Dose-Response Effects of Exercise on Glucose-Lowering Medications for Type 2 Diabetes

A Secondary Analysis of a Randomized Clinical Trial

MacDonald, Christopher S.; Johansen, Mette Y.; Nielsen, Sabrina M.; Christensen, Robin; Hansen, Katrine B.; Langberg, Henning; Vaag, Allan A.; Karstoft, Kristian; Lieberman, Daniel E.; Pedersen, Bente K.; Ried-Larsen, Mathias

Published in:
Mayo Clinic Proceedings

DOI:
10.1016/j.mayocp.2019.09.005

Publication date:
2020

Document version:
Final published version

MAYO CLINIC

Check for updates

Dose-Response Effects of Exercise on Glucose-Lowering Medications for Type 2 Diabetes: A Secondary Analysis of a Randomized Clinical Trial

Christopher S. MacDonald, MSc; Mette Y. Johansen, MSc; Sabrina M. Nielsen, MSc; Robin Christensen, MSc, PhD; Katrine B. Hansen, MD, PhD; Henning Langberg, DMSc; Allan A. Vaag, MD; Kristian Karstoft, MD, PhD; Daniel E. Lieberman, PhD; Bente K. Pedersen, MD, DMSc; and Mathias Ried-Larsen, PhD

Abstract

Objective: To investigate whether a dose-response relationship exists between volume of exercise and discontinuation of glucose-lowering medication treatment in patients with type 2 diabetes.

Patients and Methods: Secondary analyses of a randomized controlled exercise-based lifestyle intervention trial (April 29, 2015 to August 17, 2016). Patients with non−insulin-dependent type 2 diabetes were randomly assigned to an intensive lifestyle intervention (U-TURN) or standard-care group. Both groups received lifestyle advice and objective target-driven medical regulation. Additionally, the U-TURN group received supervised exercise and individualized dietary counseling. Of the 98 randomly assigned participants, 92 were included in the analysis (U-TURN, n=61, standard care, n=31). Participants in the U-TURN group were stratified into tertiles based on accumulated volumes of exercise completed during the 1-year intervention.

Results: Median exercise levels of 178 (interquartile range [IQR], 121-213; lower tertile), 296 (IQR, 261-310; intermediate tertile), and 380 minutes per week (IQR, 355-446; upper tertile) were associated with higher odds of discontinuing treatment with glucose-lowering medication, with corresponding odds ratios of 12.1 (95% CI, 1.2-119; number needed to treat: 4), 30.2 (95% CI, 2.9-318.5; 3), and 34.4 (95% CI, 4.1-290.1; 2), respectively, when comparing with standard care. Cardiovascular risk factors such as glycated hemoglobin A_{1c} levels, fitness, 2-hour glucose levels, and triglyceride levels were improved significantly in the intermediate and upper tertiles, but not the lower tertile, compared with the standard-care group.

Conclusion: Exercise volume is associated with discontinuation of glucose-lowering medication treatment in a dose-dependent manner, as are important cardiovascular risk factors in well-treated participants with type 2 diabetes and disease duration less than 10 years. Further studies are needed to support these findings.

Study Registration: ClinicalTrials.gov registration (NCT02417012).

 ■ Mayo Clin Proc. 2020;95(3):488-503

For Limelight, see page 429

Affiliations are at the end of this article.

Current treatment regimens for type 2 diabetes (T2D) include diet, physical activity, and pharmacologic therapy.[1] The latter is associated with lowered quality of life,[2] interference with the ability to live a normal life,[3] and increased economic costs.[4] Nonsurgical approaches such as lifestyle interventions have had limited efficacy in reducing the need for glucose-lowering medications and glycemic control.[5,6] Exercise volumes exceeding 150 minutes of exercise per week have been shown to induce superior improvements in glycated hemoglobin A_{1c} (HbA_{1c}) levels.[7,8]

However, a clear consensus of the existence of a dose-response relationship in relation to exercise volume is currently not established in patients with T2D.[7-12] Most studies to date have used exercise levels at or below current recommendations and therefore the limited efficacy seen in these studies may be a result of insufficient exposure to exercise. In addition, the clinical relevance of existing studies is limited because studies have largely relied on self-reported exercise levels, which are known to be sufficiently inaccurate to risk misclassification.[13] Further studies are needed to replicate the nature of any exercise dose-response relationship, if it exists, between objectively measured exercise and glucose metabolism and other cardiovascular risk factors in patients with T2D.

Recently we reported that 56% (36 of 62) of participants receiving a 12-month intensive lifestyle intervention, which prescribed exercise volumes exceeding current recommendations, achieved discontinuation of treatment with glucose-lowering medications while maintaining optimal HbA_{1c} levels.[14] A unique feature of the study was that all completed exercise was objectively measured throughout the entire intervention. However, the effect of varying exercise volumes on the need for glucose-lowering medications and effects on HbA_{1c} levels and cardiovascular risk factors were not explored.

We test the hypothesis that a positive association exists between increasing volumes of exercise and the odds of discontinuing glucose-lowering medication treatment and changes in HbA_{1c} levels in patients with T2D diagnosed within 10 years.

PATIENTS AND METHODS

Research Design

The original trial is registered at ClinicalTrials.gov (NCT02417012). Full details of the original trial protocol are published,[15] and the prespecified Supplementary Statistical Analysis Plan for these particular secondary analyses is available online at http://www.mayoclinicproceedings.org.

Study Design

The original study was a randomized (2:1), single-center, assessor-blinded, 2-arm, parallel-group trial designed to test whether an intensive lifestyle intervention was equally effective in maintaining glycemic control compared with standard care in patients with T2D, conducted in the Capital Region of Denmark (April 29, 2015 to August 17, 2016).[15] The primary results were published in 2017.[14] Guidelines from the Declaration of Helsinki were followed, and the study was approved by the Scientific Ethical Committee at the Capital Region of Denmark. All participants provided oral and written informed consent.

In this extension study, participants in the U-TURN group were divided into tertiles (lower, intermediate, and upper; described in the Supplementary Statistical Analysis Plan) based on the objective assessment of the accumulated volume of aerobic and resistance exercise completed from baseline to the 12-month follow-up.

Participants and Eligibility

Ninety-eight participants were recruited for the original study. Details about randomization and allocation procedures and sample size considerations have been published elsewhere.[15] Inclusion criteria were a diagnosis of T2D within the last 10 years, 18 years or older, body mass index (BMI; calculated as the weight in kilograms divided by the height in meters squared) of 25 or greater but 40 or less kg/m^2, and without severe comorbid conditions, insulin use, or HbA_{1c} level greater than 9%. Only participants attending the 12-month follow-up assessment and with registered exercise on the Polar watch (the latter only applied to the U-TURN group) were included in this secondary analysis.

Interventions

The intensive lifestyle intervention for the U-TURN group has previously been described in detail.[15] All participants received standard care consisting of medical counseling, lifestyle

advice, and education in T2D provided by a study nurse at baseline and every third month during the intervention period.

Prespecified algorithms for glucose-lowering medications were followed during the 12-month intervention in both groups.[15] The treatment target for glycemic control was HbA_{1c} level of 6.5%. If this target was reached at a medical consultation, the glucose-lowering medication dose was halved. In the case of unchanged values or if an additional reduction in HbA_{1c} level was observed at the following medical consultation, the treatment with medication was discontinued. The endocrinologist's regulation of all medication was blinded to group allocation.

In addition to standard care, the U-TURN group was prescribed a high-volume exercise intervention aiming for at least 240 minutes of aerobic and resistance exercise per week in phase 1 (first 4 months) and at least 300 minutes of aerobic and resistance exercise per week in phases 2 and 3 (last 8 months) with concomitant dietary counseling.

Outcomes and Measurements

The primary outcome was discontinuation according to the blinded target-driven algorithm of glucose-lowering medication treatment at the 12-month follow-up.

The mean difference for change in HbA_{1c} level from baseline to the 12-month follow-up between the exercise tertiles and standard care is a key secondary outcome. Additionally, we explored the dose-response relationship of exercise volume and body composition measures, fasting insulin level, fasting glucose and 2-hour glucose levels, fitness, energy intake, blood lipid levels, and lipid-lowering medication, blood pressure, and blood pressure—lowering medication.

Exercise volume and intensity measurement methods were described in the prepublished protocol.[15] All exercise and physical activity data were registered through a Polar V800 watch in the U-TURN group. Participants in the U-TURN group were instructed to wear the watch 24 hours a day every day of the intervention. During all exercise sessions, participants used the heart rate monitoring chest band to ensure accurate registration of exercise intensity.

Study participants were divided into tertiles based on the combined volume of aerobic and resistance exercise accumulated during the 12 months of the intervention. Bouts less than 10 minutes and aerobic exercise with a registered intensity of less than 57% of maximum heart rate, corresponding to light to very light intensity,[16] were not categorized as exercise and were excluded from the analysis. An elaborate description is found in the Supplementary Statistical Analysis Plan.

Assessments were performed in one laboratory and biochemical analyses were completed at the central laboratory (Rigshospitalet, Denmark) using standard procedures.[15]

Statistical Analyses

The original analysis plan specified a repeated-measures mixed model. However, because the model did not converge, we used the simpler model without repeated measures.[17] The primary analysis was based on the as-observed population. To account for observed confounding, all participants were assigned a propensity of being allocated to an exercise tertile. Because the original design included a standard-care group, participants in standard care were per default assigned a propensity of 0 because they did not exercise; that is, this group will continue to be a randomized control group. The propensity of belonging to a tertile was data driven, based on the baseline variables (prerandomization [ie, not influenced by post hoc elements]); sex and high-density lipoprotein cholesterol level at baseline. The propensity score was computed as a single continuous variable, ranging from 0 to 1 in the primary analyses. Variables to be associated with a high or low level of physical activity were used as a proxy for the propensity of engaging in increased exercise. Following estimation of the propensity score, the primary outcome was analyzed using multivariable logistic regression adjusted for the propensity score and an appropriate continuous baseline score (ie, glucose-lowering medication score at baseline), by including these as independent variables in the regression.

Mayo Clin Proc. ■ March 2020;95(3):488-503 ■ https://doi.org/10.1016/j.mayocp.2019.09.005
www.mayoclinicproceedings.org

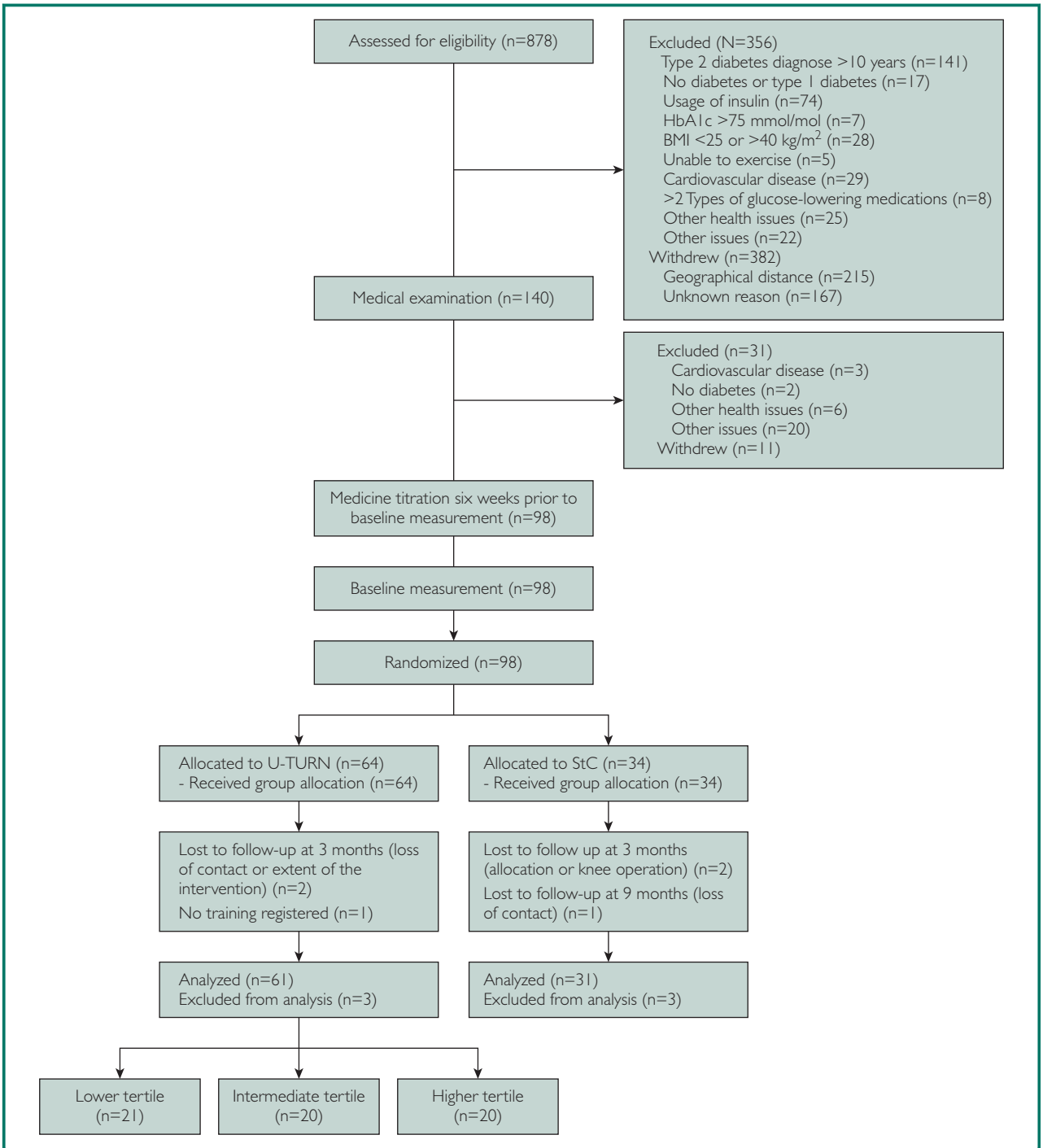

FIGURE 1. Flow of participants through the study. HbA_{1c} = glycated hemoglobin A_{1c}; BMI = body mass index; StC = standard care.

Statistical tests were conducted between different tertiles and the standard-care group in a hierarchical manner for the predefined primary and secondary analyses. A gatekeeping procedure using serial testing was applied to implicitly adjust for multiplicity.[18] We first investigated whether there was a trend in the odds ratio for discontinuation of glucose-lowering medication treatment at the 12-month follow-up between standard care

TABLE 1. Baseline Characteristics for Each Group[a,b]

	n	Standard care (n=31)	n	Lower tertile (n=21)	n	Intermediate tertile (n=20)	n	Upper tertile (n=20)
Demographic characteristics								
Age (y), mean ± SD	31	56.8±8.3	21	52.3±8.5	20	53.7±10.1	20	53.8±8.9
Female sex, No. (%)	31	14 (45)	21	14 (67)	20	7 (35)	20	8 (40)
Type 2 diabetes duration (y), median [IQR]	31	6.0 [3.0-9.0]	21	4.0 [4.0-6.0]	20	4.5 [2.0-7.3]	20	4.5 [2.8-7.3]
Glycemic control								
HbA_{1c} (%), mean ± SD	31	6.7±0.9	21	6.5±0.66	20	6.7±0.97	20	6.8±0.86
Fasting glucose (mmol/L), median [IQR]	31	7.80 [6.85-9.00]	21	6.70 [6.20-7.40]	20	7.65 [6.63-9.23]	20	8.25 [6.35-8.70]
Fasting insulin (pmol/L), median [IQR]	31	116.0 [68.0-169.0]	21	107.0 [73.0-171.0]	20	134.5 [89.0-164.8]	20	114.0 [69.3-147.8]
2-h glucose (mmol/L), mean ± SD	30	16.35±4.16	21	14.59±3.15	19	15.80±3.91	20	15.73±5.02
Lipids								
Total cholesterol (mmol/L), mean ± SD	30	3.96±0.98	21	4.32±0.56	20	4.02±0.89	20	4.19±1.05
LDL cholesterol (mmol/L), mean ± SD	30	2.21±0.85	21	2.49±0.56	20	2.41±0.84	20	2.50±0.98
HDL cholesterol (mmol/L), mean ± SD	30	1.27±0.36	21	1.36±0.40	20	1.06±0.26	20	1.24±0.30
Triglycerides (mmol/L), median [IQR]	30	1.37 [0.84-1.79]	21	1.21 [1.00-1.75]	20	1.57 [1.17-2.03]	20	1.37 [0.89-1.90]
Blood pressure								
Systolic (mm Hg), mean ± SD	23	135.7±8.2	19	130.2±12.3	19	128.8±18.3	20	123.6±9.3
Diastolic (mm Hg), mean ± SD	23	84.0±7.9	19	81.6±9.0	19	79.7±9.2	20	76.5±7.0
Body composition								
Body mass (kg), mean ± SD	31	97.6±15.2	21	92.5±15.0	20	94.3±13.4	20	99.7±13.6
BMI (kg/m^2), mean ± SD	31	32.3±4.4	21	31.8±3.6	20	30.8±4.1	20	32.3±4.0
Fat mass (kg), mean ± SD	31	35.8±10.8	21	35.9±7.9	20	33.9±9.6	20	37.3±9.3
Lean body mass (kg), mean ± SD	31	57.9±10.7	21	52.8±10.8	20	56.2±8.8	20	58.4±10.7
Abdominal fat mass (kg), mean ± SD	31	4.1±1.3	21	3.9±1.0	20	3.9±1.2	20	4.2±1.2
Body fat percentage (%), mean ± SD	31	37.9±9.2	21	40.5±6.5	20	37.3±8.1	20	38.9±8.2
Physical fitness, physical activity, and diet								
$V_{O_{2max}}$ (mL O_2/min), mean ± SD	30	2668±771	21	2648±859	20	2738±622	20	2807±691
Relative $V_{O_{2max}}$ (mL O_2/kg/min), mean ± SD	30	27.4±6.3	21	28.5±7.4	20	29.3±6.7	20	28.2±6.2
Energy intake (kJ/d), mean ± SD	25	9997±3866	20	10,294±3511	20	8814±2350	20	8767±3072

[a]BMI = body mass index; HbA_{1c} = glycated hemoglobin A_{1c}; HDL = high-density lipoprotein; IQR = interquartile range; LDL = low-density lipoprotein; $V_{O_{2max}}$ = maximun oxygen consumption.

[b]Data are presented as mean ± SD unless otherwise stated. Dichotomous and categorical data are presented as actual number (percent). Tertiles are stratified according to the observed exercise volume during the 1-year trial.

TABLE 2. Between-Group Comparisons of Changes From Baseline to 12-Month Follow-up[a,b]

	n	StC (n=31)	n	Lower tertile (n=21)	n	Intermediate tertile (n=20)	n	Upper tertile (n=20)	Comparison	Estimate (95% CI)	*P* value
Primary outcome											
Discontinuation of glucose-lowering medications, n (%)	31	5 (16)	21	10 (48)	20	12 (60)	20	14 (70)	Overall trend	—	.003
									T3-StC	OR, 34.4 (4.1 to 290.1)	.001
									T2-StC	OR, 30.2 (2.9 to 318.5)	.005
									T1-StC	OR, 12.1 (1.2 to 11.9)	.03
									T3-T1	OR, 2.8 (0.7 to 11.7)	.15
Key secondary outcomes											
Change in HbA_{1c} (%)	31	0.15 (−0.2 to 0.5)	21	−0.2 (−0.5 to 0.2)	20	−0.6 (−0.9 to −0.3)	20	−0.6 (−0.8 to −0.3)	Overall trend		.007
									T3-StC	−0.7 (−1.2 to −0.2)	.008
									T2-StC	−0.7 (−1.3 to −0.1)	.02
									T1-StC	−0.3 (−0.9 to 0.3)	.29
Reduction in glucose-lowering medications, n (%)	31	9 (29)	21	12 (57)	20	19 (95)	20	16 (80)	Overall trend	—	.003
									T3-StC	OR, 10.6 (1.2 to 91.5)	.03
									T2-StC	OR, 48. (2.5 to 928.7)	.01
									T1-StC	OR, 3.7 (0.3 to 41.4)	.29
Intensification in glucose-lowering medications, n (%)	31	15 (48)	21	4 (19)	20	1 (5)	20	2 (10)	Overall trend	—	.15
Other exploratory outcomes											
Glycemic control											
Change in fasting glucose (mmol/L)	29	−0.4 (−1.3 to 0.5)	21	−0.5 (−1.3 to 0.2)	20	−1.0 (−1.7 to −0.3)	20	−1.4 (−2.0 to −0.7)	Overall trend	—	.16
Change in fasting insulin (pmol/L)	27	−21.1 (−52.2 to 10.0)	20	−19.1 (−43.8 to 5.6)	20	−30.5 (−55.1 to −5.9)	19	−55.8 (−78.0 to −33.6)	Overall trend	—	.07
									T3-StC	−34.7 (−77.6 to 8.1)	.11
Change in 2-h glucose (mmol/L)	27	−0.4 (−2.3 to 1.5)	21	−2.2 (−3.6 to −0.7)	19	−2.7 (−4.2 to −1.2)	20	−4.0 (−5.3 to −2.7)	Overall trend	—	.02
									T3-StC	−3.6 (−6.2 to −1.1)	.006
									T2-StC	−2.3 (−5.2 to 0.6)	.11

Continued on next page

TABLE 2. Continued

	n	StC (n=31)	n	Lower tertile (n=21)	n	Intermediate tertile (n=20)	n	Upper tertile (n=20)	Comparison	Estimate (95% CI)	*P* value
Lipids											
Change in total cholesterol (mmol/L)	28	0.6 (0.1 to 1.1)	21	0.32 (−0.1 to 0.7)	20	0.6 (0.2 to 1.1)	20	0.46 (0.1 to 0.8)	Overall trend	—	.59
Change in LDL cholesterol (mmol/L)	29	0.20 (−0.24 to 0.65)	21	0.2 (−0.2 to 0.5)	20	0.6 (0.2 to 1.0)	20	0.40 (0.1 to 0.7)	Overall trend	—	.22
Change in HDL cholesterol (mmol/L)	28	0.22 (0.04 to 0.39)	21	0.1 (−0.1 to 0.2)	20	0.2 (0.1 to 0.4)	20	0.2 (0.1 to 0.4)	Overall trend	—	.33
Change in triglycerides (mmol/L)	28	0.18 (−0.16 to 0.52)	21	−0.2 (−0.4 to 0.1)	20	−0.3 (−0.6 to −0.0)	20	−0.5 (−0.8 to −0.3)	Overall trend	—	.007
									T3-StC	−0.7 (−1.2 to −0.3)	.003
									T2-StC	−0.5 (−1.0 to 0.0)	.07
Blood pressure											
Change in systolic (mm Hg)	19	−5.4 (−13.2 to 2.4)	12	−0.5 (−7.0 to 6.0)	16	0.3 (−5.4 to 5.9)	20	−2.9 (−7.3 to 1.5)	Overall trend	—	.74
Change in diastolic (mm Hg)	19	−4.1 (−9.9 to 1.7)	12	−1.7 (−6.6 to 3.2)	16	−0.0 (−4.2 to 4.2)	20	−2.0 (−5.2 to 1.3)	Overall trend	—	.77
Body composition											
Change in body mass (kg)	27	0.3 (−4.1 to 4.6)	21	−3.7 (−7.1 to −0.3)	20	−7.2 (−10.5 to −3.8)	20	−10.9 (−13.9 to −7.9)	Overall trend	—	<.001
									T3-StC	−11.2 (−17.1 to −5.3)	<.001
									T2-StC	−7.4 (−14. to −0.9)	.03
									T1-StC	−4.0 (−10.6 to 2.68)	.24
Change in BMI (kg/m^2)	27	−0.1 (−1.5 to 1.4)	21	−1.1 (−2.2 to 0.0)	20	−2.4 (−3.5 to −1.3)	20	−3.6 (−4.6 to −2.6)	Overall trend	—	<.001
									T3 StC	−3.5 (−5.5 to −1.6)	<.001
									T2-StC	−2.3 (−4.5 to −0.2)	.04
									T1-StC	−1 (−3.2 to 1.2)	.36

Continued on next page

Mayo Clin Proc. ■ March 2020;95(3):488-503 ■ https://doi.org/10.1016/j.mayocp.2019.09.005
www.mayoclinicproceedings.org

TABLE 2. Continued

	n	StC (n=31)	n	Lower tertile (n=21)	n	Intermediate tertile (n=20)	n	Upper tertile (n=20)	Comparison	Estimate (95% CI)	*P* value
Change in fat mass (kg)	27	−0.4 (−3.9 to 3.1)	21	−2.7 (−5.4 to 0.1)	20	−6.6 (−9.3 to −3.9)	20	−10.6 (−13.0 to −8.2)	Overall trend	—	<.001
									T3-StC	−10.2 (−15. to −5.5)	<.001
									T2-StC	−6.2 (−11.5 to −0.9)	.02
									T1-StC	−2.3 (−7.6 to 3.1)	.41
Change in lean body mass (kg)	27	−1.9 (−5.0 to 1.2)	21	0.9 (−1.5 to 3.4)	20	1.2 (−1.2 to 3.7)	20	−0.7 (−2.9 to 1.4)	Overall trend	—	.46
Change in abdominal fat mass (kg)	27	0.0 (−0.5 to 0.5)	21	−0.4 (−0.8 to −0.0)	20	−0.9 (−1.3 to −0.5)	20	−1.4 (−1.7 to −1.0)	Overall trend	—	<.001
									T3-StC	−1.4 (−2 to −0.7)	<.001
									T2-StC	−0.9 (−1.6 to −0.2)	.02
									T1-StC	−0.4 (−1.1 to 0.3)	.29
Change in body fat percentage (%)	27	−0.4 (−2.9 to 2.1)	21	−1.9 (−3.9 to 0.0)	20	−5.1 (−7.1 to −3.2)	20	−7.7 (−9.4 to −6.0)	Overall trend	—	<.001
									T3-StC	−7.3 (−10.6 to −3.9)	<.001
									T2-StC	−4.7 (−8.5 to −0.9)	.02
									T1-StC	−1.5 (−5.4 to 2.4)	.44
Physical fitness, physical activity, and diet											
Change in VO_{2max} (mL O_2/min)	25	40 (−257 to 337)	21	123 (−100 to 346)	20	437 (214 to 660)	19	555 (352 to 758)	Overall trend	—	.002
									T3-StC	514.9 (116.7 to 913.2)	.01
									T2-StC	397.1 (−45.7 to 839.9)	.08
Change in relative VO_{2max} (mL O_2/kg/min)	25	−0.2 (−3.5 to 3.2)	21	2.6 (0.0 to 5.1)	20	7.91 (5.4 to 10.5)	19	9.6 (7.3 to 11.9)	Overall trend	—	<.001
									T3-StC	9.8 (5.2 to 14.3)	<.001
									T2-StC	8.1 (3. to 13.1)	.002
									T1-StC	2.7 (−2.4 to 7.8)	.29
Change in energy intake (kJ/d)	23	44 (−1820 to 1908)	19	−1841 (−3247 to −435)	19	−1462 (−2854 to −71)	18	−1162 (−2435 to 112)	Overall trend	—	.61
Medication											

Continued on next page

TABLE 2. Continued

	n	StC (n=31)	n	Lower tertile (n=21)	n	Intermediate tertile (n=20)	n	Upper tertile (n=20)	Comparison	Estimate (95% CI)	*P* value
Reduction in lipid-lowering medication, n (%)	31	14 (45)	21	6 (29)	20	8 (40)	20	9 (45)	Overall trend	—	.09
									T3-StC	OR, 3.6 (0.4 to 35.5)	.28
Reduction in blood pressure—lowering medication, n (%)	31	4 (13)	21	3 (14)	20	8 (40)	20	7 (35)	Overall trend	—	.02
									T3-StC	OR, 11.1 (0.4 to 299.9)	.15

[a]BMI = body mass index; HbA_{1c} = glycated hemoglobin A_{1c}; HDL = high-density lipoprotein; LDL = low-density lipoprotein; OR = odds ratio; StC = standard care; T = tertile; Vo_{2max} = maximum oxygen consumption.
[b]Data are presented as least squares mean (95% CI) unless stated otherwise. Outcomes were analyzed using regression analyses adjusting for baseline value and propensity score. Propensity scores were estimated based on sex and HDL cholesterol level at baseline because these variables predicted group allocation. Analyses were based on a sequential analytic approach; if an overall trend was present ($P<.10$ was considered indicative), between-group comparisons for effect size estimation were initiated in a specific order, and if no difference was present ($P<.05$), the statistical inference sequence was terminated.

and each of the exercise tertiles. If present ($P<.10$ was considered indicative), formal statistical testing for the between-group comparisons and effect-size estimation was initiated in the following order until one of the end points in the hierarchy failed to be statistically significant at $\alpha=.05$: (1) standard care vs upper tertile, (2) standard care vs intermediate tertile, (3) standard care vs lower tertile, (4) upper tertile vs lower tertile, (5) upper tertile vs intermediate tertile, and (6) intermediate tertile vs lower tertile.

The secondary outcomes were analyzed using linear regression models or logistic regression models similar to the model used for the primary analysis of the primary outcome. Performance of the primary model was assessed using C statistics. A value of 0.5 suggests that the model discriminates no better than chance alone, 0.7 to 0.8 is acceptable, 0.8 to 0.9 is excellent, and greater than 0.9 is outstanding discrimination.[19]

Five sensitivity analyses were performed: (1) including energy intake at baseline and change in energy intake from baseline to the 12-month follow-up; (2) using models without adjustments; (3) including prespecified variables found to predict exercise adherence: BMI, age, fitness level, educational level, and sex[20-23]; (4) adjusted for data-driven propensity score with no adjustment for baseline value; and (5) post hoc analysis excluding participants beginning insulin treatment during the intervention. Furthermore, between-group comparisons and effect size estimation were allowed in post hoc analyses to be continued regardless of statistical significance in the gate-keeping sequence.

The statistical analysis plan was completed before any analyses were performed. All analyses were performed in the statistical program R (version 3.5.1)[24] using the packages *lme4*[25] and *drc*,[26] and statistical significance level was set at $\alpha<.05$ (2-tailed).

RESULTS

Participants

A total of 98 participants were randomly assigned to either the U-TURN intervention (n=64) or to standard care (n=34; Figure 1). Three participants in standard care did not attend the 12-month assessment. Two participants in the U-TURN group only attended the baseline assessment and 1 did not register any exercise volume (Figure 1). Hence, 92 were included in the analysis (U-TURN, n=61, standard care, n=31). Mean ± SD age at baseline was 54.4±9.0 years, and sex distribution was even (47% [43 of 92] women; Table 1).

With higher exercise volumes, the odds of discontinuing glucose-lowering medication increased (Table 2; Figure 2). The model showed acceptable or excellent discrimination (C statistic, 0.80; 95% CI, 0.71-0.91). The numbers needed to treat in the lower, intermediate, and upper tertiles were 4, 3, and 2, respectively. No statistically significant trend for intensification of glucose-lowering medication was found

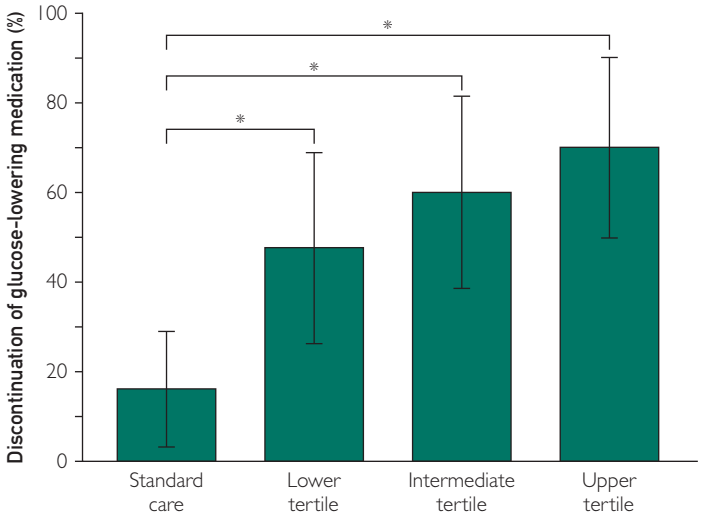

FIGURE 2. Bar chart illustrates the proportion of participants within each tertile having discontinued treatment with glucose-lowering medication at the 12-month follow-up for standard care (5/31), lower tertile (10/21), intermediate tertile (12/20), and upper tertile (14/20). Error bars indicate 95% CIs. The primary statistical model (logistic regression adjusted for glucose-lowering medication score and propensity score) showed an overall statistically significant trend ($P=.003$), as well as statistically significant differences (indicated with lines and asterisks) between upper tertile and standard care ($P=.001$), intermediate tertile and standard care ($P=.005$), and lower tertile and standard care ($P=.03$).

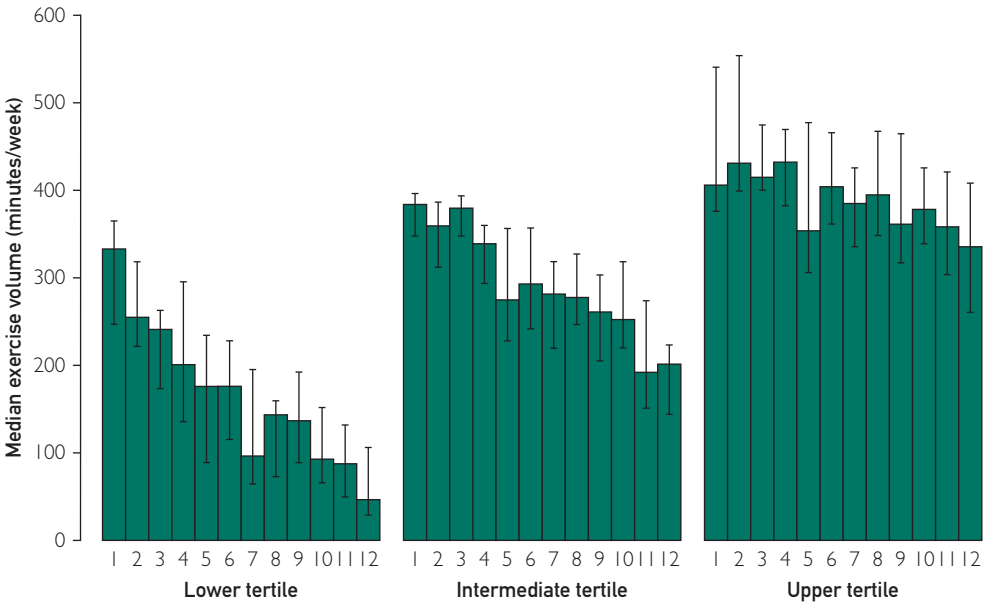

FIGURE 3. Bar chart reports the combined volume for each exercise tertile for each month of intervention. Volume is reported as median minutes per week based on all participants within a given tertile for each month of intervention. Error bars indicate interquartile range. The prescribed dosage of exercise is 240 or more minutes of exercise per week in the first phase and 300 minutes of exercise per week in the second and third phases. The upper tertile is compliant with the prescribed dose of combined exercise each month of the intervention, whereas the intermediate tertile is compliant in the first phase and the lower tertile is compliant in the first 3 months of the intervention.

(*P*=.15) (Table 2). Change in HbA_{1c} levels from baseline to the 12-month follow-up in the lower tertile was not statistically significantly reduced (−0.3%; 95% CI, −0.9% to 0.3%) (*P*=.29) compared with standard care, whereas HbA_{1c} level was reduced in the intermediate (−0.7%; 95% CI, −1.3% to −0.1%) (*P*=.02) and upper tertiles (−0.7%; 95% CI, −1.2% to −0.2%) (*P*=.008).

Sensitivity analysis adjusting for energy intake at baseline and change in energy intake from baseline to the 12-month follow-up did not affect the primary conclusions for the primary outcome materially (Supplementary Table 1, available online at http://www.mayoclinicproceedings.org). Neither did sensitivity analysis with no adjustments (Supplementary Table 2, available online at http://www.mayoclinicproceedings.org), adjusted for prespecified variables (Supplementary Table 3, available online at http://www.mayoclinicproceedings.org), or data-driven propensity (Supplementary Table 4, available online at http://www.mayoclinicproceedings.org) or excluding participants initiating insulin treatment during the intervention (Supplementary Table 5, available online at http://www.mayoclinicproceedings.org).

The trends in the explorative analysis align with the primary outcome; however, cardiovascular risk factors were only attenuated in the intermediate and upper tertiles when compared with standard care. The overall trend for fasting insulin level was significant (*P*=.07) and a reduction in 2-hour glucose level in the upper tertile was observed (*P*=.006). Reductions in body weight, BMI, and measures of fat mass was observed in the upper and intermediate tertiles, with a consistently greater reduction observed in the upper tertile. Triglyceride levels were improved in the upper tertile only. Absolute

Mayo Clin Proc. ■ March 2020;95(3):488-503 ■ https://doi.org/10.1016/j.mayocp.2019.09.005
www.mayoclinicproceedings.org

fitness (maximum oxygen consumption in milliliters of oxygen per minute) only increased in the upper tertile. No trend for change in energy intake was found.

Post hoc analyses that allowed the primary statistical testing for the between-group comparisons and effect size estimation to be continued regardless of statistical significance are found in Supplementary Table 6 (available online at http://www.mayoclinicproceedings.org). Numbers of adverse events were 5 of 31 (16%), 11 of 21 (52%), 15 of 20 (75%), and 5 of 20 (25%) for standard care and lower, intermediate, and upper tertiles, respectively. Specifically, for musculoskeletal pain, numbers were 0 of 31 (0%), 6 of 21 (29%), 7 of 20 (35%), and 1 of 20 (0.5%) for standard care and lower, intermediate, and upper tertiles, respectively.

The median volume of exercise across the intervention period in the lower tertile was 178 minutes per week (interquartile range [IQR], 121-213). The median volume of exercise in the intermediate tertile was 296 minutes per week (IQR, 261-310). Median volume of exercise in the upper tertile was 380 minutes per week (IQR, 355-446). The monthly adherence is described in Supplementary Table 7 (available online at http://www.mayoclinicproceedings.org) and Figure 3.

DISCUSSION

The main finding of the study was that exercise was associated with a decreased need for glucose-lowering medication in a dose-dependent manner. In addition, trends in the secondary outcomes align with the primary outcome. However, cardiovascular risk factors were only attenuated in the intermediate and upper tertiles. A lifestyle intervention with volumes of exercise substantially higher than current exercise recommendations was needed to generate improvements in HbA_{1c} levels, cardiorespiratory fitness, triglyceride levels, and glucose tolerance above and beyond those achieved before the intervention with higher levels of medication.[27-29]

There are only a limited number of studies exploring the dose-dependency of exercise in at-risk populations. Based on the Dose-Response to Exercise in Women studies, metabolic risk factors such as fitness, waist circumference, fasting glucose level, and systolic blood pressure are dose dependent, with greater improvements being achieved with ascending levels of exercise energy expenditure.[30,31] In a secondary analysis, Ross et al[32] found that substantial volumes of exercise with high intensity are needed to completely eliminate cardiorespiratory fitness nonresponse.

We are aware of no studies that have explored the dose dependency of exercise in relation to the need for glucose-lowering medication in patients with T2D. However, there are a limited number of studies that have explored the dose dependency of exercise on HbA_{1c} level. Di Loreto et al[7] reported that at least 10 metabolic equivalent—hours per week are needed to improve HbA_{1c} levels and reduce risk factors for diabetic complications. Furthermore, these authors report that health benefits increase with exercise levels exceeding 10 metabolic equivalent—hours per week. This result is in line with results from our study, which find additional benefits of completing a level of exercise that exceeds current recommendations.

Conversely, in the Italian Diabetes and Exercise Study (IDES), no association of exercise volume and the probability of having an HbA_{1c} level less than 6.5% was observed at the end of the study.[9] This is interesting because participants completing the highest levels of exercise in IDES reported exercise volumes that exceed the high exercise volumes of the upper tertile in our study. However, a major limitation in the IDES data is that the exercise volume was self-reported. In addition, contrary to our study, IDES included participants treated with insulin and with a longer average duration of disease, both of which are indicative of more severe disease states. Results from the Look Action for Health in Diabetes trial and Diabetes Remission Clinical Trial, as well as results from bariatric surgery trials, have established that participants with a short duration of

disease are more likely to respond to nonpharmacologic treatment.[5,6,33]

Finally, baseline HbA_{1c} levels in IDES were higher than in our study, which would have made it more difficult for IDES participants to reach the defined treatment target. Interestingly, the 3-year IDES-2 follow-up study has recently reported that an increase of 56 minutes of moderate to vigorous exercise per week was not sufficient to attenuate cardiovascular risk factors.[34] This corresponds to the findings of our lower exercise tertile.

The clinical benefits of discontinuing or reducing treatment with glucose-lowering medication are unclear. However, factors such as glycemic control, blood lipid profile, and low fitness level have consistently been associated with increased risk for diabetes-related complications.[35-38] Our analysis revealed that a lifestyle intervention including exercise volumes in the lower tertile was sufficient to introduce discontinuation of treatment with glucose-lowering medication in nearly half the participants.

However, this exercise volume failed to improve any cardiovascular disease risk markers. The data indicate that to achieve discontinuation of treatment with glucose-lowering medications while simultaneously improving clinically important markers associated with risk for T2D-related complications, exercise volumes must approach the level of the intermediate tertile. Specifically, both the intermediate and upper tertiles demonstrated significant improvements in HbA_{1c} levels, fitness, and body composition measures. Although it should be acknowledged that improvements in HbA_{1c} levels are not consistently associated with a reduction in risk for macrovascular complications and mortality,[39] the improvements in HbA_{1c} levels observed in the intermediate and upper tertiles, if maintained, likely have the potential to reduce the risk for developing microvascular complications, specifically retinopathy and nephropathy.[40] In addition, only the upper tertile increased absolute fitness and reduced both 2-hour glucose and triglyceride levels. Fitness levels, triglyceride levels, and 2-hour glucose tolerance have all been associated with risk for developing micro- and macrovascular complications.[35-38]

Diet is associated with remission of T2D,[6] and a difference in energy intake could be a possible explanation of the dose-response effect in the odds of discontinuation of glucose-lowering medication and HbA_{1c} level reduction shown in our study. We adjusted for energy intake in the analysis and this did not change the association, indicating that energy intake was not the driving factor of the effects seen on primary and secondary outcomes.

It should be acknowledged that high levels of exercise are difficult to attain and methods to increase adherence to exercise should be explored. However, a significant proportion of participants in the current study managed to perform and maintain adherence to exercise levels superceeding current recommendations.

There are some limitations to our study. First, our secondary analyses invariably involve some prognostic imbalance as randomization is lost. Specifically, patients who have a particular exercise volume could be subject to selection bias, which could lead to a difference with respect to their probability of developing the outcome. To account for potential confounding, a propensity score was created to balance out observed confounders across the groups. In addition, post hoc adjustments were applied and none of the sensitivity analyses reduced the robustness of primary results. However, the results may still be biased by different distributions of unknown prognostic factors. In relation to this, the dietary assessment in this study relied on self-reports that are subject to bias, rendering this analysis mainly exploratory. This entails that the sensitivity analysis adjusting for energy intake should be interpreted with caution.

Second, no objective measure of exercise adherence was obtained for the standard-care group. If participants in the standard-care group increase their exercise levels, this would underestimate the effect of the different exercise doses and thus the reported effects in this study may be conservative. However, because physical fitness did not increase in the standard-care

Mayo Clin Proc. ■ March 2020;95(3):488-503 ■ https://doi.org/10.1016/j.mayocp.2019.09.005
www.mayoclinicproceedings.org

group (Table 2), this indicates that the standard-care group as a whole did not increase aerobic exercise.

Third, the small number of participants in the tertiles leaves us with reduced statistical power. However, despite this, the primary analysis reached statistical significance, underscoring the notion of a very strong biological signal.

Fourth, the inclusion criteria in this study limit the generalizability of the results. In addition, there may be some form of reverse causality present, with participants potentially becoming more likely to exercise as their health improves.

In relation to discontinuations, the titration target for HbA_{1c} level at baseline was also the defined target for initiating reductions in glucose-lowering medication. This resulted in a high percentage of participants having baseline values close to or less than the target for initiating reductions in glucose-lowering medication at the onset of the intervention. This increased the odds of participants being discontinued from treatment with glucose-lowering medication. However, it would not account for the gradual increase in the odds of being discontinued from treatment with glucose-lowering medication parallel to the increase in exercise volume.

CONCLUSION

Our results indicate that exercise was associated with discontinuation of glucose-lowering medication in a dose-dependent manner, as were important cardiovascular risk factors in well-treated participants with T2D and disease duration less than 10 years. However, discontinuation of glucose-lowering medication treatment is debatable; insofar as remission is a goal, our data suggest that prescribed exercise volumes may need to exceed current recommendations to simultaneously reduce cardiovascular risk factors such as HbA_{1c} levels, fitness, body composition measures, 2-hour glucose levels, and triglyceride levels. However, the feasibility of such high volumes of exercise can be questioned. In our study, a large portion of participants managed to achieve exercise volumes exceeding current recommendations. Future high-quality randomized trials should be performed to confirm these findings and explore what could be gained by adding an even more controlled diet.

ACKNOWLEDGMENTS

The authors thank all the patients for their participation in the study.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **BMI** = body mass index; **HbA_{1c}** = glycated hemoglobin A_{1c}; **IDES** = Italian Diabetes and Exercise Study; **IQR** = interquartile range; **T2D** = type 2 diabetes

Affiliations: From The Centre of Inflammation and Metabolism and the Centre for Physical Activity Research, Rigshospitalet, (C.S.M., M.Y.J., K.B.H., K.K., B.K.P., M.R.-L.) and CopenRehab, Department of Public Health, (C.S.M., H.L.), University of Copenhagen, Copenhagen, Denmark; Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital (S.M.N., R.C.); AstraZeneca, Early Clinical Development, Cardiovascular, Renal and Metabolic Research, Mölndal, Sweden (A.A.V.); and Department of Human Evolutionary Biology, Harvard University, Cambridge, MA (D.E.L.); Musculoskeletal Statistics Unit, The Parker Institute, Bispebjerg and Frederiksberg Hospital (S.M.N., R.C.), Denmark.

Grant Support: This project was funded by TrygFonden. The Centre for Physical Activity Research is supported by a grant from TrygFonden. Centre for Inflammation and Metabolism/Centre for Physical Activity Research is a member of the Danish Centerfor Strategic Research in Type 2 Diabetes (the Danish Council for Strategic Research, grants 09-067009 and 09-075724). Contour Next glucose monitors were provided by Bayer A/S, Copenhagen, Denmark. This work was also supported by a grant from the Danish Diabetes Academy, which is supported by the Novo Nordisk Foundation (M.R.-L.). The funders had no role in design and conduct of the study; collection, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Potential Competing Interests: Dr Vaag was appointed vice president for AstraZeneca's Translational Research and Early Clinical Development during the completion of the study but remained in the scientific steering committee of this study. Dr Christensen's and Ms Nielsen's employer,

the Parker Institute, Bispebjerg and Frederiksberg Hospital, is supported by core grant OCAY-13-309 from the Oak Foundation; Dr Ried-Larsen received personal speakers fees from Novo Nordisk A/S. No other disclosures were reported.

Correspondence: Address to Christopher S. MacDonald, MSc, Rigshospitalet 7641, The Centre of Inflammation and Metabolism and the Centre for Physical Activity Research, Blegdamsvej 9, DK-2100 Copenhagen, Denmark (chmd@sund.ku.dk).

REFERENCES

1. American Diabetes Association. 6. Obesity management for the treatment of type 2 diabetes. *Diabetes Care*. 2016;39(suppl 1):S47-S51.
2. Huang ES, Brown SE, Ewigman BG, Foley EC, Meltzer DO. Patient perceptions of quality of life with diabetes-related complications and treatments. *Diabetes Care*. 2007;30(10):2478-2483.
3. Nicolucci A, Kovacs Burns K, Holt RI, et al; DAWN2 Study Group. Diabetes Attitudes, Wishes and Needs second study (DAWN2): cross-national benchmarking of diabetes-related psychosocial outcomes for people with diabetes. *Diabet Med*. 2013;30(7):767-777.
4. Espeland MA, Glick HA, Bertoni A, et al; Look AHEAD Research Group. Impact of an intensive lifestyle intervention on use and cost of medical services among overweight and obese adults with type 2 diabetes: the Action for Health in Diabetes. *Diabetes Care*. 2014;37(9):2548-2556.
5. Gregg EW, Chen H, Wagenknecht LE, et al; Look AHEAD Research Group. Association of an intensive lifestyle intervention with remission of type 2 diabetes. *JAMA*. 2012;308(23):2489-2496.
6. Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet*. 2018;391(10120):541-551.
7. Di Loreto C, Fanelli C, Lucidi P, et al. Make your diabetic patients walk: long-term impact of different amounts of physical activity on type 2 diabetes. *Diabetes Care*. 2005;28(6):1295-1302.
8. Umpierre D, Ribeiro PA, Kramer CK, et al. Physical activity advice only or structured exercise training and association with HbA1c levels in type 2 diabetes: a systematic review and meta-analysis. *JAMA*. 2011;305(17):1790-1799.
9. Balducci S, Zanuso S, Nicolucci A, et al; Italian Diabetes Exercise Study (IDES) Investigators. 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.
10. Vancea DM, Vancea JN, Pires MI, Reis MA, Moura RB, Dib SA. Effect of frequency of physical exercise on glycemic control and body composition in type 2 diabetic patients. *Arq Bras Cardiol*. 2009;92(1):23-30.
11. Boule NG, Kenny GP, Haddad E, Wells GA, Sigal RJ. Meta-analysis of the effect of structured exercise training on cardiorespiratory fitness in type 2 diabetes mellitus. *Diabetologia*. 2003;46(8):1071-1081.
12. Umpierre D, Ribeiro PA, Schaan BD, Ribeiro JP. Volume of supervised exercise training impacts glycaemic control in patients with type 2 diabetes: a systematic review with meta-regression analysis. *Diabetologia*. 2013;56(2):242-251.
13. Prince SA, Adamo KB, Hamel ME, Hardt J, Connor Gorber S, Tremblay M. A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review. *Int J Behav Nutr Phys Act*. 2008;5:56.
14. 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.
15. Ried-Larsen M, Christensen R, Hansen KB, et al. Head-to-head comparison of intensive lifestyle intervention (U-TURN) versus conventional multifactorial care in patients with type 2 diabetes: protocol and rationale for an assessor-blinded, parallel group and randomised trial. *BMJ Open*. 2015;5(12):e009764.
16. 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(7):1334-1359.
17. Laptook AR, Shankaran S, Tyson JE, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Effect of therapeutic hypothermia initiated after 6 hours of age on death or disability among newborns with hypoxic-ischemic encephalopathy: a randomized clinical trial. *JAMA*. 2017;318(16):1550-1560.
18. Dmitrienko A, D'Agostino RB Sr. Multiplicity considerations in clinical trials. *N Engl J Med*. 2018;378(22):2115-2122.
19. Hosmer DW, Lemeshow S. *Applied Logistic Regression*. 2nd ed. New York, NY: John Wiley & Sons, Inc; 2000.
20. 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.
21. Wing RR, Hamman RF, Bray GA, et al; Diabetes Prevention Program Research Group. Achieving weight and activity goals among diabetes prevention program lifestyle participants. *Obes Res*. 2004;12(9):1426-1434.
22. Forechi L, Mill JG, Griep RH, Santos I, Pitanga F, Molina M. Adherence to physical activity in adults with chronic diseases: ELSA-Brasil. *Rev Saude Publica*. 2018;52:31.
23. Eaglehouse YL, Venditti EM, Kramer MK, et al. Factors related to lifestyle goal achievement in a diabetes prevention program dissemination study. *Transl Behav Med*. 2017;7(4):873-880.
24. The R Foundation. *R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing*; 2018. https://www.R-project.org/. Accessed September 20, 2019.
25. Bates D, Maechler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. *J Stat Softw*. 2015;67(1):1-48.
26. Ritz C, Baty F, Streibig JC, Gerhard D. Dose-response analysis using R. *PLoS One*. 2015;10(12):e0146021.
27. Colberg SR, Sigal RJ, Fernhall B, et al. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement. *Diabetes Care*. 2010;33(12):e147-e167.
28. 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.
29. Piercy KL, Troiano RP. Physical Activity Guidelines for Americans From the US Department of Health and Human Services. *Circ Cardiovasc Qual Outcomes*. 2018;11(11):e005263.
30. 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(19):2081-2091.
31. Earnest CP, Johannsen NM, Swift DL, Lavie CJ, Blair SN, Church TS. Dose effect of cardiorespiratory exercise on metabolic syndrome in postmenopausal women. *Am J Cardiol*. 2013;111(12):1805-1811.
32. Ross R, de Lannoy L, Stotz PJ. Separate effects of intensity and amount of exercise on interindividual cardiorespiratory fitness response. *Mayo Clin Proc*. 2015;90(11):1506-1514.
33. Madsen LR, Baggesen LM, Richelsen B, Thomsen RW. Effect of Roux-en-Y gastric bypass surgery on diabetes remission and

complications in individuals with type 2 diabetes: a Danish population-based matched cohort study. *Diabetologia*. 2019; 62(4):611-620.

34. 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(9): 880-890.
35. Pedersen BK, Saltin B. Exercise as medicine - evidence for prescribing exercise as therapy in 26 different chronic diseases. *Scand J Med Sci Sports*. 2015;25(suppl 3):1-72.
36. Cade WT. Diabetes-related microvascular and macrovascular diseases in the physical therapy setting. *Phys Ther*. 2008; 88(11):1322-1335.
37. Sacks F, Hermans M, Fioretto P, et al. Association between plasma triglycerides and HDL-cholesterol and microvascular kidney disease and retinopathy in type 2 diabetes: a global case-control study in 13 countries. *Circulation*. 2014;129(9): 999-1008.
38. Church TS, LaMonte MJ, Barlow CE, Blair SN. Cardiorespiratory fitness and body mass index as predictors of cardiovascular disease mortality among men with diabetes. *Arch Intern Med*. 2005;165(18):2114-2120.
39. Hemmingsen B, Lund SS, Gluud C, et al. Intensive glycaemic control for patients with type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. *BMJ*. 2011;343:d6898.
40. Zoungas S, Arima H, Gerstein HC, et al; Collaborators on Trials of Lowering Glucose (CONTROL) group. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials. *Lancet Diabetes Endocrinol*. 2017;5(6):431-437.