Title: Using Propensity Scores to Estimate Effects of Treatment Initiation Decisions: State of the Science

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ABSTRACT (201/250 word limit)

Confounding can cause substantial bias in non-experimental studies that aim to estimate causal effects. Propensity score methods allow researchers to reduce bias from measured confounding by summarizing the distributions of many measured confounders in a single score based on the probability of receiving treatment. This score can then be used to mitigate imbalances in the distributions of these measured confounders between those who received the treatment of interest and those in the comparator population, resulting in less biased treatment effect estimates. This methodology was formalized by Rosenbaum and Rubin in 1983 and, since then, has been used increasingly often across a wide variety of scientific disciplines. In this review article, we provide an overview of propensity scores in the context of real world evidence generation with a focus on their use in the setting of single treatment decisions, i.e. choosing between two therapeutic options. We describe five aspects of propensity score analysis: alignment with the potential outcomes framework, implications for study design, estimation procedures, implementation options, and reporting. We add context to these concepts by highlighting how the types of comparator used, the implementation method, and balance assessment techniques have changed over time. Finally, we discuss evolving applications of propensity scores.

Generating relevant and reliable real world evidence on the comparative safety and effectiveness of medical treatments requires tools to reduce bias from confounding variables.[1,2] Both the availability of health data and the sophistication of analytic methods have increased over time due to innovations in statistics, epidemiology, digital health and computing. In the US, the 21st Century Cures Act and its paradigm-changing focus on Real World Evidence (RWE)[3] have amplified the demand for studies using routinely collected data to accelerate medical product innovation, and similar efforts are underway internationally.[4] The complexity of available data has also increased, especially with the ability to link across many data sources. While investigators in the 1950s trying to understand the causal relationship between smoking and lung cancer had access to data on only a handful of potentially confounding variables,[5] today's researchers have access to data on dozens if not hundreds of variables for users of a given drug, device or surgical therapy (though these variables are often measured with error).[6,7] The increasing number of measured confounders and the focus on marginal, rather than conditional, causal effects has rendered legacy techniques like full joint stratification increasingly unappealing.

Estimating and utilizing **propensity scores**, formally defined in 1983 as "the conditional probability of assignment to a particular treatment given a vector of observed covariates," is one way for modern researchers to make use of this rich data to reduce confounding in treatment effect estimates.[8,9] While creation of and stratification by forms of multivariable confounder scores predated this work,[10-12] some previous scores led to biased effect estimates while others were found to exaggerate precision.[13-17] Rosenbaum and Rubin's 1983 paper sharpened the focus to prediction of treatments in the entire study population and laid out a clear theoretical framework for the scores as well as three distinct ways to utilize them. Since then, propensity scores have been widely adopted as a tool to aid in estimating causal effects in applied research, and numerous excellent tutorials and orientations to aspects of propensity score analyses have been published across a variety of disciplines.[18-20]

The primary goal of this manuscript is to add to this body of work by providing an overview of the role that propensity scores currently play in generating real world evidence on treatment effects. We also highlight trends in implementation (use of active comparators, matching, and strategies to evaluate covariate balance) and recent methodological developments. To do so, we describe the theoretical framework of the propensity score in the context of

treatment decisions; study design considerations and recommendations when using propensity scores; methods for propensity score estimation and implementation; recommendations for propensity score reporting to facilitate the evaluation of the research as real world evidence; and evolving applications of propensity scores outside the context of estimating effects of a single treatment decision. To provide a foundation for this description, we conducted a literature review to quantify the increasing use of propensity score methods and examine changes in that use over time.

LITERATURE REVIEW

From 2004 to 2018, the period since the most recent systematic review by epidemiologists,[21] some 48,170 unique manuscripts were published with the phrase "propensity score" in their main text and indexed in Pubmed, Embase, Web of Science, or Scopus. From these 48,170 papers, we randomly sampled 300 articles that applied propensity scores to research questions. In the process of identifying these 300 articles, we excluded 258 articles that discussed methodological advancements, were referencing past studies, or otherwise did not apply propensity score methods. We reviewed all 300 articles to identify the type of comparator used, the type of implementation method, and any types of balance assessment.

As the 48,170 articles were not evenly distributed across calendar time and we wanted similarly precise estimates across this range of time, our set of 300 articles was made up of 75 articles randomly sampled from each of four calendar years (2004, 2009, 2014, and 2019). This strategy also allowed us to estimate the share of articles applying propensity scores for research purposes as percentages. We then applied said percentages to the raw number of articles identified in the databases to estimate the number of papers published in each calendar that used propensity scores for research. The full protocol for this literature search appears in **Appendix A.**

Figure 1 shows the 28-fold increase in the estimated number of papers applying propensity score methods per year from 220 in 2004 to 6,208 papers in 2018. For comparison, the total number of papers indexed by Medline doubled from 2004 to 2018. This widespread proliferation of propensity score methods highlights the increasing importance of understanding how to apply them.

PROPENSITY SCORE THEORY

The potential outcomes framework provides the theoretical basis for using propensity scores to control for measured confounding of treatment effects in non-randomized experiments.[8,22,23] When medical providers face a treatment decision (for example, whether to prescribe statin A or statin B to a patient), we can posit two contrasting potential outcomes for that patient: the outcome if statin A is prescribed (denoted by Y_A) and the outcome if statin B is prescribed instead (denoted by Y_B).[23] Although each of the subjects receives only one treatment, the absolute effect (i.e. the risk difference) of statin A versus statin B on each patient can then be described as $E(Y_A - Y_B)$, and the relative effect (i.e. the risk ratio) can be described as $E(Y_A/Y_B)$.

Typically, a given person or group will experience only one of their potential outcomes, $Y_{T=A}$ or $Y_{T=B}$, while the others are rendered unobservable (i.e. counterfactual). The absence of this counterfactual data makes it nearly impossible to directly observe these causal effects. We only have access to the realized potential outcomes in the two disjoint populations, which we will call $\bar{Y}_{T=A}$, the average outcome in the group that received treatment A, and $\bar{Y}_{T=B}$, the average outcome in the group that received treatment B (with the bars denoting population averages).

One way we could use these realized potential outcomes is comparing $\bar{Y}_{T=A}$ with $\bar{Y}_{T=B}$. This approach is problematic, as there may be variables that influence both treatment assignment and the outcome,[24] commonly referred to as **confounders.** If confounders are present, the population risk difference $\bar{Y}_{T=A} - \bar{Y}_{T=B}$ will generally not equal $E(\bar{Y}_A)–E(\bar{Y}_B)$; the discrepancy is known as confounding bias.

Removing this bias requires two things. First, it requires **consistency** of the treatment effects; each individual's potential outcome under a given treatment must be the outcome we observe when the individual is assigned that treatment.[25] Second, it requires patients receiving A and patients receiving B to be **exchangeable,** (i.e. the two treatment groups must possess the same covariate patterns resulting in similar baseline outcome risks except for the effect of treatment, including **positivity** for covariate patterns in both groups); if these conditions are met, then $\bar{Y}_{T=A} - \bar{Y}_{T=B}$ is equal to $E(\bar{Y}_A) - E(\bar{Y}_B)$.[26,25,27] Simple or stratified randomization to treatment A or B has become the standard to achieve exchangeability since, on average, randomization renders treatment allocation independent of other factors, whether observed or unobserved, that contribute to the outcome.

While randomization is the only way to balance unmeasured variables, there are other ways to achieve **conditional exchangeability** with respect to observed variables.[28,29] Restriction and matching have been used successfully for this purpose in scientific research for a long time. Under the assumption that all confounding variables had been measured well, restriction and matching were sometimes seen as equivalent to randomization, especially in small samples.[29] The curse of high dimensionality and rapid decrease in efficiency with simultaneous matching on many factors led to an interest in matching on summary scores.[10,14,30] Rosenbaum and Rubin[8] defined a balancing score as a function of the measured covariates *(x)* such that those with T=A and T=B have equal distributions of *(x)* given the balancing score, which thereby balances covariates across treatments A and B. Exact full stratification or perfect matching on all measured *(x)* can be thought of as the finest balancing score. The coarsest version that still balances covariates is the **propensity score**, the conditional probability of T=A given *(x)*.[8] An estimate of this conditional probability from realized data achieves balancing properties similar to the "true" probability of treatment assignment and can be used to remove confounding by measured variables through matching, stratification, modeling, weighting, or doubly-robust estimation.[23] Each of these methods creates cohorts that are exchangeable on the measured variables, estimating a variety of treatment effects with reduced bias from these factors.

There are a few caveats, however. Achieving covariate balance can require iterative fitting of the propensity score model. Unless correctly specified (e.g., by including relevant interaction or higher order terms), the propensity score may not balance univariate or multivariate distributions of *(x)* between treatment groups; moreover, it is impossible to know how complex these interaction and higher order terms need to be. Additionally, problems arise when some covariate combinations are exclusive to one treatment group (generally referred to as **non-positivity**).[31] Finally, the propensity score will not balance covariates that were not included in the score, particularly those that were unmeasured, except to the extent that unmeasured variables are correlated with those that are part of the propensity score model.[32]

Propensity score techniques have some drawbacks relative to adjustment for covariate differences via g-computation or standardization via outcome models. Most notably, propensity score analyses will generally result in less precise estimates (because they cannot approach parametric efficiency bounds) and can be more complex to implement.[33]

These drawbacks must be weighed against the benefits of using propensity scores. First, propensity score methods are preferable when it is easier or more plausible to identify the model for treatment than for the outcome, particularly in settings with few outcomes. In those cases, regression models for the outcome may be overfit with only a small number of confounding variables.[34-36] Second, unlike an outcome model, the performance of a propensity score at balancing covariates can be empirically checked (and the model refined to improve balance) without examining treatment group outcomes. Third, it is straightforward to check for covariate positivity after implementing the propensity score and to identify (and potentially exclude) types of patients who are virtually guaranteed to receive one of the treatments.[37,38]

Fourth, understanding the propensity score distribution in the treated and untreated can help researchers gain insight into whether there is insufficient overlap (empirical equipoise) between treatment groups to allow for meaningful comparative safety and effectiveness research.[39,40] Finally, if researchers wish to move beyond population level treatment effects, they can compare estimated effects across propensity score strata to identify treatment effect heterogeneity (given that providers are likely to channel specific treatment options towards those who they believe are more likely to benefit, treatments may be more beneficial for those in more extreme propensity score strata).[41] While these strata are not themselves clinically relevant, they can signal potential variability in benefit or risk; that said, it can be difficult to uncover which clinically relevant covariates are creating heterogeneous treatment effects.[42]

PROPENSITY SCORES AND STUDY DESIGN CONSIDERATIONS

Suppose, then, that the advantages of using a propensity score persuade researchers to adopt the method to estimate a treatment effect. Before deciding how to estimate or use the score, there are several key study design considerations. While these considerations are important in any study of medical treatments, the decisions below were often ignored in non-experimental work before propensity scores encouraged a focus on treatment assignment mechanisms and the importance of understanding the indications for and barriers to the use of the treatment of interest;[40,43] moreover, propensity scores can help inform some of these study design decisions, particularly with respect to identifying relevant study populations with empirical equipoise.[44]

Comparator Choice: One of the most critical decisions with respect to the analytic question and potential confounding is the choice of the treatments to be compared; typically, one is a treatment of interest and one is a **comparator**. Choice of comparator shapes and is shaped by the causal question being examined: if researchers want to estimate the effects of a treatment compared with no intervention, they should design the study to compare treated individuals with a **non-user** or **inactive comparator** group with similar health conditions. While this may seem similar to the use of placebos in randomized trials, the fact that non-users are simply continuing to receive nothing (rather than an intervention with no effect) means that the surveillance and care they receive may differ fundamentally and systematically from care received by treated individuals. Further, this difference in treatment may stem from differences in factors that are difficult to measure, such as baseline disease severity, frailty, lifestyle choices and behaviors, and risk of the outcome. While measured covariates can be integrated into the propensity score, unmeasured variables like these often contribute to **confounding by indication** (i.e. disease severity) which can bias estimates of treatment effect and yield misleading results.[45,46]

On the other hand, if the goal of the study is to compare the benefit-to-harm balance of a new drug in a class with its predecessors or other marketed products, it is likely more appropriate to use patients receiving those treatments to form an **active comparator** group.[47,48] Unlike non-user comparators[45,46], active comparators in many cases implicitly condition on the indication for treatment (and the severity of disease warranting treatment), resulting in considerable reductions in confounding by indication as well as possibly increased balance in other baseline covariates and risk of the outcome. These comparators also generally have more similar surveillance

surrounding confounding factors and contraindications, reducing the potential for differential confounder measurement error.[49] Based on our literature review (**Figure 2)**, active comparators were used in less than half of studies in 2004, 2009, and 2014, though by 2019, 57% of studies used some form of active comparator.

Starting Follow-up: Choosing when to start follow-up is also vital, as a lack of a clear time zero can result in invalid estimates of treatment effects.[50] Since propensity score theory is centered around the idea of treatment decisions, it is often useful to focus on the choice of treatment at the time of initiation by restricting the study population to **new users** of drug therapy, excluding prevalent users.[51] If instead prevalent users are included, the propensity score represents both the probability of initiating and remaining on treatment - a much more complex quantity.[48,50,52] Whether restricting to new users or prevalent users for the treatment of interest, it is often difficult to identify the start of follow-up for any non-user comparators. Properly using such non-user data is possible, but often complicates the analysis.[53] Whether studying new users, prevalent users, or non-users, improperly setting time-zero can lead to **immortal time** bias.[54]

Handling Subsequent Treatment: Another critical design decision with consequences for the causal question being examined is the extent to which subsequent treatment affects follow-up after time zero. Initial treatment designs follow individuals until the end of the study period under their first observed treatment, regardless of any stopping or switching; this is analogous to the intention-to-treat designs from randomized clinical trials. Since in non-experimental research the literal intention of the prescriber is rarely captured, it is sometimes referred to as an "initial treatment" approach. Such an analysis estimates the effect of **treatment initiation** given the population's persistence, adherence, re-initiation, and switching rates under each treatment. In real world settings, as time passes, that treatment effect will generally diverge more and more from the effects of initiation and continuous use of treatment.[55,56]

With on-treatment follow-up (i.e. as-treated follow-up), subjects are followed from treatment initiation until they deviate from some treatment protocol, typically by stopping or switching a therapy, at which point they are censored. Such a design estimates the hypothetical effect of **treatment initiation and continued persistence and adherence to a given protocol**[56,57] and produces estimates that are not conditional on the study-specific factors that shape initial-treatment estimates. The price paid, however, is that as-treated designs may show high effectiveness of treatments even if real world patients have poor treatment adherence and

persistence. Additionally, these designs open up the potential for selection bias via differential drop-out unless time-varying confounding is addressed appropriately (which is difficult, as treatment changes are often a function of subtle and not routinely captured differences in effectiveness and side effects).[58]

Study Population: Finally, the design stage requires a decision about the study population in which a treatment effect will be estimated, as heterogeneity in treatment effect can result in a difference in study findings depending on target population. Generally, investigators start by choosing from the effect of the treatment in the total population studied (population average treatment effect, or PATE) or in one of the arms being studied (average treatment effect in the treated, ATT, or average treatment effect in the comparator/untreated, ATU) or some other population entirely.[42]

Propensity scores can play a pivotal role in further refining this initial target population to a population with better exchangeability and reduced non-positivity. Are the investigators concerned about strong confounding among those with high or low probabilities of initial assignment to treatment, and if so are they planning to remove (trim) some of those individuals from the study population?[39,59,60] Excluding all those at the extremes, or "tails," of the propensity score distributions can improve the precision of estimates; moreover, if these individuals are already contraindicated or strongly indicated to receive one treatment, their best course of treatment may not be of interest to researchers. If trimming is to be used, specifying multiple trimming rules (e.g. different percentile cutpoints, symmetrical vs asymmetrical) at the design stage can help researchers protect against accusations of fishing for results while giving some insight into how much confounding (or effect heterogeneity) exists in the tails. Researchers should also be sure to describe those who were trimmed, make it clear that they have limited evidence about effects in them, and (if one characteristic is strongly predictive of being trimmed) consider explicitly reframing the study question to exclude those individuals.

PROPENSITY SCORE ESTIMATION

After design choices (including whether the propensity score will be used to shape the final target population) are made and data are gathered, the next step in a study using propensity scores is propensity score estimation. The propensity score can be used to balance treatment groups with respect to measured covariates. But which covariates should be balanced? Once we've chosen the covariates, how do we use those covariates to estimate the conditional probability of treatment? Once we have estimated this probability, what, if anything, can be done to check whether the balancing has been successful?

Variable Selection: The goal of the propensity score model is to balance the distribution of risk factors for the outcome across the treatment groups, while preserving variability in treatment assignment that is independent of outcome risk. The choice of covariates is critical, as including variables that predict only treatment in the propensity score reduces study efficiency, and that cost has to be weighted against gains in validity.[61,62]

Variable Types: Consider **Figure 3,** a directed acyclic graph that depicts assumed causal relations in the form of arrows from one variable to another. These arrows form causal paths that result in expected associations between variables.[63] Baseline covariates with open causal paths to the exposure but not the outcome, like the **instrumental** variable in **Figure 3A,** should not be included in propensity score models. These variables reduce precision[39] and amplify the effect of any unmeasured confounding (bias amplification).[64,65] Unfortunately, distinguishing these variables from confounders is usually impossible, and the comparatively small bias from including a true instrument versus excluding a variable with a very weak path to the outcome (i.e. a near-instrument) means that even near-instruments are typically worth including in the propensity score model.[66] On the other hand, including baseline variables with open causal paths to the outcome but not treatment assignment (like the risk factor variable in **Figure 3A**) can increase precision when random sampling error has led to spurious associations with treatment in the study sample.[61]

The final type of covariate, baseline variables with open causal paths to both treatment assignment and the outcome, are generally good candidates for inclusion in propensity score models. C_1 in **Figure 3A** is the archetypal example of such a variable. However, some variables meeting this description result in bias when included in the propensity score model if researchers are unable to close the paths opened by their inclusion.[67] Such variables are termed **colliders**

because they have arrows pointing into them from at least two other variables on a causal graph. That said, when a variable is both a confounder and a collider, like the "collider" variable in **Figure 3B,** the confounding bias will generally outweigh collider bias except in extreme scenarios.[68]

Notably, none of the above considerations about variable selection is specific to propensity score models. However, propensity scores have helped clarify these issues, in part because they may be prone to the inclusion of instrumental variables if misunderstood as pure treatment prediction models.

Selection Strategies: Several approaches can be used to select covariates for balancing. First, one could use *a priori* specified directed acyclic graphs like **Figure 3,** that depict assumed relations among variables based on prior knowledge, to identify adjustment sets that would render treatment assignment and the outcome independent except through effects of treatment.[63,69] These adjustment sets can be pared into what are sometimes referred to as **minimally sufficient adjustment sets**, and the sets that researchers believe can be measured with the least error can then be used to estimate the score.[70] This approach requires the causal graph to be properly specified, an untestable and often unrealistic assumption.

Another potential approach is to include all known factors that might be associated with the outcome or treatment in the data. This approach (sometimes called the **kitchen sink approach**) is often seen as a less subjective method with fewer assumptions compared with creating directed acyclic graphs to identify minimally sufficient adjustment sets, but the kitchen sink approach can induce bias from including colliders and amplify unmeasured confounding if instrumental variables are included in the propensity score model.[65] A slightly more restrictive version of this approach (including all variables that are causes of the outcome or treatment in a directed acyclic graph) has also been proposed.[71]

Finally, one can attempt to identify variables associated with treatment assignment and the outcome from the data by applying a selection algorithm to a vast quantity of potential baseline covariates. One such approach, called **high dimensional propensity scores,** identifies things like diagnosis codes or healthcare events that are associated with treatment assignment as well as the outcome and ranks them as candidates for the propensity score model based on their estimated confounding potential (including their association with treatment assignment and the outcome).[72] Notably, establishing this ranking by simply estimating marginal associations

between variables and the outcome does not always eliminate instrumental variables if treatment affects the outcome, since the instruments will, in expectation, be associated with the outcome through treatment.

Score Estimation: After the covariates are selected, they are used to estimate each participant's probability of receiving the treatment of interest. By far the most common estimation choice has been multivariable regression of treatment on the set of covariates, with the propensity score being the predicted probability of treatment for each person given their covariates.[73] Propensity score estimation usually involves logistic regression but can rely on the multinomial logit model for more than two exposure groups[74] or linear regression or more complex models for continuous treatments.[75] Multivariable regression is straightforward but requires decisions about what interactions and functional forms to use in the final model, including whether to categorize continuous covariates.

To aid in these decisions, researchers often specify a starting model and implement their analytic method (be it matching, stratification, or weighting; see **PROPENSITY SCORE IMPLEMENTATION** below), then check balance by comparing the standardized absolute mean differences (SAMDs) between the treatment groups for the covariates included in the model.[76] Larger SAMDs correspond to larger imbalances in covariates; if SAMDs are too large, researchers may re-fit the model with additional interaction terms or more flexible functional forms. Multiple iterations may be required to achieve acceptable covariate balance that reduces bias from measured confounders; to increase confidence in the results, researchers should pre-specify each step of the iterative process and avoid examining effect estimates while adjusting the model.[77,78] While such methods are used quite frequently, surprisingly little theoretical work has been done on their impact on the accuracy of standard errors of treatment effect estimates.

Another option for estimating the propensity score is the use of more flexible tools than logistic regression, especially **machine learning** approaches.[73,79,80] These classification and prediction techniques target a parameter like average standardized absolute mean difference (ASAMD) or overall performance of the prediction model and iterate through potential models and probability estimations until they identify a model or set of predictions that optimizes the target parameter. The result is a predicted probability of treatment for each individual in the data set, conditional on covariates, i.e. a propensity score. Researchers should be sure, however, to use cross-validation techniques with these data-driven approaches and to use methods that yield

appropriate standard errors and confidence limit coverage for the point estimate when using propensity scores created in this manner to avoid complications from overfitting.[81]

Regardless of propensity score estimation method, choosing the target parameter for balance assessment is difficult. While a low ASAMD typically evinces adequate overall balance, this value does not take into account that the effect of variable imbalances on bias depends on how strongly the imbalanced variables affect the risk of the outcome. Perfect balance of a near-instrument or many weak confounders in the presence of a largely imbalanced strong risk factor for the outcome can result in strong overall bias despite a low ASAMD. Given the need to balance distributions across groups, it can also be useful to assess variance ratios.[76] Currently, new methods are being developed and refined that incorporate strength of association with the outcome when assessing balance.[82-84]

PROPENSITY SCORE IMPLEMENTATION

Once each individual has a propensity score, the next step is actually using those scores to estimate a treatment effect. Propensity scores can be used in several different ways to estimate internally valid effects of treatment. Three approaches (**matching, stratification, and regression covariate adjustment**) were described by Rosenbaum and Rubin in 1983.[8] A fourth strategy, **weighting,** arose later and was combined with outcome-based approaches in the early 2000s to create a fifth category: **doubly robust** estimation.[85,86] While each of these methods can estimate a treatment effect without bias, and each will yield the same effect estimate when the treatment effect is homogeneous, their estimates may differ substantially in the presence of non-uniform treatment effects.[87,88]

Matching: Matching on the propensity score was one of the first methods to be developed as a way to improve the efficiency of matching in the presence of many covariates. After assigning propensity scores to all study participants, one group (typically the smaller, treated, group, if the comparison is between treated and untreated) is taken as the target group. Those in the comparator group whose propensity scores are "similar" to those in the target group are identified to be included in the analytic sample. Investigators have to choose what constitutes similarity: **nearest-neighbor** matching randomly chooses a target participant and matches it to the comparator participant with the closest propensity score (and repeats this process for the whole target group), while **optimal** matching algorithmically minimizes the overall distance between matched pairs in the data set. To avoid large differences in propensity scores within matched pairs, **calipers** are used to restrict the search for the nearest match to within some distance (say, 0.01, or 0.10, or 10% of the standard deviation of the propensity score) from the propensity score of the target participant.[89,90] Using calipers effectively trims from the analytic sample any target participants that are at least a half caliper width outside the zone of propensity score overlap, sometimes termed the region of common support.

Matching can be 1:1 (finding one match, at random if multiple exist, for each target group member) or one to many (finding a fixed number of matches, e.g. 2:1, or **all** matches in the comparator group within the caliper for each member of the treated group).[91] Matching can also be **with replacement** (comparator group members can match with multiple target group members) or **without replacement** (each comparator participant matches with only one target group member).[92] One to many matching with replacement typically results in the most precise

treatment effect estimates and approximates the weighting approaches discussed later; for such matching a balanced matching strategy can reduce potential bias from "one-sided" matching.[91]

After matching, outcomes in the two groups can generally be compared directly since matching leads to exchangeability on measured variables and therefore removes (measured) confounding.[93] The final treatment effect estimated after matching is the **treatment effect in the target group for which matches were found.** In settings with little similarity between groups, propensity score matching will highlight issues related to non-overlap (i.e. non-positivity) insofar as the proportion of the target that can be matched with comparator observations will be low and the estimated treatment effect may be a bad approximation of the ATT, potentially requiring a redefinition of the study population.[39,94,95] Additionally, removing the matches with the most dissimilar propensity scores runs the risk of creating more chance imbalances in the progressively smaller data set (similar to problems with small randomized samples);[96] this does not appear to be problematic in most pharmacoepidemiologic applications of the propensity score, however, given the large study sizes and types of variables used.[97]

Stratification: One alternative to matching that may lead to more precise results at the cost of additional assumptions is stratification (or, as it was referred by Rosenbaum and Rubin in 1983, subclassification) by the propensity score.[98] Just as one can reduce confounding by age by estimating treatment effects within strata of age, one can estimate treatment effects within strata of the propensity score. The narrower the strata, the less potential for residual confounding from within-stratum differences. In addition to the resulting stratum-specific treatment effects, a variety of methods (some assuming uniform treatment effects and some not, such as weights)[18] can be used to combine the results into a summary estimate**.**

Based on Cochran's work with linear confounders, [99] Rosenbaum and Rubin suggested that five strata based on propensity score quintiles would likely suffice to remove most bias in a binary treatment effect (assuming the outcome is a monotone function of the propensity score); of course, some bias is likely to remain.[8,100] While this is true with roughly equal numbers of treated and comparator patients, if the strata are derived from the overall propensity score distribution and treatment is rare, the average propensity score will be small and information will be concentrated in the higher propensity score strata where there are more treated individuals. This can lead to considerable residual confounding because of poorer within-strata balance in the low propensity score strata. In such cases, it is preferable to use **fine stratification** where a large

number of strata are formed based on the propensity score distribution in the treated; if we use the finest possible strata of the propensity score in the treated, we effectively perform a one to many matched analysis.[101] In general, regions of non-overlap should be excluded before stratification to reduce the potential for residual confounding (and the covariate distributions in those non-overlap region described), and balance within strata should be checked.

Modeling: The final method Rosenbaum and Rubin discussed in 1983 was modeling, specifically including the propensity score alongside treatment in a linear regression model. If the association between propensity score and the outcome is modeled adequately, this approach will estimate the **propensity-score conditional** treatment effect (unless g-computation is performed after adjustment).[102] Specifying the functional form correctly can be difficult, however, as the propensity score is a composite of many variables with their own effects on the outcome. This approach is therefore "doubly **un**-robust" in the sense that it requires correctly specified propensity score **and** outcome models. Bias may also arise when the variance of the propensity score estimating function differs between the treated and comparator groups.[103] Additionally, this method is one of the few propensity-score based analytic methods where the extent to which covariates were successfully balanced between treated and comparator groups is difficult to investigate and impossible to demonstrate empirically. Modeling also generally assumes uniform treatment effects. However, propensity score modeling can be combined with propensity score stratification, matching, or weighting, and researchers can reduce residual confounding from measured variables in the score by including them in the multivariable regression.[9]

Weighting: Weighting by the propensity score can be used to create a variety of exchangeable treated and comparator pseudo-populations with balanced distributions of measured covariates. Just as surveys can up- or down-weight the responses of specific groups to obtain estimates for a population of interest,[104] one can up- and down-weight treated and comparator observations to resemble some target population (and each other) using the propensity score.[105,106] The most common target populations are the total population (inverse probability of treatment weighting), the treated population (ATT, odds, or standardized mortality ratio weighting),[107] the treated population that would have been identified in a 1:1 matched analysis without replacement (match weighting),[108] or the population with an emphasis on the region of overlap (overlap weighting; this particular population can be difficult to articulate).[109]

Weights can also be stabilized to make the weighted sample size equal the unweighted sample size, improving the precision of inverse probability of treatment weighted estimators.[110]

Despite the versatility of weighted analyses, there are many potential pitfalls. First, not all statistical software is readily suited to weighted data when it comes to producing point estimates.[111] Another major concern with weighting is how researchers should deal with the problem of extremely large weights. When treated individuals have low propensity scores or untreated individuals have high propensity scores, they may receive large weights, particularly when estimating the population average treatment effect. These people, sometimes referred to as those treated **contrary to prediction**, can have a large influence on results and add considerable variance to treatment effect estimates. If they have unmeasured compelling indications or contraindications, or incorrectly measured treatment, they may cause bias as well. As a result, investigators should be careful to specify before starting the analysis whether they plan to truncate or trim (symmetrically or asymmetrically) past a certain weight (or propensity score – separate for treated and untreated) cutoff, and should decide on the final weighting model before examining outcomes.[60,112,94]

Doubly Robust Methods: Propensity scores can also be used as a component of **doubly robust** estimators that specify both outcome and treatment models, yielding an unbiased estimate if at least one of the two models is correctly specified.[86] Doubly robust estimates are typically less precise than those from outcome models but more precise than weighted estimates. While this option is appealing, it is unclear whether (or when) these estimators perform worse than the alternatives when both models are incorrect.[33] A newer form of doubly robust estimation, targeted maximum likelihood estimation (TMLE), estimates an outcome model (typically via SuperLearner, an ensemble machine learning method), then leverages a treatment assignment model to "target" the parameter of interest-the treatment effect-and reduce confounding.[113,114]

Implementation Trends: Based on our literature review, the proportion of applied papers performing matched analyses increased over time (**Figure 4).** While half of the sampled studies in 2004 and 2009 analyzed a propensity score matched dataset, three-quarters of studies in 2014 and seven-eighths of studies in 2019 used a matched approach, with a corresponding drop in the prevalence of stratified and modeled analyses. That said, our search method may have underestimated the use of weighting to some extent, as papers describing weighted analyses may not use the term "propensity score."

Estimating Variance: Up to now, we have focused on using propensity scores to obtain point estimates in the study sample. This is only half the inferential problem as variance estimation is also critical. Propensity score methods have several notable features that affect variance estimation, and researchers should be sure to use a statistically sound method for estimating standard errors. Variance and confidence intervals should also be estimated using methods that take into account any machine learning done when selecting variables for the propensity score.[115]

Despite the prevalence of propensity score matching in research, obtaining appropriate standard errors in matched studies is not straightforward. The standard solution for identifying standard errors with limited assumptions, the non-parametric bootstrap, can yield overly narrow confidence intervals when matching with replacement (as multiple copies of an individual in the bootstrap will all match to the same individual).[116] Simpler approaches to analyzing matched data can also lead to incorrect estimates of the standard error, particularly in the setting of one-to-many-matching with variable matching ratios.[93,117] Fortunately, work has recently been done to derive statistically sound estimators of standard errors after matching for continuous outcomes, survival outcomes, and time-to-event outcomes.[118-120] Only 25 of the 202 matched studies in our literature review made any mention of incorporating the matched nature of the data when estimating standard errors; hopefully, these new methods for variance estimation will be adopted by the wider community applying propensity score matching.

When using other analytic approaches, it is worth noting that some statistical software packages take weighting into account in estimating point estimates but not standard errors, yielding too-small standard errors and overly narrow confidence intervals. Nonparametric methods like the sandwich estimator (now included in SAS and many R packages) or the bootstrap (which typically has slightly more accurate confidence intervals for weighted and stratified estimates) are sometimes required to achieve appropriate confidence interval coverage.[121,122]

REPORTING RESULTS OF PROPENSITY SCORE ANALYSES

Here we provide suggestions on presentation and describe tools available to researchers for reporting and interpreting the results of studies using propensity scores. We do not intend these suggestions as a rigid checklist on what is required for scientific manuscripts, but rather as a guide to information that will help readers evaluate propensity score analyses.

Implementation: One useful principle for presenting analytic methods used in a study is providing enough detail to allow readers to repeat the study themselves.[123,124] This detail includes the variables included in the propensity score; how those variables were chosen and measured; how the propensity score was estimated; how missing and misclassified data on covariates, treatment, and the outcome were handled; whether and how the propensity score estimation was iterated to improve covariate balance based on some diagnostic; and, once the propensity score was estimated, how it was used to estimate the treatment effect (including details like caliper width and whether matching allowed for replacement in a matched study). The extent of loss to follow-up and administrative censoring should be described, as should the methods used to account for potential selection bias from these processes. When few observations are affected, bounds-based analyses can be used to explore the potential impact of restricting to observed individuals.[125] Censoring that affects many observations can be addressed using methods similar to those used to account for bias when conditioning on treatment continuation. If nothing has been done, as we frequently saw in our review, a clear reasoning behind this decision should be provided by the authors.

Because unmeasured confounding is one of the largest concerns in the non-experimental studies where propensity scores are generally used (and because the propensity score does not reduce unmeasured confounding), informing readers of key missing variables and how they may affect the final results is good practice. Researchers should also be clear about the treatment effect they are estimating with their analysis to ensure readers can understand to whom it applies and to what other populations the inference could extend. Presenting the results of pre-specified sensitivity analyses with differing propensity score models and implementation approaches can also help readers understand the effect of the specific implementation structure chosen.

Imbalance: It is important to communicate how much imbalance existed in study characteristics in the crude and, if possible, in the final analytic groups.[126] The "typical" **Table 1** includes group size, the choice of risk factors considered, and the amount of imbalance of these

factors between treatment groups at baseline, often including a metric like the standardized mean difference that shows the degree of difference between treatment groups. When combined with clear statements about the causal effect being estimated, a good **Table 1** helps readers to assess whether a given study is answering a question that is relevant to them in a study population they care about (or a study population similar to one they care about), whether the most important risk factors for the outcome have been measured, and how different the two groups were before and after propensity score implementation.

If matching, stratification, or weighting is being used, columns describing the groups after propensity score adjustment can illustrate the final covariate balance or the lack thereof, overall and within strata if applicable. These and other balance diagnostics help readers understand the degree to which the propensity score has established exchangeability on measured covariates. While SAMDs are imperfect, they are often used to examine the imbalance between treatment groups, with the aim of getting SAMDs as close to 0 as possible (with an often arbitrary cutoff for poor performance at 0.1).[76,82] In the example **Table 1,** we see that applying the SMR weights reduced the SAMDs and led to balance in all covariates presented, suggesting good performance of the propensity score. In matched or trimmed analyses, providing both crude and matched or post-trimming statistics in **Table 1** is useful for readers interested in the effect trimming or matching had on group composition. It is especially helpful to know the number, and covariate distributions of individuals in each treatment group that were excluded from the analysis due to their propensity score or a failure to find a match, as they may be important in interpreting results and defining future study populations.

From 2004 to 2019, the proportion of studies assessing group balance after some manner of confounder adjustment has increased (see **Figure 5),** with a rise in the use of both SMDs and P-values. The increase in the use of matching has likely facilitated the reporting of these balance statistics. However, it is concerning that many of the balance diagnostics rely on p-values, an inappropriate metric, as balance assessment does not involve inference about a larger population and because p-values are study-size-dependent.[127]

Population Overlap: Supplementing **Table 1** with a density plot or histogram of the propensity score distribution by treatment group (**Figure 6)** can give substantial insight into the prevalence of the treatment as well as the amount of overlap (and treatment equipoise) between treatment groups. A plot of the preference score (a transformation of the propensity score) can

help assess overlap independent of the overall prevalence of treatment.[39] While they do not describe the performance of the propensity score, the C-statistic and other measures of model discrimination can also help describe the degree of overlap between treatment groups for the variables in the propensity score model. The lower the C-statistic, the more similar the groups, and the greater the overlap; a high (>0.8) C-statistic raises concerns about positivity and equipoise between treatment groups.[94] Critically, if instruments are being included in the model, they will decrease overlap of compared groups even if the groups are perfectly balanced on risk factors for the outcome, leading to loss of precision and bias amplification as described above.[94,128,129]

Other Items to Report: As with most studies, providing crude estimates of the treatment effect (in the total population for matched studies) alongside the (propensity-score) adjusted effect estimates can contextualize the overall direction of the measured confounding, which can be compared with expectations. If time-to-event analyses are being conducted, including crude survival curves alongside weighted or matched versions is helpful, particularly in weighted analyses where observations with large weights may manifest as large vertical jumps in the curves. If stabilized weights were used, reporting mean weights (which should be close to 1) and extreme weights can provide a useful diagnostic for potential problems in the propensity score. Heavily weighted observations may signal insufficient equipoise or problems with the coding of covariates.[130]

EVOLVING USAGE OF PROPENSITY SCORES

This overview has focused on using propensity scores to assess the effect of a treatment decision between two alternatives at one fixed point in time, as originally envisioned by Rosenbaum and Rubin. However, a great deal of work has considered alternative settings.

For example, the propensity score can be helpful when there are multiple consecutive treatment decisions. The conditional probability of treatment (i.e. the propensity score) can be used to fit marginal structural models for time-varying exposures. These methods have advanced considerably over the past 20 years-including the settings of time-varying instrumental variable analysis and possible interference between study units.[105,131,132] Marginal structural models are particularly valuable for estimating alternative, more complex causal effects such as the effect of dynamic treatment regimens (i.e. treatment regimens where exposure depends on time-varying measurements and factors, like treating HIV patients when CD4 falls below a given level).[133,134] Assuming all variables that influence decisions to swap or change therapy are available in the data, these methods can estimate important treatment effects without bias. Similarly, time-conditional propensity scores have been proposed to estimate the effect of switching to novel therapies among prevalent users of older treatments and augmenting older treatment regimens with new therapeutic agents.[135]

The propensity score can also be used beyond the case of a binary treatment decision. A similar framework can be applied when treatment has three or more categories.[74,136] Matching, weights, and trimming approaches are currently being developed that take into account the issues unique to this context.[95,137,138] Work has also been done to extend propensity score methods to continuous exposures and treatments, sometimes referred to as the generalized propensity score.[43,139,140]

CONCLUSIONS

With the proliferation of real world data sources and statistical software allowing easy matched, stratified, and weighted analyses and greater reliance on routinely collected data for research, it seems likely that the coming years will see continued use and refinement of propensity score methods to generate real world evidence on comparative effectiveness and safety. Focusing on treatment assignment during study design and analysis, as suggested by Rosenbaum and Rubin in 1983, has yielded insights ranging from the best choice of comparator to what should be done in the presence of limited covariate positivity. Summarizing many potential confounders in a single statistic such as the propensity score, allows simplified presentation and easy assessment of control for measured confounders, and further, allows treatment effect estimation even for rare outcomes. Propensity scores have been and will continue to be valuable tools for non-experimental research.

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Table 1: Example Table with Distributions of Covariates and Standardized Mean Differences (SMDs) Before and After Weighting Treatment 2 Patients to Resemble Treatment 1 Patients with Standardized Mortality Ratio (SMR) Weights

Covariate	Treatment 1 N=10,717	Treatment 2 N=74,8910	Crude SMDs	Treatment 2 (SMR weighted) N=10,717	SMR weighted SMDs
Male	5,316 (50%)	32,430 (43%)	0.127	5,206 (49%)	0.005
Hypertension	10,522 (98%)	73,340 (98%)	0.018	10,523 (98%)	-0.002
Diabetes	3,334 (31%)	24,329 (33%)	-0.029	3,352 (31%)	-0.007
Coronary Artery Disease	5,178 (48%)	37,389 (49%)	-0.032	5,203 (49%)	-0.010
Congestive Heart Failure	3,839 (36%)	30,404 (41%)	-0.098	3,861 (36%)	-0.008