Kidney Medicine

The 10-Year Effects of Intensive Lifestyle Intervention on Kidney Outcomes

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Rationale & Objective: Limited data exist on longitudinal kidney outcomes after nonsurgical obesity treatments. We investigated the effects of intensive lifestyle intervention on kidney function over 10 years.

Study Design: Post hoc analysis of Action for Health in Diabetes (Look AHEAD) randomized controlled trial.

Setting & Participants: We studied 4,901 individuals with type 2 diabetes and body mass index of ≥25 kg/m^2 enrolled in Look AHEAD (2001–2015). The original Look AHEAD trial excluded individuals with 4+ urine dipstick protein, serum creatinine level of >1.4 mg/dL (women), 1.5 mg/dL (men), or dialysis dependence.

Exposures: Intensive lifestyle intervention versus diabetes support and education (ie, usual care).

Outcome: Primary outcome was estimated glomerular filtration rate (eGFR, mL/min/1.73 m^2) slope. Secondary outcomes were mean eGFR, slope, and mean urine albumin to creatinine ratio (UACR, mg/mg).

Analytical Approach: Linear mixed-effects models with random slopes and intercepts to evaluate the association between randomization arms and within-individual repeated measures of eGFR and UACR. We tested for effect modification by baseline eGFR.

Results: At baseline, mean eGFR was 89, and 83% had a normal UACR. Over 10 years, there was no difference in eGFR slope (+0.064 per year; 95% CI: −0.036 to 0.16; $P = 0.21$) between arms. Slope or mean UACR did not differ between arms. Baseline eGFR, categorized as eGFR of <80, 80-100, or >100, did not modify the intervention's effect on eGFR slope or mean.

Limitations: Loss of muscle may confound creatinine-based eGFR.

Conclusions: In patients with type 2 diabetes and preserved kidney function, intensive lifestyle intervention did not change eGFR slope over 10 years. Among participants with baseline eGFR <80, lifestyle intervention had a slightly higher longitudinal mean eGFR than usual care. Further studies evaluating the effects of intensive lifestyle intervention in people with kidney disease are needed.

Complete author and article information provided before references.

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Chronic kidney disease (CKD) affects 37 million people in the United States.[1] Obesity is a risk factor for type 2 diabetes and hypertension, the 2 leading causes of CKD.[2,3] Additionally, obesity is an independent risk factor for CKD.[4,5] Obesity treatment and improvements in obesity-related comorbid conditions may reduce the proportion of adults with CKD.[6,7]

Adverse health effects associated with obesity are perpetuated by adipose-derived factors. Upregulation of the renin-angiotensin system by adipokines facilitates systemic and glomerular hypertension, which leads to increased filtration through the glomerulus (ie, hyperfiltration), loss of protein in urine (ie, albuminuria), and maladaptive changes to the nephron over time.[8,9] Collectively, hormonal and hemodynamic perturbations, a proinflammatory environment, and direct podocyte injury may contribute to metabolic complications.[8,10,11] Weight loss benefits may include resolution of hyperfiltration, leading to normalization of estimated glomerular filtration rate (eGFR) and/or a reduction in yearly decline of kidney function over time.[12]

Lifestyle modifications alone or partnered with pharmacotherapy or bariatric surgery can augment weight loss and other health benefits.[13,14] Action for Health in Diabetes (Look AHEAD) was a multisite randomized controlled trial that demonstrated no difference between intensive lifestyle intervention and diabetes support and education in cardiovascular morbidity and mortality among adults with type 2 diabetes and overweight or obesity.[15] However, the study found benefits of intensive lifestyle intervention relative to diabetes support and education for a number of cardiovascular risk factors, including blood pressure, weight, and glycemia, which are key treatment goals for CKD management.[16-19] Look AHEAD also showed fewer incident cases of kidney disease considered very high risk of progression to end-stage kidney disease among individuals treated with intensive lifestyle intervention.[20] However, longitudinal studies are needed to understand the long-term effects of intensive lifestyle intervention on kidney function and better characterize the population in which lifestyle changes and weight loss may lower CKD risk.[21]

This study investigated the effects of intensive lifestyle intervention on change in kidney function, using creatinine-based eGFR. We also assessed whether baseline kidney function modified the effect of intensive lifestyle intervention on kidney function. We hypothesized that intensive lifestyle intervention would lead to a slower

PLAIN-LANGUAGE SUMMARY

Lifestyle interventions can improve chronic kidney disease risk factors, specifically diabetes, hypertension, and obesity. But, the effects of lifestyle intervention on change in kidney function (estimated glomerular filtration rate [eGFR]) over time are not well established. We studied Action for Health in Diabetes (Look AHEAD) trial data because all participants were affected by diabetes and overweight or obesity. Look AHEAD randomized participants to intensive lifestyle intervention or diabetes support and education (ie, usual care). We compared eGFR change over 10 years between groups, but found no difference. However, the intervention group maintained slightly higher eGFR than usual care, especially if eGFR was relatively low at baseline. Our study suggests lifestyle intervention may preserve eGFR, but dedicated studies in individuals with chronic kidney disease are needed.

decline in eGFR compared with diabetes support and education. We also hypothesized that participants with higher baseline eGFRs would have a greater benefit from lifestyle modifications because of potentially less baseline glomerulosclerosis than those with lower baseline eGFRs.

METHODS

Study Design

We performed a post hoc analysis of the Look AHEAD randomized controlled trial that occurred between June 2001 and September 2012 (median follow-up 9.6 years). Look AHEAD ended early because of futility on its primary cardiovascular outcome. Postintervention data were collected up to 2015.

Informed Consent and Internal Review Board Approval

Look AHEAD was a multisite randomized controlled trial that obtained informed consent from all study participants at their respective institutions. The University of Pennsylvania Internal Review Board determined the current post hoc analysis to be exempt from requiring internal review board approval.

Patient Population

The Look AHEAD trial enrolled adults aged 45-75 years with type 2 diabetes, body mass index (BMI) of ≥25 kg/m^2, and the ability to complete a maximal exercise test and who were under supervision by a primary care provider. The Look AHEAD trial inclusion and exclusion criteria were previously reported.[15] Exclusion criteria included lower limb amputation, urine dipstick protein of 4+ or approximately >1 g proteinuria/day, serum creatinine levels exceeding 1.4 mg/dL in women or 1.5 mg/dL in men, or dialysis dependence. The original Look AHEAD trial included 5,145 adults. We used the public access Look AHEAD dataset archived in the National Institute of Diabetes and Digestive and Kidney diseases data repository, which contains time-updated data for 4,901 consenting study participants. All 4,901 participants were included in the primary analysis (Fig 1).

Intervention

The participants were randomized to intensive lifestyle intervention or diabetes support and education, which we approximate to resemble usual care. All study participants were advised to eat a low-fat, reduced calorie diet. The goal for the intensive lifestyle intervention was to decrease initial body weight by ≥7% and increase physical activity to 175 minutes/week. Intensive lifestyle intervention consisted of individual or group sessions led by a trained interventionist to help participants meet dietary and physical activity goals using behavior modification techniques. The intensity (ie, frequency) of visits decreased over 3 phases. During phase 1, participants were offered weekly visits between months 1 and 6, which then decreased to at least 2 visits per month during months 7-12. During phase 2 (ie, months 13-48), participants had at least 1 in-person visit plus 1 additional contact per month and optional monthly open group sessions starting at month 13. After month 48, the intervention arm had one on-site monthly meeting with a counselor and optional monthly group sessions. The diabetes support and education group were offered 3 group sessions per year. Details of the Look AHEAD protocol were published by the Look AHEAD research group.[16]

Covariates

The adjusted model included the following demographics and baseline characteristics of the study cohort: age (years), sex defined as female (yes/no), race/ethnicity (categorized as non-Hispanic White, non-Hispanic Black, Hispanic, or other), BMI (kg/m^2), eGFR (mL/min/1.73 m^2), urinary albumin-creatinine ratio (UACR, mg/mg), systolic blood pressure (mm Hg), waist circumference (cm), hemoglobin A1c (%), duration of diabetes (years), smoking status (categorized as current, prior, or never), use of angiotensin-converting enzyme inhibitor (yes/no), use of angiotensin receptor blocker (yes/no), use of nonsteroidal anti-inflammatory drug (yes/no), years of education (categorized as older than 16 years, 13-16 years, or less than 13 years), employment status (categorized as full time, part-time, unemployed, or unknown), history of hypertension (yes/no), history of dyslipidemia (yes/no), and history of cardiovascular disease (yes/no). Weights were measured each year, and height was measured at baseline and years 1, 4, and 8. Covariates were selected a priori based on known associations between excess weight and adverse kidney outcomes.[22,23]

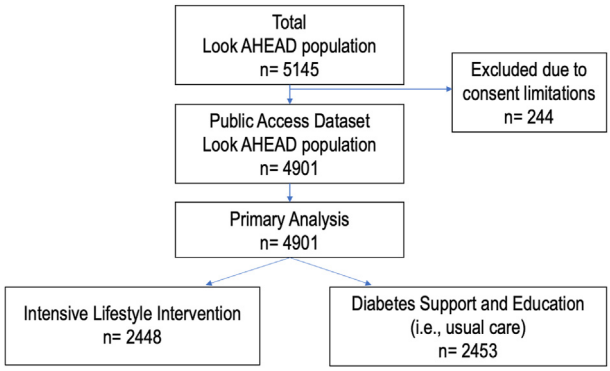


Figure 1. Study cohort.

Outcomes

Slope of eGFR (mL/min/1.73 m^2 per year) was the primary outcome. We anticipated weight and fat loss would decrease proinflammatory and nephrotoxic adipokines and facilitate lowering intraglomerular pressure. Based on prior literature, we anticipated manifestations of these physiologic changes in eGFR to vary by baseline kidney function and albuminuria.[24,25] Specifically, if hyperfiltration is present at baseline, then weight and fat loss may decrease or normalize eGFR. If kidney function is normal at baseline, then weight and fat loss may yield no change or an increase in eGFR. If kidney function is reduced at baseline, then weight and fat loss may increase eGFR. We hypothesized the long-term cumulative effect of reduced glomerular pressure would decrease eGFR slope, which we chose as our primary outcome. Furthermore, eGFR slope is recognized as an accepted surrogate endpoint for risk of end-stage kidney disease even in people with eGFR of>60 mL/min/1.73 m^2.[26,27] We included mean eGFR and slope and mean UACR (mg/mg) as secondary outcomes to assess the kidney's response to physiologic changes over the course of follow-up. Serum creatinine, urine albumin, and urine creatinine were measured at baseline, yearly for the first 5 years, and then every other year. All analyses used the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) eGFR equation using serum creatinine, without incorporating race in the equation.[28]

Statistical Analyses

We evaluated differences in baseline demographics, clinical characteristics, eGFR (first as a continuous variable and subsequently as a categorical variable using tertiles) and UACR (categorized into Kidney Disease-Improving Global Outcomes stages of albuminuria) between randomization arms using a 2-sample t test or Wilcoxon-rank sum for continuous covariates and the χ^2 test of proportions for categorical covariates.[29] We used linear mixed effects modeling with random slopes and intercepts for unique participant IDs to evaluate the association of the randomization arm with within-individual repeated measures of eGFR (primary end point) and UACR (secondary end point) over 10 years. The randomization arm and covariates were represented as baseline fixed effects. The end points, eGFR and UACR, were modeled separately. Models evaluating yearly slope included an interaction term for randomization arm and visit year. Models evaluating mean eGFR or mean UACR did not contain interaction terms. Adjusted models for effect modification by baseline eGFR on eGFR slope contained an interaction term for randomization arm, baseline eGFR tertile, and visit year. We stratified by baseline eGFR tertile (eGFR <80, 80-100, or >100 mL/min/1.73 m^2) to assess for effect modification by baseline eGFR on mean eGFR using adjusted models with an interaction term for randomization arm and baseline eGFR tertile. The current literature lacks consensus on eGFR thresholds to define hyperfiltration and single eGFR cut-points for glomerular hyperfiltration ranges from 90 to 175 mL/min/1.73 m^2 with a median value of 135 mL/min/1.73 m^2.[30] Given the low proportion in Look AHEAD with eGFR of >135ml/min/1.73 m^2, we used a mathematical cutoff to categorize glomerular hyperfiltration. We assessed for effect modification by baseline eGFR using the Wald test and a significance level of 0.05. All analyses were performed using Stata/SE version 16.1.

Missing Data

There was <3% missing data for relevant covariates. We used multiple imputation to address missing laboratory data assuming it was missing at random (ie, missingness depends only on observed data).[31]

RESULTS

Baseline Characteristics

The median age of trial participants was 58 (IQR: 55-64) years, and there was no significant difference in the proportion of intensive lifestyle intervention versus usual care participants with normal UACR (84% vs 82%), microalbuminuria (13% vs 14%), or macroalbuminuria (3% vs 3%) (Table 1). Both randomization arms were balanced with regards to sex (59% female), race/ethnicity (66% non-Hispanic White, 16% non-Hispanic Black, and 14% Hispanic), mean BMI (36 kg/m^2), eGFR (89 mL/min/1.73 m^2), and serum creatinine level (0.8 mg/dL). Most participants (75%) had an eGFR of >80 mL/min/1.73 m^2.

eGFR Slope Over 10 Years

Kidney function declined in both arms over the 10-year period. A positive difference between randomization arms (intervention vs usual care) suggested a smaller yearly decline of eGFR in the lifestyle intervention arm compared with the usual care arm. In the unadjusted and adjusted models, there was no significant difference in the eGFR slope between randomization arms (adjusted difference: +0.070 mL/min/1.73 m^2 per year; 95% confidence interval (CI), −0.032 to 0.17; P = 0.18; Table 2). In the adjusted model, the average eGFR slope was −0.86 mL/min/1.73 m^2 per year (95% CI, −0.93 to −0.79) in the

Table 1. Baseline Characteristics of Participants in the Look AHEAD Population

Characteristics[a]	Total (n = 4,901)	Diabetes Support and Education (n = 2,453)	Intensive Lifestyle Intervention (n = 2,448)
Median age (y [IQR])	59 (55-64)	59 (55-64)	58 (55-63)
Female, n (%)	2,871 (59)	1,437 (59)	1,434 (59)
Race/Ethnicity, n (%)			
White, Non-Hispanic	3,247 (66)	1,629 (66)	1,618 (66)
Black, Non-Hispanic	804 (16)	404 (16)	400 (16)
Hispanic	676 (14)	338 (14)	338 (14)
Other/Mixed	174 (4)	82 (3)	92 (4)
Weight (kg)	101 ± 19	101 ± 19	101 ± 20
BMI (kg/m^2)	36 ± 6	36 ± 8	36 ± 6
Systolic blood pressure (mm Hg)	129 ± 17	130 ± 17	128 ± 17
Waist Circumference (cm)	114 ± 14	114 ± 14	114 ± 14
Serum creatinine (mg/dL)	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2
eGFR (mL/min/1.73 m^2)	89 ± 15	89 ± 15	89 ± 15
eGFR tertiles, n (%)			
1st tertile: eGFR <80 mL/min/1.73 m^2	1,255 (26)	637 (26)	618 (25)
2nd tertile: eGFR 80-100 mL/min/1.73 m^2	2,345 (48)	1,190 (49)	1,155 (47)
3rd tertile: eGFR ≥100 mL/min/1.73 m^2	1,301 (27)	626 (26)	675 (28)
Median UACR (mcg/mg, IQR)	8.7 (5.3-18.4)	8.7 (5.4-18.8)	8.6 (5.2-18.0)
Degree of albuminuria, n (%)			
Normal, UACR <30 mcg/mg	4,076 (83)	2,022 (82)	2,054 (84)
Microalbuminuria, UACR 30-299 mcg/mg	663 (14)	350 (14)	313 (13)
Macroalbuminuria, UACR ≥300 mcg/mg	133 (3)	64 (3)	69 (3)
Missing	29 (<1)	17 (<1)	12 (<1)
Hemoglobin A1c (%)	7.3 ± 1	7.3 ± 1	7.2 ± 1
Duration of diabetes (median y, IQR)	5 (2-10)	5 (2-10)	5 (2-10)
Smoking- Current or Previous (%)	2,464 (50)	1,220 (50)	1,244 (51)
Education >12 y (%)	3,872 (79)	1,935 (79)	1,937 (79)
Employed or in school (%)	3,117 (64)	1,555 (63)	1,562 (64)
History of hypertension (%)	4,097 (84)	2,047 (83)	2,050 (84)
Use of ACE inhibitors (%)	2,113 (43)	1,072 (44)	1,041 (43)
Use of ARB (%)	778 (16)	380 (16)	398 (16)
Use of insulin (%)	748 (16)	385 (16)	363 (15)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; IQR, interquartile range; UACR, urine albumin to creatinine ratio.

[a]Mean baseline values ± SD are listed for weight, BMI, systolic blood pressure, waist circumference, serum creatinine, eGFR, UACR, hemoglobin A1c, and duration of diabetes. No significant difference in baseline characteristics between treatment arms using Wilcoxon-rank sum for continuous variables and χ^2 test for categorical variables ($P > 0.05$) except for systolic blood pressure ($P = 0.003$).

lifestyle intervention arm and −0.93 mL/min/1.73 m^2 per year (95% CI, −1.01 to −0.86) in the usual care arm.

Mean eGFR (Averaging Across Longitudinal Values)

In the unadjusted linear mixed effects model, the intensive lifestyle intervention had a slightly higher mean eGFR over 10 years of follow-up by +0.73 (95% CI, −0.068 to 1.53; P = 0.07) relative to the usual care arm. The adjusted mean difference in eGFR over 10 years was +0.40 mL/min/1.73 m^2 (95% CI, 0.060-0.74; P = 0.02; Fig 2). We explored the difference in unadjusted versus adjusted mean eGFR using a stepwise addition of covariates to the adjusted model starting with demographic covariates. The addition of age to an adjusted model with sex and race/ethnicity accounted for the observed decrease in effect size. Upon further exploration, age was identified as a significant effect modifier on mean eGFR. Participants aged 65 years or older who received intensive lifestyle intervention had a slightly higher mean eGFR (+0.99 mL/min/1.73 m^2; 95% CI, 0.16-1.82; P = 0.02) compared with their usual care counterparts.

Slope of UACR and Mean UACR

Over a 10-year follow-up period, there was no significant difference in slope of UACR (adjusted: −0.00098 mg/mg per year; 95% CI: −0.0043 to 0.0023; P = 0.57) or adjusted mean UACR (−0.0054 mg/mg; 95% CI: −0.013 to 0.0026; P = 0.19) between randomization arms (Table 3).

Effect Modification

Baseline eGFR did not modify the effect of intensive lifestyle intervention on eGFR slope (Table 4) or mean eGFR (Figs 3, 4, and 5). Relative to usual care, individuals in the

Table 2. Differences in Slope and Mean for eGFR Between Intensive Lifestyle Intervention Versus Diabetes Support and Education

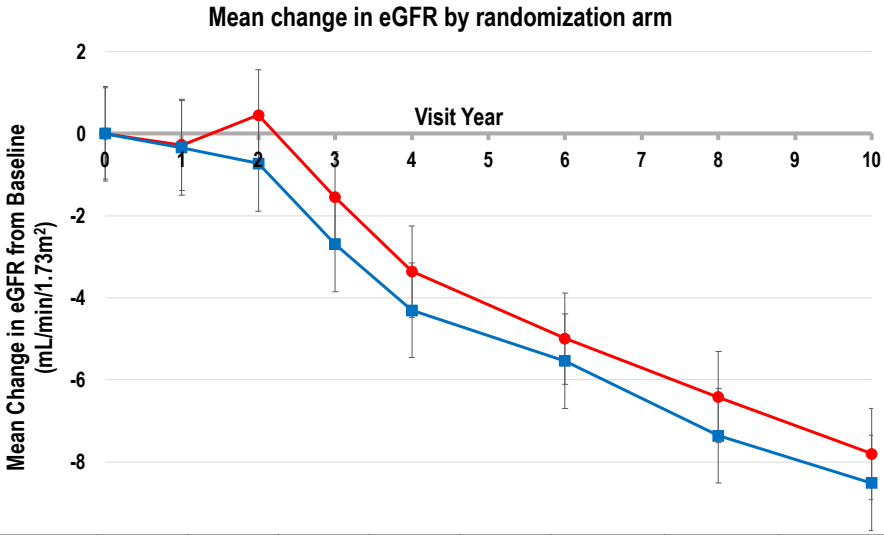
Outcome: Estimated Glomerular Filtration Rate							
		Unadjusted			Adjusted[f]		
Model[a]	Description	B (95% CI)	Intercept (95% CI)	*P*	B (95% CI)	Intercept (95% CI)	*P*
1[b]	Mean Slope (mL/min/1.73 m^2 per year)						
	Intensive Lifestyle Intervention	-0.87 (-0.94 to -0.80)	3.13 (2.56 to 3.70)		-0.86 (-0.93 to -0.79)	17.54 (14.63 to 20.45)	
	Diabetes Support and Education (Usual Care)	-0.93 (-1.00 to -0.86)		0.21	-0.93 (-1.01 to -0.86)		0.18
	Difference in Slope[c]	+0.064 (-0.036 to 0.16)			+0.070 (-0.032 to 0.17)		
2[d]	Difference in Mean[e]	+0.73 (-0.068 to 1.53)	3.10 (2.54 to 3.67)	0.07	+0.40 (0.060 to 0.74)	17.52 (14.61 to 20.43)	0.02

[a]For all models, estimated glomerular filtration rate (eGFR; primary endpoint) and urine albumin to creatinine ratio (UACR; secondary endpoint) are modeled separately. UACR was modeled using units mg/mg.
[b]Model 1 includes an interaction term for randomization arm and visit year (continuous).
[c]A positive difference in eGFR slope suggests a smaller decrease in eGFR per year over 10 years in the intensive lifestyle intervention compared with diabetes support and education arm.
[d]Model 2 is adjusted for visit year and does not have interaction terms. The difference in mean is the difference in the outcome at 10 years.
[e]A positive difference in mean eGFR suggests a higher mean eGFR over 10 years in the intensive lifestyle intervention compared with diabetes support and education arm.
[f]Adjusted models 1 and 2 include covariates for treatment arm, age, sex, race/ethnicity, diabetes duration, employment status, years of education, history of hypertension, dyslipidemia, cardiovascular disease, and baseline values for eGFR, UACR, BMI, hemoglobin A1c, waist circumference, alcohol intake per week, angiotensin-converting enzyme inhibitor use, angiotensin receptor blocker use, and nonsteroidal anti-inflammatory drug use.

lifestyle intervention arm with a baseline eGFR of <80 mL/min/1.73 m^2 had a slightly higher mean eGFR (+1.11 mL/min/1.73 m^2; 95% CI, −0.048 to 2.27; P = 0.06) over 10 years. There was no difference in mean eGFR over 10 years among individuals with a baseline eGFR 80-100 mL/min/1.73 m^2 (−0.24; 95% CI, −0.84 to 0.35, P = 0.42) or eGFR >100 mL/min/1.73 m^2 (+0.35; 95% CI, −0.24 to 0.95, P = 0.25).

DISCUSSION

In this post hoc analysis of the Look AHEAD trial, we evaluated for yearly change in kidney function after treatment with intensive lifestyle intervention or diabetes support and education (ie, usual care) in adults with type 2 diabetes, BMI of ≥25 kg/m^2 and preserved baseline kidney function. Our results complement prior Look AHEAD studies by leveraging repeated measurements to quantify



Visit Year	0	1	2	3	4	6	8	10
Intensive Lifestyle Intervention	0	-0.28	0.46	-1.55	-3.36	-4.99	-6.43	-7.80
Diabetes Support and Education	0	-0.34	-0.73	-2.70	-4.30	-5.54	-7.36	-8.52
Number of Participants	4901	4650	4507	4455	4388	4242	4029	3585

Figure 2. Mean change in eGFR by randomization arm.

Table 3. Differences in Slope and Mean for UACR Between Intensive Lifestyle Intervention Versus Diabetes Support and Education

		Outcome: Urine Albumin to Creatinine Ratio					
		Unadjusted			Adjusted[f]		
Model[a]	Description	B (95% CI)	Intercept (95% CI)	*P*	B (95% CI)	Intercept (95% CI)	*P*
1[b]	Mean Slope (mL/min/1.73 m² per year)						
	Intensive Lifestyle Intervention	+0.0073 (0.0052 to 0.0095)	0.042 (0.033 to 0.050)		+0.0071 (0.0048 to 0.0095)	-0.00010 (-0.069 to 0.069)	
	Usual Care	+0.0077 (0.0055 to 0.0098)		0.84	+0.0081 (0.0057 to 0.010)		0.57
	Difference in Slope[c]	-0.00031 (-0.0034 to 0.0028)			-0.00098 (-0.0043 to 0.0023)		
2[d]	Difference in Mean[e]	-0.011 (-0.023 to 0.0010)	0.042 (0.033 to 0.050)	0.07	-0.0054 (-0.013 to 0.0026)	-0.000092 (-0.069 to 0.069)	0.19

[a]For all models, estimated glomerular filtration rate (eGFR; primary endpoint) and urine albumin to creatinine ratio (UACR; secondary endpoint) are modeled separately. UACR was modeled using units mg/mg.
[b]Model 1 includes an interaction term for randomization arm and visit year (continuous).
[c]A positive difference in UACR slope suggests a slightly greater increase in UACR per year over 10 years in the intensive lifestyle intervention compared with diabetes support and education arm.
[d]Model 2 is adjusted for visit year and does not have interaction terms. The difference in mean is the difference in the outcome at 10 years.
[e]A negative difference in mean UACR suggests a lower mean UACR over 10 years in the intensive lifestyle intervention compared with diabetes support and education arm.
[f]Adjusted models 1 and 2 include covariates for randomization arm, age, sex, race/ethnicity, diabetes duration, employment status, years of education, history of hypertension, dyslipidemia, cardiovascular disease, and baseline values for eGFR, UACR, BMI, hemoglobin A1c, waist circumference, alcohol intake per week, angiotensin-converting enzyme inhibitor use, angiotensin receptor blocker use, and nonsteroidal anti-inflammatory drug use.

the average eGFR slope over 10 years. We found that eGFR slope was not different between participants treated with intensive lifestyle intervention versus usual care and did not differ by baseline eGFR.

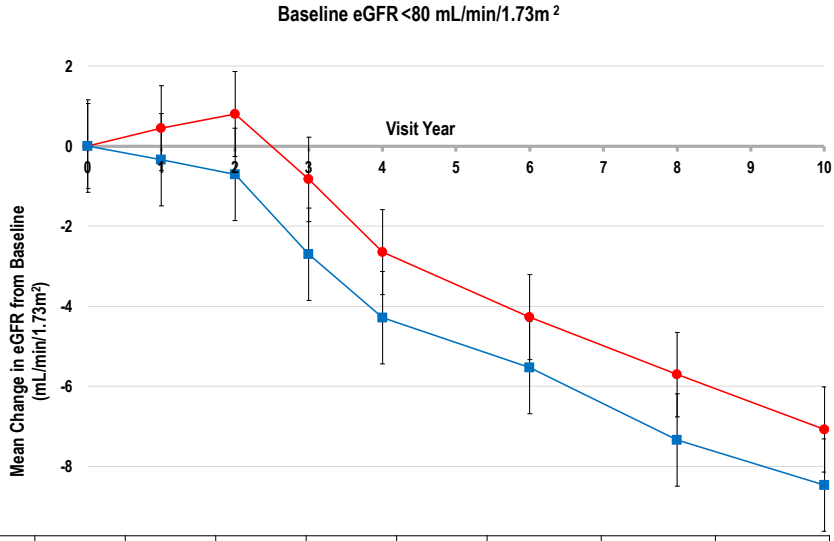
Lifestyle interventions offer several health benefits, including sustained intentional weight loss >5% of initial weight,[19] better glycemic control,[32] blood pressure, physical function,[33] and even lower incidence of very high-risk CKD.[20] However, in our analysis, a structured lifestyle intervention did not change eGFR slope, which may be explained by baseline characteristics and duration of follow-up. The average yearly eGFR slopes in both arms were less than 1 mL/min/1.73 m^2 per year, which approximates the average eGFR slope in the general US population, rather than eGFR slope in most people with type 2 diabetes (about −2.5 mL/min/1.73 m^2 per year).[34,35] Look AHEAD included a high proportion of individuals with preserved baseline kidney function, normal albuminuria, and overall well-controlled CKD risk factors (ie, diabetes, hypertension, and nonsmokers), likely contributing to a slower than average decline in eGFR and lack of an effect on UACR.[35,36] Our assessment of kidney function over 10 years is longer than prior nonsurgical weight loss studies, but microvascular changes may present even later in Look AHEAD's population. Further study is needed on the effects of a structured lifestyle program in people with uncontrolled CKD risk factors.

However, our results supplement Look AHEAD's prior observations of a lower cumulative incidence of very high-risk CKD in the intensive lifestyle intervention arm compared with usual care.[20] We estimated eGFR slope, which provides a numerical reference when clinically monitoring the potential effects of lifestyle intervention in people with the most prevalent CKD risk factors (ie, diabetes, overweight, obesity, or hypertension). Additionally, our study offers clinician support for deciding which patients (based on eGFR) may experience kidney benefit from intensive lifestyle intervention. Look AHEAD researchers previously reported a higher mean eGFR in the

Table 4. Difference in Slope of eGFR and UACR Between Randomization Arms by Baseline eGFR

	Estimated Glomerular Filtration Rate		Urine Albumin to Creatinine Ratio	
Baseline eGFR (mL/min/1.73 m²)	Difference in Slope[a] (95% CI)	Intercept (95% CI)	Difference in Slope[a] (95% CI)	Intercept (95% CI)
<80	+0.11 (-0.10 to 0.31)	6.58 (2.58 to 10.58)	-0.000085 (-0.0067 to 0.0066)	0.0053 (-0.067 to 0.077)
80-100	-0.022 (-0.28 to 0.24)		-0.0022 (-0.010 to 0.0060)	
>100	-0.11 (-0.40 to 0.17)		+0.00075 (-0.0085 to 0.010)	

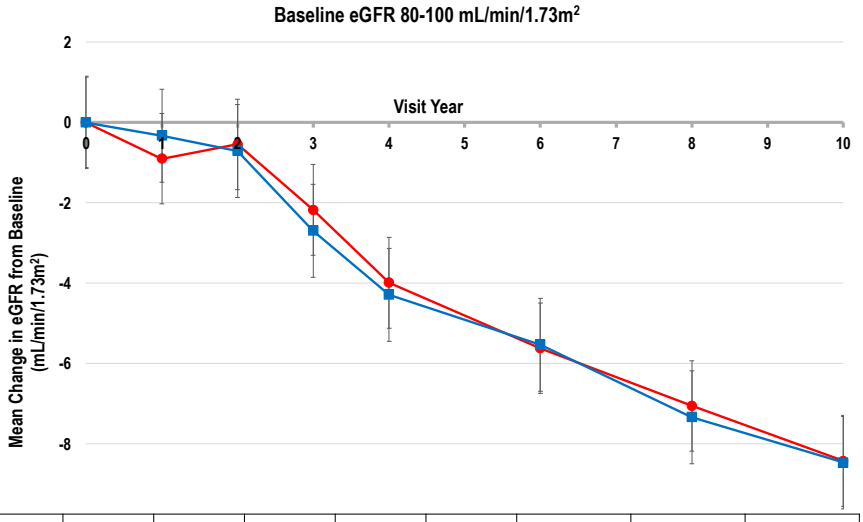
[a]Linear mixed effect models assessing for effect modification by baseline eGFR were adjusted and included a 3-way interaction term for treatment arm, visit year, and categorical variable for baseline eGFR tertiles. eGFR and UACR were modeled separately. All *P* values were >0.05.



Visit Year	0	1	2	3	4	6	8	10
Intensive Lifestyle Intervention	0	0.44	0.80	-0.83	-2.64	-4.27	-5.71	-7.08
Diabetes Support and Education	0	-0.33	-0.71	-2.69	-4.29	-5.53	-7.34	-8.47
Number of Participants	1255	1200	1165	1157	1117	1089	996	863

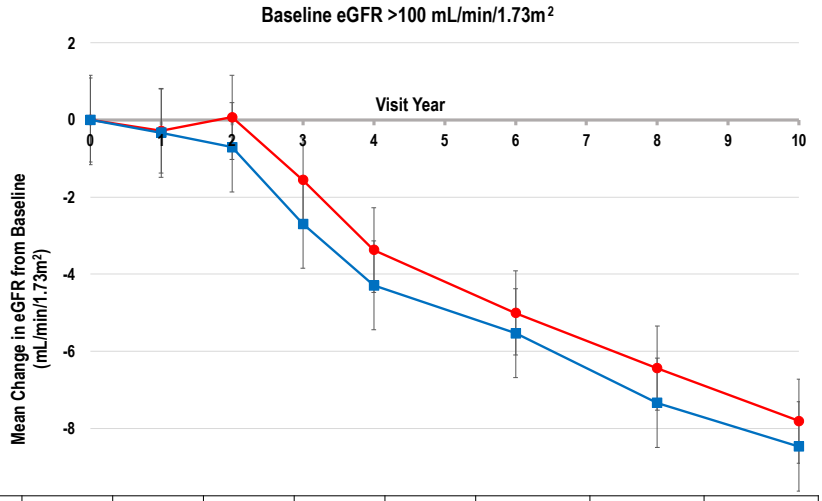
Figures 3. Mean change in eGFR from baseline by tertiles of baseline eGFR (<80, 80-100, and >100 mL/min/1.73 m²).

intervention arm compared with usual care. Our exploratory analyses characterized the slightly higher mean eGFR to occur in a subpopulation with a baseline eGFR of <80 mL/min/1.73 m^2, and a relative higher risk of progression to end-stage kidney disease. Furthermore, this subpopulation likely includes the individuals who benefited from fewer events of incident high-risk CKD. In contrast, those with higher baseline eGFR of ≥80 mL/min/1.73 m^2 and a relative lower risk of CKD progression had no absolute difference in mean eGFR between arms. All together, these results suggest kidney benefits from intensive lifestyle intervention are more likely occurring in patients with eGFR of <80 mL/min/1.73 m^2, but large pragmatic lifestyle intervention studies in patients with CKD are needed to improve generalizability and accurately identify the eGFR benefit threshold.



Visit Year	0	1	2	3	4	6	8	10
Intensive Lifestyle Intervention	0	-0.90	-0.55	-2.18	-3.99	-5.62	-7.05	-8.42
Diabetes Support and Education	0	-0.33	-0.71	-2.69	-4.29	-5.53	-7.34	-8.47
Number of Participants	2345	2223	2157	2139	2110	2044	1951	1730

Figure 4. Mean change in eGFR from baseline by tertiles of baseline eGFR (<80, 80-100, and >100 mL/min/1.73 m²).



Visit Year	0	1	2	3	4	6	8	10
Intensive Lifestyle Intervention	0	-0.29	+0.07	-1.56	-3.37	-5.00	-6.44	-7.81
Diabetes Support and Education	0	-0.33	-0.71	-2.69	-4.29	-5.53	-7.34	-8.47
Number of Participants	1301	1227	1185	1159	1161	1109	1082	992

Figure 5. Mean change in eGFR from baseline by tertiles of baseline eGFR (<80, 80-100, and >100 mL/min/1.73 m^2).

Our findings are consistent with Brenner's hyperfiltration theory.[24,25] For those in the hyperfiltration phase (ie, eGFR of >100 mL/min/1.73 m^2), a reduction in intraglomerular pressure because of fat and weight loss may normalize glomerular filtration rate (ie, decrease or maintain eGFR). Without more accurate methods to determine kidney function and pathology, we approximated participants with baseline eGFR of <100 mL/min/1.73 m^2 to have normal eGFR and no hyperfiltration. In those without hyperfiltration, response to hormonal and hemodynamic changes after weight loss may differ by the presence or absence of underlying intraglomerular pathophysiology. For instance, individuals with normal eGFR and no underlying pathophysiology may have no change in eGFR, but those with underlying pathophysiology (eg, from chronic glomerular stress or prior hyperfiltration) may have a higher eGFR. Similarly, the PREvencion con DIetaMEDiterranea Plus trial found a minimally higher eGFR despite less weight loss compared with Look AHEAD in participants with an eGFR of 60-90 mL/min/1.73 m^{2}and randomized to a lifestyle intervention with a reduced calorie Mediterranean diet vs usual care with an ad libitum Mediterranean diet.[37] Despite modest effect sizes in the Look AHEAD and PREvencion con DIetaMEDiterranea cohorts, further study is warranted in patients with CKD and albuminuria before determining whether intensive lifestyle intervention affects CKD progression, independent of weight loss.

A common limitation of weight loss studies using creatinine-based eGFR is the potential overestimation of GFR because of a lower serum creatinine when weight is lost from muscle.[38,39] In our study, higher age (ie, age 65 years or older) slightly increased the effect of intensive lifestyle intervention on mean eGFR, presumably because of age-related muscle loss confounding the interpretation of creatinine-based eGFR. Similarly, without measured GFR or cystatin C, it is difficult to determine whether reductions in eGFR are because of loss of kidney function, kidney injury, or normalization of hyperfiltration. Similar challenges using creatinine to estimate GFR were noted by Navaneethan et al[22] who observed lower creatinine-based eGFR in participants postbariatric surgery and postulated a beneficial effect with normalization of hyperfiltration rather than loss of function. In a small cohort of individuals status post Roux-en-Y gastric bypass and a mean weight loss of 27 kg, which included 6.5 kg of lean mass loss over 6 months, von Scholten et al[39] found no change in CKD-EPI-cystatin C eGFR or measured GFR corrected to standardized body surface area. However, eGFR calculated using CKD-EPI-creatinine increased by 12 mL/min/1.73 m^2 when creatinine was decreased by 9 μmol/L (∼0.1 mg/dL). A decrease in fat and adipokines with intensive lifestyle intervention may contribute to normalization of hyperfiltration, but more rigorous methods employing gold standard measures of kidney function, kidney biopsy, urinary biomarkers, body composition, and serologic measurements of cystatin C and adipokines can improve evaluation of obesity treatment effects on kidney structure and function.[40]

Our post hoc analysis of the Look AHEAD trial has several strengths, including the large sample size of nearly 5,000 participants from multiple clinical sites. The trial's high retention rate, low missingness (<3% for relevant parameters), and long follow-up allowed collection of about 7 repeated measurements of serum creatinine and UACR per individual that we analyzed with a linear mixed

effect model to estimate yearly slope. Furthermore, our study investigated the same treatments tested in Look AHEAD, which limits the potential for confounding. However, there are also several limitations. Trials, especially those with long follow-up, often recruit highly motivated individuals, limiting our study's generalizability. Additionally, exclusion of individuals with kidney disease or significant albuminuria may undermine application of our findings to many patients with type 2 diabetes and potentially underestimate the effects of intensive lifestyle intervention in people with uncontrolled CKD risk factors.[39]

In this study, we found no meaningful difference in the eGFR slope between intensive lifestyle intervention compared with usual care among people with relatively well-controlled type 2 diabetes and preserved kidney function with minimal albuminuria. Intensive lifestyle intervention is an individualized and effective approach to weight loss. However, when studying the effects of weight loss interventions on kidney function, more rigorous measures of kidney function are needed to overcome the influence of dietary and body composition changes associated with weight loss approaches. Furthermore, inclusion of more individuals with albuminuria may identify a target population in whom intensive lifestyle intervention offers greater kidney benefits. Future studies should also investigate the use of lifestyle intervention programs to improve disease awareness, medication adherence and patient-centered outcomes, such a self-efficacy and quality of life, among patients with CKD.

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