

Title: Positive Treatment Effects and High Heterogeneity of Hormonal Contraceptive Use on Women's Sexuality
Registered Report Stage 2 Based on a Programmatic Registered Report Stage 1

January 14th, 2025

Dear Prof. Dr. Evans,

Thank you very much for the quick and positive response to the revised version of our registered report stage 2 titled *Positive Treatment Effects and High Heterogeneity of Hormonal Contraceptive Use on Women's Sexuality* based on the programmatic registered report stage 1 titled *Estimating Average Treatment Effects and Treatment Heterogeneity of Hormonal Contraceptive Use on Women's Sexuality and Well-Being Based on Longitudinal Analyses*.

We really appreciate your positive evaluation of the revised version of our manuscript and the note to recommend our work after implementing a protocol of deviations from the Stage 1 registration. We think that this is a wonderful idea that will be extremely helpful to readers of our manuscript. We have briefly responded to your feedback below and provide information about the added information in the manuscript and supplement.

We have uploaded two versions of the second revised version of manuscript and supplement, including one in which all changes are presented in blue font to ease the review process.

Best regards,

Laura Botzet, on behalf of all co-authors

Editor's remarks:

Thank-you for responding to the previous feedback provided and being so comprehensive and transparent in your working. I believe the responses were appropriate and changes have indeed made the manuscript clearer and more convincing.

Thank you for your kind feedback and for acknowledging the revisions. We're pleased that the changes have improved the clarity of the manuscript. Your thoughtful comments and the reviewer's notes were very helpful in making these improvements.

Based upon a few of the changes, I'd like to suggest to you that a protocol of deviations from the Stage 1 registration is provided to readers (either as an appendices or as a supplementary doc on the OSF but explicitly signposted within the manuscript) to make sure that all the changes made are maximally visible. I have no concerns over the deviations made, however I think it was quite easy to miss them when reading the manuscript and a transparent account of them all logging where the original plans have changed, how and why, would be a valuable addiiton.

We appreciate this wonderful idea and have provided all details about the deviations from the in-principle accepted registered report stage 1, reasons for the deviations, and potential impact on the readers' interpretation in the form of Table S1 in the supplement. We have adjusted the table numbering in the supplement accordingly.

We refer to this table on page 3 of the manuscript below the information on the programmatic registered report stage 1. We have added the following sentence:

Based on the preregistration deviation table template by Willroth & Atherton (2024), Table S1 in the supplement provides all details about the deviations from the in-principle accepted registered report stage 1, the reasons for the deviations, and the potential impact on the readers' interpretation of our study.

In addition, we refer to Table S1 throughout the manuscript and the supplement when we have deviated from the registered report stage 1 (this is the case on pages 6, 21, 27, 29, 49, 57, and 58 in the manuscript and pages 42 and 43 in the supplement).

Here is the added text and the new Table S1 from the supplement:

Deviations from the Registered Report Stage 1

Based on the preregistration deviation table template by Willroth & Atherton (2024), Table S1 provides all details about the deviations from the in-principle accepted registered report stage 1, the reasons for the deviations, and the potential impact on the readers' interpretation of our study.

Table S1

Deviations from the in-principle accepted registered report stage 1, reasons for the deviations, and potential impact on the readers' interpretation

#	Mentioned in registered report stage 2	Details	Original wording in registered report stage 1 (Botzet et al., 2023)	Deviation description	Reason for deviation	Reader impact
1	Footnote 1 in <i>Empirical Evidence of Positive and Negative Effects of Hormonal Contraceptives on Sexuality</i>	<p>Type: Sample</p> <p>Reason: New knowledge</p> <p>Timing: Before data access</p>	<p>We will analyze data from up to 6,565 women who participated in PAIRFAM, a German longitudinal panel dataset consisting of 13 waves using Bayesian multilevel regressions.</p> <p>By analyzing the effects of starting and discontinuing hormonal contraceptives on sexuality and well-being in a longitudinal dataset with around 6,500 women, observed over up to 13 yearly waves (years of data collection: 2008–2021), we hope to answer questions about potentially heterogeneous average treatment effects of hormonal contraceptives in real world settings while accounting for (un)observed confounders as well as attrition effects.</p> <p>Analyses will be based on the German Family Panel (PAIRFAM), a panel dataset containing information about contraceptive use as well as women's sexuality and well-being from more than 6,500 women over 13 waves, starting in 2008 (Brüderl et al., 2021; Huinink et al., 2011).</p> <p>The longitudinal design consists of annual waves with the first data collection in 2008 and the latest available data from 2021 (wave 13).</p>	In stage 1 of this registered report we only mentioned 13 waves. The 14 th (2022) wave was released on July 31 st , 2023 and we included it in our data analysis.	We decided to include all available information up to date in our analyses.	The inclusion of the 14th wave of data increases the robustness of the study by incorporating the most recent information, potentially leading to more accurate estimates of the effects of hormonal contraceptives. This deviation does not fundamentally alter the objectives, estimates, or methodological framework of the study. Readers should interpret the results as benefiting from an expanded dataset, which may slightly increase the generalizability and precision of the results compared to what was originally described in the Stage 1 report. However, it does not introduce bias or alter the core approach or validity of the analyses.

Table S1 (continued)

Deviations from the in-principle accepted registered report stage 1, reasons for the deviations, and potential impact on the readers' interpretation

#	Mentioned in registered report stage 2	Details	Original wording in registered report stage 1 (Botzet et al., 2023)	Deviation description	Reason for deviation	Reader impact
2	<p><i>Methods – Exclusion Process and Participants</i></p> <p>Table 2</p> <p>Figure 2</p>	<p>Type: — Analysis</p> <p>Reason: Miscommunication</p> <p>Timing: Before data access</p>	—	Besides the exclusion criteria explicitly mentioned in stage 1 of this registered report, the implemented models for effects of hormonal contraception on sexuality only used information from one wave if the information from the previous wave was also available (because we used predictors from the previous waves in our models). In addition, we could only include information from participants if (1) hormonal contraception was available in the previous and the current wave (2) all additional predictors were available in the current wave and (3) one of the three outcomes was available in the previous and the current wave. To make these data exclusion steps following from modeling decisions more explicit, we now list them as additional exclusion criteria in stage 2 of this registered report.	Exclusion because of missing data was only implicitly mentioned in the registered report stage 1. In the registered report stage 2 we explicitly mention that missing data led to exclusion and list how many women and how many observations were excluded because of missing data.	The explicit listing of additional exclusion criteria related to missing data increases the transparency of the analysis process. These criteria follow logically from the modeling decisions and were implicitly necessary to perform the planned analyses. By explicitly stating these criteria and reporting the number of women and observations excluded due to missing data, we provide readers with a clearer understanding of the data preprocessing steps and the final sample composition.

Table S1 (continued)

Deviations from the in-principle accepted registered report stage 1, reasons for the deviations, and potential impact on the readers' interpretation

#	Mentioned in registered report stage 2	Details	Original wording in registered report stage 1 (Botzet et al., 2023)	Deviation description	Reason for deviation	Reader impact
3	<p><i>Methods – Analysis</i></p> <p><i>Results – Predictors of Individual Treatment Effects</i></p> <p><i>Results – Contraceptive Decisions and Individual Treatment Effects</i></p>	<p>Type: Analysis</p> <p>Reason: New knowledge</p> <p>Timing: After results known</p>	<p>To answer the question whether interindividual differences predict individual treatment effects, we will extract individual treatment effect estimates from the adjusted regression analysis and subsequently correlate them with age (continuous) and the Big Five personality traits. These correlation analyses will be weighted by the inverse of the standard error of the individual treatment effect estimates to propagate uncertainties in their estimation.</p> <p>To answer the question whether women guide their contraceptive method choices by deciding against hormonal contraceptive methods after experiencing adverse effects, we will again use individual treatment effect estimates from the adjusted regression analysis, this time correlating them with the proportion of years using hormonal contraceptives (waves in which hormonal contraceptives were used divided by total number of waves participating in PAIRFAM). This correlation analysis will again be weighted by the inverse of the standard error of the individual treatment effect estimates. This analysis can potentially provide tentative evidence for assortment based on experiences with contraceptive methods.</p>	<p>Instead of (1) summarizing individual treatment effects across draws and then (2) correlating them with interindividual differences weighted by the inverse standard error of the individual treatment effect estimates (we call this approach “average across draws, then correlate”), we (1) correlated the individual treatment effects and interindividual differences at draw level and then (2) summarized the correlations across draws (we call this approach “correlate, then average across draws”; Ly et al. (2017) for example use the term “plausible values”).</p>	<p>We realized that our approach to estimate the correlations between individual treatment effects and other interindividual differences (including age, the Big Five personality dimensions, and the proportion of years using hormonal contraceptives) overestimated the shared variance between the two constructs.</p>	<p>This deviation addresses a methodological refinement to ensure a more accurate estimation of the correlations between individual treatment effects and interindividual differences. By switching to the “correlate, then average across draws” approach, we mitigate an overestimation of shared variance that was present in the originally planned method. Readers should interpret the reported correlations as more reliable and less biased, representing a refined understanding of the relationship between individual treatment effects and interindividual differences. For transparency, the results based on the originally registered approach (“average across draws, then correlate”) are reported in the supplement.</p>

Table S1 (continued)

Deviations from the in-principle accepted registered report stage 1, reasons for the deviations, and potential impact on the readers' interpretation

#	Mentioned in registered report stage 2	Details	Original wording in registered report stage 1 (Botzet et al., 2023)	Deviation description	Reason for deviation	Reader impact
4	<p><i>Methods – Deviations from Stage 1 Concerning the Analysis Sample</i></p> <p><i>Results – Average Treatment Effect – Robustness of Results</i></p>	<p>Type: Sample</p> <p>Reason: New knowledge</p> <p>Timing: After results known</p>	<p>We plan to exclude individuals who did not identify as female. Furthermore, once a woman crossed the age of 50 or reported to be (post-)menopausal, her data (including subsequent waves) will be excluded, but previous waves of data collection will remain in the analysis. In addition, we plan to exclude all individual waves of data in which participants indicated being in a homosexual relationship or only reported homosexual relationships in the past, were pregnant, trying to become pregnant, gave birth to a child in the last year, were currently breastfeeding, or indicated using the morning-after-pill or an unknown contraceptive method.</p> <p>In further separate robustness analyses we plan to additionally exclude waves in which participants indicated that they are sterilized, as well as all subsequent waves of those participants. We will also exclude all waves in which participants indicated that their partner is sterilized and all waves in which women indicated using no contraceptive method, an intrauterine device as a contraceptive method, or hormonal methods other than the oral contraceptive pill. In addition, we will exclude all waves in which women indicated that they had never been sexually active.</p>	<p>In contrast to our registered analysis plan, we decided to report the results from robustness analysis 6 (additional exclusion of women who had never been sexually active) as our <i>main analysis</i>. All results based on the original sample for the <i>originally registered main analysis</i> are additionally presented in the supplement.</p>	<p>We did so because we realized that including women who had never been sexually active likely induces bias. This particularly applies to the IPTW approach and less so to the adjusted regression analysis, with the overall consequence that including these women makes results more dependent on modeling choices (i.e., means of covariate adjustment) that should not make a substantive difference.</p>	<p>Reporting the results of robustness analysis 6 (excluding women who had never been sexually active) as the main analysis ensures that the results are less affected by potential biases introduced by including these individuals, particularly in the IPTW approach. This shift increases the trustworthiness of the results by reducing the dependence on modeling choices for covariate adjustment. The results of the originally registered main analysis are still available in the supplement, providing transparency and allowing readers to compare results across different samples. However, readers should consider the reported main analysis to be a more accurate reflection of the study's objectives and hypotheses.</p>

Once this has been actioned (or a very strong justification for not, if you disagree), I will be very happy to provide a recommendation for this important and impactful work.

Many thanks,

Tom