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Impact of an 8-Year Intensive Lifestyle Intervention on an Index of Multimorbidity

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Abstract

Background/Objectives.—Type 2 diabetes and obesity are sometimes described as conditions that accelerate aging. Multidomain lifestyle interventions have shown promise to slow the accumulation of age-related diseases, a hallmark of aging. However they have not been assessed among at-risk individuals with these two conditions. We examined the relative impact of eight years of a multidomain lifestyle intervention on an index of multimorbidity.

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Author contributions

All authors have made substantial contributions to the manuscript. MAE conceived the manuscript, chaired the writing group, and drafted the manuscript. SAG and JB developed data sets, conducted analyses, and drafted sections. EV, WCK, FRS, HPH, KCJ, MNM, MC, and XP-S critically reviewed and edited text.

Conflict of interest

The authors report no relevant conflicts of interest.

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TITLE FOR SUPPLEMENTAL MATERIAL

Details on construction of the multimorbidity index and approaches to analysis (Supplement S1), results from analyses excluding death as a component of the multimorbidity index (Supplement S2), and a listing of the Look AHEAD study group (Supplement S3)

Design.—Randomized controlled clinical trial comparing an intensive lifestyle intervention (ILI) that targeted weight loss through caloric restriction and increased physical activity, with a control condition of diabetes support and education (DSE)

Setting.—Sixteen US academic centers

Participants.—5,145 volunteers, ages 45–76 years, with established type 2 diabetes mellitus and overweight or obesity who met eligibility criteria for a randomized controlled clinical trial

Measurements.—A multimorbidity index that included nine age-related chronic diseases and death was tracked over eight years of intervention delivery.

Results.—Among individuals assigned to DSE, the multimorbidity index scores increased by an average [95% confidence interval] of 0.98 [0.94,1.02] over eight years, compared to 0.89 [0.85,0.93] among those in the multidomain ILI, which was a 9% difference ($p=0.003$). Relative intervention effects were similar among individuals grouped by baseline body mass index, age, and sex and were greater for those with lower levels of multimorbidity index scores at baseline.

Conclusions.—Increases in multimorbidity over time among adults with overweight or obesity and type 2 diabetes may be slowed by multidomain intensive lifestyle intervention.

Keywords

Multidomain intervention; Type 2 diabetes mellitus; Obesity; Aging

INTRODUCTION

A hallmark of aging is the accumulation of age-related chronic diseases. These often co-occur with disabilities and geriatric syndromes. Their cumulative incidence is accelerated among individuals facing compressed health spans and poorer quality of late-life.^{1,2}

Two-thirds of U.S. Medicare beneficiaries have two or more chronic diseases, and the 14% who have six or more diseases account for 47% of total Medicare spending.³ Health care for these patients is clinically challenging because guidelines for individual conditions can conflict, treatment priorities can be difficult to establish, and the effectiveness of individual drugs may be altered.^{4,5}

Multimorbidity, most commonly defined as the presence of two or more age-related chronic diseases,^{6,7} is predictive of functional limitations, disability, increased health care use, and mortality.^{8,9} Increases in multimorbidity, i.e. accrual of additional chronic diseases, is recommended as an important targeted outcome for clinical trials,^{10–12} and some have viewed it as a marker for biological aging.^{13,14}

There is evidence that lifestyle interventions may slow increases in multimorbidity. For example, the FINGER randomized controlled trial of a multidomain lifestyle intervention to increase physical activity, improve diet, promote cognitive stimulation, and monitor cardiometabolic risk factors in persons aged 60–77 years reported that a two-year intervention was associated with a 67% reduction [95% confidence interval 13%–87%] in

the incidence of three or more age-related chronic diseases among individuals with at least one chronic disease at baseline.¹⁵

We examined whether a multidomain lifestyle intervention was beneficial in adults with diabetes and overweight or obesity, who are thought to be at risk for accelerated biological aging.^{16–18} We used data from the Action for Health in Diabetes (Look AHEAD) randomized controlled clinical trial to assess whether eight years of multidomain, intensive lifestyle intervention (ILI) that targeted weight loss through reduced energy intake and increased physical activity. We examined whether this intervention, compared with a control condition of diabetes support and education (DSE), slowed increases in a multimorbidity index.

METHODS

The design and methods of Look AHEAD have been published previously,^{19,20} as have its CONSORT diagram and primary results.²⁰ It was a randomized controlled trial that recruited 5,145 individuals (during 2001 to 2004) with overweight or obesity and type 2 diabetes. At enrollment, participants were ages 45–76 years and had body mass index (BMI) >25 kg/m² (>27 kg/m² if on insulin), glycated hemoglobin (HbA1c) $<11\%$, systolic/diastolic blood pressure $<160/100$ mmHg, and triglycerides <600 mg/dl, per protocol. Prior to enrollment, each prospective participant completed a two-week run-in, successfully recording information each day about diet and physical activity, and passed a maximal exercise stress test. In addition, each potential participant met with a behavioral psychologist or interventionist to confirm understanding of intervention requirements and to exclude those with significant competing life stressors or other issues (severe depression, alcohol abuse) that might impair adherence. Volunteers were recruited by use of registries, mailings, radio and television, websites, referrals and printed media.²¹

Participants provided written informed consent. Local Institutional Review Boards approved the protocol.

Interventions

The multidomain ILI targeted reducing caloric intake (1200–1800 based on initial weight) and increasing physical activity (>175 minutes per week through activities similar in intensity to brisk walking) to induce weight loss to average 7% at Year 1 and maintain this throughout follow-up.²² It also targeted improved diet ($<30\%$ calories from fat, $<10\%$ calories from saturated fat, 15% calories from protein) and provided annual monitoring of cardiometabolic risk factors (lipids, HbA1c, and blood pressure). During the first six months of ILI, participants attended three group meetings and one individual session per month. For the remainder of the first year, participants were provided two group and one individual meetings per month. During months 13–48, participants attended monthly individual meetings that were followed approximately 14 days later with phone calls or e-mails from interventionists. Optional monthly group meetings were also offered during these latter years. After this, ILI participants were encouraged to continue individual monthly sessions and annual campaigns were used to promote maintenance of weight loss. The intervention stressed self-monitoring of caloric intake and physical activity, use of liquid meal

replacements and other portion controlled approaches, and attendance at intervention sessions.²³

DSE participants were invited to attend three group sessions each year, which focused on diet, physical activity, and social support.²⁴ They did not receive specific diet, activity, or weight goals or information on behavioral strategies to lose weight but had similar cardiometabolic risk factor monitoring as ILI participants.

Interventions were terminated September, 2012. We use data accumulated during up to eight years of annual follow-up (see Supplement S1 for details), when intervention delivery was ongoing for all participants (the minimum time between randomization and intervention cessation among participants was 8.4 years).

Multimorbidity Index

As noted by Barnett, et al., “No standard approach for the measurement of multimorbidity exists, and selection and definition of multimorbidities to include is inevitably partly subjective and dependent on the data available.”²⁵ The composition of and protocols for published multimorbidity indices vary greatly.^{25–27} To construct our index, we started with the list of 20 chronic diseases developed by the United States Department of Health and Human Services.⁴ This list includes nine conditions ascertained at baseline and follow-up by Look AHEAD: cancer, cardiac arrhythmia, chronic kidney disease, congestive heart failure, coronary artery disease, depression, dyslipidemia, hypertension, and stroke. We excluded diabetes, which was common to all participants. The remaining chronic diseases from this list that we were not able to include (i.e. were not ascertained at baseline and during the first eight years of follow-up on all Look AHEAD participants) were: arthritis, asthma, autism, chronic obstructive pulmonary disease, dementia, hepatitis, human immunodeficiency virus, osteoporosis, schizophrenia, and substance abuse. Thus, the multimorbidity index we use is less inclusive than some used in other studies.

We added all-cause death as a component to our multimorbidity index. Death is often not included in such indices. However, excluding it introduces problems with differential censoring, and once it occurs, this precludes further increases in the multimorbidity index. We examined the impact of excluding death from the index in sensitivity analyses.

We used definitions of multimorbidity index components that were consistent and based on available data at baseline and during follow-up. Because some baseline conditions were drawn from self-report (i.e. not centrally adjudicated using medical records), we also used self-report of these during follow-up. Cardiac arrhythmia at baseline was based on self-reported medical history and during follow-up it was based on spontaneous report of an adverse event. At baseline and during follow-up (every six months), cancer, congestive heart failure, coronary heart disease (myocardial infarction, coronary artery bypass grafting, or angina), and stroke were queried. Serum for laboratory analyses was collected annually through Year 4 and every other year thereafter and was used to assess low density lipoprotein cholesterol (LDL-C) and estimate glomerular filtration rate (eGFR). Medication use was assessed annually. Chronic kidney disease at baseline and follow-up was based on eGFR <60 ml/min/1.73m².²⁸ Dislipidemia was defined as LDL-C concentrations ≥ 100

mg/dl and/or use of a lipid lowering medication. At each annual visit through Year 4, and then again at Year 8, participants completed the Beck Depression Inventory (BDI),²⁹ a self-report scale with reliable psychometric characteristics across clinical and nonclinical populations. Look AHEAD has adopted a BDI score ≥ 10 and/or treatment with antidepressant medications as a marker of depression symptomatology.³⁰ Hypertension was assessed annually, defined as systolic blood pressure (SBP) and diastolic blood pressure (DBP) $\geq 140/90$ mmHg and/or use of antihypertensive medications. Death was based on proxy reports, augmented with searches of the National Death Index and obituaries. Data were obtained by trained, certified staff who were masked to intervention assignment.

We distinguish between diseases based on medical history at baseline (cardiac arrhythmia, chronic kidney disease, congestive heart failure, coronary artery disease, and stroke) and those based on current status for which we had no information on their history at baseline (depression, dyslipidemia, and hypertension). For consistency, for diseases based on self-reported history, once history was reported, it was recorded as present at all future visits. However, diseases based on current status at baseline were allowed to reverse if criteria were no longer met during follow-up. Greater detail appears in Supplement S1.

Our multimorbidity index is conceptually different than the deficit accumulation frailty index that we have examined previously in Look AHEAD.³¹ Frailty indices are typically constructed of 30 or more components reflecting age-related deficits in health and functional outcomes and serve as a phenotype for individual's aging-related health status.³² The multimorbidity index reflects an individual's age-related disease status, and most individuals with multimorbidity are not phenotypically frail.³³

Baseline risk factors

Weight and height were measured in duplicate using a calibrated digital scale and stadiometer. Blood pressure was also measured in duplicate using a standardized automated device. Other self-reported characteristics and conditions were assessed using standardized questionnaires and interviews by trained and certified staff. Blood specimens for measuring HbA1c were assessed with standard laboratory procedures.

Statistical analysis

Participants were analyzed by intervention assignment, regardless of adherence. Differences in mean eight-year changes in the multimorbidity index from baseline, for those with at least some follow-up, were based on analyses of covariance with adjustment for clinical site. The consistency of mean differences among the subgroups based on sex and baseline BMI, age, and multimorbidity index was assessed by adding interaction terms to this basic model. We assessed the impact of death on results by repeating analyses, excluding it from the multimorbidity index. Analyses were performed using SAS version 9.4 (SAS Institute, Inc. Cary, NC).

RESULTS

Table 1 demonstrates the balance afforded by randomization for the two study arms at baseline with respect to risk factors and the prevalence of the individual components of the multimorbidity index.

As seen in Table 2, by Year 8 the multimorbidity score means had increased in both intervention groups. The mean [95% confidence interval] increase was 0.97 [0.94,1.07] in the DSE group and 0.89 [0.85,0.93] in the ILI group ($p=0.003$). Figure 1 portrays how increases unfolded during the eight years, with differences between groups increasing steadily during the first four years, when the ILI was most intensively delivered, and remaining fairly parallel thereafter.

At Year 8, among DSE participants the multimorbidity index had decreased from baseline for 4.9% of participants, remained unchanged for 31.8% of participants, and increased for 63.3% of participants. Among ILI participants these rates were 4.8% decreased, 35.7% unchanged, and 59.5% increased, $p<0.001$.

Figure 2 portrays how each of multimorbidity index component changed from baseline to Year 8. Incremental relative differences favoring the ILI group were seen for most components. The most prominent differences (based on a nominal $p<0.05$, unadjusted for multiple comparisons) favoring ILI were for chronic kidney disease ($p=0.04$) and hypertension ($p=0.005$). The only chronic diseases observed to increase more among ILI versus DSE participants were cardiac arrhythmia and cancer, but these differences were not significant ($p=0.38$ and $p=0.82$, respectively).

Figure 3 portrays the consistency of differences between intervention groups for the pre-specified subgroups based on sex and baseline BMI, age, and multimorbidity index score. There was little evidence that the intervention effects on the multimorbidity index differed by baseline sex or BMI. The strongest subgroup difference we saw was for ILI to be most effective in reducing increases in the multimorbidity index for participants with lower baseline scores (interaction $p=0.07$ for differences among classes; $p=0.03$ for multimorbidity index score groups as an ordinal variable).

Through Year 8, 157 (6.1%) of DSE participants and 136 (5.3%) of ILI participants had died. To assess the impact of death, we repeated analyses removing deaths from the multimorbidity index and censoring follow-up at the time of death. As seen in Supplement S2, this had little overall impact on findings: the ILI group had lower mean eight-year increases in the multimorbidity index, with mean difference 0.08 [0.02,0.13], $p=0.006$.

DISCUSSION

Our analyses of how eight-year increases in a multimorbidity index differed between ILI and DSE groups yielded three principal findings. First, over the course of eight years the index increased by an average of 0.98 among DSE participants. Second, random assignment to ILI, relative to DSE, significantly slowed this increase with the benefits accruing over the first four years of the intervention and being maintained thereafter. These benefits reflected

incremental advantages over most components of the multimorbidity index we examined, with the most pronounced contributions from chronic kidney disease, hypertension, and dyslipemia. Third, there were not significant differences in the magnitude of ILI benefits on the multimorbidity index among subgroups based on baseline BMI, age, or sex, however there was a graded relationship for more benefit of ILI for individuals who had lower baseline multimorbidity index scores.

Rate of increases in the multimorbidity index

The rate that a multimorbidity index increases over time varies depending on its components, the cohort's level of risk, and how conditions are reported. For example, Espeland, et al. drew data from three large cohorts to assess multimorbidity indices comprised of up to 13 conditions: Alzheimer's disease, arthritis (rheumatoid arthritis or osteoarthritis), atrial fibrillation, cancer (excluding non-melanoma skin cancer), cardiovascular disease, congestive heart failure, depression (treated), diabetes, emphysema/chronic bronchitis, kidney dialysis, osteoporosis, stroke, and death.¹⁴ Included were the Health and Retirement Study (HRS) cohort (which assessed 12 of the above conditions), the Rochester Epidemiology Project (REP) cohort (which assessed 10 conditions), and the Women's Health Initiative (WHI) cohort (which assessed 13 conditions).^{34–36} Increases in multimorbidity indices over time tended to be greater among males and older individuals and were highest for the REP study, which used electronic medical records rather than self-report and/or central adjudication to ascertain events. Averaged across sexes and ages 65–79, these were 0.11/year for REP, 0.07/year for HRS, and 0.04/year for the all-female WHI during six years of follow-up. In the InCHIANTI cohort of community-living adults aged 60 years and greater, multimorbidity based on 15 conditions increased by approximately 0.18/year among those with overweight and 0.25/year among those with obesity over 9 years of follow-up.⁶ In the FINGER clinical trial of community-dwelling adults ages 60–77 years, an 11-component multimorbidity index increased an average of 0.29/year across two years in the control group and 0.23/year in the intervention group.¹⁵ Thus the rate seen in the Look AHEAD cohort, e.g. 0.12/year across 10 components, most closely approximates those of the REP, but likely are influenced by the eligibility criteria, assessment schedule, self-report, components contributing to the multimorbidity index, and expected increased risks associated with diabetes and overweight/obesity.

Impact of intensive lifestyle intervention on multimorbidity index scores

At Year 8, participants assigned to ILI averaged a 9% lower increase in multimorbidity index scores compared with those assigned to DSE, corresponding roughly to about one year's average increase for the cohort. This resembles the relatively 19% slower rate reported for the FINGER multidomain lifestyle intervention over two years.¹⁵ Together, these results provide important evidence that lifestyle interventions are powerful tools to increase healthspans.

We are aware of no other clinical trials that have reported benefit from a weight loss intervention towards slowing increases in multimorbidity. However, the planned Targeting Aging with Metformin (TAME) trial is designed to assess whether metformin may achieve similar results and to test whether multimorbidity may be an outcome potentially accepted

by the US Federal Drug Administration for a drug indication.^{37,38} As seen in Figure 2, there is some evidence for heterogeneity in intervention effects among components of the multimorbidity index. This may arise from random variability across relatively small numbers of events, however it may also be that multiple mechanisms may be involved through which ILI may differentially affect diseases.

Heterogeneity of intervention effects

The benefit provided by ILI on multimorbidity index scores was statistically similar for participants grouped by sex, BMI, and age. Earlier, Look AHEAD reported that the ILI intervention benefits were relatively greater among older participants for expected disability-free life years,³⁹ total health care costs,⁴⁰ and a marker of age-related health status, a deficit accumulation frailty index.³¹ Older, compared with younger, ILI participants achieved greater average changes in BMI and comparable increases in fitness.⁴¹

The strongest evidence for heterogeneity in intervention effects was seen when participants were grouped by baseline levels of multimorbidity index scores, with relative benefits (i.e. 95% confidence intervals excluding zero) for individuals with scores of 0–1 at baseline, but no evidence for relative benefits for those with greater burdens of disease. It appears, thus, that for the greatest benefit, lifestyle intervention should be delivered to individuals before they encounter significant levels of chronic disease multimorbidity.

Strengths and limitations

We note several important strengths of our study, including the randomized, controlled study design, the large size and diversity of our cohort, the high rates of retention, and the standardized protocol for outcomes assessment. We also note some limitations. As volunteers for a clinical trial of weight loss and meeting its eligibility criteria, Look AHEAD participants may not reflect more general clinical populations of individuals with overweight or obesity and type 2 diabetes. Many of the components of the multimorbidity index we have included are based on self-report and thus may be of variable reliability. While data were collected by staff masked to intervention assignment, it is possible that participation in the Look AHEAD interventions may have differentially affected self-reporting. It is possible that the interventions differentially affected health care or follow-up, which might bias our findings, however we found no evidence for the latter. The multimorbidity index was not a pre-specified outcome for the Look AHEAD trial, and thus our analyses should be viewed as exploratory.

Summary

Multidomain intensive lifestyle interventions hold promise as potentially powerful approaches to improve later-life health and reduce the burdens of multimorbidity for individuals with overweight or obesity and type 2 diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Representatives from the National Institutes of Health collaborated on the design, conduct, and analysis of the study and the decision to submit the manuscript for publication.

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Figure 1: Changes in multimorbidity index scores from baseline: mean ($\pm$ standard deviation) by intervention assignment across eight years. Differences between intervention groups at Year 8 are statistically significant ($p < 0.001$).

Figure 2:
Changes in individual multimorbidity index components at Year 8 by intervention assignment.

Figure 3.

Consistency of differences in multimorbidity index scores between intervention groups among pre-specified subgroups. P-value for interaction trend for BMI: 0.61; P-value for interaction trend for age group: 0.08; and P-value for interaction trend for baseline multimorbidity group: 0.007.

Table 1:

Characteristics at the time of Look AHEAD enrollment of participants: mean (standard deviation) or N (percent).

	Diabetes Support and Education N=2575	Intensive Lifestyle Intervention N=2570	Chi-squared p-value
Age at enrollment			
45–54	600 (23.3%)	642 (24.9%)	0.13
55–64	1422 (55.2%)	1428 (55.6%)	
65–76	553 (21.5%)	500 (19.5%)	
Sex			
Female	1537 (59.7%)	1526 (59.4%)	0.82
Male	1038 (40.3%)	1044 (40.6%)	
Race/Ethnicity			
African-American	404 (15.7%)	400 (15.6%)	0.93
American Indian	128 (5.0%)	130 (5.1%)	
Asian/Pacific Islander	21 (0.8%)	29 (1.1%)	
Hispanic	340 (13.2%)	340 (13.2%)	
Non-Hispanic White	1631 (63.3%)	1621 (63.1%)	
Other, Multiple	51 (2.0%)	50 (1.9%)	
BMI, kg/m ²			
25–29	362 (14.1%)	403 (15.7%)	0.24
30–39	1639 (63.7%)	1592 (62.0%)	
40	574 (22.3%)	575 (22.4%)	
HbA1c, %			
<7.0	1154 (44.8%)	1197 (46.6%)	0.07
7.0–8.9	1159 (45.0%)	1157 (45.0%)	
9.0	262 (10.2%)	216 (8.4%)	
Insulin use, Miss=118	410 (16.5%)	385 (15.5%)	0.32
Diabetes Duration, yrs, Miss=40			
<5 years	1148 (44.9%)	1189 (46.7%)	0.19
Family income, Miss=505			
<\$40K	783 (33.7%)	792 (34.2%)	0.70
Components of Multimorbidity			
Cancer	223 (8.7%)	205 (8.0%)	0.37
Cardiac arrhythmia	0 (0%)	0 (0%)	---
Chronic kidney disease ^a	124 (4.8%)	130 (5.1%)	0.69
Congestive heart failure	0 (0%)	0 (0%)	---
Coronary artery disease ^b	264 (10.3%)	287 (11.2%)	0.29
Depression symptomatology ^c	734 (28.5%)	777 (30.2%)	0.17
Dyslipidemia ^d	2253 (87.5%)	2250 (87.6%)	0.95
Hypertension ^e	2015 (78.3%)	2034 (79.1%)	0.43
Stroke	58 (2.3%)	67 (2.6%)	0.41
Multimorbidity Index	2.25 (0.89)	2.28 (0.88)	0.28 ^f

^aEstimated glomerular filtration rate <60

^b Myocardial infarction, coronary artery bypass, angina

^c Beck Depression Index ≥ 10 or current antidepressant medication use

^d LDL-C ≥ 100 or current lipid-lowering drug use

^e Blood pressures ≥ 140/90 mmHg or current antihypertensive medication use

^f t-test

Table 2:

Multimorbidity index scores at baseline and Year 8 by intervention assignment, with covariate adjustment for clinic site.

	N	Mean (SE)	95% CI
Baseline			
DSE	2575	2.20 (0.02)	[2.16,2.23]
ILI	2570	2.23 (0.02)	[2.20,2.27]
Difference		-0.04 (0.03)	[-0.09,0.02] P=0.17
End of 8 years			
DSE	2529	3.17 (0.02)	[3.12,3.22]
ILI	2535	3.12 (0.02)	[3.07,3.17]
Difference		0.05 (0.03)	[-0.02,0.12] P=0.14
Change			
DSE	2529	0.98 (0.02)	[0.94,1.02]
ILI	2535	0.89 (0.02)	[0.85,0.93]
Difference		0.09 (0.03)	[0.03,0.15] P=0.003