

Statistics, Ethics, and the Promotion of Reproducible Research

Thomas F Heston¹

¹Department of Family Medicine, University of Washington

October 2, 2023

Abstract

Rigorous statistical methodology represents a vital framework for upholding research integrity and maximizing benefits in medical science. However, the misuse of statistical tools contradicts ethical tenets and compromises validity. Problematic trends like p-hacking, hyping delicate results, and overemphasizing statistical significance relative to clinical meaning introduce prejudice and impede reproducibility. Case studies, including hormone replacement therapy trials, exhibit how unsound statistics propagate doubtful conclusions and potential injury. Resolving the "reproducibility crisis" necessitates proper statistical techniques such as sufficient power, preregistration, transparent data, and Bayesian approaches. Statistics and ethics are profoundly intertwined in accountable medical inquiry. By prioritizing statistical meticulousness, investigators can satisfy their ethical duty to generate reproducible discoveries that aid patients and society. Proper statistical application is indispensable for advancing medically and socially impactful research.

Statistics, Ethics, and the Promotion of Reproducible Research

Thomas F. Heston, MD, FAAFP

Department of Family Medicine, University of Washington

Abstract. Rigorous statistical methodology represents a vital framework for upholding research integrity and maximizing benefits in medical science. However, the misuse of statistical tools contradicts ethical tenets and compromises validity. Problematic trends like p-hacking, hyping delicate results, and overemphasizing statistical significance relative to clinical meaning introduce prejudice and impede reproducibility. Case studies, including hormone replacement therapy trials, exhibit how unsound statistics propagate doubtful conclusions and potential injury. Resolving the "reproducibility crisis" necessitates proper statistical techniques such as sufficient power, preregistration, transparent data, and Bayesian approaches. Statistics and ethics are profoundly intertwined in accountable medical inquiry. By prioritizing statistical meticulousness, investigators can satisfy their ethical duty to generate reproducible discoveries that aid patients and society. Proper statistical application is indispensable for advancing medically and socially impactful research.

Keywords. reproducibility, research ethics, statistics, medical research, reproducibility crisis

Conflict of Interest. none declared

Funding. Self-funded, no external funding.

Introduction

Biostatistics, applying statistical methods to biological, medical, and public health research, is fundamental to rigorous scientific inquiry. By providing robust data analysis and interpretation frameworks, biostatistics ensures findings' validity, reliability, and generalizability and profoundly influences clinical and policy decisions (1).

The 18th century marked significant strides in probabilistic reasoning and controlled experiments. John Arbuthnot's 1710 evaluation of birth statistics in London using probability was an early breakthrough when he found with high certainty that the birth rate for males was greater than that for females (2). Concurrently, James Lind's pioneering 1753 scurvy treatment experiment established essential foundations for controlled trials by incorporating randomization and accounting for confounders (3,4). Later contributions came from mathematicians like Daniel Bernoulli, who applied statistical thinking to inoculation against smallpox (5), and Pierre-Simon Laplace, renowned for developing early Bayesian inference in his 1814 seminal work, *A Philosophical Essay on Probabilities* (6). These innovations demonstrated the growing power of statistics to produce actionable medical insights.

Key 19th-century figures include Florence Nightingale, who effectively applied statistics to demonstrate the critical role of sanitation (7), and Francis Galton, renowned for developing statistical concepts like correlation and regression broadly applicable in biology (8).

The 20th century marked increased formalization of ethical guidelines for clinical trials via documents like the Nuremberg Code, the Declaration of Helsinki, and the Belmont Report. Together, these guidelines underscored the need for rigorous statistical approaches to minimize harm and maximize benefits (9). Karl Pearson and Ronald Fisher, two prominent statisticians of the 20th century, played pivotal roles in formalizing the calculation and interpretation of the p-value (10). The advent of card tabulators and electronic computers marked a significant leap forward in statistical analysis capabilities (11). These technological advancements laid the foundation for modern-day statistical methods that continue to shape the landscape of scientific research. The advent of electronic computers and sophisticated software in the 20th century marked a pivotal leap forward, providing the computational power to develop and apply intricate statistical techniques like multivariate regression, advanced predictive modeling, and real-time data analytics.

In summary, the evolution of biostatistics from Graunt's 17th-century contributions to the technological leaps of the 20th century demonstrates its indispensable role in ensuring scientific rigor and integrity, which are fundamental to the ethical conduct of medical research. This ever-advancing field provides a moral, analytical foundation for quality clinical trials.

As Pierre-Simon Laplace famously stated, "Probability theory is nothing but common sense reduced to calculation." This succinctly captures how biostatistics brings rigor and structure to analyzing uncertainty. Florence Nightingale underscored the life-saving potential of biostatistics when she said, "To understand God's thoughts, we must study statistics, for these are the measure of His purpose." Finally, Ronald Fisher, a founder of

modern statistical science, reminded researchers, "To call in the statistician after the experiment is done may be no more than asking him to perform a post-mortem examination: he may be able to say what the experiment died of."

Statistical Hazards in Biomedical Research

In current biomedical research, statistical analyses are pivotal in validating findings and drawing evidence-based conclusions. However, the ubiquity of high-powered computing platforms has facilitated the effortless calculation of intricate statistical algorithms, sometimes leading to inappropriate and overly complex applications of statistical tools. To avoid the most common biostatistical errors, researchers should continually review the fundamentals of basic statistics to understand potential pitfalls and how to address them (12,13).

The following sections discuss several pitfalls in biostatistics that may not only skew results but also raise ethical concerns due to improper statistical planning and analysis. This is not an exhaustive list or an in-depth summary of each hazard but rather an overview of multiple areas of biostatistics that can result in flawed research.

Overreliance on Statistical Significance Versus Clinical Significance

Statistical significance is often misconstrued as indicative of clinical importance.

Researchers frequently apply an arbitrary cut-off point of 5% ($p < 0.05$) to determine the

"significance" of their findings (14). Such an approach can be misleading and lead to suboptimal patient care when the focus should be on clinical significance instead. For example, a drug may show a statistically significant reduction in blood pressure but only by an average of 1 mmHg, which is clinically irrelevant.

Over-analysis of Data: Missing the Forest for the Trees

Another pitfall is the over-analysis of data, which can cause researchers to lose sight of the broader implications of their work. With advanced computational capabilities, subjecting data to numerous statistical tests and inappropriately selecting multiple variables becomes tempting (15). However, this can result in "noise" overshadowing the "signal," thereby diluting the actual message or findings the research aims to convey.

Failure to Address Fragility of Data

The reporting of statistical outcomes often omits mention of how fragile or robust the data is. A study may tout significant findings, but the purported significance can be misleading if the results are based on fragile data sensitive to minor adjustments. Fragility indices should, therefore, be included to prevent over-hyping results (16).

Neglecting Effect Size

A common issue arises when large sample sizes are employed: p-values often fall below 0.05, thus appearing statistically significant. The reason is that statistical analysis considers standard errors, calculated as the standard deviation divided by the square root of the

sample size minus 1. Standard errors shrink as the sample size grows, and statistically significant differences that are clinically irrelevant are more likely to be identified (17). However, this can be associated with minuscule effect sizes, rendering the findings less impactful than the p-value might suggest (18).

P-Hacking: Manipulating Data to Achieve Significance

P-hacking, or data dredging, is another concerning trend in biomedical research (19). P-hacking involves manipulating data analysis to obtain statistically significant results, usually a p-value below 0.05. This can involve techniques like testing many different combinations of variables, excluding specific data points, and stopping analysis when significance is reached. These practices inflate Type I errors, the false positive rate, and undermine the validity of the findings.

Ignoring Prevalence Rates

Even when the difference in population means is statistically significant, the overall prevalence rate in a given population can override this significance. For example, a statistically significant improvement in treatment outcomes may only apply to a tiny fraction of the patient population, making the finding less meaningful in broader clinical practice (20).

Over-Reliance on Models

Statistical models are valuable tools for simplifying complex biological phenomena. However, an unwarranted faith in models, especially without ongoing updates based on new data, can lead to substantial errors in interpreting and applying research findings (21). The responsible and ethical use of models requires testing and validation before deployment.

Multiple Comparisons Problem

When a data set is subjected to numerous statistical tests, the likelihood of identifying at least one "significant" result purely by chance increases. Without proper correction methods like the Bonferroni correction or the Benjamini-Hochberg procedure, the false discovery rate could be inflated, leading to incorrect conclusions (22).

Survivorship Bias

Survivorship bias occurs when researchers focus only on subjects that "survived" a process or passed a selection filter, neglecting those who did not. It is a reporting bias that can occur due to publication bias (only publishing statistically significant findings) or selective reporting of a visible subgroup that gets mistaken for representing the entire group (23). This can skew results and conclusions, as the full range of data is not considered (24,25).

Confounding Variables

Failure to account for confounding variables can lead to incorrect inferences about causal relationships. For example, if a study finds that drug A lowers blood pressure but fails to account for lifestyle changes like diet, the study's conclusions might be inaccurate. This is a common cause for medical research that subsequently gets reversed. Randomization can help account for known and unknown confounding variables (26).

Autocorrelation

In analyzing time-series data, accounting for the likelihood of autocorrelation between measurements taken in close temporal proximity is imperative for researchers. Overlooking this statistical characteristic can bias estimates and reduce precision, compromising the validity of subsequent scientific inferences. Specialized statistical techniques, including Seasonal AutoRegressive Integrated Moving Average (SARIMA) models and Nonlinear Autoregressive Neural Networks (NANN), are often employed to mitigate this. For example, SARIMA and NANN were utilized to predict new patient admissions to a hospital so resources could be better managed (27). They found that the linear model, SARIMA, combined with NANN, was best at predicting monthly trends, but NANN alone was better at predicting daily trends.

Heteroscedasticity

The assumption that the variance of the errors is constant across all levels of the independent variables is crucial for many statistical tests. Violations of this assumption

(heteroscedasticity) can distort findings and weaken the reliability of hypothesis tests. The Harrison-McCabe test can be used to evaluate for heteroscedasticity (28).

Selection Bias

Selection bias occurs when the sample obtained does not represent the population intended for the study. For example, if a study on a drug's effectiveness only includes healthy young adults, the results may not generalize to older populations or those with comorbid conditions. Sampling bias is one type of selection bias that can occur due to non-random sampling approaches that systematically exclude certain members of the target population. For instance, convenience sampling based on easily accessible subjects may bias the sample. Another cause can be the exclusive analysis of research subjects with complete datasets and throwing out those with missing data, which in the past was common with trauma research (29). Because there is often a medical reason for missing data, this practice can skew the results, leading to incorrect conclusions from the research.

Collinearity

When two or more variables are highly correlated, it becomes difficult to separate the individual effects of these variables. This is particularly problematic in multivariate regression analyses (30).

Post-Hoc Rationalizations

After obtaining results, researchers might be tempted to explain unexpected findings with reasoning not part of the initial study design. While not always inappropriate, it can often be misleading and is generally considered poor scientific practice (31). This practice can not only lead to poor medical care, but it can have legal ramifications as well. For example, using vague symptoms at a later date to predict child abuse at an earlier date can result in grave errors in legal decisions (32).

Simpson's Paradox

Simpson's Paradox occurs when a trend that appears in separate groups disappears or reverses when the groups are combined. It highlights the importance of stratified analysis to understand subgroup effects. Adjusting disease prevalence rates appropriately can help overcome this effect in many cases (20,33)

Peer-Review and Moral Hazards

Examining the role of pre-publication peer review in perpetuating certain statistical shortcomings is imperative. Although peer review is designed to enhance research quality and mitigate the spread of misinformation, the system has limitations and ethical concerns. These include potential biases and a disproportionate emphasis on statistically significant outcomes. The definition of a "peer" within this context exhibits considerable variability, and reviewers frequently offer inconsistent feedback. The peer review process also

manifests a notable "establishment bias," leading to differential treatment of research papers based on institutional affiliation (34).

The misapplication of statistical methods can directly violate core ethical principles that guide medical research. For example, p-hacking to achieve statistical significance when the actual effect size is negligible goes against the principle of beneficence. Though it may produce an impressive p-value, the clinical benefit to patients is likely minimal. Conversely, failing to account for confounding factors correctly can overestimate an intervention's effectiveness, violating non-maleficence if it leads to patient harm. Not recognizing the fragility of findings could cause results to be over-generalized beyond what the data supports, undermining beneficence. While ethical research requires meticulous study design and execution, robust statistical practices provide the analytical framework to uphold these ethical obligations. Turning a blind eye to limitations, flexibility in data analysis, and selective reporting may achieve publication, but at the cost of breaching principles meant to protect human subjects.

In summary, as the biomedical research community increasingly relies on statistical methodologies, vigilance is essential to avoid the misuse of statistical tools. Accurate, ethical research necessitates a nuanced understanding of the complex interplay between statistical and clinical significance, among other factors, to truly advance the field.

Case Studies

These case studies demonstrate the importance of statistics in ethical medical research. The misapplication of statistical planning and analysis can result in significant harm by coming to incorrect conclusions or a significant delay in medical advances.

Hormone Replacement Therapy

In a seminal study conducted in 1991, hormone replacement therapy (HRT) was associated with reduced incidence rates of coronary heart disease among postmenopausal individuals undergoing estrogen therapy (35). This observational investigation included a significant cohort of nearly 50,000 women from the Nurses' Health Study (NHS). Over a decade-long follow-up, this research meticulously recorded 224 cases of stroke, 405 events of major coronary disease, and 1,263 total fatalities. The study's large sample size of nearly 50,000 participants provided considerable statistical power. Using multivariate regression to account for age, smoking status, cholesterol levels, and other variables was a methodological strength in assessing the independent effect of HRT on heart disease risk. The relative risks were discerned by comparing participants who had undergone HRT and those who had not. A Cox proportional hazards model was rigorously employed to control for potential confounding variables.

Within the NHS study, multivariate regression methods were utilized to account for various confounding variables, such as age (categorized in 5-year increments), cigarette smoking, hypertension, elevated serum cholesterol, and a family history of myocardial infarction

before age 60. While this methodological framework allowed for a detailed assessment of HRT's impact on coronary heart disease, its limitations must be recognized. The exclusion of data on physical activity, even when available, might have introduced bias, given the known protective effects of exercise against heart disease. The dependence on self-reported information, especially regarding crucial variables like smoking habits and medical history, might have induced recall bias. Additionally, the categorization of age and the binary distinction of specific risk factors could have led to potential misclassification, impacting the research conclusions. However, it's significant that HRT became the standard of care for postmenopausal individuals primarily based on this study's results during the 1990s. While the categorical classification of some variables may have led to misclassification, including multiple potential confounders improved upon simpler univariate analyses.

Subsequent research by the Women's Health Initiative (WHI) in 2002 contradicted these earlier findings, determining that HRT was linked with an elevated cardiovascular risk (36). This latter study employed a robust, randomized, placebo-controlled, double-blind methodology. As a result, HRT is no longer advocated as a preventive measure against cardiovascular disease.

The implications of the initial endorsement of HRT for postmenopausal individuals remain intricate. The impact was undoubtedly significant, given the visibility of the NHS article in the New England Journal of Medicine and its association with Harvard University. A more thorough examination of the statistical limitations inherent in the NHS study could have tempered the widespread, erroneous enthusiasm for HRT during the 1990s.

In the 1991 NHS research, participants mainly consisted of registered nurses from 11 U.S. states. Owing to their profession, these nurses likely had enhanced access to healthcare services and medical information compared to the broader female population of that era. This specific group might have introduced a selection bias, potentially affecting the study's findings and applicability to a more diverse demographic.

The absence of randomization made it challenging to control for confounding factors effectively. Moreover, although data on numerous variables and outcomes were accumulated, the multivariate regression model omitted protective elements such as physical activity. Paired with the biennial reset of outcome analysis, this might have potentially led to statistical errors stemming from over-analysis and p-hacking (19).

A salient takeaway from the evolution of HRT guidelines is the need for transparently addressing research limitations. Regrettably, the NHS research only provided a limited discussion on its research constraints, a pattern still prevalent in medical research. For instance, a dental literature review demonstrated that only 27% of randomized clinical trials incorporated discussions of study limitations (37).

From a statistical perspective, there are numerous ethical considerations to consider. First, observational studies suggesting significant shifts in medical therapy should be succeeded by more stringent randomized clinical trials. When adjusting an independent outcome, such as cardiovascular disease, by multivariate regression, it's imperative to include both risk and protective factors. The conclusions might not apply broadly if a study's

participants are relatively uniform. Finally, researchers should carefully examine and detail in their manuscripts the statistical limitations inherent in their investigations.

Saturated Fats and Heart Disease

A study conducted in 1957 by Keys et al. revealed an association between saturated fats and elevated cholesterol levels, prompting the recommendation in 1961 by the American Heart Association to replace saturated fats with polyunsaturated fats (38,39). Subsequently, in 2013, a meta-analysis challenged this practice, suggesting it lacked cardiovascular benefits (40). Then, a Cochrane review in 2020 concluded that there was some evidence of cardiovascular benefits of reducing saturated fat intake but found no impact on overall mortality (41). While randomized trials are more rigorous than observational studies, even RCTs can be limited by adherence, attrition, short follow-up periods, and lack of generalization to broader populations. This further emphasizes the need for caution when interpreting the results of nutrition studies since perfectly controlling diet over the long term is inherently challenging. The consensus among experts currently advocates for a balanced diet, exemplified by the Mediterranean Diet, which protects against cardiovascular issues and supports cancer prevention (42) (43). These evolving recommendations underscore the statistical advantages of employing concrete endpoints, such as diagnosed cardiovascular events, instead of surrogate endpoints. Surrogate endpoints are measures that substitute for clinical endpoints of interest. For example, a study may use a change in blood pressure as a surrogate marker for the risk of stroke. Surrogate endpoints are convenient but can be misleading if the correlation with the

clinical outcome is weak. Relying solely on them may overestimate clinical benefits or provide a false impression of efficacy. Hard clinical endpoints like mortality or cardiovascular events provide more definitive evidence. The everyday use of surrogate endpoints in dietary studies emphasizes caution when interpreting research that cannot comprehensively control for confounding variables.

Vaccinations and Autism

A study involving 12 children in 1998 suggested a potential link between autism and the measles, mumps, and rubella (MMR) vaccination (44). This study was retracted in 2010, primarily due to ethical violations related to human subjects, but notably not for statistical errors that led to poorly supported and controversial findings (45). In contrast, a comprehensive 2014 meta-analysis encompassing ten studies, which included data from over 1.2 million children, found no discernible association between the MMR vaccine and autism (46). Nevertheless, concerns regarding a potential connection between the MMR vaccine and autism persist among some parents, contributing to a significant decline in MMR vaccination rates (47). This underscores the critical importance of promptly identifying and addressing statistical errors to prevent the propagation of medical misinformation.

Notably, the original 1998 study was hindered by a limited sample size, comprising only 12 children. Additionally, it lacked proper control groups and predominantly relied on parental recall. The fact that it took 12 years to retract this study and that it continues to influence

vaccine hesitancy emphasizes the vital necessity of stringent statistical rigor before publication.

Arthroscopic Surgery for Knee Osteoarthritis

A randomized trial of 32 adults with moderate osteoarthritis found that arthroscopic knee surgery provided pain relief but was not superior to saline joint lavage alone (48). A follow-up randomized, placebo-controlled study of 180 adults with osteoarthritis in 2002 found that neither arthroscopic nor lavage was superior to sham surgery (49). These studies highlight the importance of considering the substantial placebo effects that can occur with invasive procedures (50).

Internal Mammary Artery Ligation for Angina Pectoris

Utilizing internal mammary artery ligation as a treatment for angina pectoris was widely accepted before the 1960s. This acceptance was based on a plausible hypothesis substantiated by an extensive study involving 304 patients (51) (52). An improvement was observed over a follow-up period ranging from 3 months to 4 years in 85% of the patients. However, it is essential to note that this study lacked a control group for comparative analysis, lacked blinding or randomization, and did not conduct any statistical analysis of the results.

In contrast, a follow-up study conducted in 1960, though involving only 18 participants, offered a randomized, double-blind comparison of internal mammary artery ligation versus a sham operation (53). In this study, all five participants who underwent sham surgery

reported improvement, while nine out of thirteen who underwent internal mammary ligation demonstrated improvement. Nonetheless, it is noteworthy that this follow-up study also refrained from conducting a statistical analysis. Nevertheless, when subjected to the Fisher Exact test, the data yields a p-value of 0.28, in line with the authors' conclusion that no discernible benefit was associated with internal mammary artery ligation.

Another study from the same era, albeit with a relatively small sample size of 17 participants, also employed a sham surgery approach and gained high credibility owing to its robust study design (54). In this study, five participants in the ligation group experienced improvement, three worsened, and one succumbed. In the sham group, five participants improved, two worsened, and one succumbed. Once again, this study refrained from performing a statistical analysis. Nevertheless, when the results of these 17 participants were combined with those of the other sham surgery-controlled study, the Fisher Exact p-value equated to 0.48, further supporting the notion that internal mammary artery ligation did not confer any discernible benefit. Furthermore, it's worth noting that the combined data has a robustness index of 5.75, consistent with robust statistical findings (55).

Additional subsequent studies have corroborated the findings of the two sham surgery-controlled studies, underscoring the importance of a rigorous study design. These studies also clearly demonstrated the potent placebo effect associated with invasive procedures.

Conclusion

The term "reproducibility crisis" has emerged as a pressing concern in the medical research community, spotlighting the alarming rate at which published studies—often deemed statistically significant—fail to produce the same results upon replication. Several statistical factors contribute to this ethical crisis, including but not limited to p-hacking, small sample sizes, and a publication bias that favors positive findings (56). Poor reproducibility is partly due to a lack of full access to complete data and incentives favoring novelty over replication. The ramifications are substantial, from wasted resources to suboptimal clinical guidelines and, most crucially, eroded public trust in science. Reproducibility is not just a statistical or methodological issue; it's an ethical one. When research cannot be reproduced, it threatens the core ethical imperatives of scientific integrity and societal benefit.

In addressing this crisis, the proper application of biostatistics offers a foundational solution. First, by adhering to rigorous study design and statistical planning, including power analysis, to determine appropriate sample sizes, researchers can increase the likelihood that their findings are statistically significant and clinically meaningful. Second, embracing practices like pre-registration of studies can limit the temptation or opportunities for p-hacking, thereby enhancing the validity of the findings. Transparent reporting of methods and results, including so-called 'negative findings,' would allow for more robust meta-analyses and systematic reviews, the cornerstone of evidence-based medicine. Third, advanced statistical techniques such as Bayesian analysis can offer more

nuanced interpretations of data, including integrating prior evidence. Ethical research practices and robust statistical methodology are not mutually exclusive but are, in fact, interdependent. By elevating statistical rigor, the reproducibility of research can be improved, and the ethical caliber of the science can be elevated, reinstating confidence in medical research as a trustworthy endeavor.

Upholding research ethics necessitates the proper application of statistical principles. Several strategies can promote ethical statistical practices. Broader pre-registration and data-sharing adoption fosters transparency and minimizes questionable research practices undermining integrity. Preregistration should be incentivized or required by journals and funders to limit data dredging and selective reporting. Sharing de-identified data and publishing null or negative findings reduces publication bias. This upholds the ethical obligation of disseminating all scientifically valid results, not just positive ones. Promoting collaboration between biostatisticians and researchers reinforces rigorous, ethical study design and analysis. Expanding training in statistical thinking, study design, and ethical research conduct equips more scholars to apply statistics responsibly. Embracing Bayesian approaches allows the formal integration of prior evidence, yielding more nuanced results. Through these and other efforts prioritizing statistical rigor, the research community can fulfill its ethical duty to produce reproducible findings that benefit patients and society. Statistics and ethics are fundamentally intertwined in responsible medical research.

Bibliography

1. Ahmad DA, Ahmad KN, Mohib-ul-Haq M, Nayak BG, Maqbool LM. Some applications of biostatistics to medical research. *International Journal of Advanced Research*. 2019;7(2):28–31.
2. Arbuthnott J. An argument for divine providence, taken from the constant regularity observ'd in the births of both sexes. *Philosophical Transactions (1683–1775)* 27. 1710;1683–1775(27):186–190.
3. Lind J. A treatise of the scurvy. In three parts. Containing an inquiry into the nature, causes, and cure, of that disease. Together with a critical and chronological view of what has been published on the subject. Edinburgh: Printed by Sands, Murray and Cochran for A. Kincaid & A. Donaldson; 1753.
4. Milne I. Who was James Lind, and what exactly did he achieve. *J R Soc Med*. 2012 Dec;105(12):503–8. DOI: 10.1258/jrsm.2012.12k090. PMID: 23288083. PMCID: PMC3536506.
5. Gosztonyi K. How history of mathematics can help to face a crisis situation: the case of the polemic between Bernoulli and d'Alembert about the smallpox epidemic. *Educational Studies in Mathematics*. 2021 Jul 16;108(1–2):105–22. DOI: 10.1007/s10649-021-10077-6. PMID: 34934237. PMCID: PMC8283094.
6. Laplace PS. *A Philosophical Essay on Probabilites*. New York: John Wiley & Sons; 1902.
7. Kopf EW. Florence nightingale as statistician. *Quarterly Publications of the American*

- Statistical Association. 1916 Dec 1;15(116):388–404. DOI:
10.1080/15225445.1916.10503703.
8. Stanton JM. Galton, pearson, and the peas: A brief history of linear regression for statistics instructors. *Journal of Statistics Education*. 2001 Jan;9(3). DOI:
10.1080/10691898.2001.11910537.
 9. Otte A, Maier-Lenz H, Dierckx RA. Good clinical practice: historical background and key aspects. *Nucl Med Commun*. 2005 Jul;26(7):563–74. DOI:
10.1097/01.mnm.0000168408.03133.e3. PMID: 15942475.
 10. Huberty CJ. Historical origins of statistical testing practices. *The Journal of Experimental Education*. 1993 Jul;61(4):317–33. DOI:
10.1080/00220973.1993.10806593.
 11. Grier DA. The Origins of Statistical Computing [Internet]. American Statistical Association. 2021 [cited 2023 Sep 10]. Available from:
<https://ww2.amstat.org/asa175/statcomputing.cfm>
 12. Norman GR, Streiner DL. *Pdq Statistics (PDQ Series) Third Edition*. 3rd ed. Hamilton, Ont: pmph usa; 2003.
 13. White S. *Basic & Clinical Biostatistics: Fifth Edition*. 5th ed. New York: McGraw-Hill Education / Medical; 2019.
 14. Dahlberg SE, Korn EL, Le-Rademacher J, Mandrekar SJ. Clinical versus statistical significance in studies of thoracic malignancies. *J Thorac Oncol*. 2020 Sep;15(9):1406–8. DOI: 10.1016/j.jtho.2020.06.007. PMID: 32580055.

15. Talbot D, Massamba VK. A descriptive review of variable selection methods in four epidemiologic journals: there is still room for improvement. *Eur J Epidemiol*. 2019 Aug;34(8):725–30. DOI: 10.1007/s10654-019-00529-y. PMID: 31161279.
16. Heston TF. The percent fragility index. *SSRN Journal*. 2023; DOI: 10.2139/ssrn.4482643.
17. Schober P, Bossers SM, Schwarte LA. Statistical significance versus clinical importance of observed effect sizes: what do P values and confidence intervals really represent? *Anesth Analg*. 2018 Mar;126(3):1068–72. DOI: 10.1213/ANE.0000000000002798. PMID: 29337724. PMCID: PMC5811238.
18. Goodman WM, Spruill SE, Komaroff E. A Proposed Hybrid Effect Size Plusp -Value Criterion: Empirical Evidence Supporting its Use. *The American Statistician*. 2019 Mar 29;73(sup1):168–85. DOI: 10.1080/00031305.2018.1564697.
19. Stefan AM, Schönbrodt FD. Big little lies: a compendium and simulation of p-hacking strategies. *R Soc Open Sci*. 2023 Feb 8;10(2):220346. DOI: 10.1098/rsos.220346. PMID: 36778954. PMCID: PMC9905987.
20. Heston TF. Standardizing predictive values in diagnostic imaging research. *J Magn Reson Imaging*. 2011 Feb;33(2):505–505. DOI: 10.1002/jmri.22466.
21. Sharma M. Errors in Statistical Modeling. (or why keep the human in the loop) [Internet]. *Towards Data Science*. 2021 [cited 2023 Sep 12]. Available from: <https://towardsdatascience.com/errors-in-statistical-modeling-c22978a98269>
22. Lee S, Lee DK. What is the proper way to apply the multiple comparison test? *Korean*

- Journal Anesthesiol. 2018 Oct;71(5):353–60. DOI: 10.4097/kja.d.18.00242. PMID: 30157585. PMCID: PMC6193594.
23. McGauran N, Wieseler B, Kreis J, Schüler Y-B, Kölsch H, Kaiser T. Reporting bias in medical research - a narrative review. *Trials*. 2010 Apr 13;11:37. DOI: 10.1186/1745-6215-11-37. PMID: 20388211. PMCID: PMC2867979.
 24. Thomas R. Mitigating Survivorship Bias in Scholarly Research: 10 tips to enhance data integrity [Internet]. Enago Academy. 2023 [cited 2023 Sep 12]. Available from: <https://www.enago.com/academy/survivorship-bias/>
 25. The Decision Lab. Survivorship bias [Internet]. The Decision Lab. 2020 [cited 2023 Sep 12]. Available from: <https://thedecisionlab.com/biases/survivorship-bias>
 26. Andrade C. Confounding. *Indian J Psychiatry*. 2007 Apr;49(2):129–31. DOI: 10.4103/0019-5545.33263. PMID: 20711398. PMCID: PMC2917080.
 27. Zhou L, Zhao P, Wu D, Cheng C, Huang H. Time series model for forecasting the number of new admission inpatients. *BMC Med Inform Decis Mak*. 2018 Jun 15;18(1):39. DOI: 10.1186/s12911-018-0616-8. PMID: 29907102. PMCID: PMC6003180.
 28. Uyanto SS. Monte Carlo power comparison of seven most commonly used heteroscedasticity tests. *Communications in Statistics - Simulation and Computation*. 2019 Nov 20;1–18. DOI: 10.1080/03610918.2019.1692031.
 29. Joseph L, Bélisle P, Tamim H, Sampalis JS. Selection bias found in interpreting analyses with missing data for the prehospital index for trauma. *J Clin Epidemiol*. 2004

- Feb;57(2):147–53. DOI: 10.1016/j.jclinepi.2003.08.002. PMID: 15125624.
30. Dalal DK. (multi)collinearity in behavioral sciences research. In: Oxford research encyclopedia of business and management. Oxford University Press; 2023. DOI: 10.1093/acrefore/9780190224851.013.410.
 31. Elliott HL. Post hoc analysis: use and dangers in perspective. J Hypertens Suppl. 1996 Sep;14(2):S21-4; discussion S24. DOI: 10.1097/00004872-199609002-00006. PMID: 8934374.
 32. Sbraga TP. Post hoc reasoning in possible cases of child sexual abuse: symptoms of inconclusive origins. Clin Psychol Sci Pract. 2003 Sep 1;10(3):320–34. DOI: 10.1093/clipsy/bpg029.
 33. Bonovas S, Piovani D. Simpson’s paradox in clinical research: A cautionary tale. J Clin Med. 2023 Feb 18;12(4). DOI: 10.3390/jcm12041633. PMID: 36836181. PMCID: PMC9960320.
 34. Peters DP, Ceci SJ. Peer-review practices of psychological journals: The fate of published articles, submitted again. Behav Brain Sci. 1982 Jun;5(02):187. DOI: 10.1017/S0140525X00011183.
 35. Stampfer MJ, Colditz GA, Willett WC, Manson JE, Rosner B, Speizer FE, et al. Postmenopausal estrogen therapy and cardiovascular disease. Ten-year follow-up from the nurses’ health study. N Engl J Med. 1991 Sep 12;325(11):756–62. DOI: 10.1056/NEJM199109123251102. PMID: 1870648.
 36. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al.

- Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA. 2002 Jul 17;288(3):321–33. DOI: 10.1001/jama.288.3.321. PMID: 12117397.
37. Stöckli S, Koufatzidou M, Seehra J, Pandis N. The reporting of study limitations in randomized controlled trials published in the leading dental journals: Is it sufficient? J Dent. 2023 Sep;136:104603. DOI: 10.1016/j.jdent.2023.104603. PMID: 37414393.
 38. Keys A, Anderson JT, Grande F. Prediction of serum-cholesterol responses of man to changes in fats in the diet. Lancet. 1957 Nov 16;273(7003):959–66. PMID: 13482259.
 39. Dietary fat and its relation to heart attacks and strokes. JAMA. 1961 Feb 4;175(5):389. DOI: 10.1001/jama.1961.63040050001011.
 40. Ramsden CE, Zamora D, Leelarthaepin B, Majchrzak-Hong SF, Faurot KR, Suchindran CM, et al. Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: evaluation of recovered data from the Sydney Diet Heart Study and updated meta-analysis. BMJ. 2013 Feb 4;346:e8707. DOI: 10.1136/bmj.e8707. PMID: 23386268. PMCID: PMC4688426.
 41. Hooper L, Martin N, Jimoh OF, Kirk C, Foster E, Abdelhamid AS. Reduction in saturated fat intake for cardiovascular disease. Cochrane Database Syst Rev. 2020 Aug 21;8(8):CD011737. DOI: 10.1002/14651858.CD011737.pub3. PMID: 32827219. PMCID: PMC8092457.
 42. Monllor-Tormos A, García-Vigara A, Morgan O, García-Pérez M-Á, Mendoza N, Tarín JJ, et al. Mediterranean diet for cancer prevention and survivorship. Maturitas. 2023 Aug

- 24;178:107841. DOI: 10.1016/j.maturitas.2023.107841. PMID: 37660598.
43. Delgado-Lista J, Alcala-Diaz JF, Torres-Peña JD, Quintana-Navarro GM, Fuentes F, Garcia-Rios A, et al. Long-term secondary prevention of cardiovascular disease with a Mediterranean diet and a low-fat diet (CORDIOPREV): a randomised controlled trial. *Lancet*. 2022 May 14;399(10338):1876–85. DOI: 10.1016/S0140-6736(22)00122-2. PMID: 35525255.
44. Wakefield AJ, Murch SH, Anthony A, Linnell J, Casson DM, Malik M, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet*. 1998 Feb 28;351(9103):637–41. DOI: 10.1016/s0140-6736(97)11096-0. PMID: 9500320.
45. Retraction--Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet*. 2010 Feb 6;375(9713):445. DOI: 10.1016/S0140-6736(10)60175-4. PMID: 20137807.
46. Taylor LE, Swerdfeger AL, Eslick GD. Vaccines are not associated with autism: an evidence-based meta-analysis of case-control and cohort studies. *Vaccine*. 2014 Jun 17;32(29):3623–9. DOI: 10.1016/j.vaccine.2014.04.085. PMID: 24814559.
47. Thompson S, Meyer JC, Burnett RJ, Campbell SM. Mitigating vaccine hesitancy and building trust to prevent future measles outbreaks in england. *Vaccines (Basel)*. 2023 Jan 28;11(2):288. DOI: 10.3390/vaccines11020288. PMCID: PMC9962700.
48. Chang RW, Falconer J, Stulberg SD, Arnold WJ, Manheim LM, Dyer AR. A randomized, controlled trial of arthroscopic surgery versus closed-needle joint lavage for patients

- with osteoarthritis of the knee. *Arthritis Rheum.* 1993 Mar;36(3):289–96. DOI: 10.1002/art.1780360302. PMID: 8452573.
49. Moseley JB, O'Malley K, Petersen NJ, Menke TJ, Brody BA, Kuykendall DH, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med.* 2002 Jul 11;347(2):81–8. DOI: 10.1056/NEJMoa013259. PMID: 12110735.
 50. Beecher HK. Surgery as Placebo. *JAMA.* 1961 Jul 1;176(13):1102. DOI: 10.1001/jama.1961.63040260007008.
 51. Battezzati M, Tagliaferro A, Cattaneo AD. Clinical evaluation of bilateral internal mammary artery ligation as treatment coronary heart disease. *Am J Cardiol.* 1959 Aug;4(2):180–3. DOI: 10.1016/0002-9149(59)90245-0. PMID: 13670118.
 52. Glover RP, Davila JC, Kyle RH, Beard JC, Trout RG, Kitchell JR. Ligation of the internal mammary arteries as a means of increasing blood supply to the myocardium. *Journal of Thoracic Surgery.* 1957 Nov;34(5):661–78. DOI: 10.1016/S0096-5588(20)30315-9.
 53. Dimond EG, Kittle CF, Crockett JE. Comparison of internal mammary artery ligation and sham operation for angina pectoris. *Am J Cardiol.* 1960 Apr;5:483–6. DOI: 10.1016/0002-9149(60)90105-3. PMID: 13816818.
 54. Cobb LA, Thomas GI, Dillard DH, Merendino KA, Bruce RA. An evaluation of internal-mammary-artery ligation by a double-blind technic. *N Engl J Med.* 1959 May 28;260(22):1115–8. DOI: 10.1056/NEJM195905282602204. PMID: 13657350.
 55. Heston TF. The robustness index: going beyond statistical significance by quantifying

fragility. Cureus. 2023 Aug 30; DOI: 10.7759/cureus.44397.

56. Ioannidis JPA. Why most published research findings are false. PLoS Med. 2005 Aug 30;2(8):e124. DOI: 10.1371/journal.pmed.0020124. PMID: 16060722. PMCID: PMC1182327.