Mortality Due to Cardiovascular Disease Among Apollo Lunar Astronauts

Robert J. Reynolds; Steven M. Day

INTRODUCTION: Recent research has postulated increased cardiovascular mortality for astronauts who participated in the Apollo lunar missions. The conclusions, however, are based on small numbers of astronauts, are derived from methods with known weaknesses, and are not consistent with prior research.

METHODS: Records for NASA astronauts and U.S. Air Force astronauts were analyzed to produce standardized mortality ratios. Lunar astronauts were compared to astronauts who have never flown in space (nonflight astronauts), those who have only flown missions in low Earth orbit (LEO astronauts), and the U.S. general population.

RESULTS: Lunar astronauts were significantly older at cohort entry than other astronaut group and lunar astronauts alive as of the end of 2015 were significantly older than nonflight astronauts and LEO astronauts. No significant differences in cardiovascular disease (CVD) mortality rates between astronaut groups was observed, though lunar astronauts were noted to be at significantly lower risk of death by CVD than are members of the U.S. general population (SMR = 13, 95% CI = 3–39).

DISCUSSION: The differences in age structure between lunar and nonlunar astronauts and the deaths of LEO astronauts from external causes at young ages lead to confounding in proportional mortality studies of astronauts. When age and follow-up time are properly taken into account using cohort-based methods, no significant difference in CVD mortality rates is observed. Care should be taken to select the correct study design, outcome definition, exposure classification, and analysis when answering questions involving rare occupational exposures.

KEYWORDS: spaceflight, radiation, circulatory disease.

Reynolds RJ, Day SM. *Mortality due to cardiovascular disease among Apollo lunar astronauts*. Aerosp Med Hum Perform. 2017; 88(5):492–496.

The mortality of space travelers has been studied repeatedly since the early 1990s, in both astronauts[6,8,10] and cosmonauts.[11] Researchers have examined all-cause mortality as well as mortality due to specific causes such as cancer and cardiovascular disease (CVD). Most studies show reduced risk of CVD mortality for space travelers in comparison to general populations of various nations.[8,10,11] Only one study failed to find a reduction in CVD mortality risk for space travelers, that of Delp et al.[5]

The earliest published analyses of mortality among space travelers were conducted using data from astronauts selected by the U.S. National Aeronautics and Space Administration (NASA).[8] The analysis examined mortality outcomes for NASA astronauts through 1991 and suggested that, in comparison to the U.S. general population, astronauts were at approximately half the risk of circulatory disease mortality and 64% the risk of ischemic heart disease mortality. In contrast, an analysis published in 2000 found NASA astronauts to be at approximately 1.2 times greater risk of cardiovascular mortality compared to controls selected from the civilian population of NASA's Johnson Space Center in Houston.[6] However, both of these studies were based on small numbers of astronaut deaths and thus none of the reported relative risk estimates were statistically significant. A later analysis, using data through 2009, confirmed lower risk of CVD mortality, estimating astronauts to be at less than one-third the risk in comparison to the U.S. general population.[10]

The mortality of Russian and Soviet cosmonauts has also been studied. Cosmonauts were estimated to have significantly

From Mortality Research & Consulting, Inc., City of Industry, CA.

This manuscript was received for review in September 2016. It was accepted for publication in January 2017.

Address correspondence to: Robert J. Reynolds, Ph.D., 17700 Castleton St., Ste. 586, City of Industry, CA 91748; rreynolds@mortalityresearch.com.

DOI: https://doi.org/10.3357/AMHP.4757.2017

lower mortality from all causes than the general populations of Russia, Ukraine, and other countries of cosmonaut origin. However, in comparison to U.S. astronauts, cosmonauts were found to have higher rates of all-cause and CVD mortality.[11]

A more recent analysis asserted an increased risk of CVD mortality for lunar astronauts.[5] In that study the authors used proportionate mortality ratios (PMR) to assess the excess risk of mortality by cardiovascular causes, comparing astronauts from the Apollo program to those who were trained but never flew in space and to those who flew missions in low Earth orbit (LEO) only. The authors reported that lunar astronauts had almost five times the proportion of expected CVD-related deaths when compared to nonflight astronauts, and about four times the proportion expected when compared to LEO-only astronauts. Based on this and the results of animal model experiments described in the same paper, the authors concluded that a potential explanation for the excess risk was damage to endothelial tissue from radiation exposure while in deep space. However, the studies' reliance on proportional mortality, especially when full cohort information could easily have been compiled, raises important doubts as to the interpretation of these results. Many readers, including the present authors, posted comments to the online version of the article, noting that substantial limitations of the data and methods make Delp et al.'s conclusion that Apollo astronauts experienced greater CVD mortality tenuous at best. A commentary by Cucinotta et al. raised doubts about the findings due to both the problems with a PMR analysis and the lack of detailed radiation information as an exposure in the analysis. We point the reader to the comments that follow the online version of Delp et al. and the detailed commentary by Cucinotta et al. for further details on these deficiencies.[4,13] Here we will discuss briefly one of the main limitations of the methodology employed by Delp et al.

Proportional mortality analyses have well-known and important limitations and potential biases. One problem is that an excess in proportionate cause-specific mortality for one group (say, Apollo astronauts) compared to others (say LEO astronauts or nonflight astronauts) may reflect any of 1) an excess of deaths due to the cause in question in the first group; 2) a deficit in deaths due to other causes in that group; or 3) an excess of deaths due to other causes in the latter groups. As noted in Breslow & Day,[1] proportionate mortality studies, "may indicate a fruitful orientation for later, more rigorous studies, and certainly provide a cheap and rapid way of taking an initial look at a set of data." When follow-up information is complete (with all deaths and follow-up time known), however, a full cohort analysis of mortality rates (rather than proportions of deaths without regard to exposure times) is preferable, and provides for more rigorous interpretations of what the true relationship may be between exposures and mortality.

Using a prospective cohort-based analysis, we sought to determine whether or not Apollo astronauts face greater risk of death from CVD in comparison to all other astronauts, all other flight astronauts, and all other nonflight astronauts. We also compared Apollo astronauts to the general population and compare results to those reported in earlier studies.

METHODS

Study Population

A subset of the data used here has been described previously.[10] For the current study we updated the database to include deaths and follow-up time for existing astronauts through the end of 2015 and added information on astronauts from NASA's 21st training class, selected in 2013. We also compiled information about astronauts selected for the U.S. Air Force's X-15, X-20, and Manned Orbital Laboratory (MOL) programs. All astronauts from these Air Force programs were considered to be nonflight astronauts for the purposes of this analysis (as was the case in Delp et al.[5]). The few astronauts that were selected into the NASA Astronaut Corps from earlier Air Force programs had their follow-up time start as of the date of first selection into any program.

Because the first lunar mission was flown in late 1968, follow-up for potential exposure time starts in December 1968 and ends on December 31, 2015. Similarly, we limited the sample under study to men, as only men have flown on lunar missions.

We classified a number of diseases and conditions as CVD-related, including myocardial infarctions, strokes, pulmonary edema, heart failure, thrombosis, and complications from cardiac or circulatory conditions. While not strictly all cardiac conditions, the broader term "cardio-vascular" subsumes earlier classifications such as "circulatory disease" and "ischemic heart disease." This classification is consistent with Delp et al., for example.[5] In accordance with federal regulations concerning the protection of human subjects in research, this study was exempt from institutional review, as the authors made no contact with the astronauts under study and the data used in this research are widely available public information.

General Population Mortality Rates

Mortality rates for the general population of the United States (specific to age, period, and males) were obtained from the Human Mortality Database.[12] This database compiles and publishes information on births and deaths in several countries from around the world. For the United States, data from as early as 1933 were available.

Statistical Methods

We determined standardized mortality ratios (SMRs) using the indirect method of standardization. In brief, the steps were the following:

1. Observed numbers of CVD deaths were determined separately for the Apollo and non-Apollo astronaut groups within each 5-yr age group and decade (from 1960 to 2015) stratum.
2. Beginning date of follow-up for the lunar astronaut cohort was determined based on the date of completion of each astronaut's first lunar mission (this to avoid so-called immortal time bias,[7] as an astronaut is guaranteed survival time to the end of the first lunar mission in order to be classified as

a lunar astronaut, and our focus in this study was on mortality of lunar mission astronauts). Beginning date of follow-up for nonlunar comparison astronauts was the astronaut's date of selection into the Astronaut Corps. Exposure time for each astronaut was then calculated as the time between an individual's beginning date of follow-up and the end of follow-up, the latter being either an astronaut's date of death, or the end of the study period, December 31, 2015, whichever came first.

3. Cause-specific mortality rates in each age and decade stratum were computed as the sum of the CVD deaths divided by the total follow-up time in that stratum.
4. Expected numbers of deaths for each age and decade were determined by multiplying the general population mortality rates or mortality rates determined in step 3 for nonlunar astronauts (LEO or nonflight) by the lunar exposure times determined in step 2. The resulting numbers of deaths were then summed by decade without regard to age.
5. SMRs were determined by dividing the observed numbers of deaths (step 1) by the corresponding expected numbers (step 4). Separate SMRs were thus computed for three comparisons: lunar astronauts to general population; lunar astronauts to LEO astronauts; and lunar astronauts to nonflight astronauts.
6. Confidence intervals for the SMRs were determined based on the assumption that the observed numbers of deaths follow a Poisson distribution.

Data processing and statistical analyses were performed using the R statistical computing package.[9]

RESULTS

Table I provides counts, exposure times, numbers of CVD deaths, and crude mortality rates for the different groups of astronauts used in this study. The dataset included all NASA astronauts up to and including Group 21 in 2013. This totaled to 288 astronauts who contributed 9 deaths due to CVD over approximately 7900 person-years of exposure time. Over approximately 720 person-years of observation time, 22 Air Force-selected astronauts contributed 2 additional CVD deaths.

Table I. Astronaut Data Sources and Contributions.

SOURCE OF ASTRONAUTS	COUNT	EXPOSURE	CVD*	CRUDE RATE†
All sources	310	8589.0	11	1.28
NASA Astronaut Corps	288	7869.4	9	1.14
Lunar	24	948.6	3	3.16
LEO	239	6487.3	6	0.92
Nonflight	25	433.5	0	0.00
USAF Programs	22	719.6	2	2.78
X-15	7	230.7	1	4.33
X-20	5	161.0	0	0.00
MOL	10	327.8	1	3.05

* CVD = Deaths due to cardiovascular causes.
† Crude death rate, expressed as deaths per 1000 person-years.

Crude CVD mortality rates were greatest for Air Force astronauts, at 2.78 deaths per 1000 person-years, compared with 1.14 deaths per 1000 person-years among NASA astronauts. Within the Air Force astronauts group the CVD death rate was greater for the X-15 group than the MOL group. None of the five X-20 astronauts died of CVD over the roughly 160 yr of exposure time they contributed.

The mean ages and standard deviations at various study milestones within each astronaut group are shown in **Table II**. The mean age at study start for LEO and nonflight astronauts were nearly identical, with means of 34.9 (SD = 3.6) yr and 34.6 (SD = 3.3) yr, respectively. The mean age at debut for lunar astronauts was significantly older at 39 (SD = 2.6) yr. This is to be expected as the study start for the lunar group was the date of completion of their first lunar mission, which delayed entry into the study by 6.5 (SD = 1.7) yr on average for lunar astronauts (not shown in Table II).

Surviving lunar astronauts were significantly older than the surviving nonflight and LEO astronauts at study close in December 2015. The younger age in the nonflight group is due to the addition of astronaut classes 20 and 21, both selected within the last 7 yr, many of whom have yet to be assigned to a spaceflight; the larger standard deviation results from the fact that 16 nonflight survivors were selected by NASA after 1995, and the remaining 7 were selected from the 1965 and 1967 astronaut classes (also not shown in Table II). No significant differences were seen between groups for mean age at death due to CVD, though the age at death in the lunar group was slightly lower with a larger standard deviation than the other groups. There were no significant differences in the age at death due to non-CVD causes, though lunar astronauts had a slightly higher mean age at 64.1 yr (SD = 10.1) vs. 54.9 (SD = 14.8) and 56.5 (SD = 19.5) in the other groups.

Table III presents SMRs for lunar astronauts in comparison to several groups: astronauts who never went to space (nonflight), astronauts who flew missions in LEO only, all astronauts who never flew a lunar mission (i.e., nonflight combined with LEO), and the general population of the United States. The estimated SMRs are also presented in several time periods: 1990–1999, 2000–2009, 2010–2015, and 1968–2015, the latter being the full range of the observation period for the lunar astronauts. Separate estimates for periods before 1990 are not presented as there were no CVD deaths in the lunar group and few CVD deaths in the comparison groups during those periods.

No astronaut-to-lunar astronaut SMRs were significantly different from unity in any time period or overall. We note that the direction of the SMRs pointed toward increased risk of CVD mortality for lunar astronauts in comparison to the other three astronaut groups in the 1990–1999 period, but in the 2010–2015 period, the SMRs pointed toward diminished risk or no difference for lunar astronauts. The summary SMR for 1968–2015 comparing lunar to nonflight astronauts was slightly elevated at 117, but was not significant, with a wide confidence interval. The summary SMRs from the remaining astronaut comparison groups suggest lower CVD mortality risk for lunar astronauts, but SMRs were again not statistically significant. In

Table II. Age Comparison Between Astronaut Groups for Select Study Events.

	LUNAR		LEO		NONFLIGHT		ANOVA*		
EVENT	MEAN	SD	MEAN	SD	MEAN	SD	*F*	DF	*P*-VALUE
Study start	**39.0**	2.6	34.9	3.6	34.5	3.3	15.949	2, 307	< 0.0001
Study end	**84.0**	2.5	62.6	10.0	61.1	19.5	32.5	2, 240	< 0.0001
CVD Death	66.7	13.6	72.1	11.0	70.8	3.2	0.244	2, 8	0.7888
Other Death	64.1	10.1	54.9	14.8	56.5	19.5	0.497	2, 54	0.6112

* Reference group for tests of mean differences is nonflight astronauts.
Bolded mean values significantly different from nonflight and LEO groups.

contrast, lunar astronauts were at greatly reduced risk of dying from CVD when compared to the general population. This was true over the entire 1968–2015 follow-up period, as well as in the 2000–2009 and 2010–2015 subperiods.

DISCUSSION

Results of the current analysis failed to demonstrate excess risk of mortality due to cardiovascular causes among astronauts who have flown on missions outside the Earth's magnetosphere (i.e., lunar missions). In addition, astronauts continue to demonstrate significantly (and greatly) reduced risk of CVD mortality in comparison to age-, period-, and sex-matched controls from the U.S. general population. Thus, the evidence presented here suggests that results of recent studies are still very much tenable.[6,10] Results reported by Delp et al., based on incomplete data and correspondingly limited methodology, are not supported.[5] In addition, the fact that one of the Apollo astronauts likely had pre-existing cardiovascular disease before going to the Moon further erodes support for the notion that exposure to galactic cosmic radiation on a lunar mission increases cardiovascular mortality.

Careful study of the data in Table II sheds light on the flaws inherent in Delp et al.'s PMR analysis: bias due to the age structure of the groups and deaths from competing risks in nonlunar groups. Because of the early period entry of the lunar cohort (December 1968 to December 1972), the lunar astronauts are among the oldest in the study (mean age of survivors 84.0 yr as of the end of 2015, Table II). This means that the lunar astronauts have had more time at risk for developing CVD, as CVD is typically a chronic disease which has dramatically higher age-specific risk in persons over age 65 yr compared to those under age 65.[2] Therefore, even under conditions of equal age-specific risk between lunar and nonlunar astronauts, the lunar astronauts would experience more deaths due to CVD than the younger astronauts in the cohort. Under these circumstances, the proportion of CVD deaths for the lunar astronaut group would be higher until all astronauts had died. This bias is compounded by the removal of nonlunar astronauts from the risk pool due to competing causes. Accidental deaths in the LEO and nonflight groups at relatively young ages not only mean that those astronauts are unable to die from CVD, they also mean that those astronauts experienced little to no time at high risk for death by CVD before death. Only cohort-based methods such as SMRs or Cox proportional hazard models properly capture these structural differences between groups and thus properly relate the relative risks.

A major limitation of all studies of astronaut mortality to date (including the present study) is the inability to control for lifestyle factors such as alcohol, tobacco, and relative diet and fitness levels. Of these factors, tobacco use is perhaps the most pertinent, as anecdotal information suggests that astronauts selected in the 1960s were heavy smokers. These are the astronauts who flew on Apollo lunar missions and are currently among the oldest in the astronaut cadre. If smoking habit among astronauts has changed over time in the same way in which it has in the U.S. general population (declining from 42% of adults in 1965 to under 20% of adults in 2014), then smoking may also be confounded with cohort effects, i.e., with selection year.[3] Thus, being a part of the lunar cohort would itself serve to confound the relationship between radiation exposures in deep space and mortality from CVD.

Our finding that astronauts are at lower risk of CVD mortality than the general population is consistent with prior research. However, the inclusion of X-15, X-20, and MOL astronaut

Table III. Standardized Mortality Ratios for Lunar Astronauts.

		NONFLIGHT			LEO ONLY			ALL NONLUNAR			U.S GENERAL POPULATION		
PERIOD	OBS*	EXP†	SMR‡	95% CI	EXP†	SMR‡	95% CI	EXP†	SMR‡	(95% CI)	EXP†	SMR‡	95% CI
1990-1999	2	1.2	171	21–616	0.9	213	26–770	1.0	192	(23–693)	3.9	51	6–184
2000-2009	0	1.4	0	0–267	0.9	0	0–391	1.1	0	(0–326)	6.4	0	0–57
2010-2015	1	0	–	–	1.3	77	2–427	1.0	99	(3–554)	6.6	15	0–84
1968-2015	3	2.6	117	24–343	4.2	72	15–210	3.7	81	(17–237)	20.4	15	3–43

* Observed number of deaths due to cardiovascular disease in the lunar astronaut group.
† Expected number of deaths in the lunar astronaut group based on mortality rates from the comparison group.
‡ Standardized mortality ratio comparing cardiovascular disease mortality rates in the lunar astronaut cohort (numerator) to those in the given cohort (denominator). An SMR greater than 100 indicates an excess of deaths in the lunar astronaut group.

groups by Delp et al. and in the present study differs from prior studies. In spite of this difference in study group composition we note that the SMRs reported here are similar in magnitude to those reported previously.[8,10]

In any retrospective cohort analysis of observational data, choices regarding groupings of cohort members and how exposure is classified can influence the results of the study. For example, in the present study all LEO astronauts spent time as nonflight astronauts before their first mission, and that exposure time could be attributed to the nonflight cohort. This choice would make a small difference in the SMRs in Table III for the LEO and nonflight groups, but it would not impact the all-nonlunar SMRs or the overall conclusions of this study.

Cucinotta et al. raise more important issues regarding the complexity of determining with any precision levels of radiation exposure among the various astronaut cohorts.[4] Because our analysis sought to test the conclusions of Delp et al.[5] (using appropriate cohort-based methods rather than case-control/PMR methods), we largely followed that study's choices regarding subject selection, outcome definition, and exposure classification. Different choices for any of these components could lead to different conclusions and whether any of the differences in mortality rates reported here can be attributed to different levels of radiation exposure is very much an open question.

Determining the long-term effects of space travel on mortality is a difficult task. The small numbers of people who have been space travelers, combined with the relatively small amount of time those travelers have collectively spent in space, leads to a genuinely rarified cohort with relatively small amounts of exposure to the space environment. Methodological difficulties are compounded by the temporal distribution of astronauts to date and the resulting period and cohort effects that distribution generates. Until the available data reach a critical density, cause-specific mortality analyses are, at best, an early warning surveillance system that is likely to detect only the most dramatic of health effects stemming from space travel. It is, therefore, important to continually reassess the mortality of astronauts in methodologically sound ways and reserve judgement until such a time as the evidence warrants strong conclusions. As is proper with all scientific inquiry, null results of these ongoing studies should be presented in terms of a lack of evidence of increased cause-specific mortality. In this spirit, we conclude by noting that presently there is no credible evidence of increased CVD-specific mortality among astronauts—lunar or otherwise. In fact, the evidence points toward the opposite: there is no discernible difference between astronaut subgroups and, because of the healthy worker effect, astronauts have a lower mortality rate for cardiovascular causes than does the general population as a whole. As noted, only (additional follow-up) time will tell if these conclusions persist.

ACKNOWLEDGMENTS

Authors and affiliation: Robert J. Reynolds, M.P.H., Ph.D., and Steven M. Day, M.S., Ph.D., Mortality Research & Consulting, Inc., City of Industry, CA.

REFERENCES

1. Breslow NE, Day NE. Statistical methods in cancer research. Volume I: The analysis of case-control studies. Lyon (France): International Agency for Research on Cancer; 1980. IARC Scientific Publications No. 32.
2. Centers for Disease Control and Prevention, National Center for Health Statistics. Compressed mortality file 1999–2014 on CDC WONDER Online Database, released December 2015. [Accessed Sept. 19, 2016]. Available from http://wonder.cdc.gov/cmf-icd10.html.
3. Centers for Disease Control and Prevention, Office on Smoking and Health. Trends in current cigarette smoking among high school students and adults, United States, 1965–2014. [Accessed Sept. 19, 2016]. Available from http://www.cdc.gov/tobacco/data_statistics/tables/trends/cig_smoking/.
4. Cucinotta FA, Hamada N, Little MP. No evidence for an increase in circulatory disease mortality in astronauts following space radiation exposures. Life Sci Space Res (Amst). 2016; 10:53–56.
5. Delp MD, Charvat JM, Limoli CL, Globus RK, Ghosh P. Apollo lunar astronauts show higher cardiovascular disease mortality: possible deep space radiation effects on the vascular endothelium. Sci Rep. 2016; 6:29901.
6. 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.
7. Jones M, Fowler R. Immortal time bias in observational studies of time-to-event outcomes. J Crit Care. 2016; 36:195–199.
8. 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.
9. R Core Team. R: A language and environment for statistical computing. Vienna (Austria): R Foundation for Statistical Computing; 2016. Available at https://www.R-project.org/.
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, Nurgalieva ZZ. Mortality among Soviet and Russian cosmonauts: 1960–2013. Aviat Space Environ Med. 2014; 85(7): 750–754.
12. University of California, Berkeley (USA), and Max Planck Institute for Demographic Research. Human Mortality Database. [Accessed Sept. 13, 2016]. Available at www.mortality.org or www.humanmortality.de.
13. Various authors. Comments on Delp MD, Charvat JM, Limoli CL, Globus RK, Ghosh P. Apollo lunar astronauts show higher cardiovascular disease mortality: possible deep space radiation effects on the vascular endothelium. [Accessed September 20, 2016]. Available from www.nature.com/articles/srep29901#comments.