# Potential for cancer and non-cancer risks among space workers

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**DCEG Radiation Epidemiology & Dosimetry Course 2019**

# Outline

- Radiation and other risk factors associated with space travel
- Astronaut and cosmonaut mortality [actual]
- Cataract [actual] and other morbidities [potential]
- Conclusions

- Radiation and other risk factors associated with space travel

# Radiation risks associated with space travel

- Radiation exposures in space
  - Low earth orbit – cosmic rays, radiation dose rates ~10x those on earths surface – 20-80 mSv/year (Badhwar *Health Phys* 2000 79 507-14)
  - Deep space – exposures to galactic cosmic rays (GCR) – protons, high-energy (HZE) ions, neutrons and recoil nuclei
    - GCR energy spectrum up to 1000 MeV/nucleon
    - Deep space doses of 1-2 mSv/day i.e. 1000 x background (Cucinotta & Durante *Lancet Oncol* 2006 7 431-5)

# Non-radiation risks associated with space travel

- Microgravity – effects on circulatory system and bone density
- Elevated $CO_2$ levels
- Lack of sleep (and in particular deep sleep)
- Psychological effects of confinement

# Non-radiation risks associated with space travel – NASA Twin Study

NASA Twin study (one monozygotic twin spent 340 days on International Space Station, other twin remained on earth) suggest many physiological effects even of LEO space travel:

- **cognitive function [declined – and persisted post flight]**
- **chromosomal inversions + telomere length reduction [persisted post flight]**
- epigenetic effects (DNA methylation changes)
- gut microbiome
- body weight [decrease]
- carotid artery dimension, cardiac output [increase], blood pressure [decrease], IMT [increase]
- subfoeval choroidal thickness + peripapillary retinal thickness
- levels of serum metabolites

Many but not all of these changes reverted to normal after return to earth

Garrett-Bakelman et al, *Science* 2019

- Astronaut and cosmonaut [actual] mortality

# US astronaut mortality

- Astronauts from selection class (1959/4/15) followed to 1991/9/30
- 195 astronauts
- 20 deaths
- SMR analysis
- Doses from space and medical diagnosis available – but little done with that

Peterson et al, *Radiat Res* 1993

# US astronaut mortality (2)

- Only excess is for accidents

**Standardized Mortality Ratios (SMRs) for Selected Causes of Death among Astronauts Followed from 1959 to 1991**

| Cause of death (ICD[a]) | O/E | SMR (95% CI) |
|---|---|---|
| All causes (001–999) | 20/11.06 | 181[b] (110, 279) |
| Circulatory disease (390–459) | 2/4.28 | 47 (5, 168) |
| Ischemic heart disease (410–414) | 2/3.14 | 64 (7, 230) |
| All external causes (800–998) | 16/2.01 | 796[b] (454, 1292) |
| All accidents (800–949) | 16/1.18 | 1346[b] (769, 2186) |
| Motor vehicle accidents (810–825) | 1/.60 | 165 (2, 922) |

- Per capita doses dominated by those for medical diagnosis

**Average per Capita Cumulative Radiation Doses for Astronauts Selected during 1959–1991 Follow-up Period**

| | | Per capita cumulative dose (mSv)[b] | | |
|---|---|---|---|---|
| Selection class[a] | Selection date | Space activities | Diagnostic X ray | Nuclear medicine |
| 1 (4, 6, 3) | April 1959 | 3.91 ± 2.24 | 45.54 ± 12.31 | 6.48 ± 3.60 |
| 2 (7, 7, 4) | September 1962 | 8.67 ± 3.34 | 45.84 ± 10.87 | 4.15 ± 1.24 |
| 3 (9, 9, 6) | October 1963 | 8.96 ± 4.38 | 48.89 ± 8.00 | 3.87 ± 0.85 |
| 4 (4, 4, 4) | June 1965 | 33.63 ± 14.96 | 45.72 ± 16.51 | 6.86 ± 1.01 |
| 5 (14, 14, 12) | April 1966 | 18.67 ± 6.93 | 85.21 ± 9.94 | 8.09 ± 2.19 |
| 6 (7, 7, 4) | August 1967 | 2.28 ± 0.10 | 50.85 ± 10.60 | 2.92 ± 0.46 |
| 7 (7, 7, 2) | August 1969 | 2.82 ± 0.10 | 61.52 ± 8.36 | 2.51 ± 0.11 |
| 8 (23, 23, 0) | January 1978 | 3.50 ± 0.48 | 13.10 ± 3.50 | — |
| 9 (15, 15, 1) | January 1980 | 2.41 ± 0.50 | 9.88 ± 1.74 | 1.60 ± 0.00 |
| 10 (12, 13, 0) | May 1984 | 1.13 ± 0.28 | 6.13 ± 1.52 | — |
| 11 (8, 10, 0) | June 1985 | 0.87 ± 0.32 | 4.75 ± 1.06 | — |
| 12 (8, 13, 0) | August 1987 | 0.91 ± 0.35 | 3.69 ± 0.59 | — |
| 13 (0, 16, 0) | January 1990 | — | 2.88 ± 0.55 | — |

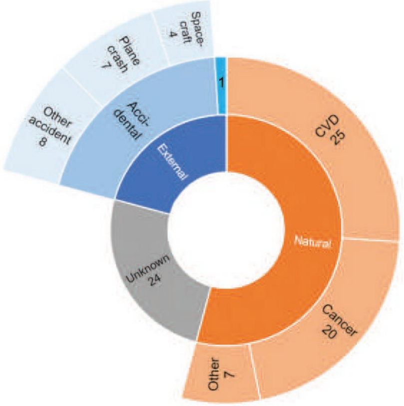
Peterson et al, *Radiat Res* 1993

# US astronaut and Russian cosmonaut mortality (1)

- NASA astronaut cohort recruited 1959/4 onwards (up to 1969 also via USAF)
- Soviet cosmonauts 1960/3 onwards (from 1989/12 via Roscosmos)
- 338 NASA astronauts, 22 USAF astronauts, 194 USSR cosmonauts, 68 Russian cosmonauts
- Relatively large number of accidental deaths in both cohorts

US astronaut deaths 1960-2017


USSR/Russian cosmonaut deaths 1960-2017



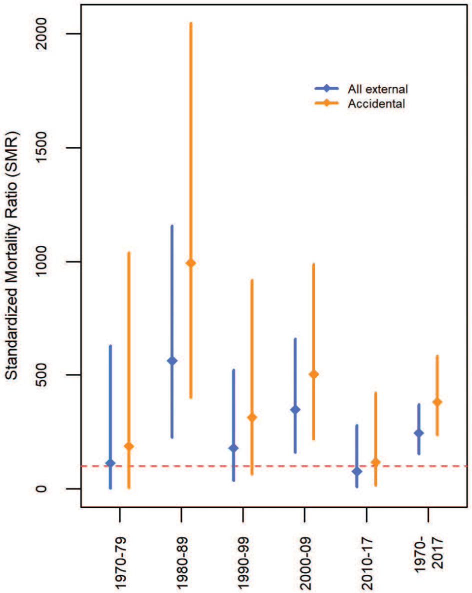



Reynolds & Day *The mortality of space explorers* 2018

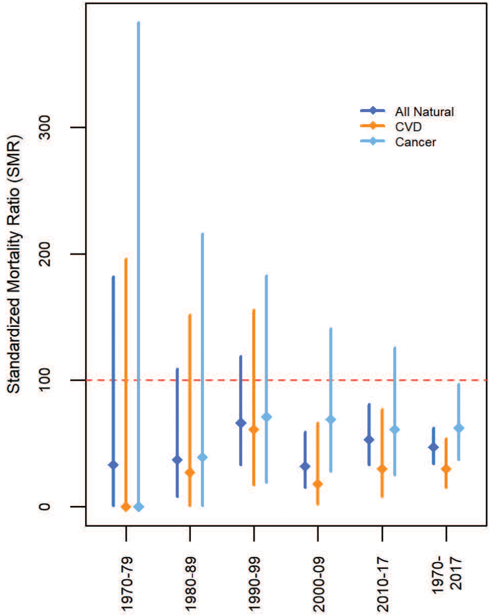
# US astronaut and Russian cosmonaut mortality (2)

- US SMRs > 100 for accidents/all external causes in all time periods, particularly 1980s [Challenger] and 2000s [Columbia]
- US SMRs < 100 for all natural causes, cancer and CVD in all time periods

All external/accidents in US astronauts




Natural causes/CVD/cancer in US astronauts

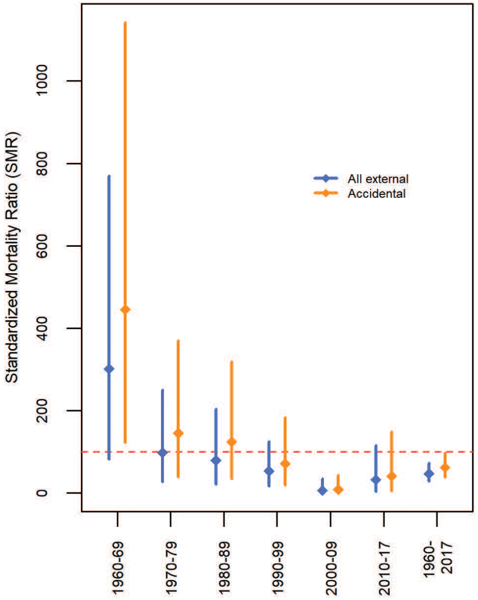



Reynolds & Day *The mort space explorers* 2018

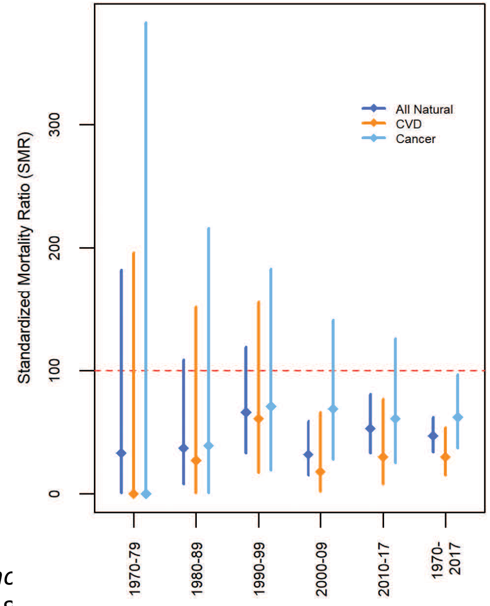
# US astronaut and Russian cosmonaut mortality (3)

- Russian SMRs > 100 for accidents/all external causes only in early period (1960s)
- Russian SMRs < 100 for all natural causes, cancer and CVD in all time periods

All external/accidents in Russian cosmonauts




Natural causes/CVD/cancer in Russian cosmonauts




Reynolds & Day *The mc of space explorers* 2018

# Interpretation of standardized mortality ratios

- SMR analysis is problematic, because comparison with the external (e.g. US, USSR/Russian national population) is likely to be misleading
- Because of the high degree of selection (both initial and continuing) in being judged fit to be an astronaut/cosmonaut, astronauts/cosmonauts likely to be much fitter than general population
- SMR analysis uninformative about possible radiation and other effects of space travel, which is likely to be small, and buried in the “noise”
- Possibly use of more comparable population can get rid of at least some of these problems

# US astronaut mortality (1)

- Longitudinal Study of Astronaut Health (LSAH) from 1959 selection class to 1991
- 210 astronauts with 3:1 matched (grouped by sex, age, BMI) among JSC ground-based employees
- RR analysis, using JSC employee comparison population, adjusted for sex, education, marital status, smoking history

| | Astronauts (N = 195) (Person-yr = 3,901) | | Comparisons (N = 575) (Person-yr = 12,471) | | | | | |
|---|---|---|---|---|---|---|---|---|
| Cause of Death | Deceased | % | Deceased | % | Crude RR | Adjusted RR* | 95% CI† | p value† |
| Cancer | 4 | 2.05 | 3 | 0.52 | 4.26 | 3.19 | 0.93–21.85 | 0.2382 |
| Cardiovascular | 3 | 1.54 | 7 | 1.22 | 1.37 | 1.20 | 0.27–5.28 | 0.8112 |
| Accidents and Injuries | 18 | 9.23 | 2 | 0.35 | 28.77 | 22.91 | 5.02–104.46 | 0.0001 |
| Other Diseases | 1 | 0.51 | 2 | 0.35 | 1.60 | 2.27 | 0.21–25.22 | 0.5040 |
| Total | 26 | 13.33 | 14 | 2.43 | 5.93 | 5.07 | 2.46–10.41 | 0.0001 |

- Most striking excess is for accidents, but also weak suggestions of excess cancer risk

Hamm et al, *Aviat Space Environ Med* 2000

# US astronaut mortality (2)

- Longitudinal Study of Astronaut Health (LSAH), male astronauts from selected from 1959/4 to 2013, excluding payload specialists
- Follow-up ended in 2018/5 - 260 astronauts
- SMR analysis using US national rates, also those of Major League Baseball (MLB) and National Basketball Association (NBA) players

| | | | US Exp | US SMR | | NBA Exp | NBA SMR | | MLB Exp | MLB SMR | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Astronauts | All | 48 | 94.0 | **51** | **(38 to 68)** | 55.3 | 87 | (64 to 115) | 63.4 | 76 | (56 to 100) |
| | External | 17 | 8.1 | **209** | **(122 to 335)** | **3.9** | **432** | **(252 to 691)** | | | |
| | All natural | 31 | 85.2 | **43** | **(31 to 60)** | **51.5** | **60** | **(41 to 86)** | | | |
| | Cancer | 13 | 25.6 | **51** | **(27 to 87)** | 14.4 | 90 | (48 to 154) | | | |
| | CVD | 8 | 31.5 | **25** | **(11 to 50)** | **22.0** | **36** | **(16 to 72)** | | | |
| | Other natural | 10 | 28.1 | **36** | **(17 to 65)** | 15.1 | 66 | (32 to 122) | | | |

- Some changes in SMR – particularly for external cause, cancer
- But are MLB and NBA really comparable to astronauts? E.g. average age at NBA vs NASA selection is 23 vs 35, and career lasts 6 vs 12 years



Reynolds & Day *Occup Environ Med* 2019

# Apollo astronaut mortality study

- Proportional mortality ratio (PMR) analysis of US astronauts divided into all flight, Low Earth Orbit, and Apollo Lunar

| | Cardiovascular Disease | Cancer | Accident | Other |
|---|---|---|---|---|
| Reference Groups | | | | |
| US Population Ages 55–64, ($n = 338, 127$) | 27% | 34% | 5% | 35% |
| Non-Flight Astronauts, ($n = 35$) | 9%* | 29% | 53%* | 9%* |
| Astronaut Groups | | | | |
| All Flight Astronauts, ($n = 42$) | 17% | 31% | 43%* | 10%* |
| Low Earth Orbit Astronauts, ($n = 35$) | 11%* | 31% | 49%* | 9%* |
| Apollo Lunar Astronauts, ($n = 7$) | 43%†‡ | 29% | 14%^ | 14% |

**Table 2. Proportional mortality rates (%) due to cardiovascular disease, cancer, accidents and all other causes.** Values are mean ± SE. $n$ = the number of individual deaths per group. *Significantly different from the US population age 55–64 group, $P \leq 0.05$; †significantly different from non-flight astronaut group, $P \leq 0.05$; ^significantly different from the non-flight astronaut group, $P \leq 0.1$; ‡significantly different from the low Earth orbit astronaut group, $P \leq 0.1$.

- Significantly elevated PMR for circulatory disease for age group 55-64 in Apollo Lunar astronauts – an effect of space radiation exposure?

Delp et al *Scientific Rep* 2016

# Problems with Apollo astronaut study of Delp *et al*

- Proportional mortality ratio (PMR) analysis is "a significant weakness … – elevated PMRs can result from increases in the cause of death under consideration, but can also arise because of decreases in mortality from the remaining causes"
- Restriction of analysis to a single age group (55-64) is an oddity – "a type of *post-hoc* data selection, and invalidates statistical inference"
- In any case comparison with the external US population is likely to be misleading, because of high degree of selection (both initial and continuing) in being judged fit to be an astronaut

Cucinotta et al, *Life Sci Pace Res* 2016

# Study of cancer and other mortality endpoints in relation to space dose in early US astronaut cohort (1)

- Because of problems with most previous analysis – comparing astronauts with external groups, need to have internal analysis of mortality vs space radiation dose
- Because medical diagnostic dose potentially swamps space radiation dose (as discussed by Peterson *et al* (*Radiat Res* 1993 133 257-64)) it is potentially important that this be taken into account in analysis
- Because of small numbers, assessment of statistical power essential
- Considered early US astronaut cohort – 73 white males selected as astronauts between 1959 and 1969 followed to 2017/2

Elgart et al, *Sci Rep* 2018

# Study of cancer and other endpoints in relation to space dose in early US astronaut cohort (2)

- As with previous analysis, accidents are only cause of death with SMR>100

| Endpoint | ICD8 range | ICD9 range | ICD10 range | Observed | Expected | SMR (95% CI) |
|---|---|---|---|---|---|---|
| All-cardiovascular disease | 390–459 | 390–459 | I00–I99 | 7 | 21.1 | 33 (14, 65) |
| Ischemic heart disease | 410–414 | 410–414 | I20–I25 | 5 | 12.5 | 40 (13, 89) |
| Cerebrovascular disease | 430–438 | 430–438 | I60–I69 | 2 | 2.6 | 77 (9, 268) |
| All-cancer (benign and malignant) | 140–239 | 140–239 | C00–C99, D00–D48 | 7 | 16.5 | 43 (18, 83) |
| Accidental mortality | E800–E929 | E800–E869, E880–E928 | V01–X59 | 12 | 2.2 | 536 (287, 1913) |
| All-cause mortality | 0-796, E800-E999 | 001-799, E800-E999 | A00-Y89 | 34 | 58.0 | 59 (44, 74) |

Elgart et al, *Sci Rep* 2018

# Study of cancer and other endpoints in relation to space dose in early US astronaut cohort (3)

- No internal radiation risks – trends with space radiation dose are all null for all endpoints considered (CVD, ischemic heart, stroke, cancer, all cause)

| | ln[OR]/Gy (95% CI) | | | | |
|---|---|---|---|---|---|
| | All-cardiovascular disease (ischemic heart and cerebrovascular disease) | Ischemic heart disease | Cerebrovascular disease | Cancer | All-cause mortality |
| Number of deaths | 7 | 5 | 2 | 7 | 34 |
| Absorbed dose adjusted for age at exit | −116.4 (−462.1, 16.1) | −60.0 (−382.9, 34.3) | −580.7 (−600.3[a], 22.9) | −43.0 (−224.3, 24.2) | −8.2 (−52.8, 24.6) |
| *p*-value | 0.14 | 0.37 | 0.10 | 0.25 | 0.70 |
| Absorbed dose adjusted for age at exit and entrance | −120.1 (−474.0, 16.1) | −60.7 (−389.3, 34.6) | −616.1 (−636.8[a], >0[a]) | −42.1 (−230.3, 25.1) | −11.4 (−58.7, 26.0) |
| *p*-value | 0.14 | 0.37 | 0.10 | 0.32 | 0.56 |
| Absorbed dose adjusted for age at exit and entrance, medical diagnostic dose[b] | −123.5 (−491.6, 16.9) | −62.7 (−411.8, 32.6) | −501.5 (−925.1[a], 32.9) | −46.3 (−230.7, 26.9) | −4.6 (−56.2, 35.6) |
| *p*-value | 0.14 | 0.35 | 0.11 | 0.30 | 0.84 |
| Absorbed dose adjusted for age at exit and entrance, year of birth, medical diagnostic dose[b] | −124.4 (−496.7, 16.9) | −68.8 (−429.6, 35.8) | −385.5[c] (−407.6[a], −363.5[a]) | −46.7 (−265.9, 36.6) | −0.5 (−70.3[a], 69.3[a]) |
| *p*-value | 0.14 | 0.35 | 0.25[c] | 0.39 | 0.57 |

- No difference made by adjustment for diagnostic dose, year birth etc



Elgart et al, *Sci Rep* 2018

# Power of cancer and other endpoints in relation to space dose in early US astronaut cohort

- Power no more than 6% for any endpoint
- Huge increase in assumed risks, or number of deaths required to achieve 80% power

| Endpoint | Deaths | EOR[a]/Gy |
|---|---|---|
| Cerebrovascular disease (CeVD) | 2 | >$10^6$ |
| | 20 | 101.52 |
| | 4479 | 3.08 |
| | 407,689 | 0.308 |
| Ischemic heart disease (IHD) | 5 | 654.31 |
| | 50 | 46.44 |
| | 18,635 | 1.47 |
| | 1,779,569 | 0.147 |
| All-cardiovascular disease (using CeVD EOR/Gy) | 7 | 353.08 |
| | 70 | 36.12 |
| | 4479 | 3.08 |
| | 407,689 | 0.308 |
| All-cardiovascular disease (using IHD EOR/Gy) | 7 | 353.08 |
| | 70 | 36.12 |
| | 18,635 | 1.47 |
| | 1,779,569 | 0.147 |
| All malignant cancer | 7 | 353.08 |
| | 70 | 36.12 |
| | 2025 | 4.70 |
| | 176,084 | 0.47 |

Elgart et al, *Sci Rep* 2018

- Cataract [actual] and other morbidities [potential] in astronauts

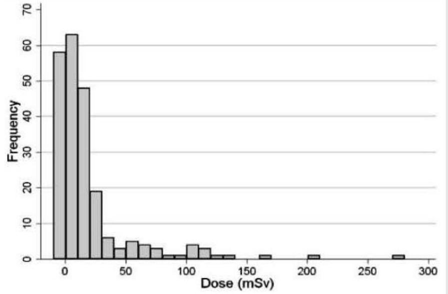
# Cataract and other ocular opacities in NASA astronauts

- 224 astronauts, 95 military aircrew and 99 ground-based subjects in Longitudinal Study of Astronaut Health (LSAH)
- Borderline significant (*p*=0.062) evidence of radiation-associated cortical opacity, but much weaker evidence of nuclear or posterior subcapsular opacity

**Progression Rate per Year per Sievert for Measures of Opacification or Changes in Visual Acuity as Determined Using Median Regression**

| Space lens dose (Sv) | Coefficient | Standard error | *P* value | 95% CI |
|---|---|---|---|---|
| Cortical opacity | 0.25 | 0.13 | 0.062 | [−0.012, 0.51] |
| Posterior subcapsular cataract opacity | $9.9 \times 10^{-4}$ | $1.85 \times 10^{-2}$ | 0.958 | [−0.0355, 0.0375] |
| Nuclear mask opacity | 2.04 | 2.75 | 0.460 | [−3.38, 7.46] |

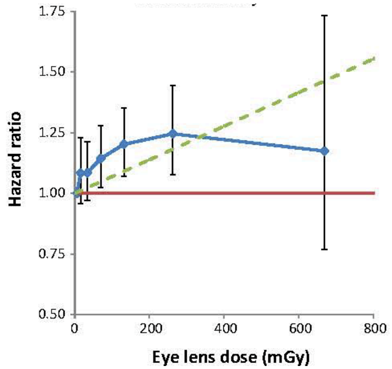
- Mostly low doses, but some >200 mSv



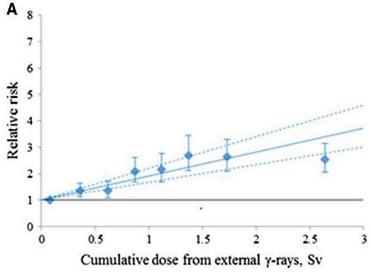

Chylack et al, *Radiat Res* 2012

# Cataract at low doses

- Accumulating evidence that cataract can be induced by low doses of ionizing radiation, albeit of different types from astronauts
- In US Radiologic Technologists (Little *et al Eur J Epidemiol* 2018 33 1179-91) there is significant trend overall and for doses < 100 mSv

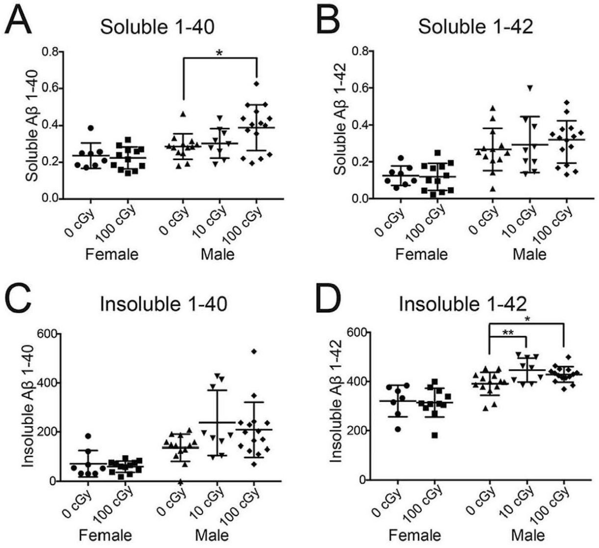



- Likewise in Mayak worker cohort (Azizova *et al Eur J Epidemiol* 2018 33 1193-1204) there is significant trend for various types of cataract, although not <100 mSv



# Neurocognitive effects observed in APP/PS1 mice exposed to 1GeV $^{56}$Fe (1)

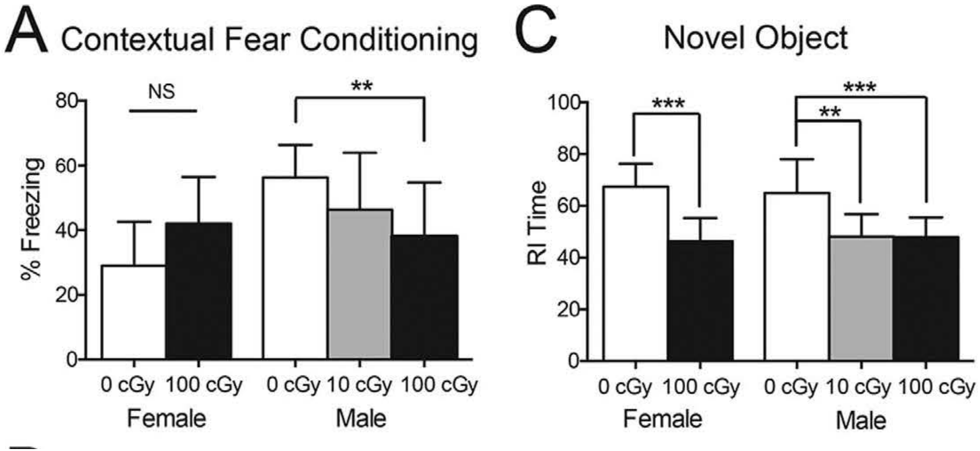
- Alzheimer's disease is characterized by buildup of amyloid β (Aβ) in brain
- Mice exposed to $^{56}$Fe 1 GeV/nucleon (analogous to GCR) 0, 0.1, 1 Gy
- Mice ~3 months old at irradiation (so young adult)
- Significant increase in Aβ in brains of male but **not** female exposed mice




Cherry et al, *PLoS ONE* 2012

# Neurocognitive effects observed in APP/PS1 mice exposed to 1GeV $^{56}Fe$ (2)

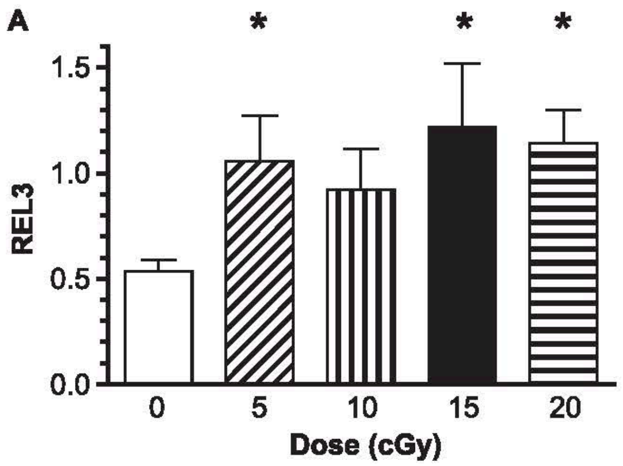
- Contextual fear conditioning (associated with electric shock to feet) and novel object recognition also affected by $^{56}Fe$ in male but **not** female exposed mice




Cherry et al, *PLoS ONE* 2012

# Neurocognitive effects observed in Wistar rats exposed to 1GeV $^{48}Ti$

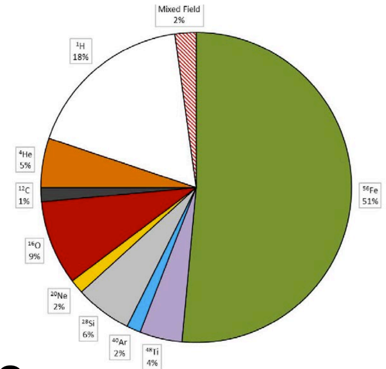
- $^{48}Ti$ 1 GeV/nucleon (analogous to GCR) 0, 0.05, 0.10, 0.15, 0.20 Gy
- Wistar rats aged 6-11 months at irradiation (so young adult to middle aged)
- Spatial memory adversely affected even by lowest dose exposure (0.05 Gy)




Britten et al, *Radiat Res* 2017

# Neurocognitive effects observed experimentally following GCR-like irradiation

- At least 50 studies have reported since Cherry *et al* (*PLoS ONE* 2012 7(12) e53275) many reviewed by Kiffer *et al* (*Life Sci Space Res* 2019 21)
- A variety of animal models are used, mostly rats or mice, but some other species (e.g. ferrets), variety of HZE ions (most $^{56}Fe$), variety of neuro-behavioural endpoints




- Not all report adverse outcomes, but many do
- Related to neurocognitive effects seen in NASA Twin Study? (Garrett-Bakelman *et al Science* 2019 364 eaau8650)
  - Exposures in Twin Study unlikely to be GCR (because ISS is in low earth orbit)

# Conclusions

- Space travel - exotic environment with some types of radiation (e.g. GCR) not seen on earth, also many other risk factors e.g. microgravity, confinement
- Little evidence of excess of any cause of death, in comparison with national and other rates, apart from external causes in US astronauts
- No evidence of excess risks for any mortality endpoint in USSR/Russian cosmonauts
- Little evidence of trend of mortality with dose in US astronauts, but power is low
- Evidence of cortical opacities in US astronauts
- Lot of experimental evidence of neurocognitive effects, specifically Alzheimer's disease, associated with quasi-GCR radiation

# Quiz 1

There is evidence of excess mortality risk in comparison with national mortality rates overall in:

- US astronauts
- USSR/Russian cosmonauts
- Both

# Quiz 1

There is evidence of excess mortality risk in comparison with national mortality rates overall in:

- US astronauts
- USSR/Russian cosmonauts
- Both

# Quiz 2

What statistically significant trends with space radiation dose have been observed in the US astronauts?

- For cancer mortality
- For circulatory disease mortality
- Both of the above
- Neither of the above

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What statistically significant trends with space radiation dose have been observed in the US astronauts?

- For cancer mortality
- For circulatory disease mortality
- Both of the above
- Neither of the above

# Quiz 3

There is evidence (at borderline levels of significance) of excess radiation-associated morbidity from which types of cataract in the US astronauts

- Cortical
- Posterior subcapsular
- Nuclear
- All of the above

# Quiz 3

There is evidence (at borderline levels of significance) of excess radiation-associated morbidity from which types of cataract in the US astronauts

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# Quiz 4

There is evidence of neuro-cognitive effects following HZE (GCR-like) radiation exposure in the following experimental models:

- Mice
- Rats
- Ferrets
- All of the above

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- All of the above

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