Oral Contraceptive Use Among Female University Students: A longitudinal Analysis of Depression, Anxiety, Stress, and Discontinuation Bias

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Research Master Thesis *Clinical and Health Psychology*

Abstract

Oral contraceptives (OC), although widely prescribed, have not been well-researched in terms of their potential effects on mental health. Some studies frequently link oral contraceptives with symptoms of depressive disorders, while others find no link. This longitudinal study, using Ecological Momentary Assessment (EMA), examined the link between oral contraceptives and depression, anxiety, and stress, as well as potential reasons to stop oral contraceptives. There appeared to be no evidence of oral contraceptives and negative effects on mental health. In addition to that, it was observed that women who discontinued OCs do not systematically differ in mental health symptoms from those who continued. The study's limitations include the utilization of self-reported data, the exclusion of vulnerable individuals, the lack of differentiation between OC types, and unmeasured confounders like age at first use and hormonal dosage. Future research should investigate OC subtypes and incorporate biological markers, as well as include potentially more vulnerable younger samples. In terms of contraceptive choice, this research showed the importance of exploring interactions between psychological, biological, and social factors influencing contraceptive choices.

Layman Abstract

Many women wonder whether taking the pill could influence their mood or mental health. Past studies have shown mixed results. Some studies say taking the pill might increase the risk of depression, stress, or anxiety, while others find no effect. This study investigated female university students over time to see if taking the pill was connected to more symptoms of depression, anxiety, or stress compared to women who don’t take the pill. The results showed no clear link between taking the pill and mental health problems. This study also looked at whether women who stopped taking the pill felt worse mentally and found no evidence for that either. These findings suggest that for most healthy young women, taking the pill may not have a noticeable impact on their mental well-being. However, the study mostly included healthy students and didn't look at different types of pills or hormone levels. Therefore, more research is needed to understand how the different pill types might affect younger or more vulnerable women.

Introduction

Oral contraceptives (OC) have been around for more than 60 years and are widely prescribed. The United Nations (2019) estimates that 151 million women use OCs worldwide. Progesterone or a combination of progesterone and estrogen are the hormones that make the OC effective (Gorenoi et al., 2007). Although the effects of progesterone and estrogen on brain structure are well-established, their impact on mental health remained largely unexplored for a long time (Pletzer & Kerschbaum, 2014). More recent research has shown inconsistent results regarding the impact of OCs on mental health, with some studies finding no significant association, whereas others report increased risks of depression and other mood disorders (Kraft et al., 2024; Skovlund et al., 2016) or positive effects on mood (Lundin et al., 2017). These conflicting findings underscore the need for more nuanced and comprehensive research on the mental health effects of OCs (De Wit et al., 2020).

Oral Contraceptives: HPA Axis and Mental Health

Several researchers have theorized that adverse effects of OC on mental health could work through alterations of the HPA axis (Hertel et al., 2017; Pletzer & Kerschbaum, 2014). The HPA axis consists of complex feedback loops between the hypothalamus, the pituitary, and the adrenal gland. This axis regulates the body's stress response, immunity, and fertility through negative and positive feedback loops (Joseph & Whirledge, 2017). OCs adjust the body's natural cortisol rhythms and responses. Some researchers suggest that OC use could change hypothalamic-pituitary-adrenal (HPA) functioning similarly to chronic psychological stressors (Hertel et al., 2017). Research has demonstrated that women on these contraceptives experience a more muted cortisol reaction to stress, hinting at the dampening effect these synthetic hormones may have on the HPA axis's sensitivity to stress (Høgsted et al., 2021). In addition, it was found that women on hormonal contraception have a smaller hippocampal volume than non-users (Hertel et al., 2017). Further evidence for an altered stress response comes from a study by Mengelkoch et al. (2024), who found

that OC users have a heightened response to a subjective stressor. In contrast, a similar study found this to be only significant among women who had initiated OC use during puberty (Sharma et al., 2020). Therefore, considering age at first use as an important factor to consider when looking at the relationship between mental health and OC use since the initiation of OC use during puberty could potentially put individuals more at risk for adverse effects.

Depression and Oral Contraceptives

Observational studies often find an association between OCs and depression (Skovlund et al. 2016), increased risk of suicide (Pérez-López et al., 2020), and poor sleep quality (Bezerra et al., 2020). Recent evidence shows that there could be specific factors that increase the vulnerability to negative influences of hormonal contraception on mental health such as starting OC at a young age, a history of premenstrual syndrome, or mood-affective disorders (Fruzzetti & Fidecicchi, 2020; Pérez-López et al., 2020; Skovlund et al., 2016).

On the other hand, evidence from randomized controlled trials and meta-analyses shows no relationship between depression and OC use (De Wit et al., 2020; Kraft et al., 2024). However, it has been proposed that the exclusion criteria for randomized controlled trials exclude individuals who might be most likely to experience negative effects from hormonal contraception on their mental health (De Wit et al., 2020; Kraft et al., 2024). When exploring the relationship between depression and OC use, the age at first use is often an important consideration that is not sufficiently addressed, since young women are not included in randomized controlled trials (RCTs) (Kraft et al., 2024). This may be one of the reasons that RCTs frequently report no effect of hormonal contraception on mental health (Kraft et al., 2024). Women with a history of mental illness are also excluded from RCTS (De Wit et al., 2020; Kraft et al., 2024). In addition, most randomized controlled trials compare a combined oral contraceptive with another version of a combined oral contraceptive (Kraft et al., 2024).

To conclude, there is a notable heterogeneity in the literature investigating the relationship of OC use and mental health, with observational studies more likely to find a significant relationship

than randomized controlled trials (De Wit et al., 2020; Kraft et al., 2024). This heterogeneity is potentially related to unaccounted confounders in observational designs or strict exclusion criteria of RCTs that may exclude the most vulnerable populations. Depression is one of the most researched mood disorders, with regard to its relationship with OC use. This stands in stark contrast with the amount of literature available for anxiety disorders.

Anxiety and OCs

To this date, no RCTs investigated the relationship between anxiety and oral contraceptives (Jahanfar et al., 2024) and most observational designs only researched one type of OCs (Standeven et al., 2020). A recent meta-analysis by Kraft et al. (2024) found four studies that investigate the relationship of oral contraceptives with anxiety disorders. Two of those four studies reported no effect (Cinar et al., 2012; Rapkin et al., 2006). One study found that among healthy women anxiety symptoms decreased after 3 months of OC intake (Paoletti et al., 2004). While the fourth study found that there was a significantly lower risk of panic disorder among women on OC compared to women not using OC (Cheslack-Postava et al., 2015).

Current study

This longitudinal study aimed to compare the mental health of female students using oral contraceptives with naturally cycling women. To make this comparison, this study investigated differences between non-OC users and OC users. First, most research on the topic utilized a cross-sectional research design (Wit et al., 2021; Kraft et al., 2023). One of the main obstacles with such a design is the missing insight into the temporal changes of symptoms and OC use. Therefore, this study added valuable information to the literature since it offered data over an extended period. Second, mental health history was an important confounder to consider in the final analysis (Wit et al., 2021). To do so, this study was guided by the following research question: *How do symptoms of generalized anxiety disorder (GAD), major depressive disorder (MDD), non-suicidal self-injury (NSSI) behaviors, and subjective stress levels change over a three-month period in female university*

students using oral contraceptives compared to naturally cycling students, controlling for age and mental health history?

Hypothesis 1 (H1): It is hypothesized that over three months, female university students using oral contraceptives will exhibit greater increases in generalized anxiety disorder (GAD) symptoms, major depressive disorder (MDD) symptoms, non-suicidal self-injury (NSSI) behaviors, and subjective stress levels compared to their naturally cycling counterparts, even when controlling for age and mental health history.

This study was able to provide valuable insights into factors that could be associated with a change in contraceptive methods. The healthy user bias, where individuals experiencing negative effects are more likely to stop using the contraceptives has been theorized to skew the samples towards users experiencing more positive or neutral effects (Johannson et al., 2023). Therefore, the second research question of this study was:

How do symptoms of generalized anxiety disorder (GAD) and major depressive disorder (MDD) differ between female university students who continue using oral contraceptives and those who discontinue their use over two years, considering the healthy user bias and controlling for age and mental health history?

Hypothesis 2 (H2): It is hypothesized that over two years, female university students using oral contraceptives, who do not discontinue use, will exhibit fewer symptoms of generalized anxiety disorder (GAD) and major depressive disorder (MDD) compared to those who discontinue.

Finally, this research was a small step toward providing knowledge to clinicians on risk factors that could predict a potential negative effect of hormonal contraception, which is not yet possible (Robakis et al., 2019).

Methods

Design

The WARN-D study employed a longitudinal, multicohort design, tracking around 2000 students from various educational institutions in the Netherlands. The study aimed to follow each of

the four cohorts of 500 people over approximately two years and was divided into three different stages. Each cohort underwent a baseline assessment (Stage 1), followed by an 8-week-long Ecological Momentary Assessment (EMA, Stage 2). Once the EMA period was over, there was a 2-year period during which the participants received follow-up questionnaires (Stage 3). The choice of a longitudinal design enabled the study to capture the dynamic nature of mood and depression, providing a rich dataset for developing a personalized early warning system for depression.

Procedure

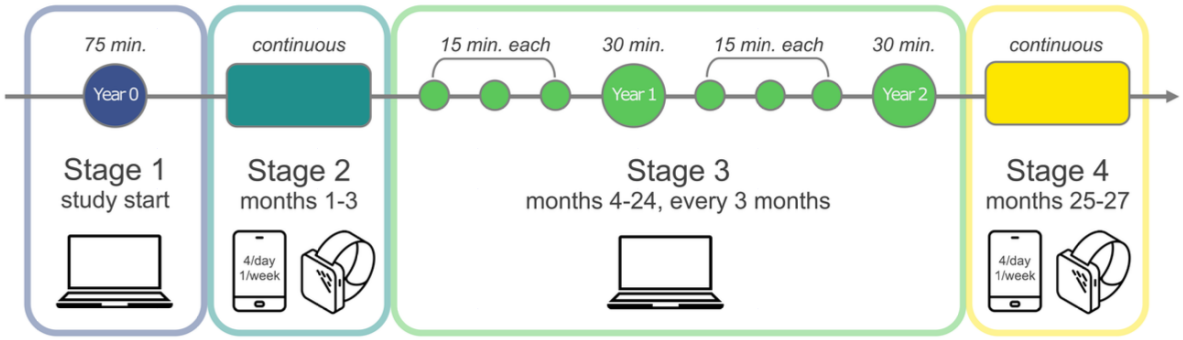
The three stages of the WARN-D study gathered different kinds of data (see Figure 1). In Stage 1, participants underwent a comprehensive baseline assessment through an online survey to collect a broad set of potential predictors for depression. Participants complete a detailed 75-minute online survey that encompasses various domains, including demographics, physical health, mental health, substance use, well-being, social factors, traits, tendencies, resilience, and more. The covariates, mental health history, and age, used for H1 and H2 were recorded during the baseline assessment.

Stage 2 involved a 3-month period of daily monitoring using smartwatches and a smartphone app to capture detailed data on participants' daily experiences and behaviors. During this period, the participants received notifications on their phones to answer small surveys every morning, during the day, and in the evening. Once a week the participants received slightly longer surveys. Those weekly surveys were used to test H1. The dependent variables MDD symptoms, GAD symptoms, Stress ratings, and NSSI were measured in those weekly surveys during stage 2. The daily measures as well as the physiological data from the smartwatches were not used for this study.

Lastly, during Stage 3, participants were followed for 21 months with online surveys in 3-month intervals to assess changes in mental health. This data was used to test H2 MDD symptoms, GAD symptoms as well as information on contraceptive use from the baseline assessment and EMA phase. More detailed information on additional variables gathered in each stage can be found in Fried et al. (2023). The data of Stage 4 (see Figure 1) was not used at all in the current study.

Figure 1

Study set-up for the different stages of the WARN-D project



Note. Overview of Design and Procedure of the WARN-D Study. From "Building an Early Warning System for Depression: Rationale, Objectives, and Methods of the WARN-D Study" Fried et al., 2023. Attribution of images: laptop, phone, and smartwatch by Mello, Rabi'ah Al Adawiyyah, and Smashicons, respectively (Noun Project, CC BY 3.0).

The study has been approved by the Leiden University Research Ethics Committee (No. 2021-09-06-E.I.Fried-V2-3406) and the European Research Council.

Participants

The study targeted students living in the Netherlands, Germany and Belgium, aged 18 and above, fluent in Dutch or English, and enrolled in a university of science or applied science. Exclusion criteria consisted of current moderate to severe depression, mania, thought disorders, substance use disorder, current treatment for mental health issues, and suicidal ideation. Students who indicated that they would be stressed by viewing burned calories on the smartwatch were also excluded. More detailed information on the in- and exclusion criteria can be found in the protocol paper of the WARN-D project (Fried et al., 2023). The current project utilized the training set of the first two cohorts. Additional exclusion criteria for this study were being male, breastfeeding, being pregnant, and having other types of hormonal contraceptive methods other than oral contraceptives. In addition, we filtered out participants that had less than 30% compliance. The rate

of insufficient responses was not statistically different between OC users and naturally cycling participants (see Supplementary Materials). After filtering out participants who answered less than 30% of the weekly measurements during stage two (for hypothesis 1), the sample consisted of 368 females, with a mean age of 22.43 years. In this sample, 107 participants said that they use oral contraceptives, whereas 261 used no contraceptives, condoms, or a copper intrauterine device. The sample for H1 was largely comparable in terms age, Subjective Social Status (SSS) and mental health history (see Table 1). However, a Pearson's Chi-squared test revealed significant differences between OC users and naturally cycling participants with $x^2(2,375) = 123.74$, $p < .001$. Dutch participants were far more likely to take OC as opposed to other nationalities. This difference between OC and non-OC in nationality did not appear to impact our results significantly.

Table 1

Sample demographics

	No OC	OC	Total Sample H1	Total Sample H2
N	267	108	368	375
Mean Age	22.62	21.97	22.43	22.3
Nationality*	135 Dutch	72 Dutch	201 Dutch	207 Dutch
	132 Other	36 Other	167 Other	168 Other
SSS	7.17	6.85	6.95	6.95
Depressive Disorder	16.48 %	15.89 %	16.30 %	16.53 %
Anxiety Disorder	22.61 %	23.36 %	22.82 %	23.70 %
Other Disorder	21.46 %	21.50 %	21.47 %	21.90 %

Note. N = Sample Size.

* Chi-square test showed that the nationality significantly differed between the OC and non-OC groups ($p < .001$).

Measures

MDD symptoms

Depression severity was quantified using the Patient Health Questionnaire-9 (PHQ-9). The PHQ-9 is a well-validated instrument consisting of nine items, each scored from 0 (not at all) to 3 (nearly every day), based on the diagnostic criteria for depressive disorders. Participants provided self-reports of depressive symptoms experienced over the previous week for H1, which meant that the scale was administered weekly during the EMA phase of the study. For H2 the first data point from the weekly surveys was used together with the data from phase 3, where the participants reported the GAD-7 symptoms over the past 3 months for a 2-year period. The sum score of the PHQ-9, ranging from 0 to 27, was used to assess the overall severity of depressive symptoms. Higher scores indicate greater depression severity (Kroenke & Spitzer, 2002).

GAD symptoms

Anxiety symptoms were assessed using the Generalized Anxiety Disorder 7-item scale (GAD-7). The GAD-7 was again, like for the PHQ-9, for H1 administered weekly during the EMA period of the study, and every three months for H2 from stage 3. The GAD-7 is a reliable measure for screening and assessing generalized anxiety disorder. It consists of seven items, each rated on a scale from 0 (not at all) to 3 (nearly every day), with the total score ranging from 0 to 21. This sum score reflects the severity of anxiety symptoms, where higher scores suggest more severe anxiety symptoms (Spitzer et al., 2006).

Stress ratings

Stress rating was assessed by letting participants rate on a scale of 1 (not at all) – 7 (very much) how stressful the week was for them. The data was recorded weekly during the EMA phase of the study.

NSSI Behavior

The weekly NSSI behavior, as a ratio binary, was set to zero if the participants answered "No" to the following question: "This week, I did something to hurt myself on purpose without

wanting to die (e.g. cutting, hitting, burning myself).". If the answer to this question was yes, the participant scored 1.

Outcome Variables: OC use and OC discontinuation

OC use was recorded during the baseline assessment and operationalized as a binary variable where the participant was categorized either as an oral contraceptive user (0) or as naturally cycling (1). Participants were classified as naturally cycling if they indicated no contraceptive use, physical contraception, or using a copper intra-uterine device.

To determine, whether there was a healthy user bias, the discontinuation of OC was measured as a binary variable. Any change from an OC to another contraceptive method was coded as 1, whereas no change was recorded as 0. This was done for both the baseline survey, the weekly surveys, and the follow-up period.

Covariates

The mental health history was recorded in three binary variables. Those are the history of depressive disorder (yes/no), a history of anxiety disorder (yes/no), and other mental disorders yes/no. In addition, age was utilized as an interval variable. Finally, for all analyses cohort was added as a binary covariate. The information on the covariates was taken from the baseline assessment (stage 1).

Statistical Analysis

First, the independent and dependent variables were not imputed. Secondly, we fitted the models using a maximum model approach. Using this approach the most complex model was fitted first and then minimized to find the model that describes the data best. In this way, we avoided underfitting (Barr et al., 2013). Outliers were investigated using boxplots and Cook's distance as well as Leverage. They were not removed, but if they lead to a bad model fit they were winsorized at the 95th percentile. Each of the models included the following covariates: age, history of depressive disorder, history of anxiety disorder, and other history of mental disorder. As a precaution, in the

case of high multicollinearity among covariates measuring mental health history, we had planned to include only a single binary variable without distinguishing between a history of depressive and anxiety disorders. This adjustment was ultimately not necessary. The effectiveness of including OC discontinuation as a predictor was assessed through likelihood ratio tests (LRT) comparing models with and without this variable, with a significance level set at $p < .05$. Assumption checks ensured the validity of the model results, including assessments for normality of residuals using Q-Q plots and the Shapiro-Wilk test, homoscedasticity checks through residual vs. fitted value plots, independence checks via residual time series plots, and evaluations of the random effects structure by comparing models with different random components using LRT. The model fit was further validated by comparing Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) across different model specifications.

Statistical tests for Hypothesis 1 – Differences between OC and NC

The first hypothesis was tested using a single multilevel model with OC use as the dependent variable and predictors including GAD symptoms, PHQ depression scores, stress ratings, cohort, age, and mental health history (depression, anxiety, and other disorders). The model included random intercepts and slopes for stress, GAD, and PHQ scores to account for within-subject variability. As previously discussed, NSSI was planned as a predictor for H1. However, NSSI had to be dropped from the maximum model since the base rate of NSSI was extremely low in the sample.
Therefore, the final general form of the maximum model was specified as follows:

$$\text{logit}(P(Y_{ij} = 1)) = \beta_0 + \beta_1(PHQ_{ij}) + \beta_2(GAD_{ij}) + \beta_3(Stress_{ij}) + \beta_4(Cohort_i) + \beta_5(Age_i) + \beta_6(Depression_i) + \beta_7(Anxiety_i) + \beta_8(Other\ Disorders_i) + u_i + \varepsilon_{ij}$$

Statistical Tests for Hypothesis 2 – Healthy User Effect

To test the second hypothesis regarding changes in contraceptive use, two separate binary logistic mixed-effects models were constructed. For the first model, the dependent variable was Change to Oral Contraceptives, with no change in contraceptive use as the reference category.

For the second model, the dependent variable was Change to Non-Hormonal Methods, with no change in contraceptive use as the reference category.

Predictors for both models included anxiety symptoms (GAD), depression symptoms (PHQ), time, age, cohort, and mental health history (depression, anxiety, and other disorders). Random intercepts and slopes for anxiety (GAD) and depression (PHQ) symptoms were included at the participant level to account for within-subject variability over time.

Model 1: $\text{logit}(P(\text{Change to Oral Contraceptives}_{ij} = 1)) = \beta_0 + \beta_1(\text{PHQ}_{ij}) + \beta_2(\text{GAD}_{ij}) + \beta_3(\text{Time}_j) + \beta_4(\text{Age}_i) + \beta_5(\text{Cohort}_i) + \beta_6(\text{Depression}_i) + \beta_7(\text{Anxiety}_i) + \beta_8(\text{Other Disorders}_i) + u_i + \varepsilon_{ij}$

Model 2: $\text{logit}(P(\text{Change to Non-Hormonal Methods}_{ij} = 1)) = \beta_0 + \beta_1(\text{PHQ}_{ij}) + \beta_2(\text{GAD}_{ij}) + \beta_3(\text{Time}_j) + \beta_4(\text{Age}_i) + \beta_5(\text{Cohort}_i) + \beta_6(\text{Depression}_i) + \beta_7(\text{Anxiety}_i) + \beta_8(\text{Other Disorders}_i) + u_i + \varepsilon_{ij}$

Results

No Evidence for Differences in Depression, Anxiety, or Stress Between OC Users and Non-Users

In the analysis of the maximum model, the calculation of function derivatives was disabled to manage computational constraints. The multilevel logistic regression model did not show significant effects (see Table 2) for any of the predictors, including PHQ-9, GAD-7 and the stress rating (all $p > .05$). This suggests that these factors do not independently explain variability in OC use. None of the covariates included in the model – age, mental health history, and cohort – seemed to explain significant variability in contraceptive use. The variance (σ^2) and standard deviation (SD) were as follows: for the random intercept $\sigma^2 = 27.491$ (*SD* = 5.243); random slope for stress ratings, $\sigma^2 = 197.006$ (*SD* = 14.036); random slope for anxiety symptoms, $\sigma^2 = 9.549$ (*SD* = 3.090); and random slope for depressive symptoms, $\sigma^2 = 3.942$ (*SD* = 1.986). The correlations between random effects were high, with values ranging from -0.99 to 0.80. The conditional $R^2 = .999$ was very large, while the marginal $R^2 = .002$ was extremely small. Therefore, we can assume that most of the variance in the outcome category of OC use or no OC use is largely explained by individual differences over time. These results indicate that the majority of the variance in the model is attributable to the random effects, with a minimal contribution from the fixed effects. Alternative models with simplified

random effect structures were tested but did not perform significantly better than chance (see Supplementary Material).

Table 2

Model of Differences Between OC users and Naturally Cycling Women; Fixed Effects

Predictors	*Estimate*	*95% CI for Estimate*		*p-value*	*OR*
		Lower	*Upper*		
Intercept	1.06	-38.70	40.83	.98	1.89
PHQ-9[a]	-0.17	-1.30	0.95	.54	0.71
GAD-7[a]	0.16	-1.66	1.99	.82	1.21
Stress	1.70	-3.79	7.19	.39	13.12
Age	0.28	-1.48	2.04	.81	1.26
Cohort	0.75	-7.80	9.29	.89	1.91
Anxiety Disorders	0.42	-12.93	13.76	.92	2.04
Depressive Disorders	-0.19	-13.50	13.17	.96	0.69
Other Disorders	0.87	-12.06	13.79	.94	1.71

Note. Total N = 368. CI = confidence interval. OR = Odds Ratio.

a. Gad-7 and Phq-9 were grand mean centered.

The comparison between the null model (random intercept only) and the full model (see Table 2) was conducted using a likelihood ratio test as well as by looking at the AIC and BIC. The null model provided a better fit to the data, as indicated by lower *AIC* = 357.80 and BIC = 370.15 compared to the full model *AIC* = 402.13 and *BIC* = 519.42. The likelihood ratio test, in agreement with the AIC and BIC, revealed no significant improvement in model fit with the inclusion of

predictors, $\chi^2(17) = 0$, $p = 1$. These results suggest that we accept the null hypothesis that generalized anxiety symptoms, depressive symptoms and stress ratings don't improve the prediction of OC use beyond chance.

Healthy User Effect: No Strong Evidence That Mental Health Predicts OC Discontinuation

In testing the H2, the reference category was no change in contraceptive method versus a change to OCs or a Change to a non-hormonal method from OC use. The two logistic models that were used were coded to refrain from the calculation of derivatives to ensure model convergence. The first model which was tested against change to no OC model that tested the change to oral contraceptives showed no significant results (see Table 4) of the fixed effects (all $p > .05$).

Table 3

No change in OC versus Change to Oral Contraceptives; Fixed Effects

Predictors	*Estimate*	*95% CI for Estimate*		*p-value*	*OR*
		Lower	*Upper*		
Intercept	-2.75	-16.21	0.06	.69	0.06
PHQ-9[a]	0.02	-0.3	1.02	.92	1.02
GAD-7[a]	-0.05	-0.5	0.95	.84	0.95
Time	-0.12	-0.33	0.89	.23	0.89
Age	-0.21	-0.84	0.81	.50	0.81
Cohort	-0.66	-3.64	0.52	.66	0.52
Anxiety Disorders	-1.21	-1.21	0.3	.64	0.3
Depressive Disorders	0.75	-3.8	2.12	.75	2.12

Table 3 (continued)

Predictors	*Estimate*	*95% CI for Estimate*		*p-value*	*OR*
		Lower	*Upper*		
Other Disorders	0.12	0.12	1.13	.95	1.13

Note. Total N = 372. CI = confidence interval. OR = Odds Ratio.

a. Gad-7 and Phq-9 were grand mean-centered.

The variance of the random intercept was $\sigma^2 = 21.26$ (*SD* = 4.61), indicating substantial variability in the outcome across participants. Additionally, the variances of the random slopes were for the GAD-7 were $\sigma^2 = 1.61$ (*SD* = 1.27) and PHQ-9 $\sigma^2 = 0.68$ (*SD* = 0.82) for show some variability in depression and anxiety scores over time. Overall, this model performed better than the null-model (see Table 6) according to the AIC and the LRT with $x^2(13) = 28.502$, $p = .008$. However, the BIC still favored the null model, indicating that the added complexity of the model may not result in much better predictions of the outcome.

Table 4

LRT for Change to Oral Contraceptives

	AIC	*BIC*	*LL*	x^2	*DF*	*p-value*
Null-Model	503.74	515.13	- 249.87			
Change to OC	501.24	586.64	-235.62	28.502	13	.008

Note. *LL* = Log likelihood; *AIC* = Akaike Information Criterion; *BIC* = Bayesian Information Criterion; x^2 = Chi-square statistic; *DF* = degrees of freedom.

Finally, when looking at the maximum model, almost all fixed effects were insignificant as well ($p > .05$), with the exception for the GAD-7 $\beta_2 = 0.31$, $p = .01$ with OR = 0.73 (see table 5). This means that provided all other variables stay constant, for each unit increase in the GAD-7 score, the odds of switching to a non-hormonal contraceptive method decreased by approximately 27%.

Table 5

Model of No Change versus Change to Non-Hormonal Method; Fixed Effects

Predictors	*Estimate*	*95% CI for Estimate*		*p-value*	*OR*
		Lower	*Upper*		
Intercept	-4.63	-11.39	2.13	.18	0.01
PHQ-9[a]	-0.02	-0.23	0.19	.85	0.98
GAD-7[a]	0.31	-0.55	-0.08	.01*	0.73
Time	0.02	-0.15	0.19	.86	1.02
Age	-0.10	-0.41	0.2	.51	0.90
Cohort	-0.43	-2.01	1.14	.59	0.65
Anxiety Disorders	-0.30	-2.67	2.07	.80	0.74
Depressive Disorders	0.19	-2.48	2.86	.89	1.21
Other Disorders	0.30	-1.83	2.42	.78	1.34

Note. Total *N* = 375. *CI* = confidence interval. *OR* = Odds Ratio.

a. Gad-7 and Phq-9 were grand mean-centered.

*$p < .05$.

The model included random intercepts 15.89 (*SD* = 3.99) and random slopes for generalized anxiety symptoms $\sigma^2 = 0.07$ (*SD* = 0.27) and depressive symptoms $\sigma^2 = 0.23$ (*SD* = 0.49) grouped by participants. The whole model explained 86.60 % of the variance with $R^2 = .866$ between change to non-hormonal method and no change, with 6.4 % of this variance being $R^2 = .064$ accounted for by the fixed effects in this model. However, even though the GAD-7 was a significant term in the

maximum model, the model did not perform statistically significantly better than chance (see table 5).

Table 6

LRT for Change to Non-hormonal Method or No Contraception

	AIC	*BIC*	*LL*	x^2	*DF*	*p-value*
Null-Model	550.93	562.32	-273.46			
Non-hormonal Method	558.99	644.43	-264.49	17.943	13	0.1597

Note. *LL* = Log likelihood; *AIC* = Akaike Information Criterion; *BIC* = Bayesian Information Criterion; x^2 = Chi-square statistic; *DF* = degrees of freedom.

Considering the results of the LRT, BIC and AIC, we conclude that there was no evidence of healthy user bias in this sample.

Discussion

The present study investigated whether oral contraceptive (OC) use is associated with symptoms of generalized anxiety disorder (GAD), major depressive disorder (MDD), and subjective stress among female university students over a three-month period. Additionally, it examined whether a healthy user effect could be observed by predicting discontinuation of OCs. Results indicated no significant differences in MDD symptoms, GAD symptoms, or stress symptoms between OC users and naturally cycling female students. Similarly, the analysis did not support the presence of a healthy user effect, although generalized anxiety symptoms showed a small, non-significant predictive trend. These findings suggest that, within this sample of healthy young women, OC use was not associated with adverse mental health outcomes over the study period.

The findings are consistent with previous evidence from randomized controlled trials, which generally show no association between OC use and symptoms of depression or anxiety (de Wit et al., 2021; Kraft et al., 2024). In contrast, they diverge from evidence from observational studies, which

often report adverse associations between OC use and mood disorders (Jahanfar et al., 2024; Monterrosa-Castro et al., 2021; Pletzer & Kerschbaum, 2014; Skovlund et al., 2016). These associations may be exaggerated due to selection biases, for example if women who experience mood side effects are more likely to start OCs (de Wit et al., 2021; Johansson et al., 2023; Kraft et al., 2024). From a biological perspective, the absence of psychological effects in our data is somewhat unexpected, since OC use has been linked to alterations in cortisol responses (Hertel et al., 2017; Gervasio et al., 2022) and increased inflammatory markers (Masama et al., 2022). A possible explanation is that OCs can modulate physiological stress systems, such as cortisol reactivity or inflammation, without necessarily leading to subjective psychological distress. This may be especially true for healthy young women, who could be resilient to physiological changes at the level of experienced mood. Finally, regarding subjective stress ratings, this study adds novel evidence, as these variables have been underexplored in the literature.

Secondly, regarding the healthy user effect our findings are contrary to previous evidence by Johannson et al. (2023). One possible explanation is that the strict exclusion criteria. In the WARN-D project, students with current moderate to severe depression, mania, thought disorders, substance use disorder, current treatment for mental health issues, and suicidal ideation could have reduced variability in mental health symptoms, leaving little room for a healthy-user effect to emerge. It is also plausible that, within a student population, discontinuation decisions are driven more by practical, social, or relational considerations. For example, multiple studies report that, especially within the first year of OC use, if women discontinue it is often due to side effects (Hall et al., 2014; Littlejohn, 2012; Westhoff et al., 2007). In the case of this study, the side effects could have included physical effects such as headaches, weight changes, moodiness, and sexual dissatisfaction (Westhoff et al., 2007). Another potential reason to discontinue OC use is that some young women have difficulty adhering to the strict regimen of OCs (Hall et al., 2014). This suggests that potential physical side effects and practical reasons may have influenced OC discontinuation in this study. The small but non-significant predictive role of generalized anxiety suggests that mental health factors

may still contribute in some cases, but likely alongside a range of other influences. Taken together, these findings highlight the complexity of contraceptive decision-making and suggest that mental health symptoms alone are unlikely to be the primary driver of discontinuation in healthy young women.

Limitations

This study had several strengths, such as its longitudinal design, the focus on multiple psychological outcomes, and careful control for important confounders such as age and mental health history. Nonetheless, several limitations should be considered when interpreting the findings. First, information on hormonal dosage, menstrual cycle, type of OC formulation, and baseline hormone levels prior to initiation was not available. All of these biological variables potentially impact the effect of OCs on the psychological outcomes measured (Kowalczyk et al., 2024; Kraft et al., 2024; Lundin et al., 2017; Pletzer & Kerschbaum, 2014).

Second, the characteristics of the study sample constrain the generalizability of results. Participants were healthy female university students, and strict exclusion criteria removed individuals with moderate-to-severe depression, current mania, substance use disorders, or those undergoing mental health treatment (Fried et al., 2023). While these criteria ensured data quality and participant safety, they reduced variability in mental health status, limiting applicability to more clinically vulnerable populations or younger adolescents, who may experience different effects from OC use (De Wit et al., 2020).

Third, there were modeling and statistical limitations. Non-suicidal self-injury, could not be included due to low base rates and models showed high random variability, indicating substantial individual differences that may have overshadowed fixed effects. Psychological symptoms fluctuate over time in response to environmental factors, which may have reduced the stability of predictive relationships (Kroenke et al., 2010).

Taken together, these limitations suggest that while the current study provides valuable longitudinal insights, its findings should be interpreted with caution, particularly when generalizing to broader or more clinically diverse populations.

Implications

The lack of a significant association between OC use and negative mental health outcomes suggests that concerns about mental health OCs do not apply broadly to healthy young women. It may also indicate that previous findings of harm are overstated due to selection or unmeasured confounding in observational designs. This research is a good example of the complexity of the considerations that women have to consider when making decisions about oral contraceptives. Future research should differentiate between different types of OC and consider a range of factors that influence the decision-making process of OC discontinuation. In addition, they should distinguish between OC formulations and integrate biological markers, such as baseline hormones or cortisol levels, to better understand the effects of OC use. Besides more longitudinal studies that can look at the fluctuations of symptoms over time, there is a need for placebo-controlled RCTs as well as more research into younger OC users. For clinicians, these findings offer some reassurance: among a healthy young population, OC use does not appear to increase the risk of depression, anxiety, or stress over time. However, individual differences and vulnerable subgroups must still be taken into account. In practice, although this study did not find an effect of OC on mental health, doctors may still want to consider the potential effects, whether positive or negative, of oral contraceptives on patients' mental health.

Conclusion

In conclusion, the present study provides longitudinal evidence that OC use does not negatively affect depression, anxiety, or stress among healthy young women, nor does it support a healthy user effect. While these findings offer reassurance, they also highlight the importance of studying more diverse and vulnerable populations, as well as integrating biological and psychosocial

variables. Such work is essential to fully understand for whom, and under which conditions, OCs may impact mental health.

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