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The HERITAGE Family Study: Quality Assurance and Quality Control

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ABSTRACT

The HERITAGE (HEalth, RIsk factors, exercise Training And GEnetics) Family Study is the first multicenter family clinical trial of its kind. Conducted by a consortium of five universities in the United States and Canada, the study has as its primary goal to document the role of the genotype in the cardiovascular, metabolic, and hormonal responses to aerobic exercise training. A comprehensive protocol was implemented at four Clinical Centers (CC) for the generation of data on sedentary subjects. This group included 450 caucasians from 90 nuclear families (father, mother, three children) and 200 black subjects from 40 to 100 family units over a 5-year period. The entire family was tested before and after a 20-week exercise training program. The fifth participating center, the Data Coordinating Center (DCC), is responsible for data management and data analysis. A Consortium Coordinating Center (CCC) responsible for the overall coordination and direction of the study was established at the Quebec CC. Quality assurance and quality control are jointly coordinated by the CCC and the DCC. A multicenter study of this magnitude requires careful standardization of all procedures and constant monitoring of quality control at all levels of operation. This report describes the quality assurance and quality control measures implemented in the HERITAGE Family Study, including some examples with real data. © 1996 by Elsevier Science Inc. Ann Epidemiol 1996;6:520–529.

KEY WORDS: Exercise training, family study, genetics, sedentary lifestyle, cardiovascular disease, diabetes, quality control.

INTRODUCTION

The overall objective of the HERITAGE Family Study is to investigate the role of the genotype in cardiovascular, metabolic, and hormonal responses to aerobic exercise training and the contribution of regular exercise to changes in several cardiovascular disease (CVD) and non-insulin-dependent diabetes mellitus (NIDDM) risk factors. Study participants consist of 90 caucasian nuclear families (father, mother, three children) and 200 black subjects from 40 to 100 family units. Participants are measured before and after a standardized exercise-training program. The protocol requires a multicenter approach so as to achieve the desired sample size within a reasonable period of time. The multicenter approach, coupled with the need to be able to detect fairly small changes in response to training, mandates that extensive quality assurance and quality control measures be implemented. This report documents our efforts in this regard and serves as a quality-control baseline paper for the HERITAGE Family Study.

STUDY DESIGN

The study design calls for recruiting, testing, training for 20 weeks, and retesting 650 sedentary subjects. This sample size was deemed necessary to yield enough power for hypothesis testing and for obtaining reasonably accurate parameter estimates for a variety of genetic models. The complexity of this study and the amount of time and effort devoted to each subject make it impossible to achieve the sample size at any single center within a reasonable period of time. Thus the study includes four Clinical Centers (CC) which generate the data over a period of 5 years (Texas, Minnesota, Arizona, [Indiana since January 1996] and Quebec) and a Data Coordinating Center (DCC), which is responsible for data management, quality control, and analysis (St. Louis, MO). The appendix provides a listing of the laboratories and people involved in the HERITAGE Family Study.

A Consortium Coordinating Center (CCC), responsible for the overall coordination and direction of the study, was

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established at the Quebec CC. The CCC is also responsible for four core laboratories located in Quebec: the Diabetes core, Lipid core, Steroid core, and DNA and Cell line core laboratories. Plasma, serum, and urine banks are established at the CCC for future (or supplementary) studies, since HERITAGE offers a unique opportunity to investigate the relationships between exercise training and risk factors. The major risk factors investigated include blood lipids, lipoproteins, apolipoproteins and enzymes; glucose tolerance and insulin metabolism; systolic and diastolic blood pressure at rest and during exercise; body weight, body fat and regional fat distribution, including abdominal visceral fat; and steroid and glucocorticoid hormone levels.

A variety of exclusion criteria are used to screen participants. For example, subjects above 65 years of age are excluded due to possible physical decline, and children below 17 years are excluded to avoid the complications of growth. Likewise, subjects essentially not in good health are excluded based upon safety and compliance concerns regarding strenuous exercise in previously sedentary subjects with major health problems. A more complete list of the inclusion/exclusion criteria was given in Bouchard et al. (1).

Measuring sedentary subjects both before and after a 20-week standardized training program provides an opportunity to assess the phenotypic expression of each individual's genotype under two well-defined environmental conditions, the pre- and post-training conditions. This study design gives us the unique ability to assess the familiality of response to a specific environmental manipulation, both in measures of fitness and concomitant effects on a wide range of cardiovascular and diabetes risk factors.

Quality Assurance and Quality Control Procedures

Quality assurance and quality control measures have become a standard part of clinical trials methodology. Entire chapters devoted to these issues can be found in many of the classical textbooks on the subject (2–4). Indeed, the importance of assuring and monitoring data quality, and promptly correcting problems as they are discovered, has been recognized from the earliest studies (5–9). The need for high-quality data is even greater for multicenter than for single-site studies because pooling of the data across sites is required to meet the sample size goals of the study, and the possibility of intercenter differences introduces yet another potential source of unwanted variation (10, 11). The need for uniformity in collection and analysis of data is magnified further in the case of multicenter family studies such as HERITAGE, where one primary goal is to understand the sources of variability within families, whether genetic, environmental, or some combination (12). Any measurement error will increase the overall variability and obscure detection of changes.

A distinction is made between quality assurance measures, which are undertaken proactively to assure that the data are of high quality (13–15), and quality control procedures, which monitor and measure the quality of the data as soon as or shortly after they are collected (16–18). In the case where other studies have found that a measurement has low reliability because many extraneous factors can influence the outcome, it is especially important to control what can be controlled so that this error is minimized. A good example is in the domain of sitting blood pressure, which has a large day-to-day variation component, nycthemeral cycles, and a notoriously high error variance, due to factors such as comfortableness of the room, arm position of the subject, previous tests conducted or anticipation of impending procedures (19–21). Nevertheless, some of this error can be reduced through meticulous design of procedures, use of repeated assessments, and careful attention to standardization. In the event that measurement error cannot be reduced to near zero, as is often the case, it is important to quantify its magnitude in the actual (or similar) study population, so that the impact on data analysis and inference can be assessed.

High quality is of particular importance in this study in order to detect relatively small changes in phenotypes in response to training and the resulting family resemblance. This report provides a description of quality assurance and quality control measures implemented in the HERITAGE Family Study, including some examples with actual data. These procedures are jointly coordinated by the CCC and the DCC and constitute the subject matter of this report. Complete details of the study design, aims, and the measurement protocol can be found in Bouchard et al. (1) and in an extensive Manual of Procedures (MOP) available from the CCC for the cost of reproduction and mailing.

Consortium Steering Committee. The five principal investigators are members of the Consortium Steering Committee, which handles all issues pertaining to the study. The Committee also includes the Project Director and the Project Administrator. The Committee meets at least twice a year to monitor the progress of the study.

Advisory Board. To provide advice and consultation periodically, an independent Advisory Board was created consisting of five experts in various subspecialties related to the study. The Consortium Steering Committee meets with the Advisory Board at least once a year.

Manual of Procedures. A major effort was made to standardize all aspects of the study protocol; the details are provided in a Manual of Procedures (MOP), which was finalized just before beginning of the data collection, which commenced 7 months after the study was funded.

Standardization and calibration of equipment. All major pieces of equipment used in testing and training have been standardized across all CCs. Specifically, the following major equipment was purchased for each CC: automated blood pressure device (STBP-780—Colin Medical Instruments

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Corporation, San Antonio, TX), (SensorMedics 2900—SensorMedics Corporation, Yorba Linda, CA), (Harpenden Calipers—Quinton Instrument Company, Seattle, WA), (Aerobicycle V—Universal Gym Equipment, Cedar Rapids, IA), and (Ergometrics-800S—SensorMedics Corporation, Yorba Linda, CA). For each piece of equipment, calibration procedures have been established and are followed routinely. For the STBP-780, the calibration is performed at the start of each testing day. For the body composition assessment, calibration of the weighing scale, load cell, and calipers/measuring tapes is performed weekly. For the SensorMedics 2900, calibration is performed before and after each test. The testing ergometer is also calibrated weekly. For the training cycle ergometers, two dynamometers are used to calibrate all ergometers and are rotated across the four CCs on a regular basis at least every 3 months.

Central training and certification of personnel. All primary personnel associated with the measurement protocol were centrally trained and certified before the study began. New personnel at each CC are trained by certified staff before being allowed to collect data. The Local Project Coordinator (LPC) has the responsibility of training and certifying the personnel at each CC. Finally, all personnel involved in subject testing are trained and certified for cardiorespiratory resuscitation procedures.

Pilot study at each clinical center. Each CC carried out a pilot study with 10 subjects for the purpose of having the personnel go through the full battery of questionnaires, interviews, and tests. These studies, performed soon after the personnel training sessions, were designed to target all areas of the HERITAGE Family Study protocol before starting official data collection. The pilot study data were recorded and sent to the DCC for analysis. Results were reviewed by the Consortium Steering Committee.

Traveling crew study to assess intercenter differences. A unique quality assurance procedure was implemented to assess intercenter differences. Before actual data collection the HERITAGE Project Director traveled with four volunteers (non-HERITAGE subjects) to each of the four CCs. All four subjects were first measured at the Quebec CC, then by each of the other three CC's, finally followed by a remeasurement period at Quebec CC. Some tests were done repeatedly at each CC. The entire four-center assessment period required approximately 3 weeks, which included 1–2 days of rest between two of the CCs. This design allowed evaluation of intercenter and intracenter reliability using the same pool of subjects. Although this traveling crew study was designed to address the full battery of measurements, it concentrated more on exercise testing and physical measurements such as anthropometry, underwater weighing, and blood pressure. Extensive evaluation of the resulting data identified a few areas of weakness requiring additional training, such as certain anthropometric measurements. After this operation, an additional training session targeting the identified areas of weakness was scheduled. The traveling crew study was repeated again a year later (1994) with four different subjects. Each time, the reliability was assessed for each measure as an intraclass correlation coefficient derived from an ANOVA (22). Although, one would expect the reliabilities to go up with time, reflecting improvement and experience, study drift is a well-known phenomenon that could lower the reliabilities over time.

In Figure 1, we present the actual intercenter reliabilities in 1993 vs. 1994 for a select group of variables from anthropometry, underwater weighing, resting blood pressure, and exercise tests. Except for resting blood pressure, all reliabilities are very high in the non-exercise test domain. For blood pressure (BP), reliabilities are known to be notoriously low because of the many external factors that influence them (19–21). The variability in BP levels is not surprising in this case since study subjects traveled from CC to CC during a relatively short period, going through a stressful period of travel and enduring considerable lifestyle variation. Moreover, as noted in a subsequent section of this report, the resting BP has high reliability when measured within each CC under standardized conditions. In the exercise domain, most reliabilities improve from 1993 to 1994, with highly reliable measurements for certain critical variables like maximal oxygen uptake ($\dot{V}O_2max$). The reliability of maximal heart rate appears to be spuriously reduced in the 1994 measurements, reflecting the small variability (2.5%) among the maximal heart rates of the four subjects.

Summary subject's file. A one-page form called the "subject's file" is used as a master inventory to log the date on which any measurement protocol is administered to each subject. All study forms, questionnaires, and procedures are listed on this form. This itemized checklist was incorporated to ensure that each procedure was properly completed according to the flow of activities specified in the MOP. It is continuously updated in the data entry system so that the DCC is aware of all procedures completed on a subject at any given time and their exact stage in the study protocol (even though the resulting data may not be in the database yet).

Data correction form. Any correction of previously recorded data needs to be documented and signed by the LPC. In case of doubt, the matter is referred to the local Principal Investigator (PI). If problems become chronic, the matter is referred to the PI responsible for the particular area of the protocol concerned. Additionally, whenever data need to be corrected after they have been transferred to the DCC, the study site initiating the correction files a form with the DCC signed by the local LPC and the PI.

Observational tour by HERITAGE Project Director. The Project Director visits each CC on a regular basis for the primary purpose of verifying that all procedures are performed according to the protocol. The major purpose

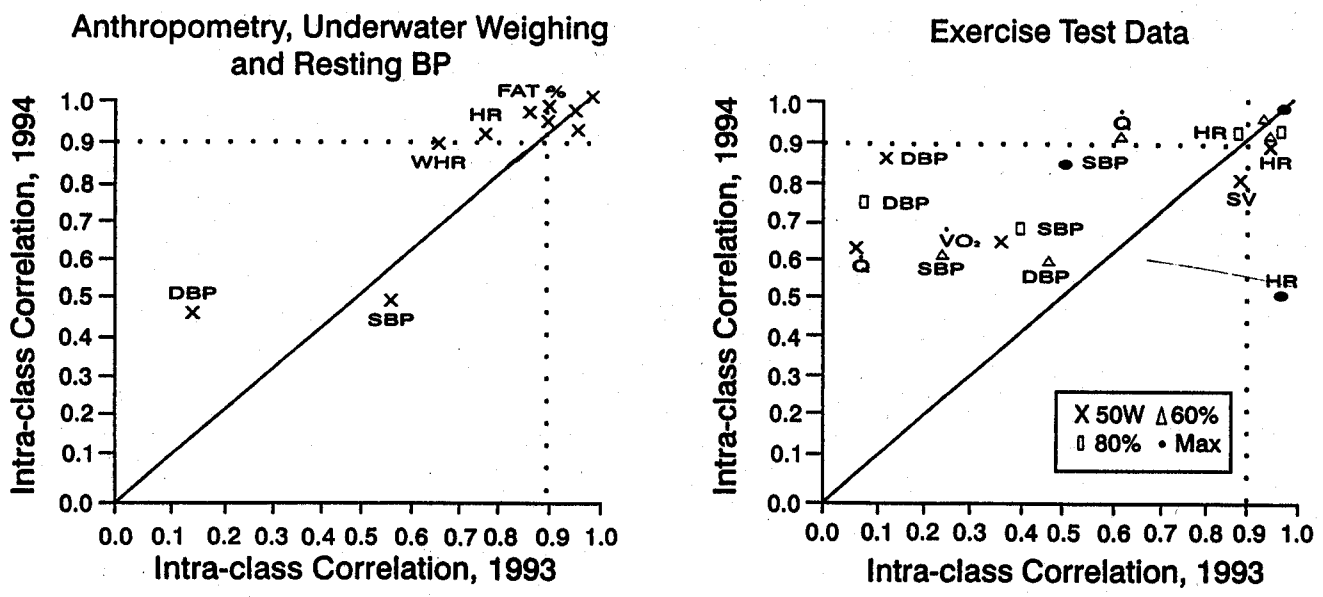

FIGURE 1. Intercenter reliability estimates for 1993–1994 traveling crew studies: (a) Anthropometry, underwater weighing, and blood pressure; (b) exercise test data. Abbreviations: HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; FAT % = percentage fat by underwater weighing; WHR = waist-to-hip ratio; $\dot{V}O_2$ = oxygen uptake; SV = stroke volume; $\dot{Q}$ = cardiac output. Variables with reliabilities over 0.9 on both occasions and not labeled in the figure are: in (a) BMI, trunk-to-extremity skinfold ratio, sum of skinfolds, stature, weight; in (b) $\dot{V}O_2$ (at 60%, 80%, and max), HR (at 60%), SV (at 60%), SBP (at 50W), DBP (at max).

of these visits was to ensure complete adherence to the experimental protocol and standardization across centers.

Central reading of exercise test data. The detailed exercise test data, which are extremely voluminous for each subject (14 variables obtained every twenty seconds for each test lasting up to 30 minutes) as well as the "analyzable" summary data (1 page report) created by a series of decisions made according to a standardized protocol, were reviewed centrally during the first year of the study by the PI responsible for this area of the study (Texas CC). Such a central review serves several important purposes. First, it evaluates the validity of the standardized decisions and hence that of the summary data. Second, the central review should minimize intercenter differences and improve the quality of the final data. As shown in Figure 2, the intercenter reliability coefficients (22) for exercise test variables at different power outputs are quite high based on data from the 1994 traveling crew study. As noted earlier, the maximal heart rate reliability is spuriously low because of low overall variance.

Central reading of exercise training data. The exercise training program is conducted on cycle ergometers for 20 weeks. The training power output is heart rate driven and is individualized by a computer system that records all training data for each person. All the training data are downloaded and reviewed centrally by the PI responsible for this area of the protocol (Indiana CC). Figure 3 illustrates the progression of heart rate and the training power output throughout the 20-week training program, for a representative HERITAGE subject. As is desirable, the actual and projected lines track very well.

Assessment of physical activity status. To be eligible for the study, subjects are required to be sedentary (physically inactive) during the last three months. They also are instructed at baseline not to change their normal lifestyle habits during the study other than the 20-week cycle ergometer training they receive. Habitual physical activity is determined at baseline and at the end of the training program with the questionnaire used in the National Institutes of Health–supported Atherosclerosis Risk in Community Study (ARIC). The high reliability and validity of the ARIC-BAECKE questionnaire was documented and confirmed in a recent study (23).

Adherence to training program. With about 600 subjects who have been enrolled in the study to date, we have a dropout rate of < 10%, which is lower than we anticipated. Our statistical power estimates were based on an expected subject attrition of 15%. Various strategies are employed to minimize dropouts and to maximize the number of participants completing the testing and training phases. Before signing an informed consent form, the LPC explains in detail all the procedures, requirements, benefits, and risks involved in the study. Subjects are told that all members of the family must complete all phases of the study. Apparently the family unit is acting as a reinforcement among the members to complete the study. In addition, several

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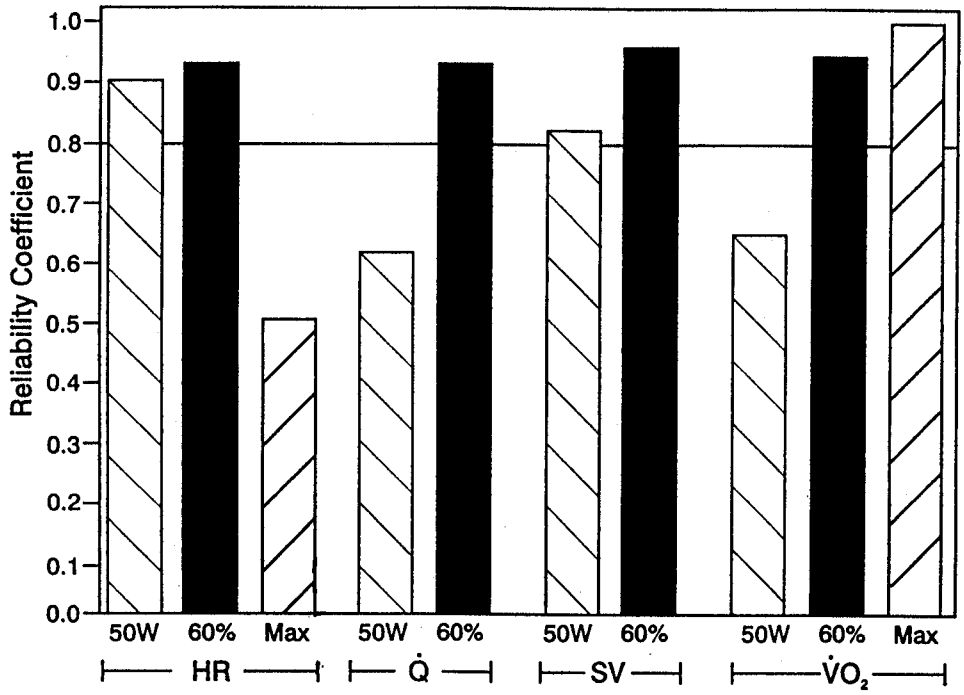

FIGURE 2. Intercenter reliability estimates for exercise test data from the 1994 traveling crew study. Each subject is evaluated at each center for heart rate (HR) at 50 W, 60%, and $\dot{V}O_2$max; cardiac output ($\dot{Q}$) at 50 W and 60% of $\dot{V}O_2$max; stroke volume (SV) at 50 W and 60% of $\dot{V}O_2$max; and oxygen uptake ($\dot{V}O_2$) at 50 W, 60%, and $\dot{V}O_2$max. Reliability for heart rate at max workload is spuriously low because the variability among the max HR of the four subjects is very low (2.5%).

factors are known to be important determinants of dropout rates during exercise training programs: (*i*) inconvenient program (24, 25); (*ii*) lack of parking (26); (*iii*) exercising alone (25, 27); (*iv*) lack of social support, especially from the spouse (28); (*v*) lack of supervision (29); (*vi*) high-intensity exercise (30); and (*vii*) excessive financial cost to participants (31). Fortunately, this study has avoided these limitations by taking the following actions. Subjects are given flexibility to schedule their own exercise timings throughout the day, seven days a week. Free parking is provided near the exercise facilities. Group workouts are routinely encouraged. Entire families are participating, which optimizes social support. All exercise sessions are supervised. Exercising is made a lot friendlier by appropriate, individualized, and gradually-increasing exercise intensities and durations. Lastly, there is no financial cost to the subjects; instead, each is compensated up to a maximum of $1000. Each family member receives $100 upon completion of the pretest phase, $600 upon completion of all 60 training sessions, and an additional $300 upon completion of the posttest phase. Such a payment schedule is designed to optimize participation in all phases of the study.

Quality assurance for handling of blood samples. A comprehensive system has been developed to standardize blood-sample handling procedures. All blood samples are prepared in a similar manner for shipment via Federal Express to the Quebec CCC. Fresh blood samples for cell lines are shipped the same day by overnight delivery. Refrigerated samples for lipid and lipoprotein analyses are stored at the local CC and shipped on a weekly basis (overnight delivery) to the CCC. Other samples are frozen and stored at −70°C at the local CC. They are shipped in batches to the CCC (also for overnight delivery). Special steps have been taken to deal with customs regulations and to ensure the timely flow of samples across United States–Canada border. Quality control measures are also undertaken to ensure that data are received by the DCC within 3 months. This is done by regularly tracking the time lag since performing the test.

Repeat measures for resting blood pressure. Resting blood pressure is measured on two different days during each of the pre- and posttraining phases. On each of these days, the first reading is discarded and the next three valid readings are recorded. The average of the three valid readings is used as the phenotype. Figure 4 presents the intracenter reliability estimates based on data obtained on the two separate days before training (based on actual study data to date on 353 subjects). As can be seen from Figure 4, the intracenter reliabilities are fairly good.

Double data entry. Data are collected on paper forms and then keyed into a data entry system written specifically for the HERITAGE Family Study in SAS OS/2 at each CC. The data entry and management system incorporates double data entry, range checks, and some error checks. During the first data entry, data range checks are made and warning messages are displayed on the screen. During the second data entry, the value is compared to that of the first data entry. Mismatches are identified and resolved at the second data entry.

Monthly data management reports. Snapshots of the cumulative CC database are sent regularly to the DCC and

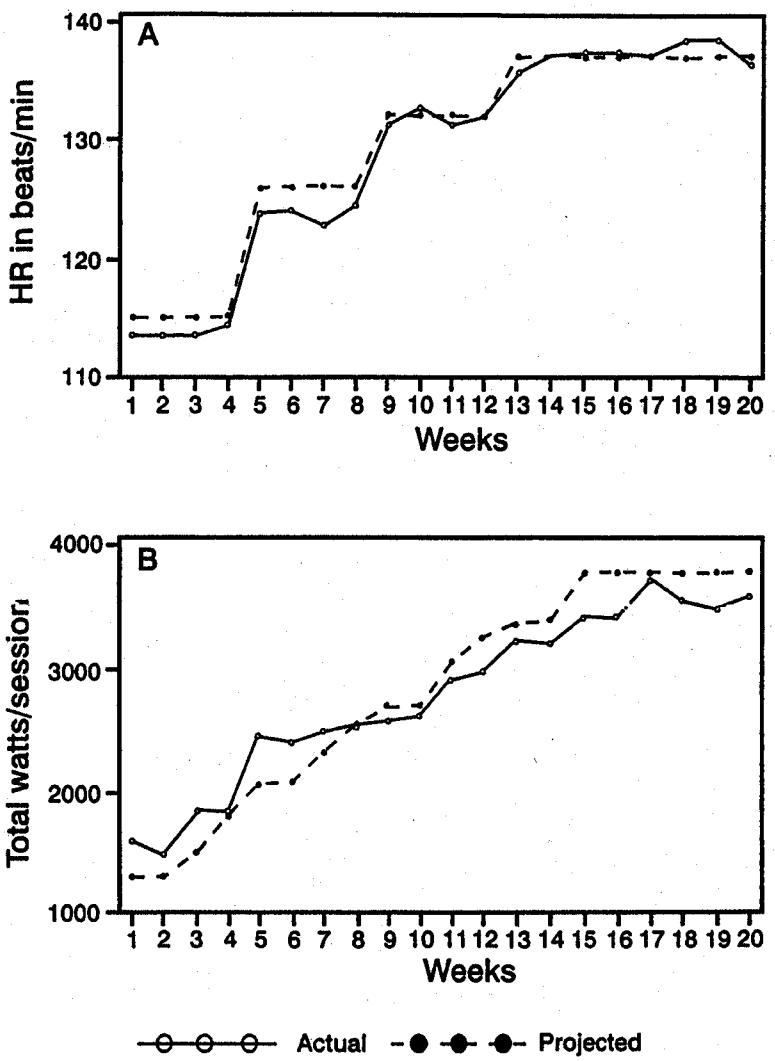

FIGURE 3. Heart rate (A) and power output (B) during the 20-week training program for a representative HERITAGE subject. Values are averaged over each week of the program. The actual and projected curves track closely. Heart rate is given in beats/min; power output in watts/session.

collated into a central database. Each month, a progress report on the current status of the study is prepared by the DCC and sent to each CC. It includes the following information: numbers of subjects and families entered in the study, status of each subject, status of each family, tests that have been completed, status of exercise training program, and status of data entry. These reports are designed to alert CCs about possible inadvertent errors or omissions of data entered.

Adverse reaction form. This form is filled out in the advent of an incident/injury during testing or the exercise training program. If any incident/injury happens (or any medical condition even if unrelated to the study), it is reported immediately to the LPC. If the medical condition affects the musculoskeletal system or any other system causing some functional incapacity, discomfort, or simply brings into question the possibility of interference with continued training or testing, it is brought to the attention of a study physician, and a medical evaluation is conducted using this form.

Intracenter reproducibility studies. Because there will always be some intercenter differences (no matter how hard one tries to standardize across centers), our primary goal is to maximize intracenter repeatability. If this is maintained, one can always statistically adjust the composite multicenter data set for possible intercenter differences in a given test result. Because families are seen together at each clinic, the intracenter differences matter more for familial resemblance models. Toward this end, we are doing an intracenter reproducibility study using 15 non-HERITAGE Family Study subjects at each center. Each subject is assessed on three separate days during a 21-day period, with a minimum of four days between successive exercise test measurements.

Cross-matching dates on subject file and tracking flow. Whenever a blood sample is collected, the CC registers the date in the subject file. Moreover, the label on each sample

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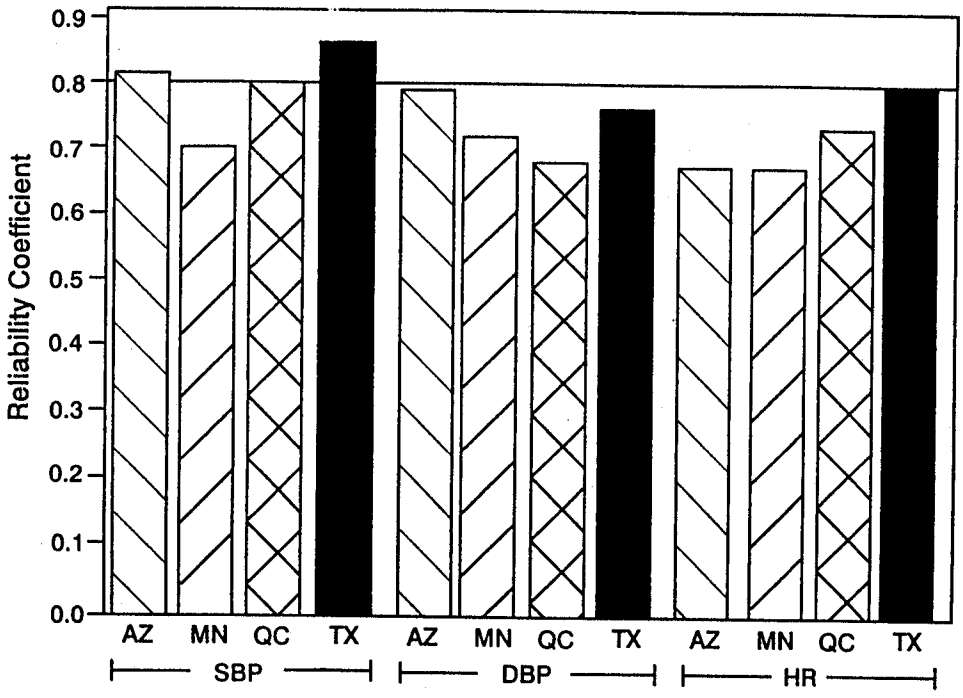

FIGURE 4. Intracenter reliability estimates for pretraining resting blood pressure (SBP = systolic; DBP = diastolic) and heart rate (HR) based on actual data on 353 HERITAGE subjects.

tube has both an ID and a date that is compared at the CCC with a packing list provided with every blood shipment. The CCC also provides a complete inventory with the samples delivered to each core laboratory for analyses. When the blood results are sent back from the core laboratories to the CCC and then to the DCC, dates are cross-matched, a process which insures that no samples are lost or mismatched in handling.

Internal Quality Control at Each Core Laboratory

Diabetes core laboratory. This core laboratory is responsible for assaying glucose, insulin, and C-peptide from the intravenous glucose tolerance test (IVGTT), and blood substrates from samples obtained during submaximal and maximal exercise. The quality of each plasma insulin determination is ensured by several measures. First, each sample is analyzed in duplicate. The sample is submitted to further repeated assays if the difference between the two individual values exceeds 30 pmol/L when the mean value for plasma insulin is < 500 pmol/L, or 60 pmol/L when the mean value for plasma insulin is > 500 pmol/L. When the mean value is > 1000 pmol/L, we accept a 10% difference. Second, one of every 20 IVGTT tests is completely reassayed for insulin so as to yield test–retest reliability data for 5% of all IVGTT tests.

Likewise, the quality of each plasma C-peptide determination is ensured by duplicate analysis. Again, the sample is reassayed if the difference between the two individual values for plasma C-peptide exceeds 50 pmol/L. Both C-peptide and glucose are also repeated in 5% of the IVGTT tests. Plasma free fatty acids, blood lactate, and plasma proteins (Technicon RA-XT—Technicon Instruments Corporation, Tarrytown, NY) are assayed from blood samples obtained during one of the exercise tests. The assays are repeated in 5% of all cases.

Lipid core laboratory. The following procedures are applied to ensure quality of plasma lipids and lipoproteins at the core laboratory.

For cholesterol and triglyceride measurements, reconstituted lyophilized control plasma is used to assess within and between-day variation. These plasma values have "lower" and "upper" normal limit levels. The two controls are used for every 20 samples run on the RA-500 Technicon robot (RA-500 Technicon—Technicon Instruments Corporation, Tarrytown, NY). In addition, both cholesterol and triglyceride are repeated in 5% of the samples.

Pooled plasma is prepared and is stabilized by the addition of protease inhibitor and antibacterial agent. This pooled plasma is used as a control for every 20 samples placed in the ultracentrifuge. The recovery of cholesterol and triglycerides in the lipoprotein fractions is monitored by this procedure. For purposes of internal quality control, the assays are repeated in 5% of all cases.

For apo A1 and B measurements, reconstituted lyophilized control plasma is used to assess within- and between-day variation. One control is used for every 10 samples, and one of every 20 samples is completely reassayed.

For measurement of post-heparin lipolytic activity, post-heparin plasma is collected from one normal subject and frozen in aliquots at −80°C. One aliquot is used for the

determination of both LPL (Lipoprotein Lipase) and HGL (Hepatic Glyceride Lipase) activities for every five samples. The assays are repeated in 5% of all cases.

Steroid core laboratory. To ensure quality control of serum steroid assays, three levels of Lyphochek control sera from Bio-Rad Laboratories, Hercules, CA are used. These control sera have low, medium, and high concentrations of free steroids, steroid esters, steroid glucuronides, and steroid sulfates. In addition, for glucuronides and esters, a commercial pool of sera from men and women is assayed by adding a known amount of pure conjugate steroid. In a typical assay, 6 low, 6 medium, and 6 high pool sera are analyzed at the beginning, at the middle, and at the end for every 100 samples. Quality control on steroid hormone–binding globulin (SHBG) is provided with 2 SHBG controls included in the kit. Finally, for purposes of internal quality control, the assays are repeated in 5% of all cases.

DNA and cell line core laboratory. Lymphoblastoid cell lines are established by transformation of B-lymphocytes with Epstein-Barr Virus (EBV). The process consists in the isolation of B-lymphocytes from blood followed by their transformation with EBV. Cells are then cultured until their freezing in liquid nitrogen. Immortalized cell lines are established for all HERITAGE subjects. Cell lines, as well as media and reagents, are routinely checked for the absence of bacteria and mycoplasma. Cell lines are routinely thawed after a few months to verify cell viability.

External Quality Control Measures

In addition to the preceding quality control measures instituted by the core laboratories, the DCC also coordinates some external quality control measures.

Split samples to core laboratories. The DCC has assigned phantom IDs to be used by each CC for shipping blinded duplicate blood samples from 15 volunteer subjects to the core laboratories. The Data Entry System provides for the identification of the pair-wise correspondence, so that the DCC can break the blind and assess the reliability of the core labs.

Data audits. Periodically, the DCC randomly audits the records of 10% of the subjects in the database. It identifies a set of IDs for each CC and asks for copies of all data forms. These data are then matched with the electronic database at the DCC. In addition, for the same subjects identified above, the exercise test data, training data, and the CT scan data are reviewed centrally as discussed below.

Central evaluation of exercise test data. The LPCs send all the raw data to the Texas CC. This center evaluates each test, provides comments to each CC, and produces a new summary report, which is then sent to the DCC. The original and the new summary reports are compared by the DCC.

Central evaluation of training data. The LPCs send all the data and graphs (such as in Figure 3) to the Indiana CC. This center evaluates each test, provides comments to each CC, and produces a new summary report, which is then sent to the DCC. The original and the new summary reports are compared by the DCC.

Central evaluation of CT scan readings. A 10% sample of the x-ray films collected at each CC for the assessment of abdominal visceral fat are sent for review by the consortium CT scan reading center at the Quebec CC. Also, a calibrated unit composed of lard, sealed in a cylinder especially designed for this purpose, is sent to each CC once a year to be scanned for the assessment of potential intercenter differences.

CONCLUSIONS

We have discussed a wide range of quality assurance and quality control measures implemented in the first multicenter clinical trial conducted at a family level, the HERITAGE Family Study. All of these procedures are in operation now, and as illustrated by Figures 1–4, the resulting data are of high quality. At the time of preparation of this manuscript, a total of 407 subjects in 80 caucasian families, and a total of 102 subjects in 27 black families have completed the protocol. We believe that the HERITAGE Family Study constitutes a unique resource for investigations of the role of genetic and environmental determinants in the response of sedentary families to regular exercise in terms of risk factors for common diseases.

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APPENDIX

The HERITAGE Family Study research consortium consists of the following personnel. A complete list of all personnel involved has been published (1).

Consortium Steering Committee

Claude Bouchard, PhD, Laval University, Chairperson; Arthur S. Leon, MD, University of Minnesota; D. C. Rao, PhD, Washington University; James S. Skinner, PhD, Indi-

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ana University; Jack H. Wilmore, PhD, The University of Texas at Austin; Jacques Gagnon, PhD, Laval University, Project Director; and Jean Paul Albert, MBA, Laval University, Administrator.

Advisory Board

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Laval University Consortium Coordinating Center and CC

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Note: Dr. Skinner was previously at the Arizona State University, Tempe, where the CC was located (with Kristine Wilmore as the LPC). Dr. Skinner moved to Indiana University in 1996, at which time the CC was also relocated to Indianapolis with significant staff changes.

The University of Texas at Austin CC

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