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Bredgade 6, 1260 København K

2. July 2021
Sagsnr. 05-0102-4

Til IRF, Sundhedsstyrelsen, irf@sst.dk

Høringssvar til Den Nationale Rekommandationsliste – baggrundsnotat for hormonal kontraception

Organon Danmark ønsker dels at takke for muligheden for at give et høringssvar og dels ønsker vi med vort høringssvar at bidrage postivt til Sundhedstyrelsens arbejde med ny rekommendationsliste for hormonal kontraception. Vi bifalder behovet for en opdatering af tidligere rekommandationer og vi sætter pris på, at baggrundsnotatet er sendt ud i en bred høring.

I vedlagte vil vi bidrage med vores input til baggrundsnotatet.

Indledende kommentarer
Vi anerkender de videnskabelige krav bag kliniske og mediciniske landvindinger, og har i vores responsum bestræbt os på at underbygge vort input ud fra det nuværende videnskabelige grundlag og særligt, hvor der ligger per reviewede videnskabeligt arbejde til grund. Vi anerkender behovet for at anvende Real World Evidence (RWE) og register studier, når der ikke forefindes per reviewede puplikationer. Vi finder RWE og register studier vigtige, såfremt data er overbevisende og samtidigt understøttes af flere lignede puplikationer. Dette uddyber vi i vores Responsum.

Til gavn for piger og kvinder vil vi argumenterer for at implantat og spiral rekommenderes som ligeværdige alternativer, således at der findes en reel valgmulighed.

Følgende 3 punkter er en opsumering af de afgørende punkter, vi gerne vil henlede arbejdsgruppens opmærksomhed på:

I. **Forholdet mellem forskellige danske rekommendationer**
Gynækologiske guidelines fra Dansk Selskab for Obstetrik og Gynækologi (DSOG); Tromboembolisk risiko ved kontraception fra 2019 overlapper i deres vejledning med målet for denne høring af de foreliggende rekommendationer. Begge rekommandationer er vejledningsdokumenter, der adresserer hormonel prævention og depression, samt hormonel prævention og trombose. Til trods for at der anvendes samme litteratur/henvisningerne, er konklusionerne og vejledningen fra DSOG forskellig fra disse rekommendationerne fra IRF. Vi anser de to vejledninger som værende i modstrid med hinanden.

II. **Forholdet mellem danske rekommendationer og internationale guidelines**
Vi konstaterer en forskel mellem de forelagte danske rekommendationer i forhold til andre internationale guidelines. Vi henleder jeres opmærksomhed på nyere guidelines udgivet i 2021 af The National Institute for Health and Care Excellence (NICE), England udarbejdet af fagudvalget under Faculty of Sexual & Reproductive Healthcare (FSRH), England. Tillige udgav WHO i 2015 deres 5. udgave af "Medical eligibility criteria for contraceptive use". Begge disse arbejder er solidt funderet og vi mener at rekommandationer i disse i højere grad, giver piger og kvinder et mere frit valg.

III. **Opdateret med de seneste internationale studier og videnskabelige puplikationer**.
Vi opfordrer til, at det videnskabelige grundlag for den samlede rekommendation bliver opdateret. I rekommendationerne bliver etonogestrel implantat grundet øget risiko for tromboemolisk sygdom, anbefalet

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til ”særlige tilfælde, når spiral er kontraindiceret, og LARC er nødvendig”. Vi savner at se understøttende entydige data for øget risiko for tromboemolisk sygdom ved anvendelse af implantat.

Se vores vedlagte responsum for input.

Tak for muligheden for at afgive et høringssvar, god arbejdslyst og de bedste hilsner

Simon Nicholson

Electronically signed by: Simon Nicholson
Reason: Approved
Date: Jul 2, 2021 09:40 GMT+1

Jul 2, 2021

Simon Nicholson
AVP, Managing Director, Regional Lead for UK, Nordic, Baltics, Ireland & Israel.

Karin Hagen

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Karin Hagen
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Responsum fra Organon Danmark

The logic in this document is as following: We have copied text from "Hormonal Kontraception, Den Nationale Rekommendationsliste 2021" (HR-DNR) with page number into a table.

- When we state "COMMENT" at the start of a new section, is it comment from Organon.
- In sections with the headline "COMMENTS AND REFERENCES TO OTHER GUIDELINES" we refer to text and/or content from NICE, DSOG or WHO.
- References within a table refers to HK-DNR's recommendation paper.
- References in the text refers to our list of references.

1. Bivirkninger: Venøse og arterielle tromboemboliske events

Fra «Hormonal Kontraception, Den Nationale Rekommendationsliste 2021«, (side 27-28)
5.4.2. Bivirkninger **Venøse og arterielle tromboemboliske events** "Herudover fandt et dansk registerstudie at den relative risiko for venøs tromboemboli var 40% forhøjet blandt kvinder, der brugte gestagen implantat (RR 1,4, 95% CI 0,6-3,4). Risikoen blev dog 40% reduceret blandt brugerne af en gestagenspiral (RR 0,6, 95% CI 0,4-0,8) i forhold til kvinder, der ikke anvendte hormonal kontraception.(14) Specialis(t)gruppen vurderer at der for gestagenpræparater er klinisk betydende lavere risiko for tromboembolisk sygdom ved anvendelse af præparater med levonorgestrel (gestagenspiraler) frem for medroxyprogesteron-injektion eller p-stav med etonogestrel. Forskellen i risiko er set i registerstudier, og skyldes formentlig forskellige de typer og dose-ringer af gestagen i de tre forskellige præparater." **Reference 14**. Lidegaard O, Nielsen LH, Skovlund CW, Lokkegaard E. Venous thrombosis in users of non-oral hormonal contraception: follow-up study, Denmark 2001-10. BMJ 2012;344:e2990.

COMMENTS AND REFERENCES TO OTHER GUIDELINES

COMMENTS: The authors of the draft on Hormonal Kontraception, Den Nationale Rekommendationsliste 2021 (HK-DNR) refer to a review and meta-analysis published in 2016 that did not find that progestin contraception was associated with increased risk of venous or arterial thrombosis [Ref 15; Tepper et al 2016]. They also refer to a review of observational studies from 2018 [Ref 10; Glisic et al 2018] that also did not find an increased risk of thromboembolic disease from the use of progestin-only contraceptives. The conclusion in these reviews is used in and are in accordance with the conclusions in recently published major guideline publications on the subject including The National Institute for Health and Care Excellence (NICE), England accredited Faculty of Sexual & Reproductive Healthcare (FSRH) Clinical Guideline on Progesterone-Implants [Ref 9] published in February 2021 (please also see comments below). However, based on data from a Danish database study that identified five confirmed first VTE events during 29.497 woman-years of exposure to the etonogestrel implant, representing a non-significant increased risk of confirmed VTE, the HK guideline authors conclude, that for progestogen preparations there is a clinically significant lower risk of

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thromboembolic disease when using preparations with levonorgestrel (progestogen coils) rather than medroxyprogesterone injection or etonogestrel implant.

Using retrospective data from a register study do not allow estimation of risks or rates as they do not have denominator data. Also, non-randomized studies tend to be at greater risk of bias Including **selection bias**, **information bias** and **reporting biases** [Ref 4; Cochrane training handbook, chapter 19, Adverse events and chapter 25, Risk of bias in non-randomized studies]. In the Lidegaard study [Ref 11], the authors failed to adequately adjust for several factors known to be associated with an increased risk of VTE: smoking, body weight, family history of VTE, and the pattern and duration of current and past hormonal contraception use. Also, choice of contraception is influenced by patient history, lifestyle and medical condition resulting in a heterogenic patient population in different groups and inclusion bias in the study. It is stated in the recommendation that the risk of VTE is 40% increased with etonogestrel implant compared to non-users. The Lidegaard data show that during 29.497-woman years, five confirmed venous thrombosis events were observed with progestogen only subcutaneous implants, corresponding to an incidence rate of 1.7 per 10.000 exposure years and an adjusted relative risk of 1.4 (0.6 to 3.4, table 2) compared with non-users of hormonal contraception. The relative risk of 1.40 (0.6-3.4) is not statistically significant and based on only 5 cases of VTE. Also, the confidence intervals of the relative risks of etonogestrel implant and the Levonorgestrel (LNG) IUS overlap: Implant 1.40 (0.58 to 3.38), LNG IUS 0.57 (0.41 to 0.81). Whether this can be translated in a statement claiming that that IUS containing LNG have significantly lower risk than Nexplanon is debatable.

EXTRACTS AND REFERENCES FROM OTHER GUIDELINES ON THE TOPIC:

We will include text from the guidelines from **NICE, DSOG and WHO.**

From NICE [Ref 9: Page 12] regarding Venous and arterial thromboembolism

> *"Key information: The very limited available evidence suggests no significant increase in risk of venous or arterial thromboembolic events associated with current use of the ENG-IMP". [Ref. 9, page12] *[1]*

Venous thromboembolism

Evidence relating to risk of venous thromboembolism (VTE) during ENG-IMP use is extremely limited but suggests no significant increased risk in the general population of implant users [Ref: 15, Tepper et al 2016].

A Danish database study identified five confirmed first VTE events during 29 497 woman-years of exposure to the ENG-IMP. After adjustment for age, this represented a non-significant increased risk of confirmed VTE (relative risk (RR) 1.4; 95% CI 0.6–3.4) during use of the ENG-IMP compared with non-

[1] *The recommendation is graded as C. A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++

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pregnant women using non-hormonal contraception [Ref: 11, Lidegaard et al 2012]. A Swedish case-control study suggested no difference between users of the ENG-IMP and non-users of hormonal contraception in the general population, but the number of implant users in the study was very small [Ref 1; Bergendahl et al 2014.]
Risk of VTE associated with use of the ENG-IMP by women who have already had a venous thromboembolic event is unknown.

Arterial thromboembolism

Evidence relating to risk of arterial thromboembolism (ATE) during use of the ENG-IMP is extremely limited but suggests no significant increased risk in the general population of implant users [Ref: 15, Tepper et al 2016].
A Danish database study identified three incidents of thrombotic stroke and three of myocardial infarction during 24 954-woman years of use of the ENG-IMP. The study reported no significant increased risk of either outcome in ENG-IMP users (for ENG-IMP use relative to non-use of hormonal contraception the relative risk for thrombotic stroke was 0.88 (95% CI 0.28–2.72) and for myocardial infarction relative risk was 2 [Ref 11:, Lidegaard et al 2012]. (95% CI 0.69–6.65).

Risk of ATE associated with use of the ENG-IMP by women who have already had an arterial thromboembolic event is unknown.

From DSOG [Ref 6; page 9]: Guidelines from Dansk Selskab for Obstetrik og Gynækologi (2019).

Parenterale gestagen-alene præparater og trombose

I et systematisk review fra 2016 med 26 artikler fandt man overordnet ingen signifikant øget risiko for tromboembolisk (arteriel og venøs) sygdom ved brug af gestagen-alene kontraception sammenlignet med ikke-brugere (inklusiv peroral gestagen) [Ref: 15, Tepper et al 2016].

For implantatet "p-stav" (etonogestrel) findes kun få studier, der samlet set, ikke finder øget risiko for tromboembolisk sygdom (ikke-signifikant); henholdsvis OR 0.9 (0.5-1.6) og OR 1.4 (0.58-3.38)

Resume af evidens	*Evidensgrad*
Gestagenspiral indebærer ikke øget risiko for tromboembolisk sygdom.	3a
Implantat "p-stav" indebærer ikke øget risiko for tromboembolisk sygdom.	3b
Depot-gestagen (MPA) indebærer en 2-3 gange øget risiko for venøs trombose sammenlignet med anvendelse af ikke-hormonel kontraception.	3a

Kliniske rekommandationer	*Styrke*
Parenteral gestagen-alene præparater med lav dosis gestagen (gestagenspiral og implantat "P-stav") indebærer ikke en øget risiko for venøs tromboembolisk sygdom, og kan med fordel især anvendes af kvinder med øget risiko herfor (>35 år, rygning, tidligere VTE eller genetisk disposition til VTE).	B

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Bredgade 6, 1260 København K

sammenlignet med ikke-brugere af hormonel kontraception [Ref: 1 Bergendahl et al 2014] [Ref: 10, Lidegaard et al 2012].

WHO: Medical Eligibility Criteria (2015)

Venous thromboembolism

Although evidence on the risk of venous thrombosis with the use of progestin oral contraceptives is inconsistent in otherwise healthy women, any small increased risk is substantially less than that with combined oral contraceptives. [Ref 16]

Same Medical Eligibility Criteria (MEC) category for Implants and Levonogestrel IUD, category 2, is set by WHO representing "condition where the advantages of using the method generally outweigh the theoretical or proven risks". [Ref 16, page 105]

COMMENT: The identical MEC classification for oral and non-oral progestin-only contraceptives in women at risk translates to a WHO judgement of a non-significant clinical risk difference and therefore an even choice, despite minor differences in DVT risk detected in individual register/epidemiological studies.

2. Øvrige bivirkninger (og ophør med behandlingen), Akne

FRA «HORMONAL KONTRACEPTION, DEN NATIONALE REKOMMENDATIONSLISTE 2021, SIDE 28

5.4.2 Øvrige bivirkninger (og ophør med behandlingen)

Akne

For gestagen-baseret kontraception er akne en kendt bivirkning. I et Cochrane-review fandt man ikke forskel på forekomst af akne mellem gestagen tabletbehandling og gestagenspiral (40). Vi fandt ikke studier, der direkte belyste eventuelle forskelle mellem præparater og administrationsvejer.

Reference 40 [Vores Ref 12] Lethaby A, Hussain M, Rishworth JR, Rees MC. Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding. Cochrane Database Syst Rev 2015;(4):CD002126. doi(4):CD002126.

COMMENTS AND REFERENCES TO OTHER GUIDELINES

COMMENTS: Reference 40 [Ref 12; Lethaby et al 2015]. This reference is not the most recent version of this Cochrane analyze. It was updated on June 12, 2020. Most current version is published by Bofill Rodriguez et al in June 2020 [Ref 2] and other references are also available on the subject, please see below.

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EXTRACT FROM OTHER GUIDELINES ON THE TOPIC:

Ad D) From NICE [Ref 9: Page 21]

> *"Key Information: Observational studies suggest that during ENG-IMP use a minority of users experience new onset acne or worsening of existing acne while others have improvement in existing acne. [2][Ref 9: Page 21]*

FSRH guideline references on acne: Mommers E et al, Am J Obstet Gynecol 2012;207:388.e1–e6; Croxatto HB,et al. Hum Reprod 1999;14:976–81; Darney P et al Fertil Steril 2009;91:1646–53. 29 Bahamondes L et al. Hum Reprod 2015;30:2527–38; Funk S et al. Contraception 2005;71:319–26. Blumenthal PD et al. Eur J Contracept Reprod Health Care 2008;13 Suppl. 1:29–36.

3. Øvrige bivirkninger (og ophør med behandlingen), Vægtøgning

FRA «HORMONAL KONTRACEPTION, DEN NATIONALE REKOMMENDATIONSLISTE 2021, SIDE 28
5.4.2 Øvrige bivirkninger (og ophør med behandlingen) **Vægtøgning** Et Cochrane-review af randomiserede kliniske studier fandt ingen betydende forskelle i vægtstigning mellem gestagentabletter, gestagenimplantat og medroxyprogesteron-injektion, men med lav evidensgrad. Flere af kontraceptionstyperne, særligt medroxyprogesteron-injektion, var associeret medvægtstigninger (41). Enkeltstudier har påvist, at gestagenimplantat også i nogle tilfælde kan medføre betydende vægtstigninger >10% af udgangsværdien (42). REFERENCE 41 Lopez LM, Edelman A, Chen-Mok M, Trussell J, Helmerhorst FM. Progestin-only contraceptives: effects on weight. Cochrane Database Syst Rev 2011;(4):CD008815. doi(4):CD008815. REFERENCE 42 DSOG. Parenteral hormonal kontraception – gestagenmetoder Dansk Selskab for Obstetrik og Gynækologi, 2015.

COMMENTS AND REFERENCES TO OTHER GUIDELINES

COMMENTS: The section in HK-DNR describes that use of implant may in some cases lead to significant weight increases > 10%. The reference is the DSOG guideline on parenteral hormonal contraception from 2015 [Ref 5]. This guideline states that a significant increase of weight (>10% of start weight) has been described in 20% of women using progesteron implant. The reference is Urbancsek et al 1998. The Urbancsek article is retracted as incorrect data were found to have been included on the study Case Report Forms and subsequently in the databases and should therefore not be used as reference. A revision of this chapter in the HK-DNR is therefore warranted.

[2] ** The recommendation is graded as C. A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++*

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Bredgade 6, 1260 København K

Also, as described in WHO Medical Eligibility Criteria on contraceptive use (2015) and the FSRH guideline for progesterone-only implant, most studies reported no statistically significant difference in weight change between the contraceptive methods. In addition, methodological differences across studies may account for any differences in findings. WHO use MEC Category 1, representing "a condition for which there is no restriction for the use of the contraceptive method" for levonorgestrel and etonogestrel implants also for women > 30 kg/m2 BMI (WHO Medical Eligibility Criteria on contraceptive use 2015). For FSRH assessment please see below.

EXTRACT FROM OTHER GUIDELINES ON THE TOPIC:
From NICE [Ref 9: Page 23]

> *"Key Information: The available evidence is too limited to confirm or exclude a causal association between ENG-IMP use and weight gain[3]. [Ref 9: Page 23]"*

In 2019, the FSRH CEU systematically reviewed the evidence relating to use of the ENG-IMP and weight change to support the FSRH statement 'Contraception and weight gain' [Ref 8]. "Weight change varied widely between individual women in the studies, but on average women gained weight during use of both the ENG-IMP and the Cu-IUD. Most studies reported no statistically significant difference in weight change between the methods."

4. Øvrige bivirkninger (og ophør med behandlingen), Humørsvingninger

FRA «HORMONAL KONTRACEPTION, DEN NATIONALE REKOMMENDATIONSLISTE 2021, SIDE 28-29
5.4.2 Øvrige bivirkninger (og ophør med behandlingen) **Humørsvingninger** For gestagen-baseret kontraception er humørsvingninger en kendt bivirkning. Et dansk registerstudie fandt at kvinder, der brugte gestagenpræparater, havde højere risiko for at modtage antidepressiv behandling. For gestagentabletter var risikoen 30% forhøjet (RR 1,3 95%CI 1,27-1,40), for gestagen-implantat 120% forhøjet (RR 2,10 95% CI 2,01-2,24); for gestagenspiral 40% forhøjet (RR 1,4 95%CI 1,31-1,42); og for medroxyprogesteron-injektion 170% forhøjet (RR 2,7 95%CI 2,45-2,87), alle vs. kvinder der ikke brugte hormonel kontraception. Resultaterne var justerede for alder, uddannelsesniveau og forekomst af visse gynækologiske sygdomme, men ikke for eksempelvis rygestatus, body mass index eller paritet. Såfremt de observerede associationer er kausale, og ved en incidens for førstegangs-brug af antidepressive lægemidler på 17 tilfælde pr. 1000 person-år blandt kvinder, der ikke anvender hormonel kontraception, svarer det til yderligere fem tilfælde pr. 1000 person-år ved anvendelse af

[3] *The recommendation is graded as C. A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++*

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gestagentabletter eller -spiral, hhv. yderligere 19 tilfælde pr.1000 person-år for gestagenimplantat og yderligere 29 tilfælde pr. 1000 person-år for medroxyprogesteron-injektion.
Spesialistgruppen vurderer at gestagenpræparater har humørsvingninger som mulig bivirkning, og at der kan være en let øget risiko for depression eller behov for antidepressiv behandling blandt brugere af gestagentabletter eller -spiraler, i størrelsesordenen ét tilfælde pr. 200 person-år. Risikoen kan være særligt øget for gestagenimplantat og medroxyprogesteron-injektion, men konfounding kan ikke udelukkes. Der er meget begrænset evidens for dette outcome.

REFERENCE: No reference presented**.**

COMMENTS AND REFERENCES TO OTHER GUIDELINES

COMMENT: No reference is provided in HK-DNR for the described Danish registry study showing that women who used progestogens were at higher risk of receive antidepressant treatment, and that the increased risk for progestogen implant was 120% elevated compared to women who did not use hormonal contraception. However, in the reference list one nationwide prospective cohort study with combined data from the National Prescription Register and the Psychiatric Central Research Register in Denmark is included. In this article, Skovlund and colleagues [ref 14; 2016] describe associations of different types of hormonal contraception with depression and compared with nonusers. The results show that users of implant experienced an RR of a first use of antidepressants of 2.1 (95% CI, 2.01-2.24). Importantly however, the authors state that they expect that institutionalized women and women with mental retardation or more severe psychiatric illness could be more likely to receive long-acting reversible contraceptive products such as medroxyprogesterone acetate depot or implants. They therefore exclude these 2 specific products in the results tables because they might be influenced by confounding by indication.

The methodological heterogenicity in studies on hormonal contraceptives and depression as well as high risk for inclusion bias (healthy user bias) is addressed in the DSOG guideline [Ref 6: Hormonel kontraception og depression, selvmord og selvmordsforsøg, 2019]

Despite the weak evidence, author of HK-DNR conclude that the risk for depression may be particularly increased for progestogen implants. This conclusion is not supported by FSRH (please see below) that states that causative association cannot be established between etonogestrel implants and depression, or WHO that use MEC Category 1, representing “A condition for which there is no restriction for the use of the contraceptive method” for women with depressive disorders in the WHO Medical Eligibility Criteria on contraceptive use (2015) [Ref 16].

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Bredgade 6, 1260 København K

EXTRACT FROM OTHER GUIDELINES ON THE TOPIC:

From NICE [Ref 9: Page 22]

> *"Key Information: The available evidence is too limited to confirm or exclude a causative association between ENG-IMP use and depression"* [4] *[Ref 9: Page 22]*

A 2018 systematic review of studies that used externally validated measures of depression [Ref. 18 Worly et al 2018] concluded that the identified data did not support a clear, general association between progestogen-only contraceptives and depression scores or incident depression diagnoses. In published data base studies, significant confounding factors cannot be excluded, and causative association is not established.

5. Sammenfatning og rekommandationer (ekstrakt fra)

FRA «HORMONAL KONTRACEPTION, DEN NATIONALE REKOMMENDATIONSLISTE 2021, SIDE 34-
5.5 Sammenfatning og rekommandationer (ekstrakt fra) Specialistgruppen vurderer desuden at gestagenspiral er forbundet med lavere risiko for tromboembolisk sygdom i forhold de øvrige gestagenpræparater. Brug af medroxyprogesteron-injektioner var muligvis forbundet med en øget risiko for alvorlige bivirkninger i form af tromboembolisk sygdom blandt kvinder med risikofaktorer, reversibelt fald i knogledensitet, og medfører ofte vægtøgning. Der er muligvis en øget risiko for depression ved anvendelse af gestagenpræparater, med en lidt lavere frekvens af behandlingskrævende depression ved anvendelse af gestagentabletter eller –spiral, i forhold til gestagenimplantat og medroxyprogesteron-injektion. Ved psykisk sårbarhed, bør man følge op på patientens psykiske tilstand efter opstart af hormonel kontraception. Etonogestrel implant rekommanderes kun til brug ved kontraindikation mod gestagenspiral, og kontraception, idet risikoen og samtidigt behov for lang-tidsvirkende reversibel kontraception, idet risikoen for tromboembolisk sygdom er større end for rekommanderede præparater.

COMMENTS AND REFERENCES TO OTHER GUIDELINES

COMMENTS: Regarding increased risk for thromboembolic events and depression in users of progesterone implants, please see comments in the sections above at page 4 under From NICE [Ref 9: Page 12] regarding Venous and arterial thromboembolism.

[4] *The recommendation is graded as C. A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++*

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6. Conclusion from Organon Denmark

- Dansk Selskab for Obstetrik og Gynækologi are providing guidance documents which overlap with the recommendations in HK-DNR regarding for example hormonal contraception and depression, and hormonal contraception and thrombosis (both published in 2019). Even though the references are also overlapping, the conclusions made, and the guidance provided differs widely. The net result is contradicting advice. Furthermore, the literature search ends December 2019, resulting in exclusion of major guidance publications as NICE accredited FSRH guidance on implants.
- LARCs are highly effective, with low annual pregnancy rates compared to other methods (Centers for Disease Control. Effectiveness of Family Planning Methods), mainly since these methods are independent of user compliance. Therefore, LARCs are recommended by multiple guidelines (e.g NICE accredited FSRH, WHO and more). This is contrast with the current recommendations of HK-DNR in terms of selection of references, interpretation and conclusion.
- We question the fact that HK-DNR is only recommending etonogestrel implants when LNG-IUS is contraindicated and LARC is needed, using low-grade evidence regarding thromboembolic disease.

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Bredgade 6, 1260 København K

16. WHO. Medical eligibility criteria for contraceptive use, 5th Edition. Guidelines Review Committee, Sexual and Reproductive Health and Research, 2015. Accessed July 1, 2021
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210702_Høringssvar_Organon Danmark_Rekommendationer_Kontraception

Final Audit Report 2021-07-02

Created:	2021-07-02
By:	Peter Wissing (peter.wissing@organon.com)
Status:	Signed
Transaction ID:	CBJCHBCAABAA3Z_6z0Kqb9UU56S8Dxn_JEb3JAyfyUDi

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Louise Bjørkholt Andersen

Fra: Ann Dalgaard Johnsen <Ann.Johnsen@stab.rm.dk>
Sendt: 5. juli 2021 17:13
Til: Sundhedsstyrelsen IRF
Emne: HØRINGSVAR: Den Nationale Rekommandationsliste (NRL) - Baggrundsnotatet for hormonal kontraception
Vedhæftede filer: Signature-20210705171344.txt

Til IRF i Sundhedsstyrelsen.

Region Midtjylland har via Danske Regioner modtaget IRFs høringsmateriale vedr. udkast til baggrundsnotat for hormonal kontraception.

Region Midtjylland har følgende bemærkninger til vedhæftede høringsmateriale:

- Diskeprans i afsnit 2.1 mellem hhv. kilde 1 og 2, ift. antal brugere af præpareter. Kilde 1 angiver hhv. 374.000 i 2014, og 458.000 i 2019. Kilde 2 giver sammenlagt hhv. 444.000 i 2014 og 422.000 i 2019.
- På side 10, tabel 1 kan ikke være på siden, en del af informationen forsvinder. Samme gør sig gældende for tabel 4, side 16.

Med venlig hilsen

Ann Dalgaard Johnsen
Farmaceut, Regional Lægemiddelkonsulent

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Sendt: 8. juni 2021 09:38
Til: Lægemiddelstyrelsen DKMA <dkma@dkma.dk>; Regioner@regioner.dk; dsam@dsam.dk; formand@dsog.dk; lise.lotte.andersen@rsyd.dk; formand@endocrinology.dk; sekretaer@endocrinology.dk; formand@dsko.org; sekretaer@dsko.org; formanden@dskf.org; tkumler@dadlnet.dk; mariann.tang@ki.au.dk; lvs@dadl.dk; info@danskepatienter.dk; info@lif.dk; info@igldk.dk
Cc: Britta Tendal Jeppesen <BRIT@SST.DK>; Simon Tarp <sita@SST.DK>; Louise Bjørkholt Andersen <LOBA@SST.DK>; Nadia Humma Ahmad <nha@SST.DK>
Emne: HØRING: Den Nationale Rekommandationsliste (NRL) - Baggrundsnotatet for hormonal kontraception - FRIST 2. juli 2021

Til høringsparter

IRF i Sundhedsstyrelsen sender hermed udkast til baggrundsnotat for hormonal kontraception, som indgår i Den Nationale Rekommandationsliste (NRL) i høring.
Se venligst vedhæftede høringsbrev og høringsliste.

Høringsversionen kan tilgås fra Høringsportalen.

Baggrundsnotatet er i høring frem til **den 2. juli 2021**.

Vi ser frem til at modtage jeres eventuelle høringssvar indsendt elektronisk til irf@sst.dk

Med venlig hilsen

Britta Tendal Jeppesen
Enhedschef

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SUNDHEDSSTYRELSEN

30. juni 2021

Til Sundhedsstyrelsen, IRF

DSAM's høringssvar vedrørende udkast til Den Nationale Rekommandationsliste (NRL) - Baggrundsnotatet for hormonal kontraception samt Den Nationale Rekommandationsliste (NRL) - Baggrundsnotatet for hormonbehandling i klimakterie og menopausen

DSAM takker for muligheden for at kommentere på ovenstående to høringsudkast vedr. hormonbehandling.

Da vores kommentarer vedrørende de to udkast overlapper en del, har vi valgt at besvare samlet.

Overordnede kommentarer:

DSAM finder det meget positivt, at der nu kommer rekommandationslister vedrørende behandling med kvindelige kønshormoner igen. Netop på dette område, hvor behandlingen er målrettet raske personer, har der været stort behov for en evidensbaseret gennemgang af balancen mellem risici og gevinster ved behandling. Rekommandationslisterne har været savnet, og diskussionen om evidens i forhold til valget af hormonpræparater har ofte været henvist til pressen, hvilket har været uhensigtsmæssigt.

Overordnet finder DSAM også, at gennemgangen af de enkelte præparatgrupper er grundig og velunderbygget og kan fungere godt som opslagsværk.

Til gengæld er DSAM skeptisk overfor formidlingen af budskaberne. Det anføres, at målet med NRL er at "støtte alment praktiserende læger i valget mellem tilgængelige lægemidler inden for en defineret lægemiddelgruppe og til en udvalgt patientgruppe".

Til dette formål finder vi, at dokumenterne ikke er særlig læsevenlige for de klinisk arbejdende læger. Derfor bør der, set med praktiserende lægers øjne, laves en forkortet og mere tilgængelig version, der sammenfatter budskaberne. Selve formidlingen af risiko – som er en meget svær opgave! - og forskellen i risiko mellem præparaterne er svært tilgængelig, hvor man bør tænke på, at lægen ikke kun skal forstå indholdet selv, men også være i stand til at videreformidle risikoen til de pågældende kvinder og deres partnere.

DSAM finder det også uhensigtsmæssigt, at man ikke kan sammenligne præparater mellem grupperne, da dette er det relevante spørgsmål for lægerne i hverdagen. Vi er klar over, at dette er et vilkår for NRL og forsøges imødekommet med udgivelsen af IRF's månedsblad. Denne fremgangsmåde kan dog være problematisk, da skiftet fra NRL til månedsblad betyder, at evidensgennemgangen ikke længere er helt så gennemsigtig, og at forfatterne af månedsbladet er "eksperter", der repræsenterer sig selv, og ikke længere er udpeget af selskaberne (selv om der selvfølgelig er sammenfald med de personer, der har siddet i arbejdsgruppen).

På samme vis kommer månedsbladet, som i princippet får større klinisk betydning end rekommandationslisten, ikke til høring, til trods for at anbefalingerne i månedsbladet kan få retsmæssig betydning fx i patientklagesager. DSAM vil anbefale, at disse principielle overvejelser videregives til organisationen bag NRL.

Specifikke kommentarer til NRL om hormonal kontraception:

Det kan undre, at der ikke er en gennemgang af de lægeligt inducerede bivirkninger ved spiral og p-stav, som man kan risikere ved selve anbringelsen. Dvs. risiko for perforation, infektion etc.

Specifikke kommentarer til NRL om hormonbehandling i klimakterie og menopausen:

Under kontraindikationer nævnes generelt - også ved rene gestagenpræparater - "kendt eller tidligere brystkræft, eller mistanke herom". Gælder dette uanset hormonfølsomhed eller ej, og uanset præparat? Eller kunne man forestille sig, at nogle præparater ikke skulle være kontraindicerede, men kunne bruges med forsigtighed?

Med venlig hilsen

Anders Beich
Formand, DSAM

Louise Bjørkholt Andersen

Fra: Aysegül Sekeroglu <ayss@regionsjaelland.dk>
Sendt: 1. juli 2021 13:31
Til: Sundhedsstyrelsen IRF
Cc: Lene Jensen; Mie Riise
Emne: Region Sjællands høringssvar: Den Nationale Rekommandationsliste (NRL) - Baggrundsnotatet for hormonal kontraception
Vedhæftede filer: Høringsbrev_hormonal kontraception_NRL_loba_03-06-21.pdf; Høringsliste_hormonal kontraception_NRL_loba_03-06-21.pdf; Signature-20210701134701.txt

Til IRF i Sundhedsstyrelsen

Region Sjælland har med interesse læst Sundhedsstyrelsens udkast til baggrundsnotat for hormonal kontraception, som indgår i Den Nationale Rekommandationsliste (NRL).
Regionen har ingen bemærkninger til udkastet.

Med venlig hilsen

Aysegül Sekeroglu
Regional Lægemiddelkonsulent - Farmaceut

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Det Nære Sundhedsvæsen
Lægemiddelenheden
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4180 Sorø

Personlig e-post: ayss@regionsjaelland.dk

Lægemiddelenheden: lmenheden@regionsjaelland.dk

www.regionsjaelland.dk

Fra: Sundhedsstyrelsen IRF <IRF@SST.DK>
Sendt: 8. juni 2021 09:38
Til: Lægemiddelstyrelsen DKMA <dkma@dkma.dk>; Regioner@regioner.dk; dsam@dsam.dk; formand@dsog.dk; lise.lotte.andersen@rsyd.dk; formand@endocrinology.dk; sekretaer@endocrinology.dk; formand@dsko.org; sekretaer@dsko.org; formanden@dskf.org; tkumler@dadlnet.dk; mariann.tang@ki.au.dk; lvs@dadl.dk; info@danskepatienter.dk; info@lif.dk; info@igldk.dk
Cc: Britta Tendal Jeppesen <BRIT@SST.DK>; Simon Tarp <sita@SST.DK>; Louise Bjørkholt Andersen <LOBA@SST.DK>; Nadia Humma Ahmad <nha@SST.DK>
Emne: HØRING: Den Nationale Rekommandationsliste (NRL) - Baggrundsnotatet for hormonal kontraception - FRIST 2. juli 2021

Til høringsparter

IRF i Sundhedsstyrelsen sender hermed udkast til baggrundsnotat for hormonal kontraception, som indgår i Den Nationale Rekommandationsliste (NRL) i høring.
Se venligst vedhæftede høringsbrev og høringsliste.

Høringsversionen kan tilgås fra Høringsportalen.
Baggrundsnotatet er i høring frem til **den 2. juli 2021**.

Vi ser frem til at modtage jeres eventuelle høringssvar indsendt elektronisk til irf@sst.dk

Med venlig hilsen

Britta Tendal Jeppesen
Enhedschef

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SUNDHEDSSTYRELSEN

Louise Bjørkholt Andersen

Fra: Wiebke Boman Hansen <wbh@rsyd.dk>
Sendt: 1. juli 2021 16:24
Til: Sundhedsstyrelsen IRF
Emne: Region Syddanmarks høringssvar: NRL - Baggrundsnotatet for hormonal kontraception
Vedhæftede filer: Høringsbrev_hormonal kontraception_NRL_loba_03-06-21.pdf; Høringsliste_hormonal kontraception_NRL_loba_03-06-21.pdf; Signature-20210701162446.txt

Fra Region Syddanmarks side takker vi for jeres udarbejdelse af NRL om hormonal kontraception.
Eneste bemærkning herfra er, at der tilsyneladende er en trykfejl i tabellen i afsnit 4.5 på side 24. I kommentarkolonnen er der byttet om på tofase- og trefase-præparat; Levonorgestrel+ethinylestradiol 50/75/125 mikrog + 30/40/30 mikrog er et trefase-præparat, mens desogestrel+ethinylestradiol 25/125 mikrogram + 40/30 mikrogram er et tofase-præparat (mærket med gul overstregning nedenfor).
(Obs også uhensigtsmæssig orddeling af ethinylestradion i kolonnen "Rekommanderet lægemiddel" t.v. – også markeret med gult)

Kombinationspræparater af flerfase type, vurderede lægemidler

Lægemiddel	Vurderet dosis	Kommentar
Rekommanderet		
Levonorgestrel[2]*, ethinylestradiol, tablet	Tablet 50/75/125 µgram + 30/40/30 µgram dagligt	Tofase-præparat. Specialistgruppen anbefaler flerfase orale kombinationspræparater med levonorgestrel som 1. valg, ud fra den eksisterende viden om bivirkningsprofil ved forskellige gestagener
Rekommanderet i særlige tilfælde		
Dienogest Ikke klassificeret*, estradiolvalerat	Tablet 2 mg/3 mg dienogest, 1 mg/2 mg/3 mg estradiolvalerat dagligt	Firefase-præparat. Dienogest er forbundet med let forøget risiko for venøs tromboembolisk sygdom ift. præparater med levonorgestrel
Desogestrel[3]*, ethinylestradiol	25/125 µgram + 40/30 µgram	Trefase-præparat. Desogestrel er forbundet med let forøget risiko for venøs tromboembolisk sygdom ift. præparater med levonorgestrel
Ikke rekommanderet		
Ingen lægemidler i denne gruppe.		

* Beskriver generationen af gestagen

Når den endelige NRL foreligger, vil vi tage udgangspunkt i anbefalingerne ved næste opdatering af vores Basisliste.
I ønskes en god sommer.

Venlig hilsen

Wiebke Boman Hansen
Lægemiddelkonsulent
Praksis

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Direkte:21818092
Mobil: 21818092

Region Syddanmark
Region Syddanmark
Damhaven 12, 7100 Vejle
Hovednummer:7663 1000
www.rsyd.dk

Praksisafdelingen behandler dine personoplysninger, og derfor skal vi give dig en række oplysninger, herunder:

- At formålet med at behandle dine personoplysninger er at sagsbehandle din henvendelse. Derfor registrerer vi dine personoplysninger i vores elektroniske sagsbehandlingssystem.
- At du kan gøre brug af en række rettigheder, herunder retten til at se dine oplysninger og retten til at gøre indsigelser mod vores behandling af dine personoplysninger

Yderligere information: www.regionsyddanmark.dk/wm509059.
Du er også velkommen til at kontakte regionens databeskyttelsesrådgiver, se nærmere her www.regionsyddanmark.dk/wm508440

Fra: Annamaria Marrero Zwinge <AZW@regioner.dk>
Sendt: 10. juni 2021 14:11
Til: kontakt@regionmidtjylland.dk; Region Syddanmark <kontakt@rsyd.dk>; Region Hovedstaden <regionh@regionh.dk>; region@rn.dk; regionsjaelland@regionsjaelland.dk
Emne: VS: HØRING: Den Nationale Rekommandationsliste (NRL) - Baggrundsnotatet for hormonal kontraception - FRIST 2. juli 2021

Til Regionerne

Hermed videresendes udkast til baggrundsnotat for hormonal kontraception fra Sundhedsstyrelsen til høring i regionerne.

Danske Regioner samler ikke et fælles høringssvar. Regionernes evt. høringssvar bedes sendt direkte til Sundhedsstyrelsen.

Med venlig hilsen

Annamaria Zwinge
Center for Sundhedsinnovation (SINO)

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E azw@regioner.dk

Danske Regioner
Dampfærgevej 22
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Sendt: 8. juni 2021 09:38
Til: Lægemiddelstyrelsen DKMA <dkma@dkma.dk>; Regioner@regioner.dk; dsam@dsam.dk; formand@dsog.dk; lise.lotte.andersen@rsyd.dk; formand@endocrinology.dk; sekretaer@endocrinology.dk; formand@dsko.org; sekretaer@dsko.org; formanden@dskf.org; tkumler@dadlnet.dk; mariann.tang@ki.au.dk; lvs@dadl.dk; info@danskepatienter.dk; info@lif.dk; info@igldk.dk
Cc: Britta Tendal Jeppesen <BRIT@SST.DK>; Simon Tarp <sita@SST.DK>; Louise Bjørkholt Andersen <LOBA@SST.DK>; Nadia Humma Ahmad <nha@SST.DK>
Emne: HØRING: Den Nationale Rekommandationsliste (NRL) - Baggrundsnotatet for hormonal kontraception - FRIST 2. juli 2021

Til høringsparter

IRF i Sundhedsstyrelsen sender hermed udkast til baggrundsnotat for hormonal kontraception, som indgår i Den Nationale Rekommandationsliste (NRL) i høring.
Se venligst vedhæftede høringsbrev og høringsliste.

Høringsversionen kan tilgås fra Høringsportalen.
Baggrundsnotatet er i høring frem til **den 2. juli 2021**.

Vi ser frem til at modtage jeres eventuelle høringssvar indsendt elektronisk til irf@sst.dk

Med venlig hilsen

Britta Tendal Jeppesen
Enhedschef

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SUNDHEDSSTYRELSEN

Kommentarer fra obsterisk gynækologsik afdeling Herlev-Gentofte til den Nationale Rekommandationsliste for Hormonal kontraception og hormonbehandling i klimakterie og menopause:

Vi betragter høringsfasen som relativ kort og har derfor valgt at kommentere rapporterne gennem nedslagspunkter på fokuserede afsnit.

I. **Hormonal kontraception**.
   a. **Introduktion**. Er generisk og svær at oversætte til en klinisk situation omkring anvendelse af hormonal kontraception. Sv.t hertil er Bilag 1, der skal understøtte den individuelle kliniske vejledning noget uklar og mindre anvendelig end WHO´s MEC
   b. **2.2 Side 7**, linje 1 ullipristal er ikke en syntetisk progesteron analog, men en selektiv progesteron modulator. Anvendelsen af gestagen "generationer" forældet og benyttes stort set ikke i international sammenhæng. Semantikken bør frarådes også i danske guidelines eller rekommandationer
   c. **3.4 side 8 Evidensgennemgang.** Det kan undre, at litteratursøgningen ophørte allerede i 2019, når flere væsentlige publikationer er fremkommet siden og Rekommandationerne formentlig først offentliggøres i 2022. Hvorfor 51 referencer (tilsvarende publikationer har ofte flere). **3.4.1** Reference savnes for typisk anvendelse af monofasepræparater
   d. **3.4.2 side 10. Østrogenindhold** En mulig modulerende effekt på arterielle tromboser af gestagenkomponenten nævnes ikke
   e. **Side 11 sidste afsnit:** om risikoen er **klinisk** signifikant ved vi jo faktisk ikke
   f. **3.4.3 Kontraindikationer.** Anvendelsen af **WHO´s MEC** kategorier synes mere klinisk anvendelig end opremsningen på side 17. Kontraindikation mod anvendelsen af kombinationspræparater ved alder >35 år uden tilstedeværelse af andre risikofaktorer er ikke aligned til andre Europæiske/Internationale guidelines, hvor anvendelse hos raske, normalvægtige og ikke-rygende kvinder er acceptabelt frem til menopausen
   g. **5. Gestagener. 5.3 virkningsmekanisme,** første afsnit. Der er tale om **Pseudodecidual** reaktion og ikke decidual som ved tidlig graviditet
   h. **5.4.2 Venøse og arterielle tromboemboliske events.** Udover selektion bias, information bias og rapporterings bias (som ved kombinationspræparaterne) findes det konklusive afsnit øverst side 28 kontradiktorisk i forhold til de referede arbejder af Tepper et al, 2016 og Glisic et al 2016. Herudover er konklusionen ikke i overenstemmelse med NICE (FSRH Clinical Guidelines 2021) og DSOG guidelines fra 2021. **Øvrige bivirkninger** og ophør med behandling side 28. **Acne** omtales ikke i den anførte reference (Lethaby et al 2015). **Vægtøgning.** DSOG referencen (42) refererer videre til artikel af Urbancsek et at, 1998, der siden er trukket tilbage pga inkonsistente data. **Humørsvingninger.** De metodologiske problemer omkring vurdering af humørsvingninger og depression er tidligere beskrevet i DSOG Guidelines. Korrektheden i det konklusive afsnit 2 side 29 kan derfor betvivles (counfounding risiko også korrekt angivet). Der findes nye referencer, der ikke støtter Rekommandationslisten f.eks FSRH Clinical Guideline: Progesterone only

implant (2021) og Worly et al. (2018). **Blødningsforstyrrelser** Tabel 5 burde indeholde information om Levosert.

i. **Sammenfatning og rekommandationer:** Udover ovennævnte nedslag burde LARC metoderne have været vurderet specifikt hos yngre kvinder. Pga kompliance er der betydelige fordele at opnå udover den mulige risikoen for osteoporose ved MPA (i.m men ikke s.c) Anbefalinger fremgår af FSRH publikationer og publikationer fra ESC (European Society for Contraception and Reproductive Health)

Herlev 01.07 2021

Sven O. Skouby
Speciallæge, dr. med, professor emeritus

Region Hovedstaden

Center for Sundhed

Enhed for Kvalitet og Patientsikkerhed i Sundhedsvæsnet

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IRF
Sundhedsstyrelsen

Journal-nr.: 21035594
Ref.: lask0005

Dato: 1. juli 2021

Høringsbidrag - Den Nationale Rekommandationsliste (NRL)

Region Hovedstaden værdsætter muligheden for at være blevet hørt. I regionen er den Regionale Lægemiddelkomité samt regionens Sundhedsfagliglige Råd for gynækologi og obstetrik (specialerådet) blevet hørt. Foruden nedenstående høringsbidrag fremsendes bemærkninger vedr. hormonel kontraception udarbejdet af professor Øyvind Lidegaard fra Afdeling for Gynækologi og Obstetrik på Rigshospitalet.

Generelle kommentar til begge NRL

Baggrundsnotaterne mangler kongruens, og bør gennemgås for gentagelser samt stave-/slåfejl. Derudover er der tabeller, som strækker sig udover højresidig margin, hvilket måske kan være sket ved konvertering til PDF-fil.

Det efterspørges, at NRL burde gøres mere læsevenlige, samt at skabes konneks/henvise til NKR (*hvor relevant*) i forbindelse med udarbejdelse af NRL.

Baggrundsnotatet for hormonal kontraception

Side 7: *Gestageners inddeling traditionelt i generationer...3 generation: …Etonogestrel (P-ring).*
Kommentar: ”P-ring” bør ledsages af ”implantat”.

Side 17 (dot 3 fra neden): *”Risikoen for tromboembolisk sygdom stiger med alderen, hvorfor kombinationspræparater ikke bør anvendes ved alder ≥35 år, uanset antallet af øvrige risikofaktorer.”*
Kommentar: Kontraindikation udelukket grundet alder? Jf. nedenstående kilder er alder alene ikke beskrevet som en kontraindikation – se:

- **DSOG guideline hormonal kontraception og tromboembolisk sygdom**: ”Parenteral gestagen-alene præparater med lav dosis gestagen (gestagenspiral og implantat ”P-stav”) indebærer ikke en øget risiko for venøs tromboembolisk sygdom, og kan med fordel især anvendes af kvinder med øget risiko herfor (>35 år, rygning, tidligere VTE eller genetisk disposition til VTE)”.
- **www.pro.medicin** ”Kontraception indeholdende ethinylestradiol bør ikke anvendes til kvinder over 35 år som ryger, har hypertension eller andre kardiovaskulære risikofaktorer, idet risikoen for myokardieinfarkt og apopleksi øges.”
- **Sundhed.dk** ”Kvinder over 35 år, som ryger, anbefales ikke at bruge p-piller på grund af øget risiko for blodprop, medmindre der er andre gode grunde til det. Dette gælder også kvinder i alle aldre, som har haft en blodprop, eller som er arvelig belastet med hensyn til risiko for blodpropper”

Forslag: Overvej at undlade, at alder >35 år *alene* skal være en absolut kontraindikation for kombinationsbehandling.

Side 19 (3.4.5. Relevante patientpræferencer): ***Monofase*** *orale kombinationspræparater administreres oralt i serier á 21 tabletter. Enkelte præparater ligger dog i pakninger til 4 ugers forbrug. I disse 4-ugers pakninger er enten 7, 4 eller* ***2 tabletter*** *virkningsløse, og tabletterne tages uden pause. Formålet med denne form for dosering er at mindske risikoen for, at tabletindtagelse glemmes*.
Kommentar: Det præparat (Qlaira) som indeholder 2 virkningsløse tabletter er ikke et monofase-præparat men et fire-fase-præparat.

Side 25: *5.2 Vurderede lægemidler… jf. tabel → Etonogestrel subkutant implantat – samlet dosis 68 mg – skiftes hver 3. år. Afgiver 75 – 25 µgram/24timer.*
Kommentar: Ret 75 – 25 til 25 - 75 µgram/24timer.

Baggrundsnotatet for hormonbehandling i klimakterie og menopausen

Side 7: ”vedr. de valgte outcomes”.
Her anføres at der er valgt at fokusere på vulvovaginal atrofi, hvor man i forhold til de systemiske præparater, har valgt at fokusere på de vasomotoriske gener.
Kommentar: Det undrer, at man har valgt vulvovaginal atrofi, der er en histologisk diagnose og ikke et symptom.

Side 9 - 11: På side 11 er der anført multiple kontraindikationer og forsigtighedsregler.
Kommentar: Disse understøttes ikke af informationen side 9 – 10 og heller ikke af information fra pro.medicin.dk mm.

Side 25: ”Oral HT”.
Kommentar: HT → antageligt hormonterapi – men der er ikke anført en definition af forkortelsen, hvilket bør gøres.

Side 25: Her fremgår det, at transdermal hormonbehandling er væsentligt dyrere end tabletter.
Kommentar: Det kan undre at pris anføres her, idet dette generelt ikke adresseres i NRL.

Side 40: Under sammenfatning af rekommandationer anføres, at der er øget risiko for cerebrovaskulær sygdom ved brug af tibolon.
Kommentar: Dette understøttes ikke entydigt af kommentarer side 38 – afsnit 2.24.2 ”Bivirkninger”, hvor følgende kan læses: ”*Der blev desuden ikke påvist en association mellem tibolon og cerebrovaskulære sygdomme. Et randomiseret klinisk studie fandt en fordobling af forekomst af cerebrovaskulær sygdom (stroke) blandt de kvinder, der fik tibolon ift. placebo (HR 2,19 95% konfidensinterval 1,14 til 4,23)* (47).”

Med venlig hilsen

Liv Askaa
Enhed for Kvalitet og Patientsikkerhed i Sundhedsvæsnet
Center for Sundhed

16/6-2021

Bemærkninger til Sundhedsstyrelsens Nationale Rekommandationsliste

Vedrørende hormonal kontraception.

Risiko for venøs trombose ved brug af kombinationsprodukter

Lad mig indledningsvist tilkendegive, at forfatterne til det udkast, som foreligger, har været ganske omfattende, taget emnets kompliksitet, antallet af publikationer, og en række ikke umiddelbart synlige dagsordener.

Kategorisering af hormonel kontraception

Allerede her er der udfordringer, da der er tale om mindst seks forskellige akser, som skal tages i betragtning:

1) Kombinationsprodukter versus gestagen only produkter
2) Østrogen dosis
3) Østrogen type (ethinylestradiol versus naturligt østrogen)
4) Gestagen type (12 forskellige)
5) Gestagendosis (mindre relevant)
6) Administrationsvej (oral, transdermal, vaginal, intrauterin, subcutan, intramuskulær)

Jeg har argumenteret for, at man for at gøre det muligt både at overskue og formidle det meget store antal mulige kombinationer vi står overfor, anvender nedenstående kategorisering:

	Progestogen types						
Oestrogen dose Microgram EE	Norethi-sterone	Levonorgestrel Norgestimate Norgestrolmin	Desogestrel Gestodene Etonogestrel	Dros-pirenone	Cypro-terone acetate	Dienogest	Other[a]
Combined products							
Oral							
30-40	1st gen.	2nd generation	3rd generation	4th generation	CPA		
15-20							
E2							
Non-oral			Vag. ring, Patch				
		Patch					
Progestogen-only products							
Oral	POP Low dose	POP Low dose	POP Middle dose	POP Middle dose			
Non-oral		LNG-IUS-H LNG-IUS-L	Implant				DMPA

DMPA = Depot Medroxy Progesterone Acetate, EE = Ethinylestradiol, E2 = Estradiol
H = High dose, L = Low dose, LNG-IUS = Levonorgestrel-releasing intrauterine system
POP = Progestogen-only pills, a) Other includes natural oestrogen combined with nomegestrolacetate

Denne opdeling anvendes bade I danske guidelines og i vores nye fælles nordiske on-line lærebog, og har vist sig ganske anvendelig til klinisk brug, som jo er det ærinde vi er ude i her.

Den vil også være at finde i en kommende oversigtsartikel i Danish Medical Journal (in press).

Det er korrekt, som det anføres flere steder, at anbringelsen af kombinationsprodukter med norgestimat i 2.generations gruppen ikke er fulgt konsekvent overalt i verden. Men det er klart forkert at hævde, at Danmark står alene med denne kategorisering, mod praksis i resten af verden. Det er primært Hollænderne, som oprindeligt fandt det mest korrekt at rubricere norgestimat som et 3. generations produkt, fordi det blev markedsført nogenlunde samtidigt med øvrige 3. generations produkter.

Forskere i England, Norge, Sverige, Finland, Frankrig og Tyskland har imidlertid i vid udstrækning rubriceret norgestimat som et 2. generationsprodukt, fordi hovedmetabolitten for norgestimat er levonorgestrel, hvorfor der kemisk er stor lighed mellem levonorgestrels og norgestimats kliniske og koagulative effekter.

Det er også en gruppe af forskere (typisk sponsoreret af industrien) som har haft en interesse i at rubricere norgestimat sammen med 3. generations produkterne, fordi forskellen i rate ratioen mellem 2. og 3. generation produkter derved blev reduceret fra omkring 2 til omkring 1.6. Det er en afgørende detalje at være opmærksom på, fordi en række metaanalyser ikke er opmærksom på denne ”bias”, som generelt indebærer en underestimering af forskellen i risiko mellem 2. generations og 3. generationsprodukterne.

Det bedste er selvfølgelig at have power nok til at opgøre hver specifikke kombination separat.

Relative risiko for venøs trombose ved kombinationsprodukter

Der er gennemført et hav af studier, og forfatterne har de væsentlige med. Dog har man ikke medtaget langt det største og et at de bedste studier, nemlig Vinogradovas BMJ studie fra 2015, som inkluderede 10.000 yngre kvinder med venøs trombose (vedhæftet denne kommentar).

Ud over en vidunderlig power, udmærkede dette studie sig også ved at have kontrolleret for BMI, som de danske studier generelt ikke har kontrolleret for. Dette studies specifikke resultater lå helt på linje med de store danske studier publiceret i årene 2009, 2011 og 2012, hvilket er bemærkelsesværdigt, fordi der var tale om forskellige datakilder, forskellige analyser, og forskellige potentielle confoundere. Også dette studie fandt en rate ratio mellem 2. generations p-piller og 3./4. generations p-piller på omkring 2.

Vinogradova vs Lidegaard

VTE confirmed	Vinogradova	Lidegaard
Non use	1 reference	1 reference
COC levonorgestrel	3.0 (2.6-3.3)	3.0 (2.2-4.0)
COC norgestimate	3.5 (2.9-4.4)	3.5 (2.9-4.3)
COC desogestrel	6.2 (5.0-7.7)	6.6 (5.6-7.8)
COC gestodene	6.5 (5.0-8.4)	6.2 (5.6-7.0)
COC drospirenone	6.1 (4.7-7.8)	6.4 (5.4-7.5)
COC cyproterone	6.0 (4.7-7.7)	6.4 (5.1-7.9)

Vinogradova et al. BMJ 2015; 350: h2135 (VT: 10,562)
Lidegaard et al. BMJ 2011; 343: d6423 (VT: 4,246)

Det er derfor misvisende i tabellen på s. 21 at tilkendegive at 3. og 4. generations produkter indebærer ”*en let forøget risiko for venøs trombose i forhold til præparater med levonorgestrel*” når der reelt er tale om en dobbelt så stor risiko (for samme østrogen dosis). Jeg foreslår derfor at man skriver, at risikoen er dobbelt så stor som ved brugen af kombinationspiller med levonorgestrel.

Et anvendeligt ”summary” af eksisterende evidens kan illustreres af nedenstående tabel.

I øvrigt er antallet af inkluderede kvinder med venøs trombose i de to studier (danske og Vinogradova) på omkring 14.000, hvilket langt overstiger mange af de metaanalyser, der er gennemført.

Relative risk of venous thrombosis with use of different types of HC Reference group: Non-users							
	Progestogen types						
	NETA	***LNG NGM***	***DSG, GSD EGS***	***DRSP***	***CPA***	***DNG***	***Others***
Combined products							
Oral EE							
30-40	3	3	6	6	6		
15-20	?	2	5	5			
E2						4 ?	?
Non-oral		Patch: 6	Vag. Ring: 6				
Progestogen only products							
Oral	1	1	1	?			
Non-oral		LNG-IUS: <1	Implant: 1				Depot: 2

Konfounder-kontrol i forskellige studier.

Her er det væsentligt at skelne mellem risikofaktorer til venøs trombose og confoundere. Eneste væsentlige confoundere at justere for, når man sammenligner brugere af forskellige typer af p-piller, er alder og kalenderår. Det skyldes at BMI og uddannelseslængde er nogenlunde ens fordelt blandt brugere af forskellige typer af p-piller – både i Danmark og i de udenlandske studier der er gennemført.

Det dokumenteres af, at korrektion for BMI ikke rokker ved estimaterne i de studier, som har gjort dette, ligesom studier, som har analyseret BMI blandt brugere af forskellige typer HC ikke finder nogen forskel. Med andre ord er BMI en risikofaktor, men ikke en konfounder. Af samme grund har det ikke nogen betydning for udregnede relative risici (i fx de danske studier) om der er korrigeret for denne oplysning eller ej.

Familiær disposition spiller måske en vis rolle i dag når p-piller udskrives, men ikke tidligere, hvor opmærksomheden på familiær disposition ikke var generel standard ved udskrivning af p-piller.

Risiko for depression ved brug af hormonel kontraception.

I refererede danske studie (ref 22) angives en relative risiko for depression til 1,2 med non-users som reference. Som det argumenteres i artiklens diskussion, er et mere retvisende estimat dem som anvender never-users som reference, hvilket gøres i Suppl. Tabel 4 (også vedhæftet). Det skyldes at non-users rummer alle de kvinder, som er holdt op med p-piller pga depressions-udvikling, og som må antages at være særligt følsomme for udvikling af depression generelt. For sjædne udfald, som fx trombose, spiller det ikke nogen stor rolle hvilken referencegruppe man anvender, men i dette tilfælde spiller det en stor rolle.

Som det fremgår at Suppl. Tabel 4 er den relative risiko for brug af antidepressiv medicin ved brug af kombinationsprodukter 1,7 (1,66-1,71) for aldersgruppen 15-34 under eet, men 2,2 (2,18-2,31) blandt unge kvinder 15-19 år.

For gestagen only-produkter er den relative rsiiko i samme aldersgrupper hhv 1,8 og 2,8.

Det gælder altså generelt at den relative risiko for depressionsudvikling er væsentligt større hos de yngste kvinder end senere.

Foreslår derfor at man anvender estimaterne i supp. Tabel 4 i stedet for de 1,2, og at man gør opmæksom på, at følsomheden synes at være særlig høj i teenage alderen.

Ellers fint arbejde!

Med venlig hilsen

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Use of combined oral contraceptives and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases

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Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/bmj.h2135)

Cite this as: *BMJ* 2015;350:h2135 doi: 10.1136/bmj.h2135

Accepted: 19 March 2015

ABSTRACT

OBJECTIVE

To investigate the association between use of combined oral contraceptives and risk of venous thromboembolism, taking the type of progestogen into account.

DESIGN

Two nested case-control studies.

SETTING

General practices in the United Kingdom contributing to the Clinical Practice Research Datalink (CPRD; 618 practices) and QResearch primary care database (722 practices).

PARTICIPANTS

Women aged 15-49 years with a first diagnosis of venous thromboembolism in 2001-13, each matched with up to five controls by age, practice, and calendar year.

MAIN OUTCOME MEASURES

Odds ratios for incident venous thromboembolism and use of combined oral contraceptives in the previous year, adjusted for smoking status, alcohol consumption, ethnic group, body mass index, comorbidities, and other contraceptive drugs. Results were combined across the two datasets.

RESULTS

5062 cases of venous thromboembolism from CPRD and 5500 from QResearch were analysed. Current exposure to any combined oral contraceptive was associated with an increased risk of venous thromboembolism (adjusted odds ratio 2.97, 95% confidence interval 2.78 to 3.17) compared with no exposure in the previous year. 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) and norethisterone (2.56, 2.15 to 3.06), and for norgestimate (2.53, 2.17 to 2.96). The number of extra cases of venous thromboembolism per year per 10 000 treated women was lowest for levonorgestrel (6, 95% confidence interval 5 to 7) and norgestimate (6, 5 to 8), and highest for desogestrel (14, 11 to 17) and cyproterone (14, 11 to 17).

CONCLUSIONS

In these population based, case-control studies using two large primary care databases, risks of venous thromboembolism associated with combined oral contraceptives were, with the exception of norgestimate, higher for newer drug preparations than for second generation drugs.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Oral contraceptive pills are known to be associated with an increased risk of thromboembolism (VTE)

Despite comparing third generation contraceptive pills with first and second generation pills, previous studies have had insufficient power to quantify VTE risk with individual drugs, particularly for new or less commonly used preparations such as drospirenone or norgestimate

WHAT THIS STUDY ADDS

This study, based on national population and prescribing practices in the UK, has sufficient power to provide reliable comparative findings for different formulations of combined oral contraceptives; its findings are comparable to those based on a Danish national cohort study

Preparations containing gestodene, desogestrel, drospirenone, and cyproterone were associated with significantly higher risks of VTE than preparations containing either levonorgestrel or norgestimate

The number of extra VTE cases per year per 10 000 treated women was lowest for levonorgestrel and norgestimate, and highest for desogestrel and cyproterone

Introduction

About 9% of women of reproductive age worldwide use oral contraceptives. This percentage rises to 18% of women in developed countries and 28% of women in the United Kingdom.[1] Combined oral contraceptives form a substantial proportion of these, particularly in more developed nations. Although combined oral contraceptives are generally effective in preventing pregnancy, they have measurable side effects such as venous thromboembolism (VTE). VTE is important, not only because of the prolonged time over which women might be exposed to such contraceptives, but also because VTEs are potentially avoidable and can be fatal.

Previous studies have shown varying risks for different types of oral contraceptives (such as third generation pills compared with first or second generation pills), but such studies were done some years ago,[2-6] and tended not to include new preparations containing drospirenone. Also, previous studies have generally had insufficient power to analyse the risks for more recent formulations[7-10] such as norgestimate. Few studies—only four of those referenced here[9 11-13]—have included any detailed analyses of dosage and, of these, only Lidegaard and colleagues[12] have covered a full range of prescribed drugs. Some studies did not control for all potential confounders (such as body mass index or smoking),[12] while others analysed only healthy users.[4 11 14] Different methodological approaches in studies have also made it difficult to compare and

combine the results.[15] Therefore, although the increased VTE risk associated with combined oral contraceptive drugs is established, the relative risks associated with different combinations remain inconclusive, especially for newer formulations.[16 17]

The UK has some of the largest sources of routinely collected data in the world, with longitudinal primary care records spanning up to 25 years and linked to secondary care data and mortality records. These databases cover many millions of patients, include data both on exposure and outcomes, and therefore are representative of the setting in which drugs are used. This makes the databases ideally suited to large scale safety studies of commonly used drugs.[18 19] In this study, we have used the two largest of these databases, QResearch (www.qresearch.org) and Clinical Practice Research Datalink (CPRD, www.cprd.com). Both have been used for earlier studies of associations between drug prescribing and VTE risks.[4 5 10 14 20 21]

Our objective was to quantify the associations between use of combined oral contraceptives and risk of VTE, adjusting for comorbidities and other available confounding factors. In particular, we were interested to analyse risks associated with newer or less used preparations such as drospirenone or norgestimate, quantify risks associated with various types of progestogen, and analyse the effect of different doses of oestrogen on VTE risks. To make the study more comparable with previous studies, we also replicated analyses for different subgroups by age and health status and for VTE cases with anticoagulation prescriptions.

Methods

Study design

The protocol for this study has already been published.[15] We undertook two similar studies using the CPRD (January 2014 version; 618 UK general practices) and QResearch database (version 38; 722 general practices) to quantify the association between prescribing of combined oral contraceptives and risk of incident VTE. We identified open cohorts of all women who had no records of VTE before the study, were aged 15-49 years, and were registered with the study practices between 2001 and 2013. Within each cohort, we designed two nested case-control studies with incident cases of VTE during the study period. This design was chosen as the most practicable, because it allowed us to work within the maximum extraction capabilities of the databases without losing any of the available cases—and therefore not compromising either the power of the study or the generalisability of the findings.[22]

The methods used in the study followed exactly those of the published protocol, with one difference related to the use of linked data. With respect to case identification, the protocol specified that "the main analysis will be run on all cases with VTE identified from the general practice data." QResearch is, however, closely linked at the individual patient level to hospital admissions data, and mortality records from the UK Office for National Statistics (ONS, www.ons.gov.uk/; complete for 99.8% of patients in QResearch, 99.9% of ONS mortality records, and 98% of hospital admissions records)[23 24]. So we identified VTE cases if, in QResearch, there was a relevant clinical code in the GP record, linked hospital record, or linked mortality record (web table 1), using the earliest recorded date on any of the three sources as the index date. For CPRD, however, not all practices were linked to these external data, so we could use only general practice records to identify VTE cases in CPRD.

For both databases, we matched each case to up to five controls by year of birth and from the same practice using incidence density sampling. Each control was allocated an index date, which was the date of first VTE diagnosis for the matched case. Eligible women had to have been registered with their practice for at least one year before the index date.

Because records of prescriptions for anticoagulant therapy (BNF 2.8.2) might indicate a previous VTE episode that was not recorded, cases with such records six or more weeks before the index date and controls with such records at any time before the index date were excluded from the analysis. We also excluded women if they had conditions such as oophorectomy, hysterectomy, and sterilisation, which normally preclude use of combined oral contraceptives. Women identified as pregnant or in the first three months after delivery at the index date were excluded, because they were less likely to be users of combined oral contraceptives and have an increased risk of VTE.[25] Cases or controls with conflicting prescriptions—two or more prescriptions for different combined oral contraceptives issued on the same date for the month before the index date—were also removed from the analysis.

Exposure to oral contraceptive drugs

Exposure to hormonal contraceptive drugs was based on prescription information in the last year before the index date. The main focus of the study was on individual combined oral contraceptives, which included all the most commonly used preparations in the UK: norethisterone, levonorgestrel, norgestimate, desogestrel, gestodene, and drospirenone (BNF 7.3.1). We included cyproterone, a hormonal treatment for acne, because it is also used as an oral contraceptive owing to its progestogen-like effect on the release of testosterone by the ovaries (BNF 13.6.2). For confounder control, the analysis included oral progestogen only contraceptives (BNF 7.3.2) and non-oral hormonal contraceptives (BNF 7.3.1 and BNF 7.3.2: implants, injections, transdermal patches, intrauterine and vaginal devices).

We investigated the recency of use by calculating the gap in days between the estimated date for the last use of a combined oral contraceptive and the index date, and categorising it as follows: used at index date or last use 1-28 days before the index date (current use); last use 29-365 days before the index date (past use); or no use in the last year before the index date. If a woman was exposed to more than one combined oral contraceptive in the last 28 days, only the latest time used was considered, but an indicator that she had switched type of oral contraceptive in the last 28 days was included in

doi: 10.1136/bmj.h2135 | *BMJ* 2015;350:h2135 | the bmj

the analysis. No use in the last year was a reference category for all analyses unless otherwise stated.

We included the category of past use in the analysis to allow for women having an increased VTE risk associated with previous drug use, either because of a very recent cessation of exposure close to the start of the current use period or because of a delayed start of drug use from a previous prescription, such that some women classified as past users were actually current users. This approach was used only to approximate short term residual and misclassification effects, and should not be interpreted as a measure of long term residual risk. To emphasise this, we have reported odds ratios for past users only in the web tables.

Use of other hormonal contraceptives (oral progestogen only and non-oral hormonal treatments) was similarly categorised into current and past exposure and added to the analysis as confounders. We aggregated the data for combined and progestogen only non-oral contraceptives, because the numbers of current users for combined non-oral contraceptives were low (13 cases and 24 controls in CPRD, 11 cases and 14 controls in QResearch) and lacked power for separate analysis.

Because VTE risk is likely to be highest in the first three months of oral contraceptive use,[26] we estimated the effect of duration of exposure on current users. We assessed exposure duration by calculating the number of days of exposure within the previous year. If the gap between the end of one prescription and the start of the next was 30 days or less, we considered exposure was continuous and combined the durations of the prescriptions. If a gap was longer than 30 days, only the latest period of exposure was considered.

Length of exposure duration was based on a period of 84 days, the most common length of a contraceptive prescription and also close to the end of the period of highest VTE risk associated with contraceptive use in other studies.[7 9] We classified duration as short term (≤84 days) and long term (>84 days), and combined it with recency of use into the following categories: short term current users (new users and restarters), long term current users (prevalent users), past use, and no use in the previous year.

In our samples, three contraceptives—norethisterone, desogestrel and gestodene—were prescribed in combinations having different doses of oestrogen. Owing to evidence of associations between higher VTE risks and higher doses of oestrogen[12], we undertook a further analysis of current users and categorised separately the oestrogen dose for these preparations (low dose (20 μg), normal dose (30-40 μg)), based on their most recent prescriptions before the index date. There was only one preparation with a high oestrogen dose (50 μg), which was combined with norethisterone. However, since there were only seven current users with this high dose preparation across both databases (one case and one control in CPRD, one case and four controls in QResearch), we included these women in the normal dose category. For all other drugs, only normal dose combinations had been prescribed.

Confounding factors

We identified the conditions affecting risk of VTE from the UK's health service guidelines related to VTE and hormonal contraceptives (web appendix 2).[27] Since these conditions might affect the prescribing decisions of doctors, we decided to adjust for these in all analyses. The chronic conditions for any patient had to be recorded before the index date in, to be included. These conditions were cancer, congestive cardiac failure, varicose veins, cardiovascular disease, rheumatoid arthritis, systemic lupus erythematosus, chronic renal disease, asthma, chronic obstructive pulmonary disease, Crohn's disease or ulcerative colitis, and coagulation disturbances (Leiden factor V, protein C and S deficiencies).

We also included traumatic events and events leading to immobilisation if recorded in the six months before the index date. These events included acute infections (upper and lower respiratory tract infections, urinary tract infections), surgery or leg/hip fracture, admission to hospital (excluding the previous 30 days before the index date). Non-idiopathic groups were formed from women with any of these chronic conditions or events, and idiopathic groups from women without them.

Obesity and smoking are also mentioned as potential risk factors in the NHS guidelines, so we adjusted all analyses for body mass index as a continuous variable, and for smoking status as the following categories: current smoker (light (1-9 cigarettes/day), medium (10-19), heavy (≥20); ex-smoker; non-smoker. We used values recorded at the closest date before the index date.

We included polycystic ovary syndrome as a confounder because it is treated with hormonal contraceptives and associated with an increased risk of VTE.[28] Other conditions treated with hormonal contraceptive prescriptions—acne, hirsutism, and menstrual disorders—were initially considered as potential confounders but their addition to analyses failed to change odds ratios for main exposures by more than 10%, so these were not included in the final study analyses.

Alcohol consumption has previously been considered as a confounder[10] and, being a potentially important lifestyle factor available from primary care data,[29] was categorised and included in the analyses (light (≤2 units/day), medium to heavy (≥3), ex-use or no use). We also adjusted for ethnic group (white or not recorded, Asian, black, or other), because women in ethnic minorities could have different patterns of contraceptive use[30] and different VTE risks from the white population.[31]

Social deprivation, which can be measured in the UK by the Townsend score, was not included as a confounder in the main analyses because it was not a significant risk factor for VTE in a previous QResearch study.[32] Furthermore, the CPRD had a large proportion of missing data for the Townsend score, so the inclusion of social deprivation would result in a loss of statistical power in that analysis. However, during the peer review process, we decided to run an additional analysis on QResearch data including the Townsend

score as a confounder, because the Townsend data were almost complete (available for 99.8% of cases and controls). We have, therefore, run an additional analysis on QResearch data including the Townsend score as a confounder.

Statistical analysis

The analyses were run on each database separately. Crude incidence was calculated by dividing the number of cases with incident VTE by the number of person years in the cohorts. Data for oral contraceptive exposure were only available for cases and matched controls rather than whole cohorts, which had higher proportions of older women than the general population. Therefore, we estimated age standardised rates of exposure to any oral contraceptives, using groups of controls before exclusions and directly standardising to the age profile for the UK general population in the relevant year based on data from the UK Office for National Statistics.

We used conditional logistic regression to obtain odds ratios with 95% confidence intervals. The differences between exposures were assessed using Wald's tests. To account for the log normal distribution for body mass index, we used the logarithm of body mass index for all analyses. Missing values for body mass index, smoking status, and alcohol consumption were imputed using chained equations.[33] Ten imputed sets were generated, and the imputation model included age, outcome (case or control), index year, all confounding factors (including acne, hirsutism, and menstrual disorders), exposure to progestogen only oral contraceptives, non-oral contraceptives (progestogen only and combined), and recency and duration of use for combined oral contraceptives. We combined the results from the imputed sets using Rubin's rules.[33]

To facilitate comparison of our results with those from earlier studies, which had analysed the associations of exposure to combined oral contraceptives by reference to levonorgestrel, we reran the analyses comparing current exposure to each drug of interest with current exposure to levonorgestrel (in combination with a normal oestrogen dose (30-40µg), the only doses prescribed in our data). Current exposures to levonorgestrel and the drug of interest were replaced with a variable coded as exposure to the drug, no exposure to the drug, and exposure to levonorgestrel. Analyses were adjusted for past exposure to levonorgestrel and the drug of interest, exposure to other combined oral contraceptives, and confounding factors.

We ran three additional analyses to look at methodological issues and allow comparisons with other published studies. Because results of diagnostic tests for VTE are not generally included in the primary care electronic records, some studies[11 14] used subsequent anticoagulation therapy to confirm VTE diagnosis, including only patients treated as such despite possible under ascertainment of VTE cases. In our study, anticoagulation records were available only for prescriptions in primary care, representing doctors' initial responses to patients presenting with VTE symptoms rather than a more complete record of initial and subsequent treatments. However, to facilitate comparison with these studies, we ran another analysis on VTE cases, supported with either prescriptions for anticoagulation therapy (BNF 2.8.2) or records of death within six weeks of the recorded date of VTE diagnosis. Links to individual mortality data from the ONS were available for all QResearch practices, so these were included in identification of deaths due to VTE. This was not the case for CPRD practices, however, so identification of deaths for the CPRD analysis was derived solely from the general practitioner record.

To distinguish whether there are different associations in idiopathic cases compared with non-idiopathic cases, an additional stratified analysis was run on subgroups of cases and matched controls. In this analysis, idiopathic cases were first analysed with any idiopathic matched controls (that is, controls with none of the chronic conditions or events listed above). Then, only non-idiopathic cases were analysed with any non-idiopathic matched controls (that is, controls with one or more of the chronic conditions or events used to identify non-idiopathic cases). The third analysis was run on subgroups of younger (15-24 years) and older (25-49 years) women, because younger women are more likely to use contraceptive clinics as a source of oral contraceptives, potentially leading to a lack of recorded exposure data for this group.[30]

In the protocol, we had proposed a sensitivity analysis for practices linked to hospital admission data, where VTE cases would be identified not only from the practice records but also from hospital admissions data. For QResearch, because the selection process used linked data sources including hospital admissions, this additional analysis became redundant. Instead, we ran a sensitivity analysis using QResearch cases identified only through general practice medical records and matched controls. For CPRD, we ran the proposed sensitivity analysis for data from the subset of practices linked to both hospital admission data and ONS mortality data, where data from all sources were used to identify VTE cases. VTE cases in hospital admission and ONS mortality data were identified by ICD-10 codes (web table 1).

To increase the power of the study and obtain more precise estimates, we combined results from the two databases using a meta-analysis technique. Adjusted odds ratios from the conditional logistical regression analyses of the two datasets were pooled by use of a fixed effect model with inverse variance weights.[34] We chose a fixed effect model because—apart from the necessarily different approaches to identification of relevant cases described above—the studies in CPRD and QResearch (which have similar sizes and similar methods of recording information) were comparable, using the same exclusion criteria, definitions of exposures and confounders, and the same models. In view of these similarities, differences in observed associations seemed most likely to derive from sampling variations, but we also ran a sensitivity analysis using a random effect model to allow for any heterogeneity.

To estimate the magnitude of VTE risk associated with combined oral contraceptives, we calculated the numbers needed to harm per year by using the adjusted odds ratios derived from the combined analyses.[35] The incidence for the unexposed female population could not be derived either from QResearch or CPRD because exposure details were not available for the whole cohorts. The rate was, therefore, derived from a Danish cohort[12] taking into account the differences in study design. We based our calculations for numbers needed to harm on the adjusted odds ratios from the combined analyses for current use and the Danish study rates of 4.18 per 10 000 women years for women aged 15-49 years and 4.91 per 10 000 women years for those aged 25-49 years. We also estimated the number of additional VTE cases expected per year per 10 000 treated women.

We used Stata version 13 for the analyses. All available cases were used from both QResearch and CPRD. A 1% level of statistical significance was used to account for multiple comparisons and 95% confidence intervals to enhance comparability with other studies. For clarity, only odds ratios from the combined analyses are presented and discussed, but the contributing odds ratios from CPRD and QResearch can be found in the tables.

Results

We identified 7334 incident VTE cases from CPRD based on clinical Read codes recorded in the general practitioner data, and 8211 incident VTE cases from QResearch within the study period, both with at least one year of medical records. Crude incidence of VTE cases per 10 000 women years was 5.9 (95% confidence interval 5.7 to 6.0) in CPRD and 6.1 (6.0 to 6.3) in QResearch. After matching cases to controls and removing ineligible participants, the final analysis included 5062 (69%) VTE cases from CPRD matched to 19 638 controls, and 5500 (67%) VTE cases from QResearch matched to 22 396 controls (fig 1). Of 5500 VTE cases from QResearch, 5088 (93%) were identified from primary care records, and an additional 284 (5%) from hospital admission data and 128 (2%) from ONS mortality data. For CPRD cases, 2917 (58%) VTE events were recorded as deep vein thrombosis only; 1626 (32%) as pulmonary embolism, with or without deep vein thrombosis; and 519 (10.3%) as other types of VTE; corresponding numbers for QResearch cases were 3156 (57%), 1613 (29%), and 731 (13%).

Proportions of cases and controls across the demographic measures and morbidities relevant to the study showed the similarities between database populations (table 1, web table 2). Median ages of women in the study were 38 years (interquartile range 30-44) for CPRD and 39 years (31-44) for QResearch. Current smoking was more common in cases than controls (27% *v* 21% for both databases), as was obesity (body mass index≥30; 30% *v* 17% for CPRD, 24% *v* 14% for QResearch). Proportions of women with established risk factors for VTE (that is, non-idiopathic cases and controls) were similar for each database (47% cases and 27% controls for CPRD, 47% and 26% for QResearch). About half of women with VTE in the study had anticoagulation prescriptions or died within six weeks of the recorded diagnosis date (2454 and 79 cases, respectively, or 50% overall in CPRD; 2749 and 207, or 54% overall in QResearch).

Exposure, main analysis

Age standardised rates of exposure to any oral contraceptive did not change over the study period (overall rates 29% in CPRD, 26% in QResearch). Use of levonorgestrel, the most common combined oral contraceptive, decreased during the study (from 15% to 11% in CPRD, and 13% to 10% in QResearch), whereas use of progestogen only oral contraceptives rose from 3% to 7% (fig 2).

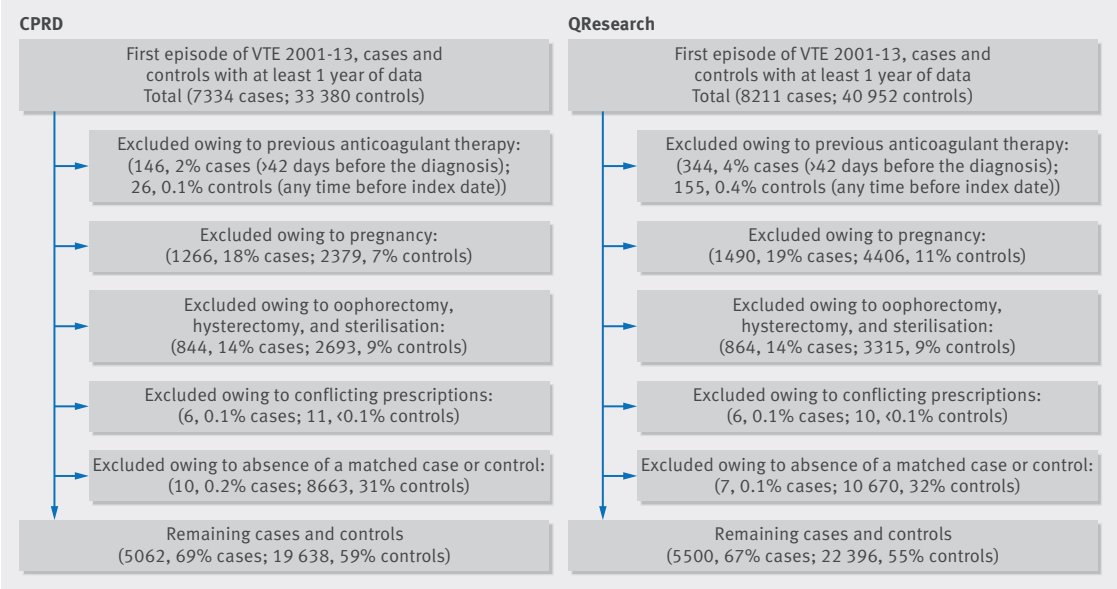

Fig 1 | Flow of included patients for CPRD and QResearch analyses with proportions of excluded observations at each point of exclusion

Table 1 | Baseline characteristics in cases and controls by database (CPRD or QResearch)

	CPRD		QResearch	
	Cases (n=5062)	Controls (n=19 638)	Cases (n=5500)	Controls (n=22 396)
Age band at index date				
15-24 years	12.6 (636)	12.7 (2496)	9.0 (493)	9.5 (2135)
25-34 years	25.5 (1290)	23.8 (4666)	25.9 (1423)	25.0 (5589)
35-39 years	17.1 (867)	17.5 (3433)	18.0 (992)	17.7 (3957)
40-44 years	20.8 (1055)	21.9 (4292)	22.5 (1239)	23.3 (5219)
45-49 years	24.0 (1214)	24.2 (4751)	24.6 (1353)	24.5 (5496)
Ethnic group				
White	36.0 (1821)	33.4 (6561)	61.6 (3386)	57.6 (12 900)
Not recorded*	60.2 (3049)	62.4 (12 249)	29.5 (1620)	32.7 (7316)
Black	1.6 (79)	1.2 (237)	4.2 (233)	3.0 (680)
Asian	1.3 (68)	1.9 (375)	2.4 (134)	4.5 (1013)
Other	0.9 (45)	1.1 (216)	2.3 (127)	2.2 (487)
Body mass index				
15-24	34.6 (1753)	44.7 (8774)	34.6 (1903)	44.2 (9895)
25-29	22.6 (1142)	22.0 (4317)	21.9 (1202)	20.0 (4473)
≥30	30.3 (1534)	17.1 (3353)	24.2 (1331)	14.3 (3196)
Not recorded	12.5 (633)	16.3 (3194)	19.3 (1064)	21.6 (4832)
Smoking status				
Non-smoker	51.1 (2586)	54.2 (10 645)	43.5 (2392)	46.5 (10 410)
Ex-smoker	17.5 (884)	16.8 (3295)	23.3 (1280)	22.1 (4952)
Current light smoker	6.3 (319)	6.0 (1188)	14.4 (790)	12.1 (2703)
Current moderate smoker	14.4 (730)	11.2 (2194)	7.7 (424)	6.4 (1433)
Current heavy smoker	6.6 (334)	4.2 (828)	4.5 (248)	2.8 (621)
Not recorded	4.1 (209)	7.6 (1488)	6.7 (366)	10.2 (2277)
Alcohol use				
No use	20.0 (1014)	17.9 (3516)	22.2 (1220)	19.3 (4315)
Ex-use	6.0 (303)	4.4 (869)	6.7 (367)	5.3 (1177)
Light (≤2 units/day)	49.0 (2479)	50.5 (9921)	32.1 (1766)	32.9 (7365)
Moderate/heavy (≥3 units/day)	5.0 (254)	5.0 (986)	17.6 (970)	18.6 (4173)
Not recorded	20.0 (1012)	22.1 (4346)	21.4 (1177)	24.0 (5366)
Non-idiopathic cases				
Proportion (no) of cases or controls	47.0 (2380)	27.2 (5340)	46.9 (2582)	26.3 (5891)
Comorbidities				
Asthma	19.1 (969)	12.9 (2530)	18.8 (1036)	12.0 (2693)
Congestive cardiac disease	0.4 (20)	0.0 (5)	0.2 (13)	0.0 (5)
Rheumatoid arthritis	1.5 (75)	0.6 (121)	2.2 (123)	0.8 (187)
Systemic lupus erythematosus	0.5 (27)	0.1 (22)	0.6 (35)	0.1 (25)
Renal disease	0.9 (48)	0.2 (35)	1.1 (62)	0.3 (65)
Stroke	0.9 (44)	0.1 (22)	0.9 (50)	0.2 (48)
Chronic obstructive pulmonary disease	0.5 (26)	0.2 (30)	0.6 (32)	0.1 (31)
Coronary vascular disease	1.0 (52)	0.3 (50)	1.5 (82)	0.3 (77)
Coagulation disturbances	0.2 (11)	0.0 (9)	0.2 (13)	0.0 (6)
Varicose veins	2.8 (143)	1.6 (314)	2.7 (151)	1.6 (359)
Hypertension	6.3 (319)	3.6 (698)	6.0 (329)	3.7 (831)
Cancer	6.6 (333)	0.9 (180)	6.6 (363)	0.9 (204)
Inflammatory bowel disease	1.9 (96)	0.6 (118)	1.8 (100)	0.6 (143)
Conditions in previous 6 months				
Infection	19.0 (964)	10.4 (2033)	17.2 (948)	9.0 (2026)
Surgery or leg/hip fracture	1.1 (54)	0.1 (16)	0.9 (51)	0.1 (24)
Hospital admission	1.4 (72)	0.2 (48)	4.1 (223)	1.1 (248)
Indications for hormonal contraceptive use				
Acne	12.6 (638)	11.7 (2307)	9.3 (514)	8.6 (1933)
Menstrual disorders	36.5 (1847)	31.0 (6091)	27.2 (1497)	23.0 (5141)
Hirsutism	2.1 (107)	1.3 (260)	1.4 (75)	1.0 (229)
Polycystic ovary syndrome	3.4 (174)	2.2 (433)	3.1 (170)	2.4 (535)
Contraceptive drug use in previous month				
Any hormonal contraceptive	32.6 (1649)	20.3 (3996)	33.4 (1838)	19.7 (4418)
Any oral combined contraceptive	24.9 (1259)	14.4 (2835)	23.8 (1309)	12.6 (2823)
Any oral progestogen only	5.1 (260)	4.4 (866)	5.1 (281)	4.0 (907)
Any non-oral hormonal contraceptive	2.6 (130)	1.5 (295)	4.5 (248)	3.1 (688)
Switch in the last month	1.9 (95)	0.6 (110)	1.9 (103)	0.5 (123)

Data are percentage (no) of cases or controls.
*Assumed as white in analyses.

doi: 10.1136/bmj.h2135 | *BMJ* 2015;350:h2135 | the bmj

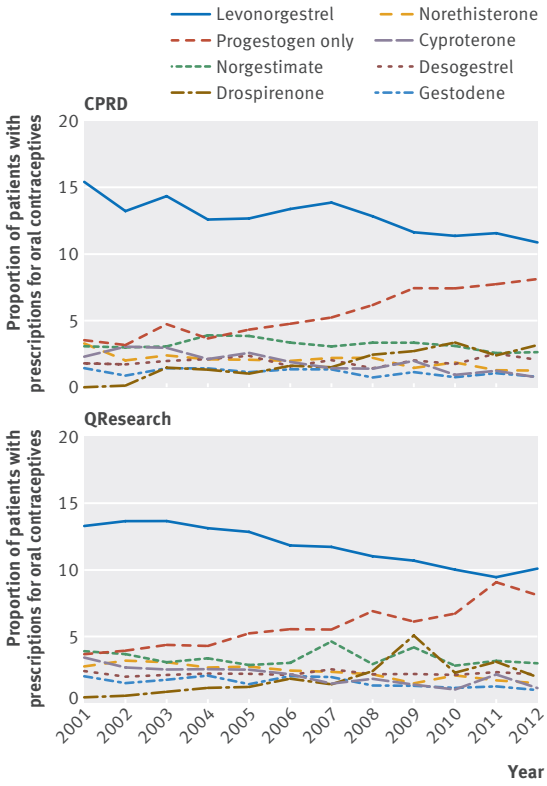

Fig 2 | **Use of different types of oral contraceptives by year and database. Data are based on age standardised exposure in controls using the UK's general population**

In the year before the index date, 30% of cases and 18% of controls in CPRD had at least one prescription for combined oral contraceptives. For QResearch, the numbers were 28% of cases and 16% of controls. Preparations with levonorgestrel seemed to be the most commonly prescribed combined oral contraceptives (45% of exposed cases, 54% of exposed controls in CPRD; 44%, 52% in QResearch). Other contraceptive types were much less used (all between 7% and 13%). Most users of combined oral contraceptives within the previous year were current users—that is, exposed in the last 28 days (84% of exposed cases, 79% of exposed controls in CPRD; 84%, 77% in QResearch; web table 3). Most of the current users were exposed for more than 84 days (across different permutations of drug type, database, and cases and controls, all between 70% and 87%).

For the analyses combining CPRD and QResearch results, current use of any combined oral contraceptive was associated with a significantly increased VTE risk (adjusted odds ratio 2.97, 95% confidence interval 2.78 to 3.17) compared with no exposure in the last year. The risks varied between different types of oral contraceptives and resulted in two clear groups: norethisterone, levonorgestrel, and norgestimate in one group; and desogestrel, gestodene, drospirenone, and cyproterone in the other. Current exposure showed that the first group had a two and a half times increased VTE risk (levonorgestrel (2.38, 2.18 to 2.59), norethisterone (2.56, 2.15 to 3.06), and norgestimate (2.53, 2.17 to 2.96), and roughly a four times increased risk for the second group (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) all compared to no exposure in the last year (table 2, fig 3, web table 4 for all variables in the model).

In our analysis to facilitate comparison with existing studies, risks associated with current use of norethisterone and norgestimate did not differ significantly from levonorgestrel. However, the risk associated with current use of gestodene was 1.5 times higher than for levonorgestrel (adjusted odds ratio 1.52, 95% confidence interval 1.24 to 1.87) and about 1.8 times higher for desogestrel, drospirenone, and cyproterone (table 3).

Table 2 | **Current exposure to combined oral contraceptives compared to non-exposure by database**

	CPRD		QResearch		Combined analysis	
Type of contraceptive	No of cases/ controls	Adjusted odds ratio (95% CI)*	No of cases/ controls	Adjusted odds ratio (95% CI)*	Pooled odds ratio (95% CI)	P
Total No	5062/19 638	—	5500/22 396	—	—	—
No use in previous year (reference)	—	1.00	—	1.00	1.00	—
Current use						
Norethisterone	96/245	2.30 (1.78 to 2.99)	109/259	2.82 (2.21 to 3.60)	2.56 (2.15 to 3.06)	<0.001
Levonorgestrel	521/1451	2.23 (1.97 to 2.52)	540/1411	2.52 (2.24 to 2.84)	2.38 (2.18 to 2.59)	<0.001
Norgestimate	122/370	1.96 (1.56 to 2.46)	160/352	3.15 (2.56 to 3.89)	2.53 (2.17 to 2.96)	<0.001
Desogestrel	165/228	4.43 (3.54 to 5.55)	163/262	4.15 (3.34 to 5.15)	4.28 (3.66 to 5.01)	<0.001
Gestodene	78/149	3.14 (2.32 to 4.24)	115/182	4.07 (3.14 to 5.26)	3.64 (3.00 to 4.43)	<0.001
Drospirenone	139/200	4.36 (3.39 to 5.60)	102/170	3.86 (2.93 to 5.08)	4.12 (3.43 to 4.96)	<0.001
Cyproterone	138/192	4.13 (3.22 to 5.31)	120/187	4.42 (3.41 to 5.73)	4.27 (3.57 to 5.11)	<0.001
Different doses of oestrogen						
Norethisterone 20 µg	44/94	2.94 (2.00 to 4.34)	36/79	2.72 (1.78 to 4.16)	2.84 (2.13 to 3.78)	<0.001
Norethisterone 30/40/50 µg	52/151	1.93 (1.36 to 2.72)	73/180	2.87 (2.14 to 3.84)	2.43 (1.94 to 3.03)	<0.001
Desogestrel 20 µg	57/88	4.43 (3.08 to 6.37)	60/97	3.80 (2.68 to 5.41)	4.10 (3.18 to 5.28)	<0.001
Desogestrel 30/40 µg	108/140	4.42 (3.34 to 5.85)	103/165	4.36 (3.33 to 5.71)	4.39 (3.62 to 5.33)	<0.001
Gestodene 20 µg	17/22	4.70 (2.41 to 9.14)	22/25	5.54 (2.99 to 10.28)	5.13 (3.26 to 8.07)	<0.001
Gestodene 30/40 µg	61/127	2.86 (2.05 to 4.00)	93/157	3.83 (2.89 to 5.08)	3.40 (2.74 to 4.21)	<0.001

*Adjusted for body mass index, smoking status, alcohol consumption, ethnic group, chronic and acute conditions, and use of other hormonal contraceptives.

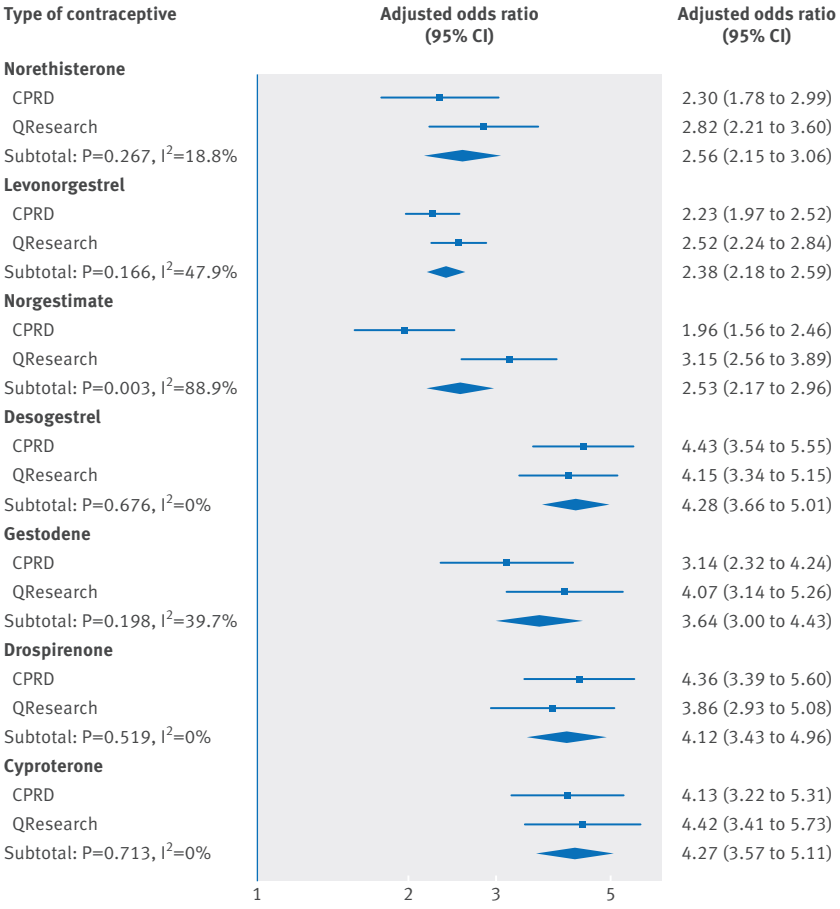

Fig 3 | Adjusted odds ratio for VTE in patients currently exposed to combined oral contraceptives compared with no use in the last year, by database. Odds ratios and 95% confidence intervals are adjusted for body mass index, smoking status, alcohol consumption, ethnic group, chronic and acute conditions, and use of other hormonal contraceptives

Analyses of oestrogen dosages were possible only for norethisterone, desogestrel, and gestodene (20 µg; 30-40 µg). Desogestrel was the most commonly prescribed of these three drugs and had slightly higher odds ratios for higher doses, whereas norethisterone and gestodene had higher odds ratios for lower doses; however, none of these differences between doses was significant (table 2).

Analysis of the duration for current users showed, only for levonorgestrel, a significantly increased risk for new users and restarters (that is, short term users) compared with long term users (adjusted odds ratios 3.38 (95% confidence interval 2.86 to 3.99) *v* 2.16 (1.97 to 2.38), P<0.001). For other drug types, the results were inconsistent, with odds ratios for shorter exposure marginally higher for norethisterone and gestodene, but marginally lower for norgestimate, desogestrel, drospirenone, and cyproterone (web table 5). Adjusted odds ratios for other confounders, including use of other hormonal contraceptives (oral progestogen only and non-oral hormonal treatments) and associations for our category of past use, are available in web table 4.

Although previous studies have not shown any confounding effect from body mass index,[11] we found that inclusion of body mass index into the model changed odds ratios for drug exposures by percentages ranging from 7% to over 10%, with the highest effect for drospirenone (web table 6). Each risk factor, when included individually, did not show a major effect on the results for drug exposures. But when all combined, the odds ratios for drug exposures changed by percentages of between 13% and 25% compared with the unadjusted values. Adjustment for deprivation information in QResearch changed odds ratios for exposures by up to 5%.

Additional analyses

When restricted to cases with anticoagulation prescriptions and matched controls, the overall pattern of risks was similar to those from the main analysis (table 4), although odds ratios were higher for all combined oral contraceptive drug types within a wide range of relative change. The differences were smaller for norethisterone (8% increase in adjusted odds ratio) and levonorgestrel (24%), and larger for norgestimate (40%), gestodene (78%), desogestrel (46%), drospirenone (48%), and cyproterone (40%). However, when tabulated by exposure, the variations shown in proportions of cases with anticoagulation prescriptions for different exposure groups (web table 7) might reflect some differential treatment of patients at initial presentation based on known drug risks.

The analysis for idiopathic cases (that is, with no risk associated conditions) and matched controls showed higher odds ratios for the oral contraceptives in the idiopathic analysis than the main analysis (table 4), but odds ratios by type of oral contraceptive were similar to the main analysis results. The odds ratios for the non-idiopathic group were correspondingly smaller (web table

Table 3 | Adjusted odds ratios for current use of different combined oral contraceptives versus levonorgestrel, by database

	CPRD		QResearch		Combined analysis	
Drug name	Adjusted odds ratio (95% CI)*	P	Adjusted odds ratio (95% CI)*	P	Adjusted odds ratio (95% CI)*	P
Levonorgestrel	1.00	—	1.00	—	1.00	—
Norethisterone	1.03 (0.78 to 1.36)	0.8	1.12 (0.86 to 1.45)	0.4	1.08 (0.89 to 1.30)	0.4
Norgestimate	0.88 (0.69 to 1.12)	0.3	1.25 (1.00 to 1.57)	0.05	1.06 (0.90 to 1.26)	0.5
Desogestrel	1.99 (1.56 to 2.54)	<0.001	1.65 (1.30 to 2.08)	<0.001	1.80 (1.52 to 2.13)	<0.001
Gestodene	1.41 (1.03 to 1.93)	0.03	1.61 (1.23 to 2.12)	<0.001	1.52 (1.24 to 1.87)	<0.001
Drospirenone	1.95 (1.50 to 2.55)	<0.001	1.53 (1.15 to 2.04)	0.004	1.75 (1.43 to 2.12)	<0.001
Cyproterone	1.85 (1.42 to 2.41)	<0.001	1.76 (1.34 to 2.31)	<0.001	1.80 (1.49 to 2.18)	<0.001

*Adjusted for body mass index, smoking status, alcohol consumption, ethnic group, chronic and acute conditions, and use of other hormonal contraceptives.

doi: 10.1136/bmj.h2135 | *BMJ* 2015;350:h2135 | the bmj

Table 4 | Additional analyses for current exposure to combined oral contraceptives compared with non-exposure by database

Type of contraceptive	CPRD		QResearch		Combined analysis	
	No of cases/ controls	Adjusted odds ratio (95% CI)*	No of cases/ controls	Adjusted odds ratio (95% CI)*	Pooled odds ratio (95% CI)	P
Women treated with anticoagulants						
Total No	2533/9882	—	2956/11 933	—	—	—
No use in previous year	—	1.00	—	1.00	1.00	—
Current use						
Norethisterone	52/131	2.70 (1.88 to 3.87)	57/143	2.82 (2.00 to 3.97)	2.76 (2.16 to 3.54)	<0.001
Levonorgestrel	260/683	2.82 (2.36 to 3.38)	297/739	3.06 (2.59 to 3.61)	2.95 (2.61 to 3.33)	<0.001
Norgestimate	71/181	2.52 (1.84 to 3.46)	99/176	4.68 (3.51 to 6.24)	3.53 (2.86 to 4.37)	<0.001
Desogestrel	113/113	7.37 (5.41 to 10.0)	95/132	5.32 (3.95 to 7.17)	6.23 (5.03 to 7.72)	<0.001
Gestodene	57/61	6.89 (4.56 to 10.4)	82/92	6.20 (4.43 to 8.67)	6.47 (4.98 to 8.39)	<0.001
Drospirenone	94/108	6.03 (4.32 to 8.41)	63/76	6.17 (4.20 to 9.05)	6.09 (4.73 to 7.83)	<0.001
Cyproterone	83/99	5.64 (3.99 to 7.97)	73/95	6.36 (4.45 to 9.08)	5.98 (4.66 to 7.66)	<0.001
Idiopathic cases/controls						
Total No	2630/7632	—	2871/8937	—	—	—
No use in previous year	—	1.00	—	1.00	1.00	—
Current use						
Norethisterone	57/96	2.55 (1.78 to 3.66)	74/117	3.08 (2.24 to 4.24)	2.84 (2.23 to 3.60)	<0.001
Levonorgestrel	321/555	2.70 (2.28 to 3.19)	333/602	2.89 (2.46 to 3.39)	2.80 (2.49 to 3.14)	<0.001
Norgestimate	72/163	1.94 (1.43 to 2.64)	104/148	3.64 (2.74 to 4.82)	2.73 (2.22 to 3.36)	<0.001
Desogestrel	107/100	5.09 (3.75 to 6.91)	98/105	4.73 (3.50 to 6.39)	4.90 (3.95 to 6.08)	<0.001
Gestodene	52/68	3.42 (2.28 to 5.12)	66/72	4.58 (3.20 to 6.58)	4.02 (3.07 to 5.27)	<0.001
Drospirenone	86/78	4.91 (3.44 to 7.01)	68/57	5.61 (3.79 to 8.32)	5.22 (4.01 to 6.79)	<0.001
Cyproterone	83/83	4.77 (3.39 to 6.71)	66/79	4.59 (3.19 to 6.61)	4.69 (3.65 to 6.01)	<0.001
Women aged 15-24 years						
Total No	636/2496	—	493/2135	—	—	—
No use in previous year	—	1.00	—	1.00	1.00	—
Current use						
Norethisterone	15/61	1.10 (0.57 to 2.10)	16/39	3.83 (1.94 to 7.57)	1.99 (1.24 to 3.18)	0.004
Levonorgestrel	150/431	2.42 (1.87 to 3.13)	88/314	2.28 (1.66 to 3.13)	2.36 (1.93 to 2.89)	<0.001
Norgestimate	31/88	2.25 (1.40 to 3.61)	36/76	4.83 (2.97 to 7.84)	3.26 (2.32 to 4.58)	<0.001
Desogestrel	30/49	4.37 (2.57 to 7.44)	24/49	3.52 (1.97 to 6.29)	3.96 (2.67 to 5.86)	<0.001
Gestodene	11/24	2.56 (1.14 to 5.73)	13/25	4.67 (2.21 to 9.88)	3.53 (2.04 to 6.12)	<0.001
Drospirenone	38/64	3.90 (2.37 to 6.40)	17/49	2.69 (1.40 to 5.17)	3.41 (2.29 to 5.05)	<0.001
Cyproterone	37/63	3.77 (2.34 to 6.07)	31/51	4.95 (2.79 to 8.78)	4.21 (2.92 to 6.08)	<0.001
Women aged 25-49 years						
Total No	4426/17142	—	5007/20 261	—	—	—
No use in previous year	—	1.00	—	1.00	1.00	—
Current use						
Norethisterone	81/184	2.75 (2.06 to 3.67)	93/220	2.73 (2.10 to 3.56)	2.74 (2.26 to 3.33)	<0.001
Levonorgestrel	371/1020	2.16 (1.87 to 2.49)	452/1097	2.63 (2.31 to 3.00)	2.40 (2.18 to 2.65)	<0.001
Norgestimate	91/282	1.93 (1.49 to 2.51)	124/276	2.92 (2.31 to 3.70)	2.43 (2.04 to 2.89)	<0.001
Desogestrel	135/179	4.62 (3.59 to 5.93)	139/213	4.26 (3.37 to 5.40)	4.43 (3.73 to 5.26)	<0.001
Gestodene	67/125	3.30 (2.38 to 4.57)	102/157	4.03 (3.06 to 5.30)	3.71 (3.00 to 4.58)	<0.001
Drospirenone	101/136	4.75 (3.53 to 6.38)	85/121	4.37 (3.21 to 5.95)	4.56 (3.69 to 5.65)	<0.001
Cyproterone	101/129	4.41 (3.28 to 5.93)	89/136	4.31 (3.20 to 5.80)	4.36 (3.53 to 5.38)	<0.001

*Adjusted for body mass index, smoking status, alcohol consumption, ethnic group, chronic and acute conditions, and use of other hormonal contraceptives.

8), but not as reliable because fewer non-idiopathic controls were available to match to non-idiopathic cases, leading to a reduction of the original matching ratio of cases to controls from 1:5 to about 1:1.5.

In the analysis of VTE cases according to age group, the proportion of the younger group was small (15-24 years; 13% in CPRD, 9% in QResearch). Odds ratios were lower for this group than for the older group (25-49 years; table 4), but again the overall pattern of risk stayed in line with the main analysis.

Risks for combined oral contraceptives compared with levonorgestrel were consistent across all the additional analyses (table 5), with no significant differences for norethisterone and norgestimate. Odds ratios for other drugs ranged from 1.4 to 2.4 (all significant apart from some drugs in the non-idiopathic group and in the younger group, which were likely to be due to low numbers).

The results from CPRD and QResearch were similar with the exception of those for norgestimate. In the CPRD analyses, risks associated with norgestimate use were similar to risks for levonorgestrel, whereas in the QResearch analyses, risks for norgestimate consistently fell between those for levonorgestrel and desogestrel across all analyses. However, the combined

Table 5 | Additional analyses for current use of different combined oral contraceptives compared with levonorgestrel by database

Drug name	CPRD Adjusted odds ratio (95% CI)*	CPRD P	QResearch Adjusted odds ratio (95% CI)*	QResearch P	Combined analysis Adjusted odds ratio (95% CI)*	Combined analysis P
Cases with anticoagulant prescription and matched controls						
Levonorgestrel	1.00	—	1.00	—	1.00	—
Norethisterone	0.96 (0.65 to 1.41)	0.8	0.92 (0.64 to 1.33)	0.7	0.94 (0.72 to 1.22)	0.6
Norgestimate	0.89 (0.64 to 1.26)	0.5	1.53 (1.12 to 2.09)	0.007	1.20 (0.95 to 1.51)	0.1
Desogestrel	2.61 (1.87 to 3.65)	<0.001	1.74 (1.26 to 2.41)	<0.001	2.11 (1.68 to 2.67)	<0.001
Gestodene	2.44 (1.58 to 3.77)	<0.001	2.03 (1.42 to 2.90)	<0.001	2.19 (1.66 to 2.88)	<0.001
Drospirenone	2.14 (1.49 to 3.06)	<0.001	2.02 (1.35 to 3.01)	<0.001	2.08 (1.59 to 2.72)	<0.001
Cyproterone	2.00 (1.38 to 2.89)	<0.001	2.08 (1.43 to 3.03)	<0.001	2.04 (1.57 to 2.65)	<0.001
Idiopathic cases and controls						
Levonorgestrel	1.00	—	1.00	—	1.00	—
Norethisterone	0.94 (0.64 to 1.39)	0.8	1.07 (0.76 to 1.50)	0.7	1.01 (0.78 to 1.30)	0.9
Norgestimate	0.72 (0.52 to 1.00)	0.05	1.26 (0.93 to 1.71)	0.1	0.97 (0.78 to 1.22)	0.8
Desogestrel	1.88 (1.35 to 2.62)	<0.001	1.64 (1.19 to 2.26)	0.003	1.75 (1.39 to 2.21)	<0.001
Gestodene	1.27 (0.83 to 1.94)	0.3	1.59 (1.09 to 2.33)	0.02	1.44 (1.08 to 1.91)	0.01
Drospirenone	1.82 (1.25 to 2.65)	0.002	1.95 (1.29 to 2.94)	0.002	1.88 (1.42 to 2.48)	<0.001
Cyproterone	1.77 (1.23 to 2.53)	0.002	1.59 (1.09 to 2.33)	0.02	1.68 (1.29 to 2.19)	<0.001
Women aged 15-24 years						
Levonorgestrel	1.00	—	1.00	—	1.00	—
Norethisterone	0.45 (0.23 to 0.89)	0.02	1.68 (0.83 to 3.38)	0.1	0.85 (0.52 to 1.38)	0.5
Norgestimate	0.93 (0.57 to 1.52)	0.8	2.12 (1.27 to 3.54)	0.004	1.38 (0.97 to 1.97)	0.08
Desogestrel	1.81 (1.05 to 3.12)	0.03	1.54 (0.85 to 2.81)	0.2	1.68 (1.12 to 2.52)	0.01
Gestodene	1.06 (0.47 to 2.40)	0.9	2.05 (0.94 to 4.44)	0.07	1.50 (0.85 to 2.63)	0.2
Drospirenone	1.61 (0.96 to 2.70)	0.07	1.18 (0.60 to 2.33)	0.6	1.44 (0.95 to 2.17)	0.08
Cyproterone	1.56 (0.95 to 2.56)	0.08	2.17 (1.19 to 3.96)	0.01	1.78 (1.21 to 2.62)	0.003
Women aged 25-49 years						
Levonorgestrel	1.00	—	1.00	—	1.00	—
Norethisterone	1.27 (0.93 to 1.74)	0.1	1.04 (0.78 to 1.38)	0.8	1.14 (0.92 to 1.40)	0.2
Norgestimate	0.89 (0.67 to 1.19)	0.4	1.11 (0.86 to 1.44)	0.4	1.01 (0.83 to 1.22)	0.9
Desogestrel	2.14 (1.62 to 2.82)	<0.001	1.62 (1.25 to 2.10)	<0.001	1.84 (1.53 to 2.23)	<0.001
Gestodene	1.53 (1.08 to 2.16)	0.02	1.53 (1.14 to 2.05)	0.004	1.53 (1.22 to 1.91)	<0.001
Drospirenone	2.20 (1.60 to 3.02)	<0.001	1.66 (1.20 to 2.30)	0.002	1.92 (1.53 to 2.41)	<0.001
Cyproterone	2.04 (1.49 to 2.80)	<0.001	1.64 (1.20 to 2.24)	0.002	1.83 (1.46 to 2.28)	<0.001

*Adjusted for body mass index, smoking status, alcohol consumption, ethnic group, chronic and acute conditions, and use of other hormonal contraceptives.

results, which gave more precise estimates, placed norgestimate in the group with levonorgestrel and norethisterone. An additional analysis for QResearch, which included adjustment for the Townsend deprivation score, showed results similar to the main analysis (web table 9).

Sensitivity analyses

When combining the results from the databases we discovered significant heterogeneity only for current use of norgestimate (I^2=89%, P=0.003). The direction of the effect was the same in both databases and, after we applied a random effect model to combine the results, the estimate for norgestimate did not change our conclusion of its association being close to the estimates for the group of earlier contraceptives (combined odds ratio 2.49, 95% confidence interval 1.56 to 3.97).

The sensitivity analysis for QResearch cases identified only through general practice medical records and matched controls delivered results in line with the main analysis (web table 10). The sensitivity analysis for CPRD practices linked to hospital admission and ONS mortality data was based on 346 general practices and covered the period between 1 January 2001 and 30 March 2012. The crude incidence of VTE per 10 000 women years in this cohort was 5.7 (95% confidence interval 5.5 to 5.8). We identified 436 extra cases from hospital admission data and 14 from ONS mortality data with at least one year of medical records. After exclusions, 2989 cases were included in the analysis, of which 2654 (89%) were identified from general practice records, 324 (11%) from hospital admission data, and 11 (0.4%) from ONS mortality data. The results were also in line with the main analysis (web table 11).

Numbers needed to harm and excess risk

Because combined oral contraceptive use was associated with increased VTE risk, additional cases of VTE would be expected across all types of combined oral contraceptives in exposed women compared with unexposed women, and particularly in those aged 25-49 years (table 6). The lowest numbers of extra cases of VTE per year per 10 000 treated women were six extra cases for levonorgestrel (6, 95% confidence interval 5 to 7) and norgestimate (6, 5 to 8) for women aged 15-49 years, and seven extra cases for levonorgestrel (7, 6 to 8)

doi: 10.1136/bmj.h2135 | BMJ 2015;350:h2135 | the bmj

and norgestimate (7, 5 to 9) for those aged 25-49 years. The highest numbers of extra cases of VTE per year per 10 000 treated women were for desogestrel (14 extra cases, 11 to 17) and cyproterone (14, 11 to 17) for ages 15-49 years, and for drospirenone (17, 13 to 23), desogestrel (17, 13 to 21), and cyproterone (17, 12 to 22) for ages 25-49 years.

Discussion

In this observational study based on two large primary care databases, women exposed to drospirenone, gestodene, cyproterone, and desogestrel within the last 28 days had around a four times increased risk of VTE. Women exposed to levonorgestrel, norethisterone, and norgestimate had about two and a half times increase in VTE risk compared with women not exposed in the past year. Risks for current use of gestodene, drospirenone, cyproterone, and desogestrel were 1.5-1.8 times higher than for levonorgestrel. Results from the additional analyses stayed in line with the main findings, although there were stronger associations in the analyses restricted to cases with anticoagulant prescriptions and matched controls. These differences were expected and can be explained by our methodological approach. We saw no significant association in the analyses of oestrogen dosages.

Strengths and limitations of the study

The main strengths of this study are its recency, comprehensiveness, and generalisability. It was based on the general female population in the UK aged 15-49 years, and explored exposure to combined oral contraceptives commonly prescribed during the past 13 years. The study also benefitted from the statistical power of large samples from the two largest UK primary care databases. Consistency in records for diagnoses, lifestyle information, and prescriptions allowed us to combine the results from both databases and achieve narrower confidence intervals for our estimates. The study also benefitted from a consistent design.

Results were adjusted for several confounding factors such as body mass index, smoking status, alcohol use, and social deprivation, which were not available to some previous studies. Education and family history might also be considered to be confounders but neither could be included in the analysis because they are not recorded sufficiently often on either the QResearch or CPRD databases. Because the exposure was based on systematically recorded prescription information, the study was free from recall bias. All eligible women were included, thus eliminating selection bias. Several additional analyses looking at conflicting methodological issues from previous studies allow readers to compare and assess the validity of the results.

A study limitation was the potential misclassification of exposure to combined oral contraceptives. According to the Contraception and Sexual Health survey in Great Britain (2000-09), between 25% and 28% of women used an oral contraceptive depending on the year.[36] Our data for both databases had similar age standardised rates of exposure to any oral contraceptive—26% for QResearch and 29% for CPRD. Because exposure information is based on prescriptions, however, there is a degree of uncertainty about actual use—when a woman started taking the drug or whether she took it at all. According to one survey from the United States, 19% of women discontinued using oral contraceptives within the first six months, more commonly younger women.[37] Because outcome information was collected prospectively, however, we do not see any reason why this effect should differ between cases and controls. Such misclassification of exposure might, however, shift odds ratios towards unity. Some uncertainty also relates to women who may have delayed use of drugs from past prescriptions (and so were actually current rather than past users), and to unaccounted residual risk associated with women who ceased use for any reason just before the current use period. However, these two potential misclassifications are likely to be small.

NHS community contraceptive clinics are also a source of oral contraceptive pills apart from general practice doctors. According to NHS Contraceptive Services reports issued between 2005 and 2013 (www.hscic.gov.uk), on average 6.9% of women under 25 years old and 1.6% of older women received oral contraceptive pills from contraceptive clinics. One report in 2005 released the numbers separately for combined and progestogen only pills, showing that the proportion of combined contraceptives prescribed was 91% of all oral contraceptives for younger women and 73% for older women.[38] From these figures, we estimated that in the population, 6.3% of younger and 1.2% of older women had exposure to combined oral contraceptives without related general practice records. These women would appear in our analyses as not exposed, creating a potential underestimation that might

Table 6 | Numbers needed to harm and excess cases per 10 000 patients for different combined oral contraceptives prescribed over one year

	Numbers needed to harm over 1 year (95% CI)		Extra cases per 10 000 treated per year (95% CI)	
Use in previous year	All ages (15-49 years)*	Age 25-49 years†	All ages (15-49 years)*	Age 25-49 years†
Norethisterone	1529 (1159 to 2086)	1169 (874 to 1620)	7 (5 to 9)	9 (6 to 11)
Levonorgestrel	1739 (1506 to 2028)	1452 (1237 to 1723)	6 (5 to 7)	7 (6 to 8)
Norgestimate	1561 (1223 to 2044)	1428 (1077 to 1966)	6 (5 to 8)	7 (5 to 9)
Desogestrel	729 (597 to 899)	594 (478 to 747)	14 (11 to 17)	17 (13 to 21)
Gestodene	905 (697 to 1198)	752 (570 to 1016)	11 (8 to 14)	13 (10 to 18)
Drospirenone	766 (604 to 986)	572 (438 to 758)	13 (10 to 17)	17 (13 to 23)
Cyproterone	731 (582 to 932)	606 (465 to 804)	14 (11 to 17)	17 (12 to 22)

*Based on combined adjusted odds ratios in table 2.
†Based on combined adjusted odds ratios in table 4.

shift odds ratios towards unity, with an effect likely to be greater in the younger group.

The additional analyses for younger women did, in fact, produce lower odds ratios for all drugs apart from levonorgestrel and norgestimate. However, in the direct comparisons of different oral contraceptives with levonorgestrel, there was no potential bias with respect to misclassification of non-users because only oral contraceptive users were involved. Other biases could arise if the prescribing regimens of contraceptive clinics differed markedly from those of general practices (with one or other being more inclined towards higher risk, lower priced drugs), or if the material circumstances of women attending general practices differed from those attending contraceptive clinics. No published data seem to support this, however, and we believe that any such effects are likely to be negligible especially given the much higher proportion of supply from general practices.

There is also some degree of uncertainty in VTE diagnoses in both CPRD and QResearch practice records, because the results of diagnostic tests needed to confirm VTE are not generally available on the primary care databases. Furthermore, these diagnoses cannot be adjudicated in our study as might happen in a clinical trial, so may be subject to misclassification bias, with some false positives for cases and some false negatives for controls. The likelihood of misclassifications is, however, much higher for cases than controls because of the low incidence of VTE in the general population from which the controls are selected—therefore, overall, such errors and misclassifications if non-differential would tend to shift odds ratios towards unity.

Further, the incidence of VTE in our cohorts were both within the estimated range of five to 10 cases per 10 000 person years for young women.[39] The slightly higher rate within the QResearch cohort can be explained partly because the data used in the database's analysis was augmented by linked mortality information from the ONS and hospital episode statistics. This link will have added extra cases to the QResearch analysis and reduced diagnostic errors. However, the relatively small difference in rates between QResearch and CPRD, and the fact that the difference is also partly explained by the slightly higher median age of the QResearch cohort, suggests that neither analysis has been substantially affected by diagnostic errors. An earlier study has also shown that the addition of "possible" cases of VTE did not materially affect results obtained using only verified cases.[40]

Patients with a diagnosis of VTE are usually treated with anticoagulant medication. In our data, however, there are several reasons why VTE cases might not be followed by an anticoagulation prescription, such as a VTE event resulting in death, or treatment unrecorded in the GP record because it was initiated and continued in a hospital or other community setting. We found that, overall, about half of patients with VTE had a record of anticoagulation prescription within their general practice record. But a more detailed breakdown by exposure and drug type revealed possible differential treatment of exposed patients depending on contraceptive drug type and roughly reflecting the known VTE risks of the drugs.

The higher odds ratios in the additional analysis restricted to cases with anticoagulation prescriptions than those from the main analysis can be explained by a combination of the exclusion of uncertain events and differential anticoagulant prescribing by doctors. Women who receive anticoagulation treatment, which is necessary for VTE, are normally more likely to be true cases than those with no treatment recorded. Therefore, inclusion of some non-cases in our main analysis probably shifted odds ratios towards unity. On the other hand, our conjecture—based on evidence in our data of differential prescribing—is that doctors are more likely immediately to prescribe and record anticoagulants for patients with VTE symptoms exposed to a high risk oral contraceptive drug than for users of lower risk drugs. As a result, use of anticoagulation records to exclude uncertain events is more problematic in this study, and we would argue that results of our restricted analysis should be read with caution, indicating little more than a general agreement with earlier findings of increased odds ratios. In particular, the range of relative increases is probably exaggerated and comparisons between drug types possibly less reliable.

Finally, the higher odds ratios obtained from the subgroups with idiopathic cases and matched idiopathic controls, compared with odds ratios from the main analysis, were also expected because the absolute risk of VTE for unexposed patients is smaller in an idiopathic subgroup than that in a non-idiopathic subgroup (and by extension a general population).[41] Although the associations seem to be stronger in the idiopathic analysis, we do not believe that they are necessarily generalisable because of the wide variation in definitions of idiopathic groups across existing studies, and the general difficulties that have been noted in defining such groups.[42]

Comparison with recent studies

In our study, we observed a reduction in prescription rates for combined oral contraceptives and an increased rate for progestogen only oral contraceptives. This is in line with NHS statistics for prescriptions in the community, and might reflect the effects of various guidelines and recommendations for patients at high risk of VTE.[43]

Prior to our study, the largest study of VTE and combined oral contraceptives was a cohort study based on medical records from the Danish general population, covering the period 2001-09 and identifying 4246 women with a first recorded VTE.[12] The Danish study adjusted for age, calendar year, and level of education. By comparison, our study had more than twice the number of VTE cases; added a further four years of data; adjusted for body mass index, smoking status, alcohol consumption, ethnic group, several chronic and acute conditions associated with increased VTE risk, and use of other hormonal contraceptives; and accounted for age, calendar year, and practice by matching. Not all types of combined contraceptives in the Danish study were available for comparison,

because some are rarely prescribed in the UK. The most used contraceptives were levonorgestrel in the UK and gestodene in Denmark. In our main analysis, the odds ratios for current use of available contraceptives were similar to the Danish relative rates. Despite a difference in the proportion of cases with anticoagulant prescriptions (52% in our study *v* 67% in the Danish study), results in these subgroups were also similar.

The most recent CPRD based study focused on a comparison of VTE risk in idiopathic cases of VTE with anticoagulant prescriptions between levonorgestrel and drospirenone.[14] It was run on records from 2002 to 2009, and so was based on fewer practices than in our study. For current users, that study showed a threefold increase in VTE risk for drospirenone compared with levonorgestrel (17 *v* 44 exposed cases; odds ratio 3.3, 95% confidence interval 1.4 to 7.6). In our study, the odds ratios for current use of drospirenone were about twice as high as for levonorgestrel in our main analysis and all additional analyses. Another study (2002-08),[11] based on pharmacological records from a US company and with a design similar to the recent CPRD study,[14] had more women with VTE exposed to drospirenone than levonorgestrel (121 *v* 65). It also showed an increased risk of VTE with drospirenone compared with levonorgestrel (odds ratio 2.4, 95% confidence interval 1.7 to 3.4). Based on the same source of data (the same US company),[11] another study showed a 70% increased risk associated with desogestrel (1.7 (1.1 to 2.4)) and no significant increase with norgestimate, both compared to levonorgestrel.[44] All three of these studies differed from ours in terms of case inclusion criteria, but their results align well with those from our additional analyses.

An Austrian case-control study (2002-06)[45] investigated gestodene-containing and second generation oral contraceptives (79 and 83 exposed cases, respectively), identifying cases from referral centres and hospitals and deriving exposure information from questionnaires. Odds ratios for contraceptive use (with reference to non-users) were two to three times higher than in our study. But, as the authors suggested, this increased risk might be due to what they termed as "hospital bias," which can lead to overestimation of VTE risks.[46] The study also compared gestodene with second generation pills but did not show any significant difference between the drugs in several sensitivity analyses. The relative differences between levonorgestrel and gestodene seen in our main and additional analysis for idiopathic cases were within the confidence interval or close to the upper confidence levels of this study.

A Dutch study (1999-2004)[9] analysed all available oral contraceptives, identifying women with VTE from anticoagulation clinics and assessing exposure from postal questionnaires and interviews. Most controls were, however, acquired by random digit dialling, a technique that might have led to selective recruitment of a less active group with a poorer health profile than the general population.[47] This technique and the higher response rates in women with VTE than in those controls (79% *v* 64%) might have introduced a selection bias and inflated odds ratios. In fact, the study did report higher odds ratios that those more generally reported elsewhere and consistently higher odds ratios with reference to non-use than our study, although relative differences with reference to levonorgestrel were again close to our findings.

An Israeli cohort study[48] (2002-08) compared VTE risks for drospirenone with those for second and third generation oral contraceptives and found significant differences for drospirenone compared with both generations (rate ratio 1.65 (95% confidence interval 1.02 to 2.65), 1.43 (1.15 to 1.78), respectively). The pattern of prescribing in this study was different from ours, with most common exposure to third generation drugs (384 exposed cases) and a lower use of levonorgestrel (23 exposed cases). Our study showed a similar association for current use of drospirenone compared with levonorgestrel (odds ratio of 1.75), but found no difference between drospirenone and third generation drugs.

Despite being a third generation drug, norgestimate (282 exposed cases) had associations with VTE risk similar to levonorgestrel in our study. But because norgestimate partly metabolises to levonorgestrel,[49] its classification as a third generation drug is not clearly established. A Danish review classified norgestimate as a second generation drug and recommended prescribing it as a first choice contraceptive along with levonorgestrel and norethisterone.[50] Norgestimate has a lower androgenic effect than levonorgestrel and had been used at a similar level to levonorgestrel in the Denmark study,[12] although in our study levonorgestrel was prescribed three times more often than norgestimate. No significant difference between norgestimate and levonorgestrel was shown in the Danish study[12] (165 exposed cases, rate ratio 1.18 (95% confidence interval 0.86 to 1.62)) or in the US study[44] (124, odds ratio 1.1 (95% confidence interval 0.8 to 1.5)).

A meta-analysis[16] including the Danish and US studies also demonstrated this non-difference between norgestimate and levonorgestrel, although it was not highlighted in the main study findings, which focused on different drug generations and oestrogen dosages. Although norgestimate had been on the market from 1995, other studies either did not consider norgestimate or were underpowered (for norgestimate, only five exposed cases in the Dutch study,[9] 15 in the CPRD study,[4] and an unclear number in a German study with lower total numbers[13]).

Our study showed no associations between VTE risk and oestrogen dose for the three types of combined contraceptives, where this could be assessed. Levonorgestrel in the UK was prescribed mostly with a 30-40 µg dose of oestrogen, so oestrogen dose analysis was not possible. Comparable preparations for norethisterone have not been analysed before, so direct comparison of our results with other studies is not possible. A lower dose of oestrogen for desogestrel preparations was associated with a slightly lower risk of VTE, which was consistent with existing literature,[12 16] but our difference was not significant. For combinations with gestodene, the numbers of current users were insufficient to draw any meaningful conclusions.

Conclusion

This study, based on two large primary care databases, investigated risks of VTE associated with combined oral contraceptives prescribed to the general female population in the UK. We believe this study has the statistical power and sufficient adjustment for relevant confounders to be regarded as an important clarifying study, which has produced the most reliable possible risk estimates using currently available UK prescription data. It has confirmed results from other recent large scale studies and added new evidence, particularly for newer or less used combined oral preparations, such as those containing drospirenone or norgestimate. Risks associated with combined oral contraceptives were, apart from norgestimate, higher for newer drug preparations than for second generation drugs.

The results from our study and the Danish study[12] provide evidence for relevant authorities concerned with prescribing guidelines or those involved with regulation of safety of medicines. In particular, along with the Danish study and a US study,[44] our results confirm the similarity of risks for levonorgestrel and norgestimate in a UK context.

We acknowledge the contribution of Egton Medical Information System (EMIS) and the University of Nottingham for expertise in creating and maintaining QResearch and to the EMIS practices which contribute data; we thank CPRD and Vision Practices for allowing access to the CPRD for this study.

Contributors: JHC had the original idea for this study. CC contributed to the development of the idea and the study design. YV reviewed the literature, contributed to the study design, undertook the primary analysis as well as the first interpretation and wrote the first draft of the paper. JHC and CC critically reviewed the paper. All authors approved the submitted version.

Funding: This research received no external funding.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any additional organisation for the submitted work; JHC is professor of clinical epidemiology at the University of Nottingham and unpaid director of QResearch, a not-for-profit organisation which is a joint partnership between the University of Nottingham and EMIS (commercial IT supplier for 60% of general practices in the UK); JHC is also a paid director of ClinRisk, which produces open and closed source software to ensure the reliable and updatable implementation of clinical risk algorithms within clinical computer systems to help improve patient care; no other relationships or activities that could appear to have influenced the submitted work.

Ethics and dissemination: The protocol for this study has been published in BMJ Open. It has also been independently peer reviewed by the QResearch Scientific Board and has been reported to Trent research ethics committee in accordance with the agreed procedure (reference no MREC/03/4/021). For CPRD data analysis, the protocol was approved by Independent Scientific Advisory Committee (reference no ISAC 13_118RA2).

Data sharing: Results for all additional analyses and descriptive statistics are already published in the web tables. Any further requests are available from the corresponding author.

The lead author and the manuscript's guarantor (YV) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

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Web appendix 1: Supplementary tables
Web appendix 2: READ codes of conditions affecting venous thromboembolism

JAMA Psychiatry | Original Investigation

Association of Hormonal Contraception With Depression

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IMPORTANCE Millions of women worldwide use hormonal contraception. Despite the clinical evidence of an influence of hormonal contraception on some women's mood, associations between the use of hormonal contraception and mood disturbances remain inadequately addressed.

OBJECTIVE To investigate whether the use of hormonal contraception is positively associated with subsequent use of antidepressants and a diagnosis of depression at a psychiatric hospital.

DESIGN, SETTING, AND PARTICIPANTS This nationwide prospective cohort study combined data from the National Prescription Register and the Psychiatric Central Research Register in Denmark. All women and adolescents aged 15 to 34 years who were living in Denmark were followed up from January 1, 2000, to December 2013, if they had no prior depression diagnosis, redeemed prescription for antidepressants, other major psychiatric diagnosis, cancer, venous thrombosis, or infertility treatment. Data were collected from January 1, 1995, to December 31, 2013, and analyzed from January 1, 2015, through April 1, 2016.

EXPOSURES Use of different types of hormonal contraception.

MAIN OUTCOMES AND MEASURES With time-varying covariates, adjusted incidence rate ratios (RRs) were calculated for first use of an antidepressant and first diagnosis of depression at a psychiatric hospital.

RESULTS A total of 1 061 997 women (mean [SD] age, 24.4 [0.001] years; mean [SD] follow-up, 6.4 [0.004] years) were included in the analysis. Compared with nonusers, users of combined oral contraceptives had an RR of first use of an antidepressant of 1.23 (95% CI, 1.22-1.25). Users of progestogen-only pills had an RR for first use of an antidepressant of 1.34 (95% CI, 1.27-1.40); users of a patch (norgestrolmin), 2.0 (95% CI, 1.76-2.18); users of a vaginal ring (etonogestrel), 1.6 (95% CI, 1.55-1.69); and users of a levonorgestrel intrauterine system, 1.4 (95% CI, 1.31-1.42). For depression diagnoses, similar or slightly lower estimates were found. The relative risks generally decreased with increasing age. Adolescents (age range, 15-19 years) using combined oral contraceptives had an RR of a first use of an antidepressant of 1.8 (95% CI, 1.75-1.84) and those using progestin-only pills, 2.2 (95% CI, 1.99-2.52). Six months after starting use of hormonal contraceptives, the RR of antidepressant use peaked at 1.4 (95% CI, 1.34-1.46). When the reference group was changed to those who never used hormonal contraception, the RR estimates for users of combined oral contraceptives increased to 1.7 (95% CI, 1.66-1.71).

CONCLUSIONS AND RELEVANCE Use of hormonal contraception, especially among adolescents, was associated with subsequent use of antidepressants and a first diagnosis of depression, suggesting depression as a potential adverse effect of hormonal contraceptive use.

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2016.2387
Published online September 28, 2016.

Supplemental content

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Depression is associated with a substantial burden in developed and developing countries.[1] The lifetime prevalence of depression is about twice as high in women as in men across different populations.[2-5] Nevertheless, before puberty, girls are found to be equally or less depressed than boys.[6,7] The 2 female sex hormones—estrogen and progesterone—have been hypothesized to play a role in the cause of depressive symptoms.[8-12] In a recent review, Toffoletto et al[13] found initial evidence that sex steroid hormones have an influence on the cortical and subcortical regions implicated in emotional and cognitive processing. Gingnell et al[14] found that use of combined oral contraceptives among women who previously had experienced emotional adverse effects resulted in mood deterioration and changes in emotional brain reactivity. The addition of progesterone to hormone therapy has been shown to induce adverse mood effects in women.[15,16] Likely mechanisms also include the action of progesterone metabolites on the γ-aminobutyric acid A receptor complex, which is the major inhibitory system in the human central nervous system.[17] Levels of neuroactive metabolites of progesterone increase during the luteal phase of the menstrual cycle in fertile women, and some experience negative mood symptoms.[17] Moreover, external progestins, probably more than natural progesterone, increase levels of monoamine oxidase, which degrades serotonin concentrations and thus potentially produces depression and irritability.[18] Clinical studies have indicated that changes in estrogen levels may trigger depressive episodes among women at risk for depression[19] and that women with major depression generally have lower estradiol levels than do control individuals.[20] Freeman et al[21] found that women with a faster transition to menopause followed by stable hormone levels had fewer depressive symptoms. In a recent double-blind placebo-controlled study,[22] women were randomized to sex hormone manipulation with groserelin (gonadotropin-releasing hormone agonist) implant or placebo, which triggered subclinical depressive symptoms in the intervention group. The depressive symptoms were positively associated with the net decrease in estradiol levels.

Few studies have quantified the effect of modern low-dose hormonal contraceptive use on the risk for depression.[23-28] Two studies[24-26] found teenage users of progestin-only contraception to be more frequent users of antidepressants than nonusers of hormonal contraceptives. One study[23] found no association between oral contraceptive use and mood symptoms, and 3 studies[25,27,28] suggested that the use of hormonal contraception was associated with better mood. We found few prior studies that assessed the effect of hormonal contraceptives on the risk for subsequent depression in a prospective cohort design and none that took into account the temporality between use of hormonal contraceptives and development of depression.

Because mood symptoms are a known reason for cessation of hormonal contraceptive use,[29-31] cross-sectional studies are vulnerable to healthy-user bias causing underestimation of a possible influence on depression. Because hormonal contraception introduces synthetic hormones and modulates the internal hormone production, an examination of the influence of hormonal contraceptives on women's mood is warranted. The aim of this study was to assess the influence of specific types of hormonal contraceptives on the risk for first use of antidepressants and first diagnosis of depression as an inpatient or an outpatient at a psychiatric hospital.

Key Points

Question Is use of hormonal contraception associated with treatment of depression?

Findings In a nationwide prospective cohort study of more than 1 million women living in Denmark, an increased risk for first use of an antidepressant and first diagnosis of depression was found among users of different types of hormonal contraception, with the highest rates among adolescents.

Meaning Health care professionals should be aware of this relatively hitherto unnoticed adverse effect of hormonal contraception.

Methods

Study Population

The Danish Sex Hormone Register Study[32] is an ongoing nationwide cohort study that includes all women living in Denmark. The cohort was identified by the unique personal identification number given to all Danish citizens at birth or immigration. This number is used in all public registers, allowing reliable linkage of data between registers. The databases were available through Statistics Denmark, and approval for their use was obtained from the Danish Data Protection Agency, which also determined that informed consent was not required because the study used deidentified data from large databases.

In the present study, we observed adolescents and women aged 15 to 34 years (hereinafter referred to as women) at any time during the 14 years from January 1, 2000, to December 31, 2013, and in the previous 5-year period. To ensure that incident events of depression were identified, all women with a depression diagnosis or use of antidepressants before January 1, 2000, or before their 15th birthday were excluded, as were all women with other major psychiatric diagnoses using the following codes from the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*: organic, DF0*; manic episode, DF30; bipolar affective disorder, DF31*; schizophrenia, DF2*; and mental retardation, DF7*. To exclude women with contraindications against the use of hormonal contraceptives, women with a diagnosis of cancer or venous thrombosis or who underwent treatment for infertility before study entry were excluded. The National Health Register provided data on discharge diagnoses of cancer and venous thrombosis since 1977, and the Psychiatric Central Research Register provided data on psychiatric diagnoses for all inpatients and outpatients since 1995. Infertility was defined as having a redeemed prescription of ovarian-stimulating drugs (Anatomical Therapeutic Chemical classification system code MG03G in the National Prescription Register). Daily updated information on immigration, emigration, and death was obtained from Statistics Denmark. Women immigrating after 1995

were excluded to ensure information on prior depression and other censoring variables for at least 5 years before study entry. The National Birth Register provided information on births since 1973 (eFigure 1 in the Supplement).

Hormonal Contraception

The National Prescription Register provided individual exposure information on prescribed and redeemed medication from all Danish pharmacies since 1995 and was categorized according to estrogen type and dose, progestin type, and route of administration (eTable 1 in the Supplement). Use of hormonal contraception was modeled as time-varying covariates, with information updated daily. All prescriptions were extended with 28 days or less if a new prescription was redeemed.[33] Hormone use was defined as current or recent use (cessation within the previous 6 months) to ensure that women who quit hormonal contraceptive use owing to depression but before any treatment was initiated were considered exposed to hormonal contraceptives. The reference group consisted of nonusers, defined as those who never used hormonal contraceptives plus former users.

Depression

Two outcome measures for incident depression were addressed. First, a first redeemed prescription of an antidepressant was recorded in the National Prescription Register (eTable 2 in the Supplement). The National Prescription Register covers all redeemed prescriptions of antidepressants from Danish pharmacies, including 98.7% of all antidepressants used in Denmark. The second outcome was a first discharge diagnosis of depression from the Psychiatric Central Research Register, defined by codes F32 to F33.9 from the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*. This outcome included all inpatients and outpatients at psychiatric departments in Denmark since 1995.

Covariates

Statistics Denmark delivered data for all women on age, length of schooling, and ongoing or completed educational level (unknown, elementary school only, high school only, skilled worker, theoretical education, and theoretical education with research qualifications). Diagnoses of polycystic ovary syndrome and endometriosis were obtained from the National Health Register. The National Birth Register provided information on body mass index (calculated as weight in kilograms divided by height in meters squared) (by categories of <18.5, 18.5-25.0, >25.0 to 30.0, and >30.0) since 2004 and smoking habits (yes or no) since 1991 for all women who had been pregnant.

Statistical Analysis

All women in the study population were followed up from entry (January 1, 2000, or 15th birthday) and until event, emigration, death, or the end of follow-up on December 31, 2013, whichever came first. Women were censored during the study period for the same reasons as the primary exclusions and temporarily during pregnancy and 6 months after delivery. To account for age and time trends in depression, we adjusted for calendar year and age using 1-year bands. We also adjusted for educational level, polycystic ovary syndrome, and endometriosis. Incidence rate ratios (RRs) and 95% CIs were calculated using Poisson regression.

Among women starting hormonal contraceptive use in the study period, we assessed the effect of duration of use compared with nonusers. Among parous women, an additional sensitivity analysis adjusted for smoking and body mass index. In 2 additional analyses, RRs among users of different hormonal contraception product types were calculated, with users of a combination of ethinyl estradiol, 30 to 40 µg, and levonorgestrel as the reference group or with those who never used hormonal contraceptives as the reference group.

Finally, sensitivity analyses were conducted on the subcohort of women who started hormonal contraceptive use sometime during the study period. Each woman contributed to the exposed and unexposed observation time. Among women who started use of hormonal contraceptives, incidence rates within 1 year after initiation of hormonal contraception were compared with the incidence rate during the time before the initiation of hormonal contraceptive use. We thereby controlled for all potential confounders, which did not change during the observation period and eliminated healthy-user bias.

Results

The study population included 1 061 997 women (mean [SD] age, 24.4 [0.001] years; mean [SD] follow-up, 6.4 [0.004] years) and 6 832 938 person-years of observation during the study period. During follow-up, 55.5% of women were current or recent users of hormonal contraception. Use of hormonal contraception according to age in 2013 is illustrated in eFigure 2 in the Supplement. Within the first year of hormonal contraceptive use, 0.04% of women changed to another product and 10% ceased using their product. A total of 133 178 first prescriptions of antidepressants and 23 077 first diagnoses of depression were detected during follow-up. Data were analyzed from January 1, 2015, through April 1, 2016.

Characteristics of Users of Hormonal Contraception

Women using hormonal contraception were a mean (SD) of 24.3 (0.01) years of age; nonusers were a mean (SD) of 24.4 (0.01) years of age. Users of the levonorgestrel intrauterine system were a mean (SD) of 31 (0.05) years of age. Women using 50 µg of combined oral contraceptives, implants, or medroxyprogesterone acetate depot were more likely to have a lower educational level than were women using other types of hormonal contraception. That tendency was most pronounced for women using medroxyprogesterone acetate depot (**Table 1**).

Hormonal Contraception and Depression

Among all users of hormonal contraceptives, the crude incidence rate of first use of antidepressants was 2.2 per 100 person-years; that of first diagnosis of depression at a psychiatric hospital, 0.3 per 100 person-years. The corresponding crude incidence rates in nonusers of hormonal contraception were 1.7 and 0.28 per 100 person-years, respectively.

Table 1. Characteristics of Users of Different Types of Hormonal Contraception[a]

Type of Hormonal Contraception	Year	Person-years	Age, Mean (SD), y	% of Women			
				Educational Level			
				Short[b]	Long[c]	PCOS	Endometriosis
Nonuse	NA	3 041 595	24.4 (0.01)	8.2	4.4	0.9	1.1
All use	NA	3 791 343	24.3 (0.01)	6.9	6.5	1	1.3
Combined products							
Oral							
Ethinyl estradiol, 50 µg							
Norethisterone	1995-2002	8060	26.3 (0.1)	17.0	2.7	1.2	2.2
Levonorgestrel	1995-2009	14 197	26.2 (0.1)	14.7	2.8	1.4	3.8
Ethinyl estradiol, 30-40 µg							
Norethisterone	1995→	38 927	25.1 (0.1)	10.6	4.4	1.0	1.5
Levonorgestrel	1995→	280 445	24.5 (0.02)	6.2	5.9	0.5	0.9
Norgestimate	1995→	339 501	24.5 (0.02)	7.2	6.6	0.9	1.1
Desogestrel	1995→	170 544	25.6 (0.03)	8.7	6.4	1.1	2.0
Gestodene	1995→	757 337	25.4 (0.01)	7.6	6.7	0.8	1.8
Drospirenone	2001→	327 930	23.4 (0.02)	6.6	7.2	1.5	1.3
Cyproterone acetate	1995→	159 931	24.1 (0.03)	6.1	8.5	3.0	1.2
Ethinyl estradiol, 20 µg							
Desogestrel	1995→	659 847	23.5 (0.01)	6.5	6.6	0.8	1.3
Gestodene	1997→	693 013	22.9 (0.01)	6.2	6.0	0.8	1.1
Drospirenone	2006→	64 894	22.2 (0.04)	4.6	7.7	1.3	0.5
Natural estrogen							
Dienogest	2009→	3711	24.1 (0.2)	4.0	8.0	1.4	2.0
Nonoral							
Patch (norgestrolmin)	2003→	8081	23.5 (0.1)	11.5	3.5	1.2	1.4
Vaginal ring (etonogestrel)	2002→	69 605	25.1 (0.04)	5.9	10.4	0.8	1.1
Progestin-only products							
Oral							
Norethisterone	1995→	33 182	27.6 (0.1)	5.2	7.4	0.7	1.4
Levonorgestrel	1995-2005	1289	28.3 (0.3)	5.4	9.8	0.7	1.7
Desogestrel	2001→	40 069	26.3 (0.1)	4.5	7.5	0.7	1.6
Nonoral							
Implant	1999→	28 867	23.0 (0.1)	16.6	1.8	0.7	0.8
Levonorgestrel IUS	1995→	81 281	31.0 (0.1)	3.8	3.5	0.5	1.5
Medroxyprogesterone acetate depot	1995→	10 587	22.7 (0.1)	26.4	0.4	1	0.7

Abbreviations: IUS, intrauterine system; PCOS, polycystic ovary syndrome; →, study end (2013).

[a] Includes 1 061 997 women aged 15 to 34 years.

[b] Indicates basic school.

[c] Indicates postgraduate degree.

Compared with nonusers, users of combined oral contraceptives experienced an RR of a first use of antidepressants of 1.2 (95% CI, 1.22 to 1.25). Women using progestin-only pills had an RR of 1.3 (95% CI, 1.27-1.40); a transdermal patch (norgestrolmin), 2.0 (95% CI, 1.76-2.18); a vaginal ring (etonogestrel), 1.6 (95% CI, 1.55-1.69); an implant, 2.1 (95% CI, 2.01-2.24); a levonorgestrel intrauterine system, 1.4 (95% CI, 1.31-1.42); and medroxyprogesterone acetate depot, 2.7 (95% CI, 2.45-2.87). The RRs of a first diagnosis of depression were slightly lower or similar (**Table 2**).

Age-stratified analyses demonstrated decreasing RRs of a first use of antidepressants with increasing age for the most commonly used products (**Figure 1**). Analyses restricted to adolescents (aged 15-19 years) showed notably higher RRs of first use of antidepressants and first diagnosis of depression. Compared with nonusers, users of combined oral contraceptives experienced a 1.8-fold higher rate (95% CI, 1.75-1.84) of first use of antidepressants; users of progestin-only pills experienced a 2.2-fold higher rate (95% CI, 1.99-2.52). Nonoral products implied a 3-fold increased risk for first use of antidepressants. The RRs for a first diagnosis of depression at a psychiatric hospital were similar or slightly lower (**Table 3**).

Assessment of the association between the duration of use and the risk for first use of antidepressants demonstrated increasing relative risks with length of use. For use of hormonal contraceptives of less than 1 month, RRs were 1.1 (95% CI, 0.95-1.15) for first use of antidepressants and 1.2 (95% CI, 1.00-1.44) for first diagnosis of depression; for 1 to less than 2

Table 2. Rate Ratio of First Use of Antidepressants and First Diagnosis of Depression in All Women[a]

		First Use of Antidepressants			First Diagnosis of Depression		
Type of Hormonal Contraception	Person-years	No. of Events	RR[b]	RR (95% CI)[c]	No. of Events	RR[b]	RR (95% CI)[c]
Nonuse	3 041 595	50 346	1	1 [Reference]	9310	1	1 [Reference]
All oral combined	3 518 381	74 126	1.2[d]	1.2 (1.22-1.25)[d]	12 211	1.0[d]	1.1 (1.08-1.14)[d]
All progestin-only	74 540	1884	1.3[d]	1.3 (1.27-1.40)[d]	296	1.1	1.2 (1.04-1.31)[d]
Combined products							
Oral							
Ethinyl estradiol, 50 µg							
Norethisterone	8060	176	1.5[d]	1.5 (1.26-1.69)[d]	22	1.3	1.2 (0.77-1.79)
Levonorgestrel	14 197	424	1.7[d]	1.6 (1.47-1.78)[d]	63	1.5[d]	1.4 (1.09-1.78)[d]
Ethinyl estradiol, 30-40 µg							
Norethisterone	38 927	583	1.0	1.1 (0.98-1.15)	77	0.9	0.9 (0.70-1.11)
Levonorgestrel	280 445	5618	1.2[d]	1.3 (1.22-1.29)[d]	1017	1.0	1.1 (1.02-1.17)[d]
Norgestimate	339 501	7017	1.1[d]	1.2 (1.18-1.24)[d]	1114	1.0	1.1 (1.00-1.14)[d]
Desogestrel	170 544	3918	1.3[d]	1.3 (1.27-1.35)[d]	604	1.1[d]	1.2 (1.07-1.27)[d]
Gestodene	757 337	15 759	1.2[d]	1.2 (1.18-1.23)[d]	2430	1.0	1.1 (1.03-1.13)[d]
Drospirenone	327 930	7843	1.3[d]	1.4 (1.34-1.41)[d]	1395	1.2[d]	1.3 (1.23-1.38)[d]
Cyproterone acetate	159 931	3914	1.3[d]	1.5 (1.43-1.52)[d]	638	1.2[d]	1.3 (1.17-1.38)[d]
Ethinyl estradiol, 20 µg							
Desogestrel	659 847	13 276	1.1[d]	1.2 (1.14-1.19)[d]	2199	1.0	1.1 (1.00-1.10)[d]
Gestodene	693 013	13 854	1.1[d]	1.2 (1.15-1.19)[d]	2314	1.0	1.1 (1.00-1.10)
Drospirenone	64 894	1623	1.2[d]	1.4 (1.31-1.44)[d]	309	1.2[d]	1.3 (1.15-1.44)[d]
Natural estrogen							
Dienogest	3711	119	1.7[d]	1.8 (1.49-2.14)[d]	29	1.8[d]	1.9 (1.31-2.72)[d]
Nonoral							
Patch (norgestrolmin)	8081	333	2.1[d]	2.0 (1.76-2.18)[d]	60	1.9[d]	1.7 (1.34-2.23)[d]
Vaginal ring (etonogestrel)	69 605	2195	1.5[d]	1.6 (1.55-1.69)[d]	421	1.5[d]	1.6 (1.45-1.77)[d]
Progestin-only products							
Oral							
Norethisterone	33 182	771	1.2[d]	1.3 (1.18-1.37)[d]	110	1.0	1.1 (0.88-1.29)
Levonorgestrel	1289	31	1.5[d]	1.7 (1.18-2.38)[d]	4	1.3	1.5 (0.54-3.86)
Desogestrel	40 069	1082	1.3[d]	1.4 (1.30-1.46)[d]	182	1.2[d]	1.2 (1.06-1.42)[d]
Nonoral							
Levonorgestrel IUS	81 281	2373	1.4[d]	1.4 (1.31-1.42)[d]	397	1.4[d]	1.4 (1.22-1.50)[d]

Abbreviations: IUS, intrauterine system; RR, incidence rate ratio.

[a] Includes 1 061 997 women aged 15 to 34 years.

[b] Adjusted for age and calendar year.

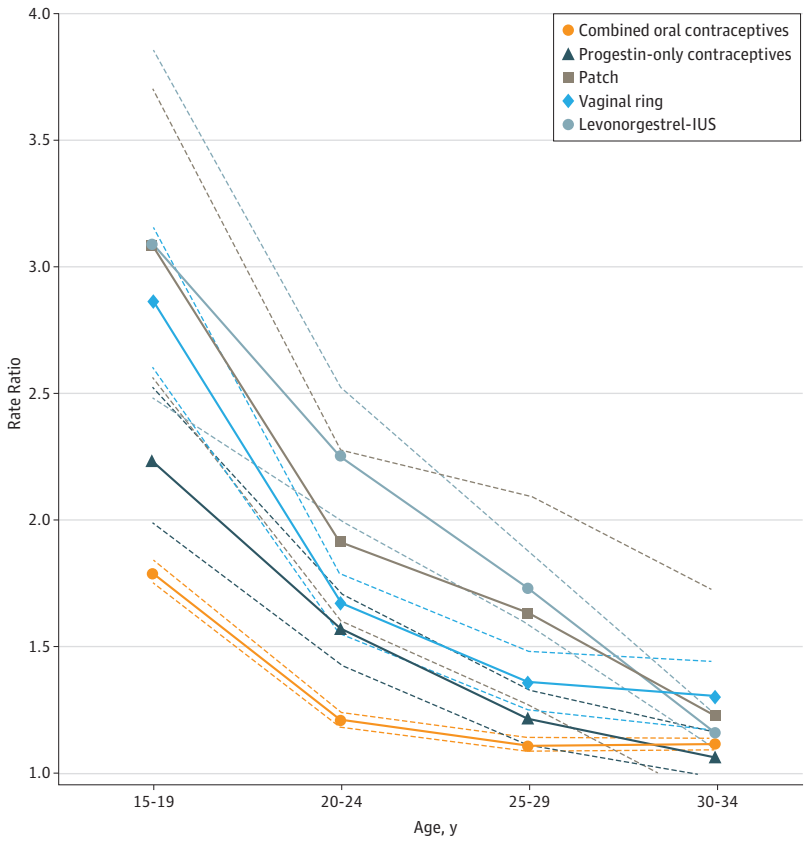
[c] Adjusted for age, calendar year, educational level, polycystic ovary syndrome, and endometrioses.

[d] Indicates statistical significance.

months, 1.1 (95% CI, 1.00-1.20) and 1.3 (95% CI, 1.07-1.54), respectively; and for 2 to less than 3 months, 1.4 (95% CI, 1.27-1.50) and 1.4 (95% CI, 1.14-1.62), respectively. Relative risks peaked after 6 months of use with an RR of 1.4 (95% CI, 1.34-1.46) for a first use of antidepressants and an RR of 1.5 (95% CI, 1.36-1.64) for a first diagnosis of depression. Thereafter relative risks decreased to RRs of 1.4 (95% CI, 1.32-1.41) and 1.4 (95% CI, 1.30-1.50), respectively, for use of 6 months to less than 1 year; 1.2 (95% CI, 1.21-1.26) and 1.2 (95% CI, 1.10-1.20), respectively, for use of 1 to less than 4 years; 1.1 (95% CI, 1.08-1.13) and 0.9 (95% CI, 0.87-0.97), respectively, for use of 4 to less than 7 years; and 1.0 (95% CI, 0.98-1.04) and 0.8 (95% CI, 0.77-0.88), respectively (unity), for use of 7 to less than 10 years (**Figure 2**).

When additionally adjusting for smoking and body mass index among parous women, the RR of first use of antidepressants did not change significantly for almost all products. An exception was the RR among women who used medroxyprogesterone acetate depot, which decreased from 2.4 (95% CI, 2.09-2.75) to 1.9 (95% CI, 1.65-2.16) with adjustment for confounders (eFigure 3 in the Supplement). When use of oral contraceptives that combined levonorgestrel and 30 to 40 µg of ethinyl estradiol constituted the reference group, a significantly higher rate of antidepressant use was found among women who used combined oral contraceptives with cyproterone acetate, natural estrogen with dienogest, and a patch or a vaginal ring (eTable 3 in the Supplement). When changing the reference group to those who never used hormonal contraceptives, all oral combined products conferred in all women an RR of 1.7 (95% CI, 1.66-1.71) for a first use of antidepressants and among adolescents an RR of 2.2 (95% CI, 2.18-2.31) (eTable 4 in the Supplement).

Figure 1. Rate Ratio of First Use of Antidepressants by Contraceptive Type



Includes all women in Denmark aged 15 to 34 years. Use of most types of hormonal contraceptives is compared with nonuse by participant age. IUS indicates intrauterine system.

Sensitivity Analyses on Starting Use of Hormonal Contraceptives

Compared with before use, the RR of antidepressant use 1 year after initiation of combined oral contraceptive use was 1.6 (95% CI, 1.58-1.69). Stratified by age groups, adolescents aged 15 to 19 years who started use of hormonal contraceptives had an RR of 1.8 (95% CI, 1.72-1.88). Women aged 20 to 30 years who started use of hormonal contraceptives had an RR of 1.4 (95% CI, 1.29-1.47) (eTable 5 in the Supplement).

Discussion

In this study, use of all types of hormonal contraceptives was positively associated with a subsequent use of antidepressants and a diagnosis of depression. That finding complies with the theory of progesterone involvement in the etiology of depression, because progestin dominates combined and progestin-only contraceptives. The high risk among women using the transdermal patch and vaginal ring compared with the corresponding pill is probably a question of dose rather than the route of administration.[34] Progestin-only products, including the levonorgestrel intrauterine system, also implied an increased risk for the use of antidepressants and a diagnosis of depression, supporting the finding that although the levonorgestrel intrauterine system primarily works locally, it also delivers levonorgestrel to the systemic circulation.[35] Adolescent women who used hormonal contraception experienced higher risks than women in general.

Strengths

Among the strengths of this study was the primarily nonselective inclusion of all adolescents and women aged 15 to 34 years living in Denmark and followed up for 14 years with no loss to follow-up and a study population of 1 million women. The information on the use of hormonal contraception and antidepressants was obtained through bar codes, eliminating recall bias. Women who used an antidepressant or had a diagnosis of depression before study entry were excluded. Next, women were temporarily censored during pregnancy and 6 months after delivery to reduce the influence of postpartum depression. Information on hormonal contraceptive use was updated daily and used as a time-varying covariate. Finally, we used alternative analysis strategies with 2 different outcomes and conducted a number of sensitivity analyses, all with consistent results.

Limitations

We do not expect general practitioners to be more likely to prescribe hormonal contraception to women at risk for depression because depression is mentioned in the leaflet as a possible adverse effect. Therefore, the opposite selection is more

Table 3. Rate Ratio of First Use of Antidepressants and First Diagnosis of Depression Among Adolescents[a]

	First Use of Antidepressants			First Diagnosis of Depression		
Type of Hormonal Contraception	Person-years	No. of Events	RR (95% CI)[b]	Person-years	No. of Events	RR (95% CI)[b]
Nonuse	1 094 654	10 257	1 [Reference]	1 106 800	2496	1 [Reference]
All oral combined	916 691	18 597	1.8 (1.75-1.84)[c]	943 325	3738	1.7 (1.63-1.81)
All progestin-only pills	10 277	287	2.2 (1.99-2.52)[c]	10 683	56	1.9 (1.49-2.53)[c]
Combined products						
Ethinyl estradiol, 50 µg						
Norethisterone	1120	22	2.6 (1.73-4.02)[c]	1137	2	1.2 (0.30-4.76)
Levonorgestrel	2042	56	2.4 (1.86-3.14)[c]	2126	10	2.2 (1.18-4.10)[c]
Oral						
Ethinyl estradiol, 30-40 µg						
Norethisterone	7735	78	1.4 (1.10-1.73)[c]	7830	17	1.5 (0.91-2.38)
Levonorgestrel	77 661	1507	1.7 (1.63-1.83)[c]	80 079	387	1.7 (1.51-1.91)[c]
Norgestimate	74 619	1559	1.9 (1.79-2.00)[c]	76 818	316	1.8 (1.61-2.05)[c]
Desogestrel	30 861	776	2.2 (2.02-2.34)[c]	32 017	143	2.0 (1.66-2.34)[c]
Gestodene	131 879	2842	1.9 (1.80-1.96)[c]	136 116	543	1.8 (1.60-1.94)[c]
Drospirenone	103 894	2174	1.9 (1.82-2.01)[c]	106 788	469	2.0 (1.85-2.27)[c]
Cyproterone acetate	38 339	834	2.0 (1.82-2.10)[c]	39 696	135	1.5 (1.27-1.80)[c]
Ethinyl estradiol, 20 µg						
Desogestrel	191 354	3720	1.7 (1.63-1.76)[c]	196 493	716	1.6 (1.46-1.74)[c]
Gestodene	228 840	4342	1.7 (1.63-1.76)[c]	234 863	859	1.6 (1.50-1.76)[c]
Drospirenone	27 244	659	1.8 (1.70-2.00)[c]	28 210	132	1.7 (1.44-2.06)[c]
Natural estrogen						
Dienogest	1093	27	2.0 (1.34-2.85)[c]	1142	9	2.6 (1.34-4.96)[c]
Nonoral						
Patch (norgestrolmin)	2526	115	3.1 (2.56-3.71)[c]	2705	23	2.8 (1.86-4.23)[c]
Vaginal ring (etonogestrel)	10 833	438	2.9 (2.60-3.16)[c]	11 513	85	2.7 (2.18-3.38)[c]
Progestin-only products						
Oral						
Norethisterone	3722	91	2.1 (1.67-2.52)[c]	3853	13	1.3 (0.76-2.27)
Desogestrel	6472	195	2.3 (2.03-2.69)[c]	6746	43	2.3 (1.68-3.08)[c]
Nonoral						
Levonorgestrel IUS	1627	80	3.1 (2.47-3.84)[c]	1832	20	3.2 (2.08-5.03)[c]

Abbreviations: IUS, intrauterine system; RR, incidence rate ratio.

[a] Includes participants aged 15 to 19 years.

[b] Adjusted for age, calendar year, educational level, polycystic ovary syndrome, and endometriosis.

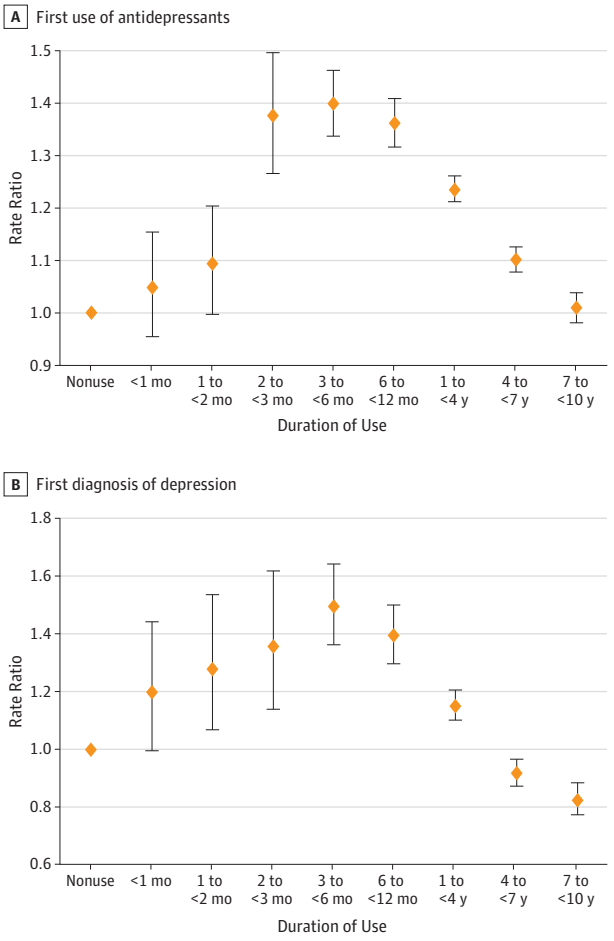
[c] Indicates statistical significance.

likely, implying a potential underestimation of the relative risks. We expect that institutionalized women and women with mental retardation or more severe psychiatric illness could be more likely to receive long-acting reversible contraceptive products such as medroxyprogesterone acetate depot or implants. Although we do not have a reference to support this concern, we decided to exclude these 2 specific products in the results tables because they might be influenced by confounding by indication. For the remaining products, these specific women account for a vanishing small fraction of all women using hormonal contraception. Thus, 80% of the female population in Denmark has used hormonal contraception some time during their reproductive life, which explains why women using hormonal contraceptives represent the general population of women in Denmark and not a selected subpopulation.

If prescribing physicians are more observant of the onset of depressive symptoms among patients to whom they have prescribed hormonal contraceptives, this could imply detection bias. Nevertheless, such bias likely cannot explain the increased risk for a first depression diagnosis at a psychiatric hospital because these diagnoses reflect the more severe depressive disorders that will be evident regardless of clinical attention. Moreover, if such a detection bias explains the increased risk, we would expect the risk estimates to be the same for all types of oral contraceptivs, which was not the case. Further, if such a detection bias was present in our data, we would expect higher risk estimates for redeemed prescriptions of antidepressants immediately after initiation of hormonal contraceptive use. However, the analyses of the duration of hormonal contraceptive use showed no significant increase in risk estimates until more than 2 months after initiation of hormonal contraceptive use.

A potential confounding factor might be the initiation of a sexual relationship because we speculate that this might

Figure 2. Rate Ratios of First Use of Antidepressants and First Diagnosis of Depression



Rate ratios are stratified by length of hormonal contraceptive use. Participants with any use of hormonal contraception were excluded at first pregnancy. Error bars indicate 95% CIs.

influence the risk for a first use of antidepressants and the diagnosis of depression. We therefore assessed the influence of sexual activity by restricting analyses to women who mostly (≥80%) have had their first intercourse (ages 20-30 years).[36] Results remained stable. Moreover, 80% of girls aged 11 to 15 years in Denmark used a condom at their first intercourse,[37] indicating that sexual relationships for many are likely to start before initiation of hormonal contraceptive use. Thus, many adolescents not using hormonal contraceptives are likely also to be sexually active. Therefore, sexual activity does not seem to be an important confounder for the association between the use of hormonal contraceptives and depression.

In a sensitivity analysis we aimed to eliminate the effect of all fixed confounders over time and attrition of susceptibility. Risk for antidepressant use 1 year after initiation of hormonal contraceptive use (disregarding discontinuation) was compared with the risk among the same women in the time before initiation of hormonal contraceptive use with adjustment for age and calendar year. This analysis found that the increased risk for first use of antidepressants was comparable with that found in the main analyses.

Our data indicate that adolescent girls are more sensitive than older women to the influence of hormonal contraceptive use on the risk for first use of antidepressants or first diagnosis of depression. This finding could be influenced by attrition of susceptibility, but also that adolescent girls are more vulnerable to risk factors for depression.[38]

We must consider that not all depressed individuals are treated with antidepressants or seen at psychiatric clinics or hospitals.[39] Moreover, antidepressants are prescribed for treatment of conditions other than depression, although depression is the main indication (approximately 80%) for the prescription of selective serotonin reuptake inhibitors.[40,41]

We identified 12 studies[23-28,42-47] with emerging conflicting results regarding use of hormonal contraceptives and the risk for depression (eTable 5 in the Supplement). These studies are reviewed in the eDiscussion in the Supplement.

Conclusions

Use of hormonal contraceptives was associated with subsequent antidepressant use and first diagnosis of depression at a psychiatric hospital among women living in Denmark. Adolescents seemed more vulnerable to this risk than women 20 to 34 years old. Further studies are warranted to examine depression as a potential adverse effect of hormonal contraceptive use.

ARTICLE INFORMATION

Accepted for Publication: August 5, 2016.

Published Online: September 28, 2016. doi:10.1001/jamapsychiatry.2016.2387

Author Contributions: Ms Skovlund and Dr Mørch had full access to all data in the study and take responsibility for the integrity of data and the accuracy of the data analyses.
Concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Skovlund, Mørch, Lidegaard.
Critical revision of the manuscript for important intellectual content: Mørch, Kessing, Lidegaard.
Statistical analysis: Skovlund, Mørch.
Obtained funding: Mørch, Lidegaard.
Administrative, technical, or material support: Lidegaard.
Study supervision: Mørch, Kessing, Lidegaard.

Conflict of Interest Disclosures: Dr Kessing reported consulting for Lundbeck and AstraZeneca and receiving honoraria for this work. Dr Lidegaard reported receiving honoraria for talks on pharmacoepidemiological issues within the past 3 years from Exeltis. No other disclosures were reported.

Funding/Support: This study was supported by the Department of Gynaecology, Rigshospitalet, University of Copenhagen, and by grant R191-2015-1356 from the Lundbeck Foundation.

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: Lars Hougaard Nielsen, PhD, consultant, provided analytical program sharing for statistical analysis. He received no financial compensation.

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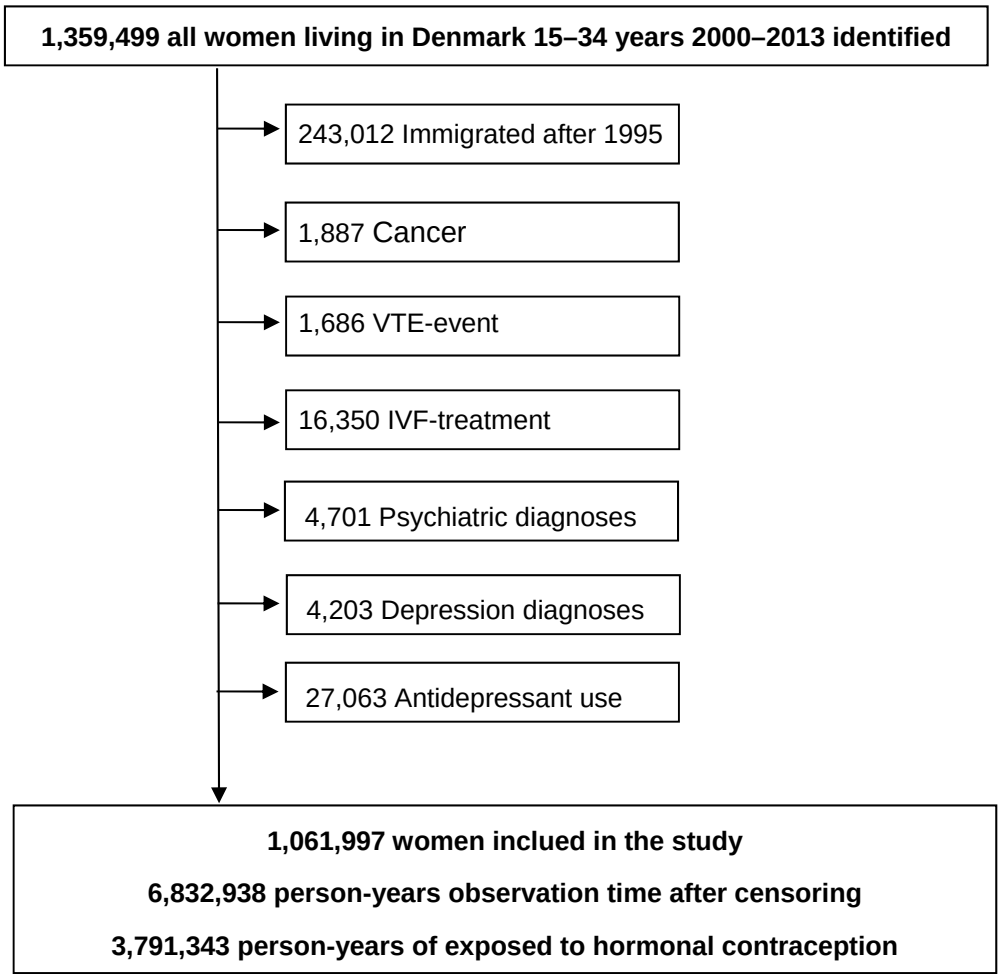
Supplementary Online Content

Skovlund CW, Mørch LS, Kessing LV, Lidegaard Ø. Association of hormonal contraception with depression. *JAMA Psychiatry*. Published online September 28, 2016. doi:10.1001/jamapsychiatry.2016.2387

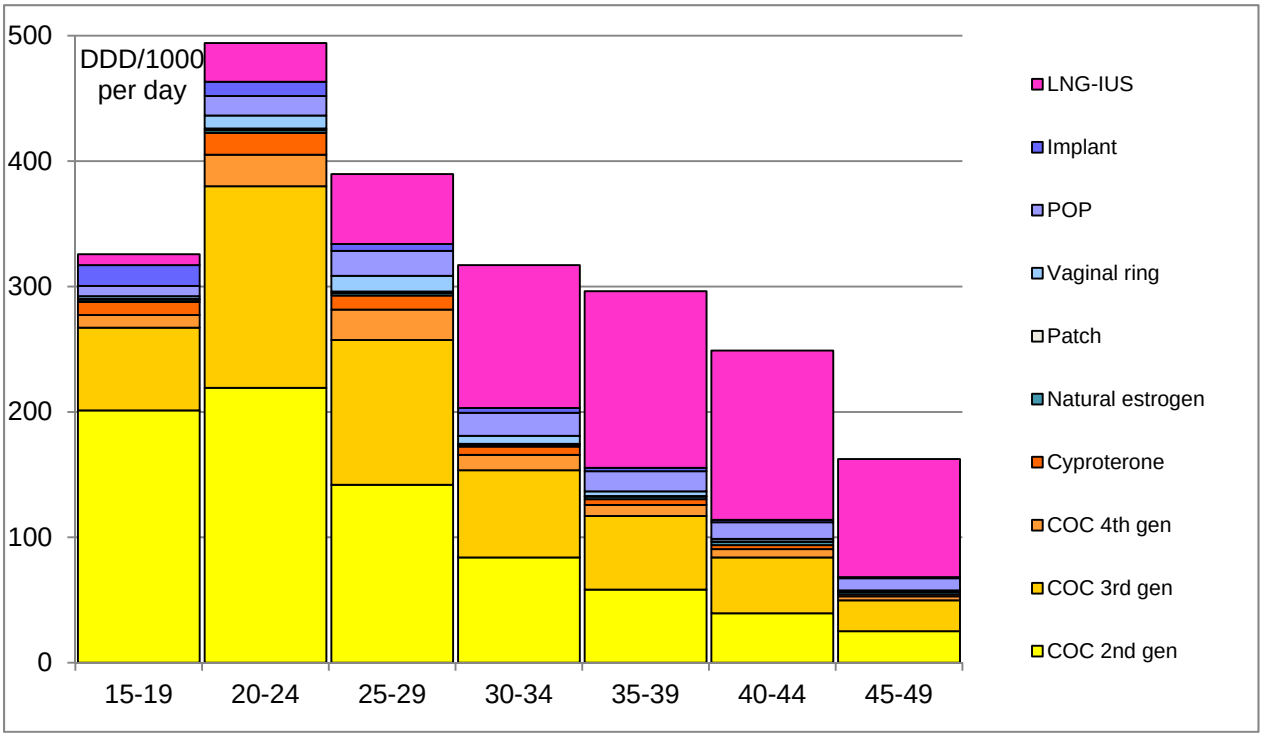
This supplementary material has been provided by the authors to give readers additional information about their work.

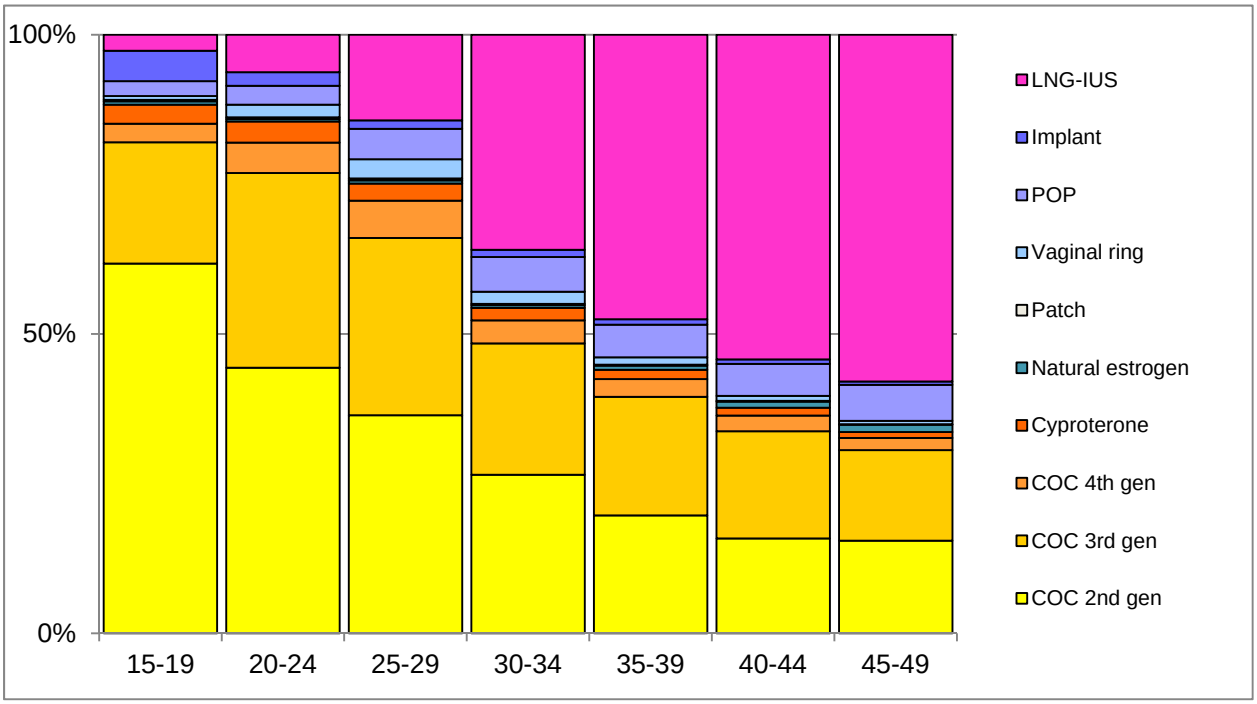
eFigure 1. Women and Person-years Fulfilling Various Inclusion and Exclusion Criteria



eFigure 2. Use of Different Types of Hormonal Contraceptives According to Age in Denmark 2013

Upper: Defined daily doses per 1000 per day, lower: Per cent distribution among users.

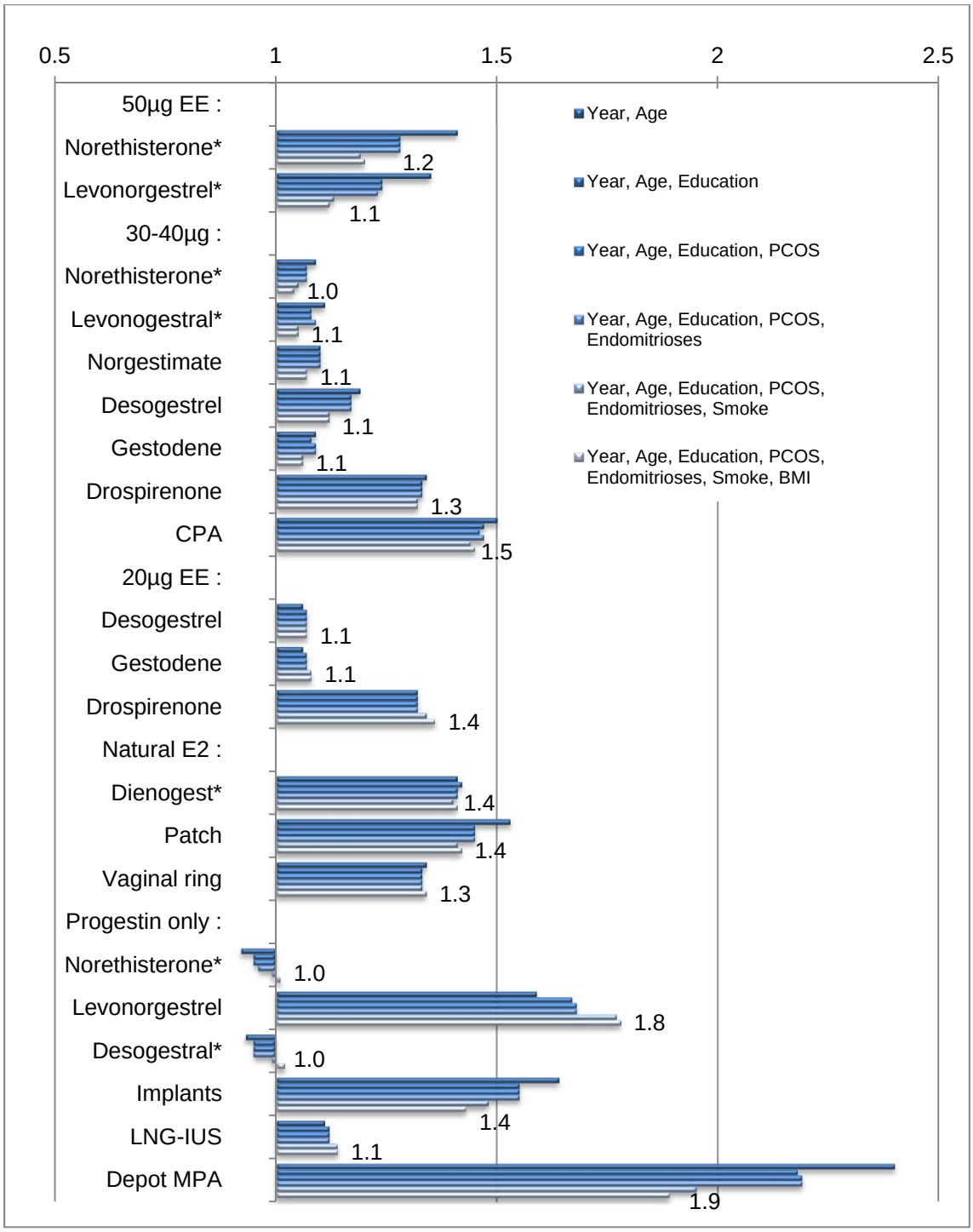




COC 2nd gen: COC with levonorgestrel or norgestimate, COC 3rd gen: COC with desogestrel or gestodene, COC 4th gen: COC with drospirenone, LNG-IUS = levonorgestrel intrauterine system

eFigure 3. Use of Antidepressants in Users of Different Types of Hormonal Contraceptives Among Parous Women 15-34 Years Old

According to adjustment for different confounders reference group nonusers of hormonal contraception.



*EE = ethinylestradiol, CPA = cyproterone acetate, LNG-IUS = levonorgestrel intrauterine system, MPA = medroxyprogesterone acetate *Not significantly different*

eTable 1. Included Groups of Hormonal Contraceptives and Corresponding Anatomic Therapeutic Chemical (ATC) Codes

Hormonal contraception group[§]	**ATC codes**
Combined products	
Oral	
50 µg EE	
Norethisterone	*G03AA03, G03AA05*
Levonorgestrel	*G03AA07,*
30-40 µg EE	
Norethisterone	*G03AA01, G03AA05, G03AB04*
Levonorgestrel	*G03AA07, G03AB03*
Norgestimate	*G03AA11*
Desogestrel	*G03AA09, G03AB05*
Gestodene	*G03AA10, G03AB06*
Drospirenone	*G03AA12*
CPA	*G03HB01*
20 µg EE	
Desogestrel	*G03AA09, G03AB05*
Gestodene	*G03AA10*
Drospirenone	*G03AA12*
Natural estrogen	
Dienogest	*G03AB*
NOMAC	*G03AA14*
Non-oral	
Patch	*G03AA13*
Vaginal ring	*G02BB01*
Progestin-only products	
Oral	
Norethisterone	*G03AC01, G03AC02,*
Levonorgestrel	*G03AC03,*
Desogestrel	*G03AC09*
Non-oral	
Implant	*G03AC08*
LNG-IUS	*G02BA03*
MPA depot	*G03DA02*

[§]) EE = ethinylestradiol, CPA = cyproterone acetate, LNG-IUS = levonorgestrel intrauterine system NOMAC = nomegestrol acetate, MPA = medroxyprogesterone acetate

eTable 2. Anatomic Therapeutic Chemical (ATC) Codes of the Included Antidepressants

ATC	Antidepressant	Group	ATC	Antidepressant	Group
N06AA	Non–selective monoamine reuptake inhibitors		N06AF	Monoamine oxidase inhibitors, non–selective	
N06AA01	Desipramine	Old	N06AF01	Isocarboxazid	Old
N06AA02	Imipramine	Old	N06AF02	Nialamide	Old
N06AA03	Imipramine oxide	Old	N06AF03	Phenelzine	Old
N06AA04	Clomipramine	Old	N06AF04	Tranylcypromine	Old
N06AA05	Opipramol	Old	N06AF05	Iproniazide	Old
N06AA06	Trimipramine	Old	N06AF06	Iproclozide	Old
N06AA07	Lofepramine	Old	N06AG	Monoamine oxidase A inhibitors	
N06AA08	Dibenzepin	Old	N06AG02	Moclobemide	Old
N06AA09	Amitriptyline	Old	N06AG03	Toloxatone	Old
N06AA10	Nortriptyline	Old	N06AX	Other antidepressants	
N06AA11	Protriptyline	Old	N06AX01	Oxitriptan	Old
N06AA12	Doxepin	Old	N06AX02	Tryptophan	Old
N06AA13	Iprindole	Old	N06AX03	Mianserin	Old
N06AA14	Melitracen	Old	N06AX04	Nomifensine	Old
N06AA15	Butriptyline	Old	N06AX05	Trazodone	Old
N06AA16	Dosulepin	Old	N06AX06	Nefazodone	New non–SSRI
N06AA17	Amoxapine	Old	N06AX07	Minaprine	Old
N06AA18	Dimetacrine	Old	N06AX08	Bifemelane	Old
N06AA19	Amineptine	Old	N06AX09	Viloxazine	Old
N06AA21	Maprotiline	Old	N06AX10	Oxaflozane	Old
N06AA23	Quinupramine	Old	N06AX11	Mirtazapine	New non–SSRI
N06AB	Selective serotonin reuptake inhibitors		*N06AX12*	*Bupropion**	Not included
			N06AX13	Medifoxamine	Old
N06AB02	Zimelidine	SSRI	N06AX14	Tianeptine	Old
N06AB03	Fluoxetine	SSRI	N06AX15	Pivagabine	Old
N06AB04	Citalopram	SSRI	N06AX16	Venlafaxine	New non–SSRI
N06AB05	Paroxetine	SSRI	N06AX17	Milnacipran	Old
N06AB06	Sertraline	SSRI	N06AX18	Reboxetine	New non–SSRI
N06AB07	Alaproclate	SSRI	N06AX19	Gepirone	Old
N06AB08	Fluvoxamine	SSRI	N06AX21	Duloxetine	New non–SSRI
N06AB09	Etoperidone	SSRI	N06AX22	Agomelatine	New non–SSRI
N06AB10	Escitalopram	SSRI	N06AX23	Desvenlafaxine	New non–SSRI

*Not included is prescribed only for smoking cessation in Denmark

Old: Mainly tricyclic antidepressants, SSRI: Selective serotonin re–uptake inhibitors

eTable 3. Relative Risk of First Use of Antidepressants in Users of Different Types of Hormonal Contraceptives Compared With Users of Combined Oral Contraceptives With Levonorgestrel

Type of		**First use of antidepressants (AD)**			
Hormonal	**Person**	**Events**		**95% CL**	
contraception[§]	**Years**	**AD**	**RR**	**Low**	**High**
Non-use	3,041,595	50,346	0.8	0.77	0.82
Combined products					
Oral					
50 µg EE					
Norethisterone	8,060	176	1.2	1.00	1.35
Levonorgestrel	14,197	424	**1.3**	1.17	1.42
30-40 µg EE					
Norethisterone	38,927	583	0.8	0.77	0.92
Levonorgestrel	280,445	5,618	1	Reference	
Norgestimate	339,501	7,017	1.0	0.93	0.99
Desogestrel	170,544	3,918	1.0	1.00	1.09
Gestodene	757,337	15,759	**1.0**	0.93	0.99
Drospirenone	327,930	7,843	**1.1**	1.06	1.13
CPA	159,931	3,914	**1.2**	1.12	1.22
20 µg EE					
Desogestrel	659,847	13,276	**0.9**	0.90	0.96
Gestodene	693,013	13,854	**0.9**	0.90	0.96
Drospirenone	64,894	1,623	**1.1**	1.03	1.15
Natural estrogen					
Dienogest	3,711	119	**1.4**	1.18	1.70
Non-oral					
Patch (norgestrolmin)	8,081	333	**1.6**	1.39	1.74
Vaginal ring (etonogestrel)	69,605	2,195	**1.3**	1.22	1.35
Progestin-only products					
Oral					
Norethisterone	33,182	771	1.0	0.94	1.09
Levonorgestrel	1,289	31	1.3	0.93	1.89
Desogestrel	40,069	1,082	**1.1**	1.02	1.17
Non-oral					
LNG-IUS	81,281	2,373	**1.1**	1.03	1.14

Levonorgestrel products are combined with 30-40 µg EE. Population includes women 15–34 years, significant results in bold.

**) Relative risk adjusted for age, calendar year, education, PCOS and endometrioses*

[§]) EE = ethinylestradiol, CPA = cyproterone acetate, LNG-IUS = levonorgestrel intrauterine system, MPA = medroxyprogesterone acetate

eTable 4. Relative Risk of First Use of Antidepressants Compared With Never-Users of Hormonal Contraceptives

Type of	**15-19**			**15-34**		
hormonal	**Person**	**Events**	**Rate ratio***	**Person**	**Events**	**Rate ratio***
contraception§	**years**	**AD**	**[95% CL]**	**Years**	**AD**	**[95% CL]**
Never user	1,019,956	7,781	Reference	2,051,290	24,308	Reference
Former	74,699	2,476	**3.1** [2.92-3.21]	990,305	26,038	**1.9** [1.90-1.97]
All oral combined	916,691	18,597	**2.2** [2.18-2.31]	3,518,381	74,126	**1.7** [1.66-1.71]
All progestin only pills	10,277	287	**2.8** [2.49-3.15]	74,540	1,884	**1.8** [1.74-1.91]
Combined products						
50 µg EE						
Norethisterone	1,120	22	**3.3** [2.16-5.01]	8,060	176	**2.0** [1.72-2.32]
Levonorgestrel	2,042	56	**3.0** [2.34-3.96]	14,197	424	**2.2** [2.04-2.47]
Oral						
30-40 ug EE						
Norethisterone	7,735	78	**1.7** [1.37-2.15]	38,927	583	**1.4** [1.33-1.57]
Levonorgestrel	77,661	1,507	**2.2** [2.03-2.29]	280,445	5618	**1.7** [1.67-1.77]
Norgestimate	74,619	1,559	**2.4** [2.24-2.50]	339,501	7017	**1.7** [1.61-1.70]
Desogestrel	30,861	776	**2.7** [2.53-2.93]	170,544	3918	**1.8** [1.74-1.87]
Gestodene	131,879	2,842	**2.4** [2.25-2.46]	757,337	15759	**1.7** [1.62-1.69]
Drospirenone	103,894	2,174	**2.4** [2.27-2.50]	327,930	7843	**1.9** [1.83-1.93]
CPA	38,339	834	**2.4** [2.27-2.63]	159,931	3914	**2.0** [1.96-2.10]
20 ug EE						
Desogestrel	191,354	3,720	**2.1** [2.03-2.20]	659,847	13,276	**1.6** [1.55-1.62]
Gestodene	228,840	4,342	**2.1** [2.03-2.20]	693,013	13,854	**1.6** [1.55-1.62]
Drospirenone	27,244	659	**2.3** [2.12-2.49]	64,894	1,623	**1.9** [1.76-1.95]
Natural estrogen						
Dienogest	1093	27	**2.4** [1.67-3.57]	3,711	119	**2.4** [2.04-2.92]
Non-oral						
Patch (norgestrolmin)	2526	115	**3.9** [3.22-4.65]	8,081	333	**2.6** [2.38-2.95]
Vaginal ring (etonogestrel)	10,833	438	**3.6** [3.30-4.01]	69,605	2,195	**2.2** [2.14-2.34]
Progestin-only products						
Oral						
Norethisterone	3,722	91	**2.6** [2.09-3.15]	33,182	771	**1.7** [1.62-1.87]
Levonorgestrel	*82*	*1*	*1.8 [0.26-13.1]*	1,289	31	**2.3** [1.62-3.27]
Desogestrel	6,472	195	**2.9** [2.54-3.37]	40,069	1,082	**1.9** [1.77-2.00]
Non-oral						
LNG-IUS	1,627	80	**4.0** [3.17-4.93]	81,281	2,373	**1.9** [1.80-1.96]

Significant results in bold.
*) Adjusted For Age, Calendar Year, Education, PCOS And Endometrioses
§) EE = Ethinylestradiol, CPA = Cyproterone Acetate, LNG-IUS = Levonorgestrel Intrauterine System, MPA = Medroxyprogesterone Acetate

eTable 5. Relative Risk of First Use of Antidepressants in Starters of Different Types of Hormonal Contraceptives: Adolescents 15-19 Years of Age and Women 20-30 Years of Age

Type of	**15-19**			**20-30**		
hormonal	**Person**	**Events**	**Rate ratio***	**Person**	**Events**	**Rate ratio***
contraception§	**years**	**DD**	**[95% CL]**	**Years**	**AD**	**[95% CL]**
Before use	633,881	4,685	Reference	158,670	2,597	Reference
All oral combined	295,063	4,316	**1.8** [1.72-1.88]	66,473	1,420	**1.4** [1.29-1.47]
All progestin only pills	3,997	70	**1.9** [1.52-2.45]	1,909	48	**1.3** [0.98-1.75]
Combined products						
Oral						
30-40 ug EE						
Norethisterone	3,313	21	1.2 [0.75-1.79]	1,067	15	1.0 [0.62-1.72]
Levonorgestrel	26,509	344	**1.5** [1.31-1.70]	4,953	99	**1.3** [1.01-1.59]
Norgestimate	21,974	294	**1.7** [1.50-1.90]	5,281	101	**1.2** [1.01-1.51]
Desogestrel	6,916	143	**2.6** [2.23-3.11]	1,766	56	**2.0** [1.50-2.54]
Gestodene	34,781	514	**1.8** [1.65-1.98]	8,205	184	1.4 [1.22-1.64]
Drospirenone	37,356	527	**1.8** [1.64-1.97]	8,861	203	**1.4** [1.23-1.64]
CPA	11,342	183	**1.9** [1.65-2.23]	3,994	108	**1.8** [1.45-2.13]
20 ug EE						
Desogestrel	65,205	962	**1.8** [1.68-1.93]	14,103	289	**1.3** [1.18-1.51]
Gestodene	77,629	1,146	**1.8** [1.70-1.93]	16,495	333	**1.3** [1.19-1.50]
Drospirenone	9,212	174	**1.9** [1.63-2.21]	1,413	25	1.0 [0.66-1.47]
Non-oral						
Patch (norgestrolmin)	694	20	**2.9** [1.85-4.45]	225	11	**2.3** [1.26-4.12]
Vaginal ring (etonogestrel)	1,759	41	**2.3** [1.70-3.16]	1,113	28	1.4 [0.98-2.06]
Progestin-only products						
Oral						
Norethisterone	1,494	26	**2.0** [1.35-2.92]	889	18	1.1 [0.68-1.71]
Desogestrel	2,436	44	**1.9** [1.40-2.54]	962	28	**1.5** [1.00-2.11]
Non-oral						
LNG-IUS	*196*	*3*	*1.3 [0.43-4.13]*	590	22	**1.6** [1.06-2.47]

Significant results in bold.
*) adjusted for age, calendar year, education, PCOS and endometriosis
§) EE = ethinylestradiol, CPA = cyproterone acetate, LNG-IUS = levonorgestrel intrauterine system, MPA = medroxyprogesterone acetate

eTable 6. Overview of Articles on Hormonal Contraception and Depression

Author Year	Study design	Exposure	Reference	Population	Age	Sample N	Outcome	Results Risk of depression
Graham[1] 1995 Scotland	Ran	CHC,POC	Placebo	Sterilised Women	32	150	Beck Depression Inventory	Increased risk in Edinburgh women on CHC. No difference for Manila women
O'Connell[2] 2007 USA	Ran	CHC	Placebo	Women with Dysmenorrhea	17	76	Depression scale	No difference
Duke[3] 2007 Australia	CS	OC	Current user	Selection of women	22-30	9,081	10-item depression Scale	No difference
Akm[4] 2010 Turkey	CS	COC	Non-user	Married women	15-49	210	Beck Depression Inventory	No difference
Kulkarni[5] 2007 Australia	CS	CHC	Non-user	Selection of healthy women	18-50	58	Hamilton Rating Scale for Depression	Increased
Wiréhn[6] 2010 Sweden	CS	CHC,POC	Non-user	All women	16-31	917,993	Use of Antidepressants	Increased risk in women on POC
Toffel[7] 2011 Finland	CS	HC	Non-user	Selection of Women	18-54	3,223	Beck Depression Inventory	No or decreased risk
Lindberg[8] 2012 Sweden	CS	HC groups	Non-user	All women	16-31	917,993	Use of antidepressants	Increased risk in women on non-oral HC or POC
Svendal[9] 2012 Australia	CS	CHC,POC	Non-user	Selection of Women	20-50	498	Clinical interview	Increased risk with POC, Decreased risk with CHC
Toffel[10] 2012 Finland	CS	HC	Non-user	Selection of Women	25-54	8,586	Beck Depression Inventory	No or decreased risk
Keyes[11] 2013 USA	Long			Sexually active Women	25-34	6,654	Depression scale	Decreased risk
Cheslack-Postava[12] 2015 USA	CS	OC	Non-user	Sample of women with known diagnoses	20-39	1,105	Diagnosed depression	No Difference
Skovlund Current study Denmark	Cohort	CHC POC	Before use/ Non-user	All Danish non-pregnant women	15-34	1,061,997	Use of AD/ Depression diagnoses	Increased risk in POC and CHC

CHC=Combined hormonal contraception, COC=Combined oral contraceptives,
POC=Progestin-only contraception, OC=Oral contraceptives, HC=Hormonal contraception,
CS= cross-sectional study, Ran=randomised study, Long=longitudinal study

eDiscussion. Comparison With Prior Studies

We identified 12 original controlled studies[1-12] specifically assessing the association between use of hormonal contraception and depression or depression indicators (eTable 5). Two studies were randomized studies, one finding no association, the other a positive association. The remaining nine of ten studies were cross-sectional studies. Because mood changes are a known reason for cessation of use of hormonal contraception, cross-sectional studies are vulnerable to healthy-user bias causing underestimation of a possible association. Of the nine studies, six were large-scale studies pointing in opposite directions and two found no association. We found no prior study assessing the impact of different types of hormonal contraception on the risk of subsequent treated depression in a prospective cohort design taking into account the temporality between use of hormonal contraception and development of a depression.

One cohort study followed adolescence women from 1994-95 and included those 6,654 women that fulfilled a fourth interview in 2007-2008, were sexually active and non-pregnant at that time.[11] The odds ratio of having a high depression score in users of hormonal contraception was 0.81 (0.58-1.14) when compared with users of less effective methods including those not using any contraception at that time. Thus, the users of hormonal contraception in this study were selected since only those women still using hormonal contraception after more than ten-year follow-up were assessed. During that time, those experiencing mood chances and ceased using hormonal contraception for that reason were selected out of the study, leaving a healthy still-user group. At the same time the depression vulnerable former-users have a high chance of being included in the comparison group of users of less effective methods, increasing the risk of depression in this reference group. Both of these selections will underestimate the relative risk of depression with hormonal contraceptive use.

It is likely, that also our main analysis was influenced by healthy user bias, as we assessed risk of treated depression among *prevalent* users of hormonal contraception which has lost the most depression sensitive women to the reference group of non-users. That is illustrated by the 38% higher risk estimates using never-users as reference, and the high risk among former users. Thus our risk estimates of antidepressant use and

depression diagnosis among prevalent users of hormonal contraception should be considered as minimum estimates.

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