THE EFFECTS OF ORAL CONTRACEPTIVES ON MOOD AND AFFECT: A META-ANALYSIS

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Abstract

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Combined oral contraceptive (COC) pills are widely used by women of reproductive age, but there is still little conclusive evidence that exists about the mood-related side effects associated with their use. This meta-analysis examined the relationship between oral contraceptive use and mood effects such as depression and anxiety to determine what role, if any, that COCs may have in the worsening or improvement of women's mood when taking them. Effect sizes compared the differences in women's mood scores before taking COCs and after one or more cycles of use. Seventeen studies made up of 25 individual samples contributed 71 effect sizes for this analysis. The results suggest that COCs tend to contribute to a small but significant improvement in women's overall moods. However, methodological challenges and inconsistencies make it difficult for researchers to establish any firm conclusions about the role COCs play in mood changes.

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and no-nonsense advice to keep me moving forward. I wouldn't be anything without them, and I hope to continue to make them proud as my life unfolds.

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Introduction

Reproduction is a function that all living creatures perform, but it is not always something they can control in terms of timing or prevention. Like any species, human beings are motivated by an innate need and desire to reproduce, but unlike other species, modern humans have gained the ability to control if and when we reproduce to a very high degree through the use of various contraceptive methods. Some more basic forms of contraception, such as condoms, have provided humans with the ability to prevent unwanted pregnancies by creating a mechanical barrier between male and female reproductive cells. But as human science and medicine have advanced, humans have now reached a point at which women are able to influence the reproductive functions of their bodies by chemical means--by disrupting the natural fluctuations of hormones within their bodies to harness the timing of a natural menstrual cycle. The result of this is that women now simply can take pills to dictate whether or not they ovulate, as well as to interrupt and tame their natural menstrual cycles at will.

While the development of combined oral contraceptive pills (COCs) has granted women a greater degree of sexual and personal freedom (Bailey, 2006; Traulsen, Haugbølle, & Bissell, 2003), there are still many aspects of hormonal contraception that remain mysterious to both pharmaceutical researchers and the women who take COCs. Although research has sought to examine some of the short and long-term effects of COCs on women's physical experiences as well as emotional experiences, there is still

much to be studied about the multitude of ways COCs could impact women's health and lives.

Combined Oral Contraceptives: An Overview

Hormones in the body perform a variety of functions related to reproduction, behavior, and development. The levels of different hormones circulating in a human body, as well as the timing of their production and release, combine to orchestrate many physical changes and behavioral motivations related to survival and reproduction. The production and release of hormones are regulated by the hypothalamic-pituitary-ovarian axis (HPO axis) in women, which sends signals in the form of "releasing hormones" from the hypothalamus to the ovaries to trigger the production of sex hormones such as estrogens and progestogens. Estrogens, often thought of popularly, and incorrectly, as the "female" hormone(s) (this is incorrect since men also produce estrogen), are one class of many endogenous hormones, and are divided into three common types: estrone (E1), estradiol (E2), and estriol (E3). A fourth type of estrogen, estetrol (E4) is only produced during pregnancy. Estrogens play a role in orchestrating behavioral motivation and bodily development by coordinating a natural menstrual cycle in organisms. Progestogens, such as progesterone, are types of steroid hormones that bind to progesterone receptors in the body, influencing other aspects of reproduction such as cervical mucus thickness and ovular release.

A natural menstrual cycle lasts around 28 days and consists of several distinct phases. The first phase of the cycle begins during bleeding, when levels of both estrogen and progesterone are low in the body. The pituitary gland then releases follicle-stimulating hormone (FSH) and a rise in estrogen levels occurs steadily during the next phase of the cycle, called the follicular phase, as immature egg follicles grow in the ovaries. Around day 14 of the cycle, a surge in luteinizing hormone (LH) triggers the release of the mature egg follicle and the corpus luteum forms at the release site, as the body enters the luteal phase of the cycle. The corpus luteum releases high levels of progesterone but is only a temporary structure, and without egg implantation, it will begin to recede as the cycle draws to its close. At the end of the cycle, both estrogen and progesterone levels decline dramatically, triggering menstruation and beginning a new cycle.

A combined oral contraceptive pill consists of two main components: a synthetic form of estrogen and a synthetic progestogen, called a progestin. These synthetic hormones block the natural activities of the HPO axis by means of a negative feedback loop--that is, the high levels of exogenous hormones signal to the pituitary that it does not need to produce FSH or LH in accordance with a natural cycle. Almost all COCs utilize the synthetic estrogen called ethinyl estradiol (although a few COCs utilize a less-common synthetic estrogen called mestranol) to artificially influence levels of estrogen in a female body and adjust a woman's menstrual cycle in accordance with a defined dosage schedule. There are numerous classes and generations of synthetic progestogens, called

progestins, that are combined with ethinyl estradiol to create an effective and simple method of contraception in the form of a small pill. These COCs are taken on a daily basis according to a schedule--often 21 days, but sometimes 28-day or other regimens--followed by a series of days of inert "placebo" pills, during which time women experience the withdrawal bleeding associated with the menstrual phase of their cycles. Doses of the pills may remain steady throughout the regimen, or they may be staggered in a "triphasic" regimen that more closely mimics the changing levels of hormones during a woman's natural cycle.

Widespread use of COCs. Thanks to the convenience and efficacy of this method, COCs are used more commonly than any other method of contraception (Mosher et al, 2004). Even if a woman does not use COCs continuously, it is still likely that she will use them at some point in her life. A longitudinal study found that, in a group of women followed over a period of 25 years, 95% of participants had used COCs as a method of contraception at some point during that period (Lindh, Ellstrom, Blohm, & Milsom, 2010). In 2004, a study investigating contraceptive use across five European countries found that over 22 million women used COCs as a contraceptive method, and that most reported high levels of satisfaction with their choice (Skouby, 2004).

COCs and side effects. As with any pharmaceutical, there have been ongoing clinical trials and studies since the introduction of COCs in the 1960s, all with the goal of examining the positive and negative effects of COCs on both physical (cycle length, cramping, bleeding, breast pain, etc.) as well as emotional (depression, anxiety, mood

swings) and psychological (mate preferences, social behavior, sexual behavior) health. Although potential health-related side effects of COC use has been the focus of much research (reviewed in Welling, 2013), relatively little has been done regarding the potential emotional or psychological (reviewed in Hahn & Cobey, 2019) side effects, with the result being that much of the existing literature about COC use mostly addresses physical effects rather than emotional effects.

And yet, many women self-report difficulties with mood changes that occur while they are taking COCs. A study by Rosenberg and Waugh (1997) found that 46% of women who discontinue oral contraceptive use do so because of mood-related side effects. Women who discontinue oral contraceptive use often turn to a less effective method of contraception, putting them at risk for an unintentional pregnancy (Segebladh, Borgström, Odlind, Bixo, & Sundström-Poromaa, 2009; Skouby, 2004). As such, it is critical to develop a better understanding of the potential mood-related side effects that may or may not exist with contraceptive use.

Examination of Literature

Anecdotally it is still a commonly held belief that COCs can have a negative effect on a woman's mood, but the literature has struggled to find a consistent effect. Some studies have found that COC use actually improves mood outcomes (Nyberg, 2013; Ott, Shew, Offner, Tu, & Fortenberry, 2008; Walker & Bancroft, 1990; Young et al., 2007) while others have found an overall worsening of mood (Gingnell et al., 2013,

Sanders, Graham, Bass, & Bancroft, 2001; Skovlund, Mørch, Kessing, & Lidegaard, 2016). Still other studies have found individual differences in a single sample population - with some women experiencing improvement in mood and others experiencing negative mood effects when taking COCs (Graham, Bancroft, Doll, Greco & Tanner, 2007; Lundin et al., 2017).

Mood improvement. Several studies have suggested that women experience an improvement in their mood symptoms when taking COCs compared to when not taking them. In 2013, an open-label prospective study using a COC containing norgestimate showed a significant improvement in negative mood symptoms compared to placebo for women who had been experiencing severe premenstrual symptoms before treatment (Nyberg, 2013). Another study by Ott and colleagues examined the effects of hormonal contraceptives on adolescents, using daily diaries and face-to-face interviews over a period of 41 months (Ott et al., 2008). They found that periods of stable oral contraceptive use correlated significantly with reports of higher positive mood and lower negative mood effects. A similar longitudinal study by Walker & Bancroft (1990) measured several factors related to contraceptive use in a sample of participants living in a setting with high rates of poverty and inconsistent use of birth control and found that COC users reported higher positive and lower negative mood during periods of use compared to periods of non-use. Another study by Young, et al. (2007) utilized data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study to compare mood symptoms across women taking COCs versus women who are not, and

found reports that women on COCs reported lower incidences of depressive symptoms and general better functioning.

Mood worsening. Conversely, several studies have suggested the opposite effect, with women experiencing negative mood side effects when they begin taking COCs. A double-blinded, placebo-controlled randomized trial examining changes in brain activity and mood in women with a history of depression found that women taking COCs scored higher on measures of depression, mood swings, and fatigue compared to those taking a placebo (Gingnell et al., 2013). Another study by Sanders and colleagues assessed 79 women before initiating OC use and again after 3, 6, and 12 months of use (Sanders et al., 2001). These researchers found that 47% of the women in the study discontinued COC use and reported significantly higher scores of emotional side effects than women who continued to take them. More recently, a nationwide prospective cohort study conducted in Denmark examined over a million women's hormonal contraceptive use and found an association between use of hormonal contraceptives and subsequent use of antidepressants and diagnoses of depression (Skovlund et al., 2016).

However, it is possible that different generations of COCs could affect women's moods differently. A 2014 randomized, double-blind study compared a group of women taking a second-generation COC to a group taking a third-generation pill formulation (Shahnazi et al., 2014). The women taking the second-generation COC showed a decrease in positive mood and an increase in negative mood after initiation, while the women in the group taking the third-generation COC showed the opposite effect.

No effect. An additional group of studies suggest that COCs have little to no effect on women's mood. A 2007 correlational study examining oral contraceptive use among Australian woman found that the odds of developing depression symptoms were not significantly different for women taking COCs compared to women who were not taking them (Duke, Sibbritt, & Young, 2007). A double-blind, placebo-controlled trial examining the side effects of COCs in adolescents also found no difference in depression symptoms between the experimental and placebo groups after three months of treatment (O'Connell, Davis, & Kerns, 2007). An observational study by Rapkin and colleagues also sought to find out whether depression symptoms developed in women who began taking a low-dose COC and were examined over the course of three months (Rapkin, Morgan, Sogliano, Biggio, & Concas, 2006). Despite a noted decrease in their levels of neuroactive steroids, which was expected to be a predictor of depression symptoms, the women in this study did not report any significant worsening of mood.

Treating PMDD with COCs. Many studies have used placebo-controlled trials to examine the positive mood effects of COCs in women with premenstrual dysphoric disorder (Eisenlohr-Moul, Girdler, Johnson, Schmidt, & Rubinow, 2017; Freeman et al., 2001; Graham & Sherwin, 1992; Pearlstein, Bachmann, Zacur, & Yonkers, 2005; Peters, Freeman, Kim, Cohen, & Joffe, 2017; Yonkers & Foegh, 2005; others) often utilizing a progestin such as drospirenone with the goal of improving premenstrual symptoms.

A small study examining 25 participants found that women taking a COC with drospirenone reported greater improvements in mood symptoms compared to the placebo

group (Pearlstein et al., 2005) while a follow-up study using a larger group of 328 participants also concluded that the same COC formulation improved PMDD symptoms compared to controls (Yonkers & Foegh, 2005). Two open-label observational studies (Borges et al., 2006; Parsey & Pong, 2000) also examined the effects of a COC containing drospirenone. These studies both found reported improvements in mood while taking the COC compared to not taking it. Study outcomes included personality traits examining dimensions of depression and social introversion, and no difference was found between baseline scores and scores at completion of the study.

Another randomized trial was conducted in women with a history of depression who experience premenstrual worsening of their mood symptoms. The women in this study were given a COC containing drospirenone, with some participants receiving a placebo during the pill-free interval, but no difference was found in the ratings of depression between the two groups (Joffe & Petrillo, 2007). A similar study by Eisenlohr-Moul and colleagues, conducted ten years later, also used a COC formulation containing drospirenone to examine its effects on women with PMDD (Eisenlohr-Moul et al., 2017). The study included administration of the COC on both continuous and intermittent dosing schedules, but still failed to find a significant improvement between the mood scores of women in those groups compared to the placebo group.

Current Issues with COC Research

A lack of standardized research regarding COC use and mood has made it difficult to report overall effects among the studies that have been conducted. As previously stated, studies have produced conflicting results about the effects of COCs on mood. Researchers have not used a "standard" pill formulation, and in some cases did not even report or record the formulations being taken by participants. To date, there is also not an agreed-upon standardized scale to measure mood/affect changes related to COCs and mood, making it difficult to analyze the data consistently across several different studies. Furthermore, no published analyses have examined variables of interest that might contribute to the overall mood effects of COCs--variables such as pill formulations, dosing schedules, individual differences, or cycle timing differences.

Lack of placebo-controlled trials in healthy women. One of the biggest barriers to COC research is that there is a lack of placebo-controlled trials that have been carried out in healthy women, as they were long considered infeasible. For many years, it was believed that placebo-controlled trials could only be carried out using sterilized women, due to the chances of placebo-group participants becoming pregnant during their research participation. The result is that few examples of placebo-controlled trials using healthy women exist.

Use of different pill formulations. It is very difficult to draw conclusions about COCs in a general way when so many different formulations of pills exist. COCs can vary in terms of the dosage of ethinyl estradiol, although the dosage typically falls

somewhere between 25 and 35 μg. They can also vary in terms of the type of progestin used, with a very large number of different types of these synthetic hormones being commonly used in pill formulations. Some of the more common progestins used are desogestrel, levonorgestrel, norgestimate, and drospirenone. In general, there are two classes of progestins: androgenic, which mimic the "masculinizing" effects of testosterone in the body such as heightened sex drive, acne, and hair growth; and antiandrogenic, which suppress these "masculinizing" activities. The androgenic properties of the progestin used in a formulation of COC could contribute to individual differences in responses to birth control pills.

Furthermore, some oral contraceptives are administered in a monophasic regimen, in which the active pills all contain the same doses of ethinyl estradiol and progestin, while others are administered in a triphasic regimen with doses of the hormones changing throughout the three active weeks of the cycle. Most COCs are administered according to a 21/7 dosing schedule (21 active days and 7 "bleeding" days) but some follow a 24/4 or extended regimen with a longer period of active pill days.

In light of these differences in both the specific synthetic progestin used, variation in the dosage (of both estrogen and progestin), and variation in the administration schedule across different brands of the combined oral contraceptive pill, collapsing data from all 'pill users' into a single, homogenous group may present a significant design concern. A large-scale study of COC use in the US recently demonstrated that women aged 15-44 report using over 80 different brands of COCs (Hall & Trussell, 2012). In this

sample of over 12,000 women, high-dose estrogen pills were more common than low-dose, 58% of women used a COC with an older generation progestin, and two-thirds used monophasic pills. This study highlights the importance of considering the specific COC used in future research, and of the need for within-participant research examining the potential differential impact of different COCs.

Despite the spectrum of pills that all fall under the umbrella of COCs, many studies have not sought to distinguish between these formulations when collecting data about women's mood symptoms and COC use (Skovlund et al., 2016; Sulak, 2000). In order to gain a large enough sample for a study, researchers may choose to forego the difficulty of obtaining information about individual formulations of pills and instead simply ask about general COC use. While this is understandable, it can make it difficult for researchers to draw nuanced conclusions about differences between types of COCs and effects on mood.

The survivor effect. Another difficulty when conducting research about COCs is that there is a high likelihood of biased reporting due to a "healthy survivor" effect. Women who participate in studies examining COC use will often drop out of the study if they experience severe adverse effects while taking the pills (Oinonen & Mazmanian, 2001). This can present a challenge when researchers examine the study's final data, since the experiences of the women who left the study cannot be properly assessed.

For example, a 2008 longitudinal study by Berenson and colleagues found that COCs provided a protective effect against nervousness and mood swings that persisted

for two years after follow-up for both an injectable form of COC as well as a 20 μg ethinyl estradiol formulation, when comparing factors across a range of users and using the Beck Depression Inventory as a measure of mood symptoms. (Berenson, Odom, Breitkopf, & Rahman, 2008). This outcome suggests that COCs contribute to the improvement of women's moods while taking them. However, the researchers also noticed that the greatest number of participants lost to follow-up were ones who had reported negative mood effects such as nervousness, depression, or loss of energy in the initial phases of the study. This "survivor effect" can cast doubt on the results of studies, since they typically only report the scores from women whose mood symptoms while taking COCs were mild enough to continue use long enough to complete the study.

Use of different scales to measure mood. While there have been many studies utilizing self-reports of mood or observer ratings to assess mood changes, there has not been a consistent scale used across COC mood studies. Many different types of scales have been used across various studies to measure changes in mood associated with COC use, with the result being that it is difficult to know whether differences in mood changes are due to actual drug effects or simply measurement differences.

Studies assessing women with PMDD have utilized the Daily Record of Severity of Problems (DRSP), which is a standard scale used to diagnose PMDD in women (Lundin et al., 2017; Yonkers & Foegh, 2005). This scale is useful because it involves mood tracking across a woman's cycle, and since it measures a wide range of symptoms related to premenstrual syndromes. Other studies have used standard scales that chiefly

measure depression symptoms, such as the Beck Depression Inventory (BDI) or the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) to measure mood changes related to COC use (Graham et al., 2007; Greco, Graham, Bancroft, Tanner, & Doll, 2007). Still others have utilized a self-made questionnaire or a combination of scales to measure mood changes (Joffe, Cohen, & Harlow, 2003; Sanders et al., 2001).

There has been a noteworthy difference found between studies utilizing a retrospective method (reporting from memory of past days) of mood reporting as compared to a prospective (reporting on a current day's state) rating of mood. Studies asking women to retrospectively report mood changes related to COC use generally found that women report a more extreme worsening of mood while using COCs than studies asking women to use prospective reports (Oddens, 1999; Joffe et al., 2003). Conversely, studies that required women to track their mood each day prospectively often found improvements in mood over time (Lundin et al., 2017; Rebollar, Balaña, & Pastor, 2017). Prospective ratings of mood have come to be seen as more reliable reports, but unfortunately, many studies have only utilized retrospective reports of mood changes.

One of the biggest challenges to measuring mood is that the subjective experience of "mood" itself is often difficult to define. Some researchers have moved away from simple scales of improvement/worsening and have begun to discuss mood in terms of dimensions of affect instead. They have found it useful to distinguish between "positive affect" and "negative affect" which can both change independently of each other or be individually subject to higher levels of variability. A scale called the Positive and

Negative Affect Schedule (PANAS) has been used in a couple of studies to measure these dimensions of affect (Jarva & Oinonen, 2006; Rebollar et al., 2017). The scale asks participants to rate the extent to which they feel a number of different emotions currently or within the past week on a 1 to 5 scale--including both positive and negative emotions. Using this scale, researchers were able to report results in terms of affect variability, and it was found in one study that COC use was associated with positive affect stabilization (Jarva & Oinonen, 2006). It is possible that use of a more nuanced scaled such as the PANAS could help to clear up the confusion in some studies that simply measured mood in terms of improvement or worsening, but at present the research is still divided by use of different scales.

Meta-analysis: A way to organize the outcomes. In light of the widespread inconclusiveness of results in this field of research, a meta-analysis is a useful way to shine a light on possible connections between variables that interact with birth control use and mood, and to direct future research toward examining the most likely possibilities for explaining these connections. Organizing and standardizing the data from several studies helps to uncover any patterns that may exist in the overall effect of COC use.

Method

After examining the existing research related to COCs and their effects on mood, a protocol for the meta-analysis was developed and pre-registered on the Open Science Framework (https://osf.io/4wfeq/), outlining the goals and methods for the project. Since this research was utilizing data drawn from human subjects, Institutional Review Board

(IRB) approval to conduct the study was obtained on March 26, 2018 (IRB 17-184) by the Humboldt State University IRB.

Following PRISMA guidelines, the major steps required were outlined as follows: searching for papers based on literature review findings, searching for papers according to keywords using several databases, excluding duplicates obtained during the searches, excluding papers from the sample based upon a set of predetermined exclusion criteria, organizing all of the papers that were not excluded, reading through each paper to record statistics and variables of interest, contacting authors to attempt to obtain statistics that were missing or reported in an unusable format, standardizing all of the statistics from different scales into uniform effect sizes, and finally running the meta-analysis on these statistics to find an overall effect.

Location of Papers

Literature review. The majority of the papers included in this meta-analysis were found using the reference sections of published articles related to COC use and mood. These were located during a literature review and recorded in a table, and then screened to determine which ones qualified for inclusion in the meta-analysis. A total of 58 papers were examined, and 23 of those papers met the criteria for inclusion in the meta-analysis. The others were excluded mostly due to their methodologies, as they were not within-subjects trials examining the effects of COCs on women's moods.

Database searching. The databases searched to locate relevant papers were Google Scholar, PubMed, PsycINFO, Web of Science and the Cochrane Central Register of Controlled Trials. To perform these searches, the keyword combinations of "contracept-," "depression," "anxiety," "birth control," "mood," and "affect," were used in different configurations of AND and OR to generate the most relevant results within a manageable sample of papers. The last date of database searching took place on 4/24/18.

These searches retrieved a total of 526 papers for potential inclusion in the study. An examination of the retrieved papers resulted in the exclusion of the majority of them, mostly due to their methodologies and aims. In particular, papers retrieved from Google Scholar and PsycINFO were most often analyses of the social effects of contraceptives, rather than studies examining their physical or emotional effects. Many of the papers retrieved from PubMed and Web of Science focused on the physical side effects of COCs rather than the emotional effects (n = 447). There were 71 duplicate papers removed from the search results, either having been retrieved from more than one database or already having been retrieved during the literature review. All told, searching of databases contributed a total of eight additional studies to be included in the meta-analysis.

Contacting researchers. Using the reference sections of published articles, key researchers in the field of COC effects were identified. These researchers were sent emails explaining the aims of the meta-analysis and requesting any unpublished data they may have. Most of the authors replied explaining that they did not have any unpublished data. One set of data was retrieved from a researcher at the University of Glasgow.

Additionally, a request for unpublished data was posted to several listservs related to this field but received no responses.

Exclusion Criteria for Papers

In order to avoid cherry-picking data and creating potential selection effect confounds in the study, a list of criteria was developed for the type of papers included in the meta-analysis. The specifications of this list were adhered to while constructing the sample to ensure the broad inclusion of as many relevant papers as possible without compromising the integrity of the analysis.

Methodology. Only papers that utilized a within-subjects design were included in the analysis, since this allowed for the examination of pre-test and post-test measures of mood. This reduced the possibility that an effect may only be due to individual differences between subjects. Ideally, the analysis would have included only randomized trials of COCs with a placebo, but since there were so few studies conducted using this methodology, this restriction would have limited the sample too much. All randomized trials of COCs with or without placebo that included mood symptoms as a primary or secondary outcome, studies comparing two or more formulations of COCs with mood symptoms as a primary or secondary outcome, and studies testing efficacy of COC formulations to treat PMDD were eligible for inclusion in the meta-analysis. This criterion was established in the hopes that it would allow for examination of the existing literature as broadly as possible without including studies likely to have confounds.

Time period. The meta-analysis only included papers published from 1985 onward. Although studies were conducted to evaluate side effects of COCs before this year, in 1985 there was a change in the standard level of estrogen in COCs after concerns about higher levels being linked to a risk of vascular disease. Since this time, doses of ethinyl estradiol in COCs have ranged only from 25 micrograms to 35 micrograms, whereas older research used doses of ethinyl estradiol encompassing a wider range. This timeframe choice was made with the intention that this meta-analysis only sampled data relevant to current practices while still encompassing a span of several decades.

Language. In regard to language of publication, only papers available in English or with an English translation were included, so that they could be read and understood fully.

Reporting of COC type and dosage. Although it would have been preferable to only include studies that reported the formulations and doses of COCs used by participants, this would have limited the meta-analysis sample size too much. Instead, all studies that adhered to the other established criteria for inclusion, even those that do not include specific pill brands, formulations, or doses were included in the analysis.

Population sample. It would have been most beneficial to the study goals to examine data from studies only looking at healthy women of reproductive age. Unfortunately, not many studies have conducted placebo-controlled trials using samples of healthy women, as it was long believed to be unethical to perform them, due to the risk of pregnancy for women in the placebo group. Consequently, much of the data was

collected from studies utilizing a sample of women with a pre-existing condition such as PMDD, and some from women who were infertile. This allowed for the collection a large enough sample of data to perform the necessary analyses.

Types of scales. Another criterion for inclusion is the type of scales used in the studies. As previously mentioned, an issue with this field of research in general is that studies have utilized many different types of scales. Consequently, a broad range of scales were included in order to avoid limiting the data. Any studies that utilized a standard scale with a primary or secondary outcome of mood ratings (for example the BDI, PANAS, Q-LES-Q, etc.) were included in the meta-analysis. A few studies that utilized a custom-made scale with mood improvement/worsening as a primary or secondary outcome were also included in the analysis.

Data Collection and Coding

After the sample of papers was selected and pared down according to the aforementioned exclusion criteria, they were scanned to find the relevant data points to record. In order to find the effect sizes, there needed to be a pre-pill mood mean and standard deviation for the sample COC group, and a post-pill mean and standard deviation reported in each paper. Many papers included a few different experimental samples within one study (e.g. a group taking one formulation of COCs and another group taking a different formulation), so these were recorded as separate samples. Many papers also used several scales to measure the same samples, or several scale items

addressing different dimensions of mood. These were also recorded separately but classified as belonging to the same sample. For studies that included several pre or post measurements (often divided by cycle phase), these scores were averaged but still separately recorded according to samples, scales, and scale items.

Several of the papers that met all other criteria for inclusion did not report the score results in a usable format. Some reported results using only visual scales or graphs (Bäckström, Hansson-Malmström, Lindhe, Cavalli-Björkman, & Nordenström, 1992; Bancroft, Sanders, Warner, & Loudon, 1986; Deijen, Duyn, Jansen, & Klitsie, 1992; Graham, Ramos, Bancroft, Maglaya, & Farley, 1995; Graham & Sherwin, 1993; Parsey & Pong, 2000); others failed to report standard deviations (Pearlstein et al., 2005; Yonkers & Foegh, 2005); others reported medians instead of means (Joffe et al., 2007; Peters et al., 2017). The authors of these papers were contacted and asked to provide the data in a usable format for the meta-analysis, but only one response resulted in the acquisition of the necessary data. This resulted in the exclusion of nine studies from the final analysis, as well as secondary scale scores from two other papers.

Two additional papers were excluded for reporting their results in the form of odds ratios (Westhoff et al., 2007; Berenson et al., 2008). This decision was based on the idea that the overall concept behind the collection of these scores were different from the pre-post measurements, as they instead were aiming to find the likelihood of developing adverse mood symptoms when taking COCs or discontinuing use of COCs due to mood

symptoms, rather than comparing magnitudes of change in mood before and after initiation of COC use. See Figure 1 for all steps related to data exclusion.

Calculating effect sizes. After all the data was collected from each paper, the effect sizes and effect size variances were calculated using an online effect size calculator. The calculator used for these computations was the Practical Meta-Analysis Effect Size Calculator, developed by David B. Wilson (Wilson, 2018). The effect sizes and variances were recorded and organized into a final table according to the coding chiefly for samples and noting scales and scale items. The scale direction for each effect size was adjusted to reflect a positive effect size to indicate an increase in negative mood symptoms (i.e. worsening of mood), and a negative effect size to indicate a decrease in negative mood symptom (i.e. improvement of mood).

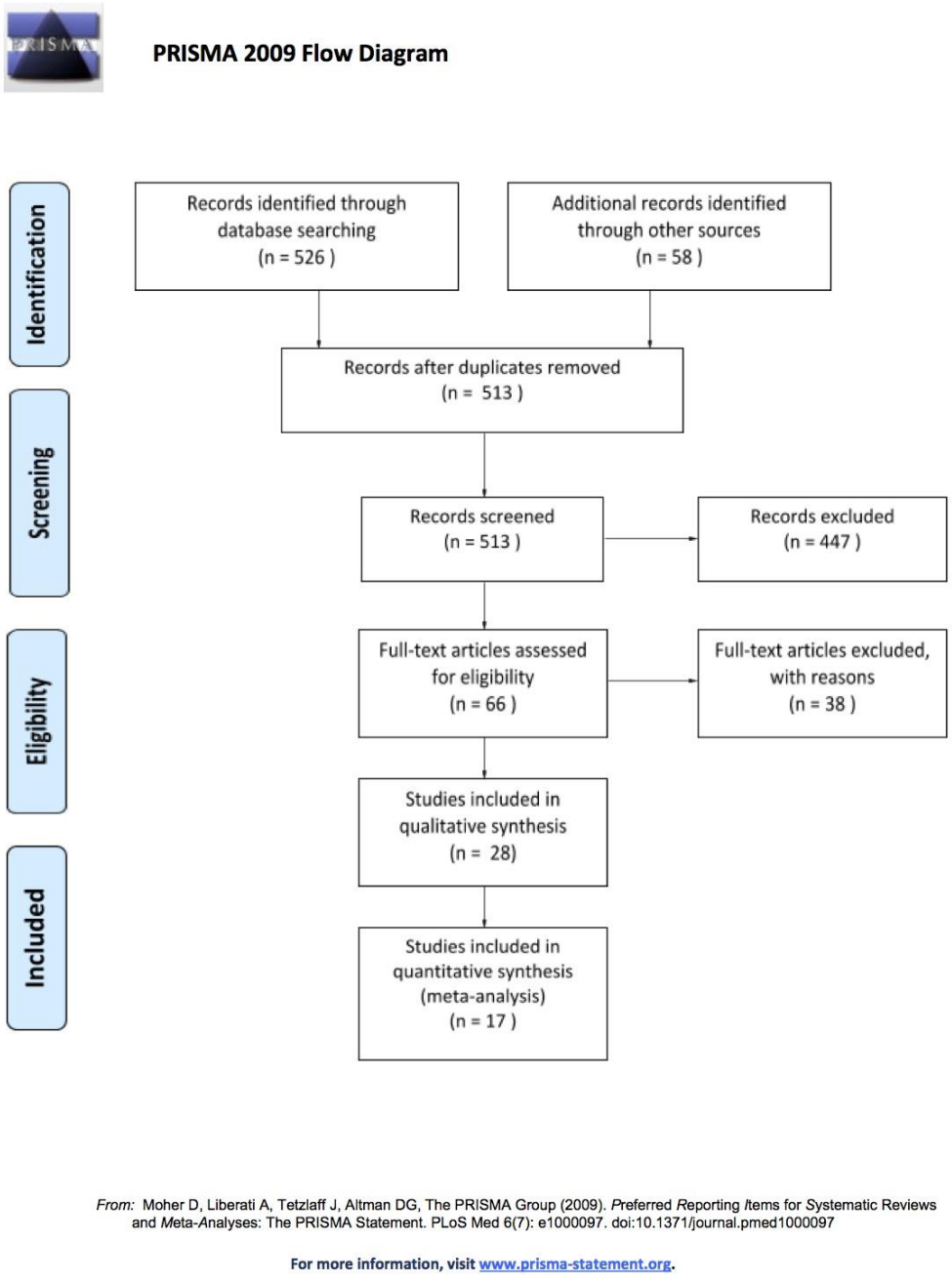

Figure 1. PRISMA flow chart showing study selection (Moher, Liberati, Tetzlaff, & Altman, 2009).

Results

A total of 17 different studies contributed data to the final analysis. These studies reflect the responses of 1268 participants from 25 unique samples. Taking into account the data points contributed by multiple scales or scale items, there were a total of 71 effect sizes that contributed to the final meta-analysis.

Since most of the samples included in this analysis contributed multiple effect sizes, these data did not meet the assumption of independence of effect sizes, which is a necessary prerequisite for most meta-analytic approaches (Gleser & Olkin, 2009). Consequently, the choice was made to use robust variance estimation (RVE), which is a way of achieving accurate estimation in meta-analysis when dependency is an issue (Hedges, Tipton, & Johnson, 2010). RVE produces the best results when used in meta-analyses that examine at least 40 samples but can still be accurate for analyses that include 20-40 samples. In light of this, the Robumeta package for R was used to run the analysis, since it allows adjustments for small sample sizes. (Fisher & Tipton, 2015).

To perform RVE, an initial estimate of the average within-sample correlation between effect sizes (designated Rho) must be made. This analysis used an initial estimate Rho value of .80, and then a sensitivity analysis was performed to determine the stability of this estimate. The sensitivity analysis produced outcomes using Rho values of .00, .20, .40, .60, and 1.0 for comparison, and the results of each were the same, suggesting a stable estimate.

The results suggest that COCs have a small, but significant, positive effect on women's mood (mean ES = -0.54, *95%CI* [-1.0200, -0.0479]). As mentioned previously, the negative direction of the effect indicates that women tend to experience improvement of mood when taking COCs compared to not taking them.

Discussion

These findings suggest that, in contrast to commonly held ideas about COCs creating mood issues, they are more likely to stabilize or improve a woman's mood when she begins taking them. Considering the existing research that focused on using COCs as a treatment for PMDD, this result is not overly surprising. However, the variability among study methodologies still makes it difficult for researchers to draw strong conclusions about the overall effects of COCs on women's moods. Rather than the statistical results obtained from this meta-analysis, the greater takeaway from this research is that the field of study regarding COCs and women's moods is still suffering from a lack of standardization in terms of study design, scales, recording of data, and definition of variables. Each individual study produced a result, but this information is not useful unless it can be considered as a whole with other studies performing the same type of research.

Limitations

The small number of studies available to include in this analysis suggests that the results may be less accurate than if there had been more data to analyze. It is unclear whether publication bias plays a role in these results, although many of the studies published non-significant results or simply included the mood scores as secondary analyses, suggesting that the current literature reflects an accurate picture of the research conducted. Attempts were made to obtain additional data from researchers in the field as well, with few contributions, which supports this idea. However, it is also possible that clinical trials conducted by pharmaceutical companies were not published, since these companies may have a lower incentive to publish research than academic researchers do.

There is also a possibility that the studies that were excluded due to data issues could have contributed to the final analysis in a way that would have affected the outcome. Many of the researchers contacted to request data reported that they no longer had access to the data for the studies in question. Perhaps if data from all the studies that met the criteria for inclusion could have been obtained in a usable format, the results might have been different.

Finally, it is worth mentioning that many of the studies included in the meta-analysis utilized samples of women suffering from PMDD and focused on using COCs containing drospirenone to treat their condition. The aim of this meta-analysis was to determine the effects of COCs on an average woman of reproductive age, taking any common formulation of COC. While drospirenone-containing COCs in particular may

improve women's moods, especially women who suffer from PMDD, it is possible that the inclusion of so many studies examining this formulation of COC using this population could have affected the results to show a more positive effect of COCs on women's mood than would be typically expected in a more generalized population.

Methodological Recommendations

The variations in the types of methodologies used to analyze COC use and mood is a major contributing factor to the difficulty in drawing any large-scale conclusions about COCs and mood effects. This meta-analysis helped to reveal the range of different methodologies that are used in this field, as well as their strengths and weaknesses. Consequently, there are some recommendations to future researchers about the best types of methodologies to use in order to draw stronger and more compelling conclusions about the roles of COCs in women's mood changes.

Study design. One of the major reasons why studies were excluded from this meta-analysis was because the methodology did not allow for comparisons before and after women began taking COCs. Some studies used a correlational design, asking women if they were taking contraceptives or not, and whether they had experienced symptoms of mood worsening. Other studies only compared groups of women taking different types of COCs, or women taking them vs. not taking them, without recording pre- and post-measurements of mood. These types of methodologies do not allow researchers to establish any sort of temporal precedence to show that the worsening of

mood could be attributed to the use of COCs, rather than some other outside variable. It is recommended that any future studies utilize a design that examines women's moods before using COCs, and again during their use.

Baseline measurements. While some studies simply administered a questionnaire immediately before the initiation of COC use, others chose to track women's moods for a month to collect baseline data. This latter method is preferred since it is more comprehensive, providing researchers with a clearer picture of each woman's "average" moods throughout a month. This is especially important considering that moods can fluctuate on a daily basis as well as alongside the different phases of a woman's menstrual cycle. It is recommended that future studies collect participants' baseline mood data for at least one month before initiating COC use. For an even more fine-tuned approach, researchers could opt to collect baseline date for several months beforehand, which would be most useful when establishing average moods as related to different phases of a woman's menstrual cycle.

Long-term assessments. In the same sense that several baseline measurements can provide a clearer picture of women's average moods before taking COCs, several post-pill assessments can help to show the effects of COCs with more accuracy, especially when looking at different phases of the menstrual cycle. Some studies perform several follow-up assessments of mood for a year or more, which would be ideal for examining the long-term effects of COCs on women's emotional health. These longer-term assessments would also be useful for studies examining cycle phases in addition to

overall effects of COCs. It is recommended that researchers assess women's moods in the first month after beginning COCs, and then make at least two or three future assessments for at least six months after the initiation of COCs, ideally more assessments over a longer period of time.

Comparison groups. It remains a methodological challenge for researchers to design studies that include a comparison group receiving a placebo, especially if blinding is included. To expect a group of healthy women to take a pill for months on end without knowing whether it is truly protecting them against pregnancy is a lot to ask of study participants, which is why so few studies exist with this type of methodology. Still, it is recommended that researchers use a double-blinded placebo-controlled methodology whenever possible to avoid concerns about validity due to a placebo effect. Failing this, a methodology that utilizes a pre-post design with a non-blinded placebo group is preferable for drawing conclusions about the mood effects of COCs, since it will still allow for comparisons between mood scores of women who begin taking COCs and women who do not. It is recommended that all studies include a comparison group of women who take a placebo COC or do not start taking COCs at all, even when studies are examining the effects of more than one type of COC.

Population samples. As mentioned previously, much of the existing research examining the mood-related effects of COCs has been conducted using women with PMDD. While this itself is an important area of study, it would also be beneficial to conduct more clinical trials using healthy women as a sample, or a combination of

healthy women and women with varying degrees of pre-existing mental health conditions. If the goal is to determine how an average woman's moods will respond to COCs, it makes sense to test this effect in a broader population sample to improve the generalizability of research results.

Types of scales. While it can be useful for researchers to use several types of scales to assess measures of mood, it would be advisable for them to include at least one measure that conducts daily ratings of moods, such as the DRSP, in addition to broader measures, such as the BDI or MADRS. Ideally, researchers should either develop or agree upon a standard scale to use for this type of research to maintain the highest level of consistency across studies. It is least advisable for studies to utilize self-made questionnaires, as these make it the most difficult to draw broader conclusions and can call into question the validity of their measurements.

With all of these considerations in mind, it seems that the most beneficial types of COC studies would be ones undertaken using a large, representative sample and executed over the course of a long timeline. These studies would ideally measure women's moods for a month or more before initiation of COCs, and then for several months after. They would also utilize standard scales with at least one prospective daily mood measurement.

Conclusions

When examining the literature related to COC use and mood, it quickly becomes clear that there is not a simple answer to the question that can apply to every woman, but

it is also clear that more standardized research methods could help researchers to effectively examine factors influencing interactions between COC use and mood.

Researching the effects of COCs on women's mood is a tricky task, but not an impossible one. At present, it appears that COCs are more likely to improve a woman's moods when she begins taking them than they are to worsen them. However, future research conducted in a more standardized way could help to either correct or reinforce these results with less ambiguity. In general, a greater number of studies would help to create a clearer picture of this effect. This is a worthwhile field of research to continue forward with, since so many women currently take COCs and so many more will likely begin taking them.

At present, women who wish to begin taking an oral contraceptive are typically prescribed a common formulation of COC and told by their doctors to report any negative side effects. If the side effects are severe enough, women are advised to switch to a different type of pill or discontinue COC use altogether. However, research efforts could aim to draw connections between variables that may work together to contribute to changes in mood, and thereby better inform women of which types of birth control may be best for an individual's circumstances prior to use. With more knowledge, women will be able to begin taking COCs with more confidence about what side effects they can expect to experience and may even be encouraged to initiate COC use to improve mood symptoms.

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Appendix A

Studies included in the final meta-analysis

Study #	Authors	Year	Title
1	Lundin et al	2017	Combined oral contraceptive use is associated with both improvement and worsening of mood in the different phases of the treatment cycle--A double-blind, placebo-controlled randomized trial
2	Gingnell et al	2013	Oral contraceptive use changes brain activity and mood in women with previous negative affect on the pill--A double-blinded, placebo-controlled randomized trial of a levonorgestrel-containing combined oral contraceptive
3	Ott et al	2008	The influence of hormonal contraception on mood and sexual interest among adolescents
4	Graham et al	2007	Does oral contraceptive-induced reduction in free testosterone adversely affect the sexuality or mood of women?
5	Greco et al	2007	The effects of oral contraceptives on androgen levels and their relevance to the premenstrual mood and sexual interest: A comparison of two triphasic formulations containing norgestimate and either 35 or 25 μg of ethinyl estradiol
6	O'Connell et al	2007	Oral contraceptives: Side effects and depression in adolescent girls
7	Borges et al	2006	Effect of a combination of ethinylestradiol 30 μg and drospirenone 3 mg on tolerance, cycle control, general well-being and fluid-related symptoms in women with premenstrual disorders requesting contraception
8	Pearlstein et al	2005	Treatment of premenstrual dysphoric disorder with a new drospirenone-containing oral contraceptive formulation

Study #	Authors	Year	Title
9	Sangthawan & Taneepanichskul	2005	A comparative study of monophasic oral contraceptives containing either drospirenone 3 mg or levonorgestrel 150 µg on premenstrual symptoms
10	Yonkers et al	2005	Efficacy of a new low-dose oral contraceptive with drospirenone in premenstrual dysphoric disorder
11	Li et al	2004	Impact of common contraceptive methods on quality of life and sexual function in Hong Kong Chinese women
12	Cinar et al	2012	Effect of an oral contraceptive on emotional distress, anxiety and depression of women with polycystic ovary syndrome: A prospective study
13	Rapkin et al	2006	Decreased neuroactive steroids induced by combined oral contraceptive pills are not associated with mood changes
14	Eisenlohr-Moul et al	2017	Treatment of premenstrual dysphoria with continuous versus intermittent dosing of oral contraceptives: Results of a three-arm randomized controlled trial.
15	Nyberg et al	2013	Mood and physical symptoms improve in women with severe cyclical changes by taking an oral contraceptive containing 250-mcg norgestimate and 35-mcg ethinyl estradiol.
16	Shanazi et al	2014	A comparison of second and third generations combined oral contraceptive pills' effect on mood.
17	Hahn & Jones	2016	OCMATE: Oral contraceptives and mate preferences project. (Unpublished raw data)