Combining Epidemiologic Information Across Space Agencies

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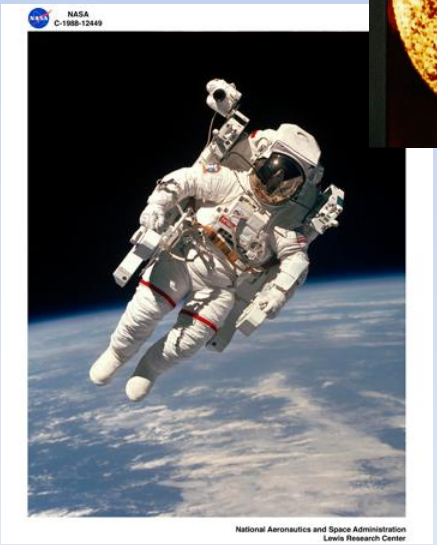
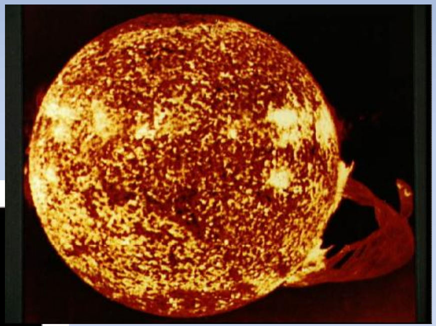
American Public Health Association Annual Meeting
Washington, D.C., 2011

Space Flight Exposure

- Space is an inherently hostile environment
- Unique occupational and environmental exposures
  - Microgravity
  - Solar particle events
  - Space radiation
  - Circadian rhythm disruption
  - Psychosocial issues
  - Confined space
  - Altered nutrition





Effects of Space Flight

- Acute and chronic effects of space flight exposure are not well understood
  - Lack of objective data
  - Limited experience of humans in space
  - Incomplete understanding of physiological effects
  - Variation in medical standards

Limited Data

- Only 302 U.S. astronauts have flown in space
- Analysis of rare events and subgroups will have likely have reduced statistical power
  - Extravehicular activities (125)
  - Mission length >30 days (45)
  - Walked on moon (12)
- Other data exists
  - Russian space agency (RSA)
  - Japan aerospace exploration agency (JAXA)
  - European space agency (ESA)
  - Others

Sharing Data Across Space Agencies

- Small, high profile population

- Sharing attributable data may violate individual agency policies and international laws
  - Privacy Act of 1974
  - Health Insurance Portability and Accountability Act (HIPAA)
  - Federal Law of the Russian Federation No. 152-FZ on Personal Data (2006)

U.S. Department of Health & Human Services

International Compilation of Human Research Protections

2011 Edition

Compiled By:
Office for Human Research Protections
U.S. Department of Health and Human Services

PURPOSE

This Compilation lists over 1,000 laws, regulations, and guidelines that govern human subjects research in 101 countries, as well as the standards from a number of international and regional organizations. This Compilation was developed for IRBs/Research Ethics Committees, researchers, sponsors, and others who are involved in international research. Its purpose is to help these groups familiarize themselves with the laws, regulations, and guidelines where the research will be conducted, to assure these standards are followed appropriately.

In addition to numerous additions and updates to the 2010 Edition provided by in-country contact persons, the 2011 Edition features:

1. A new sub-section on the laws, regulations, and guidelines on *medical device* research, which is found in the "Drugs and Devices" section.
2. The laws, regulations, and/or guidelines for five new countries: *Belarus, Grenada, Pakistan, Rwanda,* and *Tunisia*.

- http://www.hhs.gov/ohrp/international/intlcompilation/hspcompilation-v20101130.pdf

Meta-Analysis

- Meta-analytic methods may be used to combine non-attributable data
- Traditionally used to combine summary measures among multiple studies
  - Published
  - Unpublished
- We propose using meta-analytic methods to combine summary measures across space agencies
  - Non-attributable data
  - Avoids problems with sharing health related data
  - Unpublished data

Mortality Data (as of July 2009)

- For example, consider mortality data among NASA astronauts *with military experience*

Space Agency	Exposure	Deceased	Living	Risk Ratio (95% CI)	Variance*
NASA	Space flight	27	199		
	No space flight	8	12	0.30 (0.16, 0.57)	0.108

- Astronauts exposed to space flight are 0.30 times less likely to be deceased compared to those without space flight experience

*Estimated variance of the log-risk ratio

Russian Space Agency (RSA)

- How does NASA mortality data compare with RSA?

Space Agency	Exposure	Deceased	Living	Risk Ratio (95% CI)	Variance*
NASA	Space flight	27	199		
	No space flight	8	12	0.30 (0.16, 0.57)	0.108
RSA	Space flight	17	44		
	No space flight	29	41	0.67 (0.41, 1.10)	0.063

*Estimated variance of the log-risk ratio

Inverse Variance Method

- Fixed effects method
  - Widely applicable
  - Assumes common effect measure across space agencies
  - Differences between observed effect measures are due solely to random error

$$Y_i = \mu + e_i, \text{ where } e_i \sim N(0, {\sigma^2}_i)$$

Inverse Variance Method

- Effect measures are combined using a weighted average

$$\hat{\mu}_{IV} = \frac{\sum \widehat{w}_i Y_i}{\sum \widehat{w}_i}$$

where $w_i = 1/\hat{\sigma}^2{}_i$

- The standard error is given by

$$se(\hat{\mu}_{IV}) = \left(\sum \widehat{w}_i\right)^{-1/2}$$

In our example

Space Agency	Risk Ratio (95% CI)	Variance*	Weight (%)
NASA	0.30 (0.16, 0.57)	0.108	9.3 (37%)
RSA	0.67 (0.41, 1.10)	0.063	15.9 (73%)
Combined	0.50 (0.34, 0.74)	0.199	

- However, fixed effects methods assume a common effect measure.

*Estimated variance of the log-risk ratio

Heterogeneity

- A test statistic for heterogeneity of effect measures is given by

$$Q = \sum \widehat{w}_i (Y_i - \hat{\mu}_{IV})^2$$

which assumes a chi-squared distribution with $k - 1$ degrees of freedom

($k =$ number of space agencies)

In our example

Space Agency	Risk Ratio (95% CI)	Variance*	Q (P-value)
NASA	0.30 (0.16, 0.57)	0.108	
RSA	0.67 (0.41, 1.10)	0.063	
Combined	0.50 (0.34, 0.74)	0.199	3.87 (0.049)

- This suggests that variation in the effect measure may exist between space agencies

Alternative Meta-Analytic Methods

- Therefore, the IV method may not be the best option
  - Random effect methods may be more appropriate

- Furthermore, fixed effects methods yield suboptimal confidence intervals in the presence of heterogeneity and small k
  - Brockwell (2001)

Alternative Meta-Analytic Methods

- Mantel-Haenszel (fixed)
  - Low event rates
  - Small k
- DerSimonian and Laird (random)
  - Commonly used random effects model
  - Estimates τ^2, but assumed known
  - Suboptimal coverage probabilities

Alternative Meta-Analytic Methods

- Sidik (random)
  - Similar to DerSimonian and Laird
  - CIs use t-distribution, increased coverage probabilities
- Profile MLE (random)
  - Estimates τ^2 and its variability
  - Increased CI coverage probabilities

Applied to Mortality Data

Method	$\hat{\tau}^2$	(95% CI)	Risk Ratio	(95% CI)
Inverse variance	0	-	0.50	(0.34, 0.74)
Mantel-Haenszel	0	-	0.54	(0.37, 0.80)
DerSimonian and Laird	0.245	-	0.46	(0.21, 1.02)
Sidik	0.245	-	0.46	(0.00, 79.17)
Profile MLE	0.077	(0.0, 2.8)	0.47	(0.17, 1.20)

- Using data from additional space agencies
  - Improve estimates
  - Increase generalizability of results

Conclusions

- Meta-analytic methods provide a practical solution for combining data across agencies
  - Only requires non-attributable data
- The profile likelihood method offers the best solution for small *k*
- Measures of association must be clearly and uniformly defined
  - Subgroup definitions
  - Outcome measure
  - Interactions

Acknowledgements

- Wyle
  - Mary Wear, PhD
  - April Clark, DrPH
  - Sara Mason, BS
- NASA
  - Mary Van Baalen, MS
  - Kathy Johnson-Throop, PhD
- RSA
  - Lilia Simaeva
  - Rustem Kaspransky, MD