JAMA | Original Investigation

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

Stefano Balducci, MD; Valeria D'Errico, MD; Jonida Haxhi, MD, PhD; Massimo Sacchetti, PhD; Giorgio Orlando, PhD; Patrizia Cardelli, PhD; Martina Vitale, MD; Lucilla Bollanti, MD; Francesco Conti, MD, PhD; Silvano Zanuso, PhD; Giuseppe Lucisano, StatD; Antonio Nicolucci, MD, PhD; Giuseppe Pugliese, MD, PhD; for the Italian Diabetes and Exercise Study 2 (IDES_2) Investigators

IMPORTANCE There is no definitive evidence that changes in physical activity/sedentary behavior can be maintained long term in individuals with type 2 diabetes.

OBJECTIVE To investigate whether a behavioral intervention strategy can produce a sustained increase in physical activity and reduction in sedentary time among individuals with type 2 diabetes.

DESIGN, SETTING, AND PARTICIPANTS The Italian Diabetes and Exercise Study 2 was an open-label, assessor-blinded, randomized clinical superiority trial, with recruitment from October 2012 to February 2014 and follow-up until February 2017. In 3 outpatient diabetes clinics in Rome, 300 physically inactive and sedentary patients with type 2 diabetes were randomized 1:1 (stratified by center, age, and diabetes treatment) to receive a behavioral intervention or standard care for 3 years.

INTERVENTIONS All participants received usual care targeted to meet American Diabetes Association guideline recommendations. Participants in the behavioral intervention group (n = 150) received 1 individual theoretical counseling session and 8 individual biweekly theoretical and practical counseling sessions each year. Participants in the standard care group (n = 150) received only general physician recommendations.

MAIN OUTCOMES AND MEASURES Co-primary end points were sustained change in physical activity volume, time spent in light-intensity and moderate- to vigorous-intensity physical activity, and sedentary time, measured by an accelerometer.

RESULTS Of the 300 randomized participants (mean [SD] age, 61.6 [8.5] years; 116 women [38.7%]), 267 completed the study (133 in the behavioral intervention group and 134 in the standard care group). Median follow-up was 3.0 years. Participants in the behavioral intervention and standard care groups accumulated, respectively, 13.8 vs 10.5 metabolic equivalent-h/wk of physical activity volume (difference, 3.3 [95% CI, 2.2-4.4]; $P < .001$), 18.9 vs 12.5 min/d of moderate- to vigorous-intensity physical activity (difference, 6.4 [95% CI, 5.0-7.8]; $P < .001$), 4.6 vs 3.8 h/d of light-intensity physical activity (difference, 0.8 [95% CI, 0.5-1.1]; $P < .001$), and 10.9 vs 11.7 h/d of sedentary time (difference, −0.8 [95% CI, −1.0 to −0.5]; $P < .001$). Significant between-group differences were maintained throughout the study, but the between-group difference in moderate- to vigorous-intensity physical activity decreased during the third year from 6.5 to 3.6 min/d. There were 41 adverse events in the behavioral intervention group and 59 in the standard care group outside of the sessions; participants in the behavioral intervention group experienced 30 adverse events during the sessions (most commonly musculoskeletal injury/discomfort and mild hypoglycemia).

CONCLUSIONS AND RELEVANCE Among patients with type 2 diabetes at 3 diabetes clinics in Rome who were followed up for 3 years, a behavioral intervention strategy compared with standard care resulted in a sustained increase in physical activity and decrease in sedentary time. Further research is needed to assess the generalizability of these findings.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT01600937

JAMA. 2019;321(9):880-890. doi:10.1001/jama.2019.0922

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: Italian Diabetes and Exercise Study 2 (IDES_2) Investigators are listed at the end of this article.

Corresponding Author: Giuseppe Pugliese, MD, PhD, Department of Clinical and Molecular Medicine, "La Sapienza" University, Via di Grottarossa, 1035-1039 - 00189 Rome, Italy (giuseppe.pugliese@uniroma1.it).

The American Diabetes Association recommends that people with type 2 diabetes regularly perform physical activity of moderate- to vigorous-intensity.[1] In addition, the American Diabetes Association guidelines encourage reallocating as much sedentary time to light-intensity physical activity as possible and interrupting prolonged sitting with breaks of light-intensity physical activity, because these actions provide metabolic benefits independent of each other and of time spent in moderate- to vigorous-intensity physical activity.[2]

Adherence to physical activity and exercise recommendations is generally difficult. Individuals with type 2 diabetes are usually well below the recommended level of physical activity and spend a large amount of daily hours sedentary.[3] This behavior implies the need for behavioral interventions targeting both physical activity and sedentary time. Supervised exercise interventions may not be suitable for implementation in routine clinical practice[4] and, although they are successful in increasing moderate- to vigorous-intensity physical activity,[5] appear inadequate to reduce sedentary time and may trigger compensatory sedentary behavior.[6] Most of the available studies of counseling-based interventions assessed physical activity changes for no longer than 12 months[7] and used self-report measures, which are imprecise and do not accurately capture sedentary time and light-intensity physical activity.[8] The follow-up of 2 randomized clinical trials (PACE-UP and PACE-Lifts) of the general population showed maintenance of increases in objectively measured moderate- to vigorous-intensity physical activity, but no effect on sedentary time.[9] In the Look-AHEAD trial, increases in moderate- to vigorous-intensity physical activity and cardiorespiratory fitness among participants with type 2 diabetes 4 years after baseline were one-fourth of the increases 1 year after baseline.[10,11] Thus, to date, there is no definitive evidence that changes in physical activity and sedentary behavior can be maintained long term.[4,7,12]

The Italian Diabetes and Exercise Study 2 (IDES_2) investigated whether a behavioral intervention strategy was more effective than standard care in promoting a sustained increase in physical activity and reduction in sedentary time in individuals with type 2 diabetes.

Methods

This study was an open-label, assessor-blinded, parallel, superiority randomized clinical trial. The research protocol (Supplement 1 and eFigure 1 in Supplement 2)[13,14] complies with the Declaration of Helsinki and was approved by the Ethics Committee of Sant'Andrea University Hospital. Participants provided written informed consent.

Participants

The main entry criterion was type 2 diabetes (defined by the American Diabetes Association criteria[15]) for at least 1 year. Additional requirements were age 40 to 80 years, body mass index of 27 to 40, physical inactivity (ie, insufficient amounts of physical activity according to current guidelines[16]) and sedentary lifestyle (ie, >8 hours of time awake spent in a sitting or reclining posture[17]) for at least 6 months, ability to walk 1.6 km without assistance, and clearance by a cardiologist. All patients attending the study centers from October 2012 to February 2014 were evaluated for eligibility based on medical history, clinical examination, accelerometer data, and cardiologic evaluation.

Key Points

Question Can changes in physical activity/sedentary behavior be maintained in individuals with type 2 diabetes?

Findings In this randomized clinical trial of 300 patients with 3 years of follow-up, a behavioral intervention compared with standard care resulted in a significant difference over time in physical activity volume (3.3 metabolic equivalent-hours per week), moderate- to vigorous-intensity physical activity (6.4 minutes per day), and light-intensity physical activity (0.8 hours per day), as well as a difference in sedentary time (−0.8 hours per day).

Meaning A behavioral intervention may lead to a sustained increase in physical activity and decrease in sedentary time.

Investigators

A specific strategy was implemented to train physicians and exercise specialists participating in this trial to standardize procedures, improve the efficacy and safety of the intervention, promote patient adherence, and minimize dropout, as previously detailed.[5]

Randomization and Blinding

In 3 tertiary referral outpatient diabetes clinics in Rome, patients were randomized 1:1 to a behavioral intervention group to receive theoretical and practical counseling or a standard care group to receive only general physician recommendations.

Randomization was stratified by center and, within each center, by age (<65 years vs ≥65 years) and diabetes treatment (noninsulin vs insulin). Using a permuted block randomization and SAS software version 9.4, which randomly varies the block size (range, 4-8), an allocation sequence was generated and concealed, and investigators were informed of group assignment by telephone.

Physicians, exercise specialists, and participants were not blinded, whereas assessors of physical activity/sedentary time and biochemical parameters were blinded to group assignment.

Interventions

Participants in the behavioral intervention group participated in 1 individual theoretical counseling session, conducted by a diabetologist, and 8 biweekly individual theoretical and practical counseling sessions, conducted by a certified exercise specialist, per year for 3 years. This approach, derived from the original IDES protocol,[18] was conceived to promote a 2-step behavior change to decrease sedentary time by substituting it with a wide range of light-intensity physical activities and/or interrupting prolonged sitting with brief bouts of light-intensity physical activity and to reallocate sedentary time and/or light-intensity physical activity toward gradually increasing amounts of purposeful moderate- to vigorous-intensity physical activity.[13,14]

Participants in the standard care group received only general physician recommendations for increasing daily physical activity and decreasing sedentary time.

Patients from both groups received the same treatment regimen, including dietary prescription, to achieve glycemic, lipid, blood pressure, and body weight targets, according to contemporaneous American Diabetes Association guidelines.[15] Treatment regimens were adjusted at each visit using a prespecified algorithm.

Measurements

Levels of moderate- to vigorous-intensity physical activity, light-intensity physical activity, and sedentary time were measured with an accelerometer (MyWellness Key, Technogym), which had been validated against Actigraph[19] and provided accurate data of total physical activity volume and time spent at different intensities,[20] even in individuals with type 2 diabetes.[21] Participants used a daily diary for reporting time spent wearing the instrument; time spent sleeping and napping; and time spent performing nonaccelerometer-recordable activities, such as swimming, cycling, and skiing. Participants were asked to attach the device at their waist and to wear it all day (except if swimming) until going to sleep to avoid the influence of the "time accelerometer worn," which may have caused underestimation of total daily sedentary time. Because of this request, it was possible to assume that the time participants were awake without wearing the accelerometer was spent in routine morning and evening sedentary activities, unless spent doing activities that cannot be performed while wearing the accelerometer (eg, swimming). Results were expressed as total sedentary time, calculated by adding the time not wearing the accelerometer while awake to the accelerometer-recorded sedentary time. Time spent in nonaccelerometer-recordable activities, as reported in the diary, was added to time recorded by the accelerometer, according to the self-reported intensity of each activity. Participants wore the accelerometer every day from baseline to the end of month 4, and then for the last week of the month every 4 months (ie, the last week of month 8, 12, 16, 20, 24, 28, 32, and 36).[13,14]

At the same points when measurements were obtained, modifiable cardiovascular risk factors were assessed using standard methods, as reported in Supplement 1, and 10-year coronary heart disease (CHD) and stroke risk scores were calculated using the United Kingdom Prospective Diabetes Study (UKPDS) risk engine.[22]

At baseline and every year thereafter, participants were evaluated for cardiorespiratory fitness by estimating maximal oxygen uptake from peak oxygen uptake during a maximal treadmill test, upper and lower body strength from isometric tests, and flexibility using a standard bending test.[13,14]

Outcome Measures

Co-primary end points were changes in physical activity volume (metabolic equivalent [MET]-hours per week^{-1} [h/wk]), time spent in light-intensity physical activity (hours per day^{-1} [h/d]) and moderate- to vigorous-intensity physical activity (min per day^{-1} [min/d]), and sedentary-time (h/d) from baseline over the 3-year period. Secondary end points were improvements in physical fitness, including cardiorespiratory fitness, upper and lower body strength, and flexibility; modifiable cardiovascular risk factors, including hemoglobin A_{1c} (HbA_{1c}), fasting plasma glucose, triglycerides, total high-density and low-density lipoprotein cholesterol, systolic and diastolic blood pressure, estimated glomerular filtration rate, albumin:creatinine ratio, body weight, waist circumference, and high-sensitivity C-reactive protein; and 10-year CHD and stroke risk scores.[13,14] Percentage of participants achieving prespecified targets for physical activity volume (>20 MET-h/wk), light-intensity physical activity (>6 h/d), moderate- to vigorous-intensity physical activity (≥150 min/wk), and sedentary time (<10 h/d) were also calculated, and adverse events were recorded. The other secondary end points and ancillary objectives indicated in the eAppendix in Supplement 1 are not reported.

Statistical Analysis

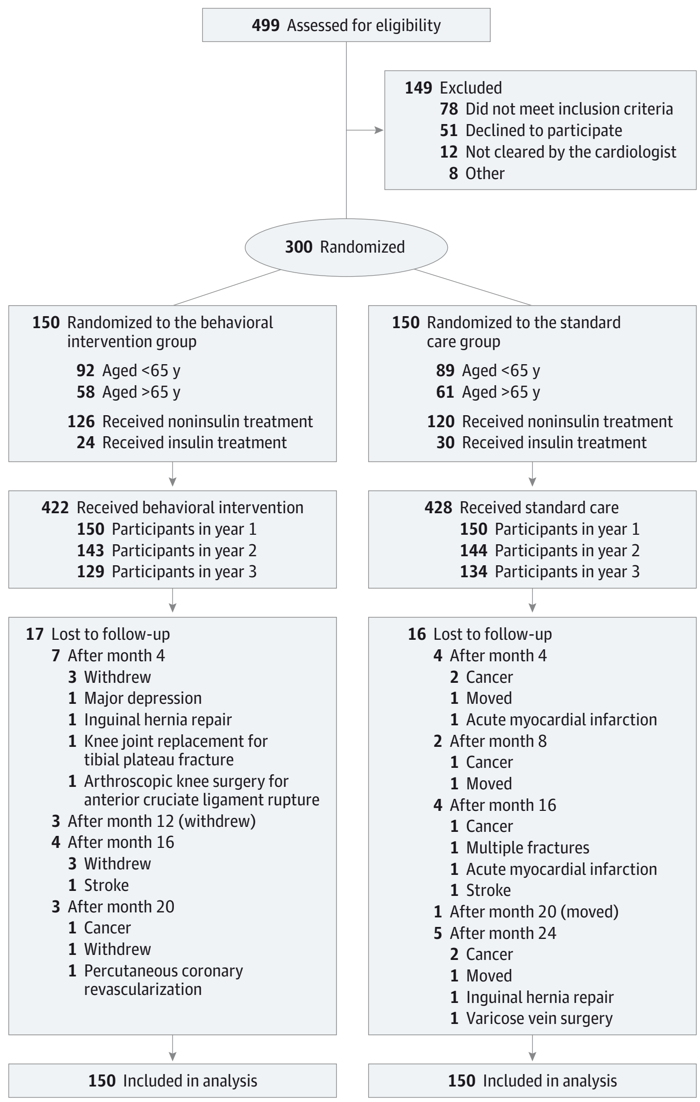
Unpublished preliminary accelerometer data, using the MyWellness Key accelerometer, showed that the mean (SD) physical activity volume in physically inactive, sedentary patients with type 2 diabetes was 10.5 (4.1) MET-h/wk. It was calculated that 142 participants per group (284 total) were needed to observe a 15% between-group difference in daily physical activity with a statistical power of 90% (α = .05) by unpaired *t* test,[13,14] and that a sample size of 300 participants allowed a 5% dropout rate, as observed in the IDES.[5] The 15% difference was considered the minimal clinically important change based on the evidence that a 15% improvement in exercise capacity is associated with a decrease in mortality.[23]

Because change in multicomponent (physical activity-related) behavior was the primary outcome measure of this study, targeting both physical activity and sedentary time, and none of the 4 primary outcome measures alone is able to capture this change, all co-primary end points were required to be significant to interpret the study as positive and the intervention as successful. Patients were analyzed according to their randomization group and per-protocol. The comparison of the intervention vs standard care on the primary and secondary end points was assessed by mixed models for repeated measures. Prespecified subgroup analyses were conducted for the primary outcomes by sex, age (<65 years vs ≥65 years), and treatment (noninsulin vs insulin), using the same models; *P* values for interaction were also estimated using type III *F* tests.

In post hoc analyses, participants in the behavioral intervention group who became physically active (ie, accumulated >150 min/wk of moderate- to vigorous-intensity physical activity throughout the 3-year period) were compared with the entire group. A separate post hoc analysis was conducted for participants with baseline HbA_{1c} values greater than or equal to 8%. In a post hoc analysis, time when not wearing the accelerometer and accelerometer-recorded sedentary time were analyzed separately, in addition to calculating accelerometer wear time and sleeping times. To account for the effect of multiple sites, the interaction with the site was also evaluated, followed by a post hoc analysis using hierarchical modeling with site as a random effect.

Models for repeated measures with an autoregressive correlation-type matrix make an assumption of missing at random and account for both missingness at random and potential correlation within participants, because they allow

Figure 1. Flow of Participants in a Study of the Effect of a Behavioral Intervention on Physical Activity in Patients With Type 2 Diabetes



evaluation of all individuals, including participants with incomplete data.[24] A per-protocol analysis was performed as a sensitivity analysis to assess the robustness of inferences about treatment effects on participants with complete data.

Statistical analyses were performed using SAS software version 9.4, and the statistical significance level was set post hoc at $\alpha < .0125$ (2-tailed) to account for the 4 co-primary end points. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory.

Results

Study Participants

A total of 449 patients were assessed for eligibility in the 3 outpatient diabetes centers. After excluding 149 patients, the remaining 300 (mean [SD] age, 61.6 [8.5] years; 116 women [38.7%]) were randomized to the behavioral intervention or standard care group. Of the 300 participants, 267 completed the study at the final evaluation (133 in the behavioral intervention group and 134 in the standard care group) and 33 participants (17 in the behavioral intervention group and 16 in the standard care group) were lost to follow-up (**Figure 1**). Participant follow-up ended in February 2017. The baseline features of study participants are reported in the **Table** and eTable 1 in Supplement 2.

Of 150 participants in the behavioral intervention group, 150 attended the theoretical counseling session in year 1, 143 in year 2, and 129 in year 3. Regarding the theoretical and practical counseling sessions, total attendance was 1133 of a possible 1200 (94.4%) in year 1, 1072 of 1144 (93.7%) in year 2, and 990 of 1032 (95.9%) in year 3.

Primary End Points

Among participants in the behavioral intervention group, physical activity volume, light-intensity physical activity, Table. Baseline Characteristics of Participants in a Study of the Effect of a Behavioral Intervention in Individuals With Type 2 Diabetes

Variable	Behavioral Intervention	Standard Care
No.	150	150
Age, mean (SD), y	61.0 (9.7)	62.3 (10.1)
Sex, No. (%)		
Women	59 (39.3)	57 (38.0)
Men	91 (60.7)	93 (62.0)
Smoking, No. (%)		
Never	64 (42.7)	58 (38.7)
Former	61 (40.7)	60 (40.0)
Current	25 (16.7)	32 (21.3)
Type 2 diabetes duration, median (IQR), y	8.0 (4.0-16.0)	9.0 (4.0-15.0)
Hemoglobin A_{1c}, mean (SD), %	7.4 (1.6)	7.3 (1.4)
Fasting plasma glucose, mean (SD), mg/dL	134.4 (44.8)	139.3 (53.7)
Body weight, mean (SD), kg	84.2 (17.1)	84.0 (15.9)
BMI, mean (SD)	30.0 (4.9)	30.1 (5.3)
Waist circumference, mean (SD), cm	103.3 (13.2)	103.9 (12.4)
Triglycerides, median (IQR), mg/dL	138.0 (94.0-203.5)	132.5 (98.0-200.0)
Total cholesterol, mean (SD), mg/dL	181.7 (39.0)	179.2 (38.9)
HDL cholesterol, mean (SD), mg/dL	48.3 (14.3)	46.3 (13.6)
LDL cholesterol, mean (SD), mg/dL	112.1 (32.8)	111.3 (34.2)
Systolic blood pressure, mm Hg	139.5 (19.7)	140.7 (21.2)
Diastolic blood pressure, mean (SD), mm Hg	82.6 (9.9)	83.1 (13.3)
hs-CRP, median (IQR), mg	2.4 (1.0-4.9)	2.3 (1.1-6.1)
eGFR, mean (SD), mL/min/1.73m^2	88.1 (18.3)	86.1 (18.5)
Albumin:creatinine ratio, mean (IQR), mg/g	7.4 (3.1-18.9)	6.9 (3.1-32.0)
CHD 10-y risk, median (IQR), %[a]	17.4 (10.1-26.5)	17.1 (12.6-27.8)
Fatal CHD 10-y risk, median (IQR), %[a]	11.7 (5.4-19.4)	12.2 (6.8-19.4)
UKPDS stroke 10-y risk, median (IQR), %[a]	8.4 (4.6-16.0)	10.6 (5.5-18.9)
UKPDS fatal stroke 10-y risk, median (IQR), %[a]	1.2 (0.7-2.6)	1.7 (0.8-3.1)
Physical activity volume, mean (SD), MET-h/wk	11.6 (4.6)	10.5 (4.8)
Light-intensity physical activity, mean (SD), h/d	4.06 (1.3)	3.79 (1.4)
Moderate- to vigorous-intensity physical activity, mean (SD), min/d	12.7 (4.2)	12.1 (5.0)
Sedentary time, mean (SD), h/d	11.5 (1.2)	11.7 (1.1)
Cardiorespiratory fitness, mean (SD), mL/min/kg	24.9 (5.9)	24.5 (7.0)
Upper body strength, median (IQR), Nm	239.0 (181.8-311.5)	244.5 (184.3-313.3)
Lower body strength, median (IQR), Nm	150.0 (116.8-211.0)	155.5 (115.0-197.3)
Flexibility, median (IQR), cm	16.0 (7.8-24.3)	17.0 (6.0-23.0)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL, low-density lipoprotein; MET, metabolic equivalent; Nm, Newton meter.

SI conversion factors: To convert glucose to mmol/L, multiply by 0.0555; triglycerides to mmol/L, multiply by 0.0113; and total, HDL, and LDL cholesterol to mmol/L, multiply by 0.0259.

[a] Based on the United Kingdom Prospective Diabetes Study (UKPDS) risk engine, which is based on the outcomes from 53 000 patient-years of data in the UKPDS.[22] In theory, the 10-year risk for each measure can range from 0% to 100%, although the maximum risk for fatal stroke is below 50%. For a white, nonsmoking man without atrial fibrillation with the median values of our sample, the risk would be 20.4% for CHD, 13.2% for fatal CHD, 8.4% for stroke, and 1.2% for fatal stroke. For a white, nonsmoking woman, the risk percentages would be 12.9%, 9.0%, 7.9%, and 1.2%, respectively.

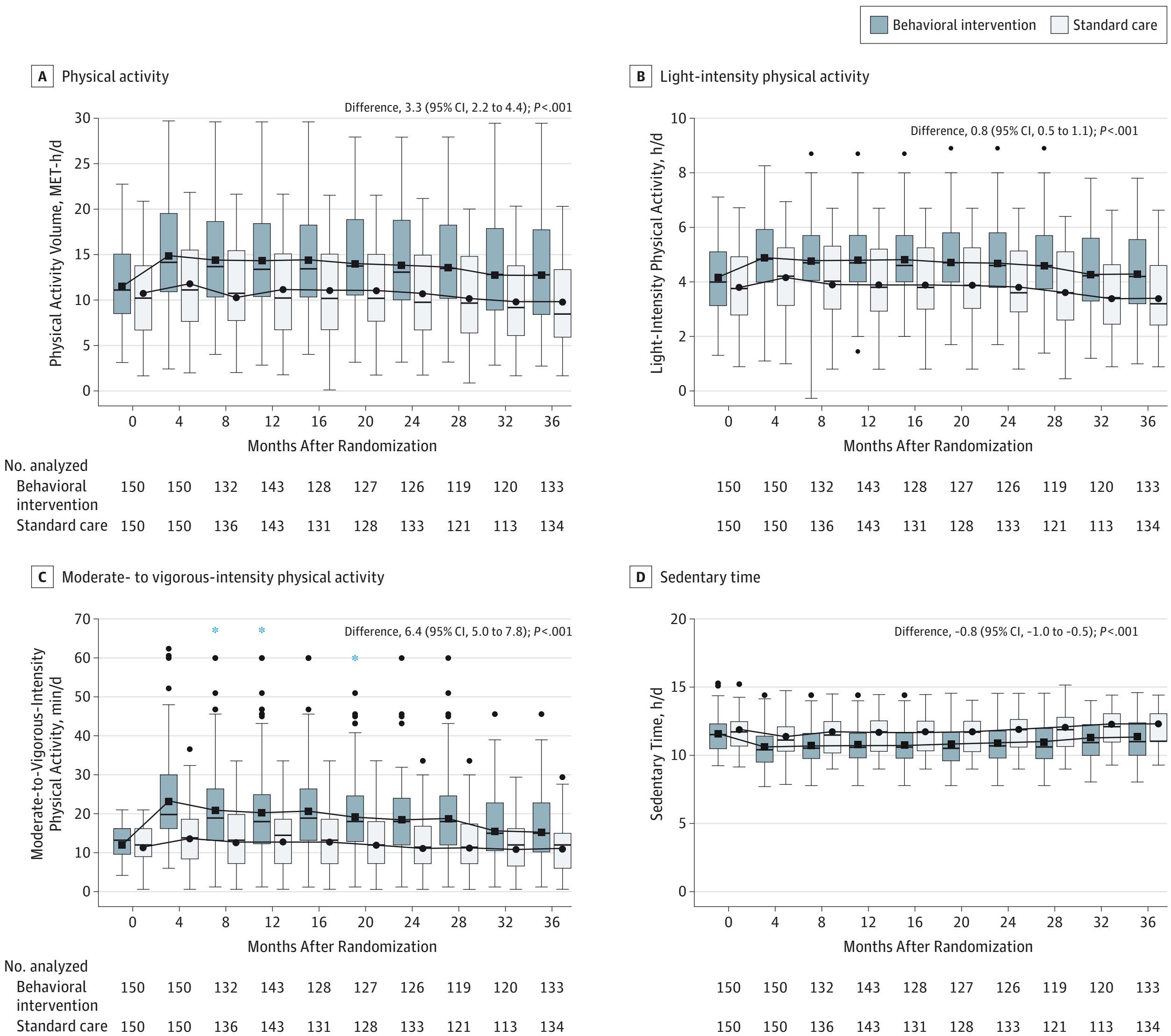
and moderate- to vigorous-intensity physical activity increased and sedentary time decreased during the initial 4 months, as previously reported,[13] then remained stable until the end of year 2. Thereafter, physical activity volume, light-intensity physical activity, and moderate- to vigorous-intensity physical activity decreased, but remained significantly higher than baseline levels, and sedentary time increased, but remained significantly lower than baseline levels. Among participants in the standard care group, increases in physical activity volume, light-intensity physical activity, and moderate- to vigorous-intensity physical activity and decreases in sedentary time were lower than in the behavioral intervention group. At the end of the study, physical activity volume, light-intensity physical activity, and moderate- to vigorous-intensity physical activity were lower and sedentary time was higher than baseline values. Over the 3-year period, participants in the behavioral intervention and standard care group accumulated 13.8 vs 10.5 MET-h/wk of physical activity volume (difference, 3.3 [95% CI, 2.2-4.4]; $P < .001$), 18.9 vs 12.5 min/d of moderate- to vigorous-intensity physical activity (difference, 6.4 [95% CI, 5.0-7.8]; $P < .001$), 4.6 vs 3.8 h/d of light-intensity physical activity (difference, 0.8 [95% CI, 0.5-1.1]; $P < .001$), and 10.9 vs 11.7 h/d of sedentary time (difference, −0.8 [95% CI, −1.0 to −0.5]; $P < .001$), respectively (**Figure 2**). Between-group differences were maintained throughout the study period, except for differences in moderate- to vigorous-intensity physical activity, which decreased during the third year from 6.5 to 3.6 min/d (eTables 2-4 in Supplement 2). Results were similar in per-protocol (eTable 5 in Supplement 2) and subgroup analyses, except for the nonsignificant between-group differences among patients receiving insulin treatment, with no significant interaction (eFigure 2 in Supplement 2). There was no effect of site on the 4 co-primary outcomes, as shown by the nonsignificant interaction and the post hoc hierarchical modeling with site as a random effect (eTable 6 in Supplement 2). In both groups, accelerometer wear time was approximately 15 h/d throughout the study, indicating that participants had likely worn the device most of the day while awake.

More participants achieved prespecified targets of physical activity volume, light-intensity physical activity, moderate- to vigorous-intensity physical activity, and sedentary time at year 1, 2, and 3 in the behavioral intervention than in the standard care group (eFigure 3 in Supplement 2). Scatterplots of preintervention vs postintervention data at the patient level are shown in eFigure 4 in Supplement 2.

Secondary End Points

In the behavioral intervention group, cardiorespiratory fitness and lower body strength improved significantly, whereas all fitness parameters worsened in the standard care group. As a consequence, the mean differences over time between participants in the behavioral intervention and standard care group in cardiorespiratory fitness (2.63 mL/min/kg [95% CI, 1.09-4.17), lower body strength (24.2 Newton meters [95% CI, 10.78-37.58]), and flexibility (−3.9 cm [95% CI, −6.40 to −1.45]) were statistically significant ($P < .001$) (**Figure 3**). Similarly, the

Figure 2. Changes Over Time in Physical Activity and Sedentary Time



Boxplots show the distribution (median, 25th and 75th percentile) of crude data (no imputation) and the lines indicate the mean values estimated by a mixed model for repeated measures. Whiskers indicate 95% CIs, circles indicate outliers (ie, values between 1.5 and 3 interquartile ranges from the end of a box), and asterisks indicate extreme values (ie, values more than 3 interquartile ranges from the end of a box). Between-group mean differences (95% CIs) over time and *P* values were calculated with a mixed model for repeated measures and are reported for each variable. MET indicates metabolic equivalent.

between-group differences in the change from baseline were significant for all parameters at year 1, 2, and 3 (eTables 2 and 3 in Supplement 2). Results were similar in the per-protocol analyses (eTable 5 in Supplement 2).

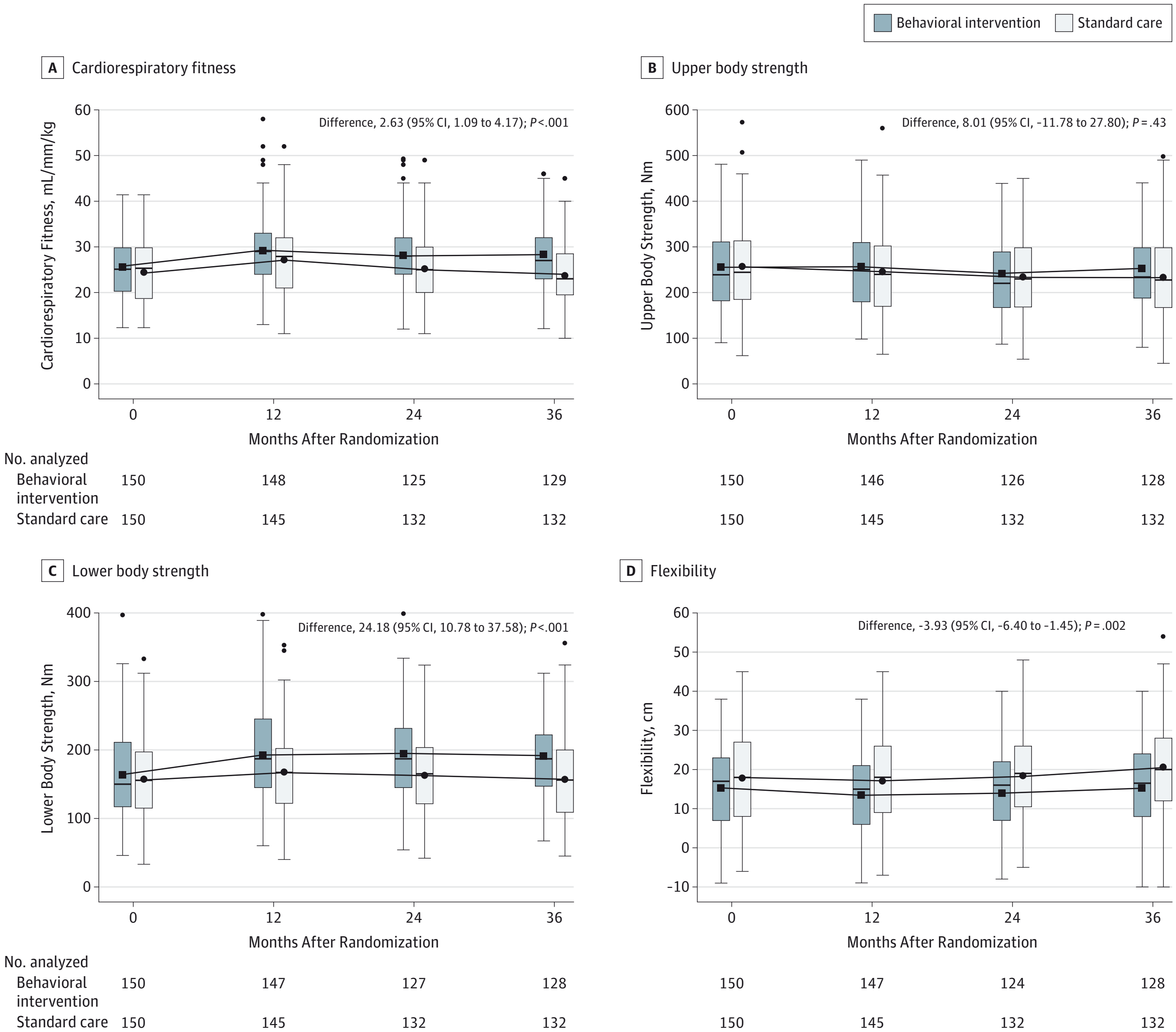
The mean difference in participants in the behavioral intervention vs standard care group was significant for fasting plasma glucose ($P = .007$), systolic blood pressure ($P = .02$), total CHD 10-year risk score ($P = .03$), and fatal CHD 10-year risk score ($P = .04$) over time, whereas the differences did not achieve statistical significance for the remaining cardiovascular risk factors and scores (**Figure 4**, **Figure 5**, and eFigure 5 in Supplement 2), including HbA_{1c}. The between-group mean difference in change from baseline was significant for total stroke risk score ($P = .04$) after 2 years and HbA_{1c} ($P = .02$), fasting plasma glucose ($P = .04$), 10-year total CHD risk score ($P = .01$), 10-year fatal CHD risk score ($P = .008$),0-year total CHD ($P = .01$), fatal CHD ($P = .008$), and total stroke ($P = .01$) after 3 years (eTables 2-4 in Supplement 2). Results were similar in the per-protocol analyses (eTable 5 in Supplement 2).

Throughout the study, changes in medication were similar in participants in the behavioral intervention and standard care groups, (eTable 7 in Supplement 2) and insulin dosage did not differ between groups (eTable 8 in Supplement 2).

Post Hoc Analyses

Results of post hoc analyses of additional accelerometer measures are reported in eFigure 6 in Supplement 2. Changes from baseline to the end of the study period in the 49 participants

Figure 3. Changes Over Time in Physical Fitness Parameters



Boxplots show the distribution (median, 25th and 75th percentile) of crude data (no imputation) and the lines indicate the mean values estimated by a mixed model for repeated measures. Whiskers indicate 95% CIs, circles indicate outliers (ie, values between 1.5 and 3 interquartile ranges from the end of a box).

Between-group mean differences (95% CIs) over time and *P* values were calculated with a mixed model for repeated measures and are reported for each variable.

in the behavioral intervention group who became physically active (≥150 min/wk of moderate- to vigorous-intensity physical activity) were higher than the change in the overall behavioral intervention group (physical activity volume, 5.1 vs 1.3 MET-h/wk; light-intensity physical activity, 0.6 vs 0.2 h/d; moderate- to vigorous-intensity physical activity, 9.5 vs 3.1 min/d; sedentary time, −0.8 vs −0.3 h/d; cardiorespiratory fitness, 4.9 vs 2.8 mL/min/kg; and HbA_{1c}, −0.59% vs −0.27%). HbA_{1c} was significantly reduced in the behavioral intervention group vs the standard care group in an analysis including only participants with baseline values greater than or equal to 8% (eFigure 7 in Supplement 2). Scatterplots of change in physical activity volume and sedentary time vs change in selected biological variables are shown in eFigure 8 in Supplement 2.

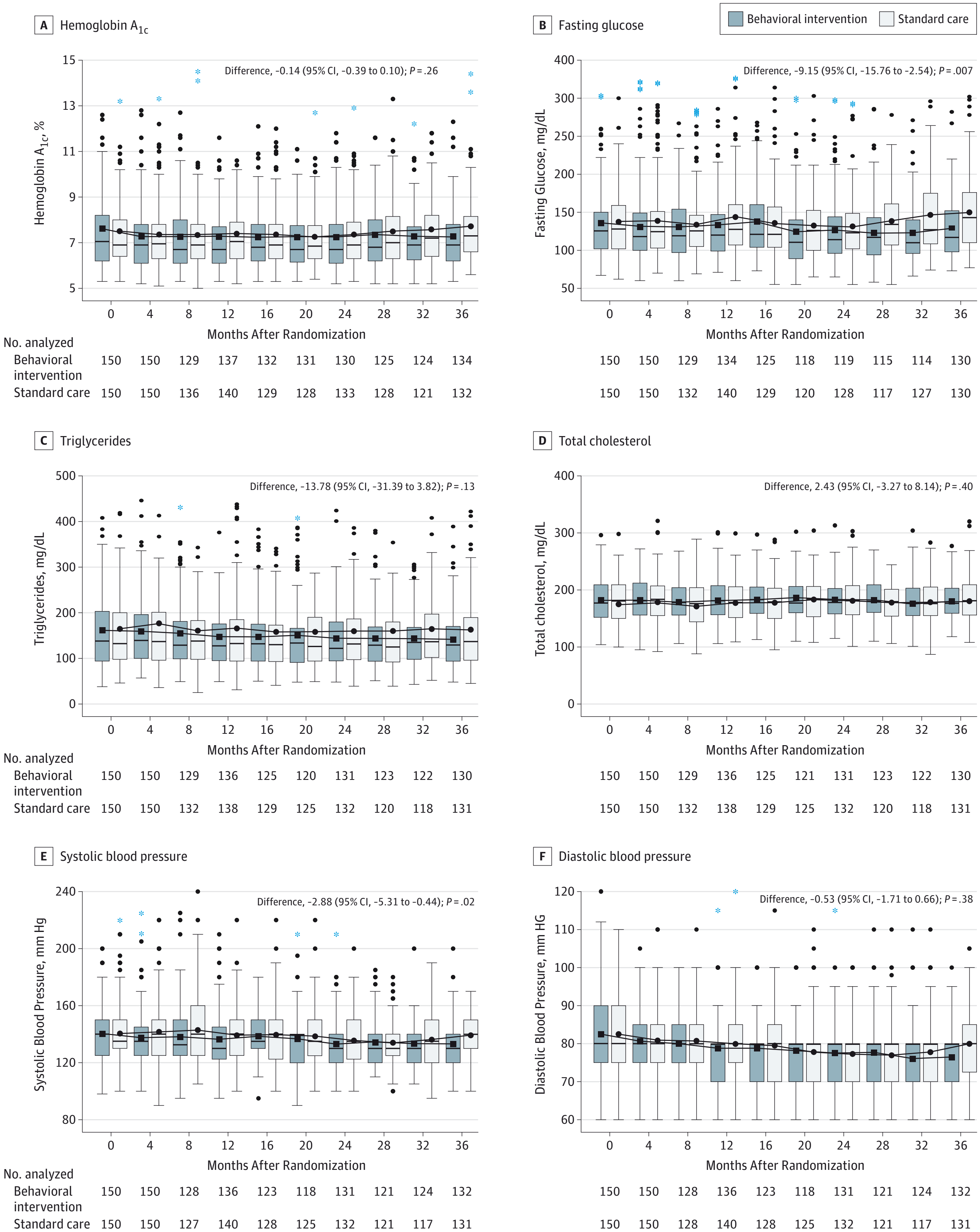
Adverse Events

Outside of sessions, 41 adverse events occurred in the behavioral intervention group vs 59 in the standard care group. Participants in the behavioral intervention group had 8 episodes of mild hypoglycemia, 3 episodes of tachycardia/arrhythmia, and 19 episodes of musculoskeletal injury/discomfort during the theoretical and practical counseling sessions (eTable 9 in Supplement 2).

Discussion

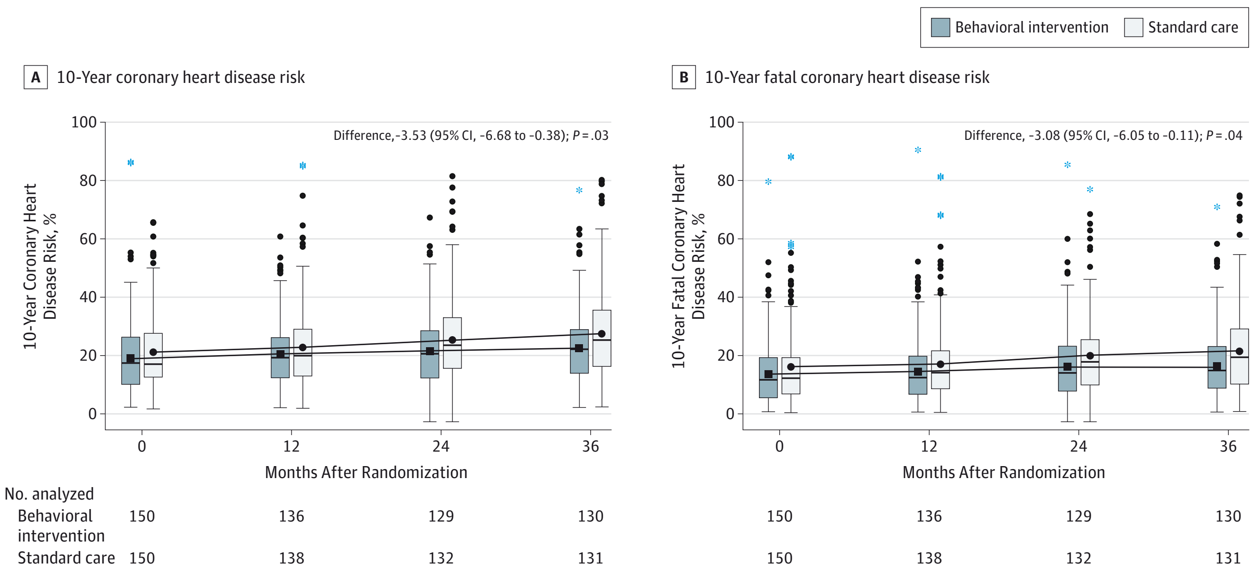
In this study, a behavioral intervention compared with standard care resulted in a sustained increase in physical activity

Figure 4. Changes Over Time in Cardiovascular Risk Factors and Scores



Boxplots show the distribution (median, 25th and 75th percentile) of crude data (no imputation) and the lines indicate the mean values estimated by a mixed model for repeated measures. Whiskers indicate 95% CIs, circles indicate outliers (ie, values between 1.5 and 3 interquartile ranges from the end of a box), and asterisks indicate extreme values (ie, values more than 3 interquartile ranges from the end of a box). Between-group mean differences (95% CIs) over time and *P* values were calculated with a mixed model for repeated measures and are reported for each variable.

Figure 5. Changes Over Time in 10-Year Coronary Heart Disease and Fatal Coronary Heart Disease Risk Scores



Boxplots show the distribution (median, 25th and 75th percentile) of crude data (no imputation) and the lines indicate the mean values estimated by a mixed model for repeated measures. Whiskers indicate 95% CIs, circles indicate outliers (ie, values between 1.5 and 3 interquartile ranges from the end of a box), and asterisks indicate extreme values (ie, values more than 3 interquartile ranges from the end of a box). Between-group mean differences (95% CIs) over time and *P* values were calculated with a mixed model for repeated measures and are reported for each variable.

and decrease in sedentary time in sedentary and physically inactive participants with type 2 diabetes.

This behavioral intervention strategy was successful in increasing physical activity volume by reallocating sedentary time to light-intensity physical activity and, to a lesser extent, moderate- to vigorous-intensity physical activity. Significant between-group differences were maintained throughout the study period for all the co-primary end points; however, the difference in moderate- to vigorous-intensity physical activity diminished during the third year, suggesting that moderate- to vigorous-intensity physical activity is more difficult to maintain with time and increasing age.

In the behavioral intervention group, the reduction in sedentary time from baseline compared with the standard care group was higher than in a previous meta-analysis of randomized clinical trials targeting both physical activity and sedentary behavior[25] (−48 vs −24 min/d), whereas the increase in moderate- to vigorous-intensity physical activity was higher than in the Look-AHEAD trial at year 4 (21.7 vs 13.0 min/wk).[11] The simultaneous increase in moderate- to vigorous-intensity physical activity and decrease in sedentary time (with reciprocal increment in light-intensity physical activity) are at variance with the Early-ACTID trial of individuals with diabetes[26] and the PACE-UP and PACE-Lifts trials of the general population,[9] which were successful in increasing moderate- to vigorous-intensity physical activity but failed to reduce sedentary time. The present findings support the need for interventions targeting all domains of behavior to obtain substantial lifestyle changes, not limited to moderate- to vigorous-intensity physical activity, which has little effect on sedentary time. This concept is consistent with a 2018 report showing that physical activity, sedentary time, and cardiorespiratory fitness are all important for cardiometabolic health.[27]

Although there was a wide range of responses to the intervention in the current study, a substantial proportion of participants ameliorated their behavior. In particular, participants who became and remained physically active throughout the follow-up achieved meaningful improvements in physical activity and sedentary time as well as in physical fitness and cardiovascular risk factors/scores.

Behavior change was associated with different changes in the exploratory secondary outcomes. There was a sustained improvement in physical fitness, supporting the concept that even relatively small increases in physical activity (primarily light-intensity physical activity) and decreases in sedentary time may result in increased cardiorespiratory fitness and muscle strength, at variance with interpretations from various intervention studies that examined the effect of light-intensity physical activity on cardiovascular disease risk factors,[28] but consistent with the results of the Maastrict Study.[29] Unlike the Look-AHEAD trial, in which the increase in cardiorespiratory fitness was 20.4% at year 1, but was significantly diminished at year 4 (5.1%) in parallel with the decreasing intensity of the intervention,[11] participants in this study maintained the increase from baseline in cardiorespiratory fitness (15% after 1 year and 11% after 3 years), possibly because the intensity of intervention, albeit lower than in the Look-Ahead trial, did not vary throughout the study period. Conversely, only minor reductions were observed in HbA_{1c}, fasting plasma glucose, and systolic blood pressure, consistent with previous studies showing only modest improvements in HbA_{1c} after behavioral or lifestyle interventions,[5,26,30] although the small HbA_{1c} reduction might be dependent on the relatively low average baseline values.

Several lines of evidence suggest that such a sustained change in behavior may be beneficial for cardiovascular and general health. First, changes in cardiovascular risk factors, though minor, resulted in a significantly lower age-dependent increase in UKPDS risk scores, which might translate into long-term cardiovascular protection. Second, increased cardiorespiratory and muscular fitness were shown to be associated with reduced total and cardiovascular mortality both in the general population and in individuals with diabetes, independently from cardiovascular risk factors.[31-33] Each 1-MET increment (3.5 mL/min/kg) in cardiorespiratory fitness has been associated with a 10% to 25% reduction in mortality, with the largest benefits occurring among low-fitness individuals, such as individuals with type 2 diabetes.[34] Third, a physically active lifestyle helps to combat reduced mobility, which is an independent risk factor for morbidity, hospitalization, disability, and mortality.[35]

The primary strength of this study is the application of an intervention targeting both physical activity and sedentary time across all settings (eg, leisure, transportation, household, and occupation), based on theoretical grounds and using several behavior change techniques. Other strengths include specific investigator training, long study duration, large sample size, objective (accelerometer-based) measurement of physical activity and sedentary time, and concurrent assessment of physical fitness.

Limitations

This study has several limitations. First, generalizability and implementation of the intervention in clinical practice require further investigation and validation of the intervention in different cohorts or settings. In particular, the effects of this strategy might be different in other cities because of climatic, socioeconomic, and cultural differences, although many other factors that may favor a physically inactive and sedentary lifestyle are common to all densely populated urban areas (eg, safety, crime, traffic, transport, walkability). Second, accelerometer use may have also promoted physical activity in the standard care group.[36] Third, because the accelerometer did not provide time-stamped data, it was not possible to obtain direct measurements of sedentary time or information on the pattern of sedentary time accumulation. Fourth, diet was not considered in the data analysis, even though patients received dietary prescriptions and adherence to diet was verified at intermediate visits.

Conclusions

Among patients with type 2 diabetes treated at 3 diabetes clinics in Rome and followed up for 3 years, a behavioral intervention compared with standard care resulted in a sustained increase in physical activity and decrease in sedentary time. Further research is needed to assess the generalizability of these findings.

ARTICLE INFORMATION

Accepted for Publication: January 28, 2019.

Author Affiliations: Department of Clinical and Molecular Medicine, "La Sapienza" University, Rome, Italy (Balducci, D'Errico, Haxhi, Cardelli, Vitale, Bollanti, Conti, Pugliese); Diabetes Unit, Sant'Andrea University Hospital, Rome, Italy (Balducci, D'Errico, Haxhi, Vitale, Bollanti, Conti, Pugliese); Metabolic Fitness Association, Monterotondo, Rome, Italy (Balducci, D'Errico, Haxhi); Department of Human Movement and Sport Sciences, "Foro Italico" University, Rome, Italy (Sacchetti, Orlando); Laboratory of Clinical Chemistry, Sant'Andrea University Hospital, Rome, Italy (Cardelli); Centre for Human Performance and Sport, University of Greenwich, Chatham Maritime, United Kingdom (Zanuso); Currently with Center for Applied Biological & Exercise Sciences, Faculty of Health & Life Sciences, Coventry University, Coventry, United Kingdom (Zanuso); Department of Clinical Pharmacology and Epidemiology, Consorzio Mario Negri Sud, S. Maria Imbaro, Italy (Lucisano, Nicolucci); Currently with Center for Outcomes Research and Clinical Epidemiology (CORESEARCH), Pescara, Italy (Lucisano, Nicolucci).

Author Contributions: Dr Pugliese had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Balducci, Sacchetti, Cardelli, Nicolucci, Pugliese.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Pugliese.
Critical revision of the manuscript for important intellectual content: Balducci, D'Errico, Haxhi, Sacchetti, Orlando, Cardelli, Vitale, Bollanti, Conti, Zanuso, Lucisano, Nicolucci.
Statistical analysis: Lucisano, Nicolucci, Pugliese.
Obtained funding: Balducci, Pugliese.
Administrative, technical, or material support: Balducci, Sacchetti, Cardelli, Zanuso, Pugliese.
Supervision: Balducci, Pugliese.

Conflict of Interest Disclosures: Dr Balducci reports personal fees from AstraZeneca, Eli Lilly, Novo Nordisk, and Takeda. Dr Zanuso is an employee of Technogym. Dr Nicolucci reports grants from Artsana, Astra-Zeneca, Eli Lilly, Novo Nordisk, and Sanofi Aventis and personal fees from Eli Lilly and Novo Nordisk. Dr Pugliese reports personal fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Mylan, Sigma-Tau, and Takeda. No other disclosures were reported.

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

Role of the Funder/Sponsor: The sponsor had no role in design and conduct of the study; collection, management, and interpretation of the data; preparation, review, approval of the manuscript; or decision to submit for publication.

The IDES_2 Investigators Steering Committee: Giuseppe Pugliese, MD, PhD, Department of Clinical and Molecular Medicine, "La Sapienza" University, and Diabetes Unit, Sant'Andrea University Hospital, Rome, Italy (principal investigator); Stefano Balducci, MD, Metabolic Fitness Association O.N.L.U.S., Monterotondo, Rome, Italy (co-investigator); Massimo Sacchetti, PhD, Department of Human Movement and Sport Sciences, "Foro Italico" University, Rome, Italy; Silvano Zanuso, PhD, Center for Applied Biological & Exercise Sciences, Faculty of Health & Life Sciences, Coventry University, Coventry, United Kingdom; Patrizia Cardelli, PhD, Department of Clinical and Molecular Medicine, "La Sapienza" University of Rome, and Laboratory of Clinical Chemistry, Sant'Andrea University Hospital, Rome, Italy; Antonio Nicolucci, MD, PhD, Center for Outcomes Research and Clinical Epidemiology (CORESEARCH), Pescara, Italy.

Data Sharing Statement: See Supplement 3.

Additional Contributions: We thank Philippa Mungra, PhD, formerly reader of English, Department of Experimental Medicine, "La Sapienza" University, Rome, Italy, for help with manuscript preparation; the diabetologists from the diabetes units at the Sant'Andrea University Hospital (Maria Cristina Ribaudo, MD, PhD, Elena Alessi, MD, Tiziana Cirrito, MD), Fatebenefratelli San Pietro Hospital (Nicolina Di Biase, MD, Filomena La Saracina, MD), and Health District, Monterotondo (Mario Ranuzzi, MD) in Rome, Italy, who recruited and followed-up patients and conducted the individual theoretical counseling session each year; and the exercise specialists from the Department of Human Movement and Sport Sciences at "Foro Italico" University, the Center for the Study of Metabolism (Luca Milo [physiotherapist], Roberto Milo, [physiotherapist]) and the Metabolic Fitness Association, Monterotondo (Gianluca Balducci [physiotherapist], Enza Spinelli [physiotherapist]), who conducted the 8 individual theoretical and practical counseling sessions each year. None of the individuals received monetary compensation.

REFERENCES

1. 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(11):2065-2079. doi:10.2337/dc16-1728

2. 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(3):589-599.

3. 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(2):203-209.

4. Balducci S, Zanuso S, Nicolucci A, et al. Effect of an intensive exercise intervention strategy on modifiable cardiovascular risk factors in subjects with type 2 diabetes mellitus: a randomized controlled trial: the Italian Diabetes and Exercise Study (IDES). *Arch Intern Med*. 2010;170(20):1794-1803. doi:10.1001/archinternmed.2010.380

5. 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(5):315-322. doi:10.1136/bjsm.2010.082495

6. Marcus BH, Williams DM, Dubbert PM, et al. Physical activity intervention studies: what we know and what we need to know: a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity); Council on Cardiovascular Disease in the Young; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research. *Circulation*. 2006;114(24):2739-2752.

7. Shephard RJ. Limits to the measurement of habitual physical activity by questionnaires. *Br J Sports Med*. 2003;37(3):197-206.

8. Hobbs N, Godfrey A, Lara J, et al. Are behavioral interventions effective in increasing physical activity at 12 to 36 months in adults aged 55 to 70 years? a systematic review and meta-analysis. *BMC Med*. 2013;11:75. doi:10.1186/1741-7015-11-75

9. 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(3):e1002526.

10. 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(12):2437-2445.

11. Look AHEAD Research Group, Wing RR. 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(17):1566-1575.

12. Ried-Larsen M, MacDonald CS, Johansen MY, et al. Why prescribe exercise as therapy in type 2 diabetes? we have a pill for that! *Diabetes Metab Res Rev*. 2018;34(5):e2999. doi:10.1002/dmrr.2999

13. Balducci S, Sacchetti M, Haxhi J, et al. 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. doi:10.1186/s13063-015-1088-0

14. Balducci S, D'Errico V, Haxhi J, et al. Effect of a behavioral intervention strategy for adoption and maintenance of a physically active lifestyle: the Italian Diabetes and Exercise Study 2 (IDES_2): a randomized controlled trial. *Diabetes Care*. 2017;40(11):1444-1452. doi:10.2337/dc17-0594

15. American Diabetes Association. Standards of medical care in diabetes—2012. *Diabetes Care*. 2012;35(suppl 1):s11-s63. doi:10.2337/dc12-s011

16. Inoue M, Iso H, Yamamoto S, et al. Daily total physical activity level and premature death in men and women: results from a large-scale population-based cohort study in Japan (JPHC study). *Ann Epidemiol*. 2008;18(7):522-530.

17. Sedentary Behaviour Research Network. Letter to the editor: standardized use of the terms "sedentary" and "sedentary behaviours". *Appl Physiol Nutr Metab*. 2012;37(3):540-542.

18. Balducci S, Zanuso S, Massarini M, et al. The Italian Diabetes and Exercise Study (IDES): design and methods for a prospective Italian multicentre trial of intensive lifestyle intervention in people with type 2 diabetes and the metabolic syndrome. *Nutr Metab Cardiovasc Dis*. 2008;18(9):585-595.

19. Herrmann SD, Hart TL, Lee CD, Ainsworth BE. Evaluation of the MyWellness Key accelerometer. *Br J Sports Med*. 2011;45(2):109-113.

20. Sieverdes JC, Wickel EE, Hand GA, Bergamin M, Moran RR, Blair SN. Reliability and validity of the Mywellness Key physical activity monitor. *Clin Epidemiol*. 2013;5:13-20. doi:10.2147/CLEP.S38370

21. McGinley SK, Armstrong MJ, Khandwala F, Zanuso S, Sigal RJ. Assessment of the MyWellness Key accelerometer in people with type 2 diabetes. *Appl Physiol Nutr Metab*. 2015;40(11):1193-1198.

22. Stevens RJ, Kothari V, Adler AI, Stratton IM; 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(6):671-679. doi:10.1042/cs1010671

23. Kodama S, Saito K, Tanaka S, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA*. 2009;301(19):2024-2035.

24. Singer JD, Willett JB. *Applied Longitudinal Data Analysis: Modeling Change and Event Occurrence*. New York, NY: Oxford University Press; 2003.

25. 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(11):905-919. doi:10.1111/obr.12215

26. 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(9786):129-139.

27. van der Velde JHPM, Schaper NC, Stehouwer CDA, et al. Which is more important for cardiometabolic health: sedentary time, higher intensity physical activity or cardiorespiratory fitness? the Maastricht Study. *Diabetologia*. 2018;61(12):2561-2569. doi:10.1007/s00125-018-4719-7

28. 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.

29. Van Der Velde JHPM, Koster A, Van Der Berg JD, et al. Sedentary behavior, physical activity, and fitness: the Maastricht Study. *Med Sci Sports Exerc*. 2017;49(8):1583-1591.

30. Johansen MY, MacDonald CS, Hansen KB, et al. Effect of an intensive lifestyle intervention on glycemic control in patients with type 2 diabetes: a randomized clinical trial. *JAMA*. 2017;318(7):637-646. doi:10.1001/jama.2017.10169

31. Blair SN, Kampert JB, Kohl HW III, et al. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. *JAMA*. 1996;276(3):205-210.

32. Ruiz JR, Sui X, Lobelo F, et al. Association between muscular strength and mortality in men: prospective cohort study. *BMJ*. 2008;337:a439. doi:10.1136/bmj.a439

33. 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(1):83-88. doi:10.2337/diacare.27.1.83

34. Ross R, Blair SN, Arena R, et al. Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the American Heart Association. *Circulation*. 2016;134(24):e653-e699.

35. Pahor M, Guralnik JM, Ambrosius WT, et al. Effect of structured physical activity on prevention of major mobility disability in older adults: the LIFE study randomized clinical trial. *JAMA*. 2014;311(23):2387-2396. doi:10.1001/jama.2014.5616

36. Baskerville R, Ricci-Cabello I, Roberts N, Farmer A. Impact of accelerometer and pedometer use on physical activity and glycaemic control in people with type 2 diabetes: a systematic review and meta-analysis. *Diabet Med*. 2017;34(5):612-620.