Biases in dermatology: A primer

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Introduction

The Cambridge English dictionary defines bias as "the action of supporting or opposing a particular person or thing in an unfair way as a result of allowing personal opinions to influence your judgement."[1] However, statistical bias is defined as any systematic error in the determination of the association between exposure and disease.[2] A point to note here is that bias is not an error in calculation or statistical analysis. It is an inbuilt feature in the study protocol. Biases are a vital aspect in any dermatological research. A thorough understanding of their types is needed to eliminate or at least minimize them, especially while designing a randomised controlled trial or performing a meta-analysis where PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) require a bias test.

Types of Bias

1. **Memory or recall bias:** This is a type of bias where sufferers of a disease, often termed cases, have a greater tendency to recall a particular habit than non-sufferers, viz controls. This results in an uneven distribution of risk factors between the cases and controls. An example of this would be a case-control study to evaluate the association between dental amalgam use and the development of oral lichen planus. Those with lichen planus are more likely to recall a history of dental amalgam use than those who do not have the disease. This difference in recall between a diseased cohort and control has resulted in difficulties in assessing the association between diet and many dermatological diseases – like milk and chocolate consumption and acne, fatty meals and psoriasis, sugary meals and psoriasis, agricultural exposure to insecticides and pemphigus and so on.[3–6]
2. **Berkesonian Bias:** Named after Dr. Joseph Berkeson, this bias reflects the variation in rates of hospital admission or clinic attendance for different diseases. For example, if a study is conducted to know the effect of pregnancy on syphilis in an antenatal clinic, we are likely to get biased data since the two conditions, viz pregnancy and syphilis, are both likely to affect clinic attendance and all observations related to the relationship between pregnancy and syphilis.[7]
3. **Collider Bias:** This is an under-appreciated bias, and often confused with a confounder. This is especially seen in observational studies where it is defined as a distortion produced by the restriction of sampling by a collider variable. A collider variable is defined as one that has an independent effect on the outcome studied apart from the studied variable. In simpler terms, collider bias occurs when exposure and development influence a common third variable. That variable or collider is controlled by study design or in the analysis. An example is the observation that psoriasis patients tend to have more depression and anxiety disorders. Since severe psoriasis patients tend to get hospitalised and also get screened for mental health issues, a spurious association between them could have been obtained due to collider bias. The two variables viz psoriasis and depression converged, i.e., collided, into a single outcome – hospitalization.[8,9]
4. **Ascertainment Bias:** This bias is commonly encountered in venereology practice. It is defined as a bias due to the tendency of some segments of the target population to get excluded due to cultural and other differences. For example, in most venereology clinics in government setups, studies show that venereal diseases are commoner in lower socioeconomic status.

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One reason might be that the higher socioeconomic status people tend to go to private practitioners and thereby get excluded from government-run clinics.[9,10] Allocation concealment and blinding are good ways to avoid this.

5. **Popularity Bias:** This bias arises when a particular disease is more popular (i.e. either more well-known or more stigmatised) among the participants than the disease with which it is compared. For example, if a study compares clinic attendance rates among various dermatological disorders, one would see vitiligo patients are over-represented over melasma. While melasma is commoner in the normal population, vitiligo, due to its popularity because of media publicity and other factors, tends to present earlier.[9]
6. **All is well bias:** It is a subjective bias where theories supported by the majority tend to get more easily published than the opposing view supported by the minority. For example, ideas on the origin of endemic pemphigus supporting autoimmunity are more likely to be published than theories exploring an infectious trigger. According to some authors, this bias is very difficult to eliminate and is a variant of publication bias.[10-12]
7. **Apprehension bias**: This results from fear and apprehensions related to an impending procedure. The classic example is the false elevation of blood pressure because the person is apprehensive of his or her blood pressure being measured.[13] A variant of this is the Hawthorne bias, where subjects modify their behavior, such as regularly taking a prescribed drug or exercising, simply because they know they are being watched, but not due to any apprehensions. Hawthorne bias is practically utilised in many leprosy clinics since regular follow-up has been shown to improve adherence to therapy based on Hawthorne bias.
8. **Attrition bias:** This occurs due to lack of follow-up. This is a common problem in studies evaluating the efficacy of biologics in psoriasis – where many patients are lost to follow-up. A remedy is performing intention to treat analysis.[9] A variation of this is non-responder bias, where non-responders to a questionnaire differ significantly from responders.[9]
9. **Availability bias:** More emphasis is placed on widely available data than scantily available data. A classic example is the use of antihistamines in pregnancy dermatoses, where nearly all standard books recommend first-generation antihistamine chlorpheniramine because more data is available.[9]
10. **Rhetoric bias:** A more charismatic piece of writing has a greater influence on the study participants than other available literature. An example is the wider use of sunscreen for polymorphous light eruption over photoprotective strategies like umbrellas, broad-brimmed hats, etc, because the lay press is more vocal about sunscreens.[14]
11. **Centripetal bias**: Patients tend to go to more reputed physicians and hospitals than others. For example, a famous or better-known cosmetologist with a good reputation tends to see more cases than other cosmetologists.
12. **Chronological bias:** This occurs in long-term studies where participants recruited earlier face different exposures and treatments than those recruited later. For example, biologics for psoriasis came later, so studies with long-term follow-up of psoriasis patients (say 30 years) will likely have this bias.[9]
13. **Confirmation bias:** This bias occurs when study participants have a preconceived notion of their disease that may not be based on facts. For example, we have observed that in North India many tinea patients report an increase in their disease due to taking meat, fish, and other so-called "hot foods". They may also present information they have collected from the internet which reinforces their beliefs.[15]
14. **Data dredging bias:** It is an entirely avoidable bias. This is subdivided into two types – Fishing type and "P-value hacking" type. It involves using multiple statistical methods to get the desired p-value and selecting the statistical model that gives the p-value the author wants. This is "lamentably common" in dermatological research.[16] To detect data dredging bias, always perform a "p-curve analysis" while performing a meta-analysis.[17,18] Much emphasis is nowadays given to the confidence interval instead of the p-value, which gives an approximate idea of the range in which one can be 95% (or 90%, depending on the confidence interval chosen) sure that the result is correct. The confidence interval remains unaffected by p-value dredging. This subject has been reviewed in depth in recent works.[18,19]
15. **Novelty bias:** The newer an intervention, the better it appears, and with time, its efficacy seems to decrease. When ligelizumab, an IgE antagonist was first discovered, ligelizumab was believed to be better than omalizumab; however, evidence soon pointed to the contrary.
16. **Diagnostic Access Bias:** Individuals in certain geographical localities have better access to medical care and, hence, may appear to have higher disease prevalence. For example, atopic dermatitis is believed to be commoner in the West – this could be due to better and earlier diagnostic facilities available than in India.[19,20]
17. **Diagnostic reference test bias:** These bias results when all individuals do not receive the same reference test. e.g., direct immunofluorescence studies may not be done for all patients with pemphigus vulgaris – some patients may receive only a skin biopsy-based diagnosis. It is a subtype of verification bias. Another variation of this type of bias is partial reference bias, where only some of the study participants receive the index and the reference tests.[21]

18. **Hot stuff bias:** Editors of journals may be less critical about topics that are "fashionable" or currently in vogue and consequently end up publishing them more frequently, resulting in publication bias as well as hot stuff bias. It can result in flawed meta-analyses based on these studies. An example is how cutaneous manifestations of COVID-19 were published. Indian Journal of Dermatology Venereology and Leprosy stood out by choosing not to publish anything and everything related to COVID-19, thus reducing hot stuff bias.[22,23]
19. **Immortal time bias:** This type of bias is commonly encountered in cohort studies where the exposure has occurred, but the outcome cannot happen. Before the participant is assigned to the treatment group, the period between the exposure and the outcome occurrence is considered immortal time. For example, if a cohort study wants to look at relapse rates following successful treatment of psoriatic erythroderma while on methotrexate, one would follow them up from hospital discharge till the first readmission occurs. Once readmission occurs, they are assigned to treatment groups. This time gap when relapse has not occurred and the patient is on methotrexate constitutes immortal time bias.[24]
20. **Incorporation bias:** This is principally relevant for diagnostic accuracy studies when the index test forms a part of the reference test, resulting in elevated sensitivity e.g., if one wants to compare the grattage test vs. dermoscopy in psoriasis and does dermoscopy only from areas of grattage positivity, one would get a very high sensitivity for the grattage test because it was incorporated into the reference test, i.e., dermoscopy.[25,26]
21. **Industry sponsorship bias:** This has now been reclassified as conflict-of-interest bias. In short, the study deliberately supports the findings expected from it by its sponsors.
22. **Informed presence bias:** Simply, a person attending a health center is more likely to get screened for other unrelated comorbidities than those not attending a health center e.g., the finding psoriasis is associated with depression has now been criticised because those having psoriasis also have a greater chance to be screened for depression since they are already attending a health center.[27]
23. **Language bias:** Articles with significant findings tend to get published more often in English (since that is the most common language in medical research) than in other languages. It is crucial in many studies involving dermatological quality of life measurements.
24. **Mimicry bias:** When an exposure causes a disease that resembles the study disease, mimicry bias can result. For example, certain drugs are known to cause a pityriasis rosea-like reaction, which, although looks like pityriasis rosea, differs from it.[28]
25. **Observer bias:** When different observers view the same observation, they report it differently e.g., different observers may give differing descriptions about subtle features in the histopathology report of a skin biopsy.[29]
26. **Unacceptable disease bias:** This occurs in socially unacceptable diseases like leprosy and STDs, which result in under-reporting.[30]
27. **Hypothetical bias:** Many dermatological researches (and some life quality questionnaires like vitiQoL) use hypothetical questions – like "What would you do when some stranger asks you about your lesion?". The responses to these questions by the study participants often do not tally with what they would do in real life. This is called hypothetical bias and is avoided by adopting the ex-ante approach.[31]
28. **Previous opinion bias:** In performing a second diagnostic test, if the result of a previous test is known, it is likely to influence the result. An extension of this is the Greenwald's law of lupus: the Sontheimer amendment – anything and everything that happens to a lupus erythematosus patient is correctly or incorrectly attributed to lupus.[32]
29. **Selection bias**: Since it is not possible to work with large populations, for most dermatological studies, samples are chosen that are said to be representative of the original population. In selection bias, the selected subgroups are not representative of their original population. A variation of this is systematic selection bias, where samples chosen differ dramatically from their representative populations. Our experience suggests, such selection bias occurs more commonly in studies conducted in regional referral centers where only the sickest or more severe patients are usually seen. For example, a study compared the efficacy of thalidomide vs. prednisolone in hospitalised patients of erythema nodosum leprosum. It derived that thalidomide was more efficacious than steroids in erythema nodosum leprosum. Such findings cannot be generalised to all erythema nodosum leprosum since patients admitted to a regional referral center will likely have more severe disease.[5,6,33]

    Selection bias is again divided into two types – endogenous selection bias and exogenous selection bias.

    The best example of endogenous selection bias in dermatology is the inclusion of non-response. If a trial tests the efficacy of a particular biologic in psoriasis, the response is usually collected from trial participants via postal services. Certain participants will not respond, although they might have substantially improved. Their exclusion will result in significant differences in efficacy evaluation.[33]

    Exogenous selection bias results when both treatment and outcome result from dependency on an external variable that is not controlled. For example, if sunlight exposure is not controlled, it will influence both the intervention and control groups since psoriasis is a photosensitive (and photoexcerbated) dermatosis.

Why must dermatologists know about biases?[34,35]

The list of biases that can occur in any research is considerably long, and certainly not all of them can be avoided. However, dermatologists should be well aware of them because:

1. While conducting systematic reviews and meta-analysis, PRISMA guidelines need to be followed, and the PRISMA checklist requires a very exhaustive list of declarations to be made by the authors as to how biases in the individual studies were detected, their types and whether they were included in the systematic review or not. This usually requires more than two authors working independently.
2. Biases can result in dramatically opposite inferences, which may not be biologically plausible; the knowledge of the biases can help detect them and thereby negate such findings.
3. The knowledge of biases is a vital part of the postgraduate dermatology curriculum and is a must-know area for thesis/dissertation purposes.
4. Since there is no fool-proof way to avoid all biases, the help of a well-qualified biostatistician might help detect and prevent many of these biases in research.

What can dermatologists do to avoid bias?

1. While designing a study, especially a randomised controlled trial, emphasis should be laid on careful randomization allocation and randomization concealment. Blinding should also be proper. This avoids many biases and, importantly, the interviewer's bias.
2. Publishers of leading dermatology journals should have an open mind and not run only after popular theories – alternative explanations should also be taken seriously. This eliminates publication bias, hot stuff bias, etc. Interestingly, nowadays, many journals have come up to encourage negative findings in biomedical research. For example, the Journal of Negative Results in Biomedical Research is dedicated to publishing negative results. This helps in eliminating publication bias while doing a systematic review.[35]
3. While performing a met a-analysis, a funnel plot is a must-know to reduce the risk of publication bias.
4. Nowadays, many automatic tools are available that automatically detect bias. They are convenient while performing meta-analysis and systematic reviews (evidence synthesis). Some of them, like the Cochrane risk of bias tool and SYRCLE's risk of bias tool, are handy tools in research.
5. To avoid previous opinion bias and popular theory biases, one should guide one's own research findings – which may well run contrary to published research yet be valid.
6. Utmost importance should be given to research ethics – both positive and negative findings are well-appreciated, and authors should not try p-value hacking or fishing techniques. That will solve the data dredging bias problem.
7. Finally, whenever in doubt, the help of a qualified statistician should be sought before designing or conducting a research study.

Concluding Thoughts

Biases represent a significant problem in dermatology, but overall, biases represent a fascinating world of mind-boggling paradoxes and cheeky loopholes that need to be tackled skillfully.

Declaration of patient consent

Patient consent is not required as there are no patients in this study.

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Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The author confirms that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

References

1. Cambridge. The Cambridge English Dictionary. https://dictionary.cambridge.org/dictionary/english/bias [Accessed January 31, 2023].
2. Park K. Principles of epidemiology and epidemiologic methods. In: Park K, ed. Park's textbook of preventive and social medicine. 22nd Ed. India: Banasridas Bhanot Publishers; 2015, pp. 70–1.
3. Penso L, Touvier M, Deschasaux M, de Edelenyi FS, Hercberg S, Ezzedine K, *et al*. Association between adult Acne and dietary behaviors: Findings from the NutriNet-Santé prospective cohort study. JAMA Dermatol. 2020;156:854–62
4. Afifi L, Danesh MJ, Lee KM, Beroukhim K, Farahnik B, Ahn RS *et al*. Dietary behaviors in psoriasis: Patient-reported outcomes from a U.S. National Survey. Dermatol Ther (Heidelb) 2017;7:227–42.
5. Kaur I, Dogra S, Narang T, De D. Comparative efficacy of thalidomide and prednisolone in the treatment of moderate to severe erythema nodosum leprosum: A randomized study. Australas J Dermatol 2009;50:181–5
6. Dawn AG, Balakrishnan R, Feldman SR. Systematic selection bias: A cause of dramatic errors in the inference of treatment effectiveness. J Dermatol Treatment 2008;19:68–71
7. Westreich D. Berkeson's bias, selection bias and missing data. Epidemiology 2013;23:159–64
8. Tönnies T, Kahl S, Kuss O. Collider bias in observational studies. Dtsch Arztebl Int 2022;119:107–12
9. Lee H, Aronson JK, Nunan D. Collider bias. In Catalogue of Bias. 2019. https://catalogofbias.org/biases/collider-bias/.
10. Culton DA, Qian Y, Li N, Rubenstein D, Aoki V, Filhio GH, *et al*. Advances in pemphigus and its endemic pemphigus foliaceus (Fogo Selvagem) phenotype: A paradigm of human autoimmunity. J Autoimmun 2008;31:311–24
11. Hans-Filho G, Aoki V, Bittner NRH, Bittner GC. Fogo selvagem: Endemic pemphigus foliaceus. An Bras Dermatol 2018;93:638–50.
12. Catalogue of Bias Collaboration, Spencer EA, Heneghan C. All's well literature bias. In: Catalogue of Biases. 2018. www.catalogueofbiases.org/biases/allswelll [Accessed January 24, 2023].

13. Catalogue of bias collaboration, Brassey J, Mahtani KR, Spencer EA. Apprehension bias. In: Catalogue of Bias. 2019. https://catalogofbias.org/biases/apprehension-bias/ [Accessed January 24, 2023].
14. Heneghan C, Spencer EA. Biases of rhetoric. In: Catalogue of Bias. 2017. https://catalogofbias.org/biases/biasesofrhetoric [Accessed January 24, 2023[.
15. Hengen C. Centripetal Bias. In: Catalogue of Bias. 2019. www.catalogueofbias.org/baises/centripetalbias. [Accessed January 24, 2023].
16. Catalogue of Bias Collaboration. Erasmus A, Holman B, Ioannidis JPA. Data-dredging Bias. In: Catalogue of Bias 2020. https://catalogofbias.org/biases/data-dredging bias/ [Accessed September 24, 2023].
17. Wagenmakers E-J, Wetzels R, Borsboom D, van der Maas, HLJ, Kievit RA. An agenda for purely confirmatory research. Perspect Psychol Sci 2012;7:632–8.
18. Sil A, Betkerur J, Das NK. P-value demystified. Indian Dermatol Online J 2019;10:745–50.
19. Simonsohn U, Nelson LD, Simmons JP. p-curve: A key to the file-drawer. J Exp Psychol Gen 2014;143:534–47.
20. Porta M, Greenland S. Hernãn M, dos Santos Silva I, Last M, eds. A Dictionary of Epidemiology. 6th ed. New York: Oxford University Press; 2014.
21. Catalogue of Bias Collaboration, Plüddemann A, McCall M. Differential reference bias. In: Catalogue of Bias. 2019. https://catalogofbias.org/biases/differential-reference-bias/ [Accessed January 24, 2023].
22. Sackett DL. Bias in analytic research. J Chron Dis 1979;32:51–63.
23. Panda S. Publishing in the time of pandemic: Editorial Policy of a Dermatology Journal during COVID-19. Indian J Dermatol Venereol Leprol 2020;86:337–40.
24. Suissa S. Immortal time bias in observational studies of drug effects. Pharmacoepidemiol Drug Saf 2007;16:241–9.
25. Gupta A., Roehrborn CG. Verification and incorporation biases in studies assessing screening tests: Prostate-specific antigen as an example. Urology 2004;64:106–11.
26. Whiting P, Rutjes AWS, Reitsma JB, Glas AS, Bossuyt PMM, Kleijnen J. Sources of variation and bias in studies of diagnostic accuracy: A systematic review. Ann Intern Med 2004;140:189–202.
27. Goldstein BA, Bhavsar NA, Phelan M, Pencina MJ. Controlling for informed presence bias due to the number of health encounters in an electronic health record. Am J Epidemiol 2016;184:847–55.
28. Lautenschlager S. Diagnosis of syphilis: Clinical and laboratory problems. J Dtsch Dermatol Ges 2006;4:1058–75.
29. Hróbjartsson A, Thomsen ASS, Emanuelsson F, Tendal B, Hilden J, Boutron I, *et al*. Observer bias in randomized clinical trials with measurement scale outcomes: A systematic review of trials with both blinded and nonblinded assessors. CMAJ 2013;185:E201–11
30. Choi BCK, Pak AWP. A catalog of biases in questionnaires. Prev Chronic Dis 2005;2:A13.
31. Özdemir S, Johnson FR, Hauber AB. Hypothetical bias, cheap talk, and stated willingness to pay for health care. J Health Econ 2009;28:894–901.
32. Sackett DL. Bias in analytic research. J Chron Dis 1979;32:51–63.
33. https://cros-legacy.ec.europa.eu/content/endogenous-selection_en [Accessed June 29, 2023].
34. Hooijmans CR, Rovers MM, de Vries RBM, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol 2014;14:43.
35. Biomed central. 2017; www.jnrbm.biomedcentral.com. [Accessed June 29, 2023].