HEALTH RELATED QUALITY OF LIFE IN CLINICAL STUDIES FOR CHRONIC DISEASES—DESIGN AND ANALYTICAL CONSIDERATIONS

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The dissertation uses health related quality of life (HRQoL) for evaluating treatment effectiveness. The research settings in the dissertation include observational cohort study and randomized clinical trial. The first research project examines the effect of Sahaja Yoga Meditation on quality of life. The study investigates whether the post intervention HRQoL, perceived anxiety assessment and hypertensive control is different in patients treated with meditation plus conventional therapy than patients treated with conventional therapy alone. The study shows that Sahaja Yoga Meditation treatment is associated with significant improvements in quality of life, anxiety reduction and blood pressure control.

The second research project examines the association of age on clinical and quality of life outcomes in the Bypass Angioplasty Revascularization Investigation 2 Diabetes Trial (BARI 2D); specifically, among patients with both type 2 diabetes and coronary heart disease, whether a treatment strategy (prompt revascularization or medical therapy for heart disease and insulin sensitizing or insulin providing drugs for type 2 diabetes) is more preferable for older individuals in terms of clinical and HRQoL endpoints. The study shows that older patients are at greater risk for cardiovascular events but the effectiveness of cardiac treatment strategies and glycemic control strategies does not differ by age. Older patients experience an accelerated decline in health status than their younger peers.

The third research project investigates the longitudinal relationship between body mass index (BMI) and heath status outcomes in BARI 2D. The study reports an inverse association between BMI and health status outcomes in patients with both stable ischemic heart disease and type 2 diabetes. Weight reduction is desirable for obese patients, but may not be necessary for overweight but non-obese patients to achieve improvements in functional capacity and perceived Energy outcomes.

The public health significance of the dissertation lies in the research findings on treatments that result in better clinical or quality of life outcomes for patients with chronic diseases, but also contrasts the strength and weakness of HRQoL studies and demonstrates strategies to overcome the methodological challenges in conducting HRQoL research in clinical studies.

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1. Dissertation overview and objectives

To evaluate the effect of treatment on the health and well being of the patients, measures of health related quality of life (HRQoL) are frequently incorporated as outcomes in clinical studies. Studying HRQoL in clinical research is complicated by the setting, therapeutic practices of interest, and design of the study. This dissertation uses HRQoL to evaluate treatment effectiveness in two different settings—a pilot study and a randomized clinical trial, and elucidates challenges in HRQoL study and approaches to address these challenges.

The dissertation is composed of three research topics. The first topic evaluates the effect of Sahaja Yoga Meditation on HRQoL. This research was conducted using an observational prospective cohort design. The second and third research topics are conducted within the framework of the Bypass Angioplasty Revascularization Investigation 2 Diabetes Trial (BARI 2D), a randomized clinical trial evaluated treatment strategies for patients with both stable ischemic heart disease and type 2 diabetes. Health status is a secondary outcome in the research to support the primary findings on clinical endpoints. The second research topic investigates the association between age, randomized treatment assignment and clinical and health status outcomes. The third research topic investigates the longitudinal relationship between body mass index (BMI) and health status.

The dissertation compares and contrasts the strengths and weaknesses of HRQoL studies in observational study and randomized clinical trial settings. In the last part of the dissertation, a research proposal for evaluating the effect of meditation on clinical and HRQoL outcomes is presented for future study.

2. Introduction

2.1 Evaluating treatment effectiveness for chronic diseases

One specific objective in epidemiology is to evaluate preventive and therapeutic interventions.[1] When a physician suggests a treatment to a patient, the decision-making is based on the experience with large groups of patients who had the same disease, the treatments these patients received, and the prognosis of the treatment being observed. Consequently, the key elements in epidemiology studies for treatment evaluation include the study design, sample population, intervention being evaluated, and effectiveness outcomes.

Study design: A randomized controlled trial remains the optimal design for evaluating therapeutic practices. Ideally, randomization will generate groups of participants that are balanced over demographic or clinic characteristics; as a result, the difference in outcomes is mainly attributed to the intervention being evaluated. Observational studies, such as longitudinal cohort and case control study, remain necessary to generate hypotheses and gather pilot data for the planning of randomized trials. Observational studies can complement or strengthen the findings of randomized trials. In general, observational studies include broader or more "generalizable" study populations since study participants do not have to consent to randomization; however, the received treatment in observational studies is often biased such that treatments are selected based on the patient's clinical profile referred to as "confounding by indication." A recent meta-analysis reported consistent findings from well-designed observational studies and randomized trials for acute or chronic diseases. The authors summarized that the results from well-designed observational studies and randomized trials were comparable.[2]

Study population: The challenge in selecting a study population in a randomized trial is to identify proper inclusion and exclusion criteria, so that the study population resembles the characteristics of the target population. In observational studies, the study population for cohort studies is either selected by recruiting the exposed and/or non-exposed individuals or by identifying a defined population before exposures occur and follow this population over time, a classic example of this is the Framingham study.[1] In case control studies, cases can be identified from hospital records or disease registries. The selection of controls usually follows one of the two approaches—either selecting controls that resemble cases in all aspects but the

disease of interest, or selecting controls that represent all persons without the disease in the target population.

Study Interventions: Drugs, medical devices, surgical practices, and lifestyle modification are examples of interventions, treatments or treatment strategies that are frequently evaluated in clinical research.[3]

Study Outcomes: The selection of study outcomes depends on biology, study setting, the intervention being evaluated, and the objective of the clinical study.[3] A good outcome has qualities such as clinical relevance, ability to be quantified, and being valid, objective, reliable, sensitive, and precise.[3] The primary outcome often determines both the study design and analysis approach. A primary outcome is usually an assessment of clinical importance, such as survival. In clinical studies, it is not uncommon to have multiple secondary outcomes to evaluate different aspects of the treatment effect. A common purpose of using secondary outcomes is to support the finding of primary outcome. Quality of life measures are often used as a secondary outcome in clinical studies.

2.2 Health related quality of life as outcomes for treatment evaluation

"Health-related quality of life" (HRQoL) integrates aspects of physical, psychological, and social health, as defined by the World Health Organization in 1948. [4,5] HRQoL can be altered by both the immediate and long-term treatment effects, especially in the chronic disease setting. Patients with chronic conditions often suffer from prolonged physical and psychological distress, which deteriorates quality of life.[6] The estimated advantage of one treatment over another can be substantially altered, or even reversed, by adjusting the primary effectiveness endpoints by quality of life. For example, Croog et al compared three anti-hypertensive therapies in a randomized clinical trial, while the three treatments showed no difference in the primary outcome, the results showed major differences in HRQoL.[7] In the cancer chemotherapy trial, Buccheri et al. suggested that small treatment benefits may be more than outweighed by the poorer quality of life and cost of therapy.[8]

In chronic diseases where a cure is not easily achieved, the goal of treatment is to stop the progress of the disease and improve the quality of life of patients.[9] It is estimated that over 100 million people live with chronic illness in the United States.[10]

Effective interventions that can alleviate the distress and improve quality of life are important to the health and well being of the patients.

2.3 Health related quality of life measurements

There are two major strategies to assess HRQoL—the assessment based on questionnaires regarding the perceived state of health and assessment based on the tradeoff between quality and quantity of life. [11,12,13] The first strategy is derived from psychometrics, where the perceived wellbeing of an individual is measured by his/her responses to a series of questions measuring different aspects of HRQoL; it is the preferable HRQoL measurement in clinical studies because of its simplicity in implementation.[11]

2.3.1 Properties of HRQoL measurements

Common properties in all forms of HRQoL measurements include coverage, validity, reliability, responsiveness and sensitivity.[4] Coverage describes the ability of a HRQoL measurement to evaluate components that are important and susceptible to change by the intervention. The components can be both objective and subjective, such as symptoms, health status, or perceived psychological or social well being. Reliability is the ability for a HRQoL measurement to yield stable values in constant conditions. In a longitudinal setting with repeated assessments, reliability also applies to the ability for an instrument to capture the true change over time. [4,11,14]

Validity is the ability of HRQoL measurements to measure what they claim to measure. Aspects of validity include face validity, construct validity and discriminant validity.[11] Face validity refers to whether the content of an instrument can be comprehended clearly without ambiguity.[11] Construct validity describes whether the results derived from the instrument are as expected to be relative to other reliable measurements assessing related characteristics. Or whether there is no association between results of measurements assessing unrelated characteristics, for example, a measurement of physical activity is expected to be correlated with another physiological measure than an measure for environment.[11,14] The comparison with other reliable measures for construct validity assessment is needed due to the lack of gold standard for measuring HRQoL. Discriminant validity represents the ability of the instrument to distinguish among subjects who experience different levels of HRQoL, for example one expects to observe worse HRQoL for patients with more

severe symptoms or other adverse disease measures. Discriminant validity is sometimes referred as responsiveness.[4,11]

Sensitivity is the ability of a measure to reflect true changes or differences in the underlying construct of wellbeing which the HRQoL measurement being used to assess. Problems such as an inadequate range, delineation of the response, ceiling and floor effects in measurements can mask important and therapeutically meaningful changes in HRQoL.[11,14] In addition, longitudinal changes within a patient are typically smaller than differences between patients, and therefore clinical studies with repeated HRQoL assessments during follow up require a greater sensitivity of the measurement.[11]

2.3.2 Generic HRQoL Measurements

Generic measurements are used in the general populations, irrespective of the heterogeneity in illness or health condition, to assess a wide range of domains applicable to a variety of health states and diseases. [15] Generic HRQoL measurements are commonly used in general health surveys and can be used to make comparisons between disease states. In clinical trials, using generic measurement also enables the investigators to compare the perceived HRQoL between study patients and other established patient or healthy populations as well as compare HRQoL between the active treatment phase and extended follow up periods after treatment has ended.[11] Examples of common generic HRQoL instruments include the Sickness Impact Profile, [16] Nottingham Health Profile, [17] Medical Outcomes Study 36-item Short Form,[15] EQ-5D, [18] and the World Health Organization Quality of Life questionnaire.[19]

2.3.3 Disease Specific HRQoL Measurement

Disease-specific instruments are developed to detect subtle effects for a particular disease and the common treatments used for this disease. These measures provide detailed information on clinically relevant HRQoL change. Items in diseases specific measurements are designed to assess aspects such as symptoms, treatment satisfaction, and the impact of the disease on emotional, physical, and social well being.[11,14] In clinical trials, disease specific instruments are chosen because it is expected to have better sensitivity to the health states that may be experienced by patients in the study. Examples of HRQoL measures for patients with

coronary artery disease include the Duke Activity Status Index,[20] the Seattle Angina Questionnaire.[21] Examples of HRQoL measures for patients with diabetes include the Appraisal of Diabetes Scale[22] and Diabetes Health Profile.[23]

2.4 Health related quality of life research in clinical studies

Important elements in HRQoL research include the specification of the study objective, design, measurement selection, data collection and statistical analysis.

2.4.1 Objective

HRQoL can be assessed as the primary, secondary, or tertiary outcome of interest, depending on the objective of the study, In clinical studies where HRQoL is a primary outcome, the efficacy of intervention is based on some or all of the dimensions of HRQoL.[11] In most studies, it is also common to use HRQoL as the secondary endpoints to support the primary clinical findings. Other than measuring effectiveness, subscales of HRQoL measurements, such as the physical functioning and bodily pain subscales of SF-36, can be used as the tertiary outcomes to monitor the safety of the therapeutic intervention.[11]

2.4.2 Design

A longitudinal design is frequently used in clinical studies to determine the effect of a therapy on changes in HRQoL status overtime.[11] The optimal number and timing of HRQoL assessments depends on the disease, therapeutic practices, and the study question. In a randomized clinical trial, the initial HRQoL assessment should occur prior to randomization, and follow-up HRQoL assessment should be frequent enough to capture meaningful change, but not to an extent that increases respondent burden, nor be more frequent than the period of recall of the measurement.[11]

2.4.3 Selection of HRQoL measurement

In the definition of Guyatt et al, a HRQoL instrument includes the questionnaire, method of administration, instructions for administration, method of scoring, data analysis and interpretation.[24] All of these aspects are important in selecting a HRQoL instrument for a clinical study. Developing a new instrument involves tasks including item generation, cognitive interviews, pre-testing, item reduction, validation studies,

translation, and cultural adaptation, a process that takes years to complete.[11,14] Therefore, it is highly recommended to use a previously validated instrument rather than a new, unvalidated one for HRQoL assessments in clinical studies.

The choice of selecting a generic measurement, disease-specific measurement or a combination of both is based on the attempt to compile a complete set of HRQoL questions that are most relevant to the disease and interventions being evaluated.[4,11] It is also common for clinical studies to use subscales of the generic or disease-specific measurements to compile a survey instrument tailored to the study question. The selection of HRQoL measurements in clinical studies is not yet standardized, largely due to the diverse HRQoL aspects being assessed in different clinical studies. Consequently, HRQoL results from different studies are not comparable, and it is difficult to interpret HRQoL results across studies.[25]

2.4.4 Conduct Assessment

In clinical studies, administration of HRQoL measurements include self-assessment, face to face assessments or centralized telephone interview with trained interviewers.[11] Different modes of administration may influence the HRQoL result. For example, self-report assessment may result in more non-response items where as direct interview methods increase the likelihood for patients to report social desirable responses during interview.[14] To manage this discrepancy, sensitivity and cares to be given to patients so that they can feel comfortable being honest with the investigator regarding HRQoL answers. It is also useful to incorporate social desirable responses measures in HRQoL questionnaires.

2.4.5 Missing Data during Implementation

Shortages in time of the research staff, lack of physician support, inadequate protocols, and unaware of the rationale for collecting HRQoL data all contribute to missing HRQoL data in the implementation stage of clinical studies.[11] Precautions for avoiding missing data during data collection include clearly specifying in the protocol the procedures for collecting HRQoL information, communication with patients about the importance to complete HRQoL assessments, and communicating with research assistants and investigators about the rationale of collecting HRQoL assessments and the importance of collecting data on all patients willing to complete the

questionnaire. Regular meeting helps identify and address the difficulty and reluctance faced by the research team in HRQoL data collection.

The secondary prevention for missing data is to gather information on factors that may contribute to missingness. Such information will be helpful in specifying the missing mechanism and accounting for the missing data in the analysis.[11]

2.4.6 Analytical Considerations

In a longitudinal study where HRQoL is measured repeatedly over time, multiple measures on the same participant tend to be correlated, and the difference in each measurement from population mean is not solely explained by random variation. Thus, simple linear regression and ANOVA/MANOVA models are not sufficient. An approach such as mixed effects models can effectively account for the within-person correlation by using a covariance structure to model the pattern of covariance between repeated observations, or by incorporating a random intercept and random coefficient to account for the deviation of the intercept and regression slope of each individual from the population averaged ones.[26]

2.4.7 Missing Data

Missing data is common in longitudinal study, due to the free will of the individual and the various levels of morbidity and treatment complication experienced by patients.[27] A broader definition of “missing data” refers to no information obtained at the time of a scheduled assessment; the assessment may or may not be required by protocol. Examples of missing data patterns include: 1) attrition, where no assessment is expected since HRQoL assessment was terminated as specified in the protocol; 2) noncompliance, where no assessment is obtained when it is expected per protocol; 3) dropout, the discontinuation of the outcome measures.[11] Missing data introduce complications in HRQoL study results, from a decrease in statistical power to detect differences to bias in study results and interpretation.[11]

Analysis strategies can adapt different assumptions on the mechanism of missing HRQoL outcomes, and remedy the effect of missingness to some extent. The common assumptions for the mechanism of missing outcomes include missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR).

MCAR assumes the reason for a missing HRQoL assessment is entirely unrelated to the HRQoL level or values.[28] It is a strong assumption and is often not appropriate in HRQoL studies, for example, if patients with prior low HRQoL are less likely to answer HRQoL questions, the MCAR assumption is violated.[14,27] MCAR is the missing assumption for longitudinal statistical procedure such as the generalized estimating equations (GEE).[28]

MAR relaxes the missing data assumption by allowing missing HRQoL data to depend on observed covariates and observed HRQoL scores. This means that missing data may be related to factors such as older age, gender, duration of diabetes as well as prior HRQoL level, but conditioning on the observed patient profile and prior HRQoL values, the future missing data is completely random. MAR is the assumption for missing outcomes in mixed model analysis.

MNAR describes missingness that is dependent not only on known covariates and prior outcomes, but also on the unobserved missing data at the time the assessment.[27] Thus, if sudden changes in health status that are not assessed cause missing HRQoL data, this results in MNAR. Strategies exist, such as utilizing pattern-mixture models, to manage the missing outcomes that are assumed to be MNAR.

Complications of missing data also arises from excluding individuals with missing baseline or no follow up assessments from the longitudinal analysis. The common practice of excluding participants who either die early or are too sick to complete the first follow-up assessment leads to HRQoL measures that may over-estimate the true values. The impact of missing outcomes from such patients on results can be evaluated by sensitivity analysis with proper imputations.

2.4.8 Multiple Testing

If analyses involve four or five HRQoL outcomes, there will be concerns about false statistical significance as a consequence of multiple testing.[14] One way of avoiding this problem is to identify in the protocol one or two primary HRQoL outcomes of principal interest, and reporting nominal p values for statistical testing with the notification of multiple testing problem in the discussion, as recommended by Pernegger[29] and Fayers and Machin.[14] It may be preferable to use a 99% confidence interval as an aid to interpretation of the results.[11]

Another common practice of managing multiple testing is to adopt an adjusted alpha level using methods such as the Bonferroni correction. For example, in a

clinical study with five HRQoL outcomes, the alpha level after Bonferroni correction is 0.05/5=0.01, can be used as the final p-value denoting “statistical significance” for the individual tests.[11,14]

3. Examples of health related quality of life research in clinical studies

This dissertation is composed of three research topics involving HRQoL research in clinical studies. The first research topic evaluated the effect of Sahaja Yoga Meditation on HRQoL with an observational prospective cohort design. The second and third projects were conducted within the framework of BARI 2D, a randomized clinical trial designed to evaluate the treatment strategies for patients with both stable ischemic heart disease and type 2 diabetes. Data on the health status aspects of HRQoL were collected as the secondary outcome in BARI 2D.

3.1 Literature review on the effect of meditation therapy on health related quality of life outcomes

Few studies in the current literature have documented the effect of meditation or yoga on quality of life. Reibel et al compared the change in quality of life before and after a mindfulness meditation program in 136 patients with various health conditions.[30] The study reported clinically meaningful improvement in quality of life, as defined by a 5 point or greater increase in SF-36 scales, in role-physical, vitality, role-emotional, mental health subscales and mental component summary measure, associated with the meditation program. Since there was no control group, however, it was difficult to know the extent of improvement in quality of life that was directly attributable to the meditation.

In a pilot study conducted by Curiati et al, elderly patients with optimally treated congestive heart failure were randomized to receive meditation or not. The meditation technique was a combination of complete yoga breathing, relaxation response and guided image of a healthy heart. Quality of life was measured by the Minnesota Living with Heart Failure Questionnaire. The study reported a higher level of quality of life associated with meditation which was equivalent to the difference achieved between enalapril treatment versus placebo in a previous study.[31] However, the inference was based on 19 patients, the small sample size increased the risk of chance finding in the study.

Another factorial randomized trial was conducted to compare the effect of adding Metta (love-kindness) meditation and massage to standard therapy on quality

of life among patients with advanced AIDS. The study reported significantly better quality of life, measured by Missoula-Vitas QoL Index, in the group that received both meditation and massage. However, adding either meditation or massage to standard therapy did not significantly improve the quality of life compared to standard therapy alone. The study did not acquire sufficient statistical power to distinguish whether the beneficial effect resulted from meditation alone, massage alone, or the synergistic effect of the two interventions.[32]

Among healthy individuals, Oken et al conducted a randomized trial, assigning healthy seniors to one of three groups: Iyengar yoga, aerobic exercise or wait-list control. Quality of life was a secondary outcome in the study. The Iyengar yoga group demonstrated significantly better scores for SF-36 vitality, role-physical, bodily pain, social functioning subscales, and the physical composite summary.[33]

In conclusion, there are few studies that explored the effect of meditation/yoga on quality of life, and the strength of evidence from most of these studies is undermined by suboptimal study designs and insufficient power. Rigorous evidence on how meditation influences quality of life, especially in clinical settings, is absent in the current literature.

3.2 Review of health related quality of life studies in randomized clinical trials for coronary heart disease or type 2 diabetes

The HRQoL study in the original BARI trial reported a greater functional capacity during the first three years for patients who had stable heart disease and were randomized to receive bypass surgery, as compared to angioplasty.[34] It is notable that the difference in HRQoL results between treatment groups was not significant at 5 or 10 years after randomization, as the rate of recurrent angina, which was negatively associated with HRQoL outcomes, converged between the treatment groups.[35] A similar trend was observed in the COURAGE trial, where patients with stable coronary artery disease were randomized to receive either percutaneous coronary interventions (PCI) or medical therapy. A greater HRQoL improvement, measured by RAND-36 survey instrument, was observed in patients with more severe angina. PCI resulted in better HRQoL outcomes than medical therapy, but the difference between treatment groups diminished after 3 years of follow-up.[36] Similarly, the ACME trial reported a better HRQoL for patients randomized to receive PCI compared with medical therapy at 6 month of follow-up.[37] In RITA-2 trial, greater

HRQoL improvement was observed in the PCI than in the medical therapy group.[38] The MASS II trial compared effectiveness among three treatment strategies—the bypass surgery, PCI and medical therapy, in patients with stable multi-vessel coronary heart disease. The greatest improvement in HRQoL was observed in patients randomly assigned to receive bypass surgery.[39] In patients with unstable angina, the RITA-3 trial reported better HRQoL outcomes in the revascularization than medical therapy group at year one.[40] The positive effect of revascularization on HRQoL outcomes may be attributable to the greater capacity of revascularization to relieve angina in patients than medical therapy. The diminishing HRQoL difference in treatment groups may be partly explained by the increasing revascularization rate in the medical group over time which results in angina relief.

For type 2 diabetes, a cross-sectional survey of follow-up HRQoL in the UKPDS study reported no difference in HRQoL by randomized treatment groups. Although HRQoL was not used to evaluate the randomized treatment effectiveness, results from the study demonstrated an inverse association between HRQoL and diabetic complications.[41]

In summary, revascularization was associated with preferable intermediate HRQoL outcomes than medical therapy in previous randomized clinical trials for patients with heart disease. However, few HRQoL results were available in randomized clinical trials for type 2 diabetes in the current literature, and information on HRQoL outcomes in trials for patients with both heart disease and type 2 diabetes are lacking.

4. Introduction of the Bypass Angioplasty Revascularization Investigation 2 Diabetes Trial (BARI 2D)

The second and third research topics of the dissertation are based on data from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. BARI 2D aimed to investigate optimal treatment strategies for patients with both stable ischemic heart disease and type 2 diabetes. BARI 2D was designed to test the two hypotheses—1) whether prompt coronary revascularization combined with medical therapy decreased the long-term mortality compared with medical therapy with the option of delayed revascularization when clinically indicated and 2) whether controlling serum glycosylated hemoglobin (HbA1c) level to a target of less than 7.0% with insulin sensitizing drugs decrease the long-term mortality compared with

insulin providing drugs.[42] To simultaneously test the two hypotheses, the BARI 2D trial used a 2 by 2 factorial design, where patients were randomly assigned to one of the two ischemic treatment strategies and one of the two glycemic treatment strategies.

4.1 Study Population

The study population in the BARI 2D trial is patients with both type 2 diabetes and angiography documented stable ischemic heart disease to be managed either by revascularization or medical therapy. The recruitment of BARI 2D trial began with seven vanguard sites in the United States on January 1, 2001 and ended on March 31, 2005 with 49 clinical sites located in the US, Canada, Mexico, Brazil, Austria and Czech Republic. A total of 2,368 patients gave written informed consent to be enrolled in BARI 2D trial. The baseline demographic and clinical characteristic of BARI 2D population is summarized in table 1.[43]

Patient Subgroups

Before randomization, each consented patient was evaluated by his/her responsible cardiologist to determine the revascularization strategy, either Percutaneous Coronary Intervention (PCI) or Coronary Artery Bypass Graft surgery (CABG), based on the patients clinical profile and extent of coronary disease. The intended revascularization strategy was an essential indicator defining the severity of coronary disease, and most importantly, the trial randomization was stratified by this intended method of revascularization variable (PCI or CABG). Other pre-specified patient subgroups were defined based on baseline characteristics including history of revascularization, insulin use, HbA_{1c} categories, left ventricular function, creatinine level, and race.[42]

4.2 Study Intervention

The randomized ischemia control strategies were comprised of: prompt revascularization with intense medical therapy versus intense medical therapy with delayed revascularization when clinically indicated. According to the protocol, patients assigned to the prompt revascularization group should receive the revascularization procedure within 4 weeks after randomization. The procedure, either coronary artery bypass graft surgery (CABG) or percutaneous coronary

intervention (PCI), was selected based on the patient's clinical and angiographic profile.[42]

The randomized glycemic control strategies for achieving a target of HbA1c less than 7.0% were comprised of: insulin sensitizing versus insulin providing drug treatment. Insulin sensitizing drugs included thiazolidinediones (TZD) and metformin. Insulin providing drugs included sulfonylurea drugs, repaglinide, nateglinide, and insulin.[42]

All BARI 2D patients received coronary risk-factor modification including target driven medical treatment for dyslipidemia and hypertension, and counseling to manage weight control, exercise and smoking cessation,[44]

4.3 Follow-up

All patients were followed at monthly clinic visits for the first 6 months and then quarterly visits until the end of the study. At each clinical visit, patient assessment included glycemic control, medication taken for diabetes, occurrence of adverse clinical events, complications, and angina status.[42] In addition, patient body weight and blood pressure were measured at clinical visit.[42] BARI 2D patients were followed until November 30, 2008. Protocol driven treatment was delivered until the 6-year annual follow-up visit or the annual follow-up visit that occurred between December 1, 2007 and November 30, 2008.

4.4 Measures

Biological Samples for Core laboratory assessments

Blood samples for core laboratory assessment on HbA_{1c}, fibrinolytic factors, and insulin was drawn at baseline, at 1 month, 3 months, 6 months, 1 year, and then every 6 months until the end of follow-up. Blood samples for lipid assessment were drawn at baseline, 6 months, 1 year, and then annually during follow up. Urine samples for core laboratory assessment on albumin and creatinine were collected at baseline and then annually during follow-up. 12-lead electrocardiography examinations were obtained at baseline, at 3 months, 1 year, and then annually for core laboratory assessment. [42]

Health Related Quality of life

Health related quality of life was assessed at baseline and at each annual clinic visit during follow up. The instrument package was a combination of complete scales or subscales of self-administered questionnaires, including the Duke Activity Status Index (DASI),[20] RAND Medical Outcome Study Energy/fatigue and health distress scales,[45] and self-rated health.[46]The Center for Epidemiologic Studies Depression Scale (CES-D)[47] was added to annual follow up assessment after recruitment ended, thus no baseline CES-D data available. The four HRQoL measures assessed both at baseline and during follow-up years (DASI, Energy, Health distress and Self-rated health) were focused on measuring the health status aspect of HRQoL. Therefore, in the dissertation, the term "health status measures", instead of "HRQoL measures" were used in the second and third research topics.

The DASI score ranged from 0-58.2. Self-rated health was measured in a five-category Likert scale and can be scored as continuous.[46] The Energy/fatigue and transformed self-rated health scores ranged from 0-100. A higher score for these 3 scales indicated better health status. In contrast, the health distress score ranged from 0-100 and the CES-D ranged form 0-60, and a higher score indicated worse health status.

4.5 Study Outcomes

The primary outcome in BARI 2D was all-cause mortality. Vital status was obtained from scheduled clinical visits and annual vital status surveys. In February 2009, a national database search was conducted to determine whether deaths had occurred for patients with unknown vital status.[48]

The principal secondary outcome was a composite of death, myocardial infarction, or stroke. Diagnosis of myocardial infarction is based on serum cardiac biomarker, such as creatine kinase MB (CK-MB) or troponin level, symptoms, and core laboratory electrocardiography assessments. Stroke and cause of death were adjudicated by an independent morbidity and mortality classification committee that were blinded from randomized treatment assignments.[48]

4.6 Main Findings of BARI 2D

The primary BARI 2D results demonstrated that there were no significant differences in five-year survival rate between the two ischemic treatment strategy groups (p=0.97), nor between the two glycemic treatment strategy groups (p=0.13).[48]

Similarly, the differences between randomized treatment groups were not statistically significant for the principal secondary outcome of the five-year cumulative rate of death/MI/stroke.[48]

Comparing the ischemia treatment strategies within the intended revascularization strata, the study reported no significant difference in mortality in either stratum. For the secondary endpoint of death/MI/Stroke, there was no treatment difference observed in PCI stratum; however, in the CABG stratum, the rate of death/MI/stroke was significantly lower in the prompt revascularization group compared with the medical therapy group (P=0.01).[48]

The study concluded that treatment strategies of prompt revascularization or medical therapy with delayed revascularization, and insulin provision or insulin sensitization result in similar rates of survival and major cardiovascular outcomes among patients with both stable ischemic heart disease and type 2 diabetes.[48] Among patients appropriate for CABG, revascularization may confer some benefits over initial medical therapy regarding major cardiovascular events.

Table 1 Selected Baseline characteristics of BARI 2D population (N = 2368) [43]

Demographic and Physical Characteristics	
Age, mean	62.4
Male, %	70.4
Race, %	
White	70.4
Black	17
Asian	4.2
Indian/Native American	4.3
Other	4.1
Hispanic ethnicity, %	12.5
Region of World, %	
USA	63.3
Canada	14.9
Brazil	15
Mexico	3.6
Europe	3.2
BMI categories (kg/m2), %	
Normal or underweight, <25	9.7
Overweight, 25 to <30	34
Class 1 obese, 30 to <35	32.1
Class 2 obese, 35 to <40	15.3
Class 3 obese, ≥40	9

Cardiac Status	
Hypertension, %	82.5
Hypercholesterolemia, %	81.9
Cigarette smoking status, %	
Current	12.5
Former	54.4
Never	33.1
Myocardial infarction, %	32
Congestive heart failure, %	6.6
Non-coronary artery disease, %	23.7
Stroke or TIA, %	9.8
Prior PCI, %	19.6
Prior stent, %	13.4
Prior CABG, %	6.4
Angina status, %	
None	17.9
Angina equivalents only	21.4
Stable CCS 1	14.3
Stable CCS 2	28.8
Stable CCS 3	7.5
Stable CCS 4	1.2
Unstable angina	9.5

Diabetes Status and Lipids	
Duration of DM categories, %	
<5 yrs	33.3
5 - <10 yrs	23.5
10 - <20 yrs	29.2
≥ 20 yrs	14.1
History of insulin use, %	29.3
Glycemia measurements, %	
HbA1c ≤ 7.0%	41.7
7.0% < HbA1c ≤ 8.0%	25.3
HbA1c >8.0%	33
Albuminuria	
Microalbuminuria	22.9
Macroalbuminuria	9.7
ABI≤0.9	20.1
MNSI clinical score >2, %	50.3
Total cholesterol ≥200 mg/dL, %	19
Triglycerides ≥200 mg/dL, %	31
HDL <40 male <50 female mg/dL, %	72.4
LDL ≥100 mg/dL, %	40.5

TIA, Transient ischemic attack; ACR, albumin to creatinine ratio; HDL, high-density lipoprotein; ABI, Ankle brachial index; MNSI, Michigan Neuropathy Screening Instrument; (Table reprint with modification from: Bypass Angioplasty Revascularization Investigation 2 Diabetes Study Group. Baseline characteristics of patients with diabetes and coronary artery disease enrolled in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. Am Heart J 2008;156:528-536.)

5. Specific aim

The aim of the first research project is to examine the effect of Sahaja Yoga Meditation on quality of life. The study investigated whether the post intervention HRQoL and perceived anxiety assessment is different in patients treated with meditation plus conventional therapy compared to patients treated with conventional therapy alone. The study also investigated differences in blood pressure and pulse for patients with self-report hypertension at baseline.

The aim of the second research project is to examine the association of age on clinical and quality of life outcomes; specifically, whether age modifies the effect of randomized treatment on clinical and HRQoL endpoints in patients with both stable ischemic heart disease and type 2 diabetes.

The aim of the third research project is to investigate the longitudinal relationship between body mass index (BMI) and heath status in patients with both stable ischemic heart disease and type 2 diabetes.

6. Paper one: effect of Sahaja Yoga Meditation on quality of life and anxiety

6.1 ABSTRACT

OBJECTIVE

This study investigated the effect of Sahaja Yoga Meditation on quality of life, anxiety level, and blood pressure control among hypertensive patients.

METHODS

A prospective observational cohort study was conducted. The meditation group was comprised of patients receiving treatment from the International Sahaja Yoga Research and Health Center. The control group was comprised of patients receiving treatment from the Mahatma Gandhi Mission Hospital, both located in New Mumbai, India. Quality of life, anxiety and blood pressure were measured before and after treatment received.

RESULTS

During August, 2008, 67 patients in the meditation group, and 62 patients in the control group completed the study. The two groups were comparable in demographic and clinical characteristics. At baseline, compared to the control group, the meditation group had higher quality of life ($p<0.001$) and similar anxiety level ($p=0.74$); among the subgroup of patients with hypertension, the meditation group had lower blood pressure ($p<0.001$). Within-group pre versus post treatment comparisons showed significant improvement in perceived quality of life, anxiety and blood pressure control in the meditation group ($p<0.001$), while quality of life deteriorated and no improvement in blood pressure was observed in controls. Between-group analyses demonstrated that the meditation group had larger improvement in quality of life, anxiety reduction and blood pressure control. The beneficial effect of meditation remained significant after adjusting for potential confounders.

CONCLUSIONS

Sahaja Yoga Meditation treatment was associated with significant improvements in quality of life, anxiety reduction and blood pressure control.

6.2 INTRODUCTION

Quality of life integrates aspects of physical, psychological, and social health.[4] Patients with chronic diseases often suffer from a prolonged physical and psychological distress, such as stress and anxiety disorders. This prolonged distress is known to affect their quality of life.[6] As over 100 million people in the United States are living with chronic illness,[10] the search for effective interventions that can alleviate the distress and improve quality of life is needed.

During the past 50 years, the use of meditation and yoga, commonly applied as an effective adjunct to conventional medical treatment, has increased rapidly in the general population. [49,50] Yet quality of life has been the focus in few studies designed to investigate the effect of meditation or yoga. One study reported improvement in quality of life after a mindfulness meditation program in patients with diverse diseases; however, the absence of control group in the study made it difficult to assess the extent of improvement attributed to the meditation.[30] Increased quality of life after yoga/relaxation treatment in elder heart failure patients was reported in a pilot study.[31] Better quality of life in advanced AIDS patients who received a combination of Metta meditation and massage treatment was observed in a factorial randomized trial.[32] Insufficient power was a drawback in both studies. Rigorous clinical research is required to strengthen the current understanding about the effect of yoga and meditation on quality of life.

Sahaja Yoga Meditation is a simple method for individuals to achieve tranquility within.[51] Beneficial effects of Sahaja Yoga Meditation in disease management have been documented in patients with epilepsy,[52] essential hypertension,[53] asthma,[54] menopausal symptoms[55] and attention deficit-hyperactivity disorder.[56] The present study was designed to evaluate the effect of Sahaja Yoga Meditation on quality of life in individuals with heterogeneous health conditions. Quality of life and anxiety level were compared between patients who meditated and sought Sahaja Yoga Meditation treatment and non-meditating patients who sought conventional therapy. Differences in blood pressure were also evaluated in the subgroup of hypertensive patients.

6.3 STUDY DESIGN AND SETTING

This prospective observational cohort study was conducted in 2008 as an international public health project through the University of Pittsburgh Graduate School of Public Health. The study was approved by the Institutional Review Board in both the University of Pittsburgh and Mahatma Gandhi Mission Medical College and Hospital before implementation.

Two groups of patients were enrolled and followed. The common eligibility criterion in the study for both the meditation and control groups was men and non-pregnant women between 18 and 65 years old who were willing to give written consent for being enrolled in the study. The meditation group was comprised of patients seeking care from the inpatient sector of the International Sahaja Yoga Research and Health Center, located at Navi Mumbai, India. The center was the first institute where treatment based on Sahaja Yoga Meditation was provided. Doctors were formally trained in Western medicine or Homeopathy and also meditated. Patients who sought treatments from the Sahaja Yoga Research and Health Center could have either major diseases or be seeking treatment for minor health issues.

The control group was comprised of patients receiving internal medicine care in the Mahatma Gandhi Mission (MGM) Medical College and Hospital located at Navi Mumbai, India. The MGM hospital provided primary to tertiary medical care for the community. Individuals who sought internal medicine care either had major diseases or were attending regular health checkups. Individuals were eligible for participating in the control group if they had not actively practiced meditation during the past 3 months and were willing to forgo any practice of meditation for the duration of the study.

6.3.1 Study Intervention

Treatment in the Sahaja Yoga Research and Health Center was daily meditation and application of Sahaja Yoga cleansing practices. The therapeutic effect of Sahaja Yoga Meditation was achieved in meditation, characterized by the state of mental silence where one could better introspect, address and resolve the distress caused by negative thoughts, emotions or behaviors. To facilitate the relaxation and mental silence (meditation), individuals could do simple exercises and cleansing practices, such as deep breathing for relieving the tension of the heart, foot-soaking with salt water for better circulation and muscle relaxation in the abdomen.[53] In the Sahaja

Yoga Health Center, patients with diseases continued their standard medical treatment during their stay. The daily schedule for the inpatient sector in the Sahaja Yoga Health Center is described in table 1. From Monday to Saturday, patients started their day at five in the morning with individual meditation, followed by collective meditation. After breakfast, each patient met with his/her responsible physician and received treatment. In the afternoon, patients attended a meditation workshop for cleansing practices, and then collective meditation in the evening. A typical day ended around 10:30 at night. This daily schedule was designed to create a disciplined lifestyle where the patient's attention and activities were focused on regaining health.

6.3.2 Measurement

Demographic and clinical characteristics were recorded at the time when participants registered to receive treatment. Quality of life and anxiety for all participants were measured both at study entry and the end of follow-up, which was at two weeks after treatment received or the time of discharge.

Quality of life in this study was measured by the shorter version of the World Health Organization Quality of life instrument (WHOQOL-BREF) [19] and World Health Organization Quality of life—Spirituality, Religion and Personal Beliefs (WHOQOL-SRPB).[57] WHOQOL-BREF is a 26-item questionnaire evaluating quality of life from 4 domains: physical health, psychological, social relationships, and environment/surroundings. WHOQOL-SRPB is a 32-item questionnaire measuring the impact of the spirituality, religion and personal beliefs on quality of life. The World Health Organization Quality of Life instruments were selected for its coverage of important quality of life aspects. Furthermore, its development and validation accounted for different cultural and value systems. The two weeks default time frame, with the flexibility to prolong or shorten for different study settings or patient populations, was appropriate for the present study.[19] Both instruments were self-administrated. If self-administration was difficult, an interviewer assisted administration by reading items to the participant. WHOQOL-BREF was summarized into 4 domain scores, and transformed to a 0-100 scale. WHOQOL-SRPB was calculated as a single domain score from 4-20. Higher score indicated better quality of life.

Anxiety was measured by the Clinical Anxiety Scale (CAS). The instrument was comprised of a 25-item self-report questionnaire measuring perceived anxiety level at the time of administration.[58] The range of CAS scores was 0 to 100. A higher score indicated more perceived anxiety.

For self-reported hypertensive patients, blood pressure and pulse were measured both at baseline and the end of follow-up. Hypertensive patients rested in sitting position for five minutes before a trained staff measured their blood pressure with a calibrated sphygmomanometer. Pulse was measured at the wrist (radial artery).

6.3.3 Analysis

Participants with both baseline and follow up assessments were included in the analysis. Baseline demographic, clinical, and quality of life characteristics in the two groups were summarized. Continuous variables were compared with Student's t-test and categorical variables with chi-square statistics.

World Health Organization Quality of life instruments and clinical anxiety scale were scored according to the manuals.[19,58,59] In the original field trial of WHOQOL-SRPB, all missing values were treated as systematic missing and excluded from the analysis. In the current study, missing data management of WHOQOL-BREF was applied to WHOQOL-SRPB, such that if less than 30% items were missing within a domain for a patient; his/her mean domain score was used for imputing the missing value. The domain score of an individual was not calculated if more than 30% items were missing.

To compare the scores before and after the treatment within each group, Sign-Rank tests were used for WHOQOL-BREF domain scores and paired T-test for other outcomes (WHOQOL-SRPB, CAS, blood pressure and pulse). To test between group differences at baseline, the end of follow-up and change from baseline to follow-up, Wilcoxon rank-sum tests and t-tests were used. The impact of meditation on follow-up quality of life measures, adjusted for essential covariates such as baseline quality of life values and social desirable response (SRDS) [60] were assessed by multivariate linear regression models. Years of hypertension and hypertension drugs use at baseline were included in models for follow-up blood pressure and pulse. Potential effect modification between meditation and patient characteristics on study outcomes were tested. If significant effect modification was

observed, the results were reported separately by levels of the characteristic. The two-sided alpha level for treatment effect and effect modification in hypertensive subgroup was set to 0.01. The analysis was performed using SAS 9.1.

6.4 RESULTS

From July to October, 2008, 70 of the 112 eligible patients admitted to the inpatient sector of the Sahaja Yoga Health Center consented to participate in the study and 67 completed follow-up. In the control group, 80 of the 120 eligible patients seeking care in the internal medicine clinic of the MGM hospital consented to participate in the study and 62 completed follow-up. 44 (70.0%) of the control patients received outpatient care. The mean follow-up time was 8.13 (±5.2) days for the meditation group and 14.25 (±2.6) days for controls. In the meditation group, the averaged years of practicing meditation was 7.4 (±4.9) years. 11 (16%) patients in the meditation group were from countries other than India, while all controls were Indians. The two groups were comparable in age, gender, marital, and working status (Table 2). The percentage of higher education was greater in the meditation group than controls. The control group had a higher physical activity level and lower BMI. At study entry, the prevalence of smoking and drinking were 16% and 13% in the control group, while none of the participants in the meditation group smoked nor consumed alcohol. The self-reported clinical history was similar in two groups, but the meditation group had higher prevalence of prior anxiety, depression, and gastrointestinal distress. One patient in the meditation group had a history of multiple scleroses, while two patients in the control group reported human immunodeficiency virus infection. At baseline, 13 (19.4%) patients in the meditation group and 28 (45.2%) patients in the control group reported a history of hypertension required treatment. For patients with self-reported hypertension, the duration and management of hypertension were comparable.

In the meditation group, after a week of Sahaja Yoga Meditation treatment, significant improvements were observed in all quality of life domains and clinical anxiety level ($p<0.001$, figure 1 and figure 2). For hypertensive participants in the meditation group, significant improvements in systolic and diastolic blood pressure were observed. Conversely, after an average two weeks of conventional treatment, the control group reported a significant decline in quality of life and greater anxiety

(p≤0.011). For hypertensive participants in the control group, no improvement in blood pressure was observed after treatment received (Figure 1 and Figure 2).

Between-group analyses showed that the meditation group had significantly higher average quality of life scores in all domains than controls at study entry. After treatment, the meditation group experienced a greater improvement in all domains of quality of life (meditation group versus controls: physical: +7 versus 0; psychological: +13 versus 0; social: +6 versus 0; environmental: +7 versus 0; spiritual: +1.2 versus -0.5 (0-20 scale), p <0.001) (Table 3). Baseline clinical anxiety scores were similar in two groups (p=0.74). After treatment, the improvement in anxiety was only observed in the meditation group, contrary to the higher levels of anxiety experienced by controls (between group difference p <0.001).

For self-reported hypertensive patients, mean blood pressure and pulse were lower in the meditation group than controls at baseline. After treatment, the reduction in diastolic blood pressure was significantly greater for hypertensive patients in the meditation group than controls (-3.3 mmHg versus 1 mmHg, p=0.0043). There was a trend for greater reduction in mean systolic blood pressure in the meditation group than controls; the trend was not statistically significant (p=0.061), possibility due to more variability in systolic blood pressure change (a 13.2 mmHg standard deviation for change from baseline) in the meditation group. The between-group difference in pulse remained before and after treatment. At the end of follow-up, the mean pulse in meditation group was significantly lower compared to controls (73.7 versus 89.8, P<0.001).

In multiple linear regression models, after adjustment for baseline value and potential confounders including age, social desirable answering pattern and self-report illness, meditation remained the strongest independent covariate for improvement in quality of life and decrease in anxiety and blood pressure. Compared to controls, meditation was associated with a mean improvement of 15.7 units in physical, 21.7 units in psychological, 16.7 units in social, 13.2 units in environmental, and 2.3 units (by a 0 to 20 scale) in spiritual quality of life (p<0.001) (Table 4). Meditation treatment resulted in a significant reduction in clinical anxiety (-8.5 units, p<0.001) (Table 5).

In hypertensive patients, meditation treatment was associated with a mean 12 mmHg reduction in systolic blood pressure (p=0.018, borderline significant at an alpha level of 0.01). The quantitative effect of meditation on diastolic blood pressure

differed by diabetes status (p for effect modification=0.0053). In patients with both hypertension and type 2 diabetes, meditation treatment decreased diastolic blood pressure by 12.32 mmHg ($p<0.001$); the effect for hypertensive patients without diabetes was not as large but still significant (6.12 mmHg decrease, $p <0.001$). Pulse was similar in the meditation or control groups in the multivariate model.

6.5 DISCUSSION

In the current study, an average of one week of Sahaja Yoga Meditation treatment was associated with significant improvement in perceived quality of life, anxiety reduction and blood pressure control. The improvements among patients receiving meditation treatment were significantly greater than the changes observed in the control group of non-meditating patients.

At baseline, individuals who practiced Sahaja Yoga Meditation had a higher level of quality of life in all domains than their non-meditating peers. In self-reported hypertensive patients, individuals who practiced Sahaja Yoga Meditation had a better blood pressure control compared to patients who received conventional treatment.

The five domains of the World Health Organization Quality of life inventory measure facets of perceived quality of life ranging from physiological health such as energy/fatigue, pain, and sleep; psychological self-esteem, memory and concentration; social relationships and support; accessibility and safety of the environment; to spiritual perceptions of wholeness, peace, hope and faith. At baseline, despite no dramatic between-group differences in demographics or clinical profile, the meditation group perceived a higher quality of life than controls. Individuals who sought Sahaja Yoga Meditation treatment had an average of seven-year meditation practice. The baseline difference in perceived quality of life might be attributed to the prior meditation experience. On the other hand, when the change from baseline in quality of life was compared, taken into account the baseline difference in two groups, the meditation group experienced significant improvement while no change was observed in controls, suggesting Sahaja Yoga Meditation treatment was also associated with betterment over an extensive spectrum of quality of life. This association was supported by comparing the perceived anxiety in the meditation groups and controls. While similar anxiety level was observed in both groups at baseline, individuals who received Sahaja Yoga Meditation treatment had

significantly reduction in anxiety levels than their peers who received conventional therapy.

In current study, there was a trend of 9.4 mmHg decrease in systolic blood pressure associated with Sahaja Yoga Meditation treatment. In current literature, a sustained 12-mm Hg decrease in systolic blood pressure for 10 years has been reported to prevent 1 death for every 11 patients treated.[61] Sahaja Yoga Meditation was associated with greater decline in diastolic blood pressure then conventional treatment, and the rate of decline was greater for patients with both hypertension and type 2 diabetes, with an estimated 12 mmHg reduction in diastolic blood pressure. Hypertension is a major risk factor for cardiovascular disease and stroke, and it is estimated that a population-wide 2-mm Hg reduction in diastolic blood pressure could prevent 6% risk of coronary heart disease and 15% risk of stroke or transient ischemic attack.[62] The decrease in blood pressure associated with Sahaja Yoga Meditation treatment could potentially lead to decrease in cardiovascular mortality and morbidity.

The burden of hypertension continues to rise. In 2000, worldwide prevalence of hypertension was 26.4%translating to 972 million adults living with hypertension. Approximately one third (29.2%) of the adult population is estimated to have hypertension in year 2025, with an estimated population of 1.56 billion.[63] In United States, 1999-2002 NHANES survey reported an estimate of 65 million adults living with hypertension.[64, 65] High blood pressure was the primary cause or contributing cause of 11.31% deaths in United States in 2003. In 2006, the estimated direct and indirect coast of high blood pressure is 63.5 billion dollars.[23] If further validation of the effectiveness of Sahaja Yoga Meditation on hypertension control are obtained, cost-effective intervention programs could result in significant lives saved and savings to individuals.

While particular causes of 96% of hypertensive cases remain unclear, research has proven that patients who are at an early stage with essential hypertension display an increase in sympathetic and a reduction in parasympathetic activity.[66,67,68] Increased overflow of sympathetic neurotransmitter (norepinephrine) is observed in kidneys and heart among patients with untreated essential hypertension.[69] The high pulse observed in hypertensive patients corresponds to a high resting cardiac output and hyperkinetic circulation associated with the imbalanced autonomic nervous system.[70] In this current study, pulse rates were lower in the meditation group than

controls at study entry and these lower levels remained in the duration of the study. The lower heart rate associated with meditation indicated a decreased sympathetic nervous system over-activity and increased parasympathetic nervous function in hypertensive patients, which might contribute to a better blood pressure control.

In addition, results from high-resolution electroencephalogram studies have shown that Sahaja Yoga Meditation was associated with an increased alpha and theta power and reduced complexity of EEG patterns over anterio-frontal and fronto-central brain regions.[71,72] It is well established that imbalance in autonomic activity causes cardiovascular diseases.[73, 74] The autonomic imbalance is marked by disinhibition of sympathoexcitatory neural circuits, which are normally under tonic inhibitory control via the prefrontal cortex.[75] By its potential of activating the limbic area for better tonic control for autonomic nervous system, Sahaja Yoga Meditation may have the beneficial effect of decreasing the occurrence of psychosomatic disorders.

The study was subject to several limitations. As an observational cohort study, participants were self-selecting into the study groups. At study entry, the meditation group had an averaged 7 years of meditation, and may influence their perceptions of quality of life. Although the results were adjusted for baseline quality of life values, duration of meditation and other confounders, between group differences could not be fully controlled. The study evaluated the effect of Sahaja Yoga Meditation within the specific setting of the health center, where patients received a regimented schedule on meditation and treatment. As a result, the effects observed in the study were attributable to the combination of meditation and life in the health center. A potential placebo effect might be of concern, in which the observed improvement was possibly due to having the regimen of treatment practices. However, at baseline, clinical history and chronic disease severity was comparable in both groups. The fact that control groups reported deterioration in outcomes while meditation group reported improvements suggest a benefit beyond placebo effect. Perceived quality of life is best measured by self-report, and the study controlled the effect of high respondent by adjusting the aptitude of reporting socially desirable answers. The sample size of hypertensive subgroup is small; nevertheless, within or between group differences in blood pressure were sufficient to result in reasonable power (The post hoc estimated statistical power of observing the 9.41 mmHg decline in systolic blood pressure in the study was 62%).

A common challenge in behavioral studies is the recruitment and retention of the participants. This challenge did not hamper the current study, and the retention rate was very high. Since the study period was brief (two weeks commitment from each subject), the burden of participation was minimized.

6.6 CONCLUSION

The current study reports that patients who received Sahaja Yoga Meditation treatment in conjugation with conventional treatment benefited in diseases management and in perceived quality of life. Further investigation is recommended for the associations between Sahaja Yoga Meditation and blood pressure reduction, especially for patients with both hypertension and type 2 diabetes. Future clinical studies with a refined experimental design on the effectiveness of Sahaja Yoga Meditation for managing chronic conditions, such as prehypertension, hypertension and type 2 diabetes are recommended.

6.7 TABLES AND FIGURES

Table 1: Daily schedule of at the Sahaja Yoga Research and Health Center for inpatient patient

05:00	Wake up, Individual meditation
8:30-9:30	Collective meditation
10:30-14:00	Doctor Consultation
16:30-18:30	Collective workshop (for example, foot-soaking)
19:00-20:30	Collective meditation

Table 2: Demographic and clinical profile of study groups at study entry

	Meditation (N=67)	Controls (n=62)	P value
Age, mean (SD)	40.53 (11.9)	42.01 (15.5)	0.6
Female, n (%)	35 (52.2)	29 (46.8)	0.49
Marital status, n (%)			0.2
Never married	17 (25.4)	10 (16.1)	
Married	46 (68.7)	50 (80.6)	
Widowed	1 (1.5)	2 (3.2)	
Divorced/separated	3 (4.5)	0 (0)	
Education level, n (%)			<0.001
< High school	0 (0)	16 (25.8)	
High school graduate or some college	19 (28.4)	17 (27.4)	
Bachelor degree	30 (44.8)	22 (35.5)	
Graduate degree	18 (26.9)	7 (11.3)	
Work status, n (%)			0.47
Working full time	36 (53.7)	35 (56.5)	
Working part-time/homemaker	21 (31.3)	22 (35.5)	
Other	10 (14.9)	5 (8.1)	
Activity level, n (%)			<0.001
Sedentary	8 (12.1)	1 (1.6)	
Mild	21 (31.8)	5 (8.1)	
Moderate	31 (47.0)	32 (51.6)	
Strenuous	6 (9.1)	24 (38.7)	
BMI, mean (SD)	23.82 (3.5)	21.86 (4.5)	0.0069
Ever smoking, n (%)	17 (25.4)	17 (27.4)	0.79
Current smoke, n (%)	0 (0)	10 (16.1)	<0.001
Alcohol consumption during the past year, n (%)	0 (0)	8 (12.9)	0.0024
History of heart disease (including angina), n (%)	4 (6.0)	7 (11.3)	0.28
History of type 2 diabetes, n (%)	10 (14.9)	9 (14.5)	0.95
History of asthma, n (%)	2 (3.0)	3 (4.8)	0.59
History of anxiety or depression, n (%)	10 (14.9)	2 (3.2)	0.022
History of gastrointestinal distress, n (%)	18 (26.9)	6 (9.7)	0.012
History of hypertension, n (%)	13 (19.4)	28 (45.2)	0.0017
Self-reported hypertension patients (n=41)			
# hypertension drugs taken, median (Q1,Q3)	1 (1,2)	2 (1,2)	0.26
Hypertensive years (n=41), mean, SD	5.62 (3.4)	3.93 (5.0)	0.28

Table 3: Outcome comparisons between meditation (n=70) and control groups (n=62) at baseline and follow-up

	WHOQOL-BREF Physical, median (Q1,Q3)			WHOQOL-BREF Psychological, median (Q1,Q3)			WHOQOL-BREF Social, median (Q1,Q3)		
	Meditation	Control	P	Meditation	Control	P	Meditation	Control	P
Baseline	69 (56, 75)	56 (44, 63)	<0.001	63 (44, 69)	56 (44, 56)	0.004	75 (56, 75)	56 (50, 75)	<0.001
Follow-up	75 (69, 81)	53 (44, 56)	<0.001	75 (69, 81)	53 (44, 56)	<0.001	75 (75, 81)	56 (50, 56)	<0.001
Difference	7 (0, 19)	0 (-6, 0)	<0.001	13 (6, 25)	0 (-6, 0)	<0.001	6 (0, 13)	0 (-13, 0)	<0.001
	WHOQOL-BREF Environmental, median (Q1,Q3)			WHOQOL-SRPB, mean (SD)			Clinical Anxiety Level, mean (SD)		
	Meditation	Control	P	Meditation	Control	P	Meditation	Control	P
Baseline	69 (56, 75)	56 (44, 63)	<0.001	15.38 (2.3)	12.44 (1.8)	<0.001	22.22 (13.8)	21.53 (9.4)	0.74
Follow-up	75 (69, 88)	56 (44, 63)	<0.001	16.57 (2.0)	11.98 (1.7)	<0.001	15.18 (10.7)	23.19 (7.7)	<0.001
Difference	7 (0, 19)	0 (0, 0)	<0.001	1.18 (1.7)	-0.47 (0.6)	<0.001	-7.07 (13.1)	1.66 (3.9)	<0.001

Hypertensive subgroup comparisons (n=41)

	Systolic blood pressure, mean (SD)			Diastolic blood pressure, mean (SD)			Pulse, mean (SD)		
	Meditation	Control	P	Meditation	Control	P	Meditation	Control	P
Baseline	134.26 (17.8)	151.19 (15.3)	0.0042	83.58 (9.4)	93.38 (7.1)	<0.001	68.20 (11.5)	85.81 (6.9)	<0.001
Follow-up	123.19 (18.9)	150.32 (13.0)	<0.001	78.21 (7.2)	94.39 (4.9)	<0.001	73.70 (10.6)	89.76 (7.0)	<0.001
Difference	-9.41 (13.2)	-0.87 (5.1)	0.061	-3.33 (4.5)	1.01 (3.7)	0.0043	3.28 (8.5)	3.67 (5.3)	0.87

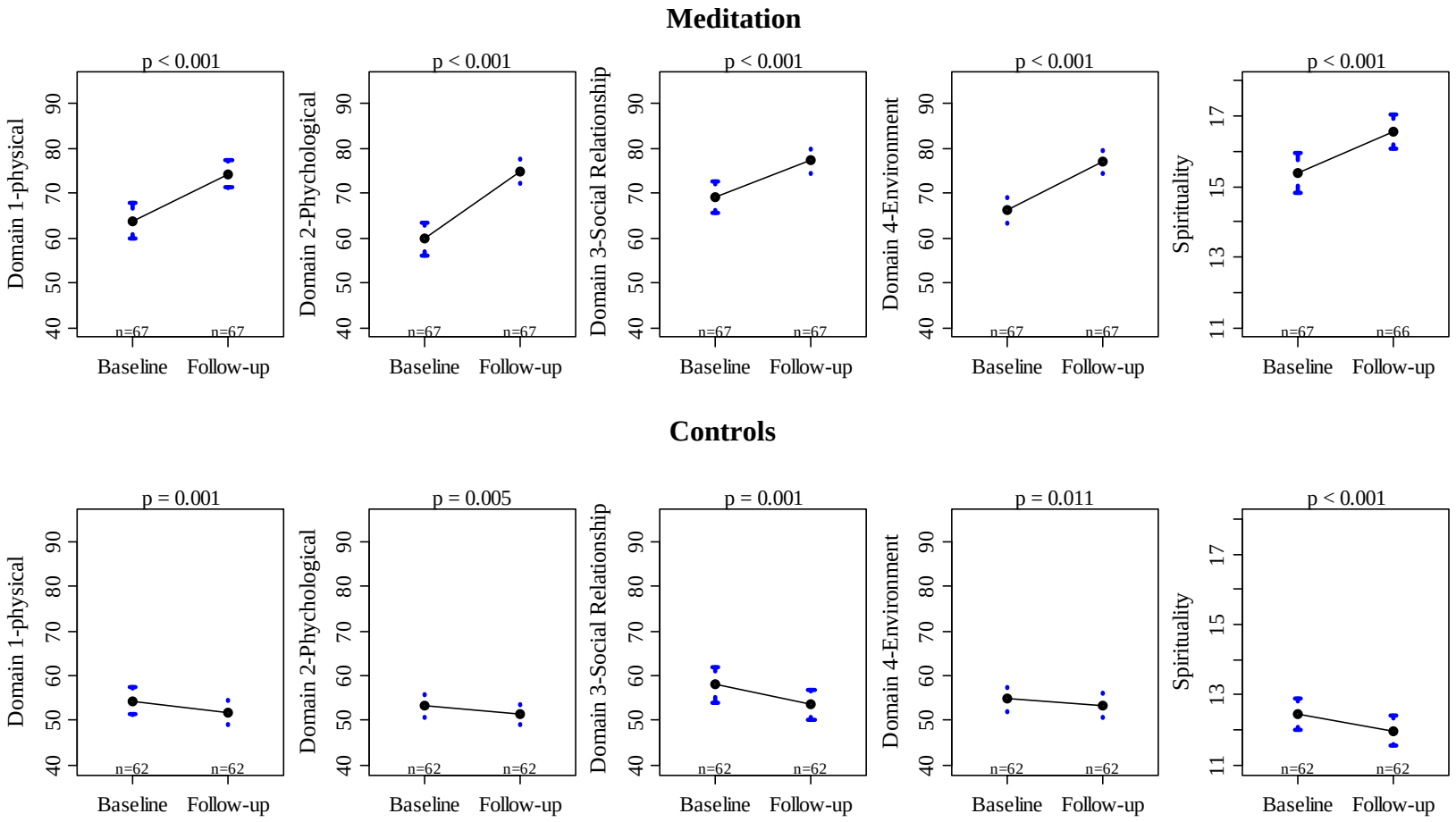


Figure 1 Baseline versus follow-up for quality of life measures within meditation and control groups (mean±1.96 SE).

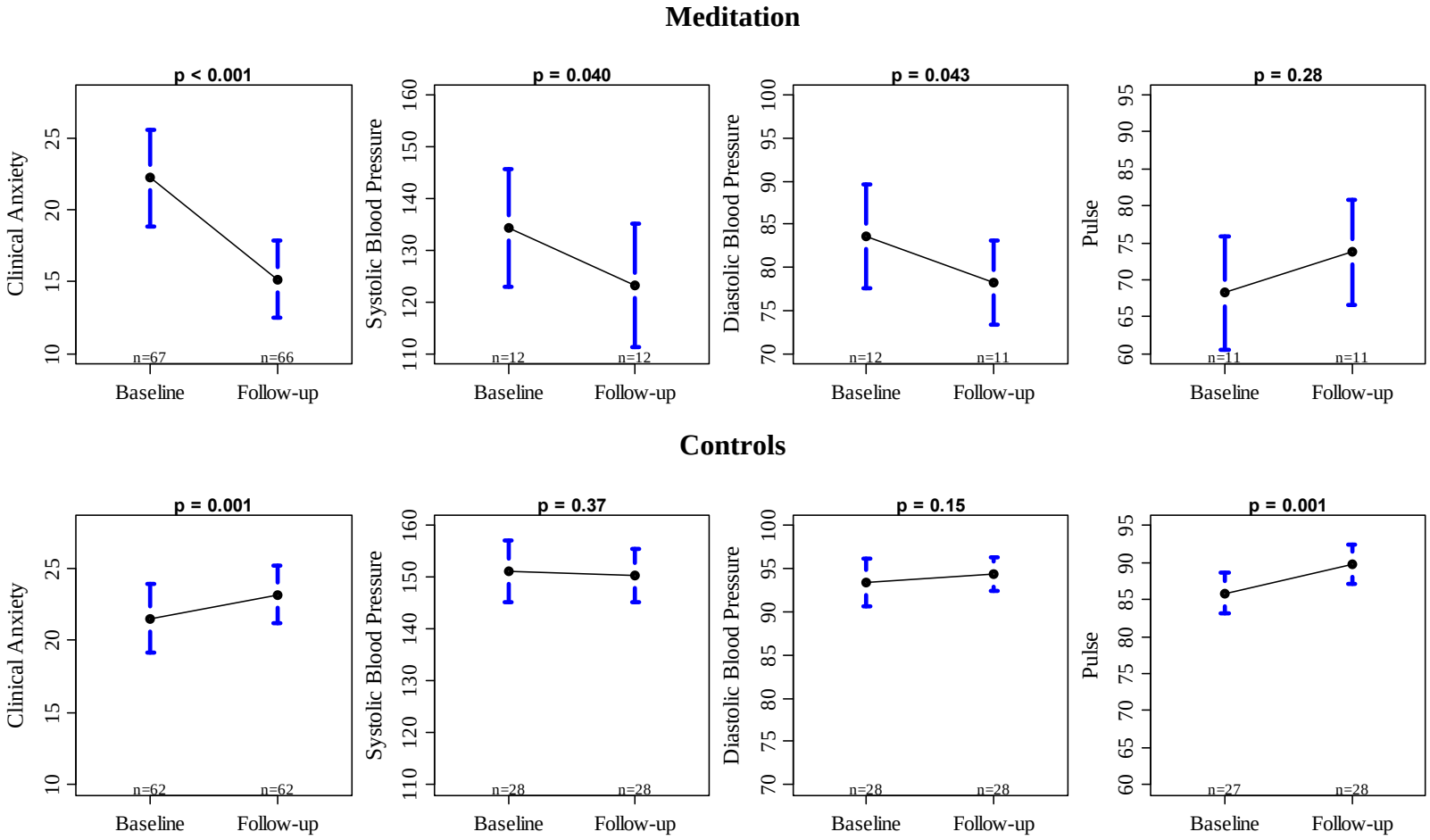


Figure 2 Baseline versus follow-up for clinical anxiety, blood pressure, and pulse within meditation and control groups (mean±1.96 SE)

Table 4 The effect of meditation on quality of life, adjusted for demographic and clinical variables (n=129)

	WHOQOL-BREF								WHOQOL SRPB (0-20)	
	Physical Domain (0-100)		Psychological domain (0-100)		Social Domain (0-100)		Environmental domain (0-100)			
R square	0.7339		0.7232		0.7358		0.8076		0.8741	
Parameters	Est.	P	Est.	P	Est.	P	Est.	P	Est.	P
Meditation (reference: controls)	15.7	<0.001	21.66	<0.001	16.66	<0.001	13.22	<0.001	2.29	<0.001
Baseline value	0.51	<0.001	0.45	<0.001	0.48	<0.001	0.71	<0.001	0.71	<0.001
SDRS[1]	2.60	0.004			2.11	0.03	2.96	<0.001	0.29	0.013
Age	-0.17	0.003					-0.10	0.032	-0.02	0.007
Indian race			5.77	0.038						
Education level (reference: high school or less)						0.023				
High school graduate or some college					-0.28					
Bachelor Degree					2.04					
Graduate Degree					6.97					
Self report history of gastrointestinal disease					-5.78	0.007				
Ever smoking									-0.47	0.034

[1]Social desirable Response measure

Table 5 The effect of meditation on anxiety level and blood pressure, adjusted for demographic and clinical variables

	Clinical Anxiety[1] (n=129)		Systolic blood Pressure (n=41)[2]		Diastolic blood Pressure[2] (n=41)		Pulse (n=41)	
R square	0.5539		0.8484		0.9326		0.7454	
Parameters	Est.	P	Est.	P	Est.	P	Est.	P
Meditation (reference: controls)	-8.46	<0.001	-12.01	0.018			-5.42	0.081
Meditation versus controls in hypertensive patients with diabetes					-12.32	<0.001		
Meditation versus controls in hypertensive patients without diabetes					-6.12	<0.001		
Baseline value	0.48	<0.001	0.83	<0.001	0.59	<0.001	0.70	<0.001
Self reported history of type 2 diabetes					-0.32	0.77		

[1] Model for clinical anxiety is also adjusted for physical activity and marital status.

[2] P value for interaction between meditation and self reported history of type 2 diabetes on diastolic blood pressure: 0.0053

7. Paper two: The effect of age on clinical and quality of life outcomes in the Bypass Angioplasty Revascularization Investigation 2 Diabetes Trial.

(The abstract was presented at the AHA 50th cardiovascular disease epidemiology and prevention conference in 2010.)

7.1 ABSTRACT

Background: Coronary revascularization in elderly patients has increased dramatically in the past decade. Previous clinical trials have reported conflicting results about the effectiveness of revascularization in older populations.

Methods: In BARI 2D, 2368 patients with stable ischemic heart disease and type 2 diabetes were randomized to 1) prompt revascularization versus medical therapy and 2) insulin sensitization versus insulin provision. Patients were followed for an average of 5.3 years. The primary outcomes were death and the composite of death, myocardial infarction (MI), and stroke. Secondary endpoints included health status. Cox regression and mixed models were used to investigate the effect of age on study outcomes and randomized treatment effectiveness.

Results: Older age was significantly associated with higher rates of death ($p<0.001$) and death/MI/stroke ($p<0.001$); however, the effect of prompt revascularization versus medical therapy on cardiovascular events did not vary by age. Compared to younger patients, older patients had lower physical function but higher energy and self-rated health, and less health distress at baseline. After an initial improvement in health status during the first year, older patients experienced an accelerated decline in health status over subsequent years (effect modification for age and follow-up time: $p <0.01$).

Conclusion: Among patients with diabetes and coronary disease, older patients were at greater risk for cardiovascular events but had similar outcomes with an invasive or conservative cardiac treatment strategy. Older patients experienced an accelerated decline in health status than their younger peers.

7.2 INTRODUCTION

Although use of coronary revascularization has increased rapidly among older adults during the past decade;[76] its effectiveness in this population has remained controversial. Concerns exist about procedural mortality risk and complications as well as long-term effectiveness in the elderly population.[77] A recent meta-analysis reported that coronary artery bypass grafting (CABG) resulted in a better survival than percutaneous coronary interventions (PCI) in older patients with multi-vessel coronary disease.[78] However, randomized clinical trials comparing revascularization to medical therapy in older patient subgroups, did not find any significant survival advantage associated with one or the other treatment approach.[79,80,81] Another area of uncertainty is the effectiveness of medical therapy and the optimal clinical approach to managing common chronic co-morbidities in the elderly such as hypertension[82] and type 2 diabetes.[83]

The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) is a randomized clinical trial that evaluated the treatment strategies for patients with stable ischemic heart disease and type 2 diabetes. Within the framework of BARI 2D, the current study hypothesized 1) older age is associated with higher incidence rates of adverse clinical outcomes, 2) the effectiveness of randomized treatment strategies for ischemic heart disease and for glycemic control differed by age, and 3) the treatment and the time effect on health status change over four years of follow-up differed by age.

7.3 METHODS

7.3.1 Study Settings

The study design and primary outcomes of BARI 2D trial have been published previously.[43, 48] In brief, 2,368 patients with stable ischemic heart disease and type 2 diabetes were randomized to receive one of the two randomized ischemia treatments—prompt revascularization (REV) or medical therapy with a delayed revascularization when necessary (MED), and simultaneously randomized to one of the two glycemic treatments— insulin sensitizing (IS) or insulin providing (IP) drug to achieve a serum Hemoglobin A1c level of less than 7.0%. Before randomization, each consented patient was evaluated by a responsible physician to determine which revascularization strategy

(CABG or PCI) was appropriate based on the extent of heart disease. In BARI 2D, the intended revascularization strategy was an important variable to define patient subgroups. The recruitment of the trial was between January 1, 2001 and March 31, 2005. The trial follow-up ended November 30, 2008 and the 2,368 patients were followed for an average of 5.3 years.

7.3.2 Outcomes

Clinical Endpoints

The clinical outcomes of interest included death from all causes, a composite of death, myocardial infarction (MI) and stroke, cardiac death and a subsequent procedure. In the prompt revascularization group, the initial procedure was carried out within four weeks after randomization. Vital status was obtained from clinical visits and regular contacts made by each clinical site, supplemented with a national database search for patients with unknown vital status after the end of follow-up. Diagnosis of MI was based on serum cardiac biomarkers and core electrocardiography laboratory assessments. Stroke and cause of death were adjudicated by an independent committee.

Repeated Health Status Measures

The health status was assessed by four instruments—the Duke Activity Status Index (DASI),[20] RAND Medical Outcome Study Energy/fatigue and health distress scales, and self-rated health. Health status was assessed at baseline and during each annual follow-up visit. The score ranged from 0-58.2 for DASI, 0-100 for the Energy/fatigue. Self-rated health was measured in a five-category Likert scale and can be scored as a 0-100 continuous score.[46] A higher score indicated better health status. Conversely, the score of health distress ranges from 0-100 and a higher score indicated worse perceived distress.

7.3.3 Statistical Analysis

Baseline demographic, clinical, and health status profile were summarized by five-year age groups (<55, 55-60, 60-65, 65-70, ≥70). Continuous variables were compared with Student's t-test and categorical variables with chi-square statistics.

For the survival analysis of each clinical outcome, data were censored at five year follow-up. Kaplan–Meier survival curves with Log-rank test statistics were used to investigate the difference in survival experiences by baseline age groups. Survival curves by randomized treatment assignments were compared within each subgroup defined by five year age category to examine whether the effect of randomized treatment on clinical outcomes differed by baseline age groups. The hazard ratio of adverse clinical outcomes associated with older age was estimated by Cox proportional-hazards regression models, where baseline age was incorporated as a continuous variable, centered at its mean. The proportional hazard assumption of Cox regression models was tested by the significance of interaction between key covariates and follow-up time. If non-proportional hazards were observed, the estimates of centered age on clinical outcomes was obtained by stratification, in which separate partial likelihood functions were constructed according to different levels of the variable where non-proportional hazards occurred, the model then find the solution that maximized the multiplication of the likelihood functions.

For the longitudinal analysis of repeated health status measures, data were truncated at year four, due to an increasing proportion of patients not having year five clinical visit due to late enrollment. Only patients with at least one follow-up health status measure were included in the analysis. The trend in health status over time was first displayed by five-year baseline age groups, and analyzed with linear mixed models to account for the correlation in repeated measures. To investigate the difference over time by age, the data were parameterized with baseline health status as the first repeated measure. Categorical variables for time and age were used in the model to compare health status at each follow-up visit to the baseline. Alternatively, to investigate the treatment effect by age, the data were re-parameterized with year 1 health status as the first repeated measure and baseline as a covariate; Follow-up time and baseline age were incorporated as continuous variables in the mixed model. The treatment effect on health status was also assessed in five-year baseline age subgroups.

To control for potential confounders in the association between age and study outcomes, multivariate models were constructed adjusting for potential confounders at baseline: CABG stratum, sex, smoking, body mass index (BMI), angina severity, insulin

use, history of hypertension, congestive heart failure, myocardial infarction, stroke, non-coronary artery disease, and clinical neuropathy. Effect modification between baseline age and randomized treatment, intended revascularization methods and follow-up time were tested in multivariate models.

Clinical sites were controlled as random effects in mixed models, where as sites were managed in the Cox models by incorporating a categorical variable for geographic region. Treatment effect was analyzed based on the intention-to-treat principle. In models evaluating prompt revascularization versus medical therapy, two variables—the intended revascularization method and baseline angina severity (not balanced between randomized ischemic treatment groups), were controlled in the analysis. A two-sided alpha level for age effect modification and subgroup analyses was set to 0.01 to control for multiple comparisons.

The assumption of a linear association between centered baseline age and study outcomes was examined by adding a quadratic age variable and tested its significance. Missing baseline covariates were managed by mean values imputation, calculated separately by the intended revascularization method. In health status analysis, missing outcomes were identified if a patient did not provide health status data at annual follow-up visit, with an exception of administrative censoring. Under the missing at random assumption in mixed model, missing outcomes were not imputed. To account for potential missing not at random, a categorical variable for three missing patterns: completers (no missing), noncompliance and dropouts was added as a covariate in the models.[27] To examine the effect of excluding patients with no follow-up health status measure, missing health status outcomes was imputed using multiple imputation for all BARI 2D patients, and parameter estimates from the imputed data were compared to those from the original data. All analyses were performed using SAS 9.0.

7.4 RESULTS

Randomized treatment was balanced among baseline age groups. A greater proportion of elderly patients (age ≥ 60) had coronary disease more suitable for bypass surgery than PCI. At baseline, younger patients had larger BMI and lower systolic blood pressure but had higher diastolic blood pressure than older patients, while patients

more than 60 years old had higher prevalence of prior cardiovascular complications. For diabetes control, the youngest patients had highest mean serum HbA1c of 8.1% while the oldest patients entered the trial with a mean HbA1c of 7.1%, which was close to the glycemic control target in BARI 2D. The highest percentage of baseline insulin use was in the 55-60 age group (30.8%). At baseline, younger patients had the higher average DASI scores but lower energy, more health distress and rated their health worse than older patients.

All 2,368 BARI 2D patients were included in the survival analysis. One year increase in age at study entry was significantly associated with higher risk of adverse events including death (hazard ratio: 1.06, $p<0.001$), death/MI/stroke (hazard ratio: 1.03, $p<0.001$), cardiac death (hazard ratio: 1.03, $p=0.0028$) and a lower risk of subsequent revascularization (hazard ratio: 0.99, $p=0.0032$). Baseline age did not modify the effect of ischemic treatment strategy at 5-year follow up (interaction p values for age and revascularization: 0.97 for death; 0.71 for death/MI/stroke; 0.99 for cardiac death and 0.19 for subsequent procedure). Survival rates were similar in prompt revascularization and medical therapy groups, except for patients aged between 65 and 70 at baseline, where medical therapy resulted in better survival rate than prompt revascularization (81.1% for REV and 89.7% for MED), with a borderline significance of 0.012 (Table 2, Figure 1).

Insulin sensitizing and insulin providing strategies resulted in similar survival in all age groups (interaction p value for age and insulin sensitizing: 0.44 for death; 0.67 for death/MI/stroke; 0.85 for cardiac death and 0.72 for subsequent procedure) (Table 2). Baseline age did not modify the effect of glycemic treatment on clinical outcomes at five-year follow up. Since the hazard rate for prompt revascularization versus medical therapy was not constant throughout follow-up time for mortality outcomes, therefore multivariate Cox regression models estimating the effect of age were stratified by cardiac treatment strategies. After controlling for potential confounders, older age was significantly associated with higher rates of death, death/MI/stroke, cardiac death and lower rate of subsequent revascularization (Table 3).

A total of 2,163 patients were included in the longitudinal analysis for health status. Health status improved significantly at the first year compared to baseline for all age

groups, yet the pattern over time differed. Younger patients had higher baseline DASI scores, and the improvement from baseline was greater and sustained longer (Figure 2). Conversely, for patient more than 70 years old at baseline, mean DASI scores after year three were significantly lower than at baseline (Table 3). For the Energy questionnaire, younger patients started with low baseline scores but experienced the largest improvement during the first year of follow-up, and the mean Energy score continued to improve through year four for the youngest age group. The trends in Health distress and self-rated health were similar to that in Energy. The age difference in DASI increased over follow-up, while it diminished for other health status measures (Figure 2).

Over four follow-up years, the effect of randomized treatment on health status did not differ by baseline age (Figure 3 and Figure 4). Subgroup analysis showed that prompt revascularization compared to medical therapy resulted in a mean 2.19 point increase in DASI score ($p=0.0090$) and a mean 4.31 point higher in Energy scores ($p=0.0016$) in the 60-65 baseline age group (Figure 3). Randomized glycemic treatment resulted in similar change in health status in all age groups (Figure 4).

In multivariable analysis, after controlling for confounders, a one year increase in baseline age was significantly associated with a 0.13 unit worsening in DASI score ($p<0.001$) at the one year follow-up. The DASI scores declined over follow-up (-0.66 per year, $p<0.001$) and older patients experienced an accelerated decline during follow-up (interaction p-value for baseline age and follow-up time: 0.0015) (Table 5, Figure 5). Older age was associated with higher Energy ($p=0.045$) and lower Health distress ($p<0.001$); however, as follow-up time increased, older patients experienced a steeper decline in Energy and accelerated increase in health distress (interaction $p <0.001$). Conversely, baseline age was not associated with change in self-rated health after adjusting for confounders ($p=0.23$).

In sensitivity analysis, the estimates of association between age and DASI score, health distress and self-rated health in the imputed data were similar to the original (Table 6). Although baseline age was not significantly associated with Energy in the imputed data, the effect modification of older age on Energy decline over time remained similar (Table 6, Figure 6).

7.5 DISCUSSION

Among patients with stable ischemic heart disease and type 2 diabetes, older patients had higher long term event rates for death and major cardiovascular events, however, the comparative treatment effect of prompt revascularization versus medical therapy, and insulin providing versus insulin sensitizing on clinical endpoints or health status outcomes did not vary by age. In health status outcomes, after initial improvements, older patients experienced an accelerated decline in health status than their younger peers. The steeper decline was most evident for functional capacity. Patients who were older than 70 perceived better Energy, less health distress and rated their health better at the end of the four year follow-up than at baseline, but, their functional capacity was significantly worse than before study enrollment.

Our results were consistent with previous clinical trials evaluating effectiveness of revascularization versus medical therapy that did not find a significant interaction between age and treatment effectiveness for clinical outcomes. In the COURAGE trial, where 2,287 patients with stable coronary artery disease were randomized to receive either PCI or medical therapy, the effect of revascularization did not differ by age.[78] The CASS study reported similar effect of bypass surgery versus medical therapy on survival in various age subgroups of patients with stable angina.[82] Concurrent to CASS, the European Coronary Surgery Study with similar study design and patient population reported a trend of greater survival benefit for bypass surgery over medical therapy in patients aged above 53 at baseline, but the effect modification between age and treatment was not statistically significant.[84]

In clinical trials for type 2 diabetes, the PROACTIVE trial randomized 5,238 patients with type 2 diabetes and macrovascular diseases to either receive pioglitazone or placebo for diabetes treatment.[85] The MICRO-HOPE trial compared hypertension drug (ramipril) versus placebo on diabetic complication or cardiovascular disease in type 2 diabetic patients.[86] In both studies, the effect of active treatment versus placebo on death and cardiovascular complications did not differ by age.

The association between age and health status outcomes was assessed in few randomized trials comparing revascularization versus medical therapy. In RITA-2 study, older patients had similar physical functioning but significantly higher vitality and general

health scores then younger patients and the effect of age was independent of randomized treatment (PCI or medical therapy).[38] In the original BARI trial, which was aimed to investigate the effectiveness of bypass surgery versus angioplasty, older age was independently associated with a decline in DASI scores and improvement in mental health.[34] The results of the current study are in agreement with the previous findings in the original BARI trial.

To determine which ischemic treatment strategy was more appropriate for the elderly, the TIME trial compared revascularization versus medical therapy in 305 patients who were more than 75 years old and had chronic ischemic diseases. The primary outcome was health-related quality of life. At six months of follow-up, the improvement in symptom relief and health-related quality of life was greater in revascularization than medical therapy, while no difference was observed in survival without MI by randomized treatment. [87] In subgroup analysis of the current study, revascularization, compared to medical therapy, did not result in a favorable improvement in health status for patients older than 70 years. The difference may be the longer follow-up time in BARI 2D for observing the association between age and health status change over time.

Limitations

BARI 2D included patients with moderate ischemic heart disease and type 2 diabetes suitable for either treatment strategies in ischemia management and glycemia control. Consequently, the study population may not fully represent all patients with heart disease and type 2 diabetes. For example, elder patients in BARI 2D had relatively good diabetes control at baseline; it is possible that the longevity due to good diabetes control enabled them to participate in the trial. In the longitudinal analysis, the association of age and health status was limited to patients with health status information available at the minimum of one follow-up. The lack of health status information is some patients may be a concern. However, when we compare the results to those in sensitivity analysis where missing health status data were imputed using multiple imputation method, the associations between age and DASI scores, health distress and self-rated health were similar in the original and imputed data. The effect modification was more sensitive to the missing data, as in the imputed data, the older

age and faster decline in DASI during follow-up became insignificant. However, the effect modification remained significant for Energy and Health distress.

7.6 CONCLUSION

In the current study, for patients with stable heart disease and type 2 diabetes, age did not modify treatment effectiveness of prompt revascularization versus medical therapy, or insulin sensitizing versus insulin providing drug for clinical and health status outcomes. After initial improvement in health status, older patients experienced an accelerated decline in health status over time compared with their younger peers. The age-accelerated decline was most prominent for functional capacity.

7.7 TABLES AND FIGURES

Table 1: Baseline characteristics by baseline 5-year age groups

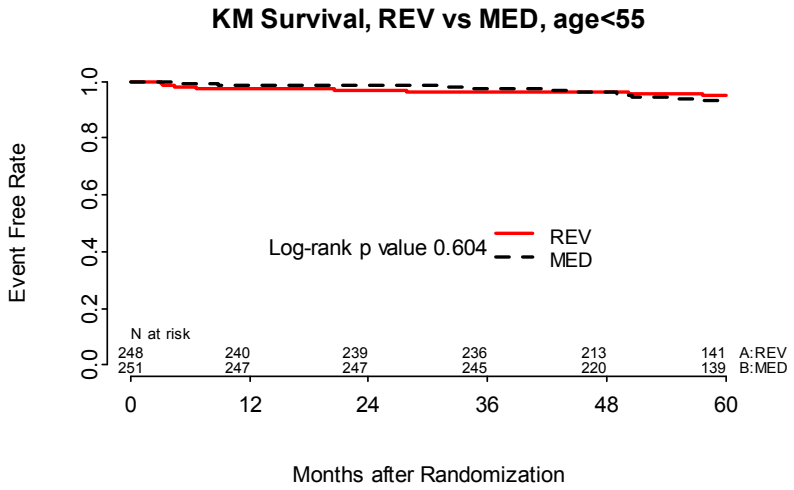
Age groups	<55	55-60	60-65	65-70	>=70	p
N	499	440	500	415	514	
Trial and demographic characteristics						
CABG Strata, %	26.7	27	36.2	38.6	33.1	<0.001
Prompt revascularization, %	49.7	52.5	47.4	51.1	48.2	0.53
Insulin Sensitizing, %	51.5	52	48.2	47.2	50.6	0.53
Male, %	69.9	71.1	73.8	72	65.4	0.046
RACE, %						
White	57.7	59.5	68.8	72.3	71.2	<0.001
Black	20.4	19.1	15.6	13.3	15.4	
Hispanic	15.2	16.6	10.6	11.3	9.3	
Other	6.6	4.8	5	3.1	4.1	
Geographic Region, %						
USA	60.7	64.1	60	60.5	70.6	0.0019
Canada	15.2	15.9	15.4	13.5	14.4	
Mexico	4.6	4.3	4	3.4	1.8	
Brazil	17.6	12	16.8	19	10.1	
Czech Republic/Austria	1.8	3.6	3.8	3.6	3.1	
Current cigarette smoker, %	23	16.9	13	7.2	2.3	<0.001
Former cigarette smoker, %	47.1	53.1	55.4	58	59	0.0014
BMI, mean	32.8	32.5	32.0	30.8	30.6	<0.001
Sitting systolic BP, mean	127.7	129.4	132.6	134.1	134.8	<0.001
Sitting diastolic BP, mean	77.7	75.7	74.9	74.5	70.0	<0.001
Cardiac characteristics						
History of MI, %	36.1	33.8	31.6	28.4	30.1	0.1
Angina Category, %						
None/Angina equivalent only	31.3	36	42.2	41.7	45.3	<0.001
Stable CCS1/CCS2	46.4	42.8	39	43.4	41.2	
Stable CCS3/CCS4/Unstable	22.4	21.2	18.8	14.9	13.4	
# of vessels with region (>=50%), %						
0	4	4.3	2.6	3.4	3.7	0.48
1	31.9	32.1	29.9	25.8	29.2	
2	35.3	36.9	34.7	37.4	35.6	
3	28.9	26.7	32.9	33.5	31.5	
Site: LVEF < 50%, %	16.4	17.4	19.5	15.9	17.8	0.66
Hypertension requiring tx, %	78.7	80.1	85.3	84.3	84.2	0.025
History of CHF req tx, %	4.5	5.3	7.8	7.3	8.2	0.073
Cerebrovascular accident TIA, %	5.9	6.8	10	13.5	12.7	<0.001
Non-coronary artery disease, %	17.5	22	27.2	25.5	26.5	0.0014
COPD, %	2.6	5.7	6.4	5.1	5.5	0.071
Prior PCI, %	19.7	20	17.6	21.2	19.8	0.73
Prior CABG, %	4.8	5.7	8	5.3	8	0.11

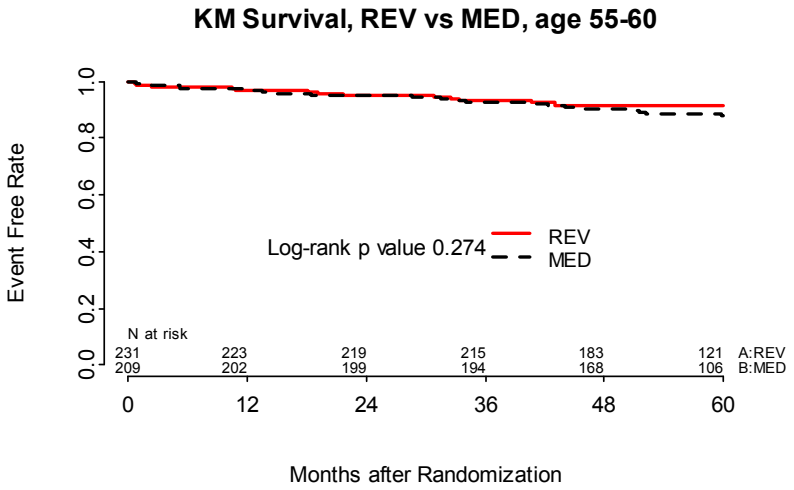
Table 1 continues:

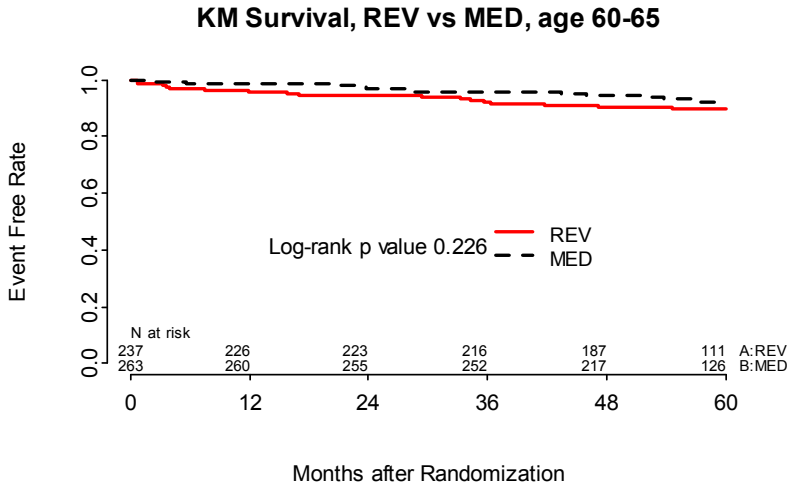
Age groups	<55	55-60	60-65	65-70	>=70	p
N	499	440	500	415	514	
Diabetic characteristics						
Duration of DM, mean	7.7	9.3	10.9	11.7	12.6	<0.001
HbA1c %: Core augmented with site estimate, mean	8.1	7.9	7.7	7.5	7.1	<0.001
Currently taking insulin, %	26.7	30.8	29.6	26.6	25.9	0.38
History of hypoglycemic episode, %	18.1	24	22.3	24.6	25.3	0.059
Neuropathy: clinical MNSI > 2, %	43.1	46.4	51.7	53	57	<0.001
Laser tx for diabetic retinopathy/macular edema, %	2.4	1.6	4.2	3.4	3.6	0.16
Legally blind, %	1	0.2	0.6	0.2	0.4	0.43
Lower extremity amputation, %	1	1.1	1	1.5	1.6	0.89
Quality of life						
DASI (0-58.2), mean	20.5	18.8	19.1	19.4	17.0	0.0017
Energy score (0-100), mean	50.4	46.7	50.5	56.2	53.2	<0.001
Health distress score (0-100), mean	48.1	46.3	39.3	35.3	33.4	<0.001
Self rated health category, mean	36.1	33.2	39.4	40.6	43.3	<0.001

Table 2: Five-year survival and free of death/MI/Stroke rate by baseline 5-year age groups and randomized treatment.

Age groups	Overall	Ischemic Randomized Treatment						Glycemic Randomized Treatment	
		Overall		CABG		PCI		IS	IP
		REV	MED	REV	MED	REV	MED		
Five year survival probability									
<55	94.1	94.9	93.4	94.0	89.8	95.2	94.6	95.5	92.6
[55,60)	89.8	91.7	87.8	93.8	78.2	91.0	91.0	87.7	92.1
[60,65)	90.8	89.5	91.9	89.6	88.5	89.5	93.6	91.7	90.0
[65,70)	85.3	81.1	89.7	76.7	89.1	83.3	90.1	84.9	85.8
>=70	80.3	83.5	77.4	78.8	72.5	85.8	79.8	80.9	79.6
Five year free of death/MI/stroke rate									
<55	83.6	82.4	84.7	81.7	84.5	82.4	85.0	86.7	80.3
[55,60)	77.1	78.0	76.3	84.0	60.0	75.6	82.1	77.4	76.7
[60,65)	79.2	79.9	78.6	78.7	76.8	80.6	79.9	80.9	77.8
[65,70)	75.4	72.7	78.1	69.5	72.5	74.2	82.0	75.4	75.4
>=70	67.6	72.3	63.4	73.6	56.3	71.7	67.0	68.0	67.1
Five year free of cardiac death rate									
<55	96.4	96.4	96.4	97.2	94.8	96.0	97.0	97.2	95.5
[55,60)	93.4	95.1	91.5	95.3	84.2	95.1	94.1	91.8	95.1
[60,65)	95.3	93.7	96.7	91.9	93.5	94.7	98.2	96.6	94.1
[65,70)	92.1	90.2	94.2	85.2	91.5	93.0	96.1	91.2	93.0
>=70	93.0	94.1	91.9	91.0	88.7	95.6	93.4	93.8	92.0
Five year free of subsequent procedure rate									
<55	63.9	69.5	58.4	90.8	62.3	61.1	57.0	64.5	63.3
[55,60)	61.4	74.8	46.1	80.8	49.4	72.4	44.8	59.7	63.1
[60,65)	70.7	79.5	62.9	91.8	63.2	72.9	62.6	75.3	66.3
[65,70)	71.3	80.0	62.8	94.5	70.5	71.8	57.7	73.9	69.0
>=70	68.6	80.3	57.6	97.2	52.7	72.9	60.3	69.9	67.2







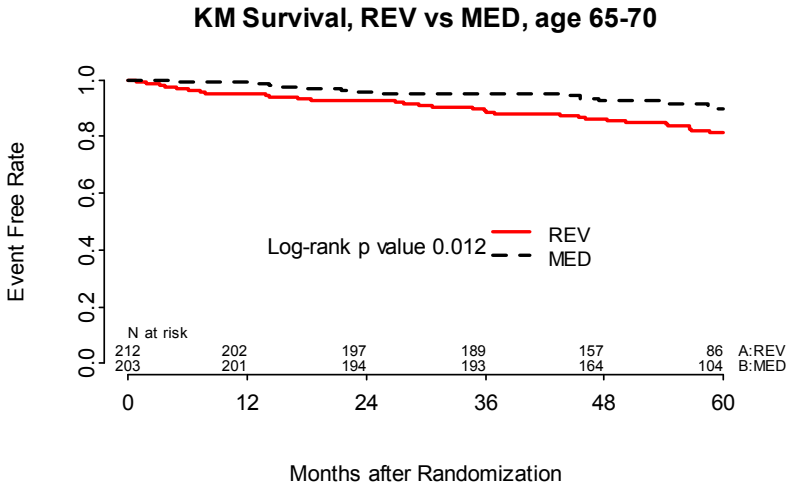


Figure 1 continues.

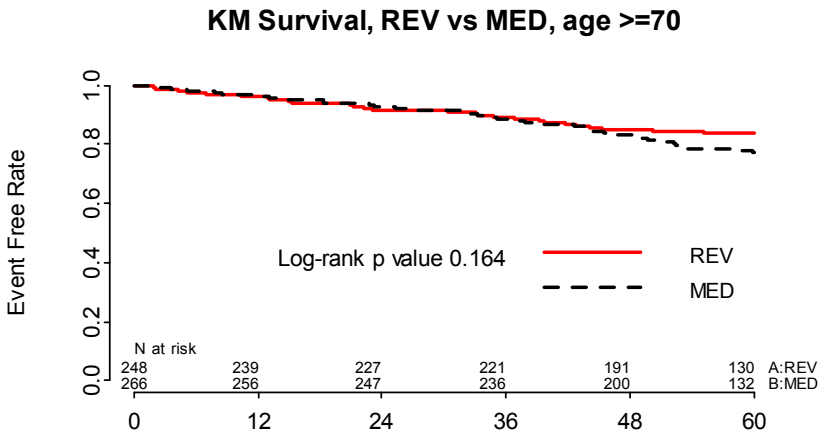


Figure 1: 5-year survival, REV versus MED, by baseline age categories. P value for the interaction between centered baseline age (continuous) and revascularization: 0.97

Table 3. Multivariable regression models for clinical outcomes during BARI 2D follow-up.

Variable	Death		Death/MI/Stroke		Cardiac death		Subsequent procedure	
	Hazard Ratio	p	Hazard Ratio	p	Hazard Ratio	p	Hazard Ratio	p
Age per 1 year increase	**1.06**	**<0.001**	**1.03**	**<0.001**	**1.03**	**0.0088**	**0.99**	**0.024**
REV versus MED in CABG stratum							0.16	<0.001
REV versus MED in PCI stratum							0.62	<0.001
IS versus IP	1.03	0.83	1.15	0.12	1.04	0.83	1.12	0.14
CABG versus PCI stratum	1.40	0.010	1.30	0.011	1.89	0.0012	1.20	0.095
Stable CCS1/CCS2	0.92	0.57	1.04	0.69	0.91	0.63	1.33	0.0016
CCS3/4 or unstable	0.96	0.83	1.15	0.29	0.96	0.87	1.84	<0.001
Currently taking insulin	1.37	0.021	1.47	<0.001	1.47	0.047	1.16	0.078
Male	1.28	0.084	0.97	0.73	1.08	0.70	0.93	0.41
BMI	1.01	0.58	1.00	1.00	0.99	0.70	1.00	0.99
Current cigarette smoker	1.16	0.48	1.06	0.70	1.37	0.26	0.97	0.80
Hypertension requiring tx	1.45	0.070	1.25	0.11	2.59	0.011	0.83	0.061
History of MI	0.97	0.83	1.18	0.096	0.99	0.96	0.98	0.78
History of CHF req tx	2.73	<0.001	1.96	<0.001	3.16	<0.001	1.04	0.82
Cerebrovascular accident, TIA	1.20	0.31	1.59	<0.001	1.05	0.86	1.24	0.083
Non-coronary artery disease	1.43	0.0079	1.18	0.10	1.54	0.027	1.09	0.38
Neuropathy: clinical MNSI > 2	1.36	0.020	1.23	0.033	1.37	0.10	1.09	0.27
Canada	0.50	0.0068	0.70	0.027	0.55	0.095	1.05	0.66
Mexico	2.07	0.036	1.97	0.0038	2.25	0.077	0.60	0.060
Brazil	1.63	0.010	0.99	0.97	1.32	0.32	0.32	<0.001
Europe	1.96	0.023	1.31	0.27	1.44	0.44	0.82	0.43

*Cox models for death, death/MI/Stroke, and cardiac death were stratified by randomized cardiac treatment strategies.

*Effect modification between prompt revascularization and CABG stratum in model for subsequent procedure: <0.001.

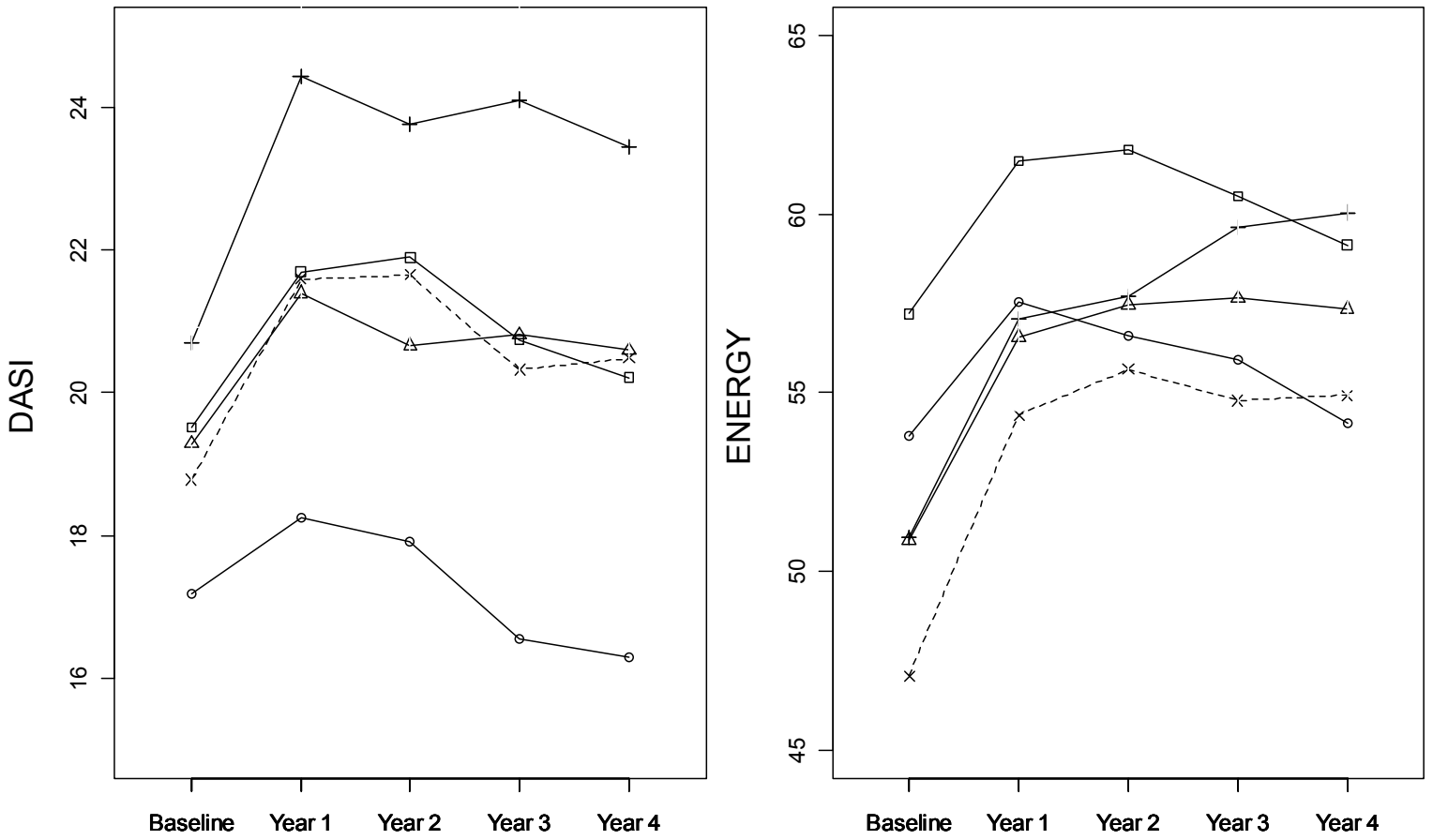


Figure 2 continues. +: age <55; -x- age: 55-60; Δ age: 60-65; □ age: 65-70; ○ age:>=70;

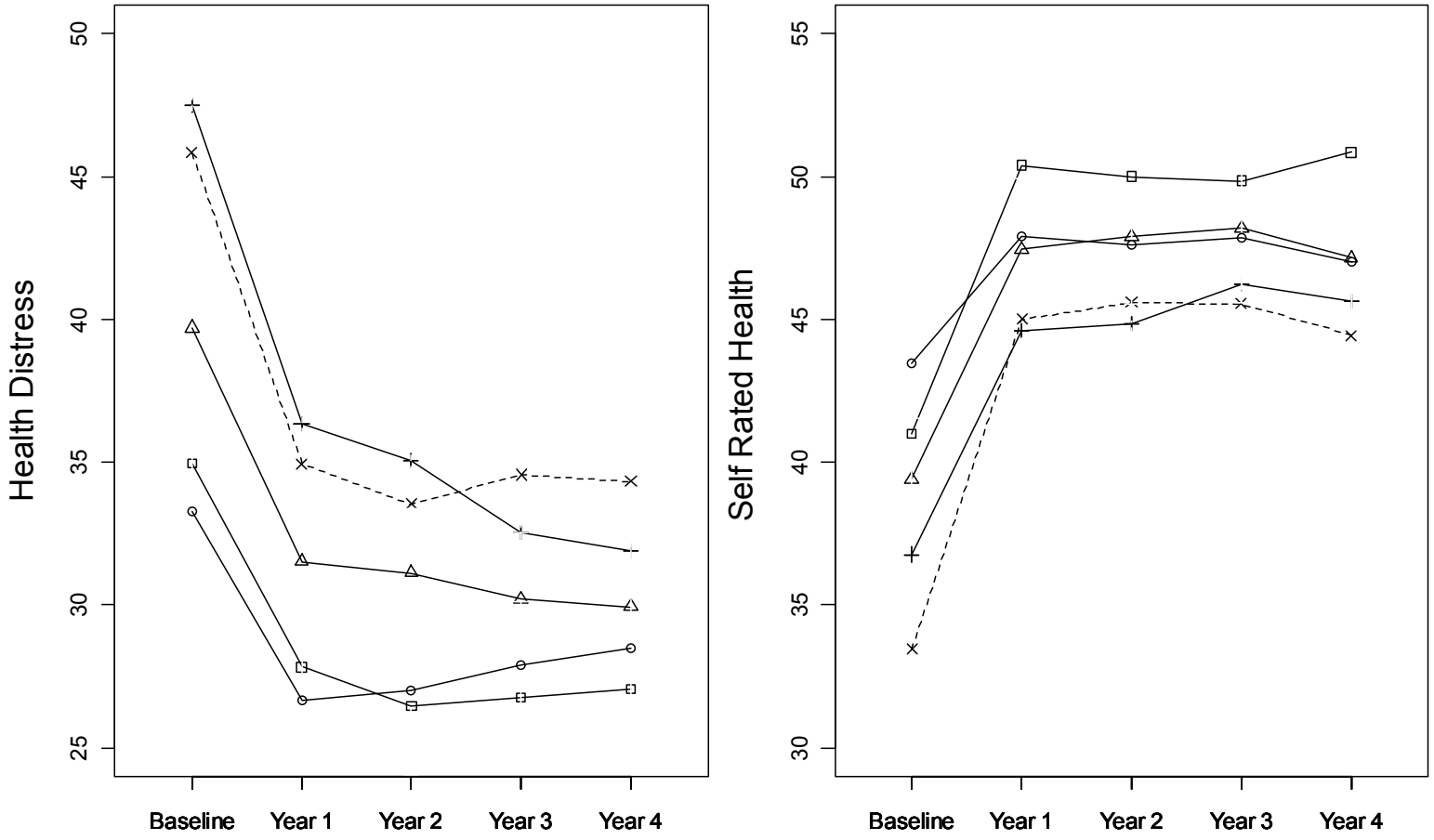


Figure 2: Health status measures by time and 5-year age categories. +: age <55; -x- age: 55-60; Δ age: 60-65; □ age: 65-70; ○ age:>=70;

Table 4: Change in health status score by 5 year age groups.

	<55		[55,60)		[60,65)		[65,70)		>=70	
	Est.	P	Est.	P	Est.	P	Est.	P	Est.	P
DASI										
Year 1 versus Baseline	3.61	*	2.82	*	1.99	*	2.17	*	1.13	0.051
Year 2 versus Baseline	3.08	*	2.48	*	1.17	0.049	2.04	0.002	0.41	0.50
Year 3 versus Baseline	3.06	*	1.15	0.087	1.35	0.032	0.85	0.22	-1.41	0.029
Year 4 versus Baseline	2.30	*	1.14	0.10	0.88	0.18	-0.13	0.86	-1.85	0.0066
Energy										
Year 1 versus Baseline	5.86	*	7.29	*	5.50	*	4.16	*	3.77	*
Year 2 versus Baseline	6.21	*	7.97	*	6.28	*	4.49	*	2.08	0.035
Year 3 versus Baseline	7.59	*	7.21	*	6.51	*	2.93	0.0061	1.45	0.14
Year 4 versus Baseline	8.10	*	7.52	*	6.22	*	1.61	0.16	-0.78	0.46
Health Distress										
Year 1 versus Baseline	-10.88	*	-10.83	*	-8.07	*	-7.11	*	-6.56	*
Year 2 versus Baseline	-11.88	*	-11.51	*	-8.18	*	-8.32	*	-5.56	*
Year 3 versus Baseline	-13.90	*	-10.45	*	-9.16	*	-7.99	*	-4.62	*
Year 4 versus Baseline	-15.14	*	-10.93	*	-8.73	*	-7.76	*	-3.38	0.011
Self-rated health										
Year 1 versus Baseline	7.64	*	11.52	*	8.01	*	9.26	*	4.41	*
Year 2 versus Baseline	7.80	*	11.42	*	8.06	*	8.80	*	3.67	0.001
Year 3 versus Baseline	8.70	*	11.56	*	8.68	*	8.64	*	4.00	*
Year 4 versus Baseline	8.03	*	10.26	*	7.08	*	9.27	*	2.59	0.033

1. * stands for p<0.001.
2. Estimates are based on models for health status controlled for 5-year baseline age groups, categorical follow-up time, and interaction between 5-year baseline age groups and follow up time, random site effect, and missing data pattern.
3. P values for interaction between 5-year baseline age groups and follow-up time on health status: 0.0021 for DAIS, <0.001 for Energy and Health Distress, and 0.0022 for self-rated health.

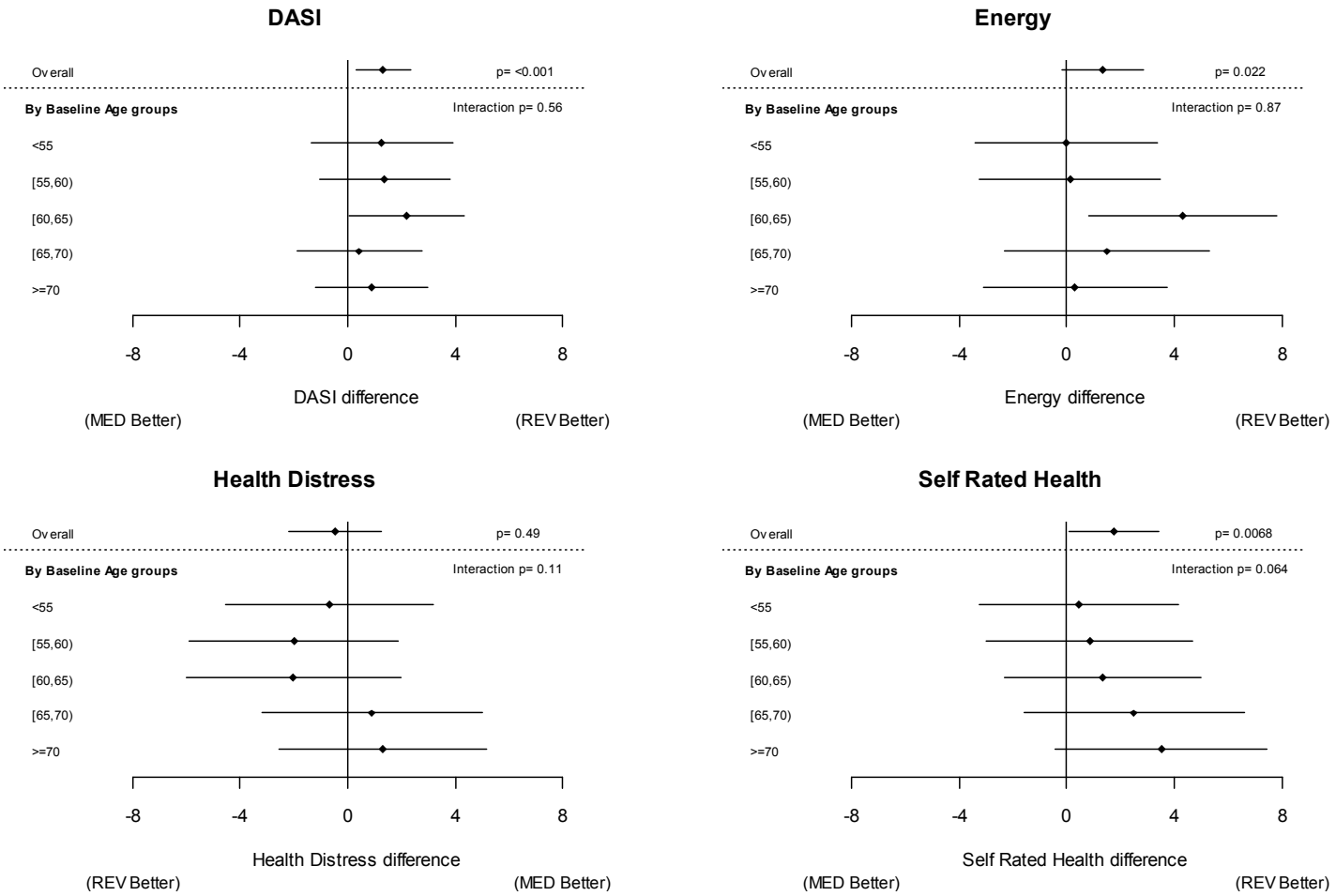


Figure 3: Effect of randomized ischemic treatment on health status, in all 2,163 patients and by 5-year baseline age groups. Interaction p values were for the interaction between centered baseline age and randomized treatment.Overall estimates were based on models controlled for strata, centered baseline age, continuous follow-up time, and interaction between centered baseline age and follow-up time(except for self-rated health), baseline health status, angina, random site effect, missing data pattern.

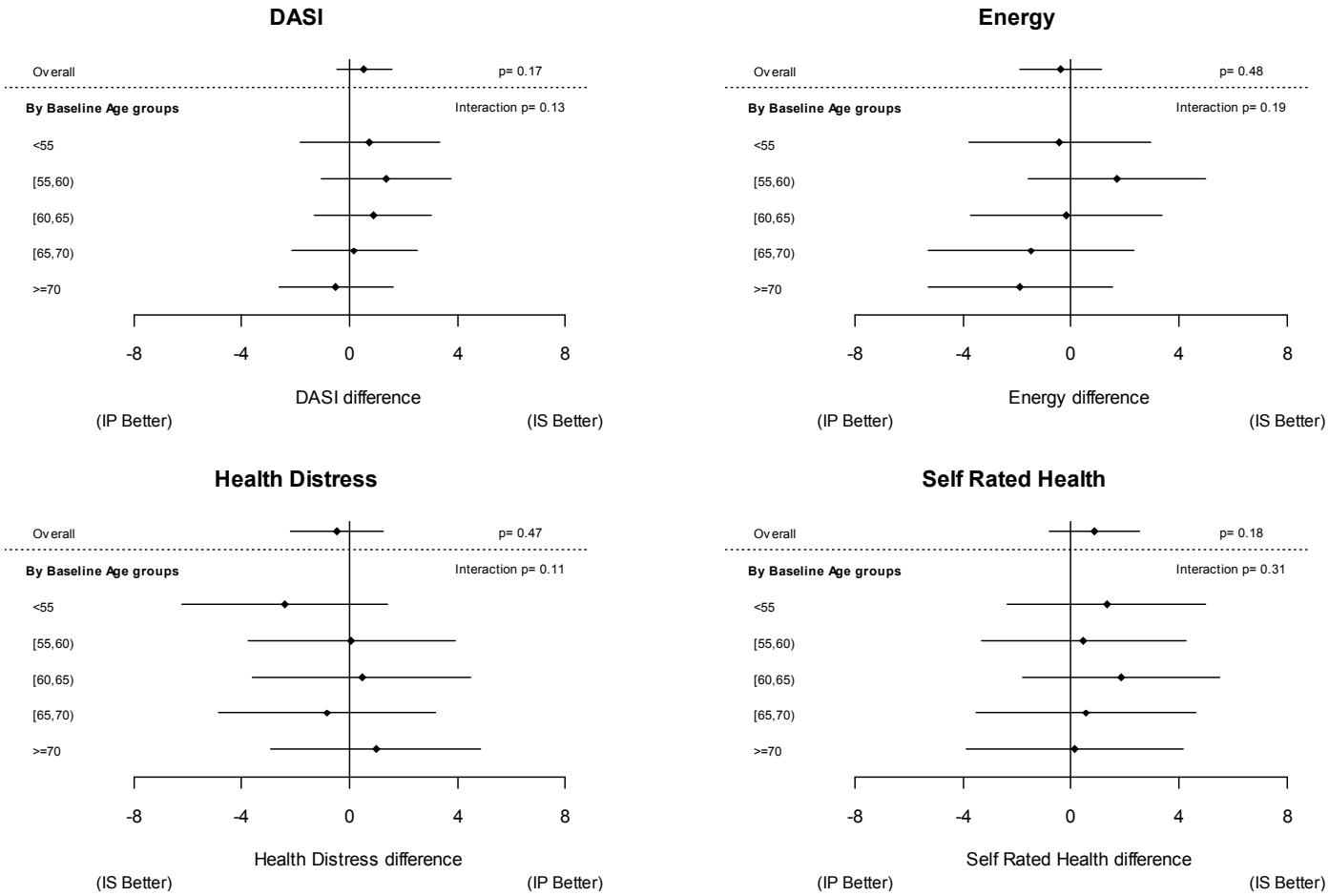
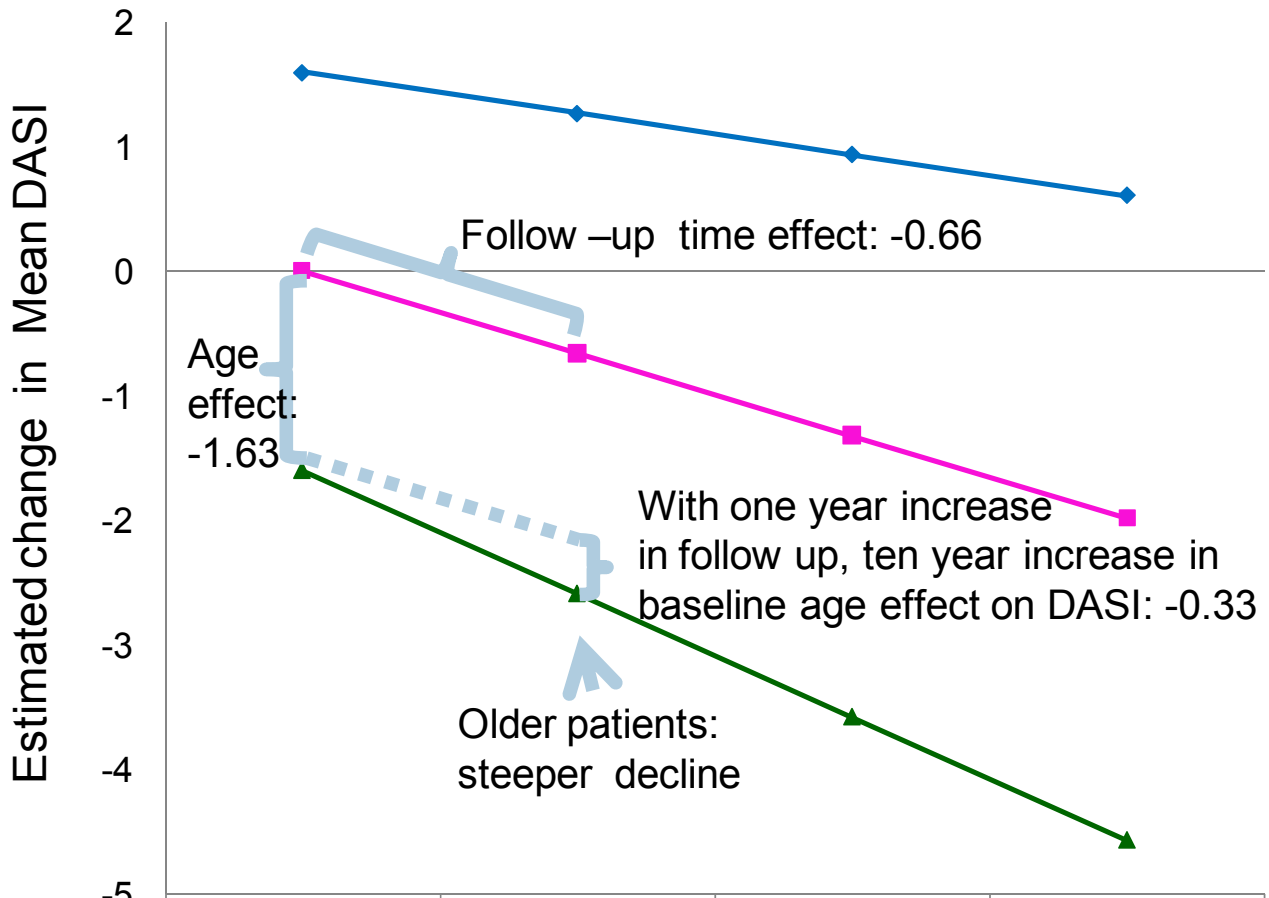


Figure 4: Effect of randomized glycemic treatment on health status, in all 2,163 patients and by 5-year baseline age groups. Interaction p values were for the interaction between centered baseline age and randomized treatment. Overall estimates were based on models controlled for centered baseline age, continuous follow-up time, and interaction between centered baseline age and follow-up time (except for self-rated health), baseline health status, random site effect, missing data pattern.

Table 5: Multivariable regression models for health status outcomes during BARI 2D follow-up.

Baseline variables	**DASI (0-58.2)**		**Energy (0-100)**		**Health Distress (0-100)**		**Self-Rated Health (0-100)**	
	Est	p	Est	p	Est	p	Est	p
1 year increase in baseline age	**-0.16**	**<0.001**	**0.013**	**0.75**	**-0.18**	**<0.001**	**-0.048**	**0.23**
Follow-up	-0.66	<0.001	-0.26	0.061	-0.16	0.34	-0.21	0.19
Interaction (baseline centered age and follow up)	-0.033	0.0015	-0.089	<0.001	0.091	<0.001		
REV versus MED	1.24	0.0012	1.16	0.043	-0.36	0.59	1.72	0.0066
IS versus IP	0.51	0.18	-0.31	0.58	-0.52	0.42	1.01	0.11
CABG stratum	0.61	0.18	1.60	0.018	-2.24	0.0038	3.08	<0.001
Baseline health status measure	0.51	<0.001	0.43	<0.001	0.41	<0.001	0.40	<0.001
Baseline angina status (reference: no angina)		0.66		<0.001		0.11		0.0062
Stable CCS1/CCS2	-0.40	0.36	-2.52	<0.001	1.55	0.037	-2.30	0.0014
CCS3/4 or unstable	-0.30	0.62	-1.40	0.12	1.22	0.23	-1.32	0.18
Insulin use at entry	-2.27	<0.001	-2.95	<0.001	2.84	<0.001	-3.10	<0.001
Male sex	2.58	<0.001	2.63	<0.001	-2.44	0.0017	2.10	0.0051
Body mass index	-0.17	<0.001	-0.17	0.0022	0.17	0.0052	-0.25	<0.001
Current smoking	-2.65	<0.001	-4.87	<0.001	4.84	<0.001	-6.42	<0.001
History of hypertension required treatment	-1.40	0.007	-1.84	0.018	1.94	0.029	-1.01	0.24
History of myocardial infarction	0.085	0.84	-1.38	0.031	0.91	0.22	-1.28	0.071
History of congestive heart failure	-1.71	0.041	-2.40	0.055	3.82	0.0078	-3.30	0.017
History of stroke	-0.87	0.20	-2.27	0.025	0.10	0.93	1.54	0.17
History of non coronary artery disease	-2.50	<0.001	-3.26	<0.001	3.35	<0.001	-3.40	<0.001
Clinical evidence of neuropathy	-1.31	0.0015	-1.37	0.027	1.31	0.065	-1.54	0.024
Missing status (reference: completers)		<0.001		0.0069		<0.001		<0.001
Noncompliance	-2.12	0.048	-2.25	0.16	3.19	0.084	-3.67	0.048
Dropout	-2.32	<0.001	-2.76	0.0032	3.84	<0.001	-4.19	<0.001
Intercept	18.2	<0.001	42.89	<0.001	7.57	0.002	40.87	<0.001

*Model controlled for random site effect.



	Year1	Year2	Year3	Year4
10 yr younger (52.4)	1.6	1.27	0.94	0.61
Mean age (62.4)	0	-0.66	-1.32	-1.98
10 yr older (72.4)	-1.6	-2.59	-3.58	-4.57

Figure 5: Interpretation of multivariate model results for health status outcomes, using DASI as an example.

7.8 SUPPLEMENT MATERIALS

7.8.1 Missing health status outcomes

Compared to participants with at least one follow-up health status measure, the 205 participants who did not have any follow-up health status measure were older, and had higher proportion of being randomized to receive prompt revascularization, higher proportion of heart failure, and more sever angina. Their perceived Energy and self-rated health were lower at baseline. (Table S1) Among the 205 participants, the baseline clinical profile and health status for those who died at first year were similar to those who survived up to at least one year. (Table S1) Although patients not included in the analysis appeared to have more severe cardiovascular conditions and lower perceived health at baseline, missingness might not be due to procedure-related death (indicating by death at first year).

All 2,163 participants in the analysis were alive at first year visit. The proportion of inactivation was much lower in participants in the analysis than those who were not included. (Table S2)For the 205 participants not included in the analysis, the proportions of death and inactivation increased with follow-up years. (Table S3)

Three strategies were used in the analysis to manage missing data, the first was using linear mixed model, and incorporated in the model covariates that were likely to contribute to missingness (for example, baseline angina status). The assumption for missingness in the model was missing at random. The second was to incorporate a categorical variable for missing pattern (completer, non-compliance and dropouts) in the linear mixed model to account for possible missing not at random. As the result, estimates of main covariates of interest, for example, age, would be averaged over missing patterns. The third strategy was to impute all missing health status outcomes for the 2,368 participants. The imputation was generated by multiple imputation method with based on important baseline covariates, baseline health status measures, and follow-up health status measures incorporated in the imputation function. Sensitivity analysis was then performed. The estimates generated from multiple imputed dataset were compared to the original data. Consistent results were showed in the sensitivity analysis. (Table S4 and S5)

Table S1: Missing health status outcomes: baseline characteristics and health related quality of life by patients with or without one follow up quality of life data.

	2,368 BARI 2D participants			205 patients not in the analysis		
	Patients with at least one follow up data	Patients without any follow up data	p	Died during yr1	Not died during yr1	p
	n=2163	n=205		n=69	n=136	
Prompt revascularization (%)	49.0	57.1	0.026	62.3	54.4	0.28
Insulin sensitizing (%)	49.9	50.2	0.93	53.6	48.5	0.49
CABG stratum (%)	32.4	30.2	0.53	39.1	25.7	0.049
Age (Mean)	62.3	63.7	0.039	64.3	63.5	0.59
Male (%)	70.6	67.3	0.32	69.6	66.2	0.63
Current Smoking (%)	12.2	16.0	0.12	9.0	19.5	0.054
BMI (Mean)	31.8	31.4	0.45	31.1	31.5	0.72
Prior MI(%)	31.6	36.7	0.14	42.6	33.6	0.21
Heart Failure (%)	6.2	11.6	0.0036	14.7	9.9	0.32
Angina (%)			0.0021			0.39
None/Angina Equivalent	39.7	35.6		40.6	33.1	
Stable CCS I or II	43.0	37.1		37.7	36.8	
Stable CCS III or IV	17.3	27.2		21.7	30.1	
Duration of Diabetes (Mean)	10.3	11.6	0.089	13.0	10.8	0.15
Insulin Use (%)	27.6	31.3	0.25	35.3	29.3	0.39
DASI (Mean)	19.1	17.3	0.081	15.6	18.2	0.22
Energy (Mean)	51.9	44.9	<0.001	46.4	44.0	0.49
Health Distress (Mean)	40.3	42.4	0.29	38.4	44.8	0.12
Self-Rated Health (Mean)	38.9	35.5	0.050	33.3	36.8	0.32

Table S2: Missing quality of life data due to death or inactivation (n=2163 patients who had at least 1 follow-up health status measure—who lived at least to year 1)

	Year 1 (33 missing)		Year 2 (140 missing)		Year 3 (229 missing)		Year 4 (312 missing)	
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent
Missing not due to death or inactivation	33	100	91	65	110	48.0	136	43.6
Death	0	0	36	25.7	83	36.2	129	41.4
Inactivation	0	0	13	9.3	36	15.7	47	15.1

* At year 4, in the 185 patients died or in the inactivation status (they may be inactivated during year 4 or had been inactivated during previous time), 5 patients (4 deaths and 1 inactivation) had quality of life information, and 4 patients died after close out, their loss of data thus not considered as missing. Therefore, only 176 death or inactivation were with missing year 4 quality of life data.

Table S3: Death and inactivation in year 1 for the 205 patients who did not have at least 1 follow-up health status measure.

	Year 1		Year 2		Year 3		Year 4	
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent
Missing not due to death or inactivation	56	27.3	27	13.2	27	13.2	23	11.2
Death	69	33.7	83	40.5	85	41.5	88	42.9
Inactivation	80	39.0	95	46.3	93	45.4	94	45.9

*During the whole BARI 2D study period, 99 deaths (including 19 deaths after inactivation), 107 inactivation (100 inactivation without reactivation) and 7 reactivations occurred in these 205 patients.

Table S4: Sensitivity analysis—compare estimates in original data (N=2,163) versus multiple imputed data (N=2,368).

	Original		Imputed	
	Est	P	Est	p
DASI				
REV vs. MED	1.32	<0.001	1.12	0.0035
Centered age	-0.14	<0.001	-0.13	<0.001
Time	-0.66	<0.001	-0.5	<0.001
Centered age and time	**-0.033**	**0.0013**	**-0.014**	**0.16**
Energy				
REV vs. MED	1.35	0.022	1.37	0.03
Centered age	0.026	0.5187	0.009	0.84
Time	-0.26	0.062	-0.23	0.12
Centered age and time	-0.089	<0.001	-0.064	<0.001
Health Distress				
REV vs. MED	-0.47	0.49	-0.21	0.76
Centered age	-0.19	<0.001	-0.14	0.0025
Time	-0.16	0.34	-0.069	0.65
Centered age and time	0.092	<0.001	0.085	0.0013
Self rated health				
REV vs. MED	1.76	0.0068	1.44	0.02
Centered age	-0.0017	0.96	-0.0051	0.9
Time	-0.21	0.19	-0.11	0.63

Table S5: Imputed data: multivariable regression models for health status outcomes during BARI 2D follow-up.

Baseline variables	**DASI (0-58.2)**		**Energy (0-100)**		**Health Distress (0-100)**		**Self-Rated Health (0-100)**	
	Est	p	Est	p	Est	p	Est	p
1 year increase in baseline age	**-0.16**	**<0.001**	**-0.0074**	**0.87**	**-0.14**	**0.0083**	**-0.051**	**0.24**
Follow-up	-0.50	<0.001	-0.23	0.12	-0.065	0.67	-0.11	0.65
Interaction (baseline centered age and follow up)	**-0.01**	**0.15**	**-0.064**	**<0.001**	**0.085**	**0.0018**		
REV versus MED	1.05	0.0049	1.20	0.062	-0.12	0.85	1.40	0.021
IS versus IP	-0.51	0.17	0.36	0.52	0.63	0.35	-1.06	0.080
CABG stratum	0.44	0.31	1.47	0.024	-2.09	0.0047	2.79	<0.001
Baseline health status measure	0.5	<0.001	0.44	<0.001	0.39	<0.001	0.39	<0.001
Stable CCS1/CCS2	-0.46	0.27	-2.23	<0.001	1.30	0.11	-1.98	0.0041
CCS3/4 or unstable	-0.30	0.59	-1.23	0.17	1.45	0.15	-1.07	0.34
Insulin use at entry	-2.00	<0.001	-2.65	<0.001	2.66	<0.001	-2.89	<0.001
Male sex	2.45	<0.001	2.48	<0.001	-2.23	0.0045	1.82	0.015
Body mass index	-0.17	<0.001	-0.15	0.0071	0.15	0.021	-0.24	<0.001
Current smoking	-2.37	<0.001	-4.45	<0.001	4.41	<0.001	-5.99	<0.001
History of hypertension required treatment	-1.28	0.012	-1.62	0.043	1.86	0.028	-0.73	0.38
History of myocardial infarction	0.16	0.70	-1.13	0.10	0.70	0.35	-1.03	0.20
History of congestive heart failure	-1.03	0.18	-1.80	0.16	3.01	0.03	-2.32	0.22
History of stroke	-0.66	0.32	-2.06	0.035	0.43	0.72	0.68	0.59
History of non coronary artery disease	-2.18	<0.001	-2.96	<0.001	3.01	<0.001	-2.94	0.0032
Clinical evidence of neuropathy	-1.32	<0.001	-1.21	0.044	1.49	0.034	-1.39	0.049

*Model controlled for random site effect.

8. Paper three: longitudinal relationship between BMI and health status in the Bypass Angioplasty Revascularization Investigation 2 Diabetes Trial.

8.1 ABSTRACT

BACKGROUND: This study investigated the longitudinal association between health status and body mass index (BMI) during 4 years of follow-up.

METHODS: Longitudinal analysis was performed on the data of the Bypass Angioplasty Revascularization Investigation 2 Diabetes trial. Health status outcomes included the Duke Activity Status, Energy/fatigue and health distress scales, and self-rated health. BMI and health status were measured concurrently at each annual follow-up visit. Variation in BMI measures was separated into between-person and within-person change when modeling the longitudinal association between repeated BMI and health status outcomes.

RESUTLS: At baseline and each follow-up year, higher BMI was associated with poorer health status outcomes. In multivariable analysis, higher mean follow-up BMI (between-person BMI) was significantly associated with lower health status outcomes. The within-person BMI change was inversely associated with DASI, Energy and self-rated health outcomes. The relationships between DASI or Energy and within-person BMI change appeared to be curvilinear, and differed by baseline obesity status.

DISCUSSION: The present study reported an inverse association between BMI and health status outcomes in patients with both stable ischemic heart disease and type 2 diabetes. Weight reduction was desirable for obese patients, but may not be necessary for overweight but non-obese patients in order to achieve improved functional capacity and perceived Energy outcomes.

8.2 BACKGROUND

The prevalence of obesity has been largely increasing during the past decades,[88] in 2000, more than half of American adults were estimated to be overweight or obese[89]. Obesity is a known risk factor for type 2 diabetes and coronary artery disease.[90] Cross-sectional studies have showed that being overweight or obese contributes to lower in health-related quality of life.[91] However, little is known about the longitudinal relationship between obesity and health status. In the baseline analysis of BARI 2D, obesity was inversely associated with health status outcomes in patients with diabetes and coronary artery disease, and the relationship was independent of baseline comorbidities and treatment.[92]

Another important aspect in the assessment of longitudinal association between obesity and health status is the within-person variability in weight. Weight fluctuation has been showed to be associate with increasing mortality and cardiovascular morbidity.[93, 94] It is unclear whether within-person weight variability associate with change in health status outcome, and if the relationship differ by obesity status.

In this study, we investigated the longitudinal relationship between obesity and health status outcomes, accounting for the between-person BMI difference, within-person BMI change, and potential interaction with obesity at baseline.

8.3 METHODS

8.3.1 Study Setting

The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) was a 2-by-2 factorial randomized trial that compared treatment strategies for patients with both stable ischemic heart disease and type 2 diabetes. The baseline characteristics and primary findings of BARI 2D had been reported in the literature.[43, 46] Briefly, patients were eligible for BARI 2D if they had type 2 diabetes, documented myocardial ischemia, and angiographically documented coronary heart disease suitable for revascularization. Consented patients were randomized to receive one of the two randomized heart disease treatments—prompt revascularization or medical therapy with a delayed revascularization when necessary, and simultaneously randomized to one of the two glycemic treatments— insulin sensitizing or insulin providing drug to achieve a serum

Hemoglobin A1c level of less than 7.0%. At total of 2368 patients were enrolled between January 2001 and March 2005, and the trial ended on November 30, 2008. The average patient follow-up was 5.3 years.

8.3.2 Variables

Body mass index (BMI) was measured for each BARI 2D participant at study entry and each clinical visit. BMI was calculated as weight (in kilograms) divided by height (in meters). Health status was assessed at baseline and at each annual follow-up visit by four instruments—the Duke Activity Status Index (DASI),[20] RAND Medical Outcome Study Energy/fatigue and health distress scales, and self-rated health. The score ranges from 0-58.2 for DASI, 0-100 for the Energy/fatigue. Self-rated health was measured in a five-category Likert scale and can be scored as a 0-100 continuous score.[46] A higher score indicates better health status. For health distress, a higher score means more distress, therefore lower scores are better.

8.3.3 Statistical Analysis

Data was truncated at year 4, since a number of patients did not have a year 5 clinical visit, since they entered late in the recruitment period. Only patients with at least one follow-up health status measure were included in the analysis. Baseline demographic, clinical, and health status profile were summarized by BMI categories of normal (BMI<25), overweight (25≤BMI<30), class I obesity (30≤BMI<35), and class II/III obesity (BMI≥35). Continuous variables were compared with Student's t-test and categorical variables with chi-square statistics. For exploratory analysis, the population means for health status and BMI were displayed at baseline and each follow-up year. The total variability in repeated health status and BMI measures were analyzed by separating the between-person and within-person variance components. [95] Nonparametric graphic display (Lowess smoothing plots) was used to show the relationship between health status and BMI. To investigate the potential feedback relationship between health status outcomes and BMI, the association between lagged BMI and health status and between lagged health status and BMI were explored.

The longitudinal analysis was performed by multilevel modeling under the structure of a linear mixed model. BMI and health status were measured concurrently at each annual follow-up visit. Year one follow-up was parameterized as the first repeated measure, and baseline health status value was included as a covariate. In modeling the association between BMI and health status, the between-person and the within-person change in repeated measured BMI was calculated. The between-person difference is defined as the difference between the overall mean BMI and the individual patient mean BMI value, averaged over follow-up years for each participant. The within-person change was calculated by subtracting the individual mean value from the BMI measures at each different follow-up year.[96,97,98]The modeling strategy was selected not only for the examination in within-person weight change and health status, but also for its ability to relax the homogeneous variance assumption in the linear mixed effect model.[99]

The model incorporated two random slopes to allow health status to differ by individuals and health status to fluctuate as BMI changes within an individual. The basic multilevel model for the longitudinal association between BMI and health status was listed in the appendix.

The assumption of linear association between BMI and health status outcomes was first graphically examined by Lowess smoothing curves, and then tested by adding a quadratic BMI variable in the model and estimated its significance. To control for potential confounders in the association between BMI and health status outcomes, multivariate models were constructed. Potential confounders at baseline including CABG stratum, sex, smoking, age, angina severity, insulin use, history of hypertension, congestive heart failure, myocardial infarction, stroke, non-coronary artery disease, and clinical neuropathy. A categorical variable for geographic region was also included in the model. Effect modification between within-person BMI change and randomized treatment, intended revascularization methods, follow-up time, sex, race, and baseline obesity were tested in multivariate models. To control for multiple comparisons, the significance level of polynomials and effect modification were set to a two-sided alpha of 0.01.

Missing baseline covariates was managed by mean values imputation, calculated separately by the intended revascularization method. In health status analysis, missing

outcomes were identified if a patient did not provide health status data at annual follow-up visit, with an exception of administrative censoring. Under the missing at random assumption in mixed model, missing outcomes were not imputed. To account for potential missing not at random, a categorical variable for three missing patterns: completers (no missing), noncompliance and dropouts was added as a covariate in the models.[27] To investigate if waist circumference can serve as an obesity measure alternative for the study, the association between health status and waist circumference was explored, and mixed effect models were constructed using either waist circumference alone or a 9-category variable combing BMI and waist circumference percent change from baseline levels (-5%<, [-5%,5%], >5%). To account for the influence of languages and cultures on health status response of participants from different countries, a sensitivity analysis was performed on data from US or Canada participants only. Analyses are performed with SAS statistical software (version 9.1; SAS Institute Inc, Cary, NC).

8.4 RESULTS

2,163 of the 2,368 (93.6%) BARI 2D participants with at least one follow-up health status measure were included in the analysis. At baseline, 1,219 (56.4%) participants were obese. Participants in higher baseline BMI categories were younger, and with higher proportions of female, African American and from sites in the United States. At baseline, obesity was associated with higher proportion of insulin use, history of congestive heart disease or chronic renal dysfunction, but inversely associated with smoking and history of myocardial infarction. The baseline distributions of serum HbA1c, duration of diabetes, and clinical history of neuropathy, angina, stroke or non-coronary artery disease were similar across BMI categories (Table 1).

Health status measures significantly improved from baseline to year one visit, and then gradually decline during follow-up years (Figure 1). The mean BMI at baseline and year one were similar, and increased gradually at later follow-up years (Figure 2). Results from lagged analysis showed one unit increase in preceding BMI was significantly associated with lower subsequent health status (-0.25 for DASI, -0.37 for Energy, 0.41 for health distress and -0.47 for self rated health, p all <0.001), while one

unit decrease in health status was associated with greater subsequent BMI (0.005 unit increase in BMI for one unit decrease in DASI ($p<0.03$), Energy ($p <0.001$), self-rated health ($p <0.001$). 0.003 unit increase in BMI for one unit increase in health distress, $p <0.001$).

The analysis of variance results showed notable within-person variability in health status outcomes (Table 2). Although the within-person variability in BMI was relatively small, as follow-up year increases, more participants had larger BMI percent change from baseline (participants with more than 5 % BMI increase from baseline: 20.5% at year 1, 28.7% at year 2, 32.8% at year 3 and 34.4% at year 4) (Figure 3). The mean BMI during follow-up, as the averaged between-person BMI value, was 32.1 for all participants, 35.7 for participants who were obese at baseline and 27.3 for participants who were non-obese at baseline. The mean within-person BMI change, as the difference in follow-up BMI measure of a participant from his/her follow-up BMI mean, averaged over the 2,163 participants, was -0.27 at year one, 0.04 at year two, 0.11 at year three, and 0.16 at year four.

At baseline and each follow-up year, higher BMI was associated with poorer health status, especially for participants with class II/III obesity at baseline (Table 3). Exploratory smoothing plots showed a nonlinear association between health status and BMI. For example, the highest mean DASI score was observed at a BMI between 26 and 30; for obese participants with BMI greater than 30 kg/m^2, higher BMI was linearly associated with lower DASI. When the variability in repeated BMI measures is separated into between and within person change, the association between DASI and within-person BMI change appeared to be curvilinear, indicating a quadratic fit (Figure 4).

In multivariable analysis, one unit increase in mean follow-up BMI, as one unit change in between-person BMI, was significantly associated with lower health status outcomes (0.28 point lower in DASI, 0.34 point lower in Energy, 0.24 point more distress and 0.36 point lower in self-rated health, p all <0.001). The within-person BMI change, as the difference in a person's follow-up BMI measures from his or her mean follow-up BMI, was inversely associated with DASI, Energy and self-rated health outcomes.

The relationships between DASI or Energy and within-person BMI change appeared to be curvilinear, and differed by baseline obesity status. For participants who were obese at baseline, increase within-person BMI by one unit was associated with worse health status (0.39 point decrease in DASI, and 0.65 point decrease in Energy), while decrease within-person BMI by one unit was associated with better health status (0.27 point increase in DASI and 0.43 point increase in Energy). For participants who were non-obese at baseline, either increase or decrease in within-person BMI was associated with lower DASI and Energy (one unit increase: -0.29 point decrease in DASI and Energy; one unit decrease: -0.61 and -1.11 point decrease in DASI and Energy) (Table 5). The association between follow-up BMI and DASI is illustrated in figure 5.

For self-rated health, a one unit increase in within-person BMI change was associated with 0.39 point decrease in averaged score ($p=0.02$). Within-person change in BMI was not significantly associated with perceptions of health distress in participants.

BMI and waist circumference was highly correlated in the current study data. Results showed that the averaged percent change in BMI had larger effect than waist circumference on health status outcomes. In sensitivity analysis restricted to only participants from the United States and Canada, similar associations between BMI and health status were observed. Although the significance for curvilinear relationship and effect modification decreased in the sensitivity analysis, the magnitudes of coefficients were similar in the two populations.

8.5 DISCUSSION

Longitudinally, higher BMI was associated with lower health status outcomes in patients with both stable coronary heart disease and type 2 diabetes, the association was independent of the effects of demographics and obesity-associated morbidity.

Differences in BMI between patients as well as changes in BMI over time within an individual patient were important determinants for health status. In the study, repeated BMI measures for each participant was separated into mean BMI during follow-up, which was constant over time for an individual, and the within-person BMI change, which represents the fluctuation in BMI over time compared to the individual patient's

mean value. To illustrate the main finding of the study, a non-obese patient with mean follow-up BMI of 27 had 2.8 point higher DASI, 2.4 point higher Energy, 2.4 point less health distress and 3.6 point higher self-rated health compared to an obese patient with mean follow-up BMI of 37. These differences are clinically important since a 3 point difference for DASI, and a 5 point difference for other health status measures are considered clinically meaningful.

BMI is a modifiable risk factor of morbidity, and lifestyle intervention programs often use percent weight change as a primary goal for overweight and obese patients. In current study, One unit reduction from individual mean follow-up BMI was significantly associated with a small increase in self-rated health for all participants, and a small increase in DASI and Energy for patients who were obese at baseline. However, both positive and negative within-person BMI changes were associated with decrease in DASI and Energy for patients who were not obese at baseline.

Obesity was prevalent in our study participants who had heart disease and diabetes. Although BARI 2D patients were counseled about weight loss and exercise, the observed trend of increasing mean BMI over time in the study was not unexpected, since diabetes treatment is known to be associated with weight gain. Moreover, at study entry, the mean age of participants was 62.3 years, and increase in BMI was expected as a result of the natural shift of body composition.[100] The present study suggests that weight reduction is desirable for obese patients. Obesity is a known risk factor for both heart disease and type 2 diabetes. The increasing adipokines secreted by excessive adipose tissue may lead to systemic inflammation and insulin resistance.[101, 102] Inflammatory factors have been showed associated with risk of sarcopenia, bone loss, and anemia,[103,104,105]leading to decline in functional capacity and health status.

It is notable that our results suggest that weight reduction may not be desirable for patients who were overweight but non-obese, since weight gain and weight loss were each associated with worsening DASI and Energy outcomes. One possible explanation is the normal increase in BMI with age. In previous literature, the Epidemiologic Studies of the Elderly reported that disability-free life expectancy was greatest among the overweight individuals with a BMI of 25-30.[106] Previous research also indicated that the body required necessary amount of fat storage to buffer the low caloric intake during

acute illness and wasting in chronic conditions.[107] The current study suggests that a stable BMI for non-obese patients was associated with better functional capacity and perceived energy outcomes.

Due to the shift in body composition and adiposity, waist circumference has been suggested as an effective measure of adnominal obesity.[108] In selecting the most appropriate method to define obesity, the associations between BMI, waist circumferences and health status were investigated. Current study reported change in BMI had larger effect on health status outcomes than waist circumference. Considering waist circumference was more susceptible to measurement error, we select BMI as the main covariate of interest in the present study.

It is also possible that health status may influence BMI measures. The study reported the association between lagged BMI and health status was greater and more significant than the association between lagged health status and BMI. Similar observations were reported in the literature, as the changes of BMI on health trajectories were more influential than the changes of health on BMI trajectory.[97] Thus, the present study used single direction model for the longitudinal association between BMI and health status outcomes.

A complication in the study would occur if participants available in the latter period of the study were likely to report better health status results. However, the association between health status and BMI were similar at each follow-up time, indicating a minor survivor effect. In addition, in multivariate analysis, the model controlled for missing patterns to adjust for possible missing not at random within the structure of mixed model, the estimates of BMI from the model thus were averaged over different missing scenarios.

Compared to previous research, the strength of the present study is to investigate the longitudinal relationship between BMI and health status outcomes, in which the subtlety of weight change dynamics overtime was captured in the analysis. The study is also informative clinically in terms of improving health status with BMI management for patients with both heart disease and type 2 diabetes.

8.6 CONCLUSION

From the results of longitudinal analysis, the present study reports an inverse association between BMI and health status outcomes in patients with both stable coronary heart disease and type 2 diabetes. The association is independent of the effects of demographics and obesity-associated diseases. Weight reduction over time is advantageous for obese patients, but may not be desirable for non-obese patients to improve functional capacity and perceived Energy outcomes.

8.7 TABLES AND FIGURES

Table 1 Baseline characteristics by BMI categories for the 2,163 BARI 2D participants included in the analysis.

Characteristic	Under/normal (N=192)	Overweight (N=743)	Class 1 obesity (N=694)	Class 2/3 obesity (N=525)	p-value
Age at study entry, mean, SD	61.7, 8.3	63.3, 8.8	62.9, 8.6	60.1, 8.9	<0.001
Male, %	71.4	75.4	72.2	61.9	<0.001
Region of World, %					<0.001
USA	44.8	50.2	65.7	78.1	
Canada	14.6	18.6	15.9	12.0	
Mexico	12.0	6.1	1.2	0.8	
Brazil	26.0	21.7	14.0	6.9	
Czech Republic/Austria	2.6	3.5	3.3	2.3	
Race/Ethnicity, %					<0.001
White non Hispanic	52.1	65.3	69.5	68.4	
Black non Hispanic	13.5	14.0	17.3	20.0	
Hispanic	23.4	13.2	11.0	9.5	
Other non Hispanic	10.9	7.5	2.3	2.1	
Current cigarette smoking	17.7	12.7	11.2	10.9	0.071
Number of years smoked, mean, SD	29.0, 13.9	28.1, 14.1	27.4, 13.6	25.4, 14.3	0.017
Insulin use at baseline, %	18.2	22.7	28.5	36.6	<0.001
Duration of DM, mean, SD	10.8, 8.4	10.3, 8.5	10.3, 8.6	10.2, 8.7	0.89
HbA1c %: Core augmented with site estimate, mean, SD	7.8, 1.7	7.6, 1.6	7.6, 1.6	7.7, 1.6	0.29
History of MI, %	37.7	34.4	29.9	27.4	0.012
History of CHF, %	5.2	4.3	5.8	9.6	0.0015
Baseline angina categories					0.16
None/Angina equivalent only	38.7	38.0	43.2	37.9	
Stable CCS1/CCS2	45.5	45.1	41.1	41.7	
Stable CCS3/CCS4/Unstable	15.7	17.0	15.7	20.4	
Clinical MNSI ≥ 2, %	47.9	48.5	51.7	51.6	0.51
Non-coronary artery disease, %	26.0	22.6	23.5	23.6	0.80
Cerebrovascular accident TIA, %	9.9	9.6	9.7	9.2	0.99
Chronic renal dysfunction, %	0.5	2.0	3.2	4.6	0.009

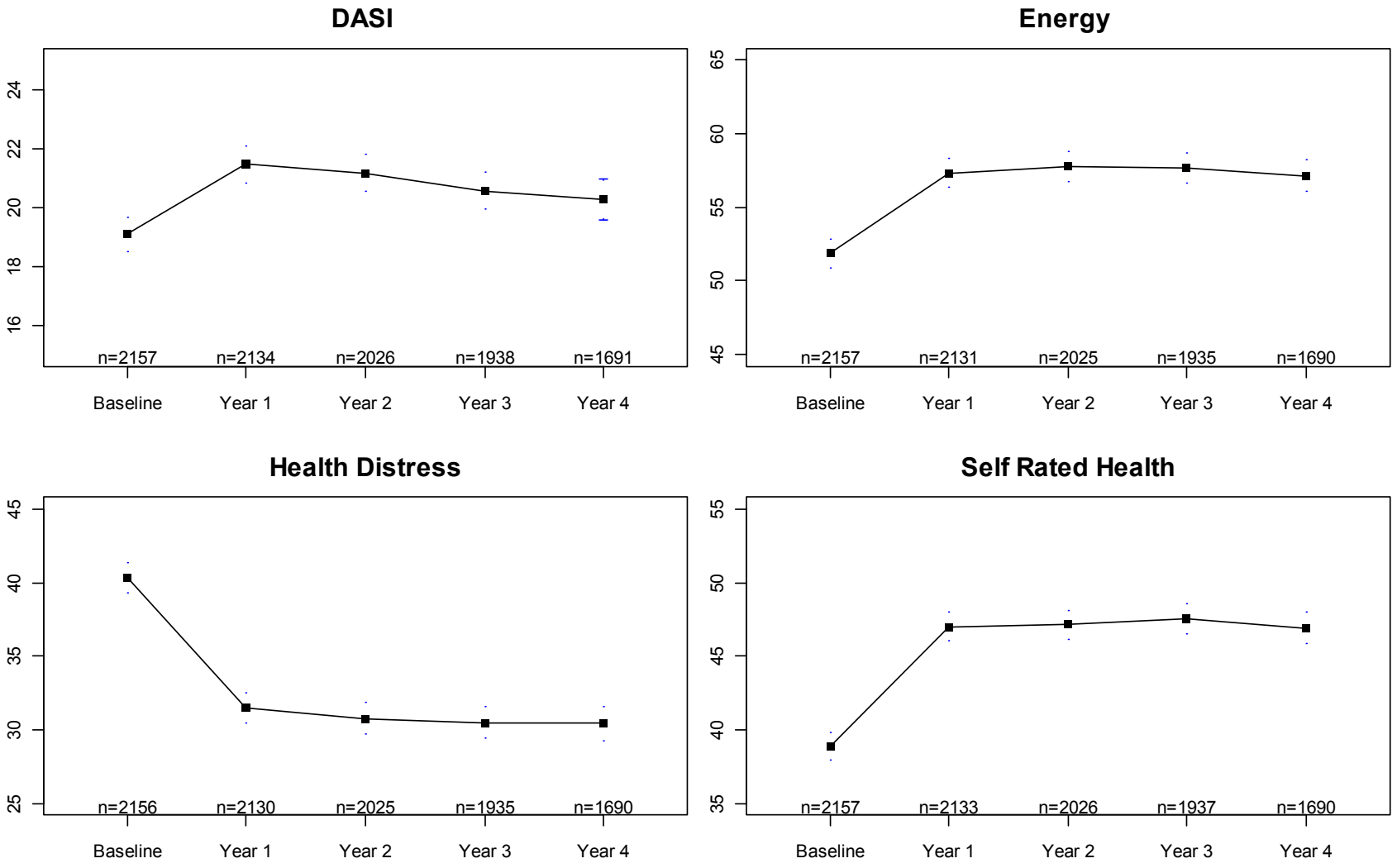


Figure 1: Mean health status by time (2,163 BARI 2D participants included in the analysis).

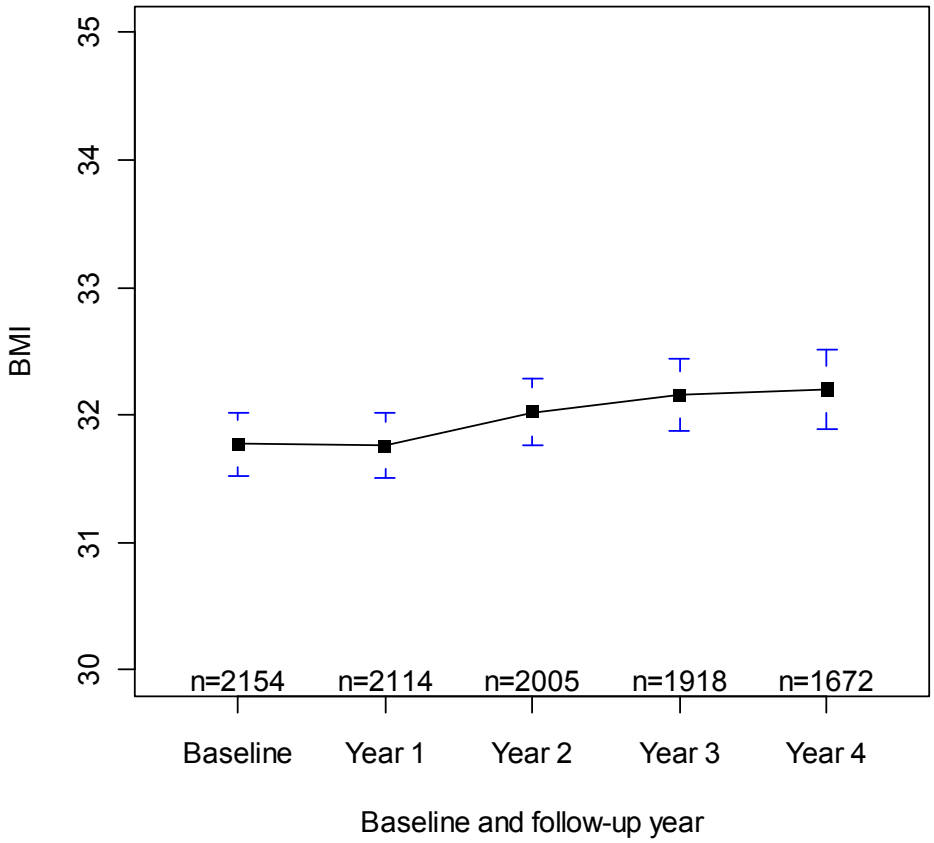


Figure 2: Mean BMI by time (2,163 BARI 2D participants included in the analysis). Bars indicating 95% confidence level of standard error of the mean.

Table 2: Between and within subject variability (Data parameterization, year 1 as the first measurement.)

Variables	Source of variability	Variance estimate
DASI	Between-participant (σ_s^2)	149.19
	Within-participant (σ^2)	59.53
Energy	Between-participant (σ_s^2)	378.90
	Within-participant (σ^2)	147.95
Health Distress	Between-participant (σ_s^2)	376.35
	Within-participant (σ^2)	217.68
Self-rated Health	Between-participant (σ_s^2)	315.84
	Within-participant (σ^2)	201.61
BMI	Between-participant (σ_s^2)	36.6
	Within-participant (σ^2)	1.98

* σ_s^2: variance due to the difference in individual mean value (averaged over repeated measures) from population mean value.
σ^2 : residual variance due to difference in individual repeated measures from individual mean.

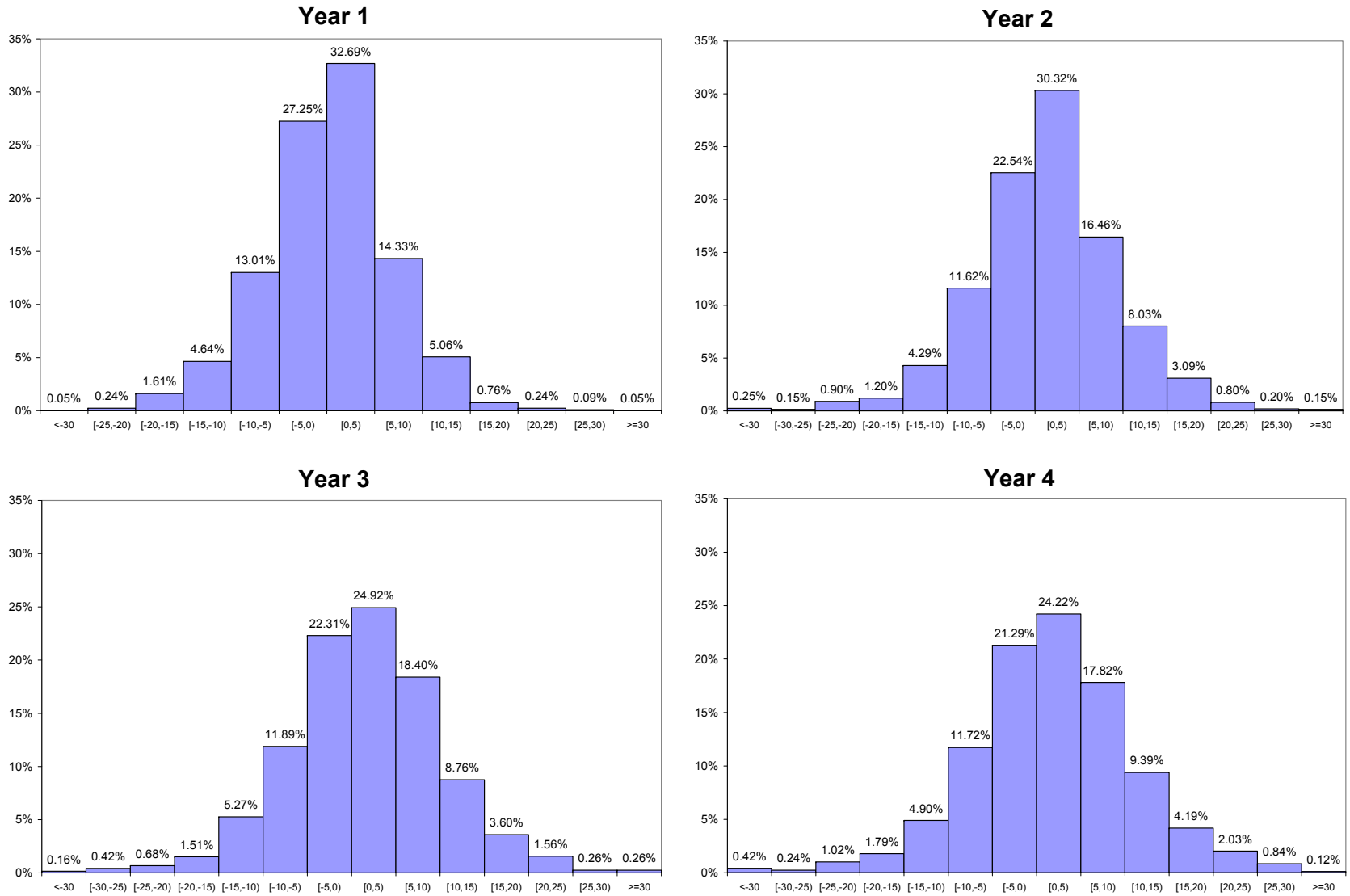


Figure 3: Distribution of percent change in BMI from baseline by follow-up time. Year 1: N=2114, year 2: N=2005, year 3: N=1918, year 4: N=1672.

Table 3: Mean health status by baseline BMI categories and time.

Health status	Under/normal (N=192)	Overweight (N=743)	Class 1 obesity (N=694)	Class 2/3 obesity (N=525)	P[1]
DASI (0-58.2)					
Baseline	20.35	20.82	19.27	16.01	<0.001
Year 1	23.29	23.50	21.52	17.87	<0.001
Year 2	23.76	23.32	20.84	17.55	<0.001
Year 3	23.20	22.46	20.67	16.71	<0.001
Year 4	22.93	22.99	20.13	15.50	<0.001
Energy (0-100)					
Baseline	57.92	56.60	50.92	44.40	<0.001
Year 1	60.66	61.79	56.76	50.61	<0.001
Year 2	62.13	62.44	56.71	50.76	<0.001
Year 3	62.71	62.33	57.96	48.72	<0.001
Year 4	61.93	62.22	56.20	49.23	<0.001
Health distress (0-100)					
Baseline	38.74	36.92	39.70	46.47	<0.001
Year 1	28.98	27.53	31.63	37.93	<0.001
Year 2	27.89	27.17	30.35	37.58	<0.001
Year 3	27.28	27.32	28.90	38.34	<0.001
Year 4	26.23	26.61	30.42	37.46	<0.001
Self-rated health (0-100)					
Baseline	36.85	42.12	39.67	34.12	<0.001
Year 1	45.92	50.34	47.30	42.26	<0.001
Year 2	47.13	50.81	47.32	41.60	<0.001
Year 3	51.76	50.77	48.03	40.52	<0.001
Year 4	50.16	50.95	47.16	39.49	<0.001

[1] p value of one-way ANOVA test at each time.

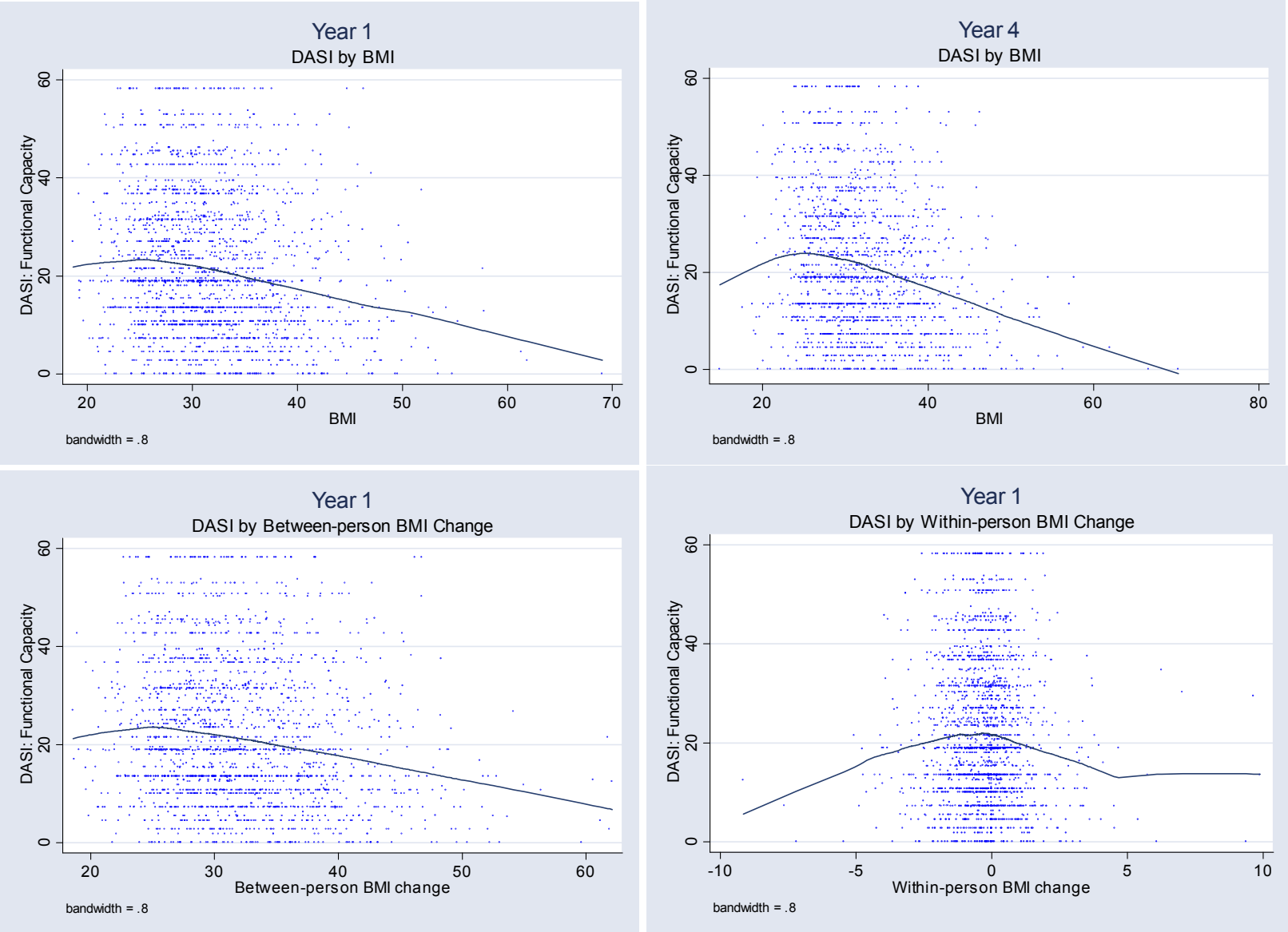


Figure 4: Lowess smoothing plots for DASI by BMI at year 1 and 4; DASI by between-person and within-person BMI change at year 1.

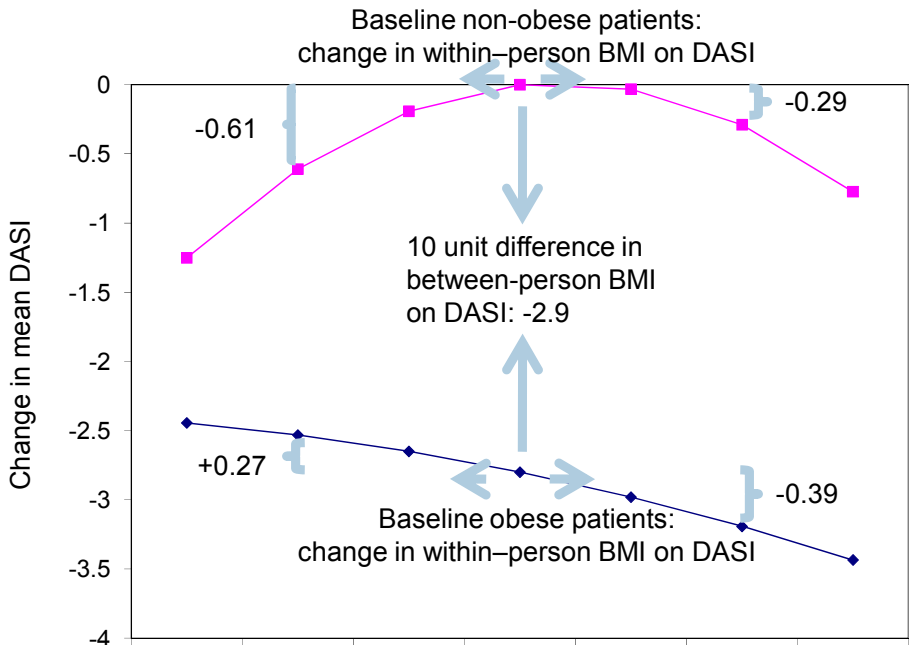
Table 5: summary results of multivariate model (N=2,163).

Effect	DASI		Energy		Health distress		Self-rated health	
	Estimate	p	Estimate	p	Estimate	p	Estimate	p
One unit increase in mean follow-up BMI (Between-person BMI difference, β_{BS}BMI)	-0.28	<0.001	-0.34	<0.001	0.24	<0.001	-0.36	<0.001
Within a person, one unit difference in each follow-up BMI measure from mean follow-up BMI (Within-person BMI difference, β_{WS}BMI)					-0.023	0.89	-0.39	0.020
β_{WS}BMI for baseline obese patients	-0.33	<0.001	-0.54	<0.001				
Quadratic β_{WS}BMI for baseline obese patients	-0.062	0.023	-0.11	0.01				
β_{WS}BMI for baseline non-obese patients	0.16	0.37	0.41	0.13				
Quadratic β_{WS}BMI for baseline non-obese patients	-0.45	<0.001	-0.7	<0.001				
IS versus IP	0.49	0.21	-0.39	0.5	-0.49	0.47	0.80	0.21
REV versus MED	1.3	<0.001	1.34	0.022	-0.52	0.43	1.79	0.0055
CABG stratum	0.45	0.31	1.6	0.018	-1.94	0.011	3.13	<0.001
Follow-up year (continuous)	-0.61	<0.001	-0.19	0.17	-0.22	0.20	-0.10	0.53
Baseline health status measure	0.52	<0.001	0.43	<0.001	0.40	<0.001	0.39	<0.001
Baseline obesity (BMI ≥ 30)	0.45	0.42	0.95	0.25				
Age at baseline	-0.23	<0.001	-0.11	0.0032	-0.065	0.14	-0.076	0.066
Male	1.94	<0.001	1.7	0.013	-1.81	0.02	1.49	0.048
Race/ethnicity (ref: white)		<0.001		<0.001		<0.001		<0.001
Black	0.39	0.5	3.77	<0.001	-1.68	0.087	0.44	0.64
Hispanic	-2.85	<0.001	-0.3	0.78	6.51	<0.001	-4.38	<0.001
Other	-2.46	0.0087	-1.55	0.27	1.61	0.31	-3.67	0.018
Angina categories (ref: None/angina equivalent only)		0.095		<0.001		0.0058		<0.001
Stable CCS1/CCS2	-0.91	0.038	-3.31	<0.001	2.35	0.0017	-2.90	<0.001
Stable CCS3/CCS4/Unstable	-0.86	0.14	-2.45	0.0058	1.9	0.058	-1.87	0.056
Baseline insulin use	-2.25	<0.001	-2.97	<0.001	2.87	<0.001	-3.23	<0.001
Current Smoking	-3.29	<0.001	-5.94	<0.001	5.69	<0.001	-7.20	<0.001
History of hypertension required treatment	-1.35	0.0099	-2.06	0.0089	2.01	0.025	-0.93	0.29
History of myocardial infarction	-0.13	0.77	-1.57	0.016	1.18	0.11	-1.49	0.038
History of congestive heart failure	-1.16	0.17	-1.29	0.31	2.88	0.046	-2.95	0.035
History of stroke	-0.95	0.16	-2.25	0.029	0.15	0.90	1.28	0.26

Table 5 continue.

History of non coronary artery disease	-2.3	<0.001	-2.72	<0.001	2.94	<0.001	-2.99	<0.001
History of chronic renal dysfunction	-1.44	0.23	-2.35	0.19	2.90	0.16	-2.03	0.31
Clinical evidence of neuropathy	-1.18	0.0034	-1.26	0.038	1.27	0.067	-1.38	0.039
Country		<0.001		<0.001		<0.001		<0.001
Brazil	0.99	0.13	16.8	<0.001	-12.47	<0.001	10.86	<0.001
Canada	1.5	0.011	3.06	<0.001	-0.31	0.76	2.13	0.031
Czech Republic/Austria	5.84	<0.001	0.28	0.87	3.26	0.10	3.32	0.086
Mexico	9.44	<0.001	6.02	0.0013	-14.95	<0.001	-3.41	0.096
Missing status (reference: completers)		<0.001		0.0029		<0.001		<0.001
Noncompliance	-1.89	0.081	-2.63	0.1	2.76	0.14	-4.29	0.022
Dropout	-2.38	<0.001	-2.96	0.0017	3.97	<0.001	-3.98	<0.001
Intercept	36.21	<0.001	54.16	<0.001	8.78	0.035	50.04	<0.001

*P value for quadratic within-person BMI change: :0.0013 for DASI and <0.001 for Energy. P value for interaction between baseline obesity and within-person BMI change: 0.0019 for DASI and <0.001 for Energy



	-1.5	-1	-0.5	0	0.5	1	1.5
Mean fup BMI: 35	-2.4445	-2.532	-2.6505	-2.8	-2.9805	-3.192	-3.4345
Mean fup BMI: 25	-1.2525	-0.61	-0.1925	0	-0.0325	-0.29	-0.7725

Figure 5: Interpretation of averaged association of follow-up BMI and DASI. Assume mean follow-up BMI is 35 for participant who were obese at baseline, and 25 for participants who were non-obese at baseline. Estimation formula: [Obese at baseline] mean DASI=-0.28*(mean BMI during follow-up-25)-0.33*(within-person BMI change)-0.062*(within-person BMI change)^2 [Non-obese at baseline] mean DASI=-0.28*(mean BMI during follow-up-25)+0.16*(within-person BMI change)-0.45*(within-person BMI change)^2*

8.8 FORMULA

Using DASI as an example, the basic multilevel model for the longitudinal association between BMI and health status outcome can be described as below.

<u>At the individual level (within individual):</u>

$DASI_{ij} = b_{0i}+b_{1i}BMI_{ij}+b_{2i}year_j+b_{3i}baseline\ DASI_i+e_{ij}$

$BMI_{ij} = BMI_{ij} + BMI_i - BMI_i = BMI_i + (BMI_{ij} - BMI_i)$

$DASI_{ij} = (b_{0i} + b_{BS}BMI_i)+b_{WS}(BMI_{ij} - BMI_i)+b_{2i}year_j+b_{3i}baseline\ DASI_i+e_{ij}$

$DASI_{ij}$: DASI for participant i at year j:
b_{0i}= year 1 DASI for participant i with both 0 in baseline and follow-up BMI.
b_{1i}= DASI difference for unit change in follow-up BMI for participant i.
b_{2i}= yearly DASI difference for participant i.
b_{3i}= DASI difference due to one unit increase in baseline value.

b_{BS}= DASI difference for unit change in mean follow-up BMI for participant i.
b_{WS}= DASI difference for unit change in follow-up BMI variability for participant i.

<u>At population level (between individual):</u>

$b_{0'} = \beta_0+\beta_{BS}BMI+v_{0i}$
$b_{1'} = \beta_{WS}BMI+v_{1i}$
$b_2 = \beta_2+v_{2i}$
$b_3 = \beta_3$

v_{0i} = individual deviation from average intercept.
v_{1i} = individual deviation from average slope of yearly DASI change.
v_{2i} = individual deviation from average slope of DASI change associated with one unit difference in within person BMI variability.

In the multilevel model, the averaged effect of follow-up BMI is $\beta_{BS}BMI_i + \beta_{WS}BMI(BMI_{ij} - BMI_i)$.

8.9 SUPPLEMENT FIGURES/TABLES

Table S1: Pearson correlation coefficients and partial correlation coefficients for BMI, waist circumference and health status measures at baseline and each follow-up visit.

	BMI	**Waist circumference**	**DASI (0-58.2)**	**Energy (0-100)**	**Health Distress (0-100)**	**Self-Rated Health (0-100)**
BMI						
Baseline	1	0.82	-0.16	-0.24	0.15	-0.11
Yr1	1	0.81	-0.18	-0.27	0.23	-0.18
Yr2	1	0.83	-0.20	-0.26	0.22	-0.18
Yr3	1	0.84	-0.18	-0.29	0.23	-0.22
Yr4	1	0.83	-0.20	-0.25	0.18	-0.22
Waist circumference						
Baseline	0.82	1	-0.12	-0.24	0.12	-0.09
Yr1	0.81	1	-0.17	-0.27	0.22	-0.16
Yr2	0.83	1	-0.18	-0.26	0.21	-0.17
Yr3	0.84	1	-0.18	-0.3	0.22	-0.23
Yr4	0.83	1	-0.21	-0.26	0.19	-0.23
BMI: Pearson Partial Correlation Coefficients						
Baseline	1		-0.12	-0.064	0.099	-0.064
Yr1	1		-0.072	-0.083	0.099	-0.083
Yr2	1		-0.096	-0.071	0.086	-0.073
Yr3	1		-0.058	-0.076	0.072	-0.070
Yr4	1		-0.056	-0.053	0.072	-0.079
Waist circumference: Pearson Partial Correlation Coefficients						
Baseline		1	0.029	-0.089	-0.009	0.003
Yr1		1	-0.046	-0.10	0.055	-0.032
Yr2		1	-0.024	-0.098	0.050	-0.039
Yr3		1	-0.050	-0.107	0.064	-0.066
Yr4		1	-0.073	-0.109	0.048	-0.065

Table S2: Health status outcomes by BMI changes, controlled for confounders (N=1,673 participants from US or Canada).

Effect	DASI		Energy		health distress		Self-rated health	
	Estimate	p	Estimate	p	Estimate	p	Estimate	p
One unit increase in mean follow-up BMI (Between-person BMI difference, **β_{BS}BMI**)	-0.26	<0.001	-0.34	<0.001	0.24	<0.001	-0.37	<0.001
Within a person, one unit difference in each follow-up BMI measure from mean follow-up BMI (Within-person BMI difference, **β_{WS}BMI**)					0.12	0.54	-0.41	0.018
β_{WS}BMI for baseline obese patients	-0.29	0.0053	-0.60	<0.001				
Quadratic β_{WS}BMI for baseline obese patients	-0.053	0.060	-0.092	0.037				
β_{WS}BMI for baseline non-obese patients	0.072	0.75	0.34	0.32				
Quadratic β_{WS}BMI for baseline non-obese patients	-0.33	0.012	-0.54	0.009				
IS versus IP	0.81	0.075	-0.47	0.48	-0.71	0.37	1.51	0.044
REV versus MED	1.00	0.028	1.11	0.095	-0.49	0.54	1.62	0.031
CABG stratum	0.46	0.40	2.28	0.0043	-2.62	0.0061	3.28	<0.001
Follow-up year (continuous)	-0.97	<0.001	-0.44	0.0052	0.042	0.83	-0.039	0.83
Baseline health status measure	0.55	<0.001	0.47	<0.001	0.42	<0.001	0.42	<0.001
Baseline obesity (BMI ≥ 30)	0.39	0.54	1.66	0.082				
Age at baseline	-0.19	<0.001	-0.078	0.067	-0.096	0.063	-0.04	0.41
Male	1.40	0.010	0.99	0.21	-0.61	0.52	1.58	0.077
Race/ethnicity (ref: white)		<0.001		<0.001		<0.001		0.0022
Black	0.55	0.39	4.31	<0.001	-1.47	0.19	-0.49	0.64
Hispanic	-2.51	0.001	0.080	0.94	6.35	<0.001	-4.2	<0.001
Other	-2.66	0.0091	-1.12	0.45	1.39	0.43	-3.51	0.036
Angina categories (ref: None/angina equivalent only)		0.080		<0.001		0.0081		0.0031
Stable CCS1/CCS2	-1.10	0.030	-4.10	<0.001	2.64	0.0027	-2.81	<0.001
Stable CCS3/CCS4/Unstable	-0.97	0.15	-2.23	0.026	2.24	0.06	-1.98	0.079
Baseline insulin use	-2.19	<0.001	-2.59	<0.001	2.81	0.002	-2.84	0.001
Current Smoking	-3.25	<0.001	-5.78	<0.001	5.68	<0.001	-7.4	<0.001
History of hypertension required treatment	-1.48	0.015	-2.05	0.022	1.81	0.087	-1.99	0.048
History of myocardial infarction	-0.43	0.40	-1.89	0.013	1.51	0.094	-1.43	0.093
History of congestive heart failure	-0.85	0.34	-1.04	0.42	2.76	0.076	-2.66	0.07
History of stroke	-1.12	0.14	-2.34	0.035	0.62	0.64	0.99	0.43

Table S2 continue.

History of non coronary artery disease	-2.07	<0.001	-2.83	<0.001	3.47	0.0003	-3.18	<0.001
History of chronic renal dysfunction	-1.27	0.32	-2.38	0.21	2.06	0.36	-1.24	0.56
Clinical evidence of neuropathy	-1.26	0.0072	-1.63	0.018	1.54	0.061	-1.74	0.026
Canada	1.72	0.0052	3.16	<0.001	-0.21	0.85	1.77	0.082
Missing status (reference: completers)		<0.001		0.0044		<0.001		<0.001
Noncompliance	-2.25	0.058	-2.68	0.12	3.36	0.11	-3.96	0.054
Dropout	-2.60	<0.001	-3.12	0.0024	4.77	<0.001	-3.92	<0.001
Intercept	33.43	<0.001	51.01	<0.001	8.83	0.072	47.37	<0.001

*P value for quadratic within-person BMI change: 0.021 for DASI and 0.013 for Energy. P value for interaction between baseline obesity and within-person BMI change: 0.10 for DASI and 0.009 for Energy.

8.9.1 Confounding due to adverse clinical event during follow-up

For all patients who experienced myocardial infarction, stroke or subsequent procedure during follow-up years, a greater proportion of participants lost weight after the event. (Table S3) Cardiovascular events appeared to be associated with reduction in BMI, especially at later follow-up years. (Table S4) Cardiovascular events also appeared to be associated with reduction in health status change from baseline, especially for functional capacity (DASI). (Table S4) Therefore, occurrence of myocardial infarction or stroke, and having subsequent procedure within a year prior to annual follow-up visit were confounders in the association between BMI and health status outcomes.

In the multivariate analysis with additional adjustment of cardiovascular event occurred within a year prior to annual visit, the quadratic association and effect modification between DASI or Energy and within-person BMI change remained similar and significant, indicating the association was independent of confounding factors. (Table S5)

Table S3: BMI change from Individual mean after clinical event occurred by baseline obese status.

Event (Person-events)	BMI change from Individual mean	Non-obese	Obese	p
MI	N=	86	110	0.74
	Decrease,%	58.1	57.3	
	No change,%	3.5	1.8	
	Increase,%	38.4	40.9	
Stroke	N=	23.0	23.0	0.95
	Decrease,%	65.2	60.9	
	No change,%	4.4	4.3	
	Increase,%	30.4	34.8	
Subsequent procedure	N=	291	503	0.66
	Decrease,%	59.8	57.6	
	No change,%	4.1	3.4	
	Increase,%	36.1	39.0	
Cancer	N=	19	25	0.32
	Decrease,%	36.8	52.0	
	Increase,%	63.2	48.0	
Chronic renal dysfunction	N=	50	113	0.62
	Decrease,%	36.0	44.2	
	No change,%	2.0	1.8	
	Increase,%	62.0	54.0	

Event (Persons)	BMI change from Individual mean	Non-obese	Obese	p
MI	N=	79	94	0.98
	Decrease,%	59.5	59.6	
	No change,%	2.5	2.1	
	Increase,%	38.0	38.3	
Stroke	N=	20	21	0.84
	Decrease,%	70.0	61.9	
	No change,%	5.0	4.8	
	Increase,%	25.0	33.3	
Subsequent procedure	N=	224	363	0.84
	Decrease,%	60.3	57.8	
	No change,%	3.6	3.6	
	Increase,%	36.1	38.6	
Cancer	N=	19	25	0.32
	Decrease,%	36.8	52.0	
	Increase,%	63.2	48.0	
Chronic renal dysfunction	N=	50	113	0.62
	Decrease,%	36.0	44.2	
	No change,%	2.0	1.8	
	Increase,%	62.0	54.0	

*Few patients had more than one event; therefore, the denominator in the upper table was person-events, and persons for the lower table.

Table S4: Health status change after clinical event occurred.

Health status	Follow-up years	MI/stroke occurred in prior year			Subsequent procedure occurred in prior year		
		No	Yes	P	No	Yes	p
BMI change from Individual mean	Year 1	-0.28	-0.052	0.22	-0.25	-0.39	0.14
	Year 2	0.05	-0.26	0.14	0.058	-0.12	0.068
	Year 3	0.13	-0.57	0.006	0.13	-0.11	0.072
	Year 4	0.16	-0.14	0.31	0.17	-0.075	0.095
BMI change from Individual mean for obese patients at baseline	Year 1	-0.29	0.13	0.16	-0.27	-0.33	0.67
	Year 2	0.025	-0.35	0.27	0.035	-0.16	0.19
	Year 3	0.13	-0.79	0.0034	0.14	-0.17	0.077
	Year 4	0.20	-0.14	0.45	0.20	0.018	0.40
BMI change from Individual mean for non-obese patients at baseline	Year 1	-0.26	-0.30	0.79	-0.23	-0.50	0.0077
	Year 2	0.082	-0.15	0.33	0.087	-0.067	0.10
	Year 3	0.12	-0.38	0.13	0.11	0.037	0.57
	Year 4	0.11	-0.14	0.46	0.13	-0.23	0.03
DASI change from baseline	Year 1	2.45	0.35	0.10	2.57	1.00	0.045
	Year 2	2.15	-6.45	<0.001	2.37	-2.73	<0.001
	Year 3	1.39	-6.47	<0.001	1.6	-4.86	<0.001
	Year 4	0.52	-2.16	0.36	0.65	-2.36	0.036
Energy change from baseline	Year 1	5.36	3.89	0.48	5.25	5.59	0.79
	Year 2	5.54	4.58	0.75	5.73	3.13	0.11
	Year 3	5.62	-1.53	0.096	5.80	0.28	0.0058
	Year 4	4.79	3.41	0.82	4.94	1.80	0.23
Health Distress change from baseline	Year 1	-8.73	-8.62	0.97	-9.18	-5.80	0.035
	Year 2	-9.33	-4.69	0.19	-9.67	-4.31	0.0058
	Year 3	-9.58	-4.86	0.38	-9.84	-3.67	0.01
	Year 4	-9.88	-0.57	0.099	-10.09	-4.12	0.032
Self-rated health change from baseline	Year 1	8.15	7.37	0.74	8.44	6.03	0.098
	Year 2	8.06	4.69	0.32	8.20	5.59	0.16
	Year 3	8.79	0.00	0.026	8.78	6.02	0.24
	Year 4	7.72	9.09	0.79	7.96	3.99	0.12

Table S5: summary results of multivariate model (N=2,163).

Effect	DASI		Energy		health distress		Self-rated health	
	Estimate	P	Estimate	p	Estimate	P	Estimate	p
One unit increase in mean follow-up BMI (Between-person BMI difference, β_{BS}BMI)	-0.27	<0.001	-0.32	<0.001	0.24	<0.001	-0.34	<0.001
Within a person, one unit difference in each follow-up BMI measure from mean follow-up BMI (Within-person BMI difference, β_{WS}BMI)					0.017	0.92	-0.39	0.017
β_{WS}BMI for baseline obese patients	-0.36	<0.001	-0.55	<0.001				
Quadratic β_{WS}BMI for baseline obese patients	-0.055	0.044	-0.10	0.02				
β_{WS}BMI for baseline non-obese patients	0.11	0.51	0.39	0.16				
Quadratic β_{WS}BMI for baseline non-obese patients	-0.44	<0.001	-0.69	<0.001				
MI/stroke occurred in prior yr	-2.36	<0.001	-1.64	0.12	2.52	0.046	-2.11	0.083
Subsequent procedure occurred in prior yr	-1.42	<0.001	-0.88	0.15	2.05	0.0046	-0.19	0.78

*P value for quadratic within-person BMI change: 0.0013 for DASI and 0.0013 for Energy. P value for interaction between baseline obesity and within-person BMI change: 0.0031 for DASI and <0.001 for Energy. P value for interaction between MI/stroke occurred in prior yr and within-person BMI change: 0.0071 for DASI

*Model control for randomized treatment, stratum, time, baseline HRQoL, sex, race, smoking, age, geographic region, angina, insulin use, history of hypertension, MI, CHF, stroke, non-coronary artery disease, renal dysfunction, clinical neuropathy, and missing data pattern.

9. Conclusion

The three HRQoL research topics in this dissertation represent the two end of epidemiology study spectrum—from pilot observational study to randomized clinical trial. As a Ph.D student, I am fortunate to have both opportunities. In conducting the observational cohort study, I had the opportunity to manage an entire study—from Institutional Review Board approval to accounting, from writing the study proposal to data collection, data analysis and drafting manuscript for publication. In working with BARI 2D, one of the most rigorously designed and conducted large scale randomized clinical trials, I had the opportunity to apply advanced statistical methods for longitudinal health status analysis, and gain the important knowledge of the different aspects in a randomized clinical trial, such as organization, implementation, and collaboration.

Meditation is often used as a supportive therapy to relief stress and discomfort caused by regular medical therapy. Thus, in the first paper, using HRQoL measures as the treatment outcome is clinically relevant. HRQoL measures are commonly continuous in scale and inexpensive to implement which makes them appealing as outcomes for small studies. Despite the limitations of pilot studies, results from paper one are informative and supportive of the beneficial effect of Sahaja Yoga Meditation on HRQoL.

HRQoL research in a large scale randomized clinical trial has a different but as important role. Class III or IV randomized clinical trials for treatment effectiveness generally compare an effective novel treatment to a well-established clinical practice, or compare two established treatment strategies, as in BARI 2D. The goal of the trial is to detect small but significant differences between two treatment alternatives, and it is not uncommon for two treatments to demonstrate equal effect on primary clinical outcomes—indicating the two treatments are as good. Under such circumstances, HRQoL and economic comparisons become important, and the treatment which leads to a better quality of life or which is more affordable will be preferred. In the randomized clinical trial for treatment efficacy, important clinical variables are measured and monitored repeatedly over time in a large study population, which makes it possible to test hypotheses other than the main treatment comparison. In BARI 2D, we are able to test whether the comparative effect of the randomized treatments on clinical and

HRQoL outcomes depend on age. We are also able to investigate the longitudinal association between change in BMI and HRQoL for patients receiving standard treatment regimens.

Selection bias remains the main threat of validity in observational study. In the meditation research, since the participants selected their own treatment, we cannot fully distinguish the extent of difference in HRQoL that is contributable to meditation therapy and the extent contributable to unobserved characters of the participants. Such concern is minimized in randomized trial, since treatment is allocated randomly, and the effect of unobserved confounders is theoretically balanced out. However, different kinds of selection bias exist in randomized trials. The potential sources of selection bias derive from the eligibility criteria and missing values. Patients with either very low or very high levels in risk factors but meet the eligibility criteria may have different physiological or pathological response. This should be kept in mind while interpreting study results to groups of patients with extreme values. For example, participants who were underweight but had both heart disease and type 2 diabetes to be eligible for BARI 2D may have a different disease mechanism that influences their HRQoL response. Thus, the association between BMI and HRQoL observed in the study may not fully apply to underweight or extremely obese individuals. Missing data is a common concern for all HRQoL studies, in the dissertation, missing data is small in the meditation study due to the manageable sample size and brief follow-up time. In large scale randomized trial with long-term follow-up, missing data is inevitable. However, if the missingess is small and the mechanism of missing is well understood, the effect of missing data can be effectively managed by current analytical methods.

To address the limitations of the meditation study, I incorporated a proposal for a randomized clinical trial to better evaluate the health benefit of Sahaja Yoga Meditation as a final chapter in this dissertation.

10. Study proposal: A randomized trial investigate Sahaja Yoga Meditation and reduced sodium DASH diet for prehypertension control

10.1 SPECIFIC AIMS

Hypertension remains a leading cause of mortality and morbidity. High blood pressure was the primary or contributing cause of death in United States.[64,65] Prehypertensive individuals are at an increased risk of developing clinical hypertension, and interventions for blood pressure control in this high risk group are of clinical and public health importance.

Previous research has shown the positive effect of Sahaja Yoga Meditation in treatment of essential hypertension. The proposed study aims to evaluate the effect of Sahaja Yoga Meditation on lowering blood pressure in prehypertensive individuals. The study also investigates potential synergic effect of Sahaja Yoga Meditation and reduced sodium DASH diet on blood pressure control.

The proposed study uses a randomized trial design with the primary outcome being change in systolic blood pressure during eight-week follow up. Secondary outcomes include change in diastolic blood pressure and health related quality of life.

10.2 BACKGROUND AND SIGNIFICANCE

10.2.1 Hypertension Disease Burden

In 2000, worldwide prevalence of hypertension was 26.4%, translating into about 972 million adults live with hypertension. It is estimated that by year 2025, about one in every three adults in the world will have hypertension, a disease burden of 1.56 billion people.[63] In the 1999-2002 NHANES survey, hypertension prevalence was 31.3% in the United States, with an estimated adult hypertensive population of 65 million.[64,65] The overall death rate from high blood pressure was 18.1 per 100,000 in United States during 2003, and high blood pressure was the contributing cause of 11.31% deaths.[65] In 2006, the estimated direct and indirect cost of high blood pressure was 63.5 billion dollars.[64] The mean total costs were $ 146,500 among mildly hypertensive and $ 219,300 among severely hypertensive men.[109]

Hypertension serves as a major risk factor for cardiovascular disease and stroke. 60% of the population-attributable risk of stroke is explained by hypertension, and 91% cognitive heart failure cases are with a history of hypertension. [110] Hypertensive individuals have four times greater risk of stroke, and two to three times higher risk of developing cognitive heart failure than individuals with normal blood pressure.[64]

Prehypertension is a state of elevated blood pressure, which is not yet reaching clinical hypertension. In the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII), prehypertension is defined as a systolic blood pressure between 120 to 139 mmHg and a diastolic blood pressure between 80 to 89 mmHg.[111] Prehypertensive individuals have a higher risk for developing hypertension. The Framingham Heart Study reported a two to four times higher odds of hypertension among participants with baseline blood pressure between 120-129/80-84 mmHg to those with below 120/70 mmHg. And a high normal blood pressure (130-139/85-89 mmHg) was associated with a five to twelve times higher odds of hypertension during four-year follow up.[112]

10.2.2 Management for Prehypertension

Prehypertension is not a disease category, but to identify individuals at high risk of developing hypertension. In the JNC VII guideline, lifestyle modification is recommended for managing prehypertension; strategies include weight loss, salt reduction, exercise and dietary intervention.[111] The effect of lifestyle modifications on lowering blood pressure has been reported in previous studies. The trials of Hypertension Prevention reported a 21% reduction in hypertension incidence in participants assigned to a weight loss counseling intervention to usual care.[113] Whelton et al[114] conducted a meta-analysis involving 1,108 normotensive persons enrolled in 27 randomized controlled trials, and reported a significant mean 4.04 mmHg systolic blood pressure reduction in those assigned to aerobic exercise than controls. Xin et al[115] summarized results of 15 randomized controlled trials and reported a dose-response association between the decreased alcohol consumption and reduction in blood pressure.

The Dietary Approaches to Stop Hypertension (DASH) trial reported a significant 3.5 mmHg systolic blood pressure reduction in normotensive or hypertensive individuals assigned to the DASH diet, as compared to a typical diet in the general US population.[116] The DASH diet is comprised with a higher intake of fruits, vegetables, and low-fat dairy products, while containing small amounts of red meat, sweets, sugar-containing beverages, and low total fat intake, especially for saturated fat and cholesterol.

A reduced sodium intake is also associated with a small but significant reduction in systolic blood pressure in normotensive persons. In a meta-analyses conducted by Cutler et al, results from 12 randomized controlled trials in normotensive participants are summarized, and an average reduction of a 77 mmol/d in dietary sodium was associated with a significant mean 1.9 mmHg decrease in systolic blood pressure.[117]

To investigate the effect of combining a healthy diet and low salt intake, the DASH-Sodium study investigated the blood pressure lowing effect of DASH diet together with different dietary sodium intake levels in normotensive or hypertensive participants. The trial reported a 7.1 mmHg reduction in systolic blood pressure in DASH diet and reduced sodium intake group to control diet and high sodium intake group.[118] The magnitude of reduction is similar to or greater than a single drug therapy.[119,120]As a result, in the United States national guidelines for hypertension prevention, DASH diet and reduced dietary sodium intake (≤ 2.3 g sodium or 5.8 g sodium chloride) are recommended.[111]

10.2.3 Outcomes for prehypertension treatment evaluation

The systolic blood pressure marked the maximum force generated by circulating blood on the vascular wall, while the diastolic blood pressure marked the minimum force. In the conditions of atherosclerosis or arterial stiffness in aging arteries, more workload is required for the heart to counterbalance the additional resistance in the hardened arteries. The resulting increment in blood pressure is more obvious in systolic than diastolic blood pressure, since diastolic blood pressure is more related to peripheral resistance.[121] The Framingham study showed that using diastolic than systolic blood

pressure to define hypertension may underestimate the number of patients requiring treatment.[122] Thus, in clinical trials, systolic blood pressure is a preferable measurement.

In patients with chronic conditions, treatment effectiveness can be substantially altered after accounting for Health-related quality of life (HRQoL).[7,8] Therefore, HRQoL is commonly assessed in clinical trials as a secondary outcome of interest.

10.2.4. The Effect of Sahaja Yoga Meditation on Lowering Blood Pressure

Sahaja Yoga Meditation is a simple method that helps individuals from any background to achieve tranquility and inner peace.[51] The therapeutic effect of Sahaja Yoga Meditation is achieved in meditation, characterized by the state of mental silence where one can better introspect, address and resolve the distress caused by negative thoughts, emotions or behaviors. Previous clinical research reported a mean 12.4 mmHg systolic blood pressure decrease and mean 10.8 mmHg diastolic blood pressure decrease in hypertensive patients received 4 months Sahaja Yoga Meditation with their anti-hypertension drug treatment than patients received anti-hypertension drug treatment only.[53] In a recent observational cohort study, a significant mean 12 mmHg systolic blood pressure reduction was observed in hypertensive patients received Sahaja Yoga Meditation treatment than those receiving conventional treatment. Sahaja Yoga Meditation therapy was associated with significant increase in quality of life.

Previous studies were subject to several limitations, including small sample sizes and confounding by indication in observational study, in which patients selected treatments based on individual or clinical difference that are difficult to rule out in non-randomized study design.

To address the limitations and better assess the effect of Sahaja Yoga Meditation on blood pressure control, the proposed study uses a randomized clinical trial with a two by two factorial design to compare Sahaja Yoga Meditation and reduced sodium DASH diet in blood pressure control for prehypertension. The secondary outcome in the study is health related quality of life (HRQoL). The proposed study also investigates possible synergy of meditation and dietary intervention on blood pressure reduction and quality of life.

10.3 STUDY HYPOTHESES:

10.3.1 Primary Hypothesis

Change in systolic blood pressure in prehyertensive individuals assigned to Sahaja Yoga Meditation is different than those who are assigned to wait-list control.

10.3.2 Secondary Hypotheses

1) Change in HRQoL in prehyertensive individuals assigned to Sahaja Yoga Meditation is different than those who are assigned to wait-list control.
2) Change in systolic blood pressure and HRQoL in prehyertensive individuals assigned to Sahaja Yoga Meditation with control diet is similar to that in prehypertensive individuals assigned to reduced sodium DASH diet with wait-list control.
3) Change in systolic blood pressure and HRQoL in prehyertensive individuals assigned to a combination of Sahaja Yoga Meditation and reduced sodium DASH diet is different from those who are assigned to either Sahaja Yoga Meditation with control diet or to the reduced sodium DASH diet with wait-list control.

10.4 STUDY DESIGN AND METHODS

The overall design of the study is an eight-week randomized two by two factorial trial in untreated prehypertensive individuals.

10.4.1 Participants and Recruitment

1) Inclusion criteria: prehypertensive individuals age more than 21 years. Prehypertension is defined as entry blood pressure of 130 to 139/≤89 or ≤139/85 to 89 mm Hg.
2) Exclusion criteria: individuals receive anti-hypertensive treatment at baseline, myocardial infarction, stroke or transient ischemic attack within the last year, or malignancy, pregnancy; the use of medications that affect blood pressure; unwillingness to stop taking vitamin and mineral supplements or antacids containing magnesium or calcium; renal insufficiency; and an alcoholic-beverage intake of more than 14 drinks per week.

3) Recruitment

The primary recruitment strategy is focus on patients seeking care for prehypertension, and recruits them from the clinic in the hospital or through referrals by family physicians. To recruit individuals with asymptotic prehypertension, mass mailing of brochures, work-site and community-based screenings are to be used for recruitment.

10.4.2 Intervention

Each of the two intervention strategies in the study comprises two treatment groups. The meditation intervention includes the wait-list control group and Sahaja Yoga Meditation group. The dietary intervention includes control diet group and reduced sodium DASH diet group.

Meditation Intervention

1. Control group: wait-list control.

There is no intervention for the wait-list control participants during the eight-week intervention period. Participants in the control group will receive the same assessments as the Sahaja Yoga Meditation group.

2. Sahaja Yoga Meditation group

The Sahaja Yoga Meditation program is a weekly 90-minute session, guided by Sahaja Yoga instructors. The session is composed of two period of 15 to 20 minutes meditation, information about how to meditate and sharing of experience. The instructor directs participants to become aware of the state of meditation within themselves by becoming silent and focusing their attention inside. Each participant will be asked to conduct shorter meditation sessions at home twice a day, and record daily meditation in the study diary.[58]

Dietary Intervention

1. Control Diet

The control diet has the nutrient composition of the typical diets in the general American population. The macronutrient profile and fiber content correspond to the

average consumption, while the potassium, magnesium, and calcium levels are close to the 25th percentile of U.S. consumption.[123] The sodium content in the diet is 100 mmol.

2, Reduced Sodium DASH Diet[118]

The combination diet is rich in fruits, vegetables, and low-fat dairy foods and has reduced amount of saturated fat, total fat, and cholesterol. This diet provides potassium, magnesium, and calcium at levels close to the 75th percentile of U.S. consumption, along with high amounts of fiber and protein.[118] The sodium content in the diet is 50 mmol.

The proposed study adopted the controlling feeding strategy from the DASH study.[116,118] The design of the menus are to be based on commonly available foods to meet the nutritional requirement of each diet. Food is to be prepared in research kitchens of every study center according to a common protocol. All centers will be instructed to use the same brand of a given food item for standardization of the diets.[116]

A seven-day menu cycle with 21 meals at four calorie levels of 1600, 2100, 2600, and 3100 kcal will be designed to meet the nutritional needs of the participants while keeping their weight steady during the period of study.[116] Participants will be requested to have either lunch or dinner on site during weekdays. At the on-site meal, the participants will be given meals to be consumed off site. Weekend meals will be given on Fridays for participants to consume off site.[116] The weight of each participant will be measured every weekday and kept stable by changing calorie levels and by adding 100-kcal snacks with nutrient contents that correspond to the assigned diets.[116]

Participants will be instructed to drink no more than three caffeinated beverages and no more than one alcoholic beverage per day. At each onsite meal, the subjects will record their beverages and additional salt intake, any non-study foods items they take or study food items they do not take.[118]

10.4.3 Measurement

Measurement for Blood Pressure

Sphygmomanometer remains the gold standard in measuring blood pressure. In the proposed study, blood pressure is measured using a calibrated sphygmomanometer

according to its standardized protocol. Systolic blood pressure is measured as the point of appearance (phase I) of Korotkoff sounds; diastolic blood pressure is measured as the point of disappearance (phase V). Measurements will be taken with participants in the sitting position after five minutes of rest. The readings are to be taken from 3 consecutive measures, which are five minutes apart.

Assessing Baseline Demographic and Clinical Profile

Demographic data and clinical history of each patient will be collected at baseline using a structured questionnaire. The Stanford 7-Day Physical Activity Recall questionnaire will be administered once during screening.[124] At baseline, weight, height, and skinfold thickness will be measured.

Laboratory Tests for Blood and Urine Sample

Routine laboratory tests are recommended by JNC VII in hypertension control, such as urinalysis and blood assay for glucose and hematocrit; serum potassium, creatinine, calcium, and a fasting lipoprotein profile. For individuals with diabetes or kidney disease, annual urinary albumin excretion or albumin/creatinine ratio monitoring are also recommended.[105] In the study, fasting blood samples will be drawn at baseline and the end of eight-week follow up for analyzing serum potassium, creatinine, calcium level, and a fasting serum profile of glucose, cholesterol, triglycerides, high-density and low-density lipoprotein cholesterol. A urine sample will be collected from each participant at baseline and the end of eight week follow up to obtain urinary sodium, potassium, phosphorus, urea nitrogen, albumin excretion, albumin/creatinine ratio. The blood and urinary samples will be assayed in corresponding core laboratories.

Health Related Quality of Life Measurements

HRQoL is measured by the WHOQOL-BREF.[19] The WHOQOL-BREF is 26-item self-administered questionnaire measuring quality of life from four domains including physical health, psychological, social relationship and environment. Two summary questions measure overall quality of life and general health.[19] The time reference for the questions is two weeks. The questionnaire generated four domain specific scores,

ranging from 4-20 or 0-100, and a higher score indicate better quality of life. A multi-countries field trial of WHOQOL-BREF demonstrates good internal consistency, reliability and constructs validity.[125] For healthy people, the questionnaire takes about five minutes to complete.

10.4.4 Outcomes

1) The primary outcome of the study is the change in resting systolic blood pressure. Change is defined as the longitudinal difference in blood pressure during follow-up. Three consecutive blood pressure measurements are to be averaged as the blood pressure result at each weekly follow up visit.
2) The secondary outcomes of interest are changes in diastolic blood pressure during follow up and HRQoL results at the end of follow up.

10.4.5 Randomization

A computer program is proposed to be used to generate the allocation sequence (StataCorp LP, College Station, TX, www.stata.com). The program generates random permuted blocks using blocks sizes 4, 6, and 8. An individual not affiliated with the conduct of the study will enter a seed number for the program to produce the allocation sequence for preparation of allocation envelopes. Consented participants will be randomly allocated to one of the following groups in a 1:1 ratio:

Group 1: Sahaja Yoga Meditation and reduced sodium DASH diet

Group 2: Sahaja Yoga Meditation and control diet

Group 3: Wait-list control and reduced sodium DASH diet

Group 4: Wait-list control and control diet

Randomization is stratified by clinical site and by self report type 2 diabetes at screening phase of the study.

10.4.6 Patient subgroups

The primary treatment comparisons will be tested in predetermined subgroups. The priori subgroups are defined by baseline characters, including type 2 diabetes, sex, and obesity categories defined by body mass index.

10.4.7 Trial Implementation

The trial is designed to have three phases—the screening, run-in, and intervention phases. If an individual desires to enter the study, the study will be explained in detail. Informed consent will be obtained by the study staff or investigator. After obtaining informed consent, an investigator or research assistant will review the inclusion and exclusion criteria of the individual. For each treatment group, during screening visits, trained and certified staff will measure the standard blood pressure of the participants with a calibrated sphygmomanometer. Three consecutive measures with five minutes interval between measures will be obtained after the subjects rested for five minutes in the seated position. Questionnaire survey on baseline characteristics, clinical history, prehypertension risk profile and health related quality of life will be administrated during the screening visit.

The run-in phase is a two-week period when all consented participants will be given control diet. Weekly blood pressure measurements composed of three consecutive measures, one fasting blood sample, one 24-hour urine sample, and information on the symptom questionnaire and HRQoL will be collected from each participant. During the second week, the participants will be randomly assigned to one of four intervention strategy combinations and learned of their assignments (meditation and diet) on the first day of the intervention.

The intervention phase is an eight-week period active intervention, in which the subjects will be following their assigned intervention. During the first six weeks, each week trained staff members who are blinded to treatment diet assignment will measure the blood pressure of study participants. Three consecutive measures with five minutes interval between measures will be obtained after the subjects rested for five minutes in the seated position. During the last two weeks, in addition to weekly blood pressure measurements, one fasting blood sample, one 24-hour urine sample, and information on the symptom questionnaire, HRQoL and physical-activity-recall questionnaire will be collected from the participants.

10.4.8 Statistical Analysis

All analyses comparing the effect of randomized treatment assignment on outcomes will be based on the intention-to-treat principle. The significance level of

randomized treatment comparisons between the four groups is set to be a 2-sided p value of 0.05. For treatment comparisons within the pre-specified subgroups, a 2-sided p value of 0.01 is used to correct for multiple testing. In multivariable models, interaction between randomized treatment and pre-specified subgroups will be tested.

To control for the correlation from repeated measures within each participant, linear mixed effect model is proposed to be used for primary outcome comparisons. For HRQoL analysis, since quality of life measured at baseline and the end of follow-up, in the analysis, follow-up quality of life measures will be used as the outcome, and adjust for baseline values. The baseline blood pressure and HRQoL measures will be the average of measurements obtained during both the screening and run-in phases.

The missing outcome measure is defined when a patient is alive and participating in the study but does not provide outcome measures expected per protocol. With the application of mixed effect model with the restricted maximum likelihood algorithm, the assumption is missing at random. However, if missing outcomes is substantial and it is suspected that missing is not at random, a random-effects pattern mixture models will be applied for analysis under the framework of mixed effect models.[27]

10.4.9 Sample Size Estimation

Sample size is calculated based on the primary hypothesis for differernce in reduction in systolic blood presure in participants randomly assigned to Sahaja Yoga Meditation and wait-list control. According to the pilot data, the standared deviation of Sahaja Yoga Meditation on change in systolic blood pressure is 13.2 mmHg. In addition, previous studies reported a 30% dropout rate in research applied Sahaja Yoga Meditation on asthma management,[56] and a 76% retention rate in the study of children with attention deficit-hyperactivity disorder.[58] Meanwhile, high adherence was reported in the DASH-Sodium trial, where 95 percent of the participants assigned to the DASH-diet group and 94 percent of those assigned to the control-diet group completed the study and provided blood-pressure measurements during each intervention period.[118] As a result, assume a dropout rate of 30 percent, 10 percent missing data, a Type I error rate of 0.05 and a Type II error rate of 0.1, the sample size estimates for testing the primary hypothesis according to different effect size are summarized in table 2. The proposed study population is 300 participants in each group of the primary treatment

comparison, which equals to a total of 600 participants. The estimated power is 90% for the study to detect a 4 mmHg or more difference in systolic blood pressure change between Sahaja Yoga meditation and wait-list control.

Effect size (mmHg)	Crude estimates	Adjusted by dropout and missing data rates
3	330	524
4	186	295
5	119	189
6	83	132

10.4.10 Timeline

The duration of the study is estimated to be 15 months, including 6 months recruiting, 3 months conducting the study, and 6 months data management and analysis.

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