

# Effectiveness of a multimodal intervention in functionally impaired older people with type 2 diabetes mellitus

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## Abstract

**Background** Type 2 diabetes, a highly prevalent chronic disease, is associated with increasing frailty and functional decline in older people. We aimed to evaluate the effectiveness of a multimodal intervention on functional performance in frail and pre-frail participants aged  $\geq 70$  years with type 2 diabetes mellitus.

**Methods** The MID-Frail study was a cluster-randomized multicenter clinical trial conducted in 74 trial sites across seven European countries. The trial recruited 964 participants who were aged  $>70$  years [mean age in intervention group, 78.4 (SD 5.6) years, 49.2% male and 77.6 (SD 5.29) years, 52.4% male in usual care group], with type 2 diabetes mellitus and determined to be frail or pre-frail using Fried's frailty phenotype. Participants were allocated by trial site to follow either usual care (UCG) or intervention procedures (IG). Intervention group participants received a multimodal intervention composed of (i) an individualized and progressive resistance exercise programme for 16 weeks; (ii) a structured diabetes and nutritional educational programme over seven sessions; and (iii) Investigator-linked training to ensure optimal diabetes care. Short Physical Performance Battery (SPPB) scores were used to assess change in functional performance at 12 months between the groups. An analysis of the cost-effectiveness of the intervention was undertaken using the incremental cost-effectiveness ratio (ICER). Secondary outcomes included mortality, hospitalization, institutionalization, quality of life, burden on caregivers, the frequency and severity of hypoglycaemia episodes, and the cost-effectiveness of the intervention.

**Results** After 12 months, IG participants had mean SPPB scores 0.85 points higher than those in the UCG (95% CI, 0.44 to 1.26,  $P < 0.0001$ ). Dropouts were higher in frail participants and in the intervention group, but significant differences in SPPB between treatment groups remained consistent after sensitivity analysis. Estimates suggest a mean saving following intervention of 428.02 EUR (2016) per patient per year, with ICER analysis indicating a consistent benefit of the described health care intervention over usual care. No statistically significant differences between groups were detected in any of the other secondary outcomes.

**Conclusions** We have demonstrated that a 12 month structured multimodal intervention programme across several clinical settings in different European countries leads to a clinically relevant and cost-effective improvement in the functional status of older frail and pre-frail participants with type 2 diabetes mellitus.

**Keywords** Diabetes; Older people; Frailty; Pre-frail; Functional status; Randomized controlled trial; Multimodal intervention

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## Introduction

Type 2 diabetes mellitus (T2DM) in older people is a complex illness that requires an individualized strategic approach to management, and it is characterized by a spectrum of medical co-morbidities including physical and cognitive functional decline and decreased survival.<sup>1,2</sup> It is also associated with an increased risk of mobility disability, instrumental activity of daily living (ADL) disability, and ADL disability.<sup>3</sup>

Frailty is emerging as a high-impact geriatric syndrome, and according to recent data from the UK Biobank Study, T2DM adds a five-fold increase in the risk of frailty in middle-aged and older people (aged 37–73 years).<sup>4</sup> Frailty is viewed as a generalized loss in physiological reserve capacity associated with functional decline and has an increased risk for negative health outcomes; it is now considered a complication of diabetes that may subsequently account for the unexplained disability excess seen in older diabetic populations.<sup>5</sup> Although the biological processes that underlie frailty are still unclear and likely to be complex and multifactorial, sarcopenia may play an important role in the accelerated decline in leg lean mass, muscle strength, and functional capacity seen in older people with diabetes compared with those without diabetes.<sup>6,7</sup>

Frailty exaggerates the challenges of managing older people and may also increase health and social burdens while also reducing quality of life in older people with diabetes.<sup>8</sup> Key objectives in managing those with functional impairment in a setting of diabetes is to prevent deterioration and activity limitation, avoid disability developing, and improve functional status from a pre-disability (impaired function) state, all of which have been broadly demonstrated in non-diabetic older populations.<sup>9</sup>

There is little evidence for the effectiveness of a single intervention in older people with diabetes at risk for developing disability with recent studies showing conflicting results. In one study, only age and frailty indices, but not co-morbidity or cardiovascular/cerebrovascular diseases, were associated with the risk of death and incident disability after adjusting for measures of frailty.<sup>5</sup> More recently, body mass index and cardio-metabolic factors were shown to explain up to 65% of the excess risk of disability (measured as changes in ADLs) over a 12 year term in those with diabetes.<sup>10</sup> A number of studies have examined the potential cost-effectiveness of either a multimodal approach or a patient-centred approach in enhancing physical function in older people with frailty or mobility problems<sup>11,12</sup> but did not report data in people with diabetes.

Physical exercise in older people is known to be associated with substantial benefits such as cardiovascular risk reduction, improvement in muscle strength and sarcopenia, and mobility disturbances and can lessen the impact of frailty and increase quality of life.<sup>12–15</sup> Tailoring the exercise prescription for physically frail older people is often not straightforward as some older people may not be able to engage regularly in exercise programmes because of their inherent physical restrictions or the associated costs of participation (attending a gym or equipment needed). For those able to participate, resistance training appears to be effective in improving functional capacity including enhancing balance, which may lessen the risk of injurious falls.<sup>16</sup> Less is known of the benefits of exercise in older people with T2DM despite evidence demonstrating that they exhibit greater declines in muscle strength and functional capacity and more rapid loss of muscle mass than do normoglycaemic controls.<sup>17</sup> However, the benefits of resistance training in terms of muscle strength and function have been shown to be comparable in diabetic and non-diabetic participants following a thrice-a-week programme of resistance exercise over 12 weeks.<sup>18</sup>

Although there had been limited evidence only of the benefits of nutritional intervention in reversing frailty, we included a nutritional component in our multimodal approach because earlier studies had suggested that low-micronutrient and low-macronutrient intakes were associated with an increased risk of frailty.<sup>19,20</sup>

We report the results of the MID-Frail randomized trial that assessed whether a multimodal intervention in pre-frail and frail older people with T2DM leads to an improvement in physical performance measured at 12 months at an individual level. We evaluated whether this multimodal approach would lead to improvements in a range of relevant secondary outcomes, whether the intervention could be delivered in both primary and secondary settings without excess difficulty, and whether the intervention was cost-effective in this population.

## Methods

### Study design

The MID-Frail study was a cluster-randomized trial in seven European countries (Belgium, Czech Republic, United Kingdom, France, Germany, Italy, and Spain), which compared the effectiveness of a multimodal intervention with usual care in frail and pre-frail subjects aged  $\geq 70$  years with

T2DM in terms of changes in physical function at 12 months (Figure 1). Randomization was at the level of hospital or primary care site owing to the nature of the intervention, which was likely to change practice for all patients within a site. The full protocol has been published previously.<sup>21</sup> Ethical approval was obtained in each participating country from a national ethics committee or from city or regionally based ethics committees and was in accordance with both national and international laws, as applicable.

The study was originally designed to assess the primary endpoint 2 years post-follow-up [a dichotomized primary outcome of whether an individual improved by one point on the Short Physical Performance Battery (SPPB<sup>22</sup>)]. However, owing to varying national regulatory challenges (mainly with delays in receiving approval to proceed) in opening sites across the European Union (EU) challenging the success of the study, a 14 month extension of the duration of the study and a formal amendment of the protocol were approved by the EU Commission in June 2016. This amendment was mainly focused on three aspects of the protocol: a change in how functional changes as assessed by the SPPB would be modelled (changing from dichotomized SPPB changes to using the SPPB score itself); a shortening in the follow-up period to 12 months for the primary endpoint, which would allow all recruited participants to achieve this time-point; and a recalculation of the sample size based on the new method of assessing the outcome. In this manuscript, we report the findings after 12 months of follow-up.

## Subjects

Subjects were aged 70 years or over, had a diagnosis of T2DM for at least 2 years, and gave informed consent. To be included in the study, subjects had to meet Fried's criteria for pre-frailty or frailty.<sup>23</sup> Reasons for exclusion included poor cognitive function (Mini-Mental State Examination < 20<sup>24</sup>);

having severe limitations in ADLs (Barthel < 60<sup>25</sup>), which would have prevented active participation (did not allow them to perform SPPB measures or follow the physical exercise programme); being unable to safely engage in the exercise component for other health-related reasons; or having a life expectancy of <6 months. Where present, caregivers were asked to provide consent.

Each cluster (hospital or primary care site) randomized was responsible for the main diabetes care element of each participant recruited. Each site was expected to be able to recruit up to 15 eligible subjects and to have the infrastructure/facilities to deliver the intervention. Each site investigator team undertook participant baseline assessments including medical history, physical examination, functional review, and laboratory biochemical and haematological testing. The intention was that participants were not informed about their group allocation (randomization) until each site had recruited seven patients into the clinical trial as part of the bias minimization approach of this cluster trial.

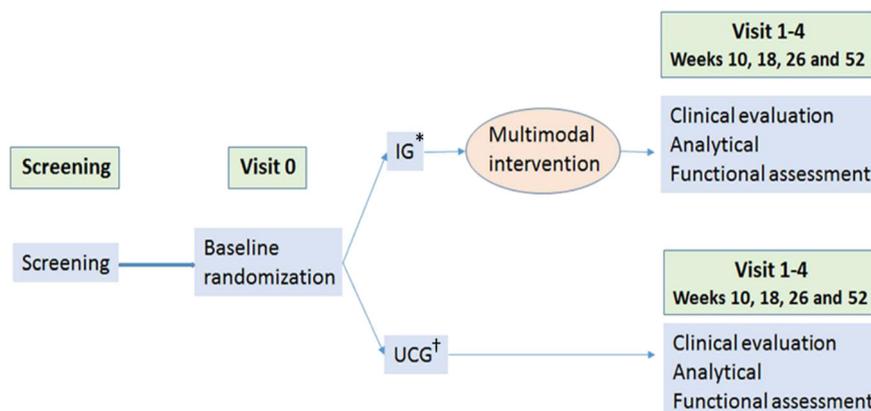
## Description of the intervention and usual care groupings

The intervention arm received a resistance exercise programme, a nutritional and educational programme, and an investigator-enhanced training (in functional assessment and clinical guideline implementation) to optimize diabetes care.

### Investigator training

This was an important component of the intervention to optimize diabetes care of participants in the intervention group. All national and site investigators received detailed training through national co-ordinator-held workshops to ensure standardization of the implementation of the protocol across all participating sites (visit assessments procedures,

**Figure 1** The MID-Frail study diagram. \*IG, intervention group. †UCG, usual care group.



functional review, exercise prescription, nutritional review, and adhering to principles of diabetes care for older people according to recent published international guidance).<sup>26</sup> Without the use of a specific protocol, site investigators were asked to attempt to achieve the following metabolic targets in participants in the IG by 6 months of follow-up: glycated haemoglobin (HbA<sub>1c</sub>; 7–8%, 53–64 mmol/mol) and blood pressure (<150/90 mmHg).

An in-house investigator DVD for training purposes was developed prior to the clinical trial. Each investigator received regular study updates, and each national co-ordinator was available for advice in the conduct of the study and interpretation of the protocol throughout the 12 months of follow-up. Two medical monitors were available at all times.

### Resistance exercise programme

The physical exercise intervention was a supervised individualized resistance exercise programme comprising a 2 week pre-training and learning phase followed by a 16 week programme with subjects undergoing two exercise sessions of 45 min per week.<sup>27</sup> Resistance exercises were appropriate ('tailored') to the individual's functional ability using variable resistance training machines (Exercycle SL, BHGroup, Vitoria, Spain) enabling each participant to achieve two to three sets of 8–10 repetitions with a load equivalent to 40–80% of the estimated one-repetition maximum (1-RM). Participants performed two exercises involving mainly lower-limb muscles (leg press and bilateral knee extension). After a baseline measure of performance at Week 2, intervention group (IG) participants began the 16 week resistance training programme as per protocol.

### Nutritional and educational programme

The nutritional and educational programme was delivered locally at each clinical intervention site and included a nutritional assessment, seven separate 45 min educational sessions delivered by a trained researcher or nutritional therapist, twice a week over 3.5–4 weeks, on the same day as the exercise intervention in the early phase of the study. Educational sessions were delivered to only small numbers of subjects (four to eight) and focused on behaviour change and key health messages such as maintaining an optimal nutritional status, avoiding hypoglycaemia, and diabetes sick-day rules. Each nutritional therapist or researcher was provided with two in-house developed manuals 'Enhancing nutritional status and diabetes knowledge' (manual for trainers) and 'Enhancing nutritional status and diabetes knowledge' (guidance for participants) to support the educational sessions.

### Usual care

Usual care was defined as the level of routine care an older participant with T2DM would normally be expected to

receive from his or her local health care system, including his or her general practitioner.

### Site allocation

Allocation of sites to intervention (IG) or usual care (UCG) was undertaken remotely using a random permuted block assignment method with a block size of four within each country with a ratio of 1:1. Sites were recruited by the Principal Investigators (PIs) in each country; patients were recruited by staff within each site. Each site was required to recruit at least seven subjects before randomization to reduce ascertainment bias. Sites continued to recruit patients after randomization, aiming to achieving 15 subjects for each site; recruitment stopped at the end of the recruiting period. Once sites had reached seven recruits, their details were passed to the statistics team in Cardiff for randomization.

### Outcomes

The primary outcome measure was the SPPB score at 12 months. The SPPB has been extensively used to assess physical performance and functional status in older frail and non-frail populations.<sup>22</sup> The SPPB score is derived from performance in three objective tests: walking speed over 4 m, five timed repeated chair rises, and a standing balance test. Each test is scored from 0 to 4 on the basis of extensive normative data, and the three scores are summed to achieve a total score, ranging from 0 to 12 (where 12 = best).

Secondary outcome measures included the following:

- activities of daily living (Barthel ADL index) and Instrumental ADLs (Lawton instrumental ADL (IADL) scale),<sup>28</sup>
- quality of life [European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5 L)],<sup>29</sup>
- permanent institutionalization,
- caregiver Burden (Modified Caregiver Strain Index<sup>30</sup>),
- episodes of symptomatic hypoglycaemia,
- episodes of hospital admission,
- mortality, and
- cost and efficiency through the incremental cost-effectiveness ratio (ICER).

### Sample size

The original sample size provided 80% power to detect a difference in proportions of functional impairment (reducing by more than one point on the SPPB) from 0.501 to 0.408 using a two-sided hypothesis test and a 5% significance threshold. The sample size was inflated for clustering with an interclass correlation coefficient of 0.05. Assuming a coefficient of variation of 0.25 and an average cluster size of 15 led to a design

effect of 1.747, which yielded a total sample size of 1718. The approved amendment to the protocol was based on a recalculation of the sample size to detect a mean difference in SPPB of one point, with the same design effect and parameters; and this showed that 1000 participants provided 97% power. This amendment to the protocol was made prior to completion of recruitment.

### Economic evaluation

The cost data considered in our analysis comprised the estimated direct health care costs used in both groups as well as those associated with the multimodal intervention during the 12 months of follow-up.

The health care resources were identified via medical records and a specific questionnaire completed by the study subjects and monetized by applying the unit costs of the health care resources of each of the participating countries in order to estimate their cost. They included the estimated costs for visits to the general practitioner and hospital specialists, nurse visits, visits to emergency services (at the health care centre, at the hospital, and domiciliary), medical tests, and hospital admissions. These resources were converted into monetary terms by multiplying them by their respective unit costs. Regarding the costs of the intervention, the multimodal intervention programme employed specific resources as personnel costs (number of professionals who participated in the programmes, their labour cost, the weekly working hours, and the mean time they devoted annually to it); location costs (type of room where the exercise and the nutritional and educational programmes took place, including estimates for the annual cost per square metre for the site); and machinery costs (acquisition cost of the two exercise machines, their transportation cost to the site, and the mean period of machinery's amortization in each country—from 3 to 5 years depending of the accountable norms of each country). All unit costs were adjusted to EUR 2016.

An analysis of cost-effectiveness was carried out comparing both health outcomes and monetary valuation of resources used in the intervention group and the usual care group. The primary outcome of interest of the cost-effectiveness analysis was the ICER. The ICER reveals the incremental cost per unit of benefit of switching from usual care to the intervention group. The health measure considered by the ICER was the difference in SPPB score between the end of the follow-up period and baseline. Univariate and probabilistic analysis were carried out to test the sensitivity of the results.

### Statistical analysis

Descriptive statistics summarized the study population by treatment group. The primary analysis was done by intention

to treat in the population who had follow-up data and compared the difference in mean SPPB score at 12 months' follow-up between the two groups, controlling for baseline SPPB, age (years), Fried criteria (frail/pre-frail), and history of hypertension, stroke/transient ischaemic attack, cancer, hip fracture, osteoporosis, Parkinson's, asthma/chronic obstructive pulmonary disease, chronic heart failure, and osteoarthritis/rheumatoid arthritis (Y/N), using a hierarchical (subjects nested within sites) analysis of covariance linear regression. Secondary analysis of the three component parts of the primary outcome (balance, gait speed, and chair stand data) was undertaken using the same model.

Secondary outcomes were analysed similarly with hierarchical logistic regression replacing hierarchical linear regression where outcomes were dichotomous. The difference between groups was presented using regression coefficients (or odds ratios as appropriate), effect sizes, 95% confidence intervals (CIs), and *P*-values. Standard diagnostics assessed model fit (e.g. inspection of fitted vs. residual plots).

Multiple imputation (MI) was employed to assess the impact of missing data. The imputation used information on all of the variables in the primary analysis to fill in missing SPPB scores. First, those with missing baseline covariates were removed from the dataset before MI was performed. Imputation respected the cluster hierarchy of this trial and imputed missing data using information about the observed covariates and the hierarchy. A second imputation analysis replicated this approach but imputed outcome (SPPB) scores for those who were missing at baseline or later during follow-up. All MI analyses were performed using 50 dataset imputations. Imputation analysis in both cases had participants who died pre-baseline excluded, whereas those who died during the follow-up had their SPPB scores set to zero (lowest possible score). All MI analyses used the 'mice' library in R.<sup>31</sup>

A subgroup analysis explored whether there was a differential treatment effect for those recruited before and after randomization (i.e. after allocation was known). This was achieved by incorporating an interaction term between treatment arm and being recruited pre-randomization or post-randomization into the primary outcome model.

Complier adjusted causal effect models were fitted to account for adherence to the intervention. Adherence to the intervention was defined as attending five of the seven nutritional and educational programme sessions, and attending 23 of the 32 resistance exercise training sessions (this represented >70% of the nutrition and exercise sessions).

## Results

Recruitment opened in December 2014 and closed in February 2016 (see Supporting Information, *Figure S1*). Overall, 964 subjects (inclusion rate, 67%) were recruited and randomized

across 74 sites (average cluster size 13). One hundred eleven subjects (89 allocated to IG and 22 allocated to UCG) withdrew from the study in the period between the randomization of the sites and the beginning of the intervention.

Characteristics of subjects in both groups at the time of randomization are shown in *Table 1*. Subjects were highly co-morbid, with an average duration of T2DM > 15 years with 37.8% being frail. Both groups were functionally well balanced (*Table 2*). Measures of daily living activity demonstrated a relatively high level of functioning despite their frailty status likely due to the exclusion criteria preventing recruitment of low-functioning participants at baseline. Medication utilization was similar in both groups (Supporting Information, *Table S1*).

In order to address concerns about recruitment bias once cluster treatment allocation was assigned, we explored differ-

ences between participants recruited pre-randomization and post-randomization. We noted some evidence that sites allocated to the intervention recruited fewer participants post-randomization than did those allocated to control (51% of pre-randomization participants were in intervention sites vs. 42% post-randomization,  $P$ -value = 0.004). Participants recruited pre-randomization and post-randomization were similar in all explored demographics, including frailty.

Overall, 828 (85.9%) subjects started the interventional phase of the study, and 614 subjects provided complete data sets after 12 months of follow-up (74.2% of those starting the interventional phase). Among those who were lost to follow-up, 48.2% were frail and 51.8% were pre-frail. Regarding group allocation, 47.7% of participants lost to follow-up were from the UCG and 53.3% belonged to the IG group.

**Table 1** Characteristics of the participants at randomization

	Intervention (IG) <i>n</i> = 451	Usual care (UCG) <i>n</i> = 513	Total <i>n</i> = 964
Male, <i>n</i> (%)	222 (49.2)	269 (52.4)	491 (50.9)
Age, mean (SD) [ <i>n</i> ]	78.4 (5.58) [451]	77.6 (5.29) [513]	78.0 (5.44) [964]
Number of years in education, mean (SD) [ <i>n</i> ]	9.5 (4.44) [448]	10.4 (5.00) [508]	10.0 (4.76) [956]
Weight, mean (SD) [ <i>n</i> ]	77.6 (14.95) [450]	79.5 (15.79) [513]	78.6 (15.43) [963]
Height, mean (SD) [ <i>n</i> ]	1.6 (0.10) [447]	1.6 (0.10) [506]	1.6 (0.10) [953]
BMI, mean (SD) [ <i>n</i> ]	29.3 (4.96) [447]	29.8 (4.96) [506]	29.6 (4.96) [953]
Frail, <i>n</i> (%)	170 (33.1)	194 (43.0)	364 (37.8)
Race, <i>n</i> (%)			
White Caucasian	482 (94.0)	400 (88.7)	882 (91.5)
Latino Hispanic	15 (2.9)	46 (10.2)	61 (6.3)
Other	16 (3.2)	5 (1.1)	21 (2.1)
Previous symptomatic hypoglycaemia? Yes, <i>n</i> (%)	40 (11.4)	50 (10.2)	90 (10.7)
Age at diagnosis, mean (SD) [ <i>n</i> ]	62.9 (12.97) [330]	59.6 (16.26) [474]	61.0 (15.07) [804]
Years since diagnosis, mean (SD) [ <i>n</i> ]	15.1 (12.15) [330]	18.1 (15.83) [474]	16.9 (14.49) [804]
Heart rate, mean (SD) [ <i>n</i> ]	73.2 (11.04) [448]	73.4 (11.29) [511]	73.3 (11.17) [959]
Systolic blood pressure, mean (SD) [ <i>n</i> ]	140.6 (18.37) [447]	139.5 (19.00) [509]	140.0 (18.71) [956]
Diastolic blood pressure, mean (SD) [ <i>n</i> ]	74.6 (10.09) [447]	75.9 (12.15) [509]	75.3 (11.25) [956]
Glycated haemoglobin %, mean (SD) [ <i>n</i> ]	7.21 (1.23) [400]	7.33 (1.18) [485]	7.28 (1.21) [885]
Co-morbidities, <i>n</i> (%)			
Hypertension	385 (85.4)	453 (88.3)	838 (86.9)
Stroke/TIA	55 (12.2)	77 (15.0)	132 (13.7)
Cancer	49 (10.9)	78 (15.2)	127 (13.2)
Hip fracture	16 (3.5)	20 (3.9)	36 (3.7)
Osteoporosis	67 (14.9)	72 (14.0)	139 (14.4)
Parkinson's disease	15 (3.3)	15 (2.9)	30 (3.1)
Asthma/COPD	56 (12.4)	80 (15.6)	136 (14.1)
CHF	41 (9.1)	41 (8.0)	82 (8.5)
OA/RA	140 (31.0)	127 (24.8)	267 (27.7)

BMI, body mass index; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; OA/RA, osteoarthritis/rheumatoid arthritis; TIA, transient ischaemic attack.

**Table 2** Functional and cognitive status of the participants at randomization

	Intervention (IG) <i>n</i> = 451	Usual care (UCG) <i>n</i> = 513	Total <i>n</i> = 964
SPPB, mean (SD) [ <i>n</i> ]	8.2 (2.61) [353]	8.6 (2.65) [491]	8.4 (2.64) [844]
Barthel, mean (SD) [ <i>n</i> ]	96.3 (7.03) [353]	95.7 (7.57) [491]	96.0 (7.35) [844]
IADL, mean (SD) [ <i>n</i> ]	7.1 (1.53) [353]	6.8 (1.76) [491]	6.9 (1.67) [844]
MMSE, mean (SD) [ <i>n</i> ]	26.9 (2.96) [451]	26.9 (3.18) [513]	26.9 (3.08) [964]

IADL, instrumental activities of daily living; MMSE, Mini-Mental State Examination; SPPB, Short Physical Performance Battery.

## Outcomes

At 12 months' follow-up, the intervention group had SPPB scores on average 0.85 points higher (indicating better function) than those of the usual care group (95% CI, 0.44 to 1.26,  $P$ -value < 0.001) after controlling for baseline values (Table 3). As described previously, imputation was performed for subjects whom baseline data were available but either follow-up data or covariate data were missing (sensitivity analysis A) and also for subjects who dropped out between screening and baseline (sensitivity analysis B). Both of these methods reduced the intervention effect minimally. The adjusted final effect marginally changed from 0.85 SPPB points (95% CI, 0.44 to 1.26,  $P$ -value < 0.001) to 0.83 (95% CI, 0.58 to 1.11,  $P$ -value = 0.003) and 0.81 (95% CI, 0.51 to 1.11,  $P$ -value = 0.003) when Sensitivity Analyses A and B were used, respectively. Findings remained both statistically significant ( $P$  = 0.003 for both sensitivity analyses). In a post hoc analysis, we assessed the percentage of subjects improving by 1 or more points during 12 months of follow-up, and this revealed a significant difference between groups (46% in IG vs. 38% in the UCG;  $P$  = 0.001). The adjusted odds ratio for this difference was 1.81 (95% CI, 1.11 to 2.94,  $P$ -value = 0.014).

Fried's frailty status (pre-frail or frail) at baseline did not have any influence on the response to treatment. There were no differences in the intervention effects between subjects of either frailty status (point estimate, 0.25; 95% CI, -0.45 to 0.94,  $P$ -value = 0.49).

Functional differences between the groups was noticeable at first follow-up (10 weeks), observable at 26 weeks, and seen through 1 year of follow-up (Tables 3 and 4). Significant differences between the groups were seen in each of the three domains of the SPPB (particularly the chair stand component) as shown in the Supporting Information (Table S2).

Eighty two per cent of participants in the intervention arm met the adherence criteria ( $n$  = 191). A complier-average causal effects<sup>32</sup> analysis estimated the intervention effect on SPPB at 12 months with full adherence to be 1.04 (95% CI, 0.66 to 1.38,  $P$ -value < 0.001), that is, just over one SPPB point for those who completed all aspects of the intervention.

In relation to the secondary outcomes, there were no clinically relevant or statistically significant effects of intervention per se for either IADL or Barthel ADL measures (Table 5). Neither was there any significant evidence of an improvement in quality of life using the EQ-5D-5L measure. No differences in carer burden were detected for the 34 participants who reported having a carer being involved in their diabetes care.

The multi-level models for the binary outcomes (episodes of hypoglycaemia, hospitalization, permanent institutionalization, and death) failed to converge, and so the unadjusted differences are presented. The number of permanent institutionalizations was low in both arms [7.3% ( $n$  = 20) IG vs. 5.8% ( $n$  = 25) UCG], without statistical significance. The

**Table 3** Result of analysis of the primary outcome (SPPB) and sensitivity analyses.

	Baseline Mean (95% CI)	1 year Mean (95% CI)	Unadjusted mean difference (1 year follow-up—baseline) (95% CI)	Adjusted <sup>a</sup> mean difference (95% CI)	$P$ -value	ICC
<b>Primary analysis</b>						
Usual care ( $n$ = 381)	8.83 (8.58 to 9.09)	8.71 (8.41 to 9.01)	0.66 (0.22 to 1.1)	0.85 (0.44 to 1.26)	<0.001	0.066
Intervention ( $n$ = 233)	8.55 (8.22 to 8.87)	9.37 (9.04 to 9.70)				
<b>Sensitivity analysis A</b>						
Usual care ( $n$ = 491)	8.62 (8.39 to 8.86)	8.32 (8.02 to 8.62)	0.46 (0.42 to 0.50)	0.83 (0.58 to 1.11)	0.003	0.062
Intervention ( $n$ = 353)	8.19 (7.91 to 8.46)	8.78 (8.44 to 9.12)				
<b>Sensitivity analysis B</b>						
Usual care ( $n$ = 513)	8.58 (8.35 to 8.81)	8.30 (8.00 to 8.59)	0.39 (0.34 to 0.43)	0.81 (0.51 to 1.11)	0.003	0.040
Intervention ( $n$ = 451)	8.07 (7.81 to 8.32)	8.69 (8.37 to 9.00)				

ICC, interclass correlation coefficient.

<sup>a</sup>Adjusted for baseline SPPB, age, gender, frailty, co-morbidities, and clustering by site.

**Table 4** Changes in SPPB along the follow-up visits

		Baseline Mean, 95% CI	Follow-up Mean, 95% CI	Unadjusted mean difference (95% CI)	Adjusted <sup>a</sup> mean difference (95% CI)	P-value	ICC
SPPB at 10 weeks	Usual care (n = 440)	8.65 (8.41 to 8.90)	8.90 (8.65 to 9.15)	0.26 (-0.12 to 0.63)	0.37 (0.04 to 0.68)	0.030	0.083
	Intervention (n = 283)	8.45 (8.14 to 8.75)	9.16 (8.88 to 9.44)				
SPPB at 18 weeks	Usual care (n = 412)	8.76 (8.51 to 9.01)	9.02 (8.76 to 9.27)	0.30 (-0.09 to 0.68)	0.35 (-0.09 to 0.77)	0.120	0.168
	Intervention (n = 264)	8.47 (8.16 to 8.77)	9.31 (9.02 to 9.60)				
SPPB at 26 weeks	Usual care (n = 399)	8.78 (8.53 to 9.04)	8.98 (8.72 to 9.25)	0.53 (0.13 to 0.93)	0.55 (0.11 to 0.98)	0.020	0.164
	Intervention (n = 241)	8.57 (8.25 to 8.90)	9.51 (9.21 to 9.81)				

ICC, interclass correlation coefficient.

<sup>a</sup>Adjusted for baseline SPPB, age, gender, frailty, co-morbidities and clustering by site.

differences between groups in rates of hypoglycaemia, hospitalization, or death did not demonstrate statistical significance.

The cost-effectiveness analysis (Table 6), however, showed that participants included at the intervention programme incurred on average lower health care cost per patient vs. usual care of 428.02 EUR (2016) per patient per year, mainly owing to minor hospitalization costs [540.93 EUR (2110.08)] in the IG group compared with the UCG group [1176.75 EUR (3730.92); saving 630.82 EUR;  $P = 0.041$ ] (Table 7), with incremental gain in SPPB score per patient included at the intervention programme vs. usual care during the follow-up period (Figure 2). Univariate and probabilistic sensibility analyses suggested that the economic evaluation conclusions remained valid (intervention remained favourable and dominant; Table 6).

The percentage of participants with HbA<sub>1c</sub> between 7% and 8% and BP  $\leq$  150/90 mmHg increased significantly in the IG (26% at baseline vs. 36.8% at 12 months,  $P = 0.02$ , and 65.4% vs. 75.5%,  $P = 0.02$ , respectively), while changes were detected in the UCG only for BP (66.2% vs. 74.1%,  $P = 0.04$ ) (Supporting Information, Table S3).

The clinical trial safety review showed no serious adverse events relating to the multicomponent intervention. Adverse events in both groups of participants are given in the Supporting Information (Table S4).

## Discussion

Type 2 diabetes mellitus, the most frequently reported metabolic disorder in Western communities, has emerged as an important co-morbidity producing functional impairment in older people. Although the effect of T2DM on risk of mortality in populations decreases with age,<sup>33</sup> its effect on functional health becomes more noticeable as the population ages.<sup>2</sup> The outcomes of intervention studies designed to improve functional status in older people at risk of disability (e.g. being frail/pre-frail) are not as clear. Whereas some studies have reported positive effects on health status from exercise and nutritional intervention,<sup>34</sup> others found little benefit and stressed for the need of a larger study to clarify the evidence.<sup>35</sup>

As the largest international trial of its kind to date, the MID-Frail study has shown significant beneficial effects of a multimodal intervention (resistance exercise, diabetes and nutritional education, investigator training to optimize diabetes care) on functional status assessed by the SPPB at 12 months of follow-up in frail and pre-frail older adults with T2DM aged 70 years and over. Our observations confirm that the multimodal intervention not only results in higher functional status (higher SPPB score) but also results in health care cost savings. The majority of the cost savings

Table 5 Effect of intervention on the secondary outcomes

		Baseline Mean, (95% CI)	1 year Mean, 95% CI	Unadjusted mean difference (95% CI)	Adjusted <sup>a</sup> mean difference (95% CI)	P-value	ICC <sup>b</sup>
IADL	Usual care (n = 387)	6.89 (6.72 to 7.06)	6.75 (6.56 to 6.93)	0.20 (-0.08 to 0.49)	0.00 (-0.27 to 0.28)	0.974	0.12
	Intervention (n = 237)	7.09 (6.89 to 7.29)	6.95 (6.73 to 7.17)				
Barthel	Usual care (n = 385)	95.95 (95.20 to 96.70)	94.91 (93.80 to 96.02)	1.23 (-0.24 to 2.70)	0.39 (-1.84 to 2.56)	0.729	0.19
	Intervention (n = 237)	96.20 (95.25 to 97.16)	96.14 (95.17 to 97.11)				
EQ-5D-5 L	Usual care (n = 343)	0.76 (0.73 to 0.78)	0.74 (0.72 to 0.77)	0.07 (0.03 to 0.11)	0.04 (-0.01 to 0.08)	0.086	0.14
	Intervention (n = 214)	0.80 (0.78 to 0.83)	0.81 (0.79 to 0.84)				
MCSI	Usual care (n = 12)	21.25 (16.68 to 25.82)	21.92 (18.99 to 24.84)	-2.46 (-6.16 to 1.24)	-1.63 (-4.78 to 1.52)	0.436	<0.01
	Intervention (n = 22)	19.64 (17.44 to 21.84)	19.45 (16.92 to 21.99)				
		% (n) (95% CI)	Unadjusted difference (intervention—usual care) (95% CI)				
Episodes of symptomatic hypoglycaemia	Usual care (n = 386)	26.9% (104)	-4.3% (-11.5 to 3.0%)				
	Intervention (n = 238)	22.7% (54)					
Episodes of hospitalization	Usual care (n = 386)	17.6% (65)	-4.2% (-10.2 to 1.7%)				
	Intervention (n = 238)	13.3% (30)					
Permanent institutional	Usual care (n = 430)	5.8% (25)	1.5% (5.6% to -2.6%)				
	Intervention (n = 273)	7.3% (20)					
Death	Usual care (n = 400)	4.6% (11.3%)	-0.4% (0 to -0.85%)				
	Intervention (n = 244)	3.2% (n = 13)					
		1.5% (to 4.9%)					
		2.8% (n = 7)					
		0.8% (to 4.9%)					

The multi-level models for the binary outcomes (episodes of hypoglycaemia, hospitalization, permanent institutionalization, and death) failed to converge, and so the unadjusted differences are presented.

EQ-5D-5L, European Quality of Life-5 Dimensions-5 Levels; MCSI, Modified Caregiver Strain Index.

<sup>a</sup>Adjusted for baseline measure, age, gender, frailty, co-morbidities, and clustering by site.

<sup>b</sup>Interclass correlation coefficient. The ICC for this logistic regression was calculated setting the residual variance to  $(\pi^2)/3$ .

**Table 6** Cost-effectiveness analysis

	ΔCosts (EUR 2016)	Incremental ratio (intervention vs. usual care)
Base case	-428.02	Intervention dominates control
Sensitivity analysis		
Optimized the mean number of patients participating in the programme (20 individuals per centre)	-478.64	Intervention dominates control
Machinery amortization period (2 years)	-373.71	Intervention dominates control
No machinery location costs	-492.55	Intervention dominates control
+10% primary care costs only in the intervention group	-377.04	Intervention dominates control
+10% specialists costs only in the intervention group	-404.08	Intervention dominates control
+10% medical tests costs only in the intervention group	-413.66	Intervention dominates control
+10% hospitalization costs only in the intervention group	-373.23	Intervention dominates control
+10% health care costs only in the intervention group	-250.88	Intervention dominates control
+20% health care costs only in the intervention group	-73.74	Intervention dominates control

Base case (principal analysis) and sensitivity according to different scenarios.

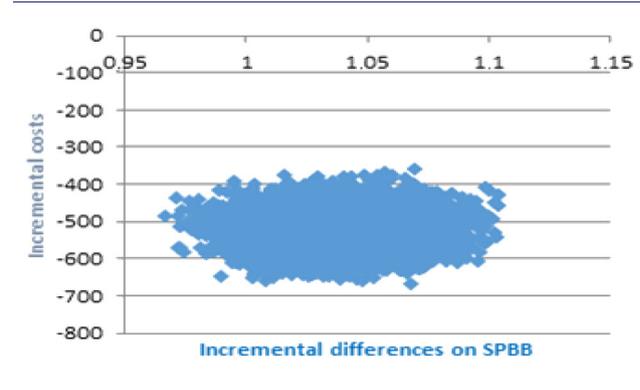
**Table 7** Mean annual direct health care cost by group during the follow-up period (EUR 2016 per patient)

	Intervention Group (n = 236) Mean (SD)	Usual clinical practice (n = 387) Mean (SD)
Intervention costs	331.75 (127.75)	0
Primary care visits	506.14 (1698.07)	611.50 (1832.78)
GP	122.58 (128.08)	153.57 (180.86)
Nursing	322.03 (1617.85)	385.72 (1721.00)
Emergencies	60.42 (154.28)	69.94 (238.33)
Medical visits to specialists	244.73 (275.51)	265.68 (316.56)
Geriatrician	49.94 (109.42)	63.49 (132.27)
Ophthalmologist	37.31 (74.46)	32.90 (83.66)
Physiotherapist	23.96 (125.43)	26.99 (71.87)
Endocrinologist	12.73 (34.93)	26.92 (71.8)
Podiatrist	19.10 (62.88)	17.31 (55.30)
Cardiologist	22.05 (38.72)	19.96 (46.09)
Medical tests/examinations	142.69 (201.15)	140.84 (179.58)
Laboratory blood tests	77.83 (111.88)	73.65 (81.31)
Echocardiography	15.01 (33.61)	8.03 (24.62)
Hospitalizations	540.93 (2113.08)*	1176.75 (3736.92)
Total direct health care costs	1766.25 (3159.89)	2194.78 (4914.18)

GP, general practitioner.

\*P < 0.05.

were based on the reduction in hospitalization, with savings for other components of the health care resource utilization being marginal. Considering that there were no statistically significant differences in the rate of hospitalizations between groups, it appears that a lower cost per episode for those allocated to the IG is the reason for the disparity. When we developed the cost-effectiveness analysis, all the scenarios supported superiority of intervention vs. the usual care (minor costs; better health outcomes). To our knowledge, this is the first economic evaluation of an intervention focused on older people who have both T2DM and frailty, and this provides a platform for further studies to determine whether community-based strategies to improve the functional status of frail older people with T2DM may lead to cost savings.

**Figure 2** The ICER considering direct health care costs (EUR 2016) and differences on SPPB.

At the end of the 12 months' follow-up, we observed that the functional status for those in the IG remained significantly higher than in the UCG. This represented a functional improvement (i.e. at least one SPPB point higher) in 53% of participants in the IG. Based on a subgroup analysis of the LIFE-P study, a change of one point on the SPPB score would be regarded as a meaningful change in an individual (the patient would benefit), although a score < 1 between groups of individuals in some cases might also be meaningful.<sup>36</sup> Future studies might consider how differences in SPPB scores following an intervention may represent different degrees of meaningful change depending on the nature of the population under study. Full adherence to the intervention programme led to higher benefits being recorded.

Although the exercise intervention ceased after 16 weeks, participants did not experience a rapid loss in physical function (deconditioning), which is observed in many studies.<sup>16,37</sup> In the MID-Frail study, the exercise routine employed is likely to have provided a sufficient stimulus to large leg muscle groups by using resistance training machines and moderate loads that ranged from 40% to 80% of individual maximal voluntary strength following a programme proven to increase muscle mass, strength, and functional ability in older people with

T2DM.<sup>27</sup> In contrast, in the LIFE study, the physical activity programme was of low intensity and focused on small muscle groups (i.e. 0.5-kg ankle weights, with subjects performing two sets of 10 repetitions) and may have been an insufficient stimulus to prevent long-term decline of physical function.<sup>9</sup> Longer-term effects of the educational programme may have also played an additional role in producing this sustained beneficial effect. These results reinforce the importance of resistance training interventions using moderate intensities (40–80% of 1-RM) as a worthwhile strategy to achieve and maintain benefits after long-term training cessation.

We did not observe any clear differences between the groups in measures of IADL or Barthel ADL, although in a period of only 12 months, this finding may have been predicted because frailty is a pre-disability state and participants with any significant measurable level of disability were excluded at the recruitment stage. As the rate of spontaneous annual conversion from pre-frailty and frailty to disability is lower than 10%<sup>38</sup> and that baseline functional status measured by IADL and basic ADL (used as measures of disability) was relatively high in both groups (indicating relatively high functioning and a potential ceiling effect), the period of follow-up (12 months) in our study was unlikely to be sufficient to capture conversions from frailty to a disability state (often identified by changes in IADL or ADL).

During the 12 months of follow-up, no significant differences between groups were observed in any of other secondary outcomes, although several of them (quality of life, hypoglycaemic events, and hospitalizations) indicated a non-statistically significant tendency towards improvement in the IG. We can only speculate that a longer period of follow-up or a further period of active intervention (proposed in the original research protocol) may have led to differences emerging between the groups.

No meaningful differences were seen in carer burden presumably influenced by the low numbers of carers reported. Because participants were relatively high functioning (despite their frailty status) at baseline based on ADL and IADL measures, it is perhaps not surprising that carer involvement was less likely. This same explanation might account for the low institutionalization rate.

Our observations appear to expand on the recent findings from the LIFE study,<sup>9</sup> which used the SPPB measure to characterize subjects and assess the effects of multicomponent physical exercise in a general older population (where 25.5% had T2DM) during a prolonged period ( $\geq 2$  years). In a recent post hoc sub-analysis of the LIFE study, the authors also reported that physical exercise is useful in both frail and non-frail individuals,<sup>39</sup> further supporting our findings in our unique diabetic population.

During the study, we experienced an unexpected high number of dropouts in both groups between the time of randomization of a clinical site and the time of intervention representing a potential limitation to the study. This was

partially explained by the long time period (often 3–4 months in some cases) for a site to reach its main target of 15 participants recruited as per protocol. Although this phenomenon is a recognized issue with cluster-randomized trials, which are known to suffer from bias introduced by a lack of allocation concealment at recruitment, we had not anticipated this problem.<sup>40</sup> The sensitivity analysis conducted to control for bias confirmed that the benefits were maintained and were highly resistant to dropouts both before and after starting the intervention, with a quite similar size effects and statistical significances in the three scenarios (the original analysis and the two sensitivity analysis). In addition, our analysis revealed no statistically significant interaction between intervention and frailty status at baseline, indicating that benefits are shown in both frail and pre-frail subjects. The loss of participants at follow-up (25.8%) is slightly higher to that originally estimated (20%) but similar to that observed in comparable studies such as the LIFE study (24.1% in the intervention arm and 27.3% in the educational arm).<sup>9</sup>

The MID-Frail study placed a great emphasis on investigator training and continued study updates and availability of advice from national co-ordinators and study medical monitors. Site investigators were provided with recently published guidelines<sup>26</sup> to guide their overall diabetes care of participants and in particular to ensure safe levels of HbA<sub>1c</sub> and blood pressure targets as previously outlined. At 12 months of follow-up, participants in the IG were significantly more likely to be in the target ranges for both HbA<sub>1c</sub> and blood pressure compared with baseline in contrast with participants in the UCG where only blood pressure was significantly more likely to be within target range. It is possible that optimizing glycaemia may have enhanced the effect of exercise and nutrition in improving functional status in the IG because this approach has been shown to preserve muscle strength in patients with dysregulated T2DM (mean age of 67 years).<sup>41</sup> Alternatively, the effect of resistance training in the IG group may have also contributed to this improved more consistent level of glycaemia via improvements in insulin action in skeletal muscle.<sup>42</sup> This is an area worthy of further investigation.

The strengths of the MID-Frail Study include the generalizability of the findings in this highly representative study population, the feasibility of practical implementation of the intervention in both primary and secondary care settings, and a legacy of benefits long after the physical and educational parts of the intervention had ceased. Once the physical exercise intervention had begun, it was associated with a high rate of adherence, demonstrating it to be acceptable to a broad range of frail older adults. Another key strength of the MID-Frail study is that it was conducted in a large sample across multiple sites in the EU and was delivered in a complex and functionally impaired group of older adults; this is a challenging population to study, but our results provide a positive impetus for other studies in this area.

In conclusion, a structured multimodal intervention composed of a short-term moderate-intensity physical resistance exercises, combined with a nutritional and educational programme and medical optimization, leads to a significant improvement in function in older adults with T2DM and varying frailty status saving costs, proving to be an efficient intervention. These findings are highly applicable to this vulnerable sector of the population at an early stage of functional decline and can be implemented in a range of routine clinical settings.

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Authors LR-M, OL and AJ S made substantial contributions to all aspects of the work described. Authors BV, GP, ET, JO-M, IB-M, MI, KH, AZ, GG, MP, TCH, MJK, IB, GA, MB,

LMP-L, SCR, RC, SDB also made important contributions to the planning, conduct, reporting, and interpretation of the work described. Authors LR-M, KH, TCH, MJK, and made substantial contributions to the writing of the manuscript including all drafts and final draft.

## Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Usage of medications in both randomization groups  
**Table S2.** Between group changes in individual domain scores of the SPPB measure

**Table S3.** Changes between baseline and the 1-year follow up stage in the percentage of participants in both groups achieving particular HbA1c and blood pressure categories

**Table S4.** Adverse Events by group and disease area

**Figure S1.** CONSORT flow diagram for the MID-Frail Study

## References

- Sinclair AJ, Dunning T, Rodríguez-Mañas L. Diabetes in older people: new insights and remaining challenges. *Lancet Diabetes Endocrinol* 2015;**3**:275–285.
- GBD 2015DALYs and HALE collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016;**388**:1603–1658.
- Wong E, Backholer K, Gearon E, Harding J, Freak-Poli R, Stevenson C, et al. Diabetes and risk of physical disability in adults: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2013;**1**:106–114.
- Hanlon P, Nicholl BI, Jani BD, Lee D, McQueenie R, Mair FS. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants. *Lancet Public Health* 2018;**3**:e323–e332.
- Castro-Rodríguez M, Carnicero JA, Garcia-Garcia FJ, Walter S, Morley JE, Rodríguez-Artalejo F, et al. Frailty as a major factor in the increased risk of death and disability in older people with diabetes. *J Am Med Dir Assoc* 2016;**17**:949–955.
- Volpato S, Bianchi L, Lauretani F, Lauretani F, Bandinelli S, Guralnik JM, et al. Role of muscle mass and muscle quality in the association between diabetes and gait speed. *Diabetes Care* 2012;**35**:1672–1679.
- Sinclair AJ, Abdelhafiz AH, Rodríguez-Mañas L. Frailty and sarcopenia—newly emerging and high impact complications of diabetes. *J Diabetes Complications* 2017 Sep;**31**:1465–1473.
- Sinclair A, Morley J. Frailty and diabetes. *Lancet* 2013;**382**:1386–1387.
- Pahor M, Guralnik JM, Ambrosius WT, Blair S, Bonds DE, Church TS, et al. Effect of structured physical activity on prevention of major mobility disability in older adults: the LIFE study randomized clinical trial. *JAMA* 2014;**311**:2387–2396.
- Koye DN, Shaw JE, Magliano DJ. Diabetes and disability in older Australians: the Australian Diabetes, Obesity and Lifestyle (AusDiab) study. *Diabetes Res Clin Pract* 2017;**126**:60–67.
- Fairhall N, Sherrington C, Kurlle SE, Lord SR, Lockwood K, Howard K, et al. Economic evaluation of a multifactorial, interdisciplinary intervention versus usual care to reduce frailty in frail older people. *J Am Med Dir Assoc* 2015;**16**:41–48.
- de Vries NM, Staal JB, van der Wees PJ, Adang EMM, Akkermans R, Olde Rikkert MGM, et al. Patient-centred physical therapy is (cost-)effective in increasing physical activity and reducing frailty in older adults with mobility problems: a randomized controlled trial with 6 months follow-up. *J Cachexia Sarcopenia Muscle* 2016;**7**:422–435.
- Cesari M, Landi F, Vellas B, Bernabei R, Marzetti E. Sarcopenia and physical frailty: two sides of the same coin. *Front Aging Neurosci* 2014;**6**:192.
- Theou O, Stathokostas L, Roland KP, Jakobi JM, Patterson C, Vandervoort AA, et al. The effectiveness of exercise interventions for the management of frailty: a systematic review. *J Aging Res* 2011;**2011**:569194.
- Cesari M, Vellas B, Hsu FC, Newman AB, Doss H, King AC, et al. A physical activity intervention to treat the frailty syndrome in older persons—results from the LIFE-P study. *J Gerontol A Biol Sci Med Sci* 2015;**70**:216–222.
- Cadore EL, Rodríguez-Manas L, Sinclair A, Izquierdo M. Effects of different exercise interventions on risk of falls, gait ability and balance in physically frail older adults. A systematic review. *Rejuvenation Res* 2013;**16**:105–114.
- Cadore EL, Izquierdo M. Exercise interventions in polypathological aging patients that coexist with diabetes mellitus: improving functional status and quality of life. *Age (Dord)* 2015;**37**:64.
- Geirsdottir OG, Amarson A, Briem K, Ramel A, Jonsson PV, Thorsdottir I. Effect of 12-week resistance exercise program on body composition, muscle strength, physical function and glucose metabolism in healthy, insulin-resistant, and diabetic elderly Icelanders. *J Gerontol A Biol Med Sci* 2012;**67**:1259–1265.
- Bartali B, Frongillo EA, Bandinelli S, Lauretani F, Semba RD, Fried LP, et al. Low nutrient intake is an essential component of frailty in older persons. *J Gerontol A Biol Sci Med Sci* 2006;**61**:589–593.
- Semba RD, Bartali B, Zhou J, Blaum C, Ko CW, Fried LP. Low serum micronutrient concentrations predict frailty among older women living in the community. *J Gerontol A Biol Sci Med Sci* 2006;**61**:594–599.

21. Rodríguez-Mañas L, Bayer AJ, Kelly M, Zeyfang A, Izquierdo M, Laosa O, et al. An evaluation of the effectiveness of a multimodal intervention in frail and pre-frail older people with type 2 diabetes—the MID-Frail study: study protocol for a randomised controlled trial. *Trials* 2014;**15**:34.
22. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. *N Engl J Med* 1995;**332**:556–562.
23. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;**56**:M146–M156.
24. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;**12**:189–198.
25. Mahoney FI, Barthel D. Functional evaluation: the Barthel Index. *Md State Med J* 1965;**14**:56–61.
26. Sinclair AJ, Paolisso G, Castro M, Bourdel-Marchasson I, Gadsby R, Rodríguez-Mañas L. European Diabetes Working Party for Older People. European Diabetes Working Party for Older People 2011 clinical guidelines for type 2 diabetes mellitus. Executive summary. *Diabetes Metab* 2011;**37**:S27–S38.
27. Ibañez J, Izquierdo M, Argüelles I, Forga L, Larrión JL, García-Unciti M, et al. Twice-weekly progressive resistance training decreases abdominal fat and improves insulin sensitivity in older men with type 2 diabetes. *Diabetes Care* 2005;**28**:662–667.
28. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* 1969;**9**:179–186.
29. Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L, et al. Measurement properties of the EQ-5D-3L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res* 2013;**22**:1717–1727.
30. Onega LL. Helping those who help others: The Modified Caregiver Strain Index. *Am J Nurs* 2008;**108**:69–70.
31. van Buuren S, Groothuis-Oudshoorn K. Multivariate imputation by chained equations in R. *Journal of Statistical Software* 2011;**45**:1–67. URL <http://www.jstatsoft.org/v45>.
32. Kasim A, ZhiMin Xiao, Higgings s, De Troyer E. R package version 1.0.6. <https://CRAN.R-project.org/package=eefAnalytics>
33. Gregg EW, Cheng YJ, Srinivasan M, Lin J, Geiss LS, Albright AL, et al. Trends in cause-specific mortality among adults with and without diagnosed diabetes in the USA: an epidemiological analysis of linked national survey and vital statistics data. *Lancet* 2018;**391**:2430–2440.
34. Fairhall N, Sherrington C, Cameron ID, Kurrle SE, Lord SR, Lockwood K, et al. A multifactorial intervention for frail older people is more than twice as effective among those who are compliant: complier average causal effect analysis of a randomised trial. *J Physiother* 2017;**63**:40–44.
35. Clegg A, Barber S, Young J, Iliffe S, Forster A. The Home-based Older People’s Exercise (HOPE) trial: a pilot randomised controlled trial of a home-based exercise intervention for older people with frailty. *Age Ageing* 2014;**43**:687–695.
36. Kwon S, Perera S, Pahor M, Katula JA, King AC, Groessl EJ, et al. What is a meaningful change in physical performance? Findings from a clinical trial in older adults (the LIFE-P study). *J Nutr Health Aging* 2009;**13**:538–544.
37. Henderson RM, Miller ME, Fielding RA, Gill TM, Glynn NW, Guralnik JM, et al. Maintenance of physical function 1 year after exercise intervention in at-risk older adults: follow-up from the LIFE Study. *J Gerontol A Biol Sci Med Sci* 2018;**73**:688–694.
38. Espinoza SE, Jung I, Hazuda H. Frailty transitions in the San Antonio Longitudinal Study of Aging. *J Am Geriatr Soc* 2012;**60**:652–660.
39. Trombetti A, Hars M, Hsu FC, Reid KF, Church TS, Gill TM, et al. Effect of physical activity on frailty: secondary analysis of a randomized controlled trial. *Ann Intern Med* 2018 Mar 6;**168**:309–316.
40. Puffer S, Torgerson D, Watson J. Evidence for risk of bias in cluster randomised trials: review of recent trials published in three general medical journals. *BMJ* 2003;**327**:785–789.
41. Nielsen R, Wiggers H, Thomsen HH, Bovin A, Refsgaard J, Abrahamsen J, et al. Effect of tighter glycemic control on cardiac function, exercise capacity, and muscle strength in heart failure patients with type 2 diabetes: a randomized study. *BMJ Open Diabetes Res Care* 2016 Apr 29;**4**:e000202.
42. Cartee GD. Mechanisms for greater insulin-stimulated glucose uptake in normal and insulin-resistant skeletal muscle after acute exercise. *Am J Physiol Endocrinol Metab* 2015 Dec 15;**309**:E949–E959.
43. von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2017. *J Cachexia Sarcopenia Muscle* 2017;**8**:1081–1083.