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Graded Resistance Exercise And Type 2 Diabetes in Older adults (The GREAT2DO study): methods and baseline cohort characteristics of a randomized controlled trial

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Abstract

Background: Type 2 diabetes (T2D) is projected to affect 439 million people by 2030. Medical management focuses on controlling blood glucose levels pharmacologically in a disease that is closely related to lifestyle factors such as diet and inactivity. Physical activity guidelines include aerobic exercise at intensities or volumes potentially unachievable for older adults limited by many co-morbidities. We aim to show for the first time the efficacy of a novel exercise modality, power training (high-velocity, high-intensity progressive resistance training or PRT), in older adults with T2D as a means for improving glycemic control and targeting many associated metabolic and physiological outcomes.

Eligibility criteria included community-dwelling men and women previously diagnosed with T2D who met the current definition of metabolic syndrome according to the International Diabetes Federation. Participants were randomized to a fully supervised power training intervention or sham exercise control group for 12 months. Intervention group participants performed whole body machine-based power training at 80%1RM, 3 days per week. The control group undertook the same volume of non-progressive, low-intensity training. Participants were assessed at baseline, 6 months and 12 months and followed for a further 5 years, during which time participants were advised to exercise at moderate-high intensity. Glycemic control (HbA1c) and insulin resistance as measured by the homeostatic model assessment 2 (HOMA2-IR) were the primary outcomes of the trial. Outcome assessors were blinded to group assignment and participants were blinded to the investigators’ hypothesis regarding the most effective intervention.

Results: We recruited 103 participants (48.5 % women, 71.6 ± 5.6 years). Participants had 5.1 ± 1.8 chronic diseases, had been diagnosed with T2D for 8 ± 6 years and had a body mass index (BMI) of 31.6 ± 4.0 kg/m². Fasting glucose and insulin were 7.3 ± 2.4 mmol/L and 10.6 ± 6.3 mU/L, respectively. HbA1c was 54 ± 12 mmol/mol. Eighty-six participants completed the 12-month assessment and follow-up is ongoing. This cohort had a lower-than-expected dropout (n = 14, 14 %) over the 12-month intervention period.

(Continued on next page)
Conclusions: Power training may be a feasible adjunctive therapy for improving glycemic control for the growing epidemic of T2D in older adults.

Trial registration: Australian and New Zealand Clinical Trials Registry ACTRN12606000436572 (24 September 2006).

Keywords: Type 2 diabetes, Resistance training, Weight lifting, Randomized controlled trial, Power training

Background
Physical activity is a critical component of optimal management for the increasing epidemic of type 2 diabetes (T2D) [1]. Although not as well studied as aerobic exercise in this cohort [2], progressive resistance training (PRT) has been shown to improve glucose homeostasis in T2D, with a clinically relevant effect size (ES) not significantly different from aerobic exercise or combined exercise or lifestyle programs [3]. It may also improve blood pressure, dyslipidemia, markers of inflammation and catabolism, and visceral obesity, thus addressing many components of metabolic syndrome [4–6]. Additionally, PRT has beneficial effects on functional exercise capacity [7, 8], osteoarthritis [9], bone health [10], depression and insomnia [11], and cognitive impairment [12], thus addressing many common co-morbidities in older adults with T2D and obesity. Importantly, PRT, in contrast to aerobic exercise, attenuates or prevents the loss of lean tissue accompanying dietary weight loss [13], thus addressing the potential adverse metabolic and clinical effects such a loss of muscle and bone mass may produce [14].

Resistance training is commonly recommended at moderate intensity and slow velocity for older adults [15]. By contrast, power training typically involves pushing a weight as quickly as possible during the concentric phase and slowly returning the weight to the start position during the eccentric phase [16]. As the rate of decline in power is greater than the rate of decline in strength with aging [17], power training may be particularly important to older adults, and has notably been shown to be more effective in improving physical function [18] and maintaining bone density [19] as compared to conventional slow-velocity resistance training. Power training has also been shown to improve functional tasks such as standing up from a chair, climbing stairs [20] and gait speed [21]. Moreover, power training specifically targets the type 2b muscle fiber atrophy that predominates in older adults and contributes to sarcopenia [22–24]. Power training thus has the potential to provide a broader spectrum of benefit than slow-velocity PRT, yet this alternative form of PRT has never been directly tested as a strategy to treat individuals with diabetes and metabolic syndrome.

With any new therapy, it is important to establish the overall risk/benefit ratio, rather than just focus upon the effect on the target symptom. Thus, our measures of other clinical problems in these individuals with metabolic syndrome, such as muscle weakness, immobility, disability, depression, cognitive impairment, sleep disturbance, postural and post-prandial hypotension, and cardiovascular symptoms will provide a balanced perspective on the unique benefits and risks of this therapeutic approach compared to usual care. It is also critically important to establish the utility of this intervention on its own, before combining it with other interventions such as weight loss diets, or aerobic exercise [4, 25] so that the independent contribution of power training to diabetes and metabolic syndrome can be definitively established.

Objectives
Our specific aim was to conduct a 12-month randomized controlled trial (RCT) to test the efficacy of power training added to the usual medical care of older adults with T2D and metabolic syndrome. In addition, the long-term feasibility and benefits of this type of exercise will be assessed over 6 years of follow-up.

Primary hypothesis
Power training will be associated with sustained improvements in insulin sensitivity and HbA1c compared to the sham exercise control group at 6-month and 12-month follow-up.

Secondary hypotheses
1. Power training will be associated with improvements in the other components of metabolic syndrome and cardiovascular risk associated with T2D, including: increased circulating high-density lipoprotein (HDL) cholesterol, decreased total and low-density lipoprotein (LDL) cholesterol and triglyceride (TG) levels, decreased ambulatory blood pressure, increased aerobic capacity, improved heart rate variability and postural hypotension compared to the sham exercise control condition.
2. Power training will be associated with a significant reduction in visceral adiposity and intramuscular lipid and increase in regional and whole body measures of lean muscle mass, bone mineral density, function, and metabolism, as well as a shift in the
anabolic milieu (decreased circulating and adipose tissue levels of inflammatory/catabolic cytokines and increased anabolic/anti-inflammatory factors) compared to the sham exercise control condition.

3. Body composition changes across the entire cohort will be related to observed metabolic/inflammatory improvements, whereas total body mass changes will not.

4. Randomization to the power training intervention as well as higher levels of participation in structured physical activity during follow-up will predict better outcomes in the above primary and secondary domains across the 6-year follow-up.

**Methods**

**Recruitment**

**Sample size estimates**

Hypothesized differences between the experimental and control participants for the primary outcomes drove sample size estimates of insulin resistance and HbA1c, based on published studies of PRT in diabetes/obesity [6, 26]. Largest available standard deviations were used for conservative estimates of ES. The most comprehensive meta-analysis at the time of study planning [27] indicated that control participants in enrolled exercise trials did not improve in metabolic outcomes, thus the control change was set at 0. Setting beta at 0.2, and alpha at 0.05, and n1 = n2, the following sample size requirements were estimated for changes from baseline at 12 months (Table 1).

Thus, 98 participants recruited, (assuming 20 % attrition), would provide 78 participants at 12 months, as required by the smaller ES hypothesized for HbA1c. Based on our pilot work, we estimated we would need to screen approximately 500 participants by phone, and 125 in person, to enroll approximately 100 eligible/interested participants. We anticipated that our loss to follow-up would actually be less than 20 %.

**Recruitment strategies**

Participants were recruited via general practitioner referral, targeted mail-outs, advertisements in local newspapers and seniors’ magazines and from brochures distributed to local medical practitioners and pharmacies. Participants were recruited from August 2006 to December 2010 with the final 12-month assessment in December 2011. Follow-up testing is due for completion in February 2016.

**Management**

All incoming responses were recorded by the research assistant and logged in a tracking database that outlined the flow of participants through the recruitment, screening and (if eligible) intervention process.

**Screening**

Potential participants contacted the research assistant and a telephone interview was conducted or scheduled for a convenient time. The telephone screening was comprised of questions to ascertain the participant’s basic demographic and contact information, current diabetic and health status, medical history, current medication use and physical activity/exercise levels. The study physician reviewed all of the individual screenings and participants were subsequently notified of their eligibility. If eligible, participants were requested to attend the University of Sydney for subsequent testing (including a health and physical examination by a physician and a 12-lead electrocardiogram (ECG) and maximal exercise stress test) to determine their eligibility.

**Participants**

**Eligibility criteria for participants**

The inclusion and exclusion criteria are listed in Fig. 1. Participants eligible for inclusion were treated with diet alone, oral medications or insulin or combination at the time of enrollment. Metabolic syndrome was defined according to the International Diabetes Federation as:

- Central obesity (defined as waist circumference ≥ 94 cm for Europid men and ≥ 80 cm for Europid women, plus any 2 of the following 4 factors:
  - Raised TG level: ≥ 1.7 mmol/L, or specific treatment for this lipid abnormality
  - Reduced HDL cholesterol: < 1.03 mmol/L in men or < 1.29 mmol/L in women, or specific treatment for this lipid abnormality
  - Raised resting blood pressure: systolic blood pressure (BP) ≥ 130 mmHg or diastolic BP ≥

**Table 1 Primary outcomes and effect sizes**

| Primary outcome | Experimental mean change | Sham control Mean change | Pooled standard deviation | Effect size (d) | Sample required (total cohort) |
|-----------------|--------------------------|--------------------------|---------------------------|----------------|-------------------------------|
| HOMA2-IR        | −0.6                     | 0                        | 0.8                       | 0.75           | 52                            |
| HbA1c (mmol/mol)| −13.1                    | 0                        | 18.6                      | 0.70           | 78                            |

Sample size estimates were driven by hypothesized differences between the experimental and control participants in the primary outcomes of the trial: insulin resistance and glucose homeostasis, as measured using HOMA2-IR and HbA1c respectively. Effect sizes were calculated based on an average of published studies of PRT in diabetes/obesity [6, 26].

HbA1c glycosylated hemoglobin, HOMA2-IR homeostatic model of assessment of insulin resistance 2
85 mmHg, or treatment of previously diagnosed hypertension
- Raised fasting plasma glucose (FPG) ≥ 5.6 mmol/L, or previously diagnosed T2D.

Exclusion criteria included significant cognitive impairment (inability to comprehend informed consent or evidence of functional impairment related to cognition on screening), non-ambulatory status or lower extremity amputation other than toes, current alcohol or substance abuse, inability to comply with study requirements over the course of 1 year due to travel plans or other commitments, or specific contraindications to resistance training exercise, such as unstable cardiovascular disease, aortic aneurysm, proliferative diabetic retinopathy, uncontrolled hypertension, or rapidly progressive or

| Inclusion Criteria | Exclusion Criteria |
|--------------------|-------------------|
| ▪ Age >60 years    | ▪ Significant cognitive impairment |
| ▪ Previously diagnosed T2D | ▪ Non-ambulatory |
| ▪ Clinically stable T2D (no change in medications in the previous 2 months) | ▪ Lower extremity amputation (other than toes) |
| ▪ BMI >25 kg/m² | ▪ Alcohol or substance abuse |
| ▪ Abnormal lipid profile | ▪ Inability to comply with study requirements over the course of one year |
| ▪ Sedentary (no PRT; structured exercise ≤ 1/week; low-moderate intensity walking or other aerobic exercise ≤ 150 min/week) | ▪ Unrepaired aortic aneurysm |
| | ▪ Proliferative diabetic retinopathy |
| | ▪ Rapidly progressive terminal illness |

T2D = Type 2 Diabetes; BMI = Body Mass Index; PRT = Progressive Resistance Training.
terminal illness. Temporary exclusions included recent laser or other ocular surgery (within 2 weeks), symptomatic hernias, acute illness, or recent fracture or other injury, until resolved.

**Settings and location where data were collected**
All assessments were carried out at the University of Sydney, Faculty of Health Sciences, Lidcombe and in the Radiology Department of Royal Prince Alfred Hospital, Sydney. Training sessions were conducted at the Harbord Diggers’ Freshwater Fitness Center, Harbord and at The Center for STRONG Medicine, Balmain Hospital, Balmain.

**Interventions**

**Experimental intervention: power training**
Experimental participants performed power training 3 days per week and using 8 major muscle groups on pneumatic resistance under supervision. We used a version of PRT called power training, in which the concentric contraction (lifting the weight) was done as fast as possible, and the lowering of the weight was done slowly (over 2–3 seconds). The exercises targeted the majority of the large muscle groups of the arms, legs, and trunk and consisted of lateral pulldown, chest press, upper back, leg press, knee extension, and knee flexion, hip extension and hip abduction. These are symmetrical muscle groups and functionally relevant to the activities of daily living, gait, and balance of older adults. For each exercise, participants performed 3 sets of 8 repetitions with a fast concentric and slow eccentric phase on pneumatic resistance training machines (approximately 6 seconds per repetition with 2 minutes of rest between sets), a regimen which has been shown to produce optimum adaptations in terms of muscle power, strength, endurance in older adults [16].

The intensity was set at 80% of the most recently determined peak strength (1 repetition maximum or 1RM). Resistances used were increased as tolerated using the Borg Scale Rating of Perceived Exertion [28, 29] on a continuous basis throughout the 12 months, and 1RM testing was repeated at 2-week intervals to ascertain progress and regulate intensity. All training was fully supervised by skilled exercise physiologists to maintain proper intensity and progression, as 2 separate trials in T2D have now shown that metabolic benefits of PRT disappear when participants are switched to semi-supervised community-based or home-based training [30, 31]. This was attributed to a drop in adherence and intensity when supervision was withdrawn. As this is a first-time efficacy trial of power training, our intent was to maximise protocol adherence.

**Control group intervention: sham PRT**
The same trainers supervised sham exercise control participants in the same facility but at different hours to avoid contamination and unblinding. These participants performed three sets of eight repetitions on the same machines, with no loading beyond the weight of the bar of the machine, using slow concentric and eccentric contraction speed. No interim 1RM testing and no progression took place. We have found that similar regimens do not improve muscle function or mass, functional status, mobility, depression, aerobic capacity, or other clinical outcomes we are measuring [32, 33]. Low-intensity resistance training has also been shown to have no effect on visceral fat [34], adiponectin [35], glucose homeostasis or insulin sensitivity, or bone mineral density [36], thus providing an ideal sham exercise control condition.

**Outcomes**
The primary outcomes of this study were insulin resistance 96 hours after the last exercise bout as assessed by the homeostatic model assessment 2 (HOMA2) computer model and HbA1c. The 96-hour time interval for HOMA2 was chosen to minimize the well-described acute bout effect of exercise on insulin sensitivity, as we are primarily interested in long-term training adaptations related to visceral fat/muscle mass.

Secondary outcomes and covariates include all of the components of metabolic syndrome, body composition, adipokines, muscle morphology and metabolism, genetic and epigenetic markers related to metabolic/cardiovascular health and exercise adaptation, measures of energy expenditure and fat oxidation, neuropsychological function, cardiovascular health status, quality of life, dietary intake and habitual physical and sedentary activity levels. Blinded assessors, at a laboratory facility separate from the training site to prevent unblinding, repeated all measurements at baseline, 6 months, and 12 months in experimental and control participants. In addition, selected measures were repeated annually during the 5 additional years of follow-up.

**Domains of assessment**
All outcome measures administered by blinded assessors at baseline, 6-month and 12-month follow-up are listed in Table 2. During the intervention phase, assessments were conducted over 3 different days to allow for the correct timing of exercise bouts and blood draws and to ensure adequate participant preparation (e.g. the cessation of blood thinning medication where possible). Figure 2 details the timing of assessments throughout the course of the study.
Table 2 Outcome measures

| Outcome                          | Outcome measure                         | Description                                                                                                                                 |
|----------------------------------|-----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| **Primary**                      | Insulin sensitivity                     | 72 hours and 96 hours post exercise  
• HOMA2 computer model for insulin sensitivity (IR, %S) [53]  
• HOMA2 computer model for beta cell function (%Beta)                                                                 |
| Glucose homeostasis              | Fasting glucose                         | Glycated hemoglobin [53]  
Insulin  
C-peptide levels  
Diabetic medication inventory and dosages  
Meal tolerance test                                                                                                                        |
| **Secondary**                    | Cardiovascular health                   | Resting heart rate variability and pulse wave velocity (arterial stiffness)  
24-hour ambulatory blood pressure  
Postural blood pressure  
Ankle brachial blood pressure index                                                                                                            |
| Lipid metabolism                | Total cholesterol                       | Low/High-density cholesterol  
Triglycerides  
Basal fat oxidation via indirect calorimetry  
Intramuscular lipid content                                                                                                                 |
| Muscle morphology and metabolism| Muscle tissue biopsy (vastus lateralis)  |  
• Glucose transporter type 4 receptor protein  
• Intramuscular insulin-like growth factor 1  
• Glycogen content  
• Muscle fiber cross-sectional area  
• Muscle fibretyping                                                                                                                         |
| Adipokines and Inflammatory markers| Adipose tissue biopsy [54]             |  
• TNF-α  
• Interleukin-6  
• High molecular weight adiponectin  
• C-Jun N-terminal kinase  
• Serum C-reactive protein [55]                                                                                                              |
| Body composition [53]            | Bioelectrical impedance analysis        |  
• Skeletal muscle mass, skeletal muscle mass index  
• Fat free mass  
• Fat mass  
• Body fat percentage  
Computed tomography scan  
• Abdominal and thigh girth, sagittal diameter  
• Abdominal total, visceral and subcutaneous fat area  
• Thigh total, intramuscular and subcutaneous fat area and muscle density (intramuscular lipid index)  
• Thigh muscle area  
Waist circumference  
Body mass index                                                                                                                             |
Randomization

Sequence generation
A computerized random-number generator (http://www.randomization.com, created by Dr Gerard E. Dallal, Tufts University) was used to randomize eligible participants at the level of the individual participant, stratified by sex and use of insulin, in blocks of four.

Allocation concealment
Sealed envelopes were prepared by an independent researcher, containing sequential treatment assignments based on a computer-generated randomization scheme, and opened by the participant’s trainer after completion of all baseline testing.

Implementation
The study was approved by the University of Sydney and the Sydney South West Area Health Service Human Research Ethics Committees (RPA HREC protocol number 04-009602/08/2006). A blinded outcomes assessor obtained informed consent from all participants enrolled in the study and informed the independent researcher

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Table 2 Outcome measures (Continued)

| Exercise capacity and Functional status | Exercise stress test (maximal treadmill test with indirect calorimetry) |
|----------------------------------------|---------------------------------------------------------------|
| • Peak aerobic capacity                |                                                               |
| • Anaerobic threshold                 |                                                               |
| • Oxygen uptake efficiency slope      |                                                               |
| • Heart rate recovery                 |                                                               |
| Muscle strength, power and endurance  |                                                               |
| Habitual and maximal gait speed       |                                                               |
| Static and dynamic balance            |                                                               |
| Chair stand and stair climb power     |                                                               |

| Neuropsychological profile            | Geriatric Depression Scale                                   |
|---------------------------------------|--------------------------------------------------------------|
|                                       | Pittsburgh Sleep Quality Index                                |
|                                       | Ewart’s Self-efficacy Scale                                   |
| Cognitive function                    |                                                               |
| • Mini Mental State Exam              |                                                               |
| • Word List Recognition and Recall   |                                                               |
| • Trail Making A and B                |                                                               |

| Actigraph sleep architecture over 7 days | • Total time in/out of bed                                |
| ----------------------------------------|-----------------------------------------------------------|
|                                         | • Sleep latency, sleep efficiency                          |
|                                         | • Total time asleep                                       |
|                                         | • Number of awakenings                                     |

Health-related quality of life

| Medical Outcomes Study 36-Item Short-Form Health Survey |
|---------------------------------------------------------|

Nutritional intake

| Food frequency questionnaire of Bloch over past 4 months |
|---------------------------------------------------------|

Energy expenditure

| Resting metabolic rate via indirect calorimetry |
|------------------------------------------------|

| Habitual physical activity and sedentary behaviour via Physical Activity Scale for the Elderly |
|------------------------------------------------------------------------------------------------|
| Actigraph accelerometers over 7 days |
| • Waking hours                        |
| • Wear time                           |
| • Total sedentary time, mean sedentary time, median sedentary time |
| • Percentage of time spent in sedentary (1 MET), light (<3 MET), moderate (3–6 MET) and vigorous (>6 MET) activity |
| • Total energy expenditure spent in sedentary (1 MET), light (<3 MET), moderate (3–6 MET) and vigorous (>6 MET) activity |
| • Physical activity level (PAL score)  |

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%S percent sensitivity, HOMA2 homeostatic model assessment 2, MET metabolic equivalent of task, TNF-α tissue necrosis factor alpha
when the participant was eligible for randomization (after completion of baseline testing). Participants were notified of their training session time by the exercise physiologist administering the intervention.

**Blinding**

This is the first truly double-blind sham exercise-controlled RCT in T2D. All outcomes assessors were blinded to treatment assignment for the duration of the study. Only the exercise physiologists and medical practitioners responsible for administering and overseeing the exercise programs were informed of participant group assignment. Participants were also blinded to the investigators’ hypothesis and only informed of their training time, not group assignment as active or sham, and were told that two different kinds of exercise were being compared for efficacy.

**Statistical methods**

All outcomes will be analyzed using all available data without imputation for missing time points via repeated measures linear mixed models, without regard to discontinuation or dropout. Secondary per-protocol analyses will be carried out on participants with ≥70% compliance as appropriate, with group by time interaction as the primary outcome of interest. Covariates will be chosen as appropriate via a priori
hypothesized confounders if there are differences between groups within relevant variables at baseline within the cohort despite randomization. Relationships between variables of interest at baseline between changes scores will be determined by simple and stepwise regression models and logistic regression models as appropriate. Statistical significance will be initially assumed at the 0.05 level, as all hypotheses were specified a priori, and Bonferroni correction is considered overly conservative in this instance [37]. Effect sizes and 95 % confidence intervals (CIs) will be calculated for all outcomes. Calculations of ES will be adjusted via Hedges’ bias-corrected ES for small sample sizes [38] and interpreted according to Cohen’s interpretation of “trivial” (0.20), “small” (0.20 < 0.50), “moderate” (0.50 < 0.80), and “large” (0.80) ES [39]. Ninety-five percent CIs for the relative ES will calculated. For ES in non-normally distributed data, median will substituted for mean, and range/4 will be substituted for SD.

Results
Participant flow
Participants were assessed at baseline, 6 and 12 months for the intervention phase of study and annually for the remaining 5-years of follow-up. Figure 3 shows the flow of participants through the study.

Recruitment
We assessed 427 people for eligibility (Fig. 3). After completing the telephone screening questionnaire, 324 people were deemed ineligible for not meeting the inclusion criteria (n = 285), declining to participate (n = 15), and a further 24 people were either unable to commit, had transport difficulties/did not live local to the training sites or had medical contraindications. A total of 103 people gave consent, met the eligibility criteria and were randomized to either the power training intervention group (n = 49) or the sham-exercise control group (n = 54).

Losses and exclusions
Three participants withdrew from the study prior to commencing the intervention. Fourteen participants dropped out of the study (did not complete follow-up assessments) after commencing the intervention (intervention group n = 10; control group n = 4). One was an adverse event related to the intervention (musculoskeletal injury in the intervention group), five felt the intervention was too hard, four were medical concerns unrelated to the intervention, three were due to commitment issues, and one was due to disinterest. Our attrition of 14 % at 12 months was less than expected for the intervention period. As expected, there has been a steady decline in participation over the follow-up phase. A total of 70 people commenced the 5-year post-intervention program with a total of 41 participants expected to complete the entire 6 years of follow-up. Currently, 35 participants have completed the 6-year follow-up, with the remaining 6 participants scheduled for their final assessment.

Baseline demographics
The baseline participant characteristics are reported in Table 3. Forty-nine and 54 participants were randomized to the intervention and control groups, respectively. Our eligibility criteria were designed so as to maximize external validity as only terminal or unstable diseases, or conditions which would permanently preclude resistance training, were exclusionary. Thus, our cohort was generally representative of older diabetic cohorts in Australia and other countries, with multiple co-morbidities and chronic medication usage. For example, the Australian Institute for Health and Welfare 2007–8 [40] report states that 58 % of individuals with diabetes also have cardiovascular disease. In our cohort, nearly one half (49 %) were being treated for cardiovascular disease. Similarly, 43 % of the Graded Resistance Exercise And Type 2 Diabetes in Older adults (GREAT2DO) cohort had hypercholesterolemia at baseline, which is not dissimilar to the Australian adult population where half of all adults over 25 years of age have high total cholesterol levels (data from 1999–2000) [41]. Among the 103 participants in this study, only 5.8 % were current smokers, similar to the 4.4 % reported in the Look AHEAD study of adults with T2D in 2006 [42]. Sixteen participants reported insulin use for control of their diabetes. In comparison to some previous trials that have excluded people with cardiovascular disease and insulin therapy, overall our cohort is more representative of the general population of older adults with T2D.

Adverse events
There were eight adverse events in six participants adjudicated by the study physician to be related to study procedures; seven in the intervention group and one in the control group. These included three syncopal episodes in a male participant with known syncope, one hamstring strain, one back pain leading to dropout, one exacerbation of pre-existing umbilical hernia requiring surgical repair, one subscapularis tear in a female participant with pre-existing grade IV osteoarthritis/rotator cuff disease requiring surgery, and one partial thickness tear of a rotator cuff muscle managed conservatively.
Discussion

We have shown for the first time that it is feasible to recruit and retain older adults with T2D and multiple chronic co-morbidities in a long-term trial of high-intensity power training. Few RCTs of PRT, as an isolated addition to usual care in middle-aged and older adults with T2D, have been published; however, the magnitude of change in glucose control (HbA1c) in these studies was comparable to the effect of aerobic exercise or oral hypoglycemic therapy [3]. One study,
### Table 3 Baseline participant characteristics

|                          | Power (n = 49) | Sham (n = 54) | Total (n = 103) |
|--------------------------|---------------|--------------|-----------------|
| **Demographics**         |               |              |                 |
| Age (years)              | 66.9 ± 4.7    | 68.8 ± 6.1   | 67.9 ± 5.5      |
| Sex (female)             | 24.0 (49.0)   | 27.0 ± (50.0)| 51.0 ± 0.5      |
| **Smoking status**       |               |              |                 |
| Current                  | 3.0 (6.1)     | 3.0 (5.6)    | 6.0 (5.8)       |
| Past                     | 31.0 (63.3)   | 33.0 (61.1)  | 64.0 (62.1)     |
| **Ethnic origin**        |               |              |                 |
| Caucasian                | 49.0 (100.0)  | 50.0 (92.6)  | 99.0 (96.1)     |
| Asian                    | 0.0 (0.0)     | 2.0 (3.7)    | 2.0 (1.9)       |
| Indian                   | 0.0 (0.0)     | 2.0 (3.7)    | 2.0 (1.9)       |
| **Chronic diseases**     |               |              |                 |
| Duration of diabetes (years) | 6.9 ± 5.1  | 9.1 ± 6.7    | 8.0 ± 6.0       |
| Number of chronic diseases | 5.1 ± 1.9    | 5.1 ± 1.8    | 5.1 ± 1.8       |
| **Hypertension**         | 37.0 (75.5)   | 39.0 (72.2)  | 76.0 (73.8)     |
| Osteoarthritis           | 35.0 (71.4)   | 33.0 (61.1)  | 68.0 (66.0)     |
| Cardiovascular diseases  | 23.0 (46.9)   | 27.0 (50.0)  | 50.0 (48.5)     |
| High cholesterol         | 24.0 (49.0)   | 21.0 (38.9)  | 45.0 (43.7)     |
| Cancer                   | 14.0 (28.6)   | 17.0 (31.5)  | 31.0 (30.1)     |
| GERD (Reflux/Barrett’s esophagus) | 8.0 (16.3) | 14.0 (25.9)  | 22.0 (21.4)     |
| PV/VD                    | 10.0 (20.4)   | 11.0 (20.4)  | 21.0 (20.4)     |
| IHD, MI, Angina          | 8.0 (16.3)    | 11.0 (20.4)  | 19.0 (18.4)     |
| Sleep apnea              | 7.0 (14.3)    | 12.0 (22.2)  | 19.0 (18.4)     |
| Depression               | 10.0 (20.4)   | 8.0 (14.8)   | 18.0 (17.5)     |
| Hypothyroidism           | 7.0 (14.3)    | 9.0 (16.7)   | 16.0 (15.5)     |
| Arrhythmia               | 8.0 (16.3)    | 6.0 (11.1)   | 14.0 (13.6)     |
| Ulcers (gastrointestinal tract) | 7.0 (14.3) | 7.0 (13.0)   | 14.0 (13.6)     |
| Osteoporosis/Osteopenia  | 5.0 (10.2)    | 8.0 (14.8)   | 13.0 (12.6)     |
| Gout                     | 7.0 (14.3)    | 5.0 (9.3)    | 12.0 (11.7)     |
| Benign prostatic hyperplasia | 3.0 (6.1)   | 8.0 (14.8)   | 11.0 (10.7)     |
| Chronic venous disease   | 4.0 (8.2)     | 6.0 (11.1)   | 10.0 (9.7)      |
| COPD/CAL                 | 2.0 (4.1)     | 7.0 (13.0)   | 9.0 (8.7)       |
| Hyperthyroidism          | 2.0 (4.1)     | 6.0 (11.1)   | 8.0 (7.8)       |
| Esophagitis              | 5.0 (10.2)    | 3.0 (5.6)    | 8.0 (7.8)       |
| **Health status**        |               |              |                 |
| Weight (kg)              | 89.5 ± 15.2   | 88.8 ± 18.8  | 89.1 ± 17.1     |
| BMI (kg/m²)              | 31.5 ± 4.7    | 31.6 ± 6.0   | 31.6 ± 5.4      |
| Waist circumference (cm) |               |              |                 |
| Men                      | 112.4 ± 9.6   | 109.3 ± 11.5 | 110.8 ± 11.7    |
| Women                    | 109.6 ± 9.6   | 108.7 ± 11.5 | 109.1 ± 12.6    |
| Resting blood pressure (mmHg) |      |              |                 |
| Systolic                 | 147.2 ± 17.9  | 145.1 ± 17.9 | 146.1 ± 17.9    |
| Diastolic                | 78.9 ± 7.5    | 77.4 ± 10.2  | 78.1 ± 9.0      |

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which directly compared isolated PRT to aerobic exercise in middle-aged type 2 adults with diabetes [26], found that PRT significantly improved 48-hour continuous glucose control, HbA1c, insulin sensitivity, and lipids, whereas aerobic exercise was ineffective. Limitations of previous studies of PRT include small sample sizes and relatively short periods of follow-up in some cases, and lack of comprehensive assessment of mechanisms of benefit, cardiovascular profile and associated clinical benefits relevant to older adults.

Thus, despite the strong theoretical rationale for its use in this cohort, and its recent advocacy by expert consensus panels internationally [1, 14, 43], PRT is not a common treatment for diabetes [2] and more evidence of feasibility, safety, and efficacy are needed. This need is highlighted by the results of the Look AHEAD trial, which reported no difference in the primary outcome of cardiovascular events following lifestyle modification in type 2 diabetics, despite clear benefits in secondary outcomes such as weight, physical activity level, fitness, quality of life, depression levels and metabolic risk [44–46]. However, most lifestyle interventions, even intensive ones such as Look AHEAD, may not attenuate losses of lean tissue mass seen with both aging and caloric restriction. In fact, bone losses were greater in men in the intensive lifestyle group in Look AHEAD compared to controls, and were proportional to weight loss achieved [47, 48]. This important issue of lean tissue loss accompanying lifestyle modification programs that do not prioritize or include anabolic exercises thus requires additional study, and is the focus of the GREAT2DO trial described here.

### Conclusion

To our knowledge no study investigating high-intensity power training has yet been published, and thus the GREAT2DO study will provide the first evidence of the safety, efficacy and long-term feasibility of this novel modality of anabolic exercise in older adults with T2D. Other studies suggest that power training is useful for osteoporosis [49, 50], balance [51], functional performance [18] and quality of life [52]. If our hypotheses are correct, improvement in metabolic health and other secondary outcomes from this trial may add to the growing rationale for this unique and robust form of exercise training for the treatment of chronic disease-related and age-related syndromes.
Acknowledgments
We would like to thank our participants for their generous contributions of time and spirit. We would like to thank Harbord Diggers’ Freshwater Fitness Center and The STRONG Clinic at Balmain Hospital for the use of their gym facilities and Keiser Sports Health Ltd for donations of resistance training equipment. The Graded Resistance Exercise and Type 2 Diabetes in Older adults (GREAT2DO) study was funded by project grant #512381 from the National Health and Medical Research Council (NHMRC), grants from The Australian Diabetes Society, Diabetes Australia and the Rebecca L. Cooper Foundation. Y. Mavros was supported by the Australian Postgraduate Award Scholarship. Y. Wang was supported by the University of Sydney International Postgraduate Research Scholarship.

This study fulfilled a portion of the postgraduate degree requirements for the following students: Shelley Kay, Yi Wang, Yorgi Mavros, Rennu Zhao, Vivienne Quo.

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Title:
Graded Resistance Exercise And Type 2 Diabetes in Older adults (The GREAT2DO study): methods and baseline cohort characteristics of a randomized controlled trial

Date:
2015-11-10

Citation:
Simpson, K. A., Mavros, Y., Kay, S., Meiklejohn, J., de Vos, N., Wang, Y., Guo, Q., Zhao, R., Climstein, M., Baune, B. T., Blair, S., O'Sullivan, A. J., Simar, D., Singh, N. & Singh, M. A. F. (2015). Graded Resistance Exercise And Type 2 Diabetes in Older adults (The GREAT2DO study): methods and baseline cohort characteristics of a randomized controlled trial. TRIALS, 16 (1), https://doi.org/10.1186/s13063-015-1037-y.

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