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Muscle grip strength predicts incident type 2 diabetes: population-based cohort study

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Muscle grip strength predicts incident type 2 diabetes: population-based cohort study

Short title: Grip strength and Type 2 Diabetes

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Abstract

Objectives: To determine the longitudinal relationship of muscle mass and strength with incident type 2 diabetes, and previously unstudied mediating effects of testosterone and inflammation.

Methods: Community-dwelling male participants (aged ≥35 years) of the Men Androgens Inflammation Lifestyle Environment and Stress (MAILES) Study underwent biomedical assessment in 2002-2006 and 2007-2010, including hand grip strength (dynamometer), testosterone and inflammatory markers. Body composition (dual-energy x-ray absorptiometry) was assessed at baseline only. Incident type 2 diabetes was defined as a self-reported doctor diagnosis, diabetes medication use, fasting plasma glucose ≥7.0 mmol/L, or glycated haemoglobin ≥6.5% (48 mmol/mol) at follow-up, that was not present at baseline.

Results: Of n=1632 men, incident type 2 diabetes occurred in 146 (8.9%). Muscle mass was not associated with incident type 2 diabetes. Grip strength was inversely associated with incident type 2 diabetes [unadjusted odds ratio (OR) per 5kg: 0.87, 95% confidence interval (CI): 0.80-0.95; adjusted OR, 95% CI: 0.87, 0.78-0.97]. Arm muscle quality (grip strength divided by arm lean mass) was similarly associated with incident type 2 diabetes. Testosterone, IL-6 and TNF-α did not significantly mediate the associations. The population attributable fraction of type 2 diabetes from low grip strength was 27% (13 to 40%), assuming intervention could increase strength by 25%.

Conclusions: Reduced muscle strength, but not reduced muscle mass, is a risk factor for incident type 2 diabetes in men. This is not mediated by testosterone or inflammation. Intervention could prevent a substantial proportion of disease.

Keywords: skeletal muscle, lean mass, dual energy x-ray absorptiometry, muscle strength, grip strength, men.
Abbreviations:

ASM: appendicular skeletal muscle mass
ASMI: appendicular skeletal muscle mass index
DXA: dual-energy xray absorptiometry
FAMAS: Florey Adelaide Male Ageing Study
FMI: fat mass index
MAILES: Men Androgen Inflammation Lifestyle Environment and Stress
NWAHS: North West Adelaide Health Study
MET: metabolic equivalent
PAF: population attributable fraction
1. Introduction

The prevalence of type 2 diabetes has been increasing worldwide [1], in association with rising obesity. However, increased adiposity contributes to only 37-77% of incident type 2 diabetes, depending on the population studied [2, 3]. Thus, identification of new and potentially modifiable risk factors is needed to inform strategies for prevention.

Multiple cross-sectional studies have shown type 2 diabetes is inversely associated with skeletal muscle mass [4, 5] and strength [6, 7]. Muscle strength is also inversely associated with the development of insulin resistance [8]. However, there are few longitudinal studies that have investigated the role of muscle mass and strength in the development of type 2 diabetes. Only three longitudinal studies have investigated muscle strength and incident type 2 diabetes, and they showed conflicting results which may due to methodological limitations from an inability to identify undiagnosed cases [9-11]. Furthermore, only one previous study has investigated muscle mass and incident type 2 diabetes, which found that changes in muscle mass did not predict incident type 2 diabetes [12]. However, that study relied on bioelectrical impedance analysis instead of gold standard measures such as dual-energy x-ray absorptiometry (DXA) [12]. The association between reduced skeletal muscle mass or strength and incident type 2 diabetes is therefore unclear.

Testosterone is a determinant of muscle mass and strength [13], and low testosterone has also been associated with type 2 diabetes in men [14]. Therefore low testosterone may mediate the association between skeletal muscle dysfunction and type 2 diabetes in men. Similarly, inflammation predicts decline in skeletal muscle mass and strength [15], while also predicting incident type 2 diabetes [16]. Hence inflammation may also mediate any association between
skeletal muscle and incident type 2 diabetes. These mechanisms have not been previously explored.

We therefore aimed to investigate the association between measures of skeletal muscle mass and strength with incident type 2 diabetes in a prospective community-dwelling cohort of men, and whether testosterone or inflammation mediate that association.
2. Methods

2.1 Cohort Participants

The Men Androgen Inflammation Lifestyle Environment and Stress (MAILES) study is a longitudinal cohort of community-dwelling men, and has been described previously [17]. In brief, MAILES consists of two concurrent prospective cohorts: the Florey Adelaide Male Ageing Study (FAMAS) [18] and the age-matched men from the North West Adelaide Health Study (NWAHS) [19]. The two cohorts are largely representative of the male population of South Australia, and used the same methodology for random population sampling.

Detailed demographic, comorbidity (doctor diagnosed diabetes, cardiovascular disease), hand dominance, and risk factor data (smoking, physical activity) were collected by self-completed questionnaire. Biomedical assessments at baseline and follow-up were conducted in 2 hospital-based clinics using standardised and reproducible study protocols, including grip strength and blood pressure measurement, anthropometry, and fasting blood samples (lipids, glucose, glycated hemoglobin, testosterone and inflammatory markers). Hypertension was defined as any of: self-report, a clinically measured systolic blood pressure of ≥140 mmHg (mean of two or three readings), diastolic blood pressure of ≥90 mmHg (mean of two or three readings), or use of anti-hypertensive medication. Metabolic syndrome was defined by International Diabetes Federation criteria. Mild (walking), moderate, and vigorous physical activity levels were determined by the Australian National Health Survey Physical Activity instrument and converted into metabolic equivalents (METs). In the NWAHS, depression was defined as a score of ≥21 on the Center for Epidemiological Studies Depression Scale, whereas in FAMAS, depression was defined as a score of ≥12 on the Beck Depression
Inventory. Cardiovascular disease was defined as a self-report of doctor-diagnosed myocardial infarction, angina, stroke or transient ischemic attack.

Approval for MAILES was obtained from the Human Research Ethics Committees of the North West Adelaide Health Service and the Royal Adelaide Hospital. All participants gave written informed consent. Baseline data were obtained in 2002-2006 and follow-up data in 2007-2010. Figure 1 shows the participant flowchart. Almost all (96%) participants were born in Australia or Western Europe (including the UK/Ireland).

2.2 Skeletal Muscle Measures

Grip strength was measured with a Jamar analog hand dynamometer in the NWAHS cohort (Lafayette Instrument Company, Lafayette, Indiana, USA) or a Smedley analog hand dynamometer (Stoelting Corporation, Wood Dale, Illinois, USA) in the FAMAS cohort [17]. To account for any systematic differences in the type of hand dynamometer used, we included cohort as a covariate in adjusted statistical analyses. Main analyses used the mean of three measurements in the dominant hand. Sensitivity analyses used the maximum (i.e. peak) measurement recorded in either hand. We also undertook sensitivity analyses to account for: 1) bodily (e.g. hand) pain, as determined by the bodily pain scale of the SF-36; 2) self-reported current smoking at baseline; and 3) use of systemic corticosteroids at follow-up.

Body composition was measured at baseline in a sub-set of the cohort (n=1181): NWAHS participants aged ≥50 years [20], and all FAMAS participants [18]. Whole-body, arms, and legs lean mass and fat mass were measured by DXA using default settings on either a pencil-beam (DPX+, Lunar software v4·7e) or fan-beam (Prodigy DF+ 14759, Encore software v9·15) densitometer. Both machines were from GE Lunar (Madison, Wisconsin, USA) and
provided similar results [21]. Appendicular skeletal muscle mass (ASM) was calculated by summing the lean mass of arms and legs. ASM and fat mass were normalised for height by dividing by height squared to generate ASM index (ASMI), and fat mass index (FMI) respectively [20, 22].

Arm muscle quality (grip strength corrected for arm lean mass) was calculated by dividing the sum of the grip strength in both hands by arms lean mass [23, 24]. Sensitivity analyses were also undertaken using arm muscle quality calculated with peak grip strength.

2.3 Type 2 Diabetes

Type 2 diabetes was defined as: previous doctor diagnosis, diabetes medication use, fasting plasma glucose (FPG) ≥7.0 mmol/L (≥126 mg/dl), or glycated haemoglobin (HbA1c) ≥6.5% (48 mmol/mol). Diabetes medication use was identified by prescription of Anatomical Therapeutic Chemical classification A10 drug(s) from the Pharmaceutical Benefits Scheme of Australia. FPG was quantified using an automated chemistry analyser system (Olympus AU5400; Olympus Corp, Tokyo, Japan). HbA1c was measured by high-performance liquid chromatography using a spherical cation exchange gel (CV, 2% at 6% of total haemoglobin).

2.4 Testosterone and Inflammatory Markers

Serum total testosterone was measured by validated stable-isotope dilution liquid chromatography-tandem mass spectrometry (API-5000, Applied Biosystems/MDS SCIEX, Ontario, Canada) [25]. All measurements were undertaken on morning samples after an overnight fast; further detail is available in previous publications [17, 26]. Serum interleukin-6 (IL-6) and serum tumour necrosis factor-alpha (TNF-α) were measured by enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Minneapolis, MN) [17].
2.5 Statistical Analysis

Statistical analysis was using SPSS version 20 (SPSS Inc., Illinois, USA) and R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria). Differences in baseline characteristics between groups were determined using t-tests (numerical variables) or \( \chi^2 \)-tests (categorical variables). The unadjusted and adjusted associations between skeletal muscle measures and incident type 2 diabetes, and any interaction effects, were determined using binary logistic regression models. Collinearity was assessed using the variance inflation factor (VIF). All VIF values in this study were less than 3.

We used binary logistic regression models further adjusted for testosterone and inflammatory markers to determine if additional adjustment for these variables attenuated the association between grip strength (or arm muscle quality) and incident type 2 diabetes. To formally quantify any mediating effect of testosterone or inflammatory markers, we undertook mediation analysis using the R mediation package. For testosterone, we also undertook a sensitivity analysis that excluded participants taking medications known to affect serum testosterone; major health problems including prostate cancer, orchidectomy, and primary testicular disease; and outlier values including total testosterone > 40 nmol/L, luteinising hormone > 12 U/L, follicular stimulating hormone > 8 U/L, and sex hormone-binding globulin > 100 nmol/L [26].

To quantify the proportion of incident type 2 diabetes cases that could be prevented if grip strength were to be increased, we calculated the population attributable fraction (PAF) using the R attribrisk package. There is no widely accepted cut-off value for low grip strength, and resistance training increases muscle strength by 25-30% after 3 months [27]. Hence we
calculated PAFs based on five potential “intervention targets”, as follows: 1) all participants increased grip strength by 25%, 2) all participants increased grip strength by 10%, 3) participants increased grip strength to our cohort’s mean (47·4kg), 4) participants increased grip strength to one standard deviation above the cohort mean (57·0kg) and 5) participants increased grip strength to one standard deviation below the cohort mean (37·2kg).

There were < 2% missing data for all confounders, except physical activity, which had 6.4% missing. Data for missing confounders, but not the primary predictor or outcome variable, were imputed as either the median (numerical variables) or the modal category (categorical variables). Data were not imputed for serum total testosterone, IL-6, or TNF-α. Sensitivity analyses using only the complete, non-imputed, dataset (n=1493) were also conducted.

2.7 Role of the Funding Source

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.
3. Results

Diabetes data were available in n=2490 men (Figure 1). Excluding n=379 men with diabetes at baseline, n=2111 were included in this study, of which follow-up data were available in n=1680 (79.6%) men. Grip strength data was available in n=1632 (77.3% of the n=2111 included in this study). Incident type 2 diabetes occurred in 146 men (8.9%) over a median follow-up of 4.95 (IQR 4.35-5.00) years. Baseline DXA measurements were available in a sub-sample of 1181 men (414 from NWAHS and 767 from FAMAS). Table 1 shows the baseline characteristics of the cohort, overall as well as grouped by whether the men developed incident type 2 diabetes or not. Compared to those that did not develop type 2 diabetes (‘never diabetes’) during follow-up, the participants that developed incident type 2 diabetes were at baseline: older, had higher body mass index (BMI), waist circumference (WC) and serum IL-6, and had higher prevalence of impaired FPG, family history of diabetes, hypertension, dyslipidaemia, metabolic syndrome and self-reported cardiovascular disease. They had lower annual income, education level, serum total testosterone and grip strength. In the DXA sub-study, compared to the participants that did not develop type 2 diabetes, participants that developed type 2 diabetes had higher total fat mass and fat mass index, and had lower lean mass percentage, and arm muscle quality. The Pearson correlation coefficient between grip strength and arm muscle quality was 0.68.

Table 2 shows the associations of grip strength, arm muscle quality, and lean mass measures with incident type 2 diabetes. In both unadjusted and adjusted logistic regression models, grip strength and arm muscle quality were significantly inversely associated with incident type 2 diabetes. In unadjusted models, lean mass percentage was inversely associated with incident type 2 diabetes, but these associations did not persist after adjustment. In models that were mutually adjusted for either grip strength or whole-body lean mass (Model 3), grip strength
and arm muscle quality were significantly inversely associated with incident type 2 diabetes independent of whole-body lean mass, but the lean mass measures were not significantly associated with incident type 2 diabetes independent of grip strength.

Table 3 shows the proportion mediated by testosterone, IL-6, and TNF-α of the associations of grip strength and arm muscle quality with incident type 2 diabetes. Further adjustment for serum total testosterone slightly attenuated the odds ratios for grip strength. The association between grip strength and incident type 2 diabetes was reduced to borderline significance (p=0.051). The association between arm muscle quality and incident type 2 diabetes remained significant after testosterone adjustment. Further adjustment for serum IL-6 and TNF-α also did not attenuate any of the associations. In mediation analysis, testosterone, IL-6, and TNF-α did not significantly mediate the association between grip strength or arm muscle quality and incident type 2 diabetes.

Table 4 shows the PAFs of incident type 2 diabetes due to low grip strength. The PAFs ranged from 3% (95% CI: 0.1 to 6%) to 29% (95% CI: 8 to 49%), depending on the intervention target chosen.

Stratified analyses are shown in Figures 2 and 3. Figure 2 shows associations of grip strength with incident type 2 diabetes, stratified by age, FPG, cohort, general adiposity, central adiposity, family history of diabetes, and serum total testosterone. The interaction effects were not significant for age, baseline FPG, cohort, family history of diabetes, or serum total testosterone. However, there were significant interaction effects for WC (p=0.002) and BMI (p=0.001). The inverse association of grip strength with type 2 diabetes was stronger in men with lower central adiposity (OR for WC<102cm, 0.80 [95% CI: 0.68-0.94] vs. WC≥102cm,
0.88 [95% CI: 0.76-1.03]) and lower general adiposity (OR for BMI<30kg/m$^2$, 0.79 [95% CI: 0.69-0.92] vs. BMI≥30kg/m$^2$, 0.94 [95% CI: 0.80-1.13]).

Figure 3 shows associations of arm muscle quality with incident type 2 diabetes, stratified by age, FPG, cohort, general adiposity, central adiposity, family history of diabetes, serum total testosterone, and lean mass per arm. The interaction effects were not significant for age, baseline FPG, cohort, family history of diabetes, serum total testosterone, or lean mass per arm. However, there were significant interaction effects for WC (p=0.001) and BMI (p<0.001). The inverse association of arm muscle quality with type 2 diabetes was stronger in men with lower central adiposity (OR for WC<102cm, 0.70 [95% CI: 0.59-0.83] vs. WC≥102cm, 0.93 [95% CI: 0.80-1.09]) and lower general adiposity (OR for BMI<30kg/m$^2$, 0.71 [95% CI: 0.62-0.83] vs. BMI≥30kg/m$^2$, 1.03 [95% CI: 0.86-1.23]).

Sensitivity analyses are presented in the online Supplemental Data (Appendix 1). Table A1 shows the analyses using peak grip strength (instead of mean dominant hand grip strength) and peak arm muscle quality (instead of overall arm muscle quality), as well as the analyses additionally adjusting for SF-36 bodily pain scale, current smoking, and systemic corticosteroid use at follow-up. Table A2 shows sensitivity analyses limited to the non-imputed complete dataset. The results of these sensitivity analyses were similar to the main analyses. The sensitivity analysis for testosterone mediation also yielded similar results to the main analysis (proportion mediated of grip strength 4% [95% CI: -70 to 71%], p=0.49; proportion mediated of arm muscle quality 1% [95% CI: -30 to 24%], p=0.90).
4. Discussion

In a large prospective community-dwelling sample of men, we found that grip strength and arm muscle quality were inversely associated with incident type 2 diabetes. Neither testosterone nor inflammation significantly mediated these associations. These associations, robust to multiple sensitivity analyses, were consistent across age, impaired fasting glucose, cohort, family history, and serum total testosterone strata. However, while these associations were especially strong in non-obese men, they were not significant in obese men. Our findings suggest that measurement of grip strength has a particularly important role in identifying non-obese men at risk of type 2 diabetes.

Only three previous studies have investigated the association between muscle strength and incident type 2 diabetes [9-11]. The largest study of those found inconclusive results: the adjusted association between grip strength and incident diabetes was not significant in the main analyses, but was significant in the sensitivity analyses [11]. However, that study relied on self-report to exclude baseline diabetes, with incident diabetes defined via self-report, identification on death case report forms, or identification on hospitalisation case report forms. Undiagnosed cases, representing 46% of diabetes worldwide [1], were not identified. Similarly, an older study defined type 2 diabetes by self-report and found no association between grip strength and incident type 2 diabetes [10]. The lack of identification of undiagnosed cases would have biased those studies towards the null. In contrast, using our comprehensive definition of type 2 diabetes, which included FPG and HbA1c criteria to identify undiagnosed cases, we found an inverse association that persisted after adjustment. When we replicated the self-reported methodology of previous studies in our own cohort, we too found no significant association after adjustment for confounders (data not shown).
In a small (n=394) study of Japanese Americans, where 75g oral glucose tolerance testing and use of diabetes medication defined type 2 diabetes, lower hand grip strength predicted incident type 2 diabetes in lean, but not in obese, participants [9]. We extend their findings by demonstrating in a larger cohort that the association is consistent across other strata (such as age, baseline FPG, family history, and serum testosterone), and is also independent of many confounding variables.

Cross-sectional studies have established an inverse association between muscle mass and type 2 diabetes [4, 5]. In contrast, the only previous longitudinal study found changes in lean mass did not predict incident type 2 diabetes [12]. However, that previous longitudinal study relied on bioelectrical impedance analysis and not gold standard methods such as DXA. Using multiple indices of skeletal muscle mass derived from DEXA, we have confirmed that skeletal muscle mass does not predict incident type 2 diabetes. The discrepancy between cross-sectional and longitudinal studies may be because low muscle mass is an effect of type 2 diabetes, instead of low muscle mass predicting type 2 diabetes development [28].

We found testosterone does not mediate the association between muscle strength and incident type 2 diabetes. This contrasts to existing knowledge that testosterone increases muscle mass and strength [29] and activates glucose metabolism-related signalling within skeletal muscle [30]. Our results suggest testosterone’s effect on cardiometabolic risk is separate from its effect on skeletal muscle. Furthermore, despite previous observations that inflammation, particularly IL-6 and TNF-α, contribute to both decreased grip strength as well as incident type 2 diabetes [15, 16], we found that IL-6 and TNF-α also do not mediate the association between grip strength and incident type 2 diabetes. Hence, much of the association between
muscle strength and incident type 2 diabetes remains unexplained, and further studies are required to elucidate other factors that may contribute.

A major strength of our study was the strong methodological basis. Measurement of grip strength by hand dynamometer is a valid and reliable measure of muscle strength [31], while DXA is an accurate measure of muscle mass [32]. Testosterone was measured using validated liquid chromatography-mass spectrometry [25]. In addition to a self-report of a doctor diagnosis, our definition of type 2 diabetes included FPG and HbA1c criteria to identify undiagnosed cases, and linkage to the Australian pharmaceutical database to identify participants who were under active pharmacological management. We did not conduct oral glucose tolerance tests and therefore some diabetes cases may have been misclassified as no diabetes, which may be a limitation of the study, however this would likely lead to the underestimation of the observed relationship. We undertook a large number of sensitivity analyses which demonstrate the robustness of our results. Another strength was our adjustment for many confounders, including age, FPG, family history of diabetes, physical activity, central adiposity, and whole-body lean mass. We also undertook analyses corrected for arm lean mass (termed ‘arm muscle quality’). Finally, our sample was a randomly selected, community-dwelling, population-representative sample of men, which aids the generalizability of our findings.

One limitation was the use of grip strength as the only measure of muscular function. However, grip strength provided similar risk estimates as quadriceps strength in a previous study of mortality risk [33]. Grip strength is a more clinically relevant measure of muscular strength compared to other measures such as quadriceps strength. We identified CVD through a self-report of doctor diagnosed conditions which may be subject to recall bias.
however large-sample validation studies (self-report compared to chart review) have found self-report of physician-diagnoses of some cardiovascular outcomes (myocardial infarction and stroke) to be highly specific and moderately sensitive measures [34-35]. Smoking and physical activity were also measured by self-report rather than objectively measured. DXA was conducted on a sub-sample of men (1181) resulting in a smaller study sample only in the final regression models but nevertheless, significant relationships were still observed. Our study is limited to men, so cannot be generalised to women. One of the aims of our study was to investigate the mediating effect of testosterone, an androgen that has sex-specific effects. Lastly, almost all participants were born in Australia or Europe, so while our findings may be generalizable to other developed countries, generalising to populations beyond these areas should be undertaken with caution.

In summary, we have found an independent, inverse association between grip strength and arm muscle quality with incident type 2 diabetes in men. This association is not mediated by circulating testosterone or inflammation biomarker levels. Future studies should elucidate other possible mechanistic explanations. There is also a need for higher quality type 2 diabetes risk prediction models which perform well at quantifying the actual magnitude of disease risk [36]. Studies developing new prediction models should examine whether inclusion of grip strength alongside traditional diabetes risk factors has value in predicting type 2 diabetes. Finally, resistance training improves muscle strength and quality [24, 37]. Our study highlights the potential importance of resistance training for the prevention of type 2 diabetes. We have found such intervention could prevent up to 29% of incident type 2 diabetes cases.
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Disclosure Statement
JJL, AV, EA, ZS, SLA, CLH, AJJ, and ASJ have no conflicts of interest to declare. GAW has received research funding from the National Health and Medical Research Council of Australia, the ResMed Foundation and equipment donations from Embla Systems. RJA has received research funding from the National Health and Medical Research Council of Australia, and The ResMed Foundation, and Equipment donations from Embla Systems.

Author Contributions
JJL, GAW, EA, and RJA designed the study. GAW, CLH, AJJ, ASJ, and RJA oversaw data collection. JJL undertook data analysis, with assistance provided by AV, SLA, and ZS. JJL, GAW, EA, AV, SLA, ZS, and RJA interpreted the results. JJL wrote the first draft of the
manuscript. All authors revised the manuscript for important intellectual content. JYL had full
access to the data and is the guarantor of this study.
References


[33] Newman AB, Kupelian V, Visser M, Simonsick EM, Goodpaster BH, Kritchevsky SB, et al. Strength, but not muscle mass, is associated with mortality in the health, aging and body


Table 1. Baseline characteristics of the cohort.

<table>
<thead>
<tr>
<th></th>
<th>Overall (n=1632)</th>
<th>Never diabetes (n=1486)</th>
<th>Incident type 2 diabetes (n=146)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54.1 ± 11.4</td>
<td>53.7 ± 11.4</td>
<td>57.7 ± 10.9</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Annual income</td>
<td></td>
<td></td>
<td></td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>&lt; $40,000</td>
<td>42.5 (694)</td>
<td>41.1 (610)</td>
<td>57.5 (84)</td>
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<td>$40,000-$79,999</td>
<td>38.8 (633)</td>
<td>39.5 (587)</td>
<td>31.5 (46)</td>
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</tr>
<tr>
<td>≥ $80,000</td>
<td>18.7 (305)</td>
<td>19.4 (289)</td>
<td>11.0 (16)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td>p=0.001</td>
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<tr>
<td>High school or lower</td>
<td>31.4 (513)</td>
<td>30.1 (447)</td>
<td>45.2 (66)</td>
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<tr>
<td>Trade</td>
<td>30.5 (498)</td>
<td>30.8 (457)</td>
<td>28.1 (41)</td>
<td></td>
</tr>
<tr>
<td>Diploma/Certificate</td>
<td>24.5 (400)</td>
<td>24.9 (370)</td>
<td>20.5 (30)</td>
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<tr>
<td>Bachelor or higher</td>
<td>13.5 (221)</td>
<td>14.3 (212)</td>
<td>6.2 (9)</td>
<td></td>
</tr>
<tr>
<td>Physical activity ≥ 600 MET min/week</td>
<td>41.3 (674)</td>
<td>41.3 (614)</td>
<td>41.1 (60)</td>
<td>p=0.958</td>
</tr>
<tr>
<td>FPG</td>
<td>41.3 (674)</td>
<td>41.3 (614)</td>
<td>41.1 (60)</td>
<td>p=0.958</td>
</tr>
<tr>
<td>&lt; 5.5 mmol/L</td>
<td>88.1 (1437)</td>
<td>90.8 (1349)</td>
<td>60.3 (88)</td>
<td>p&lt;0.001</td>
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<td>5.5-6.1 mmol/L</td>
<td>9.7 (158)</td>
<td>7.9 (117)</td>
<td>28.1 (41)</td>
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<td>6.1-6.9 mmol/L</td>
<td>2.3 (37)</td>
<td>1.3 (20)</td>
<td>11.6 (17)</td>
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<td>Family history of diabetes</td>
<td>28.2 (461)</td>
<td>27.3 (406)</td>
<td>37.7 (55)</td>
<td>p=0.008</td>
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<tr>
<td>Current smoking</td>
<td>19.4 (316)</td>
<td>19.7 (293)</td>
<td>15.8 (23)</td>
<td>p=0.247</td>
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<td>BMI (kg/m^2)</td>
<td>28.0 ± 4.2</td>
<td>27.9 ± 4.1</td>
<td>29.9 ± 4.8</td>
<td>p&lt;0.001</td>
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<td>Waist circumference (cm)</td>
<td>99.5 ± 11.2</td>
<td>99.0 ± 11.0</td>
<td>104.8 ± 12.3</td>
<td>p&lt;0.001</td>
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<td>Hypertension</td>
<td>49.5 (808)</td>
<td>47.6 (707)</td>
<td>69.2 (101)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>HDL &lt; 1.0 mmol/L</td>
<td>13.4 (218)</td>
<td>12.7 (189)</td>
<td>19.9 (29)</td>
<td>p=0.015</td>
</tr>
<tr>
<td>Triglycerides &gt;1.7mmol/L</td>
<td>34.6 (564)</td>
<td>33.4 (497)</td>
<td>45.9 (67)</td>
<td>p=0.003</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>29.5 (481)</td>
<td>27.0 (401)</td>
<td>54.8 (80)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Depression</td>
<td>8.2 (134)</td>
<td>7.9 (117)</td>
<td>11.6 (17)</td>
<td>p=0.113</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>7.2 (117)</td>
<td>6.7 (100)</td>
<td>11.6 (17)</td>
<td>p=0.028</td>
</tr>
<tr>
<td>Total testosterone(nmol/L)</td>
<td>17.3 ± 5.7</td>
<td>17.6 ± 5.7</td>
<td>15.0 ± 5.7</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Serum IL-6 (pg/mL)</td>
<td>2.0 ± 1.8</td>
<td>1.9 ± 1.7</td>
<td>2.3 ± 2.6</td>
<td>p=0.025</td>
</tr>
<tr>
<td>Serum TNF-α (pg/mL)</td>
<td>1.9 ± 2.7</td>
<td>1.9 ± 2.8</td>
<td>1.7 ± 0.9</td>
<td>p=0.494</td>
</tr>
<tr>
<td>Grip strength (kg)</td>
<td>47.1 ± 9.9</td>
<td>47.4 ± 9.9</td>
<td>44.6 ± 9.4</td>
<td>p=0.001</td>
</tr>
<tr>
<td>DXA sub-study</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total lean mass (kg)</td>
<td>58.1 ± 7.7</td>
<td>58.0 ± 7.7</td>
<td>58.7 ± 7.5</td>
<td>p=0.339</td>
</tr>
</tbody>
</table>
Lean mass percentage (%)  | 69.0 ± 6.6 | 69.3 ± 6.6 | 66.6 ± 5.5 | p<0.001
ASM (kg)                  | 26.3 ± 3.8 | 26.3 ± 3.8 | 26.2 ± 3.8 | p=0.825
ASMI (kg/m^2)             | 8.6 ± 1.1  | 8.6 ± 1.0  | 8.7 ± 1.0  | p=0.200
Total fat mass (kg)        | 23.5 ± 8.3 | 23.1 ± 8.2 | 27.0 ± 8.1 | p<0.001
Fat mass index (kg/m^2)    | 8.0 ± 2.8  | 7.6 ± 2.7  | 9.0 ± 2.7  | p<0.001
Arm muscle quality (kg/kg) | 12.4 ± 2.2 | 12.5 ± 2.2 | 11.5 ± 2.0 | p<0.001

Data are presented as % (n), or mean ± standard deviation. P-values (t-test or χ²-test) compare the incident diabetes group with the never diabetes group. MET, metabolic equivalents; FPG, fasting plasma glucose; BMI, body mass index; HDL, high density lipoprotein; DXA, dual-energy xray absorptiometry; ASM, appendicular skeletal muscle mass; ASMI, appendicular skeletal muscle mass index.
Table 2. Odds ratios (OR) and 95% confidence intervals (CI) for incident type 2 diabetes associated with grip strength, arm muscle quality, and lean mass measures.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Unadjusted OR (95%CI)</th>
<th>Model 2 OR (95%CI)</th>
<th>Model 3 OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grip strength</strong></td>
<td>1632</td>
<td>0.87 (0.80-0.95)</td>
<td>0.87 (0.78-0.97)</td>
<td>0.85 (0.74-0.98)</td>
</tr>
<tr>
<td><strong>Arm muscle quality</strong></td>
<td>1172</td>
<td>0.81 (0.74-0.89)</td>
<td>0.85 (0.75-0.95)</td>
<td>0.84 (0.75-0.94)</td>
</tr>
<tr>
<td><strong>Whole-body lean mass</strong></td>
<td>1181</td>
<td>1.06 (0.94-1.21)</td>
<td>0.96 (0.82-1.13)</td>
<td>1.03 (0.87-1.24)</td>
</tr>
<tr>
<td><strong>Lean mass percentage</strong></td>
<td>1181</td>
<td>0.76 (0.67-0.87)</td>
<td>0.91 (0.77-1.12)</td>
<td>0.96 (0.80-1.20)</td>
</tr>
<tr>
<td><strong>ASM</strong></td>
<td>1181</td>
<td>0.97 (0.76-1.25)</td>
<td>0.80 (0.57-1.11)</td>
<td>0.93 (0.64-1.34)</td>
</tr>
<tr>
<td><strong>ASMI</strong></td>
<td>1181</td>
<td>1.14 (0.94-1.38)</td>
<td>0.97 (0.76-1.24)</td>
<td>1.08 (0.83-1.39)</td>
</tr>
</tbody>
</table>

Odds ratios (95% confidence intervals) for incident diabetes are per 5kg unit increases in grip strength, lean mass and ASM, per 1kg/kg unit increases in arm muscle quality, per 5% unit increases for lean mass percentage, and per 1kg/m² increases in ASMI. Significant associations highlighted in bold. ASM, appendicular skeletal muscle mass; ASMI, appendicular skeletal muscle mass index. Model 2: adjusted for age, income, cohort, waist circumference, fasting plasma glucose, physical activity, hypertension, triglycerides and family history of diabetes. Model 3: Model 2 plus mutual adjustment for either whole-body lean mass or grip strength.
Table 3. Mediation analyses of associations [Odds ratios (OR) and 95% confidence intervals (CI)] between grip strength and arm muscle quality with incident type 2 diabetes.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Mediator</th>
<th>Reference Model*</th>
<th>Reference Model + Mediator</th>
<th>Proportion mediated (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>OR (95%CI)</td>
<td>OR (95%CI)</td>
<td></td>
</tr>
<tr>
<td>Grip strength</td>
<td>Testosterone</td>
<td>0.88 (0.78-0.99)</td>
<td>0.89 (0.79-1.001)</td>
<td>2% (-15 to 25%)</td>
</tr>
<tr>
<td>Grip strength</td>
<td>IL-6</td>
<td>0.88 (0.78-0.99)</td>
<td>0.88 (0.78-0.99)</td>
<td>1% (-6 to 9%)</td>
</tr>
<tr>
<td>Grip strength</td>
<td>TNF-α</td>
<td>0.88 (0.78-0.99)</td>
<td>0.88 (0.77-0.98)</td>
<td>1% (-6 to 9%)</td>
</tr>
<tr>
<td>Arm muscle quality</td>
<td>Testosterone</td>
<td>0.86 (0.76-0.97)</td>
<td>0.87 (0.77-0.98)</td>
<td>0% (-12 to 13%)</td>
</tr>
<tr>
<td>Arm muscle quality</td>
<td>IL-6</td>
<td>0.85 (0.76-0.96)</td>
<td>0.86 (0.76-0.96)</td>
<td>0% (-3 to 5%)</td>
</tr>
<tr>
<td>Arm muscle quality</td>
<td>TNF-α</td>
<td>0.87 (0.77-0.98)</td>
<td>0.86 (0.77-0.98)</td>
<td>0% (-10 to 13%)</td>
</tr>
</tbody>
</table>

Odds ratios (95% confidence intervals) for incident diabetes are per 5kg unit increases in grip strength, and per 1kg kg\(^{-1}\) unit increases in arm muscle quality. Significant results are highlighted in bold. IL-6, interleukin-6; TNF-α, tumour necrosis factor-alpha. *Reference Models for grip strength: adjusted for age, income, cohort, waist circumference, fasting plasma glucose, physical activity, hypertension, triglycerides and family history of diabetes. Reference Models for arm muscle quality: adjusted for age, income, cohort, waist circumference, fasting plasma glucose, and family history of diabetes. The odds ratios for the Reference Models differ slightly between testosterone, IL-6, and TNF-α because of missing data.
Table 4. Population Attributable Fractions (PAFs) of incident type 2 diabetes from low grip strength, according to intervention target.

<table>
<thead>
<tr>
<th>PAF</th>
<th>25% Target</th>
<th>10% Target</th>
<th>Mean Grip Target</th>
<th>Mean + 1 SD Target</th>
<th>Mean – 1 SD Target</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>27%</td>
<td>12%</td>
<td>13%</td>
<td>29%</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>(13 to 40%)</td>
<td>(5 to 18%)</td>
<td>(5 to 20%)</td>
<td>(10 to 47%)</td>
<td>(1 to 5%)</td>
</tr>
</tbody>
</table>

PAFs are shown as % (95% confidence interval). SD, standard deviation.

25% Target: all participants increase grip strength by 25%.
10% Target: all participants increase grip strength by 10%.
Mean Grip Target: participants with grip strength below the mean (47.4kg) have an intervention target of 47.4kg; participants with grip strength above the mean remain the same.
Mean + 1 SD Target: participants with grip strength below the mean + 1 standard deviation (57.0kg) have an intervention target of 57.0kg; participants with grip strength above 57.0kg remain the same.
Mean – 1 SD Target: participants with grip strength below the mean – 1 standard deviation (37.2kg) have an intervention target of 37.2kg; participants with grip strength above 37.2kg remain the same.
Figure 1. Flow of MAILES participants throughout the study.

MAILES participants at baseline
(Total n=2563; FAMAS n=1195 plus NWAHS n=1368)

MAILES participants with baseline diabetes data
(n=2490; 97.2%)

Exclude baseline diabetes
(n=379)

MAILES participants without diabetes at baseline
(n=2111)

MAILES participants at 5-year follow-up
(n=1680; 79.6%)

Complete grip strength data
(n=1632; 77.3%)

MAILES, Men Androgen Inflammation Lifestyle Environment and Stress study; FAMAS, Florey Adelaide Male Aging Study; NWAHS, North West Adelaide Health Study.
Figure 2. Stratified associations of grip strength with type 2 diabetes.

P-values shown are the interaction p-values for adjusted analyses. Analyses are adjusted for age, FPG, cohort, WC, and FHx, but not for the variable being stratified (in the analysis of BMI, WC was not adjusted for). FPG, fasting plasma glucose; NWAHS, North West Adelaide Health Study; FAMAS, Florey Adelaide Male Ageing Study; WC, waist circumference; BMI, body mass index; FHx, family history.
Figure 3. Stratified associations of arm muscle quality with incident type 2 diabetes.

Median lean mass per arm in this study was 3.7kg. P-values shown are the interaction p-values for adjusted analyses. Analyses are adjusted for age, FPG, cohort, WC, and FHx, but not for the variable being stratified (in the analysis of BMI, WC was not adjusted for). FPG, fasting plasma glucose; NWAHS, North West Adelaide Health Study; FAMAS, Florey Adelaide Male Ageing Study; WC, waist circumference; BMI, body mass index; FHx, family history.