The NASA-Sponsored Study of Cataract in Astronauts (NASCA). Relationship of Exposure to Radiation in Space and the Risk of Cataract Incidence and Progression. Report 1: Recruitment And Methodology

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ABSTRACT

INTRODUCTION

The NASA Study of Cataract in Astronauts (NASCA) is a five-year, multi-centered, investigation of lens opacification in populations of U.S. astronauts, military pilots, and ground-based (non-aviator) comparison participants. For astronauts, the explanatory variable of most interest is radiation exposure during space flight, however to properly evaluate its effect, the secondary effects of age, nutrition, general health, solar ocular exposure, and other confounding variables encountered in non-space flight must also be considered. NASCA contains an initial baseline, cross-sectional objective assessment of the severity of cortical (C), nuclear (N), and posterior subcapsular (PSC) lens opacification, and annual follow-on assessments of severity and progression of these opacities in the population of astronauts and in participants sampled from populations of military pilots and ground-based exposure controls. From these data, NASCA will estimate the degree to which space radiation affects lens opacification for astronauts and how the overall risks of each cataract type for astronauts compared with those of the other exposure control groups after adjusting for differences in age and other explanatory variables.

During space flight, the average lens dose of space radiation varies with the mission (see Table 1, Column 4). The highest radiation risk missions occurred on the Skylab, Russian Mir, and the International Space Station (ISS) missions because of their long duration. The Hubble telescope launch and repair missions were of moderate duration (<2 weeks), however astronauts received higher exposures from trapped protons in the Earth's radiation belts due to the location of the Hubble telescope, a distance above Earth of 600 km. The Apollo missions' orbits were outside of Earth and were of much shorter duration, however in these missions astronauts were exposed to the complete galactic cosmic ray environment during the trip to the moon. The earlier Mercury and Gemini missions were of short duration and at low orbital inclinations. The space shuttle program has been the longest occurring NASA program with over 110 missions since 1982. These missions have lasted about 14 days on average, however astronauts often participate in several missions and cumulative doses may accumulate to a higher levels with a maximum to date of seven missions flown by two astronauts. In addition, there are significant qualitative and quantitative differences between terrestrial and celestial radiation. Whereas terrestrial radiations are low LET (linear energy transfer) and derived from x-rays and gamma rays, celestial radiations are high LET and derived from heavy ions and secondary neutrons. Terrestrial x-ray and γ-ray exposures have been linked with increased cataract risk, but the precise cataractogenic risks of the various components of celestial radiation have not been defined. Many factors contribute to the average lens mission radiation dose, and if NASA is to understand the mechanism(s) by which space radiation increases the risk of cataract, a comprehensive study of astronauts and appropriate control groups is needed. To date, there has only been one systematic investigation of lens opacification among U.S. astronauts(1), which reported an increased risk of cataracts in astronauts with lens exposures of >8 mSv compared to those having lens exposures <8 mSv. Because these results were based on subjective and non-standardized lens evaluation techniques, and because NASA is planning prolonged manned space missions to the moon and to Mars, NASA funded this study to evaluate lens opacification in astronauts using standardized and validated objective techniques.

NASCA employs a longitudinal cohort study which samples on exposure in order to compare cataract prevalence and incidence among exposed astronauts with cataract prevalence and incidence among non-exposed comparison subjects (exposure controls). The most important factor considered when choosing the suitable comparison population for astronauts was the lifestyle difference surrounding health and fitness. Active astronauts are selected through stringent medical criteria and are under continual medical surveillance to sustain qualified flight

status and optimal fitness. Exposure control populations available from the local occupational aerospace community are not under such strict health surveillance, and therefore have the potential to become, on average, less healthy and fit. For this reason, we formed two subpopulations in the exposure control group: one consisting of subjects with a history of military aviation, and one without any military or commercial occupational aviation history. The former group of exposure controls is referred to as “aircrew”, since the requirement to be in this group was to be part of military aircrew (e.g., pilot, co-pilot, navigator, radar/sonar operator, loadmaster, etc.). As such, their medical history at least parallels the flight medicine experience of astronauts. The latter group is referred to as “ground-controls,” for which health and fitness was not expected to mirror the astronauts nor aircrew controls.

The operational approach to NASCA is being carried out in two stages. In the first stage, a cross-sectional analysis of baseline (Year-1) data will be performed to assess the prevalence of cataract and identify associations between cataract, space radiation, and other host/risk factors. The second stage will consist of a longitudinal analysis to identify the incidence of cataract over the repeated annual eye exams adjusted for host/risk factors. In both stages, we will perform between-group and within-astronaut comparisons and dose-response modeling. This manuscript reports on the recruitment effort, the composition of the three cohorts (astronauts, aircrew, and ground-based controls) and provides basic, baseline data by group for: general demographics, ocular and lenticular health, nutrition, solar UV- and space-radiation exposures. This first report also describes and references the methods used in the NASCA project.

The specific aims of the NASCA study are:

1. To determine the prevalence of age-related C, N, and PSC lens opacities in the complete sample of astronauts and control populations (military aviators and ground-based subjects), and determine the risk or cataract associated with radiation exposure during space flight.

2. To determine the prevalence of age-related C, N, and PSC lens opacities and risk of cataract associated with non-space flight among the control subjects.

3. To modify the ocular assessment protocol in the astronauts' regular annual medical examination to improve the assessment of the status of the crystalline lens.

4. To determine the progression of C, N, and PSC lens opacities in the complete sample of astronauts, the control populations of military aviators and ground-based subjects, and then determine the risk factors associated with cataract progression with a specific focus on the components and doses of radiation exposure during space flight.

Specific aims 1-2 will be determined using baseline data collected during the cross-sectional phase (year 1) of the study, while aim 4 on progression will be determined from the longitudinal phase (years 1-5). This report describes the recruitment effort and results for the NASCA study and provides detailed descriptions about the sampling procedures, enrollment, and statistical comparisons of the enrolled subjects. Other papers are being developed to report etiological (cause-effect) statistical modeling results and synthesize findings with current knowledge on radiobiological and clinical aspects of density opaque and cataract.

METHODS

Human Subjects Committee (HSC) Approvals: Prior to recruiting, approval of the NASCA study protocol was obtained from the HSCs at Baylor College of Medicine (BCM), Johnson Space

Center (JSC), and the Brigham and Women's Hospital (BWH). Details of the informed consent documents are available on the NASCA web site (list NASCA web site URL).

Subject enrollment. Figure 1 illustrates the distribution and enrollment of all subjects expressing an interest in participating in the NASCA project. Individuals interested in participating were either excluded because they failed to meet all of the NASCA inclusion/exclusion criteria or enrolled because they met all exclusion/inclusion criteria (designated "eligibles"). All "eligibles" were consented, scheduled for a baseline examination, and those who met all exam criteria were entered into the full protocol (and designated active subjects). Likewise, those who met exclusion criteria were excluded from the study. We anticipated that some active subjects would drop out. As the study progresses, we will report data on subjects who complete the study and also on those who drop out (including any deaths, exclusions for cause, etc.).

Instruments (Questionnaires). All astronauts are required to have standardized annual medical/ocular examinations as part of routine flight medicine surveillance. Astronaut recruitment was initiated by mailing informational packets containing informed consent forms, lay summaries, invitation letters, a Demographics-Health-Sunlight Exposure Questionnaires (DHSEQ), and Harvard Food Frequency Questionnaires (HFFQ) one month prior to the annually scheduled examination (active astronauts) or annual exam anniversary (retired astronauts). Interested subjects were asked to bring completed paperwork to their next annually scheduled appointment. We mailed similar informational packets to potential exposure controls who responded to advertisements in local newspapers and NASA-sponsored electronic newsletters sent to NASA and contractor employees. Exposure controls were asked to return their signed consent forms and completed DHSEQs and HFFQs if interested in participating in the study. The military aviation history of the aircrew exposure control group was based upon self-reporting. The details of the recruitment procedures are found on the NASCA web site [give URL].

At the time of the baseline vision exam, the study was explained in full to each subject by the optometry staff. All completed data forms for consenting subjects were given to the Data Coordinator. The Data Coordinator also merged demographic, health, and sunlight exposure data into each subject's folder and electronic medical record. All study subject folders were kept in secure files. All DHSEQs and HFFQs were delivered to the Forms Manager proper handling. The DHSEQ was administered to all subjects only at baseline; however, the HFFQ was administered to all study participants at baseline and at each follow-up visit (2). Regarding the DSHEQ, subjects were asked for basic identification data and demographic information such as birth date, age, gender, local address, and contact information. DHSEQ data were gathered on personal health history, medical conditions diagnosed by a physician, ocular medical history (cataracts, glaucoma, macular degeneration), past and current medications, ground-based ocular sunlight exposure since age 30, current use of glasses, contact lenses, (or other protective devices), percent of time sunglasses and hat were worn out doors, and time spent on the water. Smoking and ethnicity information were collected in year 2 of the study using a separate form. Subjects were asked to self-report their previous and current smoking histories and to self identify their ethnicity and racial group.

Ocular examination protocol. The optometric staff performed the standard astronaut ocular exam on all subjects during their baseline and annual visits. This protocol includes determination of the following. ***Eye color***: by inspection. ***Correction mode***: spectacles (with sphere, cylinder, and axis specified) and contact lenses (with base curves and power specified), spectacle type, contact lens type, contact lens material, contact lens design, and contact lens schedule. ***Confrontation Visual Fields***: were assessed unilaterally by finger counting in four quadrants at one meter. ***Visual acuity***: distance vision uncorrected each eye and both eyes, distance vision corrected (if required) each eye and both eyes, near vision uncorrected each eye and both eyes,

and near vision corrected (only if needed) each eye and both eyes. ***Refraction***: a manifest refraction was done in a 20 foot refracting lane to derive the best spectacle correction and the best-corrected visual acuity. High contrast, best-corrected Snellen visual acuity was measured with the Mentor B-VAT system, and high-contrast logMAR acuity was measured with the Early Treatment Diabetic Retinopathy Charts (4) (Numbers 2121,2122, 2123, 2152) according to the specified protocol. The number of letters correct (each eye) and the LogMAR acuities each eye were specified. Low contrast acuity was measured with Precision Vision back-illuminated charts. See the NASCA web site for additional details. ***Accommodation***: measured in diopters and (measured how?). ***Convergence***: (Measured how?) were recorded. ***Phorias***: (Measured how?) were recorded. *Tropias*: (Measured how?) were recorded. *Versions*: (Measured how?) were recorded. ***Intraocular pressure measurement***: IOP determination with Goldmann applanation tonometry and expressed in mm Hg. ***Biomicroscopic (slit lamp) examination***: A slit lamp evaluation of the adnexal and anterior segment tissues was done. Patients judged to have narrow angles were excluded. ***Pupillary dilatation***: Both eyes were maximally dilated with 1 gtt each of 0.5% proparacaine hydrochloride, Tropicamide 1.0%, and phenylephrine HCl 2.5%. Fundus examination was performed (With indirect ophthalmoscopy?) and findings of optic nerve, macula, retinal vessels, and periphery were recorded. ***Lens Opacities Classification System, Version III (LOCS III)*** (3): LOCS III-trained and -certified optometrists performed LOCS III grading of nuclear color (NC) after maximal pupillary dilatation was achieved. The NC scale is obtained by comparison to six standard images comprised of six standard images illustrating varying degrees of nuclear opalescence and color. The scale ranges from the lowest value of 0.1 to the highest value of 6.9. A lens given a LOCS III NC grade of 0.1 is essentially colorless. A lens with a LOCS III NC grade of 3.0 has a lemon-yellow brunescence. A lens given a LOCS III NC grade of 6.9 has advanced reddish-brown nuclear brunescence. We will ascertain if higher LOCS III NC scores contributes to the increased uncertainty associated with the objective assessment of mean pixel density in Scheimpflug slit images. ***LOCS III Training and Certification of staff***: A formal training session and a written test of competence was given to each of the NASCA optometrists (Drs. Manuel, Maxwell, Izsard, Gibson, and Choi). These training materials are found on the https://locs.webex.com web site. ***Nidek EAS 1000 Lens Imaging***: The Nidek EAS 1000 Lens Imaging System (5) was used to capture a single black/white digital Scheimpflug slit and two retroillumination images of the lens. One retro image was focused at the plane of the anterior capsule and the second was focused at the plane of the posterior capsule. Technically unsatisfactory images were rejected and new images were obtained prior to data storage. ***Image Analysis Protocols***: Both retroillumination and Scheimpflug slit images were analyzed using the Nidek EAS-1000, version 1.23E program. The details of the protocols described briefly below are available on the NASCA website. All analyses were performed by one analyst (WHT), and each analysis was checked for accuracy by LTC. Innaccurate analyses were repeated according to specific instructions by LTC. ***Image Analysis of Nidek EAS 1000 Digital Slit and Retroillumination Images***: Protocols were used to measure the total areas of cortical and PSC cataracts. We devised methods for assessing each separately in cases of mixed cataracts. We assessed ocular biometry and mean nuclear density at three nuclear loci (central clear zone, centers of the anterior, and posterior embryonal nuclei) in Scheimpflug slit images from this lens imaging system. ***Confrontation Field Testing***: Confrontation fields were assessed unilaterally by finger counting in four quadrants at 1 meter. ***Color Vision***: Color vision was assessed with Pseudo-Isochromatic 15 Color Plates under proper illumination. If 10 or more plates were correctly identified, color vision was classified as normal. ***Depth Perception***: was assessed by means of Optec 2300 (Stereo Optical) tester. Six groups of circles were presented with varying degrees of circle separation. A subject's stereopsis was designated as normal if s/he identified all circles at 20 seconds of arc. ***High and Low Contrast Sensitivity***: This was done with Precision Vision (PV) Acuity charts.

Lens space radiation dosimetry. Radiation sources in space include contributions from trapped protons in the Earth's Van Allen belts, galactic cosmic rays (GCR), and infrequent exposures from solar particle events (SPE) (7). The spatial and temporal variations of the GCR and trapped protons are determined by the sun's approximately 11-year solar activity cycle with the flux variation more than 2-fold over a cycle, and by the orbital parameters of the mission due to the variation in radiation amounts within the Earth's magnetic fields and radiation belts. The approach used at NASA is to utilize available radiation dosimetry from each mission in conjunction with space radiation transport models to estimate lens dose and dose equivalent (7-9, 20). The space radiation transport models are needed because thermoluminescence dosimeter (TLD) badges worn one on the chest or hip by astronauts measure only the absorbed dose and not the spectra components of space radiation needed to estimate biological equivalent lens doses. Spectral measurements of LET or ion charge and energy, are measured by area detectors, but not at the astronaut's body. Space doses are assumed to be made-up of two components representing GCR and trapped or solar particle contributions. The GCR contribution varies slowly with the amount of shielding and the trapped or solar radiation varies quite strongly becoming negligible at large shielding depth. This observation is used in a re-normalization procedure of transport code results first to flight specific area dosimetry and a second re-normalization to individual astronaut TLD badge doses. Checks for accuracy are also made in comparisons to area spectral data.

Assessment of ocular solar exposure. In the NASCA study, we assessed the effective ocular exposure (OE_{eff}), introduced by McCarty (10). OE_{eff}, in units of sun-years, serves as a surrogate measure of cumulative ocular solar exposure, and partitions the number of hours spent outdoors during the working week and weekend, with adjustment for protective factors such as the percentage of time wearing a hat, wearing sun glasses, contact lenses, glasses, and whether the time outdoors is over water (fishing, boating, swimming, diving and snorkeling, water skiing, windsurfing, kayaking, etc.). Data for calculating OE_{eff} were obtained during administration of the DHSEQ prior to the baseline eye exam. Subjects were asked to first construct their geographic residence history from age 30 until the current age, and provide for each geographic location the number of years lived in the location, the number of hours spent outdoors and over water during the week and on weekends, and the percentage of time wearing a brimmed hat, sunglasses, glasses, or contact lenses. Using the profile of ocular exposure throughout the residence history, a single value of OE_{eff} was determined using methods described by McCarty (10).

UV background rates for geographic areas of residence were not incorporated into OE_{eff}, since the breakdown of residence history into geographic region as was done to queue the subject's memory on lifestyle activity changes. Moreover OE_{eff} was used to reflect the combination of cumulative exposure and protective habits. The importance of assessing solar ocular exposure in the NASCA study is reflected in the known epidemiological and biological associations between ocular solar UV exposure and cataract. In 2002, McCarty and Taylor (11) reviewed 22 published epidemiologic studies on ocular solar ultraviolet (UV) exposure and cataract for biological plausibility, strength of the association, specificity, experimental evidence, temporality, dose-response relationship, and consistency of findings. Their results indicated that the majority of the studies met most of the epidemiologic criteria for causality and support an association between UV and the development of cortical cataract and perhaps posterior subcapsular cataract. They also concluded the epidemiologic data justify the implementation of public health campaigns to raise public awareness of the risk of cortical cataract due to ocular UV exposure. A molecular basis of UV-induced cataract has also been established, in which matrix metalloproteinases (12, 13), cytokines and growth factors (14-16), and beta crystallins (17) play an important role.

Statistical analysis: dimensional reduction of HFFQ data. The HFFQ resulted in 105 continuously-scaled variables representing daily intake. In order to minimize the potential for overfitting due to the curse of dimensionality (e.g., too many variables) during statistical dose-response modeling, the number of dimensions was reduced using principal components analysis (PCA). Prior to PCA, the 105 variables were partitioned into 12 a priori food groups representing fats, omega fatty acids, fatty acids, carbohydrates, amino acids, A vitamins, B vitamins, B12-folic vitamins, C vitamins, D and E vitamins, minerals, and trace elements. We left alcohol (gm), fiber (gm), caffeine (mg), and calories intact and did not assign these variables to any groups. The 12 nutrient groups and their constituent variables with units for daily intake are ***fats*** (animal fat gm, vegetable fat gm, total fat gm, saturated fat gm, monosaturated fat gm, saturated fat gm, polyunsaturated fat gm, cholesterol mg), ***omega fatty acids*** [linoleic gm, omega 3 (EPA, DHA, no alpha-linolenic acid) gm, linolenic fatty acid gm, eicosapentaenoic fatty acid (EPA) gm, docosapentaenoic fatty acid (DPA) gm, docosahexaenoic fatty acid (DHA) gm, omega 3 (EPA, DPA, DHA, alpha-linoleic) gm 2000, long chain N3 fatty acid, omega-6 (c182s, Arachadonic fatty acid gm, no gamma-linolenic acid) gm, omega-6 w/o supplements, long chain N3 fatty acid w/o supplements, omega-6 w/o supplements], ***fatty acids*** (oleic acid gm, butyric fatty acid gm, caproic fatty acid gm, caprylic fatty acid gm, capric fatty acid gm, lauric fatty acid gm, myristic fatty acid gm, palmitic fatty acid gm, stearic fatty acid gm, palmitoleic fatty acid gm, eicosenoic fatty acid gm, arachadonic fatty acid gm), ***carbohydrates*** (carbohydrates gm, lactose gm, fructose gm), ***amino acid*** (protein gm, methionine gm, animal protein gm, tryptophan gm, glutamate gm, aspartate gm), ***A vitamins*** (retinol IU, carotene IU, vitamin A IU , retinol w/o supplement, vitamin A w/o supplements, alpha carotene mcg, beta carotene mcg, beta cryptoxanthin mcg, lycopene mcg, lutein and zeaxanthin mcg, retinol equivalents of vitamin A mcg, retinol activity equivalents mcg, retinol equivalents of vitamin A without supplements, retinol activity equivalents without supplements, carotene without supplements, beta carotene without supplements), ***B vitamins*** (vitamin B-1 mg, vitamin B-2 mg, niacin mg, vitamin B-6 mg, pantothenic acid mg, vitamin B-1 without supplements, vitamin B-2 without supplements, vitamin B-6 without supplements, niacin without supplements, pantothenic acid without supplements), ***B-12 vitamins*** (total folate post 1998 mcg includes supplements and fortified foods, vitamin b12 mcg, total folate without supplements, vitamin B-12 without supplements, natural food folate 2001 mcg , folic acid from supplements and fortified foods 2001 mcg, folate equivalents mcg includes supplements and fortified foods), ***C vitamins*** (vitamin C mg, vitamin C without vitamin pills), ***D and E vitamins*** (vitamin D IU, vitamin D without vitamin pills, total vitamin E mg atoco includes supplements and fortified foods, vitamin E mg atoco from food fortification only synthetic, vitamin E mg atoco w/out vitamin supplementation mcg includes fortified foods), ***minerals*** (calcium mg, iron mg, magnesium mg, phosphorous mg, potassium mg, zinc mg, sodium mg, manganese mg, calcium without vitamin pills, iron without vitamin pills, zinc without vitamin pills , phosphorous without vitamin pills, potassium without vitamin pills, magnesium without vitamin pills, manganese without vitamin pills), and ***trace elements*** (iodine mcg, selenium mcg, copper mg, copper without supplements). Unrotated PCA (Stata 9, College Station, TX; SPSS 14, Chicago, IL) was performed on the set of variables in each of the 12 food groups described above. PC extraction was based on components for which eigenvalues exceeded a value of 2, which mostly resulted in only one PC. However, on occasion, there were 2 PCs for which the eigenvalues exceeded a value of 2.

Statistical analysis: group differences. Although the recruitment process was designed to match proportions of subjects in each study group within age decade brackets, there remain many potential cataract-causative differences between individuals that might not have been balanced in the realized study design. Further, during the cross-sectional analysis, it was imperative to identify confounding variables which were both significantly different across the three groups and potentially explanatory for the prevalence of cataract. Hypothesis testing was performed using chi-square contingency analysis for nominally-scaled variables (Table 4) and

Kruskal-Wallis non-parametric ANOVA for continuously-scaled variables (Table 5). The groupwise difference in continuously-scaled PCs for nutritional data was evaluated by performing Kruskal-Wallis non-parametric ANOVA on PC scores for only the first extracted PC for each of the 12 food groups (Stata 9, College Station, TX; SPSS 14, Chicago, IL). Measurements made on eye pairs were combined using the maximum value or measurement obtained from the "worst" eye as the dependent variable. Variables showing significant differences were flagged if p-values, adjusted for correlated multiple testing were less than 0.05 (6). It is intended that adjustment for differences in the significant variables would be made via regression models in the next analytical phase of the study. All statistical analysis involving chi-square tables, Kruskal-Wallis ANOVA, and Westfall-Young FWER were performed independently by both AF and LP and yielded identical results.

Statistical analysis: Propensity scores. An ideal goal for observational etiological studies is to randomly allocate subjects into different treatment groups in order to guarantee on average that there are no systematic differences in covariates between groups(18,19). NASCA, however, is a non-randomized study in which there is no control over group (treatment) assignment of subjects into the astronaut and control categories. Therefore, large differences could occur in observed covariates which may lead to bias in the effect of space radiation on cataract. The propensity score provides a scalar summary of covariate information and is defined as the propensity (probability) that a subject's covariate profile represents subjects truly assigned to a given treatment group. Propensity scores based on significantly different confounder variables can be used to create a quasi-randomized experiment with adjustment to the treatment effect. The BioMedStat program (http://www.chipst2c.org/BioMedStat.html) was used to perform polytomous logistic regression in which class membership was regressed on categorical and continuous confounder variables identified to be significantly different between the 3 groups. P-values for significant categorical confounder variables were determined using log-linear regression (SPSS Version 14, Chicago(IL)) with the vector of propensity scores used as a covariate. P-values for significant continuously-scaled confounder variables were assessed using univariate GLM (SPSS Version 14, Chicago, IL) with propensity scores serving as a covariate. In addition, for continuously-scaled confounder variables, log-normal transformations were performed in order to assure normality.

RESULTS

Enrollment. A major goal of NASA in funding the NASCA study was to gain additional perspective on the issues and findings of the first study of cataract in astronauts(1). The lens opacity classification method used in (1) was not standardized or validated, and the terms used to describe the type and severities of various opacities (See Column 1 of Table 3) were not the same as will be used in NASCA. There are additional differences between the original and the NASCA study populations of astronauts. These are evident in the lower half of Table 3. It is clear that in NASCA we have only 14/25 of the astronauts with non-trace cataract and only 26/48 of those with all grades of cataract. In the interim between the two studies five astronauts died, 6 had cataract surgery with IOL implantation, and 13 elected not to participate. These several differences suggest that a strict comparison of the results of the original and NASCA studies is not warranted.

Table 1, columns 2 and 3, compares the number of astronauts participating in the various NASA manned space programs who were subjects in the Cucinotta et al study(1), to the number of astronauts (and lenses) available for the NASCA study. Fifty-nine percent (59%) of those participating in the Cucinotta study (1) are participating in NASCA. Recruitment in NASCA started on May 5, 2004 and ended on May 16, 2006. Our goal was to enroll and match the 285

US astronauts living when NASCA started by gender and age group to 100 aircrew exposure controls and 100 ground-based exposure controls. This resulted in a nominal 1.4:1 matching ratio. Table 2 lists the recruitment data presented by decade for the first year of the NASCA project. The ground-based exposure control group had more young (<30y) individuals than the astronauts and aircrew exposure controls, and the aircrew exposure controls had more individuals in the 40-50y age group. Otherwise, the groups were well balanced in terms of the distribution of subjects by age decade. At this time, 230 astronauts have elected to join the NASCA study, which is lower than our original expectation.

Groupwise differences. Table 4 lists the group-specific frequencies (counts) and percentage of responses within categorical variable measured in the NASCA study. Chi-square P-values for tests of independence of categorical variables in Table 4 are listed. In order to incorporate correlation into significance tests, we ran Westfall-Young family wise error rates (FWER) for all variables. After adjusting for correlation, only 4 variables were significant: history of asthma (p=0.0041), history of hypertension (p=0.0004), history of obesity (p=0.0354), and number of medications reported taking (p=0.0017). Tests for ethnicity, racial category, tobacco usage, and all other histories of disease were not significantly different. Table 5 lists the group-specific average and standard deviation (s.d.) for each continuously scaled variable. FWER p-values for continuous variables were only significant for high contrast logMAR (p=0.0186). Solar ocular exposure was quite skewed having quartile values of 8.4, 18.1, 41.1 for astronauts of, 10.2, 22.1, and 58.3 for aircrew controls, and 9.9, 25.6, 48.6 for ground controls. Figure 2 shows the significant correlation between age at baseline and the natural logarithm of effective ocular exposure (Pearson r=0.476, P<0.0005; Spearman rank r=0.454, P<0.0005).

Propensity scores. Propensity scores for each subject were generated by using polytomous logistic regression in which the 3 binarized (1-yes,0-no) group membership variables were regressed on the significant categorical confounder variables (history of asthma, history of hypertension, history of obesity, number of medications reported taking, and the single continuously-scaled confounder (high contrast logMAR). Propensity scores for subjects in each of the 3 groups are shown in Figure 3. In Figure 3A, one can notice that there is overlap of scores and astronauts have a greater propensity for having confounder profiles similar to military aviators rather than ground controls. There were also 16 astronauts with greater propensity scores for the ground control group compared with their own group, but this rapidly degenerates since most astronauts took on propensity scores that are representative of their own group. Interestingly, almost all of the astronauts have a 0.2 propensity for having confounder profiles of military aviators. This is in agreement with the large proportion of military aviators (Figure 3B) with propensity scores greater than 0.5 for which confounder profiles represent those of the astronauts. Thus, the military aviator control group has a greater propensity for having confounder profiles similar to astronauts when compared with controls. For ground controls (Figure 3C), the majority of subjects had confounder profiles similar to astronauts and military aviators, with the remaining scores reflecting confounder profiles unique to ground controls. Lastly, Figure 3D shows the quantiles for P(astronaut) for the 3 groups, which suggests that for confounder profiles, the entire military aviator control group is more similar to the astronauts when compared with the ground controls.

The ability of propensity scores to balance differences between confounder variables across groups was evaluated using the propensity score for astronauts [i.e., P(astronaut)] for all subjects as a model covariate in log-linear regression (for categorical confounders) and GLM (for continuous confounders). Results indicate that the original chi-square p-value for history of asthma changed from <0.0005 to 0.127, for history of hypertension from <0.0005 to 0.801, for history of obesity from 0.005 to 0.080, and for number of mediciation reported talking from <0.0005 to 0.005. The Kruskal-Wallis p-value of 0.001 for the continuous confounder high

contrast logMAR changed to 0.894 after a $\log_e$ transformation (0.31+high contrast logMAR) and adjustment for propensity scores using GLM.

DISCUSSION

Radiation protection during prolonged manned flight to the moon and Mars is a major challenge that warrants continual research on bioeffects in order to minimize crew health risks. NASA places a high priority on crew radiation protection, and therefore supports the NASCA project. The primary reason for undertaking the NASCA study is to develop a more complete picture surrounding the new insights on cataract and space radiation exposure reported in Cucinotta et al.'s original paper (1). Different methods were used in NASCA, so we cannot precisely compare NASCA results to those of (1).

Efforts to recruit subjects in the NASCA study have been non-problematic and relatively straightforward. Varying levels of selection bias do exist depending on the group being considered. While many of the retired US astronauts have enrolled in NASCA, we have not been able to enroll the entire corp of retired US astronauts due to the impracticality of long-distance travel by those who have moved out of the study area. (this statement needs to be supported by comparing the distribution of dose for all astronauts vs. the distribution of NASCA astronauts - I have asked for these data from Frank during 11/15 conf call, and I will do the analysis). The majority of retired astronauts participate annually in the LSAH, returning each year via NASA-supported travel to the Lyndon B. Johnson Space Center for their annual follow-up physical -- and the majority of these are enrolled in NASCA. Several retired astronauts with previous space flight experience (i.e. space radiation exposure) were excluded from enrollment as a result of previous ophthalmological procedures.

We want to describe the success of the recruitment effort and the causes for non-participation of dropouts. [Dale and Lisa, we need a summary of disqualification reasons and dropouts assuming we know why they dropped out – include quantity of dropouts and a breakdown for astronauts and control types. Also, send their ID number so I can look at their baseline data.]

We also want to emphasize that we have gathered nutritional data with a validated instrument and describe the rationale for and the approach used in analyzing the nutritional data (principal components).

(Nutritional data were collected due to published reports on known cataractogenic risks and protective effects of certain nutrients. Need citations. Leo, based on your previous published epidemiologic studies, can you send relevant descriptions and citations for collecting the nutritional data.)

We want to comment on the solar UV and space-radiation exposure data. Leif and Frank, what are the key points to be discussed here? (I need to run correlations between age and solar to show how correlated they are).

We want to describe our goals for the short-term (cross-sectional) and the long-term phases of the NASCA program and the feasibility of reaching these goals.

(Cross-sectional) - To accurately assess the relationship of doses of space radiation, age, gender, solar UV exposure, and nutrition to the risk of lens opacification (cortical, nuclear, and posterior subcapsular) and nuclear color.
(Longitudinal) - To accurately assess the relationship of doses of space radiation, age, gender, solar UV exposure, and nutrition to the risk of progression of lens opacification (cortical, nuclear, and posterior subcapsular) and nuclear color.
(Longitudinal) -To identify nutrients or nutritional patterns that are associated with reduced risk of having lens opacification or progression of lens opacification.
To identify nutrients that may be associated with cataract and their interactions with other factors (e.g. space radiation).

The significant confounder variables used to develop propensity scores meet requirements for being pretreatment covariates related to group membership. A positive history of asthma, positive history of obesity, positive history of hypertension, number of medications reported taking, and high contrast logMAR are clinical selection criteria used during new astronaut screening.

ACKNOWLEDGEMENTS:

Grant Title: Precise Assessment of Prevalence and Progression of Lens Opacities in Astronauts as a Function of Radiation Exposure During Space Flight and Development of Improved Routine Clinical Assessment of Ocular Lens Status.
Grant Number: COOPERATIVE AGREEMENT NUMBER: NAG9-1491

JUSTIFICATION FOR CO-AUTHORS: Tung, Hardy, and Marak.

William H. Tung, B.S. performed all of the image analyses and organized the image data files for analysis by Dr. Feiveson.
Dale Hardy, M.S. was the team member at Baylor College of Medicine who recruited many of the pilots for the study, administered the Harvard Food Frequency Questionnaires (HFFQ), and organized all of the nutritional data for the project.
Lisa Marak, R.N. was the team member who was responsible for scheduling control group exams, integrating all of the study data with NASA's electronic medical record and management all of the image data.

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TABLE CAPTIONS:

Legend Table 1: Characteristics of participants in NASA missions

Legend Table 2: Recruitment for NASCA Study by Decade

Legend Table 3: (new wording): The upper half of this table compares by cataract class (as defined in the original study) the number of astronauts from the original study that are participating in the NASCA study. The lower half of the able enumerates the reasons astronauts who participated in the original study elected not to participate in NASCA.

Legend Table 4: We can provide the definitions of the various abbreviations, but we should wait until we know the results of the Kruskal-Wallis analyses since many of the comparisons may show now statistically significant differences. We would then omit the variables for which there are non-significant differences from this table.

Legend Table 5: Basic baseline data on visual function and other ocular measures.

Table 1. Characteristics of participants in NASA missions.

Mission (time periods)	**Number of Astronauts**	**NASCA Participants (# of lenses at risk)**	**Average Mission Lens Dose, mSv**
Apollo (1968 - 1972)	24	8 (16)	15.1
Skylab (1973 - 1974)	9	4 (7)	129.3
Mir (1995 - 1998)	7	6 (12)	114.3
ISS	13	10 (20)	73.5
Hubble Repair (1989 – 2003)	42	28 (56)	31.2
Total	**90**	**53 (59% overall participation)**	

[why is Shuttle ignored? If the radiation exposure is negligible, we need to state that in the text and perhaps also as a footnote to this table. Same for Mercury, Gemini and Apollo-Soyuz Test Project missions.]

Table 2: Recruitment for NASCA study by age and subject group.

Age Group	Subject Group, N(%)			
	Astronauts	Aircrew	Ground-controls	Total
<30	0(0.0)	0(0.0)	2(2.0)	2 (10.7)
30-39	20(8.7)	10(10.4)	14(14.0)	44 (37.2)
40-49	100(43.5)	24(25.0)	36(36.0)	160 (31.2)
50-59	66(28.7)	40(41.7)	28(28.0)	134 (0.9)
60-69	27(11.7)	13(13.5)	14(14.0)	54 (12.6)
70+	17(7.4)	9(9.4)	6(6.0)	32 (7.4)
Total	230(100.0)	96(100.0)	100(100.0)	426(100.0)

[I think it would be helpful to the readers to present the age distribution of the original 285 US astronauts. This would assist in comparing all three study groups to the population standard. It would also clarify why our subject distribution has this shape and why few subjects <30 were recruited. MW]

Table 3. Comparison of astronaut participation in NASCA and in study by Cucinotta et al. **(1).**

	Non-Trace		**All Cataracts**	
Cataract Type	**Cucinotta et al., 2001**	**NASCA**	**Cucinotta et al., 2001**	**NASCA**
PSC	3	2	5	3
ASC/Congenital	1	0	1	0
Cortical	9	7	20	14
Nuclear	6	1	8	2
PSC & CS	3	1	3	1
ASC& CS	1	0	1	0
CS & Nuclear	0	1	6	3
Dot Opacities	2	2	4	3
Total	25	14	48	26
	Reason for Non-Participation in NASCA			
	Non-Trace		**All cataracts**	
Deceased	-	2	-	3
Lens Implant Surgery	-	6	-	6
Other	-	1	-	3
Lack of consent or unknown	-	3	-	10
Total Non-participants	-	12	-	22

Table 4. Nominally-scaled demographic and general health variables [count(%)] assessed for confounding by using chi-square contingency table analysis.

Variable		Subject Group			Chi-square *P*-value
		Astronauts	**Aircrew**	**Ground-based controls**	
Male/Female		172/34	79/5	77/19	0.024
Ethnicity	Not Hispanic	176(95.1)	78(97.5)	68(93.2)	0.326
	Hispanic or Latino	9(4.9)	2(2.5)	4(5.5)	
	Other	-	-	1(1.4)	
Race	White	171(92.4)	73(93.1)	66(90.4)	0.912
	Black or African-American	6(3.2)	2(2.5)	2(2.7)	
	Asian	5(2.7)	2(2.5)	3(4.1)	
	American Indian/Alaskan Native	3(1.6)	2(2.5)	1(1.4)	
	Native Hawaiian or other Pacific Islander	-	-	-	
	Other	-	1(1.3)	1(1.4)	
History of asthma		2(0.1)	1(0.9)	10(10)	<0.0005[a]
History of diabetes		1(0.5)	-	1(1)	0.602
History of eye surgery		9(4.1)	6(6.3)	5(5)	0.707
History of gout		1(0.5)	3(3.2)	-	0.043
History of hypertension		13(6)	15(15.8)	24(24)	<0.0005[a]
History of macular degeneration		2(0.9)	1(1.1)	2(2)	0.706
History of obesity		-	5(5.3)	3(3)	0.005[a]
Prev. tobacco use(cigarette)		27(15)	21(26.9)	14(19.7)	0.078
Prev. tobacco use(cigar)		19(11.7)	19(27.5)	13(19.4)	0.012
#Medications reported taking	0	129(59.2)	44(46.3)	33(33)	<0.0005[a]
	1	46(21.1)	20(21.1)	24(24)	
	2	23(10.6)	12(12.6)	14(14)	
	3	7(3.2)	11(11.6)	14(14)	
	4	11(5)	6(6.3)	6(6)	
	5	2(0.9)	2(2.1)	4(4)	
	6	-	-	3(3)	
	7	-	-	1(1)	
	8	-	-	1(1)	

[a]Westfall-Young FWER p-values for history of hypertension (0.0004), #medications reported (0.0017), history of asthma (0.0041), and history of obesity (0.0354).
[b]*P*-value for groupwise difference using log-linear model with propensity score as a covariate.

Table 5. Continuously-scaled demographic, ocular, space radiation, and nutritional variables [average (s.d.)] assessed for confounding by using non-parametric Kruskal-Wallis tests.

Variable	Subject Group			Kruskal-Wallis *P*-value
	Astronauts	Aircrew	Ground-based controls	
Age (years)	51.24(9.9)	53.84(10.04)	50.57(10.78)	0.02
High contrast logMAR[a]	-0.13(0.09)	-0.11(0.09)	-0.08(0.13)	0.001[d,e]
Low contrast logMAR[a]	0.22(0.12)	0.24(0.12)	0.28(0.18)	0.015
Color vision test #1 score[a]	13.94(1.24)	13.93(0.59)	13.69(1.19)	0.008
LOCS III nuclear color[a]	1.35(0.5)	1.52(0.7)	1.53(0.85)	0.241
Intraocular pressure[a]	16.3(3.4)	16.5(3.02)	15.7(2.5)	0.199
nuc1[a,b]	52.09(18.71)	60.9(25.92)	56.35(26.31)	0.007
nuc2[a,b]	63.24(22.34)	72.63(27.47)	68.1(28.49)	0.002
nuc3[a,b]	77.16(21.45)	85.52(23.5)	79.98(24.98)	0.005
cort[a,b]	1.65(5.58)	1.33(2.64)	2.43(6.56)	0.059
PSC[a,b]	0.18(0.99)	0.28(1.08)	0.9(6.47)	0.371
Solar (OE_{eff}, sun-years)	35.28(52.47)	42.05(60.42)	40.5(52.07)	0.188
Space radiation dose (mSv)	0,8.47,19.77	-	-	-
Space radiation dose x latency (mSv-y)	0,86.92,186.02	-	-	-
Fats[c]	-0.2(2.29)	0.06(2.22)	0.4(2.54)	0.107
Omega fatty acids[c]	-0.12(2.11)	0.55(3.3)	-0.24(2.7)	0.095
Fatty acids[c]	-0.04(2.88)	-0.19(2.37)	0.28(2.97)	0.600
Carbohydrates[c]	0.03(1.57)	-0.14(1.69)	0.09(1.91)	0.538
B Vitamins[c]	-0.15(2.08)	-0.05(2.11)	0.36(2.22)	0.243
Folic Acid, Vitamin B12[c]	0.01(1.8)	-0.23(1.72)	0.18(2.19)	0.497
A Vitamins[c]	0.02(2.65)	-0.06(3.31)	-0.01(3.11)	0.595
Amino acids[c]	-0.13(2.22)	0.03(2.78)	0.28(2.51)	0.422
Minerals[c]	0.08(2.17)	-0.16(2.71)	-0.01(2.43)	0.48
Trace elements[c]	0.04(1.42)	-0.08(1.43)	-0.0042(1.5259)	0.805
D and E Vitamins[c]	-0.02(1.23)	0.16(1.52)	-0.09(1.51)	0.615
C Vitamins[c]	0.11(1.09)	-0.13(1.01)	-0.11(1.17)	0.04
Alcohol (gm-d^{-1})	20.74(8.73)	20.39(10.72)	20.62(8.69)	0.75
Fiber (gm-d^{-1})	10.31(9.74)	9.59(11.13)	10.3(13.79)	0.15
Caffeine (mg-d^{-1})	204.08(183.65)	217.43(191.05)	202.41(190.41)	0.779
Calories (-d^{-1})	1964.06(659.29)	1937.07(648)	2061.13(746.46)	0.566

[a]Mean (s.d.) of max{od,os}.
[b]Outcome variable, not used in Westfall-Young FWER analysis
[c]Mean (s.d.) of principal component scores based on first principal component extracted without rotation.
[d]Westfall-Young FWER p-value for high contrast logMAR (0.0186).
[e]*P*-value for groupwise differrence of $\log_e$(0.31+high contrast logMAR) adjusted for propensity scores using GLM was was 0.894.

FIGURE CAPTIONS:

Figure 1. Distribution and enrollment of all subjects expressing an interest in participating in the NASCA project.

Figure 2. Natural logarithm of effective ocular exposure (sun-years) as a function of age at baseline.

Figure 3. Propensity scores for astronauts and the two control groups (military aviators and ground controls). The propensity score is equal to the probability of group membership [i.e., P(Astronaut), P(Military aviator), and P(Ground control)] from polytomous logistic regression, given the covariate profile. Covariates used in polytomous logistic regression were confounder variables found to be significantly different between the 3 groups (history of asthma, history of hypertension, history of obesity, number of medications reported taking, and high contrast logMAR). 3A: Propensity scores predicted for with confounder values for astronauts. Several astronauts reflect confounder profiles more similar to military aviators or ground controls and interestingly have an invariant score of 0.2 for military aviators. 3B: scores predicted with confounder values for military aviators, showing that the majority have confounder profiles similar to astronauts, whereas (3C) ground controls have more confounder profiles unlike astronauts. 3D: Quantiles of P(Astronaut) for the 3 groups. Military aviator controls have confounder profiles more similar to astronauts when compared with ground controls.

Figure 1.

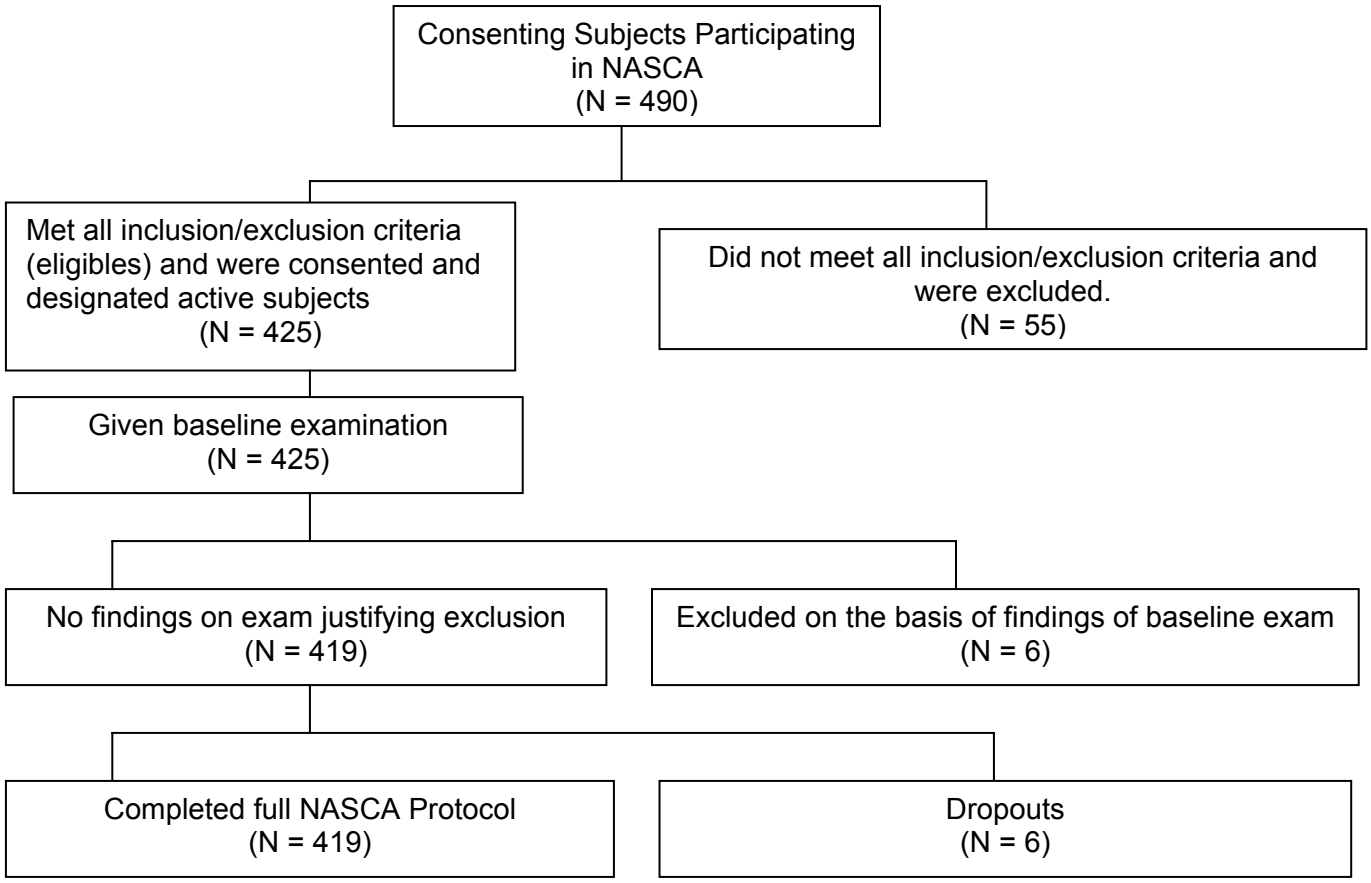
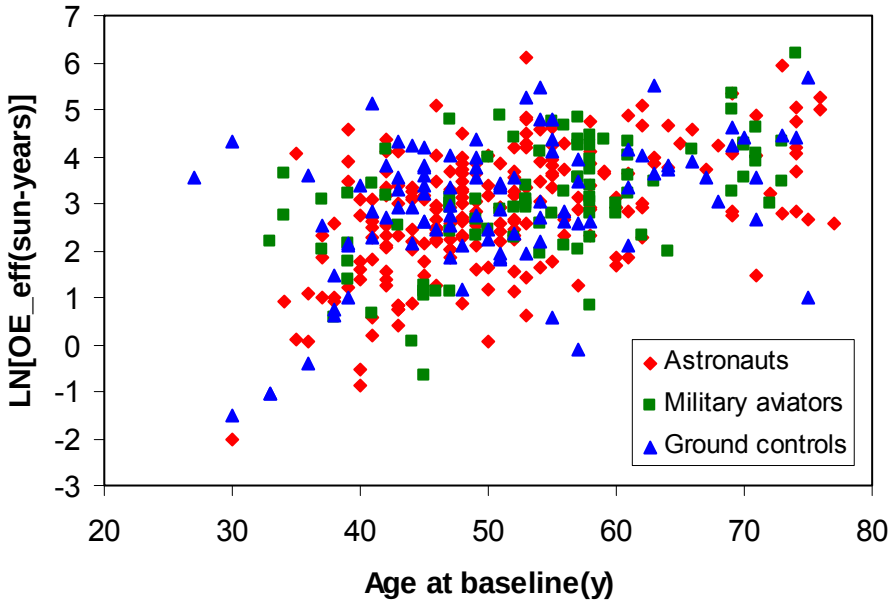
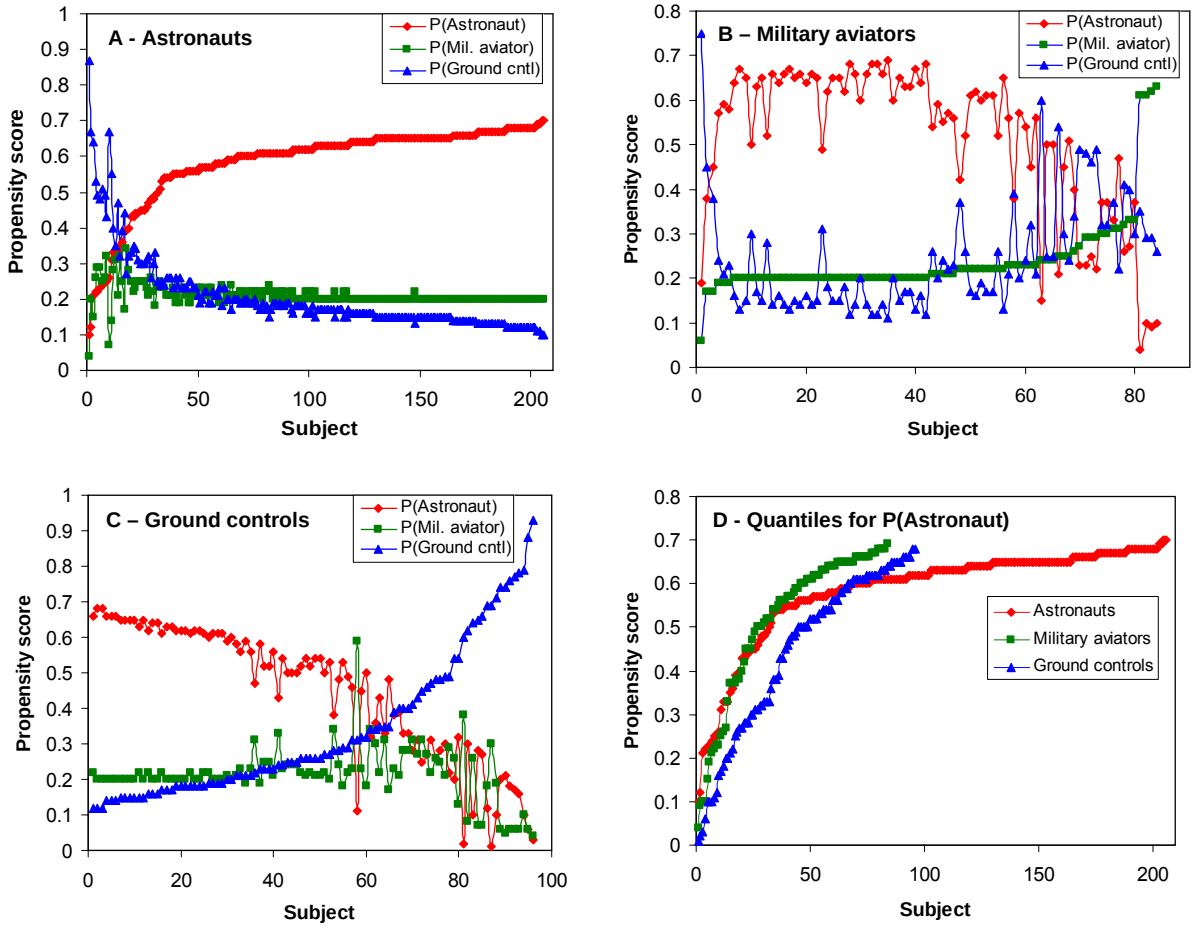

Consenting Subjects Participating in NASCA (N = 490)
Met all inclusion/exclusion criteria (eligibles) and were consented and designated active subjects (N = 425)
Did not meet all inclusion/exclusion criteria and were excluded. (N = 55)
Given baseline examination (N = 425)
No findings on exam justifying exclusion (N = 419)
Excluded on the basis of findings of baseline exam (N = 6)
Completed full NASCA Protocol (N = 419)
Dropouts (N = 6)

Figure 2.


LN[OE_eff(sun-years)]
7
6
5
4
3
2
1
0
-1
-2
-3
20
30
40
50
60
70
80
Age at baseline(y)
Astronauts
Military aviators
Ground controls



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