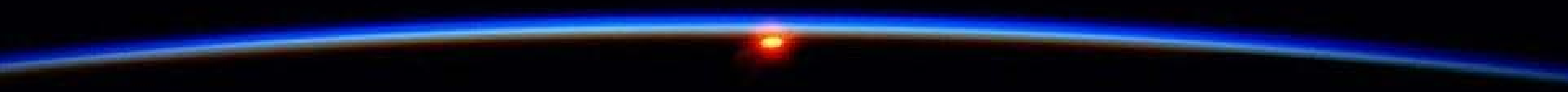
Nasal Congestion on the International Space Station



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Disclosure Information

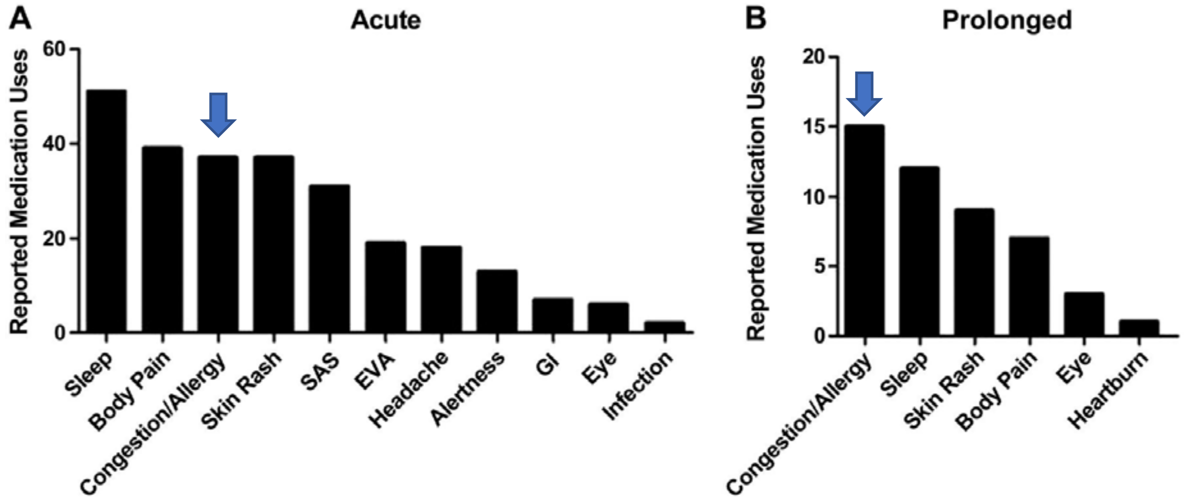
- No financial relationships to disclose
- The views expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of the National Aeronautics and Space Agency (NASA).
- This work was NOT prepared as part of my official duties as a military service member, and in no way is representative of Naval Medical Center Portsmouth, or the U.S. Navy.

Incidence

- 55% of crewmembers report use of medications for congestion

Wotring V. Medication use by U.S. crewmembers on the International Space Station. *The FASEB J.* 2015; 29:4417-4423.

Medication use by Complaint



Incidence

- Immunological related health events for 21 flight years

Medical Conditions / Clinical Symptoms	Total Events	Events / Flight Year
Allergic reaction (hypersensitivity)	2	0.1
Prolonged congestion, rhinitis, sneezing	20	1.0
Herpes viruses (cold sores)	6	0.3
Ear related: pain, congestion, itchiness	6	0.3
Pharyngitis (sore throat)	1	0.1
Skin infection (including pus forming wounds on wrist, finger, feet)	6	0.3
Skin rash/hypersensitivity (including skin conditions such as tinea versicolor, dermatitis, rosacea)	23	1.1
Urinary tract infection	2	0.1
Infections and other (including conditions such as fever, aphthous ulcer, lymphadenitis)	4	0.2
Total	**70**	**3.4**

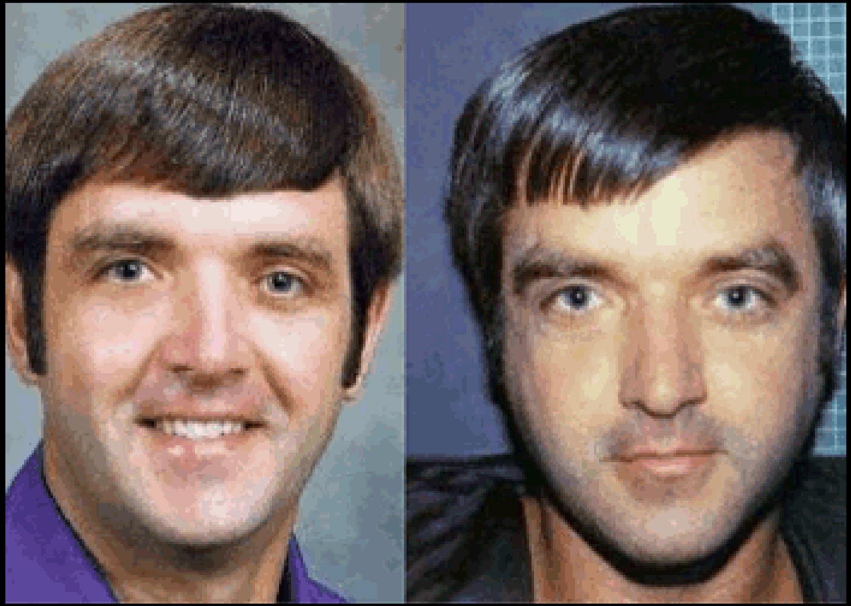
- Crucian B, Babiak-Vazquez A, Johnston S, Pierson DL, Ott CM, Sams C. Incidence of Clinical Symptoms During Long-Duration Spaceflight. *International Jounral of General Medicine*. 2016; (9) 383-391.

Why is this a concern?

- Uncomfortable/distracting
- Could contribute to poor sleep
- Prevent EVAs
- Decrease in taste
- Risk of ear/sinus infections
- Sign of underlying problems on ISS

Traditional Explanation

- Fluid shifts increase cerebral blood volume
  - Doesn't explain why congestion complaints continue throughout mission



Study Goals

Examine the relationship between nasal congestion and:

- Complaints of headache
- Carbon dioxide levels
- Age of the ISS

CO_2 Background

- Original flight rules were based on U.S. Navy submarine data and NIOSH occupational limits.
- 1970's data from U.S. subs indicated 1% (7.6mm Hg) was relatively safe.
- Physiologic effects thought to be related to 1% CO_2 in subs:
    - Respiratory minute volume
    - Blood Ph
    - Electrolytes
    - Gastric acidity
    - Sleep disturbances
- Original flight rule for ISS set at 7.6 mm Hg

Schaeffer KE. Physiologic stresses related to hypercapnia during patrols on submarines. Undersea Biomed Res. 1979;6 Suppl:S15-47.

Messier AA, Heyder E, Schaefer KE. Effect of 90-Day Exposure to 1% CO2 on Acid-Base Status of Blood. Naval Submarine Medical Research Lab, Groton, Ct. March, 02 1971.

CO_2 Background

- Reported CO_2 symptoms:
  - Headaches
  - Fatigue
  - Irritability
  - Lethargy
  - Decreased work performance
  - Sleep difficulties
- CO_2 related symptoms were anecdotally associated with large group gatherings like press conferences
- These symptoms seemed to improve when breathing 100% O_2 for EVAs.

Bacal K, Beck G, Barratt MR. "Hypoxia, Hypercarbia, and Atmospheric Control". Principles of Clinical Medicine for Space Flight. 1st ed. Barratt MR, Pool SL. New York, 2008. 445-473. Print.

CO_2 Hypothesis

- CO_2 is a potent vasodilator
  - Mediated through decreases in pH which act extracellularly to relax blood vessels and increase blood flow

- Microgravity alters venous outflow in the head and neck
  - Increases blood volume in the head and neck

Methods

- Data gathered on USOS Astronauts that flew on ISS March 14, 2001- February 16, 2018
- Complaints of congestion gathered from PMCs and SMOTs
- CO_2 data drawn from Main Constituent Analyzer
  - Missing data addressed mathematically by multiple imputation
- First 7 days of flight excluded to control for confounding variables
  - Fluid shifts occur in first week
  - Arriving vehicles have different CO_2 levels compared to ISS

PMC (Private Medical Conference)

SMOT (Space Medicine Operations Team)

• The following equation models the relationship between variables examined and the log odds where p represents the probability of reporting congestion

Statistical Analysis

- Logistic regression mixed-effects model approach
- Subject-specific random effects to addressed repeated observations of the same individuals
- Robust standard errors to address possible heteroscedasticity (model miss-specification)
- Multiple imputation used to address missing CO2 values
- Completed in SAS 9.4
- The following equation models the relationship between variables examined and the log odds where p represents the probability of reporting congestion

$$\log\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1 \times Age_{ISS} + \beta_2 \times CO_2$$

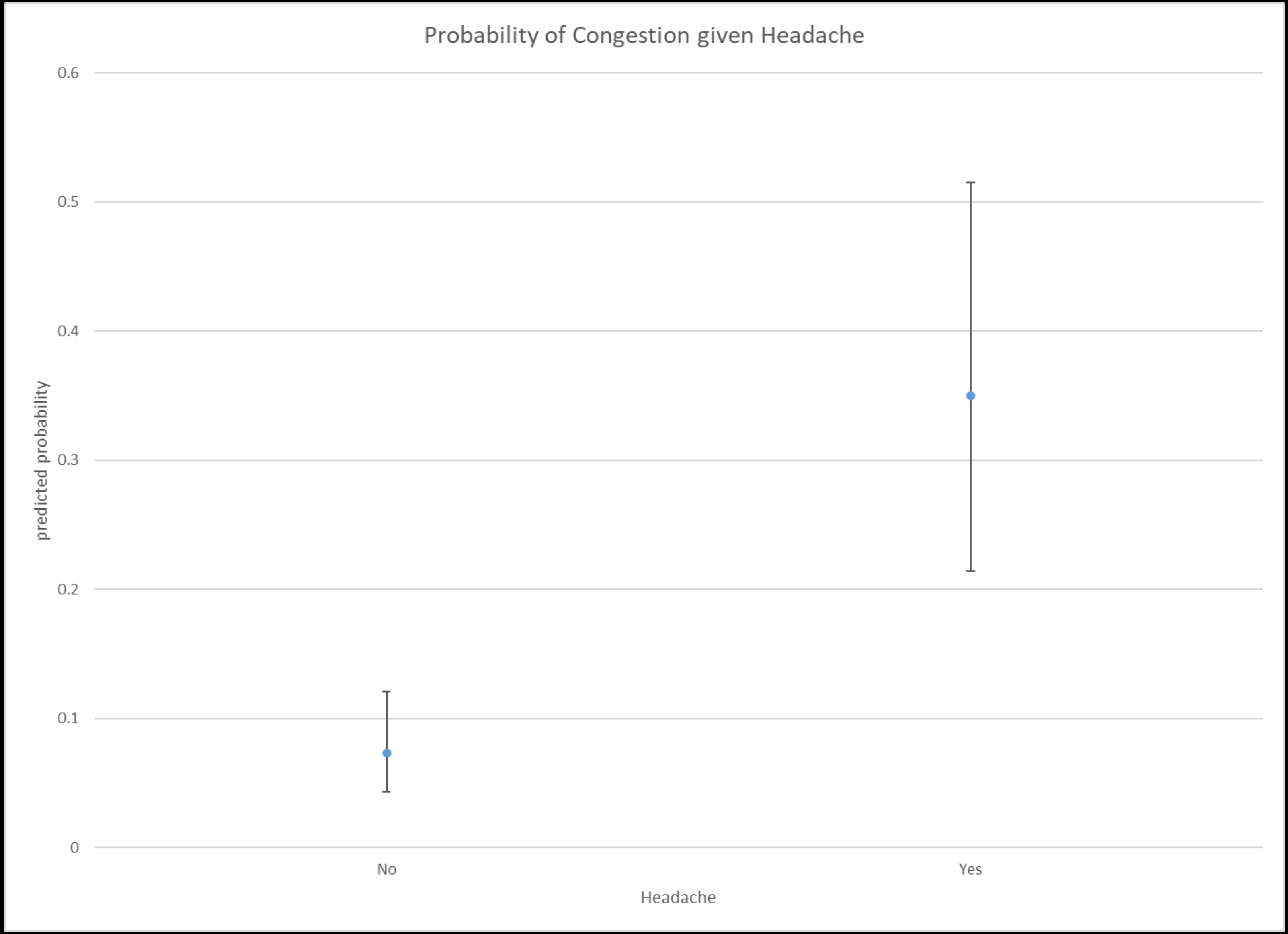
Demographics

- N= 79   Exp: 2-53

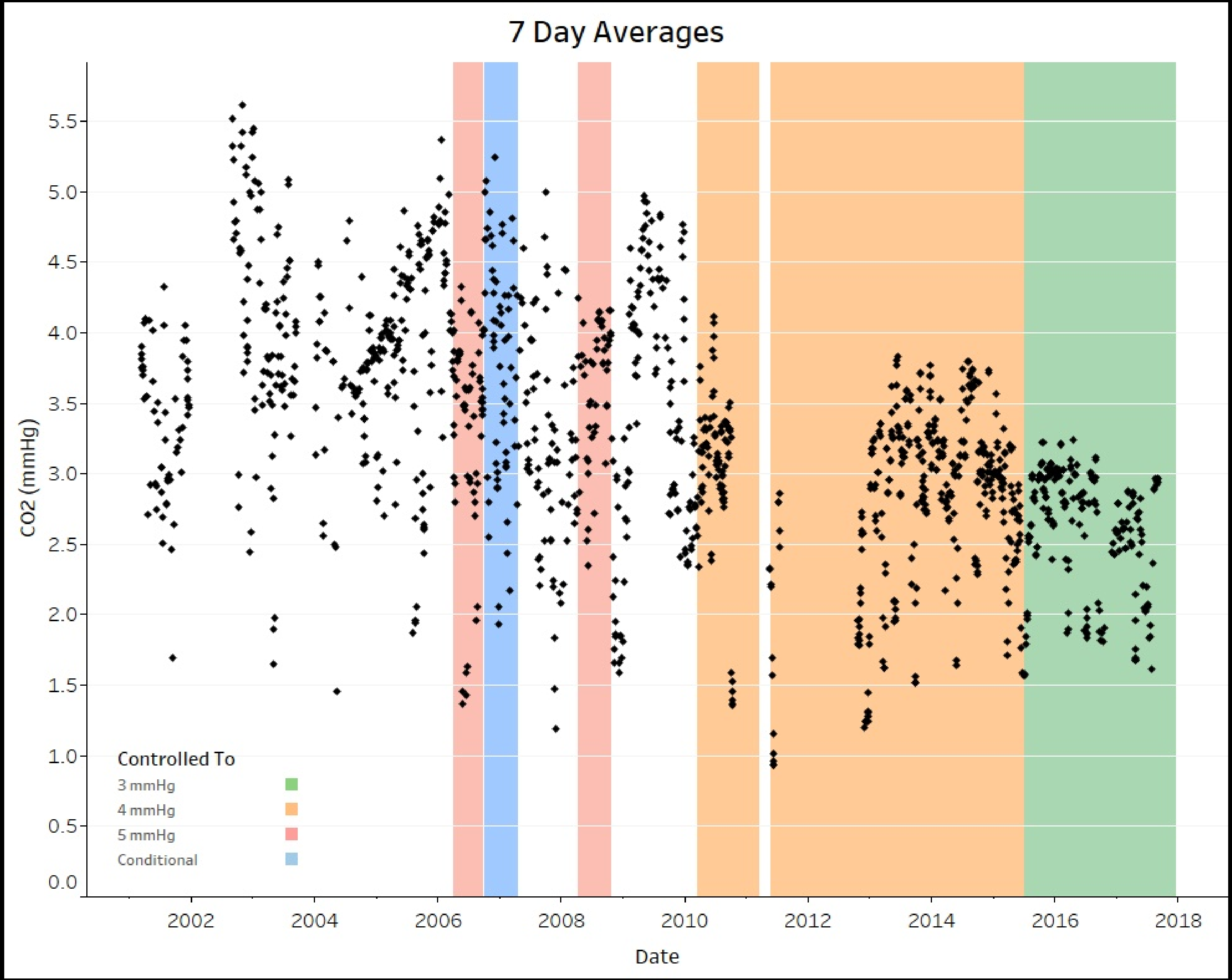
Variables	Mean ± Standard Deviation
Males, (%)	82.3
Females, (%)	17.7
Age at Launch, yr	47.3 ± 4.8
Mission duration, d	162.4 ± 40.2
Number of observations per crewmember	40.0 ± 17.2

Headache vs Congestion

(Predicted probability)

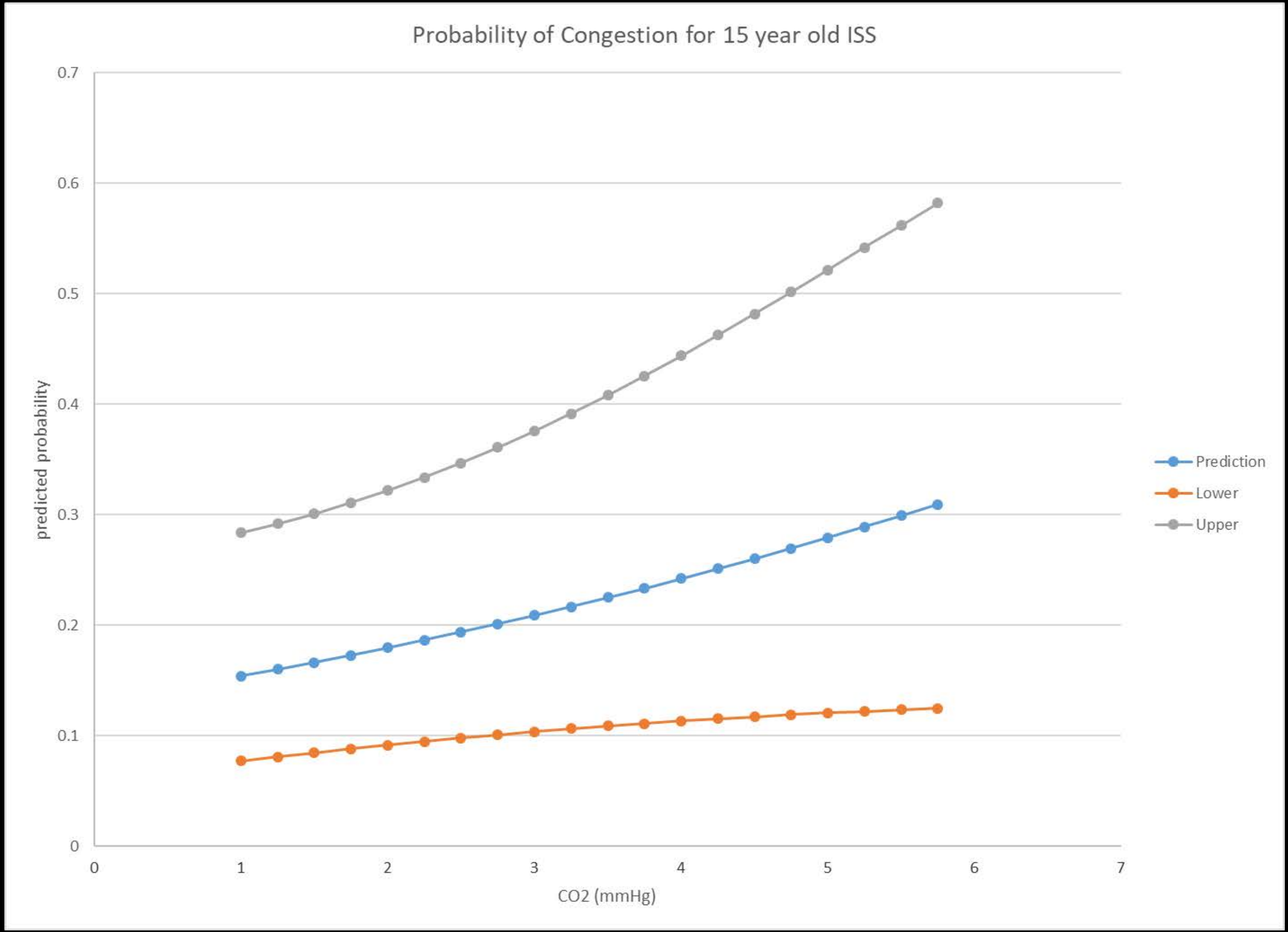


CO_2 over time



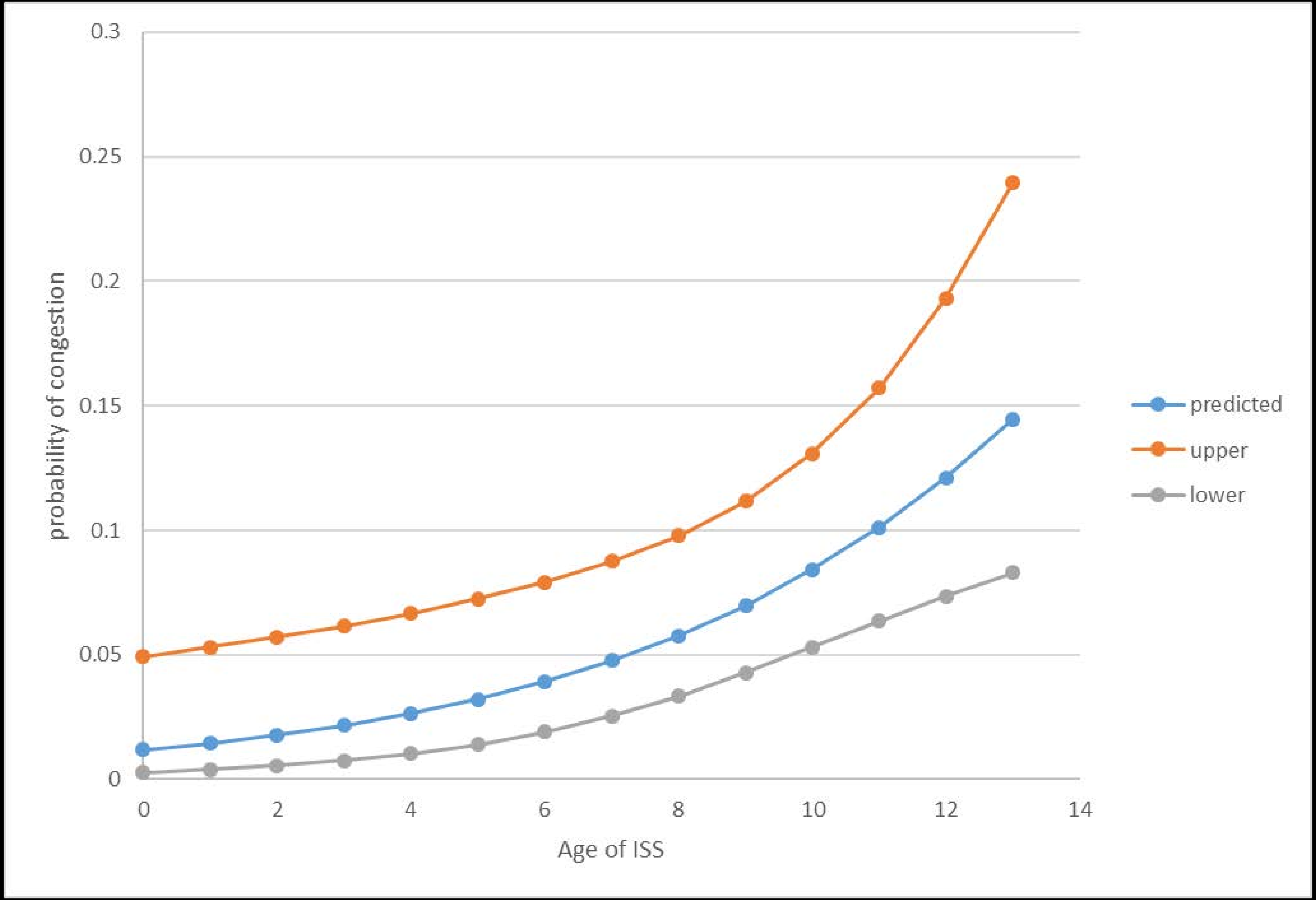
CO_2 vs. Congestion

(Predicted probability)



$p= .1582$

Age of ISS vs. Probability of Congestion



p= .0024

Potential Consequence of Aging: Physical Dust Particles

- Microgravity= floating dust
- Most ISS dust particles are large enough that they are trapped in the upper airways and nose.
- >100 microns
- Composition:
    - Dead skin
    - Hair
    - Nail clippings
    - Food particles
    - Paper
    - Plastic
    - Clothing lint
    - Other granular debris

HEPA ISS filters are designed to remove 99.7% of particles greater than .3 microns

https://ntrs.nasa.gov/archive/nasa/casi.ntrs.nasa.gov/20170008803.pdf

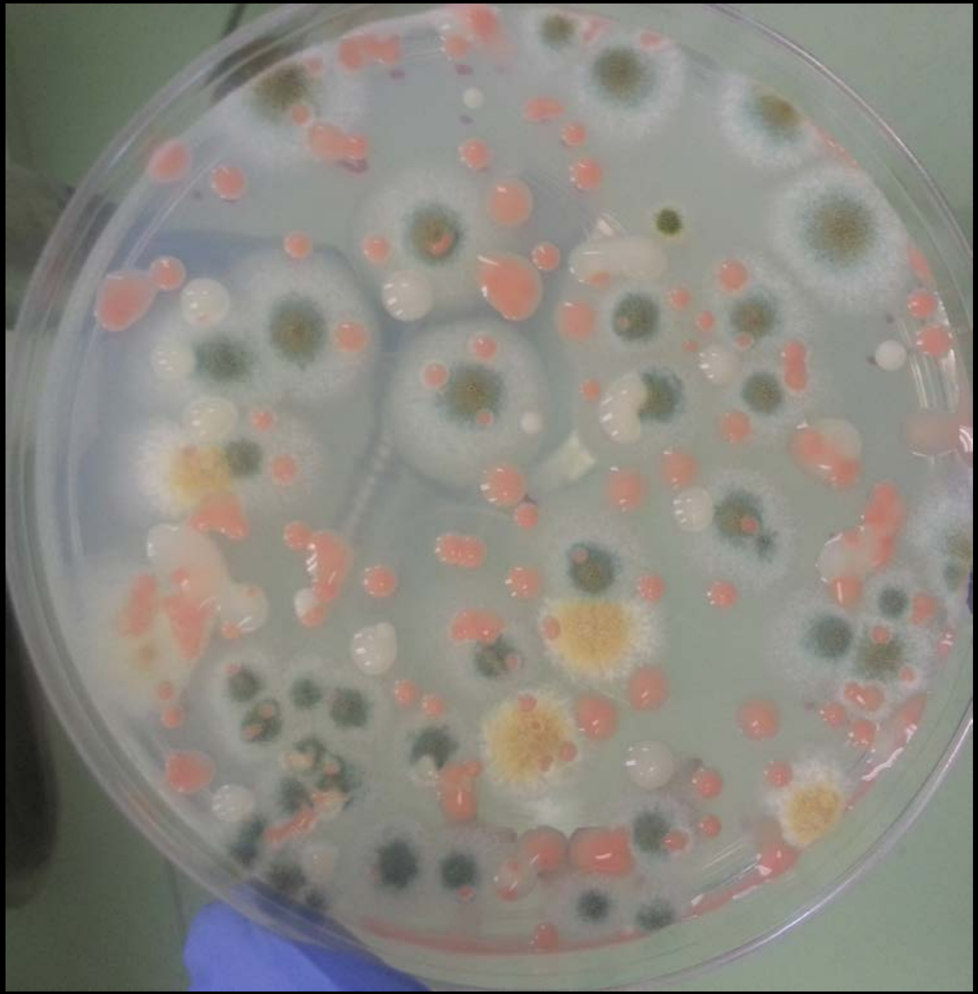
Perry JL, Coston, JE. Analysis of Particulate and Fiber Debris Samples Returned from the International Space Station. *International Conference on Environmental Systems.* July 13-17, 2014. Tucson, Arizona.

Potential Consequence of Aging: Microorganisms

- 2007: Analysis of dust collected from ISS HEPA filters by PCR returned results that included 39 species of molds, higher levels than found in most US homes.

- 2014: Risk of an astronaut reporting a medical event tripled if microbial counts were above the established limits

https://www.nasa.gov/ames/microbial-tracking



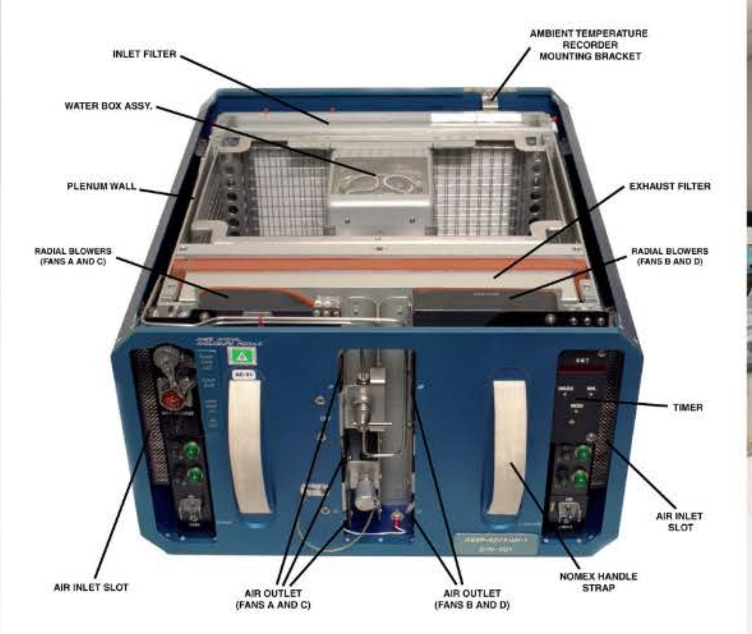
Colonies of fungi grown from a sample collected from ISS during Microbial Tracking-1

Vesper SJ, Wong W, Kuo CM, Pierson DL. Mold Species in Dust from the International Space Station Identified and Quantified by Mold Specific Quantitative PCR. *Res Microbiol*. 2008 Jul-Aug;159(6):432-5.

Oubre C, Charvat JM, Kadwa B, et al. Microbiology and Crew Medical Events on the International Space Station. National Aeronautics and Space Administration. Houston, Tx. 2014. Available at https://ntrs.nasa.gov/archive/nasa/casi.ntrs.nasa.gov/20140003763.pdf.

Potential Consequence of Aging: Rodents

- 2009: Lab mice flown to the ISS for experiments
- Research has found that up to 30% of people working with lab animals will develop an allergic response within the first year
- Did not see spike in congestion in 2009



Potential Consequence of Aging: Toxic Contaminants

- Off-Gassing of materials
  - (formaldehyde, halocarbons)
- Anticorrosives in fluid lines
  - (cadmium, nickel)
- Waste Management Systems
  - (Urea, sulfuric acid)

- Sensitive monitoring systems on board ISS have demonstrated that trace contaminants have decreased with age of station

Air Quality Monitor

Study Limitations

- CO_2 exposures vary throughout missions
  - Exercise
  - Social and work related gatherings
  - Working behind racks or in engineering spaces
  - EVAs: 100% O_2 and decreased pressure

SPHERES robot project uses CO2 bursts for propulsion

- ↑ Ventilation needed to ↓ CO_2, however also ↓ particles
- PMCs only once a week
- Individual variability in symptoms

Conclusion

- Congestion is a common ISS medical complaint
- Congestion has impacts to health and performance
  - Poor Sleep
  - Sinus Infections
  - Prevents EVAs
  - Distracting/discomfort
- Cephalic fluid shift common explanation, yet complaints continue after adaptation period
- Headaches are associated with congestion in ISS crew members
- Elevated CO2 levels may lead to congestion
- The older the ISS, the higher the predicted probability of congestion
- ISS mold levels reported higher than most US homes
- Risk of an astronaut reporting a medical event tripled if microbial counts were above the established limits

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Back up

Parameter Estimates (20 Imputations)											
Parameter	Estimate	Std Error	95% Confidence Limits		DF	Minimum	Maximum	Theta0	t for H0: Parameter= Theta0	Pr > |t|	Slope
intercept	-5.199262	1.024179	-7.20828	-3.19025	1463.7	-5.93589	-4.56054	0	-5.08	<.0001	
ISS_age	0.220178	0.072509	0.07806	0.36229	139928	0.206039	0.237137	0	3.04	0.0024	1.246299
avg_24hr	0.1885	0.132823	-0.07424	0.45124	132.02	0.035206	0.360732	0	1.42	0.1582	1.207437

HA	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper	Mean	Standard Error Mean	Lower Mean	Upper Mean	diff lower	diff upper
No	-2.5392	0.2823	2835	-8.99	<.0001	0.05	-3.0928	-1.9855	0.07316	0.01914	0.04341	0.1207	0.02975	0.04754
Yes	-0.619	0.3469	2835	-1.78	0.0745	0.05	-1.2993	0.06123	0.35	0.07893	0.2143	0.5153	0.1357	0.1653

Reporting Bias?

- No increase in complaints of congestion after publication of Law et al paper on correlation of headaches and CO_2.

FAST TRACK ARTICLE

Relationship Between Carbon Dioxide Levels and Reported Headaches on the International Space Station

Jennifer Law, MD, MPH, Mary Van Baalen, MS, Millennia Foy, PhD, Sara S. Mason, BS, Claudia Mendez, MPH, Mary L. Wear, PhD, Valerie E. Meyers, PhD, DABT, and David Alexander, MD

Objective: Because of anecdotal reports of CO_2-related symptoms onboard the International Space Station (ISS), the relationship between CO_2 and in-flight headaches was analyzed. **Methods:** Headache reports and CO_2 measurements were obtained, and arithmetic means and single-point maxima were determined for 24-hour and 7-day periods. Multiple imputation addressed missing data, and logistic regression modeled the relationship between CO_2, headache probability, and covariates. **Results:** CO_2 level, age at launch, time in-flight, and data source were significantly associated with headache. For each 1-mm Hg increase in CO_2, the odds of a crew member reporting a headache doubled. To keep the risk of headache below 1%, average 7-day CO_2 would need to be maintained below 2.5 mm Hg (current ISS range: 1 to 9 mm Hg). **Conclusions:** Although headache incidence was not high, results suggest an increased susceptibility to physiological effects of CO_2 in-flight.

On the Earth, carbon dioxide (CO_2) is a trace constituent that makes up 0.04% of the atmosphere, equating to a partial pressure ($ppCO_2$) of 0.3 mm Hg at standard pressure.[1] Nevertheless, within a spacecraft, it has been impractical to control $ppCO_2$ to such low levels because of mass constraints and consumable limitations. CO_2 levels in spacecraft have typically been 2.3 to 5.3 mm Hg, with large fluctuations occurring over hours and days.[2] The highest $ppCO_2$ recorded in a US spacecraft was 14.9 mm Hg on Apollo 13.[3] At the time of the study, the spacecraft maximum allowable concentrations (SMACs) for CO_2 were 15 mm Hg for 1 hour, 10 mm Hg for 24 hours, 5.3 mm Hg for 7 to 180 days, and 3.8 mm Hg for 1000 days.[4] The SMACs provide the basis for the operational constraints enacted by the flight rules, which are methods used by the National Aeronautics and Space Administration (NASA) for planning and executing operations.[5]

The effects of ambient CO_2 and exposure limits have been well studied on the Earth. Physiologically, when blood CO_2 levels rise, chemoreceptors in the carotid and aortic bodies quickly trigger various centers in the medulla to send signals to the intercostal muscles, diaphragm, and sinoatrial node to increase minute ventilation and heart rate to enhance the body's elimination of CO_2. CO_2 has effects on the cerebral vascular tone, primarily driven by the changes in extracellular pH. The lowering of the pH induces vasodilatation mediated by nitric oxide, cyclic nucleotides, prostanoids, potassium channels, and calcium ion exchange,[6] resulting in alteration of cerebral blood flow (CBF). Numerous studies reported an increase in CBF of 1 to 2 mL/100 g/min for each 1-mm Hg increase in arterial partial pressure of CO_2 (Pa_{CO2}),[6–8] or 5.8% to 6.7% per 1-mm Hg rise in $ppCO_2$.[9] The increase in CBF results in an elevation of intracranial pressure, presumably leading to headache, visual disturbance, impaired mental function, and other central nervous system symptoms. On longer exposures, Sliwka et al[10] found that cerebral blood flow velocity (CBFv) in the middle cerebral artery increased by 35% as detected by transcranial Doppler when subjects were exposed to 23 days of CO_2 of 5.3 or 9.1 mm Hg; although CBFv responses were similar for the two levels of exposure, headache complaints were more frequent during the early days of exposure to the higher level. Furthermore, CBFv increased at days 1 and 5 after discontinuation of hypercapnia. In addition, although CBF and cerebral blood volume (CBV) change similarly during hypercapnia on the Earth,[11] CBF and CBV may not have the same relationship in spaceflight because of impaired venous drainage caused by the cephalad fluid shift; therefore, increased flow may increase the volume.

Terrestrially, healthy males can tolerate CO_2 levels below 7.5 mm Hg indefinitely and up to 480 minutes at 11 mm Hg without acute health effects. Individuals begin to experience headache and dyspnea upon mild exertion after several hours of exposure to 15 mm Hg.[12] Sweating and dyspnea at rest may be seen after exposure to CO_2 of 23 mm Hg for 60 minutes. Dizziness, lethargy, and uncomfortable dyspnea may develop within a few minutes of exposure to CO_2 of 30 to 38 mm Hg. Still higher CO_2 concentrations will cause unconsciousness, muscle twitching, convulsions, and eventually death.[12,13]

Since the early years of the International Space Station (ISS) program, anecdotal reports have suggested that ISS crew members develop CO_2-related symptoms, such as headache, lethargy, malaise, listlessness, and fatigue, at lower CO_2 levels than would be expected terrestrially.[2] Headache was reported on two early occasions: once while crew members were working inside a confined space having reduced air flow, and the other when all of the crew members were gathered in a single location. Also, these early ISS crew members described their individual symptoms as similar to those they experienced when they were intentionally exposed to excess CO_2 during ground training.[14] On later missions, there were reports of similar symptoms when $ppCO_2$ rose above 4 mm Hg but remained under the flight rule limit of 7.6 mm Hg. The crew noted that these symptoms subsided within minutes of reducing $ppCO_2$ to the range of 2 mm Hg or when they breathed 100% oxygen (O_2) in an extravehicular activity suit. Furthermore, the crew felt better and reported improved performance when CO_2 levels were low. Similar crew observations have been periodically noted since that time. These symptoms have resulted in closer occupational surveillance and operational lowering of the ISS CO_2 limits as more data are collected and flight rules are changed.

Given the apparent increased sensitivity to CO_2 exposure during spaceflight, it is important to understand the acute and chronic effects of elevated CO_2 on orbit, particularly in light of symptoms associated with the recently described spaceflight-induced visual impairment/intracranial pressure (VIIP) syndrome.[15,16] The "VIIP syndrome" is a set of ocular structural and optic nerve changes thought to be caused by events precipitated by the cephalad fluid shift crew members experience during microgravity exposure. There is a subset of crew members who experience visual performance decrements, cotton wool spot formation, choroidal fold development, optic disc edema, optic nerve sheath distention, and/or posterior globe flattening with varying degrees of severity and permanence. It is thought that CO_2 exposure may contribute as a predisposing or exacerbating

From the NASA Johnson Space Center (Dr Law, Ms Van Baalen, Dr Meyers, and Dr Alexander), Wyle Science, Technology and Engineering (Drs Foy and Wear), and MEI Technologies (Mrs Mason and Ms Mendez), Houston, Tex.

The authors declare no conflicts of interest.

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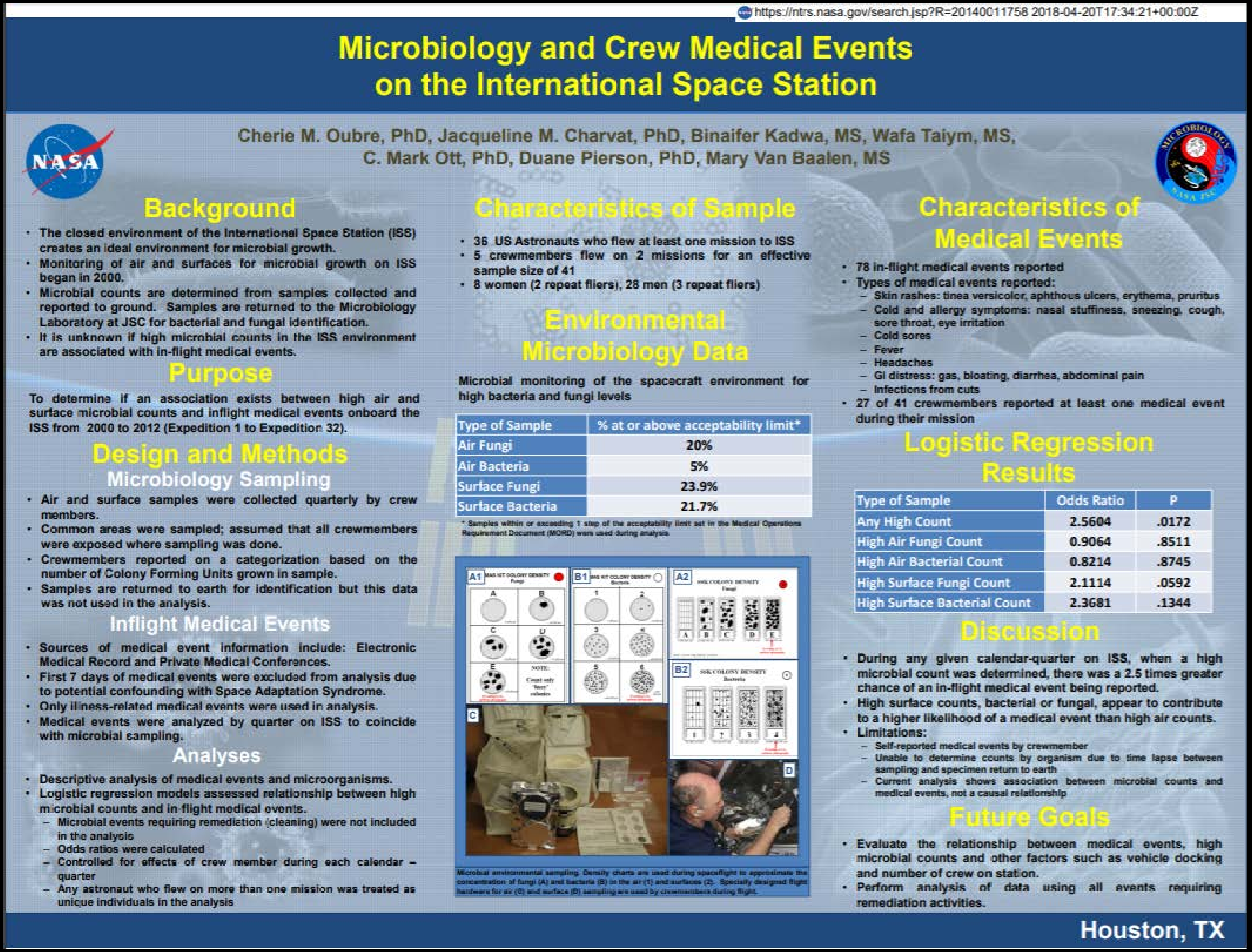
Potential Causes: Microorganisms

- 2014: Risk of an astronaut reporting a medical event tripled if microbial counts were above the established limits



https://ntrs.nasa.gov/search.jsp?R=20140011758 2018-04-20T17:34:21+00:00Z

Microbiology and Crew Medical Events on the International Space Station

Cherie M. Oubre, PhD, Jacqueline M. Charvat, PhD, Binaifer Kadwa, MS, Wafa Taiym, MS, C. Mark Ott, PhD, Duane Pierson, PhD, Mary Van Baalen, MS

Background

- The closed environment of the International Space Station (ISS) creates an ideal environment for microbial growth.
- Monitoring of air and surfaces for microbial growth on ISS began in 2000.
- Microbial counts are determined from samples collected and reported to ground. Samples are returned to the Microbiology Laboratory at JSC for bacterial and fungal identification.
- It is unknown if high microbial counts in the ISS environment are associated with in-flight medical events.

Purpose

To determine if an association exists between high air and surface microbial counts and inflight medical events onboard the ISS from 2000 to 2012 (Expedition 1 to Expedition 32).

Design and Methods

Microbiology Sampling

- Air and surface samples were collected quarterly by crew members.
- Common areas were sampled; assumed that all crewmembers were exposed where sampling was done.
- Crewmembers reported on a categorization based on the number of Colony Forming Units grown in sample.
- Samples are returned to earth for identification but this data was not used in the analysis.

Inflight Medical Events

- Sources of medical event information include: Electronic Medical Record and Private Medical Conferences.
- First 7 days of medical events were excluded from analysis due to potential confounding with Space Adaptation Syndrome.
- Only illness-related medical events were used in analysis.
- Medical events were analyzed by quarter on ISS to coincide with microbial sampling.

Analyses

- Descriptive analysis of medical events and microorganisms.
- Logistic regression models assessed relationship between high microbial counts and in-flight medical events.
  - Microbial events requiring remediation (cleaning) were not included in the analysis
  - Odds ratios were calculated
  - Controlled for effects of crew member during each calendar – quarter
  - Any astronaut who flew on more than one mission was treated as unique individuals in the analysis

Characteristics of Sample

- 36 US Astronauts who flew at least one mission to ISS
- 5 crewmembers flew on 2 missions for an effective sample size of 41
- 8 women (2 repeat fliers), 28 men (3 repeat fliers)

Environmental Microbiology Data

Microbial monitoring of the spacecraft environment for high bacteria and fungi levels

Type of Sample	% at or above acceptability limit*
Air Fungi	20%
Air Bacteria	5%
Surface Fungi	23.9%
Surface Bacteria	21.7%

* Samples within or exceeding 1 step of the acceptability limit set in the Medical Operations Requirement Document (MORD) were used during analysis.

Microbial environmental sampling. Density charts are used during spaceflight to approximate the concentration of fungi (A) and bacteria (B) in the air (1) and surfaces (2). Specially designed flight hardware for air (C) and surface (D) sampling are used by crewmembers during flight.

Characteristics of Medical Events

- 78 in-flight medical events reported
- Types of medical events reported:
  - Skin rashes: tinea versicolor, aphthous ulcers, erythema, pruritus
  - Cold and allergy symptoms: nasal stuffiness, sneezing, cough, sore throat, eye irritation
  - Cold sores
  - Fever
  - Headaches
  - GI distress: gas, bloating, diarrhea, abdominal pain
  - Infections from cuts
- 27 of 41 crewmembers reported at least one medical event during their mission

Logistic Regression Results

Type of Sample	Odds Ratio	P
Any High Count	2.5604	.0172
High Air Fungi Count	0.9064	.8511
High Air Bacterial Count	0.8214	.8745
High Surface Fungi Count	2.1114	.0592
High Surface Bacterial Count	2.3681	.1344

Discussion

- During any given calendar-quarter on ISS, when a high microbial count was determined, there was a 2.5 times greater chance of an in-flight medical event being reported.
- High surface counts, bacterial or fungal, appear to contribute to a higher likelihood of a medical event than high air counts.
- Limitations:
  - Self-reported medical events by crewmember
  - Unable to determine counts by organism due to time lapse between sampling and specimen return to earth
  - Current analysis shows association between microbial counts and medical events, not a causal relationship

Future Goals

- Evaluate the relationship between medical events, high microbial counts and other factors such as vehicle docking and number of crew on station.
- Perform analysis of data using all events requiring remediation activities.

Houston, TX

https://ntrs.nasa.gov/archive/nasa/casi.ntrs.nasa.gov/20140011758.pdf