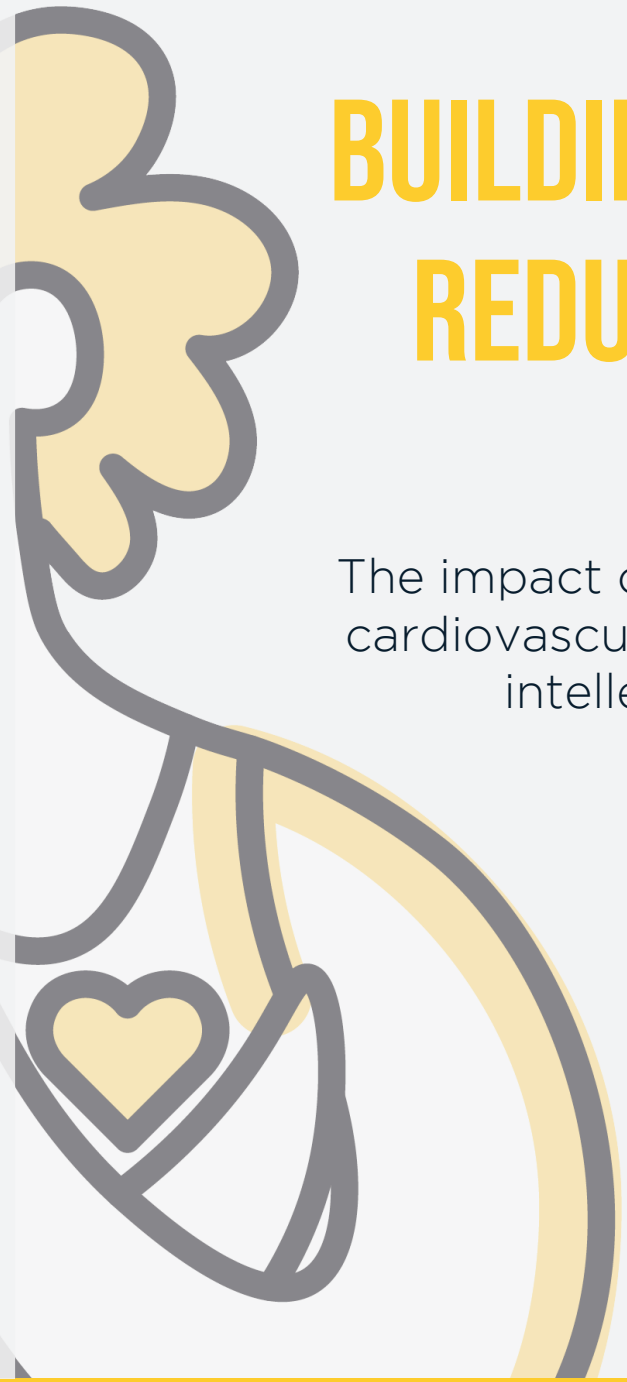

# BUILDING STRENGTH REDUCING RISKS

The impact of resistance training on cardiovascular health in adults with intellectual disabilities

KIRSTEN DE OUDE

**Stellingen behorende bij het proefschrift**

# Building Strength, Reducing Risks

The impact of resistance training on cardiovascular health
in adults with intellectual disabilities

1. De positieve effecten van krachttraining op cardiovasculaire risicofactoren laten zien dat **doen** belangrijker is dan **hoe intens**. *(dit proefschrift)*
2. Bij hoge LDL-cholesterol waarden, moet PRET overwogen worden als interventie bij volwassenen met een verstandelijke beperking. *(dit proefschrift)*
3. Krachttraining alleen is niet afdoende om verbetering in lichaamssamenstelling te bewerkstelligen. *(dit proefschrift)*
4. Het stoppen met trainen is een grotere beperkende factor voor de effectiviteit van PRET dan de trainingsintensiteit zelf bij volwassenen met een verstandelijke beperking. *(dit proefschrift)*
5. Dat PRET probleemgedrag vermindert benadrukt het bredere belang van krachttraining binnen de zorg voor mensen met een verstandelijke beperking. *(dit proefschrift)*
6. In de gehandicaptenzorg zou **niet** bewegen eerder een uitzondering dan de norm moeten zijn.
7. Als de omgeving stilzit, kun je van de cliënt geen beweging verwachten.
8. Een goede trainer in de gehandicaptenzorg heeft meer aan motivatie technieken dan aan een gewicht van 20 kilo.
9. Als beweging leven is, dan bevestigt de lage fysieke activiteit bij volwassenen met een verstandelijke beperking hoe essentieel beweeginterventies zijn in hun dagelijkse zorg. (Vrij vertaald naar de uitspraak van Leonardo da Vinci – "*Beweging is leven*.")
10. Er moeten niet nóg meer plannen voor bewegen komen, maar vooral structurele ruimte en ondersteuning gecreëerd worden om dit daadwerkelijk te doen. (Gebaseerd op Zuid-Hollandse wijsheid– "*Niet lullen maar poetsen*.")
11. Het implementeren van leefstijlinterventies voor mensen met een verstandelijke beperking wordt begrensd door een zorgsysteem dat zelf in overlevingsstand staat.

Kirsten de Oude
24 november 2026

# BUILDING STRENGTH REDUCING RISKS

The impact of resistance training on cardiovascular health in adults with intellectual disabilities

KIRSTEN DE OUDE
















The studies in this thesis were performed at the Department of General Practice, Intellectual Disability Medicine Research, Erasmus MC University Medical Center, Rotterdam, the Netherlands. The research was financially and organisationally supported by the Academic Collaboration Research Center 'Healthy Ageing and Intellectual Disabilities' (in Dutch: GOUD), which comprises Abrona, Amarant, and Ipse de Bruggen (Dutch care organisations for individuals with intellectual disabilities).

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# Building Strength, Reducing Risks

The impact of resistance training on cardiovascular risk factors
in adults with intellectual disabilities

# Sterker worden, risico's verkleinen

De impact van krachttraining op cardiovasculaire risicofactoren
bij volwassenen met een verstandelijke beperking

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr.ir. A.J. Schuit

en volgens besluit van het College voor Promoties.
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Kirsten Irina de Oude
geboren te Ter Aar.

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| | |
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| **Promotor:** | Prof.dr. S.M.A. Bierma-Zeinstra |
| **Copromotoren:** | Dr. D.A.M. Maes-Festen<br>Dr. A. Oppewal<br>Dr. G.M.H. Elbers |
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# Chapter 1

## General introduction

## Cardiovascular disease

Cardiovascular disease (CVD) remains the leading cause of mortality worldwide, representing approximately one-third of all global deaths (1). The term CVD encompasses a range of disorders affecting the heart and blood vessels, including coronary artery disease, cerebrovascular disease, and hypertension-related conditions (1). A substantial proportion of CVD cases is attributable to modifiable behavioural risk factors. Physical inactivity, poor diet, tobacco use, and excessive alcohol consumption are the leading behavioural contributors to the development of CVD, along with clinical factors such as hypertension, hypercholesterolemia, obesity and insulin resistance (1, 2).

The prevention and management of these risk factors through lifestyle modification is a cornerstone of global public health strategies aimed at reducing the incidence and impact of cardiovascular risk factors (CVRFs) (1). Among these strategies, regular physical activity has consistently been identified as one of the most effective non-pharmacological interventions for reducing CVRFs. Physical activity contributes to favourable changes in blood pressure, lipid profiles, body composition, and insulin sensitivity, while also improving vascular function and cardiorespiratory fitness (3). Both aerobic and resistance training modalities have demonstrated protective effects, with evidence highlighting the unique benefits of muscle-strengthening activities in reducing all-cause and cardiovascular mortality (4). Despite this, physical activity levels remain suboptimal in many populations, limiting the broader public health impact of exercise-based interventions (5).

## Adults with ID and health inequalities

Adults with intellectual disabilities (ID) have a neurodevelopmental disorder which is defined as a deficit in intellectual and adaptive functioning, with the onset in the developmental period before the age of 22 years (6). Globally, it is estimated that approximately 1% of the population has an ID. The severity of ID ranges from mild to profound, with varying levels of cognitive and functional abilities. While an individual with mild ID may live a relatively independent life, an individual with more severe ID may require extensive support in daily life. Therefore, this population represents a diverse group with varying levels of support needs (7).

Adults with ID face more challenges when developing health skills and need adequate support to improve their health and maintaining a healthy lifestyle. They often encounter difficulties in navigating healthcare systems, communicating health needs, and receiving adequate screening and prevention services (8). Advances in policy promoting inclusion and equality have resulted in increased health care and life expectancy (9, 10). However, despite these advances, adults with ID continue to experience marked health disparities compared to the general population (11).

## Cardiovascular risk in adults with ID

One of the most pressing health challenges faced by adults with ID is their elevated risk of developing chronic health conditions (12). The Healthy Ageing and Intellectual Disabilities (HA-ID) study has provided substantial insights in the health status of adults with ID aged 50 years and over in the Netherlands in a prospective multicentre cohort study (13). This study is conducted collaboratively by three Dutch ID care organisations (Abrona, Amarant, Ipse de Bruggen) and the Department of General Practice, Intellectual Disability Medicine Research at Erasmus MC in Rotterdam. They found that, in comparison to the general population CVRFs such as, hypertension, diabetes, and obesity were more often present in adults with ID (14, 15). Furthermore, the HA-ID cohort study revealed substantial underdiagnosis of CVRFs in this population, which suggests that their true prevalence is underestimated (16). Polypharmacy is also common among adults with ID, and psychotropic medications are frequently included, their use may contribute to weight gain, metabolic disturbances, and an increased cardiovascular risk (17-19).

Despite these well-documented risks, adults with ID are frequently underrepresented in epidemiological studies and clinical trials addressing cardiovascular prevention and intervention strategies. This limits the generalisability of evidence-based guidelines and intervention and prevention strategies developed for the general population to the ID population and contributes to persistent health inequalities (20). As such, there is a need for targeted research in adults with ID evaluating effective interventions tailored to their unique needs and capabilities.

## Cardiovascular risk management in adults with intellectual disabilities

For adults with ID, no population-specific guideline for cardiovascular risk management exists. In practice, care organisations in the Netherlands typically apply the guideline by the Dutch College of General Practitioners (Nederlands Huisartsen Genootschap) (21), originally developed for the general population, to assess risk profiles, provide lifestyle advice, and manage treatment. This guideline is in accordance with international guidelines (1). Although the NHG guideline is applicable in adults with ID it asks for individualised adjustments (22). For example, cardiovascular risk assessment and management in adults with ID is more complex, not only because comorbidities and the frequent use of psychotropic medications increase risk, but also due to polypharmacy-related interaction effects and difficulties in detecting or communicating health changes, which complicate monitoring and treatment decisions. Furthermore, treatment strategies require special attention for communication, patient motivation, monitoring of adverse effects, and multidisciplinary collaboration (22).

## Physical activity in adults with ID

One of the treatment strategies recommended by the NHG guideline is to engage in regular physical activity (21). The World Health Organization (WHO) defines physical activity as any bodily movement produced by skeletal muscles that requires energy expenditure, whereas sedentary behaviour refers to periods of low-energy expenditure while awake, such as sitting, reclining or lying (23).

For adults, the Dutch physical activity guidelines (24) recommend at least 150 minutes of moderate-to-vigorous physical activity per week, supplemented by muscle- and bone-strengthening exercises at least twice per week, while minimizing prolonged sedentary behaviour. Even small increases in physical activity, such as frequently changing posture or performing more activities in stance, can result in health benefits (25). In principle, for adults with ID, the general physical activity guidelines are applicable. However, in this population it is strongly recommended to adapt physical activity to

match individual capabilities, and to seek advice from experts when needed compared to the general population (26).

Previous research in adults with ID demonstrated that they often exhibit low levels of physical activity and high levels of sedentary behaviour (27-30). Despite the known benefits of physical activity for adults with ID, such as improved balance, muscle strength, and quality of life (31), implementing effective interventions is challenging. Due to their cognitive and functional limitations, adults with ID depend on structured guidance and support to increase physical activity levels. Previous studies have documented a range of barriers for participation in physical activity such as ageing, health problems, lack of adapted programs, attention issues, challenging behaviour, lack of support, finance, staff expertise, and transportation (32-35). Facilitators, on the other hand, include social interaction, rewards for participation, routine, and having fun (32, 35). These findings emphasise the need for tailored and structured interventions promoting physical activity and improve cardiovascular health in adults with ID.

## Resistance training for adults with ID

In the general population, the American College of Sports Medicine (ACSM) guidelines recommends both aerobic and resistance training to increase physical activity levels and improve CVRFs (3). While aerobic exercise has traditionally been emphasised in public health guidelines, resistance training has been shown to offer additional health benefits. One of these benefits is an increase in muscle mass that can lead to improvements in glycaemic control, insulin sensitivity, blood pressure, body composition, and lipid profile (36-38). Additionally, resistance training may be more feasible and engaging for adults with ID, as it involves varied, shorter bouts of effort that reduce concentration demands, while aerobic training requires longer continuous effort to benefit CVRFs (39, 40). Furthermore, resistance training can be more easily individualised, making it suitable for a population with highly varying degrees of functional capacity and ability levels.

Benefits of resistance training in adults with ID have been previously identified, such as increased muscle strength and balance, improvements in fat-free mass, fat mass, waist circumference, and Body Mass Index (BMI)

(41, 42). The HA-ID Academic Collaborative Research Center conducted a pilot study and developed in collaboration with physical activity instructors and physiotherapists in care settings a feasible Resistance Exercise Set for adults with Intellectual Disabilities (RESID) (43). In a subsequent study, they evaluated the feasibility of a 24-week progressive resistance exercise training program, using the RESID, in adults with ID and at least one CVRF and found it feasible with 58% of the participants reaching vigorous intensity (44). While in the general population the positive effects of resistance training on CVRFs have been investigated, adults with ID remain underrepresented in these studies. Therefore, this thesis will focus on the effects of the progressive resistance exercise training on CVRFs in adults with ID.

## Effect of resistance training on overall health outcomes

In addition to CVRFs, there are other health issues that are highly prevalent in adults with ID compared to the general population that may benefit from resistance training such as physical fitness, sarcopenia and falls (45, 46). Furthermore, adults with ID often experience an increased dependency in performing activities of daily living (ADL) (47) and tend to exhibit challenging behaviour more frequently (48).

Although resistance training might have positive effects on CVRFs in this population, it may also benefit these other aspects of health. Previous research has demonstrated that resistance training improves physical fitness components such as muscle strength and balance (41, 42) which can lead to increased independence in performing activities of daily living (ADL), increased gait speed, and reduced fall risk (31, 49, 50). Furthermore, resistance training could play a vital role in preventing sarcopenia, which is characterised by progressive and generalised loss of skeletal muscle mass and strength with a risk of adverse health outcomes (51). Resistance training primarily targets improvements in muscle strength, which often result in an increase in muscle mass, thereby addressing two key components of sarcopenia (52, 53). Finally, structured exercise has been reported to reduce challenging behaviour in adults with ID (54), anxiety and depression (55),

and improving overall quality of life (31, 56). In contrast to previous studies in adults with ID that primarily addressed general health outcomes or other forms of exercise, this thesis uniquely examines the combined effects of resistance training on CVRFs and a range of specific health outcomes and challenging behaviour.

## Intervention studies in adults with ID

To adequately investigate the effects of resistance training in adults with ID, a carefully designed intervention study is essential. From previous studies conducted in this population, various recommendations have been made to maximize adherence and effectiveness of interventions (33, 35, 44, 57). Considering the cognitive and functional limitations in this population, it is recommended that training protocols should include structured and supervised training sessions, supported by clear verbal instructions and visual or tactile guidance by the trainer (44). Moreover, strategies to enhance adherence, such as incentives should be integrated. Finally, collaboration with caregivers is crucial to facilitate participation, maintain consistency, and provide accurate data collection. With these recommendations, together with the experiences we gained from the HA-ID feasibility study (44), we will be able to evaluate the effectiveness of resistance training while accounting for the unique needs of adults with ID.

Previous research did not investigate the effect of resistance training on CVRFs and overall health outcomes in adults with ID. To adequately assess all these health outcomes, we will select feasible measurement instruments specifically validated for this population, drawing on evidence from the HA-ID cohort study (58-60). One challenge in this context is the accurate assessment of muscle mass in adults with ID. There are multiple methods that can determine muscle mass (61) , but their applicability for adults with ID can be questioned. Therefore, in this thesis we will also investigate a non-invasive, low cost, and low effort method to measure muscle mass and its validity.

## Aims and content of this thesis

The primary aim of this thesis, referred to as PRET (Progressive Resistance Exercise Training), is to investigate the effects of a progressive resistance training intervention, including RESID, on CVRFs and a range of specific health outcomes and challenging behaviour. To address this aim, this thesis is structured as followed:

**Chapter 2** presents the results of a systematic review and meta-analysis investigating the effects of different intensities of resistance training on CVRFs in the general population. This chapter aims to address the existing knowledge gap and provides a broader scientific context and rationale for the selection of resistance training intensity in training interventions for improving CVRFs.

**Chapter 3** outlines the study protocol for the PRET study. It describes the study design, target population, intervention characteristics, and outcome measures used to evaluate the effects of PRET in adults with ID and CVRFs.

**Chapter 4** evaluates the convergent validity of calf circumference as a proxy for muscle mass by comparing it with bioelectrical impedance analysis (BIA) measurements. This chapter explores the potential of calf circumference as a simple and accessible assessment tool for muscle mass in adults with ID.

**Chapter 5** presents the effects of the PRET study on CVRFs, including glucose metabolism, blood pressure, lipid profile, obesity, and metabolic syndrome.

**Chapter 6** presents the results on the secondary health outcomes, including body composition, physical fitness, sarcopenia, ADL, challenging behaviour, and falls. These outcomes offer a more comprehensive understanding of the broader health impacts of PRET.

**Chapter 7** provides a general discussion of the main findings, placing them in the context of existing literature. This chapter also outlines the strengths and limitations of our research, and offers recommendations for clinical practice, policy development, and future research directions aimed at improving the cardiovascular and overall health of adults with ID.

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# Chapter 2

# The effect of different resistance exercise training intensities on cardiovascular risk factors: A systematic review and meta-analysis

**K.I. de Oude**
**R.G. Elbers**
**H. Gerger**
**D.A.M. Maes-Festen**
**A. Oppewal**

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## Abstract

Resistance training effectively reduces cardiovascular risk factors (CVRFs). However, the optimal training intensity remains unclear. This systematic review investigated the effects of different resistance training intensities on glycated haemoglobin (HbA1c), systolic blood pressure (SBP), low-density-lipoprotein (LDL), and waist-hip-ratio (WHR). Secondly, we aimed to compare the effect of different resistance training intensities with each other.

We identified RCTs (N=59) investigating progressive (N=9), low (N=15), moderate (N=33), and high intensity (N=4) resistance training in adults with CVRFs. We used random-effects models to investigate the effects of each intensity on CVRFs compared to non-active controls, and meta-regression analyses to investigate differences in effect between training intensities.

Meta-analyses showed statistically significant effects of low to moderate certainty. Progressive intensity reduced SBP (-14.70 mm/Hg, 95% CI [-16.40; -13.00]) and LDL (-0.16 mmol/L, 95% CI [-0.19; -0.13]). High intensity reduced HbA1c (-0.81%, 95% CI [-1.52; -0.10]), low intensity LDL (-0.10 mmol/L, 95% CI [-0.16; -0.04]), and moderate intensity WHR (-0.02, 95% CI [-0.03; -0.01]) and HbA1c (-0.40 %, 95% CI [-0.66; -0.14]). Meta-regression analyses showed high intensity was significantly more effective in reducing WHR than low intensity.

No significant differences were found between resistance training intensities for HbA1c, SBP, and LDL. In one study high intensity was more effective than low intensity in reducing WHR. However, the limited number of studies investigating high and progressive intensity and the certainty of evidence limits the ability for definitive conclusions. More research is needed for clarification on the effect of different resistance training intensities on multiple CVRFs.

# Introduction



Cardiovascular diseases remain a global health concern, and despite preventive measures, cardiovascular diseases are still a leading cause of mortality (1). In 2009, costs related to cardiovascular disease represented 9% of the total healthcare expenditure in the European Union (1). According to the European Society of Cardiology (ESC) guidelines, major cardiovascular risk factors (CVRFs) are hypercholesterolemia, hypertension, cigarette smoking, diabetes mellitus, and obesity (1).

When managing these CVRFs, lower levels of these factors are better. For hypercholesterolemia the aim is to reduce low-density lipoprotein cholesterol (LDL). A reduction in LDL of 1 mmol/L is associated with a 25% decrease in the risk of major vascular events (2). For hypertension, a 5 mm/Hg reduction in systolic blood pressure reduces the risk of major cardiovascular events by 10% (3). In adults with type 2 diabetes mellitus (DM2), a reduction of 1% in glycated haemoglobin (HbA1c) is associated with a decrease in the risk of cardiovascular disease with 5–7% (4, 5). For obesity, a healthy body composition should be achieved with a reduction in waist-hip-ratio (WHR), which has been associated with all-cause mortality and risk of cardiovascular disease (6). A 0.01 increase in WHR has been associated with a 5% increase in risk of cardiovascular disease (6).

Resistance training has been recommended as an effective intervention for reducing CVRFs (1, 7). Muscle tissue is the primary organ for glucose uptake and triglycerides disposal, and therefore important for metabolic rate (8). Previous studies in adults with CVRFs have shown that resistance training increases skeletal muscle mass which led to improvements in glycaemic control, insulin sensitivity, blood pressure, body composition, and lipid profile (8-10). These findings emphasise the importance of resistance training in the management of CVRFs.

Although previous systematic reviews showed the importance of resistance training on physiological and metabolic parameters in adults with CVRFs (10-15), there is still a lot of variability in the training intensities used in training protocols. To increase muscle mass with resistance training, the American College of Sports Medicine (ACSM) guidelines recommend training all large muscle groups at an intensity of 70–80% of the one repetition

maximum (1RM), 2–3 times per week. However, for special populations such as adults with CVRFs the recommended intensities range between 40–50% of 1RM for older adults with hypertension to 70–85% of 1RM for adults with DM2 or hypercholesterolemia (7). These different recommendations might explain the variability in training intensities used in studies. Furthermore, multimorbidity is highly prevalent in older adults who are at high risk for cardiovascular diseases (1), which can make it difficult for clinicians to select the best intensity. This indicates the need for more clarity on the effectiveness of different resistance training intensities.

The effect of resistance training on individual CVRFs has been extensively investigated. Previous reviews investigating the effect of resistance training on CVRFs all found positive results. However, these reviews did not provide a comprehensive overview regarding different resistance training intensities for adults with multiple CVRFs. Three previous reviews (16-18) have investigated the effect of different resistance training intensities. However, one focussed only on SBP in older adults (17) and the other two focussed only on adults with DM2 (16, 18). One review investigated the effect of the duration of resistance training on multiple CVRFs (19). Other reviews (20-23) investigated the effect of resistance training on CVRFs in general and did not differentiate between different intensities. Therefore, it is still unknown if there is one resistance training intensity that can be effective in reducing all the above mentioned CVRFs and, if so, which intensity is most effective.

Therefore, the primary aim of this study was to investigate the effect of low (<60% 1RM), moderate (60–80% 1RM), and high (>80% 1RM), and progressive (50–100% 1RM) intensity resistance training on HbA1c, SBP, LDL and waist-hip ratio in adults who are at higher risk for cardiovascular disease. The secondary aim was to compare the effects of different training intensities on CVRFs with each other. This review will therefore summarise the effects of different resistance training intensities on HbA1c, SBP, LDL and waist-hip ratio and give recommendations for clinical practice.

# Methods

This systematic review is reported according to the PRISMA guidelines (Appendix 2.1) (24). The protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42022348929).



### Study selection and eligibility criteria

For this review, we included randomised, or cluster randomised controlled trials. There were no restrictions for year of publication. We excluded reports of trials that could not be adequately translated by the research team.

### Participants

The participants in the trials had to be 18 years or older and diagnosed with DM2, hypertension, hypercholesterolemia, obesity, and/or metabolic syndrome defined as the combination of abdominal obesity, insulin resistance, hypertension, and hypercholesterolemia (25). Because thresholds and definitions for CVRF have changed over time and differ between published guidelines (1, 26, 27), we used the thresholds and definitions applied by the investigators of each trial.

### Intervention

The trials had to compare different resistance training interventions with each other or with a non-active control group or usual care. We defined non-active as no additional intervention that would increase the physical activity of participants throughout the study. Usual care had to be started prior to the trial. Usual care could, for example, include lifestyle recommendations or pharmaceutical interventions. We included trials that used conventional resistance training modalities, trials that used interval training with resistance were excluded. Trials that investigated combined interventions, such as resistance training and diet or resistance training and aerobic training, were excluded. Furthermore, the intensity of the resistance training had to be characterised as low (<60% of 1RM), moderate (60–80% of 1RM), high (>80% of 1RM), or progressive (50–100%). Trials that did not report clearly on the intensity used (as in reporting the % 1RM or the number of repetitions) were excluded. Finally, the duration of the exercise programme (minimum of eight

weeks) and frequency (minimum of two training sessions with a maximum of four per week) had to meet the ACSM recommendations (7).

### Outcomes

The trials had to report one of the following outcomes: HbA1c, SBP, LDL, or WHR. We selected HbA1c as it is a reliable measurement and is recommended by the American Diabetes Association for diagnosing DM2 (28). For hypertension, we selected SBP as it is shown to be related to cardiovascular disease (27). For hypercholesterolemia, LDL was chosen because in primary care pharmaceutical interventions focus on the regulation of LDL as it is associated with CVD (29). Finally, the primary outcome for obesity was WHR as it is the best predictive measurement of obesity for CVRF (30). HbA1c was reported in all included articles as %, therefore we used this unit as reference for HbA1c to ensure accuracy with the source data. When LDL was reported as mg/dL we, converted it to mmol/L LDL (31).

### Search strategy and selection process

In collaboration with the medical library of Erasmus MC, University Medical Center Rotterdam, we developed a search strategy using a combination of relevant keywords and Medical Subject Headings (MeSH) for resistance training, CVRF, and study design. The search was conducted on November 29$^{th}$, 2019, and updated on November 11$^{th}$, 2023, in Embase, Medline Ovid, SportDiscuss, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy is provided in Appendix 2.2. Each record has been assessed by two reviewers independently. All records were assessed by KO as first reviewer and by RE or SB as second reviewers. Screening of titles and abstract was done using the Rayyan platform. The full text reports of potentially eligible studies were obtained, which were assessed based on the predefined eligibility criteria. Any discrepancies were resolved through consensus discussion or consultation with a third reviewer. Reference lists of included reports and relevant systematic reviews were hand searched in addition to the electronical database search to ensure completeness of identified studies.

### Data extraction

We used Google Forms (Google, Dublin, Ireland) to extract study characteristics (i.e., first author, year of publication, study design), participant characteristics (i.e., sample size, age, sex, population), details of the intervention (i.e., intensity, duration, frequency, type of intervention), and outcome measures related to CVRFs (i.e., HbA1c (%), SBP (mmHg), LDL (mmol/L), WHR).

The post intervention means and standard deviations (SD) from the intervention and control groups were extracted. If other statistical values were reported, we calculated the mean and SD using the available values (32). If both intention-to-treat analysis and per protocol analysis data were reported, only the data from the intention-to-treat analysis was extracted. Data extraction was done in duplicate, with the first author (KO) extracting the data for all included studies, and RE, HG, AO, and SB serving as second reviewers. Any discrepancies were resolved through consensus discussion or consultation with a third reviewer.

### Risk of bias

The risk of bias assessment was conducted using the revised Cochrane risk of bias tool (RoB 2) (33). For every domain of the tool, risk of bias was categorised into low risk (+), some concerns (±) or high risk (-). Two independent reviewers assessed the risk of bias on each domain for each outcome separately. All risk of bias assessments were completed by the first author (KO) and RE, HG, AO, SB, and LK served as second reviewers. Any discrepancies were resolved through consensus discussion or consultation with a third reviewer.

### Certainty of evidence

To determine the certainty of evidence for each outcome we used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. We assessed our results in four domains: risk of bias, inconsistency, indirectness and imprecision. The certainty of evidence for each outcome was rated as high, moderate, low, or very low (34). For the assessments, we used the GRADEpro Guideline Development Tool (McMaster University and Evidence Prime, 2024).

**Data analysis**

Initially, we planned to conduct a network meta-analysis to compare the effect of different resistance training intensities. This approach would have allowed for the simultaneous comparison of multiple intensities, incorporating both direct and indirect evidence. However, during the data collection we noticed a scarcity of multi-arm studies, which are needed for a network meta-analysis. Therefore, we performed pairwise meta-analyses and meta-regression analyses instead.

We used random-effects meta-analyses to analyse the effect estimates across studies, using a mean difference (MD). We analysed the effect estimates for each CVRF outcome and resistance training intensity. Statistical heterogeneity between studies for each analysis was assessed using $I^2$ statistics and $\tau^2$, where heterogeneity was classified as low ($I^2$<25%), moderate ($I^2$>50%) and high ($I^2$>75%) (35).

We detected outliers by checking the forest plots of each meta-analysis regarding lack of overlap between pooled 95% confidence intervals (95% CI) and 95% CI of individual studies. Additionally, we used the leave-one-out method to check for the influence of individual study results on the overall effect size (36). We checked the reports of outlier studies for possible mistakes in data extraction or methodological explanations for extreme values. Sensitivity analyses were performed excluding studies considered at high risk of bias, with baseline differences or based on type of intervention (homebased programmes or elastic band training). We presented results from the meta-analyses in a forest plot with the MD as effect size with 95% CI. In case of substantial heterogeneity ($I^2$>75%), we did not present pooled effect estimates. Additionally, we conducted meta-regression analyses to compare the effect of each training intensity on the CVRFs separately.

All statistical analyses were performed using R Statistical Software (v4.1.2; R Core Team, 2021) using the packages 'meta' (37) for meta-analyses, 'forestplot' (38) to plot the results, and 'metafor' (39) for meta regression analyses.

# Results



### Study selection

Figure 2.1 presents the study selection procedure. The search strategy identified 8,870 records after duplicate removal. Following title and abstract screening, 234 reports were selected for full text assessment. Of these, two reports could not be retrieved, one report was requested for full text with the author but was not received, 25 reports were conference abstracts, and 21 were trial registrations. Finally, 185 full text reports were assessed of which 127 reports did not meet the inclusion criteria. These reports are presented in Appendix 2.3 with reason for exclusion. From reference screening, one additional report was included which resulted in a total of 59 included studies.

### Characteristics of included studies

The characteristics of the included studies are presented in Appendix 2.4. The included studies were conducted in Asia (n=33), North America (n=10), South America (n=9), Europe (n=3), Oceania (n=2), and Africa (n=2). A total of 1,862 adults with an average age ranging from 21 to 87 years were investigated. Two studies did not report sex distribution, 24 studies included only woman, 14 studies included only men, and 19 studies included both. The duration of the interventions ranged between eight to 52 weeks, with an average of three (2–4) sessions per week. Fifteen studies (40-54) compared low intensity resistance training versus a non-active control group, 34 studies (40, 55-87) compared moderate intensity versus a non-active control group, four studies (40, 88-90) compared high intensity versus a non-active control group, and nine studies (56, 91-98) compared progressive intensity versus a non-active control group.

### Risk of bias assessment

A summary of the risk of bias assessments is reported in the forest plot for each outcome.

A total of 110 outcomes were assessed for risk of bias. Overall, 76 outcomes had some concerns of risk of bias, 31 had high risk of bias, and four had low risk of bias. The concerns are primarily due to bias within the randomisation process (n=85), bias due to missing outcome data (n=57), and bias due to selectively reported results (n=91).

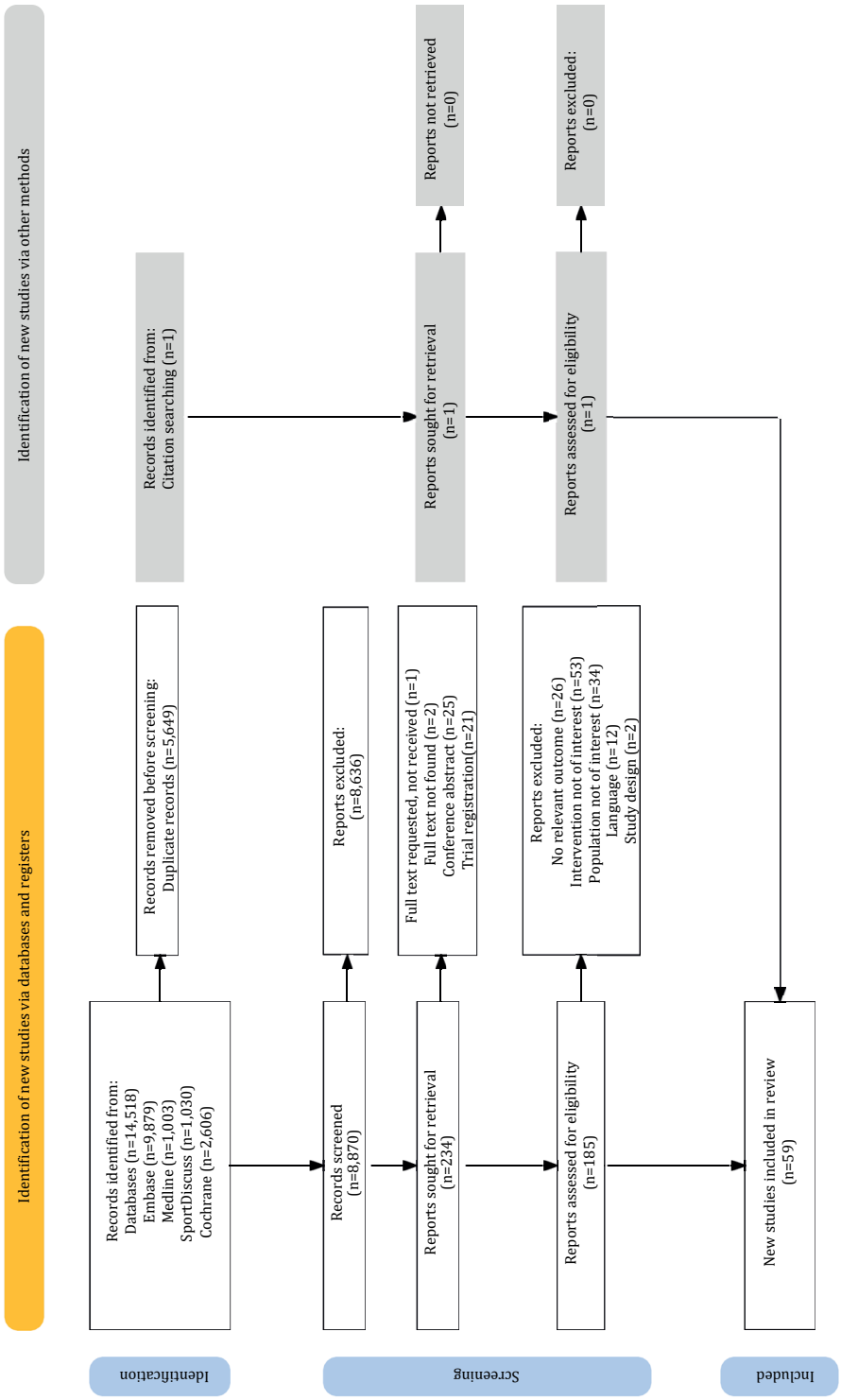


**Figure 2.1. PRISMA flowchart.**

### Glycated haemoglobin

Figure 2.2 presents the results of our meta-analysis for HbA1c. A total of 16 studies with 675 adults (54.2% male) reported HbA1c as a study outcome, of these 14 studies included adults with DM2. The average age ranged between 44 and 68 years. Of these 16 studies, two studies investigated low intensity resistance training, nine studies moderate intensity resistance training, two studies high intensity resistance training, and three studies investigated progressive resistance training.

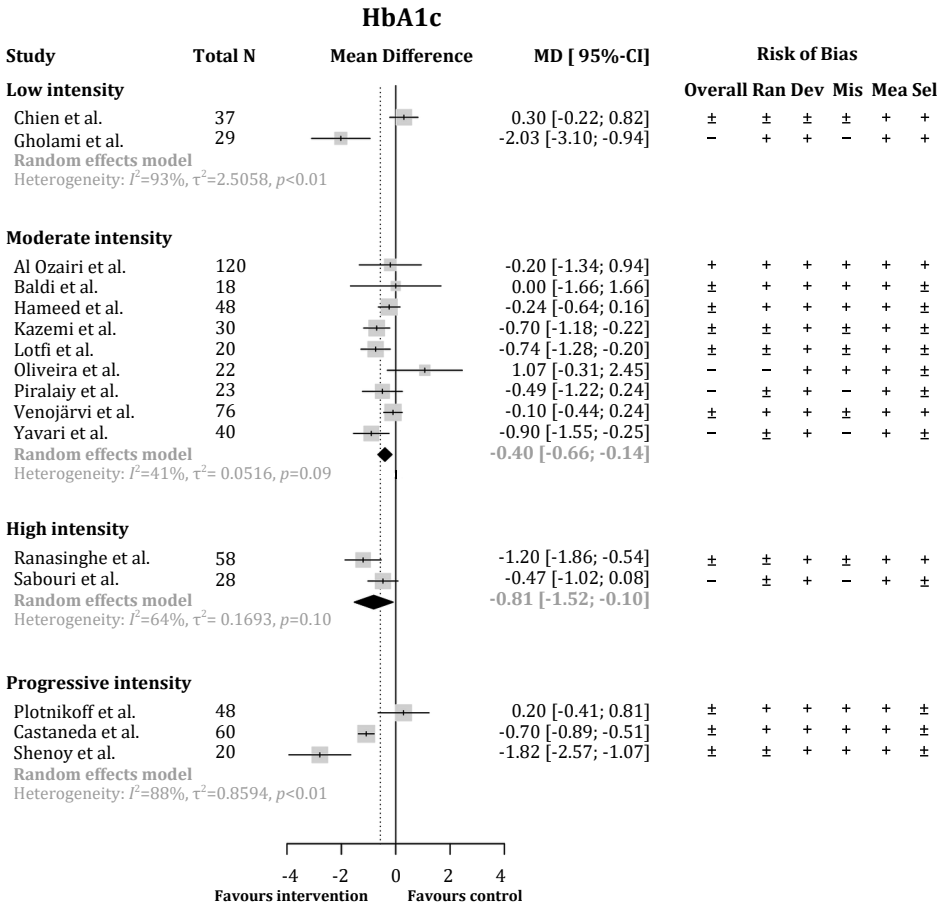


**Figure 2.2. Forestplot HbA1c.**

For all outcomes, lower values indicate improvement. Therefore, negative mean differences indicate superiority of the intervention over control in all analyses. Our meta-analyses showed statistically significant pooled effects

of -0.40 % HbA1c (95% CI [-0.66; -0.14]) for moderate intensity resistance training as compared to non-active control, and of -0.81% HbA1c (95% CI [-1.52; -0.10]) for high intensity resistance training compared to non-active control. The statistical heterogeneity for low and progressive intensity resistance training was high, therefore we did not report pooled effect estimates. The mean differences for low intensity resistance training ranged from -2.02% to 0.30% HbA1c, and for progressive intensity resistance training from -1.82% to 0.20% HbA1c.

Our meta-regression model ($I^2$=81.87%, $\tau^2$=0.40) showed no statistical differences in effect on HbA1c between training intensities. All outputs of our meta-regression analyses are presented in Appendix 2.5.

### Sensitivity analyses

We detected three outliers (44, 75, 96). In the study of Oliveira et al. we discovered baseline differences for HbA1c between intervention and control group. However, excluding this study did not change the heterogeneity or pooled effect estimate.

We found high heterogeneity for low ($I^2$=93%, $\tau^2$=2.51) and progressive intensity resistance training ($I^2$=88%, $\tau^2$=0.86). Due to the lack of studies for low intensity resistance training (n=2) we could not conduct sensitivity analysis for this intensity. For progressive intensity we excluded the study by Plotnikoff et al. based on type of intervention. This did not result in a decrease of the heterogeneity or a change in the pooled effect estimate.

Excluding the study by Plotnikoff et al. from the meta-regression analysis decreased the heterogeneity ($I^2$=77.18%, $\tau^2$=0.32) but still no statistical differences between training intensities was found.

### Systolic blood pressure

Figure 2.3 presents the results for SBP. A total of 34 studies with 1,143 adults (41.9% male) reported SBP as a study outcome, only 17 of these studies included adults with hypertension or metabolic syndrome. The average age ranged between 30 and 72 years. Of these studies, seven studies investigated low intensity resistance training, 18 studies moderate intensity resistance training, two studies high intensity resistance training, and seven studies investigated progressive resistance training.

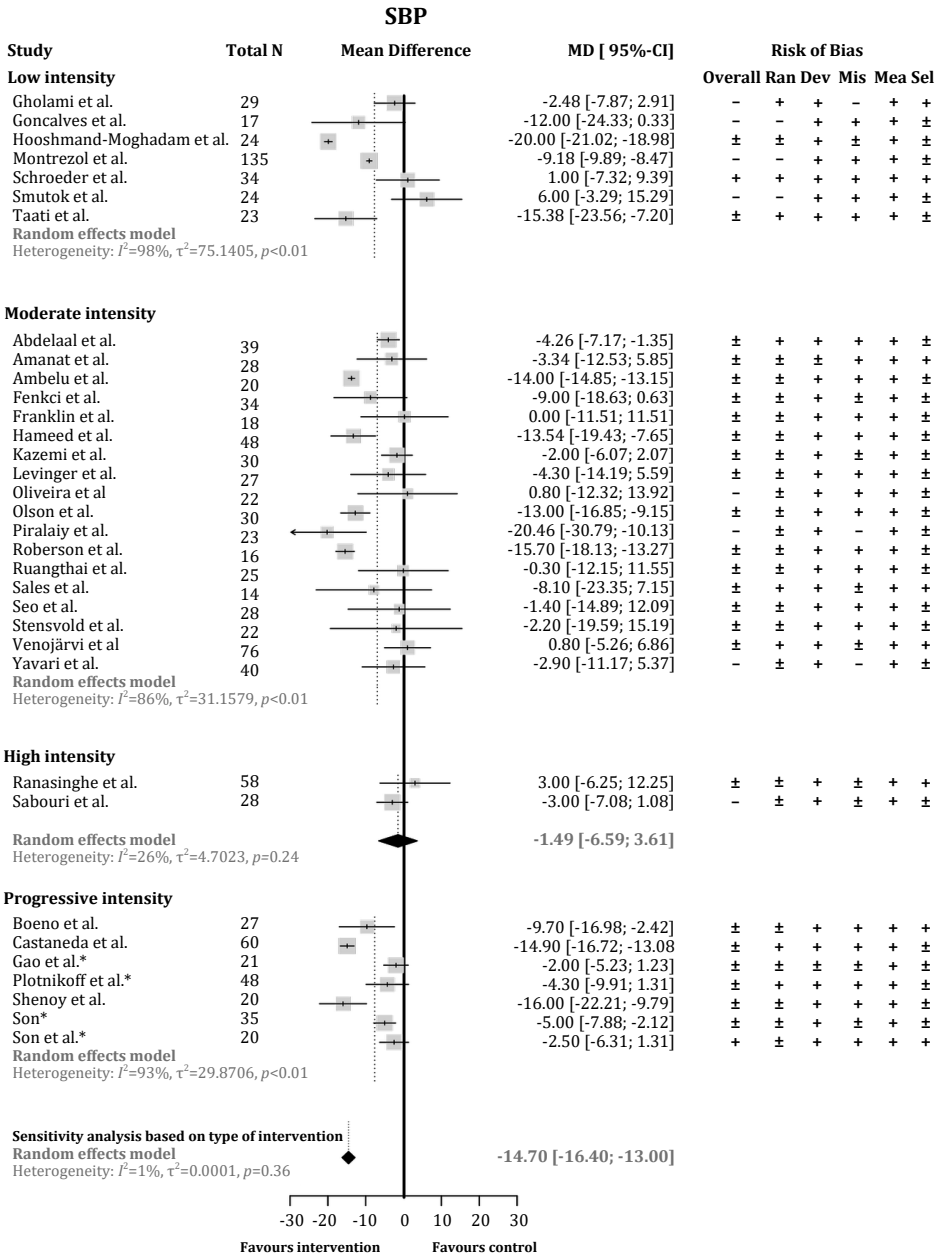


**Figure 2.3. Forestplot SBP.**

High intensity resistance training showed a non-statistically significant pooled effect of -1.49 mmHg (95% CI [-6.59; 3.61]) compared to non-active control. Progressive intensity resistance training showed a statistically

significant pooled effect of -14.70 mmHg (95% CI [-16.40; -13.00]). The heterogeneity for low and moderate intensity resistance training was high, therefore we do not report pooled effect estimates. The mean differences for low intensity resistance training ranged from -20.00 mmHg to 6.00 mmHg, and for moderate intensity resistance training from -20.46 mmHg to 0.80 mmHg.

Our meta-regression model ($I^2$=93.40%, $\tau^2$=38.76) showed no statistical differences in effect on SBP between training intensities.

### Sensitivity analyses

We checked outliers (52, 77, 88) for any mistakes in data-extraction. We found high heterogeneity for low ($I^2$=98%, $\tau^2$=75.14), moderate ($I^2$=86%, $\tau^2$=31.16), and progressive intensity resistance training ($I^2$=93%, $\tau^2$=29.87). Sensitivity analyses did not provide any explanations for low and moderate intensity.

For progressive intensity we excluded the studies by Plotnikoff et al., Son et al., Son., and Gao et al. based on type of intervention, which decreased the heterogeneity ($I^2$=1%, $\tau^2$=<0.001) and increased the pooled effect estimate from –7.62 mmHg (95% CI [-12.02; -3.22]) to -14.70 (95% CI [-16.40; -13.00]).

After excluding the above-mentioned studies in the meta-regression analysis, heterogeneity did not change. However, the estimate for progressive intensity resistance training increased from 0.45 mmHg (95% CI [-6.78; 7.68]) to -5.61 mmHg (95% CI [-14.90; 3.68]), but still no statistical differences were found between training intensities.

### Low density lipoprotein

Figure 2.4 presents the results for LDL. A total of 41 studies with 1,324 adults (32.8% male) reported LDL as a study outcome, and eight studies only included adults with hypercholesterolemia or metabolic syndrome. The average age ranged between 23 and 75 years. Of these 41 studies, 11 studies investigated low intensity resistance training, 25 studies moderate intensity training, three studies high intensity resistance training, and four studies investigated progressive intensity resistance training.

The meta-analyses showed a significant pooled effect for low intensity resistance training of -0.10 mmol/L (95% CI [-0.16; -0.04]), and progressive intensity resistance training of -0.16 mmol/L (95% CI [-0.19; -0.13]) as compared to non-active control. The heterogeneity for moderate and high

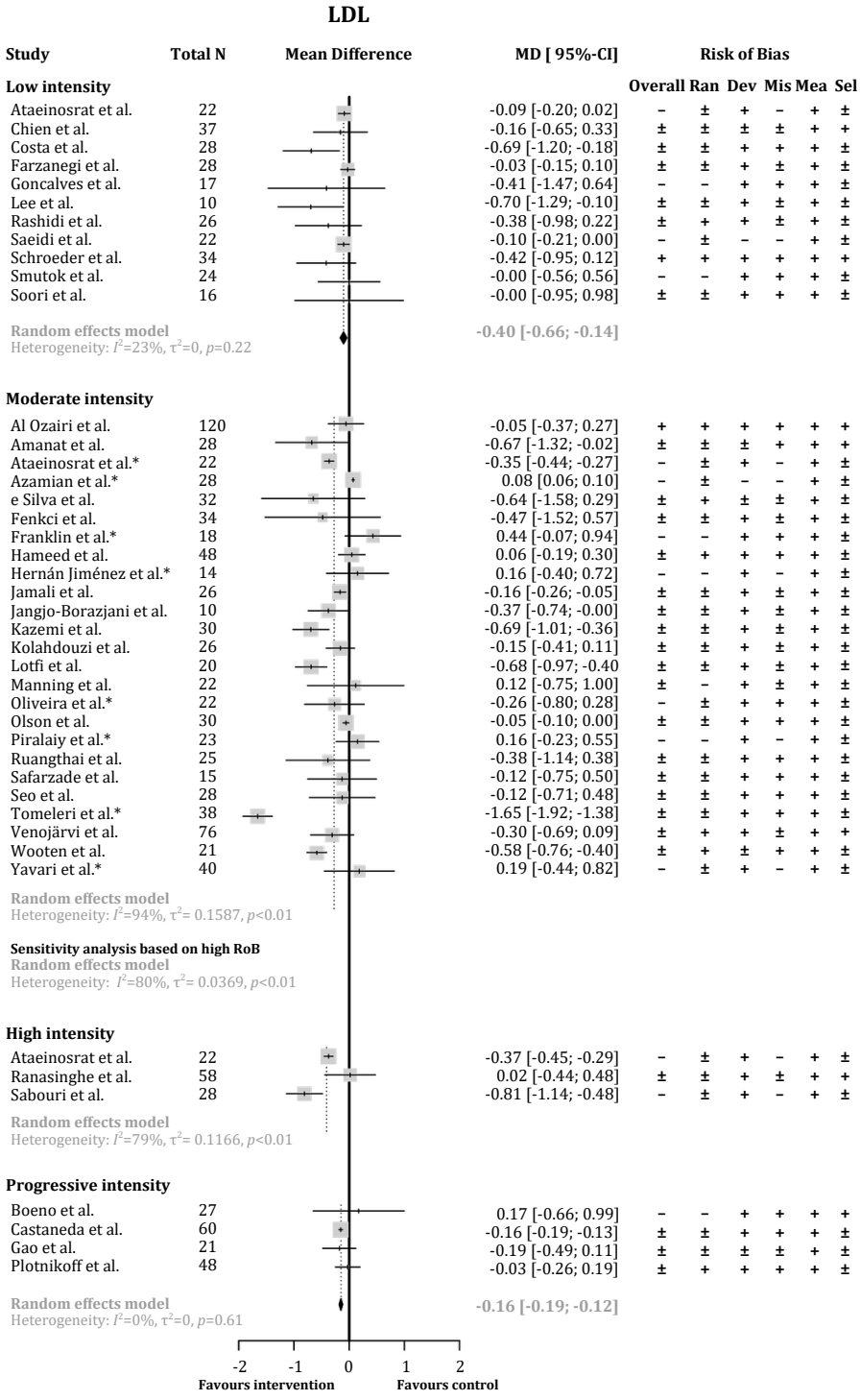


**Figure 2.4. Forestplot LDL.**

intensity resistance training was high, therefore we did not report pooled effect estimates. The mean differences for moderate intensity resistance training ranged from -1.65 mmol.L to 0.44 mmol/L, and for high intensity resistance training from -0.81 mmol/L to 0.02 mmol/L.

The meta-regression model ($I^2$=94.29%, $\tau^2$=0.11) showed no statistical differences in effect on LDL between training intensities.

### Sensitivity analyses

We found high heterogeneity for the effect of resistance training on LDL for moderate ($I^2$=94%, $\tau^2$=0.16) and high intensity resistance training ($I^2$=79%, $\tau^2$=0.12). Excluding Tomeleri et al. (highly deviant mean difference) and studies at high risk of bias (40, 60, 64, 66, 77, 86, 87) in the sensitivity analysis decreased the heterogeneity for moderate intensity resistance training ($I^2$=80% and $\tau^2$=0.04). For high intensity resistance training we could not do sensitivity analysis due to the small number of studies included (n=3).

After excluding the above-mentioned studies for moderate intensity resistance training in the meta-regression analysis, we found a decrease in heterogeneity ($I^2$=68.48%, $\tau^2$=-5.47), however, still no statistical differences were found between training intensities.

### Waist-hip-ratio

Figure 2.5 presents the results for WHR. A total of 16 studies with 426 adults (43.19% male) reported WHR as a study outcome, and 11 studies only included adults who were obese. The average age ranged between 21 and 75 years. Of these studies, three studies investigated low intensity resistance training, 10 studies moderate intensity training, one study high intensity resistance training, and three studies investigated progressive intensity resistance training.

The meta-analysis showed a significant pooled effect for moderate intensity resistance training of -0.02 (95% CI [-0.03; -0.01]) and for progressive intensity resistance training of -0.06 (95% CI [-0.10; -0.02]) compared to non-active control. A non-significant pooled effect estimate was found for low intensity resistance training of 0.01 (95% CI [-0.04; 0.05]). High intensity resistance training was investigated by only one study showing a mean difference in WHR of -0.09 (95% CI [-0.10; -0.08]).

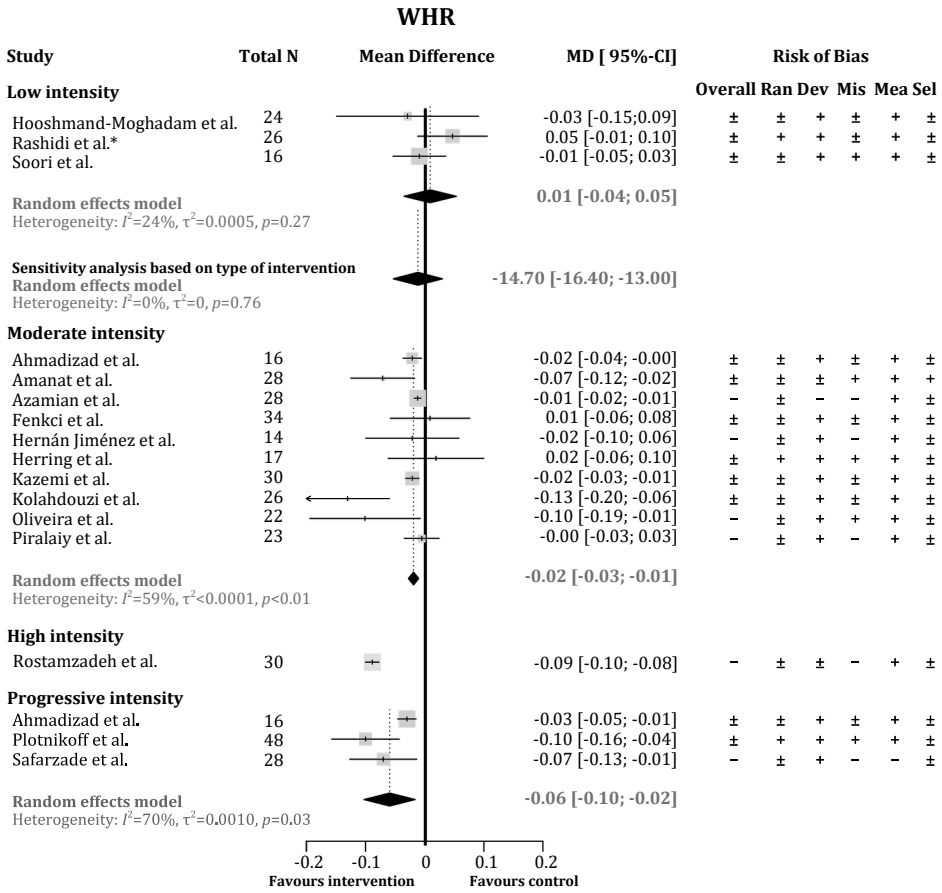


**Figure 2.5. Forestplot WHR.**

The meta-regression model ($I^2$=68.10%, $\tau^2$=51.08) showed that there was a statistical difference in effect estimates between low and high intensity resistance training and between low and progressive intensity resistance training. With high and progressive being more effective compared to low intensity resistance training.

## Sensitivity analyses

We found two outliers (71, 75) for moderate intensity resistance training in our meta-analysis. For Oliveira et al. we did not find an explanation for the larger mean difference found in this study. The mean value for WHR in the control group in the study of Kolahdouzi et al. increased between baseline and post intervention, resulting in a larger mean difference between groups.

We found high heterogeneity for progressive intensity resistance training ($I^2$=70%, $\tau^2$=0.001). However, we could not find any explanation for the observed heterogeneity.

For low intensity resistance training, we conducted a sensitivity analysis based on type of intervention, excluding Rashidi et al. Excluding this study explained all heterogeneity for low intensity resistance training. The pooled effect estimate changed from 0.01 (95% CI [-0.04; 0.05]) to -0.01 (95% CI [-0.05; 0.03]).

Excluding the study of Rashidi et al. in our meta-regression analysis increased the effect estimate of low intensity resistance training, resulting in a non-significant difference between low and progressive intensity resistance training. The effect estimate of high intensity resistance training remained significantly higher than low intensity resistance training. No change in heterogeneity of the regression model was found.

### Certainty of evidence

The certainty of evidence is presented in Table 2.1. For all resistance training intensities, the certainty of evidence was downgraded due to serious (moderate and progressive intensity) and very serious (low and high intensity) concerns for risk of bias. Subsequently, evidence for low, moderate, and progressive intensity resistance training was downgraded due to serious concerns because of inconsistency in the study results, and evidence for low and high intensity resistance training was downgraded for serious concerns because of imprecision in the study results. Resulting in an overall very low certainty of evidence for low and high intensity resistance training, low certainty for moderate intensity resistance training, and low to moderate certainty for progressive intensity resistance training.

**Table 2.1. GRADE evidence profile**

| Certainty assessment | | | | | | | Number of patients | | Pooled effect MD [95% CI] | Range of MD [95% CI] (individual studies) | Certainty ⊕⊕⊕⊕ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Outcome | N studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Other factors | I | C | | | |
| **Low intensity** | | | | | | | | | | | |
| HbA1c | 2 | Very serious[a] | Serious[b] | Not serious[c] | Serious[d] | None | 34 | 32 | | 0.30 [-0.22; 0.82] to -2.02 [-3.10; -0.94] | ⊕ Very low |
| SBP | 7 | Very serious[a] | Serious[b] | Not serious | Not serious | None | 161 | 125 | | -20.00 [-21.02; -18.98] to 6.00 [ -3.29; 15.29] | ⊕ Very low |
| LDL | 11 | Serious[e] | Not serious | Not serious | Not serious | None | 137 | 137 | -0.10 [-0.16; -0.04] | | ⊕⊕⊕ Moderate |
| WHR | 3 | Serious[e] | Not serious | Not serious | Serious[d] | None | 33 | 33 | 0.01 [-0.04; 0.05] | | ⊕⊕ Low |
| **Moderate intensity** | | | | | | | | | | | |
| HbA1c | 9 | Serious[e] | Not serious | Not serious | Not serious | None | 199 | 198 | -0.40 [-0.66; -0.14] | | ⊕⊕⊕ Moderate |
| SBP | 18 | Serious[e] | Serious[b] | Not serious | Not serious | None | 226 | 218 | | -20.46 [ -30.79; -10.13] to 0.80 [ -12.32; 13.92] | ⊕⊕ Low |
| LDL | 25 | Serious[e] | Serious[b] | Not serious | Not serious | None | 407 | 402 | | -1.65 [-1.92; -1.38] to 0.44 [-0.07; 0.94] | ⊕⊕ Low |
| WHR | 10 | Serious[e] | Serious[b] | Not serious | Not serious | None | 103 | 105 | -0.02 [-0.03; -0.01] | | ⊕⊕ Low |

*Table 2.1 continues on next page.*

**Table 2.1.** ***Continued***

| Certainty assessment | | | | | | | Number of patients | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Outcome | N studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Other factors | I | C | Pooled effect MD [95% CI] | Range of MD [95% CI] (individual studies) | Certainty ⊕⊕⊕⊕ |
| **High intensity** | | | | | | | | | | | |
| HbA1c | 2 | Very serious[a] | Not serious | Not serious | Not serious | None | 43 | 43 | -1.20 [-1.86; -0.54] | | ⊕⊕ Low |
| SBP | 2 | Very serious[a] | Not serious | Not serious[f] | Serious[d] | None | 43 | 43 | -1.49 [-6.59; 3.61] | | ⊕ Very low |
| LDL | 3 | Very serious[a] | Serious[b] | Not serious | Serious[d] | None | 54 | 54 | | -0.81 [-1.14; -0.48] to 0.02 [-0.44; 0.48] | ⊕ Very low |
| WHR | 1 | Very serious[a] | Not serious | Not serious | Not serious | None | 15 | 15 | -0.09 [-0.10; -0.08] | | ⊕⊕ Low |
| **Progressive intensity** | | | | | | | | | | | |
| HbA1c | 4 | Serious[e] | Serious[b] | Not serious | Not serious[c] | None | 66 | 62 | | -1.82 [-2.57; -1.07] to 0.20 [-0.41; 0.81] | ⊕⊕ Low |
| SBP | 8 | Serious[e] | Not serious[g] | Not serious[c] | Not serious | None | 119 | 112 | -14.70 [ -16.40; -13.00] | | ⊕⊕⊕ Moderate |
| LDL | 4 | Serious[e] | Not serious | Not serious | Not serious | None | 81 | 75 | -0.16 [-0.19; -0.13] | | ⊕⊕⊕ Moderate |
| WHR | 3 | Serious[e] | Serious[h] | Not serious | Not serious | None | 49 | 43 | | -0.10 [-0.16; -0.04] to -0.03 [-0.05; -0.01] | ⊕⊕ Low |

a. Most information is from studies at high risk of bias; b. High heterogeneity and significant; c. Different type of intervention; d. Confidence interval includes no effect; e. Most information is from studies at moderate risk of bias; f. One study had a population without hypertension; g. Heterogeneity explained by subgroup analysis for type of intervention; h. Results are not consistent.

## Discussion



The aim of this systematic review was to summarise the effects of different resistance training intensities on multiple CVRFs. We aimed to give an overview of the evidence to give clinical recommendations for the use of resistance training in adults with multiple CVRFs. This systematic review presents data from 59 trials investigating the effect of resistance training on CVRFs. To our knowledge, there has not previously been such a comprehensive review on the effect of different resistance training intensities on multiple CVRFs.

Our meta-regression analyses showed no statistically significant differences between the effect of different training intensities on HbA1c, SBP, and LDL. Our results did show a statistically significant difference between low and high intensity resistance training on WHR. The meta-regression models showed bigger effect estimates with higher training intensities. These findings show indications that a higher training intensity has a bigger effect on CVRFs. However, overall, the number of studies that investigated high (n=4) and progressive (n=9) intensity resistance training in this review was small. This could explain why we did not find statistical differences between training intensities, except for the effect of low versus high intensity resistance training on WHR.

For HbA1c our meta-analysis showed a positive significant pooled effect estimate of -0.40% for moderate intensity and -0.81% for high intensity. The systematic reviews by Fan et al. (-0.49% HbA1c) and Liu et al. (-0.61% HbA1c) found greater reductions on HbA1c for high intensity resistance training (75–100% 1RM) than for low-moderate intensity. However, these reviews categorised studies that used progressive intensity as high intensity and could therefore not differentiate between these intensities. Costa et al. conducted a subgroup analysis based on training intensity and found a positive effect on LDL of -7.70 mg/dL for studies that used a progressive training protocol. This is similar to our results where we found a positive pooled effect of progressive intensity on LDL of -0.16 mmol/L (-6.19 mg/dL).

For WHR our meta-analysis showed a significant reduction in WHR for moderate intensity of -0.02, and a non-significant increase in WHR for low intensity resistance training of 0.01. Meta-regression analysis showed that

high intensity resistance training reduced WHR significantly more compared to low intensity. However, the effect of high intensity resistance training on WHR was only investigated in one study. Previous reviews found similar results. Fan et al. found non-significant effect sizes of 0.01 for WHR for high intensity training and of -0.02 for low-moderate intensity training in adults with DM2. Lopez et al. found no association between whole body fat mass and training intensity in adults who were overweight or obese.

The results are of moderate- and low-certainty of evidence, mostly due to risk of bias and inconsistency of the results. We found substantial between-study heterogeneity in most of our results indicating that there is high variability between studies. The inclusion of studies with a variety of participant populations and intervention characteristics such as duration and supervision could explain this variability. Furthermore, although only RCTs were included in this review, our risk of bias assessment showed concerns due to bias within the randomisation process, missing outcome data, and reported results.

### Strengths and limitations

Our systematic review and meta-analysis have several strengths. We used two analytical approaches to compare the effects of different training intensities on CVRFs. First, we conducted meta-analyses according to training intensities for each CVRF. Second, we conducted meta-regression analyses to statistically compare the effects of different training intensities. Furthermore, subgroup analyses were conducted to explain heterogeneity and inconsistencies in the results. Finally, we included studies from different parts of the world which contributes to the generalisability of our results. We did exclude studies because we were not able to translate the reports adequately (n=12). However, given the number of included studies, we consider the risk of missing relevant studies to be small.

This review was conducted according to a predefined protocol. However, due to the scarcity of multi-arm studies it was not possible to conduct a network meta-analysis. Therefore, we deviated from our protocol regarding the conducted analyses. This limits the possibility to rank the training intensities and affects the certainty of evidence based on indirectness.

For our pairwise meta-analysis we used the mean post intervention scores. This method does not correct for mean baseline scores which may

have resulted in large inter-study effect size differences and imprecision of our results. We tried to account for baseline differences in sensitivity analyses by excluding outlier studies with baseline differences between study groups.

Another limitation is that WHR was the only anthropometric outcome consistently reported across the included studies. As WHR is a ratio, it does not clarify whether changes are driven by reductions in waist circumference, increases in hip circumference, or both, which limits interpretation of the specific nature of body composition changes. Although the use of WHR has its limitations, it has been shown in previous research to be a reliable and valid indicator of central adiposity and obesity-related health risk (6, 30). Moreover, there is currently no consensus on the most appropriate anthropometric measure, with ongoing debate surrounding the use of WHR, waist circumference, waist-to-height ratio, body roundness index, and other indices (99-101).

### Clinical considerations

Previous research has demonstrated that a reduction of 1% HbA1c, 5 mm/Hg SBP, 1 mmol/L LDL is of clinical relevance, as it reduces the risk of cardiovascular disease and mortality (2-5). An increase of 0.01 in WHR has been associated with a 5% increase in the risk for cardiovascular diseases (6). Considering these thresholds, the statistically significant pooled effect estimates presented in our review suggest that clinically relevant reductions can be achieved in WHR with moderate and progressive intensity resistance training, and in SBP with progressive resistance training. Our findings show positive effects of different resistance training intensities on CVRFs. However, achieving a clinically relevant reduction in the risk of cardiovascular disease, may require more than resistance training alone. In clinical practice, resistance training should be used in a broader, multicomponent intervention including changes towards a healthy lifestyle, such as healthy nutrition, no smoking, limited alcohol use, and good sleep, other training modalities, and if needed medication (1). However further research is needed in order to evaluate the effectiveness of different combinations of lifestyle interventions and medication.

Adults with CVRFs often have higher age, multiple chronic conditions and have an unhealthy lifestyle with low physical activity levels (1). These factors can increase the risk for injuries and impact the ability to perform resistance

training when not done with the right guidance and supervision (7). Multimorbidity and low levels of physical activity also can lead to deconditioning and insecurity to exercise which may impede starting with resistance training, especially at a higher intensity. Therefore, starting with low intensity resistance training can be needed (7). Furthermore, due to comorbidities, such as obesity, people might feel physically uncomfortable while exercising or have had previous negative experiences with exercise (7, 100). Starting with an easy low intensity resistance training could contribute to a positive experience with exercise. A more cautious approach in resistance training with a gradually increase in intensity can decrease the risk of injuries and increase confidence in exercising. Given that all training intensities demonstrated clinically relevant effects and considering the complexity involved in training with adults with CVRFs, progressive resistance training could be considered as a suitable resistance training intervention in clinical practice. The initial intensity and progression should be personalised by the clinician based on medical history and individual abilities.

**Future research**

For further clarification of the effectiveness of different resistance training intensities on CVRFs, future research should focus on comparing different intensities directly. Given the limited number of trials investigating the effect of low- high- and progressive intensity resistance training on CVRFs, future research should prioritize investigating these intensities. Although progressive resistance training includes all other intensities, we consider it to be both conceptually and physiologically different from protocols that use a fixed intensity. In comparison to fixed intensities, progressive resistance training avoids performance plateaus and stimulates neuromuscular and structural adaptations (99, 102). These differences could influence the effect of resistance training on CVRFs, and therefore we recommend considering progressive intensity resistance training as a separate category.

To address the observed heterogeneity in our meta-analyses, future research should also focus on the association between person-characteristics and training effects. Identifying person-characteristics that act as moderating factors will allow for better personalised training suggestions.

Additionally, future research should aim to include and report a broader range of anthropometric measurements (100, 101, 103). This will allow for a more accurate interpretation of anthropometric changes and their association with health outcomes. Using multiple measures can help clarify whether observed effects are due to changes in fat mass, muscle mass, or body shape.

Finally, as current evidence is of moderate to low quality, future studies should improve the transparency of the reported methods considering the randomisation process and missing outcome data to reduce risk of bias. Additionally, future trials should consider applying statistical methodologies that account for baseline differences between study groups. This will contribute to reducing bias and allow for a more accurate estimation of the true effect. In turn, this will enhance the quality of evidence of future meta-analyses.

## Conclusion

This review investigated the effect of low, moderate, high and progressive intensity resistance training on CVRFs in adults who are at higher risk of cardiovascular disease. Our findings showed no significant differences in effect between resistance training intensities for HbA1c, SBP, and LDL. One study showed that high intensity was more effective than low intensity in reducing WHR. These results are of low to moderate certainty of evidence. Further research is needed to explore the effect of different resistance training interventions with each other and individual characteristics, to enable personalized training recommendations in the future. The quality of the reported results must be increased. Based on the current evidence, clinicians should personalize the intensity of resistance training based on individual and medical factors.

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# Chapter 3

# The effect of progressive resistance exercise training on cardiovascular risk factors in people with intellectual disabilities: A study protocol

**R.G. Elbers**
**K.I. de Oude**
**T. Kastanidis**
**D.A.M. Maes-Festen**
**A. Oppewal**

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## Abstract

Progressive resistance exercise training (PRET) reduces cardiovascular risk factors (CVRF) in the general population. It is unknown if PRET also reduces these risk factors in adults with intellectual disabilities (ID). The aim is to present the protocol of an intervention study that investigates the effect of PRET on CVRF in adults with ID.

We will use a repeated time series design with one study group. Adults with mild-to-moderate ID and at least two CVRF are eligible (Netherlands Trial Register, NL8382). During a 12-week baseline period, measurements take place at a 6-week interval. After this, the PRET programme starts for 24 weeks, after which all measurements will be repeated. We will use hierarchical regression models, adjusted for sport activity and medication use, to estimate the effect of PRET. After the intervention, the participants will be followed-up for 12 weeks. We will evaluate factors for successful implementation of exercise in daily life. Primary outcomes are: hypertension, obesity, hypercholesterolemia, diabetes, metabolic syndrome. Secondary outcomes are: physical fitness, sarcopenia, physical activity, activities of daily living, falls, challenging behaviour.

If our results show that the PRET programme is effective, it may be a promising non-pharmacological intervention to reduce CVRF in adults with ID.

# Introduction

The life expectancy of people with intellectual disabilities (ID) is increasing and approaching that of the general population (1, 2). However, an increased life expectancy does not mean that people with ID are ageing healthy. The Healthy Ageing and Intellectual Disabilities (HA-ID) study found that cardiovascular risk factors (CVRF) were highly prevalent in adults with ID of 50 years and over. Hypertension was seen in 53% of the participants, obesity in 46–48%, hypercholesterolemia in 23%, diabetes in 13%, and metabolic syndrome in 45% (3).



When CVRF are present, it is recommended to use either medication or promotion of a healthy lifestyle to prevent the development of cardiovascular disease (4). Because adults with ID are more likely to be exposed to polypharmacy (5), promoting a healthy lifestyle and physical activity may have an even more important role in reducing cardiovascular risk. Unfortunately, most adults with ID have an inactive lifestyle with only 9% of them achieving physical activity levels needed for gaining health benefits (6).

Resistance exercise training is a well-studied intervention that reduces CVRF in the general population (7-10) and may be promising to reduce CVRF in adults with ID as well. For adults with cardiovascular and metabolic disease, the American College of Sports Medicine (ACSM) guidelines recommend a progressive resistance exercise training (PRET) programme at vigorous intensity for all large muscle groups (11). Although research has been conducted in the general population, it is still unknown whether PRET is beneficial for reducing CVRF in adults with ID. Studies indicate that the physiological responses to exercise are different in people with ID. For example, there are indicators that during exercise they have a blunted blood pressure and baroreflex sensitivity response (12, 13), and a lower maximal heart rate and peak oxygen uptake (14) than people in the general population. Therefore, the effect of exercise interventions may differ for this population, and we cannot generalize the results from the general population to people with ID.

Due to low physical activity levels (15), adults with ID are prone to other health problems. Low levels of physical activity can result in loss of muscle strength and muscle mass which can lead to sarcopenia at older age (16). Sarcopenia is a characterised by progressive and generalised loss of

skeletal muscle mass and strength with a risk of adverse health outcomes (17). Sarcopenia has been found prevalent in older people with ID, at already younger ages than in the general population (17, 18). In the general population resistance training reduces sarcopenia (19), as it increases the muscle strength and muscle mass (20). Other studies showed that people with ID have poor balance, strength, muscular endurance, and gait speed (15, 21) which can lead to difficulties in performing activities of daily living and thereby increase the dependency of caregivers (22) and falls. In addition to these health problems, challenging behaviour, such as aggression and self-injury, is common (23). Team sports seem to reduce challenging behaviour (24), but it is still unknown if resistance training is effective in reducing challenging behaviour in adults with ID.

A PRET programme may enhance physical activity and be beneficial for people's cardiovascular risk profile and health in general. In a previous study, we composed a Resistance Exercise Set for adults with ID (RESID) (25). We found that these exercises were feasible to perform by adults with mild to moderate ID and CVRF (26). Therefore, the RESID can be used in the PRET programme as the content of the training sessions. This programme may be an additional intervention to existing pharmacological treatments for CVRF in adults with ID. To our knowledge, no study investigated the effect of PRET on reducing the above-described health issues in this population. The primary aim of this study is to investigate the effect of the PRET programme on CVRF (hypertension, obesity, hypercholesterolemia, diabetes, and metabolic syndrome) in adults with ID. Second, we will investigate the effect of PRET on physical fitness, sarcopenia, physical activity, activities of daily living, falls, and challenging behaviour. This paper presents the study protocol, outcomes, and statistical analysis plan.

## Material and methods

### Study design

This study has a repeated time series design with one study group. The study period will last one year and is divided into a 12-week baseline period, a 24-week intervention period (PRET programme), and a 12-week follow-up period. We will use the baseline measurements for control comparisons.

This study follows the principles of the Declaration of Helsinki (27) and is in accordance with the Dutch Medical Research Involving Human Subjects Act. We obtained ethical approval from the Medical Ethical Committee of the Erasmus MC, University Medical Center Rotterdam in the Netherlands (MEC-2019-0544). The study is registered in the Netherlands Trial Register (NTR, NL8382). Written informed consent will be obtained from all participants or their legal representatives.

**Study population, recruitment, and inclusion**

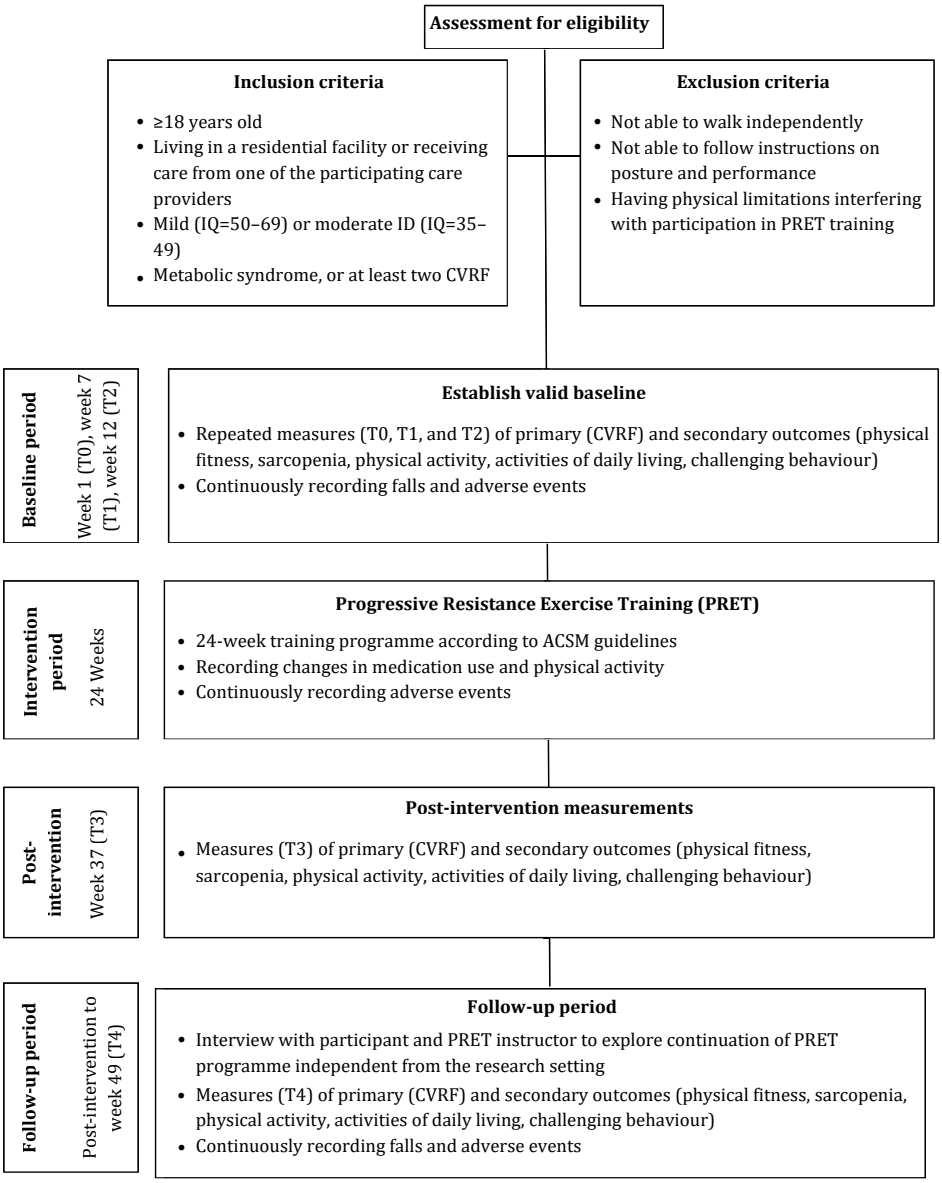


This study will be conducted within the Healthy Ageing and Intellectual Disability (HA-ID) consortium. The HA-ID consortium is a collaboration between the Chair of Intellectual Disability Medicine of the Erasmus MC, University Medical Center Rotterdam and three care providers in the Netherlands specialised in care for people with ID: Ipse de Bruggen (Zoetermeer), Abrona (Huis ter Heide), and Amarant (Tilburg).

Figure 3.1 summarises the inclusion and exclusion criteria for this study. Participants must meet the following criteria to be included: 1) being 18 years or older; 2) living in a residential facility or receiving care from one of the participating care providers; 3) diagnosed with mild (IQ=50–69) or moderate (IQ=35–49) ID (28); 4) diagnosed with metabolic syndrome (29), or at least two of the following CVRF: hypertension (30), hypercholesterolemia (4), diabetes mellitus type 2 (31), or obesity (32). Metabolic syndrome is defined as the presence of any three of the following CVRF: elevated waist circumference, elevated blood pressure, elevated fasting glucose, elevated triglycerides, and low high density lipoprotein cholesterol (29). Cut-off values for the CVRF are summarised in Table 3.1. Furthermore, participants must be able to walk independently and able to follow instructions on posture and performance for good execution of the exercises.

We will develop a query to screen medical files for potential participants. Potential participants are screened by a physical therapist for their eligibility and expected adherence to the PRET programme. To identify health issues that make participation in the PRET programme unsafe, the professional caregiver of eligible participants will fill out the Physical Activity Readiness Questionnaire (PAR-Q) (33). If a positive response to any of the items of the PAR-Q is given, the participant's physician will do a health check to assure safe

participation. Participants who do not obtain medical clearance from their physician or have physical limitations (including neurological and orthopaedic conditions) interfering with participation in the PRET programme will be excluded from the study.




ACSM: American College of Sports Medicine; CVRF: cardiovascular risk factors; ID: intellectual disability; IQ: intelligence quotient

**Figure 3.1. Study recruitment and procedures.**

**Table 3.1. Definitions of cardiovascular risk factors (CVRFs)**

| Cardiovascular risk factor | Reference | Markers | Values |
|---|---|---|---|
| Metabolic syndrome, having 3 out of 5 markers | Alberti et al. (2009) | Waist circumference | ≥94 cm (men)*<br>≥80 cm (women)* |
| | | Fasting glucose (FG) | >5.6 mmol/L |
| | | High density lipoprotein (HDL-C) | <1 mmol/L (men)<br><1.3 mmol/L (women) |
| | | Triglycerides (TG) | >1.7 mmol/L |
| | | Systolic blood pressure (SBP) and diastolic blood pressure (DBP) | ≥130 mm/Hg and ≥85 mm/Hg |
| Hypertension (Stage 2) | Whelton et al. (2017) | Systolic blood pressure (SBP) | ≥140 mm/Hg |
| | | Diastolic blood pressure (DBP) | ≥90 mm/Hg |
| Hypercholesterolemia | Piepoli et al. (2016) | Total cholesterol (TC) | >4 mmol/L |
| | | Low density lipoprotein (LDL-C) | ≥2.6 mmol/L |
| Diabetes mellitus type 2 | American Diabetes Association (2018) | Fasting glucose (FG) | ≥7 mmol/L |
| | | HbA1c | ≥48 mmol/L |
| Obesity | World Health Organisation (2008) | Waist Circumference | >94 cm (men)*<br>>80 cm (women)* |
| | | Waist-hip ratio | ≥0.90 (men)<br>≥0.85 (women) |

*European, Caucasian threshold; mm/Hg: millimetres of mercury; mmol/L: millimoles per litre.



### Informed consent procedure

All potential participants will receive study information and a consent form. A behavioural scientist will assess if potential participants understand the easy-read study information and if they are able to decide for participation themselves. If potential participants are not able to make an informed decision, we will also send the study information and a second consent form to their legal representative and ask them for a decision.

### Intervention

The PRET programme will take 24 weeks and consists of two sessions per week, with at least 48 hours between the sessions. The intervention will be led by experienced physiotherapists and physical activity instructors employed by the care providers. All instructors take part in a training prior to the study. In this training, the intervention protocol and exercises will be discussed and

practiced ensuring that the intervention is delivered according to the protocol. Every session consists of seven exercises (RESID) to train all large muscle groups (25). For each muscle group, alternative exercises will be provided for participants who are not able to perform the original exercise with a correct execution. The instructor-participant ratio will be 1 to 1 or 1 to 2.

Table 3.2 summarises the training parameters of the PRET programme. The programme is in accordance with the ACSM guidelines (11) and characterised by four mesocycles. Each mesocycle consists of six weeks of training. After each mesocycle the training intensity will increase gradually, and within each mesocycle the weights will be adjusted in a way that the intensity remains equal. Training intensity will be measured by the percentage of the heaviest load one can lift for one repetition (% of 1RM) (34). In the first mesocycle, participants are introduced to the resistance exercises and familiarised to the training protocol. They will learn to perform the exercises safely and with good posture. During mesocycles 2, 3, and 4, the number of repetitions will be gradually decreased while the training intensity will be gradually increased until vigorous intensity is reached in the fourth mesocycle (80% of 1RM). The resting time between sets will depend on the training intensity and varies between 30 seconds and 2 minutes.

The instructors will register attendance, training intensity, performed number of sets and repetitions, and the weights used for each exercise in a log. To maximise attendance and motivation, each participant receives a progression certificate to track their progress and a T-shirt to wear during the training and measurements. At completion of the programme, the participant receives a certificate and a medal.

**Table 3.2. Training parameters according to the ACSM guidelines (ACSM, 2014)**

| Mesocycle | % of 1RM | Number of sets | Number of repetitions | Rest between sets |
|---|---|---|---|---|
| 1 | - | 1-2 | 20 | 30 seconds |
| 2 | 65 | 2 | 15 | 1 minute |
| 3 | 75 | 3 | 10 | 1 minute |
| 4 | 80 | 3 | 8 | 2 minutes |

ACSM: American College of Sports Medicine; 1RM: one-repetition maximum.

### Co-interventions

Participants will continue their usual activities but cannot start another intervention or activity to improve their physical activity level during the study period. Medical interventions that are necessary for regular care are allowed to start. All changes in sport activities and medication use related to CVRF will be recorded.

### Primary outcomes

The following CVRF are the primary outcomes.



#### *Hypertension, blood pressure*

A trained researcher will use the Omron-M7 (Omron Healthcare, Kyoto, Japan) to measure blood pressure from both arms after sitting for two minutes without talking. The Omron-M7 has been found valid according to the international protocol of the European Society of Hypertension (35). We will select the arm with the highest value for the actual measurement. This arm will be measured twice, and the average score (mm/Hg) for systolic (SBP) and diastolic (DBP) blood pressure will be recorded. Participants will be classified as hypertensive if SBP ≥140 mm/Hg, and/or DBP ≥90 mm/Hg (30). If the automated blood pressure measurement repeatedly fails, for example when the reading is distorted by movement of the cuff, we will use a sphygmomanometer to manually measure the participants' blood pressure.

#### *Obesity, waist, and hip circumference*

A trained researcher will use a measuring tape (Seca 200, Seca, Hamburg, Germany) to measure waist and hip circumference (32). Waist circumference will be measured at the midpoint between the lowest palpable rib and the top of the iliac crest. Hip circumference will be measured around the widest portion of the buttocks. Each measurement will be repeated twice. If the repeated measurements are within 1 cm of one another, we will calculate an average score (cm). If the difference between the measurements exceeds 1cm, the two measurements will be repeated (32). Male participants will be classified as obese if their waist circumference >94 cm and their hip-waist ratio ≥0.90, and female participants if their waist circumference >80 cm and their hip-waist ratio ≥0.85 (32).

***Hypercholesterolemia, diabetes, and metabolic syndrome***

The medical staff of the care providers will collect blood samples after overnight fasting. The samples will be analysed at the laboratory of the Erasmus MC. We will measure total cholesterol (TC), low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), triglycerides (TG), HbA1c and fasting glucose (FG) in mmol/L. Participants will be classified as having hypercholesterolemia when TC >4 mmol/L and LDL-C ≥2.6 mmol/L (4). Cut-of values for classifying participants as having diabetes mellitus type 2 are set at ≥48 mmol/L for HbA1c and ≥7 mmol/L for FG (31). Participants will be classified as having metabolic syndrome when at least three of the following CVRF are present: elevated waist circumference (≥94 cm for men, ≥80 cm for women), elevated blood pressure (SBP ≥130 mm/Hg, and/or DBP ≥85 mm/Hg), elevated FG (>5.6 mmol/L), elevated triglycerides (>1.7 mmol/L), and low HDL-C (<1 mmol/L for men, <1.3 mmol/L for women) (29).

## Secondary outcomes

***Physical fitness, muscle endurance, muscle strength, balance***

A trained researcher will use the ID-fitscan to assess physical fitness. The ID-fitscan is a standardised set of performance tests that assesses muscle endurance (30 seconds chair stand and the five times chair stand), muscle strength (grip strength by hand-held dynamometry), and balance (four balance stances and comfortable walking speed). The set has been found feasible and reliable for adults with ID (36).

For the 30 seconds chair stand, participants are instructed to stand up and sit down as often as possible, without using their hands. We will record the number of complete stances performed in 30 seconds. For the five times chair stand, participants are instructed to stand up and sit down five times as fast as possible, without using their hands. We will record the time needed to complete five stances. For both tests, the participant starts sitting in the chair with the feet on the floor and the knees in a 90° angle.

We will use the Jamar dynamometer (Hydraulic, JAMAR, Sammons Preston Rolyan, Nottinghamshire, UK) to measure grip strength. Grip strength is tested in a seated position with the shoulder in 0° flexion and the elbow in 90° flexion. The participant is asked to squeeze the dynamometer with maximum force

three times, with one minute rest in between. Both hands will be tested. The maximum produced force of the six attempts (kg) is the final test score.

Static balance will be measured with four stances that increase in difficulty: side-by-side stand, semi-tandem stand, tandem stand, and single leg stand. The participant must try to maintain each stand independently for 10 seconds for both sides, with a maximum of five attempts. If successful, the participant continues to the next stand. We will record the time for each completed stance and use the scores for side-by-side stand, semi-tandem stand, and tandem stand to categorise static balance from 0 (worse) to 4 (best) (37). Dynamic balance will be measured as comfortable gait speed on an 11-meter walkway. The participant will start from stance and accelerate to comfortable gait speed in the first 3 meters of the walkway. When crossing the 3-meter mark, a stopwatch is put in action and gait speed will be measured over the following 5 meter. At the 8-meter mark timing will be ended, and the participant will decelerate to standing still over the last 3 meters of the walk. The test will be repeated three times. The average time of the three trials (seconds) will be converted to gait speed (m/s).



***Sarcopenia, body composition***

We will use bioelectrical impedance analysis (Tanita Body Composition Analyzer MC-780, Tanita, Tokyo, Japan) to measure body mass (kg), fat mass (kg and %), and muscle mass (kg and %). The Tanita MC-780 estimates muscle mass based on whole body conductivity and uses a conversion equation that is calibrated with Dual-energy X-ray absorptiometry as a reference (38). Muscle mass will also be measured by calf circumference. A trained researcher will use a measuring tape (Seca 200, Seca, Hamburg, Germany). Calf circumference will be measured twice at the widest point of the calf. If both measurements are within 1cm of one another, we will calculate an average score (cm). If the difference between the measurements exceeds 1cm, the two measurements will be repeated.

Table 3.3 presents the cut-off values that we will use to classify participants as being sarcopenic (17). We will classify participants that score under the cut-off values for muscle endurance, muscle strength and muscle mass as sarcopenic. If participants also score under the cut-off value for comfortable gait speed (≤0.8 m/s), they will be classified as severe sarcopenic (17).

**Table 3.3. Classification for sarcopenia cut-off (Cruz-Jentoft et al., 2019)**

| Domain | Tests | Values |
|---|---|---|
| *Sarcopenia* | | |
| Muscle strength | Five times chair stand | >15 seconds for 5 rises |
| | Grip strength | <27 kg (men)<br><16 kg (women) |
| Muscle mass | BIA | <20 kg (men)<br><15 kg (women) |
| *Severe sarcopenia* | | |
| Muscle strength | Five times chair stand | >15 seconds for 5 rises |
| | Grip strength | <27 kg (men)<br><16 kg (women) |
| Muscle mass | BIA | <20 kg (men)<br><15 kg (women) |
| Physical performance | Gait speed | ≤0.8 m/s |

BIA: bioelectrical impedance analysis; kg: kilogram; m/s: meter per second.

### *Physical activity*

To assess the physical activity levels, we will use the International Physical Activity Questionnaire (IPAQ) (39). The IPAQ assesses daily physical activity over the last seven days. The IPAQ consists of 27 items that are divided into five domains of physical activity: job-related, transportation, housework, leisure time, and sitting. For each domain, scores are provided for walking, moderate-intensity activities, and vigorous-intensity activities. Scores will be reported as the estimation of metabolic equivalent-minutes per week (MET–minutes/week) (40). The IPAQ has been found reliable and valid in the general population (39).

### *Activities of daily living*

We will use the Barthel Index (41) to assess the ability to perform basic activities of daily living. The Barthel Index consists of ten items (bowel control, bladder control, grooming, toilet use, feeding, transfer, walking, dressing, climbing stairs, and bathing) with item scoring categories ranging from two to four categories. The total score ranges from 0 (completely dependent) to 20 (completely independent) (42). The Barthel Index has good psychometric properties in the general population (42).

To assess the ability to perform instrumental activities of daily living (IADL), we will use an adapted version of the Lawton IADL scale (43). We expect that adding and rephrasing some items for preparing food, housekeeping, and doing laundry, will increase the responsiveness of the scale. In a previous study we found this version to be applicable in older adults with ID (44). The items were derived from the Groningen Activity Restriction Scale (GARS) (45). All items will be scored on a 4-point rating scale ranging from 0 (not at all, with complete help) to 3 (fully independent, without any difficulty). All items scores will be summed. A detailed description of the items and scoring is presented in Table 3.4. We will administer the Barthel Index and the adapted version of the Lawton IADL scale as an informant-based questionnaire, completed by the professional caregiver of the participant.



**Table 3.4. Items and adapted scoring based on Lawton and Brody IADL**

| Items Lawton and Brody IADL (Lawton & Brody, 1969) | Items derived from GARS (Kempen, 1996) | Items and adapted scoring used in this study |
|---|---|---|
| *Items* | | |
| Using the telephone | | Using the telephone |
| Shopping | | Shopping |
| Preparing food | Prepare breakfast or lunch | Prepare breakfast or lunch |
| | Prepare diner | Prepare dinner |
| Housekeeping | Light household activities | Light household activities |
| | Heavy household activities | Heavy household activities |
| | Make the bed | Make the bed |
| Doing laundry | Wash and iron clothes | Wash and iron clothes |
| Using transportation | | Using transportation |
| Handling medication | | Handling medications |
| Handling finances | | Handling finances |
| *Scoring of items* | | |
| 0 = Less able | 5 = Not at all, with complete help | 0 = Not at all, with complete help |
| 1 = More Able | 4 = Not fully independent, but with some help | 1 = Not fully independent, but with some help |
| | 3 = Fully independent but with great difficulty | 2 = Fully independent but with great difficulty |
| | 2 = Fully independent but with some difficulty | 3 = Fully independent without any difficulty |
| | 1 = Fully independent without any difficulty | |

GARS: Groningen Activity Restriction Scale; IADL: instrumental activities of daily living.

***Falls***

We defined a fall as an event that results in a person coming to rest inadvertently on the ground, floor, or other lower level (46). We will use a fall calendar during the baseline period and the 12–week follow-up period. Falls are logged daily by the participant or the involved professional caregiver by putting a green sticker (no fall) or a red sticker (fall) on the calendar. If a participant falls multiple times during the day, the number of falls will be written down. The professional caregiver will check the calendar for completeness. For each period, we will classify participants as a non-faller or a faller (≥1 fall).

***Challenging behaviour***

We will evaluate challenging behaviour with the Aberrant Behaviour Checklist (ABC) (47). The ABC consists of 58 items that are divided into five subscales: irritability, lethargy, stereotypic behaviour, hyperactivity, and inappropriate speech. Items are scored on a four-point scale ranging from 0 (not a problem) to 3 (severe problem) by the professional caregiver of the participant. The summed score of each subscale will be recorded separately (47). The ABC is a reliable and valid instrument in adults with ID (48).

**Adverse events**

Adverse events are defined as any undesirable experience occurring to a participant during the study. It does not matter if the event is related or unrelated to the experimental intervention. Adverse events can be reported spontaneously by the participant, trainer, or professional caregiver. All adverse events will be recorded by the researcher.

**Participant characteristics**

Age, sex, ethnicity, level of ID, aetiology of ID, family history of CVRF (yes/no), kidney disease (yes/no), and medication use related to CVRF, are collected from medical records. The level of ID will be categorised as mild (IQ=50–69) or moderate (IQ=35–49). Professional caregivers will provide information about residential setting, sport activities, smoking, and alcohol use.

## Procedures

Figure 3.1 shows a schematic representation of the study procedures. Participant characteristics will be collected at T0. During the 12-week baseline period, measurements for the primary and secondary outcomes will take place at six-week intervals (T0, T1, and T2). A minimum of three measurements is needed to establish a valid baseline and to filter out the natural variability that may exist in these parameters without applying any intervention (49). We will record changes in sport activities and medication use related to CVRF. The falls will be tracked continuously throughout the 12-week baseline period. After the baseline period, the intervention period starts for a duration of 24 weeks. We will record changes in sport activities and medication use related to CVRF. At the end of the intervention period all measurements for the primary and secondary outcomes will be repeated (T3).

The follow-up period will last 12 weeks. Directly post-intervention, we will ask all participants to fill out a questionnaire about their experiences with the PRET programme. We plan interviews with participants and their trainers who want to continue the PRET programme and evaluate facilitators and barriers for successful exercise in their daily life. At the end of the follow-up period all measurements for the primary and secondary outcomes will be repeated (T4). Falls will be tracked continuously throughout the follow-up period. Participants who drop out prematurely from the intervention, will be invited for the measurements at T3 and T4.

## Statistical analysis plan

### *Baseline characteristics*

Descriptive statistics will be used to present group characteristics for age, sex, ethnicity, level and aetiology of ID, family history of CVRF, kidney disease, use of medication, and primary and secondary outcomes at T0. We will use the mean and standard deviation (SD) to present normally distributed data, the median and interquartile range for non-normally distributed data, and the number and percentages for categorical variables.

***Effect of PRET programme (post-intervention)***

We will use two-level hierarchical linear and logistic regression models to investigate the effect of the PRET programme at the end of the intervention period (T3). The first level consists of the repeated measurements nested within a participant; the second level consists of the clustering of participants by the trainer delivering the PRET programme. We will use the likelihood ratio test (correcting for the boundary) to assess the necessity for random coefficients in the regression model. Statistical analyses will be performed with R-statistics (R Foundation for Statistical Computing, Vienna, Austria) and we will use the package Linear and Nonlinear Mixed Effects Models (nmle) (50). A two-tailed significance level of 0.05 will be used for all tests.

The variables for the PRET programme will be coded as 0 (baseline period at T0, T1, and T2) or 1 (intervention period T3). To check the assumption of stable baseline measurements, we will investigate the effect of time on each outcome variable assessed during the baseline period. Time varying variables (changes in sport activities and medication use related to CVRF) will be included as covariates in all models.

We will use the data from all participants who started the study. We will also analyse the effect of the intervention for participants who completed the intervention as planned.

***Follow-up of outcomes (12 weeks post-intervention)***

We will use two-level hierarchical linear and logistic regression models to investigate the change in primary and secondary outcomes 12 weeks after ending the PRET programme (T3–T4). Time varying variables (medication use and physical activity) will be included as covariates. We will explore if results differ based on group characteristics (age, sex, level and aetiology of ID) by adding them subsequently to the linear and logistic regression models.

***Falls during baseline and 12-week follow-up***

We will use the McNemar test to compare the numbers of non-fallers and fallers during the baseline period and the 12-week follow-up period.

***Sample size calculation***

We calculated the sample size for the outcome HbA1c using simulated data and repeated the simulation a 1000-times in a hierarchical way. To determine the effect of the trainers we used the outcome of our pilot study (25) where we found a variation of 30% for the clustering of participants by the trainer who delivered the PRET programme. The type 1 error (alpha) was set at 0.05 and power was set at 80%. We used an effect size (mean change in % HbA1c=-0.55, SD=0.47) derived from a study that examined the effect of high intensity resistance training in adults with diabetes mellitus type 2 (10). This resulted in a sample of 35 participants needed for this study. In our pilot study, 58% of the participants completed the PRET programme successfully at intended intensity (25). Therefore, we inflate the number of participants by 42% and aim to enrol 61 participants in this study.



## Discussion

In this study we will examine the effects of the PRET programme on CVRF, physical fitness, sarcopenia, activities of daily living, falls, and challenging behaviour in adults with mild to moderate ID. These health issues are highly prevalent in this population (3, 15, 21-23) and non-pharmacological treatment strategies are needed to reduce the impact of these problems on health. If the PRET programme is effective in reducing CVRF, then it may be added as a strategy to existing interventions to reduce cardiovascular risk in adults with ID. Additionally, gaining muscular strength may increase physical fitness levels, reduce sarcopenia, enhance the ability to perform activities in daily life and reduce falls. The programme may have a positive impact on challenging behaviour.

A randomised controlled trial is often considered the gold standard for intervention research and offers the ability to reduce bias due to confounding (51). We considered a randomised study design; however, randomised controlled trials in people with ID have been challenging. Obtaining informed consent from legal representatives, rather than from eligible participants themselves, often results in small sample sizes and insufficient statistical power (51). We expect that legal representatives may refuse study participation, as the participant they represent may be allocated to the control group

and will not receive the PRET programme. Therefore, we opted for a repeated time series design with one study group. Because of the single group design, we can offer all participants the PRET programme, and all participants may profit from possible health benefits. The use of the repeated measures within each participant will increase the statistical power, and the multilevel regression analyses allow us to adjust for time varying variables such as sport activities and medication use related to CVRF.

Our study design has some limitations. First, we are not able to control for elements of care that we will not measure. This may result in uncontrolled residual confounding. Second, although the measurements used to assess the primary outcomes are objective, the validity of the measurements to assess physical fitness may be influenced by the ability of the participants to follow instructions. However, the results of the physical fitness tests will only be recorded if the trained researcher is convinced that participants understand how to perform the test. Finally, the lack of blinding of the researcher performing the assessments may introduce measurement bias.

A strength of this study is the clinically applicability of the PRET programme. In a pilot study (25) we created a set of feasible resistance exercises for adults with ID (RESID) that we used in the PRET programme. Secondly, we assessed the feasibility of the PRET programme in adults with ID and CVRF (26). We found that the PRET programme was feasible when close supervision was provided to the participant, with 58% of the participants achieving vigorous training intensity.

Adherence to the PRET programme is important for the internal validity of the study. It may be challenging for adults with ID to complete a 24-week exercise programme because of motivational factors. Based on our experiences from the pilot and feasibility study, we will incorporate several strategies (a progression certificate to track progress, a T-shirt to wear during the training and measurements, and the participant receives a certificate and a medal at the end of the programme) to maximize attendance and motivation of the participants. In addition, the training will be provided by trainers who are experienced in motivating adults with ID when performing physical exercises.

## Conclusion

To our knowledge, there is no study that examined the effect of resistance training on CVRF in adults with ID. If the PRET programme can reduce CVRF, this intervention may have major implications for clinical practice. In this case, the PRET programme could be used as an additional intervention to the existing pharmacological management of CVRF in adults with ID.

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# Chapter 4

# Measuring muscle mass in adults with intellectual disabilities: The reliability and construct validity of calf circumference

**K.I. de Oude**
**R. Bonnet**
**R.G. Elbers**
**D.A.M. Maes-Festen**
**A. Oppewal**

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## Abstract

The amount of muscle mass is an important criterion to diagnose sarcopenia. Two feasible methods for measuring muscle mass in adults with intellectual disabilities (ID) are bioelectrical impedance analysis (BIA) and calf circumference (CC). CC measurements are more accessible, cheaper and easier to use than BIA in adults with ID. This study aimed to investigate the construct validity and intra-rater reliability of CC to estimate muscle mass compared to BIA in adults with mild and moderate ID and cardiovascular risk factors (CVRF).

This study was part of the PRET study (NTR, NL8382), which examined the effect of Progressive Resistance Exercise Training on cardiovascular risk factors in 36 adults with ID (55.58 years, SD: 12.89). Construct validity was analysed with Pearson's correlations between CC and BIA measurements (skeletal muscle mass ([SMM], segmental muscle mass [SegMM] and skeletal muscle index [SMI]). The intra-rater reliability was analysed with the intraclass correlation coefficient (ICC).

The correlation between CC and SMM was 0.19 (95% CI [-0.16; 0.49]), 0.60 (95% CI [0.33; 0.78]) between CC and SegMM and 0.69 (95% CI [0.47; 0.83]) between CC and SMI. The ICC was 0.94 (95% CI [0.89; 0.97]).

The excellent intra-rater reliability of CC indicates that CC-measurements are reliable within the same assessor for adults with ID and CVRF. However, the use of CC to estimate muscle mass compared to BIA remains questionable.

# Introduction

The European Working Group on Sarcopenia in Older People 2 (EWGSOP2) defined the condition sarcopenia as a progressive and generalised skeletal muscle disorder characterised by a decline of muscle strength and muscle mass. The condition is severe if physical performance is also affected (1). Sarcopenia can cause problems in daily life (2) and is associated with risks, such as falling and mortality in the general elderly population (3, 4).

A study about sarcopenia from the Academic Collaborative Research Center Healthy Ageing and Intellectual Disabilities (HA-ID) showed that 12.7% of older adults ID aged between 50 to 64 years had sarcopenia (5). An ID is a neurodevelopmental disorder and defined as a deficit in intellectual and adaptive functioning, both with onset in the developmental period before the age of 22 (6). In the general population the prevalence of sarcopenia ranges between 5–10% in elderly of 60 years and older, following the EWGSOP2 definition (7). A recent study from HA-ID found that sarcopenia and severe sarcopenia are associated with early mortality in older adults with ID (8). Thus, a timely diagnosis of sarcopenia is necessary in adults with ID.



Muscle mass is a crucial element in the diagnosis of sarcopenia (1). There are multiple methods that can determine muscle mass (9), but their applicability for adults with ID can be questioned. In the general population, the recommended method for measuring muscle mass is a dual x-ray absorptiometry (DXA) scan. CT and MRI scans can also identify muscle mass (9). However, DXA, CT and MRI scans require qualified personnel, are expensive, and time consuming. Moreover, these devices are not suitable for transport which restricts the use in a remote setting. Especially for adults with ID this can be a limitation because transferring to a research location, such as a hospital, can cause distress and limits the feasibility.

A method that appears more suitable in a remote setting is bioelectrical impedance analysis (BIA). BIA is often used to assess body composition in the general population and athletes. BIA is a portable, relatively non-invasive and quick method. In elderly, the use of BIA to assess body composition has been found reliable (intraclass correlation coefficient (ICC) ranging between 0.91 (10) and 0.99 (11) as well as valid showing a good correlation to DXA $r^2$=0.76 (12). BIA uses the electrical conductive properties of the body to

estimate muscle mass (1). Overall, BIA devices are recommended to be used for assessment of muscle mass with clinical considerations such as, age, ethnicity, and hydration status of the participant (1). Even though BIA is commonly used in the general population, the cost of a BIA device fit for professional use and the requirement of staying still without assistance can be challenging for adults with ID. Secondly, the validity and reliability of BIA measurements are sensitive to changes in the environment (temperature, humidity) and person (fasting time, hydration). Repeated measurements should therefore be performed in the same environment and at the same time whenever possible (13).

The most non-invasive, low cost, and low effort method to measure muscle mass is by measuring CC (9). The use of CC is recommended for older adults if no other diagnostic methods are available (1). CC is less sensitive than BIA to changes in the environment and person which makes the repeatability more reliable. In the general population, the intra-rater reliability has been found excellent (14, 15). Previous studies have compared CC and BIA in the general elderly population as a way of measuring muscle mass. These studies have shown moderate and strong positive correlations between CC and BIA (16-18). However, the applicability of these studies to adults with ID is uncertain. Some genetic syndromes are characterised by an altered growth (19, 20) or a different stature (21) compared to the general population, which could alter the interpretation of muscle mass. Additionally, obesity is highly prevalent in adults with ID (22), and in the general population it was found that people with a higher BMI often have a bigger CC without it representing a higher muscle mass (23). Lastly, adults with ID often have gait characteristics that differ from the general population (24), which might affect the use and development of muscles and could lead to atypical CC measurements that are not representative of overall muscle mass. Therefore, the correlation between CC and BIA could be lower in adults with ID, because of the aforementioned physical differences.

The primary aim of this study was to assess the construct validity of CC measurement for assessing muscle mass compared to BIA in adults with ID. Secondly, we assessed the intra-rater reliability of CC measurements. We expected a good intra-rater reliability for CC measurements, since the measurements are not dependent on the participant's ability to follow instructions.

# Material and methods

### Study design

This study was part of the Progressive Resistance Exercise Training (PRET) study (NTR, NL8382) (25), that was performed within the Academic Collaborative Research Center Healthy Ageing and Intellectual Disabilities (HA-ID). We obtained ethical approval from the Medical Ethics Review Committee of the Erasmus MC, University Medical Center Rotterdam in the Netherlands (MEC-2019-0544). This study is registered in the Netherlands Trail Register (NTR, NL-8382) and ClinicalTrials.gov (NCT-06579898). The PRET study uses a repeated time series design to examine the effect of PRET on cardiovascular risk factors in adults with ID. As a secondary outcome of the PRET study, muscle mass, was measured using CC and BIA. Details of the PRET study are reported in the protocol paper (25).

For this study, baseline measurements of the PRET study were used. Baseline measurements were performed at three different time points (T0, T1 and T2) with an interval of 6 weeks. The PRET study was still ongoing during the completion of this study. Data for this study was collected between December 2021 and November 2023.



### Study population and inclusion

The participants of the PRET study (n=36) were adults (≥18 years) with moderate (IQ=35–49) or mild (IQ=50–69) ID who received support or care from one of the involved care organisations (Amarant, Abrona or Ipse de Bruggen) in the Netherlands. Because of the primary objective of the PRET study, only people with a minimum of two cardiovascular risk factors (diabetes mellitus type II, hypertension, obesity, or hypercholesterolemia) or metabolic syndrome were included. Furthermore, the participants could not have any physical limitations interfering with participating in PRET. More specific information about the inclusion criteria is reported in the protocol article (25).

For this study, participants from the PRET study were included if they had two completed baseline measurements conducted by the same researcher.

## Measurements

The primary parameters of this study were muscle mass measured with BIA and CC, both measured by a trained researcher during baseline at T0, T1 and T2. Before conducting the measurements, a researcher received training in the proper application of both measurement techniques. The training involved practicing the procedures according to predefined protocols.

### *Calf circumference*

Calf circumference of each leg was measured twice at the widest point of the calf with a measuring tape (Seca 200, Germany), to the nearest half centimetre. The participant was measured in seated position with the feet flat on the ground. When a participant wore compression stockings these were not removed. If the difference between the two measurements exceeded 1 cm, the procedure was repeated (25). The result of the leg with the highest CC was used in the analysis, based on the expectation that this limb would have greater muscle mass. This selection was considered more appropriate for comparison with muscle mass measurements derived from BIA measurement.

### *Bioelectrical impedance analysis*

After measuring the CC, BIA measurements were taken with the Tanita Body Composition Analyzer MC-780MA S (Tanita, Tokyo, Japan) was used. In young healthy adults, the device has been found to correlate strongly with DXA in assessing fat free mass (26, 27). One study found a moderate sensitivity and specificity of the Tanita MC-780MA for recognizing low muscle mass in elderly compared to a DXA scan (28). The Tanita MC-780MA S is an eight-electrode and multi-frequency device that is intended for professional use. It uses electrical conductivity to estimate body composition through the hands and feet of the participant (1, 29). Additionally, the device requires height, sex, and age to estimate muscle mass.

Measurements were conducted according to the manufacturer's guidelines, and standard quality control procedures were followed to ensure reliability. No calibration statistics are available for the device used in this study. The participant stands barefoot on the BIA device without external support for the measurement to be successful. Measurements were done in the same room, at the same day of the week and at the same time for each participant.

For this study we used the following outcomes from BIA: skeletal muscle mass (SMM, kg), segmental muscle mass of each leg (SegMM, kg), and skeletal muscle index (SMI, kg/m$^2$). The SMI is equivalent to the appendicular SMM (the SMM of only the arms and legs) divided by height squared and is reported as kg/m$^2$. Considering CC strictly involves the lower extremities, SegMM of the leg is expected to show a higher correlation with CC.

### Participant characteristics

Age, sex, and level of ID were collected from medical records. During baseline measurements weight, height and BMI were also measured. Weight and BMI were measured with BIA and height with a measuring tape (25).

### Statistical analysis

We used percentages or means with standard deviations to describe the participant characteristics (age, sex, level of ID, weight, height, and BMI).

To assess the construct validity of CC, we determined the correlation between CC and BIA (SMM, SegMM, SMI) measurements at T0. If T0 was missing, we used the measurement from T1, and if T1 was missing we used the measurement from T2. We used the SegMM of the same leg as the highest CC. If both legs had the same CC, the SegMM of the left leg was used. The Pearson´s correlation coefficient was used to assess the correlation between CC, and SMM, SegMM and SMI. The correlation coefficients were classified as minor (0.0–0.1), weak (0.1–0.39), moderate (0.4–0.69), strong (0.7–0.89) or excellent (0.9–1.0) (30).

For the intra-rater reliability, we used two measurements of CC at T0, T1 or T2, done by the same trained researcher. The intra-rater reliability of the CC was analysed using the intraclass correlation coefficient (ICC, single rater, absolute agreement, two-way mixed-effects model). A confidence interval of 95% was applied. The ICC was categorised as poor (<0.5), moderate (0.5–0.75), good (0.75–0.9) or excellent (0.9>) (31). Additionally, a Bland-Altman plot was used to illustrate the agreement between the repeated CC measurements. The difference between the repeated CC measurements was plotted against the mean of both CC measurements. The systematic bias was calculated as the mean of the differences with a one-sample T-test, and the limits of agreement were set at two standard deviations above and below this mean. IBM SPSS statistics version 28.0.1.0 (32) was used for all statistical analysis.

# Results

A total of 36 participants were included in the PRET study. Of all participants two out of three baseline measurements, performed by the same researcher, were available and therefore eligible for this study. The participant characteristics are presented in Table 4.1. The participants had a mean age of 55.58 years (SD=12.89), 19 (52.8%) were men, and 21 (58.3%) had a mild ID. One participant had severe ID, which we found out after the participant completed the intervention. The inclusion criterion for level of ID was based on the anticipation that PRET would not be feasible for adults with severe

**Table 4.1. Participant characteristics (N=36)**

| | N (%) | Mean ± SD |
|---|---|---|
| Age, years | | 55.58 ± 12.89 |
| Sex | | |
| Male, n (%) | 19 (52.8%) | |
| Female, n (%) | 17 (47.2%) | |
| Level of ID | | |
| Mild, n (%) | 21 (58.3%) | |
| Moderate, n (%) | 14 (38.9%) | |
| Severe, n (%) | 1 (2.8%) | |
| Cause of ID | | |
| Congenital | 5 (13.9%) | |
| Perinatal | 3 (8.3%) | |
| Unknown | 28 (77.8%) | |
| Syndrome | | |
| Down syndrome | 1 (2.8%) | |
| Velocardiofacial | 1 (2.8%) | |
| Williams | 1 (2.8%) | |
| Other | 3 (8.3%) | |
| Unknown | 30 (83.3%) | |
| Height, cm | | 169.61 ± 10.32 |
| Weight, kg | | 86.10 ± 21.52 |
| BMI, kg/m$^2$ | | 30.12 ± 8.42 |
| Obese | 35 (97.2%) | |
| CC at T0, cm | | 39.33 ± 6.49 |
| CC at T1 or T2, cm | | 39.25 ± 7.29 |
| SMM, kg | | 29.90 ± 6.73* |
| SMI, kg | | 8.30 ± 1.54* |
| SegMM, kg | | 9.02 ± 2.08* |

ID: intellectual disability; SD: standard deviation; BMI: body mass index; CC: calf circumference; SMM: skeletal muscle mass; SMI: skeletal muscle mass index; SegMM: Segmental muscle mass. * N=35.

and profound ID. Because this participant successfully participated in PRET, we decided to include this participant in the analysis.

### Construct validity of the calf circumference

For the analysis to assess the construct validity of calf circumference, 35 participants were included. One participant was excluded from these analyses because the BIA measurement could not be completed due to ataxia. The means of the SMM, SegMM and SMI are shown in Table 4.2.

There was a statistically weak non-significant Pearson's correlation between CC and SMM (r=0.19, 95% CI [-0.16; 0.49]), a moderate significant correlation between CC and SegMM (r=0.60, 95% CI [0.33; 0.78]) and a moderate significant correlation between CC and SMI (r=0.69, 95% CI [0.47; 0.83]).

**Table 4.2. Reliability statistics**

| Outcome | Value | SD | 95% CI | p-value |
|---|---|---|---|---|
| Intraclass correlation (ICC) | 0.94 | | 0.89; 0.97 | <0.001 |
| Mean (bias) | 0.08 | 2.43 | -4.68; 4.84 | 0.419 |
| β (difference ~ mean) | -0.12 | 0.06 | | 0.05 |



### Intra-rater reliability of the calf circumference

The analysis to assess the intra-rater reliability of the CC measurement included all 36 participants. Intra-rater reliability was excellent with an ICC of 0.94 (95% CI [0.89; 0.97], p<0.001).

The Bland Altman plot (Figure 4.1) showed that on average the second CC measurement is 0.08 cm (95% CI [-0.74; 0.91]) higher than the first CC measurement. This indicates that there is relatively small systematic bias between measurements. The relatively wide range in the limits of agreement (-4.68–4.84) suggests that there was considerable variability in the differences.

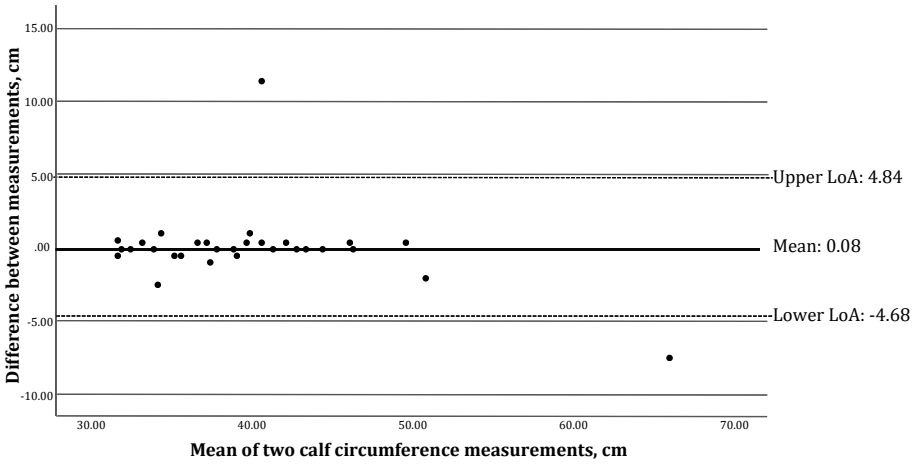


**Figure 4.1. Bland Altman plot for the calf circumference measurements.**

# Discussion

The aim of this study was to assess the construct validity of CC measurement for assessing muscle mass compared to BIA and the intra-rater reliability of CC measurements in adults with ID and CVRF. We found a statistically significant moderate correlation between CC and SegMM and CC and SMI, but a statistically non-significant weak correlation between CC and SMM. An excellent intra-rater reliability was found.

The correlation between CC and SMM was weak and non-significant. However, for both SegMM and SMI we found a moderate and significant correlation with CC. SMM represents the whole-body muscle mass, while SegMM and SMI both do not include the muscle mass of the trunk. This could explain the better correlation between CC and SegMM and SMI. Another explanation could be that truncal muscle mass is not accurately estimated by BIA. It is known that DXA has a low accuracy for estimating truncal muscle mass due to the inability to separate intra-abdominal organs, which could result in an over- or underestimation of whole-body muscle mass (33). Therefore, it is recommended by the EWGSOP2 guidelines to use SMI as a value for muscle mass when using DXA. This is probably the same for BIA measurements, which could explain why SegMM and SMI have a stronger correlation with CC.

The correlations between SMM and SMI with CC found in this study are mostly in accordance with the results that have been found previously. In

elderly of the general population, previous studies found various correlations, ranging from 0.52 to 0.81 (16, 18, 34, 35). Of these studies only Kawakami et al. (2020) also used a Tanita device (MC-980A). They found a strong correlation of 0.81 for men and 0.73 for woman in Japanese middle aged and elderly. Bohannon et al. (2016) conducted their study amongst European elderly and found similar correlations to ours. However, they used a different BIA.

It is known that BIA devices use different equations for different ethnicities. According to the EWGSOP2, for European elderly, the Sergi equation should be used for valid measurements with BIA (1). Because we do not know which equations the Tanita MC-780 uses, it is not clear if the BIA results are valid for our sample, and these can be used as a reference for CC. Before using a BIA device, it is important to know which equations are used to estimate muscle mass for a good interpretation of the results.

The intra-rater reliability of CC measurements found in this study is in agreement with other studies (14, 15). Tunc et al. (2007) and Sharkey et al. (2018) both also found an excellent intra-rater reliability. Tunc et al. (2007) found an agreement between CC measurements of 88% and Sharkey et al. (2018) found an excellent consistency of 0.94 for experts and an acceptable consistency of 0.72 for students. The difference between experts and students could indicate that knowledge and experience is important for a reliable CC measurement. These results show that there is no indication that there is a difference in intra-rater reliability between adults with ID and the general population. Our Bland Altman plot showed a mean difference of 0.08 cm which is in accordance with the found ICC that there is excellent agreement between measurements. We did find considerable variability, however this can be explained by the outliers in the data. Due to our small sample, these outliers are of great influence on the limits of agreement.



**Limitations**

This study gives insight in the correlations between CC measurements and muscle mass measured with BIA for adults with mild and moderate ID and CVRF. However, a few limitations can be identified in this study.

Firstly, we used BIA as the reference for the CC measurement. Even though EWGSOP2 recognises BIA as a method for estimating muscle mass (1), a DXA scan remains the most recommended method. For future studies, a DXA scan

as a gold standard reference measurement would give more valid results for the correlation with CC measurements. Additionally, we aimed to standardize the BIA measurement conditions as much as possible by conducting the measurements on the same day of the week, at the same location and at the same time. However, we did not report room temperature or hydration status which may have been of influence on the BIA measurement.

Secondly, participant characteristics like age are used by the BIA for the estimation of body composition. The equations used by the BIA devices are based on the general population. Because BIA devices are susceptible to different ethnicities and body types, it is possible that a specific equation for adults with ID is needed for valid BIA measurements. Despite our efforts, the exact equations used in TANITA MC-780, are unknown.

Thirdly, our study sample consisted of 36 participants, allowing outliers to be more influential on results and reducing the potential for subgroup analyses. A guideline to ensure sufficient statistical power in validation studies is at least 100 participants (36). Because this study was part of a larger study examining the effects of progressive resistance training on cardiovascular risk factors, the sample size was not determined based on a power analysis specific to the aims of this study. Although our sample equally represents level of ID and sex, our specific inclusion criteria for ID, CVRF and physical abilities limit generalisability to the entire population of adults with ID. There is a lot of diversity within the ID population. There is a great variation in the severity and aetiology of ID (6) and mobility (37). Therefore, in an additional study a larger, more diverse group of adults with ID should be included.

Another limitation is the prevalence of obesity in our sample. Because our sample consists of adults with ID and CVRF, most participants were obese. From previous studies, we know that this could influence CC and BIA measurements. BIA devices can underestimate sarcopenia in people with obesity (26, 28) and CC could overestimate muscle mass in people with obesity due to fat distribution (1).

### Clinical implications and recommendations

Considering the limitations of our study, we cannot conclude with certainty that CC is a valid measurement for muscle mass in adults with ID. The use of BIA as a reference measurement for CC measurements remains question-

able because of the uncertainty of equations used and the applicability of existing equations for adults with ID. Therefore, the validity of both BIA and CC should be further investigated using a DXA scan as a gold standard reference measurement.

When the validity of CC as a measurement for muscle mass in adults with ID is established, it is a more suitable measurement for clinical practice in remote settings. To use a BIA device in clinical practice, the assessor should be well trained in using the device and have knowledge about how the device estimates body composition. This is necessary for a good interpretation of the outcomes. Furthermore, the results of different BIA devices are not interchangeable. Lastly, BIA measurements are susceptible to changes in the environment and person (13). Therefore, to get reliable repeated measurements, each measurement should be performed at the same day, time and nutritional status. A CC measurement is easy to perform, quick, cheap, and does not need extensive instructions and preconditions.



Despite the limitations of our study, we still found a moderate correlation between CC measurement and SegMM and SMI. Therefore, CC measurement could still be used when diagnosing sarcopenia. Secondly, besides muscle mass, muscle strength is a criterion for diagnosing sarcopenia, and physical performance is an additional criterion for diagnosing severe sarcopenia (1). In a recent study in older adults with ID, Valentin et al. (2023), investigated the association between sarcopenia and 5-year mortality. For diagnosing sarcopenia, they also used CC as a measurement for muscle mass (8). They found a similar association as in the general population, which could indicate that using CC for diagnosing sarcopenia contributes to a valid diagnosis when used together with scores for muscle strength and physical performance.

In clinical practice, CC measurements provide a fast, practical, and easily implementable tool. We do not recommend CC as a sole indicator of muscle mass because it can overestimate muscle mass when used in adults with obesity. When combined with other diagnostic criteria for sarcopenia, such as muscle strength and physical performance, these measurements are valuable for early detection and allow for timely interventions.

## Conclusion

The excellent intra-rater reliability of CC indicates that CC-measurements are reliable within the same assessor for adults with ID and CVRF. However, the use of CC to estimate muscle mass compared to BIA remains questionable. We found no correlation between CC and SMM measured with BIA. The moderate correlations with BIA for SegMM and SMI, combined with the excellent intra-rater reliability, suggest that CC could potentially be used as an indicator of SegMM and SMI in adults with ID if other methods are unavailable. A DXA scan remains the preferred method. These results cannot be generalised to all adults with ID, because the participants in this study were selected based on strict inclusion criteria. Further research is necessary, with a more heterogenetic sample of adults with ID and a CT or DXA scan as reference method.

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# Chapter 5

## The effect of progressive resistance exercise training on cardiovascular risk factors in adults with intellectual disabilities

**K.I. de Oude**
**R.G. Elbers**
**D.A.M. Maes-Festen**
**S.M.A. Bierma-Zeinstra**
**A. Oppewal**

Submitted

## Abstract

Progressive resistance exercise training (PRET) has potential to decrease cardiovascular risk factors (CVRFs) in adults with intellectual disabilities (ID). This study investigated the effects of PRET on CVRFs in adults with ID at risk for cardiovascular disease.

A repeated-time-series design with one study group was used. Multilevel linear regression models examined the effect of a 24-week PRET intervention on glycated haemoglobin (HbA1c), systolic blood pressure (SBP), low density lipoprotein (LDL) and waist-to-hip-ratio (WHR), adjusted for medication use.

Thirty-six adults with mild-moderate ID (mean age 55.6 years, SD= 12.9; 52.8% men) and multiple CVRFs participated. Twenty-six participants completed the PRET intervention. LDL decreased significantly (-0.21 mmol/L (95% CI [-0.38; -0.04]). No statistically significant reductions were found for HbA1c (-2.76 mmol/mol, 95% CI [-5.93; 0.41]), SBP (-5.74 mm/Hg, 95% CI [-11.64; 0.17]), and WHR (-0.003, 95% CI [-0.01; 0.02]).

PRET led to reductions in all outcomes, however only LDL decreased significantly. Our results indicate that PRET is a promising intervention for the management of CVRFs in adults with mild to moderate ID. Clinicians could use PRET as an additional intervention for adults who can be motivated and are able to adhere to an exercise intervention.

## Introduction

Adults with intellectual disabilities (ID) face more challenges in developing health skills and maintaining a healthy lifestyle compared to adults in the general population. Adults with ID have low levels of physical activity (1, 2) with only 9% reaching adequate physical activity levels for health benefits (3). Because of their limitations in intellectual functioning and adaptive behaviour (4) adults with ID need adequate support to improve and maintain a healthy lifestyle.

Low physical activity levels increase the risk of acquiring cardiovascular risk factors (CVRFs) such as hypertension (5), hypercholesterolemia (6), diabetes mellitus type 2 (7), obesity (8), and metabolic syndrome (9). The Healthy Ageing and Intellectual Disabilities (HA-ID) cohort study found that CVRFs are highly prevalent in adults with ID who are 50 years or older. Diabetes was present in 13% of the study population, while 53% had hypertension, 23% had hypercholesterolemia, 45% had metabolic syndrome, and 26% had obesity (10, 11). The high prevalence of CVRFs and low levels of physical activity emphasise the need to explore effective interventions to improve cardiovascular health in adults with ID.

'Exercise is Medicine' was established in 2007 by the American College of Sports Medicine (ACSM) as an initiative to promote the importance of physical activity and to encourage the integration of exercise prescription as a preventive strategy for a wide range of chronic conditions (12). The initiative is particularly relevant for populations with consistently low levels of physical activity, such as adults with ID. However, the routine screening of physical activity and referral to exercise interventions remains under-prioritised in clinical practice.

Progressive resistance training (PRET) has been found effective to increase physical activity and decrease CVRFs in the general population (13-17) and is recommended by the ACSM guidelines for exercise prescription. An increase in muscle mass can lead to improvements in glycaemic control, insulin sensitivity, blood pressure, body composition, and lipid profile (18-21). Resistance training interventions have previously been investigated in adults with ID and found several beneficial effects, including increased strength and balance, and reduced waist circumference and body mass index (22, 23).

However, these studies did not specifically include adults with CVRFs, and the resistance training interventions evaluated were not based on PRET principles. Weterings et al. (24) found that PRET was feasible for adults with ID and CVRFs, with 58% of the participants achieving vigorous training intensity. These findings show the potential for PRET as an intervention to increase physical activity levels and decrease CVRFs in adults with ID.

To our knowledge, no studies investigated the effect of PRET on CVRFs in adults with ID and CVRFs. If PRET proves to be effective in reducing CVRFs in this group, this may have major implications for clinical practice. It could be incorporated into the existing management of CVRFs. Therefore, the aim of this study was to investigate the effect of PRET on diabetes, hypercholesterolemia, obesity, and hypertension in adults with ID and multiple CVRFs, using a repeated time series design.

## Methods

This study was conducted within the Academic Collaborative Research Center Healthy Ageing and Intellectual Disability (HA-ID). The HA-ID is a collaboration between the Intellectual Disability Medicine Research group of the Erasmus MC, University Medical Center Rotterdam and three care providers in the Netherlands specialised in the care for people with ID: Abrona (Huis ter Heide), Amarant (Tilburg), and Ipse de Bruggen (Zoetermeer).

This study followed the principles of the Declaration of Helsinki (25) and is in accordance with the Dutch Medical Research Involving Human Subjects Act. We obtained ethical approval from the Medical Ethics Review Committee of the Erasmus MC, University Medical Center Rotterdam in the Netherlands (MEC-2019-0544). The study, initially registered in the Netherlands Trial Register (NTR, NL8382), was re-registered in ClinicalTrials.gov (NCT06579898) following the termination of NTR services. Written informed consent was obtained from all participants or their legal representatives. Full details on the study protocol can be found in the protocol paper (26).

### Participants

Participants were eligible for this study if they were living in a residential facility or received care from one of the participating care providers. They had

to be 18 years or older with a mild (IQ = 50–69) or moderate (IQ = 35–49) ID. Finally, they had to be diagnosed with metabolic syndrome or at least two of the following CVRFs: hypertension, hypercholesterolemia, diabetes mellitus type 2 (DM2), or obesity as confirmed at the T0 baseline assessment. Cut-off values used to establish the presence of CVRFs are presented in Table 5.1. Participants who were already receiving pharmacological treatment for CVRFs were eligible for inclusion.

**Table 5.1. Definitions of cardiovascular risk factors (CVRFs) (Elbers et al. 2022)**

| Cardiovascular risk factor | Reference | Markers | Values |
|---|---|---|---|
| Metabolic syndrome, having 3 out of 5 markers | Alberti et al. (2009) | Waist circumference | ≥94 cm (men)*<br>≥80 cm (women)* |
| | | Fasting glucose (FG) | >5.6 mmol/L |
| | | High density lipoprotein (HDL-C) | <1 mmol/L (men)<br><1.3 mmol/L (women) |
| | | Triglycerides (TG) | >1.7 mmol/L |
| | | Systolic blood pressure (SBP) and diastolic blood pressure (DBP) | ≥130 mm/Hg and ≥85 mm/Hg |
| Hypertension (Stage 2) | Whelton et al. (2017) | Systolic blood pressure (SBP) | ≥140 mm/Hg |
| | | Diastolic blood pressure (DBP) | ≥90 mm/Hg |
| Hypercholesterolemia | Piepoli et al. (2016) | Total cholesterol (TC) | >4 mmol/L |
| | | Low density lipoprotein (LDL-C) | ≥2.6 mmol/L |
| Diabetes mellitus type 2 | American Diabetes Association (2018) | Fasting glucose (FG) | ≥7 mmol/L |
| | | HbA1c | ≥48 mmol/L |
| Obesity | World Health Organisation (2008) | Waist Circumference | >94 cm (men)*<br>>80 cm (women)* |
| | | Waist-hip ratio | ≥0.90 (men)<br>≥0.85 (women) |

*European, Caucasian threshold; mm/Hg: millimetres of mercury; mmol/L: millimoles per litre.

Participants were excluded if they did not obtain medical clearance from their physician, had physical limitations (including neurological and orthopaedic conditions) interfering with participation in the PRET intervention, were not able to walk independently, or were not able to follow instructions from the trainers on posture and performance.

### Study design

This study had a repeated time series design with one study group. The study period was divided into a 12-week baseline period, a 24-week intervention period (PRET programme), and a 12-week follow-up period. We used three baseline measurements to establish a valid baseline and to filter out the natural variability that may exist without applying any interventions (27). The baseline measurements were used for control comparisons.

Outcome measures were assessed at baseline (T0, T1, T2), following the intervention period (T3) and at 12 weeks follow-up (T4). For each participant, all measurements were conducted at the same location, time of the day, and day of the week. For the effect of PRET on CVRFs we compared the measurements between baseline (T0, T1, T2) and T3.

### Outcome measurements

The medical staff of the care providers collected blood samples after overnight fasting. The samples were analysed at the laboratory of the Erasmus MC. The blood samples were used to measure total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL-C), triglycerides (TG), HbA1c and fasting glucose (FG) in mmol/L.

A trained researcher measured blood pressure and waist and hip circumference. The Omron-M7 (Omron Healthcare, Kyoto, Japan) was used to measure blood pressure from both arms after sitting for two minutes without talking. Waist and hip circumference were measured to calculate the waist-to-hip ratio (WHR), which was used as an outcome indicator for obesity. Waist and hip circumference were obtained by using a Seca 200 measuring tape (Seca, Hamburg, Germany). Waist circumference was measured at the midpoint between the lowest palpable rib and the top of the iliac crest. Hip circumference was measured around the widest portion of the buttocks (8).

### Potential confounders

Changes in physical activity and medication use related to CVRFs during the intervention period were recorded. A questionnaire about physical activity (IPAQ) (28) was filled out by the professional caregiver of the participant at all timepoints (T0–T4). Participants were allowed to continue their usual activities but could not start any other intervention or activity intervening

with their physical activity levels. Medical interventions necessary for usual care were allowed. Information about medication use related to CVRFs, age, sex, ethnicity, and aetiology and level of ID was collected from medical records by the medical staff.

### Intervention

The duration of the PRET programme was 24 weeks and consisted of two sessions per week, with at least 48 hours between the sessions according to the ACSM guidelines (29). The intervention was led by physiotherapists or physical activity instructors experienced in working with adults with ID. The instructor-participant ratio was 1 to 1 or 1 to 2. Prior to the study, we trained all instructors regarding the intervention protocol, exercises and registration of each session. The intervention is based on the PRET protocol developed and investigated on feasibility in the study by Weterings et al. (22). According to the recommendations made by Weterings et al. a few small changes were made to enhance the feasibility of PRET.

The programme is characterised by four mesocycles of 6 weeks and intensity is measured by the percentage of the heaviest load one can lift for one repetition (% of 1RM). After each mesocycle the intensity is gradually increased (practice cycle, 65% 1RM, 75% 1RM, 80% 1RM). Each session consists of seven exercises (RESID) to train all large muscle groups (30). For each muscle group, alternative exercises were provided for participants who were not able to perform the original exercise correctly. A more detailed description of the intervention can be found in the protocol paper (26).

To maximise attendance and motivation we collaborated with trainers experienced in working and training with adults with ID. Additionally, each participant received a progression certificate to track their progress and a T-shirt to wear during the training and measurements. At completion of the programme, the participant received a certificate and a medal.

### Statistical analysis

We used descriptive statistics to present participant characteristics for age, sex, ethnicity, physical activity, level and aetiology of ID, presence of CVRFs, and mean values of CVRFs measurements at baseline.

We generated time-series plots for each CVRF to visualise the change in values for each participant individually, the overall sample mean, and the means of subgroups across baseline, post-intervention, and follow-up periods compared to the defined cut-off values.

Statistical analyses were performed with R-statistics (R Foundation for Statistical Computing, Vienna, Austria) and we used the package Linear and Nonlinear Mixed Effects Models (nlme) (31).

We used multilevel linear regression models to investigate the effect of the PRET programme on CVRFs at the end of the intervention period (T3) (31). We included participant identification codes as a level in the models. This level consisted of the repeated measurements nested within a participant. We planned to include a second level of clustering of participants by trainer in the models. However, due to the large number of trainers (n=15), we were not able to do so. We included the continues variable age, and the categorical variables sex, and level of ID as interaction terms in the models to explore for effect modification.

To adjust for possible confounding, we included medication and physical activity (IPAQ) as random coefficients. However, data obtained from the IPAQ questionnaire showed substantial missing data and high variability. Therefore, we determined that the data was not sufficiently reliable for analyses. Medication was included as a categorical variable (decreased, unchanged, increased) due to the wide variation in prescribed medication. A two-tailed significance level of 0.05 was used for all tests.

The variables for the PRET programme were coded as 0 (baseline period at T0, T1, and T2) or 1 (intervention period T3). To check the assumption of stable baseline measurements, we investigated the effect of time on each outcome variable assessed during the baseline period. We conducted intention-to-treat (ITT) analyses with the data from all participants who started the study. Last information carried forward was used for missing data in the ITT analyses. Subsequently, we conducted per-protocol (PP) analyses with the data from the participants who completed the intervention. Finally, we analysed the effects between baseline (T0, T1, T2) and post-intervention (T3) and the effects between post-intervention (T3) and 12 weeks of follow-up (T4) separately using the same analytical approach.

More details about the statistical analysis and sample size calculation are described in the protocol paper (26). The sample size was calculated for the outcome HbA1c and resulted in a sample of 35 participants needed for this study. Based on the feasibility results in a pilot study (30) we inflated this number by 42%, to account for potential dropout, aiming to include 61 participants.

## Results

Figure 5.1 presents an overview of the study. In total, 36 adults (52.8% male) with an average age of 55.6 years (standard deviation (SD)=12.9) participated in the study. Of all participants 13 had DM2, 12 had hypertension, 25 had hypercholesterolemia, 35 were obese, and 13 had metabolic syndrome. Most participants (66.7%) had a moderate ID and 30.6% had a mild ID. One participant had severe ID which had gone unnoticed until after ending the intervention. In this case the severe level of ID did not interfere with the ability to follow instructions. Therefore, we decided to retain this participant in the analyses. All participant characteristics are presented in Table 5.2.

Throughout the study 10 participants dropped out. One participant decided to stop after baseline measurements. During the intervention period seven participants dropped out due to motivational reasons, two of them did participate in follow-up measurements. Two participants dropped out during the intervention period due to medical reasons not related to the intervention, both participated in follow-up measurements. This resulted in a sample of 26 for the PP analyses. Of these participants, 26 participants were obese, 16 had hypercholesterolemia, 8 had hypertension, and 7 had DM2. There were no statistical differences in participant characteristics between dropouts and the PP sample.

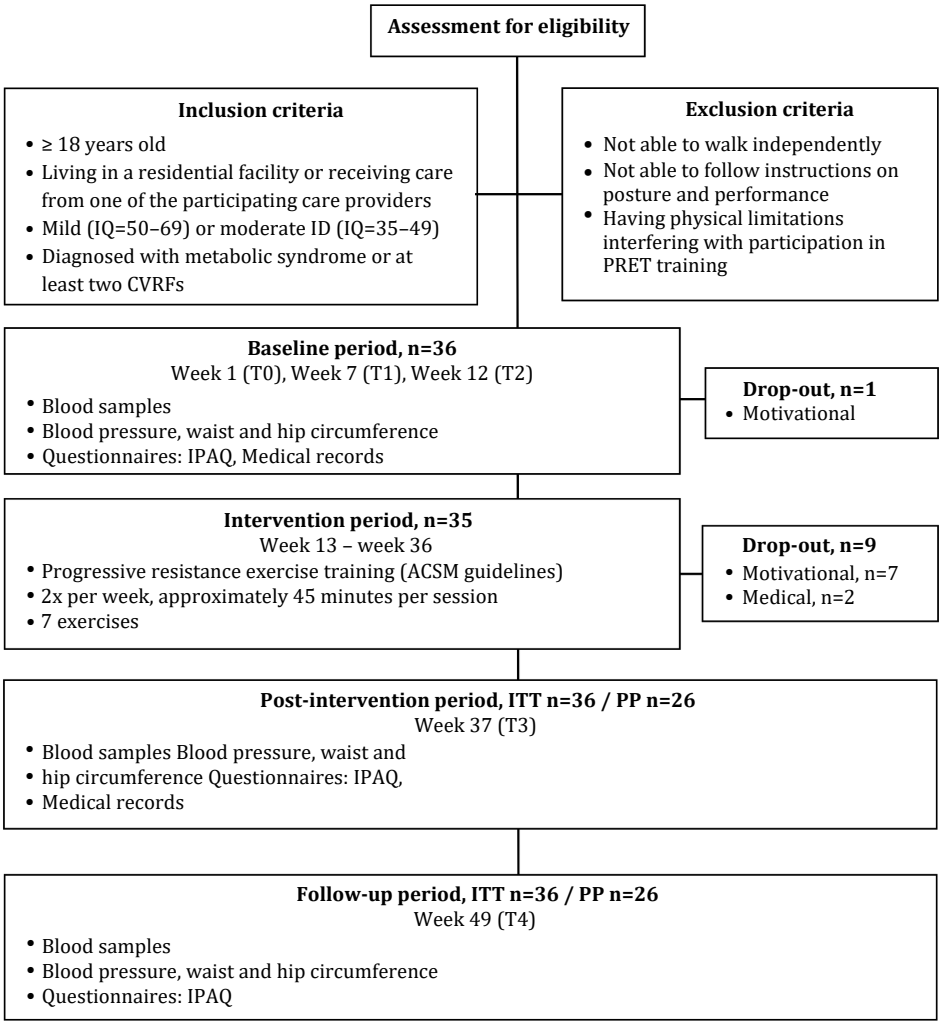


### Change in CVRFs over time

Figure 5.2 presents the mean values for each CVRF at T0, T1, T2, T3 and T4. Primarily, these plots display the individual trends for each participant, along with the mean values for the entire sample and for subsamples stratified by each CVRF. Secondly, these plots highlight the variability within the sample and identify any outliers.

**Table 5.2. Baseline participants characteristics (N=36)**

| Characteristic | N (%) | Mean (SD) |
|---|---|---|
| Age | | |
| Years | | 55.6 (12.9) |
| Sex | | |
| Men | 19 (52.8) | |
| Woman | 17 (47.2) | |
| Level of Intellectual Disability (ID) | | |
| Severe | 1 (2.7) | |
| Moderate | 11 (30.6) | |
| Mild | 24 (66.7) | |
| Aetiology of ID | | |
| Congenital | 6 (16.7) | |
| Down syndrome | 1 (2.7) | |
| Velocardiofacial syndrome | 1 (2.7) | |
| Williams syndrome | 1 (2.7) | |
| Other | 3 (8.3) | |
| Perinatal | 3 (8.3) | |
| Unknown | 27 (75.0) | |
| Ethnicity | | |
| Caucasian | 32 (88.9) | |
| Afro-American | 1 (2.7) | |
| Other | 3 (8.3) | |
| DM2 measurements | | |
| Glycated haemoglobin (mmol/mol) | | 44.6 (10.1) |
| Fasting glucose (mmol/L) | | 5.9 (1.8) |
| Cholesterol measurements | | |
| Total cholesterol (mmol/L) | | 4.6 (0.9) |
| HDL cholesterol (mmol/L) | | 1.2 (0.2) |
| LDL cholesterol (mmol/L) | | 2.6 (0.9) |
| Triglycerides (mmol/L) | | 1.7 (0.7) |
| Blood pressure measurements | | |
| Systolic blood pressure (mmHg) | | 127.6 (13.6) |
| Diastolic blood pressure (mmHg) | | 83.5 (9.3) |
| Anthropometric measurements | | |
| Weight (kg) | | 86.0 (21.8) |
| Body Mass Index ($kg/m^2$) | | 30.1 (8.5) |
| Waist circumference (cm) | | 105.8 (14.9) |
| Hip circumference (cm) | | 109.8 (14.2) |
| Waist-to-hip ratio | | 0.9 (0.1) |
| CVRFs present based on Cut-off Values* | | |
| Diabetes Mellitus Type 2 (DM2) | 13 (36.1) | |
| Hypertension | 12 (33.3) | |
| Hypercholesterolemia | 25 (69.4) | |
| Obesity | 35 (97.2) | |
| Metabolic syndrome | 13 (36.1) | |




ACSM: American College of Sports Medicine; CVRF: cardiovascular risk factors; ID: intellectual disability IQ: intelligence quotient; ITT: Intention-to-treat; PP: Per protocol.

**Figure 5.1. Study overview.**

The plots show a decline for HbA1c, SBP, and LDL, and a stable WHR throughout the study. Individual variability is notable, with some participants showing more fluctuations than others. The subsamples based on hypertension and DM2 showed a larger decline in mean values than the complete sample. For DM2, four out of 13 participants with DM2 at baseline achieved levels below cut-off value for HbA1c following the intervention. Similarly, three out of 25 participants with hypercholesterolemia at baseline achieved

levels below the cut-off for LDL after the intervention, and four out of 12 participants with hypertension at baseline achieved levels below the cut-off for SBP after the intervention. Additionally, two participants who had baseline levels below cut-off values achieved levels above cut-off for HbA1c, and two participants for SBP. No participants experienced a shift for obesity based on WHR. There were no differences in metabolic syndrome during baseline and post intervention.

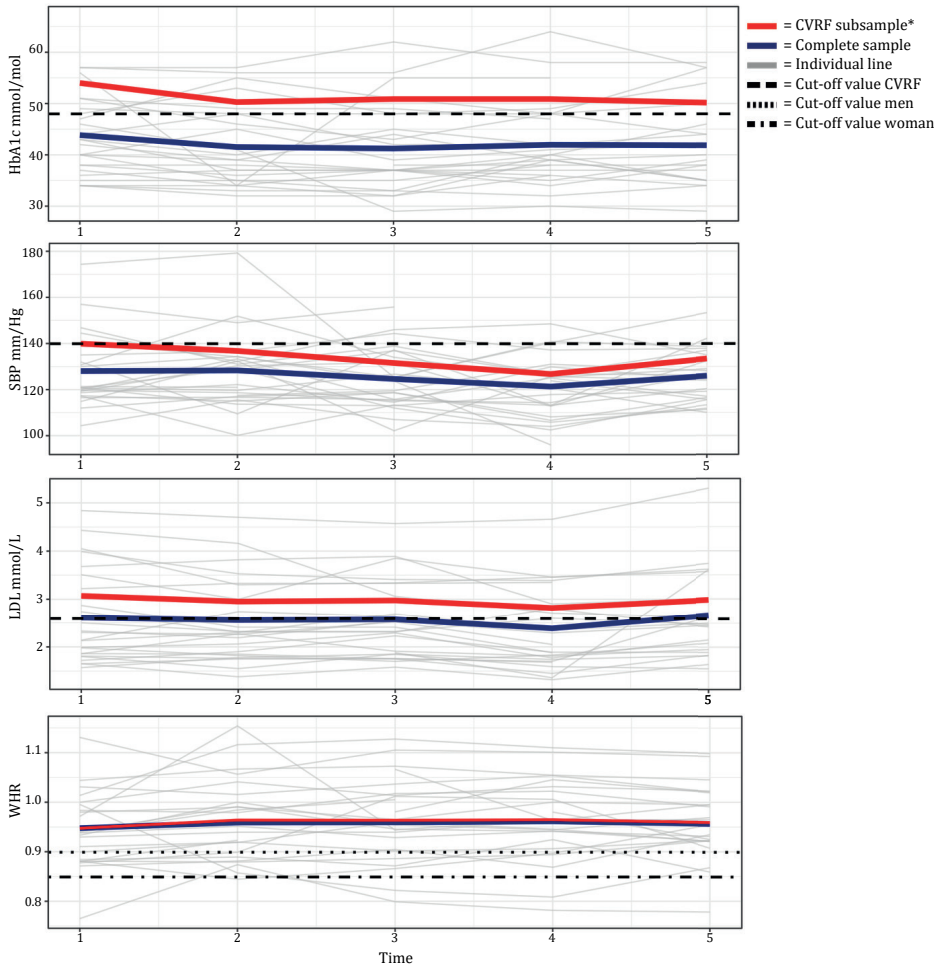



**Figure 5.2. Mean values CVRFs over time.**

## Effect of PRET programme (post-intervention)

### *Intention-to-treat*

Table 5.3 presents the effect of PRET (adjusted for medication use) on all CVRFs. All detailed results from the multilevel linear regression models are presented in Appendix 5.1. We found a statistically significant reduction of the intervention on LDL of -0.21 mmol/L (95% CI [-0.38; -0.04]). We found statistically non-significant reductions on HbA1c (-2.76 mmol/mol, 95% CI [-5.93; 0.41]), SBP (-5.74 mm/Hg, 95% CI [-11.64; 0.17]), and WHR (-0.003, 95% CI [-0.01; 0.02]) after the intervention. The added interaction terms for age, sex, and level of ID showed no statistical significance and therefore, were not included in the final models.

**Table 5.3. Multilevel linear regression models adjusted for medication use**

| Intention-to-treat analyses N=36 | | | | Per Protocol analyses N=26 | | | |
|---|---|---|---|---|---|---|---|
| **HbA1c mmol/mol** | | | | | | | |
| | β | p | 95% CI | | β | p | 95% CI |
| Intervention | -2.76 | 0.09 | -5.93; 0.41 | Intervention | -1.23 | 0.32 | -4.31; 1.86 |
| **SBP mm/Hg** | | | | | | | |
| | β | p | 95% CI | | β | p | 95% CI |
| Intervention | -5.74 | 0.06 | -11.64; 0.17 | Intervention | -6.35 | 0.06 | -12.73; 0.04 |
| **LDL mmol/L** | | | | | | | |
| | β | p | 95% CI | | β | p | 95% CI |
| Intervention | -0.21* | 0.02 | -0.38; -0.04 | Intervention | -0.22* | 0.03 | -0.42; -0.02 |
| **WHR** | | | | | | | |
| | β | p | 95% CI | | β | p | 95% CI |
| Intervention | 0.003 | 0.85 | -0.01; 0.02 | Intervention | 0.006 | 0.43 | -0.01; 0.03 |

N: number of participants in analyses; β: value; 95% CI: 95% confidence interval; p: statistical value; *: statistically significant.

### *Per-protocol*

The PP analyses showed similar results as the intention-to-treat analyses. The regression model for LDL showed a statistically significant effect of the intervention with a decrease of -0.22 mmol/L (95% CI [-0.42; -0.02]). The

other models showed statistically non-significant reductions on HbA1c (-1.23 mmol/mol, 95% CI [-4.31; 1.86]), SBP (-6.35 mm/Hg, 95% CI [-12.73; 0.04]), and WHR (-0.006, 95% CI [-0.01; 0.03]) after the intervention.

***Effect of follow-up period***

For the ITT sample the regression analyses showed a statistically significant increase after follow-up period of 0.18 mmol/L LDL (95% CI [0.02; 0.34]), and statistically non-significant increases of 0.79 mmol/mol HbA1c (95% CI [-1.23; 1.81]), and 2.54 mm/Hg (95% CI [-0.74;5.83]). For WHR a statistically non-significant decrease of –0.002 (95% CI [-0.01; 0.01]) was found.

For the PP sample the analyses showed a statistically non-significant increase after follow-up period of 0.24 mmol/mol HbA1c (95% CI [-1.53; 2.01]), 3.90 mm/Hg (95% CI [-0.25; 8.04]), and 0.22 mmol/L LDL (95% CI [-0.18; 0.62]). For WHR a statistically non-significant decrease in WHR of -0.005 (95% CI [-0.02; 0.01]) was found.

## Discussion

The aim of this study was to investigate the effect of PRET on diabetes, hypercholesterolemia, obesity, and hypertension in adults with ID and multiple CVRFs. Our results showed that LDL was significantly reduced after the PRET intervention. SBP, HbA1c, and WHR were reduced after the intervention as well; however, these were not statistically significant. Following the follow-up period, overall increases were observed in LDL, HbA1c, and SBP, while WHR showed a slight decrease. A statistically significant increase was found only in the ITT analysis for LDL.

Our results are similar to the results of Jacinto et al. (23). They investigated the effect of a combined resistance and aerobic training programme in comparison to a control group in adults with mild, moderate, and severe ID in a non-randomised experimental design. They found no statistically significant differences between exercise and control group for waist circumference, SBP, and cholesterol. Different to our study, the included participants in their study were not selected because of CVRFs. This may have resulted in a healthier sample and could explain the difference in effects found for cholesterol levels.

Previous studies in the general population have reported larger and statistically significant reductions HbA1c (32-34), SBP (32-34), LDL (34, 35), and WHR (36). These studies typically included participants with a single, well-defined CVRF. In contrast, our study included a more heterogeneous sample, resulting in a reduction of mean baseline values for each individual CVRF and potentially attenuating detectable intervention effects. For example, Castaneda et al. Reported a mean baseline of 72 mmol/mol HbA1c in a sample including solely individuals with DM2, whereas the mean baseline of HbA1c in our sample was 44.59 mmol/mol. Additionally, our sample size was small and included only 13 participants with DM2 and 12 with hypertension. However, subgroup analyses using time-series plots showed steeper declines in HbA1c and SBP. These findings support the hypothesis that the heterogeneity combined with the sample size in this study may have obscured the detection of any significant effects.

Another explanation for the differences in effects found could be the adherence to the training protocols. In this study the drop-out rate was 28%, mainly due to motivational reasons. Previous studies in the general population reported a 0% to 0.03% drop-out rate (32-36). However, the duration of the interventions in these studies was shorter, ranging from eight to 16 weeks. This may have facilitated adherence but does not provide insight into long-term commitment. Nonetheless, the higher adherence throughout the study period in the general population increases training effects which can contribute to the effectiveness of the training on CVRFs.

Adherence to exercise interventions in people with ID is a recurring challenge (23, 24). To maximize adherence to PRET in this study, we incorporated recommendations from Weterings et al. (24), who demonstrated the feasibility of PRET in adults with ID and CVRFs, into our PRET programme. We selected trainers who were experienced in training adults with ID and able to apply individualised motivational techniques. Additionally, we provided participants with a progression certificate and a T-shirt to encourage engagement. However, despite these strategies, the observed drop-out rate of 28% was higher than the 21% drop-out rate reported by Weterings et al. (24). Considering that our study sample consisted of volunteers who might have been more motivated than their peers, this is an important limitation for implementation. It emphasises the need to further explore strategies

to increase the adherence of adults with ID to a training protocol. Previous reviews (37, 38) have identified several themes related to motivation of adults with ID to exercise such as support from instructors, family, and peers, as well a preference for specific types of activities.

### Strengths and limitations

This study provides valuable insights into the effect of PRET on CVRFs in adults with ID and multiple CVRFs. In clinical practice, comorbidities are common in this population, with conditions such as metabolic syndrome being significantly more prevalent in adults with ID compared to the general population (39). Therefore, our results are particularly relevant as they represent the impact of PRET in populations with ID and multiple CVRFs, a group that is underrepresented in previous studies.

Another notable strength is the use of a repeated time series design which allows to track changes over time. Furthermore, it allows within-subject comparisons, increasing the internal validity by controlling for natural variability. Additionally, the intervention mimics a real-world intervention, characterised by its flexibility. Rather than prescribing a fixed set of exercises, trainers were provided with alternative exercises. When these alternatives were feasible, trainers were allowed to further adapt the exercises to the individual capabilities of each participant, following consultation with the researcher, provided that the progression of resistance was maintained and all targeted muscle groups were trained. This makes the intervention easily adaptable to clinical practice and provides valuable insights into the clinical applicability in real-world settings.

A limitation in this study is the sample size. The heterogeneity resulting from the inclusion of participants with multiple CVRFs and the small sample size limited the ability to detect any statistically significant effects and conduct subgroup analyses. A larger sample size would reduce the impact of sample heterogeneity. Furthermore, we aimed to quantify the physical activity levels of the participants by using the IPAQ questionnaire. However, during the statistical analyses we noted that the results of these questionnaires were unusable. The data showed a substantial number of missing values and high variability in total physical activity scores within subjects. Therefore, we could not include physical activity levels as a co-variate in our multilevel regression analyses.

We did not find any effect of PRET on WHR suggesting that PRET alone may not be enough to induce any changes in WHR. Other factors influencing a healthy lifestyle such as daily physical activity, sedentary behaviour, and healthy diet could be important factors in reducing WHR. From previous research it is known that adults with ID are more sedentary than their peers without ID (40). Furthermore, sedentary behaviour has been found related to metabolic syndrome, high cholesterol, and obesity (41). A review into the diet of adults with ID revealed that they have lower diet quality than their peers without ID (42) and may cancel out any effect PRET might have on WHR. However, in this study we did not intervene or control for diet or calorie intake. Furthermore, achieving weight reduction requires a caloric deficit, which can be achieved by increasing physical activity or reducing calorie intake. Although physical activity was increased with PRET, other factors such as calorie intake may have influenced weight, and WHR.

**Recommendations**

Future research should consider using a larger sample size to increase the ability to detect statistically significant effects of PRET. Subsequently, a larger sample size provides for the possibility to conduct subgroup analyses based on CVRF and objectively identify the impact of other factors such as, physical activity levels, sedentary behaviour, and nutrition on the effect of PRET. Furthermore, it may be valuable to explore factors that influence adherence to an exercise intervention.

We recommend that in future studies an objective measurement such as an activity tracker should be used to measure physical activity and sedentary behaviour throughout the day. A self-report or by proxy filled out questionnaire seemed not feasible to measure physical activity in our study. Additionally, diet should be included as an intervention to optimize diet quality. Investigating strategies to keep adults with ID engaged, such as through social support, personalised interventions, or other incentives, could increase the adherence and effectiveness of PRET.

This study provides important insights for clinical practice. Depending on the medical and physical possibilities, PRET could be used as a component in de management of CVRFs in adults with ID. Clinicians working with adults with ID should address the management of CVRFs multifactorial to increase

the overall lifestyle. When using PRET, clinicians should focus on the engagement of the participant and their environment to the programme to optimise its effectiveness.

## Conclusion

This is the first study investigating the effect of PRET on CVRFs in adults with ID at higher risk of cardiovascular disease. Our results found for LDL, HbA1c, and SBP indicate that PRET is a promising intervention in the management of CVRFs in adults with ID. Clinicians could use PRET as an additional intervention in adults with a mild or moderate ID who are motivated and able to adhere to an exercise intervention. Future research should aim to improve adherence to PRET in this population and further investigate the effectiveness of a multicomponent intervention including nutrition on CVRFs, as current findings only provide preliminary indications of potential effect.

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# Chapter 6

# The effect of resistance exercise training on physical fitness, behaviour, and falls in adults with intellectual disabilities

**K.I. de Oude**
**R.G. Elbers**
**A. Oppewal**
**D.A.M. Maes-Festen**

Submitted

## Abstract

This study, part of the PRET-study (NCT06579898), investigated the effect of a 24-week progressive resistance exercise training (PRET) intervention on the health outcomes: body composition, physical fitness, sarcopenia, activities of daily living (ADL), challenging behaviour, and falls in adults with intellectual disabilities (ID).

A repeated-time-series design with one study group was used. We used multilevel linear regression models and non-parametric tests to investigate changes in body composition (bioelectrical impedance), physical fitness (ID-fitscan), sarcopenia, ADL (Barthel Index, Lawton IADL scale), challenging behaviour (Aberrant Behaviour Checklist), and falls.

Thirty-six adults with mild to moderate ID (mean age 55.6 years) participated and 26 completed the intervention. Intention-to-treat and per-protocol analyses showed statistically significant improvements in physical fitness and challenging behaviour. Intention-to-treat analyses showed improvements in the 5-times chair stand (-2.40 sec, 95% CI [-4.06; -0.75]), and reductions in irritability (-1.10, 95% CI [-2.21; -0.00]) and inappropriate speech (-0.75, 95% CI [-1.22; -0.28]). No effects were observed for body composition, ADL, or falls and no cases of sarcopenia were identified.

PRET is a promising intervention to improve lower body functional muscular endurance, and challenging behaviour in adults with ID.

## Introduction

Physical activity levels are generally low in adults with intellectual disabilities (ID) (1, 2) with only 9% of them reaching adequate levels for health benefits (3). This inactivity contributes to low physical fitness, which is associated with several health conditions in this population, such as cardiovascular disease (4). Cardiovascular risk factors (CVRFs) are also highly prevalent in older adults with ID. For example, de Winter et al. (5, 6) reported hypertension in 53% of older adults with ID, obesity in 25.6%, hypercholesterolemia in 23%, diabetes in 13.7%, and metabolic syndrome in 44.7% of older adults with ID.

This study is part of the PRET-study (Progressive Resistance Exercise Training) (ClinicalTrials.gov, NCT06579898) (7), which investigated the effect of PRET on CVRFs in adults with ID. The primary outcome of the PRET study was the change in CVRFs. This report presents the effects of PRET on a range of secondary outcomes, including body composition, physical fitness, sarcopenia, activities of daily living (ADL), challenging behaviour, and falls.

Low levels of physical activity can result in sarcopenia, defined as the progressive and generalised loss of skeletal muscle mass and strength (8). In older adults with ID, sarcopenia appears earlier and is more prevalent compared to the general population (9, 10). As a result of the loss of muscle mass and strength, sarcopenia can lead to reduced mobility which impacts the ability to perform ADL, such as dressing and bathing. The study of Oppewal et al. (11) found that physical fitness is predictive for a decline in ADL over a three-year follow-up period in older adults with ID. This leads to an increased dependency on caregivers. Furthermore, falls are a major concern in older adults with ID, as they occur more frequently and often lead to serious injuries, hospitalisations, and further loss of independence (10). The combination of low physical fitness and sarcopenia increases fall risk (12). These previous findings highlight the importance of addressing physical fitness and sarcopenia in adults with ID.

In addition to physical health outcomes, behavioural aspects are also closely linked to physical activity levels in this population (9, 10). Challenging behaviour is a significant concern in adults with ID, often leading to reduced quality of life, increased caregiver burden, and limited participation in daily activities (13). While behavioural or psychopharmacological interventions

are commonly used, there is growing interest in the role of physical activity as a supportive strategy. A systematic review by Ogg-Groenendaal et al. (2014) found that participation in physical activity interventions was associated with reductions in challenging behaviour in individuals with ID (10). Furthermore, Smith and Merwin (2021) highlighted that physical activity can improve emotional regulation, executive functioning, and stress resilience in individuals with mental health disorders (14). Although there are only a limited number of studies examining exercise interventions and behaviour in this population, the findings highlight the potential of exercise interventions in managing challenging behaviour in adults with ID.

Despite the known benefits of physical activity, adults with ID face significant challenges in developing health-related skills and maintaining a healthy lifestyle due to deficits in intellectual and adaptive functioning (15, 16). They require more support and accessibility of facilities to engage in physical activity compared to the general population (17). Therefore, intervention strategies must be tailored to the specific needs and abilities of this population.

Weterings et al. (2019) developed a Resistance training Exercise Set for adults with ID (RESID) (18) and demonstrated that using RESID in a PRET intervention was feasible in adults with mild or moderate ID and CVRFs (19). Furthermore, previous studies in individuals with ID investigating the effects of resistance training have shown its benefits on body composition and physical fitness, including improvements in strength, balance, and body mass index (20, 21). However, to our knowledge no studies have examined the effect of resistance training on sarcopenia, ADL, challenging behaviour and falls in adults with ID. Therefore, the aim of this study was to investigate the effects of PRET on body composition, physical fitness, sarcopenia, ADL, challenging behaviour, and falls in adults with ID.

# Methods

### Study design

We used a repeated time series design with one study group. The study period was divided into a 12-week baseline period, a 24-week intervention period (PRET programme), and a 12-week follow-up period. We used three baseline measurements for control comparisons (22). Full details of the study

design have been published elsewhere (7). The study was conducted within the Academic Collaborative Research Center Healthy Ageing and Intellectual Disabilities (HA-ID). The HA-ID Research Center is a collaboration between the Intellectual Disability Medicine Research group of the Erasmus MC, University Medical Center Rotterdam and three care providers in the Netherlands specialised in the care for people with ID: Abrona (Huis ter Heide), Amarant (Tilburg), and Ipse de Bruggen (Zoetermeer). The PRET-study is registered in ClinicalTrials.gov (NCT06579898). Written informed consent is obtained from all participants or their legal representatives.

### Participants

Figure 6.1 presents an overview of the study procedures. The PRET study included participants who were living in a residential facility or received care from one of the participating care providers. Participants had to be 18 years or older with a mild (IQ=50–69) or moderate (IQ=35–49) ID and had to be diagnosed with metabolic syndrome or at least two of the following CVRFs: hypertension, hypercholesterolemia, diabetes mellitus type 2 (DM2), or obesity. More details about the selection of participants and consent procedure have been published in the study protocol (7).

### Measurements

Medical staff collected the participant characteristics age, sex, and aetiology and level of ID from medical records. Outcome measures were assessed at baseline (T0–week 1, T1–week 7, T2–week 12), following the intervention period (T3–week 37) and at 12 weeks follow-up (T4–week 49). Measurements consisted of bioelectrical impedance analysis (BIA), physical fitness tests, questionnaires and a fall agenda. We standardised all physical fitness measurements by conducting them at the same location, time, and day of the week. Full details on the outcome measures are reported elsewhere (7).

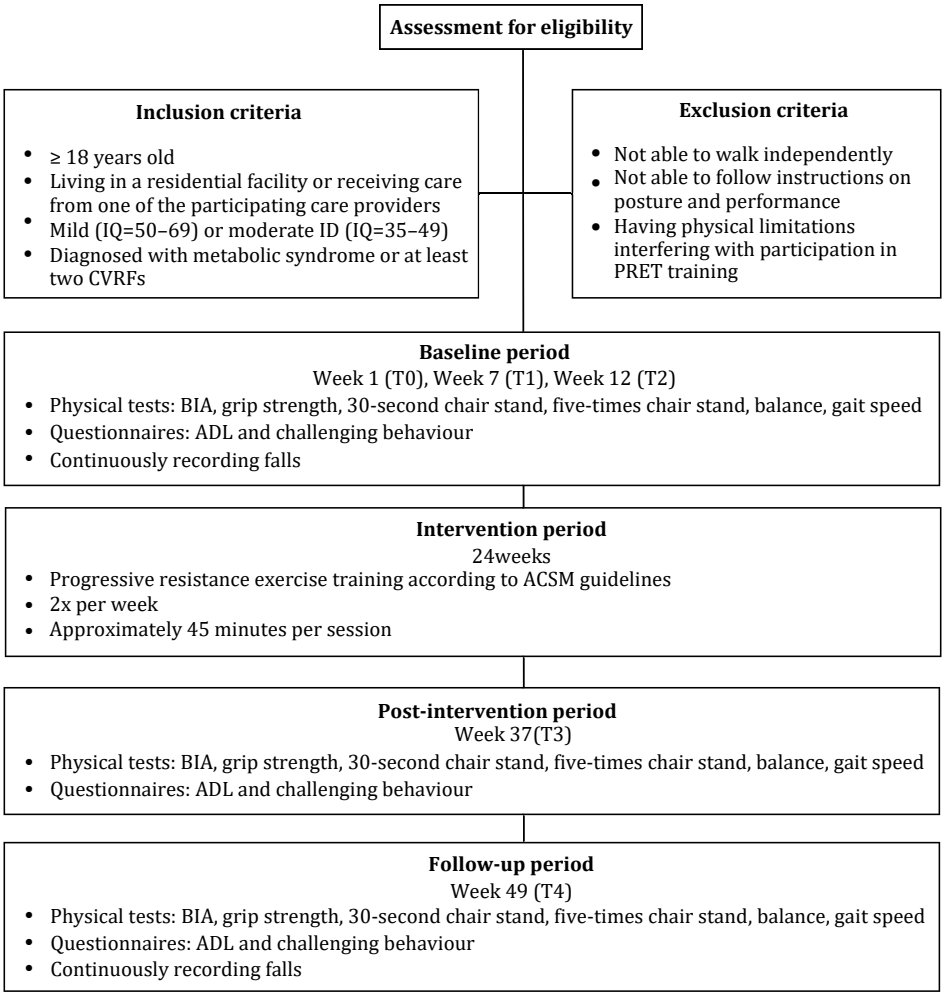


**Figure 6.1. Study overview.**
ACSM: American College of Sports Medicine; CVRF: cardiovascular risk factors; ID: intellectual disability IQ: intelligence quotient, BIA: bioelectrical impedance analysis, ADL: activities of daily living.

### *Body composition*

We used BIA (Tanita Body Composition Analyzer MC-780, Tanita, Tokyo, Japan) to measure weight (kg), BMI, fat mass (kg and %), and skeletal muscle mass (SMM; kg and %). The Tanita MC-780 estimates muscle mass based on whole body conductivity and uses a conversion equation that is calibrated with Dual-energy X-ray absorptiometry as a reference (23). Height was measured using a tape measure while participants stood barefoot against a wall, ensuring contact with the heels, back, and head.

***Physical fitness***

A trained researcher assessed physical fitness using the ID-fitscan, a standardised set of performance tests for adults with ID (24). It includes tests for lower body functional muscular endurance (30 second chair stand and 5 times chair stand) (25), general muscle strength (grip strength by hand-held dynamometry) (26), and balance (four static stances, comfortable gait speed).

For the 30 second chair stand, participants stood up and sat down as often as possible in 30 seconds, without using their hands. We recorded the number of complete stances. For the 5 times chair stand, participants stood up and sat down five times as fast as possible, without using their hands. We recorded the time needed to complete five stances.

Grip strength was measured in a seated position (shoulder 0° flexion, elbow 90° flexion) using the Jamar dynamometer (Hydraulic, JAMAR, Sammons Preston Rolyan, Nottinghamshire, UK). The participants were asked to squeeze with maximum force three times with both hands, with one minute rest in between. The highest value of six attempts (kg) was reported.

Static balance was measured with four stances, progressing in difficulty (side-by-side stand, semi-tandem stand, tandem stand, and single leg stand), which the participants had to maintain independently for 10 seconds. A maximum of five attempts was allowed. We recorded the time for each completed stance and used the scores to categorise static balance from 0 (worse) to 4 (best) (27).

Dynamic balance was measured as comfortable gait speed over the middle five meters of an 11-meter walkway. After three-meters for acceleration, the time between the three meter and eight-meter mark was measured using a stopwatch. The last three meters were used for deceleration. We converted the average time of the three trials (seconds) to gait speed (m/s).

***Sarcopenia***

We used the European cut-off values (Table 6.1) to classify participants as non-sarcopenic, sarcopenic, or severe sarcopenic (8). They were classified with sarcopenia when they scored below the cut-off value for grip strength or above cut-off value for the 5-times chair stand and below cut-off value for muscle mass. Participants were classified with severe sarcopenia when they also scored below the cut-off for physical performance, with a comfortable gait speed ≤0.8 m/s.

**Table 6.1. Classification for Sarcopenia (8)**

| Domain | Tests | Values |
|---|---|---|
| *Sarcopenia* | | |
| Muscle strength | Five times chair stand | >15 s for 5 rises |
| | Grip strength | <27 kg (men)<br><16 kg (women) |
| Muscle mass | BIA | <20 kg (men)<br><15 kg (women) |
| *Severe sarcopenia* | | |
| Muscle strength | Five times chair stand | >15 s for 5 rises |
| | Grip strength | <27 kg (men)<br><16 kg (women) |
| Muscle mass | BIA | <20 kg (men)<br><15 kg (women) |
| Physical performance | Gait speed | ≤0.8 m/s |

BIA: bioelectrical impedance analysis; kg: kilogram; m/s: meter per second.

### *Activities of daily living*

Activities of daily living were assessed with the Barthel Index for basic activities of daily living (28) and an adapted version of the Lawton scale for instrumental activities of daily living (IADL) (29). We incorporated items from the Groningen Activity Restriction Scale (GARS) (30), which was adapted to be used in adults with ID (31). Items were scored on a 4-point rating scale from 0 (complete help) to 3 (independent) and summed to get a total score.

The Barthel Index includes ten items (bowel/bladder control, grooming, toilet use, feeding, transfer, walking, dressing, climbing stairs, and bathing) with item scoring categories ranging from two to four categories. The total score ranged from 0 (completely dependent) to 20 (completely independent) (32).

### *Challenging behaviour*

Challenging behaviour was assessed with the Aberrant Behaviour Checklist (ABC) (33), a 58-item questionnaire with five subscales: irritability, lethargy, stereotypic behaviour, hyperactivity, and inappropriate speech. Professional caregivers scored the items from 0 (not a problem) to 3 (severe problem), and subscale scores were summed (34). Each subscale has its own score range: irritability (0–45), lethargy (0–48), stereotypic behaviour (0–21), hyperactivity (0–48), and inappropriate speech (0–12) (35). Higher scores indicate more severe behavioural problems.

***Falls***

A fall was defined as an unintentional event resulting in a person coming to rest on the floor, or other lower level (36). Participants or their professional caregivers recorded falls daily on a calendar during the 12-week baseline and 12-week follow-up period. Multiple falls in a day were recorded as separate events. For each period, we classified participants as non-fallers or fallers (≥1 fall), and the total number of falls were recorded.

## Intervention

The duration of the PRET intervention (7) was 24 weeks and consisted of two sessions per week, with at least 48 hours between the sessions. The intervention was led by experienced physiotherapists and physical activity instructors. The instructor-participant ratio was 1 to 1 or 1 to 2. Prior to the study, all instructors were trained in the intervention protocol, exercises and registration of each session in the training logbook.

The intervention consists of four mesocycles of six weeks (practice cycle, 65% 1RM, 75% 1RM, 80% 1RM). Each session consisted of seven exercises (RESID) to train all large muscle groups (18). For each muscle group, alternative exercises were provided for participants who could not perform the original exercise with a correct execution.

To maximise attendance and motivation, each participant received a progression logbook to track their progress and a T-shirt to wear during the training and measurements. At completion of the intervention, the participant received a certificate and a medal.

## Follow-up period

The follow-up period lasted 12 weeks. Immediately post-intervention, all participants were invited to complete a questionnaire assessing their experience with the PRET intervention programme. Although the structured training as part of the study ended, we planned an interview with participants and their trainers, who expressed interest in continuing training. The aim of this interview was to support the integration of physical activity into daily life, outside the research setting.

### Statistical analysis

We used descriptive statistics to present participant characteristics at T0 and post-intervention at T3 and for training logbook data. The same statistical analyses as for the primary outcomes of the PRET study were used (19). We used multilevel linear regression models to investigate the effect of the PRET intervention on all outcomes at the end of the intervention period (T3). The participant identification numbers were used as a level in the models. This level consisted of the repeated measurements nested within a participant. Due to a large number of trainers, we could not include the level of clustering of participants by trainer in the final model. We explored confounding by change in physical activity level, and effect modification for level of ID, age and sex.

Using the same analytical approach as described above, we separately analysed, the effects from baseline (T0, T1, T2) to post-intervention (T3) first, and second, the changes from post-intervention (T3) to 12-week follow-up (T4). We conducted intention-to-treat (ITT) analyses with the data from all participants who started the study. Last observation carried forward was used for missing data in the ITT analyses. For each outcome measure, participants were only included in the analysis if corresponding baseline data were available. Subsequently, we conducted per-protocol (PP) analyses with the data from the participants who completed the intervention.

To evaluate changes in fall incidents between the baseline (T2) and follow-up (T4), two non-parametric tests were applied, as the data were paired and not normally distributed. We used the Wilcoxon signed-rank test to compare the number of falls per participant across the two periods. Changes in fall status (faller/non-faller) between baseline and follow-up were assessed using the McNemar's test for paired nominal data.

Statistical significance was set at $p<0.05$ for all analyses. Statistical analyses were performed with R-statistics (R Foundation for Statistical Computing, Vienna, Austria) and the package Linear and Nonlinear Mixed Effects Models (nlme) (37).

## Results

In total 36 adults with ID and CVRFs participated in the PRET study. The average age was 55.6 years (SD=12.9 years) and 52.8% was male (Table 6.2).

Throughout the study 10 participants dropped out, resulting in a PP sample of 26 participants who completed the intervention. Reasons for dropout included re-evaluation of decision to participate (n=1), motivational reasons (n=7), and medical reasons not related to the intervention (n=2). There were no differences in characteristics (age, sex, level and aetiology of ID) between dropouts and participants who completed the intervention (data not shown).

**Table 6.2. Participant baseline characteristics (n=36)**

| Characteristic | N (%) | Mean (SD) |
|---|---|---|
| Age | | |
| Years | | 55.6 (12.9) |
| Sex | | |
| Men | 19 (52.8) | |
| Women | 17 (47.2) | |
| Level of ID | | |
| Severe | 1 (2.7) | |
| Moderate | 11 (30.6) | |
| Mild | 24 (66.7) | |
| Aetiology of ID | | |
| Congenital | 6 (16.7) | |
| Down syndrome | 1 (2.7) | |
| Velocardiofacial syndrome | 1 (2.7) | |
| Williams syndrome | 1 (2.7) | |
| Other | 3 (8.3) | |
| Perinatal | 3 (8.3) | |
| Unknown | 27 (75.0) | |
| Ethnicity | | |
| Caucasian | 32 (88.9) | |
| Afro/American | 1 (2.7) | |
| Other | 3 (8.3) | |

ID: Intellectual Disability; SD: standard deviation; N: number; %: percentage.



Two participants did not have any completed questionnaires for ADL and challenging behaviour resulting in an ITT sample of 34 for these questionnaires. Within the PP sample, only 19 participants had completed questionnaires.

None of the participants in the PRET study were classified with sarcopenia or severe sarcopenia. Therefore, we could not conduct any analyses for sarcopenia. Mean baseline and post-intervention scores for each outcome are presented in Table 6.3.

**Table 6.3. Mean outcome values at baseline and post-intervention (n=36)**

| Outcome | N | Baseline (T0) | Post-intervention (T3) |
|---|---|---|---|
| Body composition, mean (SD) | | | |
| Weight (kg) | 36 | 86.1 (21.5) | 85.2 (19.0) |
| BMI | 36 | 30.1 (8.4) | 29.8 (7.4) |
| Fat mass (kg) | 35 | 28.9 (15.8) | 27.3 (13.9) |
| Fat mass (%) | 35 | 32.1 (9.8) | 30.0 (8.9) |
| SMM (kg) | 35 | 29.9 (6.7) | 30.2 (6.0) |
| SMM (%) | 35 | 35.5 (7.5) | 36.2 (7.3) |
| Physical fitness, mean (SD) | | | |
| 30 second chair stand (n) | 36 | 10.6 (5.1) | 12.5 (4.6) |
| 5 times chair stand (sec) | 36 | 16.3 (9.4) | 12.9 (7.1) |
| Handgrip strength (kg) | 36 | 30.5 (11.9) | 27 (11.9) |
| Static balance | 36 | 3.8 (1.6) | 4.0 (1.8) |
| Comfortable gait speed (m/s) | 36 | 1.1 (0.4) | 1.1 (0.4) |
| Sarcopenia, N (%) | | | |
| Sarcopenic | 36 | 0 (0) | 0 (0) |
| ADL, mean (SD) | | | |
| IADL | 34 | 14.9 (9.0) | 16.0 (9.2) |
| BADL | 34 | 17.3 (3.6) | 18.0 (3.7) |
| Challenging behaviour ABC, mean (SD) | | | |
| Irritability | 34 | 7.9 (7.9) | 4.0 (6.0) |
| Lethargy | 34 | 8.4 (6.7) | 4.5 (8.1) |
| Stereotypy | 34 | 1.6 (2.3) | 0.0 (3.3) |
| Hyperactivity | 34 | 7.4 (6.9) | 5.0 (5.9) |
| Inappropriate speech | 34 | 2.9 (3.3) | 1.0 (2.8) |
| Falls, N (%) | | | |
| Fallers | 20 | 8 (22.2) | 6 (16.7) |
| Non-fallers | 20 | 28 (77.8) | 30 (83.3) |

BMI: Body Mass Index; SMM: Skeletal Muscle Mass; ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living; BADL: Basic Activities of Daily Living; ABC: Aberrant Behaviour Checklist; SD: standard deviation; kg: kilogram; %: percentage; N: number; sec: seconds; m/s: meter per second.

Results of the multilevel linear regression models for post-intervention and follow-up effects are presented for each outcome in Table 6.4.

## Effects of the intervention

### *PRET intervention*

Trainer-completed logbooks indicated that training load was progressively increased, either by introducing more challenging exercises or by increasing the lifted weight. Participants missed an average of 4.6 training sessions

(SD=3.6). Within the ITT sample, 37.1% achieved the maximum training intensity of 80% 1RM, and 31.4% reached 75% 1RM. In the PP sample, 52% achieved 80% 1RM and 44% reached 75% 1RM, while 4% did not exceed 65% 1RM.

***Body composition***

One participant could not complete BIA measurements due to ataxia and was not able to stand still for the complete measurement. Only weight and height were measured for this participant and BMI was calculated manually. Two participants did not have post-intervention BIA measurements. This resulted in an ITT sample of 35 participants for fat mass and SMM, and a PP sample of 24 participants for weight and BMI, and 23 participants for fat mass and SMM. Both the ITT and PP analyses showed no statistically significant effects of the intervention on any of the BIA measurements.

***Physical fitness***

In the ITT sample, one participant could not follow instructions to complete measurements for handgrip strength. Within the PP sample, two participants did not have post-intervention physical fitness test measurements. Of these two participants, one did not want to perform the tests, and the other was not physically able to perform the tests, resulting in a PP sample of 24.

Our results from the ITT sample showed a statistically significant positive effect of PRET on the 5 times chair stand with a reduction of -2.40 sec (95% CI [-4.06; -0.75]). No other significant effects were found in our ITT sample for physical fitness. In the PP sample, we found statistically significant positive effects on the 30 second chair stand with an increase in repetitions of 0.95 (95% CI [0.05; 1.88]), and on the 5 times chair stand with a reduction of -2.54 sec (95% CI [-4.86; -0.22]). We found no statistically significant effects on grip strength, gait speed and static balance in our PP sample.

***Activities of daily living***

We found no statistically significant effects of PRET on the outcomes IADL and BADL in both the ITT and PP sample.

**Table 6.4. Multi-level regression analyses**

| Intention-to-treat | | Post intervention | | | | Follow-up | | | |
|---|---|---|---|---|---|---|---|---|---|
| Outcome | N | β | Intervention | p | 95% CI | β | Follow-up | p | 95% CI |
| BIA | | | | | | | | | |
| Weight (kg) | 36 | 86.02 | -0.80 | 0.13 | -1.82; 0.22 | 85.22 | -0.43 | 0.17 | -1.05; 0.19 |
| BMI | 36 | 30.13 | -0.33 | 0.12 | -075; 0.09 | 29.80 | -0.15 | 0.16 | -0.37; 0.06 |
| Fat mass (kg) | 35 | 28.36 | -1.03 | 0.19 | -2.56; 0.50 | 27.33 | -0.36 | 0.44 | -1.28; 0.57 |
| Fat mass (%) | 35 | 31.55 | -0.48 | 0.22 | -1.25; 0.29 | 31.07 | -0.72 | 0.06 | -1.45; 0.01 |
| SMM (kg) | 35 | 29.99 | -0.11 | 0.78 | -0.90; 0.68 | 29.88 | 0.94 | 0.18 | -0.45; 2.33 |
| SMM (%) | 35 | 36.01 | -0.47 | 0.49 | -1.81; 0.86 | 35.54 | 1.46 | 0.18 | -0.67; 3.59 |
| Physical fitness | | | | | | | | | |
| Chair30 (repetitions) | 36 | 12.87 | -0.56 | 0.74 | -3.91; 2.79 | 12.68 | **0.44*** | 0.05 | 0.02; 0.87 |
| Chair5 (sec) | 36 | 15.79 | **-2.40*** | 0.005 | -4.06; -0.75 | 13.39 | 0.20 | 0.76 | -1.10; 1.50 |
| Hand grip strength (kg) | 35 | 30.40 | -2.40 | 0.68 | -2.48; 1.63 | 29.97 | -0.49 | 0.51 | -1.95; 0.95 |
| Balance | 36 | 3.78 | -0.25 | 0.07 | -0.52; 0.02 | 3.53 | -0.14 | 0.39 | -0.46; 0.18 |
| Gait speed (m/s) | 36 | 1.11 | 0.04 | 0.22 | -0.02; 0.09 | 1.15 | 0.01 | 0.67 | -0.05; 0.07 |
| ADL | | | | | | | | | |
| IADL | 34 | 15.19 | 0.46 | 0.17 | -0.20; 1.12 | 15.66 | -0.63 | 0.19 | -1.57; 0.32 |
| BADL | 34 | 17.19 | -0.25 | 0.07 | -0.51; 0.01 | 16.94 | 0.38 | 0.16 | -0.15; 0.89 |
| ABC | | | | | | | | | |
| Irritability | 34 | 7.63 | **-1.10*** | 0.05 | -2.21; -0.00 | 6.53 | 0.66 | 0.32 | -0.66; 1.97 |
| Lethargy | 34 | 8.61 | -0.76 | 0.25 | -2.06; 0.54 | 7.84 | 0.72 | 0.44 | -1.11; 2.54 |
| Stereotypy | 34 | 1.64 | 0.14 | 0.67 | -0.51; 0.80 | 1.78 | 0.19 | 0.60 | -0.53; 0.91 |
| Hyperactivity | 34 | 7.11 | -1.15 | 0.08 | -2.43; 0.14 | 5.97 | 0.28 | 0.72 | -1.28; 1.84 |
| Inappropriate speech | 34 | 2.99 | **-0.75*** | 0.002 | -1.22; -0.28 | 2.25 | 0.03 | 0.87 | -0.34; 0.40 |

| Per protocol | | Post intervention | | | | Follow-up | | | |
|---|---|---|---|---|---|---|---|---|---|
| Outcome | N | β | Intervention | p | 95% CI | β | Follow-up | p | 95% CI |
| BIA | | | | | | | | | |
| Weight (kg) | 24 | 83.01 | 0.19 | 0.58 | -0.49; 0.88 | 83.21 | -0.46 | 0.32 | -1.38; 0.46 |
| BMI | 24 | 28.47 | -0.07 | 0.60 | -0.34; 0.20 | 28.40 | -0.06 | 0.62 | -0.30; 0.18 |
| Fat mass (kg) | 23 | 25.65 | -0.42 | 0.50 | -1.63; 0.80 | 25.23 | -0.30 | 0.67 | -1.68; 1.09 |
| Fat mass (%) | 23 | 29.50 | 0.29 | 0.55 | -0.66; 1.24 | 29.79 | -0.91 | 0.11 | -1.99; 0.18 |
| SMM (kg) | 23 | 30.23 | -0.09 | 0.87 | -1.07; 0.91 | 30.25 | 1.28 | 0.26 | -0.95; 3.52 |
| SMM % | 23 | 37.04 | -0.71 | 0.54 | -2.97; 1.55 | 36.38 | 2.09 | 0.22 | -1.30; 5.49 |
| Physical fitness | | | | | | | | | |
| Chair30 (repetitions) | 24 | 11.68 | **0.95*** | 0.04 | 0.05; 1.86 | 12.87 | 0.65 | 0.06 | -0.00; 1.30 |
| Chair5 (sec) | 24 | 14.86 | **-2.54*** | 0.04 | -4.86; -0.22 | 12.35 | 0.04 | 0.97 | -2.07; 2.15 |
| Hand grip strength (kg) | 24 | 29.52 | 0.90 | 0.47 | -1.53; 3.33 | 30.42 | -0.71 | 0.51 | -2.86; 1.44 |
| Balance | 24 | 3.95 | -0.21 | 0.22 | -0.54; 0.12 | 3.76 | -0.20 | 0.34 | -0.62; 0.22 |
| Gait speed (m/s) | 24 | 1.18 | 0.03 | 0.38 | -0.04; 0.11 | 1.21 | 0.02 | 0.64 | -0.07; 0.11 |
| ADL | | | | | | | | | |
| IADL | 19 | 15.23 | 0.83 | 0.17 | -0.36; 2.02 | 16.05 | **-1.56*** | 0.01 | -2.68; -0.43 |
| BADL | 19 | 17.65 | -0.34 | 0.14 | -0.79; 0.11 | 17.32 | 0.12 | 0.80 | -0.78; 1.01 |
| ABC | | | | | | | | | |
| Irritability | 19 | 6.87 | **-2.13*** | 0.01 | -3.67; -0.60 | 4.74 | 1.36 | 0.20 | -0.75; 3.47 |
| Lethargy | 19 | 7.94 | **-2.37*** | 0.002 | -3.83; -0.90 | 5.58 | 0.89 | 0.40 | -1.22; 2.99 |
| Stereotypy | 19 | 1.88 | -0.30 | 0.52 | -1.21; 0.61 | 1.58 | 0.02 | 0.97 | -1.18; 1.22 |
| Hyperactivity | 19 | 5.89 | **-1.89*** | 0.04 | -3.64; -0.14 | 4.00 | 0.80 | 0.46 | -1.36; 2.95 |
| Inappropriate speech | 19 | 2.62 | **-0.94*** | 0.01 | -1.66; -0.21 | 1.69 | 0.33 | 0.28 | -0.28; 0.94 |

BIA: bio-electrical Impedance Analysis; BMI: Body Mass Index; SMM: Skeletal Muscle Mass; Chair30: 30 second chair stand; Chair5: 5 times chair stand; IADL: Instrumental Activities of Daily Living; ADL: Activities of Daily Living; BADL: Basic Activities of Daily Living; ABC: Aberrant Behaviour Checklist; N: number of sample; β: value; p: statistical value; CI: confidence interval; *: statistically significant (p<0.05).

***Challenging behaviour***

For challenging behaviour, our ITT results showed statistically significant positive effects of the intervention, reflected by decreased scores on irritability with -1.10 (95% CI [-2.21; -0.000]) and inappropriate speech with -0.75 (95% CI [-1.22; -0.28]). We found no statistically significant effects on lethargy, hyperactivity, and stereotypy. Our PP results showed statistically significant positive effects, reflected in decreased scores on irritability of -2.13, (95% CI [-3.67; -0.60]), lethargy of -2.37 (95% CI [-3.83; -0.90]), hyperactivity of -1.89 (95% CI [-3.64; -0.14]), and inappropriate speech of -0.94 95% CI [-1.66; -0.21]).

***Follow-up***

During the follow-up period our ITT analyses showed a statistically significant increase on the 30-second chair stand of 0.44 sec (95% CI [0.02; 0.87]) from post-intervention to 12 weeks post-intervention. Our PP analyses showed a statistically significant decline on IADL with -1.56 (95% CI [-2.68; -0.43]). We found no further changes on any of the other outcomes during the follow-up period for both ITT and PP analyses.

***Falls***

Fall agendas were completed by 20 participants. At baseline, eight participants were fallers (five with one fall, one with two, one with six, and one with seven falls). At follow-up six participants were fallers (three with one fall, two with two, and one with six falls). No statistically significant differences were observed in proportion of fallers (McNemar p=0.69) or the number of falls (Wilcoxon p=0.47) between baseline and the follow-up period.

## Discussion

The aim of this study was to investigate the effect of PRET on body composition, physical fitness, sarcopenia, ADL, challenging behaviour, and falls. PRET significantly improved performance on the 5 times chair stand, and challenging behaviour. We did not find any statistically significant effects for body composition, the other fitness components, ADL, and falls and no cases of sarcopenia were observed.

### Physical fitness

Regarding our results for physical fitness, statistically significant improvements were observed in the PP sample in both the 30 second chair stand and 5 times chair stand. This indicates that PRET has a positive effect on lower body functional muscular endurance.

The PRET intervention consists of progressive resistance training, with intensity increasing over time. Logbook records confirmed participants could complete exercises at higher intensities, indicating improved muscular strength. Although lower body functional muscular endurance improved, handgrip strength did not, despite its common use as an indicator of general muscle strength in the general population. This may be explained by the fact that handgrip strength primarily reflects upper limb function. Although the PRET intervention included exercises targeting all muscle groups, it is possible that improvements were more pronounced in the lower extremities, which are not captured by handgrip strength measurements (38). Although handgrip strength has been found feasible and reliable in this population (39, 40), and predictive for a decline in mobility (41) and a higher mortality risk (42), it may not be sensitive for detecting intervention related changes in general strength. Another explanation is the limited ability of adults with ID to transfer strength gains from exercises to testing tasks, as it requires cognitive and executive functions (15). This is supported by our findings observed in the chair stand tests, which resembled exercises performed in the PRET intervention, unlike handgrip strength.

Furthermore, ceiling effects might have been of influence for comfortable gait speed and balance as the included sample was able to walk independently and did not present with physical limitations that could interfere with the intervention. This is reflected in the relatively high baseline values in this study population for comfortable gait speed (1.1 m/s) and static balance (3.8 out of 4.0), suggesting limited room for measurable improvement. For comparison, de Leeuw et al. (2023) found an average comfortable gait speed of approximately 0.95 m/s in adults with ID of 50 years and older (4). These considerations highlight the importance of critically selecting tests that can detect meaningful changes.

### Challenging behaviour

We found significant improvements across multiple domains of challenging behaviour, as presented in both the ITT and PP analyses. This is particularly noteworthy given that participants were not selected based on the presence of behavioural problems, and baseline scores on the ABC subscales were generally low. Even with this limited room for improvement, reductions were still observed. This suggests that resistance training may benefit even in individuals with relatively mild behavioural issues. Our findings are in accordance with previous research showing that exercise interventions can reduce the frequency and intensity of challenging behaviour in adults with ID (10). In contrast to our study, previous studies have typically included samples selected for the presence of challenging behaviour. This highlights the unique potential of PRET to positively influence challenging behaviour in adults with ID, in addition to its benefits for other health outcomes.

### Body composition

In contrast to previous studies who found modest improvements in adults with ID (20, 21), our results showed no statistically significant changes in weight, BMI, fat mass, and SMM. A review by Jacinto et al. reported positive effects of different resistance training interventions on BMI in adults with ID. A more recent study by Gutiérrez-Cruz et al. showed decreases in body mass and body fat mass and an increase in SMM after a 14-week resistance training intervention in adults with ID (21). However, several differences between our study and those studies may explain the variation in results. While previous studies included adults with ID without specific health issues, the PRET-study required the presence of at least two CVRFs for participants to be included. For example, our sample had an average baseline BMI of 30.1 compared to 27.7 in the study by Gutiérrez-Cruz et al. The presence of multiple CVRFs in our sample may have attenuated the potential benefits of PRET. Individuals with multiple CVRFs often present with impaired vascular function (43) and/or metabolic dysregulation (44, 45). These physiological conditions may attenuate or delay adaptive responses to exercise. Furthermore, the study by Gutiérrez-Cruz et al. had a frequency of three sessions per week, compared to two in our study, and statistical analysis was conducted with data from participants who completed at least 12 weeks of the 14-week intervention.

Nearly all participants in the study by Gutiérrez-Cruz et al. completed the full 14-week intervention, which indicates better adherence. This higher adherence may have contributed to the more favourable outcomes observed in their study.

The results found in our study for SMM are consistent with previous research conducted in the general population, showing that initial gains in muscular strength are primarily due to neuromuscular adaptations rather than increases in SMM (46-48). These neural mechanisms have been extensively investigated across various populations. Although such mechanisms have not been specifically studied in adults with ID, previous findings support the notion that an increase in SMM typically occurs after a prolonged period of resistance training (48). The period of neuromuscular adaptations may be extended in adults with ID due to their low levels of physical activity (3), resulting in a greater contribution of these adaptations prior to increases in SMM compared to the general population.

To optimise body composition, diet is an important factor (49). Reductions in body weight, BMI, and fat mass generally necessitates a calorie deficit (50). In contrast, stimulating muscle growth, particularly SMM, depends on adequate protein intake (49). A recent study by Gast et al. (51) revealed that the dietary quality of adults with ID is low. Therefore, as no dietary intervention was included in the present study, the diet quality of adults with ID may have not supported the effect of PRET.

**Activities of daily living**

For both BADL and IADL no statistically significant effects of PRET were found. This could be explained by several factors. First, as noted earlier, the transferability of training-related strength gains to daily life tasks may be limited in adults with ID. Second, our sample consisted of participants who were relatively independent at baseline, as indicated by the mean baseline scores for BADL and IADL, which are in the upper range. Therefore, a ceiling effect may have obscured any improvements. This could have contributed to the lack of statistically significant changes observed in ADL, despite evidence from logbooks of increased training load, suggesting an increase in muscle strength.

We found a statistically significant decline in IADL in our PP sample after the follow-up period. This can be explained by an outlier in our data which showed a large unexplained decline of -8 for IADL.

### Falls

We found no statistically significant effect on falls. The number of participants classified as fallers decreased slightly from eight at baseline to six at follow-up, and the total number of falls showed a small reduction after the intervention. It is important to note that participants were not selected on fall status. The subgroup of fallers at baseline was small. Consequently, subgroup analyses were not possible, and any true changes within the faller group may have gone undetected.

### Sarcopenia

We identified no cases of sarcopenia in our study sample. Since participants were primarily selected based on the presence of CVRFs rather than sarcopenia, this was not unexpected. Additionally, participants were required to have no physical limitations that could interfere with the intervention, which likely reduced the likelihood of sarcopenia within the sample.

However, it is possible that cases of sarcopenia went undetected. While current sarcopenia guidelines (8) rely on fixed cut-off values for muscle mass, these thresholds may underestimate sarcopenia in individuals with obesity (52). Our sample consisted predominantly of individuals with obesity, which may have impacted the identification of sarcopenia through the cut-off values used for muscle mass in this study. Alternative indicators for muscle mass, such as muscle mass adjusted for weight, have been recommended by The European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO) (52). These indicators may have offered a more accurate representation of sarcopenia. These considerations underscore the importance of critically selecting sarcopenia cut-off values based on the characteristics of the study sample.

### Strengths and limitations

This study provides important insights into the effectiveness of a flexible, pragmatic PRET intervention for adults with ID and CVRFs. The repeated

time series design allowed us to track individual changes over time, thereby enhancing internal validity through within-subject comparisons (53). The intervention was designed to reflect real-world clinical practice, allowing for tailored adaptations based on individual capabilities while maintaining core training principles. These features support the clinical applicability of the intervention in care settings.

However, several limitations should be considered when interpreting the results of this study. First, the present report presents secondary outcomes of a study in which the intervention was specifically designed to target the primary outcomes (CVRFs). Therefore, the study population was selected based on the presence of CVRFs, rather than on the presence of behavioural problems, poor fitness, limitations in ADL, fall incidents or conditions such as sarcopenia. As a result, any effects observed in these domains may be less pronounced.

Secondly, the small sample size in this study also limits the ability to detect statistically significant changes. In addition, the sample exhibits high heterogeneity in terms of level of ID, physical abilities, and challenging behaviour influencing the outcomes. While including a heterogeneous group enhances the external validity of this study, it complicates the interpretation of the results as the heterogeneity may have obscured any effects, or the observed effects may not apply to all subgroups.

**Recommendations**

Future studies with larger sample sizes are needed to account for the heterogeneity within the population of adults with ID. A larger sample size would also increase statistical power and enable to conduct subgroup analyses, which allows for the detection of differential effects according to participant characteristics.

Future research should further explore the effects of resistance training compared to other exercise interventions on challenging behaviour in adults with ID, using samples specifically selected for the presence of challenging behaviour. This approach would allow for a more precise comparison of intervention modalities and help identify which forms of exercise are most effective in reducing challenging behaviour in this population. Challenging behaviour remains one of the most complex and demanding issues in the

care for this population, often placing a significant burden on caregivers and support systems (54). Therefore, identifying effective non-pharmacological interventions is of great importance.

Future studies targeting adults with ID should consider evaluating the feasibility and effectiveness of increased training frequency. While a higher frequency may increase the effectiveness of PRET on muscle strength and body composition (55), it may also lead to an increase in dropout in a population already prone to high dropout rates. Therefore, we recommend conducting comparative studies to assess both the feasibility and the effect of varying training frequencies.

When assessing the effectiveness of PRET in adults with ID, it is essential to critically select outcome measures that are valid, feasible, and sensitive to meaningful changes. Given the heterogeneity within the population, including variations in level of ID and physical functioning, a one-size-fits-all approach is not appropriate. For example, we observed ceiling effects in comfortable gait speed and static balance, limiting the ability to detect improvements over time. This highlights the need for selecting tests that are sufficient for higher-functioning individuals, while still feasible for a variety of level of ID.

A key strength of the PRET intervention is its adaptability of the exercises to individual capabilities and goals. However, it is crucial to align the exercise selection with the intended outcome it is used for. Therefore, to ensure an effective implementation of PRET and safe execution, it is essential that PRET is delivered by professionals with expertise in both resistance training and working with adults with ID.

## Conclusion

This study investigated the effects of PRET on multiple secondary outcomes in adults with ID and CVRFs. Statistically significant improvements were found in physical fitness and challenging behaviour. No effects were found for body composition, ADL, or falls, and no cases of sarcopenia were identified.

Given the small sample size and the fact that participants were not specifically selected based on the presence of the measured outcomes, these findings suggest that PRET has the potential to be a valuable intervention with positive effects across multiple health components in adults with ID.

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# Chapter 7

## General discussion

## Principal findings

The PRET study, as presented in **chapter 3**, investigated the effects of a progressive resistance training intervention on cardiovascular risk factors (CVRFs) and secondary health outcomes in adults with intellectual disabilities (ID). This general discussion summarises key findings, evaluates their implications, outlines the strengths and limitations of our research, and provides recommendations for future research, practice, and policy.

In **chapter 2**, we presented the results of a systematic review and meta-analysis of 59 studies in the general population, assessing the effects of low, moderate, high, and progressive resistance training intensity on CVRFs. All intensities showed beneficial effects on CVRFs with no statistically significant differences between intensities. However, only a limited number of studies focussed on low, high, or progressive intensity and the overall quality of the evidence of the included studies was low to moderate.

**Chapter 4** evaluated the convergent validity and intra-rater reliability of calf circumference as a measure of muscle mass. While calf circumference showed reliable measurements within an assessor, its validity compared to bioelectrical impedance analysis (BIA) remains uncertain.

**Chapters 5 and 6** reported the effects of the PRET intervention on CVRF and secondary health outcomes in adults with ID. Post-intervention, all CVRFs showed a trend towards improvement, with a statistically significant reduction in LDL cholesterol. At follow-up (12 weeks post-intervention), CVRF levels remained stable. Additionally, we observed significant post-intervention improvements in lower body strength and endurance (30-second chair stand and 5-times chair stand) and challenging behaviour. No other clinically meaningful effects were found for other physical fitness measurements, body composition, activities of daily living (ADL), or falls. Sarcopenia analysis was not possible, as no participants met the diagnostic criteria for sarcopenia at baseline.

## Effects of PRET on CVRFs

The findings from the PRET study largely align with the effects observed in the general population, as reported in our systematic review. This consist-

ency suggests that the effect of PRET on CVRFs are broadly applicable, even among adults with ID. However, it is important to note that the studies included in our systematic review mainly focused on individuals with a single CVRF, whereas the PRET sample included participants with multiple CVRFs. This difference in population characteristics may have attenuated the observed effects in the PRET study, suggesting that the true impact of the PRET intervention on each single CVRF could be even greater in adults with ID than our findings indicate.

Interestingly, besides the similar effects on CVRFs, the PRET study also revealed important results that differ from the general population and may reflect unique characteristics of the study population or contextual factors. In the following sections, these results will be discussed in more detail.

## Adherence

Despite strategies to enhance adherence, dropout in the PRET study remained substantial (28%), reflecting a persistent challenge in this population previously reported (1). Nevertheless, a trend towards improvement was seen across all CVRFs, suggesting health benefits are possible even with suboptimal adherence.

Systematic reviews have identified barriers to physical activity participation in adults with ID, grouped into personal, social, environmental, intervention-specifics, communication, and psychological domains (2-4). The PRET protocol addressed many of these barriers. Incentives were used to enhance motivation, exercises could be tailored to individual abilities, a familiarisation phase was included to build familiarity and confidence, training locations were accessible, and training was delivered in small groups (maximum of two participants with one trainer), with a consistent structure and the same trainer.

However, some barriers were not actively addressed. Family members and caregivers were not actively involved. Due to cognitive limitations, adults with ID often struggle to understand long-term health benefits of exercise and rely heavily on support and motivation from caregivers and family members (5). Secondly, although trainers were provided with protocol-specific guidance and materials related to the PRET intervention, motivational strategies were

not explicitly discussed or included in the protocol. All trainers had extensive experience working with and motivating adults with ID. Nonetheless, individual approaches to motivation were not assessed and likely differed across trainers. We planned to investigate the impact of individual trainers on the outcomes of the study by including a trainer level in our regression analyses. Unfortunately, this was not possible due to the large number of trainers (n=19).

Finally, while trainers can motivate participants during sessions, their influence outside the training context is limited. This suggests that a multidisciplinary approach, where trainers and other health professionals involved work closely together, may be necessary in this population to optimise adherence.

## Body composition

A noteworthy observation of this thesis was the lack of measurable changes in body composition. Despite documented progression in resistance training intensity in training logbooks, no increases in skeletal muscle mass (SMM) or reductions in weight, BMI, or fat mass were observed. This highlights a potential limitation in intervention efficacy or sensitivity of assessment methods.

Several factors may explain this. Initial strength gains are often due to neuromuscular adaptations rather than hypertrophy, which typically requires prolonged training (6-8). In adults with ID, limited motor skill development (9) and lower levels of physical activity (10) may extend this adaptation phase. Furthermore, previous studies showed improvements in body composition in adults with ID after longer exercise programs (e.g., 36 weeks) (11) and in the general population with a higher resistance training frequency (e.g., 3 times per week) (12). Therefore, the total duration of 24 weeks and frequency might have been insufficient to induce changes in body composition.

Furthermore, no nutritional interventions were included, or dietary intake was recorded in the PRET study. Previous research has shown that muscle growth depends on adequate nutrition, especially protein (13), and adults with ID often have poor dietary quality (14, 15), which may hinder

both muscle growth and weight loss. Moreover, weight loss requires a caloric deficit, which exercise alone may not achieve. This suggests a multifaceted approach, combining resistance training with a nutritional intervention, to optimise the effect of PRET.

Finally, sedentary behaviour may have had an influence on the effectiveness of the PRET intervention. Adults with ID tend to be more sedentary than the general population (16), and sedentary behaviour has been found related to metabolic syndrome, high cholesterol, and obesity in adults with ID (17). The time spent in sedentary behaviour outside the PRET intervention may have cancelled out any effect of the intervention. Although the IPAQ was used to measure physical activity, sedentary time was not assessed.

## Methodological issues

Several methodological limitations should be considered when interpreting the findings of the PRET study. Firstly, the sample size was relatively small and included only participants who were willing and possibly more motivated to take part in the intervention. This limits the generalisability of the results to the broader population of adults with ID. Furthermore, we included only adults with mild or moderate ID, further limiting the generalisability of the findings to individuals with more severe ID. Additionally, the small sample size reduced the statistical power of the study and restricted the complexity of the multilevel regression models we could apply. For example, we were unable to include additional levels in the hierarchical structure or perform subgroup analyses.

Secondly, this study used a multiple baseline measurement design in which participants served as their own controls. While this approach allows for individual-level comparisons and strengthens internal validity (18), the absence of comparing effects to a control group limits external validity and generalisability. Within-subject designs are more susceptible to time-related confounders such as seasonal effects, health changes, or external influences during the intervention period (19). Furthermore, the extended baseline period of three months may have introduced participant demotivation, potentially affecting adherence.

Finally, measurement-related limitations presented a challenge in this thesis, potentially affecting the interpretation of several outcomes. The use of the IPAQ questionnaire to assess physical activity resulted in substantial missing data and high intra-individual variability, suggesting difficulties for caregivers in accurately completing the questionnaire. Additionally, ceiling effects may have obscured changes in physical fitness and ADL outcomes, as participants demonstrated relatively high baseline scores, limiting the sensitivity of the measures to detect improvement. The assessment of sarcopenia relied on general cut-off values (20), which may have underestimated prevalence in a sample predominantly consisting of individuals with obesity. Weight-adjusted thresholds would likely have provided a more accurate classification (21). Furthermore, body composition was measured using bioelectrical impedance analysis (BIA), a method whose validity in the ID population remains uncertain (22). Even though, BIA has practical advantages and the potential to be more feasible in this population, a more precise technique, such as dual-energy X-ray absorptiometry (DXA), would have strengthened the accuracy of these measurements. Collectively, these limitations underline the need for tailored, validated measurement tools when conducting research in populations with ID.

## Implications for research

While the results from this thesis are promising, further research is needed to confirm and expand upon these findings. Future studies aiming to investigate the effect of exercise interventions such as PRET should carefully consider challenges related to study design, including achieving sufficient inclusion, ensuring both internal and external validity, maintaining participant motivation, and determining an appropriate overall duration. A well-considered approach to these design choices will help optimise feasibility and the reliability of outcomes.

To improve statistical power and detect subtle changes, larger sample sizes are recommended. Selecting a more diverse population, including individuals across all levels of ID, would allow for larger sample sizes. Although it is reasonable to assume that individuals with a milder ID may be better able to follow exercise instructions, the level of ID does not necessarily predict

physical capability or the ability to perform resistance training. Instead, successful participation may depend on adapted instructional methods, which falls within the expertise of trained professionals. Moreover, including individuals with more severe ID could potentially reduce dropout rates, as these participants are often supported by caregivers who facilitate attendance. In contrast, individuals with a milder ID may attend independently and may therefore be more likely to miss training sessions due to lack of motivation.

Integrating objective measurements for physical activity (23) and sedentary behaviour would provide a more comprehensive understanding of the mechanisms influencing intervention outcomes, particularly in relation to body composition. In the PRET study, the IPAQ was used to measure physical activity. However, this was done by proxy reporting, which requires the caregiver to have detailed and accurate knowledge of the participant's daily activities and routines (24). Accelerometers such as the ActiGraph (25) or ActivPal (26) can be used as objective measures for physical activity and sedentary behaviour (27, 28).

It is also essential for to explore multicomponent interventions that combine PRET with dietary support. Nutrition plays a critical role and integrating nutritional guidance may enhance the overall effectiveness of PRET. Combining exercise and dietary components could lead to more comprehensive health improvements and help participants gain the full benefit of the training. Furthermore, researchers should explore methods to systematically document trainer-level variables, including motivation strategies and interpersonal dynamics, as these may significantly impact adherence and outcomes.

Future research should also examine the cost-effectiveness of these multicomponent interventions for the management of CVRFs in adults with ID. In the Netherlands, health care for adults with ID is government-funded, and ongoing budget constraints within care organisations make it essential to justify new interventions not only based on health outcomes but also on economic value in comparison to current used guidelines. Although, physical activity has shown a public benefit of up to 2.7 times its cost in individuals with ID, with a socio-economic value up to 60% higher than in the general population (29), evidence on cost-effectiveness in this population remains scarce.

Conducting such evaluations in this population is challenging, as standard quality of life instruments may not be valid for adults with ID (30), and factors such as caregiver burden, and environmental adaptations make analyses complex. To address these methodological and practical challenges, collaboration with experts in health economics is essential.

## Recommendations for practice and policy

While further research is required to more comprehensively investigate the effectiveness of PRET, current evidence supports its use in practice. The PRET training provides physical therapists and physical activity trainers with a structured and feasible resistance training intervention for adults with ID and CVRF. The progressive structure of the training protocol has been shown to be practical, while also offering flexibility and creativity for adapting exercises to individual abilities.

As previously mentioned, to maximise the health benefits of PRET in adults with ID and CVRFs, it is strongly recommended that it be implemented as part of a multidisciplinary and multifaceted approach. This approach should involve close collaboration between medical staff, caregivers, family members, and allied health professionals to ensure a coordinated management of CVRFs. All professionals involved share responsibility for motivating and support, promoting adherence, and adapting to individual needs (31, 32). To support this, the recently published Dutch guideline "Bewegen als gewoonte in de langdurig zorg" (Physical Activity as a Habit in Long-Term Care) provides recommendations and supportive tools for healthcare professionals to incorporate physical activity in daily care (33).

Effective support for adults with ID requires that professionals not only possess knowledge of CVRFs and their health consequences, but most importantly, demonstrate a range of motivational skills that can be adapted to individual needs. Moreover, creativity and flexibility are essential, as there is no universal approach that suits all within this highly heterogeneous population (33, 34). Therefore, policymakers should ensure that professionals are provided with, or potentially required to undertake, specialised training in these skills. This should be part of regular professional development and supported with resources provided by the healthcare organisations. This

is in accordance with the Dutch national policy framework "Toekomstagenda: zorg en ondersteuning voor mensen met een beperking" (Future Agenda: Care and Support for People with Disabilities), outlining the need for sustainable care and support, including attention to professional development and training of health care professionals (33, 35).

## Concluding remarks

This thesis demonstrates that PRET can lead to similar health benefits in adults with ID as those observed in the general population. However, maintaining adherence to the training appears to be more challenging for this group, which likely affects the overall effectiveness of the intervention. These findings highlight the importance of a multidisciplinary approach to improve cardiovascular health in adults with ID. To support this, policymakers and healthcare organisations should focus on equipping and supporting professionals to respond effectively to the diverse needs and abilities within this population.

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# Summary

**Chapter 1: General introduction**

Although cardiovascular disease (CVD) is the leading cause of death worldwide, the risk of CVD can be reduced by addressing modifiable risk factors such as physical inactivity, poor diet, and obesity. Regular physical activity is essential for reducing cardiovascular risk factors (CVRFs).

Adults with intellectual disabilities (ID) are particularly vulnerable for CVD, experiencing higher rates of CVRFs compared to the general population. This group faces unique challenges in maintaining a healthy lifestyle, accessing healthcare, and receiving appropriate prevention and screening programmes. These difficulties result in persistent health inequalities.

In the Netherlands, cardiovascular risk management for adults with ID generally follows guidelines developed for the general population. However, these guidelines require individualised adjustments due to comorbidities, polypharmacy, and communication barriers. Increasing physical activity levels is one of the recommendations in international guidelines. However, physical activity levels among adults with ID are often low, and they encounter numerous barriers to participate in physical activity, including health problems, lack of adapted programmes, and insufficient support.

Resistance training may offer unique benefits for adults with ID, such as improvements in muscle mass, glycaemic control, blood pressure, and lipid profiles, and is more easily tailored to individual abilities than aerobic training. Despite these potential benefits, adults with ID remain underrepresented in clinical research, resulting in a lack of evidence about the effects of resistance training on health-related factors, such as CVRFs, physical fitness, body composition, sarcopenia, activities of daily living (ADL), falls, and challenging behaviour.

This thesis aims to investigate the effects of Progressive Resistance Exercise Training (PRET) on CVRFs and other health outcomes in adults with ID, addressing a significant knowledge gap and providing evidence to inform clinical practice and policy.

**Chapter 2: Effect of different training intensities on CVRFs**

This chapter presents a systematic literature review and meta-analyses on the effects of different resistance training intensities (low, moderate, high, progressive) on CVRFs in the general population. While resistance training is known to improve CVRFs, the optimal training intensity remains unclear.

Across 59 randomised controlled trials, progressive resistance training intensity showed beneficial effects on systolic blood pressure (SBP) and low-density lipoprotein cholesterol (LDL). High intensity resistance training reduced glycated haemoglobin (HbA1c), low intensity training lowered LDL, and moderate intensity resistance training improved both waist-hip ratio (WHR) and HbA1c. Comparisons between intensities revealed no statistically significant differences, apart from a stronger effect of high intensity on WHR. The certainty of evidence ranged from low to moderate.

Overall, these findings confirm that resistance training at various intensities contribute to improvements in CVRFs. However, evidence for the optimal training intensity remains limited, highlighting the need for further studies to determine optimal training prescriptions for cardiovascular risk management.

**Chapter 3: PRET study protocol: Design and methodolody**

This chapter describes the protocol for the PRET study, that aimed to evaluate the effect of progressive resistance exercise training on CVRFs in adults with ID. While resistance training has proven to be effective on reducing CVRF's in the general population, its effect in adults with ID remains unknown.

We designed a repeated time-series study with one study group. Adults with mild-to-moderate ID and at least two CVRFs were eligible for inclusion. Following a 12-week baseline period with repeated measurements, participants completed the 24-week PRET intervention, after which all outcomes were reassessed. After a12 weeks follow-up period, participants had their final assessments. Hierarchical regression models, adjusted for possible confounders, were used to evaluate intervention and follow-up effects.

The results of the PRET study are presented in chapters 5 and 6. Primary outcomes (chapter 5) included HbA1c, SBP, LDL, and WHR. Secondary outcomes (chapter 6) covered physical fitness, body composition, sarcopenia, ADL, falls, and challenging behaviour.

### Chapter 4: Measuring muscle mass in adults with ID

This chapter reports on the construct validity and intra-rater reliability of calf circumference as a proxy measurement for muscle mass in adults with ID. Compared to bioelectrical impedance analysis (BIA), calf circumference is a less expensive and a more accessible method for adults with ID. We analysed data from 36 participants in the PRET study. Pearson's correlations revealed a weak association between calf circumference and skeletal muscle mass (SMM), and moderate correlations with segmental muscle mass (SegMM) and skeletal muscle index (SMI). Intra-rater reliability of calf circumference was excellent.

Although calf circumference measurements are highly reliable within assessors, their validity in estimating muscle mass compared to BIA is limited. Calf circumference may serve as a rough indicator of muscle mass when other methods are unavailable. Due to the strict inclusion criteria for CVRFs in the PRET study, findings are not generalisable to all adults with ID. Future research should include a more heterogeneous sample and use Dual-energy X-ray Absorptiometry (DXA) or Computed Tomography (CT) scans for validation.

### Chapter 5: Effect of PRET on CVRFs

This chapter presents the results for the primary outcomes of the PRET study introduced in chapter 3. Thirty-six adults with ID participated in the study. We used multilevel linear regression models, adjusted for medication use, to investigate the effects of the PRET intervention. While improvements were observed across HbA1c, SBP, LDL, and WHR only LDL showed a statistically significant improvement. After the follow-up period, levels for HbA1c, SBP, and LDL worsened, while WHR showed a slight improvement.

The flexibility of the PRET intervention allowed trainers to adapt exercises to participant capabilities, improving real-world applicability. However, adherence was still a major challenge, as we observed a 28% drop-out rate despite the use of motivational strategies and individualised support.

The findings of this study suggest that PRET is a promising intervention for managing CVRFs in adults with ID, particularly for those who are motivated and capable of adhering to structured exercise programs. Further research is needed to improve adherence and to evaluate the effectiveness in a larger sample of adults with ID.

**Chapter 6: Effect of PRET on secondary health outcomes**

This chapter describes the effects of the PRET intervention on secondary outcomes, including body composition, physical fitness, sarcopenia, ADL, challenging behaviour, and falls, in adults with ID.

Statistically significant improvements were observed in lower body functional muscle strength and endurance and several domains of challenging behaviour (irritability, lethargy, hyperactivity, inappropriate speech). However, no changes were found in body composition, other domains of physical fitness, ADL, or falls. We aimed to investigate the effect of PRET on the presence of sarcopenia. However, no cases of sarcopenia were identified at baseline, and analysis was not possible.

Given the small sample size, and the fact that participants were not specifically recruited based on the presence of the measured secondary outcomes, these findings suggest that PRET has the potential to be a valuable intervention with positive effects across multiple health components in adults with ID.

**Chapter 7: General discussion**

This thesis shows that PRET can improve CVRFs in adults with ID, with significant reductions in LDL cholesterol and improvements in lower body performance and challenging behaviour. However, changes in body composition were minimal, and no significant effects were observed for other physical fitness measures, ADL, or falls. Adherence remained a challenge, with a 28% dropout rate, despite strategies to enhance motivation and accessibility.

Methodological limitations included a small, selected sample, restricting statistical power and generalisability. The lack of change in body composition may be attributed to the relatively short intervention duration, the modest training frequency of twice a week, the absence of dietary modifications, and potentially high levels of sedentary behaviour outside the intervention. Proxy reporting of physical activity also limited data reliability.

Future research should include larger, more diverse samples, objective measurements of physical activity and sedentary behaviour and consider multicomponent interventions combining exercise with nutritional support. For practice, the PRET intervention offers a feasible tool for resistance training in adults with ID, but optimal outcomes require a multidisciplinary approach involving caregivers, family, and other healthcare professionals to increase

adherence and motivation. Policymakers should support development in motivational and adaptive skills for healthcare professionals to address the diverse needs of this population.

Overall, PRET can improve cardiovascular health in adults with ID, but sustained adherence and a multicomponent and multidisciplinary approach is essential for maximising benefits.

# Samenvatting

**Hoofstuk 1: Algemene inleiding**

Hoewel hart- en vaatziekten wereldwijd de belangrijkste doodsoorzaak zijn, kan het risico erop verminderd worden door het aanpakken van risicofactoren zoals lichamelijke inactiviteit, een slecht dieet en obesitas. Regelmatige lichamelijke activiteit is essentieel voor het verminderen van cardiovasculaire risicofactoren (CVRF's).

Volwassenen met een verstandelijke beperking (VB) zijn kwetsbaar voor hart- en vaatziekten, en hebben vaker CVRF's in vergelijking met de algemene bevolking. Deze groep heeft te maken met unieke uitdagingen bij het handhaven van een gezonde actieve levensstijl, het op tijd verkrijgen van toegang tot gezondheidszorg en het ontvangen van passende preventie- en screeningsprogramma's. Deze uitdagingen leiden tot blijvende gezondheidsongelijkheden.

In Nederland worden voor cardiovasculair risicomanagement bij volwassenen met een VB doorgaans de richtlijnen gebruikt die ontwikkeld zijn voor de algemene bevolking. Deze richtlijnen vereisen echter individuele aanpassingen vanwege comorbiditeiten, polyfarmacie en communicatieproblemen. Het vergroten van lichamelijke activiteiten is een belangrijke aanbeveling in internationale richtlijnen. De mate van lichamelijke activiteit bij volwassenen met een VB is echter vaak laag. Ook ondervinden zij tal van barrières, zoals gezondheidsproblemen, gebrek aan aangepaste programma's en onvoldoende ondersteuning, om deel te nemen aan lichamelijke activiteit.

Deelnemen aan een krachttrainingsprogramma kan voordelen bieden voor volwassenen met een VB. Het verbetert mogelijk de spiermassa, bloedsuikercontrole, bloeddruk en cholesterol, en kan gemakkelijker worden afgestemd op individuele capaciteiten dan cardiotraining. Ondanks deze potentiële voordelen blijven volwassenen met een VB ondervertegenwoordigd in klinisch onderzoek naar krachttraining. Dit resulteert in een gebrek aan bewijs over de effecten van krachttraining op gezondheidgerelateerde factoren, zoals CVRF's, lichamelijke fitheid, lichaamssamenstelling, sarcopenie, dagelijkse activiteiten (ADL), vallen en probleemgedrag.

Dit proefschrift onderzoekt de effecten van progressieve krachttraining (PRET) op CVRF's en andere gezondheidsresultaten bij volwassenen met een VB. Hiermee wordt een belangrijk kennishiaat opgevuld en wordt wetenschappelijke onderbouwing geboden voor de klinische praktijk en beleidsvorming.

**Hoofdstuk 2: Effect van verschillende krachttrainingsintensiteiten op CVRF's**

Dit hoofdstuk presenteert een systematische literatuurstudie en meta-analyse over de effecten van verschillende intensiteiten (laag, matig, hoog, progressief) van krachttraining op CVRF's in de algemene bevolking. Hoewel krachttraining bekend staat om het verbeteren van CVRF's, blijft de optimale trainingsintensiteit onduidelijk.

De meta-analyses van 59 gerandomiseerde gecontroleerde studies toonden dat progressieve krachttraining positieve effecten heeft op systolische bloeddruk (SBP) en low-density lipoproteïnecholesterol (LDL). Hoge intensiteit krachttraining verminderde glycohemoglobine (HbA1c), lage intensiteit krachttraining verlaagde LDL, en matige intensiteit krachttraining verbeterde zowel de taille-heup ratio (WHR) als HbA1c. Het vergelijken van de verschillende intensiteiten van krachttraining vertoonde geen statistisch significante verschillen, behalve een groter effect van hoge intensiteit op WHR. De kwaliteit van het bewijs varieerde van laag tot matig.

Over het algemeen bevestigen deze bevindingen dat alle intensiteiten van krachttraining bijdragen aan verbeteringen in CVRF's. Het bewijs voor de optimale trainingsintensiteit blijft beperkt, daarom is verder onderzoek naar de optimale trainingsvoorschriften voor cardiovasculair risicomanagement noodzakelijk.

**Hoofdstuk 3: PRET studieprotocol: ontwerp en methodologie**

Dit hoofdstuk beschrijft het protocol van de PRET-studie, die het effect van progressieve krachttraining op CVRF's bij volwassenen met een VB evalueerde. Hoewel krachttraining effectief blijkt te zijn voor het verlagen van CVRF's in de algemene bevolking, blijft het effect bij volwassenen met een VB onbekend.

We hebben een herhaalde tijdsreeksstudie ontworpen met één studiegroep. Volwassenen met milde tot matige VB en ten minste twee CVRF's kwamen in aanmerking voor deelname. Na een periode van 12 weken met drie herhaalde metingen, voltooiden de deelnemers de 24 weken durende PRET-interventie, waarna alle metingen opnieuw werden uitgevoerd. Na een follow-up periode van 12 weken werden de laatste metingen uitgevoerd. Hiërarchische multi-level regressiemodellen, gecorrigeerd voor mogelijke

verstorende factoren, werden gebruikt om het effect van de PRET-interventie en veranderingen na de 12 weken follow-up te evalueren.

De resultaten van de PRET-studie worden gepresenteerd in de hoofdstukken 5 en 6. Primaire uitkomsten (hoofdstuk 5) zijn HbA1c, SBP, LDL en WHR. Bij de secundaire uitkomsten (hoofdstuk 6) is gekeken naar lichamelijke fitheid, lichaamssamenstelling, sarcopenie, ADL, vallen en probleemgedrag.

**Hoofdstuk 4: Meten van spiermassa bij volwassenen met een VB**

Dit hoofdstuk beschrijft de constructvaliditeit en intra-beoordelaarsbetrouwbaarheid van de kuitomtrek als een vervangende maat voor spiermassa bij volwassenen met een VB. In vergelijking met bio-elektrische impedantieanalyse (BIA) is kuitomtrek een goedkopere en meer toegankelijke methode voor volwassenen met een VB. We analyseerden de gegevens van 36 deelnemers van de PRET-studie. Pearson's correlaties toonden een zwakke associatie tussen kuitomtrek en skeletale spiermassa (SMM), en matige correlaties met segmentale spiermassa (SegMM) en skeletale spierindex (SMI). De intra-beoordelaarsbetrouwbaarheid van kuitomtrek was uitstekend.

Hoewel de kuitomtrekmetingen zeer betrouwbaar zijn binnen één beoordelaar, is de validiteit in het schatten van spiermassa in vergelijking met BIA beperkt. Kuitomtrek kan dienen als een ruwe indicator van spiermassa wanneer andere methoden niet beschikbaar zijn. Vanwege de strikte inclusiecriteria voor CVRF's in de PRET-studie kunnen deze bevindingen niet worden gegeneraliseerd naar alle volwassenen met een VB. Toekomstig onderzoek zou een meer heterogene steekproef moeten omvatten en een betrouwbaardere vergelijkingsmaat, zoals Dual-energy X-ray Absorptiometry (DXA) of Computed Tomography (CT)-scans, moeten gebruiken voor validatie.

**Hoofdstuk 5: Effect van PRET op CVRF's**

Dit hoofdstuk presenteert de resultaten van de primaire uitkomsten van de PRET-studie, zoals geïntroduceerd in hoofdstuk 3. Zesendertig volwassenen met een VB namen deel aan de studie. We gebruikten hiërarchische multilevel lineaire regressiemodellen, gecorrigeerd voor medicijngebruik, om de effecten van de PRET-interventie te onderzoeken. Hoewel er verbeteringen werden waargenomen in HbA1c, SBP, LDL en WHR, vertoonde alleen LDL een statistisch significante verbetering. Na de follow-up periode verslechterden

de waarden van HbA1c, SBP en LDL, terwijl WHR een lichte verbetering vertoonde.

De flexibiliteit van de PRET-interventie stelde trainers in staat om oefeningen aan te passen aan de mogelijkheden van de deelnemers, wat de praktische toepasbaarheid verbeterde. Ondanks het gebruik van motiverende strategieën en individuele ondersteuning, bleef het volhouden een grote uitdaging. Er was een uitvalpercentage van 28%.

De bevindingen van deze studie suggereren dat PRET een veelbelovende interventie is voor het managen van CVRF's bij volwassenen met een VB, met name voor degenen die gemotiveerd zijn en in staat zijn zich aan gestructureerde oefenprogramma's te houden. Verder onderzoek is nodig naar hoe het volhouden van trainingsprogramma's verbeterd kan worden, en om de effectiviteit te evalueren in een grotere steekproef van volwassenen met een VB.

**Hoofdstuk 6: Effect van PRET op secundaire gezondheidsuitkomsten**

Dit hoofdstuk beschrijft de effecten van de PRET-interventie op secundaire uitkomsten, waaronder lichaamssamenstelling, lichamelijke fitheid, sarcopenie, ADL, probleemgedrag en vallen bij volwassenen met een VB.

Er werden statistisch significante verbeteringen waargenomen in het spierkrachtuithoudingsvermogen van de benen en in verschillende domeinen van probleemgedrag (prikkelbaarheid, lusteloosheid, hyperactiviteit en ongepaste spraak). Er werden echter geen veranderingen gevonden in lichaamssamenstelling, andere domeinen van lichamelijke fitheid, ADL of vallen. Het effect van PRET op de aanwezigheid van sarcopenie kon niet onderzocht worden doordatgeen van de deelnemers sarcopenie had bij de start van het onderzoek, waardoor een analyse voor de uitkomst sarcopenie niet mogelijk was.

Gezien de kleine steekproef en het feit dat deelnemers niet specifiek waren geïncludeerd op basis van de aanwezigheid van de gemeten uitkomsten, geven deze bevindingen de potentie weer voor de PRET-interventie. De interventie heeft waardevolle positieve effecten op meerdere gezondheidscomponenten bij volwassenen met een VB.

**Hoofdstuk 7: Algemene discussie**

Dit proefschrift toont aan dat de PRET-interventie CVRF's kan verbeteren bij volwassenen met een VB. We vonden een significante verlaging van LDL-cholesterol en verbeteringen in het spierkrachtuithoudingsvermogen van de benen en probleemgedrag. De veranderingen in lichaamssamenstelling waren echter minimaal, en er werden geen significante effecten gevonden voor andere lichamelijke fitheidsmaten, ADL of vallen. Het volhouden van de interventie bleef een uitdaging, met een uitvalpercentage van 28%, ondanks verschillende maatregelen om motivatie en toegankelijkheid te verbeteren.

Beperkingen van de PRET-studie waren onder andere een kleine, geselecteerde steekproef, wat de statistische power en generaliseerbaarheid beperkt. Daarnaast kan het gebrek aan verandering in lichaamssamenstelling mogelijk worden verklaard door de relatief korte interventieduur, de lage trainingsfrequentie van twee keer per week, het ontbreken van een dieet en mogelijk hoge niveaus van sedentair gedrag (zitten, liggen, slapen) buiten de training om. Rapportage door begeleiding van fysieke activiteit beperkte de betrouwbaarheid van deze gegevens waardoor fysieke activiteit niet als level in de regressiemodellen toegevoegd kon worden.

Toekomstig onderzoek zou grotere en meer diverse steekproeven moeten includeren, objectieve maten voor fysieke activiteit en sedentair gedrag moeten gebruiken, en multifactoriële interventies moeten overwegen die fysieke activiteit combineren met een dieet. Voor de praktijk biedt de PRET-interventie een haalbaar uitgangspunt voor krachttraining bij volwassenen met een VB. Optimale resultaten vereisen een multidisciplinaire benadering met betrokkenheid van begeleiders, familie en andere zorgprofessionals om de motivatie om het programma vol te houden te vergroten. Beleidsmakers zouden de ontwikkeling van motiverende en creatieve vaardigheden van zorgprofessionals moeten ondersteunen om adequaat in te spelen op de diverse behoeften van deze populatie.

Concluderend kan PRET de cardiovasculaire gezondheid verbeteren bij volwassenen met een VB. Om de voordelen volledig te benutten zijn therapietrouw en een multidisciplinaire benadering essentieel.

# Appendices

# Appendix 2.1

## PRISMA checklist

| Section and topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review. | Title page |
| **ABSTRACT** | | | |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. | Title page |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | Page 1 manuscript |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | Page 2 manuscript |
| **METHODS** | | | |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | Page 2 manuscript |
| Information sources | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | Page 3 manuscript |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | Page 3 manuscript |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | Pages 2–3 manuscript |
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | Page 4 manuscript |

| Section and topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| Data items | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | Page 4 manuscript |
| | 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | Page 4 manuscript |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | Page 4 manuscript |
| Effect measures | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | Pages 4–5 manuscript |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | Pages 4–5 manuscript |
| | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | Pages 4–5 manuscript |
| | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | Pages 4–5 manuscript |
| | 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | Pages 4–5 manuscript |
| | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | Pages 4–5 manuscript |
| | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | Pages 4–5 manuscript |

| Section and topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | Page 4 manuscript |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | Page 4 manuscript |
| **RESULTS** | | | |
| Study selection | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | Page 5 manuscript |
| | 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | Appendix 2 |
| Study characteristics | 17 | Cite each included study and present its characteristics. | Appendix 1 |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | Figures 2–5 |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | Figures 2–5 |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | Pages 6–9 manuscript |
| | 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | Figures 2–5 Appendix 3 |
| | 20c | Present results of all investigations of possible causes of heterogeneity among study results. | Figures 2–5 Appendix 3 |
| | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | Pages 6–9 manuscript |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | Appendix 4 |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | Table 1 |

| Section and topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| **DISCUSSION** | | | |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | Page 11 manuscript |
| | 23b | Discuss any limitations of the evidence included in the review. | Pages 11–12 manuscript |
| | 23c | Discuss any limitations of the review processes used. | Pages 11–12 manuscript |
| | 23d | Discuss implications of the results for practice, policy, and future research. | Pages 12–13 manuscript |
| **OTHER INFORMATION** | | | |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | Page 2 manuscript |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | Page 2 manuscript |
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol. | Page 4 and 11 manuscript |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | Page 13 manuscript |
| Competing interests | 26 | Declare any competing interests of review authors. | Page 13 manuscript |
| Availability of data, code and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | NR |

*From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

# Appendix 2.2

## Search strategy

*Results search 29-11-2019*

| Platform | Records | Records after duplicates removed |
|---|---|---|
| Embase.com | 3,933 | 3,872 |
| Medline Ovid | 2,594 | 431 |
| SportDiscuss EBSCOhost | 981 | 411 |
| Cochrane CENTRAL | 2,928 | 850 |
| **Total** | **10,436** | **5,564** |

*Results search update 21-11-2023*

| Platform | Records | Records after duplicates removed |
|---|---|---|
| Embase.com | 6,098 | 6,007 |
| Ovid | 3,781 | 572 |
| SportDiscuss EBSCOhost | 1,428 | 619 |
| Wiley | 4,717 | 1,756 |
| **Total** | **16,024** | **8,954** |

*Manually deleted abstracts from trial registries.
No other database limits were used than those specified in the search strategies.
New references: 3,474.

### *Embase.com*

('resistance training'/exp OR (((resistance OR strength OR weight-bearing OR weightbearing OR weight-lifting OR weightlifting) NEAR/6 (training OR exercise))):ab,ti) AND ('elevated blood pressure'/exp OR 'diabetes mellitus'/exp OR 'diabetic patient'/de OR 'obesity'/exp OR 'hyperlipidemia'/exp OR 'cardiovascular risk'/exp OR 'glycosylated hemoglobin'/de OR 'glucose blood level'/exp OR 'systolic blood pressure'/exp OR 'diastolic blood pressure'/exp OR 'high density lipoprotein cholesterol'/de OR 'low density lipoprotein cholesterol'/de OR 'high density lipoprotein'/de OR 'low density lipoprotein'/de OR 'lipid blood level'/de OR 'triacylglycerol blood level'/de OR 'cholesterol blood level'/de OR 'waist hip ratio'/de OR 'metabolic syndrome X'/de OR 'insulin response'/exp OR (hypertensi* OR diabet* OR obes* OR hyperlipid* OR hypercholesterol* OR hypertriglycerid* OR ((cardiovascul* OR cardiometabol*) NEAR/3 risk*) OR (hemoglobin NEAR/3 (glycosylate* OR A1c)) OR ((glucose OR triacylglyce* OR triglyce* OR cholesterol* OR lipo-

protein*) NEAR/3 (blood OR plasma*)) OR blood-pressur* OR ((systolic* OR disatiolic) NEAR/3 pressure*) OR high-density-lipoprotein* OR low-density-lipoprotein* OR hdl OR ldl OR (waist NEAR/3 hip) OR (metabol* NEAR/3 syndrome*) OR prediabet* OR (insulin* NEAR/3 (response* OR resistance* OR depend* OR sensitiv*))):ab,ti) AND ('Controlled clinical trial'/exp OR 'Crossover procedure'/de OR 'Double-blind procedure'/de OR 'Single-blind procedure'/de OR (random* OR factorial* OR crossover* OR (cross NEXT/1 over*) OR placebo* OR ((doubl* OR singl*) NEXT/1 blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups):ab,ti,kw) NOT ([animals]/lim NOT [humans]/lim)

***Medline Ovid***

(Resistance Training / OR (((resistance OR strength OR weight-bearing OR weightbearing OR weight-lifting OR weightlifting) ADJ6 (training OR exercise))).ab,ti.) AND (exp Hypertension/ OR exp Diabetes Mellitus/ OR Obesity/ OR exp Hyperlipidemias/ OR Glycated Hemoglobin A/ OR glucose /bl OR Cholesterol, HDL/ OR Cholesterol, LDL/ OR Lipoproteins, HDL/ OR Lipoproteins, LDL/ OR lipid /bl OR Triglycerides /bl OR cholesterol /bl OR Waist-Hip Ratio/ OR Metabolic Syndrome/ OR Insulin Resistance / OR (hypertensi* OR diabet* OR obes* OR hyperlipid* OR hypercholesterol* OR hypertriglycerid* OR ((cardiovascul* OR cardiometabol*) ADJ3 risk*) OR (hemoglobin ADJ3 (glycosylate* OR A1c)) OR ((glucose OR triacylglyce* OR triglyce* OR cholesterol* OR lipoprotein*) ADJ3 (blood OR plasma*)) OR blood-pressur* OR ((systolic* OR disatiolic) ADJ3 pressure*) OR high-density-lipoprotein* OR low-density-lipoprotein* OR hdl OR ldl OR (waist ADJ3 hip) OR (metabol* ADJ3 syndrome*) OR prediabet* OR (insulin* ADJ3 (response* OR resistance* OR depend* OR sensitiv*))).ab,ti.) AND (Exp Controlled clinical trial/ OR "Double-Blind Method"/ OR "Single-Blind Method"/ OR "Random Allocation"/ OR (random* OR factorial* OR crossover* OR cross over* OR placebo* OR ((doubl* OR singl*) ADJ blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups).ab,ti,kf.) NOT (exp Animals/ NOT Humans/)

***SportDiscuss EBSCOhost***

(TI (((resistance OR strength OR weight-bearing OR weightbearing) N6 (training OR exercise))) OR AB (((resistance OR strength OR weight-bearing OR weightbearing) N6 (training OR exercise)))) AND (TI (hypertensi* OR diabet* OR obes* OR hyperlipid* OR hypercholesterol* OR hypertriglyceri d* OR ((cardiovascul* OR cardiometabol*) N3 risk*) OR (hemoglobin N3 (glycosylate* OR A1c)) OR ((glucose OR triacylglyce* OR triglyce* OR cholesterol* OR lipoprotein*) N3 (blood OR plasma*)) OR blood-pressur* OR high-density-lipoprotein* OR low-density-lipoprotein* OR hdl OR ldl OR (waist N3 hip) OR (metabol* N3 syndrome*) OR prediabet* OR (insulin* N3 (response* OR resistance* OR depend* OR sensitiv*))) OR AB (hypertensi* OR diabet* OR obes* OR hyperlipid* OR hypercholesterol* OR hypertriglyceri d* OR ((cardiovascul* OR cardiometabol*) N3 risk*) OR (hemoglobin N3 (glycosylate* OR A1c)) OR ((glucose OR triacylglyce* OR triglyce* OR cholesterol* OR lipoprotein*) N3 (blood OR plasma*)) OR blood-pressur* OR high-density-lipoprotein* OR low-density-lipoprotein* OR hdl OR ldl OR (waist N3 hip) OR (metabol* N3 syndrome*) OR prediabet* OR (insulin* N3 (response* OR resistance* OR depend* OR sensitiv*)))) AND (TI (random* OR factorial* OR crossover* OR (cross W1 over*) OR placebo* OR ((doubl* OR singl*) W1 blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups) OR AB (random* OR factorial* OR crossover* OR (cross W1 over*) OR placebo* OR ((doubl* OR singl*) W1 blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups))

*Cochrane CENTRAL*

((((resistance OR strength OR weight-bearing OR weightbearing) NEAR/6 (training OR exercise))):ab,ti) AND ((hypertensi* OR diabet* OR obes* OR hyperlipid* OR hypercholesterol* OR hypertriglyceri d* OR ((cardiovascul* OR cardiometabol*) NEAR/3 risk*) OR (hemoglobin NEAR/3 (glycosylate* OR A1c)) OR ((glucose OR triacylglyce* OR triglyce* OR cholesterol* OR lipoprotein*) NEAR/3 (blood OR plasma*)) OR blood-pressur* OR high-density-lipoprotein* OR low-density-lipoprotein* OR hdl OR ldl OR (waist NEAR/3 hip) OR (metabol* NEAR/3 syndrome*) OR prediabet* OR (insulin* NEAR/3 (response* OR resistance* OR depend* OR sensitiv*))):ab,ti)

# Appendix 2.3

## Excluded articles

| Author | Year | Title | Reason for exclusion |
|---|---|---|---|
| Abrahin et al. | 2022 | Inter-individual variations in response to aerobic and resistance training in hypertensive older adults | Intervention not of interest |
| Almenning et al. | 2015 | Effects of high intensity interval training and strength training on metabolic, cardiovascular and hormonal outcomes in women with polycystic ovary syndrome: A pilot study | Population not of interest |
| Alvarez et al. | 2012 | Effect of sprint interval training and resistance exercise on metabolic markers in overweight women | Intervention not of interest |
| An et al. | 2005 | The Effects of Aerobic Training Versus Resistance Training in Non-obese Type 2 Diabetics | Language |
| Atashak et al. | 2016 | Cardiovascular risk factors adaptation to concurrent training in overweight sedentary middle-aged men | Language |
| Banitalebi et al. | 2023 | Resistance Band Exercise: An Effective Strategy to Reverse Cardiometabolic Disorders in Women With Osteosarcopenic Obesity | No relevant outcome |
| Barcellos et al. | 2012 | Effects of exercise on kidney function among non-diabetic patients with hypertension and renal disease: Randomized controlled trial | Population not of interest |
| Barzegari et al. | 2014 | Effects of 8 weeks resistance training on plasma vaspin and lipid profile levels in adult men with type 2 diabetes | Publication type |
| Bavaresco et al. | 2023 | Impact of dynamic explosive resistance exercise with elastic bands on pulse pressure in hypertensive older adults: a randomized crossover study | Intervention not of interest |
| Berro et al. | 2019 | Effects of 12 months of resistance training vs. endurance training on bone mineral density, hip geometry indices and trabecular bone score in a group of young overweight women | Publication type |
| Bila et al. | 2023 | Body fat, cardiovascular risk factors and polymorphism in the FTO gene: randomized clinical trial and different physical exercise for adolescents | Population not of interest |
| Bittel et al. | 2020 | A single bout of resistance exercise improves postprandial lipid metabolism in overweight/obese men with prediabetes | Study design |
| Botton et al. | 2018 | Resistance training improves neuromuscular health in the elderly with type 2 diabetes: A randomised clinical trial | Intervention not of interest |

| Author | Year | Title | Reason for exclusion |
|---|---|---|---|
| Bouchonville et al. | 2014 | Weight loss, exercise or both and cardiometabolic risk factors in obese older adults: Results of a randomized controlled trial | Intervention not of interest |
| Boule et al. | 2013 | Does metformin modify the effect on glycaemic control of aerobic exercise, resistance exercise or both? | No relevant outcome |
| Brooks et al. | 2007 | Strength training improves muscle quality and insulin sensitivity in Hispanic older adults with type 2 diabetes | Intervention not of interest |
| Byrkjeland et al. | 2017 | Reduced endothelial activation after exercise is associated with improved HbA1c in patients with type 2 diabetes and coronary artery disease | Population not of interest |
| Carlson et al. | 2016 | The efficacy of isometric resistance training utilizing handgrip exercise for blood pressure management: A randomized trial | Intervention not of interest |
| Cavalcante et al. | 2018 | Effects of Different Resistance Training Frequencies on Fat in Overweight/Obese Older Women | No relevant outcome |
| Cheung et al. | 2009 | A pilot randomised controlled trial of resistance exercise bands in the management of sedentary subjects with type 2 diabetes | Intervention not of interest |
| Christensen et al. | 2019 | Effect of Aerobic and Resistance Exercise on Cardiac Adipose Tissues: Secondary Analyses from a Randomized Clinical Trial | No relevant outcome |
| Church et al. | 2010 | Effects of aerobic and resistance training on hemoglobin A1c levels in patients with type 2 diabetes: A randomized controlled trial | Intervention not of interest |
| Cohen et al. | 2008 | Improved endothelial function following a 14-month resistance exercise training program in adults with type 2 diabetes | Intervention not of interest |
| Cohen et al. | 2008 | Improved endothelial function following a 14-month resistance exercise training program in adults with type 2 diabetes | Publication type |
| Conceicao et al. | 2013 | Sixteen weeks of resistance training can decrease the risk of metabolic syndrome in healthy postmenopausal women | Population not of interest |
| Correa et al. | 2014 | Effects of high and low volume of strength training on muscle strength, muscle volume and lipid profile in postmenopausal women | Population not of interest |
| Correa et al. | 2021 | Low-load resistance training with blood flow restriction prevent renal function decline: The role of the redox balance, angiotensin 1–7 and vasopressin | Population not of interest |
| Croymans et al. | 2014 | Effects of resistance training on central blood pressure in obese young men | Population not of interest |
| Croymans et al. | 2010 | Randomized controlled trial using resistance training to improve arterial function in overweight, young adult males | Population not of interest |

| Author | Year | Title | Reason for exclusion |
|---|---|---|---|
| Cunha et al. | 2019 | Comparision of Low and High Volume of Resistance Training on Body Fat and Blood Biomarkers in Untrained Older Women: A Randomized Clinical Trial | Population not of interest |
| Cunha et al. | 2019 | Resistance training performed with single-set is sufficient to reduce cardiovascular risk factors in untrained older women: The randomized clinical trial. Active Aging Longitudinal Study | Population not of interest |
| Dantas et al. | 2016 | Effect of strength training on oxidative stress and the correlation of the same with forearm vasodilatation and blood pressure of hypertensive elderly women: A randomized clinical trial | Intervention not of interest |
| Davidson et al. | 2009 | Effects of exercise modality on insulin resistance and functional limitation in older adults: A randomized controlled trial | Intervention not of interest |
| Davis et al. | 2022 | Comparison of time-matched aerobic, resistance or combined exercise training in women living with obesity: a protocol for a pilot randomised controlled trial-the EXOFFIT (Exercise for Obesity in Females to increase Fitness) study | Publication type |
| de Oliveira Carpes et al. | 2021 | Sex Differences in Post-exercise Hypotension, Ambulatory Blood Pressure Variability, and Endothelial Function After a Power Training Session in Older Adults | Intervention not of interest |
| Diaz-Vegas et al. | 2018 | Eccentric resistance training reduces both non-response to exercise and cardiovascular risk factors in adult with overweight or obesity | Intervention not of interest |
| Dobrosielski et al. | 2012 | Effect of exercise on blood pressure in type 2 diabetes: A randomized controlled trial | Intervention not of interest |
| Dos Santos et al. | 2014 | Acute and chronic cardiovascular response to 16 weeks of combined eccentric or traditional resistance and aerobic training in elderly hypertensive women: a randomized controlled trial | No relevant outcome |
| Dunstan et al. | 2008 | Aerobic exercise and resistance training for the management of type 2 diabetes mellitus | Intervention not of interest |
| Dunstan et al. | 2006 | Community center-based resistance training for the maintenance of glycemic control in adults with type 2 diabetes | Intervention not of interest |
| Dunstan et al. | 2002 | High-intensity resistance training improves glycemic control in older patients with type 2 diabetes | Intervention not of interest |
| Dunstan et al. | 2008 | Aerobic exercise and resistance training for the management of type 2 diabetes mellitus | Publication type |
| Eatemady-Boroujeni et al. | 2014 | Comparison of the effects of 8-weeks aerobic training and resistance training on lipid profile in patients with diabetes type 2 | Language |

| Author | Year | Title | Reason for exclusion |
|---|---|---|---|
| Eriksson et al. | 1998 | Aerobic endurance exercise or circuit-type resistance training for individuals with impaired glucose tolerance? | Population not of interest |
| Fecchio et al. | 2023 | Effects of dynamic, isometric and combined resistance training on blood pressure and its mechanisms in hypertensive men | Intervention not of interest |
| Galdelha et al. | 2016 | Effects of resistance training on sarcopenic obesity index in older women: A randomized controlled trial | Population not of interest |
| Gelecek et al. | 2012 | The Effects of Resistance Training on Cardiovascular Disease Risk Factors in Postmenopausal Women: A Randomized-Controlled Trial | Population not of interest |
| Ghorbanian et al. | 2017 | Effect of progressive resistance training on serum lipocalin-2 and lipid profiles in in-active men | Language |
| Giessing et al. | 2022 | The effects of adding high-intensity of effort resistance training to routine care in persons with type II diabetes: An exploratory randomized parallel-group time-series study | No relevant outcome |
| Gomez-Tomas et al. | 2018 | Effect of a 1-year elastic band resistance exercise program on cardiovascular risk profile in postmenopausal women | Intervention not of interest |
| Guelfi et al. | 2013 | Beneficial effects of 12 weeks of aerobic compared with resistance exercise training on perceived appetite in previously sedentary overweight and obese men | No relevant outcome |
| Hangping et al. | 2019 | The impact on glycemic control through progressive resistance training with bioDensityTM in Chinese elderly patients with type 2 diabetes: The PReTTy2 (Progressive Resistance Training in Type 2 Diabetes) Trial | Intervention not of interest |
| He et al. | 2022 | β-cell function protection and metabolic effects of 6-month resistance training and aerobic training in prediabetic subjects: A randomized, multicenter controlled trial | Population not of interest |
| Heffernan et al. | 2013 | Resistance exercise training reduces arterial reservoir pressure in older adults with prehypertension and hypertension | Population not of interest |
| Ho et al. | 2012 | Resistance, aerobic, and combination training on vascular function in overweight and obese adults | Intervention not of interest |
| Ho et al. | 2012 | The effect of 12 weeks of aerobic, resistance or combination exercise training on cardiovascular risk factors in the overweight and obese in a randomized trial | Intervention not of interest |
| Hollings et al. | 2022 | High Intensity Power Training Improves Ambulatory Blood Pressure for Hypertensive Older Adults With Type 2 Diabetes: Results From the GREAT2DO Randomised Controlled Trial | Publication type |

| Author | Year | Title | Reason for exclusion |
|---|---|---|---|
| Honkola et al. | 1997 | Resistance training improves the metabolic profile in individuals with type 2 diabetes | Intervention not of interest |
| Hsieh et al. | 2018 | Resistance Training Improves Muscle Function and Cardiometabolic Risks But Not Quality of Life in Older People With Type 2 Diabetes Mellitus: A Randomized Controlled Trial | Intervention not of interest |
| Huang et al. | 2017 | Body composition influenced by progressive elastic band resistance exercise of sarcopenic obesity elderly women: a pilot randomized controlled trial | Population not of interest |
| Jang et al. | 2019 | Effects of aerobic and resistance exercises on circulating apelin-12 and apelin-36 concentrations in obese middle-aged women: A randomized controlled trial | No relevant outcome |
| Jennings et al. | 2009 | The effect of exercise training on resting metabolic rate in type 2 diabetes mellitus | No relevant outcome |
| Jorge et al. | 2011 | The effects of aerobic, resistance, and combined exercise on metabolic control, inflammatory markers, adipocytokines, and muscle insulin signaling in patients with type 2 diabetes mellitus | Intervention not of interest |
| Jose et al. | 2007 | Effect of low intensity resistance training on lipid profiles among middle aged Indian men with BMI>27 | No relevant outcome |
| Jose et al. | 2021 | Effect of weight training on triglycerides among middle aged overweight men | No relevant outcome |
| Kadoglou et al. | 2012 | The effects of resistance training on ApoB/ ApoA-I ratio, Lp(a) and inflammatory markers in patients with type 2 diabetes | Intervention not of interest |
| Kambic et al. | 2019 | Blood flow restriction resistance exercise improves muscle strength and hemodynamics, but not vascular function in coronary artery disease patients: A pilot randomized controlled trial | Population not of interest |
| Karami et al. | 2022 | The effect of different intensity circuit resistance training on gremlin-1, Macrophage migration inhibitory factor and some cardiovascular risk factors in obese men. | Language |
| Kazemi et al. | 2023 | Effect of resistance training and high-intensity interval training on metabolic parameters and serum level of Sirtuin1 in postmenopausal women with metabolic syndrome: a randomized controlled trial | Population not of interest |
| Kemmler et al. | 2016 | High intensity resistance training methods with and without protein supplementation to fight cardiometabolic risk in middle-aged males: A randomized controlled trial | Population not of interest |
| Kerksick et al. | 2010 | Changes in weight loss, body composition and cardiovascular disease risk after altering macronutrient distributions during a regular exercise program in obese women | Intervention not of interest |

| Author | Year | Title | Reason for exclusion |
|---|---|---|---|
| Kokkinos et al. | 1991 | Strength training does not improve lipoprotein-lipid profiles in men at risk for CHD | Publication type |
| Larose et al. | 2011 | Associations between physical fitness and HbA1c in type 2 diabetes mellitus | Intervention not of interest |
| Liao et al. | 2018 | Effects of elastic band exercise on lean mass and physical capacity in older women with sarcopenic obesity: A randomized controlled trial | No relevant outcome |
| Liao et al. | 2017 | Effects of elastic resistance exercise on body composition and physical capacity in older women with sarcopenic obesity: A CONSORT-compliant prospective randomized controlled trial | No relevant outcome |
| Lovell et al. | 2009 | Strength training improves submaximum cardiovascular performance in older men | Population not of interest |
| Luo et al. | 2023 | Effect of resistance vs. aerobic exercise in pre-diabetes: an RCT | Population not of interest |
| Mahdirejei et al. | 2014 | Effects of an eight-week resistance training on plasma vaspin concentrations, Metabolic parameters levels and physical fitness in patients with type 2 diabetes | Publication type |
| Mavros et al. | 2014 | Reductions in C-reactive protein in older adults with type 2 diabetes are related to improvements in body composition following a randomized controlled trial of resistance training | No relevant outcome |
| Mavros et al. | 2013 | Changes in insulin resistance and HbA1c are related to exercise-mediated changes in body composition in older adults with type 2 diabetes: Interim outcomes from the GREAT2DO trial | Publication type |
| Menezes-Cabral et al. | 2009 | Effects of differerent types of training and life styles on anthropometric and cardiocirculatory markers in aging | Intervention not of interest |
| Miri et al. | 2021 | Effect of resistance training on general health, happiness and its correlation with glycemic control in diabetic men with peripheral neuropathy | Language |
| Mondal et al. | 2021 | Effects of aerobic and resistance exercises on selected physiological biochemical and anthropometric variables among type 2 diabetic patients in dilla, Ethiopia | Intervention not of interest |
| Montrezol et al. | 2014 | Effect of a resistance training period on blood pressure, circulating levels of interleukine-6, quality of life and functional capacities in elderly hypertensive patients | Publication type |
| Mota et al. | 2013 | Acute and chronic effects of resistance exercise on blood pressure in elderly women and the possible influence of ACE I/D polymorphism | No relevant outcome |
| Mota et al. | 2013 | Acute and chronic effects of resistive exercise on blood pressure in hypertensive elderly women | No relevant outcome |

| Author | Year | Title | Reason for exclusion |
|---|---|---|---|
| Nazari et al. | 2016 | Effect of a period circuit resistance training on components ofthe metabolic syndromein females with type II diabetes | Language |
| Nikseresht et al. | 2014 | Effects of nonlinear resistance and aerobic interval training on cytokines and insulin resistance in sedentary men who are obese | Intervention not of interest |
| Nikseresht et al. | 2016 | Detraining-induced alterations in adipokines and cardiometabolic risk factors after nonlinear periodized resistance and aerobic interval training in obese men | Intervention not of interest |
| Nunes et al. | 2016 | Effect of resistance training on muscular strength and indicators of abdominal adiposity, metabolic risk, and inflammation in postmenopausal women: controlled and randomized clinical trial of efficacy of training volume | Population not of interest |
| Nybo et al. | 2010 | High-intensity training versus traditional exercise interventions for promoting health | Population not of interest |
| Oliveira-Dantas et al. | 2020 | Short-Term Resistance Training Improves Cardiac Autonomic Modulation and Blood Pressure in Hypertensive Older Women: A Randomized Controlled Trial | No relevant outcome |
| Ooi et al. | 2021 | A 16-Week Home-Based Progressive Resistance Tube Training Among Older Adults With Type-2 Diabetes Mellitus: Effect on Glycemic Control | Study design |
| Park et al. | 2014 | Effects on training and detraining on physical function, control of diabetes and anthropometrics in type 2 diabetes; a randomized controlled trial | Intervention not of interest |
| Pires et al. | 2020 | Combined Aerobic and Resistance Exercises Evokes Longer Reductions on Ambulatory Blood Pressure in Resistant Hypertension: A Randomized Crossover Trial | Intervention not of interest |
| Polito et al. | 2021 | Twelve weeks of resistance training performed with different number of sets: Effects on maximal strength and resting blood pressure of individuals with hypertension | Intervention not of interest |
| Prabhakaran et al. | 1999 | Effect of 14 weeks of resistance training on lipid profile and body fat percentage in premenopausal women | Population not of interest |
| Punia et al. | 2019 | Effect of 8 weeks body-weight resistance training on high-normal blood pressure and stage 1 hypertension subjects-pilot study to validate the protocol | Intervention not of interest |
| Rahimi et al. | 2020 | Effects of exercise training on serum preptin, undercarboxylated osteocalcin and high molecular weight adiponectin in adults with metabolic syndrome | No relevant outcome |

| Author | Year | Title | Reason for exclusion |
|---|---|---|---|
| Ramirez-Velez et al. | 2016 | High Intensity Interval- vs Resistance or Combined- Training for Improving Cardiometabolic Health in Overweight Adults (Cardiometabolic HIIT-RT Study): Study protocol for a randomised controlled trial | Publication type |
| Raso et al. | 2010 | Moderate resistance training program can reduce triglycerides in elderly women: A randomized controlled trial | Publication type |
| Ribeiro et al. | 2016 | Traditional and pyramidal resistance training systems improve muscle quality and metabolic biomarkers in older women: A randomized crossover study | Population not of interest |
| Ross et al. | 2000 | Reduction in obesity and related comorbid conditions after diet-induced weight loss or exercise-induced weight loss in men: A randomized, controlled trial | Intervention not of interest |
| Rustaden et al. | 2017 | Effects of BodyPump and resistance training with and without a personal trainer on muscle strength and body composition in overweight and obese women—A randomised controlled trial | No relevant outcome |
| Saeidi et al. | 2021 | Differential Effects of Exercise Programs on Neuregulin 4, Body Composition and Cardiometabolic Risk Factors in Men With Obesity | Intervention not of interest |
| Safarzade et al. | 2020 | The effects of circuit resistance training on plasma progranulin level, insulin resistance and body composition in obese men | Population not of interest |
| Saghebjoo et al. | 2012 | Effects of aerobic and resistance training on plasma visfatin levels in overweight women | Language |
| Salmanpour et al. | 2022 | The effect of 8 weeks of combined interval (resistance-interval training) and combined endurance (endurance-resistance training) on plasma levels of adropin and nitric oxide in males with high blood pressure | Intervention not of interest |
| Santos et al. | 2014 | Undulatory physical resistance training program increases maximal strength in elderly type 2 diabetics | No relevant outcome |
| Saremi et al. | 2011 | Effects of twelve-week strength training on serum chemerin, TNF-α and CRP level in subjects with the metabolic syndrome | Language |
| Schroeder et al. | 2019 | Comparative effectiveness of aerobic, resistance, and combined training on cardiovascular disease risk factors: A randomized controlled trial | Intervention not of interest |
| Schroeder et al. | 2015 | Independent and combined effects of aerobic and resistance training on blood pressure (ART-B) | Publication type |
| Seguin-Fowler et al. | 2022 | Improvements and Maintenance of Clinical and Functional Measures among Rural Women: Strong Hearts, Healthy Communities-2. 0 Cluster Randomized Trial | Intervention not of interest |

| Author | Year | Title | Reason for exclusion |
|---|---|---|---|
| Senechal et al. | 2013 | The impact of aerobic and resistance training on hemoglobin a1c and fitness measures in dynapenic-obese with type 2 diabetes: Results from the hart-D study | No relevant outcome |
| Senechal et al. | 2012 | The effects of lifestyle interventions in dynapenic-obese postmenopausal women | Population not of interest |
| Shaw et al. | 2006 | Consequence of resistance training on body composition and coronary artery disease risk | Population not of interest |
| Sheikholeslami-Vatani et al. | 2015 | Advanced glycation end products' response to resistance training in postmenopausal woman with type II diabetes | No relevant outcome |
| Shim et al. | 2017 | The effect of resistance exercise on fitness, blood pressure, and blood lipid of hypertensive middle-aged men | Intervention not of interest |
| Sigal et al. | 2007 | Effects of aerobic training, resistance training, or both on glycemic control in type 2 diabetes: A randomized trial | Intervention not of interest |
| Sillanpaa et al. | 2009 | Body composition, fitness, and metabolic health during strength and endurance training and their combination in middle-aged and older women | Population not of interest |
| Sillanpaa et al. | 2009 | Effects of strength and endurance training on metabolic risk factors in healthy 40-65-year-old men | Population not of interest |
| Simpson et al. | 2015 | Graded Resistance Exercise And Type 2 Diabetes in Older adults (The GREAT2DO study): Methods and baseline cohort characteristics of a randomized controlled trial | Intervention not of interest |
| Smutok et al. | 1994 | Effects of exercise training modality on glucose tolerance in men with abnormal glucose regulation | No relevant outcome |
| Soori et al. | 2011 | Effects of water-based endurance training, resistance training, and combined water and resistance training programs on visfatin and ICAM-1 levels in sedentary obese women | Language |
| Stegen et al. | 2015 | Aerobic and resistance training do not influence plasma carnosinase content or activity in type 2 diabetes | Intervention not of interest |
| Stensvold et al. | 2009 | Aerobic interval training versus strength training as a treatment for the metabolic syndrome | No relevant outcome |
| Stewart et al. | 2006 | Exercise effects on cardiac size and left ventricular diastolic function: Relationships to changes in fitness, fatness, blood pressure and insulin resistance | Intervention not of interest |
| Subasi et al. | 2012 | Effects of two different exercise trainings on plasma homocysteine levels and other cardiovascular disease risks | Population not of interest |
| Sukala et al. | 2012 | South Pacific Islanders resist type 2 diabetes: Comparison of aerobic and resistance training | Intervention not of interest |
| Sun et al. | 2010 | Qigong therapy vs progressive resistance exercise in patients with type 2 diabetes: A pilot study | Publication type |

| Author | Year | Title | Reason for exclusion |
|---|---|---|---|
| Teixeira et al. | 2010 | The effect of aerobic versus strength-based training on high-sensitivity C-reactive protein in older adults | Intervention not of interest |
| Theodorou et al. | 2016 | Aerobic, resistance and combined training and detraining on body composition, muscle strength, lipid profile and inflammation in coronary artery disease patients | Population not of interest |
| Tomeleri et al. | 2018 | Resistance training reduces metabolic syndrome and inflammatory markers in older women: A randomized controlled trial | Population not of interest |
| Tseng et al. | 2013 | A simple method for increasing levels of high-density lipoprotein cholesterol: A pilot study of combination aerobic- and resistance-exercise training | Intervention not of interest |
| Venojärvi et al. | 2013 | 12 Weeks' aerobic and resistance training without dietary intervention did not influence oxidative stress but aerobic training decreased atherogenic index in middle-aged men with impaired glucose regulation | No relevant outcome |
| Venturini et al. | 2018 | Resistant training improves fasting glucose and resistance insulin in elderly women | Publication type |
| Vikram et al. | 2022 | Randomized controlled trial to compare the impact of resistance band exercises on change in skeletal muscle mass and function in individuals with sarcopenic obesity | Publication type |
| Vincent et al. | 2006 | Resistance training lowers exercise-induced oxidative stress and homocysteine levels in overweight and obese older adults | No relevant outcome |
| Vincent et al. | 2003 | Homocysteine, and Lipoprotein Levels Following Resistance Training in Older Adults | Population not of interest |
| Vincent et al. | 2003 | Strength training and hemodynamic responses to exercise | Population not of interest |
| Wasenius et al. | 2015 | Non-structured leisure-time physical activity predicts waist circumference response to nordic walking in prediabetes | Publication type |
| Xie et al. | 2016 | Effects of exenatide combined with different modes of exercise on peak oxygen consumption in patients with type 2 diabetes and obesity | Intervention not of interest |
| Yaacob et al. | 2016 | Dumbbells and ankle-wrist weight training leads to changes in body composition and anthropometric parameters with potential cardiovascular disease risk reduction | Intervention not of interest |
| Yang et al. | 2017 | Finding the Optimal volume and intensity of Resistance Training Exercise for Type 2 Diabetes: The FORTE Study, a Randomized Trial | Intervention not of interest |
| Yang et al. | 2020 | Effect of resistance exercise on peripheral neuropathy in Type 2 diabetes mellitus | Language |
| Zapata-Lamana et al. | 2015 | Resistance exercise improves serum lipids in adult women | Intervention not of interest |

# Appendix 2.4

## Study characteristics

| Study | Country | Population | Outcome measures reported | N in analysis | % Male | N RT group | Mean age / Range | Duration | Training intensity | Description intervention |
|---|---|---|---|---|---|---|---|---|---|---|
| Abdedlaal et al. 2015 | Egypt | DM2, Hypertension, Obese | SBP | 39 | 44 | 20 | 52.10 | 12 weeks | Moderate | 3x/wk. 10 exercises, 2–3 sets, 10 repetitions, 60-75% of 1RM. |
| Ahmadizad et al. 2014 | Iran | Obese | WHR | 16 | 100 | 8 | 23.4 | 8 weeks | Progressive | 3x/wk for 50 min. 7 excercises, 2 sets, 8-18 repetitions, 50-85% of 1RM. Week 1–2: 1 set, 10 repetitions, 50% 1RM. Week 3: 2 sets, 18 repetitions, 50% 1RM. Week 4: 2 sets, 16 repetitions, 60% 1RM. Week 5: 2 sets, 14 repetitions, 65% 1RM. Week 6: 2 sets, 12 repetitions, 70% 1RM. Week 7: 2 sets, 10 repetitions, 75% 1RM. Week 8: 2 sets, 8 repetitions, 85% 1RM. |
| Al Ozairi et al. 2023 | Kuwait | DM2 | HbA1c, LDL | 120 | 62 | 64 | 60.2 | 24 weeks | Moderate | 3x/wk. 7 exercises, 2–3 sets, 15–20 repetitions. Homebased resistance exercise. |
| Amanat et al. 2020 | Iran | METS, Obese | SBP, LDL, WHR | 28 | 0 | 14 | 54.5 | 12 weeks | Moderate | 3x/wk for 60 min. 10 exercises, 2 sets, 60–80% of 1RM. |
| Ambelu et al. 2023 | Ethiopia | DM2 | SBP | 20 | 72.5 | 10 | 43,8 | 12 weeks | Moderate | 60 min. 10 exercises, 3 sets, 10 repetitions, 70–75% of 1RM. Circuit resistance training. |
| Ataeinosrat et al. 2022 | Iran | Obese | LDL | 44 | 100 | 11 | 27.5 | 12 weeks | High | 70 min. 10 exercises, 3 sets, 10 repetitions, 80% of 1RM. Resistance training using machines (Hoist Equipment, San Diego, USA) |
| Ataeinosrat et al. 2022 | Iran | Obese | LDL | 44 | 100 | 11 | 27.5 | 12 weeks | Low | 70 min. 10 exercises, 3 sets, 20 repetitions, 40% of 1RM. Resistance training using machines (Hoist Equipment, San Diego, USA) |
| Ataeinosrat et al. 2022 | Iran | Obese | LDL | 44 | 100 | 11 | 27.5 | 12 weeks | Moderate | 70 min. 10 exercises, 3 sets, 13 repetitions, 60% of 1RM. Resistance training using machines (Hoist Equipment, San Diego, USA) |

| Study | Country | Population | Outcome measures reported | N in analysis | % Male | N RT group | Mean age / Range | Duration | Training intensity | Description intervention |
|---|---|---|---|---|---|---|---|---|---|---|
| Azamian et al. 2022 | Iran | Obese | LDL, WHR | 28 | 0 | 14 | 74.04 | 12 weeks | Moderate | 3x/wk for 55 min. Exercises for arms, shoulder, abdomen, back, and legs, 3 sets, 8–12 repetitions. Resistance exercises using elastic bands (TheraBand, The Hygenic Corporation, Akron, OH, USA) |
| Baldi et al. 2003 | New Zealand | DM2 | HbA1c | 18 | 100 | 9 | 48.30 | 10 weeks | Moderate | 3x/wk. 1–2 sets, 12 repetitions, 70–75% of 1RM. Circuit strength training with ten exercises for all large muscle groups. |
| Boeno et al. 2020 | Brazil | Hypertension | SBP, LDL | 27 | 45.2 | 15 | 45.5 | 12 weeks | Progressive | 3x/wk. 9 exercises, 2–3 sets, 8–20 repetitions. 15–20 repetitions in week 1–4: 10–15 repetitions in week 4–8: 8–12 repetitions in week 8-12. Resistance training in institution's exercise facility. |
| Castaneda et al. 2002 | USA | DM2 | HbA1c, SBP, LDL | 60 | 35.5 | 29 | 66.00 | 14 weeks | Progressive | 3x/wk for 45 min. 5 exercises, 3 sets, 8 repetitions, 60–80% of 1RM. Resistance training using Keiser Sports Health Equipment, Fresno, CA. |
| Chien et al. 2022 | Taiwan | DM2 | HbA1c, LDL | 37 | 17.5 | 19 | 67.45 | 12 weeks | Low | 3x/wk for 30 min. 5 exercises, 3 sets, 20 repetitions. Homebased resistance training with sandbags. |
| Costa et al. 2011 | Brazil | Obese | LDL | 28 | 0 | 13 | 33.57 | 9 weeks | Low | 3x/wk for 60 min. 1–3 sets, 15–20 repetitions, 40–60% of 1RM. 5 mesocycles of 5 sessions. Cycle 1: 1 set, 15 repetitions. Cycle 2: 2 sets, 15 repetitions. Cycle 3: 2 sets, 18 repetitions. Cycle 4: 2 sets, 20 repetitions. Cycle 5: 3 sets, 20 repetitions. |
| Silva et al. 2020 | Brazil | DM2 | LDL | 32 | 0 | 14 | 67.78 | 16 weeks | Moderate | 2x/wk for 75 min. 9 exercises, 3 sets, 8–12 repetitions, 60–70% of 1RM. |
| Farzanegi 2022 | Iran | DM2 | LDL | 28 | 0 | 14 | 51.42 | 8 weeks | Low | 3x/wk for 40 min. 5 exercises, 40–50% of 1RM. Resistance training using elastic bands. |

| Study | Country | Population | Outcome measures reported | N in analysis | % Male | N RT group | Mean age / Range | Duration | Training intensity | Description intervention |
|---|---|---|---|---|---|---|---|---|---|---|
| Fenkci et al. 2006 | Turkey | Obese | SBP, LDL, WHR | 34 | 0 | 17 | 43.90 | 12 weeks | Moderate | 3x/wk. 6 exercises, 3 sets, 10 repetitions, 75–80% of 1RM. Resistance training using stationary exercise units (Vectra 4800; Vectra Fitness, Kent, Wash). |
| Franklin et al. 2015 | USA | Obese | SBP, LDL | 18 | 0 | 10 | 30.52 | 8 weeks | Moderate | 2x/wk. 8–10 exercises, 2–3 sets, 70–80% of 1RM. Circuit resistance training using free weights and machines. |
| Gao et al. 2023 | Iran | METS | SBP, LDL | 21 | 100 | 10 | 46.2 | 12 weeks | Progressive | 3x/wk for 45 min. 7 exercises. 2–3 sets, 8-20 repetitions, 40–80% of 1RM. Week 1: 2 sets, 15–20 repetitions, 40–45% 1RM, Week 2: 3 sets, 15–20 repetitions, 45–50% 1RM, Week 3–6: 3 sets, 12–25 repetitions, 50–60% 1RM, Week 7–10: 3 sets, 8–12 repetitions, 65–70% 1RM, Week 11–12: 3 sets, 8–12 repetitions, 70–80% 1RM. Resistance training using weight machines. |
| Gholami et al. 2021 | Iran | DM2 | HbA1c, SBP | 29 | 100 | 15 | 63.48 | 12 weeks | Low | 3x/wk for 90 min. 11 exercises, 1–3 sets, 50–60% of 1RM. Circuit resistance training using free weights and machines. |
| Goncalves et al. 2014 | Brazil | Hypertension | SBP, LDL | 17 | 0 | 7 | 65.89 | 12 weeks | Low | 8 exercises, 2 sets, 15 repetitions, 40% of 1RM. |
| Hameed et al. 2012 | India | DM2 | HbA1c, SBP, LDL | 48 | 72.9 | 24 | 44.65 | 8 weeks | Moderate | 3x/wk. 5 exercises, 3 sets, 10 repetitions, 65–70% of 1RM. Resistance training using weight machines (Body-Solid, Inc., IL, USA). |
| Hernán Jiménez et al. 2011 | Colombia | Obese | LDL, WHR | 14 | NR | 6 | 23.7 | 8 weeks | Moderate | 4x/wk. 8 exercises, 50–80% of 1RM. Resistance exercise using free weights and machines. |
| Herring et al. 2014 | USA | Obese | WHR | 17 | 29.4 | 10 | 24-68 | 12 weeks | Moderate | 3x/wk for 45–60 min. 60% of 1RM. Resistance training 2x/wk at a gym and 1x/wk at home. |

| Study | Country | Population | Outcome measures reported | N in analysis | % Male | N RT group | Mean age / Range | Duration | Training intensity | Description intervention |
|---|---|---|---|---|---|---|---|---|---|---|
| Hooshmand-Moghadam et al. 2021 | Iran | Hypertension | SBP, WHR | 24 | 100 | 12 | 60-70 | 12 weeks | Low | 3x/wk. 9 exercises, 2 sets, 40–60% of 1RM. |
| Jamali et al. 2023 | Iran | Obese | LDL | 26 | 0 | 13 | 39.68 | 8 weeks | Moderate | 3x/wk for 60 min. 8 exercises, 3 sets, 65–70% of 1RM. |
| Jangjo-Borazjani et al. 2023 | Iran | DM2 | LDL | 10 | 0 | 10 | 87.03 | 8 weeks | Moderate | 3x/wk for 65 min. 7 exercises, 3 sets, 10–12 repetitions, 60–80% of 1RM. |
| Kazemi et al. 2023 | Iran | METS | HbA1c, SBP, LDL | 30 | 0 | 15 | 45-65 | 8 weeks | Moderate | 3x/wk. 11 exercises, 3 sets, 8–10 repetitions, 75–80% of 1RM. |
| Kolahdouzi et al. 2019 | Iran | Obese | LDL, WHR | 26 | 100 | 13 | 23.50 | 8 weeks | Moderate | 3x/wk for 60 min. 8 exercises, 2 sets, 8–12 repetitions, 65–85% of 1RM. Circuit training using weight machines. |
| Lee et al. 2022 | Korea | Obese | LDL | 10 | 100 | 10 | 51.20 | 12 weeks | Low | 3x/wk for 60 min. 10 exercises, 3 sets, 15–20 repetitions, 40–50% of 1RM. Circuit resistance training using weight machines and free weights. |
| Levinger et al. 2008 | Australia | Obese, Hyper-cholester-olemia, Hyper-tension | SBP | 29 | 65.5 | 15 | 51.43 | 10 weeks | Moderate | 3x/wk. 7 exercises, 3 sets, 8–20 repetitions, 50–85% of 1RM. |
| Lotfi et al. 2023 | Iran | DM2 | HbA1c, LDL | 20 | 0 | 10 | 49.35 | 8 weeks | Moderate | 3x/wk for 60 min. 9 exercises, 2 sets, 8–10 repetitions, 60–75% of 1RM. Resistance training in university gymnasium. |
| Manning et al. 1991 | USA | Obese | LDL | 22 | 0 | 16 | 36.74 | 12 weeks | Moderate | 3x/wk. 8 exercises, 3 sets, 6–8 repetitions, 60–75% of 1RM. Resistance training using machines and free weight. |
| Montrezol et al. 2014 | Brazil | Hypertension | SBP | 135 | 32.6 | 86 | 68.03 | 16 weeks | Low | 3x/wk for 60 min. 8 exercises, 3 sets, 12 repetitions, 50% of 1RM. Resistance training using Nakagym and Biodelta (São Paulo, SP, Brazil) |

| Study | Country | Population | Outcome measures reported | N in analysis | % Male | N RT group | Mean age / Range | Duration | Training intensity | Description intervention |
|---|---|---|---|---|---|---|---|---|---|---|
| Oliveira et al. 2012 | Brazil | DM2 | HbA1c, LDL, WHR | 22 | 0 | 10 | 53.73 | 12 weeks | Moderate | 3x/wk for 60 min. 7 exercises, 2–4 sets, 10–12 repetitions, 50–80% of 1RM. Circuit resistance training. |
| Olson et al. 2006 | USA | Obese | SBP, LDL | 30 | 0 | 15 | 38.00 | 1 year | Moderate | 2x/wk. 9 exercises, 3 sets, 8–10 repetitions, 75–80% of 1RM. Resistance training using machines and free weights. |
| Piralaiy et al. 2021 | Iran | DM2 | HbA1c, SBP, LDL, WHR | 23 | 100 | 11 | 55.24 | 12 weeks | Moderate | 3x/wk. 9 exercises, 2–3 sets, 8–12 repetitions using weight machines. |
| Plotnikoff et al. 2010 | Canada | DM2 | HbA1c, SBP, LDL, WHR | 48 | 33.3 | 27 | 54.56 | 12 weeks | Progressive | 3x/wk. 8 exercises, 2–3 sets, 8–15 repetitions, 50–85% of 1RM. Home-based resistance training. Week 1: 2 sets, 10–12 repetitions, 50–60% 1RM. Week 2: 3 sets, 10–12 repetitions, 50–60% 1RM. Week 3–8,:3 sets, 10–12 repetitions, 70–80% 1RM. Week 9: 2 sets, 8–10 repetitions, 70% 1RM. Week 10–15: 3 sets, 8–10 repetitions, 70–85% 1RM. Week 16: 2 sets, 8–10 repetitions, 80% of 1RM. |
| Ranasinghe et al. 2021 | Sri Lanka | DM2 | HbA1c, SBP, LDL | 58 | 46.5 | 28 | 50.1 | 12 weeks | High | 2x/wk for 60–75 min. 7 exercises, 3 sets, 8 repetitions. |
| Rashidi et al. 2021 | Iran | Obese | LDL, WHR | 26 | 0 | 13 | 44.72 | 8 weeks | Low | 3x/wk for 60 min. 6 exercises, 3 sets, 10–20 repetitions. Resistance exercise using elastic bands (TheraBand, The Hygenic Corporation, Akron, OH, USA) |
| Roberson et al. 2018 | USA | METS | SBP | 16 | 18.8 | 9 | 71.13 | 12 weeks | Moderate | 3x/wk. 11 exercises, 3 sets, 12 repetitions, 60–70% of 1RM. Circuit training using pneumatic machines (Keiser A420, Keiser Corporation, Fresno, Calif., USA) |
| Rostamizadeh et al. 2022 | Iran | Obese | WHR | 30 | 100 | 15 | 21.00 | 24 weeks | High | 3x/wk for 90 min. 7 exercises, 4 sets, 8 repetitions, 80% of 1RM. |
| Ruangthai et al. 2019 | Thailand | Hypertension | SBP, LDL | 25 | 20 | 13 | 67.38 | 12 weeks | Moderate | 3x/wk for 60 min. 14 exercises, 3 sets, 10–15 repetitions, 50–80% of 1RM. |

| Study | Country | Population | Outcome measures reported | N in analysis | % Male | N RT group | Mean age / Range | Duration | Training intensity | Description intervention |
|---|---|---|---|---|---|---|---|---|---|---|
| Sabouri et al. 2021 | Iran | DM2 | HbA1c, SBP, LDL | 28 | 46.4 | 15 | 51.76 | 12 weeks | High | 3x/wk. 7 exercises, 3 sets, 8 repetitions. |
| Saeidi et al. 2023 | Iran | Obese | LDL | 22 | 100 | 11 | 27.5 | 12 weeks | Low | 3x/wk for 70 min. 11 exercises, 3 sets, 14 repetitions, 50% of 1RM. Resistance training using resistance machines (Huist Equipment, San Diego, CA, USA) |
| Safarzade et al. 2013 | Iran | Obese | LDL | 18 | 0 | 8 | 25-45 | 8 weeks | Moderate | 3x/wk for 45–60 min. 9 exercises, 3 sets, 8–10 repetitiions, 60–70% of 1RM. Circuit resistance training. |
| Safarzade et al. 2020 | Iran | Obese | WHR | 28 | 100 | 14 | 36 | 8 weeks | Progressive | 3x/wk for 80 min. 12 exercises, 3 sets, 8–10 repetitions, 50–85% of 1RM. Week 1: 50% 1RM, weekly increase of 5–10% 1RM with 80–85% 1RM in last 3 weeks. |
| Sales et al. 2018 | Brazil | DM2 | SBP | 14 | NR | 7 | 62.50 | 8 weeks | Moderate | 25 min. 8 exercises, 3 sets, 8–12 repetitions, 50–70% of 1RM. Circuit resistance training. |
| Schroeder et al. 2019 | USA | Hypertension | SBP, LDL | 34 | 38.2 | 17 | 57.50 | 8 weeks | Low | 3x/wk for 60min. 12 exercises, 2–3 sets, 10–20 repetitions, 40–60% of 1RM. Resistance training using TechnoGym Wellness System. |
| Seo et al. 2023 | Korea | Obese | SBP, LDL | 28 | 0 | 15 | 50.79 | 12 weeks | Moderate | 3x/wk for 60 min. 8 exercises, 3–4 sets, 8–10 repetitions, 70–80% or 1RM. At a gym. |
| Shenoy et al. 2009 | India | DM2 | HbA1c, SBP | 20 | 50 | 10 | 54.00 | 16 weeks | Progressive | 2x/wk. 7 exercises, 3 sets, 10 repetitions, 60–100% of 1RM. |
| Smutok et al. 1993 | USA | Hypercholester-olemia, Hyper-tension, DM2 | SBP, LDL | 24 | 100 | 14 | 48.83 | 20 weeks | Low | 3x/wk. 11 exercises, 2 sets, 12–15 repetitions, 60–70% of 1RM. Resistance training using Nautilus equipment (Deland, FL). |
| Son et al. 2021 | South Korea | METS, Obese | SBP | 35 | 0 | 18 | 68.20 | 12 weeks | Progressive | 3x/wk for 60 min. 10 exercises, 40–70% of 1RM. Week 1-4: 40–50% 1RM. Week 5–8: 50–60 1RM. Week 9–12: 60–70% 1RM. Resistance training using elastic bands. |

| Study | Country | Population | Outcome measures reported | N in analysis | % Male | N RT group | Mean age / Range | Duration | Training intensity | Description intervention |
|---|---|---|---|---|---|---|---|---|---|---|
| Son et al. 2020 | South Korea | Hypertension | SBP | 20 | 0 | 10 | 67.55 | 12 weeks | Progressive | 3x/wk for 60 min. 10 exercises, 40–70% of 1RM. Week 1: 40–50%, Week 5–8: 50–60% 1RM. Week 9–12: 60–70% 1RM. Resistance training using elastic bands. |
| Soori et al. 2017 | Iran | Obese | LDL, WHR | 16 | 0 | 8 | 45-60 | 10 weeks | Low | 3x/wk for 45 min. 6 exercises, 3 sets, 10–12 repetitions, 40–60% of 1RM. Resistance training using free weights. |
| Stensvold et al. 2010 | Norway | METS | SBP | 22 | 60.5 | 11 | 49.10 | 12 weeks | Moderate | 3x/wk for 40–50 min. 3–5 exercises, 3 sets, 8–12 repetitions, 80% of 1RM. Resistance training using commercial equipment. |
| Taati et al. 2020 | Iran | Hypertension | SBP | 23 | 0 | 10 | 45.78 | 9 weeks | Low | 2x/wk. 6 excercises, 2 sets, 10 repetitions, 50% of 1RM. Circuit resistance training with resistance machines. |
| Tomeleri et al. 2016 | Brazil | Obese | LDL | 38 | 0 | 19 | 68.15 | 8 weeks | Moderate | 3x/wk for 45–50 min. 8 exercises, 3 sets, 10–15 repetitions, 60–80% of 1RM. Resistance training using free weights and machines at State University facilities. |
| Venojärvi et al. 2013 | Finland | Obese | HbA1c, LDL | 76 | 100 | 36 | 54.00 | 12 weeks | Moderate | 3x/wk for 60 min. 50–85% of 1RM. Resistance training using regular resistance equipment. |
| Wooten et al. 2010 | USA | Obese | LDL | 21 | 0 | 9 | 65.89 | 12 weeks | Moderate | 3x/wk. 10 exercises, 2 sets, 8–12 repetitions, 80% of 1RM. |
| Yavari et al. 2012 | Iran | DM2 | HbA1c, SBP, LDL | 40 | 46.3 | 20 | 51.50 | 1 year | Moderate | 2–3x/wk. 10 exercises, 3 sets, 8–10 repetitions, 60–80% of 1RM. Resistance training using weight machines. |

# Appendix 2.5

## Outputs regression analyses

**Table 1: HbA1c (Mixed-Effects Model)**

| Model | Estimate | SE | Z-value | p-value | CI Lower | CI Upper |
|---|---|---|---|---|---|---|
| Intercept | -0.63 | 0.53 | -1.19 | 0.23 | -1.67 | 0.41 |
| Intensity Moderate | 0.28 | 0.59 | 0.48 | 0.63 | -0.87 | 1.43 |
| Intensity High | -0.19 | 0.73 | -0.26 | 0.79 | -1.62 | 1.23 |
| Intensity Progressive | -0.11 | 0.66 | -0.16 | 0.87 | -1.41 | 1.19 |

logLik: -14.00
$tau^2$ (residual heterogeneity): 0.40 (SE=0.22)
$I^2$ (residual heterogeneity / unaccounted variability): 81.87%
$H^2$ (unaccounted variability / sampling variability): 5.52
$R^2$ (amount of heterogeneity accounted for): 0.00%

**Table 2: Sensitivity analysis HbA1c (Mixed-Effects Model)**

| Model | Estimate | SE | Z-value | p-value | CI Lower | CI Upper |
|---|---|---|---|---|---|---|
| Intercept | -0.59 | 0.49 | -1.22 | 0.22 | -1.55 | 0.36 |
| Intensity Moderate | 0.23 | 0.54 | 0.43 | 0.66 | -0.82 | 1.29 |
| Intensity High | -0.23 | 0.67 | -0.34 | 0.73 | -1.53 | 1.08 |
| Intensity Progressive | -0.57 | 0.65 | -0.87 | 0.38 | -1.85 | 0.71 |

logLik: -12.07
$tau^2$ (residual heterogeneity): 0.31 (SE=0.19)
$I^2$ (residual heterogeneity / unaccounted variability): 77.18%
$H^2$ (unaccounted variability / sampling variability): 4.38
$R^2$ (amount of heterogeneity accounted for): 0.00%

**Table 3: SBP (Mixed-Effects Model)**

| Model | Estimate | SE | Z-value | p-value | CI Lower | CI Upper |
|---|---|---|---|---|---|---|
| Intercept | -8.10 | 2.68 | -3.00 | 0.00 | -13.39 | -2.81 |
| Intensity Moderate | 1.05 | 3.24 | 0.33 | 0.74 | -5.29 | 7.39 |
| Intensity High | 7.59 | 5.70 | 1.33 | 0.18 | -3.60 | 18.77 |
| Intensity Progressive | 0.45 | 3.69 | 0.12 | 0.90 | -6.78 | 7.68 |

logLik: -101.74
$tau^2$ (residual heterogeneity): 38.76 (SE=13.28)
$I^2$ (residual heterogeneity / unaccounted variability): 93.40%
$H^2$ (unaccounted variability / sampling variability): 15.16
$R^2$ (amount of heterogeneity accounted for): 0.00%

**Table 4: Sensitivity analysis SBP (Mixed-Effects Model)**

| Model | Estimate | SE | Z-value | p-value | CI Lower | CI Upper |
|---|---|---|---|---|---|---|
| Intercept | -8.11 | 2.68 | -3.02 | 0.00 | -13.37 | -2.85 |
| Intensity Moderate | 1.05 | 3.22 | 0.33 | 0.74 | -5.26 | 7.36 |
| Intensity High | 7.59 | 5.67 | 1.34 | 0.18 | -3.53 | 18.71 |
| Intensity Progressive | -5.61 | 4.74 | -1.18 | 0.24 | -14.90 | 3.68 |

logLik: -88.42
$tau^2$ (residual heterogeneity): 38.24 (SE=14.59)
$I^2$ (residual heterogeneity / unaccounted variability): 93.27%
$H^2$ (unaccounted variability / sampling variability): 14.87
$R^2$ (amount of heterogeneity accounted for): 6.35%

**Table 5: LDL (Mixed-Effects Model)**

| Model | Estimate | SE | Z-value | p-value | CI Lower | CI Upper |
|---|---|---|---|---|---|---|
| Intercept | -0.25 | 0.13 | -1.91 | 0.06 | -0.49 | 0.01 |
| Intensity Moderate | -0.03 | 0.15 | -0.17 | 0.87 | -0.32 | 0.27 |
| Intensity High | -0.17 | 0.25 | -0.67 | 0.50 | -0.65 | 0.32 |
| Intensity Progressive | 0.15 | 0.23 | 0.67 | 0.51 | -0.30 | 0.60 |

logLik: -19.10
$tau^2$ (residual heterogeneity): 0.11 (SE=0.04)
$I^2$ (residual heterogeneity / unaccounted variability): 94.29%
$H^2$ (unaccounted variability / sampling variability): 17.50
$R^2$ (amount of heterogeneity accounted for): 0.00%

**Table 6: Sensitivity analysis LDL (Mixed-Effects Model)**

| Model | Estimate | SE | Z-value | p-value | CI Lower | CI Upper |
|---|---|---|---|---|---|---|
| Intercept | -0.23 | 0.10 | -2.39 | 0.02 | -0.41 | -0.04 |
| Intensity Moderate | -0.02 | 0.12 | -0.21 | 0.84 | -0.25 | 0.21 |
| Intensity High | -0.24 | 0.22 | -1.13 | 0.26 | -0.66 | 0.18 |
| Intensity Progressive | 0.12 | 0.15 | 0.78 | 0.44 | -0.18 | 0.42 |

logLik: -5.47
$tau^2$ (residual heterogeneity): 0.04 (SE=0.02)
$I^2$ (residual heterogeneity / unaccounted variability): 68.48%
$H^2$ (unaccounted variability / sampling variability): 3.17
$R^2$ (amount of heterogeneity accounted for): 0.00%

**Table 7: WHR (Mixed-Effects Model)**

| Model | Estimate | SE | Z-value | p-value | CI Lower | CI Upper |
|---|---|---|---|---|---|---|
| Intercept | 0.01 | 0.02 | 0.35 | 0.7261 | -0.04 | 0.05 |
| Intensity Moderate | -0.03 | 0.03 | -1.33 | 0.1842 | -0.08 | 0.02 |
| Intensity High | -0.10 | 0.03 | -2.87 | 0.0041 | -0.17 | -0.03 |
| Intensity Progressive | -0.06 | 0.03 | -2.16 | 0.0311 | -0.12 | -0.01 |

logLik: 22.89
$tau^2$ (residual heterogeneity): 0.0006 (SE=0.0004)
$I^2$ (residual heterogeneity / unaccounted variability): 80.73%
$H^2$ (unaccounted variability / sampling variability): 5.19
$R^2$ (amount of heterogeneity accounted for): 54.02%

**Table 8: Sensitivity analysis WHR (Mixed-Effects Model)**

| Model | Estimate | SE | Z-value | p-value | CI Lower | CI Upper |
|---|---|---|---|---|---|---|
| Intercept | -0.01 | 0.03 | -0.48 | 0.6314 | -0.07 | 0.04 |
| Intensity Moderate | -0.01 | 0.03 | -0.38 | 0.7055 | -0.07 | 0.05 |
| Intensity High | -0.08 | 0.04 | -2.02 | 0.0431 | -0.15 | -0.002 |
| Intensity Progressive | -0.04 | 0.03 | -1.22 | 0.2224 | -0.11 | 0.03 |

logLik: 21.35
$tau^2$ (residual heterogeneity): 0.0005 (SE=0.0004)
$I^2$ (residual heterogeneity / unaccounted variability): 80.35%
$H^2$ (unaccounted variability / sampling variability): 5.09
$R^2$ (amount of heterogeneity accounted for): 49.44%

# Appendix 5.1

Detailed description of the results from the multilevel linear regression analyses to investigate the effect of PRET between baseline and post-intervention, adjusted for medication use for HbA1c, SBP, and LDL.

**Intention to treat analysis**

| **HbA1c mmol/mol** | | | | | |
|---|---|---|---|---|---|
| n=36 | β | SE | p-value | 95% CI | |
| (Intercept) | 43.925 | 2.610 | | 38.800 | 49.050 |
| Intervention | -2.759 | 1.615 | 0.093 | -5.929 | 0.411 |
| Medication | 6.015 | 10.940 | 0.590 | -16.689 | 28.718 |
| **SBP mm/Hg** | | | | | |
| n=36 | β | SE | p-value | 95% CI | |
| (Intercept) | 126.025 | 3.142 | | 119.852 | 132.198 |
| Intervention | -5.739 | 3.006 | 0.063 | -11.642 | 0.165 |
| Medication | 5.434 | 5.909 | 0.375 | -7.008 | 17.876 |
| **LDL mmol/L** | | | | | |
| n=36 | β | SE | p-value | 95% CI | |
| (Intercept) | 2.665 | 0.212 | | 2.248 | 3.081 |
| Intervention | -0.207 | 0.086 | 0.02* | -0.376 | -0.038 |
| Medication | -0.056 | 0.259 | 0.955 | -0.593 | 0.480 |
| **WHR** | | | | | |
| n=36 | β | SE | p-value | 95% CI | |
| (Intercept) | 0.966 | 0.012 | | 0.943 | 0.989 |
| Intervention | 0.002 | 0.008 | 0.848 | -0.012 | 0.018 |

**Per protocol analysis**

| HbA1c mmol/mol | | | | | |
|---|---|---|---|---|---|
| n=26 | β | SE | p-value | 95% CI | |
| (Intercept) | 41.127 | 1.569 | | 38.044 | 44.210 |
| Intervention | -1.738 | 1.736 | 0.323 | -5.148 | 1.672 |
| Medication | 8.558 | 5.642 | 0.155 | -3.401 | 20.517 |
| **SBP mm/Hg** | | | | | |
| n=26 | β | SE | p-value | 95% CI | |
| (Intercept) | 126.062 | 3.380 | | 119.421 | 132.702 |
| Intervention | -6.164 | 3.214 | 0.062 | -12.479 | 0.150 |
| Medication | 5.469 | 6.142 | 0.391 | -7.550 | 18.488 |
| **LDL mmol/L** | | | | | |
| n=26 | β | SE | p-value | 95% CI | |
| (Intercept) | 2.555 | 0.198 | | 2.165 | 2.944 |
| Intervention | -0.220 | 0.099 | 0.033* | -0.416 | -0.024 |
| Medication | 0.545 | 0.368 | 0.164 | -0.235 | 1.325 |
| **WHR** | | | | | |
| n=26 | Value (β) | SE | p-value | 95% CI | |
| (Intercept) | 0.956 | 0.014 | | 0.928 | 0.984 |
| Intervention | 0.007 | 0.009 | 0.432 | -0.011 | 0.025 |

# Dankwoord




## Start bij GOUD

Allereerst gaat mijn dank uit naar Dederieke en Alyt voor het vertrouwen in mij om het PRET-onderzoek uit te voeren en hiervan mijn promotietraject te maken. Ik wil Ipse de Bruggen bedanken voor de ruimte om dit op te pakken. En mijn collega's fysiotherapie in Zwammerdam, bedankt dat jullie mij hebben gesteund deze jaren.

## Opzet onderzoek

Ondanks dat de start van het onderzoek werd vertraagd door corona, gaf dat wel de kans om een mooi protocolartikel te schrijven. Heel veel dank aan de implementatiecoaches en intern coördinatoren van de zorginstelling, die in deze periode steeds meedachten in oplossingen en veel flexibiliteit toonden.

## Start eerste deelnemers

We waren dan ook ontzettend blij dat we eindelijk konden starten met de eerste deelnemers! Heel veel dank aan de implementatiecoaches en onderzoeksassistentes, die enorm veel werk hebben verzet om de deelnemers te includeren. Uiteraard ook mijn dank aan de deelnemers die enthousiast meededen en aan de trainers die hen hebben begeleid.

## Zwangerschapsverlof

Ik wil mijn fysiotherapie collega's Daan en Mariëlle heel erg bedanken dat zij tijdens mijn zwangerschapsverlof de laatste metingen hebben overgenomen. Hun inzet en betrokkenheid worden enorm gewaardeerd!

## Chicago

Tijdens mijn zwangerschapsverlof vond het wereldcongres van het IASSIDD plaats in Chicago. Ik wil mijn partner Jeroen enorm bedanken dat hij het heeft aangedurfd om alleen thuis te blijven met onze 2,5 maand oude dochter, zodat ik naar Chicago kon, wat uiteindelijk een zeer vluchtig maar efficiënt bezoek werd.

## Analyseren en schrijven

Ik wil mijn dagelijks begeleider Roy bedanken voor al zijn hulp bij het uitdenken van methodieken, zijn kritische blik op alle geschreven stukken en zijn steun gedurende het hele proces. Ook wil ik Alyt bedanken voor haar begeleiding en steun, en haar bereidheid om mee te gaan in mijn acties, zoals dat memorabele hardlooprondje door Parijs met onze GOUD-sportshirts!

## Afronden proefschrift

Uiteindelijk wil ik de rest van mijn promotieteam, Dederieke en Sita, bedanken voor al hun hulp, steun en sparringsmomenten die hebben bijgedragen aan het mooi afronden van dit proefschrift.
Kim, collega en partner in crime, bedankt voor het sparren en spuien tijdens het hele proces. Mijn familie voor hun onvoorwaardelijke steun, en in het bijzonder Jeroen voor zijn geduld tijdens de laatste loodjes, waarin ik misschien niet altijd even lief was thuis.

# Curriculum vitae



Kirsten Irina de Oude werd geboren op 29 juli 1990 in Ter Aar. Na het behalen van haar VWO-diploma aan het Scala College in Alphen aan den Rijn in 2008, volgde zij de opleiding Fysiotherapie aan de Hogeschool Leiden. In 2012 rondde zij deze opleiding af en startte direct als fysiotherapeut bij Ipse de Bruggen, een organisatie voor mensen met een verstandelijke beperking. Binnen deze organisatie is zij tot op heden werkzaam, en sinds 2024 ook als beleidsadviseur.

In 2020 behaalde zij de master Geriatriefysiotherapie aan de Hogeschool Utrecht. Tijdens haar werk als fysiotherapeut en tijdens haar masteropleiding merkte zij dat er, ondanks aanwezige expertise, weinig wetenschappelijk bewijs beschikbaar is voor interventies bij mensen met een verstandelijke beperking. Deze lacune motiveerde haar om te starten met een promotieonderzoek binnen de Academische Werkplaats GOUD, gericht op het verbeteren van zorg en gezondheid voor deze doelgroep. Haar onderzoek draagt bij aan het vergroten van doelgroepgericht wetenschappelijk bewijs, dat essentieel is voor inclusieve en passende zorg.

Kirsten woont samen met haar partner en dochter (2024) in Alphen aan den Rijn. Haar werk kenmerkt zich door betrokkenheid, nieuwsgierigheid en een sterke motivatie om bij te dragen aan inclusieve en passende zorg.

# PhD portfolio

# PhD portfolio

**Name PhD student** Kirsten Irina de Oude
Department of General Practice, Intellectual Disability Medicine Research – Erasmus MC, University of Medical Center Rotterdam

**Research School** NIHES
**PhD period** 2021–2025
**Promotor** Prof. dr. S.M.A. Bierma-Zeinstra
**Supervisors** Dr. D.A.M. Maes-Festen
Dr. A. Oppewal
Dr. G.M.H. Elbers

| | Year(s) | EC |
|---|---|---|
| **1. PhD training** | | |
| **General courses** | | |
| • Basic course Rules and Organisation for Clinical researchers (BROK) (NFU) | 2021 | 1.5 |
| • Biomedical writing for PhD candidates (EUR) | 2024 | 1.5 |
| • Scientific integrity (Graduate school, EMC) | 2022 | 0.3 |
| • EndNote (Medical library, EMC) | 2022 | 0.2 |
| **Specific courses** | | |
| • Missing data: consequences and solutions (AuMC) | 2023 | 2.0 |
| • Multilevel Modelling and Longitudinal Data Analysis (AuMC) | 2023 | 4.0 |
| • Statistical analyses with R (online) | 2023 | 0.4 |
| • ACSM clinical exercise physiology (online) | 2022 | 22.0 |
| **Presentations** | | |
| • Departmental presentations | 2021–2025 | 1.0 |
| • Departmental workshops | 2021–2025 | 1.6 |
| • Presentations healthcare organisations | 2021–2023 | 1.0 |
| • Presentation IDS-TILDA, Dublin | 2022 | 0.2 |
| **(Inter)national conferences** | | |
| • 6th IASSIDD Europe congress, Amsterdam (online symposium) | 2021 | 1.0 |
| • 17th IASSID World congress, Chicago (symposium) | 2024 | 1.0 |
| • 28th ECSS congress, Paris (poster presentation) | 2023 | 1.0 |
| • Dutch congress 'Focus on Research' (symposium) | 2023 | 0.2 |
| • Dutch Association of Intellectual Disability Physiotherapists congress (workshop) | 2024 | 0.2 |
| **2. Teaching** | | |
| **Lecturing** | | |
| • Lecture Albeda College | 2023/2024 | 1.0 |
| • Training instructors | 2021–2023 | 2.0 |
| **Supervising Master's theses** | | |
| • 2 Master Medical Science student research projects | 2022–2024 | 6.0 |
| • 2 Bachelor Physiotherapy student research projects | 2024–2025 | 8.0 |
| **Total EC** | | 52.5 |

# List of publications

**International publications (peer reviewed journals)**

1. The Effect of Progressive Resistance Exercise Training on Cardiovascular Risk Factors in People with Intellectual Disabilities: A Study Protocol. Elbers, Roy G., **Kirsten I. de Oude**, Theodore Kastanidis, Dederieke A. M. Maes-Festen, Alyt Oppewal. *International Journal of Environmental Research and Public Health* (2022);19(24):16438. doi: 10.3390/ijerph192416438. (*Rank: Q2 Public Health, Environmental and Occupational Health*)
2. The effect of different resistance exercise training intensities on cardiovascular risk factors: A systematic review and meta-analysis. **Kirsten I. de Oude**, Roy G. Elbers, Heike Gerger, Dederieke A.M. Maes-Festen, Alyt Oppewal. *European Heart Journal Open* (2025);5(5):oeaf093. doi: 10.1093/ehjopen/oeaf093. (*Rank: Q1 Cardiology and Cardiovascular Medicine*)
3. Measuring muscle mass in adults with intellectual disabilities: the convergent validity of calf circumference. **Kirsten I. de Oude**, Rosalie J.E. Bonnet, Roy G. Elbers, Dederieke A.M. Maes-Festen, Alyt Oppewal. *Journal of Intellectual Disability Research* (2025);70(1):97-104. doi: 10.1111/jir.70060. (*Rank: Q1 Rehabilitation*)
4. The effect of progressive resistance exercise training on cardiovascular risk factors in adults with intellectual disabilities. **Kirsten I. de Oude**, Roy G. Elbers, Dederieke A.M. Maes-Festen, Sita M.A. Bierma-Zeinstra, Alyt Oppewal. *Submitted*
5. The effect of progressive resistance exercise training on physical and behavioural health components: a repeated time-series design. **Kirsten I. de Oude**, Roy G. Elbers, Alyt Oppewal, Dederieke A.M. Maes-Festen. *Submitted*

**Conference proceedings**

1. Effects of resistance training on cardiovascular risk in adults with intellectual disabilities. **Kirsten I. de Oude**, Roy G. Elbers, Theodore Kastanidis, Alyt Oppewal. *Journal of Applied Research in Intellectual Disabilities* (2021);34:1297. Meeting abstract 6th IASSIDD Europe Congress.

In dit proefschrift onderzoekt Kirsten de Oude de effecten van progressieve krachttraining op de cardiovasculaire gezondheid binnen deze doelgroep. Haar onderzoek, uitgevoerd binnen het GOUD consortium, laat zien dat krachttraining bijdraagt aan het verminderen van gezondheidsrisico's.

Met een achtergrond als fysiotherapeut bij Ipse de Bruggen, combineert Kirsten praktijkervaring met wetenschappelijke inzichten. Haar werk benadrukt het belang van inclusieve gezondheids-bevordering en biedt handvatten voor professionals in de zorg van mensen met een verstandelijke beperking.

