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Oral contraceptives, depressive and insomnia symptoms in adult women with and without depression

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ABSTRACT

Background: Worldwide, oral contraceptive (OC) use is a very common form of birth control, although it has been associated with symptoms of depression and insomnia. Insomnia is a risk factor for major depressive disorder (MDD) but may also be a symptom of the disorder. Despite the large number of women who use OC, it is yet unknown whether women with previous or current diagnosis of depression are more likely to experience more severe depressive and insomnia symptoms during concurrent OC use than women without diagnosis of depression.

Aim: This study examined associations between OC use and concurrent symptoms of depression (including atypical depression) and insomnia as well as between OC and prevalences of concurrent dysthymia and MDD. Participants were adult women with and without a history of MDD or dysthymia. We hypothesized that OC use is associated with concurrent increased severity of depressive symptoms and insomnia symptoms, as well as with an increased prevalence of concurrent diagnoses of dysthymia and MDD. We also hypothesized that a history of MDD or dysthymia moderates the relationship between OC use and depressive and insomnia symptoms.

Methods: Measurements from premenopausal adult women from the Netherlands Study of Depression and Anxiety (NESDA) were grouped, based on whether participants were using OC or naturally cycling (NC). OC use, timing and regularity of the menstrual cycle were assessed with a structured interview, self-reported symptoms of depression (including atypical depression), insomnia with validated questionnaires, and MDD and dysthymia with structured diagnostic interviews.

Results: We included a total of 1301 measurements in women who reported OC use and 1913 measurements in NC women (mean age 35.6, 49.8% and 28.9% of measurements in women with a previous depression or current depression, respectively). Linear mixed models showed that overall, OC use was neither associated with more severe depressive symptoms (including atypical depressive symptoms), nor with higher prevalence of diagnoses of MDD or dysthymia. However, by disentangling the amalgamated overall effect, within-person estimates indicated increased depressive symptoms and depressive disorder prevalence during OC use, whereas between-person estimated indicated lower depressive symptoms and prevalence of depressive disorders. OC use was consistently associated with more severe concurrent insomnia symptoms, in the overall estimates as well as in the within-person and between-person estimates. Presence of current or previous MDD or dysthymia did not moderate the associations between OC use and depressive or insomnia symptoms.

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Discussion: The study findings showed consistent associations between OC use and more severe insomnia symptoms, but no consistent associations between OC and depressive symptoms or diagnoses. Instead, post-hoc analyses showed that associations between OC and depression differed between within- and between person-estimates. This indicates that, although OC shows no associations on the overall level, some individuals might experience OC-associated mood symptoms. Our findings underscore the importance of accounting for individual differences in experiences during OC use. Furthermore, it raises new questions about mechanisms underlying associations between OC, depression and insomnia.

1. Introduction

Use of oral contraceptives (OC), commonly called "the pill", is a method of birth control used by many women. It is currently the most popular form of contraception in Europe, North America and Australia with user rates in reproductive aged women between 35% and 63% (UN. Population Division, 2019). OC works through administration of exogenous sex steroids, most commonly a combination of synthetic estradiol and progesterone (e.g. combined oral contraceptives), which suppress ovulation, thus preventing pregnancy and regulating the menstrual cycle. The potential deleterious effects of OC use have gained much attention. Among reported adverse mental health effects are depressive symptoms and, to a lesser extent, sleep problems (Bezerra et al., 2020; Hall et al., 2012). Although some women may experience negative mood symptoms while using OC (Skovlund et al., 2016), most women seem unaffected (Schaffir et al., 2016).

Studies on the association between OC use and depression have shown mixed results. Skovlund et al. (2016) report that first use of OC is associated with a higher risk for a first clinical diagnosis of depression, as well as with a higher risk of first use of an antidepressant. However, most prospective studies have not shown a significant worsening in depressive symptoms in women using OC (as reviewed by Schaffir et al. (2016), Worly et al. (2018)). There are indications that variables such as young age (De Wit et al., 2020; Skovlund et al., 2016), composition of OC (Skovlund et al., 2016), but also previous experience of mood deterioration during OC use (Engman et al., 2018; Gingnell et al., 2013), may modify the risk of experiencing depressive symptoms during OC use. However, it is not yet clear whether a history of depression makes women more vulnerable for possible negative effects of current OC use such as depressive symptoms or insomnia. This information is important to enable well-informed choices on OC use.

Up till now, few studies explored the relationship between OC use and adverse mood states in women with a previous or current depressive disorder. In a randomized controlled trial, women with previous or current psychiatric disorders (anxiety, depressive and eating disorders, $n = 59$) were more likely to report adverse mood during use of combined OCs compared to placebo, although only six women in this sample had a current depressive disorder (Bengtsdotter et al., 2018). Further studies showed that women with current OC-induced mood complaints were more likely to have comorbid mood disorders than women without OC-induced mood complaints in a cross-sectional comparison (Segebladh et al., 2009). Joffe et al. (2003) retrospectively found that presence of a previous depressive episode was a significant predictor of OC-associated mood deterioration and Hall et al. (2012) found that in young women (aged 13–24) depressed moods at start of OC use increased the likelihood of reporting OC-related moodiness. However, there are only a few prospective studies on OC that specifically assessed women with diagnoses of depression. This means that clinicians and OC users currently have very limited guidance on whether OC use could affect women with a history of depression diagnoses differently than they affect non-depressed women.

Insomnia is an important component of depression, both as a symptom as well as a risk factor (Baglioni et al., 2011; Fava, 2004; Paunio et al., 2015). Previous studies showed that OC use was associated with less deep sleep as revealed with EEG measurements, and a longer time to fall asleep (Burdick et al., 2002), more frequent insomnia complaints and more daytime sleepiness compared to no use of OC (Bezerra et al., 2020). On the other hand, OC use has also been associated with longer sleep durations compared to no use in sleep EEG assessments (Guida et al., 2020). The association between OC use and insomnia has not been examined at large.

Previous studies have also not assessed the association of OC use with specific subtypes of depression. Atypical depression, which is characterized by mood reactivity and can include increased appetite and/or weight gain, hypersomnia, leaden paralysis and interpersonal sensitivity, is more prevalent in women than in men (Lamers et al., 2010), suggesting a role for sex hormones. In addition, Halbreich and Kahn (2007) noted that symptoms of postpartum depression and premenstrual dysphoric disorder strongly overlap with symptoms of atypical depression. Following their conclusion, OC use might also be associated with symptoms of atypical depression, but this has not yet been studied.

Our study firstly aimed to investigate the association between self-reported OC use and depressive symptom severity (including atypical depressive symptoms) and insomnia symptom severity in adult women, as well as the association between OC use and concurrent diagnoses of major depressive disorder (MDD) and dysthymia. Secondly, we aimed to assess if a previous or current depression diagnosis moderates the association between OC use and depressive and insomnia symptom severity. We hypothesized that measurements during OC use would show a higher depressive and insomnia symptom severity and a higher prevalence of concurrent MDD and dysthymia than women not using OC. Furthermore, we hypothesized that the association between OC use and severity of symptoms of depression and insomnia would be stronger in women with a previous or current diagnosis of a depressive disorder compared to women without a diagnosis.

2. Methods

2.1. Participants

For this study we used data from the Netherlands Study on Depression and Anxiety (NESDA). NESDA is an ongoing longitudinal cohort study assessing the long-term course and consequences of MDD and anxiety disorders in the Netherlands. From 2003 until 2007, NESDA recruited 2981 adult participants from the community, via primary healthcare and outpatient mental healthcare providers. At recruitment, 78% of participants had (past or present) depressive and/or anxiety disorders, and 22% of participants were included as non-depressed controls. Exclusion criteria were having a primary clinical diagnosis of bipolar disorder, obsessive compulsive disorder, severe substance use disorder, psychotic disorder, or organic psychiatric disorder (all confirmed by Composite International Diagnostic Interview or CIDI) or being not sufficiently proficient in Dutch language. For more details on the NESDA study and details on recruitment and methods, see Penninx et al. (2021). All participants provided informed consent and the study was approved by the Medical Ethical Committee of the VUmc (reference number 2003/183) and other participating centers.

The NESDA study followed participants 2, 4, 6 and 9 years after the baseline measurement, meaning every participant could contribute up to 5 measurements to the full dataset. At every assessment, participants underwent a structured diagnostic interview for assessment of mental disorders and questionnaires on depressive symptoms, insomnia

symptoms, lifestyle and socioeconomic factors. This included self-report questions on the presence and duration of a menstrual cycle, possible pregnancy, menopause status and contraceptive use status.

2.2. Grouping measurements based on contraceptive status

The present study included premenopausal women who had participated at least once but up to five times in assessments between baseline and follow-up, as is visualized in Fig. 1A. To exclude postmenopausal women, observations in women aged 55 years or older (n = 2391) were excluded. Observations in women who had missing data on the question of contraceptive methods (n = 263), or who used hormonal contraceptives other than OC such as a hormonal intrauterine device (IUD; n = 373), a hormone implant (n = 23), vaginal ring (n = 57) or hormone injections (n = 34) or other hormonal methods (n = 18) were also excluded. Observations during use of hormone implants, vaginal rings and hormone injections were excluded due to low sample sizes, observations in hormonal IUDs were excluded due to unknown date of placement and subsequent unknown quantity of hormone release by the IUD. Observations in women who were pregnant at the time of the assessment (n = 195), who gave birth in the last year (n = 159) or were breastfeeding (n = 7) were also excluded from the analysis.

Women who continued OC for more than 90 days, meaning they skipped multiple placebo weeks or "stop weeks", were also excluded (n = 37), as well as naturally cycling women who reported abnormal menstrual cycle durations, defined as current or regular cycles were shorter than 21 days or longer than 35 days (Nederlandse Vereniging voor Obstetrie en Gynaecologie, 2004; n = 357). To assess possible selection biases that could stem from excluding women with abnormal cycle durations, an additional sensitivity analysis was conducted on the full sample, including the women with abnormal cycle durations (reported in Appendix, see Supplementary materials B). Additionally, observations were also excluded if participants were using other hormonal medications (World Health Organization Anatomical Therapeutic Chemical (ATC) code G03, n = 22) or using hormone antagonists (ATC code L02, n = 2) at the time.

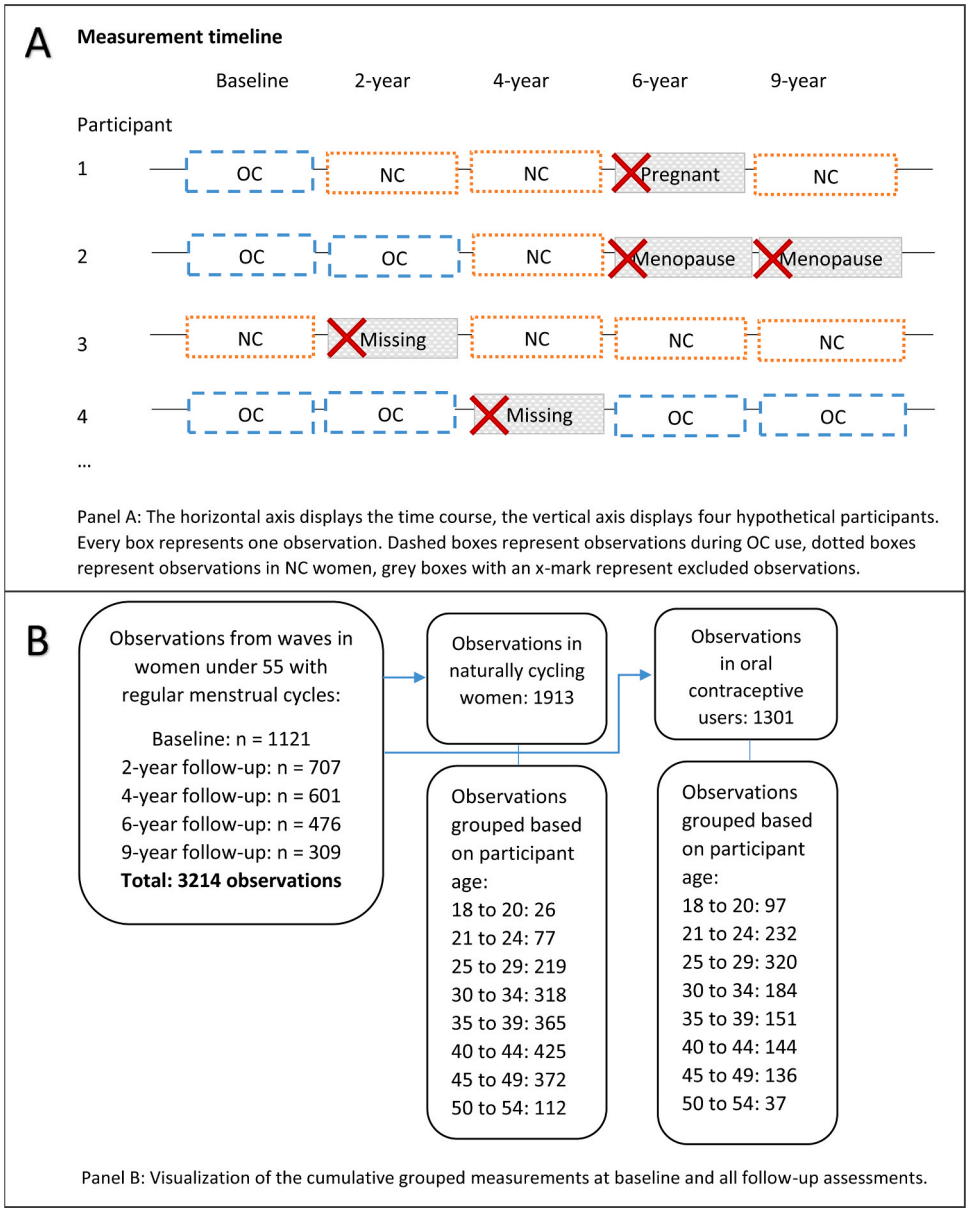

Fig. 1. Visualisation of how hypothetical participants can contribute multiple observations (panel A), and the amount of measurement observations per group (panel B). OC = oral contraceptive use, NC = naturally cycling.

The remaining observations were then grouped based on contraceptive status, into either observations during OC use (e.g. OC measurements) or observations during which participants were naturally cycling (NC measurements). Observations in women who did not use any hormonal contraceptives and reported a regular menstrual cycle were clustered in the NC observations (this included women who reported using a copper IUD or condoms for contraception), resulting in a total of 1913 observations. Observations in women who reported using OC at time of the measurement were clustered in the OC group, resulting in 1301 observations. This enabled a cross-sectional comparison of measurements based on contraceptive status (either during OC use or during non-OC use) within the longitudinal NESDA study setup. Fig. 1B shows the sample sizes of both contraceptive status groups and sample sizes over time, including the breakdown of group size. This process resulted in a total sample of 1205 women who contributed 3214 observations (mean number of observations per woman = 2.7).

2.3. Depressive disorders, and symptoms of depression and insomnia

To assess the presence of MDD or dysthymia (as defined by DSM-IV, American Psychiatric Association, 1994) the Composite International Diagnostic Interview (CIDI, version 2.1; Nelson, 1999) was used. This means that the knowledge on all current and previous diagnoses in this study was acquired using clinically validated methods. The CIDI was conducted at every assessment by trained research staff. Diagnoses of MDD and dysthymia within the last 6 months were used as an outcome measure for current depressive or dysthymic disorder.

To assess the severity of depressive symptoms, all participants filled out the well-validated Self Rated Inventory of Depressive Symptomatology (IDS-SR) at every assessment wave. The IDS-SR has excellent internal consistency (Cronbach's alpha = 0.94, Rush et al., 1996). The items in the IDS-SR are scaled on a Likert scale from 0 to 3 with 0 meaning the symptom is not present, and 3 meaning high symptom severity. The IDS-SR has 30 items, of which the scores of individual items can be summed to form a sum score that represents the depressive symptom severity. Sub-scores for atypical depression were calculated based on characteristics of atypical depression according to the DSM-IV by calculating the sum of item scores for hypersomnia (item 4), mood reactivity (item 8, reverse scored to represent absence of anhedonia), increased appetite (item 12), weight gain (item 14), leaden paralysis (item 29) and interpersonal sensitivity (item 30) from the IDS-SR, resulting in a sum score ranging from 0 to 18 (Novick et al., 2005).

To assess insomnia symptom severity, participants filled-out the Women's Health Insomnia Rating Scale (WHI-IRS) by Levine et al. (2003) at every assessment wave. The WHI-IRS consists of five items on a scale of 0–4, with a sum score ranging from 0 to 20. Items inquire about difficulty falling asleep, waking up during the night, early awakening, getting back to sleep after wakefulness and feeling rested after sleep. The WHI-IRS has an acceptable Cronbach's alpha of 0.78 (Levine et al., 2003).

2.4. Covariates

Sociodemographic variables in this study included age, highest education, country of birth, partner status and body mass index (BMI). Participants' level of education was defined as the highest number of years of education that the participant reported over the whole study duration. This was used instead of the number of years of education at each assessment because the number of years of education and participants' age were highly codependent, violating statistical assumptions. Since contraceptive choices in the Netherlands significantly differ between groups of different ethnicities (Marra et al., 2020), we adjusted for participants' birth country in the analyses. Birth country was grouped based on whether the participant was born in the Netherlands or outside the Netherlands. Partner status was reported at every assessment wave by asking about marriage and partner status (e.g., "Are you married or do you have a person you consider your long-term partner?"). Age, education level and birth country were incorporated into the multivariate adjusted model, partner status and BMI were included only if these differed between the OC and NC measurements, meaning they could be confounding effect estimates.

As an additional covariate, the course of participants' depression diagnoses (obtained through CIDI interviews) before and throughout the study was determined to categorize observations into three groups. Observations were categorized in either the never depressed control group, the remitted group or the depressed group. Observations in participants who had no MDD or dysthymia diagnoses in their lifetime were labeled as never depressed, observations in participants with a previous but no current diagnosis of MDD or dysthymia were labeled as remitted, observations in participants with a current (within the last 6 months) MDD or dysthymia diagnosis were labeled as depressed. This method of labeling meant that a participant who was recruited without a history of depression could contribute her first observations to the never depressed group, but if she were subsequently diagnosed with a depressive disorder she would contribute her next measurement to the depressed group-observations, and if she next would recover from the depressive disorder her next measurement would be grouped into the remitted group.

2.5. Statistical analyses

Statistical analyses were conducted using R (version 3.6.1; R Core Team, 2020). Demographic differences between the measurement groups were analyzed with Chi square tests for categorical variables and *t*-tests for continuous variables.

To analyze associations between OC use and symptoms of depression or insomnia, all outcomes were compared using (generalized) linear mixed models. Models were created using the 'lme4' package (Barr, 2013), and analyzed with ANOVA tests (type 3) from the 'car' package (Fox and Weisberg, 2020). Model estimates were estimated using the 'summary' function from the R package lmerTest (Kuznetsova et al., 2017) using an unstructured variance-covariance structure. In all models, a random intercept per participant was added to account for multiple measures within the same participants. This random intercept also enabled within-participant comparisons between OC and NC measurements in a subset of the measurements. Generalized linear (logistic) mixed models were used for analysis of categorical outcomes (e.g., diagnoses of MDD and dysthymia) and linear mixed models were used for the continuous variables (e.g. IDS scores, WHI-IRS scores, IDS atypical depression subscores).

2.5.1. Univariable model and multivariable model

First, outcomes were assessed using a univariable model that included only the contraceptive status (e.g., OC status or NC status at time of measurement) as fixed or independent variable and MDD or dysthymia diagnoses, depressive symptom scores (including atypical depressive symptoms) or insomnia symptom score as outcomes. Second, we used a multivariable model with adjustment for previously mentioned confounders to estimate differences between OC and NC measurements in all outcomes (e.g., MDD and dysthymia diagnoses, depressive symptoms, atypical depressive symptoms and insomnia symptoms).

2.5.2. Moderation analysis of depression status

To assess whether contraceptive status was associated with depressive symptoms (including atypical depressive symptoms) and insomnia symptoms in never depressed controls differently than in (previously) depressed participants, the psychiatric history was incorporated in two interaction terms (one for remitted depression and one for current depression). Participants' depression status (i.e., never, remitted or currently depressed) was then added through the addition of interaction terms with the OC use variable in the multivariable models.

2.5.3. Post hoc analyses

A post-hoc analysis was conducted to enable differentiation in within- and between-person estimates of OC use. Within- and between-person effects were assessed through the incorporation of two predictors for OC use instead of one: one predictor was OC use centered per participant (e.g. within cluster centering, with each participant representing one cluster of measurements), the other predictors was OC use but centered within the group mean, as recommended in Enders and Tofighi (2007) and Hamaker and Muthén (2019). These between- and within-person predictors were assessed for all main outcomes (diagnoses of depression and dysthymia, severity of depressive symptoms (including atypical symptoms of depression), and insomnia symptoms in the multivariate models which included adjustments for age, highest education and birth country.

Furthermore, in post-hoc analysis, individual sleep-related items from the IDS-SR and the WHI-IRS were analyzed per item to explore whether specific sleep complaints (e.g., trouble falling asleep, waking up during the night) were associated with contraceptive status. Results for this analysis are provided in Supplementary materials A, see Appendix.

3. Results

3.1. Demographics

We analyzed data from 1205 participants who contributed to 3214 observations. Of these observations, 1301 (40.5%) reported current OC use and 1913 (59.5%) reported they were naturally cycling at the time of measurement (see Fig. 1B). A total of 612 women contributed only to NC measurements (a total of 1467 measurements), 327 women contributed only to OC measurements (a total of 803 measurements), and 266 women contributed both to OC and NC measurements (a total of 944 measurements).

Participants were on average 35.6 (SD 9.0) years old, had received 13.5 years of education (SD 3.2), and 91.4% were born in the Netherlands. OC use was significantly associated with younger age compared to NC measurements, and measurements in OC users were more likely to be in participants born in the Netherlands, but level of education, partner status, or BMI did not differ between OC measurements and NC measurements. Means and percentages of sociodemographic variables are displayed in Table 1.

3.2. Current oral contraceptive status and depression

We observed a statistically significant difference in the IDS-SR scores between OC and NC measurements of 0.90 points (95%-CI = (0.00, 1.80); p = 0.049; Table 2), although this difference was small in terms of effect size (Cohen's $d = 0.07$) due to large differences within the groups, resulting in a high SD. This difference in IDS-SR scores was no longer significant after adjustment for the demographic covariates (B = 0.10, 95%-CI = (−0.80, 1.00), p = 0.83; Table 2). OC use was not associated with higher atypical depressive sub-scores in both the unadjusted and adjusted model.

Furthermore, measurements during OC use did not show a significantly different prevalence of MDD diagnoses in comparison to the NC measurements in the adjusted model (Odds Ratio (OR) = 0.99, 95%-CI = (0.77, 1.27), p = 0.93; Table 2). Prevalence of dysthymia diagnoses also did not differ significantly between OC and NC measurements (adjusted model: OR = 0.65, 95%-CI = (0.32, 1.27), p = 0.21; Table 2). The full model results are displayed in Table 2, and scores and estimates per depression group are visualized in Fig. 2.

3.3. Current oral contraceptive status and insomnia

We observed a higher WHI-IRS score during OC use in the unadjusted model, although this difference was not significant. The adjusted model, which included adjustments for age, country of birth and education resulted in a significant difference between OC and NC measurements of 0.54 points (B = 0.54, 95%-CI = (0.17, 0.91), p = 0.004; Table 2). The Cohen's d effect size of the difference in WHI-IRS score was 0.12, meaning the effect size for the association between OC use and insomnia symptoms is small (Cohen, 1998). The results are summarized in Table 2, and the scores per depression group are displayed in Fig. 2.

3.4. Moderation through history of depressive disorder

To assess whether vulnerability for depressive disorder (MDD and/or dysthymia) moderates the relationship between OC status and severity of depressive symptoms or insomnia symptoms, an analysis was conducted which incorporated depression group in interaction with OC status. There was no significant interaction effect of OC status X remitted depression on IDS scores (B = −0.005, 95%-CI = (−1.89, 1.78), p = 0.96), nor on atypical depression scores (B = −0.40, 95%-CI = (−1.20, 0.40), p = 0.32) or WHI-IRS scores (B = −0.34, 95%-CI = (−1.17, 0.48), p = 0.41). Similarly, no significant interaction effect of OC status X current depression was found on IDS scores (B = −0.59, 95%-CI = (−2.52, 1.34), p = 0.55), atypical depression scores (B = −0.22, 95%-CI = (−1.07, 0.63), p = 0.61) or WHI-IRS scores (B = −0.54, 95%-CI = (−1.42, 0.34), p = 0.23).

3.5. Post-hoc analysis

3.5.1. Post-hoc within- and between-participant results

The models with separate predictors for within- and between subject estimates for the IDS-SR scores, the atypical depression IDS subscores and the MDD prevalence had a better model fit (p < 0.001; ΔAIC = 19; 6 and 12, respectively) than the previous adjusted models of the main analysis. This analysis showed a disparity between the within- and between subject estimates. As displayed in Table 2, depressive symptoms (B = 1.43, 95%-CI = (0.37, 2.50), p = 0.0009), symptoms of atypical depression (B = 0.45, 95%-CI = (−0.03, 0.92), p = 0.07), as well as MDD diagnoses (OR = 1.70, 95%-CI = (1.16, 2.49), p = 0.0006) were estimated higher in OC measurements when assessing within-subject estimates. However, between-subject estimates indicated lower depression symptoms (B = −2.97, 95%-CI = (−4.57, −1.38),

Table 1
Description of the sociodemographic variables across measurements.

Contraceptive status during measurement		Naturally cycling	Oral contraceptive use	p-value
# of observations		1913	1301	–
Age in years (mean, SD)		38.1 (8.0)	31.9 (9.1)	<0.001
Highest education in years (mean, SD)		13.5 (3.2)	13.4 (3.2)	0.48
BMI in kg/m^2 (mean, SD)		25.1 (5.2)	24.7 (5.2)	0.054
Born in the Netherlands (n, %)		1703 (89.0)	1234 (94.8)	<0.001
Has a partner (n, %)		1376 (71.9)	942 (72.8)	0.62
Depression status (n, %)	No MDD or dysthymia	433 (22.6)	268 (20.6)	0.22
	Remitted from MDD or dysthymia	920 (48.1)	664 (51.0)	
	Current MDD or dysthymia	560 (29.3)	369 (28.4)	

BMI = Body Mass Index, SD = standard deviation. p-values obtained from independent samples *t*-test or from chi-square test for cross-tabulation.

Table 2
Association of oral contraceptive status with depression diagnoses and symptoms analyzed using linear mixed models.

	Contraceptive status during measurement		Estimated unadjusted difference, (OC vs. NC measurements)		Estimated adjusted difference, (OC vs. NC measurements)		Estimated adjusted difference (OC vs. NC measurements), within-and between-person estimates		
	Naturally cycling (n = 1913)	Oral contraceptive use (n = 1301)	B or OR, 95%-CI	p-value	B or OR, 95%-CI	p-value	Estimate	B or OR, 95%-CI	p-value
Depressive symptoms									
IDS score (mean, SD)	17.6 (12.9)	16.8 (12.4)	B = 0.90 (0.00, 1.80)	0.049	B = 0.10 (−0.80, 1.00)	0.83	Between-person[a]	B = −2.97 (−4.57, −1.38)	0.0003
							Within-person[a]	B = 1.43 (0.37, 2.50)	0.009
Atypical IDS subscore (mean, SD)	5.1 (4.3)	4.9 (4.2)	B = 0.03 (−0.30, 0.37)	0.86	B = −0.05 (−0.40, 0.29)	0.75	Between-person[a]	B = −0.53 (−1.04, −0.04)	0.03
							Within-person[a]	B = 0.45 (−0.03, 0.92)	0.07
Depression diagnoses									
MDD in the last 6 months (n, %)	523 (27.3)	355 (27.3)	OR = 1.10 (0.87, 1.39)	0.40	OR = 0.99 (0.77, 1.27)	0.93	Between-person[a]	OR = 0.66 (0.47, 0.92)	0.014
							Within-person[a]	OR = 1.70 (1.16, 2.49)	0.006
Dysthymia in the last 6 months (n, %)	80 (6.1)	158 (8.3)	OR = 0.76 (0.39, 1.46)	0.42	OR = 0.65 (0.32, 1.27)	0.21	Between-person	OR = 0.43 (0.13, 1.30)	0.15
							Within-person	OR = 0.81 (0.35, 1.94)	0.63
Insomnia									
WHI-IRS (mean, SD)	6.8 (4.7)	7.0 (4.7)	B = 0.29 (−0.06, 0.65)	0.11	B = 0.54 (0.17, 0.91)	0.004	Between-person	0.51 (−0.07, 1.10)	0.09
							Within-person	0.56 (0.1, 1.02)	0.02

OC = oral contraceptives, NC = naturally cycling, MDD = major depressive disorder, IDS = Inventory of Depressive Symptoms, WHI-IRS = Women's Health Inventory Insomnia Rating Scale. OR = odds ratio, B = unstandardized estimate, CI = confidence interval, SD = standard deviation. The adjusted model contains adjustment for age, education level and country of birth.

[a] =Model which includes between- and within-person estimates was significantly better than the model that estimated the general estimate as described in the text.

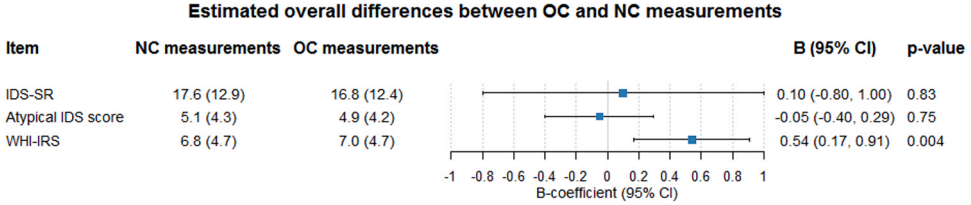

Fig. 2. Visualization of mean scores and adjusted estimations and 95% confidence intervals of the IDS score, IDS atypical depression symptom score and WHI-IRS score from the adjusted model in Table 2. The estimate is adjusted for age, education level and birth country. OC = oral contraceptives, NC = naturally cycling, IDS-SR = Self-Reported Inventory of Depressive Symptoms, WHI-IRS = Women's Health Initiative Insomnia Rating Scale, SE = Standard Error.

$p < 0.0001$), lower symptom scores for atypical depression (B = −0.53, 95%-CI = (−1.04, −0.04), p = 0.03) and lower prevalence of MDD diagnoses (OR = 0.66, 95%-CI = (0.47, 0.92), p = 0.014) in OC measurements compared to NC measurements. The models with separate predictors for within- and between-person estimates for dysthymia as well as for insomnia severity did not show a better model fit (ΔAIC = +2 and ΔAIC = +2, respectively), and estimates for dysthymia still showed no indications of associations between OC use and dysthymia prevalence. The insomnia scores were still estimated somewhat higher, both in between-participant estimates (B = 0.51, 95%-CI = (−0.07, 1.10), p = 0.09) as well as within-participant estimates (B = 0.56, 95%-CI = (0.1, 1.02), p = 0.02).

3.5.2. *Insomnia per-item analysis*

Multivariable models, conducted for the sleep-specific items from the IDS-SR (items 1, 2, 3 and 4) and all WHI-IRS items showed that specifically WHI-IRS items 2 (waking up during the night) and 3 (waking earlier than planned) were higher during OC use compared to NC measurements (B = 0.28, 95%-CI = (0.16, 0.39), $p < 0.001$ and B = 0.19, 95%-CI = (0.08, 0.31), p = 0.001, respectively). See Supplementary materials A in Appendix for the full model results for all sleep-specific IDS-SR items and WHI-IRS items.

4. Discussion

This study examined associations between current OC use and depressive disorders, severity of depressive symptoms, and insomnia symptoms in a large cohort of adult women, of whom the diagnoses and symptoms of depression were well phenotyped over the course of 9 years. Our first findings showed no indications that self-reported OC status was associated with more severe depressive symptoms (including symptoms of atypical depression), nor with higher prevalence of MDD or dysthymia. Moreover, having a previous or current diagnosis of MDD or dysthymia did not moderate the associations between OC use and insomnia or depressive symptoms. Although our overall results on OC and depression did not confirm our hypotheses, which were that OC use

would be associated with more severe depressive symptoms and higher prevalence of depressive disorders, the results from the post-hoc analysis indicated that our original lack of accounting for the within- and between-participant measurements might have obscured underlying associations between OC and depression outcomes, because the between- and within-person estimates showed opposite directions. Furthermore, insomnia symptoms were consistently found to be more severe during OC use, both in the overall analysis as well as in the between- and within person estimates, although the effect size was small.

To understand our contradictory results from between- and within-subject estimates, it is important to realize that in our study setup, OC use was not randomized or assigned, which means OC use during the study purely relied on participant's own contraceptive use choice. The choice to use or not use OC can depend on medical history or comorbidities, as seen in for example, medical advice to not use OC in women with history of thrombosis, or to use OC in women with polycystic ovary syndrome or endometriosis, as well as on personal experiences using OC: women who had adverse experiences using OC were found to be less likely to continue OC use (Westhoff et al., 2007). This implies the distribution of OC use across the participants was most likely not random. Following this reasoning, it would mean that measurements in women in our study who experience less adverse mood during OC use could be overrepresented in the OC measurements, whereas measurements in women who do experience more adverse mood effects could be overrepresented in either NC measurements or in the group of measurements in women who "switched" OC use during the study (e.g. the group of participants who contributed most to the within-subject estimates). This form of selection bias, specifically the idea that women who experience adverse effects during OC use are less likely to be present in long-term users of OC, has previously been deemed the "healthy survivor effect" (Zettermark et al., 2018).

Based on this idea of the "healthy survivor effect", our findings do seem to follow a pattern that was previously found in the literature: studies which compared population-based groups of OC users with groups of non-users found OC to be associated lower depression prevalence (as seen in Toffol et al. (2011), Keyes et al. (2013)), whereas studies that have prospectively assessed OC use over time have found adverse effects of OC on depression diagnoses and symptoms (Skovlund et al., 2016)). Within the context of this previous work, our findings accentuate some important points. First, it could be that OC negatively affects depression symptoms in some women, who might then discontinue their OC use, while other women remain unaffected. Previous work has already highlighted possible mechanisms involving progesterone and GABA receptors, in which there are strong individual differences in sensitivity to sex hormone-associated mood symptoms (Schweizer-Schubert et al., 2021) Secondly, this highlights the importance of within-person comparisons in the field of sex hormones and mood. This point has been raised before in menstrual cycle research (Schmalenberger et al., 2020) and our findings highlight the relevance of accounting for within- and between-participant comparisons.

The finding that severity of depressive symptoms were equally present in OC measurements in women with or without previous or current diagnosis of MDD or dysthymia, is not line with previous studies on mood disorders and depressive symptoms during OC use, which showed that women with previous or current mood disorders were more likely to report adverse mood during OC use (Hall et al., 2012; Joffe et al., 2003; Bengtsdotter et al., 2018). However, one should keep in mind that we found different within- and between-person estimates for the association between OC use and severity of depressive symptoms, and it is yet unclear to what extent a role history of depression might have influenced these effects.

Interestingly, we found an association between OC use and concurrent severity of insomnia symptoms, both in the overall estimates as well as in the within- and between-person estimates. Although severity of insomnia symptoms are generally higher in previously or currently depressed participants (Prather et al., 2015), psychiatric history did not significantly moderate the association between OC and insomnia scores, indicating that the OC-insomnia association is not dependent on history of a diagnosis of MDD or dysthymia. Our post hoc analyses indicate that OC use might be specifically associated with waking up multiple times during the night and earlier awakening. This suggests that differences in insomnia symptom severity during OC use (compared to non-use) could be more related to the area of maintaining sleep than initiating sleep. Our findings are in line with the study by Bezerra et al. (2020), who found that OC users report worse sleep quality than non-users. Also other studies found possible effects of OC on sleep, showing that OC users have less slow wave sleep (Burdick et al., 2002), have higher melatonin secretion and higher nocturnal body temperatures (Baker and Driver, 2007). However, the association between OC and sleep disruptions could also be caused or mediated by lifestyle factors, such as working hours, caffeine or alcohol consumption, or presence of small children (Wilsmore et al., 2013). Although the effect size of the association between OC use and insomnia was small, further studies in the domain of fundamental sleep research could offer more insight to what extent biological changes influence the association between OC use and sleep disruptions and how this may impact on health and functioning.

Our study has some particular strengths. First, our study consisted of a large sample of participants, many of whom have a history or a current depressive disorder, meaning our results can be well-generalized to women with a vulnerability for depressive disorders. As depression is common in society, this helps to generalize results to the broader population. We were able to also assess interaction effects of OC with a history of depressive disorders, which has rarely been done before. Second, psychiatric diagnoses were assessed prospectively using validated clinical interviews as well as self-reported depressive symptoms. This is fairly unique, since many studies on OC and depression rely only on self-reported depressive symptoms and retrospective questions about previous diagnoses of depression. Third, as we excluded women who breastfed, gave birth in the past year or had an abnormal cycle length, hormonal abnormalities related to pregnancy, breastfeeding or menopause did most likely not affect the analyses. Fourth, the repeated measurements within the same participants enabled within-person comparisons between OC and NC measurements within the same person, which have evidently provided novel insights into the association between OC and depression.

This study has limitations in other aspects. These limitations lie mostly in the domain of OC assessment, since the NESDA cohort originally was not aimed to assess OC use. We did not have information on the age of first use of OC, nor on the duration of current OC use. This limited the study in two ways. Firstly, recent studies found that OC use during adolescence could increase the likelihood of a depression diagnosis in adulthood, even if women did not use OC anymore (Zettermark et al., 2018; Anderl et al., 2020). The current study, however, could not take previous OC use during adolescence into account. Additionally, we only had data on concurrent OC use, meaning we did not have data on recency of OC use. We used 6 month-latency of diagnoses of MDD and dysthymia, meaning a participant could hypothetically have been depressed before they started OC use. As a consequence of these limitations we were unable to investigate exact causal relationships between OC use and depressive disorders. Furthermore, the composition or brand and dosage of the used OC and duration of use was unknown. Previous studies, such as Skovlund et al. (2016), found that progestin-only contraceptives were more strongly associated with depressive disorders than combined contraceptives. In the Netherlands, 95.8% of women use a form of combined oral contraceptives, with both estradiol and progesterone in its formulation. Moreover, ethinylestradiol/levonorgestrel 0.03/0.15 mg (or "Microgynon 30″) is the most used form of OC in the Netherlands, with 90.6% of combined OC users using this formulation (data from 2018; GIP databank, 2021). Hence, it is expected that the majority of the OC-users in our study used this form. In the current study we could only rely on population-based estimates of what forms of OC are mostly used, but future studies should take OC formulation into

account whenever possible. Another limitation is related to the exclusion of women with abnormal cycle duration, which meant that our results could not be generalized to women who report abnormally long or short cycles. Since abnormal cycle lengths can be a reason to start with OC, there was a risk of sample bias, since this meant that we mostly excluded women with abnormal cycle during NC measurements. We addressed this by conducting a sensitivity analysis on the larger sample including women with abnormal cycle lengths. The results of this sensitivity analysis show similar results to analysis in the original sample, which only included women with regular cycle lengths (see Supplementary materials B in the Appendix).

In summary, our study found consistent associations between OC use and insomnia symptoms, although effect sizes of these estimates were small. Furthermore, we found no overall associations between OC use and depression outcomes, both with regards to symptom severity and diagnosis prevalence. However, post-hoc analyses showed that the within- and between-person estimates indicated significant associations between depression and OC use. This indicates that, although OC overall was not associated with depression outcomes, some individuals might experience OC-associated depression symptoms. The effect sizes of the found associations were small, and future research should be conducted to assess whether effects of OC on depression risk are robust and clinically relevant. Nonetheless, our findings on this topic show novel results on within-person associations between OC and depression diagnoses obtained through clinical interviews, which underscore the importance of accounting for individual differences in OC research. Although our study was limited in some aspects of OC use, such as duration of use, our findings raise new questions on which women might be susceptible to possible adverse mood symptoms during OC use, and whether insomnia symptoms might be affected by OC. Future research should focus on studying underlying mechanisms between OC, insomnia and depression.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2021.105390.

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