Long-term cardiovascular risk in astronauts: Comparing NASA mission astronauts to a healthy cohort from the Cooper Center Longitudinal Study

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Abstract
Objective: To determine the long-term cardiovascular disease risk of astronauts with spaceflight exposure compared to a well-matched cohort.

Methods: NASA astronauts are selected into their profession based upon education, unique skills, and health and are exposed to cardiovascular disease risk factors during spaceflight. The Cooper Center Longitudinal Study (CCLS) is a generally healthy cohort from a preventive medicine clinic in Dallas, Texas. Using a matched cohort design, astronauts who were selected beginning April 1, 1959 (and each subsequent selection class through 2009) and exposed to spaceflight were matched to CCLS participants who met astronaut selection criteria. 1514 CCLS participants matched to 303 astronauts in a 5-to-1 ratio on sex, date of birth, and age. The outcome of cardiovascular mortality through December 31, 2016 was determined by death certificate or National Death Index.

Results: There were 11 deaths due to CVD among astronauts and 46 among CCLS participants. There was no evidence of increased mortality risk in astronauts (hazard ratio [HR]: 1.10 (95% CI: 0.50-2.45)) with adjustment for baseline cardiovascular covariates. However, the secondary outcome of CVD events showed an increased adjusted risk in astronauts (HR: 2.41 (95% CI: 1.26-4.63)).

Conclusions: No increased risk of CVD mortality was observed in astronauts with spaceflight exposure compared to a well-matched cohort, but there was evidence of increased total CVD events. Given that the duration of spaceflight will increase, particularly on missions to Mars, continued surveillance of CVD risk, and mitigation of risk is needed to ensure the safety of those who venture into space.

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Introduction

The acute effects of spaceflight on the cardiovascular system have been a primary concern of aerospace medicine to ensure completion of mission critical tasks. Astronauts are selected to have a lower overall risk of cardiovascular disease (CVD).[1,2] Those who experience spaceflight are exposed to CVD risk factors, including psycho-social stress, impaired sleep,[3] changes in exercise routines,[4] radiation exposure,[5] and altered dietary practices.[6] Subclinical manifestations of CVD during and after spaceflight may include altered lipid profiles,[7,8] increased levels of oxidative stress and inflammation,[7]and insulin resistance.[8] It is unclear whether these are short-term manifestations of spaceflight or have long-term implications for CVD risk in astronauts.

Previous studies assessed CVD risk in astronauts using publicly-available information[9-11] or through examination of medical records maintained by National Aeronautics and Space Administration (NASA).[12-14] In general, these epidemiological studies have concluded that there is no evidence of higher rates of CVD morbidity and mortality in astronauts compared to other study cohorts or the general population. Methodological concerns of these studies include comparison to cohorts without similar baseline cardiovascular health profiles or longitudinal follow-up. To specifically address these issues, NASA collaborated with The Cooper Institute (Dallas, Texas) to match astronauts who had spaceflight exposure with participants in the Cooper Center Longitudinal Study (CCLS), who represent a generally healthy population with measured cardiorespiratory fitness (CRF), a strong predictor of CVD risk. The aim of this study was to evaluate the long-term CVD risk of astronauts compared to this cohort.

Methods

Overall Study Design

This study used a matched historical cohort design. CCLS participants who met the qualifying standards of the NASA Astronaut Corps were retrospectively matched in a ratio of 5:1 on sex, date of birth (DOB) and age at entrance into the Astronaut Corps or CCLS. CVD outcomes were ascertained from records maintained by each respective group. The NASA Johnson Space Center (JSC)'s Institutional Review Board (IRB) reviewed and approved the study protocol as human subjects exempt. The CCLS is annually approved by The Cooper Institute's IRB.

Study Population

Astronaut applicants undergo comprehensive medical examinations. A distinct set of exclusion criteria are applied to select a population with the greatest chance of completing spaceflight. During their active careers, astronaut health is monitored with routine annual physical examinations occurring with greater frequency when assigned to a mission. Astronauts have prompt access to medical care through the NASA JSC Flight Medicine Clinic (FMC) and referral to medical specialists as needed. Upon retirement from active careers, astronauts may voluntarily return to the JSC FMC for annual preventive exams and provide outside medical records to augment the JSC medical record. This study included astronauts who were selected from the first astronaut class in 1959 through the class selected in 2009 and who completed at least one spaceflight mission prior to the defined end of the study. Eight astronauts who died prior to the inception of the CCLS in 1970 were not considered. No astronaut had a history of CVD at their time of selection.

The CCLS is a prospective observational study designed to evaluate the relationship between CRF, physical activity, and health.[15] The Cooper Clinic in Dallas, Texas allows patients to sign an informed consent for the use of their de-identified clinical data in the CCLS. The cohort is largely White and well educated with access to medical care. The CCLS sample pool included only those individuals without preexisting CVD.

Clinical Status

For astronauts, an aerospace medicine-trained physician conducted the selection examination, taking a detailed health history including illness, injury, and lifestyle behaviors. Interval medical history including illnesses and hospitalizations was reviewed and documented during an annual physical exam. Out-patient and hospitalization records were requested and incorporated into the JSC medical record. CCLS participants undergo a preventive examination by Cooper Clinic physicians. Examinations occur as frequently as annually but frequency is not based on a systematic research protocol. Clinic physicians conduct an extensive medical history including cardiovascular history and lifestyle behaviors.

CVD covariates were measured using standard clinical protocols per study institution. Weight in kilograms and height in meters were assessed using a standard clinical scale and stadiometer. Body mass index (BMI) was calculated as weight/height^2. Seated resting blood pressure was measured using a sphygmomanometer and reported in mmHg. After a 12-hour fast, venous blood samples were collected and assayed by respective study laboratories according to standard procedures and reported in appropriate units. For astronauts, fitness was measured using a bicycle ergometer test for the first astronauts selected in 1959,[16,17] the Balke treadmill protocol during years 1962 to 1969,[18] and the Bruce protocol starting in 1978.[19] No astronauts were selected between 1960-1961 or 1970-1977. For CCLS participants, CRF testing used the modified-Balke protocol as previously described.[15,18] Maximal VO_2 levels were estimated from exercise test results for both astronauts and CCLS participants.[20] Treadmill time has been found to be correlated with maximal oxygen uptake for both the Balke protocol (r=0.92) and the Bruce protocol (r=0.88), with significant (r=0.90) inter-test correlations.[21] Treadmill time using the modified-Balke protocol is highly correlated with measured maximal oxygen uptake in men (r=0.92) and women (r=0.94).[21,22]

Assessment of CVD Outcomes

Mortality outcomes were assessed by each group through December 31, 2016. Among astronauts, CVD deaths were derived from medical records and death certificates by an epidemiologist from the Lifetime Surveillance of Astronaut Health (LSAH) and reviewed by a second epidemiologist for quality assurance. For CCLS participants, deaths and causes of death were determined using the National Death Index. CVD death was classified with International Classification of Disease, Ninth Revision (ICD-9) codes 390-449 through 1999 and ICD-10 codes I00-I99 for deaths after 1999.

Non-fatal CVD events were available through the end of 2011, so the end of study was December 31, 2011. CVD events were comprised of CVD death, non-fatal myocardial infarction (MI), non-fatal atherosclerotic stroke, coronary artery bypass graft (CABG) surgery, and percutaneous coronary intervention (PCI). Hard CVD events were a subset of total events including only CVD death, MI, and stroke. Among astronauts, total CVD events were mined from physical examination data in JSC medical records. All records were abstracted using ICD-9 codes and Systematized Nomenclature of Medicine by an epidemiologist from the LSAH and reviewed by a second epidemiologist for quality assurance. For CCLS, non-fatal CVD events were determined by mail-back survey administered in 2011, review of Cooper Clinic medical records, or review of Medicare Administrative Claims data. Primary hospital records were obtained for incident CVD events and adjudicated independently by two board certified cardiologists with adjudication by a third cardiologist in the event of disagreement.

Matching Protocol

NASA astronauts were retrospectively matched to CCLS participants in a 1:5 ratio. In order to accommodate the privacy concerns of both organizations, matches were assigned in multiple phases. In the first phase, all CCLS participants meeting astronaut selection criteria at the time of their exam were identified.[23] Inclusion criteria were age 25-47 years, Bachelor's degree or higher, employed outside the home, height 60-76 inches, weight 103-165 pounds (women) or 124-233 pounds (men), fasting glucose < 125 mg/dL, normal ECG, normal exercise treadmill test, $VO_2max > 32.9$ mL/kg/minute, and no pre-existing conditions. CCLS participants of the same sex, within 5 years of DOB and within 10 years of selection age of each astronaut were eligible matching candidates.

In the second phase of matching, matches from each astronaut's CCLS candidate pool were assigned to minimize the total absolute difference in DOB across the cohort. Each CCLS matching candidate was assigned to at most one astronaut, and an attempt was made to assign five matching candidates to each astronaut, one from each quintile of the sex-specific distribution of astronauts' selection VO_2max.

The matching protocol was applied to two distinct analysis samples: CVD mortality through December 31, 2016 and CVD events through December 31, 2011. Figure 1a (n=1817) displays the sample selection for the CVD mortality analysis. Figure 1b (n=1772) displays the sample selection for the CVD event analysis, comprised of two separate components. The first component included astronauts alive at the end of 2011 matched to CCLS controls who responded to a follow-up survey in 2011.[24] The second component included astronauts who died prior to the end of 2011 matched to CCLS controls who died prior to the end of 2011. CCLS participants selected for the CVD event analysis were not a strict subset of those selected for the CVD mortality analysis as three additional astronauts completed a spaceflight mission between 2011 (morbidity assessment by survey & mortality assessment) and 2016 (mortality assessment only).

Statistical Analysis

Baseline characteristics were summarized by the two exposure groups. Unadjusted and adjusted hazard ratios (HR) and 95% confidence intervals (CI) for astronauts versus CCLS were estimated using proportional hazards regression stratified by matched set. Attained age was used as the time scale, so that all risk comparisons involved individuals of the same age during follow-up. Adjustments were limited by the number of CVD events in both groups; final adjustment included baseline smoking, CRF, systolic blood pressure and total cholesterol. Proportional hazards assumptions of each covariate were assessed using weighted Schoenfeld residuals. Follow-up for CVD mortality began at the date of selection for astronauts and first clinic visit for controls. Follow-up for CVD mortality was right-censored on the date of non-CVD death or December 31, 2016. Follow-up for CVD events began at the date of selection for astronauts and the first clinic visit for controls. Follow-up for CVD events was right-censored on the date of non-CVD death or December 31, 2011. A sensitivity analysis including each astronaut and their best CCLS match in VO_2max was also conducted.

Power to detect a group difference was calculated from matched data simulated from Gompertz mortality models with the same total number of events and a range of HR. The sample had 80% power to detect a HR of 2.3 (NASA versus CCLS) for CVD mortality, 2.1 for total CVD events and 2.4 for hard CVD events. Optimal matching was programmed in R, version 3.5.2,[25] using the lpSolve package[26]. All other analyses were programmed in SAS/STAT®, version 9.4 (SAS Institute Inc., Cary NC, USA).

Results

The CVD mortality analysis included 303 astronauts matched to 1514 CCLS controls. Astronauts and controls were closely matched; the average differences in DOB and age being 47 days and 5.4 years, respectively. Characteristics at baseline are displayed in Table 1a. Matched samples of astronauts and CCLS controls were similar with respect to demographic characteristics except for military experience, with more astronauts having military experience than CCLS controls. Cardiovascular risk factors such as cholesterol and blood pressure were similar between the groups. Mean CRF was nearly identical. The median cumulative spaceflight exposure for astronauts at the time of death or the end of the study period was 27 days.

The crude incidence of CVD mortality through 2016 was 1.25 events per 1,000 person-years of follow-up for astronauts versus 1.00 for CCLS (Table 2, left). There were no CVD deaths among women in either group. Table 3 displays the estimated HR for group comparisons, unadjusted and adjusted for cardiovascular covariates. All covariates satisfied the proportional hazards assumption. There was no evidence of a statistically significant difference in CVD mortality when comparing the astronauts and CCLS within matched sets (HR = 1.12 (95% CI 0.57-2.22); adjusted HR = 1.10 (95% CI 0.50-2.45)).

A sensitivity analysis for CVD mortality was conducted including the single CCLS control best matched to an astronaut on baseline VO_2max. In this sample, the mean values of VO_2max were 46.6 and 46.3 mL/kg/min for astronauts and CCLS, respectively. Each group had 11 CVD deaths. The Cox proportional hazards model included only the group variable as there were few events. The HR was 1.13 (95% CI 0.43-2.92), a similar magnitude as the full mortality analysis.

The CVD events analysis included 300 astronauts (269 living and 31 deceased) and 1472 CCLS controls. The crude incidence of CVD events through 2011 was 1.90 per 1,000 person-years of follow-up for astronauts versus 1.37 for CCLS (Table 2, right). There was only one non-fatal CVD event among women. Table 3 displays the estimated HR for group comparisons for total CVD events and hard CVD events, unadjusted and adjusted for cardiovascular covariates. NASA astronauts had increased risk of CVD events compared to their CCLS matched cohort (HR = 1.84 (95% CI 1.04-3.27)). This relationship persisted after adjustment for CVD covariates (adjusted HR = 2.41 (95% CI 1.26-4.63)).

Discussion

In the largest study of NASA astronauts with spaceflight experience to date, we evaluated the effects of spaceflight on CVD mortality and morbidity. The overall event rate in both groups was small over the 30 years of average follow-up, indicating two healthy cohorts. Astronauts with spaceflight exposure had no increased risk of cardiovascular death when compared to a well-matched cohort. This conclusion did not change after adjusting for baseline levels of important risk factors including smoking status and CRF. Conversely, astronauts had a higher risk for the combined outcome of CVD death, non-fatal MI, atherosclerotic stroke, or revascularization procedures, compared to CCLS participants. The rate of MI and stroke diagnoses among astronauts was higher than CCLS participants; however, the rate of revascularization procedures was similar. Thus, occupational exposures of spaceflight may contribute to an increased risk of CVD as astronauts age. These increased diagnoses, nonetheless, did not translate into an increased risk in mortality due to CVD. Overall, these findings support previous reports that astronauts are a healthy population with no apparent increased risk of CVD mortality due to spaceflight-related occupational exposures.

All studies of long-term risk of spaceflight face the same key obstacles: few have traveled to space, and most have done so recently. By the end of 2016, only 303 NASA astronauts completed at least one spaceflight. Consequently, an effort has been made to find the most appropriate comparison cohorts, and each comparison has added to the body of evidence. A strength of the present study is the generally healthy and fit comparison cohort, with data collected over the same approximate period as the astronaut program. The robust data collected in CCLS made it possible to (1) identify a matching candidate pool that met the same selection standards as NASA astronauts and (2) control for differences in CRF, a strong predictor of CVD risk. Further, the size of the candidate pool allowed most astronauts to be matched to five CCLS controls in the mortality analysis. Matching on birthdate and age provided tight control over the age-dependence of cardiovascular risk, secular trends in medical technology including screening and treatment for CVD, and follow-up for fatal events.

The NASA Astronaut Corps is a unique occupational population selected on the basis of their skills, educational background, and health.[27] At the time of their selection, astronauts have a low overall risk for CVD. Spaceflight exposures, while short at a median of 27 lifetime days in space for NASA astronauts, can produce physiologic changes, as well as alter levels of CVD risk factors such as physical activity, sleep, and radiation exposure. Few studies have evaluated astronauts' lifetime cardiovascular health. Several studies have assessed CVD mortality of astronauts using publicly available data and reported no difference when compared to the general population or professional athletes.[28] Most recently, a study by Ade et al. of 310 NASA astronauts, regardless of spaceflight experience, found no greater risk of cardiovascular endpoints (defined as CVD death, MI, congestive heart failure, stroke, or CABG) compared to non-astronaut NASA employees.[14] Limitations in the study by Ade et al. included the inability to analyze mortality and morbidity separately, age was only available in decades to protect the privacy of the astronauts, and fitness was not controlled.

The novel finding from the current study is that there was an increased rate of CVD events in astronauts compared to controls but no increase in mortality. The etiology for this minor difference in hard events is uncertain at this time. Based on selection criteria, at their time of entrance into the Corps, astronauts are considered very low risk for CVD. However, during spaceflight, astronauts are exposed to CVD risk factors as well as changes in physiologic factors such as stress, sleep, and diet that are known to increase risk of CVD. Finally, the question of whether there are factors inherent to spaceflight, such as radiation exposure, exists. Ultimately, though, there is no increase in CVD mortality which makes on-going evaluation of CVD events crucial.

Strengths of the current study include the extensive phenotyping of both cohorts and the similar healthy nature of all participants at baseline. Importantly, incorporation of CRF into the matching process ensured sufficient overlap of this vital risk factor and provides control for any differences between the generally healthy CCLS cohort and the astronauts. CRF is a known risk factor for cardiovascular events and mortality that is only available in a limited number of cohorts. Thus, with the addition of CRF, CCLS is the best available comparison to date for the astronaut corps.

Our study had several limitations. Astronauts who were selected before 1970, prior to the inception of CCLS, were not as well matched on both DOB and age at selection. Next, the collection of non-fatal CVD outcomes differed between the two cohorts. Specifically, the absence of non-fatal event information in CCLS controls who died prior to the survey conducted in 2011 limited the CVD event comparison to fatal events in those who died prior to 2011. As well, the relatively small numbers and generally good health of both study groups limited the number of CVD events available for analysis. Finally, the study population lacked gender, racial and ethnic diversity and may not represent the demographic of currently active NASA astronauts.

Conclusion

Our study found no difference in CVD mortality between astronauts and a matched comparison with similarly measured CRF and traditional cardiovascular risk factors. In contrast, a secondary analysis found a low but significantly higher risk of CVD events. These findings have important implications for the lifelong care of astronauts and suggest that individuals in the Astronaut Corps are not at an increased risk of CVD death but may have an increased risk of events. Currently astronauts spend six months in low Earth orbit. In coming years, missions to Mars will last over three years without the ability to promptly return to Earth or access to emergency medical care. The increased CVD morbidity warrants further study of cardiovascular risk and its mitigation for astronauts completing long duration spaceflight. The mortality findings, however, increase optimism in human tolerance for space exploration.

Potential Competing Interests: The authors report no competing interests.

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Abbreviations and Acronyms:

BMI	Body Mass Index
CABG	Coronary Artery Bypass Graft
CCLS	Cooper Center Longitudinal Study
CI	Confidence Interval
CRF	Cardiorespiratory Fitness
CV	Cardiovascular
CVD	Cardiovascular Disease
DOB	Date of Birth
FMC	Flight Medicine Clinic
HR	Hazard Ratio
ICD	International Classification of Disease
IRB	Institutional Review Board
JSC	Johnson Space Center
LSAH	Lifetime Surveillance of Astronaut Health
MI	Myocardial Infarction
NASA	National Aeronautics and Space Administration
PCI	Percutaneous Coronary Intervention
PY	Person Years

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References

1. Bogomolov VV, Duncan JM, Sargsyan AE, Pool SL. Medical Support for Crewmembers of the International Space Station. In: Sawin CF, Hanson SI, House NG, Pestov ID, eds. *Space Biology and Medicine V: US and Russian Cooperation in Space Biology and Medicine.*2009:331-394.
2. Bogomolov VV, Castrucci F, Comtois JM, et al. International Space Station medical standards and certification for space flight participants. *Aviat Space Environ Med.* 2007;78(12):1162-1169.
3. Barger LK, Flynn-Evans EE, Kubey A, et al. Prevalence of sleep deficiency and use of hypnotic drugs in astronauts before, during, and after spaceflight: an observational study. *Lancet Neurol.* 2014;13(9):904-912.
4. Moore AD, Lee SMC, Stenger MB, Platts SH. Cardiovascular exercise in the US space program: Past, present, and future. *Acta Astronautica.* 2010;66:974-988.
5. Elgart SR, Little MP, Chappell LJ, et al. Radiation Exposure and Mortality from Cardiovascular Disease and Cancer in Early NASA Astronauts. *Sci Rep.* 2018;8(1):8480.
6. Douglas GL, Zwart SR, Smith SM. Space Food for Thought: Challenges and Considerations for Food and Nutrition on Exploration Missions. *J Nutr.* 2020;150(9):2242-2244.
7. Lee SMC, Ribeiro LC, Martin DS, et al. Arterial structure and function during and after long-duration spaceflight. *J Appl Physiol (1985).* 2020;129(1):108-123.
8. Hughson RL, Robertson AD, Arbeille P, et al. Increased postflight carotid artery stiffness and inflight insulin resistance resulting from 6-mo spaceflight in male and female astronauts. *Am J Physiol Heart Circ Physiol.* 2016;310(5):H628-638.
9. Reynolds RJ, Day SM. Mortality Due to Cardiovascular Disease Among Apollo Lunar Astronauts. *Aerosp Med Hum Perform.* 2017;88(5):492-496.
10. Reynolds RJ, Day SM. Mortality among U.S. astronauts: 1980-2009. *Aviat Space Environ Med.* 2010;81(11):1024-1027.
11. Reynolds RJ, Day SM. The effect of competing risks on astronaut and cosmonaut mortality. *Life Sci Space Res (Amst).* 2018;18:35-41.
12. Peterson LE, Pepper LJ, Hamm PB, Gilbert SL. Longitudinal study of astronaut health: mortality in the years 1959-1991. *Radiat Res.* 1993;133(2):257-264.
13. Hamm PB, Nicogossian AE, Pool SL, Wear ML, Billica RD. Design and current status of the longitudinal study of astronaut health. *Aviat Space Environ Med.* 2000;71(6):564-570.
14. Ade CJ, Broxterman RM, Charvat JM, Barstow TJ. Incidence Rate of Cardiovascular Disease End Points in the National Aeronautics and Space Administration Astronaut Corps. *J Am Heart Assoc.* 2017;6(8).
15. Willis BL, Morrow JR, Jr., Jackson AW, Defina LF, Cooper KH. Secular change in cardiorespiratory fitness of men: Cooper Center Longitudinal Study. *Med Sci Sports Exerc.* 2011;43(11):2134-2139.
16. Lovelace WR, 2nd, Schwichtenberg AH, Luft UC, Secrest RR. Selection and maintenance program for astronauts for the National Aeronautics and Space Administration. *Aerosp Med.* 1962;33:667-684.
17. Von Dobeln W. A simple bicycle ergometer. *J Appl Physiol.* 1954;7(2):222-224.
18. Balke B, Ware RW. An experimental study of physical fitness of Air Force personnel. *U S Armed Forces Med J.* 1959;10(6):675-688.
19. Bruce RA, Gey GO, Jr., Cooper MN, Fisher LD, Peterson DR. Seattle Heart Watch: initial clinical, circulatory and electrocardiographic responses to maximal exercise. *Am J Cardiol.* 1974;33(4):459-469.
20. *ACSM's guidelines for exercise testing and prescription.* 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2014.
21. Pollock ML, Bohannon RL, Cooper KH, et al. A comparative analysis of four protocols for maximal treadmill stress testing. *Am Heart J.* 1976;92(1):39-46.
22. Pollock ML, Foster C, Schmidt D, Hellman C, Linnerud AC, Ward A. Comparative analysis of physiologic responses to three different maximal graded exercise test protocols in healthy women. *Am Heart J.* 1982;103(3):363-373.

23. Gray GW, Johnston SL, Saary J. Medical evaluations and standards. In: Barratt MR, Baker ES, Pool SL, eds. *Principles of Clinical Medicine for Space Flight.* 2nd ed. New York, NY: Springer Nature; 2020.
24. Radford NB, DeFina LF, Barlow CE, et al. Progression of CAC Score and Risk of Incident CVD. *JACC Cardiovasc Imaging.* 2016;9(12):1420-1429.
25. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing. https://www.R-project.org/. Published 2018. Accessed2020.
26. Berkelaar M. lpSolve: Interface to 'Lp_solve' v. 5.5 to Solve Linear/Integer Programs. https://CRAN.R-project.org/package=lpSolve. Published 2015. Accessed.
27. Hamilton DR, Murray JD, Kapoor D, Kirkpatrick AW. Cardiac health for astronauts: current selection standards and their limitations. *Aviat Space Environ Med.* 2005;76(7):615-626.
28. Reynolds RJ, Day SM. Mortality of US astronauts: comparisons with professional athletes. *Occup Environ Med.* 2019;76(2):114-117.

Figure 1a. Sample selection for NASA astronauts (blue) and matched Cooper Center Longitudinal Study (CCLS) controls (yellow) leading to analysis sample (green) for cardiovascular disease (CVD) Mortality Analysis through complete data collection, 12/31/2016

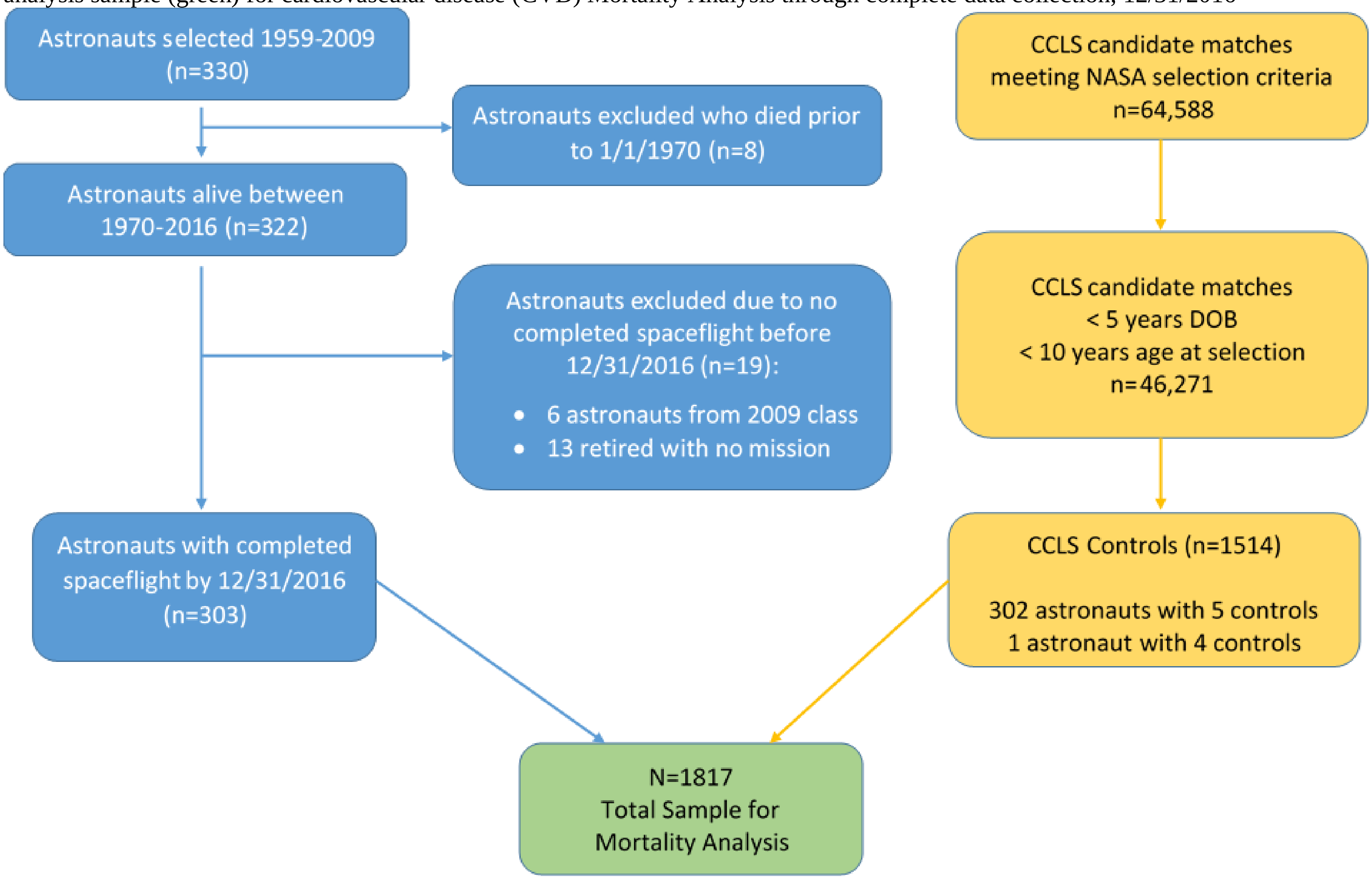

Figure 1b. Sample selection for NASA astronauts (blue) and matched Cooper Center Longitudinal Study (CCLS) controls (yellow) leading to analysis sample (green) for cardiovascular disease (CVD) event analysis through complete data collection, 12/31/2011

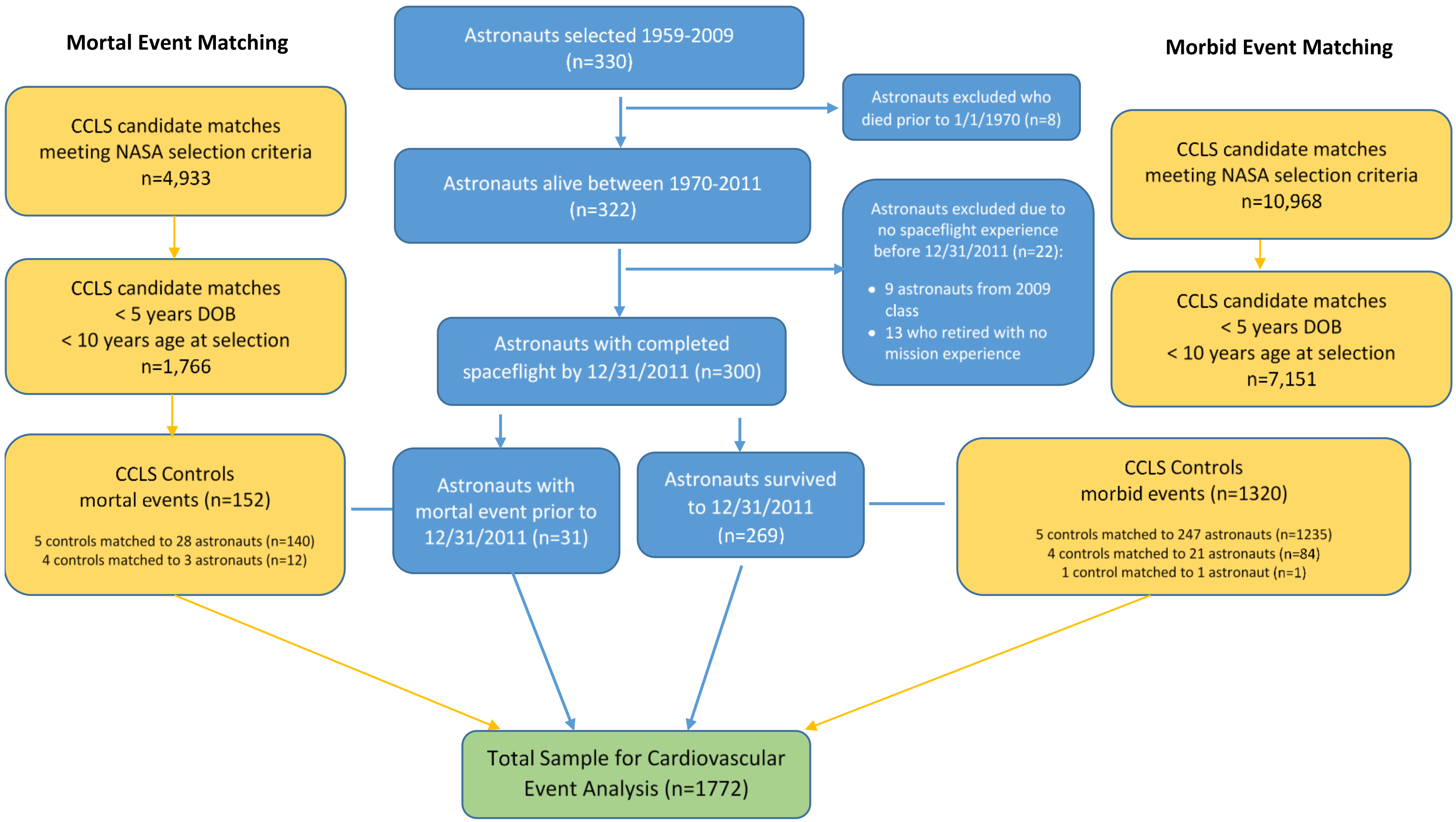
Mortal Event Matching
Astronauts selected 1959-2009 (n=330)
Morbid Event Matching
CCLS candidate matches meeting NASA selection criteria n=4,933
Astronauts excluded who died prior to 1/1/1970 (n=8)
CCLS candidate matches meeting NASA selection criteria n=10,968
Astronauts alive between 1970-2011 (n=322)
CCLS candidate matches < 5 years DOB < 10 years age at selection n=1,766
Astronauts excluded due to no spaceflight experience before 12/31/2011 (n=22):
• 9 astronauts from 2009 class
• 13 who retired with no mission experience
CCLS candidate matches < 5 years DOB < 10 years age at selection n=7,151
Astronauts with completed spaceflight by 12/31/2011 (n=300)
CCLS Controls mortal events (n=152)
5 controls matched to 28 astronauts (n=140)
4 controls matched to 3 astronauts (n=12)
Astronauts with mortal event prior to 12/31/2011 (n=31)
Astronauts survived to 12/31/2011 (n=269)
CCLS Controls morbid events (n=1320)
5 controls matched to 247 astronauts (n=1235)
4 controls matched to 21 astronauts (n=84)
1 control matched to 1 astronaut (n=1)
Total Sample for Cardiovascular Event Analysis (n=1772)

Table 1a: Baseline characteristics of NASA astronauts and Cooper Center Longitudinal Study (CCLS) participants matched on sex, date of birth, and age at baseline for cardiovascular disease mortality analysis through 12/31/2016

	Astronauts (n=303)			**CCLS (n=1514)**		
	Total N	N	%	Total N	N	%
Sex (male)	303	260	85.8	1514	1299	85.8
Military Service	303	223	73.6	1514	26	1.7
Smoking (current)	303	23	7.6	1514	182	12.0
	N	Mean[a]	SD	N	Mean[a]	SD
Birth Year	303	1951	12	1514	1951	11
Age (y)	303	34	4	1514	34	6
Framingham Risk Score	303	(0.3)	[0.1-0.8]	1514	(0.4)	[0.19-1.3]
CRF (METs)	303	13.3	2.1	1514	13.2	2.2
Total Cholesterol (mg/dL)	303	184	36	1514	195	39
HDL (mg/dL)	204	49	13	1040	49	13
LDL (mg/dL) – calculated	208	117	32	1029	119	34
Triglycerides (mg/dL)	287	(72)	[53-96]	1509	(85)	[61-122]
Blood Glucose (mg/dL)	295	94	9	1502	96	9
Systolic Blood Pressure (mm/Hg)	303	119	11	1514	118	12
Diastolic Blood Pressure (mm/Hg)	303	76	8	1514	77	9
Body Mass Index (kg/m^2)	303	23.6	2.3	1514	24.4	3.1

[a]Data presented as mean values and standard deviation or (median values) and [25th, 75th]
Abbreviations: CRF: cardiorespiratory fitness; HDL, high density lipoprotein; LDL, low density lipoprotein; MET, metabolic equivalent of task
SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; to convert triglycerides to millimoles per liter, multiply by 0.0113.
Sample sizes are smaller where a specific observation was missing.

Table 1b: Baseline characteristics of NASA astronauts and Cooper Center Longitudinal Study (CCLS) participants matched on sex, date of birth, and age at baseline for total cardiovascular disease (CVD) events through 12/31/2011

	Astronauts (N=300)			**CCLS (n=1472)**		
	Total N	N	**%**	Total N	n	%
Sex (Male)	300	257	85.7	1472	1257	85.4
Military Experience	300	220	73.3	1472	103	7.0
Smoking (Current)	300	23	7.7	1472	163	11.1
	N	Mean[a]	SD	N	Mean[a]	SD
Birth Year	300	1951	12	1472	1951	11
Age (y)	300	34	4	1472	39	5
Framingham Risk Score	300	(0.3)	[0.1-0.8]	1472	(1.0)	[0.3-2.2]
CRF (METs)	300	13.3	2.1	1472	13.3	2.1
Total Cholesterol (mg/dL)	300	185	37	1472	196	38
HDL (mg/dL)	201	49	13	1201	51	14
LDL (mg/dL) – calculated	205	118	32	1190	122	34
Triglycerides (mg/dL)	284	(72)	[53-96]	1470	(87)	[64-120]
Blood Glucose (mg/dL)	292	94	9	1464	96	9
Systolic Blood Pressure (mmHg)	300	119	11	1472	117	12
Diastolic Blood Pressure (mmHg)	300	76	8	1472	79	9
Body Mass Index (kg/m^2)	300	23.5	2.3	1472	24.7	3.0

[a]Data presented as mean values and standard deviation or (median values) and [25th, 75th]
Abbreviations: CRF, cardiorespiratory fitness; HDL, high density lipoprotein; LDL, low density lipoprotein; MET, metabolic equivalent of task
SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; to convert triglycerides to millimoles per liter, multiply by 0.0113.
Sample sizes are smaller where a specific observation was missing.

Table 2: Cardiovascular disease (CVD) mortality through 12/31/2016 and cardiovascular disease event outcomes through 12/31/2011 and follow-up for NASA astronauts and Cooper Center Longitudinal Study (CCLS) participants

	CVD Mortality (through 12/31/2016)			**CVD Events (through 12/31/2011)**		
	All	**Astronauts**	**CCLS**	**All**	**Astronauts**	**CCLS**
	Number of CVD Deaths			**Number of CVD Events**		
Total participants	1817	303	1514	1772	300	1472
Deaths	57	11	46	37	6	31
MI	--	--	--	7	4	3
Stroke	--	--	--	11	4	7
PCI	--	--	--	14	2	12
CABG	--	--	--	13	2	11
Hard CVD Events[a]	--	--	--	55	14	41
	Crude Mortality (per 1000 PY)			Crude Incidence (per 1000 PY)		
Death	1.04	1.25	1.00	0.99	0.81	1.03
All CVD Events	--	--	--	2.20	2.44	2.16
Hard CVD Events*	--	--	--	1.48	1.90	1.37
Avg follow-up time (years)	30.2 ± 10.3 (0.9-57.7)	29.1 ± 12.5 (6.1-57.7)	30.4 ± 9.7 (0.9-46.0)	21.0 ± 10.7 (0.2-52.8)	24.6 ± 12.0 (6.1-52.8)	20.3 ± 10.3 (0.2-40.8)
Avg attained age (years)	64.1 ± 11.1 (34.1-95.3)	63.1 ± 11.8 (35.1-95.3)	64.3 ± 11.0 (34.1-91.4)	58.9 ± 10.5 (24.2-90.3)	58.6 ± 11.2 (35.1-90.3)	58.9 ± 10.4 (24.2-86.3)
Avg attained age for those with an event (years)	71.8 ± 13.4 (43.4-90.3)	70.3 ± 14.5 (43.4-88.0)	72.2 ± 13.2 (45.0-90.3)	63.7 ± 10.9 (40.8-84.0)	62.8 ± 12.0 (42.7-83.0)	64.0 ± 10.6 (40.8-84.0)

[a]Hard CVD Events defined as MI, Stroke or CVD death

Abbreviations: CVD, cardiovascular disease; MI, myocardial infarction; PY, person years

Table 3: Estimated hazard ratios for cardiovascular disease (CVD) mortality and morbidity in NASA Astronauts versus Cooper Center Longitudinal Study (CCLS)

	CVD MORTALITY HR (95% CI)	**HARD CVD EVENTS[b] HR (95% CI)**	**CVD EVENTS[c] HR (95% CI)**
Number of Events / Sample Size	**57 / 1817**	**55 / 1772**	**82 / 1772**
Unadjusted Models			
Astronauts versus CCLS	**1.12 (0.57-2.22)**	**3.26 (1.04-6.90)**	**1.84 (1.04-3.27)**
Adjusted Models [a*]			
Astronauts versus CCLS	**1.10 (0.50-2.45)**	**3.22 (1.44-7.19)**	**2.41 (1.26-4.63)**
Smoking (Current Smoking vs. Nonsmoking)	1.13 (0.45-2.82)	1.42 (0.51-3.94)	1.46 (0.59-3.63)
Cardiorespiratory Fitness (per MET)	0.82 (0.70-0.97)	0.84 (0.68-1.03)	0.96 (0.83-1.10)
Systolic Blood Pressure (per 20 mmHg)	1.41 (0.88-2.26)	1.12 (0.612-2.03)	1.16 (0.72-1.86)
Total Cholesterol (per 40 mg/dL)	1.24 (0.93-1.66)	1.31 (0.89-1.92)	1.71 (1.27-2.31)

[a]Adjusted for baseline smoking, cardiorespiratory fitness, systolic blood pressure and cholesterol.
[b]Hard CVD events include death, myocardial infarction, or stroke.
[c]Total CVD events include hard events, PCI, or CABG.
Abbreviations: CABG, coronary artery bypass graft; CVD, cardiovascular disease; PCI, percutaneous coronary intervention;