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Evaluating Marginal Streuctural Model Assumptions in Assessing Hormonal Contraception on Risk of HIV Acquisition

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To the Editor

Recently, two analyses were published from the Hormonal Contraception and Risk of HIV Acquisition Study, a multicenter cohort study specifically designed to evaluate whether hormonal contraceptive use (depot-medroxyprogesterone acetate [DMPA] or combined oral contraceptives [COCs]) alters the risk of HIV acquisition among women.^{1,2} A detailed description of study participants and methods has been published elsewhere.¹ The main study analysis used conventional Cox proportional hazard models with time-varying hormonal contraceptive exposure to adjust for demographic and sexual risk factors. This analysis showed little or no evidence of increased risk of HIV acquisition with either DMPA (hazard ratio = 1.25 [95% confidence interval= 0.89 - 1.78]) or COCs (0.99 [0.69 - 1.42]) compared with the non-hormonal group.¹ A reanalysis using a marginal-structural-model (MSM) to accommodate hormonal-contraceptive exposure switching and confounding with the same set of demographic and sexual risk factors found evidence for an increased HIV acquisition risk associated with DMPA (1.48 [1.02 - 2.15]) but not COC use (1.19 [0.80 - 1.76]).² MSMs can appropriately adjust for time-dependent confounding and selection bias using the inverse-probability-of-treatment weighting (IPTW).³ Nevertheless, the model relies on certain assumptions that either cannot be verified (e.g., no unmeasured confounders) or could be problematic in the data from this study⁴ (e.g., violation of the positivity assumption due to high association between pregnancy and hormonal contraceptive use).

We conducted several sensitivity analyses to address the above concerns. First, we examined possible model misspecification in the marginal structural model by adding or removing suspected time-varying confounder(s). Second, we investigated the variability of hazard ratios estimated by MSM using a nonparametric bootstrapping procedure to obtain estimates

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from 1000 with-replacement bootstrap samples.⁵ Finally, we explored possible violations of the positivity assumption when pregnancy status was included in the MSM analyses.

We found a consistently larger effect of DMPA than COCs on HIV acquisition, compared with the nonhormonal group, across various analyses (Table). DMPA also appeared to have a larger effect with MSM analyses than with the conventional Cox model when similar covariates were included in analyses. Model misspecification can cause estimated hazard ratios to vary from 1.24 (0.85 - 1.80) to 1.51 (1.03 - 2.22) for DMPA, and from 1.00 (0.69 - 1.47) to 1.19 (0.80 - 1.76) for COCs.

Compared with the results in Model 3 (the published results¹), the bootstrapped estimates provided similar findings. We also note that the distributions of estimated weights were similar among MSM analyses that did not include pregnancy status; means and standard deviations were around 1 and 0.55, respectively, with reasonable ranges from about 0.01 to 2.64. However, when pregnancy status was included in the analysis, the distribution from untruncated weights clearly indicated the violation of positivity assumption because a large standard deviation (16.4) and a wide range of weights (from <0.01 to 3915) were observed. In general, the estimated effect becomes unstable and attenuated under that situation, with a large deviation of weights.

The validity of the MSM analysis depends on the assumption that all confounders were measured and sufficient to adjust for confounding and selection biases. The causal effect estimates could be biased if these assumptions were incorrectly specified. In these analyses we evaluated the potential issues of model specification and the positivity assumption. These findings parallel the results from a simulation study⁶ that found that inclusion of more confounders (even in the absence of complete control) resulted in a decrease in bias. This observation suggests that including all possible time-varying confounders in analyses may reduce bias, as long as no finite-sample bias is introduced. In addition, because current pregnancy clearly violated the positivity assumption for computing IPTW in the estimation of the hormonal-contraceptive effect on HIV acquisition, alternative modeling approaches (such as structural-nested-failure-time models) should be considered.⁷

Details on time-dependent confounder assessment and MSM specification are available in the eAppendix. (<http://links.lww.com>)

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table

Analysis	Time-dependent covariates/confounder included	COC			DMPA		
		Estimated weights Mean (SD)	Hazard ratio	95% Confidence interval ^d	Hazard ratio	95% Confidence interval ^d	
Standard Cox model							
Unadjusted	None	–	1.06	0.75, 1.48	1.20	0.87, 1.65	
Adjusted ^a	primary partner risk, participant behavioral risk, any condom use, and coital frequency	–	1.05	0.73, 1.52	1.25	0.89, 1.77	
MSM Analysis ^{ab}							
1	primary partner risk	0.98 (0.56)	1.00	0.69, 1.47	1.24	0.85, 1.80	
2	primary partner risk, participant behavioral risk,	0.99 (0.54)	1.08	0.74, 1.57	1.35	0.94, 1.94	
3	primary partner risk, participant behavioral risk, and any condom use	0.99 (0.54)	1.19	0.80, 1.76	1.48	1.02, 2.15	
4	primary partner risk, participant behavioral risk, any condom use, and coital frequency	1.01 (0.55)	1.18	0.78, 1.76	1.51	1.03, 2.22	
Bootstrapping ^{abc}	primary partner risk, participant behavioral risk, and any condom use	–	1.17	0.82, 1.62	1.45	1.04, 1.95	
Added pregnant status ^a	primary partner risk, participant behavioral risk, any condom use, and current pregnant status	1.20 (16.43)	1.12	0.77, 1.64	1.30	0.92, 1.85	

^a also adjusted for baseline covariates (site, age, education, STI history, breastfeeding, coital frequency and living with partner)

^b weights computing including site, baseline covariates (age, education, STI history, breastfeeding, coital frequency and living with partner) and time-varying confounders; final model adjusted for baseline covariates only.

^c based on 100 bootstrap samples with variables included in Model 3

^d robust 95% confidence interval for all weighted analyses except for the bootstrapping approach that used the quintiles of 1000 bootstrap sample estimates