PETITION ON HORMONAL CONTRACEPTIVES UPDATE 2023

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CONTRACEPTIVE STUDY GROUP

Table of Contents

List of Tables

Preliminary Statement

Hormonal contraceptives have been on the market for over 50 years and, while their formulations have changed, the basic mechanism of action has remained the same. During this time numerous studies have been performed documenting side effects, some of which appear over time, some within weeks or months, but all can have a serious impact on health. An effort was made to perform a series of comprehensive literature surveys to better understand immediate and long-term side effects of these agents. The results of this literature review have led to several recommendations. These recommendations are listed below with the documentation of the research noted on the following pages.

Action Requested

Drugs which should be removed from the market:

- Depot Medroxyprogesterone Acetate (DMPA)
    - Recommendation to remove from the market the injectable contraceptive Depot Medroxyprogesterone Acetate (DMPA; Depo Provera) based on conclusive evidence that it facilitates the transmission of HIV from men to women. Numerous alternatives are available.

Additional warnings that should be added to prescribing information.

- Breast Cancer
    - Combined estrogen-progestogen contraceptives (COCs, including oral, intravaginal and transdermal formulations) are acknowledged by IARC as Group I carcinogens. The National Cancer Institute acknowledges an increased risk of breast cancer with use of COCs. Substantial data supports an increased risk of breast cancer with the use of COCs. A warning should be added to the labeling of all COCs that they have been shown to increase the risk of breast cancer. Patient-related materials should also adequately convey this risk.
    - Progestogen-only contraceptives (POCs) have now also been extensively studied, with several large studies confirming a significantly increased risk of breast cancer with use of POCs. The National Cancer Institute acknowledges an increased risk of breast cancer with use of POCs. Additional studies confirm an increased risk for the development of breast cancer with POCs. A similar warning should be added to all POCs. Patient-related materials should also adequately convey this risk.
- Cervical Cancer
    - COCs have been linked to a significantly increased risk of cervical cancer. Similar data have been shown for POCs. More recent studies confirm this elevated risk, including for POCs. A warning should be added to the labeling of all COCs and POCs that they have been shown to increase the risk of cervical cancer. Patient-related materials should also adequately convey this risk.
- Inflammatory Bowel Disease
    - Significantly higher risk for the development of inflammatory bowel disease, especially Crohn's disease, but also ulcerative colitis, has been shown for COCs. Most recent studies confirm this increased risk, including for POCs especially with ulcerative colitis. A warning should be added to the labeling of all COCs that their use is linked to a significantly increased risk for the development of inflammatory bowel disease. Patient-related materials should also adequately convey this risk.
- Systemic Lupus Erythematosus (SLE)
    - Significantly higher risk for the development of SLE has been shown for COCs in several studies, especially the best-designed, largest cohort studies. A warning should be added to the labeling of all COCs that their use is linked to a significantly increased risk of the development of SLE. Patient-related materials should also adequately convey this risk.

- Depression and Suicide
    - Numerous studies indicate a significant relationship between hormonally active contraceptive use and depression as well as mood disorders and anxiety. Of particular concern is the high association between POCs and i) incident depression, ii) mood disorders, iii) Edinburgh Postnatal Depression Scale (EPDS) depression scores and major depression, iv) suicide/suicide attempts, v) depression, either diagnosed or anti-depressant medication prescription, and vi) depression at 3 months of use versus IUD use. A warning should be added to the labeling of all COCs and POCs that their use is linked to a significantly increased risk of the development of mood disorders and anxiety, depression, and suicide/suicide attempts. Patient-related materials should also adequately convey this risk.
- Venous Thrombosis and Cardiovascular Events
    - The current black box warning regarding thrombotic events on some formulations, notes "WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS." This is misleading and has shown to be misinterpreted by many women who infer that the increased risk only occurs with cigarette smoking and/or with being over 35 years of age. The warnings should be amended to state, "WARNING: INCREASED RISK OF SERIOUS CARDIOVASCULAR EVENTS INCLUDING BLOOD CLOTS."
    - This warning should be required for hormonal birth control products including oral, intravaginal and transdermal formulations. The patient-related materials should clearly explain the genetic risk factors, other risk factors, and the signs and symptoms. This warning should be included in ALL direct-to-consumer advertising (television, print, radio, etc.).

Additional safety information which should be added

- Multiple Sclerosis (MS)
    - Significantly higher risk for the development of MS has been shown for COCs in several studies, especially the best-designed, largest case-control studies. A warning should be added to the labeling of all COCs that their use appears to be linked to a significantly increased risk of the development of MS. Patient-related materials should also adequately convey this risk.
- Bone Fractures
    - Use of POCs is clearly associated with a higher risk of bone fractures. A black box warning should be added to the labeling of all POCs that their use is linked to a significantly increased risk of the development of bone fractures. Patient-related materials should also adequately convey this risk.
    - Protracted use of COCs has been associated with an increased risk of bone fractures. A warning should be added to the labeling of all COCs that their prolonged use may be linked to a significantly increased risk of the development of bone fractures. Patient-related materials should also adequately convey this risk.
- Body Mass Effects
    - For ANY progestin-releasing IUD:
        - Add to professional label in side effects/precautions:
            - Progestin-releasing IUDs (IUCs) have demonstrated in clinical trials to significantly increase % fat body mass with a corresponding decrease in % lean body mass over 1 year of use.
        - Add to patient-related materials:
            - Use of (Brand name) may increase the percent of fat in your body while decreasing the percent of lean body mass; this change in body composition is known to increase risk of other serious conditions such as diabetes and cardiovascular problems.

    - This warning should be included in all direct-to-consumer advertising (television, print, radio, etc.) as it demonstrates use of IUCs may contribute to other serious chronic health conditions.
    - Similar labeling should be considered for progestin-only contraceptives. Although the current evidence is less, it tends in the same direction.
- Urogenital Problems
    - Interstitial Cystitis: Significantly higher risk for the development of interstitial cystitis has been shown for COCs in two studies. A warning should be added to the labeling of all COCs that their use appears to be linked to a significantly increased risk of the development of interstitial cystitis. Patient-related materials should also adequately convey this risk.
    - COCs have also been linked to an increased risk of bacteriuria, urinary tract infections, bladder trabeculation, vulvovaginal candidiasis, vaginal dryness, vulvar vestibulitis, and Female Sexual Dysfunction (FSD) caused by OC-induced dyspareunia and reduced sexual desire and libido. These risks should be adequately conveyed in the prescribing information, especially FSD where there is substantial literature evidence.
- Autism and General Health in Offspring
    - Use of contraceptives may be associated with poorer health of offspring, and the use of progestin contraceptives at the time of conception has been associated with the development of autism in the offspring. These potential risks should be adequately conveyed in the prescribing information and patient-related materials.

List of Agents

A list of the agents discussed is shown below. Other than Depot Medroxyprogesterone Acetate (DMPA; Depo Provera) we refer in general to COCs (which refers to all combined estrogen-progestogen contraceptive formulations) and POCs (which refers to all progestin-only contraceptive formulations) regardless of the route of administration (e.g. oral, intravaginal, transdermal, implants, IUS/IUD, etc.).

Combined Estrogen-Progestin (EE-P) Pills

OVCON-35
FEMCON 35
FEMCON FE
BALZIVA 28
BRIELLYN 28
PHILITH
GILDAGIA
VYFEMLA
NEXESTA FE
and generic therapeutic equivalents
BREVICON
MODICON 28
NORMINEST FE
NORTREL 0.5/35-28
WERA
CYCLAFEM
CYONANZ
and generic therapeutic equivalents
GENERESS
KAITLIB FE
and generic therapeutic equivalents
NORINYL 1+35 28-DAY TABLETS
ORTHO-NOVUM 1/35 28 TABLETS
ALYACEN 1/35

ARANELLE
CYCLAFEM 1/35
DASETTA 1/35
NORTREL 1/35-28
NYLIA 1/35
PIRMELLA 1/35
and generic therapeutic equivalents
ORTHO-NOVUM 7/7/7-28
ALYACEN 7/7/7
CYCLAFEM 7/7/7
DASETTA 7/7/7
NORTREL 7/7/7
NYLIA 7/7/7
PIRMELLA 7/7/7
TRI-NORINYL 28-DAY
ARANELLE
NORINYL 1+50 28-DAY
LOESTRIN 21 1/20
LOESTRIN 21 1/20 FE
MINASTRIN 24 FE
TAYTULLA
MIBELAS 24 FE
MICROGESTIN 1/20
MICROGESTIN FE 1/20
JUNEL 1/20
GILDESS 1/20 and GILDESS FE 1/20
LARIN 1/20 and LARIN FE 1/20
BLISOVI 1/20 and BLISOVI FE 1/20
AUROVELA 1/20 and AUROVELA 1/20 FE
HAILEY 1/20 and HAILEY FE 1/20
and generic therapeutic equivalents
LOESTRIN 21 1.5/30
LOESTRIN FE
MICROGESTIN 1.5/30
MICROGESTIN FE
AUROVELA 1.5/30
AUROVELA FE 1.5/30
BLISOVI FE 1.5/30
GILDESS 1.5/30
GILDESS FE 1.5/30
JUNEL 1.5/30
JUNEL FE
LARIN 1.5/30
LARIN FE
ESTROSTEP 21
ESTROSTEP FE
TRI-LEGEST 21
TRI-LEGEST FE
and generic therapeutic equivalents
ZOVIA 1/35E-28

KELNOR
and generic therapeutic equivalents
LOW-OGESTREL-28
CRYSELLE
ELINEST
OGESTREL 0.5/50-28
LoSEASONIQUE
LO SIMPESSE
and generic therapeutic equivalents
ALESSE
LEVLITE
LESSINA-28
AVIANE-28
BALCOLTRA
AFIRMELLE
FALMINA
ORSYTHIA
VIENVA
and generic therapeutic equivalents
QUARTETTE—91-DAY
FAYOSIM
SEASONALE
INTROVALE
ALTAVERA
AYUNA
QUASENSE
SETLAKIN
LEVORA 0.15/30-28
KURVELO
PORTIA-28
MARLISSA
SEASONIQUE
ASHLYNA
DAYSEE
JAIMIESS
SIMPESSE
and generic therapeutic equivalents
TRIVORA-28
ENPRESSE-28
LEVONEST
ELIFEMME
MYZILRA
and generic therapeutic equivalents
DESOGEN
EMOQUETTE
ENSKYCE
ISIBLOOM
KALLIGA
and generic therapeutic equivalents
KARIVA

KIMIDESS
VIORELE
PIMTREA
VOLNEA
BEKYEE
and generic therapeutic equivalents
CYCLESSA
VELIVET
and generic therapeutic equivalents
ORTHO-CYCLEN-28
SPRINTEC
PREVIFEM
MONO-LINYAH
ESTARYLLA
MILI
and generic therapeutic equivalents
ORTHO TRICYCLEN 28
TRI-SPRINTEC
TRIPREVIFEM-28
TRI-LINYAH
TRI-ESTARYLLA
TRI-MILI
and generic therapeutic equivalents
ORTHO TRI-CYCLEN LO
TRI-PREVIFEM
TRI LO SPRINTEC
TRI-LO-ESTARYLLA
TRI-LO-MILI
and generic therapeutic equivalents
YAZ
LORYNA
NIKKI
MELAMISA
LO-ZUMANDIMINE
and generic therapeutic equivalents
BEYAZ
and generic therapeutic equivalents
YASMIN 28
SYEDA
YAELA
ZUMANDIMINE
and generic therapeutic equivalents
SAFYRAL
NATAZIA

Combined EE-P Contraceptive Patch

ORTHO EVRA
XULANE

Combined EE-P Contraceptive Ring
NUVARING

Progestin-Only Pills
MICRONOR TABLETS
NOR-QD TABLETS
CAMILA
ERRIN
HEATHER
JENCYCLA
INCASSIA
and generic therapeutic equivalents

Progestin-Only Injectable
DEPO PROVERA

Progestin-Only Implants
JADELLE
NEXPLANON

Progestin-Only IUS/IUD
MIRENA IUS
LILETTA IUD
SKYLA IUD
KYLEENA IUD

Over-The-Counter
OPILL (norgestrel)

Statement of Grounds

Risk of HIV Transmission

One of the most common forms of steroidal contraception is the injectable contraceptive: Depot medroxyprogesterone acetate (DMPA). DMPA is highly effective and requires only quarterly injections, as opposed to daily oral ingestion. As a long-acting type of effective contraceptive, it is not unique, as there are other injectable or implantable contraceptives in wide use, e.g., norethisterone enanthate (NET), as well as other delivery systems such as vaginal rings and patches.

However, evidence began emerging in the 1990s, which has become compelling in recent years, that DMPA is unique among contraceptives in its property of facilitating the transmission of HIV. This dangerous characteristic has been abundantly and unequivocally documented through several lines of evidence which are summarized below:

Epidemiological Evidence

A. Four meta-analyses (3 reports) were published in 2015. Each used different inclusion criteria and compiled the data on different numbers of studies, yet all 4 came up with essentially the same result of significantly increased risk of male-to-female HIV transmission in women using DMPA (Table 1).

Table 1 – Meta-Analyses Evaluating Risk of HIV Transmission with Depot medroxyprogesterone acetate (DMPA)

Meta-analysis	**# Included studies**	**Pooled Adj. OR or HR (95% CI)**
Ralph et al. 2015	10 (longitudinal)	HR 1.40 (1.16–1.69)
Morrison et al. 2015	18 (longitudinal)	HR 1.50 (1.24–1.83)
Brind et al. 2015	8 (cross-sectional)	OR 1.41 (1.15–1.73)
Brind et al. 2015	16 (longitudinal)	HR 1.49 (1.28–1.73)

B. Ten primary studies (all longitudinal, published between 2003 and 2014, listed in Table 2 below) were methodologically robust enough to meet the inclusion criteria of all 3 published reviews.

Table 2 – Individual Studies of the Effects of DMPA HIV Transmission

Study	Yr.(s) of study	Pop. size	Nation and locale	Subject source	Months of follow-up	Follow-up interval (months)	Type of data shown	HR or IRR (95% CI)	Weight (%)
Crook 2014	2005–2009	8,663	S Africa, Uganda, Tanzania, Zambia	Microbicide trial sero-disc. couples	12	1	Inv. Prob. W'ted HR	1.45 (1.09–1.93)	16.39
McCoy 2013	2003–2007	4,913	South Africa, Zimbabwe	Diaphragm/gel HIV prev. trial	24	3	MV HR	1.22 (0.85–1.76)	13.20
Morrison 2012	2004–2007	5,567	South Africa	General population	9–24	3	MSM HR	1.27 (0.93–1.73)	15.32
Wand 2012	Not reported	2,236	Durban, S. Africa	>90% from microbicide trial	Not reported	3	MV HR	2.02 (1.37–2.99)	12.22
Heffron 2012	2004–2010	3,790	7 African nations	Sero-discordant couples	12–24	3	MSM HR	3.93 (1.38–11.21)	2.81
Morrison 2007	1999–2004	6,109	Uganda, Zimbabwe, Thailand	Family planning clinics	21.5	3	MSM HR	1.25 (0.88–1.77)	13.86
Myer 2007	2000–2004	4,073	Cape Town, So. Africa	General population	24	6,6, & 12	MV IRR	0.75 (0.33–1.69)	4.36
Kleinschmidt 2007	1999–2001	551	Orange Farm, So. Africa	Family planning clinic	12	3	MV HR	0.46 (0.06–3.66)	0.78
Baeten 2007	1993–1997	779	Mombasa, Kenya	CSW	120	1	MV HR	1.73 (1.28–2.34)	15.69
Kiddugavu 2003	1994–1999	5,117	Rakai, Uganda	General population	31	10	IRR, MLR	0.84 (0.41–1.72)	5.37

Importantly, no consistent association has emerged with regard to oral contraceptives or other injectable or implantable contraceptives and the facilitation of HIV transmission.

Mechanistic Evidence

A. *In vivo* evidence of increased HIV transmission: Heffron et al. (2012) reported the increased presence of HIV-1 RNA in genital fluids of women using DMPA.

B. *In vitro* evidence of increased HIV replication at the cellular level: Maritz et al. (2018) reported experimental evidence of increased replication of HIV in human blood monocytes with medroxyprogesterone acetate (MPA).

C. Experimental evidence of agonistic binding to the glucocorticoid receptor (GR) as the mechanism for DMPA's immunosuppression: over the last 15 years, abundant experimental evidence of cytotoxic and immunosuppressive action of DMPA via its agonistic binding to the GR of human leukocytes has been reported (Schindler 2003; Hapgood and Tomasicchio 2010, Hapgood 2014.) Thus, Huijbregts et al. (2014) reported experimental evidence of immunosuppression of human T cells in vitro by MPA. Tomasicchio et al. (2013) reported experimental evidence of increased human T-cell destruction in vitro via the glucocorticoid receptor (GR) with MPA. Hapgood et al. (2014) reported:

> *"that MPA, unlike NET and progesterone, represses inflammatory genes in human PBMCs (peripheral blood mononuclear cells) in a dose-dependent manner, via the glucocorticoid receptor (GR), at concentrations within the physiologically relevant range. These and published results collectively suggest that the differential GR activity of MPA versus NET may be a mechanism whereby MPA, unlike NET or progesterone, differentially modulates HIV-1 acquisition and pathogenesis in target cells where the GR is the predominant steroid receptor expressed."*

D. Evidence of mechanism of MPA action at the gene expression level: experimental evidence of MPA-mediated suppression of inflammatory genes via GR in cultured human cells (Govender 2014) demonstrated the suppression of inflammatory genes in cultured human endocervical cells.

Summary and Conclusions:

DMPA, in contrast to all other steroidal contraceptives, has now conclusively been demonstrated to significantly increase the risk of HIV transmission from infected men to women. The robust epidemiological association has been supported by *in vivo* evidence of increased HIV RNA in the female genital tracts of women using DMPA. Moreover, abundant experimental evidence has shown that MPA, due to its agonistic binding of the GR, specifically represses the innate immune responses of both circulating human leukocytes and endocervical cells and allows for increasing HIV replication. The demonstration in the literature of the chain of causation is therefore compelling.

In the United States, where the availability of a wide range of contraceptive drugs and devices is virtually universal, and where, among these contraceptive choices, one and only one particular method—DMPA—is now known to increase the transmission of an often-fatal viral infection (HIV/AIDS), there can be no justification for such a drug's continued availability in the marketplace. It should be removed from the marketplace by the FDA without further delay.

Risk of HIV Transmission References

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Postscript Re: Petition for removal of DMPA from US market due to increased risk of HIV transmission:

New ECHO Trial study presents confirmation disguised as refutation

Three systematic reviews and meta-analyses (SRMAs) of studies on the risk of HIV acquisition of HIV infection by women using DMPA were published in 2015. One of them (Morrison 2015) concluded that their analysis "adds to the evidence that DMPA may increase HIV risk." They further suggested that "A randomized control trial would provide more definitive evidence about the effects of hormonal contraception, particularly DMPA, on HIV risk."

On June 13 of 2019, the results of precisely such a randomized control trial were published in the Lancet by the ECHO Trial Consortium, the trial having been designed by a group of ten that includes 3 of the authors of the 2015 Morrison SRMA (Morrison, Baeten and Rees). However, in stark contrast to their 2015 conclusion, the ECHO group, which studied DMPA in comparison to the copper IUD and the levonorgestrel (LNG) implant, concluded: "We did not find a substantial difference in HIV risk among the methods evaluated, and all methods were safe and highly effective."

However, a careful analysis of the design and results of the ECHO Trial reveals that in fact, the ECHO Trial results of 2019 provide a near perfect confirmation of the results of the 2015 Morrison SRMA, and that the authors misrepresent them as the opposite; as the exculpation of DMPA as "safe".

The performance of an appropriate randomized control trial presented the ECHO Trial Consortium with serious ethical and scientific challenges. First, the very idea of the need to conduct such a trial of a medical drug or device for an elective condition (contraception) which had already been shown to present significant risk elevation for the contraction of a potentially life-threatening infection (HIV) by three independent SRMAs, reviewing data that had been accumulated in dozens of studies dating back over a quarter century, is ethically problematic, to say the least. This is especially true in the case of DMPA, a contraceptive progestin that stands alone among many such available, in its property of being a glucocorticoid agonist, the likely mechanism by which it increases HIV risk. Indeed, the Morrison SRMA was the most mildly worded of the three 2015 SRMAs, with that of Ralph et al. suggesting that the risk might "merit complete withdrawal of depot medroxyprogesterone acetate" from the market, and that of Brind (2015), concluding that the evidence that DMPA increases the risk of HIV transmission was now "compelling".

Secondly, assuming that conducting such a study at all would be ethically valid, the WHO (2017) changed the guidance for use of DMPA from category 1 ("no restriction") to category 2 ("a condition where the advantages of using the method generally outweigh the proven or theoretical risks"), relating to the use of DMPA as a contraceptive in women at high risk of HIV acquisition. This guidance was based on the three 2015 SRMAs. At the very least, this new WHO guidance would need to be disclosed to all the ECHO study subjects, and the ECHO study notes that all participants in the study "were provided with this updated information". But the providing of such information presents a clear ethical challenge itself, in the context of a trial wherein subjects are randomly assigned to one of three groups, only one of which was clearly already known to facilitate HIV transmission. What of women who were assigned to the DMPA group? On the one hand, advising them that they were now in the highest risk group regarding HIV infection would unblind them and likely encourage them to opt out of the study, thus rendering the study scientifically invalid. On the other hand, not so advising these women would constitute withholding information on the risks of the proposed medication, a clear violation of the need to obtain informed consent. Determined to conduct a scientifically valid study, it would seem, the ECHO Consortium opted to make "concerted efforts to not provide additional or differential information or counseling to women in the DMPA-IM group."

Thirdly, assuming (*arguendo*) that the ethical challenges have been adequately met by the study design, there is the challenge of scientific validity. In such a trial a critical aspect of study design is the statistical power of the

study; to ensure that the statistical power is adequate to either confirm or reject the earlier findings. As noted in our petition, the three 2015 SRMAs arrived at virtually the same results, in the comparison of women using DMPA to those using no form of hormonal contraception. The results obtained by Morrison et al. included an overall HR = 1.50 (95% CI 1.24-1.83). But Morrison et al. also compared DMPA use to combined oral contraceptive (COC) use: HR = 1.43 (95% CI 1.23-1.67) and to use of the injectable progestin norethisterone enanthate (NET-EN). In contrast, there was no significant increase in HIV infection risk with either NET-EN (HR = 1.24; 95% CI 0.84-1.82) or COC use (HR = 1.03; 95% CI 0.88-1.20). Importantly, they also compared the use of each of the three methods to each other, and they reported that, compared to NET-EN, DMPA use was still associated with significantly elevated HIV infection risk: HR = 1.32 (95% CI 1.08-1.61). In the new ECHO study, three contraceptive methods (DMPA, copper IUD and LNG implants) were compared only to each other. Therefore, the key comparison (in regard to DMPA) was clearly between the effects of DMPA v. the effects of LNG, another long-acting, progestin only contraceptive steroid, and one which, like NET-EN and unlike DMPA, has neither been found to significantly elevate HIV infection risk, nor to interact with the glucocorticoid receptor. Since the appropriate comparison in the 2015 Morrison SRMA was between DMPA and NET-EN use, a perfect replication of the result they obtained thereby would be a statistically significant elevation in the neighborhood of HR = 1.3. Hence it is puzzling that the ECHO study was statistically designed thus:

"The trial was designed with 80% power to detect a 50% increase in the hazard of HIV for each contraceptive method compared with each of the others (ie, DMPA-IM *vs* copper IUD, DMPA-IM *vs* LNG implant, and copper IUD *vs* LNG implant). We chose a 50% increase in HIV risk on the basis of formative work with stakeholders to determine a meaningful difference that would inform policy change."

In other words, the ECHO consortium was not concerned with the scientific imperative of repeating or refuting their earlier results. Rather, they had made the decision that anything less than a 50% increase in HIV infection risk was not "a meaningful difference", thus to be ignored. Not surprisingly then, the result obtained in the ECHO study, comparing DMPA use to LNG use, was (in their "continuous use" dataset, Table 2 in ECHO 2019), HR = 1.29 (95% 0.98-1.71). Therefore, although this result is virtually identical to the result Morrison et al obtained in their 2015 SRMA, it just failed to achieve statistical significance at the 0.05 level (p=0.06), due to the study's having been underpowered to detect this difference.

Yet the ECHO Consortium seized upon this result to call DMPA "safe and effective" (along with the other two methods tested), and their literal bottom line conclusion was: "These results support continued and increased access to these three contraceptive methods."

From both a scientific and an ethical point of view, this conclusion is clearly erroneous. Six women died in the DMPA group out of the 2609 enrolled, compared to only one death in the LNG group (There were 143 v 116 cases of HIV infection in the DMPA v. LNG, respectively.) Thus DMPA appeared responsible for 5 excess deaths (and 27 excess cases of HIV infection); about 0.19% of its users, in a maximum follow-up period of only 12-18 months (average 1.33 years follow-up for the 7829 women participating with a total of 10,409 woman-years of follow-up time). If a woman's reproductive life is estimated to be about 25 times the follow-up period, from age 13 until about age 45, that would come out to a death rate of about 5% of women using DMPA compared to other injectable or implantable progestins over the course of their fertile years. The excess rate of HIV acquisition would likely cause far more excess deaths. This increased risk of death is clearly not acceptable.

We can see no justification whatsoever for the continued availability of DMPA in the US market. This detailed analysis of the ECHO Consortium study only underscores our earlier conclusion.

References cited (additional to those in the original petition)

Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial Consortium. HIV incidence among women using intramuscular depot medroxyprogesterone acetate, a copper intrauterine device, or a levonorgestrel implant for contraception: a randomised, multicentre, open-label trial. *Lancet*. 2019 Jun 13. pii: S0140-6736(19)31288-7 www.thelancet.com Published online June 13, 2019 http://dx.doi.org/10.1016/S0140-6736(19)31288-7

WHO. Hormonal contraceptive eligibility for women at high risk of HIV. Geneva: World Health Organization, 2017.

Cancer

Papers were accessed from a PubMed literature review as noted (Williams 2018). Each paper was rated based on the parameters noted in the STROBE statement (von Elm et al. 2007).

Breast Cancer

Breast cancer is the most commonly diagnosed cancer (excluding non-melanoma skin cancers) in women in developed nations, including the U.S., with 1.7 million cases diagnosed worldwide annually. It accounts for 20% of all cancers in women.[1] According to the Surveillance, Epidemiology and End Results (SEER) statistics[2], it is estimated that there are about 3,418,000 women with invasive breast cancer in the USA as well as over 60,000 cases of in situ cancers. There will be about 266,000 new cases of breast cancer in 2018, accounting for 15.3% of all new cancer cases, with about 41,000 deaths, accounting for 6.7% of all cancer deaths. Nulliparity or late childbearing and high body mass index are risk factors for breast cancer as is exposure to COCs and HRT. Any risk factors that are controllable should be minimized. The data for breast cancer is shown split into cohort studies (Table 3), case control studies (Table 4) and meta-analyses (Table 5).

The carcinogenicity of combined estrogen-progestogen contraceptives was evaluated by IARC working groups initially in 1998 (monograph published in 1999) and again in 2005 (monograph published in 2007). This was most recently updated with studies published through May 2008 (IARC 2012). Since that time, several important studies have been published, most of which are supportive of the IARC classification of COCs as Group I carcinogens and in agreement with the IARC evaluation of specific cancer types. In addition, several important studies have been published evaluating COCs and their cancer risk. In 2002 the National Toxicology Program added steroidal estrogen as a known human carcinogen (Report on Carcinogens, Fourteenth Edition available at https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html).

In agreement with IARC the recent data confirms an increased risk of breast cancer with use of COCs (Table 2). After 2005, there continue to be studies demonstrating the significant risk of breast cancer with hormonal contraception. In January 2006, the *New England Journal of Medicine* published a review article which found estrogen-progestin drugs increased breast cancer risk (Yager 2006). In October 2006 the *Mayo Clinic Proceedings* published a meta-analysis confirming estrogen-progestin drugs increase premenopausal breast cancer (Kahlenborn 2006).

The studies that looked at recent use (within 1–5 years) or current use of COCs in premenopausal women showed the most dramatic increased risk for breast cancer. In a case control study, women ages 20-49 years with use of COCs within a year had an increased risk of breast cancer (OR, 1.5; 95% CI, 1.3–1.9) (Beaber 2014). The same study showed an increase in risk depending on the formulation with triphasic COCs carrying a markedly increased risk (OR, 3.1; 95% CI, 1.4–4.7). In another large case control study of women ages 20-45 years, use of COCs for a year or more resulted in a 2.5-fold increased risk of triple-negative breast cancer (95% CI 1.4–4.3) but not for the receptor-positive breast cancers. In the same study, women 40 years or younger with a year or more use of COCs had a higher relative risk of triple-negative breast cancer (RR, 4.2; 95% CI, 1.9–

[1] https://www.wcrf.org/int/cancer-facts-figures/data...cancers/breast-cancer-statistics.
[2] https://seer.cancer.gov/statfacts/html/breast.html.

9.3) (Dolle 2009). A cohort study of over 35,000 postmenopausal women found a significantly increased risk of breast cancer in women on hormone replacement therapy (HRT) if they had used COCs in the past (RR, 2.45; 95% CI, 1.92–3.12) as compared with never users (RR, 1.67; 95% CI, 1.32–2.12) (Lund 2007). There also appears to be an increased risk for African American women on COCs within the past five years for ER+ cancers (OR, 1.46, 95% CI, 1.18–1.81), for ER- cancers (OR, 1.57; 95% CI, 1.22–1.43) and for triple-negative cancers (OR, 1.78; 95% CI, 1.25–2.53) with the risk of ER+ cancers continuing for 15–19 years after stopping the COCs (Bethea 2015).

In a French study (DeLort 2007) of 934 women who developed breast cancer, the use of COCs increased the risk of early development of breast cancer (OR, 1.84; 95% CI, 1.38–2.44). However, initiating COCs after age 23 reduced the risk (OR, 0.52; 95% CI, 0.34–0.79). Use of the levonorgestrel-releasing IUD, commonly used to treat abnormal bleeding in the perimenopause, increased the risk of developing breast cancer in postmenopausal women (OR, 1.48, 95% CI, 1.10–1.99) (Heikkinen 2016). The risk varies with the formulation as current use of a triphasic pill containing levonorgestrel carries an excess risk of causing breast cancer (RR, 3.05; 95% CI, 2.00–4.66) (Hunter 2010). In a large prospective cohort study of 1.8 million Danish women ages 15 to 49, enrolled and followed from 1995 to 2012 through various national registries, the risk of breast cancer among current or recent users increased depending on length of use from RR, 1.09 with less than one year of use (95% CI, 0.96–1.23) to an RR, 1.38 (95% CI, 1.26–1.51) for more than 10 years of use (Mørch 2017). They found the increased risk persisted after discontinuing use if COCs were used for 5 years or more. These investigators also found an increased risk in current or recent use of the progestogen-only intrauterine device (RR, 1.21; 95% CI, 1.11–1.33).

In most Western countries, 5% to 10% of all breast cancer cases are due to a main genetic cause: mutations of the BRCA1 and BRCA2 genes constitute 90% of hereditary breast cancer cases (Mehrgou 2016). These women are often begun on COCs at an early age to reduce their risk of ovarian cancer. However, in a case control study of 2,492 matched pairs of women with the *BRCA1* gene, COC use was associated with an increased risk of early onset breast cancer if begun under the age of 20 (OR, 1.45; 95% CI, 1.20–1.75) (Kotsopoulos 2014) and the risk increased by 11% for each additional year of use.

More recent publications include data from some very recent, large cohort studies (Mørch 2017, Heikkinen 2016, Poosari 2014) with RRs ranging from 1.2 to 1.37. Since breast cancer is by far the most common cancer in women, affecting 1 in 8 women at some time during their lives, this translates into a substantial number of additional cancer cases. In addition, a large registry study of POCs (Soini 2014) also showed an increased RR for breast cancer of 1.19. Increased duration of use also increases the risk of breast cancer for COCs as does use early in life (Mørch 2017).

Comments on the FDA Response

The Contraceptive Study Group greatly appreciates FDA's attention to breast cancer risk as noted in the response of 2022 May 17. Before discussing new studies, the Study Group would like to respond to some of your points.

FDA notes that, "13 studies showed no significant association with breast cancer," and that, "Three additional studies cited in the Petition found a decrease in the risk of breast cancer with CHC use." This fails to consider that 19 studies showed statistically significant increases in risk. In terms of the number of individuals in these studies, there were 1,984,184 subjects in studies that did show a statistically significant increase and 201,399 in those that did not. The FDA notes that, "Of the studies that were statistically significant, most contained issues which made the study results less reliable than the relative risk number alone suggests. For example, the study by Heikkinen does not provide a relative risk number for CHC products separately." This is true, but there is no reason to believe mechanistically that individual CHC products would have a greater or lesser risk. With multiple different estrogen agonists and two different progestins in various formulations over the years, the

observation of increased risk has been remarkably consistent. Dividing the results up by individual agents would decrease the overall power and could falsely hide a real effect. The more recent studies, summarized below, continue to confirm an effect.

Importantly, the National Cancer Institute now also recognizes a clear increased risk of breast cancer with CHCs https://www.cancer.gov/about-cancer/causes-prevention/risk/hormones/oral-contraceptives-fact-sheet. They state, "An analysis of data from more than 150,000 women who participated in 54 epidemiologic studies showed that, overall, women who had ever used oral contraceptives had a slight (7%) increase in the relative risk of breast cancer compared with women who had never used oral contraceptives. Women who were currently using oral contraceptives had a 24% increase in risk that did not increase with the duration of use. Risk declined after use of oral contraceptives stopped, and no risk increase was evident by 10 years after use had stopped." They further note, "In 2017, a large prospective Danish study reported breast cancer risks associated with more recent formulations of oral contraceptives. Overall, women who were using or had recently stopped using oral combined hormone contraceptives had a modest (about 20%) increase in the relative risk of breast cancer compared with women who had never used oral contraceptives. The risk increase varied from 0% to 60%, depending on the specific type of oral combined hormone contraceptive. The risk of breast cancer also increased the longer oral contraceptives were used." We have revised our epidemiological estimates to include this lower number of a 7% increase in risk for any use.

In the FDA analysis of the studies submitted, it is noted that there are problems with the meta-analyses and these are discussed. We acknowledge these problems but note that all the meta-analyses show some increase in risk, and in 3 of the 5 meta-analyses this reached statistical significance at least in some groups. More important are the observational cohort studies. The prior petition cited 12 cohort studies and of these, 10 showed an increase in risk, with 7 showing a statistically significant increase in relative risk at least in some sub-groups. The FDA notes that, "…studies cited in the Petition have a RR of 1.5 or less. A RR of 1.5 or less is generally considered by many epidemiologists to be a weak association." While this may be the case, the societal impact is larger for more prevalent diseases such as breast cancer. As noted in this version of the petition, Table 23, using a conservative relative risk of 1.07, this leads to over 175,000 excess cases with a cost of over 3.9 billion dollars. So, while the relative risk may appear small, the impact is large.

Perhaps the most telling remark in the FDA response is this: "FDA consideration of the appropriateness of a boxed warning may be based on, among other things, the totality of the evidence regarding a safety concern and an evaluation of the overall risk-benefit assessment. Here, the rarity of the risk of breast cancer attributable to CHCs must be considered in the context of the multiple known benefits of CHCs, most notably the prevention of pregnancy. The benefits of CHCs vastly, proportionally outweigh the small risk of breast cancer and therefore a boxed warning is not warranted here."

Several issues are of note in this statement. Firstly, there is the assumption that women who do not take contraceptives will become pregnant, presumably with an unwanted pregnancy. The CSG would like to point out that these women do not have a current disease, disorder, or pathological condition. The use of contraceptives is to prevent pregnancy, which is also not a disease, disorder or pathological condition. These are generally normal healthy women. Hormonally active contraceptives constitute a pharmacological intervention in normal women to prevent a normal condition. This must be considered in the risk-benefit calculus. It is the CSGs position that HCs should be help to a higher standard than that applied to pharmacological interventions which treat diseases, correct disorders, or ameliorate pathological conditions. They should be also held to a higher standard than vaccines, which prevent infectious diseases.

The FDA position also treats pregnancy as a pathological condition. In the risk-benefit calculus, pregnancy is clearly a risk with no benefits of pregnancy acknowledged. While pregnancy has health risks associated with it, there are also health benefits especially when carried to term, such as decreases in breast cancer risk (reviewed

in Slepicka 2019) ovarian cancer (Titus-Ernstoff 2001) and endometrial cancer (Raglan 2018) (see also https://www.cancer.gov/about-cancer/causes-prevention/risk/hormones/reproductive-history-fact-sheet). Since contraceptives do not treat a disease, correct a disorder, or ameliorate a pathology, their safety profile should be held to a higher standard than medications which have a direct impact on diseases, disorders, and pathological conditions. This is particularly the case with the many recent improvements in non-hormonally active methods, such as natural family planning and fertility awareness-based methods, which have now established themselves to be highly effective and have other notable benefits (Klaus 1982 and Brennan and Klaus H 1982 for historical information; Manhart 2013, Urrutia 2018, Fehring 2020, Manhart 2023 for more recent data). As such, the CSG strongly urges the FDA to require that users of hormonally active contraceptives should be fully informed of all potential risks for which substantive data exists. This includes the risks described herein.

Update for 2023:

Several additional studies have been published with in general confirm the effect of COCs and POCs to increase the risk of breast cancer, including 2 cohort studies, 4 case-control studies, 6 meta-analyses and a systematic review (Table 6). Of these, all of these showed increased risk at least in some sub-groups.

One large cohort study in Sweden showed a RR of 1.34 (1.24−1.44) for current or recent use of any hormonally active contraceptive, and a RR of 1.26 (1.17−1.37) for prior use for >6 months (Hultstrand 2022). This study is of particular note as a large proportion of the subjects were using POCs, which are widely available in Sweden. In subjects who were current or recent users of POCs, the RR was 1.32 (1.20−1.45), confirming other studies noted above that show and increased risk for POCs. While current or recent use of COCs was not found to be a significant risk (RR 1.03 (0.91−1.16)) this is based on only 314 cases weakening the significance of this finding. Another cohort study (Alonso-Molero 2022) evaluated the risk of death from breast cancer in breast cancer patients based on prior use of oral contraception, and while the risk was elevated this failed to reach statistical significance (HR of 1.30 (0.95-1.77) for ever use of oral contraception).

Several case-control studies evaluated the risk of developing cancer in Israeli BRCA1/2 mutation carriers (Perri 2021), in northeastern Iran (Alipour 2019), in western Iran (Moradinazar 2019) and in Chinese women (Yuan 2018). All showed elevated risk, although not all reached statistical significance. In addition, several meta-analyses (Li-Wei 2019, Khoramdad 2022, Liu 2022, Baranska 2022, van Bommel 2023) confirmed an elevated risk in various populations with the exception of one study of BRCA1/2+ patients (van Bommel 2023). A systematic review of case-control studies in India indicated elevated risk in some, but not all studies (Maurya 2022).

What is of particular significance at this juncture is the confirmation of elevated risk for breast cancer in users of POCs. With the pending launch of over the counter norgestrel this should be strongly emphasized in the patient information materials and included in all advertisements for norgestrel.

Table 3 – Breast Cancer (Cohort Studies)

Study	Study Design	OR[1] Ever Use	RR[2] Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls
Mørch et al. 2017	Cohort		1.2[3] (1.14–1.26)					1,797,932	*[4]
Heikkinen et al. 2016	Cohort		1.37 (1.12–1.68)					7,000	20,000
Lund et al. 2007	Cohort		1.33 (1.11–1.59)					11,777	23,676
Poosari et al. 2014	Cohort		1.31 (0.65–2.65)					70	11,344
Phipps et al. 2011	*[5]		0.80[6] (0.68–0.94)					5,194	
Brohet et al. 2007[7]	Cohort		1.47 (1.16–1.87)					846	747
Thorbjarnardottir et al. 2014	Cohort		1.32 (1.02–1.70)					654	16,928
Samson et al. 2017	Cohort		1.80[8] (1.29-2.55)					4816	
Rosenberg et al. 2010	Cohort		1.65 (1.19–2.30)					789	53,848
Silvera et al. 2005	Cohort		0.88[9] (0.73–1.07)					1,707	25,611
Hunter et al. 2010	Cohort		1.12 (0.95–1.33)		1.33 (1.03–1.73)			1,344	115,264
			1.42[10] (1.05–1.94)						
			3.05[11] (2.00–4.66)						

[1] OR = odds ratio (95 % confidence interval).
[2] RR = relative risk (95 % confidence interval).
[3] Initiation before age 20, greater than 10 years of use and evaluation within 5 yrs. of stopping further increased the risk.
[4] Entire population of Denmark was the cohort.
[5] Concurrent randomized clinical trials and an observational study.
[6] Hazard ratio shown. Note that women started COCs after age 25, had been off COCs for many years.
[7] Evaluation in patients carrying BRCA mutations. Hazard ratios shown.
[8] Hazard ratio shown.
[9] Hazard ratio shown.
[10] Eight or more years of use.
[11] Levonorgestrel containing combined oral contraceptives.

Study	Study Design	OR[1] Ever Use	RR[2] Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls
Trivers et al. 2007[12]	Cohort			1.57 (0.95–2.61)				292[13]	1,264[14]

[12] Looked at mortality in patients with breast cancer over 8-10 years depending on whether they were on COCs at the time of diagnosis or within one year.
[13] Deaths.
[14] Total cohort.

Table 4 – Breast Cancer (Case Control Studies)

Study	Study Design	OR[15] Ever Use	RR[16] Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls
Dolle et al. 2009	Case control	2.5 (0.9-5.24)		4.2 (1.9-9.3)				898	961
Lee et al. 2008	Case Case[17]	0.68 (0.33-1.38)						94	444
Sweeney et al. 2007	Case control	1.27 (0.99-1.63)						2,318	2,515
Beaber et al. 2014b	Case control	1.5 (1.1-2.2)						985	882
Li et al. 2012[18]	Case control	2.2 (1.2-4.2)						1,028	919
Beaber et al. 2014a	Case control			1.5[19] (1.3-1.9)				1,102	21,952
Ichida et al. 2015	Case control			0.45 (0.22-0.90)				155	12,333
Ma et al. 2010	Case control	2.87[20] (1.44-5.74)						1,197	2,015
Folger et al. 2007	Case control	1.0[21] (0.8-1.1)						4575	4682
Jernstrom et al. 2005	Case control					2.10 (1.32-3.33)		245	745
Kotsopoulos et al. 2014[22]	Case control	1.45[23] (1.20-1.75)						2,492	2,492
		1.19[24] (0.99-1.42)							
Figueiredo et al. 2010[25]	Case control					2.38 (0.72-7.83)		705	1,398
Veneroso et al. 2008	Case Case[26]	1.12 (1.03-1.23)						116	99

[15] OR = odds ratio (95 % confidence interval).
[16] RR = relative risk (95 % confidence interval).
[17] BRCA1 and BRCA2 carriers with breast cancer.
[18] Population-based case-control of women 20-44 yo with recent DMPA use for at least 12 months.
[19] Use within the past year of COCs increases risk of breast cancer.
[20] Triple negative breast cancer if less than 18 yo on COCs.
[21] Evaluated short-term use only.
[22] Study of BRCA+ patients.
[23] <20 years old.
[24] 20-25 years old.
[25] Evaluation of BRCA1 and BRCA2 carriers; controls with unilateral breast cancer compared with contralateral cases.
[26] Comparison of more aggressive with less aggressive cases.

Study	Study Design	OR[15] Ever Use	RR[16] Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls
Ma et al. 2006	Case control	1.27[27] (0.75-2.14)				0.76 (0.49-1.18)		1,366	440
		0.76[28] (0.49-1.18)							
Rosenberg et al. 2008	Case control	1.5[29] (1.2-1.8)						907	1,711
Haile et al. 2006	Case control	0.77[30] (0.53-1.12)						195	497
		1.62[31] (0.90-2.92)						128	307
Milne et al. 2005	Case control	1.52 (1.22-1.91)						1156	815
Amadou et al. 2013	Case control	1.68 (0 .67-4.21)						1,000	1,074
Ozmen et al. 2009	Case control	0.60 (0.48-0.74)						1,492	2,167
Delort et al. 2007	Population based[32]	1.84[33] (1.38-2.44)						934	
Beji et al. 2006	Case control	1.98 (1.38-2.85)						405	1,050
Veisy et al. 2015	Case control	2.11 (1.44-3.08)						235	235
Tehranian et al. 2010	Case control	2.83 (1.87-4.24)						321	321
Lumachi et al. 2010	Retrospective Review	2.06 (1.14-3.70)						404	408

[27] ER-/PR-
[28] ER+/PR+
[29] OR for 5+ years of use.
[30] BRCA1+ patients.
[31] BRCA2+ patients.
[32] Population-based study of early onset breast cancer.
[33] OR for developing breast cancer 2 years earlier than non-users.

Table 5 – Breast Cancer (Meta-Analyses)

Study	Study Design	OR[34] Ever Use	RR[35] Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
Kahlenborn et al. 2006[36]	Meta-analysis	1.19 (1.09-1.29)						18,406	27,677	91%
		1.29[37] (1.20-1.40)								
		1.24[38] (0.92-1.67)								
		1.44[39] (1.28-1.62)								
Bethea et al. 2015	Meta-analysis	1.46[40] (1.18-1.81)						1,848	10,044	85%
		1.57[41] (1.22-1.43)						1,043	10,044	
		1.78[42] (1.25-2.53)						494	10,044	
Zhu et al. 2012	Meta-analysis	1.08[43] (0.99-1.17)								54%
Friebel et al. 2014[44]	Meta-analysis	1.36[45] (0.99-1.88)								27%
		1.51[46] (1.10-2.08)								
Moorman et al. 2013	Meta-analysis	1.21[47] (0.93-1.58)								

[34] OR = odds ratio (95 % confidence interval).
[35] RR = relative risk (95 % confidence interval).
[36] Limited to case-control studies from 1980-2004.
[37] Parous women.
[38] Nulliparous women.
[39] Use before first full term pregnancy among parous women.
[40] ER+
[41] ER-
[42] Triple negative.
[43] For each 5 years on COCs the risk increased by 7%, but statistical significance not achieved.
[44] Study limited to BRCA1 and BRCA2 mutation carriers.
[45] 1-3 years of use.
[46] >3 years of use.
[47] 8 studies on BRCA1+ or BRCA2+ patients and breast cancer risk with CSC use.

Table 6 – Breast Cancer (New Studies 2023)

Study	Study Design	OR[48]	HR[49]	RR[50]	Cases	Controls
Hultstrand et al. 2022[51]	Cohort				3,842	1,500,000
Current or recent use any HC				1.34 (1.24−1.44)	1,355	
Use >6 months previously any HC				1.26 (1.17−1.37)	1,068	
Current or recent use of any combined HC				1.03 (0.91−1.16)	314	
Current or recent use of progestogen-only methods				1.32 (1.20−1.45)	523	
Alonso-Molero 2022[52]	Cohort				1685	
Ever Use			1.30 (0.95-1.77)			
<5 years of use			1.05 (0.70-1.59)			
5+ years of use			1.45 (0.92-2.28)			
Perri 2021[53]	Case control				687	1,137
Up to 1-year univariate analysis			1.16 (0.85–1.6)			
1-4 years univariate analysis			1.13 (0.9–1.44)			
5+ years univariate analysis			1.45 (1.2–1.74)			
5+ years multivariate analysis			1.62 1.27–2.06)			
Alipour 2019[54]	Case control				99	400
12-48 months		1.22 (0.64–2.33)				
49-119 months		0.76 (0.32–1.80)				
>10 years		3.17 (1.27–7.95)				
Moradinazar 2019[55]	Case control	2.02 (1.2–3.3)			212	424
Yuan 2018[56]	Case control				794	805
Pre-menopausal women		2.06 (1.39–3.04)				
Post-menopausal women		1.41 (0.76–2.64)				
Li-Wei 2019[57]	Meta-analysis	1.24 (1.10–1.41)			8,585	677,720
Khoramdad 2022[58]	Meta-analysis	1.35 (1.11-1.63)			5,675	6,785
Liu 2022[59]	Meta-analysis	1.16 (1.02-1.32)			4,321	8,025
Baranska 2022[60]	Meta-analysis	0.86 (0.70 - 1.06)			20,502	7,110

[48] OR = odds ratio (95 % confidence interval).
[49] HR = hazard ratio (95 % confidence interval).
[50] RR = relative risk (95 % confidence interval).
[51] Limited to women 15-34, followed for 12 years. Population had a high proportion of POC use (>40%).
[52] This study evaluated the risk for death from breast cancer among those with breast cancer, not the incidence of new cases of breast cancer.
[53] Jewish Israeli BRCA1/2 mutation carriers
[54] Study in northeastern Iran.
[55] Women under the age of 50 in the west of Iran
[56] Analysis of Chinese women.
[57] This study evaluated the effect of age at first use. For each one-year-old increase in the age at 1stOC was 1.007 (95% CI: 1.002–1.013, P=.003)
[58] Case-control studies in Iran.
[59] Chinese studies only.
[60] Limited to BRCA1/2+ patients.

Study	Study Design	OR[48]	HR[49]	RR[50]	Cases	Controls
van Bommel 2023[61]	Meta-analysis					
5 cohort, 1 case-control, 1 case only (no serious issues)			1.55 (1.36 - 1.76)		7,525	
4 case-control (serious inconsistencies)		1.06 (0.90 - 1.25)			9,106	
Conz 2019[62]	Meta-analysis	1.16 (1.06-1.28)			NA	NA
Women <50		1.12 (1.02-1.22)				
Women >50		1.52 (1.34-1.72)				
Maurya 2022[63]	Systematic review					
Bhadoria 2013	Case control	9.50 (3.38 - 26.7)			320	320
Lodha 2011	Case control	3.02 (1.28–7.11)			215	215
Singh 2014	Case control	0.36			138	138
Pakseresht 2009	Case control	0.46 (0.10-1.79)			115	217
Dey 200	Case control				900	1,208
ER+		0.53 (0.22 - 1.25)				
ER-		0.85 (0.48 - 1.50)				
Kamath 2013	Case control	5.99 (0.72-49.83)			94	94
Das 2012	Case control	1.975 (1.01-3.87)			105	105

[61] Limited to BRCA1/2 carriers.

[62] Levonogestral-releasing intrauterine system studies.

[63] Systematic review of papers in India. Primary references (n=7) outlined below. Note all had a very low % of patients on OCs (<5%).

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Cervical Cancer

According to the SEER statistics[1], it is estimated that there are 257,524 women in the US with cervical cancer. There will be about 13,000 new cases of cervical cancer in 2018, with about 4,000 deaths. The five-year survival for cervical cancer is 66%. The IARC evaluation of an increased risk of cervical cancer with COCs is also supported especially by a large, high-quality cohort study (Roura 2016, Table 7). The data for cervical cancer presented in Table 4 shows in particular a higher risk for invasive cervical cancer, and a higher risk with current use. All studies appear to agree that there is an increased risk of cervical cancer in users of COCs (OR apparently about 1.05 per year of use), and this risk increases with duration of use. Current use appears to confer a higher risk than past use, and the risk for invasive cancer shows the highest increase in risk (Roura 2016). A meta-analysis of case-control studies that focused on patients positive for human papilloma virus DNA (Moreno 2002) also showed an increased risk, especially with protracted (5+ years) of use of COCs. One case-control study (McFarlane-Anderson 2008) and one meta-analysis (International Collaboration 2007) also showed an increased risk with progestogen-only contraceptives. Thus, there does appear to be an increased risk of cervical cancer in users of COCs or POCs, and the risk appears to increase with duration of use.

Update for 2023

Since 2019, several studies exploring the relationship between hormonal contraceptive use and cervical cancer were published (Table 8). Of the 45 identified via the search criteria, seven directly examined the risk of cervical cancer associated with hormonal contraceptive use.

Iverson et al (2020) examined contemporary contraceptives and the risk of developing cervical cancer in a Danish population study with over 20 million patient years of observation allowing comparison between different formulations and types of Hormonal contraceptives. They found an age-adjusted incidence of cervical cancer of 14.9/100,000 person-years in non-users compared to 17.8/100,000 person-years in ever-users. Adjustment for BMI, smoking status among parous women did not materially change the risk estimates. They concluded "Overall, there was little evidence of major differences between combined products containing different progestins" and went on to state "Our results indicate that currently used combined oral contraceptives are associated with a similar pattern of cervical cancer risk as that of older preparations, at least among women not vaccinated against HPV".

Similarly, Loopik et al (2020) found in a Dutch population long term use (5 years or more) of either oral contraceptives or an IUD increased the risk of both precancerous and cancerous lesions. They also found never-use of contraceptives reduced the risk of cervical cancer when compared to the total population.

Spotnitz (2020) compared copper (CU) IUD to levonorgestrel (LNG)-IUD use and showed reduced risk of cervical Cancer with Copper containing IUDs.

Kusmiyat (2019) demonstrated increased odds of cancer with long term use (>5years) of hormonal contraceptives when compared to no use.

Singini (2021) did not show increased odds from long term use of oral contraceptives but did show increased risk from use of injectable contraceptives, which are used more commonly among this South African cohort.

In addition, two systematic reviews have been published since 2019. Asthana et al (2020) conducted a large systematic review and meta-analysis in both HPV positive women and women with unknown HPV status. They concluded both IUD and oral contraceptive use increases the risk cervical cancer and oral contraceptives pose a higher risk than IUD. More recently Anastasiou et al (2022) conducted a systematic review and concluded that 2 of 7 primary studies found a significant increased OR for precancerous lesions (cervical intraepithelial

[1] https://seer.cancer.gov/statfacts/html/corp.html

neoplasia (CIN) grade 3+) or cancer, 4 of 7 studies found no association and 1 study found no association overall but a subset suggested a reduced risk of CIN3+. Notably, all 7 of these studies were included in the Asthana et al review and the studies showing no association had follow-up periods of less than 3 years.

While not directly addressing the issue, two studies employing machine learning algorithms to improve the predictability of identifying cervical cancer were published in the period.

Asadi et al (2020) tested 5 different learning algorithms among 145 Iranian women with cervical cancer for their predictability. All five models had good area under the curve (AUC), sensitivity, and specificity (range=88% - 95% for all variables) and concluded "The important predictors in all the algorithms were found to comprise personal health level, marital status, social status, the dose of contraceptives used, level of education and number of caesarean deliveries."

Sun et al (2022) employed 858 Venezuelan women with cervical cancer and developed a screening tool with an AUC=0.877, sensitivity= 81.8%, and specificity=81.9%. They stated that the duration of hormonal contraceptive use was the single biggest predictive factor in the model.

The National Cancer Institute also acknowledges an increased risk of cervical cancer with the use of oral contraceptives https://www.cancer.gov/about-cancer/causes-prevention/risk/hormones/oral-contraceptives-fact-sheet.

Studies that have evaluated progestin-only contraceptives include McFarlane-Anderson et al (2008), International Collaboration (2007), Spotnitz et al (2020), Singini et al (2021) and Iverson et al (2020). All of these showed an increased risk of cervical cancer and/or CIN except for the Iverson (202) study, which was limited to women 15-49 years of age and may have missed effects from longer term exposure. There should be a clear warning for norgestrel users that the use of this agent has been shown to be associated with an increased risk of cervical cancer and pre-cancerous lesions.

Table 7 – Cervical Cancer

Study	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
Roura et al. 2016	Cohort Study		1.1[1] (0.9–1.3)		1.8[10] (1.4–2.4)		1[10] (0.9–1.3)	1,065	306,971	94%
			1.6[2] (1.1–2.3)		2.2[8] (1.3–4.0)		1.6[8] (1.1–2.2)	261	306,971	
Leslie et al. 2014	Case Control Study	1.35[3] (0.99-1.85)						219	2,300	87%
McFarlane-Anderson et al. 2008	Case Control Study	1.59[4] (0.87-2.82)						240	102	83%
		2.48[5] (1.30-4.74)								
Vanakankovit et al. 2008	Case Control Study	1.49 (0.79-2.64)						60	180	76%
Wilson et al. 2013	Case Control Study	1.22 (0.96–1.56)						724	3,479	76%
Matos et al. 2005	Case Control Study	1.3 (0.8–3.1)						140	157	47%
International Collaboration 2007[6]	Meta-analysis	1.057 (1.04–1.07)						16,573	35,509	97%
	<5 years of use	0.96 (0.04)[8]								
	5-9 years of use	1.2 (0.05)[5]								
	10+ years of use	1.56 (0.08)[5]								
	<5 years of use	1.07 (0.08)[9]						7,227	19,335	
	5+ years of use	1.22 (0.11)[6]								
Moreno 2002[10]	Meta-analysis							1676	255	95%
	Invasive cervical cancer (ICC)	1.29 (0.88-1.91)								
	ICC 5+ years of use	4.01 (2.01-8.02)								
	In situ carcinoma (ISC)	1.42 (0.99-2.04)								

[1] Includes Cervical Intraepithelial Neoplasia Grade 3, carcinoma in situ and invasive cervical cancer.
[2] Analysis limited to invasive cervical cancer.
[3] Study limited to HIV+ women.
[4] Combined hormonal contraceptives.
[5] Progesterone only contraceptives.
[6] Meta-analysis of 24 studies (15 cohort and 9 case-control studies).
[7] Relative risk per year of use for current users of combined hormonal contraceptives.
[8] Floating standard error shown for users of combined hormonal contraceptives.
[9] Progestin only contraceptives. Floating standard error shown. The 95% CI for 5+ years of use is 1.01-1.46.
[10] Pooled data from 8 case-control studies of invasive cervical cancer and 2 of carcinoma in situ, analyzing only the subset positive for Human Papilloma Virus DNA in cervical cells.

Study	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
	ISC 5+ years of use	3.42 (2.13-5.48)								

Table 8– Cervical Cancer Updates

Study	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
Iverson et al (2020)[11]	Population based cohort		1.19[12] (1.10-1.29)		1.30[13] (1.20-1.46)			2339	1304	
COC only					1.40 (1.28-1.53)					
Progestin only		0.91 (0.78-1.07)								
Loopik et al (2020)[14]	Retrospective population based									
OC >5yrs use vs no contraception					2.06 (1.52-2.79)			87/85,823	83/178,545	
IUD >5yrs use vs no contraception					1.21 (0.71--2.07)			16/27,509	83/178,545	
OC >5yrs vs. IUD >5yrs					1.70 (1.00-2.90)			87/85,823	16/27,509	
No contraception vs total population					0.63 (0.53-0.75)			83/178,545	559/702,037	
Grade III or worse CIN[15]										
OC >5yrs use vs no contraception					2.77 (2.56-3.00)			1478/85,823	978/178,545	
IUD >5yrs use vs no contraception					1.51 (1.32-1.74)			244/27,509	978/178,545	
OC >5yrs vs. IUD >5yrs					1.83 (1.60-2.09)			1478/85,823	244/27,509	

[11] Women 15-49 living in Denmark 1995-2014, taking part in country wide-screening program (n=1,904,094), >20million person years observation. COC used by 86% of all. current/recent users. Low rate of HPV vaccination in the population. Authors draw the following conclusions: 1) " Overall, there was little evidence of major differences between combined products containing different progestins" 2) "Our results indicate that currently used combined oral contraceptives are associated with a similar pattern of cervical cancer risk as that of older preparations, at least among women not vaccinated against HPV".

[12] Sufficient size to compare specific COC formulations and contraceptive types. Adjustment for BMI, smoking status among parous women did not materially change the risk estimates.

[13] Current or recent use defined as discontinued <12 months earlier.

[14] Population-based study among Dutch women aged 29-44 (n=702,037) with normal baseline cytology between 2005-2009 (i.e. a low risk population). Followed for up to 13 yrs., median follow-up = 9.7 yrs.

[15] Risk of developing cervical intraepithelial neoplasm grade III or worse

Study	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
No contraception vs total population					0.61 (0.58-0.64)			978/178,545	7264/702,037	
Spotnitz et al (2020)[16]	Observational cohort				0.38 (0.16-0.78)			77/8274	37/2400	
Kusmiyati et al (2019)[17]	case control			4.2 (1.01-5.69)				59/95	26/95	
Singini et al (2021)[18]	case control									
Oral HC vs no HC		1.09 (0.88-1.36)						408/ 3450	170/ 5709	
Injectable HC vs no HC		1.34 (1.11-1.61)						1226/3450	305/ 5709	
Either oral or injectable vs no HC		1.17 (1.01-1.37)						2266/3450	709/5709	
Asthana et al (2020)	systematic review & meta analysis									
Women with unknown HPV status [19]		1.51 (1.35-1.68)						9,754	39,191	
Case-controlled studies (n=14)		1.42 (1.25-1.62)								
Cohort studies (n=5)		2.32 (1.50-3.60)								
Study published after 2000 (n=5)		1.90 (1.33-2.72)								
Study published before 2000 (n=11)		1.40 (1.24-1.58)								
Duration of use (4 studies)										
<2 years use		1.27 (0.98-1.65)								
2-5 years use		1.34 (1.20-1.50)								
5-10 years		1.93 (1.56-2.36)								
>10 years		2.24 (1.45-3.48)								
HPV + women										
15 studies combined		1.66								

[16] Copper (CU) IUD vs levonorgestrel (LNG) IUD in 10,674 IUD users. High grade neoplasm rates; CU grp =2.4 (CI 1.5-4.0) cases/1,000 person years, LNG grp =5.2 (CI 3.7-7.5) cases/1,000 person years

[17] 95 Indonesian women with Cervical cancer compared to 95 women with negative PAP test, Hormone use self-reported as "consistent" over 5 or more years without differentiating between oral, injectable or implantable form. Hormonal contraceptive use >5yrs vs no use. OR adjusted for age when married <20 years old and parity >3.

[18] 3450 women with cervical cancer compared to 5709 with an unrelated cancer from the Johannesburg Cancer Study recruited 1995-2016.

[19] 19 studies combined.

Study	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
		(1.24-2.2)								
cohort studies (n=4)		1.50 (1.07-2.11)								
case controlled studies (n=11)		1.80 (1.21-2.67)								

Cervical Cancer References

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Crohn's Disease

Papers were accessed from a PubMed literature review as noted (Williams 2017). Each paper was rated based on the parameters noted in the STROBE statement (von Elm 2007).

Overall, 17 primary studies and two meta-analyses were identified which evaluated the effect of COCs on the later development of Crohn's disease (Table 9). Of the 17 primary studies, 4 showed a significantly increased risk for either ever use (Ng 2012, Sicilia 2001, Katschinski 1993) or current use (Katschinski 1993, Khalili 2013) or past use (Khalili 2013). None of the primary studies showed a significantly decreased risk. One meta-analysis (Godet 1995) gave a significantly increased RR of 1.44 (95% CI 1.12–1.86) for ever use of COCs. A meta-analysis published in 2008 showed a significantly increased risk for current use (RR of 1.46 [1.26–1.70]) compared with 1.04 (0.816–1.340) for past use. Recent studies have produced similar findings as older studies, with the highest OR published in 2012 (9.04 [1.11–73.6]). Overall, these studies indicate that use of COCs conveys an increased risk of Crohn's disease, especially current use.

New studies since the initial petition:

A prospective cohort study of 133,137 individuals between the ages of 20 and 80 from 24 countries was carried out. Country-specific validated questionnaires were used to document baseline and follow-up medication use. Participants were followed up prospectively at least every 3 years. During a median follow-up period of 11.0 years (interquartile range, 9.2–12.2 y), there were 571 incident IBD cases (143 Crohn's Disease and 428 Ulcerative Colitis).

Update for 2023

Several additional studies have been published since the original submission of the petition (Table 10). A nested case-control study in women aged 15- 49 years with a new diagnosis of IBD were matched with up to six controls (Pasvol 2022) indicated a 60% increase in risk for use of COCs but no significant increase in risk with POCs. A prospective cohort study indicated a doubling in risk for either IBD or Crohn's disease for ever use of OCs (Narula 2023). A meta-analysis (Zhao 2021) and an umbrella review of meta-analyses (Piovani 2019) both indicated a ~25% increase in the risk of Crohn's disease with ever use of OCs. A small retrospective comparative study also indicated an elevated risk (Preda 2019). Only one study failed to show a statistically significant elevated risk (Yang 2022). The retrospective cohort study was limited to "those with British White ancestry" and included self-diagnosed IBD. However, they did find an interaction with the polygenic risk score: "Specifically, we found that although previous OCT use did not exhibit a marginal association with IBD (95% CI 0.88–1.18), it elevated the risk for IBD and UC in individuals with lower polygenic risk but attenuated the risk for IBD and UC in those with higher polygenic risk (95% CI for hazard ratio of interaction term per standard deviation PRS: 0.73–0.93 for IBD, adjusted p = 0.008; 0.71–0.96 for UC, adjusted p = 0.049)." Also separated out current use and past use, reducing the power compared to use of "ever use".

Overall these studies continue to show that OCs elevated the risk for Crohn's disease in women. This should be plainly acknowledged in the prescribing information and patient materials.

Table 9 – Individual Studies of the Effects of COCs on the Development of Crohn's Disease

Study	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
Narula 2023	Prospective Cohort									
Khalili et al. 2013[1]	Cohort		1.43		2.82 (1.65–4.82)		1.39 (1.05–1.85)	315	117,060	93%
García Rodríguez et al. 2005[2]	Cohort				1.94 (0.85–4.45)		1.04 (0.50–2.17)	171	10,000	88%
Logan and Kay 1989	Cohort		1.7 (0.88–3.2)					42	45,958	54%
Vessey et al. 1986[3]	Cohort				1.33			18	17,014	46%
Boyko et al. 1994	Case-control		2 (1.0–3.7)					91	169	94%
Katschinski 1993[4]	Case-control				2.5 (0.75–4.6)					93%
Katschinski 1993[5]	Case-control				3.1 (1.1-6.7)					93%
Lashner et al. 1989	Case-control	1 (0.46–2.16)		0.73 (0.34–1.59)		1.8 (0.61–5.29)		51	51	88%
Lesko et al. 1985[6]	Case-control		1.7 (1.0–3.2)					57	2189	83%
Sandler et al. 1992	Case-control		1.49 (0.99–2.26)					184	217	81%
Persson et al. 1993	Case-control		1.7 (0.9–3.2)					152	305	81%
Halfvarson et al. 2006[7]	Case-control				1.5 (0.4–5.3)			102	102	75%
Lowe et al. 2009[8]	Case-control		1.05					21,172	754,6131	74%
Ng et al. 2012[9]	Case-control	4 (1.1–14.2)						125	125	74%

[1] Hazard ratios (RR adjusted for time).
[2] OR increased with duration of use.
[3] Authors' calculation adjusted for smoking.
[4] Adjusted RR for 1-3 years prior to disease onset.
[5] Adjusted RR for >3 years prior to disease onset.
[6] RR is from multiple logistic regression analysis.
[7] Monozygotic and dizygotic twins.
[8] Adjusted incidence rate ratio.
[9] Twins study.

Study	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
Ng et al. 2012[10]	Case-control	9.04 (1.11–73.6)								74%
Sicilia et al. 2001	Case-control	2.8 (1.01–7.77)						103	103	71%
Corrao et al. 1998	Case-control ever use			3.4 (1.0–11.9)		1.8 (0.4–7.3)		225	225	67%
Katschinski 1993[11]	Case-control		4.3 (1.3-14.4)					83	83	57%
Han et al. 2010	Case-control		0.66 (0.38–1.15)					315	536	52%
Calkins et al. 1986[12]	Case-control	1.14 (0.44–2.96)						66	67	42%
Calkins et al. 1986[13]	Case-control	1.6 (0.59–4.37)						66	71	42%
Vcev et al. 2015	Case-control	0.28 (0.03–2.46)						11	42	31%
Cornish et al. 2008	Meta-analysis				1.46 (1.26–1.70)		1.04 (0.816–.340)	1251	74,564	91%
Cornish et al. 2008[14]	Meta-analysis				1.58 (1.07–2.40)					91%
Godet et al. 1995[15]	Meta-analysis		1.44 (1.12–1.86)					531	49,156	82%

[10] Multivariate analysis.
[11] RR for use >3 years.
[12] Hospital controls.
[13] Neighborhood controls.
[14] High quality studies.
[15] Adjusted for smoking.

Table 10 – Individual Studies of the Effects of COCs on the Development of Crohn's Disease 2023 update

Study	Study Design	OR Ever Use	RR Ever Use	HR Current Use	RR Current Use	HR Past Use	RR Past Use	Cases	Controls
Pasvol 2022	Nested Case Control[16]							4,932	29,340
COCs		1.60 (1.41- 1.82)							
POCs		1.09 (0.84- 1.40)							
Narula 2023	Prospective Cohort Study								
Inflammatory Bowel Disease		2.17 (1.70–2.77)						348	79,142[17]
Crohn's Disease		1.95 (1.11-3.42)						91	
Zhao 2021	Meta-analysis[18]	1.25 (1.08-1.45)						369,385	41,775,699
Western Countries Only		1.31 (1 .12-1.53)							
Piovani 2019[19]	Umbrella Review of Meta-Analyses								
Inflammatory Bowel Disease		1.31 (1.15–1.50)							
Crohn's Disease		1.25 (1.05–1.48)							
Preda 2019[20] Inflammatory Bowel Disease	Retrospective Comparative Study							129	55
Yang 2022[21]	Retrospective cohort study								
Inflammatory Bowel Disease				(0.89–1.24)		(0.88–1.18)		2,704	175,001
Crohn's Disease				(0.92–1.53)		(0.84–1.34)		942	175,001

[16] Women aged 15- 49 years with a new diagnosis of IBD were matched with up to six controls.
[17] 24,612 on contraceptives.
[18] 255 studies in meta-analysis looking at multiple factors.
[19] Examined 183 estimates in 53 meta-analyses of 71 environmental factors related to lifestyles and hygiene, surgeries, drug exposures, diet, microorganisms, and vaccinations.
[20] Belgian IBD patients declared significantly more frequent OCP use (53% vs 9%, p <0.001). Romanian patients 11% OCP vs 0% controls.
[21] Limited to "those with British White ancestry", included self-diagnosed IBD. Looked primarily at gene-environment interactions and utilized a time-varying retrospective analysis method. Confirmation by a prospective analysis (2009-2011) unable to be performed due to low number. However, they did find an interaction with the polygenic risk score with an elevated the risk for IBD and UC in individuals with lower polygenic risk but attenuated the risk for IBD and UC in those with higher polygenic risk.

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Ulcerative Colitis

Papers were accessed from a PubMed literature review as noted (Williams 2017). Each paper was rated based on the parameters noted in the STROBE statement (von Elm 2007).

Overall 14 primary studies and one meta-analysis were identified which evaluated the effect of COCs on the later development of ulcerative colitis (Table 11). None of the primary studies has shown a statistically significant decrease in risk, while two showed a significant increase in risk for the development of ulcerative colitis with ever use of COCs (Boyko 1994, Parrello 1997). One meta-analysis examined ever use and failed to show a significant difference (Godet et al. 1995), while another meta-analysis examined current use and found a significantly increased relative risk of 1.28 (1.06–1.54). Overall these studies suggest that use of COCs conveys an increased risk of ulcerative colitis, especially current use.

Update for 2023

Several additional studies have been published since the original submission of the petition (Table 12). A nested case-control study in women aged 15- 49 years with a new diagnosis of IBD were matched with up to six controls (Pasvol 2022) indicated a 30% increase in risk for use of COCs a 35% increase in risk with the use of POCs. A prospective cohort study indicated a doubling in risk for either IBD or ulcerative colitis for "ever use" of OCs (Narula 2023). A meta-analysis (Zhao 2021) did not show an increase in the risk of ulcerative colitis with the use of OCs, but in Western countries did show an 18% increase in risk. An umbrella review of meta-analyses (Piovani 2019) indicated a ~28% increase in the risk of ulcerative colitis with ever use of OCs. A case-control study (Wang 2013) indicated an increased risk, but this did not reach statistical significance. A meta-analysis showed a 25% increase in risk for "ever use" and a 49% increase in risk for current use, but for past use the increase seen failed to reach statistical significance (Wang 2018). A small retrospective comparative study also indicated an elevated risk (Preda 2019). One other study failed to show a statistically significant elevated risk (Yang 2022). The retrospective cohort study was limited to "those with British White ancestry," and included self-diagnosed IBD. However, they did find an interaction with the polygenic risk score: "Specifically, we found that although previous OCT use did not exhibit a marginal association with IBD (95% CI 0.88–1.18), it elevated the risk for IBD and UC in individuals with lower polygenic risk but attenuated the risk for IBD and UC in those with higher polygenic risk (95% CI for hazard ratio of interaction term per standard deviation PRS: 0.73–0.93 for IBD, adjusted p = 0.008; 0.71–0.96 for UC, adjusted p = 0.049)." Also this study separated out current use and past use, reducing the power compared to use of "ever use".

Overall, these studies continue to show that OCs elevated the risk for ulcerative colitis in women, including progesterone-only agents. This should be plainly acknowledged in the prescribing information and patient materials for COCs and POCs, especially in settings where physician counseling is not required (i.e. over-the-counter availability).

Table 11 – Individual Studies of the Effects of COCs on the Development of Ulcerative Colitis

Study	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
Khalili et al. 2013[1]	Cohort		1.18 (0.92–1.52)		1.22 (0.74–2.07)		1.18 (0.91–1.52)	392	116,983	93%
García Rodríguez et al. 2005	Cohort				1.58 (0.71–3.52)		0.67 (0.32–1.39)	222	10,000	88%
Logan and Kay 1989	Cohort		1.3 (0.82–2.0)					78	45,922	54%
Vessey et al. 1986[2]	Cohort				2.1			31	17,001	46%
Boyko et al 1994	Case-control		1.7 (1.1–2.7)					211	341	94%
Lashner et al. 1990	Case-control	0.86 (0.40–1.85)		0.7 (0.27–1.83)		1.14 (0.41–.15)		46	46	81%
Sandler et al. 1992[3]	Case-control		1.1 (0.65–1.85)					89	217	81%
Persson et al. 1993	Case-control		1.7 (0.8–3.3)					145	305	81%
Halfvarson et al. 2006[4]	Case-control				0.6 (0.1–2.5)			125	125	75%
Ng et al. 2012[5]	Case-control	0.43 (0.11–1.66)						125	125	74%
Parrello et al. 1997[6]	Case-control	3.11 (1.54–6.3)						536	755	67%
Corrao et al. 1998	Case-control			1.6 (0.9–3.0)		1.3 (0.6–2.8)		594	594	67%
Calkins et al. 1986[7]	Case-control	0.62 (0.11–3.42)						35	32	42%
Calkins et al. 1986[8]	Case-control	0.57 (0.11–2.88)						35	38	42%
Vcev et al. 2015	Case-control	0.75 (0.30–1.88)						62	42	31%

[1] Hazard ratios (RR adjusted for time).
[2] Authors' calculation, adjusted for smoking.
[3] Interaction with smoking notes, higher RR in smokers (2.49).
[4] Monozygotic and dizygotic twins.
[5] Twins studies.
[6] Unclear how the calculation was done.
[7] Hospital controls.
[8] Neighborhood controls.

Study	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
Cornish et al. 2008	Meta-analysis				1.28 (1.06–1.54)		1.07 (0.702–1.640)	883	74,932	91%
Cornish et al. 2008[9]	Meta-analysis				1.24 (0.999–1.54)					91%
Godet et al. 1995[10]	Meta-analysis		1.29 (0.94–1.77)					851	49,875	82%

[9] High quality studies.
[10] Adjusted for smoking.

Table 12 – Individual Studies of the Effects of COCs on the Development of Ulcerative Colitis 2023 update

Study	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls
Pasvol 2022	Nested Case Control[11]							4,932	29,340
COCs		1.30 (1.15-1.45)							
POCs		1.35 (1.12- 1.64)							
Narula 2023	Prospective Cohort Study								
Inflammatory Bowel Disease		2.17 (1.70–2.77)						348	79,142[12]
Ulcerative Colitis		2.22 (1.70-2.91)						257	
Zhao 2021	Meta-analysis[13]	1.08 (0.90-1.29)						190,354	41,775,699
Western Countries Only		1.18 (1.03-1.35)							
Wang 2013	Case-control	2.734 (0.880-8.495)						1,308	1,308
Wang 2018	Meta-analysis	1.25 (1.04-1.51)		1.49 (1.12–1.96)		1.17 (0.95–1.43)		1,924	303,340
Piovani 2019[14]	Umbrella Review of Meta-Analyses								
Inflammatory Bowel Disease		1.31 (1.15–1.50)							
Ulcerative Colitis		1.28 (1.08–1.52)							
Preda 2019[15] Inflammatory Bowel Disease	Retrospective Comparative Study							129	55
Yang 2022[16]	Retrospective cohort study								
Inflammatory Bowel Disease				(0.89–1.24)		(0.88–1.18)		2,704	175,001
Ulcerative Colitis				(0.79–1.22)		(0.81–1.18)		1,627	175,001

[11] Women aged 15- 49 years with a new diagnosis of IBD were matched with up to six controls.
[12] 24,612 on contraceptives.
[13] 255 studies in meta-analysis looking at multiple factors.
[14] Examined 183 estimates in 53 meta-analyses of 71 environmental factors related to lifestyles and hygiene, surgeries, drug exposures, diet, microorganisms, and vaccinations.
[15] Belgian IBD patients declared significantly more frequent OCP use (53% vs 9%, p <0.001). Romanian patients 11% OCP vs 0% controls.
[16] Limited to "those with British White ancestry", included self-diagnosed IBD. Looked primarily at gene-environment interactions and utilized a time-varying retrospective analysis method. Confirmation by a prospective analysis (2009-2011) unable to be performed due to low number. However, they did find an interaction with the polygenic risk score with an elevated the risk for IBD and UC in individuals with lower polygenic risk but attenuated the risk for IBD and UC in those with higher polygenic risk.

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Systemic Lupus Erythematosus

Papers were accessed from a PubMed literature review as noted (Williams 2017). Each paper was rated based on the parameters noted in the STROBE statement (von Elm 2007).

There have been seven studies published evaluating the effect of hormonal contraceptives on susceptibility to systemic lupus erythematosus (Table 13). A significantly increased risk for development of systemic lupus erythematosus with use of COCs was shown for ever use in two studies (Costenbader 2007, Sanchez-Guerrero 1997), for current use in one study (Bernier 2009) and for past use in one study (Costenbader 2007). None of the studies showed a decreased risk. While no meta-analyses of these studies have been performed, the uniformity of the results implicate COCs as an important risk factor for the subsequent development of systemic lupus erythematosus.

Update for 2023

One additional study has been published since the original submission of the petition. A nested case-control study within the Nurses' Health Study cohorts was performed which included 86 single nucleotide polymorphisms (SNPs) and 10 human leukocyte antigen (HLA) associations showed an OR of 1.23. The authors noted that OC use is a factor in the environmental model (AUC 0.71) and the final model (genetic score, family history, environmental, lifestyle) is 0.76. A final model including SLE weighted genetic risk score, family history and eight lifestyle and environmental SLE risk factors accurately classified future SLE risk with optimism corrected AUC of 0.75. This confirms that use of OCs is associated with the risk of developing SLE. While none of these studies specifically evaluated POCs, with the decision to make norgestrel over the counter, more prevalent use is expected and a warning should be given that use of OCs may increase the risk of developing SLE.

Table 13 – Individual Studies of the Effects of COCs on the Development of Systemic Lupus Erythematosus

Study	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
Costenbader et al. 2007[1]	Cohort		1.5 (1.1–2.1)				1.7 (1.2-2.3)	262	238,046	96%
Costenbader et al. 2007[2]	Cohort		1.6 (1.1-2.2)				1.6 (1.1-2.2)	164	102,882	96%
Costenbader et al. 2007[3]	Cohort		2.3 (1.0-5.0)				2.3 (1.1-5.2)	98	107,854	96%
Bernier et al. 2009	Cohort		1.19 (0.98-1.45)		1.54 (1.15-2.07)		1.06 (0.85-1.33)	786	7817	96%
Bernier et al. 2009[4]	Cohort				2.52 (1.14-5.57)			786	7817	96%
Bernier et al. 2009[5]	Cohort				1.45 (1.06-1.99)			786	7817	96%
Sanchez-Guerrero et al. 1997	Cohort		1.4 (0.9-2.1)					99	121,546	88%
Sanchez-Guerrero et al. 1997[6]	Cohort		1.9 (1.1-3.3)					58	121,587	88%
Cooper et al. 2002	Case-control			1.5 (0.8–2.7)		1.3 (0.8–2.0)		240	321	92%
Strom et al. 1994	Case-control	0.8 (0.5-1.4)						195	143	73%
Zonana-Nacach et al. 2002[7]	Case-control	2.1 (1.18-3.6)						130	130	61%
Grimes et al. 1985	Case-control			0.5 (0.11-2.3)				109	109	58%
Cui 2023[8]	Nested case-control study	1.23 (p=0.06)[9]						138	1,136	88%

[1] Pooled RR from the Nurses' Health Study (NHS) and NHS II.
[2] RR from the NHS (data collection through 1976).
[3] RR from NHS II (data collection through 1989).
[4] RR for short term use (starting COCs within ≤3 months).
[5] RR for long term use (starting COCs over 3 months previously with current use ongoing).
[6] Using most stringent definition of systemic lupus erythematosus.
[7] Paper written in Spanish. OR is for use of oral contraceptives for more than one year.
[8] Nested case-control study within the Nurses' Health Study cohorts including 86 SNPs and 10 HLA alleles associated with SLE.
[9] Beta = 0.20, standard error 0.11.

Systemic Lupus Erythematosus References

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Risk of Depression, Mood Disorders, and Suicide

The effects of contraceptive steroid hormones on depression, mood disorders, and suicide have been investigated (Table 14). The largest study of incident depression and use of anti-depressant medication (Skovlund 2016) indicates significantly increased risks for both COCs and POCs for both outcomes. The same group studied for suicide attempts and suicides (Skovlund 2018). Elevated risks were seen, and this was the case for both COCs and POCs. The recent NCHA study (Gregory 2018) showed a similar trend. One study (Keyes 2013) showed a lower risk of depression, but was not measuring clinically diagnosed depression, but rather the presence of depressive symptoms within 7 days prior to the survey. They also found a lower rate of suicide attempts among COC users. Similar findings were seen in 2 studies that also used a questionnaire looking at current COC or POC use (Toffol 2011, Toffol 2012). An analysis of the development of mood disorders found a higher incidence with POCs but a lower incidence with COCs (Svendal 2012). A study of post-partum depression as a reported adverse drug reaction showed higher rates for levonogestrel, etonogestrel and sertraline & drospirenone (Horibe 2018). A study of post-partum DMPA versus copper IUD use showed significant increases in depression scores and major depressive episodes with DMPA (Singata-Madliki, 2016). A retrospective cohort study showed increased risk for antidepressant use in patients who used ethinyl estradiol/etonogestrel (ring), and decreased risk of depression diagnosis with norethindrone-only pills or the levonorgestrel intrauterine system. A small retrospective chart review of the effect of immediate post-partum DMPA did not show significant effects on post-partum depression (Tsai 2009). One paper did show a higher risk of post-partum depression for use of the ethinyl estradiol/etonogestrel ring, but not for other forms of contraceptives (Roberts 2017). All the papers, which have broken out the age groups of users, show maximum increased risk for depression, suicide risk, and suicide within 3 months of beginning to use the drugs and tapering off after 6 months, partly due to attenuation of symptoms, partly due to discontinuation due to adverse effects. These risks need to be adequately conveyed in prescribing information and patient-related materials.

However, little attention has been paid to the effects of blocking the important actions of estradiol and progesterone with progestins during the time of active brain remodeling. Estradiol and progesterone in normal sequence are essential for brain remodeling from ages 15–19 years particularly for myelination, dendritic pruning and establishment of new synaptic connections (Del Rio 2018). Suppressing these with synthetic progestins can have far-reaching, untoward effects. See Griksiene below in Table 14 as well as Del Rio (Del Rio 2018).

Update for 2023

The literature survey has been updated and papers with over 100 individuals are discussed (Table 15). There were 10 cohort studies of note, 2 case-control studies, 2 cross-sectional studies, one randomized study, one report on 2 phase 3 studies and 3 mechanistic studies. Articles reviewing earlier publications were omitted except for summary reviews which included explanations for the physio-pathological basis of the hormonally caused depression.

Anderl (2022) evaluated OC use in adolescence compared with no use. There was a significant impact on the risk of major depressive disorder (MDD) as adults.

Khafagy (2021) prospectively evaluated 124 females aged 18-45 who received either monthly combined injectable contraceptives (CIC), combined oral contraceptives (COC) or a copper intrauterine device (IUD). After 6 months of follow-up, there were statistically significant increases in the proportion of women who moved from the non-depression stage to mild depression in the CIC and COC groups, but not in the IUD group.

Larsen (2023), reports that a subgroup of women who have a higher susceptibility to depression and have become depressed during earlier contraceptive use, later have a higher risk of post-partum depression.

Edwards (2020) reports increased risk of suicidal behavior for adolescents especially in the early months of use from the Swedish national registry. Hazard ratios were highest among early discontinuers. The effect was seen for both COCs and POCs and was more profound for POCs.

Lundin (2021), a Swedish registry cohort study of all Nordic-born adolescents and women aged 15–25 years between 1 January 2010 and 31 December 2017, looked at new prescriptions for anti-depressants or isolated new diagnoses of depression. Notably the cohorts were unbalanced for age (median age for users was 21 years, whereas for non-users and never-users it was 20 and 17 years of age, respectively). Also, non- and never-users had a lower educational level in comparison with current users, with the difference being most profound in never users. They report no increased risk of depression among oral contraceptive users compared with non-users, but a significantly increased risk compared with never-users. Also, compared to non-users there were significantly increased risks for girls aged 15-19 years of age, with patches, LNG IUD's and implants in all age groups. Concerningly, there were increased risks for oral POPs compared with never users and for girls aged 15-19 compared with any use.

Johansson (2023) examined UK biobank participants 31-73 years of age to assess lifetime risk of depression after OC's. He found the greatest risk among adolescents within two years of initiation, less risk among adults within two years of initiation, but the lifetime relative risk was still significant 1.05 (1.01-1.09). This was confirmed by a sibling pair analysis.

Morssinkhof (2020) did not find depression in between subjects' analysis but found insomnia scores (using the Women's Health Insomnia Rating) with current OC use on within subject analysis, although the effect size was small (d=0.12). They noted that, "by disentangling the amalgamated overall effect, within-person estimates indicated increased depressive symptoms and depressive disorder prevalence during OC use."

Jung (2019) found that 15% of subjects from the Korean NHANES 2007-2016 survey reported increased risk for depression and suicidal behavior with OC use.

Fei (2021) reports that 7.5% of 212 etonogestrel implants were removed for mood issues and overall, 10% of users reported mood changes.

de Wit (2020) reported increased risk for crying, hypersomnia and eating problems of 16-year-old current users.

Anderl (2020), reports an increased risk of mood disorders, depression, suicidality, and suicide with hormonal contraceptive use among adolescents, while adolescents who did not show increased risks for depression and suicidality showed this risk when they became adults.

McKetta (2019) evaluated the relationship between OCP use and depressive disorders among female adolescents using validated, structured interview assessments in a general population sample of adolescents in the National Comorbidity Survey-Adolescent Supplement (NCS-A). The cohorts were very unbalanced for being sexually active (64% in users vs 13% in non-users). They found increased depression among adolescents using OCPs, but the associations disappeared when confounders were considered. Other analyses decreased the sample size and thus the power to detect differences.

Ejigu (2020), in a cross-sectional study of housemaids in Addis Ababa, Ethiopia, found generalized anxiety and depression was enhanced by hormonal contraception use especially in the 16-20 year age group.

Mohammadi-Pssand (2020), compared CU IUD users with DMPA users at 18 months and found higher depression among DMPA than Cu IUD users, worse sexual satisfaction with DMPA use, and more negative perceived mood effects and sexual effects over time for the DMPA users.

Singata (2021) reported from the ECHO trial which studied oral and injectable COC's, LNG and Cu IUD's. A higher proportion of oral hormonal contraceptive users reported depression at 3 months. Although this effect was not maintained through 12 months this could be in part due to symptomatic subjects dropping out from the study.

Chen (2022) reported that 3.2% of subjects and 1.2% of 3417 cycles in their phase 3 multicenter study over 13 cycles reported mild, moderate or severe mood disturbances predominantly in the first 3 cycles. 47.8% of subjects were 16-25 years of age, there was no age breakdown of reported mood disorders. 338 discontinued due to adverse events, 845 due to non-adverse events which included 328 lost to follow up and 261 consent withdrawal.

Pletzer (2019) describes temporary enlargement of the hippocampus and basal ganglia with prior hormonal contraceptives use. The changes in the basal ganglia were permanent, but disappeared in the hippocampus after hormonal contraceptives were discontinued.

Garforth (2020) reports elevated oxytocin levels were linked to higher life satisfaction among OC users compared to non-users. However, the p=0.09 in the Beck Depression Inventory may reflect the higher proportion of OC users in a relationship and sampling bias as well as survivor effect. It is notable that the much higher proportion of subjects on OCs in a relationship did not have a greater effect on the Satisfaction with Life Scale.

Larsen (2020) used brain imaging to show that OCs block 5-HT4R, the serotonin receptor, the effect was twice greater than that of selective serotonin receptor antagonists (SSRI's). The authors propose that this reflects a reduced 5-HT4R gene expression, possibly related to a blunted ovarian hormone state among OC users.

Sundström-Poromaa (2020) reviewed information on the role of progesterone and its metabolite allopregnanolone, which has been proven useful for treatment of post-partum depression. However, it may trigger negative symptoms in women with premenstrual syndrome and premenstrual dysphoric disorder. They note that progestin-contraceptives and the progestin in combined preparations block glucocorticoid as well as testosterone, estrogen, progesterone and sex-hormone binding globulin (SHBG) receptors.

Overall, these studies indicate a significant relationship between hormonally active contraceptive use and depression as well as mood disorders and anxiety. There is a plausible mechanism of action, via central nervous system neurotransmitter receptor modulation (Larsen 2020) as well as structural changes in the hippocampus and basal ganglia (Pletzer 2019). Of particular concern is the high association between progestin-only contraceptives and incident depression (Skovlund 2016), mood disorders (Svendal 2012), EPDS depression scores and major depression (Singata-Madliki 2016), suicide/suicide attempts (Edwards 2022), depression, either diagnosed or anti-depressant medication prescription (Lundin 2021), and depression at 3 months of use versus IUD use (Singata 2021). The higher risk of mood disorders, depression and suicide must be clearly stated to all potential users of POCs/POPs including in all advertising materials. A black-box warning is strongly recommended.

Table 14 – Studies of Chemical Contraceptives and Depression, Mood Disorders and Suicides

	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	Cases	Controls/Cohort Size
Skovlund 2016 incl /Worley	Prospective Cohort Incident Depression – COCs		1.1[132] (1.08-1.14)				1,061,997
	Incident Depression – POCs		1.2[133] (1.04-1.31)				
	First use of Antidepressants – COCs		1.23[134] (1.22-1.25)				
	First use of Antidepressants – POCs		1.3[135] (1.27-1.40)				
Skovlund 2018 incl /Worley	Prospective Cohort						475,802
	Prospective Cohort Suicide attempts		1.97[136] (1.85-2.10)				
	Suicides		3.08[137] (1.34-7.08)				
Gregory 2018	NCHA survey					146,938	202,759
	Ever Diagnosed with Depression	1.558 (1.506-1.612)					
	Academic performance affected by depression	1.282 (1.245-1.321)					
Keyes 2013	COC reduced depression among women 25-34 years of age.[138] 4 waves of L-Hanes			-1.04[139] (-1.73 - -0.35)		3224	1219
	Suicide attempts			0.38 (0.15-0.97)			
Toffol 2011	Population/choice			-0.988[141] (-1.917 – -0.059)			2,310

[132] First diagnosis of depression for combined oral contraceptive users.
[133] First diagnosis of depression for all progestin-only method users.
[134] First use of an antidepressant for combined oral contraceptive users.
[135] First use of an antidepressant for all progestin-only method users.
[136] Hazard ratio for suicide attempts; all hormonal contraceptives.
[137] Hazard ratio for suicides; all hormonal contraceptives.
[138] "The presence of depressive symptoms during the past 7 days was assessed in all waves using the Center for Epidemiologic Studies Depression Scale (CES-D)."
[139] β statistic shown.
[141] β statistic shown for the Beck Depression Inventory (BDI). None of the other parameters assessed was statistically significant (including any psychiatric diagnosis, alcohol dependence, major depressive episode or disorder, dysthymic disorder, or anxiety disorder).

	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	Cases	Controls/Cohort Size
	Cross sectional 30-54 yrs. of age[140]						
Toffol 2012	Population-based cross-sectional study[142]			-0.42 (--1.79 - -0.04)[143]			8,586
Svendal 2012[144]	Population-based cross-sectional study					40	458
	POC Use – mood disorder			3.0 (1.1-7.8)			
	COC Use – mood disorder			0.3 (0.1-0.9)			
Horibe 2018	Retrospective[145]					253	6,157,897
	Post-partum depression w/ levonorgestrel			12.5 (8.7-18)			
	Post-partum depression w/ etonogestrel			14.0 (8.5-22.8)			
	Post-partum depression w/ sertraline & drospirenone			5.4 (2.7-10.9)			
Singata-Madliki 2016	Single-blind randomized controlled trial of post-partum DMPA vs. copper IUD			[146]		111[147]	117[148]
Kulkarni 2005[149]	Case-control pilot study COCs vs non-users			p=0.001 depression for all scales[150]		26	32

[140] "The associations between the current use of COCs and the LNG-IUS, and their duration versus mood symptoms [Beck Depression Inventory (BDI)], psychological well-being [(General Health Questionnaire-12 (GHQ-12)] and recent psychiatric diagnoses [(Composite International Diagnostic Interview (CIDI)] were examined among women who participated in the Finnish-population-based Health 2000 study." "Overall, hormonal contraception was well tolerated with few significant effects on psychological well-being."

[142] Data were collected in the context of the National FINRISK Study Survey, a cross-sectional population-based health survey carried out in Finland every 5 years since 1972. For the purpose of this study, data collected in the years 1997, 2002 and 2007 were analyzed for ages 25–54. OC vs. LNG. inconsistent questions between surveys, BDI, recall bias, etc. "Presence of somatic and psychological symptoms was assessed by asking the participants how often (often, sometimes, not at all) in the previous month they had had one or more out of 13 symptoms." Also administered the Beck Depression Inventory-13. "A negative association between the current use of COCs and Beck Depression Inventory-13 (BDI-13) score was found. Some other negative associations, all characterized by a small effect size, were detected between current use of COCs and the BDI items feelings of dissatisfaction, feelings of uselessness, irritability, lost interest in people and lost appetite."

[143] Results for the BDI-13 shown. Other parameters (including BDI-21, low mood last year, anhedonia last year, recent diagnosis of depression and recent other psychiatric diagnosis) did not reach statistical significance.

[144] Women in Australia 20-50 years of age. Evaluated for the occurrence of mood disorders, including major depressive disorder (MDD), minor depression, bipolar disorder, dysthymia, mood disorder due to a general medical condition and substance induced mood disorder.

[145] Data is from the FDA Adverse Event Reporting System (FAERS) database. Reporting Odds Ratios (ROR) are shown.

[146] Beck Depression Inventory (BDI-II) and the Edinburgh Postnatal Depression Scale (EPDS) evaluated. The one-month EPDS depression scores were statistically significantly higher in the DMPA arm compared with the IUD arm (p=0.04). Three-month BDI-II scores were significantly higher in the DMPA arm than in the IUD arm (p=0.002) and, according to the BDI-II but not the EPDS, more women in the DMPA arm had major depression at this time-point (8 vs 2; p=0.05).

[147] 111 randomized to DMPA.

[148] 117 randomized to IUDs.

[149] Assessment tools included three depression rating scales: Beck Depression Inventory (BDI), Hamilton Rating Scale for Depression (HAMD) and Montgomery-Asberg Depression Rating Scale (MADRS); also used the Global Assessment of Functioning (GAF) Scale.

[150] ANOVA of GAF, BDI, HAMD &MADR scales all significantly different.

	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	Cases	Controls/Cohort Size
Roberts 2017	Retrospective cohort study[151]			With Dx of depression[152]	w/anti depressant use[153]	31,506[154]	44,022[155]
	Norethindrone-only pills			0.56 (0.49-0.64)	0.58 (0.52-0.64)		
	Levonorgestrel intrauterine system			0.65 (0.52–0.82)	1.01 (0.87–1.18)		
	Etonogestrel subdermal implant			1.01 (0.83–1.22)	1.22 (1.06–1.41)		
	Ethinyl estradiol/ norgestimate (pill)			0.89 (0.70–1.14)	1.02 (0.85–1.22)		
	Ethinyl estradiol/norethindrone (pill)			0.82 (0.59–1.12)	0.88 (0.69–1.13)		
	Ethinyl estradiol/etonogestrel (ring)			1.09 (0.80–1.50)	1.45 (1.16–1.80)		
Tsai 2010	Retrospective chart review[156]	DMPA	Controls			55	192
	Mean EPDS scores at 6 weeks postpartum	5.02	6.17				
Griksiene 2011	Case-control study[157]	[158]				23[159]	20[160]

[151]Post-partum depression with hormonal contraception.

[152] Adjusted hazard ratios shown.

[153] Adjusted hazard ratios shown.

[154] Number on hormonal contraceptives.

[155] Number not on hormonal contraceptives.

[156]Depot medroxyprogesterone in the immediate post-partum period and depression. Evaluated the Edinburgh Postnatal Depression Scale (EPDS).

[157] Verbal fluency and mental rotation (spatial perception) are affected by progestins w/androgenic or antiandrogenic properties.

[158] Naturally cycling women performed better on verbal fluency task as compared to OC users. Subjects who used the third generation (androgenic) COCs generated significantly fewer words as compared to new generation (anti-androgenic) OC users and non-users. The third generation OC users demonstrated significantly longer RT in MRT task as compared to non-users. The MRT, verbal fluency and mood parameters did not depend on the phase of menstrual cycle.

[159] Women on hormonal contraception.

[160] Control women not on hormonal contraception.

Table 15 – Studies of Chemical Contraceptives and Depression, Mood Disorders and Suicides Updated 2023

	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	Cases	Controls/Cohort Size
Anderl 2022[161]	Prospective cohort study	1.41 (1.08-2.18)				534	191
	Only those with no history of major depressive disorder	1.72 (1.21-2.18)					
Khafagy 2021[162]	Prospective cohort study						124
	Combined injectable contraceptives			34.1%			44
	Combined oral contraceptives			27.5%			40
	Copper IUD			15%			40
Larsen 2023[163]	Cohort study	1.35 (1.17-1.56)				5,722/18,431	188,648
Edwards 2022[164]	Cohort study						216,702
	COCs 1 month		1.56 (1.30–1.88)				
	COCs 3 months		1.47 (1.26–1.72)				
	COCs 6 months		1.36 (1.18–1.56)				
	COCs 12 months		1.19 (1.01–1.40)				
	POCs 1 month		2.13 (1.64–2.77)				
	POCs 3 months		1.96 (1.57–2.44)				
	POCs 6 months		1.75 (1.44–2.12)				
	POCs 12 months		1.48 (1.17–1.87)				
Lundin 2021	Cohort study[165]	**RR Any Use vs Ever Use**	**RR Any Use vs Never Use**	**RR Any Use vs Ever Use 15-19**	**RR Any Use vs Ever Use 20-25**		739,585
	Any use	1.01 (1.00–1.03)	1.29 (1.27–1.32)	1.10 (1.08–1.13)	0.91 (0.89–0.93)		
	Combined oral contraceptives	0.89 (0.87–0.91)	1.01 (0.98–1.02)	0.96 (0.93–0.98)	0.80 (0.78–0.82)		
	Oral progestin only contraceptives	1.03 (0.99–1.06)	1.11 (1.07–1.14)	1.13 (1.07–1.19)	0.96 (0.92–0.99)		
	Patch/Ring	1.27 (1.21–1.33)	1.33 (1.27–1.39)	1.43 (1.30–1.58)	1.21 (1.14–1.27)		
	Implant	1.23 (1.19–1.27)	1.28 (1.23–1.32)	1.38 (1.30–1–45)	1.11 (1.07–1.16)		
	Depot medroxyprogesterone acetate	0.82 (0.70–0.98)	0.86 (0.73–1.01)	0.67 (0.44–1.02)	0.90 (0.75–1.08)		

[161] OC use in adolescence compared with no use impact on the risk of major depressive disorder (MDD) as adults.
[162] Study of females aged 18-45 in El-Kalyubia, Egypt. The percentage of those who moved from the non-depression stage to mild depression after 6 months is shown.
[163] Evaluation of the risk of developing post-partum depression in women with a history of depression. Prior depression associated with hormonal contraceptive use defined as onset of depression within 6 months of starting hormonal contraceptives (n=5,722) or not associated with hormonal contraceptives (n=18,431).
[164] Swedish national registry study of women born between 1991 and 1995 whether they retrieved prescriptions for oral contraceptives. Cox proportional hazards models used to test the association between contraceptive use and first observed suicidal event (suicide attempt or death) from age 15 until the end of follow-up in 2014 (maximum age 22.4). Results are shown for Model 3, which was the most stringent, based on time from initiation of use.
[165] All Nordic-born (i.e. born in Sweden, Norway, Finland, Denmark or Iceland) adolescents and women aged 15–25 years between 1 January 2010 and 31 December 2017 and residing in Sweden were identified through the Total Population Register and included in the study. 77 613 events included 66,455 by an antidepressant prescription, and 16,111 by a depression diagnosis only.

	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	Cases	Controls/Cohort Size
	LNG-IUD	1.34 (1.29–1.39)	1.37 (1.32–1.42)	1.59 (1.46–1.73)	1.28 (1.23–1.34)		
Johansson 2023[166]	Population-based cohort study		**HR Ever Use**				264,557
	Within 2 years of initiation		1.79 (1.63-1.96)				
	Adolescents		1.95 (1.64-2.32)				
	Adults		1.74 (1.54-1.95)				
	Lifetime Risk		1.05 (1.01-1.09)				
Morssinkhof 2021[167]	Longitudinal cohort study	**B**[168]					1,121
	IDS-SR Score[169]	0.10 (-0.80-1.00)					
	Major Depressive Disorder diagnoses			0.99 (0.77-1.27)			
	Dysthymia Diagnosis			0.65 (0.32-1.27)			
	WHI-IRS score[170]			B= 0.54 (0.17, 0.91)			
Jung 2019[171]	Retrospective cohort study	1.13 (1.00-1.24)				4,067	27,067
Fei 2021[172]	Retrospective cohort study	11 (7.5%)				212	
de Wit 2020[173]	Retrospective cohort study				NS[174]		1010
	Adolescents[175]				p = 0.001	309 Score 0.4. (0.30)	536 Score 0.33 (0.30)
	Crying in adolescents			1.89 (1.38-2.58)			
	Hypersomnia in adolescents			1.68 (1.14-2.48)			

[166] Data from the UK Biobank. Incidence of depression was addressed via interviews, inpatient hospital or primary care data. 205,860 ever users; 49,645 never users. To validate causality, familial confounding was examined in 7,354 sibling pairs.
[167] Data from the Netherlands Study on Depression and Anxiety, an ongoing longitudinal cohort study assessing the long-term course and consequences of MDD and anxiety disorders in the Netherlands. 78% of participants (women under 55) had (past or present) depressive and/or anxiety disorders, and 22% of participants were included as non-depressed controls. 1913 observations in normally cycling women, 1301 observations in women on OCs.
[168] Unstandardized estimate.
[169] Self-Rated Inventory of Depressive Symptomatology.
[170] Women's Health Insomnia Rating Scale.
[171] Study in Korea in the Korean National Health and Nutrition Examination Survey (KNHANES) (2007-2016). Endpoints were suicide attempt/ideation with the analysis stratified by a history of depression.
[172] Study of female patients under 18 years who had an implant placed from 2013 to 2018, number (%) or patients who had the implant removed for mood issues reported.
[173] Data from the Dutch Tracking Adolescents' Individual Lives Survey (TRAILS).
[174] Depressive Symptom Score. NS = not significant in the overall population.
[175] Mean values (standard deviation) shown.

	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	Cases	Controls/Cohort Size
	Eating problems in adolescents			1.54 (1.13-2.10)			
Anderl 2020[176]	Case-control					561	322
	Never use/ Adolescent use	0.31 (0.16–0.60)				353	
	Adult use/ Adolescent use	0.54 (0.30-0.95)					
McKetta 2019[177]	Structured interview – case control			671	4,094		
	OR for ever having a depressive disorder						
	Unadjusted	1.86 (1.54 – 2.24)		1.60 (1.26 – 2.02)			
	Adjusted for age	1.52 (1.24 – 1.86)		1.29 (1.01 – 1.65)			
	Adjusted for smoking history	1.52 (1.25 – 1.85)		1.33 (1.04 – 1.69)			
	Adjusted for BMI category	1.85 (1.53 – 2.23)		1.59 (1.25 – 2.02)			
	Adjusted for age at sexual debut	1.28 (1.03 – 1.58)		1.11 (0.86 – 1.43)			
	Adjusted for socioeconomic status	1.85 (1.54 – 2.24)		1.59 (1.26 – 2.02)			
	Adjusted for all	1.10 (0.88 – 1.37)		1.00 (0.77 – 1.29)			
Ejigu 2020[178]	Community based cross-sectional study			2.03 (1.18-3.50)			826
Mohammadi-Pasand 2020	Cross-sectional study of DMPA vs. IUD users			DMPA Mean ± SD	IUD Mean ± SD	150	150
	Current Depression[179]			6.1 ± 3.5	4.4 ± 3.4		
	Current Sexual Satisfaction[180]			45.5 ± 15.2	38.1 ± 18.1		
	Negative perceived mood effects over time			31 ± 20.7	11 ± 7.3		
	Negative perceived sexual effects over time			25 ± 16.7	3 ± 2		
Singata 2021[181]	Randomized to Contraceptive Method	**Any Depression**	**Moderate/Severe Depression**				
	DMPA-IM 3 months	33.5%	17.0%			188	
	IUD 3 months	25.6%	16.1%			180	
	LNG Implant 3 months	27.7%	18.5%			184	
	DMPA-IM 12 months	17.4%	9.6%			167	

[176] OC use in adolescence predicts lasting vulnerability to adult depression.40
[177] Validated, structured interview data of adolescents in the National Comorbidity Survey-Adolescent Supplement. Cohort very unbalanced for being sexually active (64% in users vs 13% in non-users.
[178] Evaluated determinants of anxiety and depression.
[179] Measured by Patient Health Questionnaire (PHQ-9), higher is worse.
[180] Measured by Index of Sexual Satisfaction, higher is worse
[181] Follow-up of patients in South Africa in the ECHO trial.

	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	Cases	Controls/Cohort Size
	IUD 12 months	24.7%	17.7%			158	
	LNG Implant 12 months	20.4%	13.0%			162	
Chen 2022	2 multicenter phase 3 trials of estetrol/drospirenone	**% of Subjects**				3,417	
	Treatment-related mood disturbance	3.2%					
	Discontinued for treatment-related mood disturbances	1.1%					
Pletzer 2019[182]	Correlations with duration of prior OC use	Correlation Coefficient	p value			79	52
	Hippocampal volumes	Left: r=0.29 Right: r=0.31	0.02 0.02				
	Basal ganglia volumes	Left: r=0.37 Right: r=0.37	0.01 0.01				
Garforth 2020[183]	Comparative hormonal & mood evaluation	**OC Users**	**Non-OC Users**	**p value**		71	114
	Oxytocin	1.1±0.5	0.6±0.5	<0.0001		49	87
	ACTH	1.3±0.4	1.5±0.4	<0.05		49	87
	Estradiol	0.8±0.3	1.5±0.5	<0.0001		49	87
	Progesterone	0.2±0.1	0.4±0.3	<0.05		49	87
	Testosterone	0.2±0.1	0.3±0.1	<0.05		49	87
	In a relationship	55.1%	35.6%	0.007		49	87
	Satisfaction with Life Scale	26.9±5.3	24.8±6.1	0.04		49	87
	Positive and Negative Affect Schedule	2.8±0.8 1.4±0.3	2.9±0.7 1.4±0.4	NS		49	87
	Beck Depression Inventory	24.2±3.9	27.1±7.0	0.09		22	27
Larsen 2020[184]	[^{11}C]SB207145-PET imaging of 5-HT4R binding			% Change vs non-users (95% CI)		16	37
	Pallidostriatum			-8.4 (-14.8 to -1.5)			
	Caudate			-10.7 (-17.1 to -3.9)			
	Hippocampus			-12.8 (-21.0 to -3.9)			
	Amygdala			-6.9 (-16.1 to 3.3)			
	Anterior Cingulate Cortex			-10.5 (-18.0 to -2.4)			
	Neocortex			-10.9 (-18.2 to -3.0)			

[182] Women aged 18-35 who participated in one of three functional imaging studies (MRI) and provided information about their previous contraceptive use.
[183] All data from Dataset 1 except the Beck Depression Inventory which is from the (smaller) Dataset 2.
[184] The 5-HT4R is a potential target in major depressive disorder as 5-HT4R stimulation has fast acting antidepressant-like properties.

Depression, Mood Disorders, and Suicide References.

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Multiple Sclerosis

Papers were accessed from a PubMed literature review as noted (Williams 2017). Each paper was rated based on the parameters noted in the STROBE statement (von Elm 2007).

A total of 6 studies (3 cohort studies and 3 case-control studies) were identified which evaluated the impact of COCs on the subsequent development of multiple sclerosis (Table 16). Two studies showed a significantly increased risk for the development of multiple sclerosis with ever use of COCs (Hellwig 2016, Kotzamani 2012) with a similarly increased risk noted in one study for current use or past use (Hellwig 2016). Overall these studies suggest that use of COCs may convey an increased risk for the subsequent development of multiple sclerosis.

Table 16 – Individual Studies of the Effects of COCs on the Development of Multiple Sclerosis

Study	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
Hernán et al. 2000[185]	Cohort		1.1 (0.9-1.5)		1 (0.6-1.6)		1.2 (0.9-1.5)	313	237,318	90%
Thorogood et al. 1998[186]	Cohort				1.2 (0.7-2.0)		1.3 (0.9-2.0)	114	46,000	75%
Villard-Mackintosh et al. 1993	Cohort		0.8 (0.5-1.4)					63	16,969	65%
Hellwig et al. 2016	Case-control	1.51 (1.12-2.03)		1.47 1.05-2.05		1.55 (1.20-2.00)		400	3804	92%
Kotzamani et al. 2012	Case-control	1.6 (1.1-2.4)						254	314	81%
Alonso et al. 2005[187]	Case-control	0.6 (0.4-1.0)		0.5 (0.3-1.2)		0.6 (0.4-1.0)		106	1001	77%

[185] NHS I and II cohorts.
[186] Funded by drug companies that make HCs.
[187] OC use over the 3 years prior to the index date. Limited to women ≤50 years of age.

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Interstitial Cystitis

A case-control study (Konkle 2012) showed significantly higher use of birth control pills in cases versus controls: 88% versus 82%; P = 0.019. Another case-control study showed that use of COCs markedly increased the risk of the disease whether past (OR 4.6, 95% CI 1.74-12.1) or current use (OR 6.9, 95% CI 2.1–22.1). Interstitial cystitis was associated with vulvodynia and sexual dysfunction in a high number of cases (Gardella 2011). Another study showed that use of COCs in patients with interstitial cystitis was associated with a decrease in quality of life (El Khoudary 2009). One meta-analysis (Champaneria 2015) showed that ever use of COCs significantly increased the risk of interstitial cystitis (OR 2.31, 95% CI 1.03–5.16).

Overall, use of COCs appears to be associated with an increased risk for the development of interstitial cystitis.

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Osteoporotic Bone Fractures

Prescribing information for POCs typically includes a warning regarding the development of osteoporosis. However, the more relevant outcome is fracture risk. Therefore, articles were sought that looked at the effect of COCs and POCs on fracture risk. Data were initially derived from a systematic review of the evidence from observational studies of hormonal contraceptive use for contraception and the risk of fracture in women by Lopez (Lopez 2015). They noted that in 2004, the US Food and Drug Administration added a warning to depot medroxyprogesterone acetate (DMPA) labeling about the potential loss of BMD (FDA 2004), which might limit long-term use. A systematic review of progestin-only methods found an association between DMPA use and loss of bone mineral density (Curtis 2006). Lopez identified 559 records, 524 of which did not meet their inclusion criteria. Thirty-five full-text reports remained, 11 of which were excluded. Of the remaining 24, 10 were secondary articles. That left 14 articles: the 14 studies examined oral contraceptives (N = 12), DMPA (N = 4) and the hormonal IUD (N = 1). Similar search terms to Lopez were used for papers published since 2015 and 2 additional papers were retrieved. The resulting studies are shown in Table 17.

COCs: Three early studies (Cooper 1993, Tuppurainen 1993, Vessey 1998) showed an increase risk of fracture with use of COCs. These studies predominately evaluated pre-menopausal fracture risk. Others that evaluated wrist fracture linked to falling had few cases but showed a trend to decreased risk (O'Neill 1996). One study that evaluated post-menopausal fracture risk based on prior oral contraceptive use (Barad 2005) also found an increased fracture risk. Another study looking at hip fracture risk in elderly women (Michaëlsson 1999) showed a decreased risk but is compromised in that "The exposure time for oral contraceptives may thus maximally have spanned 5 years…" Two studies by Vestergaard (Vestergaard 2006 and Vestergaard 2008) looked at any fracture with OC use and did not show a significant effect when multivariate analyses were performed. However, these studies only looked at use within the past 5 years and did not take into account remote use or cumulative lifetime use. A small cross-sectional study in southern Tasmania (Wei 2011) was stratified by duration of use and showed a reduction in vertebral deformities for 5-10 years of use, but no effect for shorter or longer duration of use and no effect on number of vertebral deformities. A large case-control study which evaluated incident fracture risk with varying numbers of COC prescriptions showed an increased risk for 10+ prescriptions with current use (Meier 2010). A similar study failed to confirm this for most prescription numbers (Kyvernitakis 2017) but this study had fewer subjects reducing its power. A case-control study (Memon 2011) nested in an earlier cohort study (Cooper 1993) failed to show an effect.

Overall the weight of evidence for use of COCs suggests an increased risk of bone fracture with protracted use. The study by Barad (2005) appears to have the largest number of subjects, was a cohort study, and was the only study that evaluated post-menopausal fracture risk with prior use of COCs.

In contrast, virtually all the studies evaluating POCs show an elevated risk (Lanza 2013, Vestergaard 2008b, Meier 2010, Kyvernitakis 2017). This risk appears to increase with duration of use.

Table 17 – Individual Studies of the Effects of Contraceptives on the Development of Osteoporotic Fractures

Study	Study Design	Intervention	OR	RR		Cases	Controls or Cohort Size	Outcome
Cooper 1993[188]	Cohort	COCs		1.20 (1.08-1.34)		1365	46,000	All fractures
Vessey 1998[189]	Cohort	COCs		1.5 (1.1-2.1)		1308	17,032	First fracture: radius or ulna
Vessey 1998[190]	Cohort	COCs		1.2 (1.1-1.4)				First fracture: all sites
Vessey 1998[191]	Cohort	COCs		2.5 (1.5-4.0)				First fracture: radius or ulna
Vessey 1998[192]	Cohort	COCs		1.3 (1.1-1.5)				First fracture: all sites
Vessey 1998[193]	Cohort	COCs		5.7 (p=0.017)				First fracture: radius or ulna
Vessey 1998[194]	Cohort	COCs		11.2 (p<0.001)				First fracture: all sites
Barad 2005[195]	Cohort	OCs[196]		1.07 (1.01–1.15)		4,674	80,947	First fracture
Barad 2005[197]	Cohort	OCs		1.15 (1.04-1.27)		4,674	80,947	First fracture
Barad 2005[198]	Cohort	OCs		1.09 (0.97–1.23)		4,674	80,947	First fracture
Lanza 2013[199]	Retrospective cohort study	DMPA[200]		1.41 (1.35–1.47)		11,822	312,395	Incident fractures

[188] From the Royal College of General Practitioners (RCGP) Oral Contraception Study.
[189] OC use > 97 months vs no use. Recruited age 25 to 39 years; followed to 45 years.
[190] OC use > 97 months vs no use. Recruited age 25 to 39 years; followed to 45 years.
[191] Interval since use: 73 to 96 months vs no use (radius or ulna). Recruited age 25 to 39 years; followed to 45 years.
[192] < 12 months vs no use (all fractures). Recruited age 25 to 39 years; followed to 45 years.
[193] X^2 trend.
[194] X^2 trend.
[195] Recruited age 50 to 74 years; OC use: any vs none.
[196] The patients were asked about oral contraceptive use, which likely was predominantly COCs but was not broken down with regard to COCs or POCs.
[197] Among women without any postmenopausal hormone treatment, past OC use for 5 years or less.
[198] Among women without any postmenopausal hormone treatment, past OC use for more than 5 years.
[199] They note that, "Although DMPA users experienced more fractures than nonusers, this association may be the result of confounding by a pre-existing higher risk for fractures in women who chose DMPA for contraception." However, this is based on analysis of relatively few fractures prior to DMPA use.
[200] Depot medroxyprogesterone acetate = DMPA.

Study	Study Design	Intervention	OR	RR		Cases	Controls or Cohort Size	Outcome
	Past use[201]	DMPA		1.32 (1.24–1.41)				Incident fractures
	Recent use[202]	DMPA		1.41 (1.31–1.50)				Incident fractures
	Current use[203]	DMPA		1.51 (1.41–1.61)				Incident fractures
Tuppurainen 1993[204]	Case-control	OCs	1.21 (0.93-1.57)			629	13,100	All fractures
Tuppurainen 1993[205]	Case-control	OCs	1.35 (0.88-2.05)			210	13,100	Wrist fractures
O'Neill 1996	Case-control	OCs	0.3 (0.1-0.9)			62	116	Distal forearm fractures only Population controls
O'Neill 1996	Case-control	OCs	0.7 (0.2-2.4)			62	50	Distal forearm fractures only Fall controls
Michaëlsson 1999[206]	Case-control	Any[207]	0.75 (0.59–0.96)			1327	3312	Hip fractures
Vestergaard 2006[208]	Case-control	OCs	<0.3 DDD/day	0.3–0.99 DDD/day	1+ DDD/day	64,548	193,641	Any fracture in the year 2000
	<25 years[209]	OCs	0.97 (0.91–1.03)	0.96 (0.92–1.01)	0.92 (0.86–0.98)			Any fracture in the year 2000
	25-49 years	OCs	0.91 (0.82–1.00)	0.90 (0.77–1.05)	0.87 (0.64–1.18)			Any fracture in the year 2000
	50+ years	OCs	0.92 (0.77–1.10)	0.69 (0.45–1.05)	0.62 (0.27–1.41)			Any fracture in the year 2000
Vestergaard 2008a[210]	Case-control	OCs	<0.3 DDD/day	0.3–0.99 DDD/day	1+ DDD/day	64,548	193,641	Any fracture in the year 2000
	<15	OCs	1.02 (0.75–1.37)	1.17 (1.01–1.37)	0.97 (0.85–1.11)			Any fracture in the year 2000
	15.1-17	OCs	1.22 (1.02–1.47)	1.14 (1.00–1.30)	1.04 (0.90–1.19)			Any fracture in the year 2000

[201] Active DMPA use based on the interleaving of active 90-day exposures generated by each injection.
[202] Recent exposure is 640 or fewer days after the last active exposure.
[203] Past exposure begins after "recent" exposure (641 or more days after the last active exposure).
[204] Oral contraceptive use for 6+ years.
[205] Oral contraceptive use for 6+ years.
[206] No significant correlation was seen with duration of use, time since last use or time between last use and menopause.
[207] Any type of chemical contraceptive was evaluated, not separated as COCs or POCs.
[208] "The exposure time for oral contraceptives may thus maximally have spanned 5 years (from January 1, 1996, to December 31, 2000)." This and the other Vestergaard study are not useful as they do not take into account remote use or cumulative lifetime use. ORs shown.
[209] Defined daily dosages = DDD.
[210] Similar to Vestergaard 2006; only looked at use within the past 5 years. A younger group examined here. ORs shown.

Study	Study Design	Intervention	OR	RR		Cases	Controls or Cohort Size	Outcome
	17.1-19	OCs	0.97 (0.87–1.09)	0.93 (0.84–1.02)	1.02 (0.89–1.18)			Any fracture in the year 2000
	>19	OCs	0.99 (0.93–1.05)	1.00 (0.93–1.08)	0.88 (0.78–0.99)			Any fracture in the year 2000
Vestergaard 2008b[211]	Case-control	DMPA	1.44 (1.01–2.06)			64,548	193,641	Any fracture in the year 2000 DMPA use
Wei 2011[212]	Cross-sectional		<5 years of use	5-10 years of use	>10 years of use		491	
		OCs	0.85 (0.45–1.58)	0.45 (0.21–0.93)	0.75 (0.36–1.54)			Presence of vertebral deformity
		OCs	0.96 (0.62–1.48)	0.63 (0.37–1.07)	0.94 (0.56–1.56)			Number of vertebral deformities
Meier 2010[213]	Case-control		Current Use	Past Use		17,527	70,130	Incident fracture
	1-2 DMPA Scripts	DMPA	1.18 (0.93–1.49)	1.17 (1.07–1.29)				Incident fracture
	3-9 DMPA scripts	DMPA	1.36 (1.15–1.60)	1.23 (1.11–1.36)				Incident fracture
	10+ DMPA scripts	DMPA	1.54 (1.33–1.78)	1.30 (1.09 –1.55)				Incident fracture
	1-2 COC Scripts	COCs	1.01 (0.87–1.18)	1.00 (0.95–1.07)				Incident fracture
	3-9 COC scripts	COCs	1.01 (0.94 –1.09)	0.99 (0.94 –1.04)				Incident fracture
	10+ COC scripts	COCs	1.09 (1.03–1.16)	1.03 (0.97–1.10)				Incident fracture
Memon 2011[214]	Case-control	COCs	1.05 (0.86-1.29)			651	1302	Any fracture
Kyvernitakis 2017[215]	Case-control		OR Current Use	OR Past Use		4189	4189	First-time fracture diagnosis
	1-2 DMPA scripts	DMPA	0.97 (0.51–1.86)	0.96 (0.73–1.26)				
	3-9 DMPA scripts	DMPA	2.41 (1.42–4.08)	1.14 (0.86–1.51)				
	10+ DMPA scripts	DMPA	1.46 (0.96–2.23)	1.55 (1.07–2.27)				
	1-2 COC scripts	COCs	0.98 (0.73–1.31)	0.90 (0.77–1.05)				
	3-9 COC scripts	COCs	1.39 (1.12–1.73)	0.90 (0.78–1.03)				

[211] Similar to Vestergaard 2006; only looked at use within the past 5 years. DMPA examined here. ORs shown.

[212] Small cross-sectional study. ORs shown.

[213] Females aged 20–44 years with an incident fracture diagnosis between 1995 and 2008.

[214] Nested case-control study of the Cooper study from the Royal College of General Practitioners (RCGP) Oral Contraception Study. Last OC use > 10 years vs never.

[215] Women between 20 and 44 years of age with a first-time fracture diagnosis, matched with random controls using the Disease Analyzer database.

Study	Study Design	Intervention	OR	RR		Cases	Controls or Cohort Size	Outcome
	10+ COC scripts	COCs	1.07 (0.88–1.30)	1.04 (0.90–1.21)				

Osteoporotic Fracture References

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Impact of Contraceptives on Body Mass

Weight gain is a common complaint among contraceptive users but whether use of contraceptives is causally related remains undefined. Progestin-only contraceptives are most commonly associated with weight gain complaints and discontinuation. A recent Cochrane review (Gallo et al. 2014) examined the effect of combined oral contraceptives on weight gain and concluded existing data does not support a causal relationship. A second review of progestin-only contraceptives on weight gain (Lopez et al. 2016) found most studies of low to moderate quality but did conclude weight gain of up to 2kg (4.4 lbs) within the first year of use with continued increases thereafter. The authors advised appropriate counselling on expected weight changes to minimize discontinuation due to perceived weight gain.

The attached table (Table 18) summarizes studies of 1 year or longer that examined weight and body mass changes in contraceptive users in comparison to non-hormonal contraceptives or no method. Several additional studies compare various contraceptives for their effect on weight or body composition, but these do not directly address our focus.

The strongest data appear to be the deleterious effects of levonorgestrel-releasing IUDs on percent lean and fat body mass. Total body weight change does not appear different between groups and several large studies have shown no significant differences. However, a significant increase in % fat mass with a corresponding decrease in % lean body mass was observed in both studies where these were measured. A similar effect was seen from oral desogestrel in a single study.

Thus, while limited to date, data suggest that use of progestin-only contraceptives may have deleterious effects on % fat and % lean body mass with no significant overall effect on total body weight.

A review of current Mirena labeling makes no mention of changes in lean or fat body mass composition.

Retrospective, but not more recent, prospective studies also show DMPA use is associated with significant gains in weight. The data appear too mixed to draw firm conclusions.

Table 18 – Effect of Chemical Contraceptives on Weight Gain

Study	Design	Comparison	N	Time	Weight change (Kg)	Fat mass change	Lean mass change	Comments
Pantoja 2010	Retrospec.	DMPA 150 vs CuIUC	758	1yr	1.76 vs-0.42*			Largest differences noted in normal and overweight BMI subgroups, minimal differences in obese BMI subgroup
				2yr	3.1 vs 0.4*			
				3yr	3.9 vs 0.8*			
Modesto 2015	Retrospec.	DMPA150 vs CuIUC	1277	1yr	1.3 vs 0.2*			Adjusted for years of school & # children. 20% loss @4yrs 84% @ 10yr.
				4yr	3.5 vs 1.9*			
				10yr	6.6 vs 4.9*			
Taneepanichuskul 1998	Retrospec.	DMPA 150 vs CuIUC	100	10yr	10.9 vs 11.2			Included women 37-50 years (no younger women)
Vickery 2013	Prospec.	DMPA 150 vs CuIUC	167	1yr	2.2 vs 0.16			CHOICE study subgroup
Dal'Ava 2014	Prospec.	DMPA 150 vs CuIUC	110	1yr	1.9vs 1.1	1.6 vs -0.9 (Kg)	0.3 vs 1.2 (kg)	Paired by age (+/-2yr) & weight (+/-2kg)
Dos Santos 2014	Prospec.	DMPA 150 vs CuIUC	71	1yr	1.4 vs 0.3	1.57 vs 0.52 (kg)	(0.31) vs (0.26) (kg)	Matched by age & BMI
								()= negative value
Studies comparing LNG IUC to non-hormonal contraceptive								
Study	**Design**	**Comparison**	**N**	**Time**	**Weight change (Kg)**	**Total body fat**	**Lean body mass**	
Dal'Ava 2012	Prospec.	LNG-IUC vs non-hormonal IUC	76	1yr	2.9 vs 1.4	2.5% vs -1.3%*	(1.4%) vs 1.0%*	Paired by age & BMI
Napolitano 2015	Prospec.	LNG IUC vs no method	60	1yr	0.6 vs (0.2)	1.1% vs (0.5%)*	(1.1%) vs 0.5*	
Vickery 2013	Prospec.	LNG-IUC vs Cu IUC	230	1yr	1.03 vs 0.16	nd	nd	
Modesto 2015	Retrospec.	LNG-IUC vs CuIUC	1204	1yr	0.7 vs 0.2	nd	nd	

				4yr	2.7 vs1.9			
				10yr	4.0 vs 4.9			
Studies comparing progestin-only COCs to non-hormonal								
Study	**Design**	**Comparison**	**N**	**Time**	**Weight change (Kg)**	**Total body fat**	**Lean body mass**	
Napolitano 2015	Prospec.	Desogestrel 75ug vs no hormonal	68	1yr	0.3 vs -0.2	1.1% vs -0.5%*	(2.8%) vs 0.5%*	
Studies comparing combined COCs to non-hormonal								
None found-								
Abstract from 2014 Cochrane review of combined oral contraceptives on weight gain: "We found 49 trials that met our inclusion criteria. The trials included 85 weight change comparisons for 52 distinct contraceptive pairs (or placebos). *The four trials with a placebo or no intervention group did not find evidence supporting a causal association* between combination oral contraceptives or a combination skin patch and weight change. Most comparisons of different combination contraceptives showed no substantial difference in weight. In addition, discontinuation of combination contraceptives because of weight change did not differ between groups where this was studied. Gallo MF, Lopez LM, Grimes DA, Carayon F, Schulz KF, Helmerhorst FM. Combination contraceptives: effects on weight. Cochrane Database of Systematic Reviews 2014, Issue 1. Art. No.: CD003987.								

* Significant difference ($p<0.05$).

Impact of Contraceptives on Body Mass References

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Urogenital Effects of Contraceptives

In addition to cervical cancer and interstitial cystitis, noted above, there are other adverse urogenital effects of COCs that should be communicated to patients. These include bacteriuria (Zahran 1976; calculated OR 3.57), urinary tract infection (Engel 1979: 27–50% incidence), bladder trabeculation (Zahran 1976; calculated OR 11.7), recurrent vulvovaginal candidiasis (Spinollo 1995, Yusuf 2007; OR 2.08), vaginal dryness (Lee 2017), vulvar vestibulitis (Champaneria 2016: OR 2.1 95 % CI 1.26–3.49; also noted in Lee 2017), and Female Sexual Dysfunction (FSD) (Lee 2017). FSD appears related to OC-induced dyspareunia, reduced sexual desire and libido (Lee 2017). This risk is increased if COCs are used in adolescents and the duration of OC use is at least 2 years (Lee 2017), although some newer COCs containing drospirenone 3 mg plus EE 30 mg and gestodene 75 mg plus EE 20 mg appear to have a reduction in these risks (Lee 2017).

These urogenital risks, especially FSD where there is substantial literature, should be referenced in prescribing information and patient pamphlets.

Urogenital Effects References

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Venous Thromboembolism and Contraceptives

The current language on the black box warning of certain contraceptives regarding risk of cardiovascular events clearly misleads women about the real risks of these drugs. It says: WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS. A study (Gomer 2009) conducted among 300 women concluded "that most of them believe that certain risks are only associated with being over 35 years of age and/or smoking." Instead, the label should clearly state that anyone taking the medications without good knowledge of the risk factors could experience a potentially life-threatening cardiovascular event and should discuss the risks with a medical provider.

The incidence of venous thromboembolism (VTE) for healthy women can significantly increase with the use of hormonal contraceptives, even women under 35 and not-smoking. In a 2012 article about birth control side effects, Dr. Rebecca Peck (Peck R 2012) reports that "Oral contraceptives are associated with a three to five times higher risk of VTE (Van Hylckama VA 2009)." Third and fourth generation combined hormonal contraceptives (CHC) have been found to put women at an even much higher risk, leading to major lawsuits against some manufacturers and changes in regulations in several countries. In his opinion published in Drug Safety, Dr. Lidegaard, the author of several studies on the subject, states: "Of 14 studies specifically assessing the risk in users of CHC with desogestrel or gestodene, 13 found a higher risk with use of these products when compared to the use of CHC with levonorgestrel" (Lidegaard 2014). Drospirenone, the progestin contained in Yaz and Jasmine, also increases the risk of VTE over levonorgestrel by a factor of 1.5 to 2.8. "The relative risk [of Drospirenone was 6.3 as compared with nonusers in both the large Dutch (Van Hylckama 2009) and Danish (Lidegaard 2011) study." The author comments that "the studies demonstrating risk differences between CHC with different progestins are generally methodologically more transparent and more robust than those demonstrating no difference, especially concerning exclusion of women with predispositions for VTE." Another large study published in 2015 (Vinogradova 2015) reviewed 10,552 cases of VTE reported between 2001 and 2013 in the UK and found similar elevated risks of VTE with these CHC: "Corresponding risks associated with current exposure to desogestrel (4.28, 3.66 to 5.01), gestodene (3.64, 3.00 to 4.43), drospirenone (4.12, 3.43 to 4.96), and cyproterone (4.27, 3.57 to 5.11) were significantly higher than those for second generation contraceptives levonorgestrel (2.38, 2.18 to 2.59)." Note that the odds ratios were "adjusted for smoking status, alcohol consumption, ethnic group, body mass index, comorbidities, and other contraceptive drugs."

Most importantly, the risk levels are multiplied if women have other risk factors. For instance, women who have the genetic blood condition known as Factor V Leiden could have a risk as high as 18 per 10,000 woman-years. If these women stay on the product for 10 years, their risks could be 250 per 10,000 woman-years, or 2.5% as risks increase with aging (Lidegaard 2014).

Dr. Lidegaard concludes: "Therefore, women with known risk factors of VTE are advised to be reluctant to use CHC. The relative risk of VTE with different dispositions is as follows: previous thrombosis: > 50 (Le Moigne2013), genetic abnormalities such as factor V Leiden mutation (heterozygous): 6, deficiency of protein C: 10, of protein S: 10, of antithrombin: 25, and of prothrombin 20210A: 3 (Phillippe 2014). Pregnancy with delivery on average: 8, adiposity: 2–3 and immobilization 2–5 depending on how long time you are immobilized. Family disposition (first-degree relatives with VTE before their 50th year) doubles the risk of VTE. Women with such dispositions are generally recommended to use progestin-only contraception, which does not increase the risk of VTE except perhaps for medroxyprogesterone depots. A genetic screening should until further also be restricted to women with a family disposition" (Lidegaard 2014).

In a 2018 systematic review (Keenan 2018) of the most evidenced-based articles from the 1960s to 2018 comparing users of COCs to nonusers, with a confirmed diagnosis of VTE, and including more than 17 million woman-years of observation, women on HC increase their risk by 3- to 9-fold. However, the first year of use has the highest risk for clot formation, and if a woman is younger than 30, her risk is increased 13-fold in the first year. Obesity can increase the risk of being on hormonal contraception, about doubling the risk compared

to a woman of normal weight on the pill. It is not considered cost-effective to check for thrombophilia, a genetic disposition to form blood clots, but for those with thrombophilia, the risk can be as high as 62-fold in the first year.

This systematic review of the literature concludes that 136–260 women die from VTE a year in the United States from hormonal contraception. Combined with the added risk of stroke and heart attack from the COCs, 300–400 women die each year in the United States simply due to their choice of using HC for family planning (Keenan 2018). To give some perspective, meningitis killed 45 people (of all ages) in 2017: most US States mandate meningitis vaccination for college and university students.

A summary of studies is shown in Table 19.

Table 19 – Relative Risk of Venous Thromboembolism in Current Users of Different Combined Hormonal Contraceptives as Compared with Nonusers Unless Otherwise Specified

Study	Data Sampling Period	VTE (number)	CHCs with levonorgestrel RR (95% CI)	CHCs with desogestrel/gestodene RR (95% CI)	CHCs with drospirenone RR (95% CI)
Blomenkamp 1995	1988 - 1992	126	3.8 (1.7 - 8.4)	8.7 (3.9 - 19.3)	-
WHO 1995a, 1995b	1989 - 1993	433	3.6 (2.5 - 5.1)	7.4 (4.2 - 12.9)	-
Jick 1995	1991 - 1994	80	1 (reference)	1.8 (1.0 - 3.2)	-
Spitzer 1996	1991 - 1995	471	3.7 (2.2 - 6.2)	6.7 (3.4 - 13.0)	-
Lewis 1999	1993 - 1995	502	2.9 (1.9 - 4.2)	2.3 (1.5 - 3.5)	-
Farmer 1997	1991 - 1995	85	3.1‡ (2.1 - 4.5)	5.0‡ (3.7 - 6.5)	-
Todd 1999	1992 - 1997	99	1 (reference)	1.4 (0.7 - 2.8)	-
Bloemenkamp 1999	1994 - 1998	185	3.7 (1.9 - 7.2)	5.6 (not given)	-
Parkin 2000	1990 - 1998	26	5.1 (1.2 - 21.4)	14.9 (3.5 - 64.3)	-
Lidegaard 2002	1994 - 1998	987	2.9 (2.2 - 3.8)	4.0 (3.2 - 4.9)	-
Dinger 2007	2000 - 2004	118	1 (reference)	1.3 (NA)	1.0 (0.6 - 1.8)
Vlieg 2009	1999 - 2004	1524	3.6 (2.9 - 4.6)	7.3 (5.3 - 10.0)/5.6 (3.7 - 8.4)	6.3 (2.9 - 13.7)
Lidegaard 2009	1995 - 2005	4213	2.0 (1.8 - 2.3)	3.6 (3.3 - 3.8)	4.0 (3.3 - 4.9)
Dinger 2010	2002 - 2008	680	1 (reference)	NA	1.0 (0.6 - 1.8)
Parkin 2011	2002 - 2009	61	1 (reference)	NA	2.7 (1.5 - 4.7)
Jick 2011	2002 - 2008	186	1 (reference)	NA	2.8 (2.1 - 3.8)
Lidegaard 2011	2001 - 2009	4246	2.2 (1.7 - 2.8)	4.2 (3.6 - 4.9)	4.5 (3.9 - 5.1)
Confirmed only	2001 - 2009	2707	2.9 (2.2 - 3.8)	6.8 (5.7 - 8.1)	6.3 (5.4 - 7.5)
FDA Kaiser 2011	2001 - 2007	625	1 (reference)	NA	1.5 (1.2 - 1.9)
Gronich 2011	2002 - 2008	518	1 (reference)	1.4 (0.9 - 2.1)	1.7 (1.0 - 2.7)
Lidegaard 2012	2001 - 2010	5287	3.2 (2.7 - 3.8)	6.5 (4.7 - 8.9)*	NA
Dinger 2014	2005 - 2010	162	1 (reference)	NA	0.8 (0.5 - 1.6)

‡ Absolute risk per 10,000 years.
* Vaginal ring with the third-generation progestin etonogestrel.

Venous Thromboembolism References

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Atherosclerosis and Cardiovascular Events

Noting that previous studies had demonstrated women on oral contraceptives (OC) faced a fourfold increased risk of heart attack (Hennekens 1977; Vessey 1976; Beral 1976), researchers in 1982 set out to understand the pathogenesis of vascular disease related to COCs. They found that combination oral contraceptives (COC) caused "greater cell proliferation and incorporation…in both human arterial smooth muscle cells and dermal fibroblasts." Smooth muscle cell proliferation is an integral feature of all atherosclerotic lesions (Bagdade 1982).

In 2007, a presentation at the American Heart Association meeting described a study of 1,301 Belgian women, which showed that women had a 20 to 30 percent increase of plaque for every decade on COCs (Rietzschel 2007). They performed a multivariate adjustment for age, smoking, blood pressure, lipids, obesity, diabetes, physical activity, fruit, vegetable and alcohol intake, educational level and drug therapy (lipid-lowering, antihypertensive, aspirin). Use of OC was associated with a significant increase in carotid or femoral unilateral plaque (OR per 10 years of OC exposure were: carotid plaque 1.17 (1.00 –1.33) and femoral plaque 1.28 (1.10 – 1.47). When evaluating the prevalence of bilateral disease (involvement of right and left carotid/femoral artery) as a more stringent phenotype of atherosclerosis, the OR per 10 years OC exposure were 1.42 (1.03–1.84) for carotid plaque and 1.34 (1.05–1.63) for femoral plaque.

They later noted that active OC users had elevated C-reactive protein levels, three times higher than non-users. C-reactive protein is a biomarker for many inflammation-related arterial (and autoimmune) diseases, which was recently the subject of another presentation (Rietzschel 2018). After a similar multivariate analysis, they found the hs-CRP levels were (adjusted geometric means [95% CI]) were: non-users (NoH) 1.0 [0.9 –1.1]; hormone replacement therapy (HRT) users 1.2 [1.1–1.5] and OC users 3.3 [3.0 –3.6]; (OC vs NoH: $p<0.001$; HRT vs NoH: $p<0.05$).

This group also evaluated the carotid and femoral pulse wave velocity (PWV), a measure of arterial stiffness (Rietzschel 2008). They found the average PWV among non-users was 6.6 m/sec, while the average among current OC users was 6.75 m/sec. The blood pressure (BP) of current OC users was also significantly higher (systolic BP (+4.4 ± 0.9 mmHg; $p < 0.001$), diastolic BP (+2.3 ± 0.6 mmHg; $p < 0.001$)). They noted that duration of OC use is a significant determinant of PWV, even after adjustment for age, BP, lipid levels, body size, heart rate, drug therapy (lipid-lowering, antihypertensive), glycemic status and smoking: $F = 6.1$; $p = 0.013$. Per 10 years of OC exposure PWV increased by 0.1 m/s (0.02– 0.18; $p = 0.013$). They concluded that current OC use is associated with increased PWV because OC's increase blood pressure, while long-term use is an independent determinant of PWV, increasing PWV by 0.10 m/s per 10 years exposure (probably through structural remodelling of the vessels). These findings were supported by an evaluation of large artery stiffness in the ENIGMA study (Hickson 2011) although other smaller studies have shown conflicting data (Yu 2014, Priest 2018).

A study of homocysteine and nitric oxide levels compared 50 healthy women with normal menstrual cycles as a control group and 50 healthy women receiving oral contraceptive pills for at least three menstrual cycles (Fallah 2012). They noted that after 3 months of treatment, homocysteine levels were significantly increased ($P = 0.027$), and there was a significant and considerable decrease ($P = 0.048$) in NO concentration of oral contraceptive pill (OCP) consumers. Another study evaluated the effect of COCs on homocysteine and C-reactive protein levels in women (Norouzi 2011). This observational cross-sectional analysis included 90 healthy, non-obese women (mean age 25 years). Forty-five healthy women on OCP and 45 healthy controls were studied. COC users had a minimum of 3 cycles on COCs. The results showed that the homocysteine (13.268±3.475 vs. 7.288±2.621 µmol/L) and CRP (5863.0±1349.5 vs. 1138.3±691.12 ng/ml) levels were significantly higher in women receiving OCP in comparison with the control group ($p=0.027$ and $p<0.001$, respectively). Similarly, a cross-sectional study, in 2011-2012, evaluated 60 healthy premenopausal women (30 cases of COC consumers and 30 controls as nonconsumers), aged between 25 and 45 years who were current

users for at least a 3-year period. They evaluated brachial artery endothelial function (using flow-mediated dilatation (FMD)) and common carotid artery intima–media thickness (Heidarzadeh 2014). They noted that there was a significant FMD% difference between 2 groups of cases and controls: 11 ± 3.53 versus 15.80 ± 9.22 (P = 0.01). In addition, a significant mean CCA-IMT thickness difference was detected: 0.53 ± 0.07 versus 0.44 ± 0.08 (P = 0.00). Although these results were not significant after multiple regression analysis, the authors noted that their results were in favor of early atherosclerotic changes in prolonged users of COCs.

The Danish Heart Association released the results of a 15-year historic cohort study looking at thrombotic stroke and myocardial infarction, which observed over 1.6 million women. The results demonstrated that women taking COCs with ethinyl estradiol at a dose of 20 µg had a risk of arterial thrombosis that was 0.9 to 1.7 times higher than non-users, while those taking a dose of 30 to 40 µg had a 1.3 to 2.3 higher risk (Lidegaard 2012). The risk of thrombotic stroke appeared to be independent of duration of use, while the risk for myocardial infarction increased with duration of use (Table 20).

Together, these studies suggest that protracted use of COCs can induce atherosclerotic changes independent of any pro-thrombotic effect. These changes may contribute to the increase in thrombotic stroke and myocardial infarction seen in COC users.

Table 20 – Relative Risk of Thrombotic Stroke and Myocardial Infarction among Users of Selected Types of Combined Oral Contraception with Ethinyl Estradiol at a Dose of 30 to 40 µg, as Compared with Nonusers, According to Duration of Use (from Lidegaard 2012).

		Thrombotic Stroke		**Myocardial infarction**	
Duration of use	No. of person-yrs.	No. of events	Relative Risk (95% CI)	No. of events	Relative Risk (95% CI)
<1 year	987,564	213	1.90 (1.64–2.20)	86	1.85 (1.48–2.31)
1-4 years	992,825	194	1.55 (1.33–1.80)	108	1.99 (1.63–2.43)
>4 years	399,461	173	1.93 (1.65–2.26)	91	2.11 (1.70–2.62)

Atherosclerosis and Cardiovascular Events References

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Effects on the Children of Women who use Hormonally active Contraceptives

General Health of Offspring

A 2016 study (Birnbaum 2016), "Can Contraceptive Pill Affect Future Offspring's Health? The Implications of Using Hormonal Birth Control for Human Evolution" concluded that "Our findings show that children of women who were on the pill during relationship onset are more often reported by their mothers to be infection-prone and require medical care, suffer from a higher frequency of common sicknesses, and are perceived as generally less healthy than their peers as compared with children of women who were not on contraceptive pill during relationship onset." There were no significant differences in perceived health and perceived duration of recovery from illnesses in comparison with peers. Overall, the analysis explained between 2.4 and 7.8%of the health indicators' variance. In the analysis they found no link to breast feeding, nor exposure to other children at school. They did find that that 11.5% of the couples who met during regular contraceptive pill use got divorced as compared with 3.5% of the couples who met under natural.

Autism spectrum disorder (ASD) in Offspring

A 2014 review (Strifert 2014) posited the increase in the prevalence of oral contraceptive use in the past 60 years coincides with the recent dramatic rise in autism and autism spectrum disorder (ASD) prevalence,

indicating a link between oral contraceptive and ASD. This was reinforced in 2017 with a Chinese study (Zou 2017) which concluded that prenatal levonorgestrel (LVG, a progestin which is contained in norgestrel) exposure induces autism-like behavior in rat offspring through ERβ suppression in the amygdale, the first time the potential effect of oral contraceptives on the contribution of autism-like behavior in offspring had been discovered. The authors also noted that LVG was also present in farmed fish eaten by Chinese women. The following year in 2018 a population-based case-control epidemiology study was conducted in China (Li 2018) which confirmed that following factors were strongly associated with ASD prevalence: use of progestin to prevent threatened abortion, use of progestin contraceptives at the time of conception, and prenatal consumption of progestin-contaminated seafood during the first trimester of pregnancy. All the above factors were directly or indirectly involved with prenatal progestin exposure. Additionally, in vivo experiments in rats further confirmed the findings. Either endogenous (progesterone) or synthetic progestin (norethindrone)-treated seafood zebrafish was used to feed pregnant rats, and the subsequent offspring showed autism-like behavior.

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Conclusion

Hormonal agents have a variety of effects on various organs and organ systems which may result in a deleterious impact on women's health. It is important to stress that these agents are generally not used to treat a disease, disorder or pathology but are used by healthy women to suppress ovulation. As such, the safety requirements for these agents should be much more stringent than other medications which are used to treat a disease, disorder or pathology. The data reviewed above reflect a vast body of information which has come to light since the introduction of these agents as contraceptives over 50 years ago. While the information for patients and prescribers currently reflects many of the known side effects, others have come to light which are not adequately represented in the current prescribing information. These should be added and made obvious to patients. In one instance, that of venous thromboembolism, while the warning information is present, it is phrased in a misleading manner which misleads the patients into drawing the incorrect conclusion regarding the risks. In addition, one agent (DMPA) appears to convey a specific risk for HIV transmission which is not shared by other agents. DMPA should be considered for revoking of marketing authorization and removed from the market. The risks of depression, mood disorders, and suicide have not been adequately emphasized.

We further encourage the Agency to require the manufacturers of these agents to widely publicize these additional risks. Many millions of women are currently receiving COCs and POCs. Many millions more have been exposed to these agents at some point in their lives. They should receive updated information regarding risks which have not been conveyed, or not adequately conveyed, in the past. All women who have been exposed to COCs or POCs should be informed so that they can take this information into account as they may encounter some of these adverse effects in some cases many years after cessation of use.

Environmental Impact

Based on data from the Guttmacher Institute, a conservative estimate of 11 million women aged 15-44 in the US take some form of hormonal contraceptive each day[216]. A 2015 study reports that about 21 percent of women of reproductive years are using some form of hormonal contraceptive, which equates to about 13 million women (Daniels 2015). This has resulted in a significant increase in the release of synthetic progestagens (such as levonorgestrel) and synthetic estrogens (such as ethinylestradiol [EE2]) into the aquatic environment via wastewater treatment plant discharges (Besse 2009, King 2016). EE2 is metabolized in the liver undergoing first pass metabolism, but ~6% of the administered dose appears as untransformed EE2 in the urine and ~9% in the

[216] https://www.guttmacher.org/fact-sheet/contraceptive-use-united-states.

feces (Stanczyk 2013). As noted by King (King 2016), even at low concentrations, these compounds can act as potent endocrine disruptors, affecting the growth, development, and reproduction of exposed aquatic organisms (Tyler 1998, Larsson 1999). EE2 is one of the most studied synthetic hormones in aquatic environments, for which assessments of environmental concentrations and the quantification of endocrine-related effects have been documented in a range of aquatic species (Purdom 1994, Jobling 1998, Kirby 2004, Jobling 2006). In fact, the numerous studies on the effects of EE2 on aquatic organisms have led to the derivation of a reliable predicted no-effect concentration of 0.1 ng/L for EE2 (Caldwell 2012).

In 1993, the first publication appeared which brought attention to the issue of synthetic chemicals mimicking natural estrogen in the environment (Sharpe 1993). The study pointed to environmental pollutants, which were having a deleterious effect on male fetuses in utero – endocrine disruptors like polychlorinated biphenyls, detergents, dioxins, and hormonal contraceptives. In 1995, another paper (Sumpter 1995) noted that male fish in 28 rivers across Britain were being "feminized" by pollutants. In 2002, a paper was published that focused specifically on the effects of endocrine-disrupting chemicals in the environment (Jobling 2002). They demonstrated reduced fertility in fish populations in areas downstream of effluent from sewage plants located along tributaries of the Thames River. In 2007, the results of a seven-year Canadian lake study were published which examined the effects of EE2 (Kidd 2007). The researchers released a quantity of EE2 equivalent to what would come into the waterways via sewage from a city of 200,000 people. They witnessed an immediate feminization and transgendering of male fish, which resulted in the "near extinction" of the fathead minnow population (Kidd 2007). Although the minnow populations neared extinction, they rebounded as soon as the researchers stopped adding EE2 to the lake. A 2006 study from the United States Geological Survey on smallmouth bass in the Shenandoah and Monocacy Rivers found that more than 80-percent of all the male bass living in these waterways were growing eggs in their testes[217].

A study was carried out of fish populations relative to the sewage treatment plants of three major Colorado cities: Denver, Boulder, and Colorado Springs (Woodling 2006). At each municipality, they set up a location just upstream from where the effluent was released, and another just downstream. The fish in the upstream locations enjoyed a balanced 1:1 female-to-male sex ratio. Downstream there were five female fish for every one male, and twenty percent of the reduced male population demonstrated intersex characteristics, such as eggs in their testes and the presence of vitellogenin, an egg yolk protein normally found only in fertile females. The consequences also appeared to ascend up the food chain in a measurable way, specifically with the feminization of trout, mink frogs and green frogs (Parke 2009). Both the predicted and the measured concentrations of EE2 in the US, including effluent of waste water treatment plants, surface water, or ground water, exceeds the predicted no-effect concentrations on fish populations (Kostich 2013).

Environmental factors have been implicated in declining fertility rates (Skakkebaek 2016). A 2017 study out of Hebrew University and Mount Sinai Medical School found that sperm counts in human men have dropped by more than 50 percent since 1973 (Levine 2017). While it has been noted that environmental exposure to individual steroidal estrogens, as well as their mixtures, are unlikely to dramatically affect endocrine signaling in humans, it is not clear whether more subtle effects are possible (Kostich 2013). More recently, environmental effects of levonorgestrel have been postulated (King 2016) but there is less hard data.

There is a clear effect of environmental EE2 on fish populations as well as species higher in the food chain such as frogs. An effect on humans is also possible.

[217] https://dep.wv.gov/WWE/watershed/wqmonitoring/Documents/Potomac-Intersex/USGS_FishHealthReproductiveIssuesPotomac_2006.pdf.

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Economic Impact

For the diseases noted below, in some cases we have calculated the estimated economic impact taking into account those who are currently using COCs and those who have ever used COCs. According to the CDC[218] 15.9% of women aged 15–44 in the US use "the pill." There are 61 million US women of reproductive age (15–44)[219]. This yields 9,699,000 women in the USA currently on COCs. Note that this is a low estimate as it does not include women using intravaginal and transdermal formulations and is lower than the estimate by Daniels (Daniels 2015).

According to the National Survey of Family Growth[220], 79.3% of women surveyed from 2011–2015 have ever used "the pill." This is down from 81.9% in the 2006-2010 survey and 82.3% in the 2002 survey. The lower number for "ever use" of 79.3% is used in subsequent calculations. According to the 2010 census (Howden 2011), there were 156,964,212 women in the US, of whom 24% were under 18 years of age. Thus, there were 119,292,801 women 18 years of age or older. This implies that 119,292,801 x 0.793 = 94,599,191 women in the USA have ever used the pill. As noted above, this does not include women using intravaginal and transdermal formulations.

The numbers 9,699,000 for current use and 94,599,191 for ever use of COCs were used in some of these calculations. In other cases, the census data for specific age groups was used if they were the groups most likely to be impacted by current or recent use of COCs.

For progesterone-only contraceptives (POCs), the National Survey of Family Growth[221], notes that 25.4% of women aged 15–44 in 2011–2015 have ever used "3-month injectable (Depo-Provera™)." This is up from 23.2% in 2006–2010 and 16.8% in 2002. For a conservative estimate, we will use the lowest of these numbers (16.8% or 20,041,191 women) who have ever used POCs. This would not include POCs administered by other routes and is thus a conservative estimate.

HIV Costs

According to the CDC[222], an estimated 255,900 women were living with HIV at the end of 2014. Of these it is estimated 87% were via sexual contact (this proportion was relatively stable from 2011–2016; CDC HIV Surveillance Table 1a). Annual medical cost estimates for HIV-infected persons, adjusted for age, sex, race/ethnicity, and transmission risk group, were from the HIV Research Network (range $1,854–

[218] https://www.cdc.gov/nchs/fastats/contraceptive.htm.
[219] https://www.cdc.gov/nchs/data/nhsr/nhsr086.pdf.
[220] https://www.cdc.gov/nchs/nsfg/key_statistics/c.htm#everused.
[221] https://www.cdc.gov/nchs/nsfg/key_statistics/c.htm#everused.
[222] https://www.cdc.gov/hiv/group/gender/women/index.html.

$4,545/month) and for HIV-uninfected persons were from the Medical Expenditure Panel Survey (range $73–$628/month) (Schackman 2015). Using this information along with the prevalence of DMPA use of 16.8%, this suggests an annual cost of treatment for HIV infection due to DMPA use of ~$157-573 million (

Table 21).

Table 21 – Estimated Economic Impact of DMPA due to Increased Prevalence of HIV Infection

Women with HIV	255,900
Sexual transmission	87%
Cases due to sexual transmission	222,633
Ever use of DMPA	16.80%
Women with HIV with DMPA use	37,402
RR of HIV with DMPA use	1.4
Adjusted estimate →	26,716
Excess cases →	10,686
Highest estimated individual annual costs →	$53,664
Lowest estimated individual annual costs →	$14,712
Highest estimated total annual costs →	$573,474,111
Lowest estimated total annual costs →	$157,218,081

Breast Cancer

A recent study in the US (Blumen 2016) notes, "The average costs per patient allowed by the insurance company in the year after diagnosis were $60,637, $82,121, $129,387, and $134,682 for disease stage 0, I/II, III, and IV, respectively. The average costs allowed per patient in the 24 months after the index diagnosis were $71,909, $97,066, $159,442, and $182,655 for disease stage 0, I/II, III, and IV, respectively." For all patients, they note that the average cost for the first 12 months following diagnosis is $85,772, and for the second 12 months is $22,127 with a total of $103,735 for the 24 months following diagnosis. For these calculations we will use the first-year costs to estimate costs for incident cases among current users of COCs and will use the second-year cost to approximate the average annual cost of care for a patient diagnosed with breast cancer. According to the NIH SEER statistics[223], the incidence of breast cancer is 126.0 per 100,000 person-years. Approximately 12.4 percent of women will be diagnosed with female breast cancer at some point during their lifetime. According to the best epidemiology studies noted in Table 3 (Mørch 2017; Heikkinen 2016, Lund 2007), and the best meta-analysis in Table 5 (Kahlenborn 2006) the relative risk of ever use of COCs for the development of breast cancer is 1.19–1.37. Based on this information, the estimated increase in cost from use of COCs due to incident cases of breast cancer is between $199 million and $387 million (Table 22).

Table 22 – Estimated Economic Impact of COCs due to Increased Incidence of Breast Cancer

Women of reproductive age	Number on the pill	Incidence		
61,000,000	9,699,000	0.00126		
Estimated women on the pill at risk →		12,221		
Adjusted estimate of cases →		14,543	1.19	Low RR
Adjusted estimate of cases →		16,742	1.37	High RR
Excess cases →		2,322	Low RR	
Excess cases →		4,522	High RR	
Annual cost per patient of breast cancer →		$85,772		

[223] https://seer.cancer.gov/statfacts/html/breast.html.

Estimated annual costs →	$199,157,489	Low RR
Estimated annual costs →	$387,833,005	High RR

To evaluate the impact of "ever use" of COCs on prevalent breast cancer, we noted that the best meta-analysis (Kahlenborn 2006) showed a 1.19 odds ratio of breast cancer with COCs. In addition, the lower estimate of 7% increase from the National Cancer Institute is added as a lower bound. According to the SEER statistics, there are currently 3,418,124 prevalent cases of breast cancer in the USA. The estimated increase in cost from treatment of the excess cases of breast cancer is estimated to be ~$9.6 billion annually (Table 23).

Table 23 – Estimated Economic Impact of COCs due to Increased Prevalence of Breast Cancer

Prevalent cases of breast cancer	Ever use of COCs	Breast cancer ever users		
3,418,124	79.3%	2,710,572		
Adjusted estimate of cases if no use of COCs →		2,277,792	1.19	High RR
Adjusted estimate of cases if no use of COCs →		2,2,533,245	1.07	Low RR
Excess cases →		432,780	High RR	
Excess cases →		177,327	Low RR	
Annual cost per patient of breast cancer →		$22,127		
Estimated total costs →		$9,576,133,158	High RR	
Estimated total costs →		$3,923,714,529	Low RR	

Cervical Cancer

A recent study in Canada (Pendrith 2016) on the costs of invasive cervical cancer treatment noted: "The mean overall medical care cost was $39,187 [standard error (se): $1,327] in the 1st year after diagnosis. … At 5 years after diagnosis, the mean overall unadjusted cost was $63,131 (se: $3,131), and the cost adjusted for censoring was $68,745 (se: $2,963)." For these calculations we will assume a cost of $39,187 annually for incident cases and $13,749 (=$68,745/5) annually for prevalent cases of invasive cervical cancer. According to the NIH SEER statistics[224], the incidence of invasive cervical cancer is 7.4 per 100,000 person-years. According to the American Cancer Society[225], it is estimated that 13,170 women will be diagnosed with invasive cervical cancer in the USA in 2019. In 2015, there were an estimated 257,524 women living with invasive cervical cancer in the United States. According to the best epidemiology studies noted in Table 7 (Roura 2016) the relative risk of ever use of COCs for the development of invasive cervical cancer is 1.6 and the RR for current use is 2.2. Based on this information, the estimated increase in cost from use of COCs due to incident cases of cervical cancer is ~$33 million (Table 24).

Table 24 – Estimated Economic Impact of COCs due to Increased Incidence of Cervical Cancer

Women of reproductive age	Number on the pill	Incidence		
61,000,000	9,699,000	0.000074		
Estimated women on the pill at risk →		718		
Adjusted estimate of cases →		1,579	2.2	RR
Excess cases →		861		
Annual cost per patient of cervical cancer →		$39,187		
Estimated annual costs →		$33,750,635		

To evaluate the impact of "ever use" of COCs on prevalent cervical cancer, we noted that the best study (Roura 2016) showed a 1.6 relative risk of cervical cancer with COCs. According to the SEER statistics, there are

[224] https://seer.cancer.gov/statfacts/html/cervix.html.
[225] https://www.cancer.org/cancer/cervical-cancer/about/key-statistics.html.

currently 257,524 prevalent cases of cervical cancer in the USA. The estimated increase in cost from treatment of the excess cases of cervical cancer is estimated to be ~$1 billion annually (

Table 25)

Table 25 – Estimated Economic Impact of COCs due to Increased Prevalence of Cervical Cancer

Prevalent cases of breast cancer	Ever use of COCs	Cervical cancer ever users		
3,418,124	79.3%	257,524		
Adjusted estimate of cases if no use of COCs →		204,217	1.6	RR
Excess cases →		76,581		
Annual cost per patient of cervical cancer →			$13,749	
Estimated total costs →			$1,052,914,912	

Crohn's Disease

A recent study in the US (Rao 2018) estimated the 5-year cost of the treatment of Crohn's disease as $116,838 per patient (interquartile range of $45,643–$240,398; annual cost $23,368). This was higher with worsening disease activity. According to the Centers for Disease Control (CDC), the incidence of Crohn's disease is 3.1 to 14.6 cases per 100,000 person-years[226]. According to the best epidemiology studies noted in Table 9 (Khalili 2013; García Rodríguez 2005), and the best meta-analysis (Cornish 2008), the relative risk of current COC use is 1.46–2.82 for the development of Crohn's disease. Based on this information, the estimated increase in cost just from treatment of the excess cases of Crohn's disease, only looking at current use and not past use of COCs, is between $3 million and $60 million annually (Table 26).

Table 26 – Estimated Economic Impact of COCs due to Increased Incidence of Crohn's Disease

Women of reproductive age	Number on the pill	Low incidence	High incidence		
61,000,000	9,699,000	0.000031	0.000146		
Estimated women on the pill at risk →		301	1,416		
Adjusted estimate →		439	2,067	1.46	Low RR
Adjusted estimate →		848	3,993	2.82	High RR
Excess cases →		138	651	Low RR	
Excess cases →		547	2,577	High RR	
Annual cost per patient of Crohn's disease →		$23,368			
Estimated annual costs →		$3,231,920	$15,221,300	Low RR	
Estimated annual costs →		$12,787,162	$60,223,406	High RR	

To evaluate the impact of "ever use" of COCs, we noted that the best cohort study (Khalili 2013) and meta-analysis (Cornish 2008) showed a 1.43 and 1.44 relative risk of Crohn's disease. According to the Centers for Disease Control (CDC), the prevalence of Crohn's disease in adults is 201 cases per 100,000 person-years[227]. Taking the lower number of 1.43, the estimated increase in cost from treatment of the excess cases of Crohn's disease due to COC use is approximately $1.9 billion annually (Table 27).

Table 27 – Estimated Economic Impact of COCs due to Increased Prevalence of Crohn's Disease

Women ≥ 18 in 2010 Census	Ever use of COCs	Prevalence		
119,292,801	94,599,191	0.000201		
Estimated women on the pill at risk →		190,144		
Adjusted estimate →		271,906	1.44	RR

[226] https://www.cdc.gov/ibd/IBD-epidemiology.htm.
[227] https://www.cdc.gov/ibd/IBD-epidemiology.htm.

Excess cases →	81,762	1.44	RR
Annual cost per patient of Crohn's disease →	$23,368		
Estimated total costs →	$1,910,583,605	1.44	RR

Ulcerative Colitis

A recent study in the US (Cohen 2015) noted that compared with controls, patients with UC had higher adjusted total direct ($15,548 vs $4812) and indirect costs ($4125 vs $1961) annually. This implies a total annual increase in cost of ~$12,900 for UC. This was higher with worsening disease activity. According to the Centers for Disease Control (CDC), the incidence of UC is 2.2 to 14.3 cases per 100,000 person-years[228]. According to the best epidemiology studies noted in Table 11 (Khalili 2013; García Rodríguez 2005), and the best meta-analysis (Cornish 2008) the relative risk of current COC use 1.22–1.58 for the development of UC. Based on this information, the estimated increase in cost just from treatment of the excess cases of UC, only looking at current use and not past use of COCs is between $605,000 and $10 million per year (Table 28).

Table 28 – Estimated Economic Impact of COCs due to Increased Incidence of Ulcerative Colitis

Women of reproductive age	Number on the pill	Low incidence	High incidence		
61,000,000	9,699,000	0.000022	0.000143		
Estimated women on the pill at risk →		213	1,387		
Adjusted estimate →		260	1,692	1.22	Low RR
Adjusted estimate →		337	2,191	1.58	High RR
Excess cases →		47	305	Low RR	
Excess cases →		124	804	High RR	
Annual cost per patient of ulcerative colitis →		$12,900			
Estimated annual costs →		$605,567	$3,936,184	Low RR	
Estimated annual costs →		$1,596,494	$10,377,212	High RR	

To evaluate the impact of "ever use" of COCs, we noted that the best cohort study (Khalili 2013) showed a 1.18 relative risk of UC. The estimated increase in cost of the excess cases of UC due to use of COCs is approximately $522 million annually (Table 29).

Table 29 – Estimated Economic Impact of COCs due to Increased Prevalence of Ulcerative Colitis

Women ≥ 18 in 2010 Census	Ever use of COCs	Prevalence		
119,292,801	94,599,191	0.000238		
Estimated women on the pill at risk →		225,146		
Adjusted estimate →		265,672	1.18	RR
Excess cases →		40,526	1.18	RR
Annual cost per patient of ulcerative colitis →		$12,900		
Estimated total costs →		$522,789,187	1.18	RR

Systemic Lupus Erythematosus

A recent study in the US (Chen 2015) noted that mean total health care costs were $21,535 among all SLE patients over the 1-year study period. According to the Centers for Disease Control (CDC), the incidence of SLE is 6.5–10.6 cases per 100,000 women-years[229]. In terms of prevalence, "A conservative estimate suggests a prevalence of 161,000 with definite SLE and 322,000 with definite or probable SLE." According to the best epidemiology studies noted in Table 13 that evaluated current use of COCs (Bernier 2009), the relative risk of

[228] https://www.cdc.gov/ibd/IBD-epidemiology.htm.
[229] https://www.cdc.gov/lupus/facts/detailed.html.

current COC use is 1.45 – 2.52 for the development of SLE. Based on this information, the estimated increase in cost just from treatment of the excess cases of SLE, only looking at current use and not past use of COCs, is $6.1 million to $33.6 million annually (Table 30).

Table 30 – Estimated Economic Impact of COCs due to Increased Incidence of Systemic Lupus Erythematosus.

Women of reproductive age	Number on the pill	Low incidence	High incidence		
61,000,000	9,699,000	0.000065	0.0001065		
Estimated women on the pill at risk →		630	1,028		
Adjusted estimate →		914	1,491	1.45	Low RR
Adjusted estimate →		1,589	2,591	2.52	High RR
Excess cases →		284	463	Low RR	
Excess cases →		958	1,563	High RR	
Annual cost per patient of SLE →		$21,535			
Estimated annual costs →		$6,109,388	$9,963,002	Low RR	
Estimated annual costs →		$20,636,155	$33,652,807	High RR	

To evaluate the impact of "ever use" of COCs, we noted that the best cohort studies (Costenbader 2007; Bernier 2009) showed a relative risk of SLE 1.19–2.3. The estimated increase in cost of the excess cases of SLE due to use of COCs is approximately $439 million–$1.55 billion annually (Table 31).

Table 31 – Estimated Economic Impact of COCs due to Increased Prevalence of Systemic Lupus Erythematosus.

Women ≥ 18 in 2010 Census	Ever use of COCs	Prevalence		
119,292,801	94,599,191	161,000		
Estimated women on the pill at risk →		127,673		
Adjusted estimate →		107,288	1.19	Low RR
Adjusted estimate →		55,510	2.3	High RR
Excess cases →		20,385	1.19	Low RR
Excess cases →		72,163	2.3	High RR
Annual cost per patient of SLE →		$21,535		
Estimated total costs →		$438,985,908	1.19	Low RR
Estimated total costs →		$1,554,030,205	2.3	High RR

Depression

The most reliable study (Skovlund 2016) indicated a 1.1 RR for depression with COCs and a 1.2 RR with POCs. This study evaluated women aged 15-34 and then followed them for a mean of 5 years. According to the information from Brody (Brody 2018), the prevalence of depression in women aged 20-39 is 10.1%. An analysis of medical claims conducted by insurer Blue Cross Blue Shield (Blue Cross Blue Shield 2018) found that "in 2016, Blue Cross plans spent $10,673 on those diagnosed with 'major depression' compared to $4,283 on those without a depression diagnosis." With this information, and noting from the census data (Howden 2011) that there are ~52 million women aged 15-39, we calculate that the excess annual cost of depression attributable to COCs is ~$2.4 billion (

Table 32) and from POCs is ~$937 million (Table 33).

Table 32 – Estimated Economic Impact of COCs due to Increased Prevalence of Depression

Women aged 15-39	51,877,977
Percent with depression	10.1%
Women aged 15-39 with depression	5,239,675.68
Ever use of COCs	79.30%
15-39 y.o. COC users with depression	4,155,063
RR of depression with COC use	1.1
Adjusted estimate →	3,777,330
Excess cases →	377,733
Estimated individual annual costs →	$6,390
Estimated total annual costs →	$2,413,713,761

Table 33 – Estimated Economic Impact of POCs due to Increased Prevalence of Depression

Women aged 15-39	51,877,977
Percent with depression	10.1%
Women aged 15-39 with depression	5,239,675.68
Ever use of POCs	16.80%
15-39 y.o. COC users with depression	880,266
RR of depression with POC use	1.2
Adjusted estimate →	733,555
Excess cases →	146,711
Estimated individual annual costs →	$6,390
Estimated total annual costs →	$937,482,772

Multiple Sclerosis

As the most rigorous cohort studies did not show an increase in the risk of developing multiple sclerosis a rigorous cost analysis was not performed. However, using the information from the best case-control study (Hellwig 2016), an increased odds ratio of 1.51 was noted. If this is assumed to be accurate, this can be used along with a study of total MS costs from 1997-2013 (Chen 2017). They noted that, "The total charges on managing MS range from $161 million in 1997 to $755 million in 2013." Conservatively assuming steady costs since 2013, we can calculate that 79.3% of those costs were incurred by women who were "ever users" of COCs. This yields $598,715,000. If these women had not used COCs there would have been a proportionate reduction in costs of $202,215,000 ($598,715,000–($598,715,000/1.51)).

Interstitial Cystitis

According to one recent paper (Tung 2017) on average, having interstitial cystitis was associated with $7,223 higher total health care costs annually than not having IC. The prevalence of interstitial cystitis has been estimated at 2.7% using a high specificity definition (McLennan 2014) while another study in a managed care population (Clemens 2005) indicated (depending on the definition) a prevalence between 45 and 197 per 100,000 women. Using the most conservative estimate (Champaneria 2015) "ever use" of COCs is associated with an OR of 2.31 for interstitial cystitis. Assuming 61 million women of reproductive age, with a 79.3% of exposure to COCs, this suggests ~11,500 excess cases (using a prevalence of interstitial cystitis of 45/100,000) to ~50,500 (using a prevalence of interstitial cystitis of 197/100,000). This yields an annual cost of $83–$365 million (Table 34).

Table 34 – Estimated Annual Economic Impact of COCs due to Increased Prevalence of Interstitial Cystitis

Low prevalence of interstitial cystitis	0.00045
High prevalence of interstitial cystitis	0.00197
Women of reproductive age	61,000,000
Number with ever use of the pill	48,373,000
# of Women with interstitial cystitis low prevalence	21,768
# of Women with interstitial cystitis high prevalence	95,295
OR	2.13
Excess cases of interstitial cystitis low prevalence	11,548
Excess cases of interstitial cystitis high prevalence	50,555
Annual cost	$7,223
Annual cost of interstitial cystitis low prevalence	$83,412,664
Annual cost of interstitial cystitis high prevalence	$365,162,106

Osteoporotic Bone Fracture Risk

According to a recent review (Ballane 2017), in North America the incidence of osteoporotic vertebral fractures is 837 to 1,083 cases per 100,000 women per year (mean of 960 per 100,000 per year) as standardized to 2015. The annual excess cost of care for women with osteoporotic vertebral fractures was estimated to be $11,655 per year (Kilgore 2009). Using the most relevant relative risk of 1.07 (Barad 2005), this implies an annual cost of ~$308 million dollars in the US from COC use (Table 35).

Table 35 – Estimated Economic Impact of COCs due to Increased Annual Incidence of Vertebral Fractures

Women ≥ 50 in 2010 Census	Ever use of COCs	Incidence of osteoporotic vertebral fractures		
53,151,456	42,149,105	0.0096		
Estimated women on the pill with Fx →		404,631		
Adjusted estimate →		378,160	1.07	RR
Excess cases →		26,471		
Annual cost per patient of osteoporotic vertebral fractures →		$11,655		
Estimated total annual costs →		$308,521,992		

The best cohort study on fracture risk with progesterone-only contraceptives (POCs) showed a RR of 1.51 for ever use of DMPA (Lanza 2013), the most widely used POC. Assuming 16.8% of women have used POCs this yields an annual cost of ~$290 million dollars in the US from POC use (

Table 36).

Table 36 – Estimated Economic Impact of POCs due to Increased Aal Incidence of Vertebral Fractures

Women ≥ 50 in 2010 Census	Ever use of POCs	Incidence of osteoporotic vertebral fractures		
53,151,456	8,929,445	0.0096		
Estimated women on the pill with Fx →		85,723		
Adjusted estimate →		60,796	1.41	RR
Excess cases →		24,926		

Annual cost per patient of osteoporotic vertebral fractures →	$11,655	
Estimated total annual costs →	$290,517,770	

Body Mass

The costs of the effects on body mass were not calculated, but these effects are contributory to atherosclerosis and cardiovascular events, which are discussed below.

Urogenital Effects

The medical and societal costs of the urogenital effects of hormonal contraceptives were not calculated as, although there are measurable costs, they are not felt to be significant.

Venous Thromboembolism, Atherosclerosis and Cardiovascular Disease

About 1 in every 4 female deaths is due to heart disease; it is the leading cause of death for women in the U.S.[230] A review of recent population studies revealed that the overall prevalence of Peripheral Arterial Disease (PAD) for women is 15.6% (compared to 13.4% for men).[231] In 2008, coronary heart disease was prevalent in 7.5 million women.[232] The total mean direct medical costs for cardiovascular disease (CVD) is $18,953 annually (Nichols 2010). Using the median relative risk of the most popular birth control brands, the RR is 1.8 (Table 37).

Table 37 – Estimated Economic Impact of COCs due to Increased Incidence of Cardiovascular Disease

Coronary heart disease	Ever use of COCs	CHD in ever users		
7,500,000	79.3%	5,947,500		
Adjusted estimate of cases if no use of COCs →		3,304,167	1.8	RR
Excess cases →		2,643,333		
Annual cost per patient for CVD →		$18,953		
Estimated total costs →		$50,099,090,349		

A more conservative estimate would assume that the increased risk for cardiovascular disease is limited to women aged 15–49 years, which was the group studied by Lidegaard (Lidegaard 2012). According to the US Census in 2010, population is broken down by age group (Howden 2011). The rate of cardiovascular events is similarly broken down by Lidegaard (Lidegaard 2012). Thus, the number of cases by age group is shown in Table 38.

Table 38 – Cardiovascular Events in Women by Age Group

[230] https://www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_women_heart.htm.
[231] https://www.medscape.org/viewarticle/711179_2.
[232] https://www.healthline.com/health/heart-disease/women-statistics-facts#1.

Census data		Events per 100,000 person-years (Lidegaard 2012)		Events per year	
Age group	Number of women	Myocardial infarction	Stroke	Myocardial infarction #	Stroke #
15 to 19 years	10,736,677	0.4	3.4	43	365
20 to 24 years	10,571,823	0.7	5.6	74	592
25 to 29 years	10,466,258	2.2	10.5	230	1,099
30 to 34 years	9,965,599	5	15.4	498	1,535
35 to 39 years	10,137,620	12.2	23.3	1,237	2,362
40 to 44 years	10,496,987	25.4	39.2	2,666	4,115
45 to 49 years	11,499,506	38.2	64.4	4,393	7,406
Total number of events per year				9,141	17,473

Using these estimates, with the annual cost of care for cardiovascular disease and the relative risk noted above, this calculates to ~$61 million in excess costs for myocardial infarctions and ~$117 million in excess costs for strokes (Table 39).

Table 39 – Cost of Cardiovascular Events in Women Attributable to COC use.

	Myocardial infarction	Stroke		
Total events per year	9,141	17,473		
Ever use of the pill	79.30%			
# with events on COCs	7,249	13,856	1.8	RR Ever Use
Adjusted estimate →	4,027	7,697.96		
Excess cases →	3,222	6,158		
Estimated annual costs →	$18,953	$18,953		
Estimated Excess annual costs →	$61,062,935	$116,719,504		

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Certification

We certify that this petition contains all relevant information, including any that may be unfavorable to the petition, that we were able to obtain.

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