Sex Differences in Major Bleeding With Glycoprotein IIb/IIIa Inhibitors
Results From the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) Initiative

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Background—Glycoprotein (GP) IIb/IIIa inhibitors are beneficial in patients with non–ST-segment elevation acute coronary syndromes (NSTE ACS); their safe use in women, however, remains a concern. The contribution of dosing to the observed sex-related differences in bleeding is unknown.

Methods and Results—We explored the relationship between patient sex, GP IIb/IIIa inhibitor use, dose, and bleeding in 32 601 patients with NSTE ACS across 400 CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) hospitals, of whom 18 436 were treated. GP IIb/IIIa inhibitor dose was defined as excessive if not reduced when creatinine clearance was \( >50 \text{ mL/min} \) for eptifibatide or \( >30 \text{ mL/min} \) for tirofiban. Major bleeding was defined as a hematocrit drop \( >0.12 \), need for transfusion, or intracranial bleeding. Major bleeding was adjusted for clinical factors and antithrombotic dose. The risk for bleeding attributable to excess GP IIb/IIIa dose was determined by sex using prevalence and adjusted odds ratios (ORs). Women had higher rates of major bleeding than men among those treated with GP IIb/IIIa inhibitors (15.7% versus 7.3%, \( P < 0.0001 \)) and among those not treated (8.5% versus 5.4%, \( P < 0.0001 \)). Despite similar serum creatinine levels, creatinine clearance averaged 20 points lower among treated women than men. Treated women were also more likely to receive excess GP IIb/IIIa doses than men (46.4% versus 17.2%, \( P < 0.0001 \); adjusted OR 3.81, 95% confidence interval [CI] 3.39 to 4.27). Excess dosing was associated with increased risk of bleeding in women (OR 1.72, 95% CI 1.30 to 2.28) and men (OR 1.27, 95% CI 0.97 to 1.66); however, bleeding risk attributable to dosing was much higher in women (25.0% versus 4.4%).

Conclusions—Women experience more bleeding than men whether or not they are treated with GP IIb/IIIa inhibitors; however, because of frequent excessive dosing in women, up to one fourth of this sex-related risk difference in bleeding is avoidable. Appropriate dosing will improve care of all patients with NSTE ACS, with a particular benefit for women.

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Key Words: glycoproteins ■ hemorrhage ■ drugs ■ sex ■ women

Women represent a large proportion of patients treated for non–ST-segment elevation acute coronary syndromes (NSTE ACS), particularly among older patient subgroups. In fact, there are now more deaths annually due to cardiovascular disease among women than men.1 Much of the higher risk in women has been attributed to baseline differences, because women are often older and have more comorbidity at the time of presentation.2 Glycoprotein (GP) IIb/IIIa inhibitors have been demonstrated to be beneficial in such high-risk NSTE ACS patients3–5; however, several trials and a meta-analysis have raised concerns about their relative benefits and risks in women versus men.4,6–9 Specifically, in several clinical trials, women had twice the rate of bleeding.
when treated with GP IIb/IIIa inhibitors. The use of GP IIb/IIIa inhibitors in community-treated women may pose greater risks due to older age, greater comorbidity, and observed variation in delivered doses across practice settings.

Using data from the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) initiative, we investigated bleeding risk for women compared with men when treated with GP IIb/IIIa inhibitors after accounting for baseline factors, invasive care, anti-thrombin therapy, and GP IIb/IIIa dosing. Among patients eligible for GP IIb/IIIa treatment, we describe the association between GP IIb/IIIa treatment, dose, and major bleeding in women and in men.

Methods

CRUSADE

The CRUSADE initiative is an ongoing database of patients with high-risk NSTE ACS admitted to US hospitals since November 2001. Eligibility requires ischemic symptoms lasting ≥10 minutes combined with positive cardiac markers (troponin or creatine kinase-MB) or ischemic ST-segment ECG changes (ST-segment depression or transient ST-segment elevation) <24 hours after admission. CRUSADE hospitals are diverse in size, teaching status, capacity, and regional location. Relative to national averages, CRUSADE hospitals are larger and more likely to have catheterization laboratories and surgical capabilities. Participating hospitals collect data through retrospective chart review using standardized data collection tools. Data collected include patient characteristics, the immediate use of medications (<24 hours from presentation), use and timing of invasive cardiac procedures, laboratory results, physician and hospital characteristics, and discharge therapies and interventions. The institutional review board of each hospital approves their organization’s participation in CRUSADE. Individual informed consent is not required because data are collected anonymously, without unique patient identifiers.

Study Population

The starting population included all patients with recorded sex (missing n = 203) enrolled at 400 CRUSADE hospitals from January through December 2004 (n = 39,730). Patients were excluded if they had contraindications to GP IIb/IIIa inhibitors (n = 7129; 49.2% women, 50.8% men). Contraindications for GP IIb/IIIa inhibitors were recorded by site investigators and included platelet count <100,000/µL, creatinine >4.0 mg/dL, recent major surgery or hemorrage, prior stroke, prior allergic reaction, or severe hypertension or comorbidity. The remaining analysis population included patients eligible for treatment with GP IIb/IIIa inhibitors (n = 32,601), 56.6% of whom were treated (n = 18,915). We compared baseline characteristics and outcomes for women (n = 6054) and men (n = 12,352) who received GP IIb/IIIa inhibitors with those of women (n = 6068) and men (n = 8097) who did not. For GP IIb/IIIa inhibitor dosing analyses, we excluded patients without recorded dose or creatinine clearance (n = 4266). For major bleeding analyses, we excluded patients transferred out of a participating hospital (n = 4913), undergoing coronary artery bypass grafting (n = 3592), or with baseline hematocrit <0.26 (n = 1541). The median (25th, 75th percentile) number of patients from each participating hospital was 78 (33, 131).

Definitions

Dosing adjustments for GP IIb/IIIa inhibitors and heparins were based on US Food and Drug Administration–approved manufacturer’s recommendations in package inserts, as well as published practice guidelines. For GP IIb/IIIa inhibitors, the initial dose was collected as full or reduced as follows: eptifibatide, full dose (2 µg · kg⁻¹ · min⁻¹) or reduced dose (1 µg · kg⁻¹ · min⁻¹); tirofiban, full dose (0.1 µg · kg⁻¹ · min⁻¹) or reduced dose (0.05 µg · kg⁻¹ · min⁻¹). Creatine clearance was estimated with the Cockcroft-Gault formula, using age, sex, creatinine, and body weight. The dose of GP IIb/IIIa inhibitors was considered excessive for full-dose tirofiban when creatine clearance was <30 mL/min and for full-dose eptifibatide when creatine clearance was <50 mL/min.

Analysis

Baseline characteristics, signs at presentation, treatment variables, and in-hospital major bleeding are shown for eligible patients who were treated with GP IIb/IIIa inhibitors and for those who were not. Continuous variables are reported as mean±SD, and categorical variables are reported as percentages. Significance of observed differences was tested with Wilcoxon rank sum tests for continuous variables and χ² tests for categorical variables. Among patients treated with GP IIb/IIIa inhibitors, the proportion who received them in excess dose is presented overall and by demographic subgroups (ie, sex, age, and serum creatinine if creatine clearance was <50 mL/min).

To explore factors associated with excess dosing, we developed a model using generalized estimating equations that accounted for within-hospital clustering of responses, because patients at the same hospital are more likely to be similar to each other than to those at other hospitals. Variables included age, sex, creatine clearance per 10 mL/min, diabetes mellitus, nonwhite race (versus white), prior congestive heart failure (CHF), positive cardiac markers, weight, insurance category, hospital score for adherence to guideline-recommended medications, total hospital beds, treatment by cardiologist (versus noncardiologist), and academic (versus nonacademic) hospitals (“excess dosing model”).

To explore the relationship between major bleeding and GP IIb/IIIa for sex, we developed a series of major bleeding models that shared the same covariates with the exception of the population and GP IIb/IIIa dosing variables. First, core clinical risk factors for bleeding (eg, age per 10 years, renal insufficiency, female sex, signs of CHF on admission, and systolic blood pressure per 10 mm Hg) and dosing of heparins were considered with treatment with GP IIb/IIIa inhibitor (versus no GP IIb/IIIa inhibitor) for major bleeding model 1. Second, the core model was modified to include GP IIb/IIIa inhibitor use as a 2-level variable (either appropriate dose [versus not treated] or excess dose [versus appropriate dose]) for major bleeding model 2a and 2b. Finally, we used a 3-level variable for dose (excess dose or appropriate dose versus not treated) for major bleeding model 3. To further explore interactions between sex, GP IIb/IIIa inhibitor use, and major bleeding, we ran each model in women and men separately and tested sex and GP IIb/IIIa inhibitor interaction terms in each model as well.

Finally, we estimated the population attributable risk percentage (PAR%) for major bleeding resulting from excess dosing by weighting the sex-specific odds ratios (ORs) from major bleeding model 2 for each sex subgroup by sex-specific exposure to excess dosing. This PAR% describes the proportion of major bleeding events that would not have occurred if the factor of interest (excess dosing) had been absent in each sex subgroup. This was estimated by

\[ \text{PAR%} = \frac{P_e(OR_e - 1)}{1 + P_e(OR_e - 1)} \times 100\% \]

where \( P_e \) is the prevalence of excess dosing in each group and \( OR_e \) is the increased odds of bleeding associated with excess dosing in women and men, respectively. A probability value <0.05 was considered significant for all tests. All analyses were performed with SAS software (version 8.2, SAS Institute, Cary, NC).
The authors had full access to the data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

Results

Women constituted 37.3% of the population eligible for treatment with GP IIb/IIIa inhibitors. The most commonly used GP IIb/IIIa inhibitor was eptifibatide (88.5%), and the median (25th, 75th percentile) duration of GP IIb/IIIa treatment was 19.95 hours (15.13, 32.52). Among eligible patients, women were less likely to receive GP IIb/IIIa inhibitors than men (50% versus 60.4%, \( P<0.0001 \)).

Baseline characteristics of men and women eligible to receive GP IIb/IIIa inhibitors are shown by whether they were treated with GP IIb/IIIa inhibitors or not (Table 1). Compared with treated men, treated women were older, weighed less, and had more diabetes mellitus, hypertension, prior stroke, prior myocardial infarction, and prior CHF. Treated women were equally likely to have a serum creatinine \( \geq 2.0 \) mg/dL but had an average creatinine clearance 20 points lower than men. In addition, treated women were equally likely to have positive cardiac markers, to receive heparin, and to undergo diagnostic catheterization during hospitalization but less likely to undergo percutaneous or surgical revascularization (Table 1).

Compared with same-sex patients who were treated, eligible patients not treated with GP IIb/IIIa inhibitors were older and had lower creatinine clearance, lighter body weight, and more past cardiac history and comorbidity. In addition, untreated patients were less likely to have ECG changes or positive cardiac markers and more likely to have signs of CHF at admission (Table 1). Untreated patients were also less likely than treated patients to receive other antiplatelet and heparin therapies or to undergo cardiac catheterization or revascularization.

Excess Dosing

Among patients treated with GP IIb/IIIa inhibitors, 26.9% overall received them in an excessive dose (Figure 1). The risk of excess dosing in those with estimated creatine clearance \(<50 \) mL/min was most pronounced when serum creatinine was \( \leq 2.0 \) mg/dL (90.8% versus 62.9% for serum creatinine \( >2.0 \) mg/dL). In addition, excess dosing was more common in women (46.4% versus 17.2% in men) and in patients aged \( \geq 75 \) years (64.2% versus 16.0% in those aged \( <75 \) years). Women had a 4-fold higher unadjusted likelihood of receiving an excessive dose than men (OR 4.11, 95% confidence interval [CI] 3.78 to 4.48), which persisted after full adjustment for variables in the excess dosing model (OR 1.47, 95% CI 1.31 to 1.64). Older age (OR 1.26, 95% CI 1.19 to 1.34) and body weight (OR 1.02, 95% CI 1.00 to 1.03) also increased the likelihood of excess dosing, whereas higher creatinine clearance (OR per 10-mL/min increase 0.25, 95% CI 0.22 to 0.29) and prior CHF (OR 0.69, 95% CI 0.56 to 0.86) decreased the likelihood in this model.

Major Bleeding by Sex and Treatment

Major bleeding events occurred in 10.1% of patients treated with GP IIb/IIIa inhibitors versus 6.8% of those not treated (\( P<0.0001 \)). Among treated patients, major bleeding occurred more often in women than in men (15.8% versus 7.3%, \( P<0.0001 \)). Among those not treated, major bleeding was also more common in women than in men (8.5% versus 5.4%, \( P<0.0001 \)). Early initiation (within 24 hours) of GP IIb/IIIa inhibitors was associated with a slightly lower rate of bleeding in the overall population compared with initiation after 24 hours (9.8% versus 10.9%), and this pattern persisted for women (15.0% versus 17.4%) and men (7.3% versus 7.5%). Major bleeding was also more common in invasively managed women regardless of treatment with GP IIb/IIIa inhibitors (Table 2). Overall, treatment with GP IIb/IIIa inhibitors (versus not treated; OR 2.38, 95% CI 2.08 to 2.71) remained independently associated with major bleeding after adjustment for variables in major bleeding model 1. In addition, the sex interaction between GP IIb/IIIa inhibitor treatment and bleeding was significant (\( P=0.014 \)), which reflects the fact that although there was a positive association between bleeding and GP IIb/IIIa inhibitor use in both sexes, this relationship was more pronounced among women. The adjusted OR for major bleeding in those treated with GP IIb/IIIa inhibitors (versus those not treated) was 2.78 (95% CI 2.34 to 3.31) for women and 1.98 (95% CI 1.61 to 2.42) for men (major bleeding model 1 by sex subgroups).

Major Bleeding by Sex and Excess Dosing

Major bleeding was higher in women than in men in subgroups receiving excess doses or appropriate doses and among those not treated (Figure 2). Although the crude rates of major bleeding were only slightly higher in appropriately dosed men compared with those not treated, this difference was significant after adjustment for variables in major bleeding model 2a (adjusted OR 1.83, 95% CI 1.45 to 2.32). Men also had 3 times the rate of bleeding if given an excessive versus an appropriate dose, but after adjustment for variables in major bleeding model 2b, this was no longer significant (adjusted OR 1.27, 95% CI 0.97 to 1.66). In women, the crude rates of major bleeding were higher in appropriately dosed patients than in those not treated, as well as in those given an excessive dose compared with an appropriate dose, and these differences remained significant after adjustment for variables in major bleeding model 2a (adjusted OR 2.16, 95% CI 1.69 to 2.76) and 2b (adjusted OR 1.72, 95% CI 1.30 to 2.28). When we considered appropriate or excessive dose versus those not treated along with clinical factors and treatment with heparins (major bleeding model 3), the ORs for bleeding in the overall population that was related to excessive dosing of GP IIb/IIIa inhibitors versus lack of treatment (adjusted OR 2.84, 95% CI 2.46 to 3.28) and for appropriate dose versus no treatment (adjusted OR 1.85, 95% CI 1.57 to 2.17) were more pronounced, and the sex-by-treatment interaction was no longer significant (\( P=0.27 \)), which suggests that the previously noted sex interaction was due to dosing.

In sex-specific models among treated patients, excess dose was associated with a 46% increased odds of major bleeding overall (adjusted OR 1.46, 95% CI 1.22 to 1.73),
a 27% increased odds of bleeding among men (adjusted OR 1.27, 95% CI 0.97 to 1.66), and a 72% increased odds of bleeding among women (adjusted OR 1.72, 95% CI 1.30 to 2.28) compared with appropriate dose when adjusted with major bleeding model 2b in each sex subgroup (Figure 3). When we considered the OR for bleeding with excess dose among men (OR 1.27) with the prevalence of excess dosing among men (17.2%), a 4.4% risk attributable to excess dosing was observed. However, when we considered the OR for bleeding associated with excess dose among women (OR 1.72) with the prevalence of excess dosing among women (46.4%), a much higher 25.0%
increased risk attributable to excess dosing was observed among women.

Discussion
Women experience more bleeding than men in the course of routine care for NSTE ACS. This higher relative risk in women is apparent with or without treatment with GP IIb/IIIa inhibitors. In addition, treatment with appropriately dosed GP IIb/IIIa inhibitors is associated with a greater bleeding risk than no treatment, and excess dosing is associated with further elevation in this risk among women and men alike. However, women are significantly more likely to receive excess doses of GP IIb/IIIa inhibitors despite their obvious differences in body size, age, and comorbidity. The average creatinine clearance for women treated with GP IIb/IIIa inhibitors was 20 points lower than for men, and excess dosing with creatinine clearance <50 mL/min most often occurred when serum creatinine was also <2 mg/dL. After adjustment for patient factors and excess dose, sex differences in bleeding remain. Although other treatment factors may also contribute to risk differences, the proportion of bleeding attributable to excess dosing in community practice is 5-fold higher among women than among men (25.0% versus 4.4%).

The net benefit of GP IIb/IIIa inhibitors is determined by a balance between therapeutic benefits and risks. Women are at greater risk for death and myocardial infarction after NSTE ACS owing to comorbidity and treatment differences. Likewise, in the present study population, women were older and had more comorbidity. However, women who were treated with GP IIb/IIIa inhibitors were younger, healthier, and more likely to receive other acute care than their untreated counterparts. This suggests that women treated with GP IIb/IIIa inhibitors in the community were at lower risk than all women with NSTE ACS. However, treated women were still at higher risk and were less likely to undergo revascularization than treated men. Differences between treated groups in comorbidity and ACS management may explain some of the observed differences in risk.

**TABLE 2.** Major Bleeding by Treatment and Sex Among Patients Eligible for GP IIb/IIIa Inhibitors

<table>
<thead>
<tr>
<th>Group</th>
<th>No GP IIb/IIIa Inhibitor</th>
<th>GP IIb/IIIa Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women (n=6068)</td>
<td>Men (n=8097)</td>
</tr>
<tr>
<td>Overall</td>
<td>8.5 (380)</td>
<td>5.4 (294)</td>
</tr>
<tr>
<td>No PCI*</td>
<td>8.3 (303)</td>
<td>5.6 (229)</td>
</tr>
<tr>
<td>PCI†</td>
<td>10.0 (76)</td>
<td>4.6 (59)</td>
</tr>
</tbody>
</table>

*PCI* indicates percutaneous coronary intervention. Values are % (n).

**Figure 1.** Excess dosing for overall population, by sex, serum creatinine level (*) among those with creatine clearance <50 mL/min, and age.

**Figure 2.** Major bleeding by sex in patients not receiving GP IIb/IIIa inhibitors compared with those receiving appropriate dose and those receiving excess dose. Probability values represent unadjusted comparisons.

**Figure 3.** Adjusted relationship between excess dose of GP IIb/IIIa inhibitors vs no excess dose and major bleeding (major bleeding model 2b); OR with 95% CIs for major bleeding overall and by sex subgroup among treated patients.
and benefit with GP IIb/IIIa inhibitors across patient sex.76–28 In GP IIb/IIIa inhibitor clinical trials, female sex independently predicted risk of major bleeding after accounting for age, weight, and renal function.7,10 In post-marketing studies, nearly half (48%) of the early deaths from GP IIb/IIIa inhibitors also occurred in women, with the majority of those deaths (80%) attributed to major bleeding.29 Although key patient factors that elevate risk have been enumerated, dosing has not previously been considered as an explanatory variable.

We found that female sex remains a significant risk factor for bleeding after adjustment for baseline differences, GP IIb/IIIa treatment, and GP IIb/IIIa dose. Female sex has also been linked to bleeding risk in other clinical settings with a variety of antithrombotic agents (ie, thrombolytics, unfractionated heparin, and low-molecular-weight heparin).12,22,30–33 Women are also vulnerable to bleeding owing to their smaller body size. Differences in platelet reactivity have also been suggested to exist in relation to levels of sex hormones, but these are speculative.34–36 Thus, higher rates of bleeding observed in women are not unique to the use of GP IIb/IIIa inhibitors and may not be entirely attributable to any 1 antithrombotic therapy. Combinations of antithrombotic agents may pose more risk in women, or the dichotomous cutpoints used to determine excess dose may not account for the continuous nature of the dose-response curve. Pharmacological responses to therapeutic agents may also differ between the sexes.37–39

Bleeding with GP IIb/IIIa inhibitors is more common among patients with diminished renal function.40 The strong relationship between serum levels of GP IIb/IIIa inhibitors and platelet inhibition establishes the link between drug clearance and pharmacodynamic effects.41,42 Although the independent contribution of excess dosing does not differ by sex, the attributable risk is much greater in women, who are more likely to have their renal insufficiency overlooked. In practical terms, a 70-year-old woman (155 pounds) with apparently normal serum creatinine of 1.3 mg/dl still requires adjustment of GP IIb/IIIa inhibitor dose (creatinine clearance of 42 mL/min). The relationship between creatinine clearance and dose-related risk may also be continuous, or other sex-related differences may alter the ideal thresholds for adjustment. However, dosing GP IIb/IIIa inhibitors within the recommended range remains an immediate target for improving safety and would benefit half the women currently being treated in community practice.

In conclusion, routine estimation of creatinine clearance and dose adjustment of narrow therapeutic index drugs during loading and infusion protocols must be prioritized. Even with appropriate adjustment, providers must remain vigilant for bleeding in women. GP IIb/IIIa inhibitor dose likely represents just 1 of several sex-related treatment risks, so continued investigation into other contributing causes for bleeding in women is warranted.

Study Limitations
In CRUSADE, the use of GP IIb/IIIa inhibitors is not randomized; therefore, unrecognized differences between treated groups may persist. In addition, hospitals participate voluntarily in CRUSADE and may represent a subset of community practice more interested in quality. We describe only major bleeding as a complication; the inclusion of minor bleeding would likely increase the association between dosing and bleeding in women. In addition, other aspects of bleeding risk, such as history of bleeding diathesis, concomitant use of drugs that affect coagulation (eg, nonsteroidal anti-inflammatory drugs or warfarin), and specific timing in relation to procedures and duration of therapy were not assessed. Dose adjustments made after the initial dose were not considered. Finally, consecutive patient enrollment in CRUSADE is requested but not monitored, and data elements are not adjudicated by source documents. Interval assessments of chart abstraction have demonstrated a high level of correlation between the case report form and actual care.

Conclusions
Women are at higher risk of bleeding during treatment for NSTE ACS. Use of GP IIb/IIIa inhibitors is associated with increased bleeding risk in women and men alike; however, 25% of the bleeding risk with GP IIb/IIIa inhibitors among women is attributable to excess dosing. Although dosing of GP IIb/IIIa inhibitors may be just 1 of several explanations for this bleeding risk in women, appropriate dose adjustment should be prioritized to increase the safe use of these agents.

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References


**CLINICAL PERSPECTIVE**

Women represent a large proportion of patients treated for non–ST-segment elevation acute coronary syndromes and are known to experience more bleeding than men in the course of routine care. Although glycoprotein (GP) Ilb/IIia inhibitors are beneficial in this population, their safe use in women remains a concern, with trials and meta-analyses demonstrating twice the rate of bleeding in treated women. We show that among 32 601 community non–ST-segment elevation acute coronary syndromes patients in 400 CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) hospitals, 18 436 of whom received treatment, excess dosing of GP Ilb/IIia inhibitors was common in women (46.4% versus 17.2% of men). Excess dosing was associated with increased risk of bleeding in women and men alike, and women had higher rates of major bleeding than men if treated (15.8% versus 7.3%, \( P<0.0001 \)) or not treated (8.5% versus 5.4%, \( P<0.0001 \)). Most important, the risk attributable to dosing excess was much higher in women (25.0% versus 4.4%) because of their greater exposure to excess dosing. Therefore, variations in dosing among high-risk subgroups may be sufficient to alter the risk profile of therapeutics and limit benefits. We demonstrate that one fourth of the risk difference between women and men in bleeding with GP Ilb/IIia inhibitors would be avoidable with appropriate dosing without invoking any other major contributor to these sex differences.
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