Despite growing awareness of the burden of cardiovascular disease (CVD) in women over the past 2 decades, reports of disparities in the delivery of health care for these diseases have persisted over time. \(^7\) Under-treatment of women as compared with men has been described for primary prevention, stable coronary artery disease (CAD) and suspected or diagnosed acute coronary syndromes in both observational studies and controlled experiments.\(^2-6\) However, because men and women are nonidentical in many ways that might be relevant for treatment decisions, a critical question for policy makers and clinicians is whether these gender-based variations in treatment correspond to lower quality care. A demonstration of clinical inequity (unequal treatment despite equal clinical need) rather than strict inequality (unequal treatment regardless of need or condition) has been proposed as a framework to identify inappropriate variations in healthcare utilization.\(^7\) Following this model, it is important to consider whether observed gender differences correspond to inequities or may reflect appropriate variations explained by differences in treatment indications and contraindications or patient preferences.\(^7\)

In a well-known study published over a decade ago, investigators devised a clever experiment to address just this question of identifying inappropriate healthcare variations.\(^8\) Using actors posing as patients with chest pain, primary care physicians were less likely to refer women for cardiac catheterization than men. Because these patients were carefully designed to be identical in age, cardiac risk factors, and symptoms, followed a script standardizing patient communication, and only differed by gender (and race), it seemed obvious that biased decision-making must account for treatment differences.

In this commentary, we illustrate why analyses that attempt to control for all known cardiac risk factors that affect treatment decisions might still yield misleading findings about the presence, magnitude, and causes of gender disparities. This residual bias occurs in the setting of cardiovascular care research because CVD itself is a sexually dimorphic disease, where sex alone might be an important determinant of outcomes and of treatment benefit. Here and throughout, we are using the term sex differences broadly to encompass both the biological factors normally subsumed under this term, but also socially influenced behavioral factors, usually described as gender differences.\(^9\)

Well-recognized sex differences in the risk of future CVD events could justify differences in healthcare practice even when all other patient factors are identical. We emphasize that consideration of sex-based risk differences is necessary to understand when variation by gender in decision-making might represent inappropriate, versus appropriate, disparities in health care.

**Otherwise Similar Men and Women May Receive Different, Yet Appropriate, Care: Some Examples**

To illustrate how sex differences in outcome risks could lead to variation in referral for diagnostic services, we applied the Duke Clinical Score,\(^10\) a clinical prediction model, to estimate the risk of CAD among hypothetical patients like the ones in the above experiment. The Duke Clinical Score predicts risk of significant CAD at catheterization among symptomatic patients. A physician participating in the experiment could have encountered both male and female versions of a 55-year-old fictional patient with hyperlipidemia, type 2 diabetes mellitus, and a history of smoking. According to the Duke algorithm, the female patient has a 25% risk of CAD, as compared with 59% for the male. Other risk calculators give similarly divergent predictions across patients differing only by gender.\(^11,12\) One need not be able to derive Bayes’ theorem to appreciate that patients with such dramatically different pretest probabilities should have different rates of referral for costly or risky diagnostic tests like cardiac catheterization. We expect that adjustment for CAD risk would have attenuated—or fully nullified—the Schulman finding of apparent gender bias in cardiac catheterization referral rates.

In fact, outcome risk–guided decision-making is promoted in many clinical guidelines. For example, the 2010 Cardiac CT Appropriate Use Criteria encourage physicians to assess pretest CAD probability using algorithms like the Duke or Diamond Forrester scores and to follow referral recommendations that incorporate whether a patient’s risk of CAD is low (<10%), intermediate (10%–90%), or high (>90%).\(^13\)
Applying the Duke prediction model to lower risk patients from the above experiment—55 year olds with none of the above-mentioned cardiac risk factors—reveals that the female patient has a 4% risk of CAD versus 23% for her male counterpart. Following the appropriate use criteria, referral for cardiac CT would be deemed appropriate for a symptomatic male patient with an interpretable ECG who is able to exercise, but of uncertain benefit for the female. Although these patients were matched with respect to all available baseline clinical information, the lower risk of CAD inherently associated with being a woman would generate rational gender differences in referral rates. In this case, observed gender variation in referral to cardiac CT that did not account for sex differences in CAD risk would not be able to distinguish biased decision-making, or true disparity, from appropriate differences that arise in management of sexually dimorphic conditions. Moreover, even when guidelines do not explicitly recommend the use of risk models in decision-making, implicit sex stratification is often appropriate, especially where diagnostic tests or therapeutic interventions are costly or invasive. In contrast to the experimental study above, most research related to disparities in clinical decision-making use observational designs. A typical approach to isolating inappropriate variations is to compare treatment in men and women although controlling for differences in cardiac risk factors, appropriateness of treatment, and patient preferences (when available) using multivariable regression methods. Yet these studies typically have the same design flaw as the experiment because well-known sex differences in the risk of a CVD event will naturally still guide rational decision-making in real-world settings. Without specifically accounting for the effect of sex itself on future risk, untangling the amount of gender-based disparity is impossible because the effect of sex would be justifiably incorporated in the decision-making process.

To illustrate how differences in healthcare utilization can arise without bias and persist with the conventional analytic approach of controlling for confounding risk factors, we performed a simple simulation applying guidelines and risk prediction models to the 2009 to 2010 National Health and Nutrition Examination Survey (NHANES) population. We modeled the association between gender and the likelihood of receiving statin therapy in a hypothetical scenario in which the recently published American College of Cardiology/American Heart Association (ACC/AHA) criteria for lipoprotein lowering therapy were perfectly adhered to. The ACC/AHA guideline supports the use of statins for primary prevention among individuals with a 10-year atherosclerotic CVD (ASCVD) risk >7.5% or diabetes mellitus. We used the recently developed Pooled Cohort Equations CV Risk Calculator to estimate risk based on each person’s age, sex, race, blood pressure, cholesterol (total and high-density lipoprotein), type 2 diabetes mellitus, smoking status, and use of antihypertensive medication. Details of the analysis and descriptive characteristics of the NHANES population (Appendix Table I in the Data Supplement) are available in the Appendix in the Data Supplement.

Among the NHANES population over age 50 years without prior coronary artery disease, we estimated that ACC/AHA guideline-congruent care would result in statin therapy for 40% of men versus 34% of women. Even after controlling for all influential baseline cardiac risk factors (age, race, hypertension, high-density lipoprotein and total cholesterol, diabetes mellitus, and smoking), the odds of receiving statin treatment is 44% lower in women compared with men (odds ratio 0.56, 95% confidence interval 0.43–0.73) in this scenario. However, when we instead adjust for the 10-year risk of ASCVD (using the risk equation, but not the individual risk factors), no effect of gender on the odds of receiving statin therapy is seen (odds ratio 1.06, 95% confidence interval 0.71–1.60), as would be

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**Figure.** Apparent gender disparity in statin treatment explained by sex differences in 10 year atherosclerotic cardiovascular disease (ASCVD) risk. A. An apparent inappropriate treatment disparity because a male patient is recommended for blood lipid lowering therapy, whereas a female patient with identical cardiac risk factors (age, race, SBP, HDL, and LDL and no history of smoking history, Type 2 diabetes mellitus, or antihypertension treatment) is not. B. Reveals how this apparent treatment disparity is actually an appropriate treatment difference explained by sex differences in 10-year risk of ASCVD in the setting of a risk-guided clinical decision. Although the male and female patients have identical risk factors at baseline, the male would warrant treatment because male sex itself is associated with a higher risk of ASCVD. His overall risk consequently exceeds the treatment guideline threshold, whereas the female patient’s risk does not. Analyses that control for all cardiac risk factors would (like A) leave the treatment disparity unexplained. DM indicates diabetes mellitus; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and SBP, systolic blood pressure.
expected in this analysis where the treatment decision is dictated by an objective risk-based guideline. Adjustment with the risk score allows isolation of the effect of gender bias on treatment decisions (in this case null), independent of ASCVD risk. Controlling for baseline risk factors alone does not do this because men and women are inherently not the same in terms of future risk, even when all other things are equal (illustrated in the Figure).

Approaches to Identify Gender Inequity Rather Than Inequality

Although adjustment with risk scores should allow more accurate evaluation of clinical inequities, to date, such risk models have rarely been applied in studies of gender disparities in cardiovascular care. One of the few studies that did so found that gender variation in cardiac catheterization disappeared after adjusting for cardiologist-generated pretest estimates of CAD risk.\(^7\) Thankfully, there are a proliferation of risk models that can help us appropriately account for the intrinsic effect of sex on outcome risk. When sexual dimorphism is recognized for a given disease, as is the case for many cardiovascular conditions, predicted probabilities from a corresponding risk model containing sex could be applied as a covariate or stratification variable in analyses of gender disparities. In our Tufts PACE clinical prediction model Registry, a systematic review of cardiovascular and cerebrovascular clinical prediction models published from 1990 to 2012, 36% of the 579 models identified includes coefficient terms for sex, suggesting that meaningful sex differences in risk are indeed common in these diseases and that estimates of these differences are often readily available in the medical literature.

To be sure, bias plays a role in physician decision-making. The interaction of a physician’s personal and professional experiences with highly salient patient characteristics, such as gender or race, surely influences behavior, both consciously and unconsciously, and can result in healthcare disparities. In our simulation where the treatment decision was fixed by an objective guideline and thus was unbiased by definition, we observed no apparent gender disparity after adjusting for the risk score. However, in real world clinical practice, we do not expect that our explanation completely accounts for all of the gender differences observed in the utilization of cardiac services reported in the literature. A key next question to address is the degree to which accounting for the influence of sex on disease risk through the use of risk models alters estimates of gender disparities for sexually dimorphic conditions. We expect this will depend on several factors, including the magnitude of the effect of sex on risk, the degree of physician awareness of sex differences in risk, and the nature of the risk differences (women being at higher or lower risk, for instance). Additionally, it is important to note that sex differences in outcome risk can themselves arise from treatment disparities. For example, higher risk of CAD in men could in theory arise because of better primary prevention in women, but we doubt this is at play. Despite these caveats, we think that differences in risk need to be considered in gender disparities research and analytically accounted for when possible. In these scenarios, sex differences in risk can lurk as a hidden variable, though we recognize that this is just one aspect of the complex socio-cultural and biological interactions between sex, gender, and healthcare services. Consequently, as a patient’s sex and gender identity encompass factors that change and interact over the life course with shifting biological forces and experience, efforts to quantify these complexities using statistical models should be careful to consider assumptions about the temporal sequence of risk factors and possible interactions that could inform the analytic approach.

Conclusions

As heart disease represents the most common cause of death of both women and men, understanding the drivers of the substantial gender variations in cardiac care that have been documented is a top public health priority. It is been pointed out that differences in care do not necessarily mean inferior care if clinical equity, not equality, is to be the criterion for disparity.\(^7\) Currently, the most common approach to isolating shortfalls in appropriate care involves accounting for eligibility criteria and adjustment by all other baseline risk factors. A recent framework acknowledged the importance of accounting for these differences, as well as patient preferences.\(^7\) We propose that this framework be updated to reflect the fact that differences in outcome risk represent another appropriate determinant of decision-making. Although we have framed this discussion around the example of sex and gender differences in cardiac care—because sex is a well-established determinant of the incidence and prognosis of several common cardiovascular conditions—this updated framework would in theory also apply to the study of racial and ethnic disparities. For example, because African Americans are at higher CAD risk, an analysis showing similar statin treatment rates in white and black patients (even after controlling for other risk factors besides race) might obscure an actual racial disparity (undertreatment of black patients) that would be revealed when their higher risk is appropriately accounted for—although the full implications of this framework are undoubtedly complex and merit more attention. In either case, where there is sexual or racial/ethnic dimorphism in risk, studies that endeavor to quantify inappropriate variations in care should account for known differences in outcome risk or therapy response in addition to baseline patient factors and preferences.

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Disclosures

None.

References


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All Else Being Equal, Men and Women Are Still Not the Same: Using Risk Models to Understand Gender Disparities in Care
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SUPPLEMENTAL MATERIAL

APPENDIX: Risk models to understand gender disparities in care

OVERVIEW OF RISK PREDICTION MODELS
A risk model is a statistical mechanism for assigning to an individual a probability of developing a future health outcome in a given time period. This assignment is made based on his or her values for a set of risk-determining variables and the estimated impact of the variables on the outcome.

TUFTS-PACE CPM Registry
The Tufts PACE Clinical Prediction Model (CPM) Registry is based on a systematic review of cerebrovascular and cardiovascular CPMs published in English-language articles from 1/1990-5/2012. All included CPMs permit calculation of outcome probabilities from information provided in the form of an equation, point score or nomogram. The registry includes 506 articles describing 796 models, of which 717 are development CPMs, and 585 are unique primary models (one primary model was selected in cases where multiple nested models were presented). We calculated the proportion of models with coefficients for the effect of sex on disease incidence or prognosis.

NHANES SIMULATION METHODS
Study Population
Participants aged between 21-80 years from National Health and Nutrition Examination Survey (NHANES) 2009-2010 were included in our analysis. Demographic and clinical characteristics of the participants are presented in Appendix Table 1 below. NHANES uses stratified multistage probability cluster sampling to ensure adequate representation of the nation’s noninstitutionalized civilian population. Individuals with prior coronary heart disease were excluded from this analysis as the focus was on primary prevention.

Risk Prediction Models
We implemented a 10-year ASCVD (atherosclerotic cardiovascular disease) risk model for the NHANES population. NHANES contains extensive survey, laboratory and vital signs data including the measures needed for calculating ASCVD risk: age, sex, race, blood pressure, cholesterol (total and high density lipoprotein), Type 2 diabetes mellitus, smoking status, family history of MI, and use of medications for the treatment of hypertension.

Guidelines
We focused on a recently published guideline that will be commonly used in clinical practice: American College of Cardiology/American Heart Association (ACC/AHA). The ACC/AHA guidelines support the use of statins for primary prevention among individuals with a 10-year ASCVD risk greater than 7.5%, or diabetes.

Statistical Analysis
The combination of guidelines and risk prediction models were applied to the NHANES population. All descriptive statistics for related to recommendations for the use of statins were calculated by applying the
sampling weights. To account for NHANES participants who are already on statins, lipid levels were adjusted to reflect the impact of prevalent therapy by increasing total cholesterol by 20% and reducing HDL by 5%. Logistic regression models were used to estimate odds ratios and their 95% confidence intervals for the association between gender and likelihood of meeting ACC/AHA recommended criteria for lipid lowering therapy. The cardiac risk factor adjusted multivariate model included the effect of gender and age (years), current smoking status (yes/no), race (black vs. non-black), self reported high blood pressure (yes/no), self reported diabetes (yes/no), HDL<45, (yes/no), and total cholesterol>200 (yes/no). For sensitivity analyses, this model was also run with continuous HDL and total cholesterol values with very similar results. The risk-adjusted model included the effect of gender and the 10-year ASCVD risk score (continuous).

Appendix Table 1. Demographic and clinical characteristics of NHANES participants

<table>
<thead>
<tr>
<th></th>
<th>Female n=3352</th>
<th>Male n=3175</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>48.0 (18.7)</td>
<td>48.3 (18.7)</td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>47.0 (32.0-63.0)</td>
<td>48.0 (32.0-63.0)</td>
</tr>
<tr>
<td>Cardiovascular disease, %</td>
<td>2.2</td>
<td>5.6</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>10.6</td>
<td>11.7</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>15.3</td>
<td>18.6</td>
</tr>
<tr>
<td>Currently on statin, %</td>
<td>14.6</td>
<td>18.9</td>
</tr>
<tr>
<td>Cholesterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total, mean (SD)</td>
<td>192.3 (42.6)</td>
<td>195.7 (40.4)</td>
</tr>
<tr>
<td>HDL, mean (SD)</td>
<td>56.7 (15.9)</td>
<td>48.2 (15.5)</td>
</tr>
<tr>
<td>Blood pressure</td>
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<td></td>
</tr>
<tr>
<td>Systolic, mean (SD)</td>
<td>121.2 (19.9)</td>
<td>125.6 (17.3)</td>
</tr>
</tbody>
</table>

SD: standard deviation, IQR: interquartile range

References