slow the progression of CKD and the development of CV complications [20] [21].

Angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs), which block the renin-angiotensin-aldosterone system (RAAS), have long been the recommended medications for treating hypertension and proteinuria [21] [22]. The lowering of T2DM endpoints with the angiotensin II antagonist losartan and irbesartan was detailed in different trials [23] [24]. Despite the beneficial effects of these drugs, there is still a sizable residual risk of kidney function decline and the emergence of CV problems [21] [22]. Patients with CKD benefit from CV benefits of lipid-lowering treatments but do not have renoprotective effects [21]. Endothelin receptor antagonists, at the cost of unac-

ceptable high side effects risk, can reduce proteinuria, arterial stiffness, and blood pressure in patients with CKD [23]-[28].

The effects of bardoxolone methyl, a synthetic triterpenoid with antioxidant and anti-inflammatory properties, on the risk of kidney failure or death from CV causes were examined in the Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes (BEACON) trial, which included 2185 patients with T2DM and stage 4 CKD. The study was terminated because the intervention was linked to a greater rate of CV events than the placebo [29]. Other strategies, such as treating anemia and acidosis and reducing uric acid, haven't been 100% successful [30]. As a result, patients with CKD continue to have a significant absolute risk of CV and renal morbidity and death. Therefore, it is highly desired to develop novel therapeutics for reducing renal problems [21].

### 4.2. Potential Pharmacologic Mechanisms of Renal Effects of SGLT2i

The potential mechanism of the renal benefits of SGLT2is is an area of ongoing investigation (**Figure 1**). Increased proximal tubular glucose and sodium reabsorption in DM may be due to overexpression of SGLT2 mRNA and increased transporter activity. As a result, decreased sodium transport to the macula densa inhibits tubuloglomerular feedback, which decreases the estimated glomerular filtration rate (eGFR) by causing afferent arteriolar vasodilation, hyperfiltration, and hyperperfusion. Therefore, SGLT2is decrease the workload on the glomeruli and tubules. Additionally, SGLT2is prevent proximal sodium and glucose reabsorption, which causes natriuresis. Acute reductions in BP and body weight, as

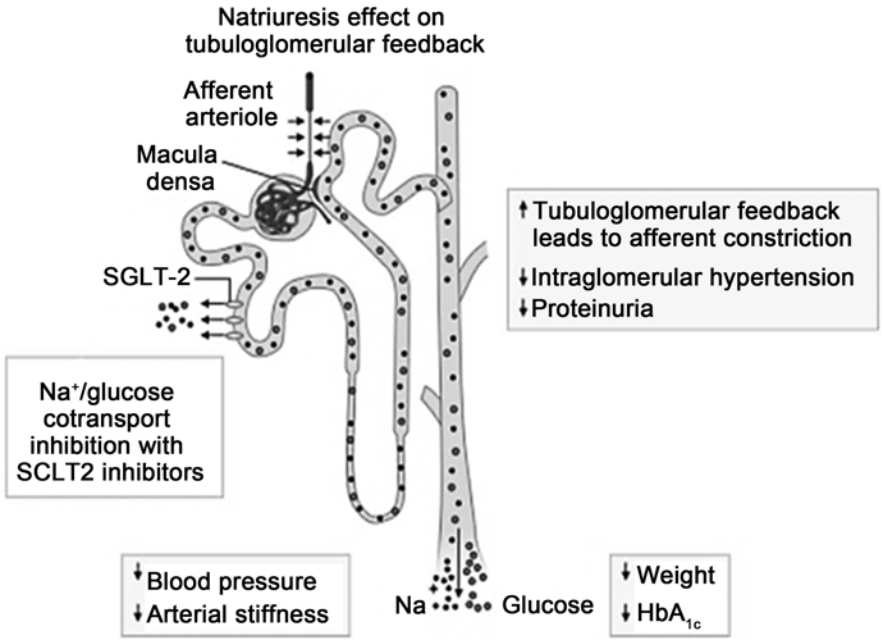


**Figure 1.** The potential effects of SGLT2is on renal structure and function: underlying mechanism [33].

well as contraction of the plasma volume, are linked to increased sodium excretion. SGLT2is reduce arterial stiffness, an indicator of both renal and cardiovascular risk. In addition to promoting anti-inflammatory and antifibrotic pathways, SGLT2i enhances the positive effects of decreased glomerular hypertension, hyperfiltration, and renal oxygenation. Therefore, SGLT2is have also been shown to reduce albuminuria [31] [32] [33].

Additionally, there is less histologic evidence of nephropathy when SGLT2i is present. There are assessments elsewhere, and more recent studies are shedding more insight into the mechanism underlying SGLT2i's advantageous effects [34] [35] [36].

### 4.3. Effectiveness of SGLT2 Inhibitors in CKD

The beneficial effects of SGLT2is on kidney function have been demonstrated in several large clinical trials, including the CREDENCE and DAPA-CKD trials [7] [12]. In these trials, patients with CKD treated with SGLT2is had a significantly lower risk of progression to end-stage kidney disease (ESKD) and a lower risk of cardiovascular events and mortality.

The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (**CREDENCE**) trial was a randomized, double-blind, placebo-controlled trial that evaluated the efficacy and safety of canagliflozin, an SGLT2i, in patients with T2DM and albuminuric CKD. The trial demonstrated a significant reduction in the risk of the primary composite outcome of ESKD, doubling of serum creatinine, and renal or cardiovascular (CV) death in the canagliflozin group compared to the placebo group [7]. Canagliflozin also reduced the risk of secondary CV outcomes.

The "Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease" (**DAPA-CKD**) trial was a multinational, multicenter, event-driven, randomized, double-blind, placebo-controlled trial that evaluated the efficacy and safety of dapagliflozin, an SGLT2i, in patients with CKD, with or without T2DM. The trial demonstrated a significant reduction by 39% (resulting in a number needed to treat of 19) in the risk of the primary composite outcome of sustained decline in eGFR, ESKD, or death from renal or CV causes in the dapagliflozin group compared to the placebo group. Dapagliflozin also reduced the risk of secondary outcomes, including all-cause mortality (reduced by 31%; HR, 0.69; 95% CI, 0.53 to 0.88; P = 0.004) and a composite of cardiovascular death and hospitalization for heart failure (reduced by 29%; HR, 0.71; 95% CI, 0.55 to 0.92; P = 0.009). The benefit was consistent for the primary endpoint regardless of the T2DM status, emphasizing the central principle that dapagliflozin benefits were independent of glycemic status, *i.e.*, dapagliflozin showed a kidney protective effect in patients with or without T2DM [12] [37].

The Study of Heart and Kidney Protection with Empagliflozin trial (**EMPA-KIDNEY**) was a randomized, double-blind, placebo-controlled trial that evaluated the efficacy and safety of empagliflozin, an SGLT2i, in patients with CKD, with or without T2DM. The trial demonstrated a significant reduction in the risk

of the primary composite outcome of sustained decline in eGFR, renal death, or ESKD in the empagliflozin group compared to the placebo group [38]. Progression of kidney disease or death from CV causes occurred in 13.1% of the empagliflozin group and in 16.9% of the placebo group (HR, 0.72; 95% CI, 0.64 - 0.82; $P < 0.001$). Results were consistent among patients with or without diabetes and across subgroups defined according to eGFR ranges. However, there were no significant differences between the two groups in hospitalization for heart failure or death from CV cause (composite outcome) (4.0% of the empagliflozin group and 4.6% of the placebo group; HR, 0.84; 95% CI, 0.67 - 1.07; $P = 0.15$) or with respect to death from any cause (4.5% and 5.1%, respectively; HR, 0.87; 95% CI, 0.70 - 1.08; $P = 0.21$) [38].

These trials provide strong evidence for the efficacy of SGLT2is in managing CKD, particularly in patients with T2DM and albuminuria. The results of these trials have led to the inclusion of SGLT2is in guidelines for managing CKD in patients with DM [8].

Therefore, among the different available molecules of SGLT2is, only dapagliflozin is recommended by the NICE for CKD with or without T2DM. It is recommended for those with albuminuria (urine albumin: creatinine ratio (ACR) ≥ 22.6 mg/mmol and eGFR 25 - 75 ml/min/1.73m$^2$), either attributed to diabetic or non-diabetic causes. Also, dapagliflozin is recommended for those with ACR < 22.6 mg/mmol and eGFR 25 - 75 ml/min/1.73m$^2$ [39].

## 5. Safety and Side Effects

Although SGLT2is have demonstrated efficacy in reducing glucose levels and cardiovascular events in patients with T2DM [37], their safety profile in patients with CKD has been a topic of concern due to the potential adverse effects.

Although SGLT2is could cause volume depletion, previous studies believed that patients receiving SGLT2i may have a lower risk of acute kidney injury [40] [41].

Previous studies recommended that the concern of SGLT2is causing acute kidney injury should not impact the decision of healthcare professionals to prescribe or continue SGLT2is. However, some experts advise patients to temporarily withhold these agents during any illness that increases the risk of dehydration and to carefully monitor the patient's volume status by physical examination, blood pressure measurements, and laboratory tests, including haematocrit and electrolytes [42].

Previously, potential concerns of SGLT2i adverse effects existed in CKD patients, including hypoglycemia, urinary tract infections, and lower limb amputations. However, the later was a historical concern that was proven wrong by many studies as shown in the following paragraphs [43] [44].

However, no increase in serious hypoglycemia was observed with canagliflozin and dapagliflozin in the CREDENCE or DAPA-CKD trials, respectively [7] [12].

In addition, despite initial concerns, routine use of SGLT2 inhibitors was not found to increase urinary tract infections, as observed in a previous meta-analysis

(RR, 1.02; 95% CI, 0.95 - 1.09; I2 = 0.0%) [45].

Regarding the risk of lower limb complications, only patients receiving canagliflozin showed an increased risk of amputation (OR = 1.60; 95% CI, 1.04 - 2.46) and peripheral arterial disease development (OR = 1.53; 95% CI, 1.14 - 2.05) [44]. However, whether this constitutes a class effect or is strictly related to canagliflozin is unknown. Therefore, it is important to counsel patients with diabetes on routine preventative foot care.

## 6. Clinical Considerations

### 6.1. Patient Selection and Monitoring for SGLT2 Inhibitor Therapy in CKD

The use of SGLT2is in patients with CKD requires careful consideration due to the potential adverse effects. Patient selection and monitoring are critical in ensuring the safe and effective use of SGLT2is in CKD. Patient selection involves identifying patients most likely to benefit from SGLT2is therapy while minimizing the potential risks. SGLT2is should not be initiated in CKD patients with an eGFR of less than 20 mL/min/1.73m$^2$ or patients with ESKD requiring dialysis [46].

However, according to the 2022 KDIGO guidelines, once patients with CKD start SGLT2i treatment, it is favorable to continue on the prescribed agent even if the eGFR falls below 20 ml/min per 1.73 m$^2$ unless it is intolerable or KRT is initiated [47].

Additionally, patients with a history of AKI, hypotension, or dehydration should be closely monitored if SGLT2 inhibitors are used. Generally, regular monitoring is essential for patients with CKD who are receiving SGLT2is. Patients should monitor their eGFR and serum creatinine levels before initiating therapy and periodically thereafter to assess renal function [37]. In patients with eGFR < 60 mL/min/1.73m$^2$, the risk of AKI may be increased, and close monitoring is recommended [48].

Additionally, patients should be monitored for signs and symptoms of volume depletion, including orthostatic hypotension and electrolyte abnormalities, such as hyponatremia and hyperkalemia [39].

High-risk patients with CKD should be closely monitored with the presence of risk factors, including prior acute kidney injury [49], risk of volume depletion [39], exposure to nephrotoxic agents (such as nonsteroidal anti-inflammatory drugs (NSAIDs), contrast agents, and aminoglycoside antibiotics) [50], and other comorbidities (such as liver disease, heart failure, and sepsis) [39]. These risk factors should be considered when evaluating the potential use of SGLT2is in patients with CKD. Close monitoring of renal function is also recommended in those patients [51].

### 6.2. Dosage Adjustments for Patients with CKD

SGLT2is are renally cleared medications, and therefore, dosage adjustments are

necessary for patients with impaired kidney function to reduce the risk of adverse effects [37]. According to the Saudi FDA, the recommended starting dose of dapagliflozin is 10 mg once daily and empagliflozin is 10 mg once daily in CKD patients [52]. According to the Saudi FDA recommendations, for patients with an eGFR 60 to <90 or CrCl 60 to <90, the recommended starting dose of canagliflozin is 100 mg or 300 mg. In patients with an eGFR 45 to <60 or CrCl 45 to <60, the dose of is limited to 100 mg once daily. Canagliflozin should not be initiated in patients with an eGFR < 45 or CrCl < 45. Canagliflozin should be discontinued when eGFR is persistently < 45 or CrCl < 45. Canagliflozin should also not be used in patients with end stage renal disease (ESRD) or in patients on dialysis [52].

Dosage adjustment for SGLT2is is generally not required in elderly patients with CKD. Previous studies observed that body weight decreased more with higher doses of SGLT2 inhibitors, especially dapagliflozin [53].

However, patients with a higher body weight may require higher doses of some SGLT2i agents, such as canagliflozin, to achieve therapeutic efficacy [54]. Caution should also be exercised with the coadministration of certain medications, such as diuretics and angiotensin-converting enzyme inhibitors (ACEIs), which may affect renal function and increase the risk of hypovolemia [9]. Patients with hepatic impairment may require dosage adjustments of SGLT2is due to their effects on metabolism and clearance [55]. SGLT2is are not recommended during pregnancy and breastfeeding due to limited data on their safety and efficacy in these populations [8].

### 6.3. Potential Drug-Drug Interactions in Patients with CKD

SGLT2is can interact with other medications commonly used in CKD patients, potentially leading to adverse effects. They may enhance the diuretic effect of loop diuretics, leading to dehydration and electrolyte imbalances [56] [57]. NSAIDs can reduce renal blood flow and impair renal function, and concomitant use with SGLT2is may increase the risk of AKI [58]. Although only a few case studies were reported, SGLT2is could be linked to an increasing the risk of statin-induced myopathy, as they can increase the plasma concentration of statins [59]. However, these interactions should be handled in an individual base while monitoring fluid status, electrolytes status, renal functions, and myopathy. Also, this topic needs more investigation.

## 7. Conclusion

In conclusion, the role of SGLT2is in CKD is self-evident. Therefore, their utilization in CKD, DM or non-DM cases is recommended (use dapagliflozin, empagliflozin, then canagliflozin in sequence). Patient selection is one important factor when prescribing SGLT2is.

## 8. Recommendations

| *Recommendations* |
|---|
| Assess all individuals with T2DM for established CVD and/or CKD or risk for them using standard diagnostic criteria. Initate SGLT2i in those with established CVD and/or CKD and in those with three or more CVD and/or CKD risk factors without established CVD and/or CKD. |
| Assess all CKD patients for risk of progression. Those with stages 3 - 5 CKD and high progression risk (urine albumin-to-creatinine ratio: UACR > 300 mg/g) should be considered for SGLT2i<br>Adults with CKD and heart failure or eGFR ≥ 20 mL/min/1.73m$^2$ with UACR ≥ 200 mg/g should be treated with an SGLT2 inhibitor.<br>Adults with eGFR ≥ 20 - 45 mL/min/1.73m$^2$ with UACR < 200 mg/g should be treated with an SGLT2 inhibitor. |
| Do not initiate SGLT2i if eGFR is below 20 mL/min/1.73m$^2$ but continue SGLT2i if the patient is already on it. |
| Regular monitoring is also essential for patients with CKD who are receiving SGLT2is. |
| Patients with a history of AKI, hypotension, or dehydration should be monitored closely if SGLT2 inhibitors are used. |
| Patients on SGLT2is should have their eGFR and serum creatinine levels monitored before initiating therapy and periodically thereafter to assess renal function. Close monitoring is recommended in patients with eGFR < 60 mL/min/1.73m$^2$. |
| Patients should be monitored for signs and symptoms of volume depletion, including orthostatic hypotension and electrolyte abnormalities, such as hyponatremia and hyperkalemia. |
| Assess for risk factors for AKI while on SGLT2is. |
| Use SGLT2i with caution in those with a history of genital or urinary tract infections. |
| Counseling for patients with regards genital infections, and volume status is recommended for those on SGLT2is. |
| Patients should be advised to withhold SGLT2is during an acute illness that can lead to dehydration. |
| Drug-to-drug interactions should be considered when prescribing SGLT2is with loop diuretics, ACEIs, ARBs, other anti-DM medications, NSAIDs, and statins. |
| Dosage adjustments are necessary. The recommended dosage adjustments for SGLT2is in patients with impaired kidney function are as follows:<br>- Dapagliflozin is 10 mg once daily, and it should not be used in patients with an eGFR less than 25 mL/min/1.73m$^2$.<br>- The recommended starting dose of Empagliflozin is 10 mg once daily, and it should not be used in patients with an eGFR less than 20 mL/min/1.73m$^2$.<br>- The recommended starting dose of Canagliflozin is 100 mg once daily, and it should not be used in patients with an eGFR less than 45 mL/min/1.73 m$^2$. |
| ***Future directions and ongoing research in this field.*** |
| More research is needed to establish the role of SGLT2is therapy in specific populations with kidney diseases, such as kidney transplant recipients, those with lower grades of proteinuria (A2, e.g. those with chronic interstitial nephritis or CKD of unknown etiology), and those with lower eGFR. |
| Saudi cost-benefit analyses need to be undertaking to define the place of SGLT2is in standard treatment algorithms. |
| More research studies are needed to highlight the drug-drug interaction of SGLT2is in different population. |

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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# Exercise Intolerance and Excessive Chronotropic Response Due to Possible Autonomic Dysfunction Post COVID-19 Infection

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## Abstract

**Introduction and Objectives:** In patients with Post-Acute Sequelae of Coronavirus 2 infection (PASC), a post infectious autonomic dysfunction may be one of the underlying mechanisms. Patients often present with exercise intolerance and exaggerated heart rate response to exercise. We report a single centre experience of patients with PACS and suspected autonomic dysfunction. **Methods:** Forty-two patients evaluated in the Outpatient Cardiology Department with suspected PASC were included in the study. Patients complained of compromised exercise performance persisting >3 months after recovery from COVID-19 infection, compared to the pre-COVID-19 period. The patients were evaluated with 12-lead electrocardiogram, echocardiography, 24-hour ECG ambulatory monitoring and either exercise stress test or a 6-minute walk test. **Results:** All 42 patients demonstrated an exaggerated chronotropic response, defined as the inappropriate increase in heart rate before the 6$^{th}$ minute of exercise >100% of the age-predicted maximal heart rate value with reproduction of clinical symptoms. In addition, 24-hour ambulatory electrocardiography revealed an increased mean heart rate of 92 beats/minute and decreased mean standard deviation of sequential 5-minute N-N interval (SDNN) of 74.4 ms. Pharmaceutical treatment with b-blockers, ivabradine or both was administrated in 29 (69%) resulting in symptomatic improvement in 82.8% of those under treatment. However, residual symptoms persisted in 69% of patients after 3 months. **Conclusions:** In patients

with "Post-acute COVID-19" syndrome, we found an excessive chronotropic response to exercise suggesting autonomic dysfunction as the underlying mechanism of symptoms. Treatment with beta blockers or ivabradine resulted in clinical improvement but a substantial proportion of patients remained symptomatic.

## Keywords

COVID-19, Autonomic Neuropathy, Exertional Intolerance, Exaggerated Chronotropic Response, POTS, Dysautonomia

## 1. Introduction

Over 630 million cases of SARS CoV-2 (SARS CoV-2) infection had been confirmed on November 2022, since the beginning of the pandemic, representing a significant challenge for health systems worldwide [1]. In addition to the short-term increased mortality and morbidity rates in these patients, recent studies revealed an increased incidence of symptoms persisting for weeks or months following acute infection, often referred to as Post-Acute Sequelae of Coronavirus 2 infection (PASC) or "long COVID-19" [2]. Symptoms such as fatigue, headache, postural tachycardia, orthostatic intolerance, dizziness and cognitive impairment, palpitations, gastrointestinal dysfunction and exercise intolerance presumed to represent the long-term effect of the disease [2] are identified in 10% - 20% of COVID-19 infection survivors [3]. For most of these manifestations, autonomic dysfunction appears to be one of the underlying mechanisms, especially in patients presenting with orthostatic intolerance, POTS, neurocardiogenic syncope or orthostatic hypotension [4] [5] [6], especially in the case of Orthostatic Intolerance and Postural Orthostatic Tachycardia Syndrome (POTS) [7]-[13].

## 2. Objectives

In the present case series, we report a single centre experience of diagnostic and therapeutic management of patients with suspected PACS.

## 3. Methods

This retrospective study was performed in a single centre in Greece. Informed consent was obtained from each patient. In addition, the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by our institution's human research committee. Cases were collected retrospectively after reviewing the outpatient clinic database for the time-period between May 2021 and April 2022.

Patients were either self-referred or referred to our outpatient clinic by their healthcare provider for cardiovascular evaluation following COVID-19 infec-

tion. Inclusion criteria were: 1) fully asymptomatic patients prior to COVID infection, 2) the presence of exercise intolerance persisting >3 months post COVID-19 recovery, and 3) recording of an exaggerated chronotropic response. Patients with pre-existed cardiac disease, implantable cardiac devices, uncontrolled hypertension, or other serious medical condition were excluded.

Basic cardiovascular assessment included obtaining a thorough medical history and physical examination, laboratory tests (including full blood count, biochemistry, and thyroid function tests), 12-lead electrocardiogram (ECG) and echocardiogram in all cases. Next, patients underwent either a treadmill exercise stress test (EST) (45.2%) or a 6-minute walk test to assess the functional status more accurately. Tilt Table Test was performed in 2 cases and where appropriate a 10-min stand test was performed to assess orthostatic intolerance (n = 20). In addition, all 42 patients underwent a 24-hour ambulatory electrocardiographic assessment.

Details obtained from the medical record included demographics, medical history, laboratory investigations, radiological findings (chest radiograph and/or computed tomography, CT), cardiovascular assessment tests, clinical management and patient outcome and survival.

Autonomic dysfunction was indicated by the presence of excessive increase in heart rate upon standing accompanied by orthostatic intolerance or by the presence of an abnormally high resting heart rate higher than 100 bpm or by recording a disproportional increase of heart rate compared to the status of exercise. When clinically relevant, the presence of POTS, defined as the orthostatic increase of the heart rate (HR) of >30/min (>40/min in patients of 12 - 19 years of age) in the absence of concomitant blood pressure drop in patients with duration of symptoms of orthostatic intolerance for at least 3 months, was assessed.

COVID-19 infection was confirmed by positive reverse transcription-polymerase chain reaction results on respiratory samples.

## 4. Results

The records of forty-two patients (37 female) fulfilling the above-mentioned inclusion criteria were further investigated. Demographic data are presented in Table 1. Median age was 41.2 ± 11.3 years (range: 26 - 66 years). All patients were older than 20 years of age, whereas 11 were between 21 and 30 years old, 10 were between 31 and 40 years old, 11 were between 41 and 50 years old, 7 were between 51 and 60 years old and 3 were older than 61 years. Three male patients were between 31 and 40 years old, 1 was between 41 and 50 years old, whereas 2 were between 51 and 60 years old. Mean time-period between COVID-19 infection and 1st appointment was 3.7 months. Prior to COVID-19 all patients were fully functional and asymptomatic without significant co-morbidities. Thirty-nine of the 42 patients were fully vaccinated, whereas 3 were not vaccinated.

During COVID-19 infection, 28 patients presented with mild symptoms of acute respiratory infection, 10 patients reported moderate symptoms such as

**Table 1.** Demographics of the patient study group.

| | N = 42 (%) |
|---|---|
| **Age** (years old) | 41.2 ± 11.3<br>Range: 26 - 66 |
| **Sex** | |
| • Female | 37 (88.1%) |
| • Male | 3 (11.9%) |
| **Risk factors** | |
| • Arterial Hypertension | 9 (21.4%) |
| • Diabetes Mellitus | 2 (4.8%) |
| • Dyslipidaemia | 9 (21.4%) |
| • Smoking | 14 (33.3%) |

high fever lasting for >3 days, breathlessness and coughing whereas 4 patients were diagnosed with pneumonia, however none of the patients was hospitalised. Nine patients reported anosmia and/or ageusia.

All patients were referred to our Outpatient Department for exercise intolerance at mild exertion and a significant impairment of their quality of life, persisting at least 3 months after recovery from COVID-19 infection. Other symptoms were fatigue (69%), palpitations during exercise (76.2%), syncope (14.3%), presyncope (23.8%) and postural intolerance (26.2%) without fulfilling the diagnostic criteria of POTS (**Table 2**).

Twenty-four patients had a respiratory assessment prior to their visit in our department whereas the rest were referred to respiratory clinic by us to rule out a respiratory condition associated with their symptoms. All patients underwent a chest x-ray (n = 33) and/or chest computerised tomography (n = 24).

Following the assessment scheme (**Figure 1**), we did not reveal structural heart disease in any case in this group of patients, based on the clinical, electrocardiographic, and echocardiographic findings. On the other hand, we revealed an exaggerated chronotropic response defined as the inappropriate increase in heart rate before the 6$^{th}$ minute of exercise >100% of the age-predicted maximal heart rate value (APMHR) in all 42 patients with reproduction of clinical symptoms. In addition, 24-hour ambulatory electrocardiography revealed an increased mean heart rate and a decreased mean standard deviation of sequential 5-minute N-N interval (SDNN) of 74.4 ms (range: 52 - 112 ms) (**Table 3**, **Figure 2**).

Twenty-nine patients (69%) received pharmacotherapy for the treatment of the presumed autonomic dysfunction attributed to the post-acute sequelae of COVID-19 infection which included beta blockers, (n = 16), either Metoprolol (75 - 125 mg/day) or Bisoprolol (10 mg/day), or ivabradine 5 mg bid (n = 11) or a beta-blocker/ivabradine combination (n = 2). Thirteen patients did not wish to receive medication after reassurance, and remained on non-pharmacological measures only.

All 42 patients had a regular follow-up 1 month and 3 months after the initial

**Table 2.** Clinical symptoms.

| Symptom | N (%) |
|---|---|
| *Exertional Intolerance* | 42 (100%) |
| *Orthostatic Intolerance* | 11 (26.2%) |
| *Fatigue* | 29 (69%) |
| *Palpitations* | 32 (76.2%) |
| *Pre-syncope* | 10 (23.8%) |
| *Syncope* | 6 (14.3%) |

**Table 3.** Diagnostic and therapeutic interventions.

| Intervention | N (%) |
|---|---|
| **History/Physical Examination** | 42 (100%) |
| **Assessment at Respiratory Department** | |
| • Referral to Respiratory Department | 18 (42.8%) |
| • Referral from Respiratory Department | 24 (57.2%) |
| **Pulmonary Imaging** | |
| • Chest X-ray | 33 (78.6%) |
| • Chest Computerised Tomography (CT) | 24 (57.1%) |
| **Laboratory Tests** (full blood count/liver function tests/blood glucose/thyroid function tests/renal function tests) | 42 (100%) |
| **Electrocardiogram** | 42 (100%) |
| **Echocardiogram** | 42 (100%) |
| • Mean Ejection Fraction: | 62% |
| **24-hour ambulatory ECG-recording** | 42 (100%) |
| • Mean SDNN | 74.4 ms (range: 52 - 112 ms) |
| • Mean Heart Rate | 92 beats/minute |
| **Functional status assessment** | |
| • Exercise Stress Test | 19 (45.2%) |
| • 6-Minute Walk Test | 23 (54.8%) |
| **Orthostatic Test** | 20 (47.6%) |
| **Tilt Table Test** | 2 (4.8%) |
| **Pharmaceutical Therapy** | 29 (69%) |
| • b-blockers | 16 (38.1%) |
| • Ivabradine | 11 (26.2%) |
| • b-blockers/ivabradine combination | 2 (4.8%) |
| **Response to treatment** | 24/29 patients (82.8%) |
| **Residual symptoms** | 29/42 patients (69%) |

assessment. Most patients (69%) reported residual symptoms 3 months after the first visit in our department. However, in most of the cases (24 of 29 patients, 82.8%), patients showed a significant improvement with treatment, reporting a

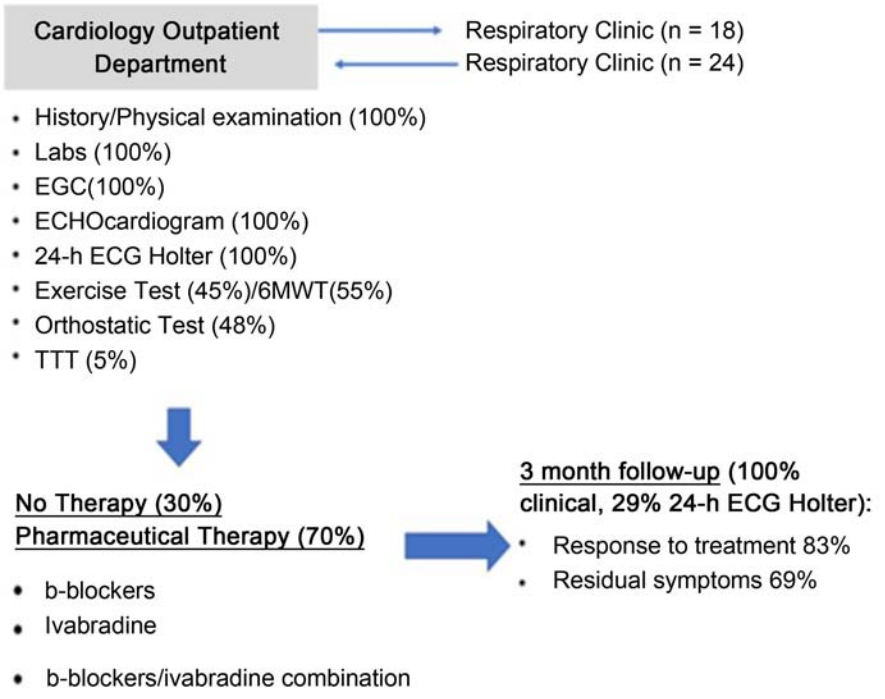


**Figure 1.** 24-hour ambulatory electrocardiographic recording of a 33 years-old female patient with exertional intolerance persisting 3.5 months after recovery of COVID-19 infection.

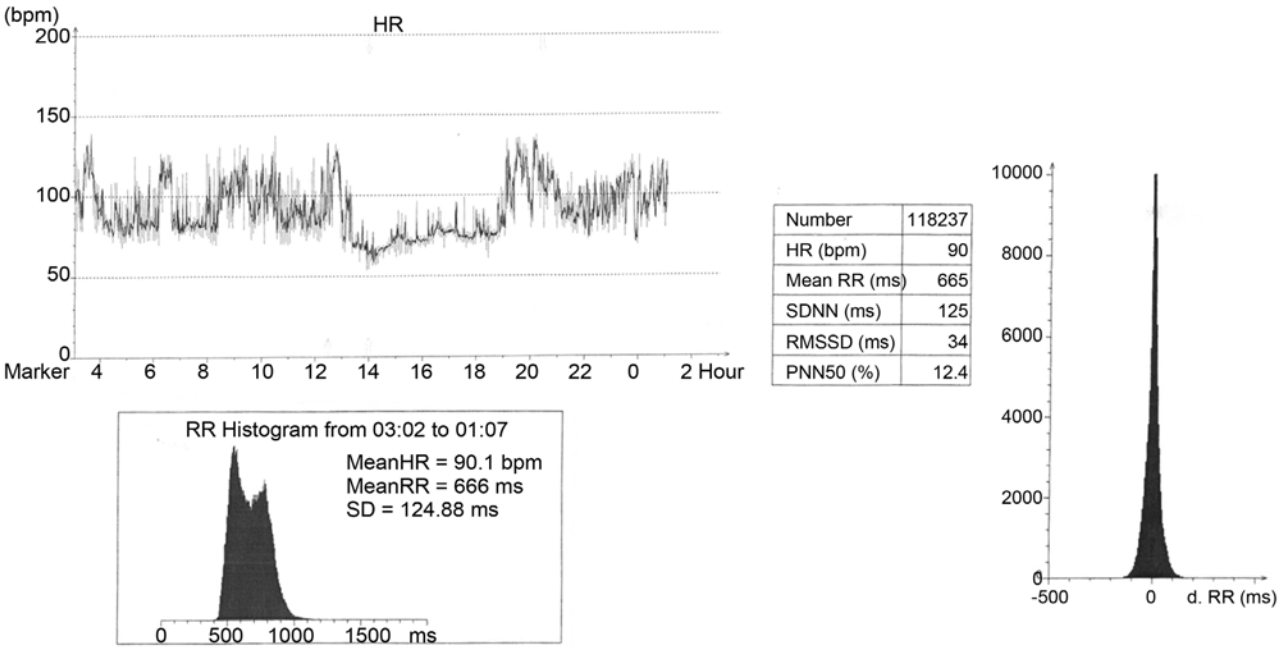


**Figure 2.** 24-hour ambulatory electrocardiographic recording of a 52 years-old female patient with exertional intolerance persisting 3 months after recovery of COVID-19 infection.

better functional status and quality of life. Beta-blocker/ivabradine combination was effective and significantly reduced symptoms. Moreover, ivabradine administration resulted in a significant improvement in 10 of the 11 patients. Beta-

blockers were effective in 12 of the 16 patients. No significant side effects or significant variations in response among individuals was recorded. Interestingly, a 24-hour ambulatory ECG test was repeated in 12 patients (28.6%) showing a significant decrease in mean heart rate compared to the subject's 24-hour Holter performed during the initial assessment.

## 5. Discussion

Various neurologic manifestations have been described in patients previously infected by SARS CoV-2 virus [2]. Among those, several disorders of the Autonomic Nervous System such as POTS may occur in previously healthy individuals. Symptoms may persist for weeks after recovery from the acute infection and are encompassed in the so-called "Post-acute COVID-19" or "long COVID-19" syndrome [7] [9] [11] [14] [15] [16]. Many symptoms of post-acute COVID syndrome appear to be autonomic in nature, suggesting that autonomic impairment may play a central role in the underlying patho-physiology [17]. Some authors suggest that a combination of orthostatic tachycardia and symptoms such as dyspnoea or palpitations, persisting in the post COVID-19 infection period, may indicate the presence of POTS [2] [11]. In a large case series, authors reported that POTS and other common autonomic disorders can follow COVID-19 in previously healthy non-hospitalized patients who experience significant disability 6 - 8 months after an acute infection [10].

In the present study, we specifically detected and retrospectively investigated a group of patients presenting in the Outpatient Cardiology Department with persistent symptoms of exercise intolerance after COVID-19 infection, who were proved to manifest an exaggerated chronotropic response. All patients were previously healthy and reported long-lasting symptoms, in most of the cases fatigue and palpitations during mild to moderate exercise, post-acute COVID-19 infection recovery, severely decapacitating their quality of life. In general, physical exercise increases oxygen demand and subsequently leads to increased heart rate due to an enhanced sympathetic activity and an inhibition of the parasympathetic limb. On the other hand, an excessive rise in heart rate, in the post-COVID period in previously healthy and asymptomatic patients, may represent a possible autonomic imbalance resulting from sympathetic hyperactivity as well as a reduced vagal activity. In this situation, heart rate reaches its peak early, resulting in limitation of maximum exercise capacity.

In the present study we used two methods to assess the presence of excessive chronotropic response to physical activities, namely traditional treadmill exercise testing in 45% and 6-minute walk test in 55% of the patients. In all cases the APMHR was reached before the 6$^{th}$ minute of exercise, with reproduction of clinical symptoms. Therefore, based on the clinical and diagnostic findings we may assume that these patients represent a group with an autonomic imbalance variant presenting with exercise intolerance due to an excessive chronontropic response. We believe that these findings may suggest an underlying autonomic

dysfunction due to the COVID-19 infection. Clinical symptoms may be classified in the spectrum of "Post-acute COVID" entity, since symptomatology onset was closely related to it.

Patients were highly symptomatic and sought for medical advice despite of the fact that none required hospitalization. Therefore, our data suggest that even mild cases of COVID-19 infection can lead to "Post-acute COVID" symptoms.

Furthermore, 24-hour ECG recording recorded an increased mean HR of 92 beats/minute indicating, presumably, a worst autonomic balance with increased chronotropic response to exercise. In addition, SDNN (standard deviation of normal-to-normal R-R intervals), an essential variable of heart rate variability measures, is considered as the "gold standard" for medical stratification of cardiac risk when recorded over a 24 h period, predicting both morbidity and mortality. In our study, mean SDNN was calculated at 74.4 ms with a range of 52 - 112 ms, indicating a deteriorated Heart rate Variability.

Several studies demonstrate that a rapid HR increase at the beginning of a standard EST is a strong and independent predictor of cardiac death and non-fatal myocardial infarction in patients with coronary artery disease as well as heart failure, probably via an increase in electrical instability and thus enhancing life-threatening arrhythmias [18] [19]. On the other hand, a prospective study recruiting 149 patients did not find evidence of excess cardiovascular risk in COVID-19 survivors, after a 6-month follow-up period, compared to patients who had no history of the disease [20]. Similarly, in our study, no death was recorded, and most of the patients reported an improvement in symptoms after a 3-month follow-up period.

Recently, investigators highlighted the phenomenon of abnormal sinus tachycardia in patients previously infected by SARS CoV-2 virus, and proposed that "post-COVID-19 tachycardia syndrome" should be considered a phenotype or sub-syndrome of post-acute COVID-19 syndrome [21]. Post-COVID-19 tachycardia syndrome may represent a POTS or inappropriate sinus tachycardia subset contributing to several symptoms in this patient group [21]. Furthermore, Aranyo *et al*., recently, reported that Inappropriate Sinus Tachycardia (IST) is prevalent among post-acute COVID-19 patients. In their study, among 200 patients, 40 (20%) fulfilled the diagnostic criteria for IST, namely a symptomatic sinus rhythm rate ≥ 100 bpm at rest with a mean 24-h heart rate above 90 beats/min in the absence of any acute physiological demand or conditions known to commonly produce sinus tachycardia [22] [23]. Additionally, IST was accompanied by a decrease in most heart rate variability parameters such as pNN50 and HF band, whereas the disorder was more common in young women without previous comorbidities and with mild SARS-CoV-2 infection [22]. Authors, suggest that cardiac Autonomic Nervous System imbalance with decreased parasympathetic activity seems to be a plausible pathophysiological explanation for this phenomenon [22]. Due to the similarities in the demographics of our patient group as well as the findings of the 24-hour ambulatory electrocardio-

graphic assessment, it can be speculated that IST may also be the diagnosis, at least, in a subset of our patients. However, a significant difference with our study is that in this patient group (that also included mostly young or middle age women), individuals had a persistently increased heart rate, whereas in our study, patients had a predominantly exaggerated heart rate response to exercise, and symptoms occurred mostly during exercise. The exact mechanisms leading in these dysautonomic subtypes remain to be investigated in future research. however clinical doctors should recognise and treat them at an early stage.

Medical therapy was initiated in 29 of the 42 patients, however in the total group of the 42 patients 69% reported residual symptoms 3 months after the first visit. Nevertheless, 83% of the patients who received medical treatment reported a significant improvement. Beta blockers and/or ivabradine was initiated in a dose depending on the 24-hour ambulatory electrocardiography results, and was further increased according to patient's symptoms. Beta-blocker/ivabradine combination or ivabradine monotherapy administration appear to be more effective compared to b-blocker monotherapy, however the patient sample is small, and no definite conclusions can be extracted. Even though there is not a uniform approach to managing cardiac dysautonomias, pharmacologic agents should be prescribed as adjuncts to existing non-pharmacological therapies on a case-by-case basis. Non-pharmacological measures include patient education (*i.e.* avoiding triggers and activities that might aggravate their symptoms, performing counter-pressure maneuvers), increase in water and salt intake to promote volume expansion, avoiding medication that reduces blood volume or decreases blood vessel tone (such as antihypertensives, diuretics and nitrates), using compression garments that reach the abdomen to enhance venous return and attending exercise training programs introduced gradually to avoid aggravating symptoms and slowly progress from non-upright activities (e.g. rowing machines, recumbent cycles) to upright aerobic exercises.

Autonomic dysfunction is not rare in those affected by COVID-19, and patients are often highly symptomatic with a severely compromised quality of life in the short and probably in the long term. A better understanding of the complex and various pathophysiological mechanisms that affect the autonomic nervous system as well as an early recognition of the dysautonomia subtypes and administration of medical treatment at an early stage could help reduce the sequelae of COVID-19.

The study has several limitations. First of all, this is a retrospective, non-randomised, single centre case series report and therefore results must be evaluated from this perspective. In addition, the size of the sample population studied is small comprising of only 42 patients. The population of this study is, additionally, restricted to those patients who sought medical assistance due to their symptoms at the Cardiology Outpatient Department of our hospital, and therefore findings cannot be expanded to the general population or to all COVID patients. Moreover, long-term follow-up is absent. Presence of long-term follow-up data remains a critical aspect of this type of research since only a few data exist in li-

terature regarding long-term prognosis of dysautonomias as well as the exact mechanisms leading to persisting symptoms. Therefore, future research should incorporate extended observation periods. Fourth, the symptom-limited maximal exercise test or 6-minute walk test that was used to assess the patients' functional status may be influenced by several factors. This strategy does not provide information regarding the metabolic and oxygen demand during exercise. Fifth, the presence of an autonomic disorder is only speculated and is not proven by autonomic laboratory testing, neither patients assessed in specialized neurology departments in order to confirm diagnosis. Sixth, an exaggerated chronotropic response was defined as the inappropriate increase in heart rate before the 6$^{th}$ minute of exercise >100% of the age-predicted maximal heart rate value (APMHR) with a concomitant reproduction of clinical symptoms. This definition, although clinically relevant for this specific patient group, is arbitrary. In addition, a 10-min stand test was only performed in 20 patients, when considered to be clinically relevant (such as in the case of reported orthostatic intolerance or syncope), leading in inhomogeneity in the diagnostic procedure. A Tilt Table test may be considered for patients assessed for POTS. On the other hand, an active stand test is a simple evaluation for POTS (and orthostatic hypotension) that can be done at the bedside or in the clinic with only an automated or manual BP cuff and therefore, most authors consider it as being the standard of care for assessing patients with orthostatic complaints [24] [25]. However, the inhomogeneity in the diagnostic procedure, including patients not assessed for orthostatic intolerance, patients assessed with Tilt Table Test and patients assessed with a 10 minutes active stand test, may have compromised the results of the present study. Finally, improvement in symptoms was not recorded with a repeated exercise test or 6-minute walk test.

## 6. Conclusion

In this retrospective study of patients recovered from SARS CoV-2 virus infection, we identified a subgroup of patients with "Post-acute COVID-19" syndrome with exercise intolerance due to excessive chronotropic response. Our findings provide more evidence on the mechanism of, at least, a subset of patients with "Post-acute COVID" symptoms, suggesting the presence of autonomic dysfunction. Although that, in most cases, this is a temporary, gradually resolving phenomenon, clinical doctors should suspect and diagnose this variety of PASC in patients with a previous COVID-19 infection complaining for exercise intolerance.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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# Different Resistance Exercise Interventions for Handgrip Strength in Apparently Healthy Adults: A Systematic Review

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## Abstract

**Background**: Although handgrip strength is a biomarker for morbidity/mortality, there is lack of evidence on the effects of resistance training on handgrip strength in healthy adults of all ages. **Objective**: The aim of this systematic review was to assess the impact of resistance training on handgrip strength in healthy adults. **Methods**: Five databases/search engines were searched. Studies comparing different types of resistance exercise interventions versus a non-exercised control group on handgrip strength were included. The available data did not allow us to conduct the pre-planned meta-analyses; therefore, only descriptive statistics were performed to summarize the data. **Results**: Twenty studies (17 randomized and three non-randomized controlled trials) were included, most of which were conducted in older adults. Twelve studies reported no significant difference in the change in handgrip strength between the resistance training and control groups. Two studies showed increases in handgrip strength in the resistance training group compared with the control group. Other studies included results for multi-training groups or left/right hands and found increasing handgrip strength compared to controls, but only in one training group or one hand. Overall, the randomized and non-randomized clinical trials presented moderate risk of bias. **Conclusions**: Due to the lack of low risk-of-bias randomized controlled trials of young and middle-aged adults, different training protocols, and small sample sizes, the existing evidence appears insufficient to support resistance training for increasing handgrip strength in healthy adults. Future studies may seek to discern

the optimal way to develop and employ resistance training to improve handgrip strength.

## Keywords

Grip Strength, Strength Training, Biomarker, Healthy Adults

## 1. Introduction

Studies published over the last quarter century clearly show that better health (reduced morbidity and mortality) is associated with higher handgrip strength in adults [1] [2] [3] [4] [5]. Specifically, large-scale longitudinal studies published in the past two years have repeatedly reported inverse associations between handgrip strength and the risk of various diseases and accidents, such as heart diseases [6], diabetes [7] [8], cancer [9] [10], dementia [11] [12], and falls [13]. These associations remain even when adjusting for age, education level, body mass index, alcohol, tobacco, medical history, etc. If handgrip strength is a valid biomarker of health, we need to find out how best to increase this biomarker. This would allow studies to explore whether increasing that biomarker actually confers health benefits.

The debate about the possible factors of the causal association between handgrip strength and morbidity risks has not been well-studied. Some of these factors are difficult to assess because they are not always constant, especially over long-term follow-up. For example, several studies have discussed the impact of physical activity as a mediating factor between handgrip strength and morbidity/mortality [5] [14] [15] [16] [17]. However, although the association between handgrip strength and physical activity is evident in cross-sectional studies, it has not been confirmed in longitudinal studies [18]. Additionally, many types of physical activity (e.g., aerobic- or resistance-type training with upper body and/or lower body movements) may impact handgrip strength differently [19] [20]. Therefore, it is essential to investigate the interventional effects of different types of physical activity on handgrip strength.

A recent systematic review and meta-analysis reported statistically significant but small intervention effects (standardized mean difference: 0.28, $p < 0.001$) of different training types on handgrip strength in healthy community-dwelling older adults [19]. Other systematic reviews and meta-analyses reported on the impact of resistance training on handgrip strength, but the participants of these studies were older than 60 years [21] [22] [23] [24]. Therefore, investigating the effects of resistance training on handgrip strength in adults of all ages, including young adults, is warranted to understand the effects of physical activity on handgrip strength. Thus, this study investigated the impact of various types of resistance training interventions on handgrip strength in apparently healthy adults. Similar to the results for older adults, we hypothesized that although the

impact of resistance training on handgrip strength would be statistically significant in younger adults, the impact of the intervention would be negligible.

## 2. Methods

We performed this systematic review according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement [25]. The study was pre-registered (February 5, 2023) in the International Prospective Register of Systematic Review (PROSPERO) (CRD42023394028).

### 2.1. Search Strategy

English-language searches of the electronic databases and search engines Medline (PubMed), Scopus, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar were conducted from inception to February 15, 2023, by two independent researchers (T.A. and R.V.). The reference lists of included studies were searched to locate any further relevant articles not found with the initial search.

Articles were retrieved from electronic databases and search engines combining the following terms: (handgrip strength OR grip strength OR physical function OR sarcopenia) AND (resistance training OR strength training OR home-based exercise OR power training OR elastic band) AND (healthy adults OR elderly OR older people OR community-dwelling). No filters were applied to the searched databases to prevent omitting irrelevant articles.

Initially, all files were extracted from databases in either RIS format (Scopus, Web of Science, CENTRAL, and Google Scholar) or nbib format (Medline). The files were then uploaded into Rayyan software, where the titles and abstracts of identified articles were checked for relevance. Subsequently, the reviewers independently reviewed the full text of potentially eligible papers. Any disagreements between the reviewers on inclusion were resolved by a consensus between both researchers (T.A. and R.B.V.). After that, all files selected for inclusion were retrieved from Rayyan software and uploaded into Mendeley software, which was used as a reference management tool to write the first draft of this manuscript.

### 2.2. Inclusion and Exclusion Criteria: Participants, Interventions, Comparators, Outcomes, and Study Design

The PICOS (population, intervention, comparison, outcome, and study design) framework [25] was used to guide this systematic review. *Population:* Healthy individuals (≥18 years) with and without sarcopenia (low handgrip strength, slow walking speed, and low muscle mass). *Intervention* (*exposure*): Different types of resistance training interventions with any session duration (e.g., 30 minutes, 45 minutes), and any weekly frequency (e.g., number of days per week). *Comparison*: Non-intervention control group. A group of individuals who were not exposed to any exercise or active intervention. *Outcome*: Changes in handgrip strength. *Study design*: Any randomized or non-randomized clinical trials com-

paring different types of resistance exercise intervention versus a non-intervention control group on handgrip strength. Studies enrolling individuals with obesity and/or chronic diseases (e.g., heart disease, diabetes, cancer, chronic lung disease, stroke, Alzheimer, chronic kidney disease) were excluded from this review.

Randomized clinical trials were included in the review if they met the following selection criteria: 1) a research question on the effects of a resistance training intervention, 2) adults or older adult participants without chronic disease (e.g., heart disease, diabetes, cancer, chronic lung disease, stroke, Alzheimer, chronic kidney disease), 3) compared the resistance training intervention with a non-intervention control group, 4) reported at least one outcome related to handgrip strength, and 5) written in English language. Studies were excluded based on the following file types: abstracts, study protocols, conference papers, books, book sections, theses, opinion articles, observational studies, letters to editor, and reviews. Furthermore, studies that used combined interventions (e.g., resistance training plus any other type of intervention [drug, nutritional supplement…]) were excluded from this systematic review. To address our main purpose, studies applying only handgrip strength training were excluded from this review. Comparison groups and study types were not included in the search strategy but were used as inclusion criteria.

### 2.3. Data Extraction

The following study characteristics were extracted: authors, publication year, study design, participants' characteristics (sample size, age, sex, and health status), changes in handgrip strength, device used to test handgrip strength, and characteristics of the exercise intervention program (type and intensity of exercise program, exercise frequency, and duration of intervention program). These data were extracted manually and independently by two researchers (T.A. and R.V.), with disagreements resolved by consensus between both researchers. All data were typed into an excel spreadsheet file and later manually transferred to a word file. When the data reported in the articles were insufficient, additional information was requested from the corresponding authors.

### 2.4. Risk of Bias Assessment

Two authors (R.V. and S.D.) independently assessed the risk of bias in randomized and non-randomized included studies using version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) [26] and the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) [27], respectively. RoB 2 assess randomized trials in the following aspects: 1) bias arising from the randomization process, 2) bias due to deviations from the intended interventions, 3) bias due to missing outcome data, 4) bias in the measurement of the outcome, and 5) bias in the selection of the reported results. The overall risk of bias was expressed as "low risk of bias" if all domains were rated as low risk, "some con-

cerns" if some concern was raised in at least one domain but not rated as high risk in any other, or "high risk of bias" if at least one domain was rated as high risk or has several domains with some concerns [26]. ROBINS-I assess non-randomized trials in the following aspects: a) bias due to confounding, b) bias in selection of participants into the study, c) bias in classification of interventions, d) bias due to deviations from intended interventions, e) bias due to missing data, f) bias in measurement of outcomes, g) bias in selection of the reported result [27]. Traffic light and weighted summary risk-of-bias plots for randomized and non-randomized included studies were produced by the online Risk of bias (robvis) tool (https://mcguinlu.shinyapps.io/robvis/). Any discrepancies were resolved through discussion between both researchers (R.V. and S.D.).

### 2.5. Statistical Analysis

The available data did not allow us to conduct the pre-planned meta-analyses. Thus, only descriptive statistics were performed to summarize data, including the main participants' characteristics, interventions characteristics, handgrip measurements, and main results reported by the included studies.

## 3. Results

### 3.1. Included Studies

Twenty studies were included in this systematic review [28]-[47]. **Figure 1** presents the flow of papers through the study selection process. The included studies were published from 1995 [42] up to 2021 [34], in which six are randomized controlled trials [28] [34] [36] [40] [45] [47], ten are randomized trials [30] [31] [32] [33] [35] [37] [39] [42] [43] [46], one is cluster randomized controlled trial [29], and three are non-randomized trials [38] [41] [44] (**Table 1**).

### 3.2. Participant Characteristics

Participants' characteristics are summarised in **Table 1**. Most of the included studies (95%, n = 19) were conducted with older adults [28]-[42] [44] [45] [46] [47], while only one study was conducted with young adults [43]. Almost half (45%, n = 9) of the included studies clearly stated that were conducted with healthy individuals [30] [31] [32] [33] [36] [37] [39] [42] [43], the remaining studies were conducted with older adults without experience in resistance training [38] [40] [45], older women with cognitive impairment [35], prefrail and frail older adults [44], sedentary older men [34], community-dwelling older adults receiving home care [29], community-dwelling and independent older adults [47], sarcopenic and recreationally active older adults [46], postmenopausal women [28], and older inner-city African American women [41].

The number of participants in each study varied from 22 [41] to 419 [37]. Eight studies examined exclusively women [28] [33] [35] [36] [38] [39] [41] [42], one exclusively men [34], whilst 11 studies assessed men and women [29] [30]

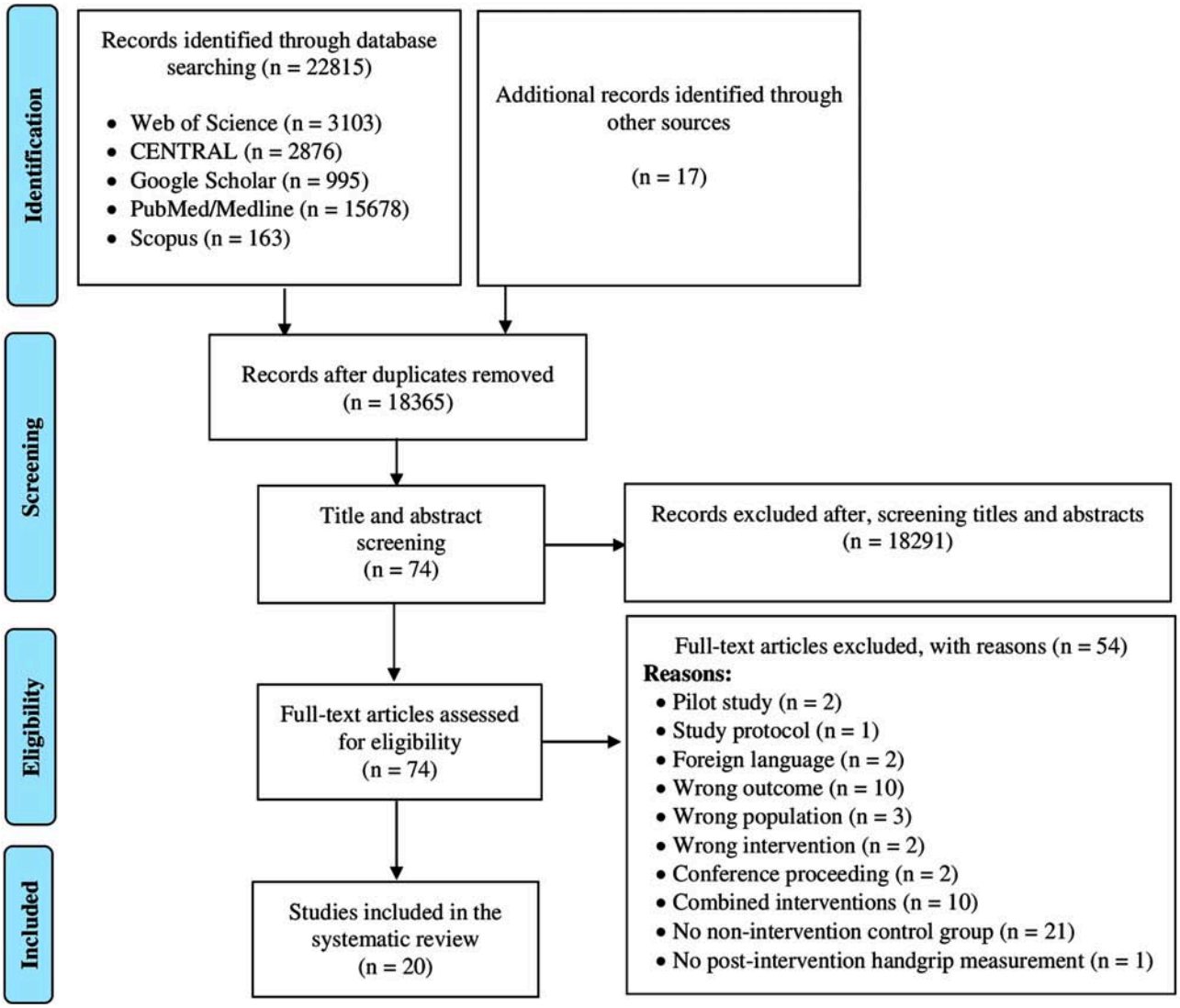


**Figure 1.** Flowchart of the study selection process.

[31] [32] [37] [40] [43] [44] [45] [46] [47].

### 3.3. Intervention Characteristics

Resistance training programmes are summarised in **Table 2**. Most of the studies (70%, n = 14) applied one resistance training intervention [29] [31] [32] [33] [35] [38] [39] [41]-[47], five studies (25%) applied two different resistance training interventions [28] [30] [34] [36] [37], and the remaining study applied four different resistance training interventions [40]. Resistance training protocols were composed of heavy or moderate intensity or slow eccentric/concentric resistance exercises with rubber bands, elastic band, water canes and/or own body weight [29] [31] [37] [45] [46], whole-body resistance exercises [39] [44], home-based resistance exercises [42] [43], functional-task exercises [28] [36], suspension resistance exercises [33] [34], chair-based elastic resistance exercises [35] [41], traditional moderate/high-intensity resistance exercises [32] [47],

**Table 1.** Characteristics of the participants of the included studies (n = 20).

| Study | Study design | Sex (n) | Age (years)[a] | Body mass (kg)[a] | Height (cm)[a] | BMI (kg/m$^2$)[a] | Health status |
|---|---|---|---|---|---|---|---|
| Aragão-Santos *et al.* (2020) | Randomized controlled trial | EBFT: 13F<br>TSBFT: 15F<br>CON: 11F | EBFT: 65.2 (4.3)<br>TSBFT: 66.0 (5.2)<br>CON: 66.1 (4.1) | EBFT: 67.4 (12.9)<br>TSBFT: 69.8 (13.5)<br>CON: 70.4 (9.5) | EBFT: 153.9 (6.2)<br>TSBFT: 151.7 (4.8)<br>CON: 154.3 (3.3) | EBFT: 28.47 (5.22)<br>TSBFT: 30.31 (5.65)<br>CON: 29.54 (3.62) | Postmenopausal women |
| Bårdstu *et al.* (2020) | Cluster randomized controlled trial | RT: 42F/22M<br>CON: 22F/21M | RT: 86.5 [80 - 90]<br>CON: 86.0 [80 - 90] (median & IQR) | RT: 66.5 [55.5 - 79.5]<br>CON: 70.4 [62.4 - 80.2] (median & IQR) | RT: 160 (9)<br>CON: 164 (9) | RT: 25.1 [23.6 - 28.1]<br>CON: 27.0 [23.7 - 30.3] (median & IQR) | Community-dwelling older adults receiving home care |
| Bezerra *et al.* (2018) | Randomized trial | MJ: 7F/4M<br>MJ+SJ: 5F/6M<br>CON: 4F/4M | MJ: 63.2 (5.7)<br>MJ + SJ: 64.6 (4.8)<br>CON: 65.0 (6.0) | MJ: 76.7 (13.9)<br>MJ + SJ: 76.1 (18.0)<br>CON: 68.4 (12.4) | MJ: 1.69 (0.86) m<br>MJ+SJ: 1.66 (0.11) m<br>CON: 1.65 (0.71) m | Not reported | Untrained healthy aging adults |
| Bunout *et al.* (2004) | Randomized trial | SE: 21F/10M<br>SN: 16F/12M<br>NE: 12F/4M<br>NN: 17F/16M | SE: 74.0 (3.6)<br>SN: 74.7 (3.8)<br>NE: 74.4 (3.27)<br>NN: 73.7 (3.6) | SE: 66.2 ± 11.9<br>SN: 61.9 ± 11.2<br>NE: 62.2 ± 10.11<br>NN: 68.7 ± 12 | SE: 155.7 ± 9.1<br>SN: 153.8 ± 9.1<br>NE: 151.5 ± 8.76<br>NN: 154.1 ± 10.3 | 27.4 (4.6)<br>Reported total sample value | Healthy, non-institutionalized older adults |
| Bunout *et al.* (2005) | Randomized trial | RT: 94F/17M<br>CON: 92F/38M | RT-F: 75.1 (4.5)<br>RT-M: 74.6 (5.8)<br>CON-F: 74.8 (4.6)<br>CON-M: 75.2 (4.4) | RT-F: 60.4 (10.0)<br>RT-M: 71.2 (11.8)<br>CON-F: 59.3 (9.7)<br>CON-M: 68.3 (10.4) | RT-F: 147.5 (6.2)<br>RT-M: 165.2 (5.6)<br>CON-F: 146.8 (6.1)<br>CON-M: 162.3 (6.6) | Not reported | Healthy Chilean older adults |
| Campa *et al.* (2021) | Randomized controlled trial | 36M | 67.4 (5.1) | 76.6 (10.7) | 1.68 (0.72) m | 27.1 (3.3) | Sedentary older men |
| Campa *et al.* (2018) | Randomized trial | RT: 15F<br>CON: 15F | RT: 66.5 (4.3)<br>CON: 65.6 (5.2) | RT: 72.7 (12.1)<br>CON: 77.1 (7.1) | RT: 158.7 (4.7)<br>CON: 155.3 (10.2) | RT: 28.8 (4.6)<br>CON: 32.4 (5.6) | Healthy older women |

**Continued**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Chupel *et al.* (2017) | Randomized trial | RT: 16F CON: 17F | RT: 83.50 (5.13) CON: 82.12 (6.41) | RT: 66.26 (16.35) CON: 67.45 (14.57) | RT: 150.4 (0.08) CON: 150.8 (0.06) | RT: 29.27 (7.10) CON: 29.67 (5.98) | Older women with mild cognitive impairment |
| de Vreede *et al.* (2005) | Randomized controlled trial | RT: 34F FT: 33F CON: 31F | RT: 74.8 (4.0) FT: 74.7 (3.5) CON: 73.0 (3.2) | RT: 70.7 (12.1) FT: 69.4 (9.0) CON: 71.3 (11.4) | RT: 1.62 (0.08) m FT: 1.63 (0.06) m CON: 1.62 (0.06) m | Not reported | Community-dwelling healthy older women |
| Gylling *et al.* (2020) | Randomized trial | HRT: 143FM MRT: 144FM CON: 132FM | 62 - 70 Reported total sample value | 75.5 (14.3)[c] Reported total sample value | Not reported | 25.8 (4.1)[c] Reported total sample value | Independently healthy and chronically diseased men and women |
| Pereira *et al.* (2012) | Non-randomized trial | RT: 28F CON: 28F | RT: 62.5 (5.4) CON: 62.2 (4.3) | RT: 68.2 (11.2) CON: 66.2 (10.9) | RT: 1.55 (0.06) CON: 1.57 (0.06) | RT: 28.2 (4.0) CON: 27.0 (3.2) | Older women without experience in resistance training |
| Rhodes *et al.* (2000) | Randomized trial | RT: 22F CON: 22F | RT: 68.8 (3.2) CON: 68.2 (3.5) | RT: 68.4 (12.0) CON: 61.7 (12.9) | RT: 160.9 (5.5) CON: 159.3 (4.5) | Not reported | Healthy sedentary older women |
| Richardson *et al.* (2019) | Randomized controlled trial | HVLL1: 5F/5M HVLL2: 5F/5M LVHL1: 5F/5M LVHL2: 5F/5M CON: 5F/5M | HVLL1: 66 (5) HVLL2: 67 (6) LVHL1: 67 (4) LVHL2: 66 (6) CON: 65 (5) | HVLL1: 80.0 (16.9) HVLL2: 83.2 (13.5) LVHL1: 76.3 (11.8) LVHL2: 73.0 (13.4) CON: 71.4 (12.7) | HVLL1: 168.7 (7.4) HVLL2: 173.3 (9.7) LVHL1: 167.2 (11.1) LVHL2: 166.8 (8.9) CON: 170.4 (9.5) | HVLL1: 28 (5) HVLL2: 28 (5) LVHL1: 28 (5) LVHL2: 26 (4) CON: 24 (3) | Moderately-highly active, but resistance exercise naïve older adults |
| Rogers *et al.* (2002) | Non-randomized trial | RT: 16F CON: 6F | RT: 74.8 (8.8) CON: 74.7 (4.5) | Not reported | Not reported | RT: 24.4 (1.9) CON: 24.1 (2.3) | Older African American women |

**Continued**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Skelton *et al.* (1995) | Randomized trial | RT: 20F CON: 20F | RT: median 79.5 (range: 76 - 93) CON: median 79.5 (range: 75 - 90) | RT: 54.1 (9.1) CON: 61.5 (11.4) | RT: 1.54 (0.07) m CON: 1.57 (0.07) m | Not reported | Healthy older women |
| Thomas *et al.* (2008) | Randomized trial | RT: 9F[b] CON: 11F[b] | F: 24.6 (2.6) M: 25.9 (3.0) | F: 60.6 (7.5) M: 77.4 (10.1) | F: 168.2 (4.3) M: 180.9 (5.5) | Not reported | Young healthy adults |
| Tieland *et al.* (2015) | Non-randomized trial | RT: 41F/21M CON: 36F/29M | RT: 78.4 (8.1)[c] CON: 79.5 (7.9)[c] | RT: 78.5 (14.2)[c] CON: 74.0 (12.9)[c] | RT: 1.66 (0.08) m[c] CON: 1.66 (0.08) m[c] | Not reported | Prefrail and frail older adults |
| Tsuzuku *et al.* (2018) | Randomized controlled trial | RT: 17F/25M CON: 18F/26M | RT: 72.5 (2.1) CON: 73.2 (2.1) | RT: 57.2 (9.9) CON: 55.7 (9.6) | Not reported | RT: 23.2 (2.6) CON: 22.4 (2.4) | Older adults without experience in resistance training |
| Vezzoli *et al.* (2019) | Randomized trial | RT: 10F/10M CON: 9F/6M | RT: 73.0 (5.5) CON: 71.7 (3.4) | RT: 76.3 (16) CON: 69.8 (15.0) | RT: 1.65 (0.1) m CON: 1.62 (0.1) m | RT: 27.7 (4.4) CON: 26.6 (3.5) | Sarcopenic and recreationally active older adults |
| Wanderley *et al.* (2015) | Randomized controlled trial | AT: 18F/6M RT: 7F/12M CON: 24F/7M | AT: 70.0 (5.7) RT: 67.3 (4.9) CON: 67.8 (5.5) | AT: 65.6 (3.0) RT: 71.7 (3.5) CON: 71.6 (2.6) | Not reported | AT: 27.5 (0.9) RT: 28.9 (1.0) CON: 28.5 (0.8) | Community-dwelling and independent older adults |

RT: resistance training. CON: control group. EBFT: element-based functional training. TSBFT: task-specific-based functional training. FT: function training. MJ: multi-joint resistance training. MJ+SJ: multi-plus single-joint resistance training. SE: supplemented and trained. SN: supplemented and non-trained. NE: non-supplemented and trained. NN: non-supplemented and non-trained. HVLL1: high-velocity, low-load once-weekly. LVHL1: low-velocity, high-load once-weekly. HVLL2: high-velocity, low-load twice-weekly. LVHL2: low-velocity, high-load twice-weekly. F: female. M: male. FM: female and male, m: meters. [a]Data presented as mean (standard deviation) or median [interquartile range] or amplitude (minimum – maximum). [b]Total sample size was 41 individuals (27 females and 14 males), but only females were enrolled in the interventions (resistance training [n = 15] or control group [12]). [c]Standard error was converted to standard deviation.

high-speed power exercises [38], high-velocity low-load and low-velocity high-load resistance exercise,40 and low volume multi-joint resistance exercises or a combination of multi- and single-joint resistance exercises [30].

**Table 2.** Characteristics of the resistance training interventions of the included studies (n = 20).

| Study | Groups (n) | RT interventions | #weeks (#sessions) | Sets (repetitions) | Session duration | Rest interval | Supervision | Intensity control/ monitoring |
|---|---|---|---|---|---|---|---|---|
| Aragão-Santos *et al.* (2020) | EBFT: 13<br>TSBFT: 15<br>CON: 11 | EBFT: 1 - 18 sessions composed by 8 exercises (squat in the smith, seated row, leg press 45˚, upright bench press, hamstring curl bilateral, lat pull-down, standing calf raises, and stiff) at RPE of 7 - 9. 18 - 36 sessions composed by 8 exercises (squat, seated row, knee extension, bench press, hamstring curl unilateral, seated row, leg press calf raises, and abdominal sit up) at RPE of 7 - 9.<br>TSBFT: 1 - 18 sessions composed by 8 exercises (deadlift with kettlebell, suspension strap row, sit and stand up, push with elastic, farmers walk [kettlebell], row with elastics, hip lift bilateral, and plank front [bench 40 cm]) at RPE of 7-9. 18-36 sessions composed by 8 exercises (deadlift with sandbag, suspension strap row, squat with kettlebell, push-ups in a bench of 60 cm, farmers walk [kettlebell], row with knee elevation, hip lift unilateral, and plank front [step 15 cm]) at RPE of 7-9. | 14 weeks (3x/week) | 2 sets (8 - 10 repetitions) | ~50 min (25 min for RT exercises) | Not clearly reported | Yes | RPE of 7 - 9 (scale was not clearly reported) |
| Bårdstu *et al.* (2020) | RT: 64<br>CON: 42 | RT: 5-7 exercises (rowing, chest press, squats, biceps curl, knee extension, shoulder press, and up-and-go) using elastic bands, body weight, and water canes. | 35 weeks (2x/week) | 2 - 4 sets (8 - 12 repetitions) | 30 - 45 min | Not clearly reported | Yes | Until fatigue (*i.e.*, unable to complete more repetitions with proper technique) |

**Continued**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Bezerra *et al.* (2018) | MJ: 11<br>MJ+SJ: 11<br>CON: 8 | MJ: cable chest press and seated row.<br>MJ+SJ: cable chest press, seated row, elbow flexion, and elbow extension.<br>Complementary program was performed by both MS and MJ+SJ groups: horizontal leg press and seated leg curl. | 8 weeks (3x/week) | MJ: 2 sets (12 RM)<br>MJ+SJ: 1 set (12 RM)<br>Complementary program: 1 set of 10, 5, and 6 repetitions | Not clearly reported | MJ or MJ+SJ: 1 min<br>Complementary program: 2 min | Yes | Until momentary failure (in the final set) |
| Bunout *et al.* (2004) | SE: 31<br>SN: 28<br>NE: 16<br>NN: 33 | Exercise: Training consisted in a period of warming up and 3 levels of chair stands, 3 levels of modified squats (5 sets of 10 repetitions; levels included squats without therabands or with therabands to increase gravitational force), 3 levels of step ups in a stair (10 sets of 10 repetitions; levels included one step, two steps and two steps without using the hand rails) and 6 sets of 15 repetitions of arm pull-ups using rubber bands that are color coded to confer progressive resistance. | 1 year (2x/week) | 5 - 10 sets (10 - 15 repetitions) | 60 min | Not clearly reported | Yes | Until fatigue (not clearly defined) |
| Bunout *et al.* (2005) | RT: 111<br>CON: 130 | RT: moderate intensity resistance exercise training (functional weight bearing exercises, chair stands, modified squats, arm pull-ups using rubber bands, 15 min walking before and after resistance exercises). | 1 year (2x/week) | 5 - 10 sets (10 - 15 repetitions) | 60 min | Not clearly reported | Yes | Until fatigue (not clearly defined) |
| Campa *et al.* (2021) | ST: 11<br>TT: 11<br>CON: 11 | Suspension training (ST): squat, biceps curl, chest press, low row, rotational ward, squat with Y deltoid fly, and triceps pushdown.<br>Traditional training (TT): squat, alternating lunge, alternating curl with elastic tube, push up, plank, row with elastic tube, and alternating lateral raise with elastic tub. | 12 weeks (3x/week) | 3 sets (12 repetitions) | ~60 min | 1 min | Yes | RPE of 13 (from 6 to 20 Borg scale) |

**Continued**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Campa *et al.* (2018) | RT: 15<br>CON: 15 | RT: program initially included very low-load joint mobility exercises, then squat, rear deltoid row, biceps curl, chest press, low row, rotational ward, and stretching. | 12 weeks (2x/week) | 4 sets (12 repetitions) | 60 min | 1 min | Yes | Partici-pants were free to modulate the exercise intensity by changing the body's inclina-tions |
| Chupel *et al.* (2017) | RT: 16<br>CON: 17 | Chair-based elastic band RT group: warm-up (body mobilization and dynamic stretching), 8 - 10 elastic-band exercises using the yellow and red colors levels of elastic bands, and cool-down (specific exercises with easy stretching). | 28 weeks (2x/week for 8 weeks, 3x/week for 12 weeks, and 2x/week for 8 weeks) | Phase 1: 1 - 2 sets (10 - 12 repetitions) Phase 2: 2 - 3 sets (10 repetitions) | 45 min | 45 sec | Yes | RPE of 6 to 8 (from 0 to 10 OMNI scale) |
| de Vreede *et al.* (2005) | RT: 34<br>FT: 33<br>CON: 31 | RT: core resistance exercises included elbow flexors and extensors, shoulder abductors adductors and rotators, trunk flexors and extensors, hip flexors extensors abductors and adductors, knee flexors and extensors, and ankle dorsal and plantar flexors. FT: The program was divided into a practice phase (2 weeks), a variation phase (4 weeks), and a daily tasks phase (6 weeks). | 12 weeks (3x/week) | 3 sets (10 repetitions) | 60 min | ~2 min | Yes | RPE of 7 to 8 (from 0 to 10 OMNI scale |
| Gylling *et al.* (2020) | Heavy RT: 143<br>Moderate RT: 144<br>CON: 132 | A progressive whole-body training program with increasing load was performed in both training groups. Heavy RT was a linear periodized regime using fitness machines. Moderate RT performed with rubber bands and own body weight. | 1 year (3x/week) | Heavy RT: 3 sets (6 - 12 repetitions) Moderate RT: 3 sets (10 - 18 repetitions) | Not clearly reported | Not clearly reported | Yes | Heavy RT: ~70% - 85% of 1RM Moderate RT: ~50% - 60% of 1RM |

**Continued**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Pereira *et al.* (2012) | RT: 28<br>CON: 28 | RT: high-speed power training composed by 10-minute warm-up (brisk walking and several joint mobilization exercises), followed by the leg extension and bench press training was initiated. In each session, they performed curl-ups (3 sets of 12 reps) and lumbar exercises (3 sets of 10 reps). Two power exercises were then performed: the counter movement jump and medicine ball throw (1.5 kg). | 12 weeks (3x/week) | RT: 3 sets (4 - 12 repetitions) | 60 min | 2 min (between sets)<br>3 min (between exercises) | Yes | 40% - 75% of 1RM |
| Rhodes *et al.* (2000) | RT: 22[b]<br>CON: 22[b] | RT: a whole-body progressive resistance training was applied in a circuit fashion. The circuit included large muscle exercises—for example, chest press, leg press, biceps curl, triceps extension, quadriceps curl, hamstrings curl. The first 3 months were performed under fully supervision and for the remaining nine months, subjects exercised in recreation facilities close to their homes. homes. They continued with the same volume (three sets, eight repetitions) of weight lifted while the training stimulus exact weight was adjusted every two weeks. | 1 year (3x/week) | RT: 3 sets (8 repetitions) | 60 min | Not clearly reported | Yes (in the first 3 months) | 75% of 1RM |
| Richardson *et al.* (2019) | HVLL1: 10<br>HVLL2: 10<br>LVHL1: 10<br>LVHL2: 10<br>CON: 10 | HVLL1 and HVLL2: concentric phase was performed "as fast as possible" followed by a 3-sec eccentric phase. LVHL1 and LVHL2: concentric phase was performed over 2-sec with a 3-sec eccentric phase. | HVLL1 and LVHL1: 10 weeks (1x/week)<br>HVLL2 and LVHL2: 10 weeks (2x/week) | HVLL1 and HVLL2: 3 sets (14 repetitions)<br>LVHL1 and LVHL2: 3 sets (7 repetitions) | Not clearly reported | 1.5 min (between sets)<br>3 min (between exercises) | Yes | HVLL1 and HVLL2: 40% predicted 1RM<br>LVHL1 and LVHL2: 80% predicted 1RM |

**Continued**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Rogers *et al.* (2002) | RT: 16<br>CON: 6 | RT: Warm-up (range of motion) activities, followed by strength training exercises (chair-based exercises for the upper body [chest, back, biceps, and triceps] using elastic fabands/dumbbells and the lower body [knee extension, knee flexion, leg press, toe raises, heel raises, foot abduction, and side leg lifts] using elastic bands), and relaxation activities. | 4 weeks (3x/week) | 3 sets (8 - 15 repetitions) | 50 min | Not clearly reported | Yes (an exercise science student instructed the classes) | When subjects could easily complete 15 repetitions of an exercise, they were encouraged to increase load (rubber band or dumbbells) |
| Skelton *et al.* (1995) | RT: 20<br>CON: 20 | RT: Groups of four to six women performed progressive resistance training once a week and were also asked to complete two unsupervised home sessions per week following an exercise prescription. Each class began with a 10-minute warm-up and stretch of the main muscle groups being trained; correct posture was stressed. The 30 to 40-minute strengthening component of the class involved exercises for shoulder and hip abductors, adductors, flexors and extensors, elbow flexors and extensors, and knee flexors and extensors. There was a 10-minute warm-down component at the end of the class. | 12 weeks (3x/week) | 3 sets (4 - 8 repetitions with body weight, rice bags [1 - 1.5 kg], or elastic tubing) | 50 - 60 min | Not clearly reported | Partially (1 of the 3 weekly sessions) | Resistances were initially chosen so that the subject could almost complete 3 sets of 4 repetitions. As soon as a subject could complete 3 sets of 8 repetitions of an exercise, the resistance was increased, and the number of repetitions was reduced. |
| Thomas *et al.* (2008) | RT: 9[a]<br>CON: 11[a] | RT: home-based resistance training program for the upper extremities (push-ups in the prone position, dips in the supine position, and shoulder stabilization in the prone position). | 8 weeks (3x/week) | First 4 weeks: 3 sets (10 repetitions) Remaining weeks: 3 sets (15 repetitions) | Not clearly reported | Not clearly reported | Not clearly reported | Not clearly reported. |

**Continued**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Tieland *et al.* (2015) | RT: 62<br>CON: 65 | RT: whole body resistance-type exercise training program (leg press, leg extension, chest press, lat pull-down, pec-dec, and vertical row). | 24 weeks (2x/week) | 3 - 4 sets (started 10 - 15 repetitions, changed to 8 - 10 repetitions due to workload increase) | Not clearly reported. | 1 min (between sets)<br>2 min (between exercises) | Yes | Started at 50% and increased to 75% of 1RM |
| Tsuzuku *et al.* (2018) | RT: 42<br>CON: 44 | RT: squat, tabletop push-up, and sit-up, performing slowly eccentric and concentric phase (4 sec for each movement) using body weight as a load. | 12 weeks (median of 5x/week) | 2 sets (10 - 14 repetitions) | 15 min | Not clearly reported | Yes (clinic session only, but not at home) | Exercise load varies from person to person due to body mass-based resistance exercise. |
| Vezzoli *et al.* (2019) | RT: 20<br>CON: 15 | RT: chest press, horizontal leg-press, vertical row, and shoulder exercises with free weights (lateral raise) exercises. | 12 weeks (3x/week) | 3 sets (14 - 16 repetitions) | Not clearly reported. | 1 min | Yes | 60% of 1RM |
| Wanderley *et al.* (2015) | AT: 24<br>RT: 19<br>CON: 31 | RT: 10-min warm-up that included stretching, gymnastics, and low intensity exercises (walking, biking), nine resistance exercises (leg press, chest press, leg extension, seated row, seated leg curl, abdominal flexion, biceps curl, low-back extension, and triceps extension), and a 10-min cooldown. | 8 months (3x/week) | 1st month: 2 sets (12 - 15 repetitions)<br>2nd to 8th month: 2 sets (8 - 12 repetitions) | 50 min | 2 min | Yes | 1st month: 50% - 60% of 1RM; RPE of 4 to 6 (from 0 to 10 Borg scale)<br>2nd to 8th month: 80% of 1RM; RPE of 7 (from 0 to 10 Borg scale) |

RT: resistance training. CON: control group. EBFT: element-based functional training. TSBFT: task-specific-based functional training. FT: functional-task exercise. ST: suspension training. TT: traditional training. MJ: multi-joint resistance training. MJ+SJ: multi- plus single-joint resistance training. SE: supplemented and trained. SN: supplemented and non-trained. NE: non-supplemented and trained. NN: non-supplemented and non-trained. HVLL1: high-velocity, low-load once-weekly. LVHL1: low-velocity, high-load once-weekly. HVLL2: high-velocity, low-load twice-weekly. LVHL2: low-velocity, high-load twice-weekly. RPE: rating of perceived exertion. 1RM: one-maximum repetition. AT: aerobic training. $HR_{reserve}$: reserve heart rate. min: minute. sec: seconds. [a]Total sample size was 41 individuals (27 females and 14 males), but only females were enrolled in the interventions (resistance training [n = 15] or control group [12]). [b]The final testing, one year later, included 20 exercisers and 18 control subjects.

Intervention duration ranged from four weeks [41] to one year [31] [32] [37] [39], with 12 weeks being the most common (35%, n = 7) [33] [34] [36] [38] [42] [45] [46]. More than half of the resistance training protocols (60%, n = 12) were performed thrice a week [28] [30] [34] [36] [37] [38] [39] [41] [42] [43] [46] [47]. Five protocols were performed two times per week [29] [31] [32] [33] [44],

one protocol was performed one to two times per week [40], one protocol was performed two to three times per week [35], and one protocol was performed five times per week [45]. Session duration ranged from 15 [45] to 60 minutes [31] [32] [33] [34] [36] [38] [39], with 60 minutes being the most common (35%, n = 7), followed by 50 minutes (15%, n = 3) [28] [41] [47]. Six studies (30%) did not clearly report the session duration [30] [37] [40] [43] [44] [46].

The number of sets per exercise ranged from one [35] to 10 [31] [32], with three sets (50%, n = 10) being the most common [34] [36]-[43] [46] (**Table 2**). Most of the studies (75%, n = 15) adopted a range of eight to 15 repetitions per set [28]-[36] [39] [41] [43] [44] [45] [47].

The intensity of effort for resistance training protocols was mostly prescribed and monitored by the percentage of one-repetition maximum (35%, n = 7) [37] [38] [39] [40] [44] [46] [47], and rating of perceived exertion (20%, n = 4) [28] [34] [35] [36]. The remaining studies used participants' body weight, rubber bands, rice bags, or dumbbells [33] [41] [42] [43] [45] or encouraged the participants to perform the repetitions until fatigue/momentary failure [29] [30] [31] [32].

Half of the studies (50%, n = 10) did not clearly report the rest interval between sets and/or exercises [28] [29] [31] [32] [37] [39] [41] [42] [43] [45]. Five studies (25%) applied a one-minute rest interval between sets [30] [33] [34] [40] [46], three studies (15%) applied two minutes [36] [38] [47], and one study applied 45 seconds [35]. Three studies clearly reported a rest interval between exercises of three minutes [38] [40] and only one study reported two minutes [44].

Sixteen studies (80%) provide supervision for all training sessions [28]-[38] [40] [41] [44] [46] [47], one study for the first three months of one-year intervention period [39], one study for one of three weekly sessions [42], and one study for only clinic session, but not home sessions [45]. The remaining study [43] did not clearly report the information about supervision.

### 3.4. Handgrip Measurements

Settings of the handgrip strength measurements are summarised in **Table 3**. Eighteen studies (90%) used electronic, digital, or mechanical hand dynamometers, while the remaining two studies [28] [42] did not clearly report what instrument was used to measure handgrip strength. Half of the included studies (50%, n = 10) did not clearly report which position (e.g., standing or sitting) and elbow angle were adopted for handgrip strength measurement [29] [31] [32] [36] [37] [39] [40] [41] [42] [47], seven studies (35%) adopted a sitting position with a 90˚ elbow flexion position [28] [30] [33] [34] [38] [43] [44], and three studies (15%) adopted a standing position [35] [45] [46], in which two of these three studies asked for participants to keep their upper limbs along the side of the body [35] [46], and one study did not report the arm and/or elbow position [45].

Most of the studies (55%, n = 11) measured both left and right participants'

**Table 3.** Main results of the resistance training and control groups of the included studies (n = 20).

| Study | Handgrip measurement | Position | Hand | Handgrip strength results | | RT group compared to control group |
|---|---|---|---|---|---|---|
| Aragão-Santos *et al.* (2020) | Not clearly reported | Sitting position at a 90˚ elbow flexion position | Left<br>Right | EBFT: ↔<br>TSBFT: ↑<br>CON: ↓<br>No significant between-group differences. | - | ↔<br>↔ |
| Bårdstu *et al.* (2020) | Handheld dynamometer (Baseline® Hydraulic Hand Dynamometer, Elmsford, NY, USA) | Not clearly reported | Preferred arm | RT: ↔<br>CON: ↔<br>No significant between-group differences. | - | ↔ |
| Bezerra *et al.* (2018) | Hand dynamometer (Saehan Corporation®, 973, Yangdeok-Dong, Masan, Korea) | Sitting position at a 90˚ elbow flexion position | Left<br>Right | MJ: ↑<br>MJ+SJ: ↑<br>CON: ↔<br>No significant group effect. No significant group × time interaction. | - | ↔<br>↔ |
| Bunout *et al.* (2004) | Hand grip dynamometer (Therapeutic Instruments, Clifton NJ, USA) | Not clearly reported | Left<br>Right | Right hand:<br>NE: ↑<br>NN (CON): ↔<br>No significant between-group differences. | Left hand:<br>NE: ↑<br>NN (CON): ↔<br>No significant between-group differences. | ↔↔ |
| Bunout *et al.* (2005) | Hand grip dynamometer (Therapeutic Instruments, Clifton NJ, USA) | Not clearly reported | Dominant | RT: ↔<br>CON: ↔<br>No significant between-group differences. | - | ↔ |
| Campa *et al.* (2021) | Dynamometer (Takei Scientific Instruments Co., Niigata, Japan) | Sitting position at a 90˚ elbow flexion position | Dominant | ST: ↑<br>TT: ↔<br>CON: ↓<br>Significant group × time interaction. | - | ↑<br>↔ |
| Campa *et al.* (2018) | Dynamometer (Takei K.K. 5001, Takei Scientific Instruments Ltd., Niigata, Japan) | Sitting position at a 90˚ elbow flexion position | Dominant | ST: ↑<br>CON: ↓<br>Significant group by time interaction. | - | ? |

**Continued**

| | | | | | | |
|---|---|---|---|---|---|---|
| Chupel *et al.* (2017) | Dynamometer (Lafayette, 78010, Indiana, USA) | Standing position with the elbow at the side of the body | Left<br>Right | RT: ↑<br>CON: ↔<br>Significant difference between groups. | - | ↑ |
| de Vreede *et al.* (2005) | Handgrip dynamometer (Takei Kiki Kogyo 5101, Tokyo, Japan) | Not clearly reported | Left<br>Right | RT: ↔<br>FT: ↔<br>CON: ↔<br>No significant between-group differences. | - | ↔<br>↔ |
| Gylling *et al.* (2020) | SAEHAN DHD-1 Digital Hand Dynamometer | Not clearly reported | Not clearly reported | Heavy RT: ↔<br>Moderate RT: ↔<br>CON: ↔<br>No significant group × time interaction. | - | ↔<br>↔ |
| Pereira *et al.* (2012) | Hand dynamometer (Lafayette Instrument, Lafayette, IN) | Sitting position at a 90˚ elbow flexion position | Dominant<br>Non-dominant | Dominant hand:<br>RT: ↑<br>CON: ↔<br>No significant between-group differences. | Non-dominant hand:<br>RT: ↑<br>CON: ↔<br>Significant between-group differences. | ↔↑ |
| Rhodes *et al.* (2000) | Hand dynamometer | Not clearly reported | Dominant | RT: ↔<br>CON: ↔<br>No significant between-group differences. | - | ↔ |
| Richardson *et al.* (2019) | Digital strain-gauge dynamometer (Takei TKK 5401, Takei Scientific Instruments, Tokyo, Japan) | Not clearly reported | Dominant<br>Non-dominant | Dominant hand:<br>HVLL1: ↔<br>HVLL2: ↔<br>LVHL1: ↔<br>LVHL2: ↔<br>CON: ↔<br>No significant between-group differences. | Non-dominant hand:<br>HVLL1: ↔<br>HVLL2: ↔<br>LVHL1: ↔<br>LVHL2: ↑<br>CON: ↔<br>Significant difference between LVHL2 and CON. | ↔↔<br>↔↔<br>↔↔<br>↔↑ |
| Rogers *et al.* (2002) | Handgrip dynamometer (Jamar, Inc.) | Not clearly reported | Not clearly reported | RT: ↑<br>CON: ↔<br>Between group statistics were not clearly reported. | - | ? |

**Continued**

| | | | | | | |
|---|---|---|---|---|---|---|
| Skelton *et al.* (1995) | Not clearly reported | Not clearly reported | Left<br>Right | RT: ↑<br>CON: ↔<br>Significant between-group differences. | - | ↑ |
| Thomas *et al.* (2008) | Grippit® dynamometer (AB Detector, Gothenburg, Sweden) | Sitting position at a 90˚ elbow flexion position | Left<br>Right | Right hand<br>RT: ↑<br>CON: ↔<br>Significant between-group differences. | Left hand<br>RT: ↔<br>CON: ↔<br>No significant between-group differences | ↑↔ |
| Tieland *et al.* (2015) | Hydraulic hand dynamometer (Jamar, Jackson, MI, USA) | Sitting position with the arm in a 90˚ angle position | Dominant<br>Non-dominant | Dominant hand<br>RT: ↑<br>CON: ↑<br>Significant time effect. No significant group effect. No significant group × time interaction. | Non-dominant hand<br>RT: ↑<br>CON: ↑<br>Significant time effect. No significant group effect. No significant group × time interaction. | ↔↔ |
| Tsuzuku *et al.* (2018) | Hand grip dynamometer (Grip-D; Takei Instruments, Niigata, Japan) | Standing position | Right | RT: ↔<br>CON: ↔<br>No significant between-group differences | - | ↔ |
| Vezzoli *et al.* (2019) | Dynamometer (JAMAR PLUS+, Sammors Preston, Rolyon, Bolingbrook, IL, USA) | Standing position, the upper limbs along the sides, and the legs slightly apart | Left<br>Right | RT: ↔<br>CON: ↔<br>No significant between-group differences | - | ↔ |
| Wanderley *et al.* (2015) | Handgrip dynamometer (Takei, TKK 5101 Grip-D) | Held the dynamometer in the dominant hand with his/her arm by his/her side and had to squeeze using maximum force | Dominant | RT: ↔<br>CON: ↔<br>No significant group × time interaction. | - | ↔ |

RT: resistance training. CON: control group. EBFT: element-based functional training. TSBFT: task-specific-based functional training. FT: function training. ST: suspension training. TT: traditional training. MJ: multi-joint resistance training. MJ+SJ: multi- plus single-joint resistance training. SE: supplemented and trained. SN: supplemented and non-trained. NE: non-supplemented and trained. NN: non-supplemented and non-trained. HVLL1: high-velocity, low-load once-weekly. LVHL1: low-velocity, high-load once-weekly. HVLL2: high-velocity, low-load twice-weekly. LVHL2: low-velocity, high-load twice-weekly. Note: only resistance training and control groups were included in this table? authors did not clearly reported the between-group statistics. ↑: increased. ↓: decreased. ↔: not changed/different.

handgrip strength [28] [30] [31] [35] [36] [38] [40] [42] [43] [44] [46], five studies (25%) measured only dominant participants' handgrip strength [32] [33] [34] [39] [47], one study (5%) measured only right participants' handgrip strength [45], one study (5%) measured participants' preferred arm [29], and the remaining two studies (10%) did not clearly report which hand (e.g., left, right or both and/or dominant, non-dominant or both) was used to measure handgrip strength [37] [41].

### 3.5. Impact of Intervention

Twelve studies (60%) reported no significant difference in handgrip strength change between the resistance training group and control group following an intervention study [28] [29] [30] [31] [32] [36] [37] [39] [44] [45] [46] [47]. Two studies (10%) included results for multi-training groups and found increased handgrip strength compared to controls, but only in one training group [34] [40]. Two studies (10%) measured the handgrip strength of the right and left or dominant and non-dominant hands and reported a training effect on one hand but not on the other [38] [43]. Two studies (10%) showed increased handgrip strength in the resistance training group compared with the control group [35] [42]. Finally, two studies (10%) did not clearly report differences in intervention effects [33] [41].

### 3.6. Risk of Bias

Overall, the randomized and non-randomized clinical trials presented moderate ("some concerns") risk of bias (**Figure 2(a)** and **Figure 2(b)**, respectively). Among the randomized trials in the risk of bias assessment, only three studies (17.6%) reported that the allocation sequence was concealed until participants were enrolled and assigned to interventions [33] [34] [47]. Only four studies (23.5%) used blind assessors [28] [36] [37] [47]. The remaining studies (n = 13) did not blind the assessors, or this information was unclear. Only two studies analyzed the data in accordance with a pre-specified plan [37] [47]. Among the three non-randomized studies included in the risk of bias assessment, none of them used blind assessors [38] [41] [44]. All the non-randomized studies presented a low risk of bias in the classification of interventions due to deviations from intended interventions. Due to the characteristics of the intervention studies, none of the randomized and non-randomized studies could blind participants and personnel (trainers). **Supplementary Material** shows traffic light risk-of-bias plots for randomized and non-randomized included studies.

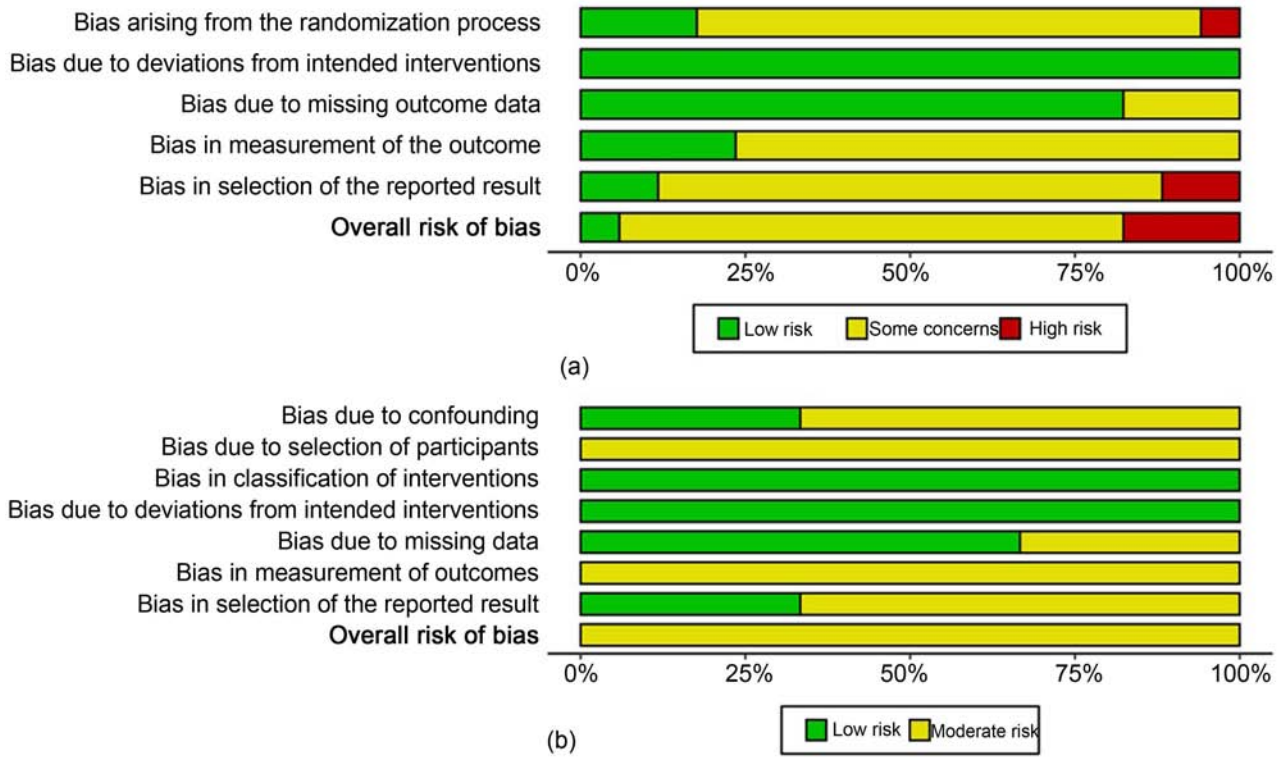


**Figure 2.** Assessment of risk of bias.

## 4. Discussion

This systematic review aimed to search and understand the impact of resistance training intervention on handgrip strength in adults of all ages, including young adulthood. However, contrary to our expectations, we found only one study that examined the impact of resistance training on handgrip strength in study participants with a mean age of less than 60. Even though low and decreasing handgrip strength is inversely associated with morbidity/mortality, there is limited interest and emphasis on the impact of resistance training on handgrip strength in young and middle-aged adults. Therefore, most of the studies selected in this review had participants with a mean age of 60 years or older.

### 4.1. Training Program and Its Impact on Handgrip Strength

Handgrip exercise training may improve handgrip strength in middle-aged and older adults [48] [49], but this systematic review did not include studies involving such exercise programs. However, when resistance exercise is offered using resistance training machines, study participants sit on a chair. The participants' hands often grip a bar to maintain body position during the exercise. Even when training with a rubber band, participants may hold onto one end of the band during exercise. This type of exercise makes determining exercise intensity or contraction time difficult but indicates an indirect handgrip exercise. In this systematic review, twelve of the 20 selected studies found no difference in handgrip strength changes between the resistance training and control groups. Most of

those studies employed moderate- to high-intensity resistance exercises using resistance training machines and rubber/elastic bands [28] [29] [30] [31] [32] [36] [37] [39] [44] [46] [47]. On the other hand, two studies that reported a significant increase in handgrip strength in the resistance training group compared to the control group involved training programs using their body weight and rubber/elastic bands [35] [42]. These results did not explain the difference in the impact of resistance training on handgrip strength due to differences in exercise modes. Furthermore, there were no differences in other training variables, such as the volume of exercise (number of repetitions and sets) and intervention period, depending on whether they affected handgrip strength. Participants in the two studies [35] [42] that observed a significant increase in handgrip strength with resistance training were older adults with a mean age of about 80. Of the two, in the study where resistance training had the most change in handgrip strength, an increase of approximately 3 kg was observed in the training group [35]. While Labott and colleagues [19] recently concluded in a meta-analysis that different types of exercise training were capable of increasing handgrip strength compared to different control groups (e.g., other exercise interventions or non-exercise control groups), the observed effect size was small. Of the studies included in the analysis, Labott and colleagues [19] observed that only four of the 24 included studies found statistically significant increases in handgrip strength relative to the control group; however, only one of these four studies in fact compared resistance training intervention to a non-exercise control group. Thus, had we been able to perform a meta-analysis, it is possible that pooling all studies together would demonstrate a statistically significant effect of resistance training on handgrip strength relative to the control group, but the effect size would be expected to be small.

### 4.2. Discrepancies in Handgrip Strength Changes between Training Groups within a Study

When a single study includes two or more training groups, and there is a difference in handgrip strength change between the groups, knowing the factors behind this difference is meaningful from the perspective of handgrip strength improvement strategies. Our selected studies included two [34] or four [40] training groups that found increasing handgrip strength compared to controls in only one training group within each study. Campa and colleagues [34] compared the impact of suspension and traditional resistance training on handgrip strength and found that only suspension training produced increasing handgrip strength. The elastic bands employed in the traditional training program used different tube sizes specific to the given exercise. The suspension training was carried out using gripping straps attached to the tip of the elastic tube, which helped to grip firmly. A predicted factor for the difference in impact on handgrip strength could be attributed to the need for repeated firmer grip during the suspension exercise. Richardson and colleagues [40] observed the impact on handgrip

strength when resistance training was performed in eight whole-body exercises (four in the upper body and four in the lower body) at high load (80% 1RM)-low velocity or low load (30% 1RM)-high velocity. In addition to each load-velocity condition, four training conditions differing in frequency (once a week vs. twice a week) were compared. As a result, handgrip strength increased only under the training program with high load-low velocity twice a week. The reasons for these results are unclear, but some possibilities exist. When performing high-load, low-velocity exercises using training machines, the time required to grip the movable bar during upper-body exercise is more extended than under other conditions. For lower-body movements, the time needed to hold the bar to stabilize the body is also longer than other conditions. Training load, volume, and frequency in resistance training using machines may impact the grasping movements of the machine's bar, which may train handgrip strength indirectly. However, this issue has yet to be investigated.

## 5. Limitations of the Study

The present systematic review is not without limitations. First, several studies included in this review were classified as having "moderate" risk of bias. Second, there is a paucity of studies on the present topic using randomized controlled trials that compared a resistance training group versus a control group comprising older adults. Hence, we were unable to provide a strong discussion for studies comprising middle-aged adults. Third, the included studies applied different resistance training protocol settings (e.g., exercises, intervention duration, weekly frequency, session duration, number of sets and repetitions, rest interval between sets and exercises, and intensity control/monitoring), which makes difficult to compare the handgrip strength results. Fourth, the available data in the included studies did not allow us to perform all pre-planned main meta-analysis, subgroup analysis, and sensitivity analysis.

## 6. Perspectives

The impact of resistance training interventions on handgrip strength has been primarily observed in older adults, and there needs to be more studies in young and middle-aged adults. From a meta-analysis perspective, we recommend that future randomized controlled trials with low risk of bias and larger sample sizes evaluating the effects of different resistance training protocols on handgrip strength compared to a non-exercise control group in middle-aged and older adults report the mean difference between groups and their standard deviation or at least mean changes within groups and its standard deviation. Furthermore, although handgrip strength is a biomarker [50], whether it can improve morbidity and mortality when increased by environmental factors such as resistance training has yet to be demonstrated [51] [52]. When handgrip strength is increased through whole-body resistance training or through select sports (*i.e.*, whether or not an athlete plays with sports equipment in their hands) [53], the

effects on risk factors for lifestyle-related diseases are complex, but the impact on risk factors that occur when handgrip strength is directly increased by handgrip exercise has not been fully elucidated [54]. These studies are considered important in helping to elucidate the mechanisms of the inverse association between handgrip strength and morbidity/mortality.

## 7. Conclusion

The present systematic review showed that due to the lack of low risk of bias randomized controlled trials, different research designs, different resistance training protocols, small sample sizes, and different populations investigated, the existing evidence is insufficient to support resistance training for increasing handgrip strength in apparently healthy middle-aged and older adults. Furthermore, as the included studies presented an overall "moderate" risk of bias, future low-risk-of-bias randomized clinical trials comprising middle-aged and older adults are required. Finally, future studies may build upon these limitations to discern the optimal manner by which to develop and employ resistance training to improve handgrip strength.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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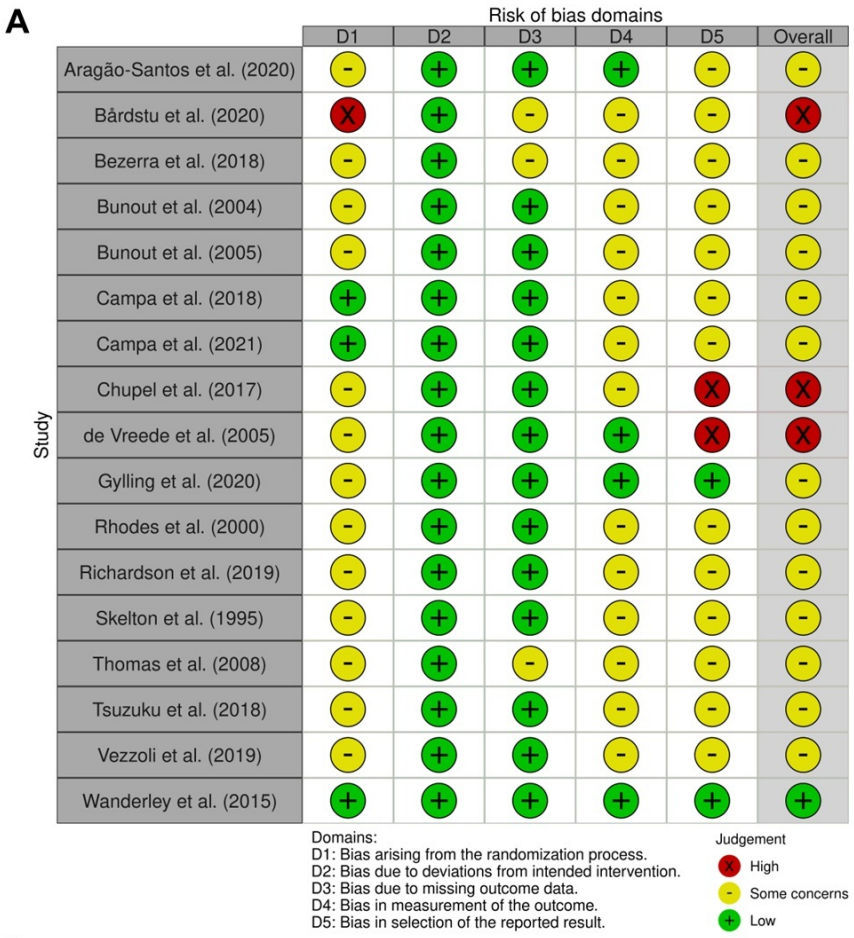
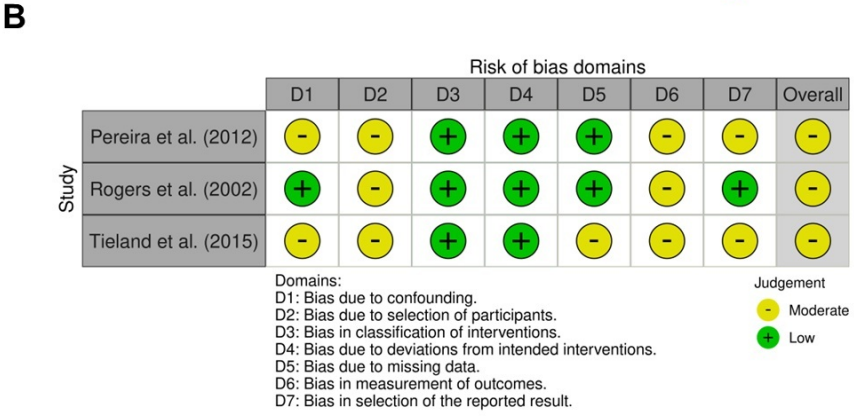
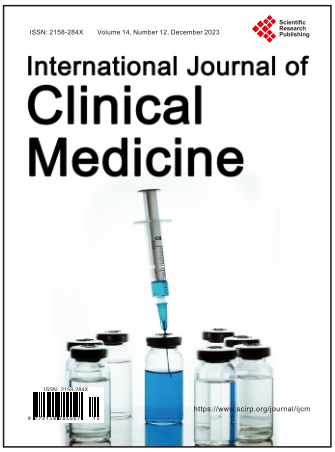
## Supplementary Material: Traffic-Light Plots for the Randomized (A) and Non-Randomized (B) Included Studies



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