

ORIGINAL ARTICLE

Lifestyle Change and Mobility in Obese Adults with Type 2 Diabetes

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ABSTRACT

BACKGROUND

Adults with type 2 diabetes mellitus often have limitations in mobility that increase with age. An intensive lifestyle intervention that produces weight loss and improves fitness could slow the loss of mobility in such patients.

METHODS

We randomly assigned 5145 overweight or obese adults between the ages of 45 and 74 years with type 2 diabetes to either an intensive lifestyle intervention or a diabetes support-and-education program; 5016 participants contributed data. We used hidden Markov models to characterize disability states and mixed-effects ordinal logistic regression to estimate the probability of functional decline. The primary outcome was self-reported limitation in mobility, with annual assessments for 4 years.

RESULTS

At year 4, among 2514 adults in the lifestyle-intervention group, 517 (20.6%) had severe disability and 969 (38.5%) had good mobility; the numbers among 2502 participants in the support group were 656 (26.2%) and 798 (31.9%), respectively. The lifestyle-intervention group had a relative reduction of 48% in the risk of loss of mobility, as compared with the support group (odds ratio, 0.52; 95% confidence interval, 0.44 to 0.63; $P < 0.001$). Both weight loss and improved fitness (as assessed on treadmill testing) were significant mediators of this effect ($P < 0.001$ for both variables). Adverse events that were related to the lifestyle intervention included a slightly higher frequency of musculoskeletal symptoms at year 1.

CONCLUSIONS

Weight loss and improved fitness slowed the decline in mobility in overweight adults with type 2 diabetes. (Funded by the Department of Health and Human Services and others; ClinicalTrials.gov number, NCT00017953.)

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THE GROWING PREVALENCE OF TYPE 2 diabetes mellitus is an ominous health threat in the United States^{1,2} and globally.³ Surveillance data from the Centers for Disease Control and Prevention cite type 2 diabetes as largely a disease of aging,⁴ and its prevalence may escalate as the population gets older.^{5,6} An insidious consequence of aging in persons with type 2 diabetes is physical disability,⁷ particularly the loss of mobility.⁸ Reduced mobility puts patients at risk for loss of independence,⁹ leads to muscle loss (which compromises glucose storage and clearance),¹⁰ and compromises the quality of life.¹¹

With increasing age in the general population, the risk of mobility-related problems increases with the level of obesity¹²⁻¹⁴ and physical inactivity.^{15,16} Equally compelling data show that older adults with type 2 diabetes have twice the prevalence of disability in mobility-related activities, as compared with those without the disease.¹⁷ An increasing body-mass index further increases the risk.¹⁸

The ongoing Look AHEAD (Action for Health in Diabetes) study, a multicenter, randomized, controlled trial enrolling more than 5000 overweight or obese persons with type 2 diabetes, was designed to determine whether intentional weight loss would reduce morbidity and mortality from cardiovascular causes. In this phase of the study, we assigned participants to one of two treatments: an intensive lifestyle intervention or a diabetes support-and-education program to lower and then maintain body weight and improve fitness.¹⁹ We examined the decline in self-reported limitations in mobility during the first 4 years of the study using a multistaged statistical approach^{20,21} and evaluated how the decline in mobility was influenced by the intervention and whether observed differences were mediated by weight loss or an improvement in fitness.

METHODS

STUDY PARTICIPANTS

We enrolled overweight or obese adults between the ages of 45 and 74 years with type 2 diabetes. Major reasons for exclusion included a glycated hemoglobin level of more than 11%, a blood pressure of more than 160/100 mm Hg, a triglyceride level of more than 600 mg per deciliter (6.8 mmol

per liter), inadequate control of coexisting medical conditions, underlying diseases that were likely to limit life span or affect safety, and failure to pass a baseline graded exercise stress test. At baseline, the cohort had deficits in mobility as determined by self-report²² and performance on a treadmill test.²³

Written informed consent was obtained before screening. Further details on the inclusion and exclusion criteria have been reported previously.¹⁹ A diagram showing enrollment and outcomes for the first 4 years of the trial was originally published by Wing et al.²⁴ (Fig. 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

STUDY DESIGN

From 2001 through 2004, we randomly assigned participants to an intensive lifestyle intervention or to a diabetes support-and-education program. Wadden et al.²⁵ have described the key components of the intensive lifestyle intervention (see the study protocol, available at NEJM.org). The two primary goals were to induce a mean weight loss from baseline of more than 7% and to increase the duration of physical activity to more than 175 minutes a week. Diabetes support and education involved three group sessions a year focusing on nutrition, physical activity, and support.

The study was approved by the institutional review board at each participating center, with review by an independent data and safety monitoring board. Data were gathered by staff members who were unaware of study-group assignments.

STATUS ASSESSMENT

Mobility

Mobility was assessed on the basis of 6 of 11 items on the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) Physical Functioning subscale.^{26,27} The items included vigorous activity, such as running and lifting heavy objects; moderate activity, such as pushing a vacuum cleaner or playing golf; climbing one flight of stairs; bending, kneeling, or stooping; walking more than a mile; and walking one block. Participants were assigned a score of 1 on items for which they reported not being limited at all or a score of 0 on items for which they indicated having any limitation.

Weight Loss and Fitness

Weight was assessed at each annual visit, and peak metabolic-equivalent (MET) capacity was estimated from performance on a graded exercise treadmill test²³ administered at baseline, year 1, and year 4. Data for years 2 and 3 were estimated with the use of a carry-forward method. METs were estimated from treadmill speed and elevation with the use of standardized equations.^{23,28}

STATISTICAL ANALYSIS

To analyze the results, we used discrete hidden Markov modeling,^{20,29} which conceptualizes disability as two distinct but parallel processes, a sequence of multiple indicators of disability driven by an underlying sequence of latent states. The state at time “t+1” depends only on the state at time “t” and not on the history before “t.” Thus, hidden Markov modeling produces three sets of estimated measurements. First, the model of the longitudinal data set resulted in a set of disability states, each characterized by scoring on the six mobility criteria. The number of states was determined by a goodness-of-fit criterion.³⁰ Each subject could be classified as a member of any one of the several disability states at any given time point; it was assumed that the number and structure of the states was constant across time. Second, the model provided estimates of the prevalence of each latent state at a given time point. Finally, the model produced estimates for the transition probabilities from one state to another at any given time point except the last state, which is one minus the other probabilities. Technical details are provided in reports by Ip et al.²⁹ and Zhang et al.³¹

The analysis proceeded in two phases. First, we evaluated a main effect of the intervention on the decline in the mobility state. Second, we examined whether weight loss, improved fitness, or both explained this effect. Phase 1 used the cumulative logit mixed-effects regression model for an ordinal outcome with the use of PROC GLIMMIX (SAS). The mixed-effects model accounted for the correlation among observations from the same subject during the 4-year study period with adjustment for the baseline disability status. This model assumes proportional odds, implying that the odds for cumulative logits among disability categories are uniform. Phase 2 followed standard procedures for mediational analysis.^{32,33} All analyses were

performed on an intention-to-treat principle. In cases in which some values were missing, we assumed that the data were missing at random.

RESULTS**STUDY PARTICIPANTS**

Of the 5145 participants who underwent randomization in Look AHEAD, 5016 were included in this analysis. To be included in the analysis, participants had to have data from at least 1 follow-up visit. The rate of loss to follow-up was 0.97%. The characteristics of the participants in the analysis were similar to those of participants in the entire study (Table 1).³⁴

CHANGES IN ENERGY EXPENDITURE

Data from the Paffenbarger Physical Activity Index³⁵ that were collected on a subgroup of subjects confirmed that 1105 participants in the lifestyle-intervention group had a greater increase in the mean (\pm SE) energy expenditure from baseline for leisure-time physical activity than did 1120 participants in the support group. At year 1, the mean increase in energy expenditure was 881.0 ± 48.3 kcal per week in the lifestyle-intervention group and 99.2 ± 39.5 kcal per week in the support group; at year 4, the mean per-week increases in energy expenditure were 357.7 ± 47.1 kcal and 95.9 ± 42.5 kcal, respectively ($P<0.001$ for both comparisons). The average weight loss during this period was far greater in the lifestyle-intervention group than in the support group (6.15% vs. 0.88%, $P<0.001$).²⁴

FOUR STATES OF DISABILITY*Criteria for Each State*

The best-fitting model included nine states of disability (Fig. 2 in the Supplementary Appendix). To render the model more clinically useful, it was reduced to four states that were sequential and progressively ordered from the healthiest to the most severe state of disability (Fig. 1). In state 1 (good mobility), participants were somewhat unable to perform vigorous physical activities. In state 2 (mild mobility-related disability), participants had problems in bending and long-distance walking. In state 3 (moderate mobility-related disability), participants had deficits in many tasks and some deterioration in the ability to climb

Table 1. Baseline Characteristics of the Participants.*

Characteristic	Diabetes Support and Education		Intensive Lifestyle Intervention	
	Current Sample	Complete Sample†	Current Sample	Complete Sample†
No. of participants	2502	2575	2514	2570
Age (yr)	58.9±6.9	58.8±6.9	58.6±6.8	58.6±6.8
Female sex (%)	59.7	59.7	59.4	59.4
Race or ethnic group (%)‡				
Black	15.6	15.7	15.6	15.6
American Indian or Alaska Native	5.1	5.0	5.2	5.1
Asian or Pacific Islander	0.8	0.8	1.2	1.1
White	63.4	63.4	63.0	63.1
Hispanic	13.1	13.2	13.1	13.2
Other	2.0	1.9	2.0	1.9
Weight (kg)	100.9±18.9	100.8±18.8	100.6±19.7	100.5±19.6
Height (cm)	167.2±9.9	167.3±9.9	167.2±9.6	167.2±9.6
Body-mass index§	36.0±5.8	36.0±5.8	35.9±6.0	35.9±6.0
Glycated hemoglobin (%)	7.30±1.19	7.31±1.20	7.25±1.15	7.25±1.15
Cardiovascular fitness¶	7.18±1.99	7.18±1.99	7.20±1.95	7.20±1.95
History of cardiovascular disease (%)	13.4	13.6	14.2	14.4
Hypertension (%)	83.4	84.0	84.5	84.5
Use of medication for diabetes (%)				
Oral	75.3	75.4	76.5	76.5
Insulin	19.1	19.4	18.7	18.7
None	12.2	12.2	12.8	12.8
Knee pain (%)	43.2	43.2	43.0	42.7

* Plus–minus values are means ±SD. There were no significant differences between groups in any category.

† Data for the complete Look AHEAD sample are taken from Bray et al.³⁴

‡ Race or ethnic group was self-reported.

§ Body-mass index is the weight in kilograms divided by square of the height in meters.

¶ The level of cardiovascular fitness is the estimated metabolic-equivalents value from a graded exercise test, with scores ranging from 3.3 to 16.7 and higher scores indicating better cardiovascular fitness.

|| Subjects could have been taking both oral medications and insulin.

stairs and engage in moderately demanding activities. In state 4, participants had severe limitations, with difficulty in nearly all tasks.

Clinical Relevance

Using baseline data, we examined the clinical relevance of the four-state model. Moving from state 1 to state 4, the average body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) increased progressively (33.83, 36.07, 37.39, and 38.79, respectively), as did the number of coexisting medical conditions (1.18, 1.44, 1.70, and 1.84). The estimated maximal MET capacity from state 1 to state 4 decreased linearly (8.16, 7.13, 6.52, and 5.94, respectively), and the ratio of women was disproportionately higher in state 4 than in state 1: although women consti-

tuted 50.0% of the good-mobility category, they constituted 72.0% of the severe-disability category.

RISK OF LOSS OF MOBILITY

Changes in the prevalence of severe disability during the 4-year period differed significantly in the two groups, with a higher proportion of participants in the lifestyle-intervention group who had good mobility than in the support group during all 4 years (Fig. 2). After adjustment for baseline prevalence, numbers of subjects with severe mobility-related disability in the lifestyle-intervention group were 308 of 2514 (12.3%) at 1 year and 517 of 2514 (20.6%) at 4 years, as compared with 474 of 2502 (18.9%) at 1 year and 656 of 2502 (26.2%) at 4 years, respectively, in the support group. At year 4, the prevalence of good mobility

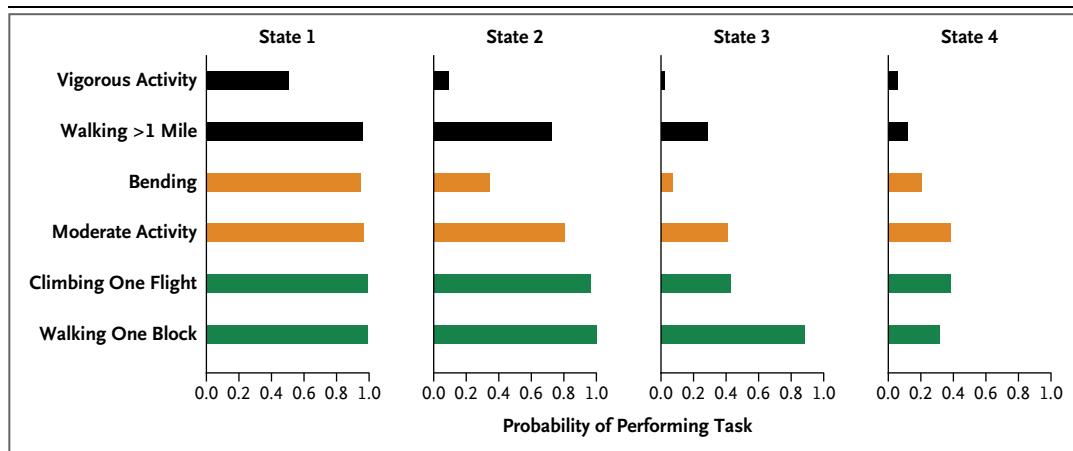


Figure 1. Model of Four States of Clinical Disability.

In state 1 (good mobility), participants had some difficulty in performing vigorous physical activities. In state 2 (mild mobility-related disability), participants had problems in bending and long-distance walking. In state 3 (moderate mobility-related disability), participants had deficits in many tasks and some deterioration in the ability to climb stairs and engage in moderately demanding activities. In state 4 (severe limitations), participants had difficulty in nearly all tasks. In each category, the longer the horizontal bar, the higher the probability that participants could perform that task without difficulty.

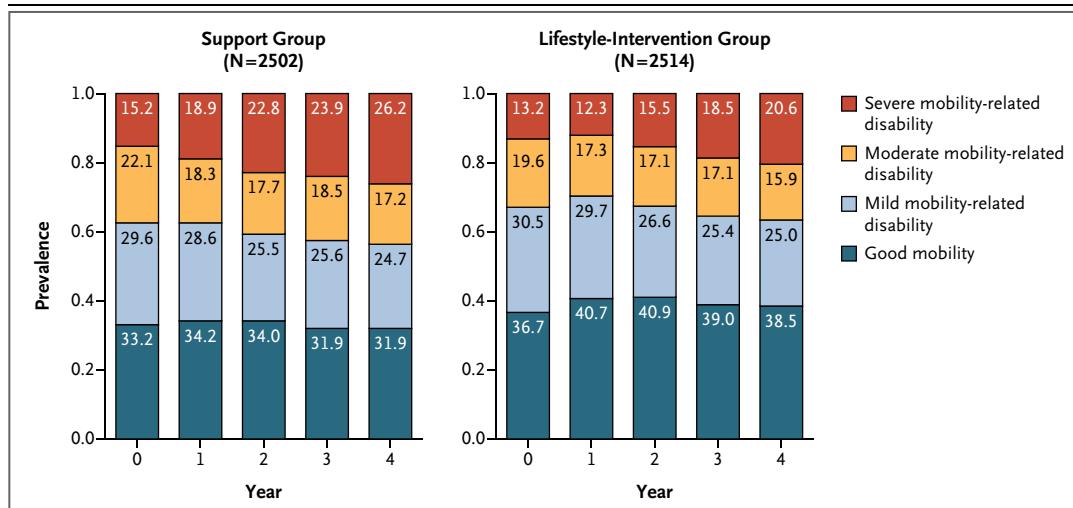


Figure 2. Prevalence of the Four States of Clinical Disability during the 4-Year Study.

The numbers in each color block are the percentages of participants at each state of mobility-related disability among those receiving diabetes support and education and those receiving an intensive lifestyle intervention. Values at follow-up visits for years 1 to 4 have been adjusted for baseline values.

was 38.5% in the lifestyle-intervention group, as compared with 31.9% in the support group. When expressed as a summary odds ratio, participants in the lifestyle-intervention group had a 48% reduction in mobility-related disability, as compared with those in the support group (odds ratio, 0.52; 95% confidence interval, 0.44 to 0.63; $P < 0.001$).

TEST OF MEDIATION

Table 2 provides the steps in the test for mediation,³² with results presented as odds ratios or percentages with lower and upper limits. Step A established that the intensive lifestyle intervention resulted in significant weight loss and improved fitness during the 4-year study period, whereas step B showed that loss of weight and improved fitness

Effect	Value	Lower Limit	Upper Limit	P Value
Effect of intervention on risk of loss of mobility: base model (odds ratio)	0.52	0.44	0.63	<0.001
Step A: Effect of intervention on weight loss and improved fitness (%)				
Effect of intervention on weight loss	5.4	5.0	5.8	<0.001
Effect of intervention on improved fitness	11.9	10.6	13.1	<0.001
Step B: Effect of weight loss and improved fitness on mobility (odds ratios)				
Effect of weight loss on mobility	0.99	0.98	0.99	<0.001
Effect of improved fitness on mobility	1.08	1.07	1.09	<0.001
Step C: Effect of weight loss, improved fitness, and intervention on mobility (odds ratios)				
Effect of weight loss on mobility	0.93	0.92	0.94	<0.001
Effect of improved fitness on mobility	0.99	0.98	0.99	<0.001
Effect of intervention on mobility	0.82	0.68	1.00	0.049

* The three steps in the test for mediation were designed to show which aspects of the lifestyle intervention were the drivers of improved mobility, as compared with diabetes support and education. Step A illustrates that the intensive lifestyle intervention resulted in a relative reduction of 5.4% in weight and a relative improvement of 11.9% in fitness, whereas the odds ratio in step B shows that both weight loss and fitness were related to improved mobility status. The odds ratios in step C show that when changes in weight and fitness were included in a model with treatment and mobility, the intervention effect was marginally significant, suggesting that the protective effect of the intervention on change in disability status was almost totally explained by weight loss and improved fitness.

both resulted in a lower risk of loss of mobility ($P < 0.001$). In step C, loss of weight and improved fitness were included in the base model with the intervention effect. Both loss of weight and improved fitness were significant mediators for the effect of the lifestyle intervention on slowing the loss of mobility ($P < 0.001$). Moreover, the magnitude of the effect of weight loss was larger than that of improvement in fitness.

Both mediation effects were highly significant, as verified by means of a Sobel test ($P < 0.001$) (Fig. 3). In this model, for every relative reduction of 1% in weight and relative improvement of 1% in fitness, the risk of the loss of mobility was reduced by 7.3% and 1.4%, respectively.

ADVERSE EVENTS

An examination of symptoms that were pertinent to increased exercise behavior revealed few between-group differences. There was a slightly higher incidence of pulled or strained muscles reported by participants in the lifestyle-intervention group than in the support group (18.6% vs. 15.7%, $P = 0.006$) but only at year 1 (Table 1 in the Supplementary Appendix).

DISCUSSION

Among overweight and obese adults with type 2 diabetes, an intensive lifestyle intervention led to a relative reduction of 48% in the severity of mobility-related disability, as compared with diabetes support and education. This effect was mediated by both weight loss and improvement in fitness. Group differences that favored the lifestyle-intervention group were most striking in the severe-disability category. However, as shown by prevalence rates in the good-mobility category during all 4 years of the study, participants in the lifestyle-intervention group also retained higher levels of healthy functioning than those in the support group. The proportion of participants with the highest level of functioning at baseline in the support group was generally stable until year 3 and then declined. By contrast, in the lifestyle-intervention group, there was an increase in the prevalence in the good-mobility category by year 2, and rates never fell below baseline. Difficulty in bending over was a harbinger for the loss of mobility, possibly because older adults who have difficulty with such movement are at risk for being sedentary. Deficits

in mobility are a risk factor for the onset and progression of most chronic diseases, including cardiovascular disease.³⁶ Mobility is an important component of quality of life,²² and severe mobility-related disability increases rates of institutionalization.³⁷

The role of weight loss and improved fitness in reducing rates of mobility-related disability is underscored by the mediation analysis.³² Although weight loss was slightly more influential in preventing the loss of mobility than was improved fitness, both factors contributed independently to the observed effect. One plausible explanation for this pattern is that weight loss may improve relative strength in the lower limbs and even facilitate balance, two components of fitness that are important to mobility.³⁸ Not surprisingly, weight loss was found to be related to dietary adherence. Wadden et al.³⁹ recently reported that participants in the lifestyle-intervention group who lost at least 10% of their initial weight at the 4-year assessment consumed fewer calories than those who gained weight ($P < 0.001$). The mean daily caloric intake of participants who lost at least 10% of their initial weight was 1565.5 kcal, a value that is consistent with the intervention goals.³⁹

Our findings support other 4-year analyses of data from the Look AHEAD study that attest to the long-term efficacy of the intensive lifestyle intervention on weight loss, increased fitness, and improvement in the risk profile for cardiovascular disease.²⁴ Although the current findings may seem limited in light of this previous work and related reports that are based on 1-year data,^{40,41} these are the first data from Look AHEAD to show that the intensive lifestyle intervention also reduced the risk of loss of mobility. This is an important finding for clinical medicine, given the importance of disability in patients with type 2 diabetes⁸ and the fact that the prevalence of type 2 diabetes will increase as the population ages.^{5,6} The findings also reinforce results from related research. For example, an 18-month study involving older, overweight or obese adults with knee osteoarthritis showed that a combined treatment of weight loss and exercise was superior to either exercise or diet alone in improving measures of disability.⁴² In a 12-month study involving older adults with mild-to-moderate frailty, Villareal and colleagues³⁸ recently reported that exercise and weight loss each reduced rates of physical disability, as compared with a control intervention that was restricted to

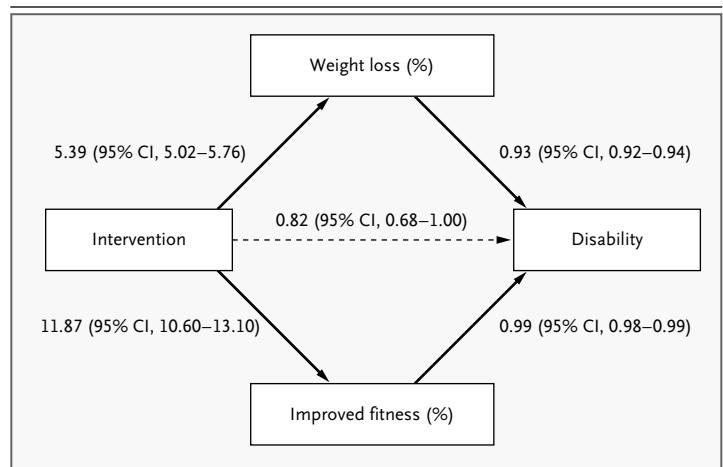


Figure 3. Path Diagram for Mediation Model.

The four solid arrows represent significant indirect effects, and the dashed arrow represents a marginally significant direct effect of the intervention on mobility after adjustment for the mediators. The coefficients and 95% confidence intervals are positioned at the middle of each arrow; those on the arrows leading from the intervention to each mediator represent the percent weight loss and fitness improvement owing to the intervention. The coefficients for the effect that weight loss and improved fitness had on disability show that for every 1% loss in weight there was a 7.3% reduction in the odds ratio for disability $[(1.00 - 0.927) \times 100]$, and for every 1% improvement in fitness $[(1.00 - 0.986) \times 100]$, the odds ratio was reduced by 1.4%.

the provision of general information about a healthy diet, but the combination of the two interventions was superior to either one alone. Finally, an 18-month weight-management and exercise study among older, overweight or obese adults with metabolic dysfunction compared the effects of three treatments (exercise only, weight loss plus exercise, and successful-aging education) on the results of a 400-m walk test. Exercise benefited mobility, as compared with successful-aging education, but the most favorable effect occurred when participants lost weight in conjunction with exercise.⁴³

In summary, our findings confirm the clinical importance of declining mobility as adults with type 2 diabetes age. Although our measure of mobility was not based on performance, it had considerable clinical relevance with expected relationships to BMI, coexisting illnesses, baseline estimated metabolic equivalents, and sex. Furthermore, both weight loss and improved fitness were determinants of this effect.

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REFERENCES

- Engelgau MM, Geiss LS, Saaddine JB, et al. The evolving diabetes burden in the United States. *Ann Intern Med* 2004;140:945-50.
- Boyle JP, Thompson TJ, Gregg EW, Barker LE, Williamson DF. Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality, and prediabetes prevalence. *Popul Health Metr* 2010;8:29.
- Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004;27:1047-53.
- Centers for Disease Control and Prevention. Percentage of civilian, non-institutionalized population with diagnosed diabetes, by age, United States, 1980-2010 (<http://www.cdc.gov/diabetes/statistics/prevnational/figbyage.htm>).
- Boyle JP, Honeycutt AA, Narayan KM, et al. Projection of diabetes burden through 2050: impact of changing demography and disease prevalence in the U.S. *Diabetes Care* 2001;24:1936-40.
- Cowie CC, Rust KF, Byrd-Holt DD, et al. Prevalence of diabetes and impaired fasting glucose in adults in the U.S. population: National Health and Nutrition Examination Survey 1999-2002. *Diabetes Care* 2006;29:1263-8.
- Gregg EW, Beckles GL, Williamson DF, et al. Diabetes and physical disability among older U.S. adults. *Diabetes Care* 2000;23:1272-7.
- Gregg EW, Gerzoff RB, Caspersen CJ, Williamson DF, Narayan KM. Relationship of walking to mortality among US adults with diabetes. *Arch Intern Med* 2003;163:1440-7.
- Fried LP, Bandeen-Roche K, Chaves PH, Johnson BA. Preclinical mobility disability predicts incident mobility disability in older women. *J Gerontol A Biol Sci Med Sci* 2000;55:M43-M52.
- Park SW, Goodpaster BH, Lee JS, et al. Excessive loss of skeletal muscle mass in older adults with type 2 diabetes. *Diabetes Care* 2009;32:1993-7.
- Rejeski WJ, Focht BC, Messier SP, Morgan T, Pahor M, Penninx B. Obese, older adults with knee osteoarthritis: weight loss, exercise, and quality of life. *Health Psychol* 2002;21:419-26.
- Koster A, Patel KV, Visser M, et al. Joint effects of adiposity and physical activity on incident mobility limitation in older adults. *J Am Geriatr Soc* 2008;56:636-43.
- Lang IA, Llewellyn DJ, Alexander K, Melzer D. Obesity, physical function, and mortality in older adults. *J Am Geriatr Soc* 2008;56:1474-8.
- Rejeski WJ, Marsh AP, Chmelo E, Rejeski JJ. Obesity, intentional weight loss and physical disability in older adults. *Obes Rev* 2010;11:671-85.
- LaCroix AZ, Guralnik JM, Berkman LF, Wallace RB, Satterfield S. Maintaining mobility in late life. II. Smoking, alcohol consumption, physical activity, and body mass index. *Am J Epidemiol* 1993;137:858-69.
- Miller ME, Rejeski WJ, Reboussin BA, Ten Have TR, Ettinger WH. Physical activity, functional limitations, and disability in older adults. *J Am Geriatr Soc* 2000;48:1264-72.
- Gregg EW, Beckles GL, Williamson DF, et al. Diabetes and physical disability among older U.S. adults. *Diabetes Care* 2000;23:1272-7.
- Imai K, Gregg EW, Chen YJ, Zhang P, de Rekeneire N, Williamson DF. The association of BMI with functional status and self-rated health in US adults. *Obesity (Silver Spring)* 2008;16:402-8.
- Ryan DH, Espeland MA, Foster GD, et al. Look AHEAD (Action for Health in Diabetes): design and methods for a clinical trial of weight loss for the prevention of cardiovascular disease in type 2 diabetes. *Control Clin Trials* 2003;24:610-28.
- MacDonald IL, Zucchini W. Hidden Markov and other models for discrete-valued time series. London: Chapman and Hall, 1997.
- Rejeski WJ, Ip EH, Marsh AP, Zhang Q, Miller ME. Obesity influences transitional states of disability in older adults with knee pain. *Arch Phys Med Rehabil* 2008;89:2102-7.
- Rejeski WJ, Lang W, Neiberg RH, et al. Correlates of health-related quality of life in overweight and obese adults with type 2 diabetes. *Obesity (Silver Spring)* 2006;14:870-83.
- Ribisl PM, Lang W, Jaramillo SA, et al. Exercise capacity and cardiovascular/metabolic characteristics of overweight and obese individuals with type 2 diabetes: the Look AHEAD clinical trial. *Diabetes Care* 2007;30:2679-84.
- Wing RR, Bahnson JL, Bray GA, et al. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus four-year results of the Look AHEAD trial. *Arch Intern Med* 2010;170:1566-75.
- Wadden TA, West DS, Delahanty L, et al. The Look AHEAD study: a description of the lifestyle intervention and the evidence supporting it. *Obesity (Silver Spring)* 2006;14:737-52.
- Ware JE, Keller SD, Hatoum HT, Kong SXD. The SF-36 Arthritis-Specific Health Index (ASHI). I. Development and cross-validation of scoring algorithms. *Med Care* 1999;37:MS40-MS50.
- Bruce B, Fries JF, Ambrosini D, et al. Better assessment of physical function: item improvement is neglected but essential. *Arthritis Res Ther* 2009;11:R191.
- American College of Sports Medicine. ASCM's guidelines for exercise testing and prescription. 7th ed. Philadelphia: Lippincott Williams & Wilkins, 2006.
- Ip EH, Snow Jones A, Heckert DA, Zhang Q, Gondolf ED. Latent Markov model for analyzing temporal configuration for violence profiles and trajectories in a sample of batterers. *Sociol Methods Res* 2010;39:222-55.
- Schwartz G. Estimating the dimensions of a model. *Ann Stat* 1978;6:461-4.
- Zhang Q, Snow Jones A, Rijmen F, Ip EH. Multivariate discrete hidden Markov

- models for domain-based measurements and assessment of risk factors in child development. *J Comput Graph Stat* 2010; 19:746-65.
32. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol* 1986;51:1173-82.
33. MacKinnon DP. Introduction to statistical mediation analysis. New York: Lawrence Erlbaum Associates, 2008.
34. Bray G, Gregg E, Haffner S, et al. Baseline characteristics of the randomised cohort from the Look AHEAD (Action for Health in Diabetes) study. *Diab Vasc Dis Res* 2006;3:202-15.
35. Paffenbarger RS Jr, Wing AL, Hyde RT. Physical activity as an index of heart attack risk in college alumni. *Am J Epidemiol* 1978;108:161-75.
36. Mensah GA, Brown DW. An overview of cardiovascular disease burden in the United States. *Health Aff (Millwood)* 2007; 26:38-48.
37. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol* 1994;49:M85-M94.
38. Villareal DT, Chode S, Parimi N, et al. Weight loss, exercise, or both and physical function in obese older adults. *N Engl J Med* 2011;364:1218-29.
39. Wadden TA, Neiberg RH, Wing RR, et al. Four-year weight losses in the Look AHEAD study: factors associated with long-term success. *Obesity (Silver Spring)* 2011; 19:1987-98.
40. Jakicic J, Jaramillo S, Balasubramanyam A, et al. Effect of a lifestyle intervention on change on cardiorespiratory fitness in adults with type 2 diabetes: results from the Look AHEAD Study. *Int J Obes (Lond)* 2009;33:305-16.
41. Williamson D, Rejeski WJ, Lang W, Van Dorsten B, Fabricatore A, Toledo K. Impact of a weight management program on health-related quality of life in overweight adults with type 2 diabetes. *Arch Intern Med* 2009;169:163-71.
42. Messier SM, Loeser RF, Miller GD, et al. Exercise and dietary weight in overweight and obese older adults with knee osteoarthritis: the Arthritis, Diet, and Activity Promotion Trial. *Arthritis Rheum* 2004;50:1501-10.
43. Rejeski W, Brubaker P, Goff DC Jr, et al. Translating weight loss and physical activity programs into the community to preserve mobility in older, obese adults in poor cardiovascular health. *Arch Intern Med* 2011;171:880-6.

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