

M.S. SEMINAR SERIES

THANKS TO OUR SPONSORS:



OUR AGENDA

- 4PM Live Music: Helena Holleran
- 5PM Keynote Presenter: Dr Revere Kinkel
- 6PM Guest Presenter: Dr Emily Schorr
- 7PM Event Concludes





Helena Holleran

Musical
Performer



Dr Revere Kinkel

Keynote Speaker



Dr Emily Schorr

Guest
Presenter

MEET OUR TEAM

Our team of
presenters and
artists for MS
Seminar: Part II



HELENA HOLLERAN

PRESENTED BY
BARNTIME MUSIC

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DR REVERE KINKLE

CLINICAL NEUROLOGIST
MS PRACTICE DIRECTOR
UCSD

Seminars in Integrative Management of MS
Seminar III
Decision making in Chronic Disease?

Revere (Rip) Kinkel MD, FAAN, FANA
Professor of Clinical Neurosciences
Director of the Multiple Sclerosis Program
Chief of Clinical Neurology, Hillcrest



Overview: Handling Perturbations in Health

- 100 % probability of occurrence
 - Goal: minimize frequency and severity of events & develop effective problem solving while remaining positive
 - Evaluate and overcome cognitive distortions that interfere with logical decision making and behaviors required to achieve goals
 - Learn to apply deliberate decision making
 - Understand the limitations and distortions of mental shortcuts (heuristics)
 - Requires education, training, planning
 - Know how to recognize BS, including the BS we tell ourselves
 - Build self efficacy : learn through failures and successes

Heuristics: *Amos Tversky & Daniel Kahneman*

- Mental shortcuts to facilitate understanding and problem solving
 - Makes problems less complex by ignoring information consciously or unconsciously
 - Allows for quick decision making under uncertain situations
- 3 main types
 - Representativeness: allows people to judge the likelihood that a place, object, idea or event belongs in a general category or class based on its similarity to members in that category
 - Anchoring & Adjustment: allows people to estimate a number or value by selecting a starting point (“anchor”) and adjusting the value up or down
 - Availability: allows people to estimate the likelihood of an event based on how easily that event can be brought to mind
- Heuristics are useful to survival but subject to bias & distortion that can interfere with decision making and make it easier to spread bullshit

1. Tversky, A., and Kahneman, D. [“Judgment under uncertainty: Heuristics and biases.”](#) *Science* 1974, vol. 185, no. 4157, pp. 1124-1131.
2. Kahneman, D. *Thinking, Fast and Slow*, 2011. Farrar, Straus and Giroux, New York
3. Bergstrom CT & West JD. *Calling Bullshit*, 2021, Random House, New York



System 1 and 2: Dan Kahneman's conceptualization

Heuristics are the byproduct of this interacting system

- System 1

- Quick and intuitive
- Little or no effort

- A
- C
- L
- H
- S
- a

Complex decisions with incomplete information and serious consequences require energy and create stress. It is even worse if you have difficulty staying focused (ADD or MS!) or dealing with anxiety and/or depression

- Generates suggestions for system 2 (impressions, intuitions, intentions, feelings); if endorsed these turn into beliefs or actions

- System 2

- Deliberate, effortful, orderly
- Requires concentration & attention

- Helps to program system 1 but it takes too much energy to constantly monitor system 1
- Easier to recognize other peoples' system 1 mistakes than your own

The Problem: Defining BS

- Bullshit: Using an individual's or a group's mindset or mental state to distract, confuse or mislead through actions, emotions, pictures, words or numbers
 - Bullshit is common because everyone is trying to sell you something (for good or misleading reasons); bullshit can also be fun, interesting and entertaining (“Bullshit artist”):
 - Lying is meant to evade the truth; bullshit is meant to alter the perception of the truth, mislead you or confuse you by overwhelming you and leaving you with no trust in anything. So-called “alternative truths”
 - Evasive and Persuasive Bullshit
- Brandolini's principle (2014)
 - “The amount of energy needed to refute bullshit is an order of magnitude bigger than [that needed] to produce it”: *think about going viral on social media*

Example of BS in Medicine: vaccines cause autism

- 1998 article in Lancet by Andrew Wakefield et al
 - Raised the possibility that a syndrome involving autism and inflammatory bowel disease may be associated with MMR vaccine
 - Tiny sample size
 - Case history
 - Refuted by
 - Mechanism
 - Despite Millers' investigations showing no link with autism, professional misconduct, and retraction of the original article as a fraud, the belief of a link persists
 - Why? Brandolini's Principle: it is easy to spread bullshit on social media. In this case antivaxxers invented a story about a big pharma conspiracy to hid the truth

Bullshit as Fraud

The Problem with Press Releases

Bullshit by Association

“Physical Activity Linked to Reduced Cancer Risk”. *NIH News*

Original Investigation

Association of Leisure-Time Physical Activity With Risk of 26 Types of Cancer in 1.44 Million Adults

Steven C. Moore, PhD, MPH; I-Min Lee, MBBCh, ScD; Elisabete Weiderpass, PhD; Peter T. Campbell, PhD; Joshua N. Sampson, PhD; Carl M. Kitahara, PhD; Sarah K. Keadle, PhD, MPH; Hannah Arendt, PhD; Amy Berrington de Gonzalez, DPhil; Patricia Hartge, ScD; Hans-Olov Adami, MD, PhD; Cindy K. Blair, PhD; Kristin B. Borch, PhD; Eric Boyd, BS; David P. Check, BS; Agnès Fournier, PhD; Neal D. Freedman, PhD; Marc Gunter, PhD; Mattias Johansson, PhD; Kay-Tee Khaw, MD, MSc, PhD; Martha S. Linet, MD; Nicola Orsini, PhD; Yikyung Park, ScD; Elio Riboli, MD; Kim Robien, PhD; Catherine Schairer, PhD; Howard Sesso, ScD, MPH; Michael Spriggs, BS; Roy Van Dusen, MS; Alicja Wolk, DMSc; Charles E. Matthews, PhD; Alpa V. Patel, PhD

- Representative Heuristic

- “It is human nature to infer that when two things are associated, one causes the other.”

“300 Minutes a Week of Moderate Exercise May Help Ward Off Cancer. More than 46,000 cancers in America each year, or about 3 percent of cases, could be prevented by meeting physical activity guidelines”. *New York Times*

Exercise
at

RESULTS A total of 1.44 million participants (median [range] age, 59 [19-98] years; 57% female) and 186 932 cancers were included. High vs low levels of leisure-time physical activity were associated with lower risks of 13 cancers: esophageal adenocarcinoma (HR, 0.58; 95% CI, 0.37-0.89), liver (HR, 0.73; 95% CI, 0.55-0.98), lung (HR, 0.74; 95% CI, 0.71-0.77), kidney (HR, 0.77; 95% CI, 0.70-0.85), gastric cardia (HR, 0.78; 95% CI, 0.64-0.95), endometrial (HR, 0.79; 95% CI, 0.68-0.92), myeloid leukemia (HR, 0.80; 95% CI, 0.70-0.92), myeloma (HR, 0.83; 95% CI, 0.72-0.95), colon (HR, 0.84; 95% CI, 0.77-0.91), head and neck (HR, 0.85; 95% CI, 0.78-0.93), rectal (HR, 0.87; 95% CI, 0.80-0.95), bladder (HR, 0.87; 95% CI, 0.82-0.92), and breast (HR, 0.90; 95% CI, 0.87-0.93). Body mass index adjustment modestly attenuated associations for several cancers, but 10 of 13 inverse associations remained statistically significant after this adjustment. Leisure-time physical activity was associated with higher risks of malignant melanoma (HR, 1.27; 95% CI, 1.16-1.40) and prostate cancer (HR, 1.05; 95% CI, 1.03-1.08). Associations were generally similar between overweight/obese and normal-weight individuals. Smoking status modified the association for lung cancer but not other smoking-related cancers.

CONCLUSIONS AND RELEVANCE This study found that leisure-time physical activity was associated with lower risks of many cancer types. However, the study also found that most of these associations were not statistically significant, supporting broad generalizability.

JAMA Intern Med. 2016;176(6):656-664. doi:10.1001/jamainternmed.2016.0176. Published online May 16, 2016.

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jamainternalmedicine.com

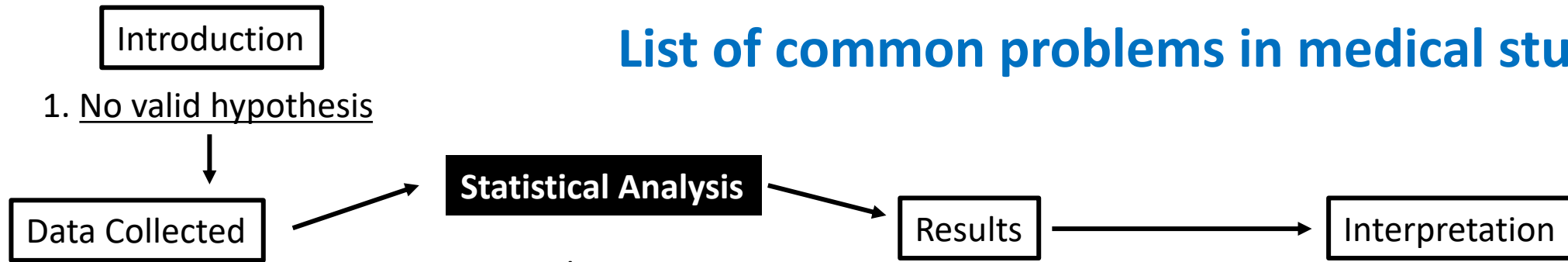
- Be wary of media reports with prescriptive claims

- Go to Tyler.Vigen.com for an entertaining list of spurious correlations

“Exercise Cuts Cancer Risk, Huge Study Finds”, *US News & World report*

Understanding Medical Studies

List of common problems in medical studies



1. No valid hypothesis

Statistical Analysis

Results

Interpretation

1. P-value misuse
2. Not taking into

1. Data mining

1. Inadequate Design and Methodology
 2. N is too small
 3. Selection bias
 4. Failure to account for missing data or dropout
 5. Control group
 6. Use of non validated
 7. Non-Randomized
- determine a meaningful result

- 1. Focus on human RCTs**
- 2. Make sure you are represented in study population**
- 3. N =50 per group for MRI outcome, 400 for relapse outcome (RMS) and 800 for disability outcome (PMS)**
- 4. Adequate duration to address safety & efficacy**
- 5. Published in high index factor journal (> 10)**

Associations or correlations

presented as causation

distorting the body of evidence

pointing out pitfalls

limited external validity not

appropriate

press releases & Commentary

based on incomplete data present-

ing just plain Bullshit

Interpretation or headlines not

representative of issue studied (e.g. animal studies reported as cure for MS)

7. Publication bias

Jumping to conclusions

How the spread of BS can have severe consequence

A prospective open-label study of endovascular treatment of chronic cerebrospinal venous insufficiency

“CCSVI is strongly associated with multiple sclerosis (MS)”

Objective: Chronic cerebrospinal venous insufficiency (CCSVI) is characterized by combined stenoses of the principal pathways of extracranial venous drainage, including the internal jugular veins (IJVs) and the azygous (AZY) vein, with development of collateral circles and insufficient drainage shown by increased mean transit time in cerebral magnetic

“CCSVI endovascular treatment significantly improved MS clinical outcome Measures, especially in the RR group; rate of relapse-free patients changed From 27 % to 50 % postoperatively ($P < .001$) and MR Gad + Lesions from 50 % to 12 %; $p < .001$)”

$P < .0001$). CCSVI endovascular treatment significantly improved MS clinical outcome measures, especially in the RR group: the rate of relapse-free patients changed from 27% to 50% postoperatively ($P < .001$) and of MR Gad+ lesions from 50% to 12% ($P < .0001$). The Multiple Sclerosis Functional Composite at 1 year improved significantly in RR patients ($P < .008$) but not in PP or SP. Physical QOL improved significantly in RR ($P < .01$) and in PP patients ($P < .03$), with a positive trend in SP ($P < .08$). Mental QOL showed significant improvement in RR ($P < .003$) and in PP ($P < .01$), but not in SP.

Conclusions: PTA of venous strictures in patients with CCSVI is safe, and especially in patients with RR, the clinical course positively influenced clinical and QOL parameters of the associated MS compared with the preoperative assessment. Restenosis rates are elevated in the IJVs but very promising in the AZY, suggesting the need to improve endovascular techniques in the former. The results of this pilot study warrant a subsequent randomized control study. (J Vasc Surg 2009;50:1348-58.)

Problems with the Zamboni study

- Hypothesis: claimed a non-established relationship (“CCSVI” is strongly associated with MS”)
- N too small (65 patients)
- No control group
- Neither patients or evaluators of outcome were blind to treatment
- Only a single run-up evaluation for pre- post- comparisons
- Apparent improvements in clinical outcomes do not account for placebo effects and regression to the mean

Why did Zamboni's results cause such a stir and why was it so difficult to correct?

- The outsider with no apparent bias: a vascular surgeon struggling to find a cure for his wife with MS
- The allure of a one-time treatment
- Far less regulation of surgical procedures than pharmacological treatments
- The perfect storm in 2009
 - MS patients realizing that old injectables were not meeting their needs
 - Skepticism directed at the MS establishment was maximal at the time because of safety concerns with the only high efficacy MS treatment.
 - NMSS, desperate for survival at the culmination of the great recession, was forced to fund CCSVI research or face a major loss in philanthropic funding
 - Social media exploded between 2009 and 2014 when studies refuting the link between CCSVI and MS appeared. Investigators castigated as biased



Prevalence of extracranial venous narrowing on catheter venography in people with multiple sclerosis, their siblings, and unrelated healthy controls: a blinded, case-control study

Anthony L Traboulsee, Katherine B Knox, Lindsay Machan, Yinshan Zhao, Irene Yee, Alexander Rauscher, Darren Klass, Peter Szkup, Robert Otani, David Kopriva, Shanti Lala, David K Li, Dessa Sadovnick

“Catheter venography criteria for [CCSVI] were positive for one of 65 (2%) people with Multiple Sclerosis, one of 46 (2%) siblings, and one of 32 (3%) unrelated controls (p=1.0)”

Department of Radiology (L Machan MD, A Rauscher PhD, D Klass MD, Prof D K Li MD), and Department of Medical Genetics (I Yee MSc, D Sadovnick), University of British Columbia, Vancouver,

and they comprised 177 adults: 79 with multiple sclerosis, 55 siblings, and 43 unrelated controls, from three centres in Canada. We assessed narrowing of the internal jugular and azygous veins with catheter venography and ultrasound criteria for chronic cerebrospinal venous insufficiency proposed by Zamboni and colleagues. Catheter venography data were available for 149 participants and ultrasound data for 171 participants.

Findings Catheter venography criteria for chronic cerebrospinal venous insufficiency were positive for one of 65 (2%)

“Extracranial venous narrowing of greater than 50 % is a frequent finding in people.....”

Canada; and Department of Surgery, University of Saskatchewan, Regina, Saskatchewan, Canada (D Kopriva MD, S Lala MD)

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criteria for detection of greater than 50% narrowing on catheter venography was 0.406 (95% CI 0.311–0.508), and specificity was 0.643 (0.480–0.780).

Interpretation This study shows that chronic cerebrospinal venous insufficiency occurs rarely in both patients with multiple sclerosis and in healthy people. Extracranial venous narrowing of greater than 50% is a frequent finding in patients with multiple sclerosis, unaffected siblings, and unrelated controls. The ultrasound criteria are neither sensitive nor specific for narrowing on catheter venography. The significance of venous narrowing to multiple sclerosis symptomatology remains unknown.

Funding MS Society of Canada, Saskatoon City Hospital Foundation, Lotte and John Hecht Memorial Foundation, Vancouver Coastal Health Foundation, and the Wolridge Foundation.

Efficacy and Safety of Extracranial Vein Angioplasty in Multiple Sclerosis

A Randomized Clinical Trial

Paolo Zamboni, MD; Luigi Tesio, MD; Stefania Galimberti, PhD; Luca Massacesi, MD; Fabrizio Salvi, MD; Roberto D'Alessandro, MD; Patrizia Cenni, MD; Roberto Galeotti, MD; Donato Papini, PhD; Roberto D'Amico, PhD; Silvana Simi, PhD; Maria Grazia Valsecchi, PhD; Graziella Filippini, MD, for the Brave Dreams Research Group

IMPORTANCE Chronic cerebrospinal venous insufficiency (CCSVI) is characterized by restricted venous outflow from the brain and spinal cord. Whether this condition is associated with multiple sclerosis (MS) and whether venous percutaneous transluminal angioplasty (PTA) is beneficial in persons with MS and CCSVI is controversial.

Editorial page 15

Supplemental content

A very unlikely hypothesis remains unlikely even after someone obtains experimental results with a very small *p*-value

In 2017 Dr Paolo Zamboni officially retracted his claim that his “Liberation Procedure” benefited MS. He continues to study the relationship between cerebral vasculature and Multiple Sclerosis. This retraction occurred after thousands of patients underwent this procedure, with SAEs up to 10 %, and millions of dollars were spent to disprove a treatment for which there was no theoretical benefit.

They had 100% and 10 of 37 (27%) in the sham group were free of new lesions on magnetic resonance imaging (odds ratio, 1.80; 95% CI, 0.81-4.01; *P* = .15; adjusted *P* = .30).

CONCLUSION AND RELEVANCE Venous PTA has proven to be a safe but largely ineffective technique; the treatment cannot be recommended in patients with MS.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01371760

JAMA Neurol. 2018;75(1):35-43. doi:10.1001/jamaneurol.2017.3825
Published online November 18, 2017.

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The members of the Brave Dreams Research Group are listed at the end of the article.

Corresponding Author: Paolo Zamboni, MD, Translational Surgery and Vascular Diseases Centre, University of Ferrara Hospital, Via Aldo Moro 8, 44124 Cona, Ferrara, Italy (paolozamboni@icloud.com).

Diagnostic Testing

- Patient comes to you with concerns of lyme disease because of recent tick exposure (no known bite or rash), and increased fatigue. His lyme test is positive & he asks for treatment
- Lyme testing false positive rate is 5 %
- False negative rate is 10 %
- What is the chance he has lyme disease?

Base Rate Fallacy

	Positive test	Negative test	Total # people
Lyme disease +	9	1 (false -)	10
Lyme disease -	495 (false +)	9405	9,990
Total # people	504	9406	10,000

The probability of disease is based on the pretest probability of the disease. There is < 2 % chance the patient is infected (9/504)

Prevalence of Lyme disease in endemic areas is 1/1000

Now let's pretend the pretest probability of Lyme disease is 50 %

	Positive test	Negative test	Total # people
Lyme disease +	4500	500 (false negative)	5,000
Lyme disease -	250 (false positive)	4750	5,000
Total # people	4750	5250	10,000

Now there is almost a 95 % chance the patient is infected ($4500/4750=94.7\%$)

Rules for Decision Making

- Think positively but be skeptical
 - Who (is telling me), how (do they know) and why (are they trying to sell me) ?
 - Go to the source (peer reviewed journal article) and make sure info matches
 - Use Snopes.com, PolitiFact.com to check internet, social media or other news reports
- Beware of unfair comparisons (inappropriate control group) or lack of external validity (if you are not in the control group)
- If it seems too good to be true, it probably is. Think represented but not necessarily your
- Be aware of precognition. Neuroscience is particularly true of correlations or associations (tylervigen.com)
- For Decision making, “Trust someone who likes you but doesn’t care too much about your feelings”: Dan Kahneman
- Break decisions into steps (Dysconjugate (A or B) probabilities higher than conjugate (A and B) probabilities)
- Expect to make wrong decisions. These are ways to learn and grow

All breakthrough data will be reported in the most important journals

Think

NEJM, Lancet, JAMA, Nature, Science, Cell, Brain,

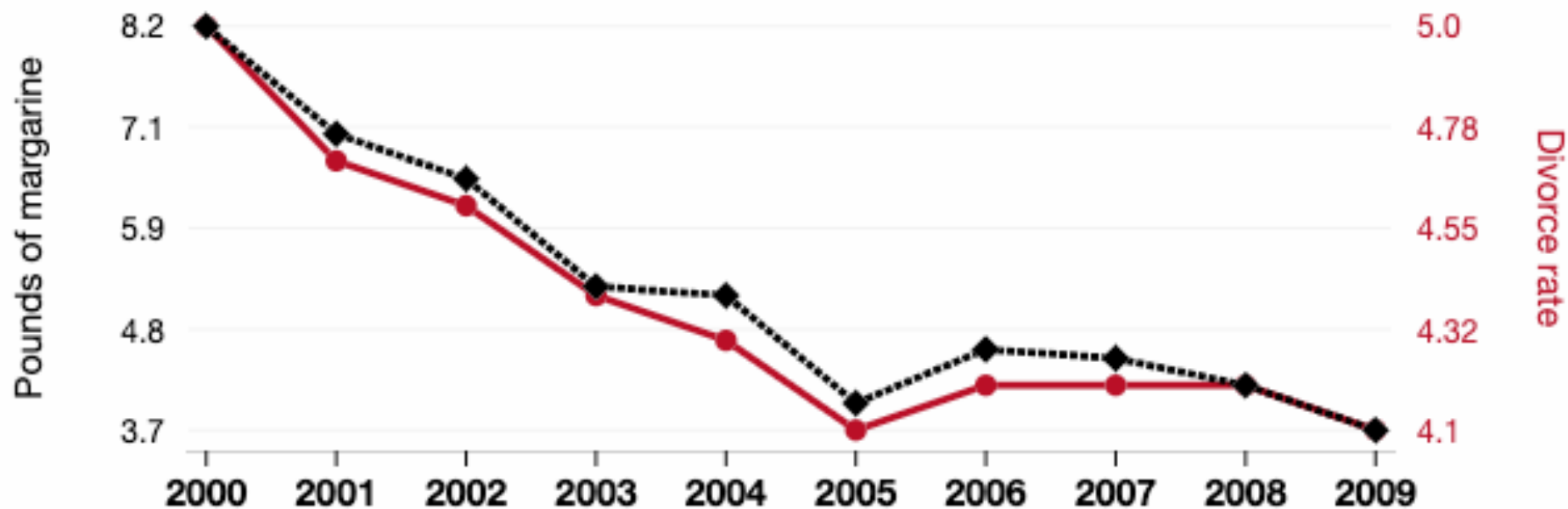
Neuron, Neuroimage, Annals of Neurol., J of

Neuroscience

Per capita consumption of margarine

correlates with

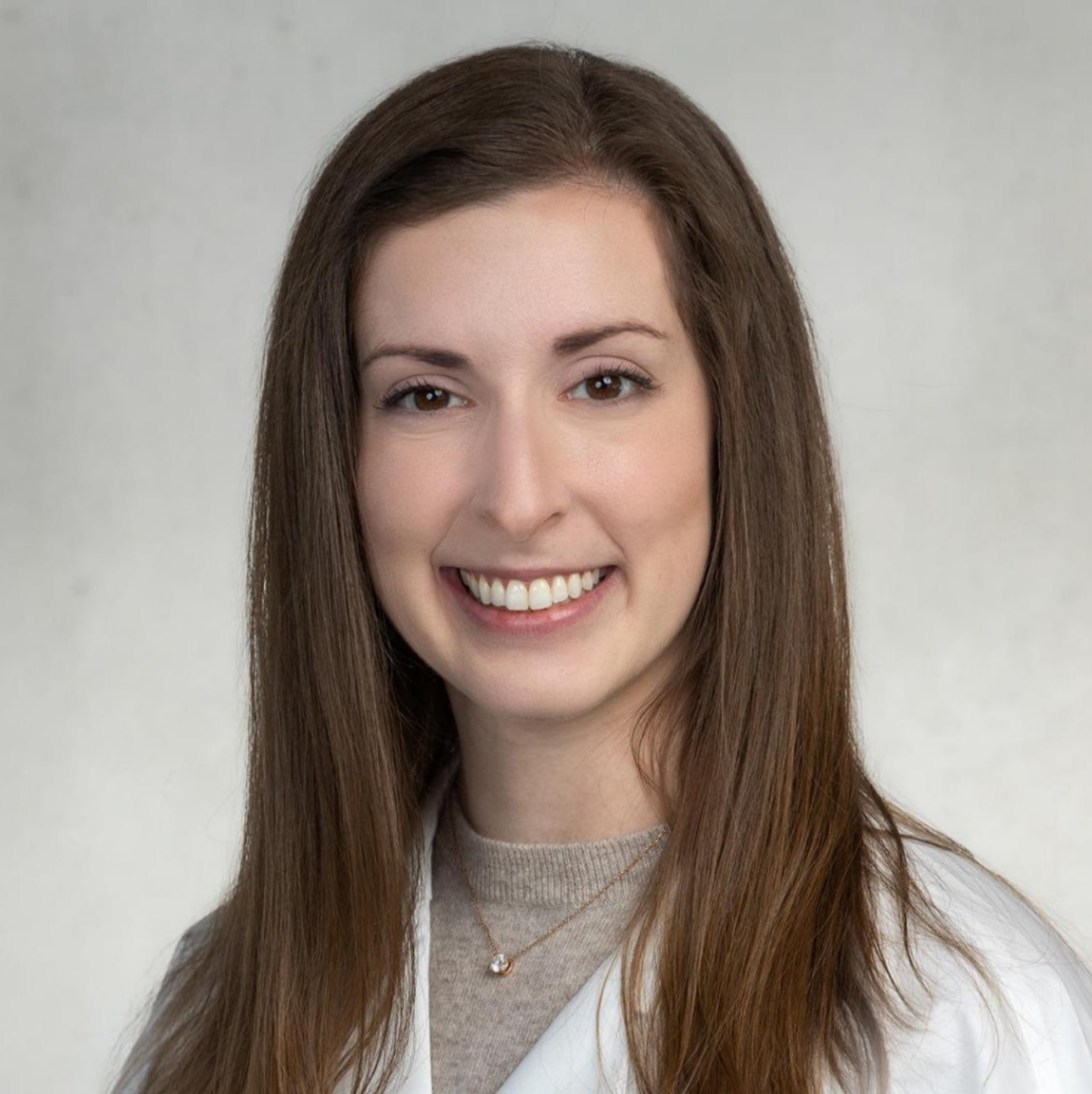
The divorce rate in Maine



◆ Per capita consumption of margarine in the United States · Source: US Department of Agriculture

● The divorce rate in Maine · Source: CDC National Vital Statistics

2000-2009, $r=0.993$, $r^2=0.985$, $p<0.01$ · tylervigen.com/spurious/correlation/5920



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