

*The Viability of Lifestyle Intervention for Remission and  
Reduction of Diabetes-Related Morbidity*

*Edward W. Gregg, PhD  
School of Public Health  
Imperial College London*

# Summary of Evidence and Effect Sizes for the Benefits of Weight Loss Interventions on Major Morbidity

Morbidity	Adult Prevalence	RR Reduction	3-year NNT	Evidence for Benefit
Diabetes	12%	40-60%	7	Strong
Hypertension	29%	20%	13	Strong
Moderate Disability	25%	50%	14	Moderate
Chronic Kidney Disease	16%	30%	119	Moderate
CVD Incidence		----	----	Unclear

References: <sup>1</sup>Knowler et al., NEJM, 2002; <sup>2</sup>Welton et al., Arch Intern Med, 1997;

<sup>3</sup>Rejeski et al., NEJM, 2012, <sup>4</sup>Look AHEAD Study Group, 2014; <sup>5</sup>Look AHEAD Study Group, 2013

<sup>6</sup>National Diabetes Fact Sheet; <sup>7</sup>National Chronic Kidney Disease Fact Sheet.

# Potential for Remission of Type 2 Diabetes with Lifestyle Intervention

- Background assumption that diabetes irreversible.
- Studies of bariatric surgery demonstrate ~60% remission rate after 5 years.
- Early type 2 diabetes characterized by an extended period of continued insulin production and action.
- Lifestyle intervention is effective on multiple pathways of insulin resistance.
- The Look AHEAD Study was the largest, intensive lifestyle-based weight loss intervention ever conducted.

## Historical Perspective: Evidence and Epidemiology when *Look AHEAD* was Designed: Year 2000

- Adult U.S. obesity prevalence: 32%
- Diabetes prevalence 9%
- CVD accounting for almost half of deaths.
- ~ 34% of the population attempting weight loss.
- Weight loss associated with many short-term benefits.
- Cohort studies associated weight loss with increased mortality risk.
- Studies of “intentional” weight loss were inconclusive.

# Study Population (Inclusion Criteria)

- Overweight/obese (*mean BMI=36*)
- Type 2 diabetes
- Age 45-75 (*mean 59*).
- With (13%) or without prior CVD (87%)
- Passed graded exercise test.
- Metabolically controlled
  - (A1c<11%; trig <600; BP<160/90)
- *Pragmatic choice due to power concerns.*
- *Population with conceivably much to gain from weight loss.*

# Intensive lifestyle intervention on CVD events over 11.5 y: The Look AHEAD Study: Study Design

Diabetes  
Support &  
Education

*3-4 educational sessions  
per year related to self-care  
and diabetes management*

Baseline

*Outcomes*

11.5-yr

*Follow-up*

Intensive  
Lifestyle

Year 1: Weekly Counseling

*Goal=10% wt. loss*

*1200-1800 kcal/day*

*175 minus Phys. Activity*

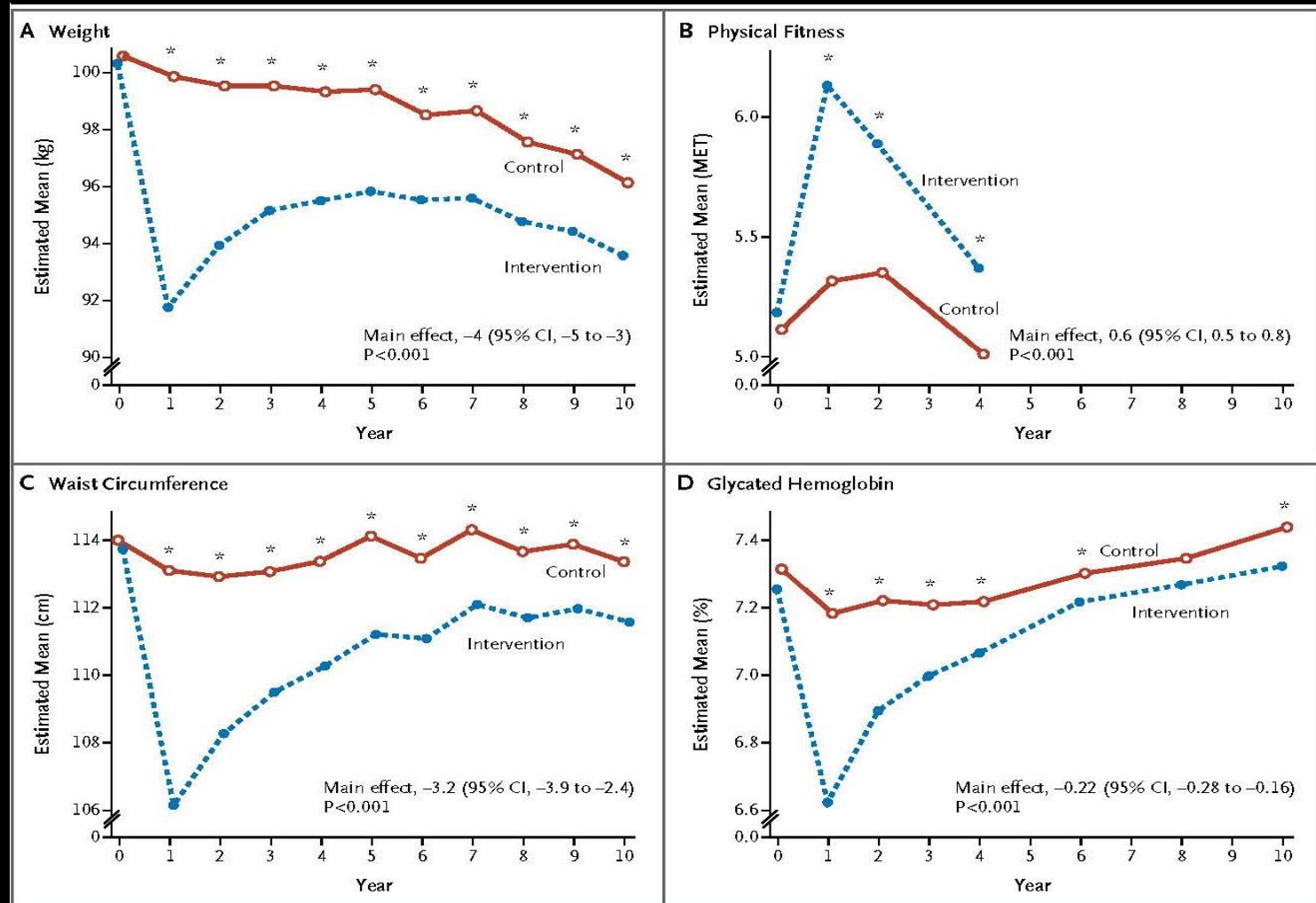
*Comprehensive Behavior Support*

Years 2-4: Monthly contact  
for maintenance.

Years 5+: Quarterly contact  
to prevent re-gain.

*Refresher Sessions throughout*

# Changes in weight, physical fitness, waist circumference, and A1c levels over 10 years: The Look AHEAD Study



**Figure 1. Changes in Weight, Physical Fitness, Waist Circumference, and Glycated Hemoglobin Levels during 10 Years of Follow-up.** Shown are the changes from baseline in overweight or obese patients with type 2 diabetes who participated in an intensive lifestyle intervention (intervention group) or who received diabetes support and education (control group). The reported main effect is the average of all between-group differences after baseline. Means were estimated with the use of generalized linear models for continuous measures. MET denotes metabolic equivalents; asterisks indicate P<0.05 for the between-group comparison. Data from 107 visits during year 11 were not included in the analyses.

# Effect of intensive lifestyle intervention on CVD events over 11.5 y: The Look AHEAD Study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes

The Look AHEAD Research Group\*

ABSTRACT

### BACKGROUND

Weight loss is recommended for overweight or obese patients with type 2 diabetes on the basis of short-term studies, but long-term effects on cardiovascular disease remain unknown. We examined whether an intensive lifestyle intervention for weight loss would decrease cardiovascular morbidity and mortality among such patients.

### METHODS

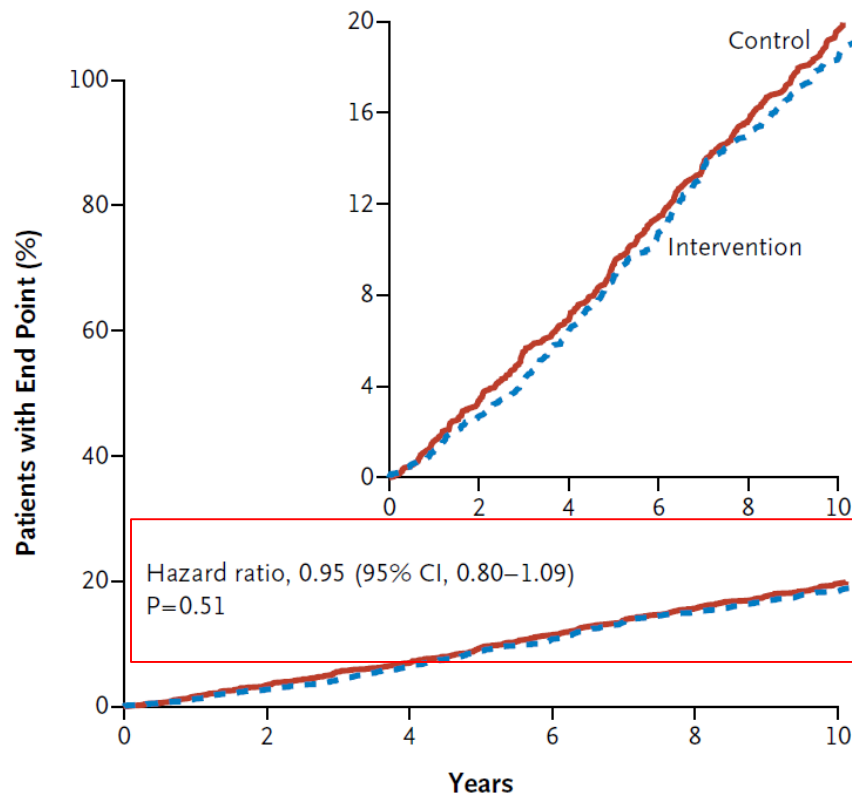
In 16 study centers in the United States, we randomly assigned 5145 overweight or obese patients with type 2 diabetes to participate in an intensive lifestyle intervention that promoted weight loss through decreased caloric intake and increased physical activity (intervention group) or to receive diabetes support and education (control group). The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina during a maximum follow-up of 13.5 years.

### RESULTS

The trial was stopped early on the basis of a futility analysis when the median follow-up was 9.6 years. Weight loss was greater in the intervention group than in the control group throughout the study (8.6% vs. 0.7% at 1 year; 6.0% vs. 3.5% at study end). The intensive lifestyle intervention also produced greater reductions in glycated hemoglobin and greater initial improvements in fitness and all cardiovascular risk factors, except for low-density-lipoprotein cholesterol levels. The primary outcome occurred in 403 patients in the intervention group and in 418 in the control group (1.83 and 1.92 events per 100 person-years, respectively; hazard ratio in the intervention group, 0.95; 95% confidence interval, 0.83 to 1.09;  $P=0.51$ ).

### CONCLUSIONS

An intensive lifestyle intervention focusing on weight loss did not reduce the rate of cardiovascular events in overweight or obese adults with type 2 diabetes. (Funded by the National Institutes of Health and others; Look AHEAD ClinicalTrials.gov number, NCT00017953.)



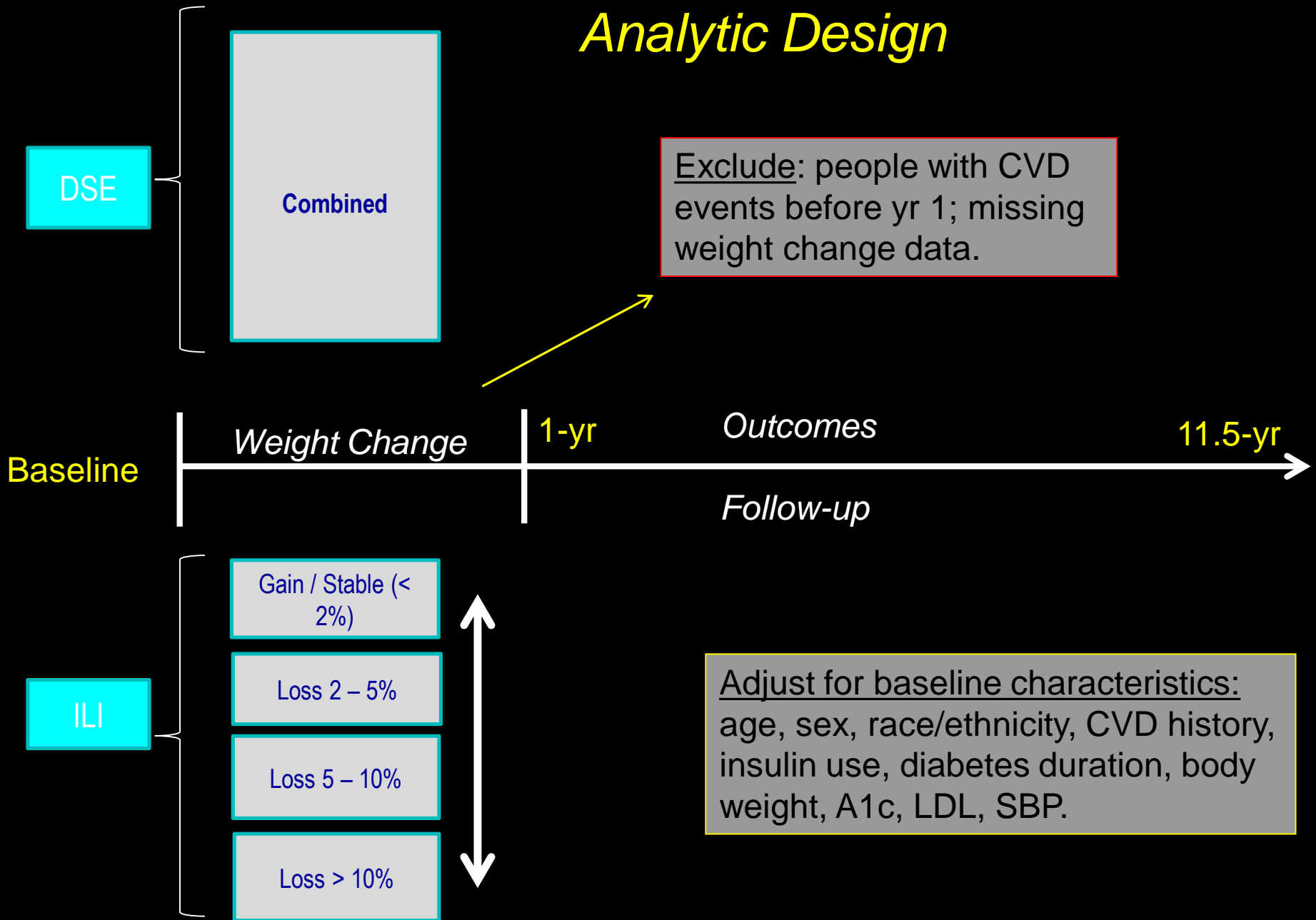
### No. at Risk

Control	2575	2425	2296	2156	2019	688
Intervention	2570	2447	2326	2192	2049	505

Figure 2. Cumulative Hazard Curves for the Primary Composite End Point.



# Analytic Design

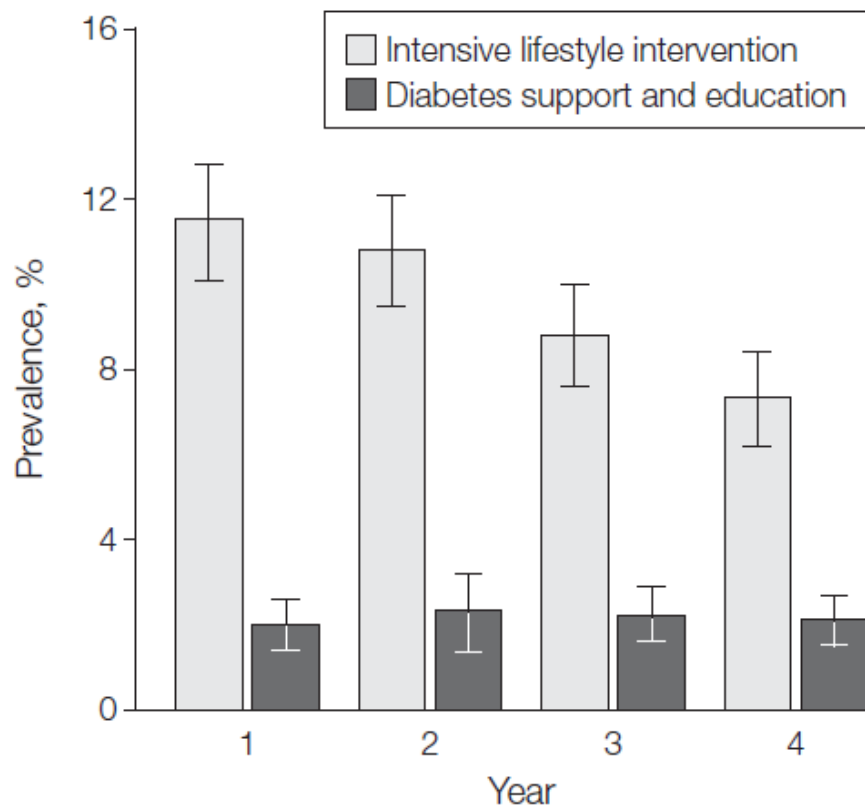


# Comparison of control group (reference) with intensive weight-loss intervention weight loss categories: The Look AHEAD Study

	Intensive lifestyle intervention weight-change categories (percentage weight loss in first year)						p value
	Overall control group (reference)	Gain or stable (<2% loss)	Small loss ( $\geq 2$ –<5%)	Medium loss ( $\geq 5$ –<10%)	Large loss ( $\geq 10$ %)	Hazard ratio per SD weight change	
<b>Primary outcome</b>							
Events per person-years	351/20 891	58/3087	69/3766	114/6446	120/8266	..	..
Crude rate per 100 person-years	1.68	1.88	1.83	1.77	1.45	..	..
Unadjusted hazard ratio (95% CI)	1.00	1.14 (0.86–1.51)	1.09 (0.85–1.42)	1.06 (0.86–1.31)	0.84 (0.68–1.04)	0.88 (0.79–0.98)	0.02
Adjusted hazard ratio* (95% CI)	1.00	1.29 (0.96–1.72)	1.04 (0.80–1.36)	1.15 (0.92–1.43)	0.80 (0.65–0.99), p=0.039†	0.85 (0.76–0.95)	0.006
<b>Secondary outcome</b>							
Events per person-years	503/20 436	82/3009	108/3643	151/6335	173/8136	..	..
Crude rate per 100 person-years	2.46	2.72	2.96	2.38	2.13	..	..
Unadjusted hazard ratio (95% CI)	1.00	1.14 (0.90–1.44)	1.22 (0.99–1.50)	0.97 (0.81–1.17)	0.85 (0.72–1.02)	0.86 (0.78–0.94)	0.0007
Adjusted hazard ratio* (95% CI)	1.00	1.28 (1.01–1.64), p=0.045†	1.19 (0.96–1.47)	1.02 (0.84–1.23)	0.79 (0.66–0.95), p=0.011†	0.82 (0.74–0.90)	<0.0001

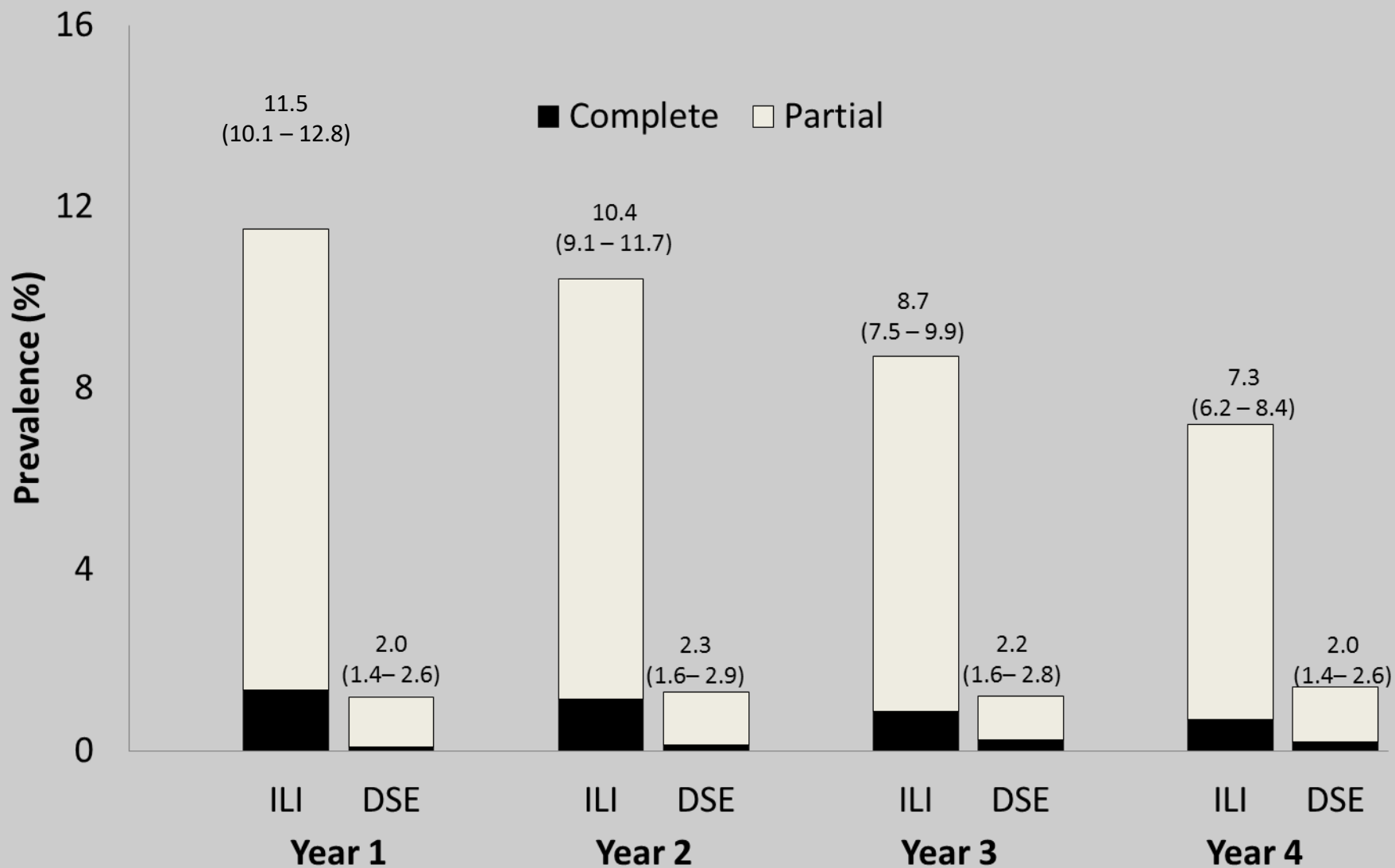
# Association of an Intensive Lifestyle Intervention With Remission of Type 2 Diabetes

**Figure 2.** Prevalence of Any Remission (Partial or Complete) by Intervention Condition and Year

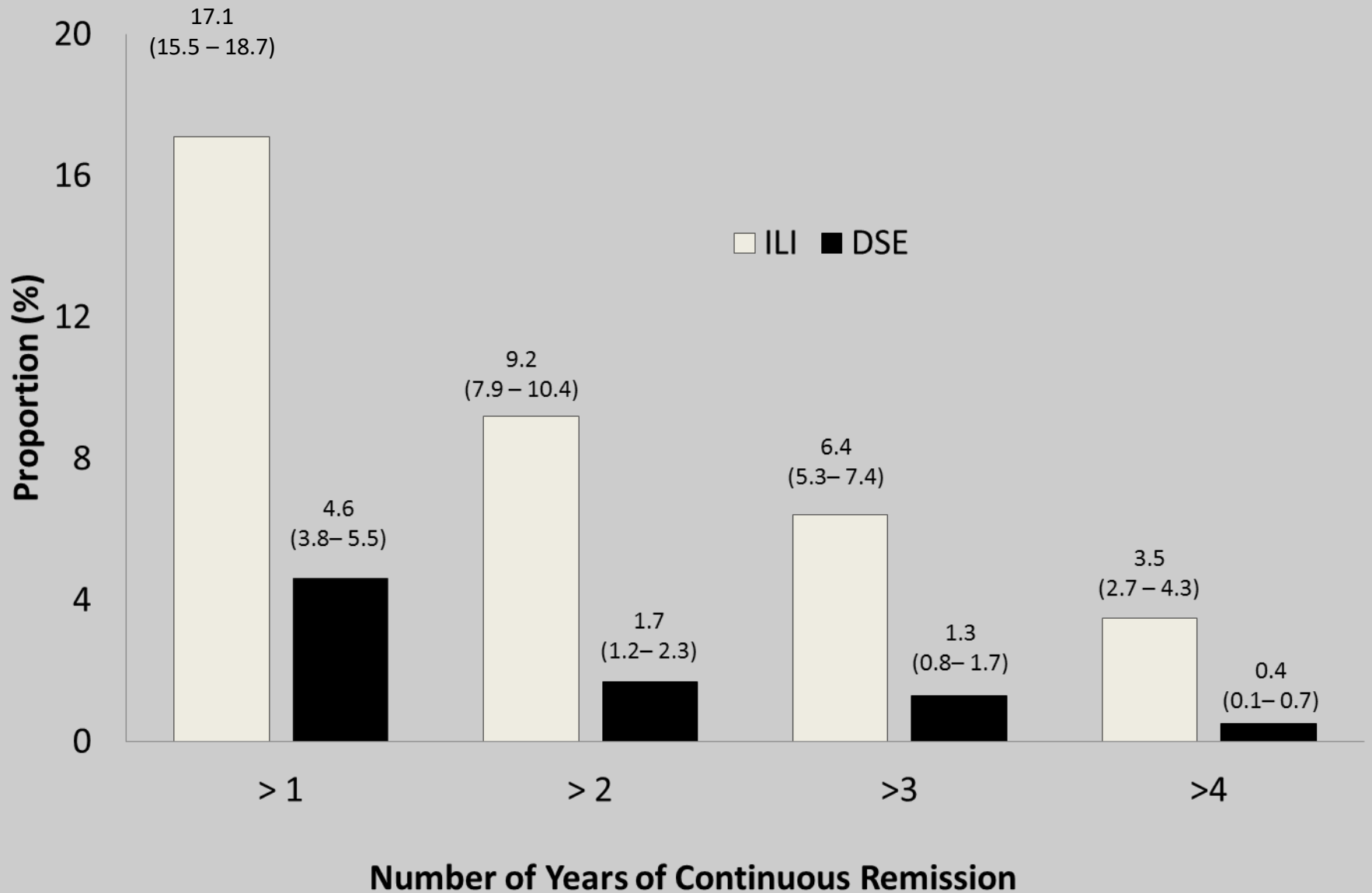


- RCT of 4503 overweight adults with diabetes.
- Net weight loss 7.9% at 1 y; 3.9% at 4y.
- Net fitness improvement of 15.3% at 1 y; 6.4 % at 4 y.
- 1-year remission greatest for ILI subgroups with < 2 yrs DM duration (21%) and low initial A1c (17%).

# Impact of Look AHEAD Intervention on Probability of Remission from Diabetes (Partial or Complete) by Year



# Impact of Look AHEAD Intervention on Number of Years of Continuous Remission from Diabetes (Partial or Complete)



**Table 2.** Odds Ratios and Probability of Any Remission Associated With Key Demographic and Health Status Predictors for the Overall Sample and by Intervention Group<sup>a</sup>

						Overall /	DSE /	ILI
Diabetes duration tertile, y								
Low: 0 to <2	1168 (26.1)	1 [Reference]		1 [Reference]		13.5 (11.6-15.6)	5.1 (3.5-7.3)	21.2 (18.0-24.7)
Middle: 2 to <7	1707 (38.2)	0.42 (0.32-0.54)	<.001	0.43 (0.32-0.58)	<.001	6.1 (5.0-7.4)	1.4 (0.8-2.5)	11.1 (9.1-13.4)
High: ≥7	1597 (35.7)	0.15 (0.10-0.22)	<.001	0.21 (0.14-0.33)	<.001	2.2 (1.6-3.1)	0.5 (0.2-1.4)	4.1 (2.9-5.7)
Body mass index tertile								
Low: <32.5	1501 (33.3)	1 [Reference]		1 [Reference]		7.0 (6.3-8.7)	2.0 (1.2-3.3)	12.4 (10.2-15.0)
Middle: 32.5-37.7	1501 (33.3)	1.02 (0.77-1.35)	.89	0.92 (0.66-1.28)	.62	7.4 (6.2-8.9)	1.8 (1.0-3.0)	13.2 (10.9-15.8)
High: >37.7	1501 (33.3)	0.73 (0.54-0.99)	.04	0.75 (0.53-1.07)	.11	5.4 (4.3-6.7)	2.2 (1.4-3.6)	8.8 (6.9-11.1)
Hemoglobin A <sub>1c</sub> tertile, %								
Low: <6.7	1300 (28.9)	1 [Reference]		1 [Reference]		10.4 (8.9-12.3)	3.6 (2.4-5.4)	17.1 (14.4-20.3)
Middle: 6.7-7.6	1634 (38.2)	0.70 (0.54-0.90)	<.001	0.76 (0.56-1.03)	.07	7.5 (6.3-9.0)	2.0 (1.3-3.3)	13.0 (10.8-15.5)
High: >7.6	1569 (35.7)	0.24 (0.17-0.34)	<.001	0.40 (0.27-0.60)	<.001	2.7 (2.0-3.6)	0.7 (0.3-1.5)	4.9 (3.6-6.7)
No insulin use	2251 (80.7)	1 [Reference]		1 [Reference]		8.1 (7.2-9.0)	2.3 (1.7-3.1)	13.8 (12.3-15.6)
Insulin use	864 (19.3)	0.10 (0.05-0.21)	<.001	0.23 (0.11-0.51)	<.001	0.8 (0.4-1.8)	0.5 (0.1-1.9)	1.2 (0.5-2.9)
1-y Weight loss tertile, %								
Low: <1 (including weight gain)	1464 (33.3)	0.08 (0.05-0.12)	<.001	0.15 (0.08-0.27)	<.001	1.4 (0.9-2.1)	1.1 (0.7-1.9)	2.7 (1.2-5.9)
Middle: 1 to 6.5	1465 (33.4)	0.21 (0.16-0.29)	<.001	0.37 (0.26-0.53)	<.001	3.7 (2.8-4.8)	2.1 (1.3-3.4)	5.4 (3.9-7.3)
High: >6.5	1464 (33.3)	1 [Reference]		1 [Reference]		15.2 (13.4-17.2)	7.1 (4.9-11.1)	16.4 (14.5-18.6)
1-y Fitness change tertile, %								
Low: <-2.3	925 (24.4)	1 [Reference]		1 [Reference]		3.1 (2.1-4.4)	1.1 (0.5-2.4)	7.1 (4.7-10.6)
Middle: 2.3 to <17.9	1593 (42.0)	1.83 (0.77-1.96)	<.001	1.23 (0.77-1.96)	.39	5.5 (4.5-6.7)	2.0 (1.3-3.3)	9.4 (7.5-11.7)
High: ≥17.9	1274 (33.6)	4.31 (1.14-2.86)	<.001	1.80 (1.14-2.86)	.01	12.0 (10.3-13.9)	3.7 (2.2-6.2)	15.6 (13.3-18.1)

# Summary: Findings from Look AHEAD

- **No significant effect** of on the primary outcome of *cardiovascular disease incidence in ITT*.
- **However**, the impact of weight loss intervention on CVD may depend upon the magnitude of response to the intervention.
- **Significant, strong benefits** of the ILI on *physical disability and partial diabetes remission and sleep apnea*.
- **Significant, moderate benefits of ILI** on *chronic kidney disease and depression*.

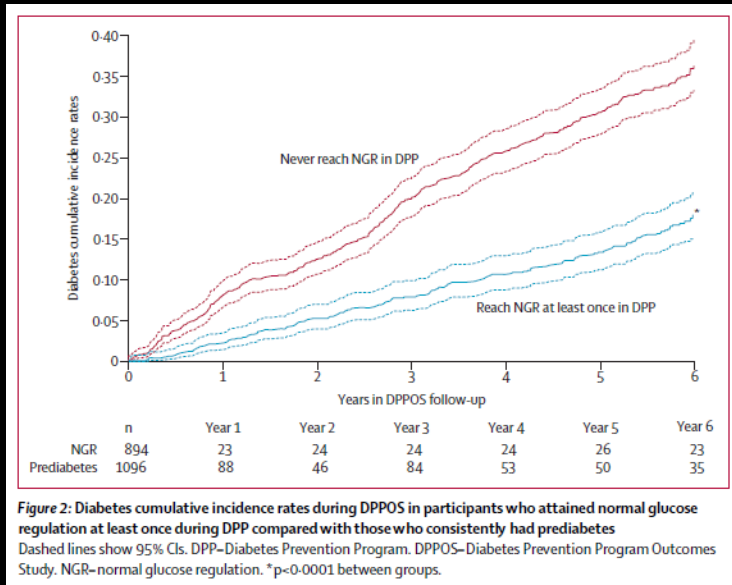
# Challenges (and Special Opportunities for REWIND)

- Engagement and participation in major public health implementation of intensive lifestyle intervention.
- Sustainability of intervention
- Sustainability of effect.
- Unique design opportunities for REWIND:
  - Unique definition of remission (and advantage of maintaining metformin).
  - Multiple clusters (units) with staggered roll-out.
  - Multi-level measurement.
  - 2+ levels of comparable controls.
  - Real World data and real-world implementation.

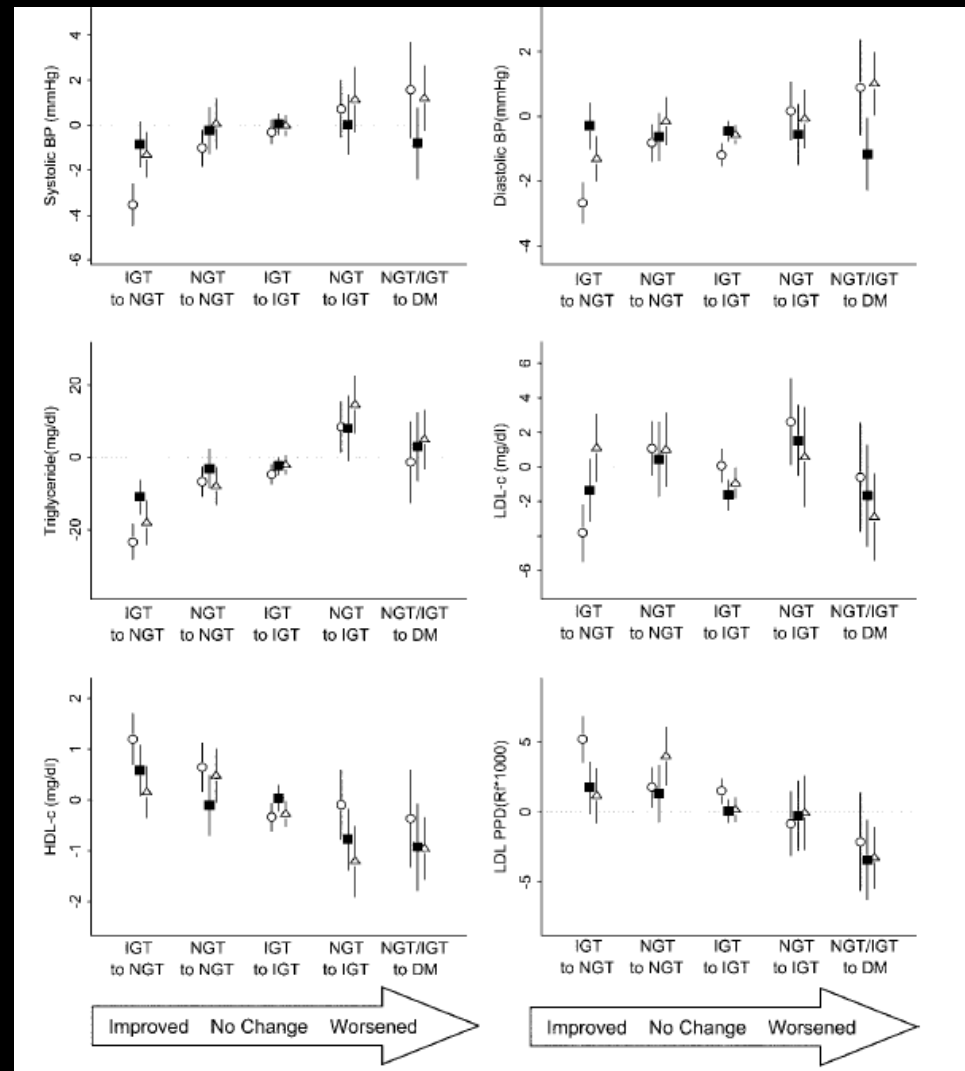


**EXTRAS**

# Effect of Progression From Impaired Glucose Tolerance to Diabetes on Cardiovascular Risk Factors and Its Amelioration by Lifestyle and Metformin



**Findings:** Reversion from IGT to NGT has a large impact on subsequent diabetes incidence and improvement in CVD risk factors.



# Behavioral strategies in diabetes prevention programs: A systematic review of randomized controlled trials

Michael K. Baker<sup>a,\*</sup>, Kylie Simpson<sup>b</sup>, Bradley Lloyd<sup>b</sup>,  
Adrian E. Bauman<sup>c</sup>, Maria A. Fiatarone Singh<sup>a,d</sup>

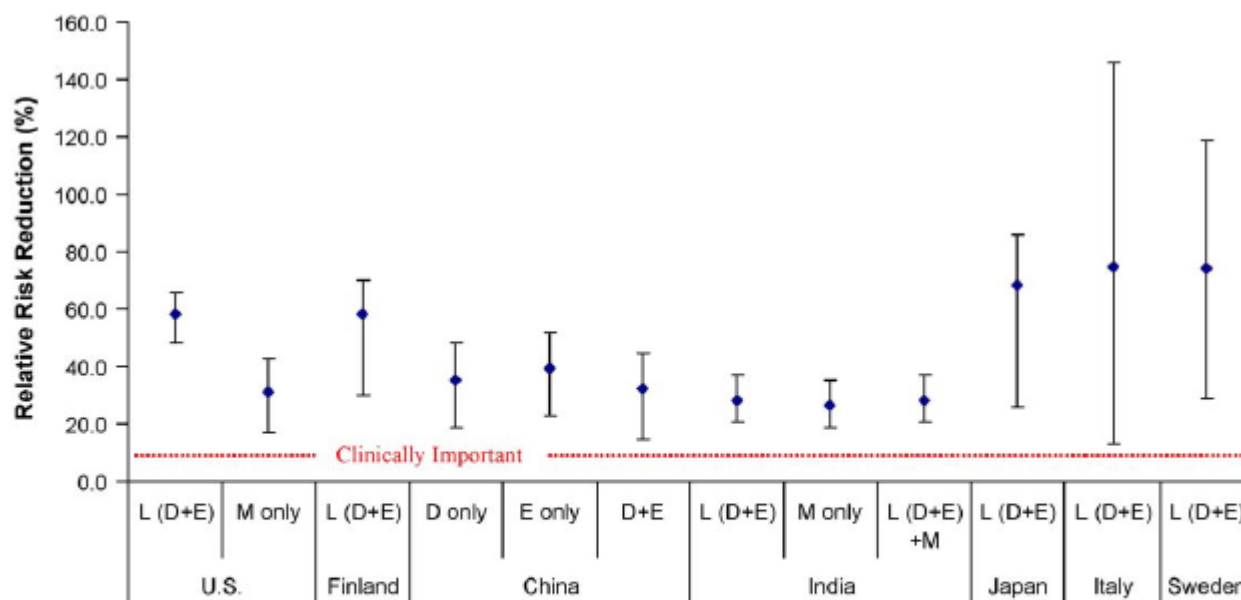
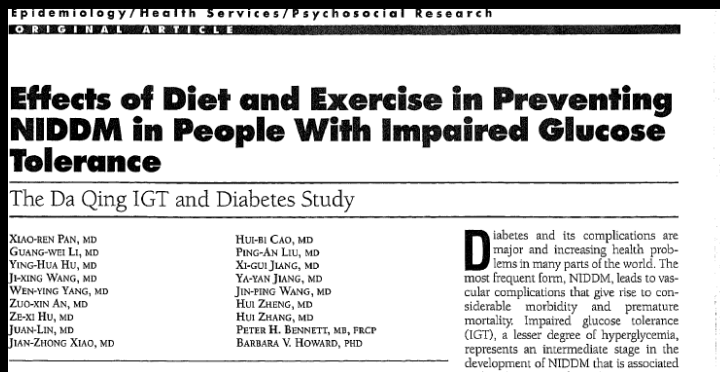


Fig. 2 – Relative risk reduction in all groups. Reported relative risk reduction (95% confidence intervals). \*RRR is calculated at the 95% CI for the studies that did not report a CI. L, lifestyle; D, diet; E, exercise; M, metformin; DPP, Diabetes Prevention Program (USA); DPS, Diabetes Prevention Study (Finland); DQS, Da Qing IGT and Diabetes Study (China); IDPP, Diabetes Prevention Program (India); JDPP, Diabetes Prevention Program (Japan); ADPP, Asti Diabetes Prevention Program (Italy); VIP, Västerbotten Intervention Program (Sweden).

# Diabetes Prevention Studies from China, India and Japan



- 31-46% reduced incidence over 6 years with no weight change

A. Ramachandran · C. Snehalatha · S. Mary ·  
B. Mukesh · A. D. Bhaskar · V. Vijay ·  
Indian Diabetes Prevention Programme (IDPP)

**The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1)**

- 28% reduced incidence over 3yrs with no wt loss.

## Lifestyle Modification and Prevention of Type 2 Diabetes in Overweight Japanese With Impaired Fasting Glucose Levels

*A Randomized Controlled Trial*

Toshikazu Saito, MD, PhD; Makoto Watanabe, MD, PhD; Junko Nishida, MD; Tomono Izumi, BA; Masao Omura, MD, PhD; Toshikazu Takagi, MD; Ryuzo Fukunaga, MD, PhD; Yasutsugu Bandai, MD, PhD; Naoko Tajima, MD, PhD; Yosikazu Nakamura, MD, MPH, FFPH; Masaharu Ito, MD; for the Zensharen Study for Prevention of Lifestyle Diseases Group

- 44% reduced incidence over 4 years with 1.8 % wt loss).

Prevention of type 2 diabetes by lifestyle intervention:  
a Japanese trial in IGT males

Kinori Kosaka<sup>a</sup>, Mitsuihiko Noda<sup>a,\*</sup>, Takeshi Kuzuya<sup>b</sup>

- 67% reduced incidence over 4 years with no wt change.

# Impact of Intensive Lifestyle Intervention on Disability-Free Life Expectancy: The Look AHEAD Study

Edward W. Gregg,<sup>1</sup> Ji Lin,<sup>1</sup>  
Barbara Bardenheier,<sup>1</sup> Haiying Chen,<sup>2</sup>  
W. Jack Rejeski,<sup>2</sup> Xiaohui Zhuo,<sup>3</sup>  
Andrea L. Hergenroeder,<sup>4</sup>  
Stephen B. Kritchevsky,<sup>2</sup> Anne Peters,<sup>5</sup>  
Lynne Wagenknecht,<sup>2</sup> Edward H. Ip,<sup>2</sup> and  
Mark A. Espeland,<sup>2</sup> for the Look AHEAD  
Study Group\*

Diabetes Care 2018;41:1–9 | <https://doi.org/10.2337/dc17-2110>

**Age**

50

ILI

15.3

20.7

DSE

14.4

21.5

60

ILI

12

15.2

DSE

11.1

15.7

70

ILI

9.2

9.9

DSE

8.4

10.2

■ Active ■ Disabled

0

5

10

15

20

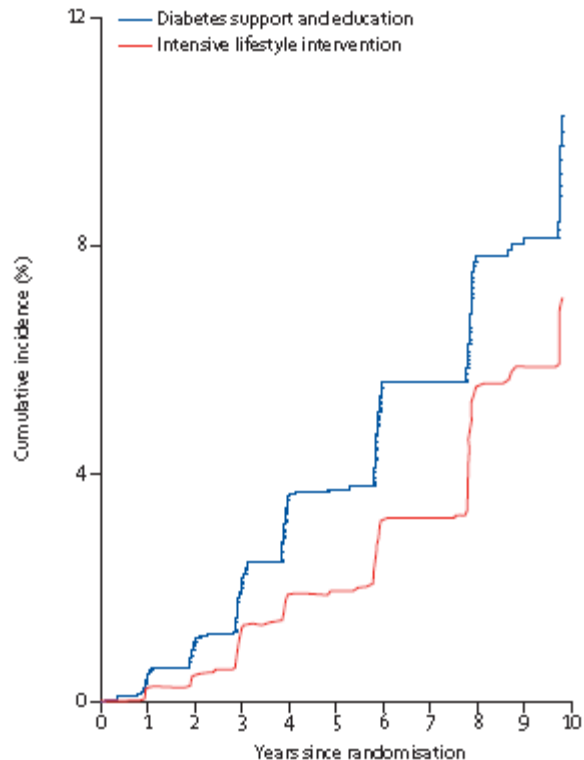
25

30

35

40

# Effect of Lifestyle-Based Weight Loss Intervention on Nephropathy: The Look AHEAD Study



Number at risk	0	1	2	3	4	5	6	7	8	9	10
Diabetes support and education	2408	2325	2203	2092	1914	854					
Intensive lifestyle intervention	2423	2371	2275	2180	1987	889					

Figure 2: Cumulative incidence of very-high-risk chronic kidney disease. Too few observations were available beyond year 10 for reliable estimates.

*Very high risk CKD* defined as:

a) eGFR < 30mL/min

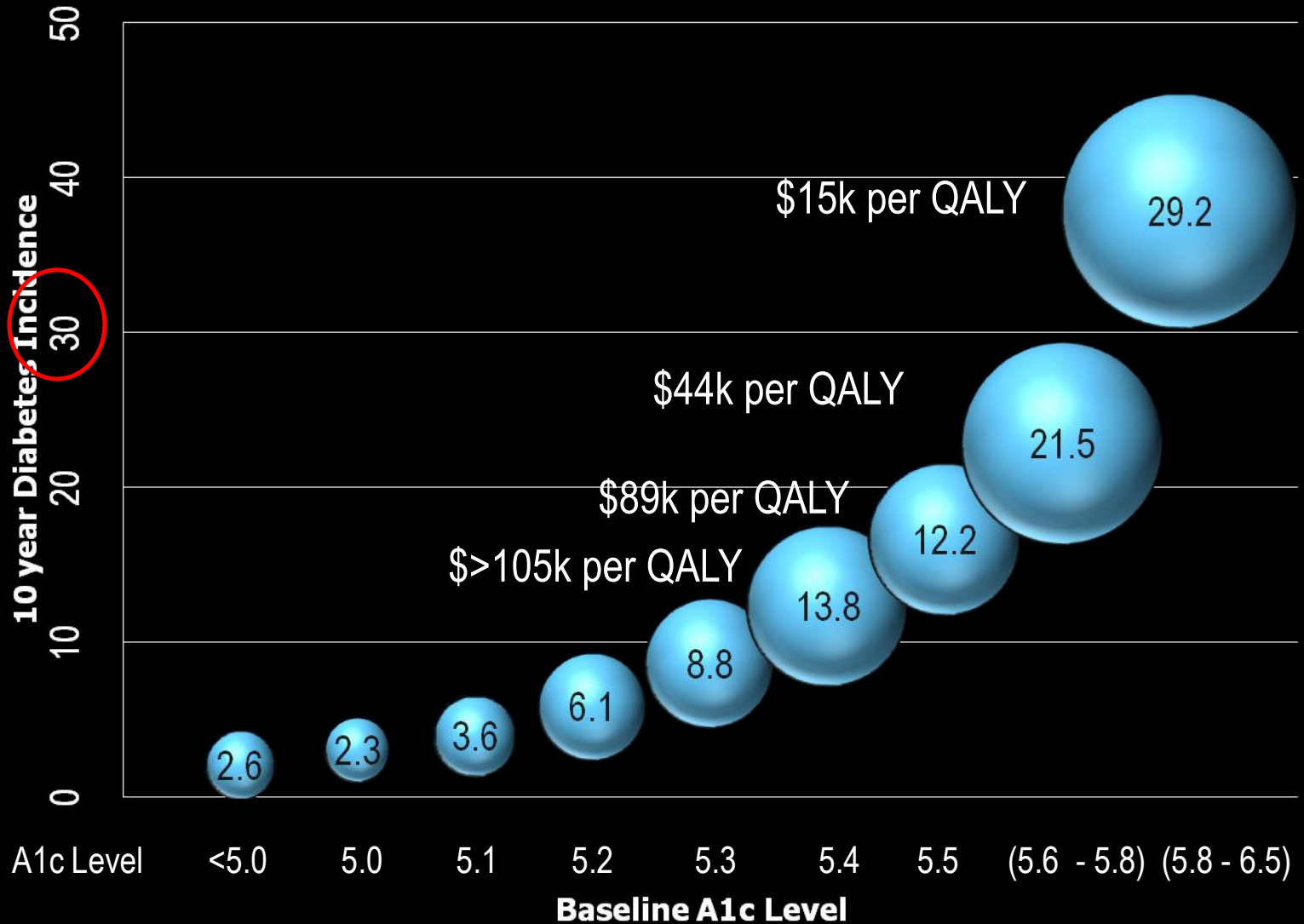
regardless of urine ACR.

a) eGFR < 45 ml/mn and urine ACR  $\geq$  30

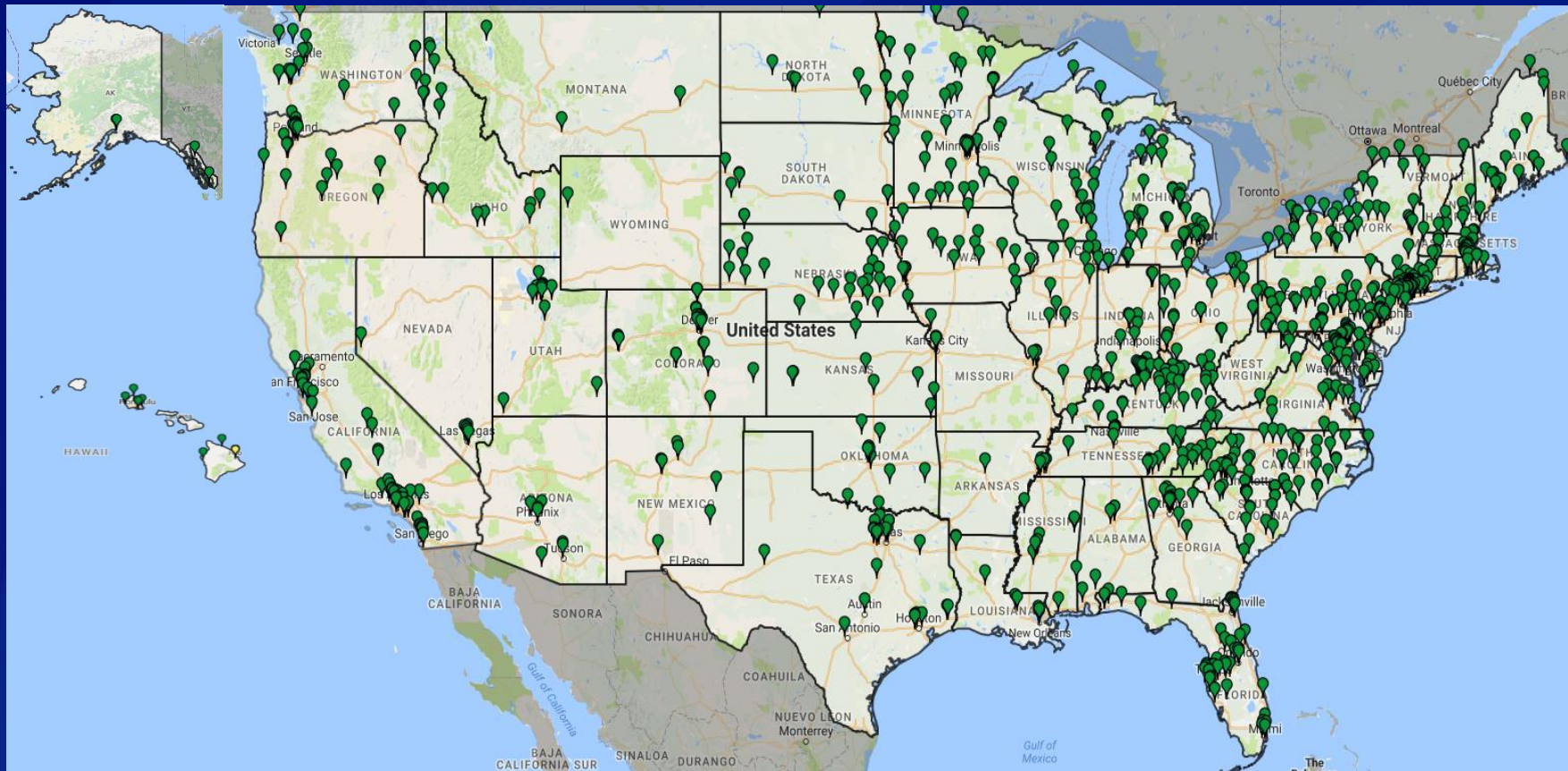
b) eGFR < 60 mL/min and urine ACR > 300

c) Renal replacement therapy

**Relationship of A1c (x-axis) and 10-year Diabetes Incidence (y axis).  
Circle size represents the proportion of total diabetes cases over 10 years.**



# CDC Diabetes Prevention Recognition Program



- 1557 CDC-recognized programs across 50 states/territories.
- >10,300 coaches (lay people; health professionals) trained.
- Serving 156,935 eligible participants.
- 65 commercial health plans providing some coverage for 3M in 11 states



**Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial**

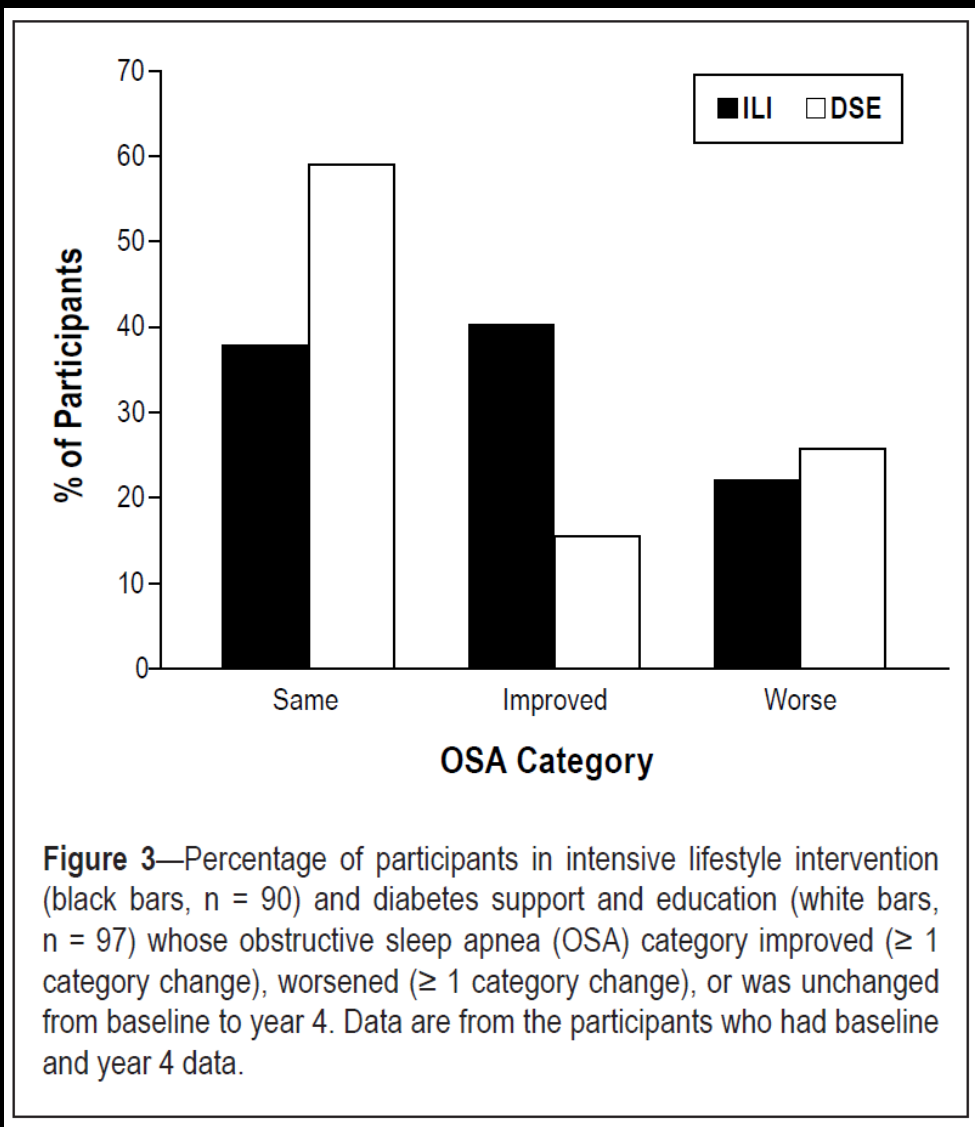
**Intensive lifestyle intervention weight-change categories (percentage weight loss in first year)**

	Overall control group (reference)	Gain or stable (<2% loss)	Small loss (≥2–<5%)	Medium loss (≥5–<10%)	Large loss (≥10%)	Hazard ratio per SD weight change	p value
--	-----------------------------------	---------------------------	---------------------	-----------------------	-------------------	-----------------------------------	---------

**Primary outcome**

Events per person-years	351/20 891	58/3087	69/3766	114/6446	120/8266	..	..
Crude rate per 100 person-years	1.68	1.88	1.83	1.77	1.45	..	..
Unadjusted hazard ratio (95% CI)	1.00	1.14 (0.86–1.51)	1.09 (0.85–1.42)	1.06 (0.86–1.31)	0.84 (0.68–1.04)	0.88 (0.79–0.98)	0.02
Adjusted hazard ratio* (95% CI)	1.00	1.29 (0.96–1.72)	1.04 (0.80–1.36)	1.15 (0.92–1.43)	0.80 (0.65–0.99), p=0.039†	0.85 (0.76–0.95)	0.006

# Long-Term Effect of Weight Loss on Obstructive Sleep Apnea Severity in Obese Patients with Type 2 Diabetes



- Sub-sample of 264 adults With type 2 diabetes and previously diagnosed obstructive sleep apnea
- 4-year assessment of apnea-hypopnea index

## 4-year OSA Remission:

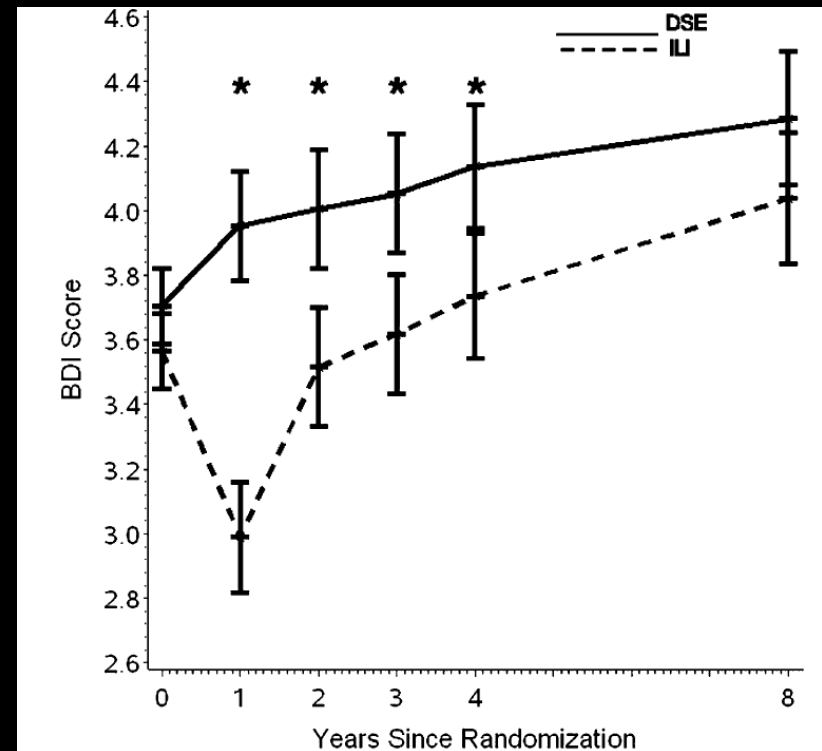
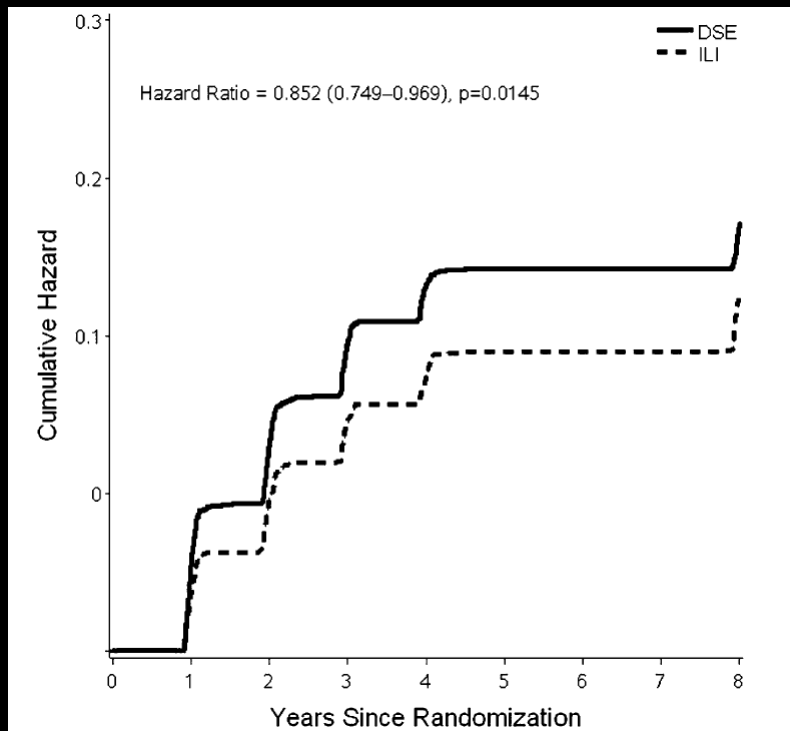
ILI: 20.7%

DSE: 3.6%

# Impact of Look AHEAD Beyond CVD

- Complete/Partial Remission from Diabetes
- Chronic Kidney Disease
- Sleep apnea
- Depression
- Disability and disability-free life expectancy

# Impact of Intensive Lifestyle Intervention on Depression in Type 2 Diabetes: The Look AHEAD Trial



- Reduced depression incidence (RR=0.85) and better BDI scores among ILI participants with no depression.
- No effect of ILI on progression or remission from depression.