Relationships of Changes in Physical Activity and Sedentary Behavior With Changes in Physical Fitness and Cardiometabolic Risk Profile in Individuals With Type 2 Diabetes: The Italian Diabetes and Exercise Study 2 (IDES_2)

Diabetes Care 2022;45:213–221 | https://doi.org/10.2337/dc21-1505

*Stefano Balducci,[1,2,3] Jonida Haxhi,[1,2,3] Massimo Sacchetti,[4] Giorgio Orlando,[4,5] Patrizia Cardelli,[1,6] Martina Vitale,[1,2] Lorenza Mattia,[1,2] Carla Iacobini,[1,2] Lucilla Bollanti,[1,2] Francesco Conti,[1,2] Silvano Zanuso,[7,8] Antonio Nicolucci,[9,10] and Giuseppe Pugliese,[1,2] for the Italian Diabetes and Exercise Study 2 (IDES_2) Investigators**

[1]Department of Clinical and Molecular Medicine, University of Rome La Sapienza, Rome, Italy
[2]Diabetes Unit, Sant'Andrea University Hospital, Rome, Italy
[3]Metabolic Fitness Association, Monterotondo, Rome, Italy
[4]Department of Human Movement and Sport Sciences, University of Rome "Foro Italico," Rome, Italy
[5]Research Centre for Musculoskeletal Science & Sports Medicine, Department of Life Sciences, Faculty of Science and Engineering, Manchester Metropolitan University, Manchester, U.K.
[6]Laboratory of Clinical Chemistry, Sant'Andrea University Hospital, Rome, Italy
[7]Center for Applied Biological and Exercise Sciences, Faculty of Health and Life Sciences, Coventry University, Coventry, U.K.
[8]Centre for Human Performance and Sport, University of Greenwich, Chatham Maritime, U.K.
[9]Center for Outcomes Research and Clinical Epidemiology (CORESEARCH), Pescara, Italy
[10]Department of Clinical Pharmacology and Epidemiology, Consorzio Mario Negri Sud, S. Maria Imbaro, Italy

Corresponding author: Giuseppe Pugliese, giuseppe.pugliese@uniroma1.it

Received 19 July 2021 and accepted 1 October 2021

Clinical trial reg. no. NCT01600937, clinicaltrials.gov

This article contains supplementary material online at https://doi.org/10.2337/figshare.16746262.

This article is featured in a podcast available at https://diabetesjournals.org/journals/pages/diabetes-core-update-podcasts.

S.B. and J.H. contributed equally to this work.

**A complete list of the Italian Diabetes and Exercise Study 2 (IDES_2) Investigators can be found in the supplementary material online.*

OBJECTIVE

In the Italian Diabetes and Exercise Study_2 (IDES_2), behavioral counseling promoted a sustained increase in physical activity (PA) volume (+3.3 MET h · week^{-1}), moderate- to vigorous-intensity PA (MVPA) (+6.4 min · day^{-1}), and light-intensity PA (LPA) (+0.8 h · day^{-1}) and decrease in sedentary time (SED-time) (−0.8 h · day^{-1}). Here, we investigated the relationships of changes in PA/SED-time with changes in physical fitness and cardiometabolic risk profile in individuals with type 2 diabetes.

RESEARCH DESIGN AND METHODS

In this 3-year randomized clinical trial, 300 physically inactive and sedentary patients were randomized 1:1 to receive 1-month theoretical and practical counseling once a year or standard care. Changes in physical fitness and cardiovascular risk factors/scores according to quartiles of accelerometer-measured changes in PA/SED-time were assessed, together with univariate and multivariable associations between these parameters, in the whole cohort and by study arm.

RESULTS

Physical fitness increased and HbA_{1c} and coronary heart disease 10-year risk scores decreased with quartiles of MVPA and SED-time change. In quartile IV of MVPA increase and SED-time decrease, cardiorespiratory fitness increased by 5.23 and 4.49 mL · min^{-1} · kg^{-1} and HbA_{1c} decreased by 0.73 and 0.85%, respectively. Univariate correlations confirmed these relationships, and mean changes in both MPVA and SED-time predicted changes in physical fitness and cardiovascular risk factors/scores independently of one another and of other confounders. Similar findings were observed with LPA and PA volume and in each group separately.

CONCLUSIONS

Even modest increments in MVPA may have a clinically meaningful impact, and reallocating SED-time to LPA may also contribute to improved outcomes, possibly by increasing total energy expenditure.

Both physical inactivity and sedentary behavior are independently associated with increased mortality from any cause and cardiovascular disease (CVD) in the general population (1,2) and also in people with type 2 diabetes (3,4), who are usually well below the recommended level of physical activity (PA) and spend many daily hours as sedentary time (SED-time) (5). Being physically inactive is not the same as being sedentary, as it refers to an individual accumulating an insufficient amount of moderate- to vigorous-intensity PA (MVPA) according to current guidelines (i.e., $<$150 min $\cdot$ week^{-1}) (6). Conversely, sedentary individuals are those spending too much time (generally $>$8 h $\cdot$ day^{-1}) in any waking behavior characterized by an energy expenditure $\leq$1.5 MET (6). As the recommended amount of daily MVPA ($\sim$21.5 min) represents $<$3% of the time spent awake, even a physically active individual may be sedentary if he or she does not accumulate enough light-intensity PA (LPA) during the remaining daily hours in place of SED-time.

These observations represent the basis for the current American Diabetes Association guidelines that recommend that individuals with type 2 diabetes regularly perform the indicated amount of MVPA and also reallocate as much as possible of SED-time to LPA and interrupt prolonged sitting with breaks of LPA (7). Unfortunately, adherence to guideline recommendations is generally poor among individuals with diabetes, especially in the long-term, though only a few studies have investigated maintenance of changes in PA/sedentary behavior over time.

Counseling interventions designed to promote walking through the provision of pedometers in the general population (8) or in individuals with prediabetes (9) or type 2 diabetes (10,11) resulted in up to $\sim$8 min $\cdot$ day^{-1} increases in MVPA after 1 year and smaller ($\sim$4 min $\cdot$ day^{-1}), or even no, increments after longer follow-up, together with no change in SED-time. However, in these studies, the intervention failed to significantly improve CVD risk factors and other surrogate outcomes (8–10) or to produce sustained increases in cardiorespiratory fitness (12), raising the question of whether increments in MVPA of this extent and/or duration are sufficient to produce clinically meaningful effects. Conversely, in the Italian Diabetes and Exercise Study 2 (IDES_2), a counseling intervention targeting both PA and sedentary behavior, which was effective in promoting a sustained increase in PA and decrease in SED-time, resulted in clinically meaningful improvements in physical fitness and, to a lesser extent, in CVD risk factors and scores over a 3-year follow-up (13). However, while the increase versus control in MVPA was only 6.4 min $\cdot$ day^{-1} during the 3-year period and 3.6 min $\cdot$ day^{-1} at the end of the study, the reduction in SED-time and the reciprocal increment in time spent in LPA in comparisons with individuals receiving standard care were 0.8 h $\cdot$ day^{-1} over time, with the increase in LPA substantially contributing to the 3.3 MET h $\cdot$ week^{-1} increase in total PA volume (13). Therefore, it is unclear whether the improvements in physical fitness and CVD risk profile were attributable to the increase in MVPA, despite being as modest as in the walking-based intervention studies, or to the relatively greater changes in SED-time and LPA.

In the present prespecified ancillary analysis of the IDES_2, we investigated the relationships of changes in MVPA and SED-time (and the relative importance of each of them) with changes in physical fitness and CVD risk profile in patients with type 2 diabetes participating in this trial.

RESEARCH DESIGN AND METHODS

Study design and methods have previously been described (13,14) and will be briefly reported here. The IDES_2 was an open-label, assessor-blinded, parallel, superiority randomized clinical trial that assessed the efficacy of a behavioral intervention in increasing daily PA and reducing SED-time over a 3-year follow-up in patients with type 2 diabetes.

The research protocol complies with the Declaration of Helsinki. It was approved by the Ethics Committee of Sant'Andrea University Hospital, and participants provided written informed consent.

Participants

The main entry criterion was type 2 diabetes (defined according to the American Diabetes Association criteria) of at least 1-year duration. Additional requirements were age 40–80 years, BMI 27–40 kg/m^2, physically inactivity and sedentary lifestyle for at least 6 months, ability to walk 1.6 km without assistance, and eligibility after cardiologic evaluation.

Randomization and Blinding

In three tertiary referral, outpatient diabetes clinics in Rome, patients were randomized 1:1 to either an intervention (INT) group, receiving theoretical and practical exercise counseling, or a control (CON) group, receiving only general physician recommendations. Randomization was stratified by center and, within each center, by age $<$ vs. $\geq$65 years and noninsulin versus insulin treatment, with use of permuted-block randomization SAS 9.4 software that randomly varied the block size (range 4, 8).

Patients from both groups received the same treatment regimen, including dietary prescription, to achieve glycemic, lipid, blood pressure (BP), and body weight targets, according to current guidelines. Treatment was adjusted at each visit with a prespecified algorithm.

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

Intervention

The intervention in the INT group consisted of one individual theoretical counseling session, held by a diabetologist, plus eight twice-weekly individual theoretical and practical counseling sessions, held by a certified exercise specialist, once a year for 3 years. This approach was based on the Social Cognitive Theory Model and Health Belief Model and used several behavior change techniques. It was designed to promote a two-step behavior change, i.e., *1*) decreasing SED-time by substituting it with a wide range of LPAs and/or interrupting prolonged sitting at home or work with brief bouts of LPA and *2*) gradually increasing the time spent in purposeful MVPA by reallocating time from sedentary behavior and/or LPA.

Outcome Measures

Coprimary end points were changes from baseline in total PA volume, LPA, MVPA, and SED-time over the 3-year period. Secondary end points were changes from baseline in physical fitness and modifiable CVD factors and scores. Results for these end points have been presented in a previous publication (13). Here, we report on the relationships between changes in primary and secondary end points.

Measurements

Levels of total PA volume, time spent in LPA and MVPA, and SED-time were measured with use of an accelerometer (mywellness key; Technogym, Cesena, Italy) and a daily diary for reporting the time spent wearing the instrument, sleeping, and napping and performing nonaccelerometer recordable activities such as swimming, cycling, skiing, etc. Participants were asked to attach the device at the waist and to wear it all day (except if swimming) up to bedtime to avoid the influence of the "time accelerometer worn," which may cause underestimation of total daily SED-time. In this way, it was possible to assume that the time patients were awake without wearing the accelerometer was spent in routine morning and evening sedentary activities, unless it was spent in activities that cannot be performed while wearing the accelerometer (e.g., swimming). Results were expressed as total SED-time, calculated by addition of the accelerometer nonwear time in the awake state to the accelerometer-based SED-time. Diary-reported time spent in non-accelerometer-recordable activities was added to that recorded by the accelerometer, according to the intensity of each activity. 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 to detail the short-term effect of intervention.

At the same time points, the modifiable cardiovascular risk factors BMI, waist circumference, diabetes duration, fasting plasma glucose (FPG), HbA_{1c}, triglycerides, total, HDL, and LDL cholesterol, systolic and diastolic BP, and hs-CRP were assessed with standard methods, and total and fatal coronary heart disease (CHD) and stroke 10-year risk scores were calculated with the UK Prospective Diabetes Study risk engine (15).

At baseline and every year thereafter, participants were evaluated for physical fitness. Cardiorespiratory fitness was assessed as VO_{2max} by maximal treadmill exercise test with use of the Balke protocol. Isometric muscle strength was assessed as maximal voluntary contractions performed at a shoulder press (Technogym) for the upper body and a leg extension machine (Technogym) for the lower body and measured by a strain gauge tensiometer (Digimax; Mechatronic GmbH, Darmstadt, Germany). Hip and trunk flexibility was assessed by a standard bending test.

Statistical Analysis

Mean changes over baseline throughout the 3-year follow-up in PA/SED-time, physical fitness, and CVD risk factors/scores were calculated for participants who completed the study. These individuals were then stratified by quartiles of changes in MVPA, SED-time, LPA, and PA volume, and data were expressed as mean ± SD. One-way ANOVA was used for assessing differences among quartiles.

Univariate correlations between changes in MVPA, SED-time, LPA, and PA volume and changes in physical fitness and CVD risk factors/scores were assessed by Spearman ρ. Multivariable linear regression analyses were applied to assess the independent correlates of changes in physical fitness and CVD risk factors/scores over the 3-year period. Age, sex, study arm, the baseline value of the dependent variable, and changes in MVPA and SED-time were included as covariates in model 1. As SED-time was almost entirely reallocated to LPA, which contributed significantly to the increase in total PA volume, LPA was substituted for SED-time in model 2, whereas PA volume was substituted for MVPA and SED-time in model 3.

All of the above analyses were performed in the whole cohort and in the two groups separately. All P values <0.05 were considered statistically significant. Statistical analyses were performed with SPSS, version 20 (SPSS, Chicago, IL).

RESULTS

As previously described (13), 449 patients were assessed for eligibility from October 2012 to February 2014 in the three centers, and after exclusion of 149 patients for various reasons, the remaining 300 were randomized to the CON or INT group (n = 150 each). Of these 300, 267 patients completed the study at the final evaluation (CON = 134 and INT = 133), whereas 33 patients (CON = 16 and INT = 17) dropped out for various reasons; of those in the INT group, >90% attended the counseling sessions.

The baseline features of study participants and results for coprimary and secondary outcomes have previously been reported, together with adverse events, which did not differ between groups and were unrelated to PA (13).

Changes in Physical Fitness and CVD Risk Factors and Scores by Quartiles of Changes in MVPA and SED-Time

There were no significant differences in age and sex among quartiles of MVPA and SED-time change (not shown). Patients falling in quartile I of MVPA and SED-time change showed a substantial decrease in MVPA and increase in SED-time (on average, -10.8 min $\cdot$ day^{-1} and $+0.72$ h $\cdot$ day^{-1}, respectively), those in quartile II showed virtually no change, and those in quartiles III and IV showed modest (on average, $+4.0$ min $\cdot$ day^{-1} and -0.60 h $\cdot$ day^{-1}, respectively) and marked (on average, $+14.3$ min $\cdot$ day^{-1} and -1.53 h $\cdot$ day^{-1}, respectively) improvements, respectively (Table 1). There was only a partial correspondence between quartiles of MVPA change and quartiles of SED-time change; in fact, though 47.8% and 60.6% of patients assigned to quartiles I and IV of MVPA change fell into quartiles I and IV of SED-time, respectively, there were also a few individuals in the highest quartile of MVPA change who fell in the lowest quartile of SED-time change and vice versa (Table 1). Moreover, most of the participants falling in the highest quartile (IV) of MVPA and SED-time change were from the INT group, whereas those in quartile III were almost in equal number from the two groups and those in the lowest quartiles (I and II) were mainly from the CON group (Supplementary Table 1). Therefore, while >40% of INT participants and almost 40% of CON participants showed a marked improvement and worsening, respectively, in both MVPA and SED-time, ~30% of INT participants showed no meaningful change or

Table 1—Distribution of study participants by quartiles of mean changes from baseline in MVPA versus SED-time

	Quartiles of mean change in SED-time vs. baseline (h·day^{-1})			
Quartiles of mean change in MVPA vs. baseline (min·day^{-1})	I: *N* = 67; mean 0.72 ± 0.39 (1.94, 0.2)	II: *N* = 66; mean 0.09 ± 0.17 (0.22, −0.33)	III: *N* = 68; mean −0.60 ± 0.18 (−0.34, −0.99)	IV: *N* = 66; mean −1.53 ± 0.43 (−1.00, −3.08)
I: *N* = 67; mean −3.33 ± 2.17 (−10.81, −1.09)	32 (47.8)	19 (28.8)	12 (17.6)	4 (6.1)
II: *N* = 67; mean 0.27 ± 0.84 (−1.08, 1.87)	24 (35.8)	20 (30.3)	15 (22.1)	8 (12.1)
III: *N* = 67; mean 4.02 ± 1.58 (1.88, 7.20)	10 (14.9)	20 (30.3)	23 (33.8)	14 (21.2)
IV: *N* = 66; mean 14.32 ± 6.59 (7.24, 34.95)	1 (1.5)	7 (10.6)	18 (26.5)	40 (60.6)

Data are *n* (%) unless otherwise indicated.

even substantial worsening and ∼30% of CON participants showed modest or even striking improvements in these parameters (Supplementary Table 1).

Improvements with quartiles of mean change over baseline in MVPA were observed for PA/SED-time and physical fitness parameters as well as for HbA_{1c}, FPG, BMI, triglycerides, and total and fatal CHD 10-year risk (Table 2). Improvements with quartiles of mean change over baseline in SED-time were observed for PA and physical fitness parameters as well as for HbA_{1c} and total and fatal CHD 10-year risk (Table 3). Similar results were obtained for quartiles of mean change over baseline in LPA (Supplementary Table 2) and PA volume (Supplementary Table 3). Improvements in physical fitness parameters and CVD risk factors/scores with quartiles of changes in accelerometer-based measures were observed also in the two groups separately (not shown).

Correlations of Changes in MVPA/SED-Time With Changes in Physical Fitness and CVD Risk Factors/Scores

Upon univariate analysis, changes in MVPA and SED-time correlated significantly with those in physical fitness parameters as well as in HbA_{1c}, FPG, hs-CRP, total and fatal CHD 10-risk, BMI and waist circumference (for MVPA changes only), and total stroke 10-risk score (for SED-time changes only) (Supplementary Table 4). Similar results were obtained for changes in LPA and PA volume (Supplementary Table 4) and in the two groups separately (not shown).

In model 1, changes in MVPA and SED-time were both independent predictors of change in VO_{2max} (especially MVPA change) and HbA_{1c} (especially SED-time change) (Table 4). Removal of either one from the model resulted in a stronger association of the other one with VO_{2max} (especially for 1 h · day^{-1} change in SED-time: β −1.608, $P < 0.0001$) and HbA_{1c} (especially for 1 min·day^{-1} change in MVPA: β −0.047, $P < 0.0001$). Only change in MVPA was an independent predictor of change in upper and lower body strength and inversely of change in waist circumference, triglycerides, and systolic BP (Table 4); when MVPA change was removed from the model, change in SED-time became an independent predictor of change in lower-body strength and triglycerides but not in upper-body strength and waist circumference (not shown). Only change in SED-time was an independent predictor of change in bending, FPG, diastolic BP, and CHD 10-year risk scores and, inversely, of change in HDL cholesterol (Table 4); when SED-time change was removed from the model, change in MVPA became an independent predictor of change in FPG, HDL cholesterol, and CHD 10-year risk scores but not in bending and diastolic BP (not shown). In replacing of SED-time changes with LPA changes (model 2), the latter was an independent predictor of changes in the same parameters as for SED-time, except bending (Supplementary Table 5). Likewise, in replacing of MVPA and LPA changes with PA volume changes (model 3), PA volume changes were an independent predictor of changes in the same variables as for MVPA and/or SED-time (Supplementary Table 6). Results were similar when the multivariable linear regression analyses were conducted separately in CON (Supplementary Table 7) and INT (Supplementary Table 8) participants.

The baseline value of the dependent variable was always significantly associated with its change over the study follow-up, except for VO_{2max}, and the other covariates (age, sex, and study arm) were also variably associated with changes in the dependent variables (Table 4 and Supplementary Tables 5 and 6).

CONCLUSIONS

This prespecified ancillary analysis of the IDES_2 showed that both increases in MVPA and decreases in SED-time contributed to the associated improvements in physical fitness and CVD risk profile. These findings provide important insights into the understanding of the relative roles of changes in PA and sedentary behavior promoted by counseling interventions on these surrogate outcomes, the improvement of which may translate into long-term benefits in terms of morbidity and mortality (16,17). In fact, it has long been debated whether increasing (MV)PA volume below the recommended targets and/or reallocating SED-time mainly to LPA, as occurred in the IDES_2, has a meaningful impact on physical fitness and CVD risk profile. Several studies support the concept that increasing PA volume and/or intensity below a certain threshold (i.e., that recommended by guidelines) would not be effective in improving these outcomes, according to the overload principle of training (18). The current study provides strong support to the concept that this may not apply to physically inactive and sedentary or unfit individuals, including most of those suffering from type 2 diabetes. In particular, our data suggest that even modest increments in MVPA may have a clinically meaningful impact for these people, provided that they are associated with larger decrements in SED-time and

Table 2—Mean changes over baseline in study parameters according to quartiles of mean changes from baseline in MVPA

	Quartiles of mean change in MVPA versus baseline				
	I	II	III	IV	*P*
N	67	67	67	66	
MVPA, min · day^{-1}	−3.33 ± 2.17	0.27 ± 0.84	4.02 ± 1.58	14.32 ± 6.59	
Range	−10.81, −1.09	−1.08, 1.87	1.88, 7.20	7.24, 34.95	
SED-time, h · day^{-1}	0.22 ± 0.74	−0.14 ± 0.79	−0.44 ± 0.65	−1.14 ± 0.68	<0.0001
LPA, h · day^{-1}	−0.20 ± 0.76	0.17 ± 0.78	0.38 ± 0.75	0.91 ± 0.65	<0.0001
PA volume, MET h · week^{-1}	−0.89 ± 1.98	0.38 ± 1.85	1.36 ± 1.88	4.25 ± 1.97	<0.0001
VO_{2max}, mL · min^{-1} · kg^{-1}	−0.43 ± 2.85	0.78 ± 2.68	2.86 ± 3.01	5.23 ± 3.88	<0.0001
Upper-body muscle strength, Nm	−17.9 ± 24.2	−15.5 ± 22.4	−6.5 ± 25.0	4.8 ± 29.8	<0.0001
Lower-body muscle strength, Nm	11.5 ± 24.8	5.7 ± 21.9	18.0 ± 20.9	39.3 ± 37.7	<0.0001
Bending, cm	0.99 ± 4.03	0.61 ± 3.81	−0.30 ± 3.87	−1.45 ± 2.63	0.001
HbA_{1c}, % mmol · mol^{-1}	0.40 ± 0.99 4.4 ± 10.8	0.04 ± 0.64 0.4 ± 7.0	−0.23 ± 0.81 −2.5 ± 8.9	−0.73 ± 1.22 −8.0 ± 13.3	<0.0001
FPG, mmol · L^{-1}	0.45 ± 1.92	0.23 ± 2.99	−0.31 ± 1.81	−0.66 ± 1.75	0.014
BMI, kg/m^2	0.26 ± 1.30	0.03 ± 1.10	−0.36 ± 1.35	−0.33 ± 1.25	0.011
Waist circumference, cm	1.90 ± 4.78	1.72 ± 9.00	−0.72 ± 4.93	−0.64 ± 6.35	0.021
Triglycerides, mmol · L^{-1}	0.11 ± 0.93	0.02 ± 0.44	−0.26 ± 1.00	−0.05 ± 0.56	0.044
Total cholesterol, mmol · L^{-1}	0.15 ± 0.83	0.00 ± 0.82	−0.01 ± 0.70	0.02 ± 0.61	0.572
HDL cholesterol, mmol · L^{-1}	−0.06 ± 0.15	−0.11 ± 0.18	−0.05 ± 0.19	−0.06 ± 0.17	0.110
LDL cholesterol, mmol · L^{-1}	0.00 ± 0.79	−0.05 ± 0.75	−0.09 ± 0.56	0.00 ± 0.60	0.866
Systolic BP, mmHg	−3.22 ± 16.84	−4.62 ± 18.43	−2.37 ± 13.17	−4.27 ± 16.71	0.854
Diastolic BP, mmHg	−2.98 ± 8.75	−5.68 ± 13.67	−3.84 ± 10.31	−2.90 ± 7.52	0.373
hs-CRP, mg · L^{-1}	−0.04 ± 0.70	−0.16 ± 0.90	−0.04 ± 0.45	−0.12 ± 0.53	0.654
CHD 10-year risk score, %	−0.04 ± 0.70	−0.16 ± 0.90	−0.04 ± 0.45	−0.12 ± 0.53	0.002
Fatal CHD 10-year risk score, %	0.60 ± 2.58	−0.45 ± 4.48	0.08 ± 0.94	−0.24 ± 1.21	0.003
Stroke 10-year risk score, %	5.33 ± 6.88	4.15 ± 6.06	2.39 ± 5.21	1.62 ± 6.15	0.387
Fatal stroke 10-year risk score, %	4.81 ± 6.30	3.77 ± 5.15	2.45 ± 4.51	1.57 ± 5.07	0.895

Data are means ± SD unless otherwise indicated.

reciprocal increments in LPA resulting in substantial increases in total PA volume, which also contribute to improve outcomes.

This offers a possible explanation for the discrepancies between the IDES_2 and studies specifically designed to increase MVPA by promoting walking through the provision of pedometers, most of which failed to show significant improvements in surrogate outcomes, despite similar increases in MVPA but with no change in SED-time. No effect was in fact reported on HbA_{1c} or other CVD risk factors (9,10) or pain, depression, anxiety, or health-related quality of life (8), regardless of whether increases in MVPA were maintained, albeit to a lesser extent (8), or not (9), in the long-term. In addition, at variance with the IDES_2, the initial improvement in cardiorespiratory fitness was not maintained in the Look AHEAD (Action for Health in Diabetes) trial, as after 4 years it was approximately one-fourth of that observed after 1 year (12), just like the increment in MVPA (11). Taken together, these findings indicate that a behavioral counseling targeting both MVPA and SED-time, such as in the IDES_2, is more effective in promoting a sustained behavior change than interventions focusing only on PA (19), which appear inadequate to reduce SED-time and might even trigger compensatory sedentary behavior (20). However, it is unclear whether the additional contribution of decreasing sedentary behavior is related to the reduction and/or interruption of SED-time per se. On the one hand, these actions were in fact shown to provide metabolic benefits independent of one another, in addition to time spent in MVPA (21); furthermore, prolonged sitting time was associated with increased risk of CVD events independent of leisure-time PA in postmenopausal women without a history of CVD (22), and not only the amount but also the pattern of SED-time was associated with mortality (23). On the other hand, change in LPA was independently associated with change in the same variables as change in SED-time and change in PA volume was independently associated with change in the same variables as change in MVPA and LPA. This suggests that the

Table 3—Mean changes from baseline in study parameters according to quartiles of mean changes from baseline in SED-time

	Quartiles of mean change in SED-time versus baseline				
	I	II	III	IV	*P*
N	67	66	68	66	
SED time, h · day^{-1}	0.72 ± 0.39	−0.09 ± 0.17	−0.60 ± 0.18	−1.53 ± 0.43	
Range	1.94, 0.23	0.22, −0.33	−0.34, −0.99	−1.00, −3.08	
MVPA, min · day^{-1}	−0.92 ± 4.64	1.24 ± 4.17	4.50 ± 6.23	10.35 ± 8.73	<0.0001
LPA, h · day^{-1}	−0.64 ± 0.50	0.08 ± 0.34	0.51 ± 0.36	1.30 ± 0.57	<0.0001
PA volume, MET h · week^{-1}	−1.69 ± 1.50	0.37 ± 1.00	1.83 ± 1.25	4.58 ± 1.84	<0.0001
VO_{2max}, mL · min^{-1} · kg^{-1}	−0.08 ± 2.45	1.49 ± 3.04	2.61 ± 3.91	4.49 ± 4.03	<0.0001
Upper-body muscle strength, Nm	−15.4 ± 22.0	−7.7 ± 22.9	−12.0 ± 25.7	0.54 ± 33.7	0.005
Lower-body muscle strength, Nm	5.8 ± 23.9	17.5 ± 24.0	17.9 ± 24.5	33.8 ± 38.5	<0.0001
Bending, cm	1.46 ± 3.53	0.43 ± 3.79	−0.84 ± 3.75	−1.24 ± 3.28	<0.0001
HbA_{1c}, %	0.46 ± 0.78	0.00 ± 0.99	−0.13 ± 0.71	−0.85 ± 1.11	<0.0001
mmol · mol^{-1}	5.0 ± 8.5	0.0 ± 10.8	−1.4 ± 7.8	−9.3 ± 12.1	
FPG, mmol · L^{-1}	0.61 ± 2.66	−0.17 ± 2.40	−0.06 ± 1.51	−0.68 ± 1.86	0.009
BMI, kg/m^2	0.05 ± 1.26	−0.03 ± 1.25	0.01 ± 1.33	−0.44 ± 1.21	0.099
Waist circumference, cm	1.40 ± 8.68	0.94 ± 6.02	0.79 ± 6.11	−0.87 ± 4.73	0.208
Triglycerides, mmol · L^{-1}	0.07 ± 0.90	−0.12 ± 0.93	−0.09 ± 0.58	−0.04 ± 0.66	0.503
Total cholesterol, mmol · L^{-1}	0.19 ± 0.89	0.05 ± 0.55	−0.08 ± 0.75	0.00 ± 0.74	0.205
HDL cholesterol, mmol · L^{-1}	−0.08 ± 0.16	−0.09 ± 0.20	−0.06 ± 0.17	−0.05 ± 0.17	0.512
LDL cholesterol, mmol · L^{-1}	0.06 ± 0.82	−0.02 ± 0.46	−0.13 ± 0.66	−0.05 ± 0.73	0.429
Systolic BP, mmHg	−4.36 ± 15.19	−1.54 ± 14.22	−4.37 ± 17.26	−4.16 ± 18.49	0.701
Diastolic BP, mmHg	−3.54 ± 14.13	−2.80 ± 6.56	−4.96 ± 8.30	−4.07 ± 10.85	0.671
hs-CRP, mg · L^{-1}	−0.10 ± 0.83	0.05 ± 0.44	−0.15 ± 0.76	−0.16 ± 0.55	0.237
CHD 10-year risk score, %	5.89 ± 6.54	4.09 ± 6.03	2.84 ± 4.89	0.59 ± 6.29	<0.0001
Fatal CHD 10-year risk score, %	5.17 ± 5.78	3.82 ± 5.57	2.88 ± 4.09	0.67 ± 5.16	<0.0001
Stroke 10-year risk score, %	3.75 ± 3.46	4.29 ± 3.90	4.09 ± 9.15	2.67 ± 3.27	0.353
Fatal stroke 10-year risk score, %	0.30 ± 1.14	0.59 ± 1.09	0.50 ± 1.60	0.25 ± 1.07	0.364

Data are means ± SD unless otherwise indicated.

additional contribution of reduced SED-time might be attributed to the reciprocal ∼0.8 h·day^{-1} increment in LPA, which impacted more than the ∼6 min·day^{-1} increment in MVPA on the increase in total PA volume and energy expenditure. There is in fact growing evidence that higher LPA is also associated with better outcomes. In healthy sedentary older adults, VO_{2max} improved significantly at 35–50% heart rate reserve and continued improving at a greater rate up to heart rate reserve of 75–80% (24). An analysis of 18 studies in healthy subjects showed that exercising intensities below ∼45% VO_2 reserve were consistently ineffective at increasing VO_{2max} in individuals with mean initial VO_{2max} >40 mL · min^{-1} · kg^{-1} but not in those with mean initial VO_{2max} <40 mL · min^{-1} · kg^{-1}, though the lowest intensities examined were ∼30% VO_2 reserve (25). Though a systematic review of 33 intervention studies failed to detect a significant effect of LPA on CVD risk factors (26), other reports showed a favorable impact (27–30). Moreover, two meta-analyses showed that LPA was associated with improved cardiometabolic health and reduced total and CVD mortality risk (31,32). Finally, the curvilinear relationship between LPA/SED-time and mortality risk was attenuated, but not abolished, by MVPA, except for very high levels (33), and an inverse association was reported between number but not intensity of daily steps and all-cause death (34,35) and CVD events (36).

Another plausible, not mutually exclusive explanation for the discrepancies between the IDES_2 and walking-based intervention studies is that the relative extent of increases over baseline in MVPA is as relevant as the absolute increase for the effect on clinical outcomes. In fact, in the IDES_2, time spent in MVPA was only ∼12 min · day^{-1} at baseline and, hence, increased by >50% throughout the 3-year follow-up and was still 30% over baseline at end of study (13). Conversely, in walking-based intervention studies, percent increments were much smaller as MVPA ranged from ∼25 to ∼45 min · day^{-1} at baseline and increased by up to ∼8 min · day^{-1} after 1 year and by one-half or less after longer follow-up (8–11). This interpretation

Table 4—Independent predictors of mean changes from baseline in physical fitness and CVD risk factors and scores (model 1)

	Independent variables											
	Mean change in MVPA, min · day^{-1}		Mean change in SED-time, h · day^{-1}		Baseline value of dependent variable		Age, years		Male sex		INT study arm	
Dependent variables	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*
VO_{2max}, mL · min^{-1} · kg^{-1}	0.218	<0.0001	−0.684	0.013							0.810	0.062
Upper-body muscle strength, Nm	0.944	<0.0001			−0.139	<0.0001	−0.507	0.001	11.980	<0.0001	5.411	0.089
Lower-body muscle strength, Nm	0.996	<0.0001			−0.161	<0.0001	−0.639	<0.0001	9.473	0.010	19.432	<0.0001
Bending, cm			0.511	0.033	−0.143	<0.0001	0.087	<0.0001	−1.135	0.004	−1.804	<0.0001
HbA_{1c}, %	−0.025	0.001	0.449	<0.0001	−0.342	<0.0001			0.176	0.048	0.283	0.005
FPG, mmol · L^{-1}	−0.031	0.069	0.294	0.048	−0.520	<0.0001	−0.018	0.088	0.524	0.014		
BMI, kg/m^2			0.160	0.069	−0.032	0.029	−0.018	0.022				
Waist circumference, cm	−0.109	0.028			−0.187	<0.0001			1.881	0.013		
Triglycerides, mmol · L^{-1}	−0.013	0.008			−0.373	<0.0001	−0.011	0.004				
Total cholesterol, mmol · L^{-1}					−0.516	<0.0001	−0.008	0.032	−0.192	0.007		
HDL cholesterol, mmol · L^{-1}			−0.023	0.017	−0.314	<0.0001			−0.044	0.014		
LDL cholesterol, mmol · L^{-1}					−0.533	<0.0001	−0.007	0.032	−0.111	0.087		
Systolic BP, mmHg	−0.199	0.018			−0.653	<0.0001	0.347	<0.0001				
Diastolic BP, mmHg			0.794	0.035	−0.747	<0.0001	−0.081	0.017				
hs-CRP, mg · L^{-1}					−0.250	<0.0001	−0.150	0.004	3.909	<0.0001		
CHD 10-year risk score, %			2.256	<0.0001	−0.185	<0.0001	0.269	<0.0001	4.394	<0.0001		
Fatal CHD 10-year risk score, %			1.918	<0.0001	−0.126	<0.0001	0.221	<0.0001	3.301	<0.0001		
Stroke 10-year risk score, %					0.083	0.020	0.149	0.001	1.135	0.088		
Fatal stroke 10-year risk score, %					−0.222	<0.0001	0.058	<0.0001	0.474	0.001		

is consistent with a recent UK Biobank longitudinal study showing that, in inactive people, a 6 min · day^{-1} difference in brisk walking (corresponding to ∼500 steps in 5 min [37]) was associated with significant health benefits (∼4 life years gained) (38). Likewise, in adults at high risk for type 2 diabetes and CVD, every 2,000 step · day^{-1} increment in ambulatory activity at baseline was associated with a 10% lower risk of CVD events and each 2,000 step · day^{-1} change from baseline to 12 months was associated with an additional 8% difference (36). Moreover, among older women, as few as ∼4,400 steps · day^{-1} were significantly related to lower mortality rates compared with ∼2,700 steps · day^{-1} (35) and, among sedentary, overweight postmenopausal women, one-half the currently recommended PA volume was sufficient to improve cardiorespiratory fitness (39). A pronouncement of the American College of Sports Medicine concluded that the benefits of PA on CVD events and all-cause and CVD mortality start with very modest amounts (approximately one-third the amount recommended by guidelines) (1).

This analysis of the IDES_2 also showed differences in the relative importance of increases in MVPA and decreases in SED-time depending on the variable tested. Changes in both MVPA and SED-time were independently associated with changes in VO_{2max}, though the relationship was stronger for the former, which was the only independent predictor of muscle strength, in keeping with the concept that PA of higher intensity is required for a significant impact on cardiorespiratory and muscle fitness (18). Conversely, the association of bending with SED-time indicates the beneficial effect of reducing sitting (and increasing the total amount of PA) on flexibility. The much stronger association of glycemic control with SED-time than with MVPA may be related to the greater amount of energy expenditure produced the associated larger increase in LPA with reduction of SED-time, compared with the modest increase in MVPA. Moreover, while it is plausible that waist circumference, triglycerides, and systolic BP were preferentially associated with MVPA (28), it is difficult to explain the findings that HDL cholesterol and diastolic BP were independently predicted by SED-time only, though they are in keeping with previous observations (30,40). Finally, the independent association of CHD 10-year risk scores with both MVPA and SED-time reflects their relationships with parameters used for calculating these scores, with the stronger relationship with SED-time likely depending on its higher strength of association with HbA_{1c} compared with MVPA.

The main strengths of this study concern the trial design, i.e., the application of an intervention targeting both PA and SED-time, based on solid theoretical grounds, and using several behavioral change techniques, the specific training of investigators, the long study duration, and the large sample size. Other strengths include the objective (accelerometer-based) measurement of PA/SED-time and the concurrent assessment of physical fitness and CVD risk factors. However, this study has some limitations. First, generalizability requires further investigation and validation in different cohorts or settings. Second, this trial was not designed to assess the impact of changes in MVPA and SED-time on physical fitness and CVD risk factors/scores, which were secondary end points, and specific studies should be designed to assess the effect of different extents of increases in MVPA and/or decreases in SED-time on these variables. Third, results might have been affected by unmeasured confounders, e.g., diet, which were not considered in data analysis, though patients received dietary prescriptions and adherence to diet was verified at intermediate visits.

In conclusion, this analysis of the IDES_2 indicates that, in physically inactive and sedentary patients with type 2 diabetes, even modest increments in MVPA may have a clinically meaningful impact on physical fitness and cardiovascular risk profile and that reallocating SED-time to LPA may also contribute to improve these outcomes, possibly by increasing total energy expenditure. This implies that, in these individuals, the behavior change produced by counseling interventions targeting both MVPA and SED-time/LPA may be sufficient to ensure long-term benefits in terms of morbidity and mortality.

Acknowledgments. The authors thank the patients and the IDES_2 Investigators for participating in this study.

Funding. This work was supported by the Metabolic Fitness Association, Monterotondo, Rome, Italy.

The sponsor had no role in design or conduct of the study; collection, management, or interpretation of data; or preparation, review, or approval of the manuscript.

Duality of Interest. S.B. reported personal fees from AstraZeneca, Eli Lilly, Novo Nordisk, and Takeda. S.Z. is an employee of Technogym. A.N. reported grants from AstraZeneca, Eli Lilly, Novo Nordisk, and Sanofi and personal fees from Eli Lilly and Novo Nordisk. G.P. reported personal fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Mylan, Sigma-Tau Pharmaceuticals, and Takeda. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. S.B. and J.H. conceived and designed the study, researched data, and reviewed and edited the manuscript. M.S., G.O., P.C., M.V., L.M., C.I., L.B., F.C., and S.Z. researched data and contributed to the discussion. A.N. conceived and designed the study, performed statistical analysis, and reviewed and edited the manuscript. G.P. conceived and designed the study, researched data, performed statistical analysis, and drafted the manuscript. G.P. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Kraus WE, Powell KE, Haskell WL, et al.; 2018 PHYSICAL ACTIVITY GUIDELINES ADVISORY COMMITTEE. Physical activity, all-cause and cardiovascular mortality, and cardiovascular disease. Med Sci Sports Exerc 2019;51:1270–1281

2. Matthews CE, George SM, Moore SC, et al. Amount of time spent in sedentary behaviors and cause-specific mortality in US adults. Am J Clin Nutr 2012;95:437–445

3. Church TS, Cheng YJ, Earnest CP, et al. Exercise capacity and body composition as predictors of mortality among men with diabetes. Diabetes Care 2004;27:83–88

4. Loprinzi PD, Sng E. The effects of objectively measured sedentary behavior on all-cause mortality in a national sample of adults with diabetes. Prev Med 2016;86:55–57

5. Morrato EH, Hill JO, Wyatt HR, Ghushchyan V, Sullivan PW. Physical activity in U.S. adults with diabetes and at risk for developing diabetes, 2003. Diabetes Care 2007;30:203–209

6. World Health Organization. WHO Guidelines on Physical Activity and Sedentary Behaviour, 2020. Accessed 25 June 2021. Available from https://www.who.int/publications/i/item/9789240015128

7. Colberg SR, Sigal RJ, Yardley JE, et al. Physical activity/exercise and diabetes: a Position Statement of the American Diabetes Association. Diabetes Care 2016;39:2065–2079

8. Harris T, Kerry SM, Limb ES, et al. Physical activity levels in adults and older adults 3-4 years after pedometer-based walking interventions: long-term follow-up of participants from two randomised controlled trials in UK primary care. PLoS Med 2018;15:e1002526

9. Khunti K, Griffin S, Brennan A, et al. Promoting physical activity in a multi-ethnic population at high risk of diabetes: the 48-month PROPELS randomised controlled trial. BMC Med 2021;19:130
10. Andrews RC, Cooper AR, Montgomery AA, et al. Diet or diet plus physical activity versus usual care in patients with newly diagnosed type 2 diabetes: the Early ACTID randomised controlled trial. Lancet 2011;378:129–139
11. Unick JL, Gaussoin SA, Hill JO, et al. Four-year physical activity levels among intervention participants with type 2 diabetes. Med Sci Sports Exerc 2016;48:2437–2445
12. ; Look AHEAD Research Group. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. Arch Intern Med 2010;170: 1566–1575
13. Balducci S, D'Errico V, Haxhi J, et al.; Italian Diabetes and Exercise Study 2 (IDES_2) Investigators. Effect of a behavioral intervention strategy on sustained change in physical activity and sedentary behavior in patients with type 2 diabetes: the IDES_2 randomized clinical trial. JAMA 2019;321:880–890
14. Balducci S, Sacchetti M, Haxhi J, et al.; Italian Diabetes and Exercise Study 2 (IDES_2) Investigators. The Italian Diabetes and Exercise Study 2 (IDES-2): a long-term behavioral intervention for adoption and maintenance of a physically active lifestyle. Trials 2015;16:569
15. Stevens RJ, Kothari V, Adler AI; United Kingdom Prospective Diabetes Study (UKPDS) Group. The UKPDS risk engine: a model for the risk of coronary heart disease in type II diabetes (UKPDS 56). Clin Sci (Lond) 2001;101:671–679
16. Blair SN, Kampert JB, Kohl HW 3rd, et al. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. JAMA 1996;276:205–210
17. Ruiz JR, Sui X, Lobelo F, et al. Association between muscular strength and mortality in men: prospective cohort study. BMJ 2008;337: a439
18. Garber CE, Blissmer B, Deschenes MR, et al.; American College of Sports Medicine. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc 2011;43:1334–1359
19. Prince SA, Saunders TJ, Gresty K, Reid RD. A comparison of the effectiveness of physical activity and sedentary behaviour interventions in reducing sedentary time in adults: a systematic review and meta-analysis of controlled trials. Obes Rev 2014;15:905–919
20. King NA, Horner K, Hills AP, et al. Exercise, appetite and weight management: understanding the compensatory responses in eating behaviour and how they contribute to variability in exercise-induced weight loss. Br J Sports Med 2012;46:315–322
21. Cooper AR, Sebire S, Montgomery AA, et al. Sedentary time, breaks in sedentary time and metabolic variables in people with newly diagnosed type 2 diabetes. Diabetologia 2012; 55:589–599
22. Chomistek AK, Manson JE, Stefanick ML, et al. Relationship of sedentary behavior and physical activity to incident cardiovascular disease: results from the Women's Health Initiative. J Am Coll Cardiol 2013;61:2346–2354
23. Diaz KM, Howard VJ, Hutto B, et al. Patterns of sedentary behavior and mortality in U.S. middle-aged and older adults: a national cohort study. Ann Intern Med 2017;167:465–475
24. Huang G, Wang R, Chen P, Huang SC, Donnelly JE, Mehlferber JP. Dose-response relationship of cardiorespiratory fitness adaptation to controlled endurance training in sedentary older adults. Eur J Prev Cardiol 2016;23:518–529
25. Swain DP, Franklin BA. VO(2) reserve and the minimal intensity for improving cardiorespiratory fitness. Med Sci Sports Exerc 2002;34:152–157
26. Batacan RB Jr, Duncan MJ, Dalbo VJ, Tucker PS, Fenning AS. Effects of light intensity activity on CVD risk factors: a systematic review of intervention studies. BioMed Res Int 2015;2015: 596367
27. Lamb MJE, Westgate K, Brage S, et al.; ADDITION-Plus study team. Prospective associations between sedentary time, physical activity, fitness and cardiometabolic risk factors in people with type 2 diabetes. Diabetologia 2016;59:110–120
28. LaMonte MJ, Lewis CE, Buchner DM, et al. Both light intensity and moderate-to-vigorous physical activity measured by accelerometry are favorably associated with cardiometabolic risk factors in older women: the Objective Physical Activity and Cardiovascular Health (OPACH) Study. J Am Heart Assoc 2017;6:e007064
29. Whitaker KM, Pettee Gabriel K, Buman MP, et al. Associations of accelerometer-measured sedentary time and physical activity with prospectively assessed cardiometabolic risk factors: the CARDIA study. J Am Heart Assoc 2019;8:e010212
30. German C, Makarem N, Fanning J, et al. Sleep, sedentary behavior, physical activity, and cardiovascular health: MESA. Med Sci Sports Exerc 2021;53:724–731
31. Chastin SFM, De Craemer M, De Cocker K, et al. How does light-intensity physical activity associate with adult cardiometabolic health and mortality? Systematic review with meta-analysis of experimental and observational studies. Br J Sports Med 2019;53:370–376
32. Qiu S, Cai X, Jia L, et al. Does objectively-measured light-intensity physical activity reduce the risk of cardiovascular mortality? A meta-analysis. Eur Heart J Qual Care Clin Outcomes 2021;7:496–504
33. Matthews CE, Keadle SK, Troiano RP, et al. Accelerometer-measured dose-response for physical activity, sedentary time, and mortality in US adults. Am J Clin Nutr 2016;104:1424–1432
34. Saint-Maurice PF, Troiano RP, Bassett DR Jr, et al. Association of daily step count and step intensity with mortality among us adults. JAMA 2020;323:1151–1160
35. Lee IM, Shiroma EJ, Kamada M, Bassett DR, Matthews CE, Buring JE. Association of step volume and intensity with all-cause mortality in older women. JAMA Intern Med 2019;179: 1105–1112
36. Yates T, Haffner SM, Schulte PJ, et al. Association between change in daily ambulatory activity and cardiovascular events in people with impaired glucose tolerance (NAVIGATOR trial): a cohort analysis. Lancet 2014;383:1059–1066
37. Rowlands A, Davies M, Dempsey P, Edwardson C, Razieh C, Yates T. Wrist-worn accelerometers: recommending ~1.0 m *g* as the minimum clinically important difference (MCID) in daily average acceleration for inactive adults. Br J Sports Med 2021;55:814–815
38. Chudasama YV, Khunti KK, Zaccardi F, et al. Physical activity, multimorbidity, and life expectancy: a UK Biobank longitudinal study. BMC Med 2019;17:108
39. Church TS, Earnest CP, Skinner JS, Blair SN. Effects of different doses of physical activity on cardiorespiratory fitness among sedentary, overweight or obese postmenopausal women with elevated blood pressure: a randomized controlled trial. JAMA 2007;297:2081–2091
40. Mann S, Beedie C, Jimenez A. Differential effects of aerobic exercise, resistance training and combined exercise modalities on cholesterol and the lipid profile: review, synthesis and recommendations. Sports Med 2014;44:211–221