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Research Article

Is Sex More than A Risk Factor? Sex as Biological Variable and Oral Health

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Abstract

This perspective paper examines the critical importance of incorporating Sex as a Biological Variable (SABV) in dental research, with particular focus on restorative dentistry. While medical research has increasingly recognized sex differences as crucial for understanding disease etiology, progression, and treatment, dentistry has lagged behind. The authors highlight how sex is typically relegated to a "confounding variable" or "risk factor" in dental studies rather than being used for stratified analysis. The paper outlines methodological considerations for sex-specific study design, including factorial design approaches, appropriate sample size calculations, and statistical power requirements for detecting sex differences. Drawing parallels from medical research, the authors demonstrate how understanding sex differences could lead to more personalized and effective dental treatments. The manuscript concludes that implementing sex and gender-based analysis in dental research is essential for advancing from generalized to personalized dentistry, noting that unlike medicine, there is currently no recognizable trend toward sex-specific research in dentistry.

Keywords: Sex as a biological variable; Sex differences; Sex-related differences; Sex as a stratified factor; Sex as a confounding factor; Sex dimorphism

Introduction

Within the last three decades there is an increasing interest in medicine to explore sex differences. While historically medical research has frequently regarded the physical and anatomical characteristics typically associated with the male body as the norm, studies began to unveil the detrimental consequences of relying on data collected from males when assessing symptoms in females, including inaccurate diagnoses, ineffective treatments, and disparities in health outcomes such as delayed heart disease diagnosis in women [1-6]. In dental research, this topic has hardly been addressed and is currently still on the fringes of attention.

While at first the approach was to minimize data variance by enrolling study participants with similar characteristics as age, sex or weight, women were excluded from clinical trials in medicine due to their hormone differences [7]. Rising attention of funding agencies is seen since 1986 as the National Institute of Health (NIH) encouraged researchers to include woman in clinical trials to critically investigate sex and gender differences in regard to diagnosis, prevention, and treatment of diseases. In 2016 the USA National institute of Health (NIH) mandated that all preclinical research (i.e., animal research, e.g. in dentistry implant Osseo-integration or soft-tissue healing in beagle dogs which are typically used as "animal model") must include "sex as a biological variable" (SABV), unless strongly justified otherwise. This has substantially increased attention to "sex differences research" in medicine as in neuroendocrinology, with good reasons. Studying how biological sex contributed to our health can help to understand disease etiology, manifestation, progression, and treatment of disease [8]. However, in dentistry and more specific in restorative dentistry one can find one an few attempts to deal with this aspect. Sex differences have often been reduced to binary measures (i.e. female or male) and have often been used interchangeably and in a simplistic binary measure [9]. However, sex and gender are two distinct terms, that interact continuously [10]. As stated by Joel and Fine 2022 [9] sex can be described by at least 3 definitions:

1. Sex belonging to one of the two categories of male and female;

2. Sex as a Biological Variable (SABV) characterized by a set of chromosomes (XX or XY), genes, and hormones that lead to a different functioning of the reproductive system;

3. Phenotypic sex related to the physical phenotypes of male and female including external sex characteristics, genital organs, and other body morphology [9].

In contrast, gender is a social construct that refers to an individual's identity, self- perception, and self-identification in sex-related roles in response to cultural influences, social roles, and expectations [11]. Importantly, both sex and gender influence molecular and cellular processes, immune response, and disease predisposition [7], which makes it important to take it to account.

Thus, sex related research is not a life style, trend or hype, but a personalized dental/ medical approach to personalized dental care.

What's Behind Sex Differences

To date there is no clear understanding regarding the underlaying pathophysiology of sex differences in oral diseases. This may be due to the complex interaction between biological, i.e. hormones, genetics, immune response, gender roles and psychological, or environmental modifiable factors [7]. Males and females have the same immunological cells, proteins, and pathways in place to protect against the development of disease. However, the kinetics, magnitude, and skewing of the responses mounted against pathogens, allergens, toxins, or self- antigens, can differ dramatically between sexes [12]. As described in a recent scoping review [7] there are important sex differences in the predisposition of oral diseases. Females present a higher caries predilection and oral facial pain conditions, while conversely, males are more predisposed to periodontal disease. Additionally, current evidence points towards sexual dimorphism as a potential modifier in disease predisposition and progression of pulpal and periapical disease. It is concluded that a more comprehensive evaluation of the interplay of sex and gender and other associated risk factors with oral disease predisposition is certainly needed [7].

For the field of restorative dentistry, the number of remaining teeth on a dentition level or tooth destruction on a single-tooth level define the type and load capability of restorations needed. It makes intuitive sense, that there will intersection of sex and bite force, since there is sex-dependent bite-force differences. Thus, persons with higher bite force need more load capable restorations. To the best of our knowledge this topic was not addressed so far beyond the rather statistical approach of seeing sex as a risk factor [13-16].

The number of teeth is a surrogate which indicates successful oral aging (which is also termed "functional dentition" by the WHO). In case of tooth loss prosthetic restoration increases the number of functional tooth pairs by tooth- or implant-borne Fixed Dental Prosthesis (iFDP/FDP) or Removable Partial Dentures (RPDs), which subsequently increases Oral Health Related Quality of Life (OHRQoL) [17,18], and even happiness [19].

While both, tooth- and implant-based FDP respectively, have a short- and long-term positive effect on OHRQoL, RPDs positively affected the latter only in the short term. IFDP showed also greater short-term improvement in OHRQoL than RPDs and tooth- based FDPs [20]. However, none of these studies report sex differences nor discuss SABV.

Recently two practice-based clinical studies with a time of observation of 10.9 and 16.9 years, respectively on the performance and outcome of lithium-disilicate glass-ceramic inlays, onlays, complete and partial coverage restorations in posterior teeth were published. While it is highlighted that both sex and age are considered "confounding variables" or "risk factors" - as it is most likely regarded as surrogate for occlusal force, oral hygiene, and diet - none of these both clinical studies reported sex and age influence on outcome. Since sex and age were assessed as confounding factor, and no significant effect on survival of lithium-disilicate restorations was found the authors conclude that these types of restorations investigated are eligible for both female and male patients. However, a relative risk ratio of about 3:1 for male compared to female subjects is reported [13]. Thus, it remains open for discussion, whether sex is not more than a confounding or risk factor and whether a stratified analysis by sex wouldn't be more appropriate to provide a more differentiated picture. Due to the very limited amount of sex-specific evidence in dentistry, in the following we will focus on methodological aspects of study design and strive for analogies to medical research and emphasize certain aspects that we consider essential. The aim is to improve sex-specific restorative dental research and reporting in particular when meaningful differences occur.

Study Both Sexes or Study Sex Differences?

A heading found in "The promises and pitfalls of sex difference research" [8] can be adapted to restorative dentistry as "It is vital to study both sexes response to restorative dental treatments, but is it also important to study sex differences? Will mandating SABV effectively change our understanding of oral health and disease?"

Unfortunately, the NIH mandate on clinical trials did not extend to presentation of the dental data by sex nor did it mandate sample size. Thus, there has been little progress in terms of reporting and analyzing outcomes of sex in dental research. Even though researchers were required to include both sexes in these trials, the majority have not analyzed the data with sex as a consideration [8]. It is an issue in general: Clinical trials with the Food and Drug

Administration (FDA) did not analyze or even report the outcome data by sex [21].

The same is obviously true for restorative dentistry. Stratified presentation of clinical data by sex is scarce. Until studies are mandated to report their data disaggregated by sex and analyzed for the effect of sex, and/or make the data freely available to all, the inequities will continue [8].

Compelling evidence from human (and animal model) studies implicate sex (and gender) as crucial factor influencing (oral) health and disease. Understanding the underlaying sex difference in oral disease can yield important considerations in tailored preventive strategies, distinct occurrence and progression, personalized, individualized and more effective treatment approaches [7] (Table 1).

Research Step	Best Practices
Motivation	Consider known sex differences in disease incidence, prevalence, and survival. Review existing literature on sex and gender differences, alert to the fact that many hypotheses have not been well tested. Read carefully to consider likelihood of false-positives (especially in context of multiple testing) and false-negatives (especially where statistical power is low). Apply a life course perspective to consider the timing of exposures that might interact with sex and gender in specific developmental windows.
Subject selection	Consider sex-specific age incidence of disease to maximize statistical power. Consider reproductive stages and cycles, particularly where they may modify the impact of the main exposure being investigated. Consider the impact of gendered social environment for the distribution of factors that may interact with the main exposure. For basic and preclinical studies, review options for classical gonadectomy, knockouts, or four-core genotype experiments. Consider whether sex of cell lines is known, relevant, and generalizable.
Randomization (if applicable)	In smaller studies, stratified randomization by sex or gender will ensure balance, even if different numbers of males and females are included.
Sample size	True tests of sex differences need to be large enough to test interaction between sex and the main exposure or treatment; such tests typically require several times the sample size to be adequately powered, compared with studies of main effects. Studies too small to detect interaction can still report the main effects of the exposure or treatment by sex; however, they cannot claim to have tested a sex difference. Be alert to the risk of false-negatives in underpowered sex strata. Studies too small to detect even the main effects of sex can provide sex- specific data to generate hypotheses or contribute to meta- analyses of sex differences. “Big data” studies, where the variable of sex is often available, need to be conducted thoughtfully to avoid contributing false-positives to the sex difference literature.
Data collection	Consider sex and gender differences in disease presentation. Consider whether exposures mean the same thing in both sexes and genders. Be aware of sex and gender differences in pharmacokinetics and pharmacodynamics; the same dose may have different impact in males and females or may vary by body size. Collect data on exogenous hormones: contraceptives, menopausal hormone therapy, testosterone, and other steroid use. Consider recording data on reproductive cycle (follicular/ luteal), and stage (prepuberty, puberty, pregnancy, lactation, premenopause, and postmenopause). Collect data on influential covariates that may vary by sex and gender in the study population.
Analysis, reporting, and interpretation	Prespecify tests of sex differences to reduce type I error. Account for confounding by factors associated with sex and gender. Investigate intermediate “pathway” variables to understand apparent sex differences. Admit when sex differences were tested as post hoc exploratory analyses. Make opportunities to replicate sex difference findings. Interpret apparent sex and gender differences in the light of biological plausibility and social context.

Table 1: Sex and Gender Differences Research Design for Basic, Clinical, and Population Studies: Essentials for Investigators [27].

Essentials for research designs for *in-vitro*, preclinical and clinical studies (Sex and gender differences research designs): Statistical implications as for power and sample size

Although incorporating sex differences is important, to study sex differences requires nuanced approaches and considerations to ensure successful transition of the SABV mandate into fruitful discovery [8]. Statistical simulations show that scientists need **NOT** increase overall sample size by default when including both sexes in *in-vivo* studies [22].

Important and common statistical terms adapted from du Sert et al. [23], which are typically placed in the context of *in-vivo* research are detailed below to complete the set-up for relevant information in the context of sex and gender research are displayed in Table 2 [22].

Term	Definition
Effect size	Quantitative measure of differences between groups or strength of relationships between variables.
Factor	Factors are independent categorical variables that the experimenter controls during an experiment in order to determine their effect on the outcome variable. Example factors include sex or treatment.
Factorial design	An experimental design that is used to study 2 or more factors, each with multiple discrete possible values or levels.
Independent variable	A variable that either the experimenter controls (e.g., treatment given or dose) or is a property of the sample (sex) or a technical feature (e.g., batch or cage) that can potentially affect the outcome variable.
Interaction effect	When the effect of one independent variable (factor) depends on the level of another. For example, the observed treatment effect depends on the sex of the animals.
Levels	Are the values that the factor can take. For example, for the factor sex the levels are male and female.
Main effect	A main effect is the overall effect of one independent variable on the outcome variable averaging across the levels of the other independent variable.
Outcome variable	A variable captured during a study to assess the effects of a treatment. Also known as dependent variable or response variable.
Power	For a predefined, biologically meaningful effect size, the probability that the statistical test will detect the effect if it exists (i.e., the null hypothesis is rejected correctly). Can also be called sensitivity.
Treatment	A process or action that is the focus of the experiment. For example, a drug treatment or a genetic modification.
Sex as a biological variable (SABV)	The research philosophy that emphasizes the importance of including both sexes in in vivo studies in such a way that a generalizable treatment effect is detectable. Critically, sex should be treated as a variable of primary biological interest. There is no requirement to prospectively power a study to detect a baseline difference between the sexes or treatment by sex interaction, but studies will detect large differences where they exist.

Table 2: Common statistical terms adapted from du Sert et al. typically placed in the context of *in-vivo* research [23].

As highlighted by Buch et al [24] researchers are naturally resistant to the idea that they need to increase or even double their sample size and perform the same research with effectively less money. The funding agencies have responded by indicating that sample size does not need to be doubled or even changed to investigate sex differences in research (http://www.cihr-irsc.gc.ca/e/51257.html). A recent paper showed that doubling of sample size was not necessary if one did not predict main effects of sex [24]. However, if one has never tested an effect in both sexes it would be impossible to predict whether main or interaction effects may be expected. Thus, for best practices, it is important to ensure that studies are statistically powered for interactions with sex differences to be detectable. There are numerous instances in neuroscience, and other areas, of underpowered studies [25,26]. Of course, it does not make statistical sense to assume the same sample size will be informative, if for example you previously used a sample size of 6 males, you could instead use 3 males and 3 females). Perhaps a doubling of sample size is not required but more subjects will be required to have enough power to inform on a sex difference if one exists.

However, to use the same number of animals split between the sexes is predicated on two implicit assumptions

1. that the numbers will be split equally between males and females (balanced design), and

2. that any sex difference in the effect of the main intervention under examination is either extremely large or non-existent. Assumption one should be feasible to achieve in practice. However, the second assumption for the most part would prevent the detection of smaller but still important differences in effects between the sexes [24].

Button et al. [25] highlight that the average statistical power of studies in the neurosciences (and we have no pain to assume in dental research) is very low. The consequences of this include overestimates of effect size and low reproducibility of results. There are also ethical dimensions to this problem, as unreliable research is inefficient and wasteful [25]. Insufficient statistical power and use of combined sexes in studies is often used as a reason to not examine sex as a factor.

However, the use of sex as a stratified factor in the analyses can lead to **increased** statistical power in particular when there are interaction effects. Thus, it is important that researchers not just consider that sex differences will result in overall main effects, but that they may result in interaction effects, i.e. when a treatment has different effects in one sex vs. another, a point that is lost in the recommendation to not increase overall sample size when including both sexes [8,24]. Well summarized, one can also say that the absence of evidence for sex differences is not necessarily evidence of the absence of sex differences [27].

Another comprehensive description of essentials for investigators regarding research designs in this field is nicely presented elsewhere [27] and should be in part cited in our SABV research perspective as we consider it helpful:

Randomization by sex and/or gender

Investigators, particularly those in these rare instances of conducting studies with >100 subjects, may wish to randomize the sexes separately to ensure similar distributions of treated and untreated males and females. In preclinical experiments, this is known as a factorial design [28]. Such stratified randomization retains the advantages of standard random allocation, effectively creating a mini-trial within each sex stratum [29]. Stratified randomization can accommodate a study plan with unequal numbers of male and female subjects, especially helpful when men and women join a study at different rates or in different time periods [27].

In a fully randomized design, subjects that share the same characteristics (sex, age etc.) are allocated at random to control or treated groups. In a factorial design, subjects that may categorically vary in some respect (sex, age) are allocated in equal number to control and treated groups. The key advantage of the factorial design is that it allows for the testing of both the main effects (e.g., treatment, sex) and an interaction between the factors (e.g., does the effect of treatment depend on sex?).

Factorial data should be analyzed by method that considers both factors, such as two-way analysis of variance (two-way ANOVA) (Figure 1a).

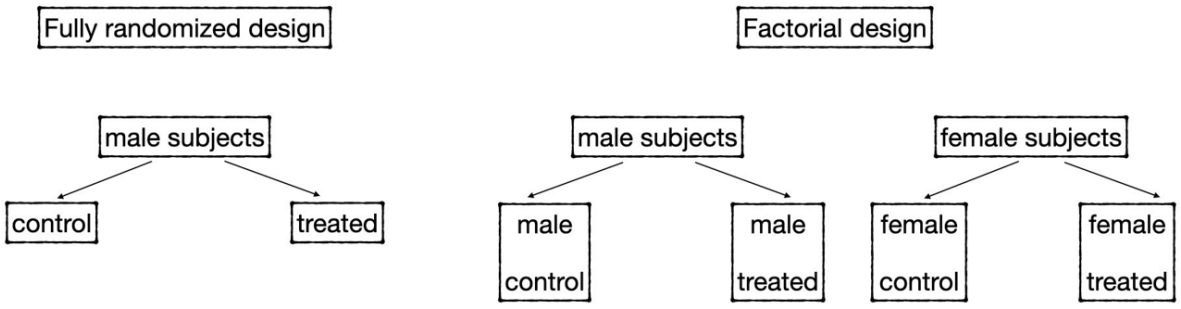

Figure 1a: Explainer on factorial design compared to fully randomized design [22].

The outcome of this type of analysis is independent estimates of significance for the main effects (e.g., treatment, sex), and the interaction term. Critically, the estimates for the main effects are derived from all the data. For example, the treatment estimate returns an average treatment effect as it uses the data from both sexes, and the sex estimate returns an average sex effect as it uses the data from both control and treated. Typically, where there is a significant interaction between factors in a factorial analysis, a set of post-hoc pairwise tests can also be carried out. This involves testing between pairs of factors in the data to estimate the effect for each sex independently. For example, where there is a sex by treatment interaction, post-hoc tests between control and treated might be carried out for each sex separately (Figure 1b).

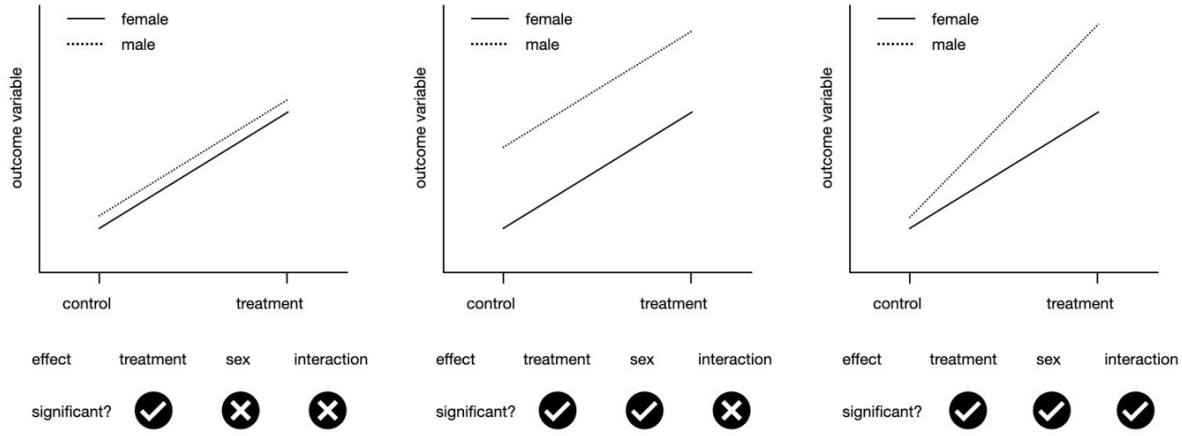

Figure 1b: Explainer on factorial design analysis. Adapted from Phillips et al. (2023) [22]. Potential outcomes from a factorial study. The graphs show the mean for each treatment group with a line highlighting the treatment effect by sex.

Non-parallel lines highlight that the treatment effect may depend on sex. Beneath each plot, is a summary of which terms in the model explain variation in the data.

Sample Size Considerations for Studies Including Males and Females

Most studies are planned from the outset with a sample size just large enough to afford 80% statistical power to detect the main effect of the primary exposure. Unless preplanned, most studies are underpowered to examine associations separately for males and females. This is particularly true of secondary data analyses of studies never designed to examine subgroup differences. This lack of statistical power to detect sex and gender differences can lead to the premature conclusion that such differences do not exist. In fact, most studies are simply too small to fairly test all but the most pronounced sex and gender differences. In the current era of accountability to analyze and present sex-stratified data, it is worth considering ideal practice and reality with respect to power and sample sizes to detect sex differences. Although most researchers will find that limited samples and funds constrain their ability to investigate sex and gender differences, it is also to address the special case of "big data," where problems may ensue from an abundance of statistical power to detect trivial differences, rather than too little power to detect meaningful differences [27].

Ideal: statistical power to detect interaction by sex [27]. The sample size required to detect statistically significant sex differences (interactions by sex) is considerably larger than that required to detect the main effects of treatment or sex alone. Statistical power to detect a sex difference depends on the prevalence of the exposure, outcome, and sex, as well as the strength of the associations between them. Software is freely available to calculate sample sizes to detect interactions. However, the rule of thumb is that it takes fourfold the sample size to detect an interaction than it does to detect main effects (i.e. treatment or sex alone) [30]. Investigators need to take into account differential disease rate by sex and the expected magnitude of the main effect in each sex; statistical power to detect either main effects or a sex interaction may not be optimized by recruiting half women and half men. In planning, investigators may have to make "best guesses" at the magnitude of expected sex differences, based on the literature and biologic understanding. As with any power calculation, it is best to input a range of likely main effects and interactions to evaluate the impact of sample size on the ability to detect a sex interaction. A study that is large enough to detect a sex interaction, if one exists, represents the "ideal" in sex difference studies. Few studies are planned with the power to detect statistically significant sex

differences. Many studies that have attempted to test interactions by sex have been underpowered to do so. Unfortunately, researchers easily forget that an interaction P value >0.05 often says as much about the design and size of the study as it does about the presence or absence of a sex difference.

Next Best: Statistical Power to Detect Main Effects Within Sex Strata

Even where a study is too small to test for sex interaction effects, it may still have enough statistical power to examine the main effects of exposure within sex strata. This is simple sex stratification to examine exposure–disease associations for each sex. For example: Does diabetes predict periodontitis among males? Does diabetes predict periodontitis among females? A study may find a statistically significant beneficial impact of treatment on disease among males and fail to find a significant effect of treatment among females or - in extreme cases - find statistically significant benefits or harms that vary by sex. However, if the study lacks power to test an interaction by sex, investigators cannot claim that they have detected a difference between males and females that meets conventional standards for ruling out chance.

To plan a study with adequate statistical power to detect main effects by sex is straightforward: simply calculate sample sizes needed to detect main effects in men and women separately (and add them up), taking into account sex differences in rates of disease, expected size of impact of exposure, and, for observational studies, expected prevalence of exposure. Many studies analyze their data by sex as an afterthought. Such subgroup analyses of main effects stratified by sex are often underpowered, which heightens the risk of type II error, or false-negative results. This is true even when the original analysis, in which all subjects are analyzed together, regardless of sex, reports a statistically significant association of exposure with disease. The danger of such underpowered comparison of "main effects" among males and females is that, by chance alone, one out of every six studies reporting an overall effect in the combined sample will, on sex stratification, report a significant effect in females (but not males) and one out of six will report a significant effect among males (but not females).

Better than Nothing: Representation of Sex

Studies underpowered to detect even sex-stratified main effects can still make available data and/or analyses stratified by sex, particularly in supplemental material, without making inferences regarding sex differences per se. Such data may serve as preliminary analyses for future studies adequately powered to detect sex differences and may be used in meta-analyses [27].

Discussion

In dentistry, there is currently little evidence of research that recognizes Sex as a Biological Variable (SABV). There is some evidence of sex differences or sex-related differences in oral health and oral disease with regard to periodontitis, caries, oro-facial pain and other aspects of oral health and Oral Health Related Quality of Life, while gender as social variable as a topic virtually does not exist. In periodontology, restorative, prosthetic and implant dentistry, the binary biological sex (male/female), i.e. so-called "sex dimorphism", is usually statistically considered as "confounding variable" or "risk factor" rather than a variable used for stratified randomization (factorial design) and data analysis. Sex-specific stratification has not yet taken place *in vitro*, in preclinical (animal) and clinical study planning and analysis. It is therefore not possible to answer for whom - men and/or women - which dental treatment would be appropriate and useful, as the question is not even asked.

Despite progress towards a broader understanding of sex and gender in medicine there is still a significant gap between the recommendations from sex and gender experts and the "mainstream" movement, which did not even reached dentistry. While experts advocate for incorporating a wider range of non-binary sex and gender categories in data collection and demographic forms [31], the 'general' fields of health research are only beginning to recognize the importance of including both males and females in study designs (e.g., the recent call for integrating 'traditional' binary sex and gender in analysis by Nature journals; Nature 605, 396 (2022) https://doi.org/10.1038/ d41586-022-01218-9) [6,32].

A scoping review [7] highlights that sex has not been considered as biological variable in controlled studies. Studies lacking to consider gender in addition to sex differences in health and disease. Including sex and gender as host-centric variables in clinical and solely for sex in *in-vitro* and/or preclinical studies will allow oral and dental research to move beyond the descriptive binary comparisons that preclude conclusive findings and translation to clinical care.

Moreover, by considering sex as a binary variable, i.e. male vs. female, other measurements of sex and gender identity and sexual orientation are left overlooked and excluded from consideration (e.g. transgender, cisgender, nonbinary) [9]. The NIH Office of Research on Woman's Health defines "sex" as a multi- dimensional biological construct and "gender" as a multi-dimensional social and structural construct. Assessing both in human research is critical, yet the distinction between both are imperfect [33]. Klein [12] calls for journal policies that require authors to report the sex of their cells, animals, and subjects to improve our understanding of the pathogenesis of disease with the long-term goal of personalizing treatments for males and females in an effort to protect both equally.

Stachenfeld in Aguado, et al. [33] stated that it is also critical that we investigate how sex, gender, genetic differences, race, and other social determinants of health intersect when exploring scientific questions. Research demonstrates the impact of gender by showing us the many ways in which social experience impacts health. Recently it was highlighted that acute care trials in leading medical journals infrequently include SABV, female/woman and non-white trial participants, reported race or ethnicity, and never reported gender-related factors. They conclude that there exists substantial opportunity to improve Sex and Gender-Based Analysis (SGBA) and diversity metric reporting in acute care trials [34].

Conclusion

This perspective paper examines the methodology of sex-specific research and proposes applying medical research frameworks to dentistry, aiming to establish sex as a biological variable (SABV) in dental research. Unlike medicine, dentistry lacks a clear trend toward sex-specific research and treatment. Stratified analysis by biological sex should be implemented across clinical, preclinical, and *in-vitro* studies to enable evidence-based, personalized treatment approaches. Integrating Sex and Gender-Based Analysis (SGBA) would enhance scientific quality and lead to targeted prevention and treatment strategies, ultimately contributing to more effective, patient- centered care that addresses the specific needs of all sex and genders.

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