Title: Oral Contraceptive Use in Adolescence Predicts Lasting Vulnerability to
Depression in Adulthood

Abbreviated title: Oral Contraceptives and Depression

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Abstract

Background

Previous evidence suggests that use of oral contraceptives (OCs), especially during adolescence, may increase women's vulnerability to depression in the short term. Here we investigate whether women who had first used OC in adolescence show an increased prevalence of depression in the long term.

Methods

We examined 1,236 women in the United States National Health and Nutrition Examination Survey for whom information on depression and age at first OC use was publicly available. We compared women who reported first use of OCs in adolescence to women who had never used OCs and women who had first used OCs in adulthood on 1-year prevalence of major depressive disorder (MDD) assessed by trained interviewers.

Results

Compared to women who had used OCs during adolescence, women who had never used OCs were less likely to meet the criteria for MDD within the past year in adulthood (odds ratio [OR] = 0.31, 95% CI = 0.16–0.60), and so were women who only started using OCs in adulthood (OR = 0.54, 95% CI = 0.30–0.95). Third factors that have previously been proposed to explain the relationship between OC use and depression risk such as age at sexual debut, and, importantly, current OC use, did not account for the results in propensity score analyses.

Conclusions

We show a long-term association between adolescent OC use and depression risk in adulthood regardless of current OC use. Our findings suggest that adolescence may be a sensitive period during which OC use could increase women's risk for depression, years after first exposure.

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Keywords: oral contraceptive use, depression, adolescence, sensitive period, NHANES

Abbreviations: MDD: major depressive disorder; OC: oral contraceptive; OR: odds ratio

Introduction

Depression is the leading cause of disability and suicide deaths worldwide (World Health Organization, 2017). Beginning in adolescence, women are twice as likely as men to develop depression (World Health Organization, 2017; Skovlund, Mørch, Kessing, & Lidegaard, 2016). Converging evidence from animal models and humans also suggests that the gonadal hormones oestrogen, progestogen, and testosterone may be important biological contributors to the observed sex differences in depression risk (Montoya & Bos, 2017; Naninck, Lucassen, & Bakker, 2011; Skovlund et al., 2016), in addition to psychosocial and environmental factors (Mendle, Turkheimer, & Emery, 2007).

Oral contraceptives (OCs) contain synthetic forms of oestrogen and/or progestogen while suppressing the endogenous production of oestrogen, progestogen, and testosterone (Montoya & Bos, 2017), and may, therefore, alter a woman's vulnerability to depression. Such hormone-induced changes may be particularly pronounced in adolescence, a life period that is characterised by intensive social, cognitive, reproductive, and physiological development (Crone & Dahl, 2012). Indeed, a recent prospective population-based analysis of over 1 million women (all women living in Denmark aged 15 to 34 years) indicates that, in the short term, use of OCs or other forms of hormonal contraceptives is associated with increased use of antidepressants and a higher likelihood of a first diagnosis of depression; the observed relationship was strongest in adolescents (Skovlund et al., 2016). In another prospective population-based study on over 800,000 women aged 12 to 30 years residing in Sweden, adolescents, but not young adults, who used hormonal contraception were more likely to use other drugs commonly prescribed for mental health impairments (anxiolytics, hypnotics, and sedatives) (Zettermark, Vicente, & Merlo, 2018). These results are further supported by two large-scale cross-sectional studies, which showed increased use of antidepressants (Lindberg, Foldemo, Josefsson, & Wiréhn, 2012) and higher rates of

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diagnosed depression (McKetta & Keyes, 2019) in adolescent OC users in bivariate

associations. In contrast, findings in adults are more equivocal (e.g., Cheslack-Postava,

Keyes, Lowe, &, Koenen, 2015; Skovlund et al., 2016; Wiréhn, Foldemo, Josefsson, &

Lindberg, 2010; Zettermark et al., 2018).

Critically, and especially during important developmental periods such as adolescence,

gonadal hormones may contribute to the organisation of brain structures and thereby generate

enduring changes and differences between individuals (Berenbaum & Beltz, 2011; Cahill,

2018; Schulz, Molenda-Figueira, & Sisk, 2009). These hormone-induced long-term changes

involve systems that are known to be dysregulated in depression such as the hypothalamic–

pituitary–adrenal stress axis and limbic regions (Berenbaum & Beltz, 2011; Schulz et al.,

2009). The vast majority of studies demonstrating organising effects of pubertal/adolescent

gonadal hormone exposure on brain development and behaviour used animal models (Schulz

et al., 2009). In rats, pubertal androgens organise synaptic plasticity in the hippocampus,

leading to enduring changes in hippocampal functioning that can still be observed in

adulthood (Hebbard, King, Malsbury, & Harley, 2003). Similarly, eliminating the sex-specific

gonadal hormone surge through prepubertal gonadectomy (ovariectomy in females and

castration in males) abolishes typically observed sexual dimorphisms in cell numbers and

volume of the medial amygdala (Ahmed et al., 2008).Initial evidence in humans supports

these findings. For instance, a recent study showed that earlier pubertal timing, which is

tightly coupled with exposure to gonadal hormones (Shirtcliff, Dahl, & Pollak, 2009),

prospectively predicted altered white matter microstructure in the uncinate fasciculus and the

cingulum bundle at age 19 (Chahal et al., 2018); both altered miscrostructure in the uncinate

fasciculus and in the cingulum bundle have been linked to depression risk (reviewed in

Bracht, Linden, & Keedwell, 2015). Furthermore, both oestradiol and testosterone levels in

adolescent women predicted white matter and right amygdala size measured two years later in

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a prospective study, independent of age (Herting et al., 2014). In contrast, we are not aware of any studies that have investigated organising effects of hormonal contraceptives on adolescent brain development.

Given the above evidence of the role of gonadal hormones in behaviour and cognition related to depression and the organisational effects of gonadal hormones during adolescence, the question arises of whether adolescence may be a sensitive period during which OC use could produce enduring change in a woman's risk for depression by altering her hormonal milieu during this important phase of behavioural and brain development (Cahill, 2018). Millions of women worldwide use OCs, and OCs are particularly popular among adolescents: In the United States, over half of the sexually active women aged 15–19 years now use OCs (Jones, Mosher, & Daniels, 2012). Additionally, one-third of the adolescent women who use OCs do so solely for non-contraceptive reasons (reducing cramps or menstrual pain, menstrual regulation, treatment of acne, etc.) (Jones, 2011). While the benefits of OC use for adolescent and adult women have been well-documented (e.g., Lindberg, Santelli, & Desai, 2016), it is crucial to also understand their potential side-effects in the short and long terms. While a number of prior studies have investigated short-term associations between OC use and depression risk (generally within the subsequent year), the present study focuses on whether use of OCs might have lasting effects on depression risk, potentially even years later.

Finally, an important limitation of most large-scale studies investigating the relationship between hormonal contraceptive use and depression is the unavailability of data on potential baseline differences between OC users and non-users that may account for the observed effect (e.g., age at sexual debut and age at first period). In the few studies that did control for behavioural and demographic factors that may explain the link between OC use and depression (Cheslack-Postava et al., 2015; McKetta & Keyes, 2019), all available potential confounders have been entered simultaneously into the regression model predicting

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depression from OC use. However, this approach can obscure potential true effects, especially when covariates are substantially correlated with the predictor variable (e.g., history of OC use and age at sexual debut are highly correlated; McKetta & Keyes, 2019), resulting in multicollinearity (Vatcheva, Lee, McCormick, & Rahbar, 2016). Moreover, this approach can reduce test power by consuming many degrees of freedom when estimating covariate-outcome associations that are not the researchers' core interest (Connelly, Sackett, & Waters, 2013). In recent years, the propensity score weighting approach has become an increasingly acknowledged alternative for balancing exposure and control groups in observational studies, thereby improving causal inferences (Connelly et al., 2013; Miller & Chapman, 2001; Sbarra, Emery, Beam, & Ocker, 2014).

Here, we examined whether prior OC use in adolescence is associated with a higher 1-year prevalence of major depressive disorder (MDD) in adulthood. We also controlled for a large number of potential confounding variables that have previously been associated with OC use and/or depression, using a propensity score weighting approach.

Methods

Study population

We analysed data from women in the United States National Health and Nutrition Examination Survey (NHANES) (CDC National Center for Health Statistics, 2017) for whom information on mental health and age at first OC use was publicly available (NHANES 1999–2004). NHANES is a continuous program of cross-sectional surveys which combines interviews and physical examinations to assess the health and nutritional status of the U.S. population; it uses a complex, multistage, probability sampling design to select participants representative of the non-institutionalised population in the U.S. A sampling weight is assigned to each sampled person to control for the unequal probability of selection, nonresponse adjustment, and adjustment to independent population controls (CDC National

Center for Health Statistics, 2017). From 1999–2004, half of the NHANES sample aged 20–39 years was selected to receive interview modules assessing psychiatric disorders ($N =$ 1,243). We excluded women from our analyses who had incomplete data for either the depression module ($n = 3$) or in questions assessing OC use ($n = 4$), resulting in a final sample of $N = 1,236$ women (age: $M = 29.11$; $SD = 5.70$). Women with missing information on covariates were retained for unadjusted analyses but excluded from analyses involving propensity score weighting. Most of the covariates had $< 5\%$ missing data; the remaining four had $\leq 10\%$ missingness.

Ethical considerations

The study was approved by the National Center for Health Statistics Institutional Review Board and all participants provided informed consent.

Oral contraceptive use

Current and past OC use was determined via self-report in the reproductive health module of NHANES 1999–2004. Participants reported on whether they had ever used OCs, and if so, at what age they had first started using OCs, and whether they were currently using OCs. If they reported that they were not currently using OCs, they were asked at what age they had last taken OCs. We defined first OC use in adolescence as first intake of OCs at an age ≤ 19 years (Skovlund et al., 2016) and first OC use in adulthood as first intake of OCs at an age > 19 years. Women who reported that they had never taken any birth control pills were defined as never users of OCs. Following the procedures described in prior research with the same data set (Cheslack-Postava et al., 2015), we defined women as current OC users if they reported currently taking OCs or having recently taken OCs but stopped at an age equal to or one year lower than their current age; this definition of "current use" thus covered the same time period as the MDD diagnosis measure (i.e., 1-year prevalence).

Depression

A computer-assisted version of the World Health Organization Composite International Diagnostic Interview (CIDI) was administered to participants by trained interviewers to assess depression in the past 12 months (CDC National Center for Health Statistics, 2017). The CIDI is a fully standardised interview that is used to assess mental disorders. Because it can be administered by lay interviewers and does not assume the presence of a current disorder, it is considered to be especially suitable for large epidemiological studies (CDC National Center for Health Statistics, 2017). The CIDI has been demonstrated to show high concordance with standardised clinical assessment for 12-month prevalence estimates of mood disorders as reflected by an area under the curve of 0.83 (Haro et al., 2006). For all our analyses, diagnostic status for clinical depression was defined as meeting DSM-5 diagnostic criteria for MDD. None of the main results changed considerably when we used DSM-IV criteria instead.

Covariate selection

Covariates for the propensity score model were selected in a two-step procedure. First, we identified central demographic and sample characteristics (NHANES cohort, age, and educational level (high school graduate [reference]; less than high school education; education beyond high school), marital status (married or living with partner [reference]; never married; widowed, divorced or separated), poverty income ratio (a ratio of family income to poverty threshold), and ethnicity (non-Hispanic white [reference]; non-Hispanic black; Hispanic; other), and other variables that are theoretically or empirically linked to OC use and/or depression and were available in the dataset: body mass index (BMI; weight in kilograms divided by height in meters squared) (Luppino et al., 2010), age at menarche (Kaltiala-Heino, Kosunen, & Rimpelä, 2003), age at sexual debut (Kaltiala-Heino et al., 2003), smoking history (no [reference]; yes) (Kendler et al., 1993), sex of sexual partners (other-sex only [reference]; same-sex only or both sexes) (Charlton et al., 2013; Marshal et al., 2011),

diagnosed endometriosis (no [reference]; yes) (Chen et al., 2016), ever use of Depo-Provera or injectables to prevent pregnancy (no [reference]; yes) (Skovlund et al., 2016), ever use of other medication containing female hormones such as oestrogen and progesterone (no [reference]; yes) (Soares, Almeida, Joffe, & Cohen, 2001), current use of OCs for ever users (no [reference]; yes) (Skovlund et al., 2016), total duration of lifetime OC use (ever users only), and pregnancy in the past year (no [reference]; yes) (O'Hara, Schlechte, Lewis, & Varner, 1991). Second, following recommendations in the literature (DuGoff, Schuler, & Stuart, 2014), we selected those variables for our propensity score model that were related to the outcome (MDD), independently of whether they were also related to the exposure (history of OC use). Simulation studies show that inclusion of variables that are related to the outcome increases the precision of the estimated exposure effect without increasing bias; in contrast, including variables that are related to the exposure but not the outcome decrease the precision of the estimated exposure effect without decreasing bias (Brookhart et al., 2006).

We used $p < .20$ as a conservative threshold for variables to be selected as covariates (Cheslack-Postava et al., 2015). This resulted in 11 covariates being included in the propensity score model: age at menarche ($p = .15$), age at sexual debut ($p = .012$), education ($p = .10$), marital status ($p < .001$), BMI ($p = .003$), diagnosis of endometriosis ($p = .036$), ever use of other medication containing female hormones such as oestrogen and progesterone ($p = .012$), pregnancy in the past year ($p = .071$), smoking history ($p = .007$), sex of sexual partners ($p = .064$), and current OC use ($p = .17$) (ever users of OCs only). NHANES cohort, age, poverty income ratio, ethnicity, ever use of Depo-Provera or injectables to prevent pregnancy, and total duration of lifetime OC use were unrelated to MDD (all ps $> .38$) and were therefore not entered into the propensity score model.

Data analysis

Analyses were performed using the "survey" package in R (version 3.32-1; https://CRAN.R-project.org/package=survey) to account for the complex NHANES sampling design and sampling weights. We used a logistic regression model to estimate odds ratios (OR) and 95% confidence intervals (CI) of 1-year prevalence of MDD from onset of OC use. To allow concurrent comparison of the treatment group (first OC use in adolescence) with both comparison groups (first OC use in adulthood and never users of OCs) within the same statistical model, the treatment group was set as reference.

To balance pre-existing differences between the groups, we used a propensity score weighting approach. Propensity scores were obtained using the "twang" package in R (https://CRAN.R-project.org/package=twang) with the following specifications: (1) the target estimand was set to measure average treatment effect on the treated, with adolescent OC users specified as the treatment group; (2) method of measuring balance across covariates was the standardised effect size; (3) the number of iterations in the generalised boosted models were 3,000; and (4) sampling weights in the propensity score model were specified by NHANES sampling weights (Ridgeway, Kovalchik, Griffin, & Kabeto, 2015). Following the recommendations in the literature, sampling weights and propensity weights were then multiplied, and this combined weight was entered into the final analysis model (DuGoff et al., 2014). The final analysis model also accounted for other survey design features, including clustering and strata (DuGoff et al., 2014).

As a more stringent test to rule out the confound of early sexual activity, we then conducted a sensitivity analysis among women who had their sexual debut in adolescence. Moreover, to rule out that the presented results were an artefact of our specific age-based categories, we tested whether early OC use predicted MDD by using age at first OC use in years as a continuous (as opposed to categorical) predictor both across the whole sample and among women who had their sexual debut in adolescence.

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Results

Of the 1,236 eligible women, 561 (45%) had first used OCs in adolescence, 353 (29%) had first used OCs as adults, and 322 (26%) had never used OCs. Overall, 131 (11%) met the criteria for MMD according to DSM-5. Sample characteristics by history of OCs use are displayed in Table 1.

Addressing the proposed relationship between history of OC use and depression, adult women who had used OCs during adolescence showed a higher 1-year prevalence of MDD compared to both adult women who had never used OCs (odds ratio [OR] = 0.31, 95% CI = 0.16–0.60) as well as women who had only started using OCs in adulthood (OR = 0.54, 95% CI = 0.30–0.95) in the unadjusted model. These effects remained stable when controlling for a large number of potential confounders using propensity score weighting (Table 2). Balancing of potential confounders was successful: Except for diagnosis of endometriosis ($p = .14$), ever use of other medication containing female hormones ($p = .001$), and pregnancy in the past year ($p = .11$), all variables were well-balanced after applying propensity weighting (all ps > .26). Excluding women who had been pregnant in the past year, women with a diagnosis of endometriosis, and ever users of other medication containing female hormones from analyses did not change the core results.

Our sensitivity analysis among women who had their sexual debut in adolescence confirmed the results of our main analysis: Women who had used OCs during adolescence showed a significant increase in 1-year prevalence of MDD compared to both women who had only started using OCs as adults as well as women who had never used OC, both in the unadjusted and the propensity score weighted models (Table 3). Moreover, the effect was robust to using age at first OC use (in years) as a continuous predictor for ever users of OCs, both across the whole sample (OR = 0.90, 95% CI = 0.83–0.98) and women who had their sexual debut in adolescence (OR=0.89, 95% CI =0.81–0.98).

Discussion

In a U.S.-representative sample of 1,236 women, we found that prior OC use in adolescence predicted a higher 1-year prevalence of MDD in adulthood compared to both women who had never used OCs and women who had only started using OCs after adolescence. Specifically, compared to women who had used OCs during adolescence, women who had never used OCs had 0.31 times the odds (95% CI = 0.16–0.60) of meeting the criteria for MDD within the past year, and women who only started using OCs in adulthood had 0.54 times the odds (95% CI = 0.30–0.95). These disparities held after controlling for potential confounds in propensity score weighted models and in a subsample of women who had their sexual debut in adolescence. Our findings are consistent with a recent large-scale prospective study showing that OC use in adolescence is associated with increased depression (Skovlund et al., 2016). Critically, by indicating that women who had used OCs during adolescence were at heightened risk for depression in adulthood even when controlling for current OC use, our findings suggest that adolescence may represent a sensitive period during which the use of OCs could increase women's likelihood to develop depression until years after first exposure. This interpretation is in accordance with the abundant evidence from animal models showing that gonadal hormones can cause long-lasting changes in brain and behaviour especially during critical developmental periods such as puberty/adolescence (Berenbaum & Beltz, 2011; Schulz et al., 2009).

Interestingly, some other researchers using the NHANES or other cross-sectional datasets have come to a different conclusion: Namely, that there are no differences in depression between current users and non-users of OCs, or even a protective effect of OC use on depression (Cheslack-Postava et al., 2015; Toffol et al., 2011, 2012; Wiréhn et al., 2010). We believe that the seeming inconsistencies in these conclusions may be explained by key differences in how women are grouped. Specifically, all previous studies were primarily

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focused on investigating short-term, as opposed to long-term, effects of OC use. The majority of these studies therefore did not differentiate between never users and former users of OCs, instead combining them into a single non-user reference group which was then compared to current users (Toffol et al., 2011, 2012; Wiréhn et al., 2010). This practice of classifying both former and never users of OCs as non-users may lead to a substantial underestimation of both potential short and long-term effects of OC use on depression risk for at least two reasons that we discuss below.

First, adverse effects on mood are a known cause for discontinuation of OC use (Rosenberg & Waugh, 1998), potentially leading to a higher likelihood for women who are vulnerable to depression to discontinue OC use. With the common practice of combining both former and never users of OCs into one single non-user reference group, these depression-sensitive women would therefore be more likely to be included in the non-user reference group ("survivor effect"), which would result in an underestimation of a possible association between OC use and depression (Skovlund et al., 2016; Zettermark et al., 2018). Because we focus on first use of OCs rather than on current use, our study categorises comparison groups in a way that eliminates the possibility of our effects being driven by a survivor effect. Instead of assigning women who may have discontinued OC use due to adverse effects to the non-user reference group, we assigned all women who had first used OCs in adolescence to the first use in adolescence group and all women who had first used OCs in adulthood to the first use in adulthood group in our study, irrespective of whether they had ceased treatment in the meantime or not.

Second, a large majority (68%) of the former users in the current NHANES sample—a U.S.-representative sample—first used OCs during adolescence. Presumably, a similarly substantial percentage of women who are classified as "non-users" in the studies discussed above, are in fact former users who had first used OCs in adolescence. Assuming that there is

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indeed a detrimental long-term effect of adolescent use on depression risk as our data suggest, the practice of combining never users and former users into a single group of "non-users" could hinder the detection of any effects of OCs on adult women's mental health because the estimated depression risk for the reference group would be artificially inflated by the former users. Combining women in this way could in fact even lead to an apparent protective effect, especially in purely adult samples. Indeed, the few studies that reclassified groups into never users, former users, and current users in supplemental analyses support our interpretation: In these studies, never users of hormonal contraceptives showed a substantially lower incident rate of depression to both current and former users (Cheslack-Postava et al., 2015; Skovlund et al., 2016). Whereas others have interpreted this result as likely reflecting unmeasured baseline differences between women who never versus ever used hormonal contraception (Cheslack-Postava et al., 2015; Skovlund et al., 2016), the evidence presented here suggests that this pattern may rather (or in addition) be a sign of long-lasting effects of adolescent hormonal contraceptive use on mental health. In line with this interpretation, the only published study that reported comparisons between former and never users stratified by age group found that the increased depression risk for former compared to never users of hormonal contraceptives was more pronounced in adolescents (whose former use must have necessarily been in adolescence) compared to adults (whose former use may have been either in adolescence or adulthood) (Skovlund et al., 2016). Furthermore, all studies that compared current users with non-users (combining both former and never users) separately for different age groups including adolescents found stronger and substantially more consistent negative effects of OC use in adolescents than in adults (Lindberg et al., 2012; Skovlund et al., 2016; Zettermark et al., 2018).

Strengths and Limitations

We used a large and U.S.-representative sample to examine the hypothesised relationship between prior OC use in adolescence and 1-year prevalence of depression in adulthood. In contrast to previous large-scale studies investigating the relationship between OC use and depression, presence of depression in our sample was determined using a standardised diagnostic interview procedure for all participants, thereby providing a more precise measure of clinically relevant depression than proxies such as use of antidepressants or other psychotropic drugs (Lindberg et al., 2012; Skovlund et al., 2016; Wiréhn et al., 2010; Zettermark et al., 2018) or self-report surveys (Toffol et al., 2011, 2012). Because not all depressed individuals seek or have access to clinical help, our study may furthermore provide a less biased estimate of real depression risk than registry data on diagnoses of depression at a psychiatric hospital (Skovlund et al., 2016).

An apparent limitation of our study is that first use of OCs was assessed via retrospective self-report, which may be susceptible to recall bias. However, we found consistent results both when using age at first OC use in years as a continuous predictor and when using relatively broad age categories (age of first OC use at an age ≤ 19 years versus age of first OC use at an age > 19 years). As the latter analysis only requires participants to recall whether they started using OCs as teenagers or not, it seems unlikely that biased reporting would explain the observed patterns of results. In other words, even if participants were not able to recall the exact age at which they started using OCs, it seems unlikely that systematic biases would exist in their general recall of whether they had started using it as teenagers or not.

Further, we did not have access to information on the specific hormonal contraceptive formulations used by women in this study. This is a limitation, as OCs differ in whether they contain synthetic forms of oestrogen and progestogen or progestogen only, as well as in the specific types and dosages of synthetic oestrogen and progestogen used (Skovlund et al. 2016;

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Montoya & Bos, 2017). However, several large-scale studies indicate that even though effect sizes vary, depression rates in hormonal contraceptive users are consistently higher than in non-users across formulations at least in adolescents (Lindberg et al., 2012; Skovlund et al., 2016), thereby suggesting that a common (or similar) mechanism might be at play leading to the observed differences in depression risk. For instance, both combined OCs (containing both oestrogen and progestogen), as well as formulations containing only progestogen, suppress endogenous oestrogen and progestogen levels via negative feedback mechanisms, and both types of OCs additionally suppress endogenous testosterone production (Montoya & Bos, 2017). Because lowered levels of each of these hormones have been demonstrated to modify a variety of social-emotional behaviours and brain functions in animal models (Berenbaum & Beltz, 2011; Montoya & Bos, 2017; Schulz et al., 2009), suppression of endogenous hormone levels could be one plausible common mechanism that may contribute to the altered depression risk across OC formulations. Alternatively, the increased 1-year prevalence of MDD for adolescent OC users may be a more direct result of the administered synthetic sex hormones, which are not only available in higher levels but also more potent than their natural counterparts (Gebel Berg, 2015), or due to a suppression of the naturally fluctuating pattern. Indeed, natural variability in oestradiol levels in the menopause transition has been linked to depression symptoms (although it should be noted that greater variability predicted higher depression symptomology in this study; Gordon, Rubinow, Eisenlohr-Moul, Leserman, & Girdler, 2016). Future studies should systematically document short- and long-term effects of using different types of OCs (and other forms of hormonal contraceptives) in adolescence on mental health; this may also help to identify the specific biochemical mechanisms underlying the observed association.

Moreover, information on the duration of adolescent OC use was not available in our sample. Because the strength of potential adverse effects of adolescent OC use on long-term

depression risk may depend on duration of use, future studies should aim at investigating the effects of different treatment durations on long-term alterations in depression risk systematically, as has recently been done for first-time diagnoses (Skovlund et al., 2016).

Finally, it is important to acknowledge that the correlational nature of epidemiological data precludes causal conclusions. Although we show in our study that factors that have previously been proposed to explain the relationship between OC use and depression risk (e.g., age at sexual debut) do not account for the pattern of results, additional factors may still underlie the reported association between adolescent OC use and depression risk in adulthood.

Conclusion

In this study, we found that women who had used OC during adolescence show an increased risk to have a depressive episode in adulthood, years after first exposure. Critically, these findings were not accounted for by a large number of third variables that have previously been used to explain observed relationships between OC use and depression.

While providing women of all ages with access to effective methods of birth control is and should continue to be a major global health priority (Temmerman et al., 2015), the presented findings reveal an urgent need for future studies to address whether there is indeed a causal link between use of OCs and other forms of hormonal contraception in adolescence and the risk of developing depression and other psychopathologies in the short and long terms.

Key Points and Relevance

- Gonadal hormones during adolescence generate enduring neural and behavioural changes and contribute to differences between individuals

- We found that women who had used OCs during adolescence had a higher 1-year prevalence of depression in adulthood than both never users of OCs and women who only started using OCs in adulthood.

- The associations remained robust when a large number of potential third factors were accounted for using propensity score weighting.

- These findings suggest that OC use during adolescence may increase a woman's risk for depression years after first use.

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Table 1. Study sample characteristics depending on history of oral contraceptive use (weighted for the stratified sampling procedure if not noted otherwise).

	1st OC Use in Adolescence	1st OC Use in Adulthood	Never Users of OCs
Participants, unweighted, N (%)	561 (45%)	353 (29%)	322 (26%)
OC users, current, %	38%	48%	N/A
Age, mean (95% CI)	29.82 (29.26–30.38)	31.61 (30.77–32.24)	26.91 (26.01–27.81)
Age at menarche, mean (95% CI)	12.60 (12.44–12.76)	12.67 (12.49–12.83)	12.49 (12.28–12.71)
Age at sexual debut			
Mean (95% CI)	15.75 (15.54–15.96)	18.85 (18.82–19.37)	18.14 (17.64–18.93)
Categories			
Sexual debut in adolescence	97%	60%	55%
Sexual debut in adulthood	3%	39%	21%
Never	1%	1%	24%
Sexual partners, sex			
Men only	94%	95%	92%
Women only or both men and women	6%	5%	8%
Marital status			
Married/living with partner	66%	66%	39%
Separated, divorced, or widowed	13%	11%	5%
Never married	22%	23%	56%
Pregnant in past year	25%	28%	21%
Ethnicity			
Non-Hispanic white	72%	65%	46%

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Non-Hispanic black	14%	11%	17%
Mexican or other Hispanic	12%	20%	28%
Other	2%	4%	9%
Education			
College or above	60%	67%	53%
High school graduate	14%	12%	25%
Below high school	26%	22%	22%
Body mass index, kg/m^2, mean (95% CI)	26.74 (25.93–27.55)	25.75 (24.89–26.61)	27.09 (26.05–28.12)
Poverty income ratio, mean (95% CI)	2.70 (2.53–2.87)	3.03 (2.82–3.24)	1.98 (1.69–2.27)
Smoking history	51%	32%	29%
Diagnosis of endometriosis	11%	4%	2%
Ever use of Depo-Provera or injectables to prevent pregnancy	20%	15%	9%
Ever use of other medication containing female hormones	6%	3%	3%

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Table 2. Sample-weighted vulnerability to depression depending on history of oral contraceptive use.

	1st OC Use in Adolescence	1st OC Use in Adulthood	Never Users of OCs
Major Depressive Disorder			
1-Year Prevalence, % (95% CI)	16.1 (12.5–19.7)	9.3 (5.5–13.1)	5.7 (2.6–8.8)
Unadjusted association, OR (95% CI)	1.00 [Reference]	0.54 (0.30–0.95)	0.31 (0.16–0.60)
PS-adjusted association not controlling for current OC use, OR (95% CI)	1.00 [Reference]	0.34 (0.17–0.69)	0.31 (0.10–0.94)
PS-adjusted association controlling for current OC use, OR (95% CI)	1.00 [Reference]	0.36 (0.18–0.75)	N/A

Abbreviations: OC: oral contraceptive; PS: propensity score

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Table 3. Sensitivity analysis: Sample-weighted vulnerability to depression depending on history of oral contraceptive use among women who had their sexual debut in adolescence.

	1st OC Use in Adolescence	1st OC Use in Adulthood	Never Users of OCs
Major Depressive Disorder			
1-Year Prevalence, % (95% CI)	16.2 (12.5–19.8)	7.7 (3.3–12.1)	6.5 (2.5–10.4)
Unadjusted association, OR (95% CI)	1.00 [Reference]	0.43 (0.22–0.87)	0.36 (0.17–0.73)
PS-adjusted association not controlling for current OC use, OR (95% CI)	1.00 [Reference]	0.30 (0.14–0.65)	0.31 (0.10–0.92)
PS-adjusted association controlling for current OC use, OR (95% CI)	1.00 [Reference]	0.32 (0.15–0.70)	N/A

Abbreviations: OC: oral contraceptive; PS: propensity score

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