Supplemental Material:

History of cardiovascular disease, intensive lifestyle intervention, and cardiovascular outcomes in the Look AHEAD Trial

The Look AHEAD Research Group, Cora E. Lewis, MD, MSPH; John P. Bantle, MD; Alain G. Bertoni, MD, MPH; George Blackburn, MD,* PhD; Frederick L. Brancati, MD*, MHS; George A. Bray, MD; Lawrence J. Cheskin, MD; Jeffrey M. Curtis, MD, MPH; Caitlin Egan, MS; Mary Evans, PhD; John P. Foreyt, PhD[10]; Siran Ghazarian, MD; Bethany Barone Gibbs, PhD, FAHA; Stephen Glasser, MD; Edward W. Gregg, PhD; Helen P. Hazuda, PhD; Louise Hesson, MSN, CRNP; James O. Hill, PhD; Edward S. Horton, MD; Van S. Hubbard, MD;John M. Jakicic, PhD; Robert W. Jeffery, PhD; Karen C. Johnson, MD, MPH; Steven E. Kahn, MB, ChB; Abbas E. Kitabchi, PhD, MD*; Dalane Kitzman, MD; William C. Knowler, MD, DrPH; Edward Lipkin, MD, PhD; Sara Michaels, MD; Maria G. Montez, RN, MSHP, CDE; David M. Nathan, MD; Ebenezer Nyenwe, MD; Jennifer Patricio, MS; Anne Peters, MD; Xavier Pi-Sunyer, MD; Henry Pownall, PhD; David Reboussin, PhD; Donna H. Ryan, MD; Thomas A. Wadden, PhD; Lynne E. Wagenknecht, DrPH; Holly Wyatt, MD; Rena R. Wing, PhD; Susan Z. Yanovski, MD

Correspondence to: Cora E. Lewis, MD, MSPH
Department of Epidemiology
School of Public Health
University of Alabama at Birmingham
RPHB 210C
1720 2nd Ave S
Birmingham, AL, 35294-0022

Short title: Look AHEAD Research Group, CVD subgroups findings

Look AHEAD Research Group

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]; Kerry Stewart, EdD[3]; Richard Rubin, PhD[3]; Jean Arceci, RN; Susanne Danus; David Bolen; Danielle Diggins; Sara Evans; Mia Johnson; Joyce Lambert; Sarah Longenecker; Kathy Michalski, RD; Dawn Jiggetts; Chanchai Sapun; Maria Sowers; Kathy Tyler

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, MPH[2]; Monika Safford, MD[3]; Stephen Glasser, MD[3]; Vicki DiLillo, PhD[3]; Charlotte Bragg, MS, RD, LD; Amy Dobelstein; Sara Hannum, MA; 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]; Kathryn Hayward, MD[3]; Heather Turgeon, RN, BS, CDE[2]; Valerie Goldman, MS, RD[2]; Linda Delahanty, MS, RD[3]; Ellen Anderson, MS, RD[3]; Laurie Bissett, MS, RD; Virginia Harlan, MSW; Theresa Michel, DPT, DSc, CCS; Mary Larkin, RN; Christine Stevens, RN

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

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University of Tennessee East. Karen C. Johnson, MD, MPH[1]; Carolyn Gresham, RN[2]; Mace Coday, PhD; Lisa Jones, RN; Lynne Lichtermann, RN, BSN; J. Lee Taylor, MEd, MBA; Beate Griffin, RN; Donna Valenski

University of Tennessee Downtown. Abbas E. Kitabchi, PhD, MD[1]; Ebenezer Nyenwe, MD[3]; Helen Lambeth, RN, BSN[2]; Moana Mosby, RN; Amy Brewer, MS, RD,LDN; Debra Clark, LPN; Andrea Crisler, MT; Gracie Cunningham; Debra Force, MS, RD, LDN; Donna Green, RN; Robert Kores, PhD; Renate Rosenthal, PhD; Elizabeth Smith, MS, RD, LDN

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The Miriam Hospital/Brown Medical School Rena R. Wing, PhD[1]; Renee Bright, MS[2]; Vincent Pera, MD[3]; John Jakicic, PhD[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 Steven M. Haffner, MD[1]; 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 Murillo, BS[2]; Robert Knopp, MD[3]; Edward Lipkin, MD, PhD[3]; Dace Trence, MD[3]; Elaine Tsai, MD[3]; Basma Fattaleh, BA; Diane Greenberg, PhD; Brenda Montgomery, RN, MS, CDE; Ivy Morgan-Taggart; Betty Ann Richmond, MEd; Jolanta Socha, BS; April Thomas, MPH, RD; Alan Wesley, BA; Diane Wheeler, RD, CDE

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]; 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; Patricia Poorthunder; Sandra Sangster; Leigh A. Shovestull, RD, CDE; Miranda Smart; Janelia Smiley; Teddy Thomas, BS; Katie Toledo, MS, LPC

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[3]; David Reboussin, PhD[3]; W. Jack Rejeski, PhD[3]; Alain G. Bertoni, MD, MPH[3]; Wei Lang, PhD[3]; Michael S. Lawlor, PhD[3]; David Lefkowitz, MD[3]; Gary D. Miller, PhD[3]; Patrick S. Reynolds, MD[3]; Paul M. Ribisl, PhD[3]; Mara Vitolins, DrPH[3]; Daniel Beavers, PhD[3]; Haiying Chen, PhD, MM[3]; Dalane Kitzman, MD[3]; Delia S. West, PhD[3]; Lawrence M. Friedman, MD[3]; Ron Prineas, MD[3]; Tandaw Samdarshi, MD[3];Kathy M. Dotson, BA[2]; Amelia Hodges, BS, CCRP[2]; Dominique Limprevil-Divers, MA, MEd[2]; Karen Wall[2]; Carrie C. Williams, MA, CCRP[2]; Andrea Anderson, MS; Jerry M. Barnes, MA; Mary Barr; Tara D. Beckner; Cralen Davis, MS; Thania Del Valle-Fagan, MD; Tamika Earl, Melanie Franks, BBA; Candace Goode; Jason Griffin, BS; Lea Harvin, BS; Mary A. Hontz, BA; Sarah A. Gaussoin, MS; Don G. Hire, BS; Patricia Hogan, MS; Mark King, BS; Kathy Lane, BS; Rebecca H. Neiberg, MS; Julia T. Rushing, MS; Valery S. Effoe, MD,MS; Michael P. Walkup, MS; Terri Windham

Central Resources Centers

DXA Reading Center, University of California at San Francisco Michael Nevitt, PhD[1]; Ann Schwartz, PhD[2]; John Shepherd, PhD[3]; Michaela Rahorst; Lisa Palermo, MS, MA; Susan Ewing, MS; Cynthia Hayashi; Jason Maeda, MPH

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

Diet Assessment Center, University of South Carolina, Arnold School of Public Health, Center for Research in Nutrition and Health Disparities Elizabeth J Mayer-Davis, PhD[1]; Robert Moran, PhD[1]

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; Barbara Harrison, MS; 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

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[1] Principal Investigator
[2] Program Coordinator
[3] Co-Investigator
All other Look AHEAD staffs are listed alphabetically by site.

Supplemental Material: Methods supplement

Detailed inclusion/exclusion criteria.

Gender Men and women are eligible. Look AHEAD will endeavor to recruit approximately equal numbers of men and women.

Type 2 diabetes mellitus Diabetes mellitus will be determined by self-report with verification (medical records, current treatment, verification from personal health care provider, or test results meeting the 1997 American Diabetes Association criteria of fasting glucose > 126 mg/dl, symptoms of hyperglycemia with casual plasma glucose > 200 mg/dl or two-hour plasma glucose > 200 mg/dl after a 75 gram oral glucose load). In an effort to identify individuals with type 2 diabetes (the population that would be most responsive to weight loss), individuals who have a clinical history strongly suggestive of Type 1 diabetes will be excluded. Individuals taking oral hypoglycemic medication or insulin and those who are treated with diet and exercise are eligible. No more than 30% of the study population will be using insulin at entry into the study.

Body mass index Overweight individuals, with body mass index of 25 kg/m2 or greater (27 kg/m2 if currently taking insulin) are eligible. Weight loss is recommended for overweight individuals with one or more cardiovascular risk factors, including diabetes mellitus. There is no upper eligibility criterion for body mass index, however an upper limit on weight has been set (Protocol Section 4.2.1).

Age Individuals aged 45-75 years old are eligible. Older individuals are excluded due to their increased risk of competing mortality and potential safety concerns related to weight loss. Starting in August 2002, applicants aged 45-54 were only eligible if they reported CVD a history; those 55-75 years were eligible regardless of their history of CVD.

Ethnicity All ethnic groups are eligible for the study. Look AHEAD has the goal of recruiting 33% of the study cohort from ethnic minority groups including African Americans, Hispanic Americans, American Indians, and Asian Americans. Data from NHANES III indicate that approximately 23% of individuals meeting the eligibility criteria for Look AHEAD will be from ethnic minorities.

Blood pressure Look AHEAD will enroll individuals whose blood pressure is under at least moderate control: treated or untreated resting systolic/diastolic blood pressure less than 160/100 mmHg. Individuals whose blood pressure exceeds these levels during screening will be told to seek treatment. Such individuals may be rescreened after three months to re-assess blood pressure eligibility.

Glycemic control Look AHEAD will enroll individuals whose HbA1c is less than 11% or equal to 11%. Individuals whose HbA1c exceeds this level may require more urgent care and will be told to seek treatment. Such individuals may be re-screened after three months to re-assess HbA1c eligibility.

Lipid control Individuals with a fasting triglycerides concentration less than 600 mg/dl are eligible. Individuals whose fasting triglycerides concentration exceeds this level may be rescreened after three months to re-assess triglycerides eligibility.

History of cardiovascular disease Look AHEAD will recruit individuals both with and without a history of cardiovascular disease. Data from NHANES III indicate that approximately 29% of individuals meeting the eligibility criteria defined by the trial will have a history of cardiovascular disease. Cardiovascular event rates in diabetic individuals with heart disease are expected to be approximately twice those of diabetic individuals without a history of heart disease.

Eligible participants include those with a history of uncomplicated myocardial infarction, coronary artery bypass surgery, percutaneous coronary angiography, atherectomy or stent placement, chronic stable angina pectoris, no resting or exercise induced complex arrhythmias, and stable NYHA Class I or Class II congestive heart failure if they are beyond three months. Participants with a history of carotid or peripheral artery atherectomy, angioplasty, or bypass surgery are also eligible for inclusion if they meet functional criteria for inclusion.

All participants will undergo a supervised maximum exercise stress test using the established study protocol. The exercise stress test will be conducted while the participant is continued on any prescribed medication for cardiovascular disease. Abnormalities will result in exclusion or in further evaluation. Individuals who develop exercise induced angina pectoris or significant

ST segment depression of 1.5 mm or greater at low to moderate workloads (less than 7 METs) may be included if they have been evaluated by a cardiologist and considered safe for participation in the Lifestyle Intervention protocol.

Willingness to participate Participants must be willing to be randomized to either Diabetes Support and Education or the Lifestyle Intervention and to follow the protocol to which they have been assigned. Individuals who are unwilling to consider using weight loss medications are eligible for the study, however they must be willing to modify their diet and their activity and to attempt to lose 7% of their body weight if they are assigned to the Lifestyle Intervention.

Detailed description of intensive lifestyle intervention. The lifestyle intervention used in Look AHEAD was based on the most recent research on the strategies for inducing and maintaining weight loss (1). The intervention was similar to that used in the Diabetes Prevention Program (DPP), but differed in the following ways: the Look AHEAD intervention included both group and individual sessions, participants were given a weight loss goal of 10% (rather than 7%), meal replacement products were provided to improve adherence, weight loss medication was used as an option for a short period of time, the physical activity goal was 175 minutes (compared to 150 minutes in DPP), and a specific algorithm for adjustment of diabetes medications was followed to reduce the risk of hypoglycemia.

The Look AHEAD intervention sought to achieve and maintain at least a mean 7% weight loss. In order to achieve this, each individual participant was encouraged to lose and maintain at least 10% of their body weight. Weight loss was attained through decreased caloric intake and increased physical activity.

Participants attended both group and individual sessions, with decreasing frequency of contact over the course of the trial. The sessions were conducted by nutritionists, exercise specialists, and behavior therapists certified by Look AHEAD. All participants were assigned a lifestyle counselor who worked with the individual throughout the program. Participants completed the first year of treatment with an assigned group of 10-20 persons. For months 1-6, participants were provided weekly treatment, with three group sessions and one individual session each month; for months 7-12, they were provided two group sessions and one individual session each month. During Years 2 to 4, the intervention was delivered more on an

individual basis, with at least one in-person contact each month and an additional monthly phone or email contact. After year 4, there was one individual contact each month. In addition, participants were offered two or three group classes and courses each year to help maintain interest and the weight and activity goals.

ILI participants were given a calorie goal of 1200-1500 kcal/day for those who weighed less than 114 kg (250 lbs) and 1500 to 1800kcal/day for those over 114 kg. They were encouraged to consume 30% of total calories from fat and at least 15% of calories from protein. Meal replacement products were provided at no cost to help participants adhere to their dietary goals. During weeks 3 to 19 of the program, individuals were encouraged to replace two meals each day with a liquid shake and one snack with a bar. The other meal (typically dinner) consisted of conventional foods; fruits and vegetables were added to reach the calorie goal. From week 20 on, meal replacements were typically used for one meal per day with conventional foods consumed at the other times.

Physical activity was gradually increased to a goal of at least 175 minutes/week. This activity goal was achieved in bouts of at least 10 minutes in duration and used moderate intensity activities such as brisk walking. Group sessions discussed methods for exercising safely and reducing barriers to exercise and introduced participants to strength training which could comprise up to 25% of the weekly goal. In addition to structured activity done in bouts of at least 10 minutes, participants were also encouraged to increase their lifestyle activity. They were provided with pedometers and encouraged to walk 10,000 steps each day.

Behavioral strategies were stressed throughout the program. Self-monitoring of food and physical activity was emphasized as the most important behavioral strategy, and self-monitoring logs were reviewed regularly by the lifestyle counselors to assist participants with their behavior changes. Participants were weighed at each session, self-monitoring books were reviewed, and a new lesson topic presented. Lessons were prepared centrally and are available at the web address provided at the end of this appendix. These lessons included topics such as limiting times and places of eating, coping with negative thoughts, and relapse prevention.

Hypoglycemia was of particular concern during the first 6 months of the program when caloric restriction and meal replacement products were started. To minimize the risk of hypoglycemia,

participants taking insulin or other medications that might cause hypoglycemia, monitored their blood sugar for at least one week. These readings were used by the medical staff to adjust medications following a preset algorithm (2, 3). The same approach to adjusting medications was used in later years when campaigns or refresher groups included more structured dietary approaches and meal replacement products designed to promote weight loss.

To maximize weight loss, a tool box of additional strategies was available for use with participants after month 6 if the individual had not achieved the 10% weight loss. The tool box included orlistat, a weight loss medication (4). A total of 451 participants elected to use this medication between month 7 and 12 for a mean of 16.7 $\pm$ 8.8 weeks. However, since minimal weight loss benefit was observed with orlistat, the use of this medication was discontinued in 2008.

From Year 2 on, participants were invited to participate in a periodic group refresher courses and national campaigns. (Refreshers typically lasted 4-6 weeks, while campaigns were usually 8-10 weeks.) Both were designed to re-engage participants and increase commitment of lifestyle changes. The national campaigns were implemented at all sites and the same time and often included a small prize (e.g. a windbreaker or stadium blanket) for achieving campaign goals. Monthly open group meetings and reunion groups, where participants met with the members of their original year 1 treatment group, were also provided.

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Supplemental Material: Results Tables and Figures

Table S1. Intervention effects by randomized assignment and baseline history of CVD subgroup: median weight change and fitness change

Figure S1. Distributions of percent change in fitness by randomization group from baseline to follow-up year 1 and follow-up year 4 in those without (S1A) and with (S1B) history of CVD at baseline.

Figure S2. Aspirin use by randomized assignment and by year, among those without history of cardiovascular disease (A) and with history of cardiovascular disease at baseline (B).*†

*p<0.05 for ILI vs DSE difference at time point with CVD subgroup
† Significant differences between the intensive lifestyle intervention and the diabetes support and education control groups were present only at follow-up years 1 and 2 among those without a cardiovascular history at baseline.

Figure S3. Mean HbA1C levels by baseline history of cardiovascular disease and treatment assignment by year.*

*Overall difference between treatment arms in both those with and without history of cardiovascular disease at baseline ($p < 0.001$); significant differences between the intensive lifestyle intervention and the diabetes support and education control groups were present at follow-up years 1, 2, 3, and 4 in both cardiovascular disease history groups.

Figure S4. Insulin use by randomized assignment and year, among those without history of cardiovascular disease (A) and with history of cardiovascular disease at baseline (B).*†

*p<0.05 for ILI vs DSE difference at time point with CVD subgroup
† Overall difference between arms in the group without history of cardiovascular disease at baseline ($p < 0.001$); significant differences between the intensive lifestyle intervention and the diabetes support and education control groups were present at all follow-up timepoints except year 10 in this group. There were no differences by treatment assignment among those with cardiovascular disease history at baseline.

Figure S5. Mean HDL-Cholesterol levels by baseline history of cardiovascular disease and treatment assignment by year.*

*Overall difference between treatment arms in those without history of cardiovascular disease at baseline ($p < 0.003$); significant differences between the intensive lifestyle intervention and the diabetes support and education control groups were present at follow-up years 1, 2, 3, and 4 in those without cardiovascular disease and at years 1 and 3 in those with history cardiovascular disease.

Figure S6. Mean systolic blood pressure levels by baseline history of cardiovascular disease and treatment assignment by year.*

*Overall difference between treatment arms in those with ($p=0.063$) and without ($p < 0.001$) history of cardiovascular disease at baseline; significant differences between the intensive lifestyle intervention and the diabetes support and education control groups were present at baseline and follow-up years 1, 2, 3, 4, 7, and 8 in those without cardiovascular disease history group and at follow-up year 1 in those with baseline cardiovascular disease.

Figure S7. Mean diastolic blood pressure levels by baseline history of cardiovascular disease and treatment assignment by year.

Figure S8. Mean log triglyceride levels by baseline history of cardiovascular disease and treatment assignment by year

Figure S9. Cumulative hazard plots for hypoglycemic serious adverse events by history of cardiovascular disease at baseline and randomized treatment assignment.*

*ILI indicates the intensive lifestyle intervention group (dashed blue line) and DSE indicates the diabetes support and education control group (solid red line).

Table S1. Intervention effects by randomized assignment and baseline history of CVD subgroup: median weight change and fitness change (METs)

Follow-up visit (year)		1	2	3	4	6	8	10
Median percent weight change (kg)								
CVD history subgroup	Intervention group							
No	DSE	-0.5	-0.6	-0.6	-0.7	-1.7	-2.3	-3.3
	ILI	-8.0	-5.7	-4.7	-4.1	-4.2	-5.2	-6.1
Yes	DSE	-0.1	-0.6	-1.0	-0.4	-2.1	-2.6	-3.1
	ILI	-7.5	-5.6	-4.9	-5.0	-4.9	-6.1	-7.5
Median percent fitness change								
No	DSE	0.0			-4.0			
	ILI	15.6			0.0			
Yes	DSE	0.0			-7.9			
	ILI	12.2			-3.6			

ILI: intensive lifestyle intervention

DSE: diabetes support and education control

Fitness from graded exercise test available at years 1 and 4 post-randomization only

Figure S1. Distributions of percent change in fitness by randomization group from baseline to follow-up year 1 and follow-up year 4 in those without (S1A) and with (S1B) history of CVD at baseline.

Figure S1A

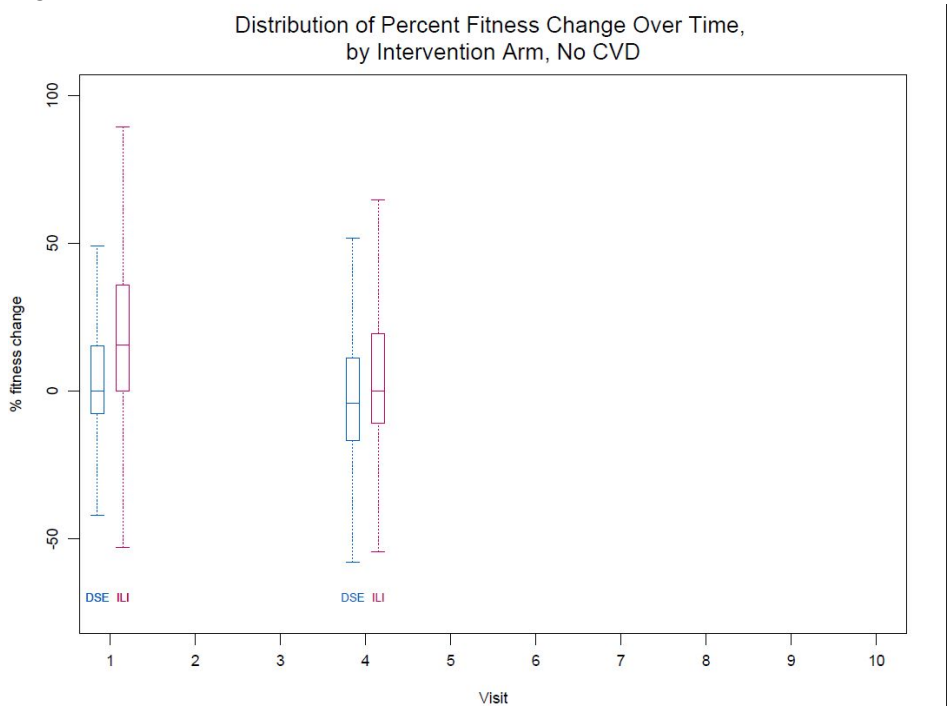

Figure S1B

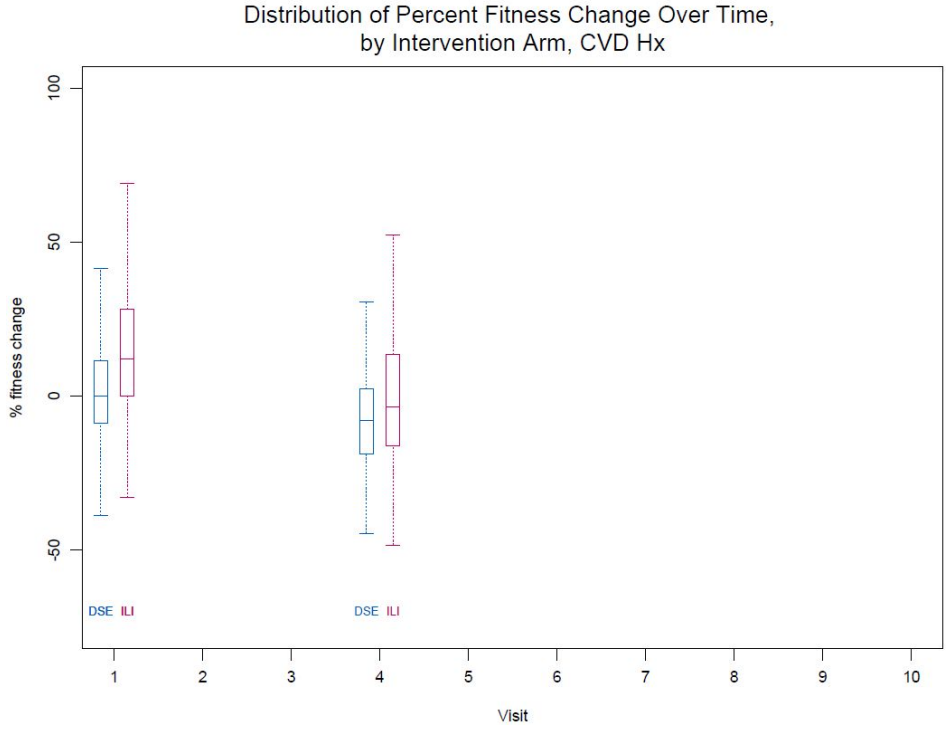

Figure S2a. Aspirin use: no history of CVD history at baseline

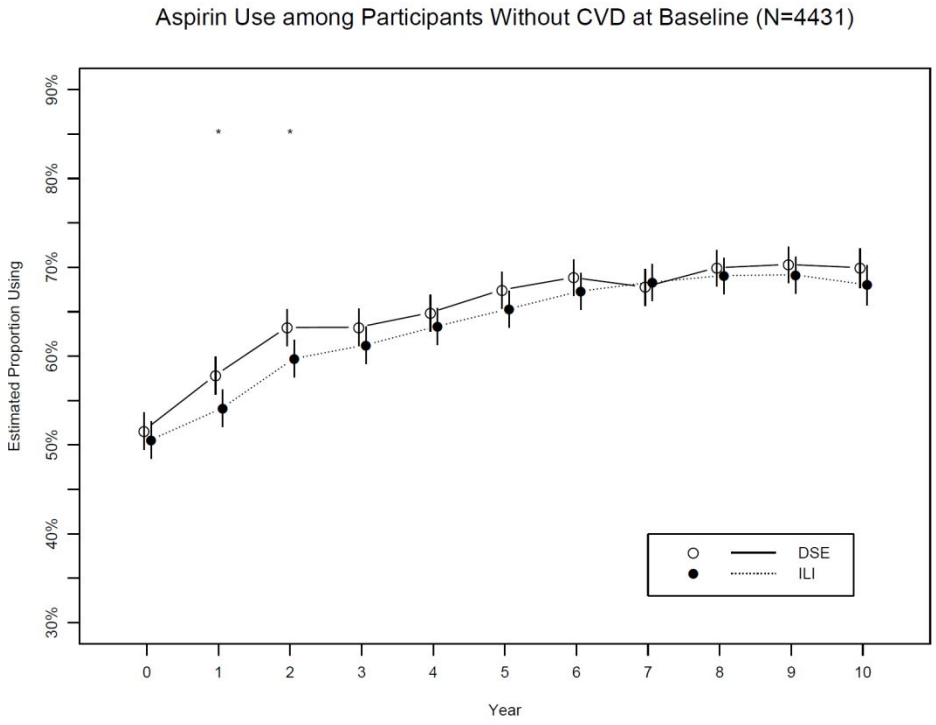

Figure S2b. Aspirin use: baseline CVD history

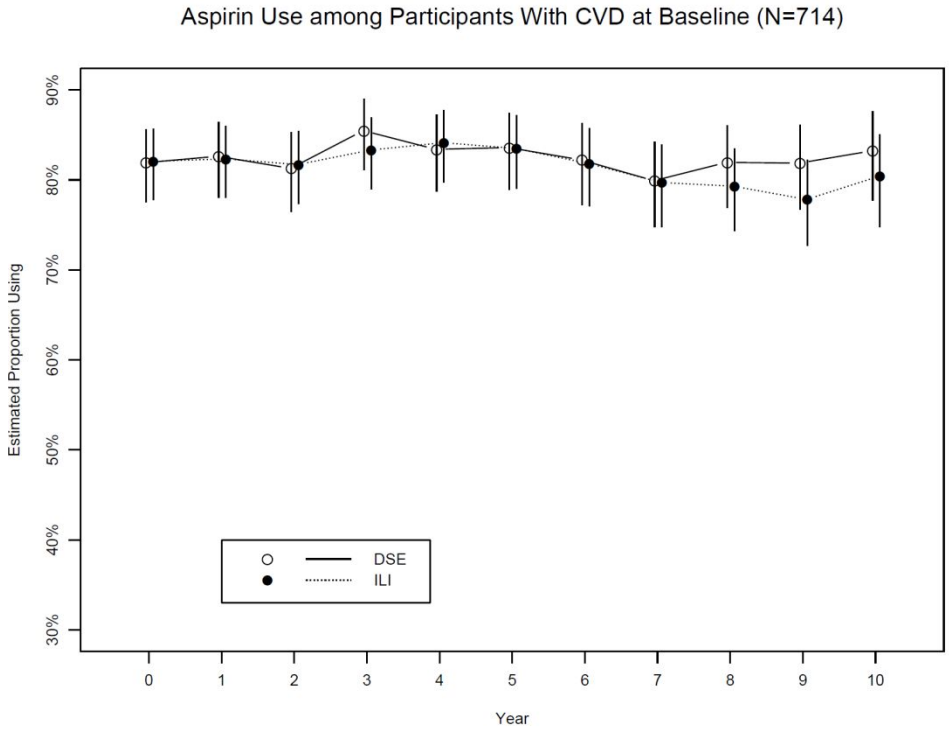

Figure S3. Mean HbA1c

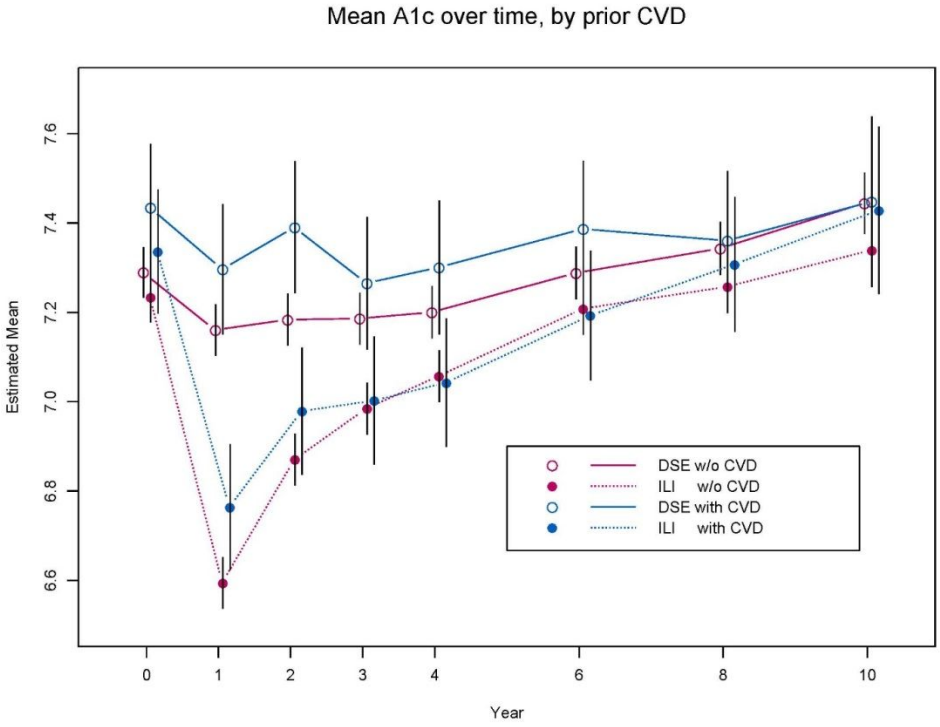

Figure S4a. Insulin use: no history of CVD at baseline

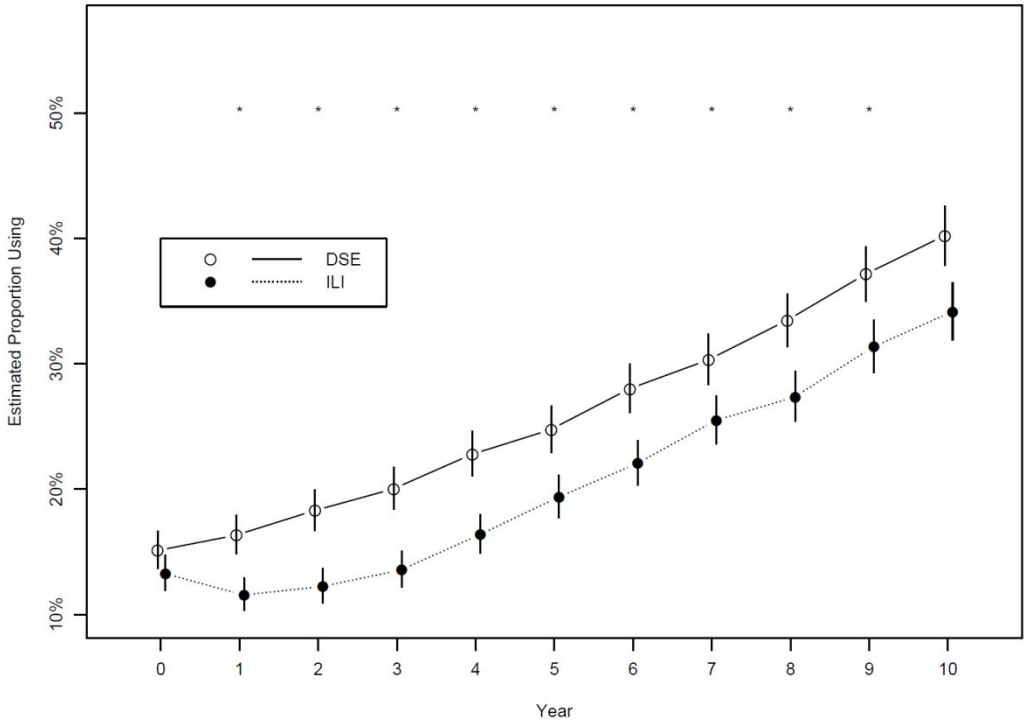

Figure S4b. Insulin use: baseline CVD history

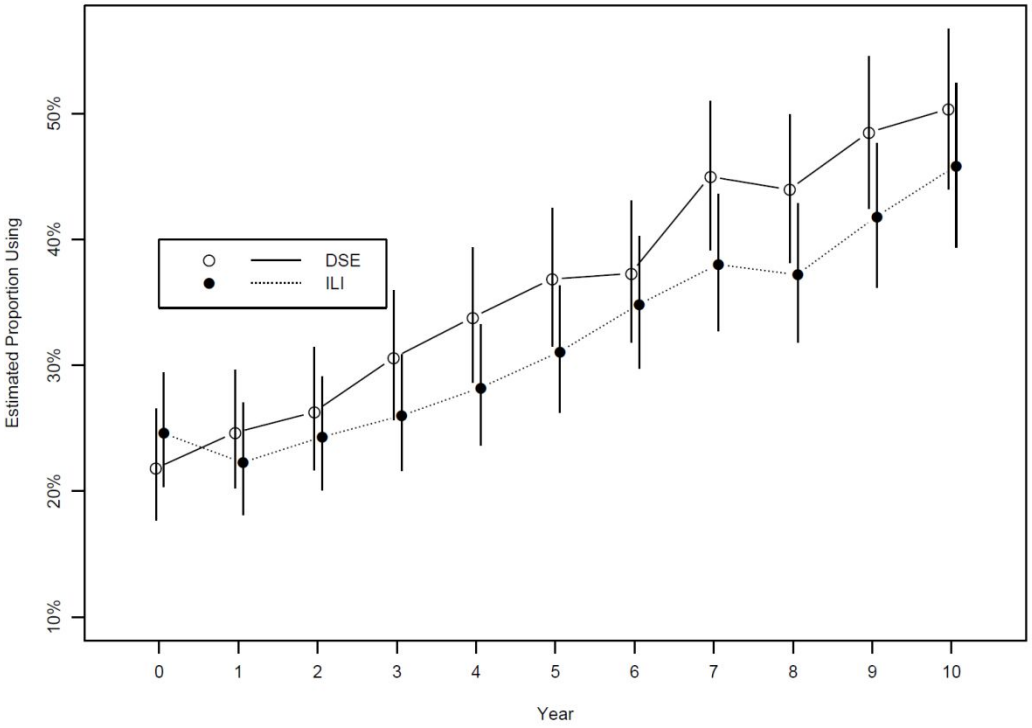

Figure S5. Mean HDL-C

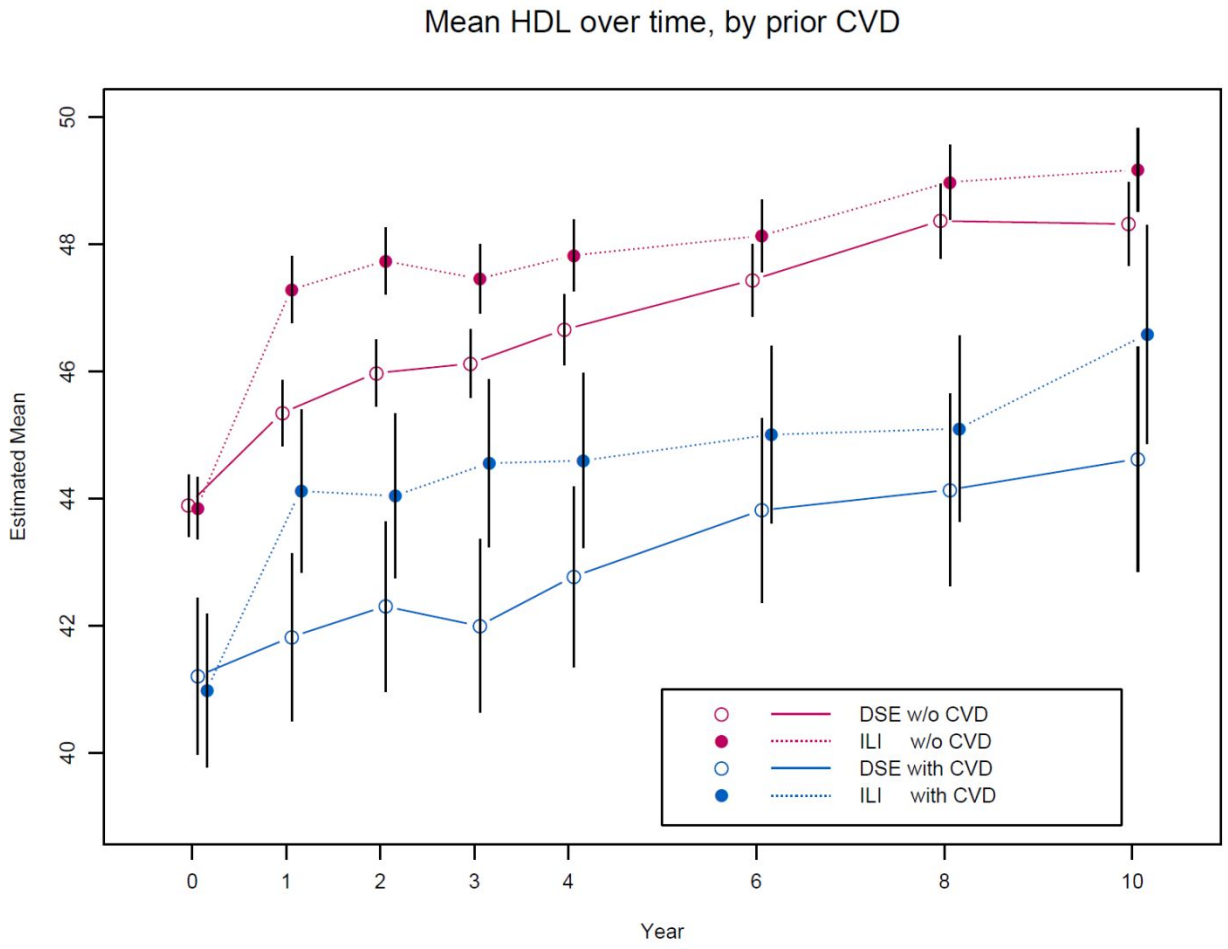

Figure S6. Mean systolic blood pressure

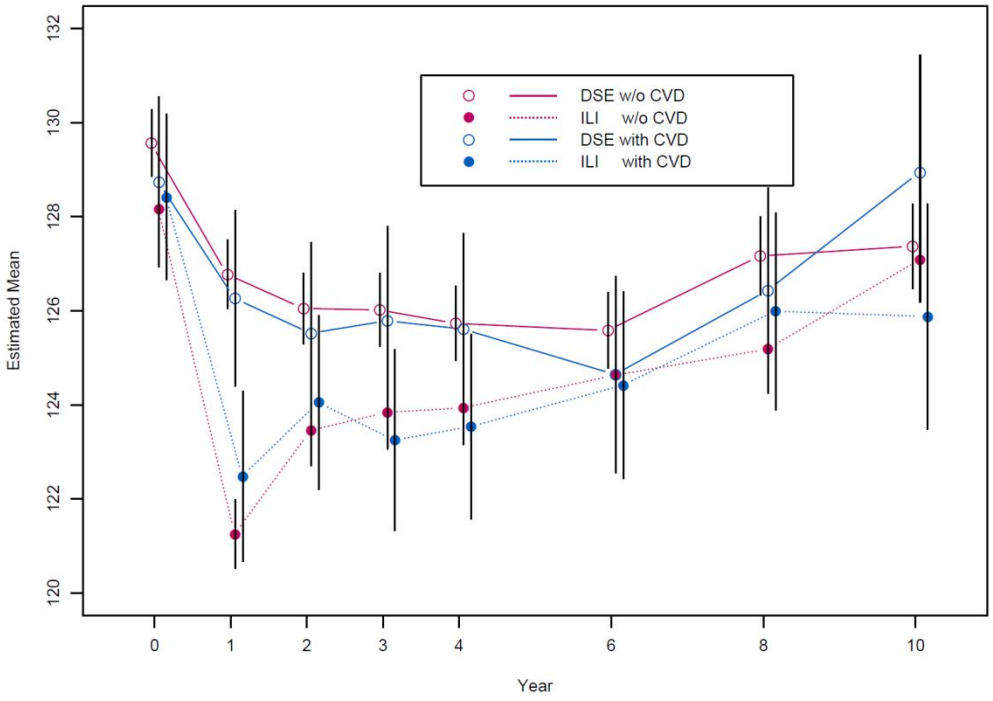

Figure S7. Mean diastolic blood pressure

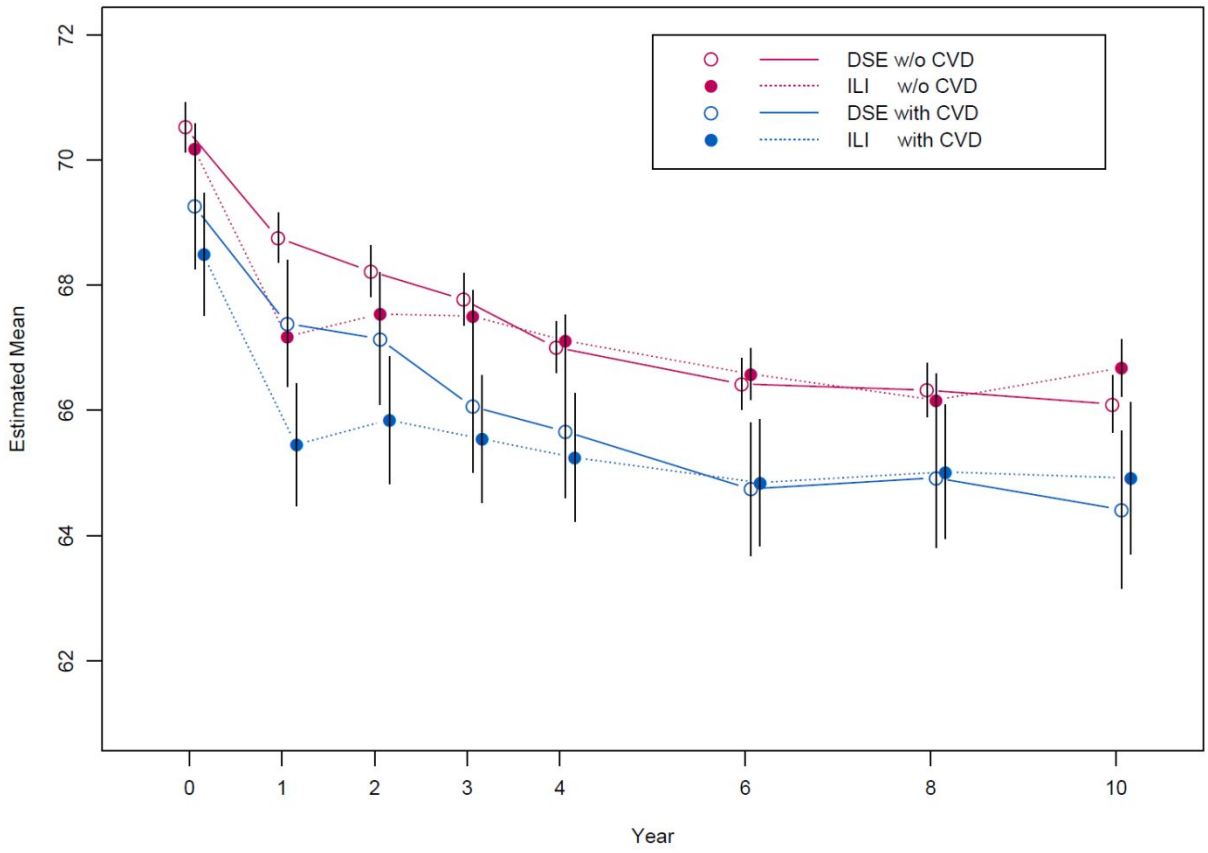

Figure S8. Mean log triglycerides

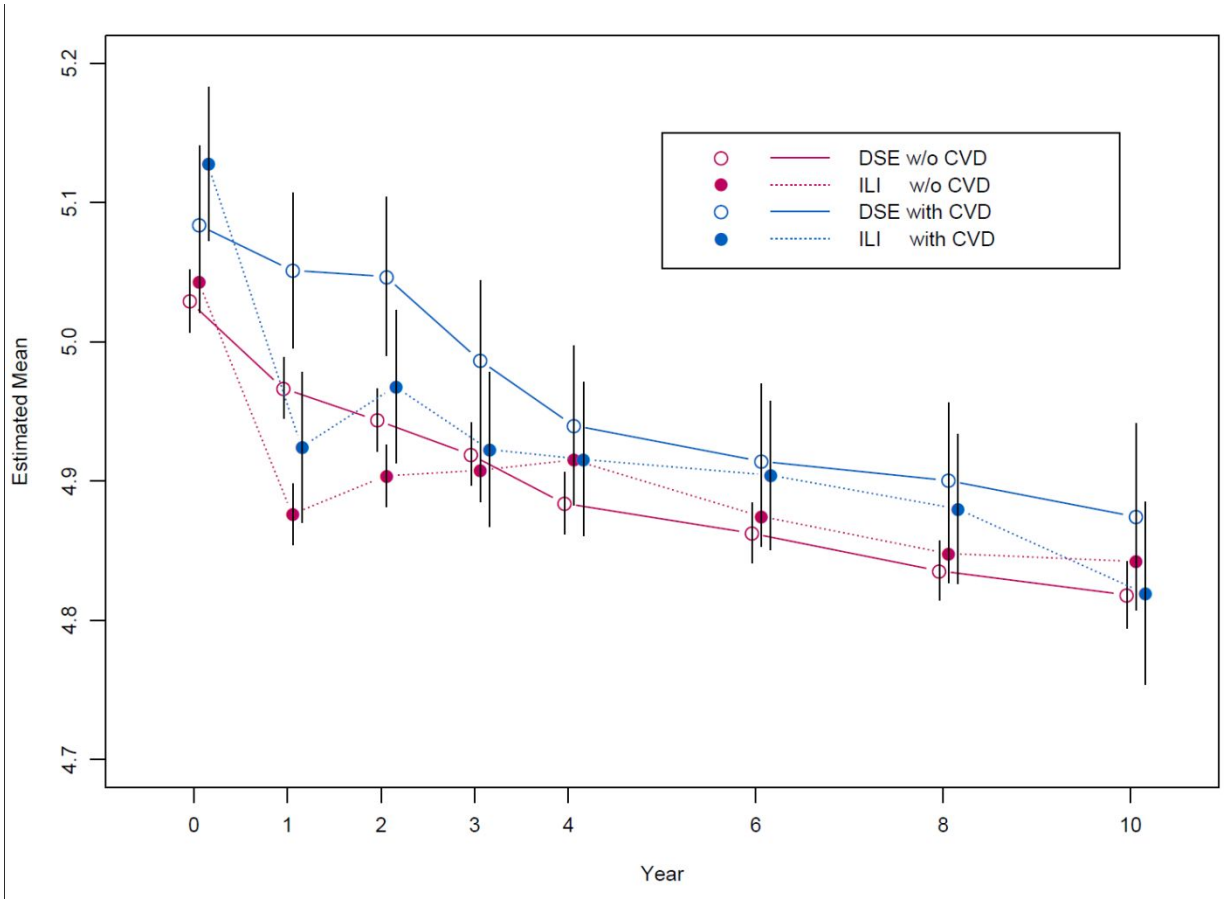

Figure S9. Cumulative hazards for hypoglycemia SAE