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Effect of an Intensive Lifestyle Intervention on Glycemic Control in Patients With Type 2 Diabetes
A Randomized Clinical Trial

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➕ **Supplemental content**

IMPORTANCE It is unclear whether a lifestyle intervention can maintain glycemic control in patients with type 2 diabetes.

OBJECTIVE To test whether an intensive lifestyle intervention results in equivalent glycemic control compared with standard care and, secondarily, leads to a reduction in glucose-lowering medication in participants with type 2 diabetes.

DESIGN, SETTING, AND PARTICIPANTS Randomized, assessor-blinded, single-center study within Region Zealand and the Capital Region of Denmark (April 2015-August 2016). Ninety-eight adult participants with non–insulin-dependent type 2 diabetes who were diagnosed for less than 10 years were included. Participants were randomly assigned (2:1; stratified by sex) to the lifestyle group (n = 64) or the standard care group (n = 34).

INTERVENTIONS All participants received standard care with individual counseling and standardized, blinded, target-driven medical therapy. Additionally, the lifestyle intervention included 5 to 6 weekly aerobic training sessions (duration 30-60 minutes), of which 2 to 3 sessions were combined with resistance training. The lifestyle participants received dietary plans aiming for a body mass index of 25 or less. Participants were followed up for 12 months.

MAIN OUTCOMES AND MEASURES Primary outcome was change in hemoglobin A_{1c} (HbA_{1c}) from baseline to 12-month follow-up, and equivalence was prespecified by a CI margin of ±0.4% based on the intention-to-treat population. Superiority analysis was performed on the secondary outcome reductions in glucose-lowering medication.

RESULTS Among 98 randomized participants (mean age, 54.6 years [SD, 8.9]; women, 47 [48%]; mean baseline HbA_{1c}, 6.7%), 93 participants completed the trial. From baseline to 12-month follow-up, the mean HbA_{1c} level changed from 6.65% to 6.34% in the lifestyle group and from 6.74% to 6.66% in the standard care group (mean between-group difference in change of −0.26% [95% CI, −0.52% to −0.01%]), not meeting the criteria for equivalence (P = .15). Reduction in glucose-lowering medications occurred in 47 participants (73.5%) in the lifestyle group and 9 participants (26.4%) in the standard care group (difference, 47.1 percentage points [95% CI, 28.6-65.3]). There were 32 adverse events (most commonly musculoskeletal pain or discomfort and mild hypoglycemia) in the lifestyle group and 5 in the standard care group.

CONCLUSIONS AND RELEVANCE Among adults with type 2 diabetes diagnosed for less than 10 years, a lifestyle intervention compared with standard care resulted in a change in glycemic control that did not reach the criterion for equivalence, but was in a direction consistent with benefit. Further research is needed to assess superiority, as well as generalizability and durability of findings.

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First-line treatment of type 2 diabetes includes diet, physical activity, and weight loss prior to or in parallel with initiation of pharmacological therapy.[1] Whereas medication is effective in lowering hemoglobin A_{1c} (HbA_{1c})[2] in patients with type 2 diabetes, it is also associated with potential adverse drug interactions,[3] discomforts,[4] increased economic costs[5] and decreased quality of life.[6] Therefore, lifestyle interventions are needed that are able to maintain glycemic control to at least the same extent as medication.

In the Action for Health in Diabetes (Look AHEAD) study, reductions in HbA_{1c} and glucose-lowering medication were observed after 12 months of lifestyle intervention compared with diabetes support and education.[7] However, the clinical relevance of this and other lifestyle interventions is limited due to self-reported medication changes, use of drug-assisted weight loss and weight maintenance, and the subjective nature of unblinded, target-driven regulation of glucose-lowering medication.[8-10] To our knowledge, only 2 studies have implemented objective target-driven regulation of glucose-lowering medication when assessing the effect of lifestyle in patients with type 2 diabetes.[11,12] A randomized clinical trial showed that an intensive diet intervention maintained glycemic control in patients with type 2 diabetes, preventing an increased need for glucose-lowering medication.[11] The addition of walking provided no further improvements.[11] In contrast, improvement in glycemic control was reported when adding supervised exercise, but with no concurrent reduction in glucose-lowering medication.[12]

The objective of this randomized clinical trial was to test the hypothesis that an intensive lifestyle intervention is equivalent compared with standard care in maintaining glycemic control in participants with type 2 diabetes diagnosed less than 10 years, and secondarily leads to a reduction in glucose-lowering medication.

Methods

Study Design
This study was a single-center, assessor-blinded, randomized clinical trial that took place in Region Zealand and the Capital Region of Denmark from April 2015 to August 2016. The full protocol is included in Supplement 1. This study was approved by the Scientific Ethical Committee at the Capital Region of Denmark. Guidelines from the Helsinki Declaration were followed and reporting in this article is aligned with CONSORT standards. All participants provided oral and written informed consent.

Participants and Eligibility Criteria
Participants were recruited via media and the Danish Diabetes Association and screened through telephone interview and medical examination. Inclusion criteria were type 2 diabetes diagnosed less than 10 years, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) of 25 to 40, and taking 2 or fewer glucose-lowering medications. Exclusion criteria were HbA_{1c} level greater than 9%, insulin-dependence, or presence of 1 or more of the fol-

Key Points

Question Can an intensive lifestyle intervention achieve glycemic control comparable with standard care in patients with type 2 diabetes?

Findings In this randomized clinical trial of 98 adults with type 2 diabetes diagnosed for less than 10 years, and which was designed to assess equivalence, the lifestyle intervention vs standard care resulted in a mean change in hemoglobin A_{1c} level of −0.31% vs −0.04%, respectively. The 95% CI around the difference (−0.52% to −0.01%) exceeded the prespecified equivalence margin of ±0.4%.

Meaning An intensive lifestyle intervention did not meet the criterion for equivalence for glycemic control, but the direction of findings suggests potential benefit.

lowing complications: diabetic retinopathy, macroalbuminuria (urine albumin-creatinine ratio ≥300 mg/g) or nephropathy (plasma creatinine ≥1.47 mg/dL [to convert to μmol/L, multiply by 88.4]). At least 6 weeks prior to baseline measurements, all participants had their glucose-lowering, lipid-lowering, and blood pressure-lowering medications titrated by the study endocrinologist to obtain prespecified treatment targets.[13] Response to the medical standardization did not constitute reason for exclusion. Medical standardization was performed to assess the effect of the lifestyle intervention without amplifying the result due to poorly regulated HbA_{1c} levels at baseline. The data were collected at Rigshospitalet, Copenhagen, Denmark.

Randomization and Blinding
Participants were randomized in permuted blocks of 3 and 6, stratified by sex, to either the lifestyle group or the standard care group in a 2:1 ratio. A computer-generated random number sequence was created by an independent statistician. The sequence was given to an external data manager with no involvement in the study procedures and concealed on a password-protected computer. After baseline measurements, participants were given consecutive numbers, which were forwarded to the external data manager, who subsequently returned the corresponding allocation to the study nurse. Blinding of the participants and the study nurse was not possible after group allocation. However, the study nurse solely delivered the standard care treatment and had no role in assessing the treatment actions, analyzing, or interpreting the data. All test personnel and adjudicators of outcomes were blinded.

Interventions
All participants received standard care that included medical counseling, education in type 2 diabetes, and lifestyle advice by the study nurse at baseline and every 3 months for 12 months. The study endocrinologist, who regulated all glucose-lowering, lipid-lowering, and blood pressure-lowering medication, was blinded to group allocation and received all clinical variables from the study nurse. To minimize the risk of bias, prespecified treatment targets and algorithms[13] for glucose-lowering, lipid-lowering, and blood pressure-lowering medication were followed by the study endocrinologist to reach standardization across groups. The treatment target for glycemic

control was 6.5% for HbA_{1c} level, and if this target was reached, the glucose-lowering medication dose was halved. If the HbA_{1c} level was unchanged or lower at the following medical consultation, the glucose-lowering medication was discontinued. If the participant experienced hypoglycemic events between medical consultations, they would contact the study nurse, and the blinded study endocrinologist would consider whether a reduction in glucose-lowering medication was necessary. If HbA_{1c} level exceeded 7.5%, the glucose-lowering medication was increased according to the prespecified algorithm.[13]

The lifestyle participants additionally received an intensive lifestyle intervention, described in detail previously,[13] which consisted of 5 to 6 weekly aerobic sessions (duration 30-60 minutes), of which 2 to 3 sessions were combined with resistance training. For the first 4 months, all exercise sessions were supervised, and supervision was progressively reduced during the 12 months. All supervised training was performed in groups of 4 to 8 participants. Participants were given an individual dietary plan with a macronutrient distribution of 45% to 60% carbohydrate, 15% to 20% protein, and 20% to 35% fat (<7% saturated fat). During the first 4 months the total energy intake was restricted. Individual and group-based dietary counseling were offered by clinical dieticians and progressively reduced during the 12 months. Additionally, participants were encouraged to be physically active in their leisure time (≥10 000 steps per day). Steps and exercise sessions were objectively monitored with a smartwatch (Polar V800).

Outcomes

The primary outcome was change in HbA_{1c} level from baseline to 12-month follow-up. The secondary outcome was reduction in glucose-lowering medication from baseline to 12-month follow-up. Exploratory outcomes included changes from baseline to 12-month follow-up in total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, systolic and diastolic blood pressure, fasting insulin, fasting glucose, 2-hour glucose concentration following an oral glucose tolerance test, maximal oxygen uptake ($\dot{V}o_{2max}$), weight, BMI, fat mass (total and abdominal), and lean body mass. We also explored the reduction in blood pressure lowering and lipid-lowering medication. Additionally, we analyzed the proportions of participants who discontinued their blinded, target-driven, glucose-lowering medical therapy between baseline to 12-month follow-up as well as the proportion of participants who increased their treatment according to the same prespecified algorithm between baseline to 12-month follow-up. In case of any adverse events the participants in the lifestyle group were encouraged to contact the intervention center and those in the standard care group were advised to contact the study nurse. At each medical consultation, the study nurse interviewed all participants about potential adverse events. All outcomes were presented to a blinded, adjudicated writing committee and group allocation was only revealed when consensus was achieved.

Measurements were performed in 1 laboratory and biochemical analyses were completed at the central laboratory (Rigshospitalet, Denmark) using standard procedures (Supplement 1). Primary, secondary, and exploratory measurements were performed in 1 day, except the 2-hour oral glucose tolerance test, which was performed on a separate day 48 hours after discontinuation of glucose-lowering medication and exercise cessation.

Sample Size

The predefined margin of equivalences was ±0.4% for HbA_{1c} level in relation to between-group comparison and was decided by 2 clinical content experts (AAV and KBH). This margin was based on half of the effect that was considered a clinically relevant reduction in HbA_{1c} level leading to a reduction in the risk of microvascular complications in patients with newly diagnosed type 2 diabetes.[14,15] Moreover, the minimum detectable significant change in HbA_{1c} level and what is recommended as an acceptable noninferiority margin defined by the US Food and Drug Administration were considered.[16,17] This margin has been widely used in trials testing glucose-lowering medications in patients with type 2 diabetes.[18-21]

In a two 1-sided test analysis for additive equivalence of 2-sample normal means with bounds ±0.4% [95% CI] for the mean difference and a significance level of .05, assuming a mean difference of 0 and a common SD of 0.9%, a total sample size of 120 participants assuming an allocation ratio of 2:1 would correspond to a power less than 50% (0.476). However, based on a superiority approach (in potential favor of standard care) it was decided (MR-L and RC) that a 95% CI excluding differences between groups of greater than 0.4 units would be interpreted as indicating the absence of a clinically meaningful difference.[22] According to the principle of sensitivity, a concept that refers to the sensitivity of the overall conclusions to various limitations of the data, assumptions, and analytic approaches to data analysis,[23] our estimates showed that including only 90 participants (60:30) would result in reasonable confidence limits. Thus, the sample size was based on feasibility within the local context enabling up to 120 participants to be enrolled. The sample size was truncated based on a formal stop rule defined as 24 months (August 2015) prior to the study end date of the preplanned 24-month follow-up (August 2017).[13]

Statistical Analysis

The full statistical analysis plan is available in Supplement 2. The analysis of the primary outcome was performed according to the intention-to-treat principle. Imputations were not used to replace missing data in the primary analysis, but were included in a sensitivity analysis to assess missing data. According to Piaggio et al,[24] equivalence is declared if the entire 2-sided CI ([1-α] × 100%) is included within the equivalence margin. Accordingly, a 2-sided 95% CI for the difference in change in HbA_{1c} level from baseline to 12-month follow-up between groups was derived from a repeated-measures mixed linear model and equivalence was declared if the 95% CI of HbA_{1c} level change was completely within the prespecified equivalence range (−0.4% to +0.4%).[25] Equivalence was tested using two 1-sided tests.[26] The repeated-measures mixed linear models included participants as a random effect, with fixed factors for group (2 levels), time (4 levels for the continuous outcomes [ie, change in HbA_{1c} level from baseline]), and the

Figure 1. Flow of Participants Through the Study
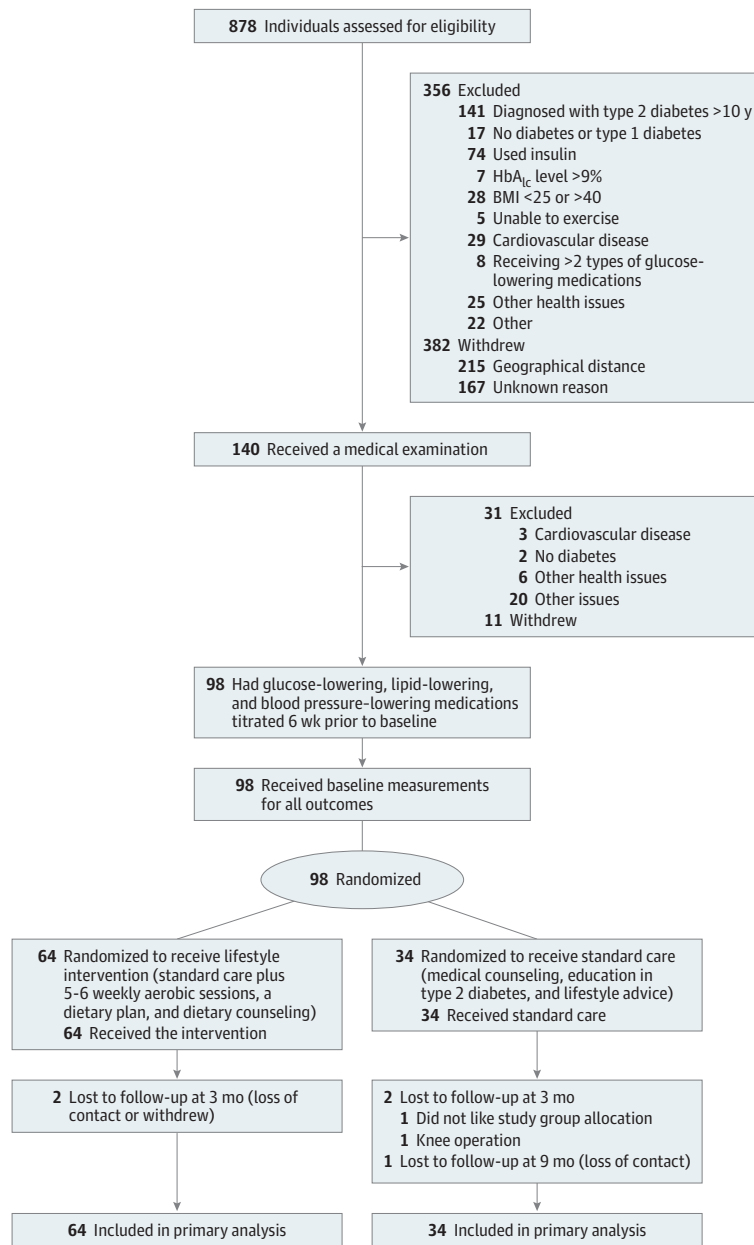
BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared).

corresponding interactions (adjusted for baseline values and sex). To assess the adequacy of the linear models, features were investigated via the predicted values and the residuals. Equivalence results are expressed with estimates of the group differences in the change from baseline and 95% CIs to represent precision of the estimates and P values for equivalence.

The analyses of the secondary outcome and the exploratory outcomes were based on a superiority assumption and presented as mean difference with 95% CI and P values for superiority. The secondary outcome (reduction in glucose-lowering medication) was reported as the between-group difference in the proportion of the participants (risk difference, percentage point), who reduced their need for glucose-

lowering medication according to the prespecified algorithm from baseline to 12-month follow-up.[13] A reduction from baseline was scored as 0 (no reduction) or 1 (a reduction). Additionally, we explored the between-group difference in the proportion of participants, who completely discontinued their blinded, target-driven, glucose-lowering medical therapy from baseline to 12-month follow-up as well as the difference in the proportion of participants who increased their treatment from baseline to 12-month follow-up according to the same prespecified algorithm. The difference in proportion between the groups reducing, discontinuing, or increasing their medication at 12-month follow-up compared with baseline was tested using a χ^2 test. Difference in the median change of the

Table 1. Baseline Characteristics of Participants With Non–Insulin-Dependent Type 2 Diabetes Allocated to the Lifestyle vs Standard Care Groups

	Lifestyle Group, Mean (SD) (n = 64)	Standard Care Group, Mean (SD) (n = 34)
Demographics		
Age at consent, y	53.6 (9.1)	56.6 (8.1)
Female, No. (%)	31 (48)	16 (47)
Type 2 diabetes duration, median (IQR), y	5 (3 to 8)	6 (3 to 9)
Glycemic control		
Hemoglobin A_{1c}, %	6.65 (0.8)	6.74 (0.9)
Fasting glucose, median (IQR), mg/dL	131.5 (115.3 to 152.3)	140.5 (124.3 to 171.2)
Fasting insulin, median (IQR), μIU/mL	16 (11 to 23)	18 (9 to 29)
2-h glucose, mg/dL (n = 62/33)	15.1 (4.1)	16.3 (4.0)
Lipids		
Total cholesterol, mg/dL	160.2 (33.1)	154.2 (37.0)
LDL, median (IQR), mg/dL	92.7 (71.4 to 112.0)	81.1 (69.5 to 96.5)
HDL, mg/dL	47.3 (13.2)	49.1 (13.3)
Triglycerides, median (IQR), mg/dL	54.8 (39.2 to 74.9)	55.6 (34.7 to 69.9)
Blood pressure		
Systolic, mm Hg	127 (14) (n = 60)	136 (8) (n = 24)
Diastolic, mm Hg	79 (8) (n = 60)	84 (8) (n = 24)
Body composition		
Body mass, kg	94.7 (14.0)	98.1 (15.0)
BMI	31.4 (3.9)	32.5 (4.5)
Fat mass, kg	35.2 (9.2)	36.4 (9.2)
Lean body mass, kg	58.7 (10.8)	61.0 (10.7)
Abdominal fat mass, kg	4.0 (1.2)	4.2 (1.2)
Physical fitness, physical activity, and diet		
$\dot{V}O_{2max}$, mL O_2/min	2713 (717) (n = 64)	2636 (742) (n = 33)
Relative $\dot{V}O_{2max}$, mL O_2/kg/min	28.7 (6.6) (n = 64)	26.9 (6.2) (n = 33)
Physical activity, median (IQR), met h/wk	61.9 (44.2 to 95.9) (n = 59)	60.5 (50.1 to 121.5) (n = 32)
Energy intake, median (IQR), kcal/d	2130 (1697 to 2563) (n = 61)	2146 (1599 to 2637) (n = 27)

(continued)

medication score from baseline to 12-month follow-up was tested using a Wilcoxon rank-sum test.

Sensitivity analyses included the baseline-observation carried forward imputation technique, complete-case and multiple linear imputation analysis. In the multiple imputation procedure the missing values at 12-month follow-up were imputed including all covariates from the main model (eTable 2 in Supplement 3). β-Coefficients and standard errors were obtained from 30 imputed data sets and adjusted for the variability between imputations.[27] A per-protocol population was defined by adherence to medication and attendance at medical consultations in both groups and the completion of 70% or more of the prescribed exercise sessions for the lifestyle participants.

Table 1. Baseline Characteristics of Participants With Non–Insulin-Dependent Type 2 Diabetes Allocated to the Lifestyle vs Standard Care Groups (continued)

	Lifestyle Group, Mean (SD) (n = 64)	Standard Care Group, Mean (SD) (n = 34)
Medication and Medication Scores[a]		
Glucose-lowering medication, No. (%)		
None	1 (2)	0
Biguanide	50 (79)	27 (79)
Biguanide and GLP-1 analogue	13 (19)	7 (21)
Biguanide, GLP-1 analogue, and insulin	0	0
Glucose-lowering medication score, median (IQR)	3.0 (2.0 to 3.0)	3.0 (2.0 to 3.0)
Lipid-lowering medication, No. (%)		
None	13 (20)	4 (12)
Statin	51 (80)	30 (88)
Lipid-lowering medication score, median (IQR)	3.0 (2.0 to 3.0)	4.0 (3.0 to 4.0)
Blood pressure-lowering medication, No. (%)		
None	33 (52)	15 (44)
ARB	11 (17)	4 (12)
ARB and thiazide	11 (17)	8 (24)
ARB, thiazide, and calcium-channel blocker	9 (14)	7 (20)
Blood pressure-lowering medication score, median (IQR)	0.5 (0.0 to 4.0)	2.0 (0.0 to 5.0)

Abbreviations: ARB, angiotensin receptor blocker; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); GLP-1, glucagon-like peptide 1; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; $\dot{V}O_{2max}$, maximal oxygen uptake.

SI conversion factors: To convert total, HDL, and LDL cholesterol to mmol/L, multiply by 0.0259; glucose to mmol/L, multiply by 0.0555; insulin to pmol/L, multiply by 6.945; triglycerides to mmol/L, multiply by 0.0113.

[a] Medication score ranges: glucose-lowering medication, 0 to 7; blood pressure–lowering medication, 0 to 8; and lipid-lowering medication, 0 to 6. A higher medication score indicates a more-intensive pharmacological treatment.

Statistical analyses were performed using STATA/IC (StataCorp), version 13.1, and the statistical significance level was set at α <.05 (2-tailed). A statistical analysis plan was described prior to analysis.

Results

Between April 2015 and August 2015, a total of 878 participants were screened for inclusion, and, of these, 356 were excluded primarily due to having a diagnosis of type 2 diabetes for more than 10 years and insulin-dependence. Additionally, 382 participants withdrew primarily because of geographical distance. Of the 98 participants who were enrolled in the study, 64 participants were allocated to the lifestyle group and 34 participants to the standard care group (**Figure 1**). At baseline, the participants had a mean age of 54.6 years (SD, 8.9) and mean HbA_{1c} level of 6.7% (**Table 1**).

Table 2. Primary, Secondary, and Exploratory Outcomes From Baseline to 12-Month Follow-up for Lifestyle vs Standard Care Groups Among Participants With Non–Insulin-Dependent Type 2 Diabetes, Intention-to-Treat Population

	Lifestyle Group		Standard Care Group		Between-Group Difference (95% CI)	P Value[a]
	No. of Patients	Change (95% CI)	No. of Patients	Change (95% CI)		
Primary Outcome						
Hemoglobin A$_{1c}$,%	64	−0.31(−0.45 to −0.16)	34	−0.04 (−0.25 to 1.17)	−0.26 (−0.52 to −0.01)	.15
Secondary Outcome						
Proportion of participants with reduction in glucose-lowering medication[b]	62	No. (%) 47 (73.5)	31	No. (%) 9 (26.4)	47.1 (28.6 to 65.3)	<.001
Exploratory Outcomes						
Glucose-lowering medication score, median change (IQR)[c,d]	62	−2.0 (−3.0 to −1.0)	31	0.0 (−1.0 to 2.0)	−2.0 (−4.0 to 0.0)	<.001
Glycemic control						
Fasting insulin, µIU/mL[e]	59	−7.0 (−8.6 to −5.4)	26	−5.0 (−7.5 – 2.5)	−2.0 (−5.0 to 1.0)	.18
Fasting glucose, mg/dL[e]	62	−7.8 (−22.8 to −10.6)	29	−7.8 (−16.8 to 1.1)	−8.8 (−19.7 to 2.1)	.11
2-h glucose, mg/dL[e]	61	−48.3 (−60.9 to −35.6)	27	−15.4 (−34.5 to 3.7)	−32.9 (−55.8 to −9.9)	.005
Lipids						
Total cholesterol, mg/dL		19.29 (11.85 to 26.73)	34	19.68 (8.61 to 30.74)	−0.39 (−13.9 to 12.96)	.95
LDL, mg/dL	64	12.76 (6.22 to 19.31)	34	11.18 (1.61 to 20.76)	1.58 (−10.03 to 13.19)	.79
HDL, mg/dL	64	8.27 (6.21 to 10.34)	34	5.38 (2.32 to 8.44)	2.89 (−0.80 to 6.59)	.13
Triglycerides, mg/dL	64	−8.45 (−14.03 to −2.88)	34	−2.61 (−10.82 to 5.61)	−5.85 (−15.77 to 4.08)	.26
Blood pressure						
Systolic, mm Hg	60	−1.5 (−4.0 to 1.0)	24	−3.7 (−7.7 to 0.3)	2.2 (−2.6 to 7.0)	.37
Diastolic, mm Hg	60	−1.4 (−3.2 to 0.5)	24	−3.4 (−6.4 to −0.4)	2.0 (−1.6 to 5.6)	.28
Body composition						
Body mass, kg	64	−6.11 (−7.50 to −4.72)	34	−1.97 (−4.02 to 0.10)	−4.14 (−6.63 to −1.66)	.001
BMI	64	−2.01 (−2.46 to −1.56)	34	−0.69 (−1.35 to −0.02)	−1.32 (−2.13 to −0.51)	.001
Fat mass, kg	64	−6.13 (−7.33 to −4.93)	34	−1.16 (−2.94 to 0.66)	−4.97 (−7.11 to −2.82)	.004
Lean body mass, kg	64	0.62 (0.12 to 1.11)	34	−0.71 (−1.44 to 0.03)	1.32 (0.44 to 2.21)	.003
Abdominal fat mass, kg	64	−0.81 (−0.98 to −0.65)	34	−0.10 (−0.34 to 0.14)	−0.71 (−1.00 to −0.42)	<.001
Physical fitness						
V̇o$_{2max}$, mL o$_2$/min	61	394.8 (293.0 to 496.7)	25	−36.4 (−196.0 to 123.1)	421.2 (214.4 to 621.1)	<.001
Relative V̇o$_{2max}$, mL o$_2$/kg/min	61	6.52 (5.25 to 7.78)	25	−0.11 (−2.10 to 1.87)	6.63 (4.27 to 8.99)	<.001
Medication						
Proportion of participants with reduction in lipid-lowering medication[b]	62	No. (%) 23 (35.9)	31	No. (%) 14 (41.2)	Risk Difference (95% CI), % −5.0 (−25.5 to 15.1)	.61
Lipid-lowering medication score, median change (IQR)[c,e]	62	0 (−1 to 0)	31	0 (−1 to 0)	0 (−1 to 2)	.49
Proportion of participants with reduction in blood pressure-lowering medication[b]	62	No. (%) 18 (28.1)	31	No. (%) 4 (11.8)	Risk Difference (95% CI), % 16.4 (−0.9 to 31.8)	.06
Blood pressure-lowering medication score, median change (IQR)[c,e]	62	0 (−1 to 0)	31	0 (0 to 0)	0 (−2 to 0)	.02
Post Hoc Analyses		No. (%)		No. (%)		
Proportion of participants with an increase of glucose-lowering medication[b]	62	7 (10.9)	31	15 (44.1)	Risk Difference (95% CI), % −33.2 (−51.5 to −14.8)	<.001
Proportion of participants with discontinuation of glucose-lowering medication[b]	62	36 (56.3)	31	5 (14.7)	Risk Difference (95% CI), % 41.5 (24.5 to 58.6)	<.001
5% body weight reduction	62	36 (56.3)	31	5 (14.7)	41.5 (24.5 to 58.6)	<.001
10% body weight reduction	62	20 (31.3)	31	1 (2.9)	28.3 (15.6 to 41.0)	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HDL, high-density lipoprotein; LDL, low-density lipoprotein; V̇o$_{2max}$, maximal oxygen uptake.

SI conversion factors: To convert total, HDL, and LDL cholesterol to mmol/L, multiply by 0.0259; glucose to mmol/L, multiply by 0.0555; insulin to pmol/L, multiply by 6.945; triglycerides to mmol/L, multiply by 0.0113.

[a] P value is derived from a two 1-sided test analysis for equivalence for the primary outcome. All other P values are for superiority.

[b] If the prespecified treatment target was reached at the medical consultation the pharmacological treatment was halved, and if unchanged values or an additional reduction was observed at the following medical consultation the medical treatment was paused. Treatment targets were 6.5% or less for

hemoglobin A$_{1c}$ level, 130/80 mm Hg or less for blood pressure, 5 mmol/L or less for triglyceride level, and 2 mmol/L or less for LDL cholesterol level. If hemoglobin A$_{1c}$ level was more than 7.5%, blood pressure more than 140/85 mm Hg, triglyceride level more than 5 mmol/L, or LDL cholesterol level more than 2 mmol/L, medication was increased.

[c] Between-group difference tested using the Wilcoxon rank-sum test.

[d] Medication score ranges: glucose-lowering medication, 0-7; blood pressure-lowering medication, 0-8; and lipid-lowering medication, 0-6. A medication score of 0 indicates discontinuation and a high medication score indicates a more-intensive pharmacological treatment.

[e] Based on baseline to 12-month follow-up values.

Figure 2. Hemoglobin A$_{1c}$ Levels for the Lifestyle vs Standard Care Groups Among Participants With Non–Insulin-Dependent Type 2 Diabetes, Intention-to-Treat Analysis


No. of participants					
Lifestyle	64	61	61	60	62
Standard care	34	27	28	26	31
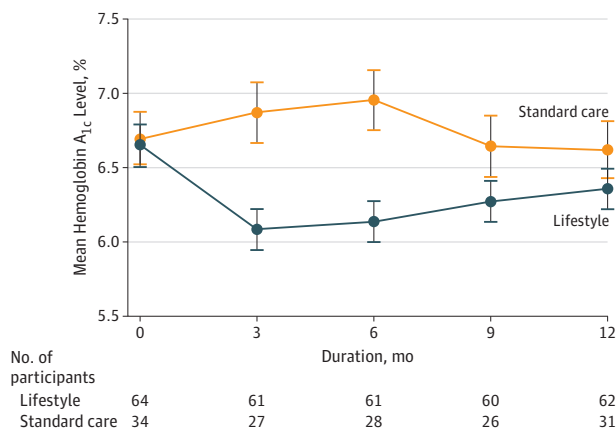
Data are least squares means derived from mixed linear models and adjusted for baseline hemoglobin A$_{1c}$ and sex. Error bars indicate 95% CIs.

Figure 3. Proportion of Participants With Non–Insulin-Dependent Type 2 Diabetes With a Reduction in Glucose-Lowering Medication From Baseline in the Lifestyle vs Standard Care Groups

Error bars indicate 95% CIs. If the prespecified treatment target was reached at the medical consultation, the pharmacological treatment was halved. If unchanged values or an additional reduction was observed at the following medical consultation, the medical treatment was paused.

At 12-month follow-up, no significant difference (*P* = .22) in retention rates was observed between the groups (97% for the lifestyle group and 91% for the standard care group).

From baseline to 12-month follow-up, the mean HbA$_{1c}$ level changed from 6.65% to 6.34% in the lifestyle group, and from 6.74% to 6.66% in the standard care group, with a mean between-group difference for change of −0.26% (95% CI, −0.52% to −0.01%). For the primary outcome, the difference in change for HbA$_{1c}$ level from baseline to 12-month follow-up was not contained within the equivalence margin of ±0.4%, thus equivalence could not be declared in the intention-to-treat analysis (*P* = .15) (**Table 2**). In the per-protocol analysis the mean change in HbA$_{1c}$ level decreased from 6.71% to 6.15% in the lifestyle group, and from 6.71% to 6.50% in the standard care group with a mean between-group difference of −0.36% [95% CI, −0.65% to −0.08%] (*P* = .18). Thus, equivalence could not be declared (eTable 1 in Supplement 3). The analysis of the secondary outcome showed that the proportion of participants, who reduced the use of glucose-lowering medication from baseline to 12-month follow-up was higher in the lifestyle group (73%) compared with the standard care group (26%) (risk difference, 47.1% [95% CI, 28.6% to 65.3%]) (Table 2), with a number needed to treat of 2.1 (95% CI, 1.6 to 3.5). The least-squares mean of HbA$_{1c}$ level is shown in **Figure 2**, and the mean reduction in glucose-lowering medication from baseline to 12-month follow-up is shown in **Figure 3**.

Exploratory outcomes are presented in Table 2. No group differences were observed in relation to reductions in lipid-lowering or blood pressure-lowering medication during the 12 months. Adherence to lipid-lowering and blood pressure-lowering medication are reported in eTables 4 and 5 in Supplement 3, whereas the proportion of participants that reduced the use of lipid-lowering and blood pressure-lowering medication is illustrated in eFigures 1 and 2 in
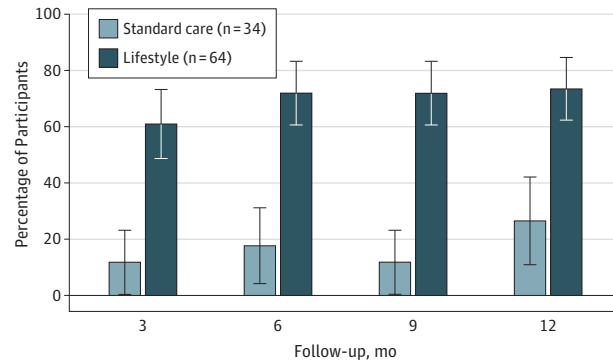
Supplement 3. Post hoc analysis showed that more participants in the lifestyle group eliminated the use of glucose-lowering medication (56.3%) than the standard care group (14.7%) from baseline to 12-month follow-up (risk difference, 41.5% [95% CI, 24.5% to 58.6%]). A larger proportion of the standard care participants increased the use of glucose-lowering medication (44.1%) compared with lifestyle participants (10.9%) (risk difference, 33.2% [95% CI, 51.5% to 14.8%]). Thirty-two adverse events occurred in the lifestyle group (**Table 3**). One participant in the lifestyle group experienced atrial fibrillation. Several sensitivity analyses confirmed the robustness of the primary analysis (eTable 2 in Supplement 3).

At 12-month follow-up, 71% of lifestyle participants and 83% of standard care participants adhered to the prescribed glucose-lowering medication (eTable 3 in Supplement 3). The lifestyle participants completed 82% of the prescribed exercise sessions, both aerobic and resistance training, during the 12 months (eTable 6 in Supplement 3) and attendance was 78% at the individual and dietary group sessions throughout year 1 (eTable 7 in Supplement 3).

Discussion

The main finding was that an intensive lifestyle intervention was nonequivalent compared with standard care in relation to maintaining glycemic control, with the modest reduction in HbA$_{1c}$ favoring the lifestyle group. Additionally, the lifestyle intervention led to a substantial and parallel reduction in glucose-lowering medication.

The finding that the lifestyle intervention resulted in a rejection of the equivalence hypothesis may appear unexpected as the utilized initial medical titration resulted in all participants being very close to the HbA$_{1c}$ level treatment target at baseline measurement prior to the lifestyle

Table 3. Adverse Events From Baseline to 12-Month Follow-up for Lifestyle vs Standard Care Groups Among Participants With Non–Insulin-Dependent Type 2 Diabetes

	Lifestyle Group, No. (%) (n = 64)	Standard Care Group, No. (%) (n = 34)	Between-Group Risk Difference, % (95% CI)
Serious Adverse Events			
Overall	1 (2)	0	2 (−6.5 to 9.7)
Deaths	0	0	0
Severe hypoglycemic events[a]	0	0	0
Adverse Events			
Mild hypoglycemia[b]	8 (12.5)	0	12.5 (0.0 to 20.6)
Any musculoskeletal pain or discomfort[c]	14 (21.9)	0	21.9 (13.8 to 30.0)
Acute injury during exercise[d]	1 (1)	NA	NA
Musculoskeletal pain or discomfort resulting in inability to exercise for ≥7d[e]	13 (20.3)	NA	NA
Gastrointestinal problems[f]	4 (6.3)	3 (9)	−2.6 (−10.7 to 5.5)
Mild hypotension	4 (6.3)	0	6.3 (−1.9 to 14.4)
Insomnia	0	1 (3)	−1.4 (−9.5 to 6.7)
Peripheral edema	1 (2)	1 (3)	−2.9 (−11.0 to 5.1)

Abbreviation: NA, not applicable.

[a] Plasma glucose less than 54 mgL/dL, episodes requiring third party assistance or medical intervention.

[b] Signs of hypoglycemia reported to the study nurse. They include hunger, sweating, increased nonexercise heart rate, feeling uncomfortable, dizziness, and confusion.

[c] Any musculoskeletal pain or discomfort reported to the diabetes nurse or intervention center.

[d] An immediate sensation of pain, discomfort, or loss of functioning during exercise reported to the intervention center.

[e] Musculoskeletal pain or discomfort causing cessation of exercise for 7 consecutive days or more, which were reported to the intervention center.

[f] Includes nausea, vomiting, diarrhea, constipation, and dyspepsia.

intervention. Additionally, the treat-to-target approach intentionally induced a ceiling effect on HbA$_{1c}$ level in both groups. Earlier studies have also addressed the effect of lifestyle on glycemic control and target-driven regulation of glucose-lowering medication. However, the results have been conflicting[11,12] and may to some extent be explained by reliance on advice-based exercise interventions[11] as opposed to supervision of exercise.[28] Furthermore, greater improvement in glycemic control is associated with higher levels of physical activity,[29] beyond the current physical activity recommendations for patients with type 2 diabetes.[30]

In the Look AHEAD study, a baseline HbA$_{1c}$ level of 7.2% was reduced by 0.6% in the lifestyle group after 1 year.[7] The corresponding numbers in the current study were 6.7% at baseline and −0.3% at year 1. The proportion of participants in the lifestyle group who reduced the use of glucose-lowering medication after 12 months was 73.5% in this study compared with 7.8% in the Look AHEAD study.[7] This may be due to several factors including different levels of supervised exercise and total exercise volume (duration, frequency, and intensity), which in this study far exceeded what was implemented in the Look AHEAD study.[31] The use of drug-assisted weight loss in Look AHEAD also differed markedly from this study and may limit the true effect of lifestyle intervention. Besides an extensive exercise intervention, the blinded, highly standardized, algorithm and target-driven approach to regulate glucose-lowering medication in both the lifestyle and standard care group was

a major strength of this study compared with other studies. However, more adverse events were observed in the lifestyle group compared with standard care, which may be ascribed to higher susceptibility in this group in relation to, for example, mild hypoglycemia because of the combination of lifestyle and medical therapy.

Limitations

This study has several limitations. First, only participants with type 2 diabetes diagnosed for less than 10 years were included. Prolonged diabetes duration, poor glycemic control, and insulin dependence[8,12,32] may reflect a more progressive disease state. As observed in the Look AHEAD study, better glycemic control and short diabetes duration at baseline were associated with a higher probability of meeting optimal care goals and remission of type 2 diabetes at 1-year follow-up.[8,33] Thus, the inclusion criteria in this study may limit generalizability. Second, the lifestyle intervention included several lifestyle elements, which challenges the interpretation of individual effects of each intervention component. Third, the self-reported dietary intake in this study is subject to biases and limitations.[34] Fourth, to be able to discriminate between the combined effect of medication and lifestyle in contrast to medication alone, a prespecified treatment algorithm using recommended first-line medical treatments[35] was employed, which led to a limited number of medications. Therefore, it is not possible to generalize the results to other combinations of glucose-lowering medications.

Conclusions

Among adults with type 2 diabetes diagnosed for less than 10 years, a lifestyle intervention compared with standard care resulted in a change in glycemic control that did not reach the criterion for equivalence, but was in a direction consistent with benefit. Further research is needed to assess superiority, as well as generalizability and durability of findings.

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