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David L. Mount, *Wake Forest University*
Patricia Feeney, *Wake Forest University*
Anthony N. Fabricatore, *University of Pennsylvania*
Mace Coday, *The University of Tennessee*
Judy Bahnson, *Wake Forest University*
Robert Byington, *Wake Forest University*
Suzanne Phelan, *The Miriam Hospital*
Sharon Wilmoth, *Wake Forest University*
William C. Knowler, *NIDDK, Phoenix*
Irene Hramiak, *St. Joseph's Health Care, London*

Only first 10 authors above; see publication for full author list.

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Constructing Common Cohorts From Trials with Overlapping Eligibility Criteria: Implications for Comparing Effect Sizes Between Trials

David L. Mount, Psy.D.[a], **Patricia Feeney, MS**[a], **Anthony N. Fabricatore, PhD**[b], **Mace Coday, PhD**[c], **Judy Bahnson, BA**[a], **Robert Byington, PhD**[a], **Suzanne Phelan, PhD**[d], **Sharon Wilmoth, BA**[a], **William C. Knowler, MD, DrPH**[e], **Irene Hramiak, MD**[f], **Kwame Osei, MD**[g], **Mary Ellen Sweeney, MD**[h], and **Mark A. Espeland, PhD**[a] **for the Look AHEAD and ACCORD Research Groups**

David L. Mount: dmount@wfubmc.edu; Patricia Feeney: pfeeney@wfubmc.edu; Anthony N. Fabricatore: fabricat@mail.med.upenn.edu; Mace Coday: mcoday@utmem.edu; Judy Bahnson: jbahnson@wfubmc.edu; Robert Byington: bbyingto@wfubmc.edu; Suzanne Phelan: sphelan@lifespan.org; Sharon Wilmoth: swilmoth@wfubmc.edu; William C. Knowler: knowler@nih.gov; Irene Hramiak: irene.hramiak@sjhc.london.on.ca; Kwame Osei: kwame.osei@osumc.edu; Mary Ellen Sweeney: msweene@emory.edu; Mark A. Espeland: mespelan@wfubmc.edu

[a]Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA, 27157

[b]University of Pennsylvania, Philadelphia, Pennsylvania, USA, 19104

[c]The University of Tennessee Health Science Center, Memphis, Tennessee, USA, 38163

[d]The Miriam Hospital, Providence, Rhode Island, USA, 02903

[e]Diabetes Epidemiology and Clinical Research Section, NIDDK, Phoenix, Arizona, USA, 85014

[f]St. Joseph's Health Care, London, Ontario, Canada, N6A4V2

[g]Ohio State University School of Medicine, Columbus, Ohio, USA, 43210

[h]Emory University School of Medicine/Atlanta VAMC, Atlanta, Georgia, USA, 30033

Abstract

Background—Comparing findings from separate trials is necessary to choose among treatment options, however differences among study cohorts may impede these comparisons.

Purpose—As a case study, to examine the overlap of study cohorts in two large randomized controlled clinical trials that assess interventions to reduce risk of major cardiovascular disease events in adults with type 2 diabetes in order to explore the feasibility of cross-trial comparisons

Methods—The Action for Health in Diabetes (Look AHEAD) and The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trials enrolled 5,145 and 10,251 adults with type 2 diabetes, respectively. Look AHEAD assesses the efficacy of an intensive lifestyle intervention designed to produce weight loss; ACCORD tests pharmacological therapies for control of glycemia, hyperlipidemia, and hypertension. Incidence of major cardiovascular disease events is the primary outcome for both trials. A sample was constructed to include participants from each trial who appeared to meet eligibility criteria and be appropriate candidates for the other trial's interventions. Demographic characteristics, health status, and outcomes of members and non-members of this constructed sample were compared.

Corresponding Author: Mark A. Espeland, PhD, Department of Biostatistical Sciences, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, North Carolina 27157, mespelan@wfubmc.edu.

Results—Nearly 80% of Look AHEAD participants were projected to be ineligible for ACCORD; ineligibility was primarily due to better glycemic control or no early history of cardiovascular disease. Approximately 30% of ACCORD participants were projected to be ineligible for Look AHEAD, often for reasons linked to poorer health. The characteristics of participants projected to be jointly eligible for both trials continued to reflect differences between trials according to factors likely linked to retention, adherence, and study outcomes.

Limitations—Accurate ascertainment of cross-trial eligibility was hampered by differences between protocols.

Conclusions—Despite several similarities, the Look AHEAD and ACCORD cohorts represent distinct populations. Even within the subsets of participants who appear to be eligible and appropriate candidates for trials of both modes of intervention, differences remained. Direct comparisons of results from separate trials of lifestyle and pharmacologic interventions are compromised by marked differences in enrolled cohorts.

Keywords

Randomized clinical trials; Cross-trial comparisons; Type 2 diabetes

INTRODUCTION

To integrate results from separate trials into clinical practice and health policy, it is necessary to compare and contrast their findings. Common tools are meta-analyses to pool effect sizes of similar interventions and cost-effectiveness analyses to contrast relative effect sizes of different interventions. Yet the magnitudes and distributions of effect sizes among trials differ, in part, because their cohorts vary [1,2]. The degree to which differences among trial cohorts exist and have the potential to influence cross-trial comparisons may be under appreciated.

To demonstrate this, we conducted a case study of two trials that shared many design features. Each assesses interventions to reduce cardiovascular morbidity and mortality in adults with type 2 diabetes. The Action for Health in Diabetes (Look AHEAD) study tests an intensive lifestyle intervention designed to induce modest weight loss (i.e., 7% of initial body weight) and increase physical activity. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study tests pharmacological strategies to improve glucose control, lipid profiles, and hypertension. Results of these trials are likely to be compared to determine the relative benefits and costs of behavioral and pharmacological treatments in persons with type 2 diabetes.

As we describe, despite the many similarities of these two trials, marked differences between their cohorts exist with respect to many factors that may modify the magnitudes of intervention effects. To examine the degree to which differences were based on the target populations for pharmacologic versus non-pharmacologic interventions, we constructed a sample of participants who appeared to meet criteria for both trials and assessed whether between-trial differences remained within this subset. This exercise leads us to consider, more generally, how the comparison of results from trials that feature markedly different interventions may be hampered by differences among cohorts prior to randomization and how examining the intersection between trial cohorts may inform these comparisons.

METHODS

Look AHEAD is a randomized controlled behavioral trial designed to test whether assignment to an intensive lifestyle intervention featuring weight loss through diet, exercise,

and behavior change techniques will reduce the risk of major cardiovascular events in 5,145 overweight or obese individuals with Type 2 diabetes [3,4]. The comparison condition is standardized diabetes support and education. Up to 13.5 years of follow-up is planned across 16 participating US centers.

ACCORD is a randomized, multicenter trial designed to assess the efficacy of three complementary medical treatment strategies for reducing the risk of major cardiovascular events in individuals with type 2 diabetes [5,6]. It has a double 2 X 2 factorial design in which three approaches are being tested: 1) intensive glycemia control [7], 2) treatment to increase HDL-cholesterol and lower triglycerides (in the context of good LDL-cholesterol and glycemia control) [8], and 3) intensive blood pressure control (in the context of glycemia control) [9]. All of its 10,251 participants were included in the overarching glycemia trial in which participants were randomized to an intensive A1C goal of less than 6% or a standard goal of between 7 and 7.9%. In addition, one 2 X 2 trial also addresses the lipid question comparing fibrate versus placebo in 5,518 participants with background statin therapy and the other 2 X 2 trial addresses the blood pressure question comparing an intensive systolic blood pressure goal of less than 120 mmHg versus a standard goal of less than 140 mmHg in 4,733 participants. Planned treatment and follow-up is between four to eight years across 77 US and Canadian clinical sites. The glycemia trial was stopped early in February 2008 due to an increased risk of mortality among participants assigned to intensive goal; all intensive group participants were then transitioned to the standard A1C goal with the lipid and blood pressure trials continuing through June 2009 [10].

Look AHEAD enrolled participants from July 2001 to April 2004. ACCORD enrolled participants across two waves of recruitment: 1,174 were enrolled from January to June, 2001 and 9,077 from February, 2003 to September, 2005 [11]. The trials used similar approaches to recruitment, which featured community mailings, advertisements, and other local recruitment strategies.

Inclusion criteria for both trials defined a broad population of adults with Type 2 diabetes established by ADA criteria[12] and who were at relatively high risk for cardiovascular events.

Exclusion criteria were used to identify individuals who were appropriate targets for, and judged likely to adhere to, the separate interventions. These are summarized below; additional details appear elsewhere [4,5]. The study protocols are published at https://www.lookaheadtrial.org and http://www.accordtrial.org. Both trials used glucose monitoring diaries to select likely adherers; Look AHEAD added food and exercise diaries. Look AHEAD excluded for substance abuse, medical and psychological conditions that could affect adherence; ACCORD had similar exclusions and, additionally, non-adherence to medication prescriptions.

The major differences between eligibility criteria defined individuals who were targets (i.e. warranted treatment and for whom treatment was sufficiently safe) for the separate therapies. For the lifestyle intervention in Look AHEAD, targets were individuals whose BMI was ≥25 kg/m^2 (≥27 kg/m^2 if on insulin), whose diabetes and hypertension were at least moderately controlled, and whose cardiovascular status (including performance on a graded exercise test) supported the prescription of physical activity. For the drug therapies in ACCORD, targets were individuals whose diabetes, hypertension, and/or lipid/lipoprotein levels were sufficiently uncontrolled to warrant pharmacological treatment. Thus, ACCORD included individuals with prior angina, ischemic changes on resting ECG, ECG changes on graded exercise tests, positive cardiac criteria imaging studies, and ≥50% coronary or carotid stenosis, all exclusions for Look AHEAD. ACCORD criteria excluded many

individuals with LDL-cholesterol <130 mg/dl, HDL-cholesterol >40 (males) or >50 mg/dl (females), or blood pressures <140/95 mmHg, all of whom might be eligible for Look AHEAD.

Development of the Constructed Sample

It is impossible to identify accurately whether participants in one trial would be recruited, be eligible, and agree to enroll in the other trial, in part due to differences in the information collected during screening and to unmeasured or unknown factors. Instead, we constructed a sample comprised of participants from each trial whose baseline information appeared to be consistent with eligibility criteria of the other trial, within the confines of the available information. Both studies collected data via interview-administered forms, self-report, and clinical measures. When available, biomarkers from the common central laboratory rather than locally obtained measures were used to define the constructed sample for consistency, even if eligibility was established by local measures.

Many exclusion criteria were common to both trials, such as pregnancy, participation in another trial, Class III or IV congestive heart failure, and major organ transplant. Some depended on data that were collected during screening with very similar protocols in both trials, such as body mass index, age, laboratory markers (e.g. HbA1c, serum creatinine), and blood pressure. Other criteria depended on data for which the measurement protocols between trials were not identical, but for which eligibility could be reasonably inferred. For example:

- When exclusion criteria were based on measures up to two years prior to randomization, the current presence of a condition in the other trial was considered sufficient for exclusion from the constructed sample.
- ACCORD did not ascertain by interview if a participant had a pacemaker or a left bundle branch block, so exclusion was based on ECG data.
- ACCORD queried individuals about amputations due to diabetes while Look AHEAD queried about amputations of the leg: these were treated as common exclusion criteria because amputations of the lower limbs are more common than other appendages in diabetes.

Proxies for some of the Look AHEAD exclusion criteria were not always available in ACCORD. Examples include myocarditis, pericarditis, and ability to pass a behavioral run-in that involved diet and physical activity record keeping. Likewise, proxies did not exist within Look AHEAD for some ACCORD criteria, such as hypoglycemia requiring assistance. For all but one of these cases we judged the prevalence to be sufficiently low to disregard these eligibility criteria. Most problematic for constructing the pooling criteria was the use of graded exercise testing by Look AHEAD [13]. Eligibility for Look AHEAD required completion of a valid maximal graded exercise test: ≥85% of age-predicted maximal heart rate and ≥4 metabolic equivalents (METS) if not taking medications affecting heart rate response or Rating of Perceived Exertion (RPE) score ≥18 and ≥4 METS otherwise [13]. There exist no comparable current cardiovascular health indicators in ACCORD. We attempted to develop rules for predicting graded exercise test results that could be used to predict the performance of ACCORD participants. Both discriminant analysis and nearest neighbor matching [14] were applied to data from Look AHEAD screenees, however the generated rules had inadequate accuracy. It is a limitation of our findings that we are unable to identify ACCORD participants who would not have met the Look AHEAD graded exercise test exclusion criterion.

Data Analysis

The major reasons that participants from each trial were not included in the constructed sample were tallied. If there were multiple reasons, each was counted as a separate occasion. Within each trial, participants who were included in the constructed sample were compared, using chi squared tests and t-tests, to those who were excluded with respect to factors thought to be associated with cardiovascular disease risk, adherence, and the relative effectiveness of the interventions. No adjustments for multiple comparisons were made in this descriptive analysis. Within the constructed sample, participants from the two individual trials were similarly compared.

RESULTS

Members of the Constructed Sample

As described in Table 1, only 1,082 (21.0%) of Look AHEAD participants were selected for inclusion in the constructed sample. The major reasons participants were not included were related to diabetes control: 3,272 (63.6%) were excluded because of HbA1c <7.5% and 124 (2.4%) were excluded because their diabetes was either inadequately controlled and/or because too many drugs were being used for its control. Additional reasons participants were excluded were 1) being younger than 55 years of age and having no history of cardiovascular disease (N=1,153; 22.4%) or 2) having a body mass index ≥45 kg/m^2 (N=426; 8.3%).

Comparatively, a larger portion of ACCORD participants (N=7,330; 71.5%) were included in the constructed sample ($p<0.001$). Table 2 summarizes the reasons that ACCORD participants were excluded. The most common reasons for exclusion were failure to meet weight criteria (N=1,134; 11.1%), primarily a body mass index below the Look AHEAD thresholds; elevated blood pressures (N=899; 8.8%); cardiologic safety concerns (N=518; 5.1%); and adverse laboratory findings (N=400; 3.9%).

Within-Trial Comparisons of Included vs. Excluded Participants

Many of the baseline characteristics of the Look AHEAD participants in the constructed sample differed from those who were excluded (see Table 3). Overall, those included were older, less likely to be women or to have a college education, and more likely to be from racial/ethnic minorities. Despite having a lower mean BMI and waist circumference, Look AHEAD participants in the constructed sample had poorer cardiovascular disease risk factor profiles than their excluded counterparts. Included participants were more likely to be current smokers and have longer diabetes duration, higher HbA1c or elevated fasting glucose, higher blood pressures, and higher triglycerides. They tended to have lower HDL-cholesterol and to use more medications. Included participants were more likely to be uninsured or on Medicare.

ACCORD participants included in the constructed sample also differed in many respects from those who were not included (Table 3). Included participants tended to be slightly younger, better educated, and were more likely to be Caucasian. Although included participants had a greater mean BMI and waist circumference, and lower HDL-cholesterol, they tended to have more favorable risk profiles than excluded participants. Specifically, ACCORD participants in the constructed sample had a shorter duration of diabetes, lower HbA1c, lower fasting glucose, lower blood pressure, lower total cholesterol, lower LDL-cholesterol, and lower triglycerides on average than those who were excluded. Additionally, included participants were less likely to use insulin and more likely to use thiazolidinediones, statins, and antihypertensive medications (i.e. ace-inhibitors and

diuretics). Fewer included participants were uninsured and more had health care provided by the Veteran's Administration.

Between Trial Comparisons of Participants Included in the Constructed Sample

Look AHEAD and ACCORD participants in the constructed sample differed from each other in many respects. The most pronounced difference appeared to be gender: 55.5% of the Look AHEAD participants in the constructed sample were female compared to 38.3% of the ACCORD participants. Look AHEAD participants were more likely to be Hispanic/Latino. They were more highly educated and less likely to be current smokers. They had diabetes for fewer years, but had slightly poorer diabetes control. They were heavier and had higher mean total cholesterol, LDL-cholesterol and triglycerides, but lower mean blood pressures along with less prior history of cardiovascular disease. Look AHEAD participants were less likely to be using insulin, statins, and ACE-inhibitors, and more likely to be taking thiazolidinediones. They were less likely to be on Medicaid and less likely to be uninsured or have Veteran's Administration health care coverage, but more likely to be on Medicare.

DISCUSSION

Choices in clinical interventions and public health strategies require integrating results across studies. There are many examples of direct comparisons of effect sizes and cost-effectiveness among diverse trials and interventions [e.g. 15–20]. These are necessary exercises, however the degree to which differences among trial cohorts may erode the validity of comparisons requires consideration.

As we have demonstrated, despite sharing a diagnosis of type 2 diabetes, the Look AHEAD and ACCORD study participants differ in important ways. Many differences derive from the targets for the trial interventions. For Look AHEAD, these are overweight and obese individuals for whom weight loss and physical activity are safe; for ACCORD, these are appropriate candidates for intensive pharmacologic treatment. We attempted to identify a subsample of participants in each trial who would likely be eligible for participation in the other and thus appropriate targets for both types of interventions. These participants, who comprised the constructed sample, were systematically different from the other participants in their respective trials with respect to many characteristics often linked to retention, adherence, and outcomes, many of which have been shown to be linked to the early success of Look AHEAD interventions [21,22].

Fewer than 30% of Look AHEAD participants may have been eligible to participate in the ACCORD trial. These individuals were less obese, but had generally poorer health, than their counterparts who would not have qualified for ACCORD. By contrast, ACCORD participants who appeared eligible for Look AHEAD (approximately 70% of the ACCORD sample) were heavier at baseline, but in broadly better health, than those who would have been excluded from Look AHEAD. We note, however, that we were unable to determine whether ACCORD participants would have the valid maximal graded exercise test required by Look AHEAD. Because of the higher prevalence of cardiovascular disease in the ACCORD sample, we suspect that our findings give an overestimation of the percentage of ACCORD participants who would have been eligible for Look AHEAD.

The limited overlap of the trial cohorts impedes many cross-trial comparisons. Critically, differences between Look AHEAD and ACCORD participants in disease severity, complications, and health insurance status would be expected to translate to differences in the distribution of health-related benefits and costs.

The reasons Look AHEAD and ACCORD participants included in the constructed sample, who all appeared to be appropriate targets for nonpharmacologic and pharmacologic therapy, remain markedly different are unclear. As we use this sample to compare more fairly the intervention effects of lifestyle versus pharmacologic strategies on cardiovascular events, we must acknowledge these differences. We expect that the intervention effect sizes for participants in this intersection will differ meaningfully from those for the whole cohorts and that covariate-adjustment will not be sufficient to account for these differences. Whether this is so can be assessed with formal tests of interactions and whether differential adherence or other mechanisms are important can be explored, however these findings await the trials' completions. Within the constructed sample itself, analytical approaches (e.g. covariate-adjustment, matching, or propensity scores adjustment [23]) will be required to reduce biases of cross-trial comparisons based on this constructed sample, but may produce the most relevant comparisons of the interventions.

Many authors have described differences between individuals who do and do not volunteer for clinical trial participation and how this may influence results [2,24–27]. Less understood is how the nature of the intervention being tested in a clinical trial may influence the pool of volunteers. We speculate, for example, that the greater proportion of women enrolled in the Look AHEAD trial may derive, in part, from a greater willingness for women to volunteer for a trial focused on weight loss. Look AHEAD required participants to have a degree of good health sufficient to participate in physical activity interventions and ACCORD required a cardiovascular risk profile that was sufficiently unhealthy to warrant intensive drug interventions: these influences may not be fully captured by the trials' eligibility criteria. Certainly the sites selected to participate in a clinical trial and their approaches to enrollment influence study cohorts. For example, the ACCORD trial included more sites affiliated with Veterans' Administration hospitals, which may also have reduced the number of women in the trial cohort.

Limitations

In many cases, we were not able to ascertain with complete accuracy whether participants were ineligible for the parallel trial due to differences in the set of screening measures that were employed. Therefore, some individuals were erroneously included in our constructed sample, inflating inclusion rates. Another limitation was due to differences in participating clinical sites, such as location and enrollment practices. If different sites had participated in the trials, the estimated inclusion rates may have been altered. Differences in the effect sizes of controlled trials may also be influenced by the comparison conditions, which we do not address.

Conclusions

Direct comparisons of findings between clinical trials may be limited by known or unknown dissimilarities between their enrolled cohorts. While we have analyzed only two trials, our results may have more general implications about the impact that research questions, eligibility criteria, and enrollment may have on cross-trial comparisons. In most settings, there is meaningful heterogeneity in responses to trial interventions. Often, this may be linked to eligibility criteria and enrollment practices: indeed, these are often chosen to affect adherence and outcomes. We expect that when markedly different interventions are involved, e.g. pharmacologic versus non-pharmacologic approaches, the intersection of trial cohorts will be most constrained and cost effectiveness comparisons may be most compromised. A better understanding of how factors that shape trial cohorts influence their results is needed. Developing methods for sampling the intersection between trial cohorts could result in more direct cost/benefit outcome comparisons among diverse treatment approaches, such as pharmacologic therapy versus lifestyle change. A single estimate of an

effect size may be insufficient to inform treatment choices. If relative effect sizes are published for subgroups, at least some of these subgroups should be defined as appropriate targets for alternative therapies.

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Look AHEAD Research Group at Baseline

Clinical Sites

The Johns Hopkins Medical Institutions Frederick Brancati, MD, MHS; Debi Celnik, MS, RD, LD; Jeff Honas, MS; Jeanne Clark, MD, MPH; Jeanne Charleston, RN; Lawrence Cheskin, MD; Kerry Stewart, EdD; Richard Rubin, PhD; Kathy Horak, RD

Pennington Biomedical Research Center George A. Bray, MD; Kristi Rau; Allison Strate, RN; Frank L. Greenway, MD; Donna H. Ryan, MD; Donald Williamson, PhD; Elizabeth Tucker; Brandi Armand, LPN; Mandy Shipp, RD; Kim Landry; Jennifer Perault

The University of Alabama at Birmingham Cora E. Lewis, MD, MSPH; Sheikilya Thomas MPH; Vicki DiLillo, PhD; Monika Safford, MD; Stephen Glasser, MD; Clara Smith, MPH; Cathy Roche, RN; Charlotte Bragg, MS, RD, LD; Nita Webb, MA; Staci Gilbert, MPH; Amy Dobelstein; L. Christie Oden; Trena Johnsey

Harvard Center

Massachusetts General Hospital: David M. Nathan, MD; Heather Turgeon, RN; Kristina P. Schumann, BA; Enrico Cagliero, MD; Kathryn Hayward, MD; Linda Delahanty, MS, RD; Barbara Steiner, EdM; Valerie Goldman, MS, RD; Ellen Anderson, MS, RD; Laurie Bissett, MS, RD; Alan McNamara, BS; Richard Ginsburg, PhD; Virginia Harlan, MSW; Theresa Michel, MS

Joslin Diabetes Center: Edward S. Horton, MD; Sharon D. Jackson, MS, RD, CDE; Osama Hamdy, MD, PhD; A. Enrique Caballero, MD; Sarah Ledbury, MEd, RD; Maureen Malloy, BS; Ann Goebel-Fabbri, PhD; Kerry Ovalle, MS, RCEP, CDE; Sarah Bain, BS; Elizabeth Bovaird, BSN,RN; Lori Lambert, MS, RD

Beth Israel Deaconess Medical Center: George Blackburn, MD, PhD; Christos Mantzoros, MD, DSc; Ann McNamara, RN; Heather McCormick, RD

University of Colorado Health Sciences Center James O. Hill, PhD; Marsha Miller, MS, RD; Brent VanDorsten, PhD; Judith Regensteiner, PhD; Robert Schwartz, MD; Richard Hamman, MD, DrPH; Michael McDermott, MD; JoAnn Phillipp, MS; Patrick Reddin, BA; Kristin Wallace, MPH; Paulette Cohrs, RN, BSN; April Hamilton, BS; Salma Benchekroun, BS; Susan Green; Loretta Rome, TRS; Lindsey Munkwitz, BS

Baylor College of Medicine John P. Foreyt, PhD; Rebecca S. Reeves, DrPH, RD; Henry Pownall, PhD; Peter Jones, MD; Ashok Balasubramanyam, MD; Molly Gee, MEd, RD

University of California at Los Angeles School of Medicine Mohammed F. Saad, MD; Ken C. Chiu, MD; Siran Ghazarian, MD; Kati Szamos, RD; Magpuri Perpetua, RD; Michelle Chan, BS; Medhat Botrous

The University of Tennessee Health Science Center

University of Tennessee East. Karen C. Johnson, MD, MPH; Leeann Carmichael, RN; Lynne Lichtermann, RN, BSN

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*No longer affiliated with study unit.

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Peremislov, K. Gunyou, R. Passi. *University of Minnesota, Minneapolis, MN:* E.R. Seaquist, M.V. Mech, L.E. Benedict*, D.J. Demmon*, A.F. Kumar, S.M. Martinson*, S.A. Miller, C. Pease*, J.P. Rao*, J.B. Redmon, J.E. Swanson†, J.K. Wimmer*. *University of Minnesota, Phalen Village Clinic, St. Paul, MN:* K. Peterson, L.A. Seaquist, C. Boese*, M. Cruciani, E. Dodds, F. Parenteau Ek*, J.L. Feldman, P. Fontaine, C.J. Lange, T.J. Mendenhall*, A.M. Peterson, A. Rudelt, T.M. Schrock*, D.P. Spielman*, S. Velasco*, J.C. Weinhandl. *Riverside Health Partners Clinic, Department of Endocrinology, Minneapolis, MN:* J.M. Sperl-Hillen, P.J. O'Connor, M.E. Busch, A. Chung, B.K. Klein, N. Krugen, T. Bunkers-Lawson*, H.L. Ekstrom*, H.S. Gunderson*, B.M. Johnson*, J.H. MacIndoe*, D.J. Prewedo*, J.L. Rawl*, C.M. Roethke*, Mary Spencer. *University of Iowa, Health Care Diabetes Clinical Research and Programs, Iowa City, IA:* W.I. Sivitz, S.M. Wayson, T.A. Lower*, L. Larson, L.A. Ahrens*, M. Bayless, S.E. Beck*, J. Chahal, C. Chenard, G.C. Doelle, V.M. Guzman, U.M. Kabadi*, K.A. Ochs*, A. Rahhal, R.G. Spanheimer*, L. Snetselaar*, K. Smith*, D. Wells. ***Ohio-Michigan CCN:*** *Case Western Reserve University, Division of Clinical and Molecular Endocrinology, Cleveland, OH:* S. Genuth, F. Ismail-Beigi, M. Thibonnier*, L. Vargo*, C. Kelly*, T. Bongorno*, A. Dolish*, L. Pavlik, M. Tiktin, S. Isteitieh. ***Ohio-Michigan clinical sites:*** *University Hospitals of Cleveland, Division of Endocrinology, and University Hospitals Westlake Medical, Cleveland, OH:* F. Ismail-Beigi, A. Krikorian, L. Moore, L. Richardson, E. Coles-Herman, K. Yee, J. Frankino, M. Jing, A. Sood, L. Hustak*, M. Julius*, L. Pavlik*, T. Ross*, L. Long*, W. Schwing*, M. Tiktin*, M.K. Sullivan*, L. Strauss*, K. Behm*, F. Eskandari*, C. Hall*, D. Hayes*, K. Horowitz, S. Isteitieh*, Z. Madhun*, E. Seeholzer*, J. Shina*, H. Taylor*, A. Schnall*, S. Huang, M. Heeg, J. Tang, J. Belkin*, M.S. Lee*, T. Joly*. *St. Vincent Charity Hospital, Lipid Research Center, Cleveland, OH:* L.S. Sadler, M. Griffith*, A. Hornsby*, K. Klyn, E. Ospelt, L. Long, M. DeSmit*, P. McCann, N.P. Schmidt*, C. Gottfried, T. Kulow, J. Zaletal, M.S. Kapadia. *University Suburban Health Center, South Euclid, OH:* A.M. Schnall, L. Dragmen, R. Ellert*, J. Smith, J. Leksan, T. Sussman, S. Huang, M. Heeg, J. Tang, J. Belkin*, M.S. Lee*, T. Joly*. *Cleveland Veterans Affairs (VA) Medical Center (VAMC), Department of Medicine, and Ravenna Community Based Outpatient Clinic, Cleveland, OH:* F. Ismail-Beigi, L. Hustak, M. Julius*, W. Schwing, M. Tiktin*, J. Anselmo*, F. Eskandari*, S. Daymeyer*, C. Hall, D. Hayes*, K. Horowitz, S. Isteitieh*, C. Johnson*, E. Kern, M.A. Richmond*, L. Richardson, K. Roberts*, J. Shina*, A. Sood, P. Suhan*, H. Taylor, S. Watts*, J. Martin, L. Moor*, B. Burtch*, S. Ober, G.J. Strauss, A. Leone, J. Belkin*, S. Huang*, K. Frank*, D. Stephens*, M.S. Lee*, T. Joly*. *The Cleveland Clinic Foundation, Cleveland, OH:* B.J. Hoogwerf, J. Brakeman, M. Matzinger *, J. Newsome*, J. Becker*, S. Bizjack*, B. Clingman*, S. Curtas, G. Depietro*, R. Ellert*, C. Horner, G. Bunae *, A. Hamrahian*, A. Hawkins, T. Head, S. Iannica, L. Jones, P. Kaiser, R. McCoy, A. Mehta, L. Olansky, A. Orasko, S. Reddy *, D. Ross*, L. Shockley*, E. Siraj*, M. Williams*, R. Zimmerman. *Your Diabetes Endocrine Nutrition Group, Mentor, OH:* D. Weiss, K.A. Fagan, T.M. Hanslik, J. Farrell, P. Brys, M. Oligny, K. Prokop, K. Lenardic, T. Karapanzcik, S. Huang, M. Heeg, J. Tang, J. Belkin*, M.S. Lee*, T. Joly*. *Medical University of Ohio, Department of Medicine, Ruppert Health Center, Toledo, OH:* B. Akpunonu, R. Franco-Saenz†, J. Gilmore, M. Gilmore, L. Godfrey, P. Ross, B. Bauer, M. Chrisstie*, A. Lopez, P. Mulrow, C. Peters*, R. Pop-Busui*, J. Roman*, C. Smith*, J. Bick*, Z. Blust*, P.T. Nelsen, D. Marcus*. *The Ohio State University Medical Center, Division of Endocrinology, Diabetes and Metabolism, Columbus, OH:* K. Osei, E.A. Dziengelewski*, H. Breedlove, D. Boland*, C. Casey Boyer, S. Cataland, P. A. Green, J.E. Irwin, D.P. Schuster, J.L. Varga-Spangler, T. Bowles, K. Weiland, K. Arnold; T. Evans*, J. Bouttamy, A. Letson, E. Craig, F. Davidorf. *University of Cincinnati/VA Medical Center, Research Service, Cincinnati, OH:* R.M. Cohen, K. Burton, J. Craig, B. Carter*, J. Harrer*, R. Hurd*, D. Lopez-Stickney*, C. Pritchard*, A. Pfefferman*, B.A. Ramlo-Halsted*, C. McCormick, C. Riley, M. Strominger*, A. Knittel, G. Groff, C. Bailey, A. Howald, N. Anderson, J. Laver Bierschbach, M. Tyzinski*, B. Smith*, S. Krug, V. Hershberger*, R.K.

Hutchins*, L.A. Raymond*. *Henry Ford Health System–New Center One, Detroit, MI:* D.M. Kahkonen*, T. Cushman, M. Roman, A.M. Stys, K. White, M. Austin*, C. Chatterton, J.K. Francis*, C. Jones*, D. Kruger, A. McLellan*, F. Whitehouse, E. Higgins*, S. Levy, A. Schoenherr*, P. Edwards. *Grunberger Diabetes Institute, Bloomfield Hills, MI:* G. Grunberger, L.C. Aman*, A.H. Bandagi*, K.M. Russell, C. Tucker, Y. Abidova, A. Amirikia. ***Northeastern CCN:*** *Columbia University College of Physicians and Surgeons, New York, NY:* J.T. Bigger, C.R. Lopez-Jimenez, R. Bornholdt, L. Busaca, H.N. Ginsberg, P. Gonzales, D. Gosh*, P. Love†, A. Kosok*, E. Robinson*, R. Steinman, C. Watson, G. Reyes. ***Northeastern clinical sites:*** *Jacobi Medical Center, Bronx, NY:* U.K. Schubart, M. Mendoza, G. Goswami, A. Laufer*, J. Russo, N. Vincenty. *Albert Einstein General Clinical Research Center, Bronx, NY:* M.H. Alderman, L. Carroll, M.J. Sanguily, J.U. Gorkin, A.C. Mayer, L. Ramos, V. Sessoms, A. Fritts Stewart*. *Cornell Internal Medicine Associates, New York, NY:* D. Brillon, J. Cordero, M.A. Richardson, E. Wei, F. Ganz, B.R. Meyer, J. Paley*, S. Anderson*, C. Charles*, A. Dwoskin*, R. Chiong, K. Hyams. *The Diabetes Care and Information Center of New York, Flushing, NY:* D.L. Lorber, T. Arenstein, P. Depree, A.A. Elmorsy*, J.M. Wendel, L.L. Zintl, P. August, M. Beck*, M.D. Goldberg, M.J. Hofacker*, M. Marotta-Kollarus*, E.J.L. Ocampo, C.A. Resta, J.M. Tibaldi. *The Cooper Health System, Cherry Hill, NJ:* A. Bastien*, S. Grudzinski, P. Niblack, L. Abreu, T. Brobyn, K. Brown*, M. Casale*, D. Dougherty*, G. Haddad, K. Heintz, M. Kelly,* D. Linneman*, C. Olivia, M.A. Salvador*, P. Zee*, D. Hyman. *The Cooper Health System, Cherry Hill, NJ:* A. Bastien*, S. Grudzinski, P. Niblack, L. Abreu, T. Brobyn, K. Brown*, M. Casale*, D. Dougherty*, G. Haddad, K. Heintz, M. Kelly,* D. Linneman*, C. Olivia, M.A. Salvador*, P. Zee*, D. Hyman. *Great Lakes Medical Clinic Research, Westfield, NY:* D.F. Brautigam, R. Fischer, J.M. Chiarot, D.M. Scharf, B. Nunn*, J. Carlson, C. Flanders*, M.R. Hagen, S. Newman, T.A. Gordon. *Naomi Berrie Diabetes Center, New York, NY:* R. Goland, C.H. Tuck†, P. Kringas, J. Hey-Hadavi*, J. Montes*, J. Vargas-Jerez, J. Salas-Spiegel. *Ambulatory Care Network at Columbia University, New York, NY*: A. Getaneh, J. Ramirez*, E.F. Vasquez*, G. Kranwinkel. *Irving Diabetes Research Unit, New York, NY:* D.S. Donovan, G. Febres*, C. Hernandez*, M.A. Jonaitis, L. Mesa. *State University of New York Downstate Medical Center, Brooklyn, NY:* M.A. Banerji, M. Norton, P. Patel, V. Daly, S. Hirsch, C. Jazmin, R. Khillan, D. Mendonca, A. Relingado, E. Sandoval, M. Tiewala. *Kings County, Brooklyn, NY:* M.A. Banerji, M. Norton, P. Patel, V. Daly, S. Hirsch, C. Jazmin, R. Khillan, D. Mendonca, A. Relingado, E. Sandoval, M. Tiewala. *The Cooper Health System, Cherry Hill, NJ:* A. Bastien*, S. Grudzinski, P. Niblack, L. Abreu, T. Brobyn, K. Brown*, M. Casale*, D. Dougherty*, G. Haddad, K. Heintz, M. Kelly,* D. Linneman*, C. Olivia, M.A. Salvador*, P. Zee*, D. Hyman. ***Southeastern CCN:*** *Wake Forest University School of Medicine, Department of Public Health Sciences, Winston-Salem, NC:* D.C. Goff, Jr, J.H. Summerson, L. Crago, C.S. Blackwell*, A. Bertoni, R.L. Blaine, J.K. Kirk, R.L. Spach, J. Williamson, J. Calles, J. Katula, D.B. Wishnietsky*. ***Southeastern clinical sites:*** *Duke University Medical Center, Durham, NC:* M.N. Feinglos, J. Jones, M.B. Mason, M.A. Furst, W.J. Bean*, G. Gedon-Lipscomb, J.B. Green, T. Parham*, B.M. Satterwhite*, C.R. Thacker. *Constant Care, Inc., Valdosta, GA:* D. Padhiar, R. Noel*, N. Padhiar, S. West*, J. Braden, A. Francis*. *Wake Forest University School of Medicine, Department of Geriatrics/Gerontology, Winston-Salem, NC:* H.H. Atkinson, M. Dibari*, J. Allen, J. Stanfield, T. Delvalle-Fagan, L.J. Gordineer, L. Gordon, M. Gordon*, S.L. Smith*, H. Yates*. *Downtown Health Plaza, Winston-Salem, NC:* C.F. Pedley, G. Zurek, M. Baird, B. Dunn*, W. Kinder*, S. Mauney. *University of North Carolina, Diabetes Care Center, Chapel Hill, NC:* J.B. Buse, M.D. Duclos, R.E. Kirby*, J.F. Largay, N.M. McDermott*, A. Goley, S.S. Braithwaite, J.M. Dostou, E.A. Fasy*, D.C. Kelly*, C.E. Metz*, J. Jeffries, D. Rubin*. *Holston Medical Group, Kingsport, TN:* J.L. Miller, S.M. Norton, J. Weatherly*, S. Bishop*, B. Cross, K. Nuss, M. Surgenor, Y. Wood. *Carolinas Medical Center Family Practice, Charlotte, NC:* T. Barringer, C. Hoffman*, C. Morris, P. Tochiki*, G. Reinblatt, P. Bruner*. *Robeson Health Care Corporation, Fairmont Clinic,*

Fairmont, NC: R. Peace, D.O. Stuart*, J. Strickland, L. Cummings, D. Craig*, J. Stanfield*. *Robeson Health Care Corporation, Julian T. Pierce Clinic, Pembroke, NC:* R. Peace, D.O. Stuart*, J. Strickland, L. Cummings, D. Craig*, J. Stanfield*. *Wake Forest University School of Medicine, Departments of Internal Medicine and Endocrinology, Winston-Salem, NC:* J.R. Crouse, L. Menon, S. Marion*, D. Davis*, B. Cabrera*, J. Calles, T. Chandler, J. Ellis, E. Kouba, P. Riddle, E. Myers*. *Tulane University Health Science Center, New Orleans, LA:* V. Fonseca, R.H. McDuffie, N.O. Asafu-Adjaye, S.M. Leger, P. Reilly, G. Afner, F. Arrey*, S. Asnani, E. Borshard*, D. Boyd*, A.Cemo, S. Chennur*, P. Dupart, R. Garg*, G.P. Girindra*, B. Gouda*, W. Itoua-N'Ganongo*, I. Innocent-Ituah*, C. Johnson*, N. Kuhadiya, M. Kukreja*, I. Mangan-Mbondi*, S. Mason*, C. McLain, J. Naylyanya*, K. Nazereth*, S. Nazereth*, S. Singh, T. Thethi, K. Varnado*, R. Williams*. *Kaiser Permanente, Clinic Atlanta Crescent Medical Center, Tucker, GA:* J.I. Barzilay, M. Eley*, K. Bader, D. Curry-Ball, S. Goodman*, M. Stevens. ***VA CCN:*** *Memphis VAMC, Memphis, TN:* W.C. Cushman, T.S. Geraci, S.M. Walsh, L.G. Coley, M.B. Elam, D.I. Pickering*. ***VA clinical sites:*** *Memphis VAMC, Hypertension/Lipid Research Clinic, Memphis, TN:* M.B. Elam, C.W. Thompson, L. Lichtermann, S. Peeples, J. Turner-Bates*, M. Heimberg, D. Childress, J. Turner, J. Jasper, J. Coley. *Baltimore VAMC, Baltimore, MD:* B.P. Hamilton, J. Hamilton, G. Kuzbida, W. Hatten, Jr, A. Lancaster, J. Haywood. *Carl T. Hayden VAMC, Phoenix, AZ:* J. Felicetta, M. Bourne- Collo, M.E. Svoboda, D. Clothier, M. Deitz†, C. Flaugher*, P. Hayward*, T. Scheibe*, S. Velarde, S. Heritage, J.P. Nelson. *Atlanta VAMC Medical Service, Decatur, GA:* M.E. Sweeney, D. Harrelson, S. McConnell, F. Watson, R. Johnson, L. Whittington, M. Nanes, M. Salles. *Ralph H. Johnson VAMC, Primary Care, Charleston, SC:* J. Basile, D.B. Ham, B. North-Lee, H.A. Baig, S.U. Rehman, J. Mixson. *G. V. (Sonny) Montgomery VAMC, Research Department, Jackson, MS:* K.A. Kirchner, L.A. Hinton, L. Mack, C. Adair*, B. James*, A. Spencer, A. Jones. *VA NY Harbor Healthcare System, New York, NY:* L. Katz, E.A. Richardson, A.G. Goldberg*, A. Nieves, J.E. Russo*, S.A. Sochalski, D. Hoffman. *Washington VAMC, Washington, DC:* V. Papademetriou, B. Gregory, R. Alignay*, E. Nylen, B. Rajendran, R. Hodges. *St. Louis VAMC, St. Louis, MO:* S. Giddings, E. Clark, A. Pittler, R. Davis, P. Harris. *Central Arkansas Clinic Healthcare System, Little Rock, AR:* D.L. Simmons, J.J. Cooper*, K. Dishongh, R. Bates*, K. Bhaghayath*, P. Choksi*, S. Conley*, S. Elbein, F. Faas, Z. Hamid, J. Johnson, P. Johnson, A. Mayo*, M.S. Moriarty, G. Nair*, D. Rani*, N. Rasouli, S. Said*, N. Rassouli*, M. Rodriguez*, K. Thomas*, K. Watson, D. Williams, A. Makdissi. ***Coordinating Center:*** *Wake Forest University School of Medicine, Winston-Salem, NC:* R.P. Byington, W.T. Ambrosius, R.T. Anderson*, J. Barnes, J. Beal, C. Bell, D.E. Bonds, S. Burton,* C. Collins, D. Cook, B. Craven, T. Craven, D. Dunbar, G. W. Evans, P. Feeney, C. D. Furberg, C. M. Greven, J. Griffin, L. Harvin, J. Hepler, L. Howard*, L.T. Howard-Perdue, M. Hough, W. Hwang, A. Kimel, D. Lefkowitz, A. Lopina*, J. Lovato, L.C. Lovato, M.E. Miller, D. Reboussin*, S. Rushing, L. Sanders, L. Sims, C. Stowe, M. Walkup*, S. Wilmoth, K. Wilson, N. Woolard. ***Drug Distribution Center:*** *Albuquerque VAMC, Albuquerque, NM:* D. Raisch, R. Ringer, M. Sather, B. DelCurto, D. Garnand. ***ECG Reading Center:*** *Wake Forest University School of Medicine, Winston-Salem, NC:* R. Prineas, C. Campbell, Z. Zhang, L. Selph, S. Hall*, S. Hensley, Y. Li, M. Mills. ***Central Chemistry Laboratory:*** *Northwest Lipid Research Laboratories, Seattle, WA:* S. Marcovina, J. Chmielewski, K. Gadbois, V. Gaur, G. Strylewicz, M. Ramirez, S. Waddell, M. Mehan*. ***ACCORD-MIND MRI Reading Center:*** *University of Pennsylvania, Philadelphia, PA:* R.N. Bryan, C. Davatzkios, G. Moonis, L. Desiderio, S. D'Arcy*. ***Fundus Photograph Reading Center:*** *University of Wisconsin Medical School, Madison, WI:* M. Davis, R. Danis, S. Johnson*, N. Robinson, L. Hubbard, B. Esser, D. Thayer, M. Neider, K. Glader, M. Burger. ***Project Office:*** *National Heart, Lung, and Blood Institute (NHLBI), Bethesda, MD:* D.G. Simons-Morton, L. Cooper*, M. Domanski, C. Nwachuku*, Y. Rosenberg, M. Salive*, P. Savage, J.L. Fleg, J.A. Cutler, N. Geller, D. Follmann*, M. Proschan*, C. Jennings, E. Schaeffer*, P. Mills,* J. Bittner*, R. Kirby, P. Frommer†, L. Fine, J. Chan. *National Institute of Diabetes and*

Digestive and Kidney Diseases (NIDDK), Bethesda, MD: J. Fradkin, S. Malozowski, C. Meyers, T. Hostetter*. *National Institute on Aging (NIA), Bethesda, MD:* L. Launer. *National Eye Institute (NEI), Bethesda, MD:* E.Y. Chew. *Centers for Disease Control and Prevention (CDC), Atlanta, GA:* A. Albright, K.M.V. Narayan, M. Engelgau*, P. Zhang.

Table 1

Factors eliminating Look AHEAD participants from the constructed sample: note that some individuals were excluded for multiple reasons.

ACCORD Exclusion Criteria	Number excluded
Glycemic control	
HbA1c <7.5%	3272 (63.6%)
HbA1c >11 %	39 (0.8%)
Insulin and 3 oral medications	90 (1.7%)
HbA1c >9.0%, No insulin & 3 oral medications	33 (1.5%)
More than 3 oral medications	17 (0.3%)
Total	3396 (66.7%)
Age <55 years and no history of cardiovascular disease	1153 (22.4%)
Body mass index ≥45 kg/m^2	426 (8.3%)
Insufficient risk factor profile	83 (1.6%)
Serum creatinine >1.5 mg/dl	27 (0.5%)
Total number excluded	4063 (79.0%)
Total number included in constructed sample	1082 (21.0%)

Table 2

Factors eliminating ACCORD participants from the constructed sample: note that some individuals were excluded for multiple reasons.

Look AHEAD Exclusion Criteria	Number excluded
Weight	
BMI <25.0 kg/m^2	870 (8.4%)
On insulin and BMI between 25.0 and 27.0 kg/m^2	255 (2.5%)
Weight >350 lbs	9 (0.1%)
Total	1134 (11.1%)
Blood pressure	
Systolic >160 mmHg	899 (8.8%)
Diastolic >100 mmHg	162 (1.6%)
Total	1061 (10.4%)
Cardiologic factors	
Use of pacemaker	64 (0.6%)
Heart rate <45 b/m	76 (0.7%)
Heart rate >100 b/m	136 (1.3%)
ECG Left bundle branch block	68 (0.7%)
ECG uncontrolled atrial fibrillation	106 (1.0%)
ECG ventricular tachycardia	68 (0.7%)
Total	518 (5.1%)
Central laboratory results	
Serum creatinine >1.4 and female	46 (0.4%)
HbA1c >11.0%	183 (1.8%)
Triglycerides >600 mg/dl	171 (1.7%)
Total	400 (3.9%)
Amputation due to diabetes	185 (1.8%)
Alcohol intake >14 drinks per week	98 (1.0%)
Oral steroids	21 (0.2%)
Total number excluded	2921 (28.5%)
Total number included in constructed sample	7330 (71.5%)

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Table 3

Baseline characteristics of Look AHEAD and ACCORD participants grouped by inclusion or exclusion in the constructed sample: mean (SD) or percent.

Baseline Characteristic	Look AHEAD Participants			ACCORD Participants			Constructed Sample: Look AHEAD vs ACCORD (p-value)
	Not Included in Constructed Sample N=4063 (79.0%)	Included in Constructed Sample N=1082 (21.0%)	Included vs Not Included (p-value)	Not Included in Constructed Sample N= 2921 (28.5%)	Included in Constructed Sample N=7330 (71.5%)	Included vs Not Included (p-value)	
Age, years	58.1 (7.1)	61.0 (5.2)	<0.001	62.6 (7.1)	62.1 (6.7)	0.006	<0.001
Female sex	60.6%	55.5%	0.003	39.1%	38.3%	0.50	<0.001
Race/Ethnicity							
African-American	15.7%	18.8%	0.009	19.2%	19.3%	0.92	0.71
Hispanic/Latino	12.8%	15.0%	0.059	7.2%	7.2%	0.98	<0.001
Caucasian	69.7%	64.9%	0.002	59.4%	66.9%	<0.001	0.19
Education							
Less than HS	6.3%	9.6%		16.6%	14.1%		
HS/GED	13.1%	16.5%	<0.001	26.3%	26.4%	<0.001	<0.001
Some college	39.7%	36.6%		30.2%	33.8%		
College grad	40.8%	37.3%		26.9%	25.6%		
Smoking status							
Current	4.1%	5.7%	0.01	16.3%	13.0%		
Former	44.8%	47.5%		39.7%	46.0%	<0.001	<0.001
Never	51.1%	46.9%		44.0%	40.9%		
Prior CVD*	11.4%	23.5%	<0.001	36.2%	34.2%	0.20	<0.001
Diabetes duration, yrs	6.2 (6.3)	9.1 (7.0)	<0.001	11.7 (7.8)	10.5 (7.6)	<0.001	<0.001
HbA1c, %	7.0 (1.1)	8.4 (0.8)	<0.001	8.5 (1.3)	8.2 (1.0)	<0.001	<0.001
Fasting blood glucose, mg/dl	145.5 (41.9)	182.2 (47.5)	<0.001	181.5 (65.4)	172.8 (51.9)	<0.001	<0.001
BMI, kg/m^2	36.2 (6.2)	35.0 (4.4)	<0.001	29.7 (6.2)	33.2 (4.8)	<0.001	<0.001

Baseline Characteristic	Look AHEAD Participants			ACCORD Participants			Constructed Sample: Look AHEAD vs ACCORD (p-value)
	Not Included in Constructed Sample N=4063 (79.0%)	Included in Constructed Sample N=1082 (21.0%)	Included vs Not Included (p-value)	Not Included in Constructed Sample N= 2921 (28.5%)	Included in Constructed Sample N=7330 (71.5%)	Included vs Not Included (p-value)	
Waist circumference, cm	114.1 (14.4)	113.4 (12.2)	0.12	101.3 (15.4)	109.0 (12.8)	<0.001	<0.001
Blood pressure, mmHg							
Systolic	128.1 (17.0)	131.6 (17.4)	<0.001	144.9 (21.4)	133.0 (13.7)	<0.001	<0.001
Diastolic	70.0 (9.5)	70.6 (9.7)	<0.001	77.3 (12.5)	73.9 (9.7)	<0.001	<0.001
Lipids/lipoproteins, mg/dl							
Total cholesterol	190.4 (37.1)	193.3 (39.0)	0.02	188.5 (47.5)	181.2 (39.2)	<0.001	<0.001
LDL-cholesterol	112.2 (32.0)	112.9 (33.2)	0.54	106.4 (35.6)	104.3 (33.2)	0.005	<0.001
HDL-cholesterol	43.8 (11.9)	42.4 (11.5)	<0.001	42.9 (13.0)	41.5 (11.0)	<0.001	0.01
Triglycerides	177.6 (113.2)	197.1 (129.8)	<0.001	212.1 (227.7)	184.1 (99.5)	<0.001	<0.001
Medication use							
Insulin	16.5%	28.6%	<0.001	37.8%	33.8%	<0.001	<0.001
Thiazolidinediones	26.3%	23.8%	0.11	16.4%	20.5%	<0.001	0.01
Statins	42.5%	48.3%	<0.001	58.0%	63.7%	<0.001	<0.001
Any antihypertensive	73.2%	79.9%	<0.001	83.8%	86.1%	0.003	0.43
Ace-inhibitors	41.4%	46.7%	0.002	51.0%	53.8%	0.01	<0.001
Beta-blockers	19.6%	27.3%	<0.001	29.5%	29.2%	0.76	0.20
Diuretics	33.4%	35.9%	0.13	32.7%	37.0%	<0.001	0.43
Insurance Status**							
Uninsured	8.0%	11.2%	0.001	26.8%	28.8%	0.04	<0.001
Medicare	18.6%	23.9%	<0.001	5.4%	5.1%	0.63	<0.001
Medicaid	2.4%	3.3%	0.106	12.6%	17.6%	<0.001	0.008
Covered by VA	4.4%	4.1%	0.675	18.6%	12.3%	<0.001	<0.001

* MI, stroke, coronary bypass surgery, angioplasty, carotid endarterectomy, angioplasty lower extremity artery, aortic aneurysm repair, and heart failure

** Does not include Canadian citizens