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There is no association between combined oral hormonal contraceptives and depression: a Swedish register-based cohort study

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Objective To investigate whether users of hormonal contraceptives (HCs) are at increased risk of depression compared with non-users.

Design Register-based cohort study.

Setting Sweden.

Sample Women aged 15–25 years between 2010 and 2017 with no prior antidepressant treatment, psychiatric diagnose or contraindication for HCs (n = 739 585).

Methods Women with a prescription of HC were identified via the Swedish Prescribed Drug Register (SPDR). Relative risks (RRs) for first depression diagnosis in current HC-users compared with non-users were modelled by Poisson regression. Adjustments included age, medical indication for HC-use and parental history of mental disorders, among others.

Main outcome measures Depression, captured by a redeemed prescription of antidepressant treatment, or a first depression diagnosis in the SPDR and the National Patient Register.

Results Compared with non-users, women on combined oral contraceptives (COCs) and oral progestogen-only products had lower or no increased risk of depression, relative risk (RR) 0.89 (95% CI 0.87–0.91) and 1.03 (95% CI 0.99–1.06) after adjustments, respectively. Age-stratified analyses demonstrated that COC use in adolescents conferred no increase in risk (RR 0.96, 95% CI 0.93–0.98), whereas use of progestogen-only pills (RR 1.13, 95% CI 1.07–1.19), contraceptive patch/vaginal ring (RR 1.43, 95% CI 1.30–1.58), implant (RR 1.38, 95% CI 1.30–1.45) or a levonorgestrel intrauterine device (RR 1.59, 95% CI 1.46–1.73) were associated with increased risks.

Conclusions This study did not find any association between use of COCs, which is the dominating HC in first time users, and depression. Non-oral products were associated with increased risks. Residual confounding must be addressed in the interpretation of the results.

Keywords Antidepressant treatment, combined oral contraceptives, depression, hormonal contraceptives, mental effects, pharmaco-epidemiology.

Tweetable abstract There is no association between combined hormonal contraceptives and depression.

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Introduction

Hormonal contraceptives (HCs) enable fertility control and alleviation of menstrual symptoms and are used by millions of women worldwide.[1] Combined oral contraceptives (COCs) are the most commonly used HCs in Europe and Northern America.[2,3] Although several studies have investigated the association between HCs and mental effects, there is as yet no consensus on the role of HCs on adverse mood symptoms.[4,5] Given that adverse mood continues to be one

of the main reasons for cessation, this matter causes considerable uncertainty for the woman and her physician during contraceptive counselling.[6,7]

Two randomised controlled trials (RCTs) suggested minor, yet significant worsening in anxiety, mood swings, irritation and general well-being in women allocated to a COC compared with women allocated to placebo.[8,9] No deterioration in depressive symptoms was noted in either RCT. Instead, women treated with COC had lower levels of depressive symptoms during the premenstrual phase.[8] Further, adverse mood during treatment was relatively common among placebo users, suggesting that adverse mood effects are not always causally related to HC exposure.[8,9] Although this study design enables control of known and unknown confounders, RCTs in this field are so far underpowered to detect rare outcomes such as mental health problems requiring treatment.

As for rare outcomes, two recent large-scale Nordic observational studies found an increase in psychotropic drug treatment or a first depression diagnosis in women who started HC.[10,11] The risk was most pronounced during adolescence, with continuously decreasing risks with age. The risk was present across all types of HCs, but greater risk estimates were noted for the non-oral regimens such as the vaginal ring or contraceptive patch – a finding with no obvious biological plausibility.

A large body of evidence highlights the importance of genetic and environmental contribution in affective disorders.[12,13] The Nordic studies have met with criticism; one limitation brought forward being that parental history of mental health problems was not considered.[14] To our knowledge, no study in this field has considered the influence of parents' mental health on the outcome.

The aim of this study was to investigate the association between HC use and depression, measured as antidepressant treatment or a first depression diagnosis subsequent to HC use. We wanted to use the strengths of a large-scale epidemiological study design but to improve the control of various confounders, including parental history of mental disease.

Methods

This was a cohort study based on data from six Swedish national population-based registers. The Swedish National Board of Health and Welfare provided data from the Swedish Prescribed Drug Register, the National Patient Register, the Swedish Medical Birth Register and the Cause of Death Register. Statistics Sweden provided data from the Total Population Register, the Multi-Generation Register and the Education Register.

The Prescribed Drug Register enables drug identification through Anatomical Therapeutic Chemical (ATC) classification codes and provides data on dispensed prescriptions for the entire Swedish population since July 2005, including prescriptions issued from the primary healthcare.[15] The National Patient Register was established in 1964 and contains information on dates of hospital enrolments and corresponding somatic and psychiatric diagnoses classified according to the International Classification of Diseases and Related Health Problems (ICD), with complete national coverage since 1987.[16] Since 2001, the National Patient Register has also recorded specialist outpatient visits. However, data from primary healthcare visits is not yet covered within the register.[16]

The Medical Birth Register covers deliveries in Sweden since 1973 and includes prospectively collected pregnancy and delivery-related data regarding mothers and newborn children.[17]

The Cause of Death Register provides dates and causes of all registered deaths since 1952.[18]

The Total Population Register is provided by Statistics Sweden and covers information on the identity of all Swedish residents registered as living in Sweden at some point since 1961. The Multi-Generation Register emanates from the Total Population Register and provides information on individuals born since 1932 and any relation to biological or adoptive parents.[19] The Education Register contains information on the highest achieved level of education in all Swedish individuals. The personal identity number (PIN) allocated to each Swedish citizen at birth or immigration allows reliable linkage of data across registries.[20]

Each somatic or psychiatric diagnosis referred to in the study was classified according to the International Statistical Classification of Diseases and Related Health Problems (ICD), with different revisions being adopted depending on which year the data (i.e. the diagnosis) was initially registered.[21]

Study population

All Nordic-born (i.e. born in Sweden, Norway, Finland, Denmark or Iceland) adolescents and women (referred to as women hereafter) aged 15–25 years at any time between 1 January 2010 and 31 December 2017 and residing in Sweden were identified through the Total Population Register and included in the study (Figure S1).

Women with a medical condition existing 5 years before entering the study that constitutes a contradiction to the use of HCs were excluded from the study: malignancies in breast or genital organs (ICD-10 codes D05, C50–C58), any cardiovascular disease including deep vein thrombosis (ICD-10 codes I10–I50, I20–I25, I26–I28, I42–I46, I49, I63, I74, I81–I82, O00–O007, O22, O87), infertility including redeemed prescription of ovarian-stimulating drugs (ICD-10 code N97, ATC code G03G), systemic lupus erythematosus (ICD-10 code M32) and migraine with aura (ICD-10 code G43.1).

Hormonal contraceptives are rarely used before age 15 in Sweden. Less than 1% of 13-year old girls are prescribed HC, and the corresponding number in 14-year-old girls is approximately 5%. As prescription in early adolescence often is due to unrecorded medical indications or targeted to vulnerable girls, we also excluded all women who had used any HC prior to age 15.

To capture only incident events of depression, women with any diagnosis of mental or behavioural disorders (ICD-10 code F05–F99) or antidepressant treatment (ATC classification N06A) 5 years before study start were excluded (4.5 years for women who entered the study in 2010). In addition, women who were prescribed any psychostimulant or non-psychostimulant medication (ATC classification code N06B) 5 years before study start were excluded.

Exposure

Women who were treated with any HC between 1 January 2010 and 31 December 31 2017 were identified through The Swedish Prescribed Drug Register. As HC can only be dispensed using a prescription issued by a physician or a midwife, all users during the time period have been included in the study.

Hormonal contraceptive use was defined as never, current or former use and was modelled as time-varying variables. Non-users formed the primary reference group, and included women who were never-users or former users. Never-users were used as reference group in secondary analyses, and consisted of women who had never used HC during the study period and the person-years women contributed with prior to their first HC prescription.

As any study-specific outcome due to hormonal exposure is unlikely in the first month of treatment, women were considered unexposed for the first 28 days after they had their HC prescription redeemed. Oral HCs and contraceptive patch/vaginal ring can be prescribed for 3 or 12 months. The length of prescription was available from the defined daily dose (DDD) information. The hormonal intrauterine device (IUD), implant and injection exposures were estimated as 5 years, 3 years and 3 months, respectively. All dispensed prescriptions were extended after 28 days.

Hormonal contraceptives were categorised according to route of administration (oral or non-oral) and as combined or progestogen-only products (POPs). COC products included ethinyl estradiol (EE) + levonorgestrel (LNG) (ATC codes G03AA07, G03AB03), EE + norgestimate (NGT) (ATC code G03AA11), EE + drospirenone (DRSP) (ATC code G03AA12), EE + desogestrel (DSG) (ATC code G03AA09), EE + dienogest (DNG) (ATC code G03AA16), EE + cyproterone acetate (CPA) (ATC code G03HB01), estradiol (E2) + nomegestrol acetate) and E2 + DNG (ATC code G03AB08). Oral POPs included norethisterone (ATC classification code G03AC01), lynesterole (ATC classification code G03AC03) and DSG (ATC classification code G03AC09). Non-oral combined products included contraceptive patch with EE + norgestrolmin (ATC code G03AA13) and vaginal ring with EE + etonogestrel (ATC code G02BB01). Non-oral POPs included injectable medroxyprogesterone acetate (DMPA) (ATC code G03AC06), implant (G03AC08) and LNG-IUD (ATC code G02BA03).

Outcomes

Depression was defined as either a redeemed prescription for antidepressant treatment (ATC code N06A) or a first depression diagnosis (ICD-10 codes F32–F33.9) between 1 January 2010 and 31 December 2017.

Covariates

The highest attained educational level at the end of the study period was categorised as ≤12 years, >12 years or unknown.

Medical indication for HC use included polycystic ovary syndrome (PCOS) (ICD-10 codes E282, L68), endometriosis (ICD-10 codes N80), heavy menstrual bleeding (ICD-10 codes N92), acne (ICD-10 codes L70), premenstrual syndrome (ICD-10 code N943) and dysmenorrhoea (ICD-10 codes N944–946).

Parental origin was categorised as (1) both parents born in the Nordic countries, (2) one parent born in the Nordic countries, (3) both parents born outside of Europe or (4) other. If any one of the parents of the women had been diagnosed with mental or behavioural disorders, or had committed suicide (ICD-8 codes 290–309, E9509–9599, ICD-9 codes 290–316, E950–E959, ICD-10 codes F05–99, X60–84) we considered this to be a parental history of mental disorders. We retrieved information on the parents from specialised inpatient care between 1971 and 2016 or specialised outpatient care between 2001 and 2016, and the information was linked to the women in the cohort using the Multi-Generation Register.

Data on body mass index (BMI) and smoking habits were collected from the Medical Birth Register and thus only included women who became pregnant during the study period. BMI (calculated as weight in kilograms divided by height in meters squared) was registered as a continuous variable. Smoking, if present, was categorised as yes (regardless of quantity) or no.

Statistical analyses

All women were followed upon entry in the study (1 January 2010, or on their 15th birthday) until event, emigration, death or the end of the follow up in (31 December 2017, or on their 26th birthday). We excluded women who developed a medical condition that constituted a contradiction to use of HCs. Further, women who developed any

mental or behavioural disorders during the study period were excluded (same diagnoses and psychostimulant treatment that were used for exclusion). Women with an event occurring simultaneously as a criterion for censoring were excluded. Women were temporarily censored 12 months before and 6 months after delivery.

Relative risks (RRs) for developing depression were modelled by Poisson regression on time split data. By formulating the model as a Poisson regression on time split data, several time-scales can be used and time-dependent associations are interactions between covariates and the time-scale (s).

Adjustments in the first model (Model 1) included age, calendar year, level of education, parental origin, and any diagnosis that suggested HC was used on medical indication. Age and calendar time were used as time scales and follow-up time within each woman was split into 1-year intervals, during which the rate was assumed to be constant. Continuous variables were modelled using restricted cubic splines with four knots placed at the 5th, 35th, 65th and 95th percentiles of each variable's marginal distribution.[22]

Adjustments in the second model (Model 2) included all the covariates in Model 1 and a parental history of mental or behavioural disorders and parental suicide.

Analyses included outcome incidence in relation to (1) type of HC exposure with non-users as reference group (2) type of HC exposure with never-users as reference group (2) the age of the woman (15–19 or 20–25 years). Supplementary analyses tested whether (1) adjustment for BMI and smoking changed the results (information only available in the 7.8% of women who had given birth) (2); the risk of HC-associated depression differed due to how the outcome was obtained, separating (i) women who filled a prescription for antidepressants and (ii) women who were diagnosed with depression; (3) whether start of exposure mattered for outcome incidence, assuming that (i) women started on the same day that they filled the prescription, (ii) 14 days after filled prescription or (iii) 28 days after filled prescription).

All analyses were performed using the freely available software R[23] version 3.6.1 using the Epi[24,25] and rms[26] packages.

Patient and public involvement

Neither patients nor the public was involved in the design, conduct, reporting or dissemination plans of the research.

Ethics

The study was approved by the Independent Research Ethics Board in Uppsala, Dnr 2017/546. The study was designed, conducted and consequently reported adhering to the 22-item STROBE-checklist.[27] No patient or patient organisation was involved in the planning or execution of the study.

Results

The cohort included 739 585 women, and 304 438 person-years, Table 1. A total of 77 613 events were recorded; 66 455 by an antidepressant prescription, and 16 111 by a depression diagnosis only. Demographic, medical and psychiatric variables in users, non-users, never-users and former users are shown in Table 1. The median age for users was 21 years, whereas for non-users and never-users it was 20 and 17 years of age, respectively. Non- and never-users had a lower educational level in comparison with current users, with the difference being most profound in never-users. Non- and never-users less often had parents who had been born in Sweden in comparison with current users, with the lowest number in never-users (Table 1). Current HC users had more often been diagnosed with dysfunctional uterine bleeding, dysmenorrhoea, endometriosis or polycystic ovary syndrome in comparison with non- and never-users, the difference with non-users being less profound.

Depression in relation to type of HC

Depression in relation to type of HC is shown in Table 2. In the fully adjusted model (model 2), women on COC had a lower risk of depression than non-users (RR 0.89, 95% CI 0.87–0.91). Women who used oral POPs or DMPA had no increased risk of depression compared with non-users: RR 1.03 (95% CI 0.99–1.06) and RR 0.82 (95% CI 0.70–0.98), respectively. Small risk increases were noted in patch/vaginal ring users (RR 1.27, 95% CI 1.21–1.33), in implant users (RR 1.23, 95% CI 1.19–1.27) and in LNG-IUD users (RR 1.34, 95% CI 1.29–1.39). The risk estimates were only marginally higher when never-users were used as reference group. For instance, the risk of developing depression in women on COC was not increased (RR 1.01, 95% CI 0.98–1.02), whereas a small increased risk was evident in women on oral POP (RR 1.11, 95% CI 1.07–1.14).

Sensitivity analyses with adjustment for BMI and smoking did not yield any marked changes to the risk estimates (Table S1). Analyses stratified by type of event (antidepressant prescription or depression diagnosis) yielded similar results (Table S2). Similar results were found in analyses where we assumed that women started using HC on the same day as they filled their prescription, 14 days after filled prescription or 28 days after filled prescription (Table S3).

Depression in relation to type of HC and age

Depression in relation to type of HC and age is shown in Table 3. In the fully adjusted model (model 2), age-stratified analyses showed that any HC use in women 15–

Table 1. Demographic, medical and psychiatric variables in users, non-users, never-users and former users

	Users	Non-users	Never users	Former users
Median age	21	20	17	22
Education				
>12 years	2 076 166 (86.5)	2 829 278 (78.2)	1 165 850 (68.0)	1 663 428 (87.5)
≤12 years	278 651 (11.6)	641 756 (17.7)	439 228 (25.6)	202 528 (10.7)
Unknown	44 635 (1.9)	145 198 (4.0)	109 510 (6.4)	35 688 (1.9)
Family				
Both parents from the Nordic countries	2 147 613 (89.5)	3 002 107 (83.0)	1 322 663 (77.1)	1 679 444 (88.3)
One parent from the Nordic countries	149 361 (6.2)	254 841 (7.0)	130 053 (7.6)	124 788 (6.6)
Both parents from outside EU	44 335 (1.8)	191 522 (5.3)	148 765 (8.7)	42 757 (2.3)
Other	58 656 (2.4)	168 432 (4.7)	113 378 (6.6)	55 054 (2.9)
Parental history of mental disorder	597 992 (24.9)	941 075 (26.0)	433 493 (25.3)	507 582 (26.7)
Parental history of suicide	11 843 (0.5)	16 603 (0.5)	6341 (0.4)	10 262 (0.5)
Medical indication for HC				
Acne	120 089 (5.0)	180 521 (5.0)	78 252 (4.6)	102 269 (5.4)
Dysfunctional bleeding	118 684 (4.9)	161 625 (4.5)	48 316 (2.8)	113 309 (6.0)
Dysmenorrhoea	92 253 (3.8)	128 134 (3.5)	42 681 (2.5)	85 453 (4.5)
Endometriosis	16 164 (0.7)	20 179 (0.6)	4290 (0.3)	15 889 (0.8)
Polycystic ovary syndrome	37 695 (1.6)	61 211 (1.7)	22 744 (1.3)	38 467 (2.0)
Depression	29 175 (1.2)	48 438 (1.4)	23 220 (1.4)	25 218 (1.4)
Prescribed antidepressants	26 071 (1.1)	41 592 (1.1)	18 292 (1.1)	23 300 (1.2)
Diagnosed in specialised psychiatric care	5100 (0.2)	11 327 (0.3)	7155 (0.4)	4172 (0.2)

Data presented in relation to person-years.

19 years old was associated with a minor increased risk compared with no use (RR 1.10, 95% CI 1.08–1.13). However, COC use in women 15–19 years conferred no risk increase (RR 0.96, 95% CI 0.93–0.98).

In contrast, use of oral POPs (RR 1.13, 95% CI 1.07–1.19), contraceptive patch/vaginal ring (RR 1.43, 95% CI 1.30–1.58), implant (RR 1.38, 95% CI 1.30–1.45) and LNG-IUD (RR 1.58, 95% CI 1.48–1.68) was associated with increased risks. Among women 20–24 years of age, use of COC and oral POPs was associated with a decreased risk, whereas use of any non-oral HC was associated with slightly increased risks (Table 3).

Discussion

Main findings

In this study, including almost 740 000 women, use of COC was associated with no risk of depression, independent of age and irrespective of which reference group was used in the analyses. Use of oral POPs conferred no overall increased risk of depression but was associated with a minor increased risk among adolescents. Non-oral HCs were associated with a small increased risk of depression compared with non-use across all age groups.

Strengths and limitations

This study has some major limitations that should be addressed. First, and most importantly, the observational design only allows us to find possible associations, and we cannot establish any causal relationships. Secondly, we collected depression diagnoses from the National Patient Register, which only covers specialised in- and outpatient care. To mitigate the fact that most women are diagnosed with depression in primary care, we also used prescriptions of antidepressants to establish our primary outcome.[28] However, antidepressants are not only used for treatment of depression but are also prescribed to women with various anxiety syndromes.[29] Using antidepressant treatment as a proxy for depression might thus be misleading, but should nonetheless capture women who develop mental health problems from HC-use. Similarly, medical indication for HC use was established through diagnoses from specialised care. Women with dysmenorrhoea, acne and PCOS are often not treated within specialised care. Consequently, some of these women who were prescribed HC for medical reasons might be categorised as healthy. This might lead to misclassification of confounders in the study, ultimately resulting in overestimation of risk.

The strength in this register-based study is the size of the study population, which allows for high power and good

Table 2. Risk of depression in relation to type of HC

Type of HC	Person-years	Events *n* (%)	Crude RR (95% CI)	Model 1* RR (95% CI)	Model 2** RR (95% CI)
(A) Risk of depression in relation to type of HC with non-users as reference group					
No use	1 947 129	48 438 (1.4)	ref	ref	ref
Any use	1 097 243	29 175 (1.2)	1.06 (1.04–1.08)	1.01 (0.99–1.03)	1.01 (1.00–1.03)
COC	707 468	16 281 (1.2)	0.87 (0.86–0.89)	0.88 (0.87–0.89)	0.89 (0.87–0.91)
Oral POPs	159 583	4468 (1.0)	1.08 (1.05–1.11)	1.04 (1.00–1.08)	1.03 (0.99–1.06)
Patch/Ring	52 847	1799 (1.2)	1.32 (1.26–1.38)	1.29 (1.23–1.35)	1.27 (1.21–1.33)
Implant	110 517	3834 (1.9)	1.39 (1.34–1.43)	1.28 (1.23–1.32)	1.23 (1.19–1.27)
DMPA	3400	136 (1.7)	1.56 (1.32–1.84)	0.88 (0.74–1.04)	0.82 (0.70–0.98)
LNG-IUD	65 596	2747 (2.1)	1.67 (1.60–1.73)	1.36 (1.31–1.41)	1.34 (1.29–1.39)
Type of HC	**Person-years**	**Events, *n* (%)**	**Crude RR (95% CI)**	**Model 1* RR (95% CI)**	**Model 2** RR (95% CI)**
(B) Risk of depression in relation to type of HC with never-users as reference group					
Never use	1 208 084	23 220 (1.4)	ref	ref	ref
Any use	1 097 243	29 175 (1.2)	1.38 (1.35–1.40)	1.30 (1.28–1.33)	1.29 (1.27–1.32)
COC	707 468	16 281 (1.2)	1.02 (1.00–1.04)	1.00 (0.98–1.02)	1.01 (0.98–1.02)
Oral POPs	159 583	4468 (1.0)	1.18 (1.14–1.22)	1.12 (1.09–1.16)	1.11 (1.07–1.14)
Patch/Ring	52 847	1799 (1.2)	1.36 (1.30–1.42)	1.33 (1.27–1.39)	1.33 (1.27–1.39)
Implant	110 517	3834 (1.9)	1.43 (1.39–1.48)	1.31 (1.27–1.35)	1.28 (1.23–1.32)
DMPA	3400	136 (1.7)	1.56 (1.32–1.85)	0.88 (0.75–1.04)	0.86 (0.73–1.01)
LNG-IUD	65 596	2747 (2.1)	1.69 (1.63–1.76)	1.38 (1.33–1.44)	1.37 (1.32–1.42)

COC, combined oral contraceptive; DMPA, medroxyprogesterone acetate depot; HC, hormonal contraceptive; LNG-IUD, levonorgestrel intrauterine device; POP, progestin-only products; RR, relative risk.

*Adjusted for age, calendar year, level of education, parental country of origin, and polycystic ovarian syndrome, endometriosis, dysfunctional uterine bleeding, acne and dysmenorrhoea.

**Adjusted for all the covariates in Model 1 plus parental diagnoses of mental or behavioural disorders and parental suicide. Non-users consisted of women who were never-users and former users. Never-users consisted of women who had never used HC during the study period and the person-years women contributed prior to their first HC prescription.

precision, and a small risk of false-positive findings. In addition, recall bias is non-existent when data are based on ATC- and ICD-codes.[30] The longitudinal design and the focus on relatively young women may provide some protection against healthy user bias, which is otherwise common in cross-sectional studies.[7]

In comparison with previous longitudinal studies in the field, our study is strengthened by controlling for the impact of parents' mental health history. Numerous studies have emphasised the genetic component in mental illness, and this should be taken into account when mental health is the outcome. The impact of parents' mental health did not, however, change the risk estimates in this study and the importance of this confounder might thus be questioned. Again, diagnoses of mental and behavioural disorders in the participant's parents were only collected from specialised care and thus more moderate forms of mental health problems were not accounted for. Similarly, information on mental health in parents born outside of Sweden may be incomplete. If this is the case, there is a possibility that the impact of this potential confounder might be underestimated.

Finally, we have tested both non-users and never-users as reference group. Although none of these groups may be completely ideal as they differed in background variables and gynecological diagnoses from the users, non-users differed less from the users than never-users did. For that reason, non-users was kept as reference group for the primary analyses.

Interpretation

The results in our study are both at odds and comparable to previous longitudinal register-based studies in the field.[10,11] In our study, COC use was associated with no risk of depression compared with non-use (and never-use), and we found no COC-induced risk for depression among the adolescents. In contrast, a Danish study reported small increased risks of antidepressant treatment or a first diagnosis of depression with COC use, and a greater risk among the adolescents.[10] This discrepancy points to an

Table 3. Risk of depression in relation to type of HC and age

Type of HC 15–19 years+	Person-years	Events, *n* (%)	Crude RR (95% CI)	Model 1* RR (95% CI)	Model 2** RR (95% CI)
No use	1 001 900	20 876 (1.3)	ref	ref	ref
Any use	370 864	10 111 (1.3)	1.29 (1.21–1.26)	1.11 (1.08–1.14)	1.10 (1.08–1.13)
COC	266 677	6337 (1.2)	1.06 (1.03–1.09)	0.95 (0.92–0.97)	0.96 (0.93–0.98)
Oral POPs	49 914	1494 (1.1)	1.30 (1.23–1.37)	1.15 (1.09–1.21)	1.13 (1.07–1.19)
Patch/Ring	10 565	401 (1.2)	1.61 (1.46–1.78)	1.45 (1.37–1.53)	1.43 (1.30–1.58)
Implant	33 455	1349 (2.1)	1.82 (1.73–1.93)	1.45 (1.40–1.51)	1.38 (1.30–1–45)
DMPA	522	22 (1.7)	1.83 (1.21–2.78)	0.73 (0.48–1.10)	0.67 (0.44–1.02)
LNG-IUD	10 356	539 (2.2)	2.32 (2.13–2.52)	1.62 (1.49–1.77)	1.59 (1.46–1.73)
Type of HC **20–25 years**	**Person-years**	**Events, *n* (%)**	**Crude** **RR (95% CI)**	**Model 1*** **RR (95% CI)**	**Model 2**** **RR (95% CI)**
No use	945 229	27 562 (1.5)	ref	ref	ref
Any use	726 379	19 064 (1.2)	0.90 (0.88–0.91)	0.91 (0.89–0.92)	0.91 (0.89–0.93)
COC	440 790	9944 (1.2)	0.76 (0.74–0.77)	0.79 (0.77–0.81)	0.80 (0.78–0.82)
Oral POPs	109 669	2974 (1.0)	0.96 (0.92–1.00)	0.96 (0.93–0.99)	0.96 (0.92–0.99)
Patch/Ring	42 281	1398 (1.2)	1.17 (1.11–1.24)	1.20 (1.14–1.27)	1.21 (1.14–1.27)
Implant	77 062	2485 (1.9)	1.17 (1.12–1.22)	1.13 (1.09–1.18)	1.11 (1.07–1.16)
DMPA	2878	114 (1.7)	1.41 (1.17–1.70)	0.92 (0.76–1.10)	0.90 (0.75–1.08)
LNG-IUD	55 240	2208 (2.1)	1.46 (1.40–1.52)	1.29 (1.23–1.35)	1.28 (1.23–1.34)

COC, combined oral contraceptive; DMPA, medroxyprogesterone acetate depot; HC, hormonal contraceptive; LNG-IUD, levonorgestrel intrauterine device; POP, progestin-only products; RR, relative risk.
*Adjusted for age, calendar year, level of education, parental origin, and any diagnosise that indicate HC use due to medical conditions (polycystic ovarian syndrome, endometriosis, dysfunctional uterine bleeding, acne and dysmenorrhoea).
**Adjusted for all the covariates in Model 1 plus parental diagnoses of mental or behavioural disorders and parental suicide.

important limitation within the hormonal contraceptive pharmaco-epidemiology field, where we assess effects of treatments women can choose themselves (or are advised to choose for reasons that cannot be captured by register information). The women in this study have the same physical characteristics as the women of previous studies and the same contraceptives have been used, yet the results for COCs are different among the two Nordic countries. The only conclusion from this is that there is residual confounding, and that factors that we, and others, have not accounted for, may have influenced the results. Such factors may include overall prescription patterns, the prescribers, women's preconception of HC, personality and medical use of HC.

In line with previous data, non-oral products yielded greater risk estimates compared with oral products, evident for both the combined and progestogen-only methods.[10] With small pharmacokinetic and pharmacodynamic differences, there is no clear biological explanation for the higher risk estimates for non-oral products.[31] Similarly, the lack of dose-related response to progestogen-only exposure calls for caution. Previous studies indicate that women who present with elevated depressive symptoms are more inclined (or, perhaps, are advised) to choose more effective and user-independent contraceptive methods such as IUDs and implants.[10,32,33] Further, the assumption that women who fill a prescription for an LNG-IUD will continue using it for 5 years (and, similarly, that an implant user will have the implant in place for 3 years) may contribute to the somewhat higher estimates in the LNG-IUD and implant users.

In line with previous studies, we found greater risk estimates in adolescents than non-adolescents when stratifying for age.[10,11] Several studies highlight that adolescents who use HCs differ in various aspects from their non-using peers. A study including 4765 American adolescents found that the increased risk of depressive symptoms among oral contraceptive users vanished after adjustments for sexual debut and smoking.[4] Early sexual debut and early start of HC use have previously been associated with an increased risk of depression.[34,35] Relationship- and social status should therefore be adequately addressed as potential

confounders. Another interpretation is that adolescents more often use HCs for medical reasons. These medical reasons, such as acne, can themselves constitute a risk factor for depressive symptoms.[36] In support of this, one longitudinal Australian study demonstrated that women who used oral contraceptives for reasons other than birth control were more likely to experience depressive symptoms compared with women who do not.[37]

Conclusions

Pharmaco-epidemiological studies are subject to multiple known and unknown confounders, and possible caveats must be considered when the results are interpreted. Our study, with a similar design to previous studies, found lower risk for depression in COC users, and no increased risk in oral POP users. The discrepancies with previous longitudinal register-based studies are likely explained by residual confounding, i.e. individual-level confounding that was not possible to capture from the registers used, than by an actual (positive or negative) association between exposure and the outcome.

Disclosure of interests

Marie Bixo serves occasionally as medical advisor for Asarina Pharma. Kristina Gemzell Danielsson reports honoraria for occasional lectures from MSD/Merck, Bayer AG, Gedeon Richter, Exeltis, Azanta, HRA-Pharma, Mithra, NaturalCycles, Campus Pharma and Exelgyn and her clinic has participated in clinical trials conducted by Exeltis, Mithra, Bayer, MSD, Removaid and Myovant. Over the past 5 years, I. Sundstrom-Poromaa has served occasionally on advisory boards or acted as invited speaker at scientific meetings for MSD, Bayer Health Care, Gedeon Richter, Peptonics, Shire/Takeda, and Lundbeck A/S. Rickard Ljung reports honoraria for occasional lectures from Pfizer. Rickard Ljung is also at the Swedish Medical Products Agency, SE-751 03 Uppsala, Sweden. The views expressed in this paper do not necessarily represent the views of the Government agency. Cecilia Lundin, Anna Wikman, Erik Lampa and Per Wikman have no conflicts of interest.

Contribution to authorship

Conception, planning, design and carrying out of the study: CL, AW, RL, KGD, ISP. Acquisition, data curation, interpretation of data: CL, PW, RL, ISP. Statistical analysis: EL. Drafting of the manuscript: CL, EL, ISP. Critical revision of the manuscript: AW, RL, MB, KGD.

Details of ethics approval

The study was approved by the Regional Ethical Review Authority in Uppsala, 14 February 2018. Reference number 2017/546.

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None.

Data availability

Data available from the authors on request.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Cohort recruitment flowchart.

Table S1. Risk of depression in relation to type of HC with non-users as reference group. Sensitivity analysis in women who had given birth, in whom information on BMI and smoking was available.

Table S2. Risk of antidepressant treatment or risk of being diagnosed with depression in specialist care in relation to type of HC. Non-users are used as reference group.

Table S3. Risk of depression in relation to hormonal contraceptive start, assuming that women started on the day they filled the prescription, 14 days after filled prescription or 28 days after filled prescription. Non-users are used as reference group. ■

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