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RESEARCH ARTICLE

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Sustained increase in physical fitness independently predicts improvements in cardiometabolic risk profile in type 2 diabetes

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Abstract

Aims: To investigate the relationship between changes in physical fitness and cardiovascular risk factors and scores in patients with type 2 diabetes receiving either a behavioural counselling intervention to increase moderate-to-vigorous-intensity physical activity (MVPA) and decrease sedentary-time (SED-time) or standard care.

Materials and Methods: This is a pre-specified ancillary analysis of the Italian Diabetes and Exercise Study_2, a 3-year randomized clinical trial in which 300 physically inactive and sedentary patients were randomized 1:1 to receive either a one-month theoretical and practical counselling each year or standard care. Mean changes from baseline throughout the 3-year period in MVPA, SED-time, cardiorespiratory fitness (VO_{2max}), muscle strength, flexibility, cardiovascular risk factors and scores were calculated for study completers (n = 267) and considered irrespective of study arm.

Results: Haemoglobin (Hb) A_{1c} and coronary heart disease (CHD) risk scores decreased with quartiles of VO_{2max} and lower body muscle strength changes. Multivariable linear regression analysis showed that increases in VO_{2max} independently predicted decreases in HbA_{1c}, blood glucose, diastolic blood pressure (BP), CHD and total stroke 10-year risk and increases in HDL cholesterol, whereas increases in lower body muscle strength independently predicted decreases in body mass index (BMI), waist circumference, triglycerides, systolic BP, CHD and fatal stroke 10-year risk. These associations remained after including changes in BMI,

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See Supporting Information, The IDES_2 Investigators.

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waist circumference, fat mass and fat-free mass, or MVPA and SED-time as covariates.

Conclusions: Improvement in physical fitness predicts favourable changes in cardiometabolic risk profile, independent of changes not only in (central) adiposity or body composition but also in MVPA and SED-time.

Trial Registration: ClinicalTrials.gov; NCT01600937; URL https://clinicaltrials.gov/ct2/show/NCT01600937.

KEYWORDS
cardiovascular risk, physical activity, physical fitness, sedentary behaviour, type 2 diabetes

1 | INTRODUCTION

Adopting and maintaining a physically active lifestyle provides significant health benefits to people with type 2 diabetes through multiple mechanisms. Increased energy expenditure from physical activity (PA)/exercise is associated with improvements in blood glucose levels and other risk factors for cardiovascular disease (CVD).[1] In addition, increasing PA and decreasing sedentary (SED)-time result in improved health-related physical fitness, which includes cardiorespiratory fitness, muscle strength and endurance, flexibility, and body composition.[2] In fact, aerobic, resistance, and flexibility training increase cardiorespiratory fitness, muscular fitness, and flexibility, respectively.[3] Moreover, aerobic and resistance training contribute to improving body composition through a decrease in fat mass (FM) (which however requires large volumes of moderate-to-vigorous-intensity PA, MVPA[4]) and an increase in muscle mass, respectively.[3] Thus, in addition to ameliorating cardiometabolic risk profile, PA/exercise exerts direct beneficial effects on cardiorespiratory, neuromuscular and skeletal systems, which include improvements in left ventricular structure and function (especially diastolic function), pulmonary ventilation and diffusion, peripheral blood flow and muscle oxygen utilization, bone mass and strength, and body stability, balance, and flexibility.[1] All these effects account for the ability of fitness, especially cardiorespiratory, to mitigate the health risks of "fatness"[5] and to predict all-cause and CVD mortality[6–11] independently of (and better than) traditional CVD risk factors and other exercise test variables.[8,12,13]

A number of studies have shown an association between various components of physical fitness and cardiometabolic risk profile in healthy people and those with obesity or diabetes.[14–25] In the Italian Diabetes and Exercise Study (IDES), patients with type 2 diabetes engaged in a supervised aerobic and resistance training programme accumulated large amounts of MVPA.[26] The associated improvements in physical fitness predicted amelioration of CVD risk factors independently of changes in body weight and, in case of muscular fitness, also of waist circumference, but not of changes in PA/exercise volume.[27] In the Italian Diabetes and Exercise Study_2 (IDES_2), a counselling intervention targeting both PA and sedentary behaviour was effective in promoting increases in MVPA, which were modest (+6.4 min·day^{-1}) but sustained over a three-year follow-up and associated with larger decreases in SED-time (−0.8 h·day^{-1}) and corresponding increases in light-intensity PA (LPA).[28] This resulted in larger than expected increases in physical fitness, especially cardiorespiratory fitness and lower body muscle strength, and less marked improvements in glucose and blood pressure (BP) control and CVD risk scores. All these changes were predicted by changes in MVPA and/or SED-time (or LPA) independently of one another and of other confounders.[29]

The present pre-specified ancillary analysis of the IDES_2 was aimed at (a) investigating the relationships of changes in cardiorespiratory fitness and lower body muscle strength (and the relative importance of each of them) with changes in CVD risk factors and scores; and (b) assessing whether sustained improvements in fitness predict favourable changes in cardiometabolic risk profile independently of changes in adiposity or MVPA and SED-time.

2 | MATERIALS AND METHODS

Design and methods have been detailed elsewhere[28,30] and will be briefly reported here.

2.1 | Design

IDES_2 was an open-label, assessor-blinded, parallel, superiority randomized clinical trial that assessed the efficacy of a behavioural intervention in increasing daily PA and reducing SED-time over a 3-year follow-up in patients with type 2 diabetes versus standard care.

2.2 | Participants

Inclusion criteria were type 2 diabetes of at least one-year duration, age 40–80 years, body mass index (BMI) 27–40 kg/m^2, physically inactivity (i.e., insufficient amounts of PA according to current guidelines[31]) and sedentary lifestyle (i.e., more than 8 h/day spent in any waking behaviour characterised by an energy expenditure ≤1.5 metabolic equivalents while in a sitting or reclining posture[32]) for at least 6 months, ability to walk 1.6 Km without assistance, and

eligibility after cardiologic evaluation. The latter included a resting electrocardiogram (ECG) and eventually an echocardiogram and/or an ECG treadmill test; then, participants who received medical clearance were further evaluated by ECG monitoring during the maximal treadmill exercise test for the assessment of cardiorespiratory fitness. Exclusion criteria were conditions limiting or contraindicating PA, affecting the conduct of the trial, reducing lifespan, and/or affecting the safety of intervention (Table S1 in Supporting Information).

2.3 | Randomisation and blinding

Three-hundred patients with type 2 diabetes were recruited in three tertiary referral outpatient Diabetes Clinics in Rome and randomized 1:1 to either an intervention (INT) group, receiving theoretical and practical exercise counselling, or a control (CON) group, receiving only general physician recommendations. Randomisation was stratified by centre and within each centre by age < versus ≥65 years and non-insulin versus insulin treatment using a permuted-block randomisation software.

Patients from both groups received the same treatment regimen, including dietary prescription, to achieve glycaemic, lipid, BP, and body weight targets according to current guidelines.[33] Dietary and pharmacological treatment was adjusted at each visit using a prespecified algorithm.

Physicians, exercise specialists, and participants were not blinded, whereas assessors of accelerometer/diary and biochemical parameters were blinded to group assignment.

2.4 | Intervention

Participants in the INT group were engaged in a one-month theoretical and practical counselling, each year for 3 years. Specifically, the intervention consisted of one individual theoretical counselling session plus eight twice-weekly individual theoretical and practical counselling sessions.

The 30-min theoretical, individual, face-to-face counselling session was held by a diabetologist and consisted of seven steps.

Each theoretical and practical counselling session was held by a certified exercise specialist. The theoretical part was aimed at improving patients' knowledge of the effects of exercise on health, conditions contraindicating exercise, difference between habitual and occasional exercise, and essential parameters of wellness such as BP, heart rate, and blood glucose. The practical part served to instruct patients to distinguish the different types of exercise, evaluate exercise intensity, and monitor and correct blood glucose imbalances during and after the session. This approach was designed to promote an increase in any kind of PA, based on the patient's preference, and a decrease in SED-time through a two-step behaviour change, that is, (1) decreasing SED-time by substituting and/or interrupting it with a wide range of LPAs; and (2) gradually increasing the time spent in purposeful MVPA.

2.5 | Measurements

Total PA volume, time spent in LPA and MVPA, and SED-time were measured by the use of an accelerometer (MyWellness Key, Technogym, Cesena, Italy) and a daily diary for non-accelerometer recordable activities. Measurements were obtained at baseline and every 4 months thereafter for seven consecutive days, except for the initial 4 months, during which the device was worn for the entire period.

At the same time points, the modifiable CVD risk factors haemoglobin (Hb) A_{1c}, fasting plasma glucose (FPG), BMI, waist circumference, triglycerides, total, HDL, and LDL cholesterol, and systolic and diastolic BP, were measured using standard methods; fat mass (FM) and fat-free mass (FFM) were assessed by bioimpedance analysis using Tanita BF664 (Vernon Hills, IL, USA); and total and fatal coronary heart disease (CHD) and stroke 10-year risk scores were calculated using the United Kingdom Prospective Diabetes Study risk engine.[34]

At baseline and every year thereafter, participants were evaluated for physical fitness by assessing cardiorespiratory fitness (as maximal oxygen uptake, VO_{2max}), upper and lower body muscle strength, and flexibility by maximal treadmill exercise test, isometric test, and bending test, respectively.

2.6 | Statistical analysis

All the analyses were conducted in the whole cohort, irrespective of the study arm.

Mean changes from baseline throughout the three-year follow-up in physical fitness, CVD risk factors and scores, and PA/SED-time were calculated for participants who completed the study as the mean values of changes from baseline at each time point (i.e., at 4, 8, 12, 16, 20, 24, 28, 32, and 36 months). To describe changes in CVD risk factors and scores with those in physical fitness parameters, the mean values of changes in HbA_{1c}, FPG, BMI, waist circumference, FM, FFM, triglycerides, total, HDL and LDL cholesterol, systolic and diastolic BP, and total and fatal CHD and stroke 10-year risk scores were then stratified by quartiles of changes in VO_{2max} and lower body muscle strength and data were expressed as mean ± SD and analysed by one-way ANOVA.

Multivariable linear regression analyses with stepwise backward selection of variables were performed to assess the independent predictors of changes in CVD risk factors and scores over the three-year period. Age, sex, study arm, the baseline value of the dependent variable, and changes in VO_{2max} and lower body muscle strength were included as covariates in Model 1. Changes in MVPA and SED-time were also included as covariates in Model 2, whereas changes in BMI, waist circumference, and FM plus FFM were included as covariates in Models 3, 4, and 5, respectively.

All the p-values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS version 20 (SPSS Inc., Chicago, IL, USA).

3 | RESULTS

As previously reported,[28] 267 patients completed the study at the final evaluation (CON = 134; INT = 133), whereas 33 patients (CON = 16; INT = 17) dropped out for various reasons; of those in the INT group, >90% attended the counselling sessions.

The baseline features of study participants and the effects of intervention on the main outcomes of the trial have been reported elsewhere, together with adverse events and change in medication use, which did not differ between the two groups.[28]

3.1 | Relationships between changes in VO_{2max} and changes in lower body muscle strength

There were no significant differences in age and sex among quartiles of MVPA and SED-time change (data not shown). Patients falling in quartile I of VO_{2max} and lower body muscle strength change showed substantial decreases in VO_{2max} and lower body muscle strength, those in quartile II showed virtually no change, and those in quartiles III and IV showed clinically modest and marked improvements, respectively (Supplementary Table S2 in Supporting Information). Though VO_{2max} change and lower body muscle strength change were significantly correlated ($r = -0.597$, $p < 0.0001$), there was only a partial correspondence between quartiles of each other. In fact, 41.3% and 50.0% of patients assigned to quartiles I and IV of VO_{2max} change fell into quartiles I and IV of lower body muscle strength, respectively, but there were also a few individuals in the highest quartile of VO_{2max} change who fell in the lowest quartile of lower body muscle strength change (1.6%) and vice versa (9.7%) (Supplementary Table S2 in Supporting Information).

Most of the participants falling in the quartiles IV and, to a lesser extent, III of VO_{2max} and lower body muscle strength change were from the INT group, whereas those in quartile II of VO_{2max} change were almost in equal number from the two groups, and those in quartile I of VO_{2max} change and in quartiles II and I of lower body muscle strength change were mainly from the CON group. Therefore, while ~40% of INT and CON participants showed a marked improvement and worsening, respectively, in both VO_{2max} and lower body muscle strength, ~30% of INT participants showed

TABLE 1 Descriptive analyses of mean changes over from baseline in study parameters throughout the three-year follow-up according to quartiles of mean changes over the baseline in VO_{2max}, irrespective of study arm.

	Quartiles of mean change in VO_{2max} versus baseline				
Variables: Change in	**I**	**II**	**III**	**IV**	***p***
N	66	66	65	65	
VO_{2max}, ml·min^{-1} kg^{-1}	−2.18 ± 1.61	0.79 ± 0.68	2.89 ± 0.57	6.98 ± 3.05	
(range)	(−7.7; −0.3)	(−0.3; 1.9)	(2.0; 3.8)	(3.9; 17.2)	
HbA_{1c}, %	0.27 ± 0.91	−0.05 ± 1.02	−0.26 ± 0.87	−0.46 ± 1.10	<0.0001
FPG, mmol·l^{-1}	0.10 ± 2.50	0.06 ± 2.78	−0.41 ± 1.80	−0.10 ± 1.60	0.556
BMI, kg/m^2	0.10 ± 1.12	−0.04 ± 1.26	−0.20 ± 1.55	−0.29 ± 1.13	0.307
Waist circumference, cm	1.23 ± 4.05	1.83 ± 8.80	−0.37 ± 5.83	−0.83 ± 6.14	0.056
FM, %	0.41 ± 2.36	0.35 ± 2.50	−0.19 ± 2.76	−0.22 ± 2.25	0.299
FFM, kg	0.05 ± 2.31	−0.01 ± 3.29	−0.31 ± 1.55	0.22 ± 4.72	0.818
Triglycerides, mmol·l^{-1}	0.20 ± 0.85	−0.20 ± 0.70	−0.14 ± 0.92	−0.06 ± 0.57	0.014
Total cholesterol, mmol·l^{-1}	0.10 ± 0.78	0.04 ± 0.87	0.01 ± 0.61	−0.03 ± 0.65	0.767
HDL cholesterol, mmol·l^{-1}	−0.08 ± 0.17	−0.06 ± 0.16	−0.08 ± 0.19	−0.06 ± 0.19	0.723
LDL cholesterol, mmol·l^{-1}	−0.04 ± 0.73	−0.04 ± 0.82	−0.05 ± 0.60	−0.03 ± 0.52	0.999
Systolic BP, mmHg	−3.22 ± 16.74	−2.57 ± 15.19	−6.38 ± 17.42	−2.02 ± 16.45	0.435
Diastolic BP, mmHg	−3.67 ± 11.09	−3.40 ± 12.11	−4.55 ± 9.42	−3.53 ± 8.84	0.922
CHD 10-year risk score, %	5.57 ± 6.84	3.83 ± 6.06	2.35 ± 5.69	1.75 ± 5.80	0.002
Fatal CHD 10-year risk score, %	4.99 ± 6.04	3.70 ± 5.13	2.18 ± 5.02	1.76 ± 4.97	0.002
Stroke 10-year risk score, %	4.78 ± 9.31	3.93 ± 3.11	3.09 ± 3.95	3.10 ± 3.43	0.250
Fatal stroke 10-year risk score, %	0.49 ± 1.76	0.42 ± 0.90	0.33 ± 1.19	0.40 ± 1.02	0.910

Note: Values are mean ± SD, unless otherwise specified; *p* values by one-way ANOVA.

Abbreviations: BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; FFM, fat-free mass; FM, fat mass; FPG, fasting plasma glucose; HbA_{1c}, haemoglobin A_{1c}; VO_{2max}, maximal oxygen uptake.

no meaningful change or even substantial worsening and ~30% of CON participants showed modest or even striking improvements in these parameters (Supplementary Table S3 in Supporting Information).

3.2 | Relationships between changes in physical fitness and changes in CVD risk factors and scores

The descriptive analyses of changes in CVD risk factors and scores by changes in physical fitness parameters showed improvements with quartiles of VO_{2max} change for HbA_{1c} and triglycerides and total and fatal CHD 10-year risk (Table 1), whereas improvements with quartiles of lower body muscle strength change were observed for total and fatal CHD and total stroke 10-year risk (Table 2). Participants falling in quartile IV of VO_{2max} and lower body muscle strength showed average decreases in HbA_{1c} of 0.46% and 0.28% and increases in total CHD 10-year risk of 1.75% and 2.09% and in fatal CHD 10-year risk of 1.76% and 1.79%, respectively, compared with an increase of 0.27% or no change in HbA_{1c}, increases in total CHD 10-year risk of 5.57% and 4.77%, and increases in fatal CHD 10-year risk of 4.99% and 5.25%, respectively, in those falling in quartile I.

3.3 | Changes in physical fitness as independent predictors of changes in CVD risk factors and scores

In Model 1, increases in VO_{2max} were independent predictors of decreases in HbA_{1c}, FPG, diastolic BP, total and fatal CHD and total stroke 10-year risk, and increases in HDL cholesterol, whereas increases in lower body muscle strength independently predicted decreases in BMI, waist circumference, triglycerides, systolic BP, and total and fatal CHD and fatal stroke 10-year risk (Table 3). Based on multivariable linear regression analysis, each 5 $mL \cdot min^{-1}$ kg^{-1} increase in VO_{2max} was estimated to independently predict a decrement in HbA_{1c} of 0.44%, in FPG of 0.56 $mmol \cdot l^{-1}$, in diastolic BP of 1.26 mmHg, in total CHD 10-year risk of 2.23%, in fatal CHD 10-year risk of 1.90%, and in total stroke 10-year risk of 1.02%, and an increment in HDL cholesterol of 0.03 $mmol \cdot l^{-1}$, whereas each 50

TABLE 2 Descriptive analyses of mean changes over from baseline in study parameters throughout the three-year follow-up according to quartiles of mean changes over the baseline in lower body muscle strength, irrespective of study arm.

	Quartiles of mean change in lower body strength versus baseline				
Variables; change in	**I**	**II**	**III**	**IV**	***p***
N	65	64	66	66	
Lower body muscle strength, Nm	−13.76 ± 11.37	6.58 ± 5.05	23.56 ± 5.37	56.69 ± 25.91	
(range)	(−55.7; −3.00)	(−2.67; 14.67)	(15.00; 34.00)	(35.3; 206.3)	
HbA_{1c}, %	0.00 ± 1.01	0.00 ± 0.86	−0.22 ± 0.86	−0.28 ± 1.26	0.263
FPG, $mmol \cdot l^{-1}$	0.17 ± 3.10	−0.02 ± 1.85	−0.36 ± 1.68	−0.13 ± 2.01	0.595
BMI, kg/m^2	0.07 ± 1.23	−0.15 ± 1.21	−0.14 ± 1.31	−0.22 ± 1.37	0.602
Waist circumference, cm	1.79 ± 8.61	0.33 ± 4.73	0.28 ± 5.32	−0.45 ± 6.61	0.254
FM, %	0.63 ± 2.33	−0.21 ± 2.69	0.11 ± 2.51	−0.20 ± 2.35	0.178
FFM, kg	0.16 ± 3.69	−0.17 ± 1.82	−0.50 ± 1.52	0.49 ± 4.59	0.319
Triglycerides, $mmol \cdot l^{-1}$	0.00 ± 0.98	−0.06 ± 0.60	−0.14 ± 0.86	−0.01 ± 0.64	0.738
Total cholesterol, $mmol \cdot l^{-1}$	0.24 ± 0.80	−0.03 ± 0.80	−0.18 ± 0.72	0.09 ± 0.54	0.009
HDL cholesterol, $mmol \cdot l^{-1}$	−0.07 ± 0.18	−0.04 ± 0.17	−0.09 ± 0.16	−0.08 ± 0.19	0.285
LDL cholesterol, $mmol \cdot l^{-1}$	0.16 ± 0.67	−0.17 ± 0.74	−0.17 ± 0.75	0.02 ± 0.47	0.010
Systolic BP, mmHg	0.20 ± 17.43	−5.96 ± 17.21	−4.53 ± 14.26	−4.12 ± 16.53	0.168
Diastolic BP, mmHg	−3.26 ± 14.49	−5.18 ± 9.60	−3.73 ± 8.25	−3.15 ± 8.17	0.673
CHD 10-year risk score, %	5.30 ± 6.63	3.43 ± 6.64	2.71 ± 5.55	2.09 ± 5.89	0.021
Fatal CHD 10-year risk score, %	4.77 ± 5.70	3.39 ± 5.96	2.68 ± 4.71	1.79 ± 4.97	0.014
Stroke 10-year risk score, %	5.25 ± 9.46	3.77 ± 4.19	3.37 ± 3.21	2.50 ± 2.38	0.040
Fatal stroke 10-year risk score, %	0.59 ± 1.87	0.41 ± 1.29	0.36 ± 0.72	0.24 ± 0.75	0.438

Note: Values are mean ± SD, unless otherwise specified; *p* values by one-way ANOVA.

Abbreviations: BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; FFM = fat-free mass; FM; fat mass; FPG, fasting plasma glucose; HbA_{1c}; haemoglobin A_{1c}.

TABLE 3 Independent relationship of mean changes from baseline in CVD risk factors and scores with mean changes from baseline in cardiorespiratory fitness and lower body muscle strength, as assessed by multivariable linear regression analysis with stepwise backward selection of variables in the whole cohort (Model 1).

Independent variables: Change in →	VO_{2max}, $ml \cdot min^{-1} \cdot kg^{-1}$		Lower body muscle strength, Nm		Baseline value of dependent variable		Age, years		Sex, male	
Dependent variables: Change in ↓	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*
HbA_{1c}, %	−0.088	<0.0001	-	-	−0.420	<0.0001	-	-	−0.177	0.067
FPG, $mmol \cdot l^{-1}$	−0.113	<0.0001	-	-	−0.574	<0.0001	-	-	−0.620	0.004
BMI, kg/m^2	-	-	−0.006	0.030	−0.034	0.025	−0.020	0.014	-	-
Waist circumference, cm	-	-	−0.035	0.004	−0.185	<0.0001	-	-	−2.071	0.006
FM, %	-	-	-	-	−0.052	<0.0001	−0.030	0.056	-	-
FFM, kg	-	-	-	-	−0.143	<0.0001	−0.039	0.040	−2.499	<0.0001
Triglycerides, $mmol \cdot l^{-1}$	−0.021	0.051	−0.003	0.036	−0.374	<0.0001	−0.012	0.002	-	-
Total cholesterol, $mmol \cdot l^{-1}$	-	-	-	-	−0.506	<0.0001	−0.007	0.034	0.165	0.019
HDL cholesterol, $mmol \cdot l^{-1}$	0.006	0.007	-	-	−0.312	<0.0001	−0.002	0.084	0.045	0.012
LDL cholesterol, $mmol \cdot l^{-1}$	-	-	-	-	−0.524	<0.0001	−0.007	0.050	-	-
Systolic BP, mmHg	-	-	−0.066	0.002	−0.650	<0.0001	0.300	<0.0001	-	-
Diastolic BP, mmHg	−0.252	0.004	-	-	−0.755	<0.0001	−0.089	0.009	-	-
CHD 10-year risk score, %	−0.446	<0.0001	−0.031	0.017	−0.213	<0.0001	0.285	<0.0001	−4.739	<0.0001
Fatal CHD 10-year risk score, %	−0.379	<0.0001	−0.027	0.022	−0.150	<0.0001	0.233	<0.0001	−3.507	<0.0001
Stroke 10-year risk score, %	−0.204	0.016	-	-	0.071	0.049	0.158	0.001	−1.340	0.047
Fatal stroke 10-year risk score, %	-	-	−0.006	0.011	−0.230	<0.0001	0.055	<0.0001	−0.463	0.002

Note: The table reports the beta estimates and the corresponding *p* values for the variables remaining in the model in the last step.

Abbreviations: BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CVD, cardiovascular disease; FFM, fat-free mass; FM, fat mass; FPG, fasting plasma glucose; HbA_{1c}, haemoglobin A_{1c}; VO_{2max}, maximal oxygen uptake.

Nm increase in lower body muscle strength was estimated to independently predict a decrement in BMI of 3 Kg/m^2, in waist circumference of 1.8 cm, in triglycerides of 0.15 $mmol \cdot l^{-1}$, in systolic BP of 3.3 mmHg, in total CHD 10-year risk of 1.57%, in fatal CHD 10-year risk of 1.33%, and in fatal stroke 10-year risk of 0.31%.

These associations were slightly attenuated when including MVPA and SED-time changes among the covariates (Model 2), with only SED-time change being independently associated with HbA_{1c} change, FPG, FM, and total and fatal CHD 10-year risk (Table 5). In addition, the independent associations of VO_{2max} and lower body muscle strength were unchanged when including BMI (Model 3), waist circumference (Model 4), or FM+FFM (Model 5) changes as covariates, except for triglycerides in Models 3 and 5. Changes in all these measures were independently associated with each other as well as with several CVD risk factors (Table 5 and Supplementary Tables S4–5 in Supporting Information).

In all models, the baseline value of the dependent variable was always significantly and inversely associated with its change, whereas age and sex were variably associated with changes in the dependent variables (Tables 3–5 and Supplementary Tables S4–5 in Supporting Information). When included in the models, the study arm was associated solely with changes in HbA_{1c} and total and fatal CHD 10-year risk, the relationship of which with physical fitness parameters was only modestly attenuated (data not shown).

4 | DISCUSSION

This pre-specified ancillary analysis of the IDES_2 shows that sustained improvements in physical fitness produced by modest increments in MVPA and larger decrements in SED-time (with reallocation to time spent in LPA) are associated with a better cardiometabolic risk profile. More importantly, this report suggests for the first time that the contribution of improved fitness to the amelioration of CVD risk factors and scores may be additional to that attributable not only to changes in (central) adiposity and body composition but also to the increases in MVPA and decreases in SED-time.

The increases in VO_{2max} and lower body muscle strength observed in participants falling in quartile IV were associated with clinically meaningful improvements in CVD risk factors and scores. Likewise, the improvements in CVD risk factors and scores

TABLE 4 Independent relationship of mean changes from baseline in CVD risk factors and scores with mean changes from baseline in cardiorespiratory fitness, lower body muscle strength, MVPA, and SED-time, as assessed by multivariable linear regression analysis with stepwise backward selection of variables in the whole cohort (Model 2).

Independent variables: Change in → Dependent variables: Change in ↓	VO_{2max}, $ml \cdot min^{-1} \cdot kg^{-1}$		Lower body muscle strength, Nm		MVPA, $min \cdot day^{-1}$		SED-time, $h \cdot day^{-1}$		Baseline value of dependent variable		Age, years		Sex, male	
	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*
HbA_{1c}, %	−0.050	<0.0001	-	-	-	-	0.478	<0.0001	−0.378	<0.0001	−0.007	0.091	-	-
FPG, $mmol \cdot l^{-1}$	−0.077	0.015	-	-	-	-	0.335	0.013	−0.561	<0.0001	−0.019	0.078	−0.615	0.004
BMI, kg/m^2	-	-	−0.006	0.030	-	-	-	-	−0.034	0.025	−0.020	0.014	-	-
Waist circumference, cm	-	-	−0.035	0.004	-	-	-	-	−0.185	<0.0001	-	-	−2.071	0.006
FM, %	-	-	-	-	-	-	0.411	0.019	−0.052	<0.0001	−0.033	0.034	-	-
FFM, kg	-	-	-	-	-	-	-	-	−0.143	<0.0001	−0.039	0.040	−2.499	<0.0001
Triglycerides, $mmol \cdot l^{-1}$	−0.021	0.051	−0.003	0.036	-	-	-	-	−0.374	<0.0001	−0.012	0.002	-	-
Total cholesterol, $mmol \cdot l^{-1}$	-	-	-	-	-	-	-	-	−0.506	<0.0001	−0.007	0.034	0.165	0.019
HDL cholesterol, $mmol \cdot l^{-1}$	0.006	0.007	-	-	-	-	-	-	−0.312	<0.0001	−0.002	0.084	0.045	0.012
LDL cholesterol, $mmol \cdot l^{-1}$	-	-	-	-	-	-	-	-	−0.524	<0.0001	−0.007	0.050	-	-
Systolic BP, mmHg	-	-	−0.066	0.002	-	-	-	-	−0.650	<0.0001	0.300	<0.0001	-	-
Diastolic BP, mmHg	−0.252	0.004	-	-	-	-	-	-	−0.755	<0.0001	−0.089	0.009	-	-
CHD 10-year risk score, %	−0.334	0.002	−0.036	0.008	-	-	1.616	<0.0001	−0.203	<0.0001	0.271	<0.0001	−4.792	<0.0001
Fatal CHD 10-year risk score, %	−0.283	0.003	−0.030	0.011	-	-	1.392	<0.0001	−0.143	<0.0001	0.222	<0.0001	−3.601	<0.0001
Stroke 10-year risk score, %	−0.204	0.016	-	-	-	-	-	-	0.071	0.049	0.158	0.001	−1.340	0.047
Fatal stroke 10-year risk score, %	-	-	−0.006	0.011	-	-	-	-	−0.230	<0.0001	0.055	<0.0001	−0.463	0.002

Note: The table reports the beta estimates and the corresponding *p* values for the variables remaining in the model in the last step.

Abbreviations: BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CVD, cardiovascular disease; FFM, fat-free mass; FM, fat mass; FPG, fasting plasma glucose; HbA_{1c}, haemoglobin A_{1c}; VO_{2max}, maximal oxygen uptake.

TABLE 5 Independent relationship of mean changes from baseline in CVD risk factors and scores with mean changes from baseline in cardiorespiratory fitness, lower body muscle strength, and body mass index (BMI), as assessed by multivariable linear regression analysis with stepwise backward selection of variables in the whole cohort (Model 3).

Independent variables: Change in →	VO_{2max}, $ml \cdot min^{-1} \cdot kg^{-1}$		Lower body muscle strength, Nm		BMI, kg/m^2		Baseline value of dependent variable		Age, years		Sex, male	
Dependent variables: Change in ↓	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*
HbA_{1c}, %	−0.083	<0.0001	-	-	0.106	0.004	−0.419	<0.0001	-	-	-	-
FPG, $mmol \cdot l^{-1}$	−0.102	<0.0001	-	-	0.321	<0.0001	−0.565	<0.0001	-	-	−0.532	0.011
Waist circumference, cm	-	-	−0.026	0.022	1.917	<0.0001	−0.159	<0.0001	-	-	−1.649	0.017
FM, %	-	-	-	-	1.185	<0.0001	−0.028	0.016	-	-	-	-
FFM, kg	-	-	-	-	0.310	0.031	−0.143	<0.0001	−0.034	0.071	−2.421	<0.0001
Triglycerides, $mmol \cdot l^{-1}$	−0.021	0.055	−0.003	0.053	0.047	0.092	−0.378	<0.0001	−0.011	0.004	-	-
Total cholesterol, $mmol \cdot l^{-1}$	-	-	-	-	-	-	−0.506	<0.0001	−0.007	0.034	0.165	0.019
HDL cholesterol, $mmol \cdot l^{-1}$	0.006	0.011	-	-	−0.011	0.091	−0.309	<0.0001	−0.002	0.052	0.042	0.020
LDL cholesterol, $mmol \cdot l^{-1}$	-	-	-	-	-	-	−0.524	<0.0001	−0.007	0.050	-	-
Systolic BP, mmHg	-	-	−0.061	0.004	0.906	0.062	−0.650	<0.0001	0.317	<0.0001	-	-
Diastolic BP, mmHg	−0.252	0.004	-	-	-	-	−0.755	<0.0001	−0.089	0.009	-	-
CHD 10-year risk score, %	−0.439	<0.0001	−0.029	0.026	0.463	0.081	−0.213	<0.0001	0.293	<0.0001	−4.631	<0.0001
Fatal CHD 10-year risk score, %	−0.374	<0.0001	−0.025	0.034	0.426	0.069	−0.152	<0.0001	0.242	<0.0001	−3.421	<0.0001
Stroke 10-year risk score, %	−0.204	0.016	-	-	-	-	0.071	0.049	0.158	0.001	−1.340	0.047
Fatal stroke 10-year risk score, %	-	-	−0.006	0.011	-	-	−0.230	<0.0001	0.055	<0.0001	−0.463	0.002

Note: The table reports the beta estimates and the corresponding *p* values for the variables remaining in the model in the last step.

Abbreviations: BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CVD, cardiovascular disease; FFM, fat-free mass; FM, fat mass; FPG, fasting plasma glucose; HbA_{1c}, haemoglobin A_{1c}; VO_{2max}, maximal oxygen uptake.

independently predicted by increases in VO_{2max} and lower body muscle strength, as estimated by multivariable linear regression analysis, were clinically meaningful. The strong and independent relationships between changes in physical fitness and cardiometabolic risk profile in people with type 2 diabetes confirm and extend those previously reported in the IDES[27] and other studies.[14–25] All together, these findings indicate that fitness may represent a surrogate outcome in PA-based lifestyle interventions, as larger improvements in cardiorespiratory and muscular fitness predict larger reductions in CVD risk factors and scores. This has important clinical implications as the level of physical fitness, which is mainly determined by the amount and type of PA, is also dependent on the individual genetic background.[35] Thus, genetically low-fit individuals might respond less to training programs also in terms of reductions in CVD risk factors and scores and, hence, require higher PA volumes and/or intensities to achieve meaningful improvements in cardiometabolic risk profile.[36] In addition, our findings indicate a different spectrum of CVD risk factors that are favourably affected by improvements in cardiorespiratory versus muscular fitness, both of which contribute to the reduction of CVD risk scores.

The strength of association between changes in physical fitness with changes in CVD risk factors and scores was not modified by further adjusting for measures of total and central adiposity and body composition, possibly suggesting that the impact of improving fitness on cardiometabolic risk profile is independent of weight loss and reductions in central fat distribution or FM:FFM ratio. This finding is consistent with previous reports in people with type 2 diabetes from the IDES who were engaged in a supervised exercise training programme,[27] and in healthy individuals from the Cooper Centre Longitudinal Study who were examined at least 4 times over a 10-year period.[17] Taken together, these observations reflect the fact that the body weight- and fat-lowering effect of PA/exercise is limited unless larger volumes are achieved.[4] This is at variance with the diet, which produces meaningful weight loss, though the reduction of FM is associated with a loss of muscle mass unless dietary restrictions are combined with exercise.[37]

A unique finding of this study is that the associations of changes in physical fitness with those in CVD risk factors and scores were only slightly attenuated, if anything, by further adjusting for MVPA and SED-time. This is at variance with the IDES, in which associations disappeared after adjusting for PA/exercise volume. However, in the IDES, patients with type 2 diabetes were engaged in a supervised exercise programme and accumulated large amounts of MVPA with proportionate improvements in physical fitness,[26] consistent with the finding that adherence was shown to be high in interventions using supervised training.[38] In the IDES_2, the counselling intervention

produced only modest, though sustained increases in MVPA, which resulted in disproportionate increases in physical fitness that could be explained by the larger increases in total energy expenditure, due to the significant contribution of reallocation of SED-time to LPA.[28] Under these circumstances, it might be possible to separate the favourable effects on cardiometabolic risk profile of improvements in physical fitness from those of changes in MVPA/SED-time that resulted in improved fitness, though no causal inference can be made in an association study. The mechanisms underlying the potential direct effects of increases in fitness may include vasodilation and angiogenesis with augmented oxygen delivery, increased mitochondrial biogenesis with enhanced tissue aerobic respiration, and myokine release with improved insulin sensitivity and anti-inflammatory effect.[1,12,39]

The observations that improvements in physical fitness predict amelioration of cardiometabolic risk profile beyond the extent of weight loss and the level of PA/SED-time further supports the concept that cardiorespiratory fitness[12] (and possibly also muscular fitness[40]) should be considered a vital sign and added to traditional CVD risk factors to improve prediction of CVD mortality.[41] Targeting increases in fitness in PA-based interventions is particularly important in people with type 2 diabetes, who are usually low-fit, as the most favourable effects of improving fitness on outcomes were observed when moving from the least fit group to the next least fit group.[6,8]

The main strengths of this study include the objective (accelerometer-based) measurement of PA/SED-time, the concurrent assessment of physical fitness and CVD risk factors, the long study duration, and the large sample size. However, this study has some limitations. First, generalisability requires further investigation and validation in different cohorts or settings. Second, this trial was not designed to assess the impact of changes in physical fitness on CVD risk factors and scores, which were both secondary endpoints, and specific studies should be designed to assess the relationships between each other. Third, results might have been affected by unmeasured confounders, for instance diet, that were not considered in data analysis, though patients received dietary prescriptions. Finally, no cause-effect relationships can be derived from simple associations.

In conclusion, this analysis of the IDES_2 indicates that, in physically inactive and sedentary patients with type 2 diabetes, sustained improvements in physical fitness resulting from modest increases in PA and larger reductions in sedentary behaviour predict a favourable cardiometabolic risk profile. These associations are independent not only of changes in (central) adiposity and body composition but also of changes in MVPA/SED-time. These findings suggest that increasing fitness may have a beneficial effect on CVD risk factors per se, further supporting the concept of physical fitness as a vital sign and the importance of improving fitness in people with type 2 diabetes.

AUTHOR CONTRIBUTIONS

Conception or design: Stefano Balducci, Jonida Haxhi, Martina Vitale, Massimo Sacchetti, Silvano Zanuso, Antonio Nicolucci, and Giuseppe Pugliese; acquisition, analysis, or interpretation of data: Stefano Balducci, Jonida Haxhi, Martina Vitale, Lorenza Mattia, Massimo Sacchetti, Giorgio Orlando, Patrizia Cardelli, Carla Iacobini, Lucilla Bollanti, Francesco Conti, Silvano Zanuso, Antonio Nicolucci, and Giuseppe Pugliese; drafting of the manuscript: Giuseppe Pugliese; critical revision of the manuscript for important intellectual content: Stefano Balducci and Jonida Haxhi; screening and contacting patients: Jonida Haxhi, Martina Vitale, Lorenza Mattia, Lucilla Bollanti, and Francesco Conti; biochemical testing: Patrizia Cardelli; statistical analysis: Antonio Nicolucci and Giuseppe Pugliese: obtaining funding: Stefano Balducci; administrative, technical, or material support: Stefano Balducci, Massimo Sacchetti, Giorgio Orlando, Patrizia Cardelli, Carla Iacobini, and Silvano Zanuso; supervision: Stefano Balducci and Giuseppe Pugliese. All authors read, provided feedback, and approved the final version.

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CONFLICT OF INTEREST STATEMENT

All authors have completed and submitted the Conflicts of Interest Disclosure form. Stefano Balducci reported lecture fees from AstraZeneca, Eli Lilly, Novo Nordisk, and Takeda. Jonida Haxhi reported lecture fees from Boehringer Ingelheim. Martina Vitale reported lecture fees from MundiPharma and Novo Nordisk. Silvano Zanuso is an employee of Technogym. Antonio Nicolucci reported consultant fees from AstraZeneca, lecture fees from Eli Lilly, Medtronic, and Novo Nordisk, and grant support from AlfaSigma, Novo Nordisk, Pikdare, Sanofi, Shionogi, SOBI, and Theras. Giuseppe Pugliese reported consultant fees from Abbot, Bayer, and Novo Nordisk, and lecture fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, and Novo Nordisk. No other disclosures were reported.

ETHICS STATEMENT

The study protocol was approved by the Ethics Committee of Sant'Andrea University Hospital (Prot. n. 212/2012) and was conducted in accordance with the Declaration of Helsinki. Participants provided written informed consent.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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PEER REVIEW

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SUPPORTING INFORMATION

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