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Original Research

Effects of multicomponent exercise on frailty in older adults with type 2 diabetes: Differential responses by metabolic frailty phenotype

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ABSTRACT

Background: Frailty in older adults with type 2 diabetes mellitus (T2DM) is metabolically heterogeneous, but whether multicomponent exercise (MCE) produces phenotype-specific functional benefit remains unclear. We asked two linked clinical questions: does a supervised 24-week MCE program improve physical function and frailty versus usual care, and are those effects modified by metabolic frailty phenotype (anorexic–malnourished [AM] phenotype vs sarcopenic–obese [SO] phenotype)?

Methods: In this 24-week, phenotype-stratified, parallel-group randomized controlled trial, 146 community-dwelling adults aged ≥65 years with long-standing T2DM and frailty/pre-frailty who met predefined AM or SO criteria were randomized within phenotype to supervised MCE or usual care (AM-Control/MCE 31; SO—Control/MCE 42). Co-primary outcomes were Short Physical Performance Battery (SPPB) score and Fried frailty phenotype count. Key secondary outcomes were 4-m gait speed, five-chair-stand time, and grip strength. Covariate-adjusted generalized estimating equation models of change from baseline to 12 and 24 weeks included intervention, phenotype, visit, and all interactions, and adjusted for baseline outcome, age, sex, BMI, baseline HbA1c, metformin, SGLT2 inhibitor, GLP-1RA, insulin, diabetic retinopathy, diabetic peripheral neuropathy, chronic kidney disease stage ≥3, and hypertension. Benjamini-Hochberg false-discovery-rate correction was applied across functional outcome comparisons.

Results: Arm-level baseline balance was good overall, whereas AM and SO were intentionally distinct at baseline in adiposity, nutrition, glycemia, inflammation, and insulin resistance. Compared with usual care, MCE improved all functional outcomes at both follow-up visits. At 24 weeks, adjusted MCE-control differences were +1.14 points for SPPB (95 % CI 0.99 to 1.28), -0.64 for Fried count (95 % CI -0.77 to -0.51), +0.111 m/s for gait speed (95 % CI 0.095 to 0.127), -1.42 s for chair-stand time (95 % CI -1.70 to -1.14), and +0.94 kg for grip strength (95 % CI 0.72 to 1.16); all BH $q < 0.001$. Treatment-by-phenotype interactions at 24 weeks favored SO for SPPB (+0.50 points, 95 % CI 0.22 to 0.79; $q = 0.005$), gait speed (+0.048 m/s, 95 % CI 0.016 to 0.080; $q = 0.012$), and chair-stand time (-0.82 s, 95 % CI -1.37 to -0.27; $q = 0.012$), whereas the Fried-count interaction was not significant.

Conclusions: A supervised 24-week MCE program improved physical function and frailty in older adults with T2DM and frailty/pre-frailty. Functional gains were larger in the SO than AM phenotype for several performance-based outcomes, suggesting phenotype-dependent responsiveness. Because this trial deliberately focused on two endpoint phenotypes and excluded intermediate presentations, the findings should be interpreted as clinically informative but not definitive for phenotype-guided care.

Trial Registration: Registered prospectively in the Chinese Clinical Trial Registry (ChiCTR), a WHO ICTRP primary registry (registration no ChiCTR2400090109; http://www.chictr.org.cn/), on 24 September 2024, before enrollment.

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1. Introduction

Frailty is highly prevalent among older adults with type 2 diabetes mellitus (T2DM) and is associated with accelerated functional decline, increased hospitalization, and mortality [1–3]. However, frailty in this population is increasingly recognized as a biologically and clinically heterogeneous condition that cannot be adequately explained by chronological age or glycemic control alone [4–6]. Substantial interindividual differences in body composition, nutritional status, inflammatory burden, and insulin sensitivity shape both the mechanisms and clinical expression of frailty in older adults with T2DM [7,8]. These observations challenge the traditional view of frailty as a uniform syndrome and highlight the need for a metabolically informed framework.

In recent years, the concept of metabolic frailty has been proposed to capture this heterogeneity, conceptualizing frailty as a continuum driven by opposing disturbances in energy balance and muscle–fat interactions [9–11]. At one end of this spectrum are individuals characterized by negative energy balance, malnutrition, and muscle wasting; at the other are those with excess adiposity, ectopic fat accumulation, chronic low-grade inflammation, and pronounced insulin resistance [10–12]. This framework provides a biologically plausible explanation for the diverse frailty phenotypes observed in older adults with diabetes.

Within this continuum, two prototypical metabolic frailty phenotypes are commonly described. The AM phenotype is characterized by low or declining body mass, reduced muscle mass and strength, inadequate energy and protein intake, and limited metabolic reserves, conferring heightened vulnerability to catabolic stress and rapid functional deterioration [13–15]. In contrast, the SO phenotype combines reduced muscle quantity and function with excess, predominantly visceral, adiposity, and is accompanied by systemic inflammation, insulin resistance, and adverse lipid profiles [12,16–18]. Although individuals with both phenotypes may meet criteria for frailty or pre-frailty, they differ fundamentally in underlying pathophysiology, clinical trajectories, and potentially in responsiveness to intervention [9,19].

MCE programs incorporating resistance, aerobic, and balance training are among the most effective interventions to prevent or reverse frailty and improve physical performance in older adults [20,21]. In people with T2DM, structured exercise additionally improves insulin sensitivity, glycemic control, and inflammatory status [22,23]. However, emerging evidence suggests that the efficacy of exercise interventions may depend critically on the underlying metabolic milieu [11,24]. In individuals with the SO phenotype, exercise may simultaneously enhance muscle function, reduce visceral adiposity, and attenuate inflammation, resulting in substantial functional gains [16]. In contrast, in those with the AM phenotype, chronic undernutrition and limited energy availability may constrain adaptive responses to exercise unless accompanied by adequate nutritional support [14,25]. Whether identical exercise prescriptions yield comparable benefits across these contrasting metabolic frailty phenotypes remains unclear.

In this phenotype-stratified randomized trial, we asked a single primary clinical question: compared with usual care, does a 24-week supervised multicomponent exercise (MCE) program improve physical function and frailty in community-dwelling adults aged ≥65 years with long-standing T2DM and frailty/pre-frailty, and are those effects modified by metabolic frailty phenotype (AM vs SO)? We hypothesized that MCE would improve SPPB and Fried frailty count overall, with larger performance gains in SO than in AM; this question is most relevant to clinicians, rehabilitation teams, and service planners deciding whether a standard exercise prescription is likely to be sufficient or should be combined with nutritional support.

2. Methods

2.1. Study design and participants

2.1.1. Design

This was a 24-week, phenotype-stratified, parallel-group randomized controlled trial in community-dwelling older adults with long-standing type 2 diabetes mellitus (T2DM) and frailty or pre-frailty. The prespecified primary scientific question was whether responsiveness to a standardized multicomponent exercise (MCE) program differed between two contrasting metabolic frailty phenotypes: the anorexic–malnourished (AM) phenotype and the sarcopenic–obese (SO) phenotype.

2.1.2. Trial registration

This trial was registered prospectively in the Chinese Clinical Trial Registry (ChiCTR), a WHO ICTRP primary registry, on 24 September 2024 (registration no ChiCTR2400090109; http://www.chictr.org.cn/), prior to enrollment of the first participant.

2.1.3. Participants and recruitment setting

In October 2024, we initiated collaboration with physicians from three community health service centers (Shuibei, Tongtai, and Zhaoyang) in Shaowu, Fujian Province, China, and conducted recruitment across the centers' catchment communities. By 30 October, 244 community residents met screening criteria for physician-diagnosed T2DM and the Fried frailty phenotype (frailty or pre-frailty). Screening counts by center were: Shuibei ($n = 67$), Tongtai ($n = 96$), and Zhaoyang ($n = 81$). Detailed screening and exclusion information is presented in the flow diagram.

2.1.4. Assessment and delivery setting

Baseline assessments and follow-up outcome measurements were performed through the collaborating community and hospital network. Supervised exercise sessions and standardized health education were delivered at the community health service centers by trained rehabilitation therapists and geriatric physicians. Community workers assisted with participant contact, appointment reminders, and adherence monitoring.

2.1.5. Eligibility criteria

Eligible participants were aged ≥65 years, had physician-diagnosed T2DM for at least 10 years, lived independently in the community, and met criteria for frailty or pre-frailty according to the Fried frailty phenotype (≥3 or 1–2 criteria, respectively) [26]. Exclusion criteria included severe cognitive impairment, major neurological or musculoskeletal disorders limiting mobility, unstable cardiovascular disease, acute illness or hospitalization within the preceding 3 months, or other contraindications to exercise as determined by a study physician, in line with established exercise safety guidance for older adults with chronic disease [27].

2.1.6. Randomization, allocation concealment, and blinding

After phenotype classification, participants within each phenotype stratum were randomized in a 1:1 ratio to either the MCE intervention or control group. Randomization sequences were generated by an independent statistician using a computer-based algorithm with variable block sizes of 4–8. Allocation concealment was ensured using sequentially numbered, opaque, sealed envelopes prepared off-site. Outcome assessors and laboratory personnel were blinded to group assignment. Because of the nature of the intervention, participants and exercise instructors were not blinded.

2.1.7. Definition of metabolic frailty phenotypes

The AM phenotype was defined as:

(1) malnutrition according to the Global Leadership Initiative on Malnutrition (GLIM) criteria [28];
(2) possible sarcopenia according to the 2019 Asian Working Group for Sarcopenia (AWGS) definition (low muscle strength with SPPB <9) [29]; and
(3) absence of central obesity (waist circumference <90 cm in men and <80–85 cm in women) [30].

Supportive features included unintentional weight loss ≥5 % within the previous 6 months, low serum albumin, or documented insufficient energy and/or protein intake, consistent with prior descriptions of malnutrition-driven frailty and cachexia-related muscle loss [14,15].

The SO phenotype was defined as:

(1) general and/or central obesity (BMI ≥25 kg/m^2 for Asian populations and/or elevated waist circumference);
(2) possible sarcopenia according to AWGS 2019; and
(3) metabolic dysregulation, indicated by metabolic syndrome defined using International Diabetes Federation (IDF) criteria [31].

These criteria reflect the coexistence of excess adiposity, impaired muscle function, insulin resistance, and low-grade inflammation, as described in prior studies of sarcopenic obesity and metabolic frailty in older adults with T2DM [11,16,18].

2.2. Intervention

2.2.1. MCE intervention

The MCE intervention was delivered at the community health service centers by trained rehabilitation therapists in collaboration with geriatric physicians, following established recommendations for frail older adults and individuals with T2DM [20,22,27]. Participants attended supervised group sessions three times per week for 24 weeks; each session lasted approximately 60 min and included 4–8 participants. Sessions comprised (1) 5–10 min of warm-up; (2) 20–25 min of moderate-intensity aerobic exercise (walking or cycling) at 50–70 % of heart-rate reserve; (3) 20 min of progressive resistance training for major upper- and lower-limb muscle groups, initiated at approximately 60 % of one-repetition maximum and increased by 5–10 % as tolerated; (4) 5–10 min of balance and functional training; and (5) cool-down. Intensity and progression were individualized based on symptoms, perceived exertion, and performance, with on-site monitoring of heart rate and adverse symptoms [27]. Intervention delivery was continuous apart from brief pauses during major Chinese statutory holidays (e.g., Spring Festival and National Day), after which sessions resumed according to the same prescription (reported in the Supplementary Appendix).

2.2.2. Adherence and safety

Attendance was recorded at each session. Community workers supported adherence through reminders and follow-up contacts. Vital signs and capillary glucose were monitored according to site procedures, and adverse events were reviewed by study physicians.

2.2.3. Control condition

Control participants continued usual medical care for T2DM and received standardized monthly health education sessions at the community centers (e.g., diabetes self-management, fall prevention, and nutrition advice), but did not receive a structured exercise program.

2.3. Outcomes

2.3.1. Primary, secondary, and exploratory outcomes

Primary outcomes were lower-extremity physical function assessed by the Short Physical Performance Battery (SPPB) and frailty severity assessed by the Fried frailty phenotype count [26].

Secondary outcomes included gait speed, chair-stand performance, and handgrip strength, which are validated indicators of mobility and frailty severity in older adults [32,33].

Exploratory outcomes included glycated hemoglobin (HbA1c), high-sensitivity C-reactive protein (hsCRP), triglyceride-to-HDL cholesterol ratio, and homeostatic model assessment of insulin resistance (HOMA-IR); these were used to contextualize phenotype biology and were interpreted cautiously.

2.3.2. Assessment time points

Assessments were performed at baseline, week 12, and week 24 for SPPB, Fried frailty count, gait speed, chair-stand time, grip strength, and the exploratory biochemical markers.

2.3.3. Sample size considerations

The trial was designed as a phenotype-stratified randomized study focused on whether response to MCE differs between AM and SO, rather than as a definitive implementation trial. Based on previous studies on the relationship between exercise and frailty, we assumed that the standard deviation estimate of the change in SPPB score was 1.6 points. If we have approximately 40 participants per phenotype-by-treatment cell, the study provides a certain precision for overall treatment effects but only moderate precision for interaction estimates and limited precision for mechanistic inference. Accordingly, phenotype-by-treatment interaction analyses were prespecified and emphasized, but they remain inferentially more fragile than the overall treatment contrasts.

2.4. Statistical analysis

Baseline characteristics were summarized as mean ± SD for continuous variables and n (%) for categorical variables. Because significance testing alone can be misleading for randomized baseline comparisons, baseline tables report both P values and absolute standardized differences (ASDs) for the overall MCE-versus-control comparison; phenotype-stratified baseline values are also presented descriptively by the four randomized cells (AM-Control, AM-MCE, SO—Control, SO-MCE). All randomized participants were analyzed according to assigned group.

The primary analysis followed the intention-to-treat principle. For the five functional outcomes (SPPB, Fried frailty count, 4-m gait speed, five-chair-stand time, and grip strength), the main analysis modeled change from baseline at weeks 12 and 24 using generalized estimating equations with an exchangeable working correlation structure and robust sandwich standard errors. Each model included intervention group, phenotype, visit, all two-way interactions, the three-way intervention-by-phenotype-by-visit interaction, the corresponding baseline outcome value, and the following prespecified baseline covariates: age, sex, BMI, baseline HbA1c, metformin use, SGLT2 inhibitor use, GLP-1RA use, insulin use, diabetic retinopathy, diabetic peripheral neuropathy, chronic kidney disease stage ≥3, and hypertension. From these models we estimated adjusted mean changes for each phenotype-by-treatment cell and derived three contrasts at each visit: (i) overall MCE versus control, (ii) SO versus AM within the MCE arm, and (iii) the treatment-by-phenotype interaction (difference-in-differences).

To address multiplicity, Benjamini-Hochberg false-discovery-rate (BH-FDR) correction was applied separately to the overall treatment contrasts and the treatment-by-phenotype interaction contrasts across the five functional outcomes at two follow-up visits. Within-MCE SO-versus-AM comparisons were presented as supportive analyses. Exploratory biomarker analyses (HbA1c, hsCRP, TG/HDL ratio, and HOMA-IR) used analogous adjusted models and were interpreted as hypothesis-generating rather than confirmatory. As sensitivity analyses, we conducted multiple imputations for missing outcomes. All tests were two-sided and analyses were performed in Python.

3. Results

3.1. Participant flow, intervention delivery, adherence, and safety

Between October 1 and 30, 2024, eligible community-dwelling older adults were recruited via three community health service centers in Shaowu City (Shuibei, Tongtai, and Zhaoyang). A total of 244 individuals with T2DM and Fried-defined frailty or pre-frailty were screened; 146 met criteria for either the anorexic–malnourished (AM) phenotype ($n = 62$) or the sarcopenic–obese (SO) phenotype ($n = 84$) and were randomized within phenotype strata to MCE or usual care (73 per group; Fig. 1). Follow-up assessments at 12 and 24 weeks were completed by 97.3 % and 96.6 % of all randomized participants, respectively; within the MCE arm, 69/73 (94.5 %) and 68/73 (93.2 %) completed the 12- and 24-week assessments. Among all randomized MCE participants, median attendance over the 24-week program was 86.1 % of prescribed sessions (range 43.1 %–98.6 %). Primary analyses followed the intention-to-treat principle. Exercise-related adverse events were uncommon and nonserious, consisting of mild hypoglycemia, transient dizziness/lightheadedness, and musculoskeletal discomfort; no exercise-related serious adverse events were recorded in the trial dataset.

3.2. Baseline characteristics

Overall baseline balance between MCE and control was good, including demographic factors, functional status, glucose-lowering medications, hypertension, chronic kidney disease stage ≥3, diabetic peripheral neuropathy, and diabetic retinopathy; all ASDs were small (Table 1). By contrast, the two metabolic frailty phenotypes were intentionally distinct at baseline. Relative to AM, SO participants had higher BMI, waist circumference, HbA1c, hsCRP, TG/HDL ratio, and HOMA-IR, whereas AM participants had lower MNA-SF scores and worse chair-stand performance. Baseline values by the four randomized phenotype-by-treatment cells are shown in Table 2 and indicate that randomization remained broadly balanced within phenotype strata.

3.3. Overall covariate-adjusted functional effects of MCE

In the covariate-adjusted models, MCE improved both co-primary outcomes and all key secondary functional outcomes compared with usual care at 12 and 24 weeks (Table 3). At 12 weeks, adjusted MCE-control differences were +0.758 for SPPB, −0.346 for Fried frailty count, +0.068 m/s for gait speed, −0.997 s for chair-stand time, and +0.737 kg for grip strength; all BH $q < 0.001$. At 24 weeks, the corresponding adjusted differences were +1.137 for SPPB (95 % CI 0.989 to 1.284), −0.644 for Fried frailty count (95 % CI −0.773 to −0.515), +0.111 m/s for gait speed (95 % CI 0.095 to 0.127), −1.420 s for chair-stand time (95 % CI −1.700 to −1.140), and +0.942 kg for grip strength (95 % CI 0.721 to 1.163); again, all BH $q < 0.001$. Because these outcomes were measured repeatedly at baseline, 12 weeks, and 24 weeks, the results describe performance trajectories over 24 weeks rather than isolated endpoint differences. The consistent separation at 12 weeks with further gains by 24 weeks supports a progressive training response under continued supervision.

3.4. Differential response by metabolic frailty phenotype

The phenotype-response analyses are shown in Table 4. At 24 weeks, formal treatment-by-phenotype interactions indicated larger SO-than-AM treatment effects for SPPB (+0.505, 95 % CI 0.221 to 0.789; $q = 0.005$), gait speed (+0.048 m/s, 95 % CI 0.016 to 0.080; $q = 0.012$), and chair-stand time (−0.820 s, 95 % CI −1.371 to −0.269; $q = 0.012$). The interaction was not significant for Fried frailty count, and the 24-week grip-strength interaction did not survive multiplicity correction. Within the MCE arm, SO participants showed directionally larger gains than AM participants at 24 weeks for SPPB, gait speed, chair-stand time, and grip strength, but these within-arm contrasts were less precise and should be interpreted as supportive rather than primary evidence.

3.5. Exploratory metabolic and inflammatory outcomes

Exploratory adjusted biomarker analyses at 24 weeks also favored MCE, with MCE-control differences of −0.320 % for HbA1c, −0.725 mg/L for hsCRP, −0.322 for TG/HDL ratio, and −1.059 for HOMA-IR (all nominal $P < 0.001$). Nominal treatment-by-phenotype interactions for these biomarkers generally favored SO, but because these analyses were exploratory, underpowered for hard metabolic endpoints, and were not intended to establish mechanism, we do not foreground them in the abstract or conclusion.

4. Discussion

In this phenotype-stratified randomized trial of 146 older adults with

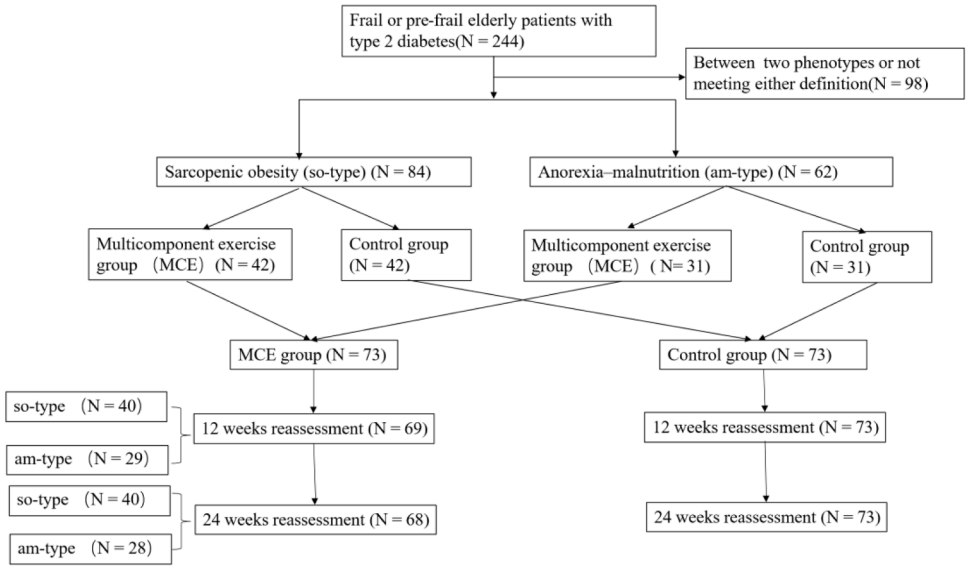

Fig. 1. CONSORT flow diagram of participant progress through phenotype screening, randomization, and follow-up.

Table 1
Baseline characteristics: MCE vs control.

Variable	MCE (n = 73)	Control (n = 73)	P value	Absolute standardized difference
Age, years	74.18 ± 4.63	74.45 ± 4.87	0.656	0.057
Female, n (%)	40 (54.8 %)	41 (56.2 %)	1.000	0.016
BMI, kg/m^2	25.19 ± 4.04	25.33 ± 3.94	0.786	0.035
Waist circumference, cm	87.93 ± 9.01	88.67 ± 9.95	0.537	0.079
SPPB score	6.96 ± 1.66	6.91 ± 1.66	0.819	0.029
Fried phenotype count	3.14 ± 1.42	3.14 ± 1.26	1.000	0.000
4-m gait speed, m/s	0.83 ± 0.12	0.80 ± 0.11	0.061	0.239
Five-chair-stand time, s	15.32 ± 2.16	15.28 ± 2.18	0.891	0.017
Grip strength, kg	18.91 ± 5.62	18.34 ± 5.34	0.409	0.105
MNA-SF score	11.36 ± 1.54	11.45 ± 1.44	0.637	0.060
HbA1c, %	7.81 ± 0.79	7.68 ± 0.62	0.171	0.174
hsCRP, mg/L	3.22 ± 1.73	3.36 ± 1.74	0.529	0.080
TG/HDL ratio	4.63 ± 2.04	4.36 ± 1.98	0.289	0.135
HOMA-IR	4.75 ± 2.76	4.48 ± 2.22	0.395	0.108
Metformin use, n (%)	60 (82.3 %)	53 (72.6 %)	0.126	0.214
SGLT2 inhibitor use, n (%)	24 (32.9 %)	21 (28.8 %)	0.583	0.087
GLP-1RA use, n (%)	12 (16.4 %)	15 (20.5 %)	0.510	0.105
Insulin use, n (%)	25 (34.2 %)	27 (37.0 %)	0.691	0.067
Hypertension, n (%)	50 (68.5 %)	48 (65.8 %)	0.787	0.052
Chronic kidney disease stage ≥3, n (%)	22 (30.1 %)	15 (20.5 %)	0.107	0.223
Diabetic peripheral neuropathy, n (%)	24 (32.9 %)	25 (34.2 %)	0.788	0.051
Diabetic retinopathy, n (%)	19 (26.0 %)	16 (21.9 %)	0.453	0.114

Note: ASD, absolute standardized difference; SPPB, Short Physical Performance Battery; MNA-SF, Mini Nutritional Assessment Short-Form; hsCRP, high-sensitivity C-reactive protein; HOMA-IR, homeostatic model assessment of insulin resistance; GLP-1RA, glucagon-like peptide-1 receptor agonist.

T2DM and frailty/pre-frailty, a 24-week supervised MCE program improved both co-primary outcomes and all key secondary functional outcomes compared with usual care. Repeated assessments at baseline, 12 weeks, and 24 weeks showed favorable performance trajectories over time, with early improvement by 12 weeks and further separation by 24 weeks. The phenotype question also received a qualified positive answer: participants with the SO phenotype showed larger gains than those with the AM phenotype for performance-based outcomes at 24 weeks, particularly SPPB, gait speed, and chair-stand time, whereas improvement in Fried frailty count was similar across phenotypes.

The contrast between performance measures and Fried frailty count is clinically important. SPPB, gait speed, and chair-stand time changed in a phenotype-dependent way, but Fried count did not. This suggests that metabolic frailty phenotype may influence the magnitude of neuromuscular and mobility adaptation more than short-term transition across the relatively coarse Fried categories. Accordingly, the most convincing evidence for phenotype-dependent responsiveness in this trial comes from the formal treatment-by-phenotype interaction terms for performance-based outcomes, not from within-arm subgroup contrasts alone. The magnitude of change also appears clinically meaningful: the adjusted 24-week between-group differences of 1.14 points in SPPB and 0.111 m/s in gait speed are within or above commonly cited ranges for substantial meaningful improvement in lower-extremity performance and walking speed [34]. Given that slow gait is consistently associated with disability, falls, institutionalization, and mortality in community-dwelling older adults, the observed gait-speed trajectory is potentially relevant for mobility-related risk stratification [35].

Table 2
Baseline characteristics by metabolic phenotype and randomized group.

Variable	AM-Control (n = 31)	AM-MCE (n = 31)	SO—Control (n = 42)	SO-MCE (n = 42)
Age, years	74.23 ± 5.00	73.81 ± 4.67	74.67 ± 4.76	74.55 ± 4.60
Female, n (%)	18 (58.1 %)	17 (54.8 %)	23 (54.8 %)	23 (54.8 %)
BMI, kg/m^2	22.24 ± 1.81	21.91 ± 2.17	28.41 ± 2.95	28.47 ± 2.53
SPPB score	6.76 ± 1.58	6.61 ± 1.57	7.06 ± 1.74	7.11 ± 1.72
Fried phenotype count	3.18 ± 1.32	3.16 ± 1.36	3.10 ± 1.21	3.11 ± 1.40
4-m gait speed, m/s	0.78 ± 0.11	0.80 ± 0.12	0.82 ± 0.11	0.85 ± 0.11
Five-chair-stand time, s	15.53 ± 2.15	15.83 ± 1.96	15.03 ± 2.19	14.80 ± 2.25
Grip strength, kg	18.41 ± 5.20	18.64 ± 5.95	18.26 ± 5.51	19.19 ± 5.30
MNA-SF score	10.90 ± 1.45	10.77 ± 1.45	12.00 ± 1.22	11.96 ± 1.39
HbA1c, %	7.53 ± 0.60	7.53 ± 0.71	7.84 ± 0.61	8.09 ± 0.78
hsCRP, mg/L	1.88 ± 0.64	1.77 ± 0.59	4.83 ± 1.13	4.66 ± 1.19
TG/HDL ratio	2.95 ± 1.00	3.37 ± 0.98	5.76 ± 1.71	5.88 ± 2.06
HOMA-IR	3.10 ± 1.22	2.76 ± 1.15	5.86 ± 2.14	6.74 ± 2.45
Chronic kidney disease stage ≥3, n (%)	7 (22.6 %)	11 (35.5 %)	8 (19.0 %)	11 (26.2 %)

Note: This table is descriptive and shows phenotype-stratified baseline values in the four randomized cells. AM, anorexic–malnourished phenotype; SO, sarcopenic–obese phenotype; MNA-SF, Mini Nutritional Assessment Short-Form; hsCRP, high-sensitivity C-reactive protein; HOMA-IR, homeostatic model assessment of insulin resistance.

The larger SO response is biologically plausible. The SO phenotype combines reduced muscle function with excess adiposity, insulin resistance, and low-grade inflammation, all of which are plausible targets of combined aerobic and resistance exercise. The exploratory biomarker results were directionally consistent with this interpretation, because MCE was associated with overall improvements in HbA1c, hsCRP, TG/HDL ratio, and HOMA-IR and the nominal biomarker interactions generally favored SO. However, these biomarker findings remain hypothesis-generating, the study was not powered for hard metabolic endpoints or mediation analyses, and they should not be interpreted as demonstrating mechanism.

In participants with the AM phenotype, lower nutritional reserve may limit adaptation to exercise alone. The smaller gains observed in the AM phenotype should therefore not be interpreted as absence of benefit; rather, they suggest that a standard MCE prescription may be insufficient when undernutrition, reduced protein intake, or catabolic burden are prominent. From a clinical standpoint, patients with AM features may need lower initial training loads, closer monitoring, and earlier nutritional optimization alongside exercise.

A central design choice was to focus on the two endpoint metabolic frailty phenotypes, the anorexic–malnourished (AM) phenotype and the sarcopenic–obese (SO) phenotype, rather than the much larger middle

Table 3
Covariate-adjusted change from baseline: MCE vs control.

Outcome	Week	Adjusted difference (MCE - Control)	95 % CI	P value	BH q value
SPPB score	12 weeks	0.758	0.758 (0.618, 0.897)	<0.001	<0.001
SPPB score	24 weeks	1.137	1.137 (0.989, 1.284)	<0.001	<0.001
Fried phenotype count	12 weeks	−0.345	−0.345 (−0.484, −0.207)	<0.001	<0.001
Fried phenotype count	24 weeks	−0.644	−0.644 (−0.773, −0.515)	<0.001	<0.001
4-m gait speed, m/s	12 weeks	0.068	0.068 (0.051, 0.085)	<0.001	<0.001
4-m gait speed, m/s	24 weeks	0.111	0.111 (0.095, 0.127)	<0.001	<0.001
Five-chair-stand time, s	12 weeks	−0.997	−0.997 (−1.283, −0.710)	<0.001	<0.001
Five-chair-stand time, s	24 weeks	−1.420	−1.420 (−1.700, −1.140)	<0.001	<0.001
Grip strength, kg	12 weeks	0.737	0.737 (0.511, 0.963)	<0.001	<0.001
Grip strength, kg	24 weeks	0.942	0.942 (0.721, 1.163)	<0.001	<0.001

Note: Adjusted differences are estimated from intention-to-treat generalized estimating equation (GEE) models of change from baseline with an exchangeable working correlation structure and robust standard errors, adjusted for baseline outcome value, age, sex, BMI, baseline HbA1c, metformin use, SGLT2 inhibitor use, GLP-1RA use, insulin use, diabetic retinopathy, diabetic peripheral neuropathy, chronic kidney disease stage ≥3, and hypertension. BH q values were derived from Benjamini-Hochberg false-discovery-rate correction across the five functional outcomes at two visits.

spectrum of metabolic frailty. We made that choice intentionally to maximize biological contrast and improve the chance of detecting effect modification. These definitions should therefore be understood as endpoint phenotypes on an underlying metabolic-frailty continuum, not as an exhaustive classification of frailty in older adults with T2DM. This strengthens interpretability as a proof-of-concept phenotype trial, but it also narrows external validity and may accentuate phenotype differences relative to routine practice, where many older adults with T2DM have mixed or intermediate features. Accordingly, the present estimates should not be generalized to intermediate or mixed phenotypes without further study. Their practical value is more modest and more realistic: phenotype tendency may help clinicians and rehabilitation teams judge whether a standard MCE program is likely to be sufficient, or whether exercise should be moderated and paired with nutritional support.

Several other limitations deserve emphasis. First, this was a single-city, community-based, highly supervised program; our sample consisted of relatively old (mean age ~74 years), community-dwelling adults with ≥10-year T2DM, moderate comorbidity burden, and reduced but still ambulatory baseline function (mean SPPB ~6.9; gait speed ~0.81 m/s). External validity is therefore greatest for similar outpatient/community cohorts rather than nursing-home residents, recently hospitalized patients, or individuals with very advanced disability. Second, follow-up was limited to 24 weeks, so we cannot infer durability or effects on disability, falls, hospitalization, or mortality. Third, although we applied full covariate adjustment, BMI and HbA1c are close to the phenotype construct itself; this conservative strategy may have attenuated, rather than exaggerated, phenotype contrasts. Fourth, no structured nutritional co-intervention was provided, which is especially relevant for the AM phenotype. Finally, the biomarker panel was limited and no imaging-based body-composition measures were available, so causal or mechanistic inference remains weak. From an implementation perspective, median attendance in the MCE arm was 86.1 % over 24 weeks, and delivery depended on existing community health service centers, therapist-led supervision, and coordination with geriatric physicians and community workers for safety and adherence monitoring; these features may help other outpatient/community systems judge transferability.

For future work, the most useful next step is a multicenter phenotype-stratified trial that either includes intermediate phenotypes or models phenotype as a continuum, extends follow-up beyond 12 months, and tests exercise-plus-nutrition support in AM. Using the observed 24-week SPPB interaction in this dataset (~0.47–0.50 points),

Table 4
Covariate-adjusted phenotype-response analyses.

Outcome	Week	Analysis	Adjusted difference	95 % CI	P value	BH q value
SPPB score	12 weeks	SO vs AM within MCE	0.069	0.069 (−0.225, 0.363)	0.644	0.805
SPPB score	12 weeks	Treatment × phenotype interaction	0.069	0.069 (−0.197, 0.335)	0.609	0.677
SPPB score	24 weeks	SO vs AM within MCE	0.376	0.376 (0.054, 0.697)	0.022	0.055
SPPB score	24 weeks	Treatment × phenotype interaction	0.505	0.505 (0.221, 0.788)	<0.001	0.005
Fried phenotype count	12 weeks	SO vs AM within MCE	−0.008	−0.008 (−0.272, 0.257)	0.955	0.955
Fried phenotype count	12 weeks	Treatment × phenotype interaction	−0.018	−0.018 (−0.284, 0.249)	0.897	0.897
Fried phenotype count	24 weeks	SO vs AM within MCE	−0.121	−0.121 (−0.373, 0.132)	0.350	0.500
Fried phenotype count	24 weeks	Treatment × phenotype interaction	−0.131	−0.131 (−0.374, 0.113)	0.294	0.491
4-m gait speed, m/s	12 weeks	SO vs AM within MCE	0.019	0.019 (−0.017, 0.054)	0.307	0.500
4-m gait speed, m/s	12 weeks	Treatment × phenotype interaction	0.015	0.015 (−0.018, 0.048)	0.381	0.545
4-m gait speed, m/s	24 weeks	SO vs AM within MCE	0.054	0.054 (0.023, 0.086)	<0.001	0.007
4-m gait speed, m/s	24 weeks	Treatment × phenotype interaction	0.048	0.048 (0.016, 0.080)	0.003	0.012
Five-chair-stand time, s	12 weeks	SO vs AM within MCE	−0.091	−0.091 (−0.651, 0.468)	0.749	0.833
Five-chair-stand time, s	12 weeks	Treatment × phenotype interaction	−0.205	−0.205 (−0.763, 0.352)	0.471	0.589
Five-chair-stand time, s	24 weeks	SO vs AM within MCE	−0.661	−0.661 (−1.208, −0.114)	0.018	0.055
Five-chair-stand time, s	24 weeks	Treatment × phenotype interaction	−0.820	−0.820 (−1.371, −0.269)	0.004	0.012
Grip strength, kg	12 weeks	SO vs AM within MCE	0.654	0.654 (0.155, 1.153)	0.010	0.051
Grip strength, kg	12 weeks	Treatment × phenotype interaction	0.547	0.547 (0.093, 1.001)	0.018	0.045
Grip strength, kg	24 weeks	SO vs AM within MCE	0.478	0.478 (0.022, 0.933)	0.040	0.079
Grip strength, kg	24 weeks	Treatment × phenotype interaction	0.283	0.283 (−0.156, 0.722)	0.206	0.412

Note: Adjusted differences are estimated from the same intention-to-treat generalized estimating equation (GEE) models described for Table 3. "Treatment × phenotype interaction" denotes the difference-in-differences contrast. Within-MCE SO-versus-AM comparisons are supportive analyses. BH q values were derived from Benjamini-Hochberg false-discovery-rate correction across the five functional outcomes at two visits. AM, anorexic–malnourished phenotype; SO, sarcopenic–obese phenotype.

a confirmatory 2 × 2 trial would require roughly 100 participants per cell (about 400 total) for 80 % power. Until such data are available, the clinical message is cautious but actionable: supervised MCE can be recommended as a core component of frailty care in older adults with T2DM, while phenotype information may help tailor intensity and the need for concurrent nutritional support rather than dictate a rigid yes/no treatment decision.

5. Conclusions

Among community-dwelling older adults with T2DM and frailty/pre-frailty who met AM or SO criteria, 24 weeks of supervised MCE improved physical function and reduced frailty relative to usual care. The response was larger in the SO than AM phenotype for performance-based outcomes, especially at 24 weeks. Because the trial deliberately focused on two endpoint phenotypes and excluded intermediate presentations, these findings should be interpreted as preliminary guidance for tailoring care within endpoint phenotypes, not definitive evidence for phenotype-guided protocols across the full metabolic-frailty spectrum.

Abbreviations

T2DM, type 2 diabetes mellitus; MCE, multicomponent exercise; AM, anorexic–malnourished phenotype; SO, sarcopenic–obese phenotype; SPPB, Short Physical Performance Battery; MNA-SF, Mini Nutritional Assessment Short-Form; GLIM, Global Leadership Initiative on Malnutrition; AWGS, Asian Working Group for Sarcopenia; IDF, International Diabetes Federation; HbA1c, glycated hemoglobin; hsCRP, high-sensitivity C-reactive protein; HOMA-IR, homeostatic model assessment of insulin resistance; TG/HDL, triglyceride-to-high-density lipoprotein cholesterol ratio; BH-FDR, Benjamini-Hochberg false-discovery-rate; FPG, fasting plasma glucose.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Shaowu Municipal Hospital, Fujian Province, China (No. 2024,008). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment. This study adheres to the CONSORT guidelines.

Consent for publication

Written informed consent was obtained from all participants prior to enrollment. All participants consented to the publication of anonymized data for research purposes. No individual-level identifiable data are presented in this manuscript.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration on the use of generative AI and AI-assisted technologies

During revision, the authors used generative AI-assisted technology (ChatGPT, OpenAI) to support language editing and translation. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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CRediT authorship contribution statement

Xiaojing Zha: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Zhengyang Wang:** Software, Methodology, Investigation. **Yiqing Huang:** Software, Investigation, Data curation. **Liping Huang:** Investigation, Data curation. **Lianbin Huang:** Software, Data curation. **Jiwen Zeng:** Software, Methodology, Formal analysis, Data curation. **Yonghong Ding:** Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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