Supplementary Results

Baseline characteristics by sex and by study arms are shown in **Table S1.** There were no significant differences between DSE and ILI in site-specific cancer incidence rates (**Tables S2**). In men, risk reductions were greatest for lymphoma (HR, 0.06, 95% CI, 0.01 to 0.45) and pancreatic cancer (HR, 0.36, 95% CI, 0.13, 0.99) **(Table S3**), but the number of cases was very small. There were no differences in site-specific cancer incidence rates among women (**Table S4**). No significant differences were observed between the study arms in site-specific or sex-specific cancer mortality outcomes (**Tables S5-S7**).

Table S1. Baseline characteristics by sex and study arm in 4,859 Look AHEAD participants

	Male (N = 1980)		Female (N = 2879)	
Characteristics	**DSE (N = 985)**	**ILI (N = 995)**	**DSE (N = 1439)**	**ILI (N = 1440)**
Age (years)	59.8±6.68	59.7±6.71	58±6.82	57.6±6.66
Race	.	.	.	.
African American	89 (9.04)	93 (9.35)	292 (20.29)	290 (20.15)
White	749 (76.04)	745 (74.87)	767 (53.3)	777 (54)
Hispanic	96 (9.75)	99 (9.95)	236 (16.4)	232 (16.12)
Other	51 (5.18)	58 (5.83)	144 (10.01)	140 (9.73)
Education	.	.	.	.
<13 years	116 (12.1)	138 (13.98)	377 (26.91)	345 (24.57)
13-16 years	333 (34.72)	325 (32.93)	580 (41.4)	566 (40.31)
>16 years	510 (53.18)	524 (53.09)	444 (31.69)	493 (35.11)
Smoking	.	.	.	.
Never	380 (38.78)	367 (36.96)	847 (58.94)	851 (59.18)
Past	559 (57.04)	575 (57.91)	528 (36.74)	526 (36.58)
Current	41 (4.18)	51 (5.14)	62 (4.31)	61 (4.24)
Drinking	.	.	.	.
None/wk	508 (51.68)	533 (53.62)	1129 (78.79)	1118 (78.07)
1-3/wk	238 (24.21)	237 (23.84)	222 (15.49)	242 (16.9)
4+/wk	237 (24.11)	224 (22.54)	82 (5.72)	72 (5.03)
Height (feet)	5.8±0.22	5.8±0.22	5.3±0.21	5.3±0.21
Weight (lbs)	240.7±40.14	240.4±42.01	209.5±38.32	208.8±39.39
BMI (kg/m^2)	35.2±5.28	35.3±5.69	36.6±6.02	36.3±6.2
Waist Circumference (cm)	118.5±13	118.8±14.01	111.1±13.32	110.5±13.59
SBP (mmHg)	129.2±16.86	127.9±16.46	129.8±17.22	128.2±17.67
DBP (mmHg)	73.6±9.18	73±9.06	68.3±9.22	67.8±9.28
HbA1c (%)	7.3±1.23	7.2±1.15	7.3±1.2	7.3±1.14
eGFR (mL/min/1.73 m2)*	92.2±20.11	92.1±20.3	95.2±23.49	96.4±24.81
Cholesterol (mg/dL)	181.2±35.75	181.8±36.27	196.5±36.67	197.5±38.42
Triglycerides (mg/dL)	162 (111, 233)	162 (113, 231)	145 (105, 206)	150 (107.5, 212)
Insulin Use	154 (16.11)	155 (16.16)	231 (16.76)	216 (15.46)

	Male (N = 1980)		Female (N = 2879)	
Characteristics	**DSE (N = 985)**	**ILI (N = 995)**	**DSE (N = 1439)**	**ILI (N = 1440)**
Statin Use	486 (50.31)	509 (52.31)	566 (40.49)	571 (40.73)
History of CVD	200 (20.3)	213 (21.41)	124 (8.62)	130 (9.03)
Hypertension	824 (83.65)	840 (84.42)	1182 (82.14)	1196 (83.06)
Family History of Diabetes	596 (60.51)	577 (57.99)	1035 (71.92)	963 (66.88)
Self-Reported Diabetes Duration	5 (3, 10)	5 (2, 10)	5 (2, 10)	5 (2, 9)

DSE: Diabetes Support and Education. ILI: Intensive Lifestyle Intervention.

N(%) or mean ± standard deviation (SD) or Median (Q1,Q3).

*eGFR calculated by the Modification of Diet in Renal Disease (MDRD) Study equation.

Table S2. Site-specific cancer incidence by study arm in 4,859 Look AHEAD participants

	DSE		ILI			
Cancer Type	**Number of Events**	**Rate***	**Number of Events**	**Rate***	**HR (95% CI)**	**P-value**
Site						
Esophageal	4	0.2	4	0.2	0.98 (0.25, 3.93)	0.98
Stomach	7	0.3	5	0.2	0.70 (0.22, 2.22)	0.55
Colon/Rectal	30	1.2	28	1.1	0.92 (0.55, 1.53)	0.74
Gallbladder or Liver	3	0.1	7	0.3	2.28 (0.59, 8.83)	0.23
Pancreas	20	0.8	11	0.4	0.55 (0.26, 1.14)	0.11
Lung	17	0.7	19	0.7	1.09 (0.57, 2.10)	0.79
Melanoma	17	0.7	16	0.6	0.92 (0.47, 1.82)	0.82
Post-menopause breast (women only)	78	5.1	62	4.0	0.78 (0.56, 1.09)	0.14
Ovary or Uterine, including co-existing (women only)	15	1.0	16	1.0	1.04 (0.52, 2.11)	0.91
Prostate (men only)	58	5.7	68	6.6	1.15 (0.81, 1.64)	0.42
Bladder	17	0.7	12	0.5	0.69 (0.33, 1.45)	0.33
Kidney	17	0.7	11	0.4	0.63 (0.3, 1.35)	0.24
Thyroid	10	0.4	7	0.3	0.69 (0.26, 1.8)	0.44
Lymphoma	23	0.9	12	0.5	0.51 (0.25, 1.02)	0.06
Myeloma	1	0.0	7	0.3	6.88 (0.85, 55.96)	0.07
Leukemia	11	0.4	9	0.3	0.80 (0.33, 1.93)	0.62
Other	24	0.9	38	1.4	1.56 (0.93, 2.60)	0.09

DSE: Diabetes Support and Education. ILI: Intensive Lifestyle Intervention. HR: hazard ratio

*Rate per 1,000 person-years

Table S3. Site-specific cancer Incidence by study arm in 1,980 male Look AHEAD participants

	DSE		ILI			
Cancer Type	**Number of Events**	**Rate***	**Number of Events**	**Rate***	**HR (95% CI)**	**P-value**
Site						
Esophageal	4	0.4	4	0.4	0.97(0.24, 3.89)	0.97
Stomach	3	0.3	1	0.1	0.33(0.03, 3.15)	0.33
Colon/Rectal	15	1.4	17	1.6	1.11(0.55, 2.22)	0.77
Gallbladder or liver	3	0.3	2	0.2	0.65(0.11, 3.86)	0.63
Pancreas	14	1.3	5	0.5	0.36(0.13, 0.99)	0.05
Lung	11	1.1	8	0.7	0.70(0.28, 1.74)	0.45
Melanoma	11	1.1	13	1.2	1.15(0.52, 2.57)	0.73
Prostate	58	5.7	68	6.6	1.15(0.81, 1.63)	0.43
Bladder	13	1.3	9	0.8	0.67(0.29, 1.57)	0.36
Kidney	7	0.7	6	0.6	0.84(0.28, 2.49)	0.75
Thyroid	2	0.2	0	0.0	-	-
Lymphoma	16	1.5	1	0.1	0.06(0.01, 0.45)	0.006
Myeloma	1	0.1	4	0.4	3.93(0.44, 35.20)	0.22
Leukemia	5	0.5	4	0.4	0.77(0.21, 2.88)	0.7
Other	14	1.3	23	2.2	1.60(0.82, 3.10)	0.17

DSE: Diabetes Support and Education. ILI: Intensive Lifestyle Intervention. HR: hazard ratio

*Rate per 1,000 person-years

Table S4. Site-specific cancer Incidence by study arm in 2,879 female Look AHEAD participants

	DSE		ILI			
Cancer Site	**Number of Events**	**Rate***	**Number of Events**	**Rate***	**HR (95% CI)**	**P-value**
Site						
Stomach	4	0.3	4	0.3	0.99(0.25, 3.95)	0.99
Colon/Rectal	15	1.0	11	0.7	0.72(0.33, 1.58)	0.42
Gallbladder or Liver	0	0.0	5	0.3	-	-
Pancreas	6	0.4	6	0.4	0.98(0.32, 3.04)	0.97
Lung	6	0.4	11	0.7	1.81(0.67, 4.89)	0.24
Melanoma	6	0.4	3	0.2	0.49(0.12, 1.97)	0.32
Breast (Post-Menopause)	78	5.1	62	4.0	0.78(0.56, 1.09)	0.15
Ovary or Uterine, including co-existing	15	1.0	16	1.0	1.05(0.52, 2.12)	0.89
Bladder	4	0.3	3	0.2	0.74(0.16, 3.29)	0.69
Kidney	10	0.6	5	0.3	0.49(0.17, 1.44)	0.19
Thyroid	8	0.5	7	0.4	0.86(0.31, 2.38)	0.78
Lymphoma	7	0.4	11	0.7	1.55(0.60, 4.00)	0.36
Myeloma	0	0.0	3	0.2	-	-
Leukemia	6	0.4	5	0.3	0.82(0.25, 2.69)	0.75
Other	10	0.6	15	0.9	1.48(0.66, 3.29)	0.34

DSE: Diabetes Support and Education. ILI: Intensive Lifestyle Intervention. HR: hazard ratio

*Rate per 1,000 person-years

Table S5. Site-specific cancer Mortality by study arm in 4,859 Look AHEAD participants

	DSE		**ILI**			
Cancer Type	**Number of Events**	**Rate***	**Number of Events**	**Rate***	**HR (95% CI)**	**P-value**
Site						
Esophageal	2	0.1	3	0.1	1.46 (0.24, 8.73)	0.68
Stomach	4	0.2	4	0.1	0.98 (0.24, 3.91)	0.97
Colon/Rectal	7	0.3	7	0.3	0.98 (0.34, 2.79)	0.97
Gallbladder or Liver	5	0.2	7	0.3	1.36 (0.43, 4.30)	0.60
Pancreas	15	0.6	8	0.3	0.52 (0.22, 1.23)	0.14
Lung	12	0.5	12	0.4	0.90 (0.40, 2.03)	0.79
Melanoma	0	0	2	0.1	--	-
Post-menopause breast (women only)	6	0.4	3	0.2	0.49 (0.12, 1.96)	0.31
Ovary/Uterine, including co-existing (women only)	3	0.2	5	0.3	1.63 (0.39, 6.81)	0.51
Prostate (men only)	3	0.3	3	0.3	0.97 (0.20, 4.80)	0.97
Bladder	4	0.2	0	0	--	-
Kidney	3	0.1	2	0.1	0.65 (0.11, 3.88)	0.64
Myeloma	0	0	3	0.1	--	-
Leukemia	2	0.1	3	0.1	1.47 (0.25, 8.79)	0.67
Lymphoma	6	0.2	0	0	--	-
Others	13	0.5	19	0.7	1.43 (0.71, 2.9)	0.32

DSE: Diabetes Support and Education. ILI: Intensive Lifestyle Intervention. HR: hazard ratio

*Rate per 1,000 person-years

Table S6. Site-specific cancer mortality by study arm in 1,980 male Look AHEAD participants

	DSE		ILI			
Cancer Type	**Number of Events**	**Rate***	**Number of Events**	**Rate***	**HR (95% CI)**	**P-value**
Site						
Esophageal	2	0.2	3	0.3	1.44(0.24, 8.62)	0.69
Stomach/Gastric	2	0.2	1	0.1	0.48(0.04, 5.31)	0.55
Colon/Rectal	3	0.3	3	0.3	0.97(0.20, 4.83)	0.97
Gallbladder or Liver	5	0.5	3	0.3	0.59(0.14, 2.45)	0.46
Pancreas	10	1.0	5	0.5	0.48(0.17, 1.42)	0.19
Lung	8	0.8	5	0.5	0.60(0.20, 1.85)	0.38
Melanoma	0	0.0	2	0.2	-	-
Prostate	3	0.3	3	0.3	0.95(0.19, 4.70)	0.95
Bladder	4	0.4	0	0.0	-	-
Kidney	2	0.2	0	0.0	-	-
Lymphoma	3	0.3	0	0.0	-	-
Myeloma	0	0.0	2	0.2	-	-
Leukemia	1	0.1	1	0.1	0.97(0.06, 15.56)	0.98
Other	7	0.7	11	1.0	1.51(0.59, 3.90)	0.39

DSE: Diabetes Support and Education. ILI: Intensive Lifestyle Intervention. HR: hazard ratio

*Rate per 1,000 person-years

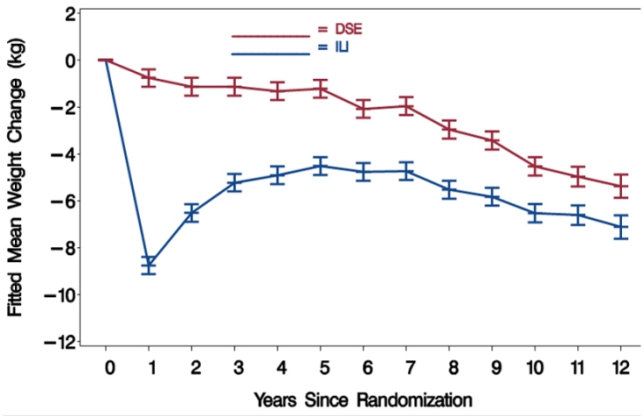
Table S7. Site-specific cancer mortality by study arm in 2,879 female Look AHEAD participants

	DSE		ILI			
Cancer Type	**Number of Events**	**Rate***	**Number of Events**	**Rate***	**HR (95% CI)**	**P-value**
Site						
Stomach	2	0.1	3	0.2	1.47(0.25, 8.80)	0.67
Colon/Rectal	4	0.3	4	0.3	0.98(0.24, 3.92)	0.98
Gallbladder/Liver	0	0.0	4	0.3	-	-
Pancreas	5	0.3	3	0.2	0.58(0.14, 2.45)	0.46
Lung	4	0.3	6	0.4	1.48(0.42, 5.25)	0.54
Breast (Post-Menopause)	6	0.4	3	0.2	0.49(0.12, 1.97)	0.32
Ovary/Uterine, including co-existing	3	0.2	5	0.3	1.64(0.39, 6.85)	0.50
Kidney	1	0.1	2	0.1	1.97(0.18, 21.67)	0.58
Lymphoma	3	0.2	0	0.0	-	-
Myeloma	0	0.0	1	0.1	-	-
Leukemia	1	0.1	2	0.1	1.96(0.18, 21.61)	0.58
Other	6	0.4	8	0.5	1.32(0.46, 3.79)	0.61

DSE: Diabetes Support and Education. ILI: Intensive Lifestyle Intervention. HR: hazard ratio

*Rate per 1,000 person-years

Appendix Figure 1: Weight Change Over 12 Years of Follow−up



338x190mm (96 x 96 DPI)

Appendix: Look AHEAD Research Group at End of Continuation

Clinical Sites

The Johns Hopkins University Frederick L. Brancati, MD, MHS[1*]; Jeanne M. Clark, MD, MPH[1] (Co-Principal Investigators); Lee Swartz[2]; Jeanne Charleston, RN[3]; Lawrence Cheskin, MD[3]; Richard Rubin, PhD[3*]; Jean Arceci, RN; David Bolen; Danielle Diggins; Mia Johnson; Joyce Lambert; Sarah Longenecker; Kathy Michalski, RD; Dawn Jiggetts; Chanchai Sapun; Maria Sowers; Kathy Tyler

*deceased

Pennington Biomedical Research Center George A. Bray, MD[1]; Allison Strate, RN[2]; Frank L. Greenway, MD[3]; Donna H. Ryan, MD[3]; Donald Williamson, PhD[3]; Timothy Church, MD[3] ; Catherine Champagne, PhD, RD; Valerie Myers, PhD; Jennifer Arceneaux, RN; Kristi Rau; Michelle Begnaud, LDN, RD, CDE; Barbara Cerniauskas, LDN, RD, CDE; Crystal Duncan, LPN; Helen Guay, LDN, LPC, RD; Carolyn Johnson, LPN, Lisa Jones; Kim Landry; Missy Lingle; Jennifer Perault; Cindy Puckett; Marisa Smith; Lauren Cox; Monica Lockett, LPN

The University of Alabama at Birmingham Cora E. Lewis, MD, MSPH[1]; Sheikilya Thomas, PhD,MPH[2]; Monika Safford, MD[3]; Stephen Glasser, MD[3]; Vicki DiLillo, PhD[3]; Gareth Dutton, PhD, Charlotte Bragg, MS, RD, LD; Amy Dobelstein; Sara Hannum; Anne Hubbell, MS; Jane King, MLT; DeLavallade Lee; Andre Morgan; L. Christie Oden; Janet Wallace, MS; Cathy Roche, PhD, RN, BSN; Jackie Roche; Janet Turman

Harvard Center

Massachusetts General Hospital. David M. Nathan, MD[1]; Enrico Cagliero, MD[3]; Heather Turgeon, RN, BS, CDE[2]; Barbara Steiner, EdM; Valerie Goldman, MS, RDN[2]; Linda Delahanty, MS, RDN[3]; Ellen Anderson, MS, RDN[3]; Laurie Bissett, MS, RDN; Christine Stevens, RN; Mary Larkin, RN; Kristen Dalton, BS, Roshni Singh, BS

Joslin Diabetes Center: Edward S. Horton, MD[1]; Sharon D. Jackson, MS, RD, CDE[2]; Osama Hamdy, MD, PhD[3]; A. Enrique Caballero, MD[3]; Sarah Bain, BS; Elizabeth McKinney, BSN, RN; Barbara Fargnoli, MS,RD; Jeanne Spellman, BS, RD; Kari Galuski, RN; Ann Goebel-Fabbri, PhD; Lori Lambert, MS, RD; Sarah Ledbury, MEd, RD; Maureen Malloy, BS; Kerry Ovalle, MS, RCEP, CDE

Beth Israel Deaconess Medical Center: George Blackburn, MD, PhD[1]; Christos Mantzoros, MD, DSc[3]; Ann McNamara, RN

University of Colorado Anschutz Medical Campus James O. Hill, PhD[1]; Marsha Miller, MS RD[2]; Holly Wyatt, MD[3] , Brent Van Dorsten, PhD[3]; Judith Regensteiner, PhD[3]; Debbie Bochert; Gina Claxton-Malloy RD Ligia Coelho, BS; Paulette Cohrs, RN, BSN; Susan Green; April Hamilton, BS, CCRC; Jere Hamilton, BA; Eugene Leshchinskiy; Loretta Rome, TRS; Terra Thompson, BA, Kirstie Craul, RD, CDE; Cecilia Wang, MD

Baylor College of Medicine John P. Foreyt, PhD[1]; Rebecca S. Reeves, DrPH, RD[2];

Molly Gee, MEd, RD[2]; Henry Pownall, PhD[3]; Ashok Balasubramanyam, MBBS[3]; Chu-Huang Chen, MD, PhD[3]; Peter Jones, MD[3]; Michele Burrington, RD, RN; Allyson Clark Gardner, MS, RD; Sharon Griggs; Michelle Hamilton; Veronica Holley; Sarah Lee; Sarah Lane Liscum, RN, MPH; Susan Cantu-Lumbreras; Julieta Palencia, RN; Jennifer Schmidt; Jayne Thomas, RD; Carolyn White; Charlyne Wright, RN; Monica Alvarez, PCT

The University of Tennessee Health Science Center
University of Tennessee East. Karen C. Johnson, MD, MPH; Karen L. Wilson, BSN; Mace Coday, PhD[3]; Beate Griffin, RN, BS; Donna Valenski; Polly Edwards; Brenda Fonda; Kim Ward

University of Tennessee Downtown. Helmut Steinburg, MD[3]; Carolyn Gresham, BSN; Moana Mosby, RN; Debra Clark, LPN; Donna Green RN; Abbas E. Kitabchi, PhD, MD (retired)

University of Minnesota Robert W. Jeffery, PhD[1]; Tricia Skarphol, MA[2]; John P. Bantle, MD[3]; J. Bruce Redmon, MD[3]; Richard S. Crow, MD[3]; Scott J. Crow, MD[3]; Manami Bhattacharya, BS; Cindy Bjerk, MS, RD; Kerrin Brelje, MPH, RD; Carolyne Campbell; Mary Ann Forseth, BA; Melanie Jaeb, MPH, RD; Philip Lacher, BBA; Patti Laqua, BS, RD; Birgitta I. Rice, MS, RPh, CHES; Ann D. Tucker, BA; Mary Susan Voeller, BA

St. Luke's Roosevelt Hospital Center F. Xavier Pi-Sunyer, MD[1]; Jennifer Patricio, MS[2]; Carmen Pal, MD[3]; Lynn Allen, MD; Janet Crane, MA, RD, CDN; Lolline Chong, BS, RD; Diane Hirsch, RNC, MS, CDE; Mary Anne Holowaty, MS, CN; Michelle Horowitz, MS, RD; Les James; Raashi Mamtani, MS

University of Pennsylvania Thomas A. Wadden, PhD[1]; Barbara J. Maschak-Carey, MSN, CDE[2]; Robert I. Berkowitz, MD[3]; Gary Foster, PhD[3]; Henry Glick, PhD[3]; Shiriki Kumanyika, PhD RD, MPH[3]; Yuliis Bell, BA ; Raymond Carvajal, PsyD; Helen Chomentowski; Renee Davenport; Lucy Faulconbridge, PhD;
Louise Hesson, MSN, CRNP; Sharon Leonard, RD; Monica Mullen, RD, MPH

University of Pittsburgh John M. Jakicic, PhD[1]; David E. Kelley, MD[1]; Jacqueline Wesche-Thobaben, RN, BSN, CDE[2]; Daniel Edmundowicz, MD[3]; Lin Ewing, PhD, RN[3]; Andrea Hergenroeder, PhD, PT, CCS[3]; Mary L. Klem, PhD, MLIS[3]; Mary Korytkowski, MD[3]; Andrea Kriska, PhD[3]; Lewis H. Kuller, MD, DrPH[3]; Amy D. Rickman, PhD, RD, LDN[3]; Rose Salata, MD[3]; Monica E. Yamamoto, DrPH, RD, FADA[3]; Janet Bonk, RN, MPH; Susan Copelli, BS, CTR; Rebecca Danchenko, BS; Tammy DeBruce, BA; Barbara Elnyczky; David O. Garcia, PhD; George A. Grove, MS; Patricia H. Harper, MS, RD, LDN; Susan Harrier, BS; Diane Heidingsfelder, MS, RD, CDE, LDN; Nicole L. Helbling, MS, RN; Diane Ives, MPH; Janet Krulia, RN, BSN, CDE; Juliet Mancino, MS, RD, CDE, LDN; Anne Mathews, PhD, RD, LDN; Lisa Martich, BS, RD, LDN; Meghan McGuire, MS; Tracey Y. Murray, BS; Anna Peluso, MS; Karen Quirin; Jennifer Rush, MPH; Joan R. Ritchea; Linda Semler, MS, RD, LDN; Karen Vujevich, RN-BC, MSN, CRNP; Kathy Williams, RN, MHA; Donna L. Wolf, PhD

The Miriam Hospital/Brown Medical School Rena R. Wing, PhD[1]; Renee Bright, MS[2]; Vincent Pera, MD[3]; Deborah Tate, PhD[3]; Amy Gorin, PhD[3]; Kara Gallagher, PhD[3]; Amy Bach, PhD; Barbara Bancroft, RN, MS; Anna Bertorelli, MBA, RD; Richard Carey, BS; Tatum Charron, BS; Heather Chenot, MS; Kimberley Chula-Maguire, MS; Pamela Coward, MS, RD; Lisa Cronkite, BS; Julie Currin, MD; Maureen Daly, RN; Caitlin Egan, MS; Erica Ferguson, BS, RD; Linda Foss, MPH; Jennifer Gauvin, BS; Don Kieffer, PhD; Lauren Lessard, BS; Deborah Maier, MS; JP Massaro, BS; Tammy Monk, MS; Rob Nicholson, PhD; Erin Patterson, BS; Suzanne Phelan, PhD; Hollie Raynor, PhD, RD; Douglas Raynor, PhD; Natalie Robinson, MS, RD; Deborah Robles; Jane Tavares, BS

The University of Texas Health Science Center at San Antonio Helen P. Hazuda, PhD[1]; Maria G. Montez, RN, MSHP, CDE[2]; Carlos Lorenzo, MD[3]; Charles F. Coleman, MS, RD; Domingo Granado, RN; Kathy Hathaway, MS, RD; Juan Carlos Isaac, RC, BSN; Nora Ramirez, RN, BSN

VA Puget Sound Health Care System / University of Washington Steven E. Kahn, MB, ChB[1]; Anne Kure, BS[2]; Edward J. Boyko, MD, MPH[3]; Edward Lipkin, MD, PhD[3]; Dace Trence, MD[3]; Subbulaxmi Trikudanathan, MD, MRCP, MMSc[3]; Elaine Tsai, MD[3]; Brenda Montgomery, RN, MS, CDE; Ivy Morgan-Taggart; Jolanta Socha, BS; Lonnese Taylor, RN, BS; Alan Wesley, BA

Southwestern American Indian Center, Phoenix, Arizona and Shiprock, New Mexico William C. Knowler, MD, DrPH[1]; Paula Bolin, RN, MC[2]; Tina Killean, BS[2]; Maria Cassidy-Begay, BSND, RND [2]; Katie Toledo, MS, LPC[2]; Cathy Manus, LPN[3]; Jonathan Krakoff, MD[3]; Jeffrey M. Curtis, MD, MPH[3]; Sara Michaels, MD[3]; Paul Bloomquist, MD[3]; Peter H. Bennett, MB, FRCP[3]; Bernadita Fallis, RN, RHIT, CCS; Diane F. Hollowbreast; Ruby Johnson; Maria Meacham, BSN, RN, CDE; Christina Morris, BA; Julie Nelson, RD; Carol Percy, RN, MS; Patricia Poorthunder; Sandra Sangster; Leigh A. Shovestull, RD, CDE; Miranda Smart; Janelia Smiley; Teddy Thomas, BS

University of Southern California Anne Peters, MD[1]; Siran Ghazarian, MD[2]; Elizabeth Beale, MD[3]; Kati Konersman, RD, CDE; Brenda Quintero-Varela; Edgar Ramirez; Gabriela Rios, RD; Gabriela Rodriguez, MA; Valerie Ruelas MSW, LCSW; Sara Serafin-Dokhan; Martha Walker, RD

Coordinating Center

Wake Forest University Mark A. Espeland, PhD[1]; Judy L. Bahnson, BA, CCRP[3]; Lynne E. Wagenknecht, DrPH[1]; David Reboussin, PhD[3]; W. Jack Rejeski, PhD[3]; Alain G. Bertoni, MD, MPH[3]; Wei Lang, PhD[3]; David Lefkowitz, MD[3]; Patrick S. Reynolds, MD[3]; Denise Houston, PhD[3]; Mike E. Miller, PhD[3]; Laura D. Baker, PhD[3]; Nicholas Pajewski, PhD[3]; Stephen R. Rapp, PhD[3]; Stephen Kritchevsky, PhD[3]; Haiying Chen, PhD, MM[3]; Valerie Wilson, MD[3]; Delia S. West, PhD[3]; Ron Prineas, MD[3]; Tandaw Samdarshi, MD[3]; Amelia Hodges, BS, CCRP[2]; Karen Wall[2]; Carrie C. Williams, MA, CCRP[2]; Andrea Anderson, MS; Jerry M. Barnes, MA; Tara D. Beckner; Delilah R. Cook; Valery S. Effoe, MD, MS; Melanie Franks, BBA; Katie Garcia, MS; Sarah A. Gaussoin, MS; Candace

Goode; Michelle Gordon, MS; Lea Harvin, BS; Mary A. Hontz, BA; Don G. Hire, BS; Patricia Hogan, MS; Mark King, BS; Kathy Lane, BS; Rebecca H. Neiberg, MS; Julia T. Rushing, MS; Debbie Steinberg, BS; Jennifer Walker, MS; Michael P. Walkup, MS;

Central Resources Centers

Central Laboratory, Northwest Lipid Metabolism and Diabetes Research Laboratories
Santica M. Marcovina, PhD, ScD[1]; Jessica Hurting[2]; John J. Albers, PhD[3], Vinod Gaur, PhD[4]

ECG Reading Center, EPICARE, Wake Forest University School of Medicine
Elsayed Z. Soliman MD, MSc, MS[1]; Charles Campbell [2]; Zhu-Ming Zhang, MD[3]; Mary Barr; Susan Hensley; Julie Hu; Lisa Keasler; Yabing Li, MD

Hall-Foushee Communications, Inc.
Richard Foushee, PhD; Nancy J. Hall, MA

Federal Sponsors

National Institute of Diabetes and Digestive and Kidney Diseases Mary Evans, PhD; Van S. Hubbard, MD, PhD; Susan Z. Yanovski, MD

National Heart, Lung, and Blood Institute Lawton S. Cooper, MD, MPH; Peter Kaufman, PhD, FABMR; Mario Stylianou, PhD

Centers for Disease Control and Prevention Edward W. Gregg, PhD; Ping Zhang, PhD

---

1 Principal Investigator
2 Program Coordinator
3 Co-Investigator
All other Look AHEAD staff members are listed alphabetically by site.

PROTOCOL

ACTION FOR HEALTH IN DIABETES

Revised Look AHEAD – Continuation Trial

Approved by the Look AHEAD
Protocol Review Committee
First Issue February 06, 2001
First Revision, May 10, 2001
Second Revision, October 28, 2002
Third Revision, May 16, 2003
Fourth Revision, July 28, 2005
Amendment to Fourth Revision, September 1, 2005
Fifth Revision, November 4, 2005
Sixth Revision, August 20, 2007
Seventh Revision, April 29, 2009
Eighth Revision, October 23, 2009
Ninth Revision, September 5, 2011
Tenth Revision, November 7, 2012
Eleventh Revision, June 27, 2013
Twelfth Revision, August 26, 2013

ADDENDUM TO Look AHEAD PROTOCOL:

Action for Health in Diabetes Continuation (Look AHEAD-C)

1. EXECUTIVE SUMMARY

Background

The aging of the population and the epidemic of obesity have led to a rapid increase in the number of older, obese individuals with diabetes. Little is known about the long-term health effects of lifestyle interventions designed to lower weight and increase physical activity in this population. The Look AHEAD Continuation (Look AHEAD-C) builds on the extraordinary retention and adherence of the Look AHEAD trial to continue it, adding assessments of critical outcomes, to determine the long-term impact of 9-11 years of intensive lifestyle intervention (ILI) on the health problems of greatest concern in older, obese individuals with type 2 diabetes.

Objectives

The primary objectives of Look AHEAD-C are to examine the relative impact of random assignment to 9-11 years of intensive lifestyle intervention to promote and maintain weight loss and increased physical activity on 1) physical function and mobility disability and 2) cognitive function and cognitive impairment. Secondary objectives include additional health-related outcomes of importance to older individuals and to accrue additional power to evaluate secondary and tertiary outcomes of Look AHEAD.

Study Cohort

All participants currently participating in the Look AHEAD trial will be invited to enroll in Look AHEAD-C.

Study Interventions

No interventions will be provided as part of Look AHEAD-C.

Outcomes

The primary physical function outcome is a composite based on a battery of physical function measures and a timed 400 meter walk. The primary cognitive outcome measure is a composite developed from a battery of standardized tests. Important secondary outcomes include adjudicated mobility disability and cognitive impairment (i.e. either mild cognitive impairment or dementia) and individual physical function and cognitive function measures. Other measures include measures of microvascular complications (including renal disease and neuropathy), depression, fractures, and cancers. Look AHEAD-C will continue to assess cardiovascular disease events, weight, physical activity, cardiovascular risk factors, health related quality of life, health care utilization and costs, medications, falls, biomarkers from blood and urine, and weight control strategies.

Analyses

The primary analyses will follow intention to treat to compare cohorts formed by the original randomization. All longitudinal data will be used in these analyses, including any measures collected during the intervention phase of the Look AHEAD trial on individuals who do not contribute data to Look AHEAD-C.

2. BACKGROUND AND RATIONALE

History of Look AHEAD

Look AHEAD is a two-arm randomized clinical trial to examine the health effects of ILI to achieve and maintain weight loss by decreasing caloric intake and increasing physical activity. It enrolled 5,145 overweight/obese volunteers with type 2 diabetes. Its primary hypothesis was that the incidence rate of the first post-randomization occurrence of a composite outcome, which included fatal and non-fatal myocardial infarction and stroke, hospitalization for angina, and cardiovascular disease (CVD) death, over a planned follow-up period of up to 13.5 years would be reduced among participants assigned to the ILI compared to those assigned to DSE. Three composite secondary outcomes were also examined: 1) cardiovascular death, myocardial infarction (fatal or non-fatal), and stroke (fatal or non-fatal); 2) death (all causes), myocardial infarction, stroke, and hospitalization for angina; and 3) death (all causes), myocardial infarction, stroke, hospitalization for angina, coronary artery bypass grafting, percutaneous coronary angioplasty, hospitalization for heart failure, carotid endarterectomy, or peripheral vascular procedures such as bypass or angioplasty. On 9/14/12, the Data and Safety Monitoring Board (DSMB) informed the study group: "The DSMB recommends that the study proceed, but with a major modification. Based on preliminary analyses of the data currently being collected, there is sufficient evidence to conclude that the Intense Lifestyle Intervention (ILI) and Diabetes Support and Education (DSE) arms are not significantly different for the primary and secondary study hypotheses and pre-specified subgroup analyses. This is corroborated by formal futility analyses... Because of the potential importance of completion of ancillary studies and additional data collection that could be valuable for exploratory analyses, the DSMB recommends conversion of the study to a longitudinal cohort study without continuation of the ILI intervention…." The NIDDK concurred with the recommendation. Since this date, Look AHEAD has modified its protocol, informed participants of these changes, and developed the first set of high priority publications from the trial.

Rationale for Continuing to Follow Look AHEAD

Of the 5,145 overweight and obese participants with diabetes that Look AHEAD enrolled, 59% were female, 37% were from traditionally under-represented ethnic/racial groups, 14% had a history of CVD, and 15% were taking insulin. Participants averaged 59 years of age and a BMI 35.9 kg/m^2 at baseline. After 9-11 years of follow-up, the trial had retained 93% of its surviving participants. In 2011, 99% consented to participate in a 2 year trial extension. The ILI group lost an average of 8.6% of their body weight at Year 1 compared to 0.7% in DSE [Look AHEAD, 2007] and has maintained significantly greater weight losses throughout follow-up. At Year 8, 50% of the ILI participants had maintained $\geq$5% weight loss. These losses are the best long-term results ever obtained with lifestyle intervention; follow-up of the cohort to determine whether weight losses can be maintained without further intervention is critical. In addition, the ILI produced marked differences in cardiovascular fitness at Years 1 and 4 as measured by exercise treadmill test (when fitness was last assessed) [Jakicic, 2010]. Individuals assigned to ILI had greater improvements in HbA1c throughout all years of the study, with less use of insulin [Look AHEAD, 2007; Redmon, 2010; Look AHEAD 2010]. They were also more likely to experience "partial remission" of diabetes [Gregg, 2012]. Continued follow-up is needed to determine if these benefits are sustained and lead to other positive outcomes, e.g. reduced diabetes complications. Previous publications have documented benefits of ILI relative to DSE through 4 years for symptoms of sleep apnea, physical function, depressive symptoms, systolic blood pressure and HDL-cholesterol [Look AHEAD, 2007; Jakicic, 2009; Williamson, 2009; Foster, 2009; Look AHEAD, 2010; Wing, 2011; Phelan, 2012; Rejeski, 2012; Faulconbridge, 2012].

The number of individuals in the US aged 65 years or older is projected to double from 35 million in 2000 to 71 million in 2030 [Houston, 2009; MMWR, 2003]. Now, nearly 40% of US seniors are obese [Flegal, 2010] and over half have diabetes [Villareal, 2005]. These trends

have altered the clinical landscape dramatically so that older individuals who are obese and have diabetes now comprise one of the most rapidly growing patient groups that clinicians see. As they represent a relatively new phenomenon, these individuals are understudied and have represented only small proportions of prior cohort studies and clinical trials [Halter, 2012; Cruz-Jentoft, 2013]. Continuing to follow the Look AHEAD cohort provides a unique opportunity to examine the effects of 9-11 years of lifestyle intervention, relative to a control condition, on the health issues of great relevance to older obese individuals with type 2 diabetes.

Preservation of physical function and independence in later life is a primary goal of health care [Lu, 2013]. Diabetes and mid-life obesity independently convey marked increased risk for physical impairment and disability due to declines in strength and mobility [Levine, 2012; Guralnik, 1993; LaCroix, 1993; Lu, 2013; Stenholm, 2012]. The co-occurrence of diabetes and obesity increases the prospect of lost physical independence, greater health care utilization, and greater societal costs [CDC, 2008; CDC, 2009; CDC, 2005; Hogan, 2003; Lu, 2013; Stuart, 2008; von Lengerke, 2010].

Midlife obesity and diabetes each are associated with doubling of the risk for dementia [Kloppenborg, 2008]. Unless major advances are made, the successive epidemics of obesity and diabetes may overwhelm the resources in the US for treating and caring for the millions of excess cases of dementia and its prodrome, mild cognitive impairment (MCI), that these conditions are projected to produce. Despite considerable effort and progress, no effective strategies for preventing cognitive impairment are currently available [Desai, 2010; Plassman, 2010]. Weight loss and increased physical activity have been identified as among the most likely strategies to have major impacts on preservation of cognitive function in the US [Barnes, 2011].

Chronic kidney disease (CKD) imposes a large and growing burden on the health of the US population. Persons with CKD are at elevated risk for myocardial infarction, heart failure, stroke, adverse drug effects, end stage renal disease (ESRD) requiring dialysis, and mortality. Diabetes mellitus is the leading cause of CKD in US adults. In some cohort studies, BMI is an independent risk factor for incident CKD, and in Look AHEAD, baseline BMI was associated with greater albuminuria [Kramer, 2009]. However, there is no evidence from randomized controlled clinical trials that weight loss reduces the risk of incident CKD or progression of CKD in obese adults with type 2 diabetes. Nutritional guidelines for CKD and CKD prevention have traditionally focused on limiting sodium and protein intake and maintaining or not gaining weight in late stage CKD -- not on intentional weight loss. In addition, diabetic peripheral neuropathies affect as many as 50% of individuals with diabetes [Deshpande, 2008]. Diabetic foot problems represent the most common cause of health care visits and inability to work for individuals with diabetes [Deshpande, 2008]. Approximately 20% of these individuals have autonomic neuropathy, which increases their risk of cardiovascular mortality [Vinik, 2003].

There are few longitudinal studies of aging and depression in the general population [Frasure-Smith, 1995], and none among people with type 2 diabetes. In 2004, the burden of depression as measured by disability adjusted life years was greater for unipolar depression than for all but two other diseases, and by 2030 it is expected to be greater than for any other disease [WHI, 2004]. Both obesity and type 2 diabetes are associated with increased risk of depression [Knol, 2006; Robert, 2003; Scott, 2008; Zhao, 1987], which increases the risk of developing CVD [Rugulies, 2002; Wulsin, 2003] and mortality in those with existing CVD [Barefoot, 1996; Carney, 1988; Frasure-Smith, 1995]. In a large observational study, over a 3-year follow-up, both minor and major depression were associated with >40% increased mortality, controlling for other mortality risk factors [Katon, 2004]. In addition, late-life depression is an established risk

factor for cognitive impairment and dementia [Barnes, 2011; Chen, 1999; Geda, 2006; Goveas, 2011].

Osteoporotic fractures are prevalent, serious events that can result in substantial morbidity and increased mortality [Toteson, 2001; Vigneri, 2009]. Persons with type 2 diabetes often have higher BMI and bone mineral density than persons without diabetes and thus might be expected to be at lower risk for the development of osteoporosis and fracture [Barrett-Connor, 1992; Isaia, 1999; Schwartz, 2001; van Daele, 1995]. However, since the rate of bone loss is higher in older adults with diabetes compared to others [CDC, 2009; Schwartz, 2005; Strotmeyer, 2005], the risk for fractures is actually increased [Bonds, 2006; Ottenbacher, 2002; Schwartz, 2002; Strotmeyer, 2005]. Weight loss is also an important risk factor for bone loss and thus may increase the risk of fracture in older adults with diabetes [Ensrud, 2003; Jensen, 2001; Riedt, 2005; Villareal, 2008].

Obesity [Brach, 2004; Joslin, 1959] and type 2 diabetes [Vigneri, 2009] both increase risk for cancer. For example, the proportion of cancers attributable to obesity is 17% for breast cancers, 24% for kidney cancers, 28% for pancreas cancers, and 49% of endometrial cancers [WCRF, 2007]. The risk for death is also greater in cancer patients who have type 2 diabetes compared to those who do not [Calle, 2003; Barone, 2008; Hsin-chieh, 2012]. While the association between overweight/obesity and risk for cancer is well established, there is less certainty that intentional weight loss reduces risk [McTiernan, 2010]. In observational studies there are generally inverse associations between the amount of weight intentionally lost and cancer risk, but a randomized controlled clinical trial is needed for a definitive assessment whether weight loss reduces cancer in older overweight/obese adults.

Over the past decades, intensive lifestyle interventions have become increasingly effective at producing initial weight losses. However, the maintenance of weight loss remains problematic. Ongoing treatment has been shown to reduce the risk of weight regain, but such studies have typically not lasted beyond 18-24 months, and it remains unclear whether individuals who have been in treatment long-term are subsequently able to maintain weight loss on their own. Analyses comparing those individuals who lost 10% of their body weight at Year 1 in ILI and maintained it at Year 8 (N=324) to those who regained their weight (N=117) showed the maintainers continued to engage in higher levels of physical activity than regainers (1472 vs 800 kcal/wk at Year 8); they also reported weighing themselves more frequently and endorsed using the following strategies more often than regainers: reducing calorie intake, reducing fat, and increasing exercise. These data are similar to those reported in the National Weight Control Registry (NWCR), a registry of over 10,000 people who have lost 70 lbs on average and kept it off over 5 years. Data from the NWCR suggest that after 2-3 years of successful weight loss maintenance the odds of continued success are increased, but that continued maintenance of behavior changes is necessary for weight loss maintenance. Look AHEAD-C provides an opportunity to examine the effects of intervention termination following 9-11 years of ILI on subsequent changes in body weight.

Look AHEAD-C will continue to record major cardiovascular disease events. While the primary aims of the intervention phase of Look AHEAD were on a composite of these events, continued follow-up allows focus on specific types of events, such as congestive heart failure. Adults with diabetes have a high incidence of congestive heart failure (CHF), the fastest growing cardiovascular disorder in the US [Bertoni, 2004; Nichols, 2004]. Epidemiologic evidence suggests higher hemoglobin A1c (HbA1c), greater obesity, and older age are risk factors for incident CHF among those with diabetes [Bell, 2003]. However, a recent meta-analysis suggests tight glycemic control does not prevent CHF [Castago, 2011]. Since in most trials,

tight glycemic control is associated with weight gain and/or use of agents that increase CHF risk (e.g. TZDs), Look AHEAD provides the opportunity to examine the effects of improvements in glycemic control achieved by weight loss, and by weight loss and improved physical fitness per se, on the development of CHF.

Look AHEAD-C also provides the opportunity for more focused study of the consistency of intervention effects among important subgroups. Look AHEAD data suggest that the long-term impact of ILI on CVD and health care costs may vary depending on CVD history. If evidence for these findings strengthens during Look AHEAD-C, it will have a major influence on future treatment recommendations. Similarly, data from a Look AHEAD ancillary study suggest that the impact of ILI on physical and cognitive function may vary depending on participant's initial weight: this, too, requires further study and replication.

Look AHEAD-C capitalizes on the outstanding level of participant retention in this RCT; the centralized adjudication of a large panel of CVD events, including CVD procedures, deaths, cancers, and fractures; the state-of-the-art medication classification system that, from annual visits, tracks use of all prescription medications; and the extensive systems for assigning costs to hospitalizations, outpatient medical care, nursing home stays, and medication use that have been developed. Look AHEAD has developed a vigorous program of ancillary studies: its continuation will enable ongoing ground-breaking ancillary studies to meet their goals and for new applications based on emerging findings to be developed. Further, Look AHEAD has a large biorepository that can be used to examine biologic pathways that may have influenced the outcome of the main trial.

3. SPECIFIC AIMS

Primary Hypotheses

Participants will have better profiles of healthy aging following 9-11 years of random assignment to ILI compared to DSE, as indicated by differences on the following parameters:

Physical function and mobility disability. The primary physical function outcome is a composite measure of physical function based on the Short Physical Performance Battery (SPPB) and a timed 400 meter walk. The adjudicated construct of mobility disability, individual physical function measures, and assessments of physical impairments will be important secondary outcomes.

Cognitive function and cognitive impairment. The primary cognitive function outcome is a composite measure developed from a battery of standardized tests. The adjudicated construct of cognitive impairment (i.e. either mild cognitive impairment or dementia) and individual cognitive function measures will be important secondary outcomes.

Secondary Aims

Look AHEAD-C will examine whether participants assigned to ILI compared to DSE have better long-term profiles for the following markers of healthy aging.

Diabetes control and microvascular complications. Compared to DSE, ILI was associated with better glycemic control with less medication and better profiles of kidney disease markers in Look AHEAD. Look AHEAD-C will determine whether these benefits are maintained long-term and translate to fewer clinical events. The assessment of microvascular complications is strengthened by adding an objective measure of peripheral neuropathy and continuing

surveillance for amputations, end stage renal disease, retinal laser surgery and autonomic neuropathy (by ECG).

Depression. Because obesity and diabetes both increase the risk of depression, which has important associations with cardiovascular disease and mortality, the assessment of depression will be strengthened by adding the Patient Health Questionnaire-9 (PHQ-9), which provides information to permit diagnosis of major and minor depression using DSM-IV criteria, and continue to use Beck Depression Index.

Fractures and cancers. Look AHEAD included the assessment of intervention effects on the incidence of fractures and cancers as important tertiary aims but was not powered to make this assessment adequately. Further follow-up is needed to accrue sufficient power to test these hypotheses.

Additional Aims

Subgroup comparisons. Look AHEAD pre-specified comparisons of the consistency of intervention effects on its primary outcome between participants who had pre-existing cardiovascular disease (CVD) at enrollment to those who had no history of cardiovascular disease, but was not designed to have sufficient power to test this interaction. It has observed differences in the risk of CVD events, hypoglycemia, and use of medical care and costs between these two groups of individuals: ILI appeared to be beneficial for those with no history of CVD but not for those with a history of CVD. Continued follow-up of incident CVD events and other safety outcomes is critical to determine whether these differences between individuals grouped by CVD history diminish or increase over time and depend on whether ILI occurs before or after the events. This is necessary to determine whether it is appropriate to recommend weight loss lifestyle interventions to overweight and obese individuals with diabetes who have prior history of CVD. Two other pre-specified subgroups were gender and race/ethnicity; additional data can provide improved power to assess the consistency of the intervention effects across these subgroups.

Weight maintenance. The ILI produced impressive sustained weight losses, with 50% maintaining 5% weight loss through 8 years. With stopping the ILI, there is an opportunity to determine whether those individuals who have successfully maintained weight loss throughout the trial are now able to maintain these weight losses on their own.

Dissemination. Look AHEAD-C provides the opportunity to complete additional publications of Look AHEAD data. It creates a backbone for currently funded ancillary studies (described below) and infrastructure for new ancillary studies and for pooling data with other studies such as the Diabetes Prevention Program (DPP) and the Action to Control Cardiovascular Risk in Diabetes (ACCORD). Most participants have been genotyped on the Human CVD (IBC) and Metabochip and genetic analyses (some with DPP) are ongoing.

4. APPROACH

Overview of Look AHEAD-C

Look AHEAD-C continues data collection from 8/1/13 to 12/31/14 with the addition of new measures of greatest importance to this aging cohort, continues analyses of data from the intervention phase of Look AHEAD, and conducts close-out and analyses from 1/1/15-7/31/15. During this continuation, one clinic assessment visit (taking approximately 3 hours) is planned for each participant. In addition, all participants will have 2 or 3 6-month phone calls for outcomes assessments.

Re-Enrollment of Participants
All participants currently enrolled and being followed in Look AHEAD will be approached for recruitment into Look AHEAD-C.

Informed Consent
All studies with extended follow-up of older individuals face issues related to assuring informed consent for participants who might have cognitive impairment. Look AHEAD-C is not designed to provide a clinical diagnosis of cognitive impairment and its protocol features no procedures that place participants at greater than minimal risk (i.e. these procedures are limited to the risk that one typically encounters with venipuncture, standing up from a seated position, or walking in a corridor). Its process for obtaining informed consent is drawn from models provided by other clinical trials in older individuals.

Staff will receive central training in the administration of informed consent. Participants will be contacted prior to the consenting session and the procedures for Look AHEAD-C will be briefly reviewed with the participant. If, based on prior interactions with the participant or responses during the call, the staff member has any concerns about whether the participant will be able to complete the consent process (described below), the participant will be asked to have a surrogate (e.g. partner or trusted friend) accompany them to the visit to assist in the consent process.

Obtaining informed consent. The program coordinator or other qualified research staff will be responsible for leading the potential participant through the entire consent process. This means:

- All aspects of the study, as described in the consent form, are first discussed with the potential participant. The consent form is thoroughly reviewed and answers to the potential participant's questions are provided.
- After reviewing the consent form, the staff person obtaining consent will complete a form with the participant to assess the potential participant's understanding of the material. The staff person will specifically state this intent to the potential participant (i.e., the staff member is making sure the potential participant appreciates what s/he is being asked to do, and why). Guided by the form, the staff member will ask the participant about critical elements in the informed consent, e.g. why the study is being conducted, ability to withdraw at any time, consequences of withdrawing, possible risks and benefits of participation, procedures involved, time required, confidentiality, and whom to call with any questions. Answers provided by the participant will be documented.
- If the participant does not demonstrate sufficient capacity to answer the questions about the study and thus may not be able to provide informed consent, a formal surrogate will be needed to consent to ongoing study participation, Staff persons will ascertain that the following can serve as a surrogate: first-degree family members (parent, spouse, or an adult son or daughter), health care proxy, legally appointed guardian, or participant-chosen surrogate, in accordance with local, state and IRB regulations.

Procedures for obtaining surrogate consent for future participation. Participants who have the capacity to consent will be given the opportunity to decide in advance whether they do or do not want a surrogate to make decisions for them to continue their participation in the study should they lose capacity to consent in the future. This will be documented on the procedures consent note in their research chart. For those participants who choose not to have a surrogate make enrollment decisions for them in the future and lose the capacity to consent, this will be

documented and the participant will be excluded from further participation after losing the capacity to consent.

- Staff persons will discuss with the participant who they have chosen as a surrogate or who they would like to serve as a surrogate decision maker.
- Staff persons will ascertain that the following can serve as a surrogate: first-degree family members (sibling, spouse, or an adult son or daughter), health care proxy, legally appointed guardian, or participant-chosen surrogate, in accordance with local, state and IRB regulations.
- Participants will be encouraged to discuss their future research participation with the surrogate.

Consent to have protected health information shared with the coordinating center. In addition, participants will be asked to consent to having their Protected Health information shared with and electronically transferred to the Coordinating Center at Wake Forest University Health Sciences. Participants are not required to consent to this sharing of information; their decision not to share this information will not affect their participation in the Look AHEAD Continuation. However, if provided, this shared information will be used at the Coordinating Center in the event of natural or other major disaster affecting a clinical site (for example, if a clinic were destroyed by a hurricane or tornado the Coordinating Center would be able to provide contact information for the participant to the clinics). Second, the information would be used to allow searches of national databases such as the National Death Index (NDI) or Centers for Medicare and Medicaid Services (CMS) for the purpose of determining date and cause of death, and diagnosis codes and dates for health care utilization. These would require that the Coordinating Center have access to names, addresses, birth dates, social security number and/or medicare number. Third, in the event that future funding is not available for the clinics to contact their participants, this information would be used to allow direct contact by the Coordinating Center with the participant, by telephone or mail, for the following purposes: to invite the participant to take part in an ancillary study; to conduct the study outcomes interview; to conduct other types of interviews, e.g., to inquire about current health status, body weight, others and to update contact information on informants/proxies.

5. DATA COLLECTION

Outcomes and Assessments

The Look AHEAD-C clinical battery requires approximately three hours and will typically be completed in a single clinic visit. This battery will be completed once for each participant during the Look AHEAD continuation on the same schedule as during the intervention phase of the trial; however, an expanded window will be allowed for these visits. In addition, participants will continue to be called at 6 month intervals throughout the continuation. Again, these calls will continue to be conducted on the same schedule as during the intervention phase of the trial. All participants will have at least 2 calls, and some will have 3 during the Look AHEAD continuation. These calls will be used to assess and identify outcomes for central adjudication.

The clinic exam will be conducted by certified staff who will continue to be masked to former intervention assignment. Measures from the original Look AHEAD trial that will continue to be collected include: study outcomes, medical history, costs, HRQL, BDI-1, collection of fasting blood/urine, blood pressure, weight, waist, height , ECG (on those who did not have it the prior year), self-reported neuropathy, questionnaire on weight control practices and eating habits, and the Paffenbarger activity questionnaire. Repeated blood/urine assays will include HbA_1C, urine

albumin, and urine and serum creatinine. Specimens will be stored to enable additional measurements to be made.

New measures to be collected in the Look AHEAD-C clinic exam(s) include measures of physical and cognitive function necessary to determine the prevalence of physical impairment, physical disability and cognitive impairment; the Patient Health Questionnaire (PHQ-9) for determining the prevalence of depression; and mono-filament, tuning fork screening and testing of reflexes for peripheral neuropathy. Participants will receive a $200 honorarium for completing the assessments.

Measures Obtained During Clinic Visit

Component	Elements and Associated Form(s)	Time
Consent	Consent Form Consent Understanding Form	20 min
Physical Measures obtained in fasting state	Blood and Urine ECG (50%)	10 - 30 min
Physical Measures not requiring fasting state	Blood pressure WeightWaist, Height Neuropathy monofilament, reflexes and tuning fork tests	12 min
Physical Function/Activity Battery	400 meter walk Short Physical Performance Battery (SPPB) Disability questionnaire (PAT-D) Health ABC physical function questionnaire Grip strength Paffenbarger	45 min
Cognitive Function Battery	Interviewer Administered Battery (45 min) Digit Symbol Substitution Rey Auditory Verbal Learning Modified MiniMental State Exam Trails A&B Stroop Color-Word Test Shipley Vocabulary Test	45 min
Interviewer-administered questionnaires	Thoughts and Feelings (including Beck depression) PHQ-9 My Health A (revised) Hypoglycemia Medical Events (in lieu of SAE)	20 min
Self-administered questionnaires	My Health B (revised) Michigan Screening (for neuropathy) Weight Control Strategies Questionnaire	10 min
Study outcomes (interviewer-administered) These will be done at 6 month intervals by phone and either at the time of the LookAHEAD-C clinic visit or by an additional phone call	Study Outcomes Overnight Hospital Administration (FU-A) Heart Blood Vessels (FU-B) Gall Bladder Surgery (FU-C) New Broken Bones (FU-D) Outpatient New Cancers or Malignant Tumors (FU-E) Unknown Cancer Biopsy (FU-F)	5 – 40 min (highly variable)

Measures related to physical function. The proposed measures of physical function were selected because they predict the onset of disability, morbidity and death; are reliable, sensitive to change, and safe; and have low participant burden [Newman, 2006; Ostir, 2007; Perera, 2005]. The physical function measures have been used extensively in large-scale clinical trials and epidemiological studies of function in older adults. These measurements can predict health outcomes even in middle-aged adults [Fielding, 2011; Sasaki, 2007; Wilcox, 2006]. The **Short Physical Performance Battery** (SPPB) includes a timed short walk, time for standing from a chair 5 times without the use of arms, and the ability to maintain certain postures for the testing of balance [Guralnik, 1993]. A **400 m walk test** will be administered, as a validated measure of mobility disability [Espeland, 2007]. **Grip strength** will be measured twice in each hand to the nearest 2 kg using an isometric Hydraulic Hand Dynamometer (Jamar, Bolingbrook, IL). The **Health ABC Physical Function Questionnaire** assesses the participant's ability and ease or difficulty to walk different distances [Brach, 2004].

Impaired physical function, impaired strength and mobility disability. Impairment in physical function is defined as an SPPB score less than 10 and gait speeds less than age/gender-specific 10%ile. Impairment in grip strength is defined based on age- and gender-adjusted 10%iles. Mobility disability is defined as the unwillingness or inability to complete a 400 meter walk test within 15 minutes without sitting, leaning against the wall, or the assistance of another person or walker [Fielding, 2011]. Individuals who complete the walk in more than 15 minutes have an extremely slow pace (<0.45 m/sec), which would make their walking capacity of little utility in daily life. Standard protocols will be used to adjudicate the status of individuals who are not able to attend clinic visits due to hospitalizations or institutionalization [Fielding, 2011]. Self-reported physical function and disability will be assessed with a modified version of a disability instrument called the **Pepper Assessment Tool for Disability** (PAT-D) [Rejeski, 2008; Rejeski, 2010]. It includes 19 items, covering 3 domains: basic activities of daily living (ADL), mobility, and instrumental ADLs.

Measures of cognitive function. The cognitive function tests were chosen to: 1) extend the battery of cognitive tests collected in the Look AHEAD Movement and Memory and Look AHEAD Brain MRI ancillary studies to the full cohort and 2) support the adjudication of cognitive impairment classification (MCI and dementia). **Attention and concentration** will be assessed with the Trail Making Test-Part A [Reitan, 1958]. **Verbal memory** will be assessed with immediate and delayed recall on the Rey Auditory Verbal Learning Test [Lesak, 1995]. **Working memory** will be assessed with the Digit-Symbol Substitution Test [Wechsler, 1981]. Other abilities involving executive control such as **response inhibition, selective attention,** and **cognitive flexibility** will be assessed with the Modified Stroop Color Word Interference Test [Houx, 1993; Stroop, 1935] and the Trail-Making Test-Part B (TMT-B) [Reitan, 1958]. **Global cognitive functioning** will be assessed with the Modified Mini-Mental Status Exam (3MSE) [Teng, 1987] and a brief vocabulary test (Shipley-2) will be administered to estimate **intellectual capacity**. Age- and education-appropriate normative reference values are available for the Shipley-2, and scores are relatively resilient to the effects of aging and disease [Yuspeh, 1998]. Thus, performance on the Shipley-2 will serve as a benchmark against which *change* in function across specific cognitive domains can be estimated [Yuspeh, 1998].

Assessment of cognitive impairment. The adjudicated outcomes of 'No Cognitive Impairment,' 'Mild Cognitive Impairment' and 'Probable Dementia' add discrete, clinically relevant outcomes to Look AHEAD-C, outcomes that are used in many other studies involving cognitive function. By adding these discrete, adjudicated outcomes, investigators will be able to characterize the impact of the intervention on a fuller gradient of cognitive outcomes that includes domain specific cognitive functions (e.g., attention, verbal memory, response inhibition,

processing speed), global cognitive functioning (i.e., battery composite score) and discrete clinical syndromes (mild cognitive impairment and dementia).

The proxies of participants who score below pre-set cutpoints on the 3MSE [Teng, 1987] will be telephoned by trained clinic staff who will administer the **Functional Activities Questionnaire (FAQ),** a 10-minute validated measure of functional impairment related to cognitive impairment [Pfeffer, 1982]. If permission has been granted by participants who are not subsequently assessed due to declining health or death, their proxies will be administered the **Dementia Questionnaire (DQ**) [Kawas, 1994], a validated, semi-structured interview assessing cognitive and behavioral impairment and other relevant information needed to identify dementia and mild cognitive impairment [Gaussoin, 2012]. It is anticipated that about 15% of the cohort would obtain scores low enough to trigger screening phone calls.

The cognitive adjudication process involves having experts in the diagnosis of mild cognitive impairment and dementia who are blind to treatment assignment review cognitive and functional data using established diagnostic criteria [Albert, 2011; McKhann, 2011]. Each participant meeting study criteria for adjudication will have their data independently reviewed by two experts. When adjudicators agree on the classification, it will become final for study purposes. In instances where adjudicators disagree, the entire Adjudication Committee will also review the data and discuss the case until consensus is achieved. This process has been successfully used in other large, multi-site clinical trials and observational studies.

Depression. During the intervention phase of the Look AHEAD trial, participants completed the **Beck Depression Inventory** (BDI-1) and reported prescription medication use (including antidepressants) annually. At the Look AHEAD-C clinical visit, all participants will also complete the **Patient Health Questionnaire-9 (PHQ-9**). The PHQ-9 is a 9-item questionnaire [Kroenke, 2001] based on Diagnostic and Statistical Manual-IV criteria for depression. It permits a reliable and valid categorical classification (depressed vs non-depressed) as well as a continuous score for symptom severity. The PHQ-9 can be administered by self-report questionnaire or telephone (if needed) in about 5 minutes. Continuing to administer the BDI-1 allows depressive symptoms to be tracked consistently across the entire course of follow-up.

Microvascular disease. Collection of urine and blood samples will be continued to assess changes in **urine albumin to creatinine ratio, eGFR,** and **serum creatinine**. Look AHEAD-C will continue to collect self-report and hospital records related to the development of ESRD and renal replacement therapy. An objective measure of **peripheral neuropathy** will be added to Look AHEAD-C using the protocol of the Diabetes Prevention Program Outcomes Study. This includes a Semmes Weinstein 10 gram monofilament examination, the Michigan Neuropathy Screening Instrument, and symptom assessment. Twelve-lead resting ECGs will continue to be collected on even years; these will be read and past ECGs re-read to assess **neuropathy-related heart rate variability**. Collection of self-report of retinal laser therapy will be continued, which has been shown to provide a valid assessment of clinical retinopathy [Grassi, 2009; Patty, 2012].

Weight loss maintenance. Look AHEAD-C will examine behavioral measures associated with long-term weight loss in this cohort of overweight/obese individuals with type 2 diabetes. Both overall weight change (baseline to continued follow-up) and weight change after intervention cessation for ILI with DSE participants will be compared. Administration of the Weight Control Strategies Questionnaire will continue.

Physical activity. Physical activity is an important predictor of prevention of many of the health problems under investigation in Look AHEAD-C (e.g. physical and cognitive function, CVD, and depression). It is also the single most consistent predictor of weight loss maintenance. The **Paffenbarger questionnaire** [Jakicic, 2010] will be administered to all participants (it was administered at baseline, and Years 1 and 4 in a subset of participants and to all participants at Year 8). This assessment will be used to gauge long-term adherence to physical activity recommendations.

Outcomes assessment. Collection of study outcomes will continue at 6-month phone calls. To shorten the annual clinic assessment, these outcomes will typically not be assessed during the clinic visit, but will be assessed by a phone call at approximately the same time as the Look AHEAD-C clinic visit. Thus, during Look AHEAD-C, all outcome assessments will be by phone and depending on the timing of these calls, each participant will receive 2 or 3 outcomes calls. These calls inquire about hospitalizations, nursing home admissions, rehabilitation services, outpatient care, dialysis, amputations, and home health care. Additional details are obtained on overnight hospital admissions, outpatient care for cardiovascular events and procedures, gall bladder surgeries, fractures, and cancers. Hospital records related to CVD events, fractures, and cancers will continue to be collected. These outcomes will be centrally adjudicated using procedures currently in place.

Home visits and alternative assessment protocols. In an aging cohort, provisions must be made for alternatives to clinic visits to enhance cohort follow-up. These alternative visits will include, at minimum, consent, those aspects of the physical function and cognitive function battery that can be administered in the alternative setting, and body weight.

Outcomes adjudication. The following outcomes will be adjudicated in Look AHEAD-C by panels of experts according to protocols pre-specified in Look AHEAD.

- Death (including specifically cardiovascular death)
- Myocardial infarction
- Stroke
- Hospitalization for angina
- Congestive heart failure
- Venous thrombo-embolic disease
- Revascularization
- Cancer (excluding nonmelanoma skin cancer)
- Fracture (excluding ribs, chest/sternum, skull, face, fingers, toes, and cervical vertebrae)

Look AHEAD-C adds the following adjudicated outcomes, for which protocols are being developed.

- Mobility disability
- Mild cognitive impairment
- Dementia

Other outcomes of interest (e.g. gallbladder surgery, recurrent cancers, recurrent fractures) will be classified by coordinating center staff.

6. EDUCATION AND RETENTION ACTIVITIES

During the continuation, there will be no differences in the education and retention activities provided to the original randomization groups. Rather all participants will be offered the same activities. This will include the following:

Educational Class
All participants will be invited to one educational class during the Look AHEAD continuation. . This class will include members of both the original ILI and DSE groups, who will be treated together in the "Look AHEAD Together" program. In order to accommodate participants at each site who might like to attend, it is anticipated that the group class will need to be offered 3 – 5 times at different times (day/evening). Each session is expected to include about 10 – 20 participants and be led by 2 individuals. Each class will include a presentation related to nutrition, a discussion/activity related to physical activity, and an update on the study and research from the trial. The materials for these classes will be prepared centrally, and all centers will offer the same basic class. It is anticipated that the class will last 2 hours and in many sites will include lunch or snack.

Retention Activity
Each site will offer one retention activity during the Look AHEAD Continuation. Participants from both the ILI and DSE original groups will be invited to attend this activity, and in most cases be invited to bring their spouse or a friend. The activities may include a lunch or dinner and some type of social activity. The purpose of these events is to thank participants for their ongoing participation in Look AHEAD and provide an opportunity for social interaction among participants and with research staff.

7. SAFETY

The potential risks to individuals participating in this non-intervention phase of the trial are very few. Protocols for tests of physical function have been chosen to maximize safety. To minimize the risk of falling, the area where the activity will take place will be as free of clutter and distractions as possible. An emergency plan of action will be in place at each site to address injury or emergency situations.

Staff will be trained in obtaining physical measurements. Participants will receive reports with the results of follow-up measurements (weight, body mass index, blood pressure) including explanations as to what is considered normal or abnormal, and if they authorize it, a copy of their results will be sent to their primary care provider. Participants with abnormalities needing medical management will be referred to their primary care provider.

Safety Alerts
Look AHEAD-C will continue the alert systems and procedures for responding to abnormal weight changes and blood pressures. As detailed below, it will adopt the following alert systems and procedures for cognitive deficits and depressive symptoms. Following alerts, a determination will be made about the safety of continued participation in Look AHEAD in consultation with the participants' surrogate, primary health care provider, and/ or mental health care professional.

Cognitive deficits. The database system compares the participant's scores to age-and education-specific norms for each test. If scores are ≥ 2 standard deviation units below normal, the Cognitive Impairment Adjudication Committee will review the scores and other relevant data to determine whether the participant meets the study definition for cognitive impairment. It so, clinic staff will be notified and will be responsible for informing the participant and, if the participant has provided a Release of Information form, informing the physician and/or surrogate as well. Template letters for participants and physicians are available on the website. Documentation of follow-up is required for all alerts. On-line reports are available for monitoring alerts.

Depressive symptoms. Look AHEAD has been administering the Beck Depression Inventory throughout the trial so procedures are in place for responding to elevated total scores or positive responses to the item related to suicide. The procedures will be similar for responding to elevated scores on the PHQ-9. If the BDI is ≥ 24 or PHQ-9 is ≥ 15, the participant will be informed that they may be depressed and referred to their PCP for further evaluation and possible treatment. If the PHQ-9 is >20 and the suicide question on either instrument is endorsed, the participant MUST be evaluated immediately by Look AHEAD medical staff or by a PhD level clinical psychologist and appropriate intervention initiated (e.g. ensure immediate psychiatric consultation or if the participant is considering suicide at this time, accompanying the participant to the emergency room).

Confidentiality

Protected health information will be collected as part of this project. HIPAA authorization will be requested from all participants. Look AHEAD-C will carefully adhere to all HIPAA standards. Study participants face risks related to inadvertent release of confidential information. This will be minimized through careful adherence to best practices for data collection and management. All research staff will be trained in principles and methods for assuring participant confidentiality and safety.

Data will be used only in aggregate and no identifying characteristics of individuals will be published or presented. Results of testing will be sent to participants' private physicians if participants agree to this. Confidentiality of data will be maintained by using research identification numbers that uniquely identify each individual. Safeguards will be established to ensure the security and privacy of participants' study records. Databases will not use participants' names as identifiers: the Look AHEAD research ID number will be used. The research records will be kept in a locked room in the Look AHEAD-C clinic. The files matching participants' names and demographic information with research ID numbers will be kept in a separate room and will be stored in a locked file that uses a different key from that of all other files. Only study personnel will have access to these files, and they will be asked to sign a document that they agree to maintain the confidentiality of the information. After the study is completed, local data will be stored with other completed research studies in a secured storage vault.

Consent will cover the use of confidential data collected by the study and will permit sharing these data among the study sites, incorporation in the Look AHEAD databases, and the distribution of de-identified data for public use databases. A certificate of confidentiality will be sought prior to be beginning of recruitment to offer further protection of privacy. Handling of research data will follow Look AHEAD policies, which include approved security procedures.

A model informed consent document for use at all local sites is in Appendix 1. Sites will be able to make minor modifications to the document as required for local IRB approval. Once IRB approval is obtained locally, active Look AHEAD subjects will be contacted by local staff and asked if they would like discuss participation in Look AHEAD-C. As part of the consent process, participants will be educated about safety and potential risks will be explained. Before making the decision to participate, each potential subject will be given an IRB-approved informed consent document to review. Before signing the consent, all participants will be given the opportunity to read the entire document and have their questions answered. Written informed consent will be obtained before any study procedures may be performed.

Data and Safety Monitoring Plan

The Coordinating Center will maintain safety monitoring of all serious events related to data collection and data management. These will be reviewed regularly by the study group and sponsor. IRB reports will be prepared, as needed. A Data and Safety Monitoring Board will regularly review study progress and safety.

8. ANALYSIS PLANS

This section describes some of the major statistical approaches and analyses that will be performed for the aims that are new to Look AHEAD-C. Aims that are part of the original Look AHEAD protocol continue to be governed by its analysis plan.

Primary Hypotheses

The primary study hypotheses for Look AHEAD-C will be tested based on a two-tailed significance level of 0.025, i.e. using a Bonferroni correction to control type 1 error. In this analysis, the "intention to treat" approach will be used in which participants are grouped according to randomization assignment. Additional, secondary analyses may be performed that account for crossover from the assigned intervention group and loss to endpoint ascertainment.

Physical function. The primary hypothesis for physical function is that random assignment to ILI, compared to DSE, will have resulted in a mean difference in a composite measure of physical function, based on physical function assessments collected as part of the Look AHEAD-C battery. This composite will be formed from two measures: 400 meter walk times and the short physical performance battery (SPPB). Composite summaries will be calculated separately for males and females as the average of the estimated means of these two measures in each arm, with each divided by estimate of its standard deviation. The two gender specific summaries will then be combined into a single composite by computing a weighted average of the summaries for men and women. Estimates will be obtained using multivariate analysis of covariance with adjustment for clinic site (the stratification factor used in the original randomization), time since randomization, and the following covariates measured at the time of the original Look AHEAD enrollment that are included to recapture power associated with the lack of a baseline measure of physical function: BMI, age, the physical score from the SF-36, and history of cardiovascular disease. In this model, all observed data can be included without special procedures for missing data, provided they are missing at random. The composite will be assessed with (two-sided) Type 1 error set at 0.025. This estimate is a modification of O'Brien's OLS test [O'Brien 1984] which has been discussed favorably for use in clinical trials when there is no clear single endpoint [Tang, 1993]. Although this approach is typically implemented as a one-sided test, it can be implemented as a two-sided test, allowing rejection of the null hypothesis when all outcome measures indicated adverse effects of the intervention.

Cognitive function. The primary hypothesis for cognitive function is that random assignment to ILI, compared to DSE, will have result in a mean difference in a composite measure based on cognitive function assessments collected as part of the Look AHEAD-C battery. This composite will be formed from the following measures: delayed recall from the Rey Auditory Verbal Learning test, Digit Symbol Substitution Test score, the Modified Stroop Color Word Interference Test, the Trail-Making Test-Part B, and the Modified Mini-Mental Status Exam.

A composite summary will be estimated in the same way as proposed for the measures of physical function. Mean differences between the ILI and DSE groups will be tested using analysis of covariance, with adjustment for clinic site, time since randomization, and the following covariates measured at the time of the original Look AHEAD enrollment that are included to recapture power associated with the lack of a baseline measure of cognitive

function: age, the mental score from the SF-36, gender, education, and race/ethnicity, with (two-sided) Type 1 error set at 0.025.

Secondary Outcomes
Secondary study hypotheses will be considered supporting and exploratory analyses, so tests will be conducted using a two-tailed significance level of 0.05. The main analyses for the secondary outcomes will follow an intention to treat approach.

Secondary outcomes related to physical function and disability. The prevalence of adjudicated mobility disability will be assessed as a secondary outcome for physical function between intervention groups using logistic regression with adjustment for clinic site and time from randomization. Other secondary analyses will describe differences between interventions groups with respect to the individual measures contributing to the composite (400 m walk time and SPPB), grip strength, Health ABC physical function questionnaire scores, impaired physical function, impaired strength, and the Pepper Assessment Tool for Disability (PAT-D).

Secondary outcomes related to cognitive function. Differences in the prevalence of adjudicated cognitive impairment (mild cognitive impairment or dementia) will be assessed as a secondary hypothesis using logistic regression with the same set of covariates, as a secondary outcome for cognitive function. Secondary analyses will also describe differences in the individual components of the cognitive function composite and additional measures of cognitive function (i.e. Trails A, intellectual capacity, and test subscores).

Depression. The primary analysis of depressive symptoms will be based on a composite measure formed by averaging z-scores of the Beck Depression Inventory (BDI) and the Patient Health Questionnaire-9 (PHQ-9) scores collected at the Look AHEAD-C visit. Mean differences between intervention groups will be compared using analysis of covariance with adjustment for clinic site and time since randomization. Additional analyses will compare intervention groups with respect to scores on each of these measures, the prevalence of depression based on established cutpoints from these instruments, the longitudinal trajectory of BDI scores and antidepressant medication use throughout Look AHEAD and Look AHEAD-C. Proportional hazards models will be used to compare the incidence of depression cutpoints based on BDI>10 between the intervention groups throughout follow-up.

Microvascular disease. Mean differences between intervention groups in urine albumin to creatinine ratio, eGFR, and serum creatinine over time will be assessed using general linear models for repeated measures, with adjustment for clinical site and time from randomization. Differences in the prevalence of heart rate variability over time will be assessed using generalized estimating equations. Differences in the incidence of ESRD and renal replacement therapy throughout follow-up will be assessed using proportional hazards regression.

Fractures and cancers. The main comparisons of intervention groups with respect to the distribution of time until the first post-randomization occurrence of fractures and cancers will be based on survival analysis. To compare intervention arms, a Mantel-Haenszel test with unit weighting will be used, stratified by clinical center. Cox proportional hazards models will be used to compare intervention groups in supporting analyses involving additional covariates, if the underlying assumptions appear warranted. Markers indicating clinical centers will be used as covariates. Log/log plots of survival will be used to examine the assumption of proportional hazards. Failure time is measured from the time of randomization. Some minor biases may occur due to this choice, for example if there is a differential drop-out rate between randomization and the start of interventions. The period of time between randomization and the

first intervention session is kept as short as possible by not performing the randomization until groups of potential eligible participants accrue. Censoring will be defined by the time when participant status was last known. Each outcome will be assessed at significance level 0.05 using similar approaches.

General Statistical Approach for Additional Analyses

The objectives of AHEAD-C require a broad range of analytical techniques. In reporting results, Look AHEAD-C manuscripts will clearly distinguish between the primary hypothesis and secondary objectives and will discuss results from these different outcome measures appropriately. In this context, the Look AHEAD-C study group is comfortable with performing significance tests of secondary objectives at 0.05 levels of significance.

To examine how the termination of the interventions may have influenced trajectories of weight and self-reported physical activity, change-point models will be used in which patterns of change in these variables prior to Look AHEAD-C are compared with the values collected during Look AHEAD-C.

Additional analyses will document how the cohort has been altered by the re-consenting process over time. These will identify characteristics of individuals related to drop-out and also characteristics that may be related to any differential re-consenting between intervention groups. If evidence emerges that this may influence findings, propensity scores analyses will be used to project the magnitude of associated biases and support findings.

At the end of Look AHEAD-C, analyses for the results from Look AHEAD with respect to its primary and secondary CVD outcomes will be updated to examine whether trends have continued.

Subgroup Analyses

Look AHEAD-C will assess the consistency of intervention effects for outcomes that are continued from Look AHEAD with respect to the subgroups pre-specified in the Look AHEAD protocol: gender, race/ethnicity, and history of CVD at the time of Look AHEAD enrollment. These include myocardial infarctions and congestive heart failure. For the new measures introduced in Look AHEAD-C related to physical and cognitive function, two subgroups of primary interest are pre-specified: age and BMI at the time of Look AHEAD enrollment, using cutpoints defined at the time of Look AHEAD enrollment of 65 years and 30 kg/m^2 for these measures to define subgroups.

9. PROJECTIONS OF STATISTICAL POWER

At the termination of the Look AHEAD ILI, 4,452 participants were currently active. Power calculations are based on the conservative assumption that 90% of these participants will enroll in Look AHEAD-C, i.e. approximately N=4000 participants.

Physical Function and Mobility Disability

Look AHEAD-C will examine both levels of physical function measures and the prevalence of physical impairment/mobility disability. The composite that forms the primary physical function outcome is expressed in standard deviation units. N=4000 participants is projected to provide 90% power to detect a mean difference of 0.11 standard deviation units. This is a relatively small intervention effect, well within the magnitude of findings from the Look AHEAD Movement and Memory Study for measures of mobility-related physical function (unpublished data), so that Look AHEAD-C is well-powered to detect differences in this composite. More critical, is the

power projected to be available to detect differences in the prevalence of mobility disability. The potential magnitude of intervention effects on this outcome is framed by findings at Year 4 in Look AHEAD, when 30% fewer ILI participants compared to DSE participants were classified as having severe mobility disability according to a construct developed from questionnaire responses [Rejeski, 2012]. Further, at Year 8 the Look AHEAD Movement and Memory ancillary study found 25% reductions in the odds for 20 and 400 meter gait speeds falling below 10%iles, cutpoints that denote accepted markers of functional impairment. This ancillary study also found a 19% reduction in completing a 400 meter walk in <15 minutes, a validated measure of mobility disability [Espeland, 2007; Fielding, 2011]. Using the rates observed in Look AHEAD Movement and Memory, 96% (83%) power is projected to detect intervention effects of 20% (25%) for physical impairment based on gait speed. With the risk factors for mobility disability from Look AHEAD Movement and Memory (age, gender, SPPB, 400 meter gait speed, BMI, and grip strength), a risk factor prediction model from the LIFE pilot study [Marsh, 2011; LIFE, 2006] projects an annual incidence of 3.3%/year for mobility disability within the Look AHEAD Movement and Memory cohort. If the cohort from the ancillary study is representative of the full cohort, 396 (3 years x 3.3% x N=4000) cases of mobility disability are projected to have occurred since the Look AHEAD Movement and Memory ancillary study was conducted, i.e. about 9.9% of the cohort. Given this, 80% power is projected to detect a difference in the prevalence of mobility disability of 2.9%, i.e. approximately a 29% reduction.

Cognitive Function and Cognitive Impairment

In calculations that parallel those for the physical function composite, Look AHEAD-C is projected to provide 90% power to detect a mean difference of 0.11 standard deviation units between intervention groups for the cognitive function composite. More critical is the power available to detect differences in cognitive impairment. Cognitive function scores and risk factors from Look AHEAD Movement and Memory ancillary study can be used to project the prevalence of mild cognitive impairment or dementia using prediction models from other cohorts. Using a prediction model from the Women's Health Initiative Memory Study (WHIMS) [Espeland, 2007], which has been validated using data from the Ginkgo Evaluation of Memory (GEM) trial [Dekosky, 2008], a prevalence of 12% mild cognitive impairment or dementia is projected for its cohort in 2014 (unpublished data). If these results extend to the full cohort, approximately 480 cases of mild cognitive impairment or dementia is projected for the Look AHEAD-C cohort (among its approximately N=4000 participants, i.e. a prevalence of 12%). This yields 80% power to detect a difference in prevalence of 3.2% between intervention groups (i.e. a 27% intervention effect).

Microvascular Complications

Chronic kidney disease is one of the important microvascular complications for individuals with diabetes. ILI participants tend to have lower incidence of ACR>30 or eGFR<60ml/min compared to the DSE (HR=0.90; p=0.07 for both). Look AHEAD-C is projected to provide 65% power to detect an approximate 10% reduction in the hazard ratio for both indicators. To date, 624 Look AHEAD participants have had laser eye surgeries: Look AHEAD-C is projected to provide 68% power for detecting a 20% difference in rates between intervention groups with the additional follow-up provided by Look AHEAD-C.

Depression

Through 8 years, ILI was associated with a hazard ratio of 0.59 (p=0.04) for incident moderate-to-worse depressive symptoms (BDI>20) among older participants. No benefit was seen for younger participants. Look AHEAD-C includes a more accurate assessment of late-life depression using the PHQ-9 instrument (and repeating BDI) and will provide greater statistical power for assessing the potential interaction with age. If rates of PHQ-9 defined late-life

depression parallel those seen with BDI>20, the prevalence in the Look AHEAD-C cohort will be 6% among DSE vs 4% among ILI participants (approximately 200 incident cases overall). From this, Look AHEAD-C is projected to provide 81% power to detect a 33% reduction associated with ILI [Schoenfeld, 1993]. The PHQ-9 provides a continuous score for depressive symptom severity, for which greater power is projected.

Cardiovascular Disease Events
Assessing the interaction between history of CVD and ILI on incident myocardial infarction is a critical Look AHEAD-C goal. If the current trend continues, Look AHEAD-C is projected to provide ≥85% power for the interaction to reach significance at the 0.05/3 level, which would adjust for comparisons in the three subgroups pre-specified in the Look AHEAD protocol for CVD event analyses, i.e. gender, ethnicity, and CVD history. In reporting this finding, it will be noted that Type 1 error has not been controlled for the monitoring (for safety) of these potential interaction during the course of the trial.

Other Outcomes
Sufficient power is also projected for the goals related to costs, medication use, and weight maintenance. Look AHEAD-C goals related to amputations, use of dialysis, and hypoglycemia episodes have less power, however it is important to track these events.

10. DATA AND INFORMATION MANAGEMENT

Look AHEAD features an integrated web-based system for managing operations and capturing data. At entry, data are immediately validated against sets of validation rules. Some identify errors that must be corrected immediately. For less critical concerns, other rules present validation warnings for review, which are saved to the database for later reconciliation that is tracked with reminders and reports. Data are immediately available in alert/tracking systems and dynamic reports based on relational databases. No records are ever deleted, all changes produce audit trails, and back-ups are created hourly. This provides a high degree of integrity, detail and flexibility in responding to unexpected study needs related to report generation, auditing, and monitoring. A comprehensive security program is in place that integrates policy and practice.

Training, Certification, and Quality Control
Look AHEAD-C will continue the successful quality assurance program of the trial that includes extensive manuals, central training, certification/recertification, and monitoring and reporting. The web-based data management, reporting, and document archive is an extraordinary resource for maintaining exceptional quality control.

Central Adjudication
Look AHEAD has a robust system for central adjudication of cardiovascular, cancer and fracture outcomes. These systems will be maintained through Look AHEAD-C. Adjudication of mobility disability, mild cognitive impairment, and dementia will be based on successful protocols from other trials.

Ancillary Studies
Look AHEAD has maintained a robust program of ancillary studies that has extended the scientific breadth of the trial and which will serve as a model for Look AHEAD-C. Guidelines for the development and conduct of ancillary studies appear on the study website. The Ancillary Studies Committee reviews applications, which are approved by the Steering Committee, and monitors progress.

Dissemination Plan
Look AHEAD-C will publicize the results of the study to practicing clinicians, policy makers, research study participants and the general public. Widespread dissemination will occur during the year following trial completion and publication with the main results, and secondary and ancillary results by employing the following techniques: (a) media coverage through press releases and interviews targeted to local and national newspapers, television and radio outlets; (b) production of the research summary document and facts sheet targeted to the general public which clearly and concisely summarizes the key conclusions of the trial; (c) production of flyers, posters, brochures, and research briefs targeted to broad audiences; (d) use of new media and social networking approaches to widely disseminate videos of the techniques of the physical activity intervention to trainers and the public; (e) study newsletters targeted to study participants; (f) distribution of dissemination materials to community agencies, professional societies and health-related websites and list-serves; (g) hosting and attending seminars, conferences, community forums and health fairs; and (h) mailing personal thank you letters to research study participants.

Data Sharing
Look AHEAD-C will follow the general NIH data sharing guidance and provide a data sharing plan to be reviewed and approved by the NIDDK. Data sharing will be accomplished using mixed modes with more than one version of a dataset, each providing a different level of access. This will include data enclave (controlled, secure environment in which eligible researchers can perform analyses using data resources), data archive (place where machine-readable data are acquired, manipulated, documented, and distributed), researcher's efforts (investigator responds directly to data requests by mailing a CD-ROM containing data or posting data on a Web site), and publishing articles in scientific publications. Limited support will be available to outside investigators by phone or email to facilitate the usability of the data, and more extensive support may be negotiated with individual investigators on a fee for service basis. Protecting the rights and privacy of human subjects is the first priority. The final datasets will be de-identified prior to release for sharing.

Data and associated documentation available to users only under a **data-sharing agreement** that provides for: (1) a commitment to using the data only for research purposes and not to identify any individual human participant; (2) a commitment to securing the data using appropriate computer technology; and (3) a commitment to destroying or returning the data after analyses are completed.

Look AHEAD-C will continue to provide de-identified databases to the NIDDK Data Repository for public use, under a schedule set by the sponsors and the study group.

11. STUDY GOVERNANCE AND TRIAL COORDINATION

Study governance during Look AHEAD-C will continue as described in the Look AHEAD protocol. The responsibilities of the clinical centers and coordinating center are maintained. The Steering Committee is the governing body that provides the leadership for Look AHEAD-C and establishes scientific and administrative policy for the study. It holds the primary responsibility for developing the protocol, recommending appropriate procedures to manage the conduct and monitoring of study operations, and reporting the study results. The Steering Committee is comprised of the Principal Investigators of each clinical center, the Principal Investigator of the coordinating center, and the NIDDK Project Scientist. Each member of the Steering Committee will have one vote. All major scientific decisions will be determined by

majority vote of the Steering Committee. The Executive Committee comprised of the Study Chair and Co-Chair, the Principal Investigator of the Coordinating Center, and the NIDDK Project Scientist and Program Official is convened to effect management decisions required between Steering Committee meetings, as needed, for efficient progress of the trial. The Executive Committee reports its actions to the Steering Committee on a regular basis. Meetings of the Executive Committee will generally be held by conference call according to a regular schedule. This Committee also develops timelines for the accomplishment of tasks, selects committee members and chairs, presents information to the Data and Safety Monitoring Board, and develops Steering Committee meeting agendas. The Look AHEAD-C Executive Committee will constitute committees of investigators and staff throughout the trial, as needed. Among these will be working groups that are tasked with oversight of key scientific areas that are new to the trial, including physical function, cognitive function, late-life depression, post-intervention behavioral changes, and geriatrics/gerontology. The Look AHEAD Publications Policy will continue to be maintained.

An independent Data Safety and Monitoring Board (DSMB) has been appointed by the NIDDK Director to review periodically the progress of Look AHEAD-C. The activities of the DSMB are outlined in the DSMB charter.

12. Look AHEAD-C TIMELINE

Look AHEAD-C will be conducted over a two-year period from August 1, 2013 to July 31, 2015.

Trial Activities	Calendar Time
Re-enrollment and Look AHEAD-C data collection	8/1/13 - 12/31/14
Close-out and analysis	1/1/15 – 7/31/15

BIBLIOGRAPHY

Albert MS, Dekosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alz Dement 2011;7:270-9.

ASPE.HHS.GOV. Draft National Plan to Address Alzheimer's Disease (apse.hhs.gov/daltcp/napa/NatlPlan.shtml.)

Barefoot JC, Schroll M. Symptoms of depression, acute myocardial infarction and total mortality in a community sample. Circulation 1996;93:1976-80.

Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol 2011;10:819-28.

Barone BB, Yeh HC, Snyder CF, et al. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. JAMA 2008;300:2754-64.

Barrett-Connor E, Holbrook TL. Sex differences in osteoporosis in older adults with non-insulin-dependent diabetes mellitus. JAMA 1992;268:3333–7.

Bell DS. Heart failure: the frequent, forgotten, and often fatal consequence of diabetes. Diab Care 2003;26:2433-41.

Bertoni AG, Hundlery WG, Massing MW, et al. Heart failure prevalence, incidence, and mortality in the elderly with diabetes. Diab Care 2004;27:699-703.

Bonds DE, Larson JC, Schwartz AV, et al. Risk of fracture in women with type 2 diabetes: The Women's Health Initiative Observational Study. J Clin Endocrinol Metab 2006;91(9):3404-10.

Brach JS, Simonsick EM, Kritchevsky S, et al. The association between physical function and lifestyle activity in the Health, Aging, and Body Composition study. J Am Geriatr Soc 2004;52:502-9.

Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of US adults. N Engl J Med 2003;348:1625-38.

Carney RM, Rich MW, Freedland KE, et al. Major depressive disorder predicts cardiac events in patients with coronary heart disease. Psychosom Med 1988;50:627-33.

Castago D, Baird-Gunning J, Jhund PS, et al. Intensive glycemic control has no impact on the risk of heart failure in type 2 diabetic patients: evidence from a 37,229 patient meta-analysis. Am Heart J 2011;162:938-48.

Centers for Disease Control and Prevention. Percentage of civilian, non-institutionalized population with diagnosed diabetes by age, United States, 1980-2009. (http://www.cdc.gov/diabetes/statistics/prev/national/figbyage.htm).

Centers for Disease Control and Prevention. Prevalence and most common causes of disability among adults--United States, 2005. MMWR Morb Mortal Wkly Rep 2009;58:421-6.

Centers for Disease Control and Prevention. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention (2005) National diabetes fact sheet: general information and national estimates on diabetes in the United States.

Chen P, Ganguli M, Mulsant BH, Dekosky ST. The temporal relationship between depressive symptoms and dementia: a community-based prospective study. Arch Gen Psychiatry 1999;56(3):261-266.

Cruz-Jentoft AJ, Carpena-Ruiz M, Montero-Errasqin R, Sanchez-Castellano C, Sanchez-Garcia E. Exclusion of older adults from ongoing clinical trials about type 2 diabetes mellitus. J Am Geriatr Assoc 2013;16:734-738.

Dekosky ST, Williamson JD, Fitzpatrick AL, et al. Gingko biloba for the prevention of dementia. JAMA 2008;300:2253-62.

Desai AK, Grossberg GT, Chibnail JT. Healthy brain aging: a road map. Clin Geriatr Med 2010;26:1-16.

Deshpande AD, Harris-Hayes M, Schootman M. Epidemiology of diabetes and diabetes-related complications. Phys Ther 2008;88:1254-64.

Duckworth AL, Peterson C, Matthews MD, et al. GRIT: perseverance and passion for long-term goals. K Personal Soc Psychol 2007;92:1087-1101.

Ensrud KE, Ewing SK, Stone KL, et al. Intentional and unintentional weight loss increase bone loss and hip fracture risk in older women. J Am Geriatr Soc 2003;51:1740-7.

Espeland MA, Gill TM, Guralnik J, et al. Designing clinical trials of intervention for mobility disorder: results from the Lifestyle Interventions and Independence for Elders Study Group. J Gerontol Med Sci 2007;62A;1237-43.

Espeland MA, Rapp SR, Robertson R, et al. Benchmarks for designing two-stage studies using Modified Mini-Mental State Examinations: Experience from the Women's Health Initiative Memory Study. Clin Trials 2006;3:99-106.

Faulconbridge LF, Wadden TA, Rubin RR, et al. One-year changes in symptoms of depression and weight in overweight/obese individuals with type 2 diabetes in the Look AHEAD study. Obesity 2012;20:783-793.

Fielding RA, Rejeski WJ, Church T, et al. The Lifestyle Interventions and Independence for Elders (LIFE) Study: Design and methods. J Gerontol Med Sci 2011;66A(11):1226-37.

Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999-2008. JAMA 2010;303:235-41.

Foster GD, Borradaile KE, Sanders MH, et al. A randomized study on the effect of weight loss on obstructive sleep apnea among obese patients with type 2 diabetes: the Sleep AHEAD Study. Arch Intern Med 2009;169(17):1619-26.

Frasure-Smith, N, Lesperance F, Talajic M. Depression and 18-month prognosis after myocardial infarction. Circulation 1995;91:999-1105.

Gaussoin SA, Espeland MA, Absher J, et al. Ascertaining dementia related outcomes from deceased or proxy-dependent participants: an overview of the Women's Health Initiative Memory Study Supplemental Case Ascertainment Protocol. Int J Geriatr Psychiatry 2012;27:205-14.

Geda YE, Knopman DS, Mrazek DA, et al. Depression, apolipoprotein E genotype, and the incidence of mild cognitive impairment: a prospective cohort study. Arch Neurol. 2006;63:435-40.

Goveas JS, Espeland MA, Woods NF, et al. Depression and incidence of mild cognitive impairment and dementia in elderly women: The Women's Health Initiative Memory Study. J Am Geriatr Soc 2011;59:57-66.

Grassi MA, Mazzulla DA, Knudtson MD, et al. Patient self-report of prior laser treatment reliably indicates presence of severe diabetic retinopathy. Am J Ophthalmol 2009;147:501-4.

Gregg E, Chen H, Wagenknecht L, et al. Impact of intensive lifestyle intervention on the remission of type 2 diabetes: The Look AHEAD Study. JAMA 2012;308(23):2489-2496.

Guralnik JM, LaCroix AZ, Abbott RD, et al. Maintaining mobility in late life. I. Demographic characteristics and chronic conditions. Am J Epidemiol 1993;137:845-57.

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;49a:M85-94.

Halter JB. Diabetes mellitus in an aging population: the challenge ahead. J Gerontol A Bio Sci Med Sci 2012;67:1297-9.

Hogan P, Dall T, Nikolov P. Economic costs of diabetes in the US in 2002. Diab Care 2003;26:919-32.

Houston DK, Nicklas BJ, Zizza CA. Weighty concerns: the growing prevalence of obesity among older adults. J Am Dietet Assoc 2009;109:1886-95.

Houx PJ, Jolles J, Vreeling FW. Stroop interference: aging effects assessed with the Stroop Color-Word Test. Exp Aging Res 1993;19:209-24.

Hsin-Chieh Y, Platz EA, Wang NY, et al. A prospective study of the associations between treated diabetes and cancer outcomes. Diab Care 2012;35:113-8.

Isaia GC, Ardissone P, Di Stefano M, et al. Bone metabolism in type 2 diabetes mellitus. Acta Diabetol 1999;36:35–8.

Jakicic JM, Gregg E, Knowler W, et al. Activity patterns of obese adults with type 2 diabetes in the Look AHEAD Study. Med Sci Sports Exerc 2010;42(11):1995-2005.

Jakicic JM, Jaramillo SA, Balasubramanyam A, et al. Effect of a lifestyle intervention on change in cardiorespiratory fitness in adults with type 2 diabetes: results from the Look AHEAD Study. Int J Obes 2009;33(3):305-16.

Jensen LB, Kollerup G, Quaade F, et al. Bone minerals changes in obese women during a moderate weight loss with and without calcium supplementation. J Bone Miner Res 2001;16:141-7.

Joslin EP, Lombard HL, Burrows RE, et al. Diabetes and cancer. N Eng J Med 1959;260:486-8.

Katon WJ, Simon G, Russo J, et al. Quality of depression care in a population-based sample of patients with diabetes and major depression. Med Care 2004;42:1222-9.

Kawas C, Segal J, Stewart, WF, et al. A validation study of the Dementia Questionnaire. Arch Neurol 1994;51:901-6.

Kloppenborg RP, van den Berg E, Kappelle LJ, et al. Diabetes and other vascular risk factors for dementia: Which matters most? A systematic review. Eur J Pharmacol 2008;585:97-108.

Knol, MJ, Twisk, JW, Beekman, AT, et al. Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. Diabetologia 2006;49:837-45.

Kramer H, Reboussin D, Bertoni AG, et al. Obesity and albuminuria among adults with type 2 diabetes. Diab Care. 2009;32(5):851-3.

Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16:606-13.

LaCroix AZ, Guralnik JM, Berkman LF, et al. Maintaining mobility in late life. II. Smoking, alcohol consumption, physical activity, and body mass index. Am J Epidemiol 1993;137:858-69.

Lesak MD. Neuropsychological Assessment. New York: Oxford University Press, 1995.

Levine ME, Crimmins E. The impact of insulin resistance and inflammation on the association between sarcopenic obesity and physical functioning. Obesity 2012;20:2101-6.

Little RJA, Rubin DB. Statistical Analysis With Missing Data, 2nd ed. New York : John Wiley and Sons, 2002.

Look AHEAD Research Group. 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(17):1566-1575.

Lowe MR, Butryn ML, Didie ER, et al. The Power of Food Scale: a new measure of the psychological influence of the food environment. Appetite 2009;53:114-118.

Lu FP, Lin KP, Kuo HK. Diabetes and the risk of multi-system aging phenotypes: a systematic revise and meta-analysis. PloS One 4(1):e4144. Doi:10.1371/journal.pone.0004144.

Marsh AP, Rejeski WJ, Espeland MA, et al. Muscle strength and BMI as predictors of major mobility disability in the Lifestyle and Independence for Elders pilot. J Geront 2011;66:1376-83.

McKhann GM. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alz Dement 2011;7:263-9.

McTiernan A, Irwin M, Vongruenigen V. Weight, physical activity, diet, and prognosis in breast and gynecologic cancers. J Clin Oncol 2010;28:4074-80.

MMWR Weekly. Public health and aging: trends in aging - United States and worldwide. 2003;52:101-6.

Newman AB, Simonsick EM, Naydeck EM, et al. Association of long-distance corridor walk performance with mortality, cardiovascular disease, mobility limitation, and disability. JAMA 2006;295:2018-26.

Nichols GA, Guillion CM, Koro CE, et al. The incidence of congestive heart failure in type 2 diabetes: an update. Diab Care 2004;27:1879-84.

O'Brien PC. Procedures for comparing samples with multiple endpoints. Biometrics 1984;40:1079-1087.

Ostir GV, Kuo YF, Berges IM, Markides KS, Ottenbacher KJ. Measures of lower body function and risk of mortality over 7 years of follow-up. Am J Epidemiol 2007;166:599-605.

Ottenbacher KJ, Ostir GV, Peek MK, et al. Diabetes mellitus as a risk factor for hip fracture in Mexican American older adults. J Gerontol 2002;57:M648–53.

Patty L, Wu C, Torres M, et al. Validity of self-reported eye disease and treatment in a population-based study: The Los Angeles Latino Eye Study. Ophthalmology 2012;119:1725-30.

Perera S, Studenski S, Chandler JM, Guralnik JM. Magnitude and patterns of decline in health and function in 1 year affect subsequent 5-year survival. J Gerontol A Biol Sci Med Sci 2005;60:894-900.

Pfeffer RI, Kurosaki TT, Harrah CH, et al. Measurement of functional activities in older adults in the community. J Geront 1982;37:323-9.

Phelan S, Kanaya AM, Subak LL, et al. Weight loss prevents urinary incontinence in women with type 2 diabetes: results from the Look AHEAD Trial. J Urol 2012;187:939-944.

Plassman BL, Williams JW, Burke JR, et al. Systematic review: NIH state-of-the-science conference: factors associated with risk for and prevention of cognitive decline in later life. Ann Intern Med 2010;153:182-93.

Redmon JB, Bertoni AG, Connelly S, et al. Effect of the Look AHEAD study intervention on medication use and related cost to treat cardiovascular disease risk factors in individuals with type 2 diabetes. Diab Care 2010;33(6):1153-8.

Reitan RM. The validity of the Trail Making Test as an indicator of organic brain damage. Percept Motor Skills 1958;8:271-6.

Rejeski WJ, Ip EH, Bertoni AG, et al. Lifestyle change and mobility in obese adults with type 2 diabetes. N Engl J Med 2012;366:1209-17.

Rejeski WJ, Ip EH, Marsh AP, et al. Measuring disability in older adults: the International Classification System of Functioning, Disability, and Health Framework. Geriatr Gerontol Int 2008;8:48-54.

Rejeski WJ, Marsh AP, Chmelo E, Rejeski JJ. Obesity, intentional weight loss, and physical disability in older adults. Obes Rev 2010;11:671-85.

Riedt CS, Cifuentes M, Stahl T, et al. Overweight postmenopausal women lose bone with moderate weight reduction and 1 g/day calcium intake. J Bone Miner Res 2005;20:455-63.

Roberts, RE, Deleger, S, Strawbridge, WJ, et al. Prospective association between obesity and depression: evidence from the Alameda County Study. Int J Obes Relat Metab Disord 2003;27:514-21.

Rugulies R. Depression as a predictor of coronary heart disease: a review and meta-analysis. Am J Prev Med 2002;23;51-61.

Sasaki H, Kasagi F, Yamada M, Fujita S. Grip strength predicts cause-specific mortality in middle-aged and elderly persons. Am J Med 2007;120:337-42.

Schoenfeld DA. Sample-size formula for the proportional-hazards regression model. Biometrics 1993;39:499-503.

Schwartz AV, Hillier TA, Sellmeyer DE, et al. Older women with diabetes have a higher risk of falls: a prospective study. Diabetes Care 2002;25:1749–54.

Schwartz AV, Sellmeyer DE, Ensrud KE, et al. Older women with diabetes have an increased risk of fracture: a prospective study. J Clin Endocrinol Metab 2001;86:32-8.

Schwartz AV, Sellmeyer DE, Strotmeyer ES, et al. Diabetes and bone loss at the hip in older black and white adults. J Bone Miner Res 2005;20:596-603.

Scott KM, McGee MA, Wells JE, et al. Obesity and mental health disorders in the adult general population. J Psychosom Res 2008;64:97-105.

Shlipak MG, Katz R, Kestenbaum B, et al. Rapid decline of kidney function increases cardiovascular risk in the elderly. J Am Soc Nephrol 2009;20:2625-30.

Stenholm S, Tiainen K, Rantanen T, et al. Long-term determinants of muscle strength decline: prospective evidence from the 22-year mini-Finland follow-up survey. J Am Geriatr Soc 2012;69:77-85.

Stroop JR. Studies of interference in serial verbal reactions. Exp Psychol 1935;18:643-62.

Strotmeyer ES, Cauley JA, Schwartz AV, et al. Nontraumatic fracture risk with diabetes mellitus and impaired fasting glucose in older white and black adults: the health, aging, and body composition study. Arch Intern Med 2005;165:1612-7.

Stuart B, Lloyd J, Zhao L, et al. Obesity, disease burden, and prescription spending by community-dwelling Medicare beneficiaries. Curr Med Res Opin 2008;24:2377-87.

Stunkard AJ, Messick S. The Three-Factor Eating Questionnaire to measure dietary restraint, disinhibition and hunger. J Psychosomatic Res 1985;29:71-83.

Sumithran P, Prendergast LA, Delbridge E, et al. Long-term persistence of hormonal adaptations to weight loss. N Engl J Med 2011;365:1597-604.

Tang DI, Geller NL, Pocock SJ. On the design and analysis of randomized clinical trials with multiple endpoints. Biometrics 1993;49:23-20..

Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. J Clin Psychiatry 1987;48:3148.

The LIFE Study Investigators. Effects of a physical activity intervention on measures of physical performance: results of the Lifestyle Interventions and Independence in Elders (LIFE) pilot study. J Gerontol Med Sci 2006;61A:1157-65.

The Look AHEAD Research Group. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the Look AHEAD trial. Diab Care 2007;30(6):1374-83.

Tosteson AN, Gabriel SE, Grove MR, et al. Impact of hip and vertebral fractures on quality-adjusted life years. Osteoporos Int 2001;12:1042-9.

van Daele PL, Stolk RP, Burger H, et al. Bone density in non-insulin-dependent diabetes mellitus. The Rotterdam Study. Ann Intern Med 1995;122:409-14.

Vigneri P, Frasca F, Sciaca L, et al. Diabetes and cancer. Endocrin Relat Cancer 2009;16:1103-23.

Villareal DT, Shah K, Banks MR, et al. Effect of weight loss and exercise therapy on bone metabolism and mass in obese older adults: a one-year randomized controlled trial. J Clin Endocrin Metab 2008;93:2181-7.

Vinik AI, Maser RE, Mitchell BR, Freeman R. Diabetic autonomic neuropathy. Diabetes Care 2003;26:1553-79.

von Lengerke T, Hagenmeyer EG, Gothe H, et al. Excess health care costs of obesity in adults with diabetes mellitus: a claims data analysis. Exp Clin Endocrinol Diab 2010;118:496-504.

Wechsler D. WAIS-R manual. New York: Psychological Corporation, 1981.

Weintraub S, Dikmen S, Heaton RK, et al. Cognitive assessment using the NIH Toolbox. Neurol 2013;80;S54-S64.

Wilcox BJ, He Q, Chen R, et al. Midlife risk factors and healthy survival in men. JAMA 2006;296:2343-50.

Williamson DA, Rejeski J, Lang W, et al. Impact of a weight management program on health-related quality of life in overweight adults with type 2 diabetes. Arch Intern Med. 2009;169(2):163-71.

Wing RR, Lang W, Wadden TA, et al. Benefits of modest weight loss in improving cardiovascular risk factors in type 2 diabetes. Diab Care 2011;34(7):1481-6.

World Cancer Research Fund/American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective. Washington DC:AICR, 2007.

World Health Organization
http://www.who.int/healthinfo/global_burden_disease/2004_report_update/en/index.html, 2004.

Wulsin, LR, Singal, BM. Do depressive symptoms increase the risk for onset of coronary disease? A systematic quantitative review. Pyschosom Med 2003;65:201-10.

Yuspeh RL, Vanderploeg RD, Kershaw KA. Normative data on a measure of estimated premorbid abilities as part of a dementia evaluation. Appl Neurphsychol 1998;5:149-53.

Zhao G, Ford, ES, Dhingra, S, et al. Depression and anxiety among US adults: associations with body mass index. Int J Obes 2009;33:257-66.