

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

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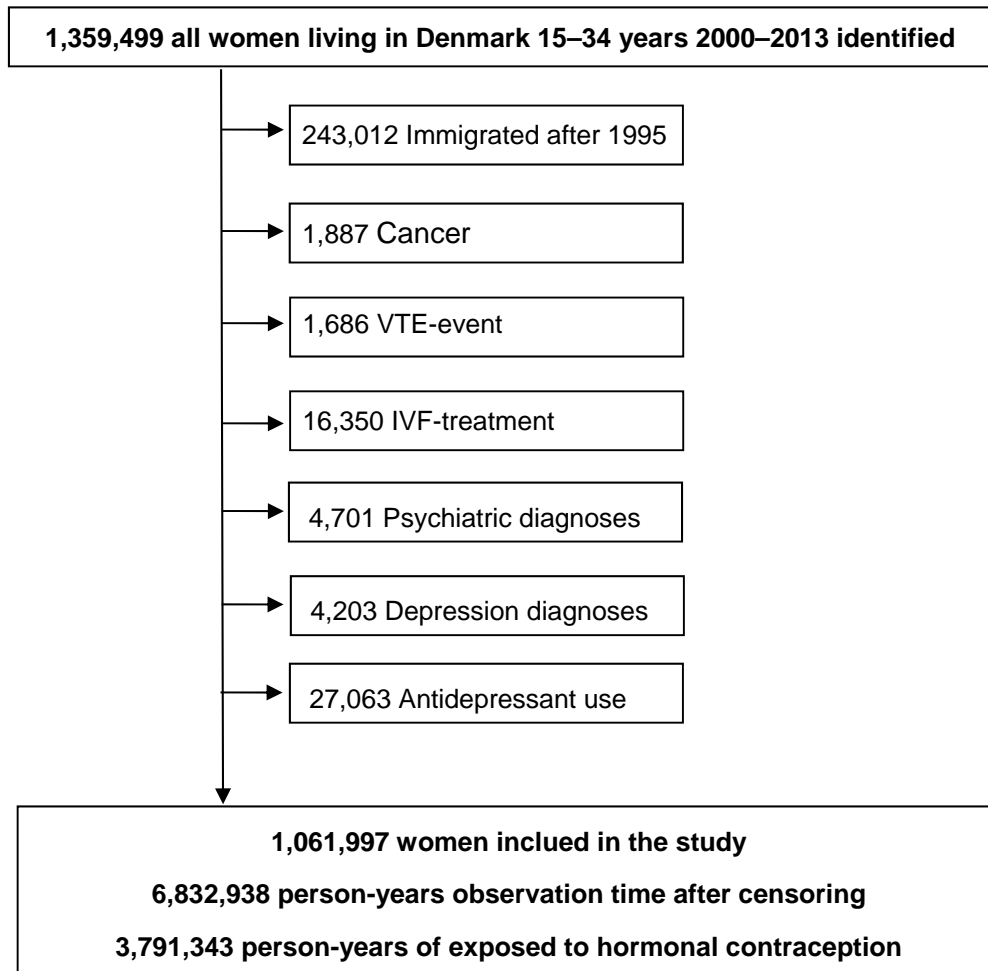
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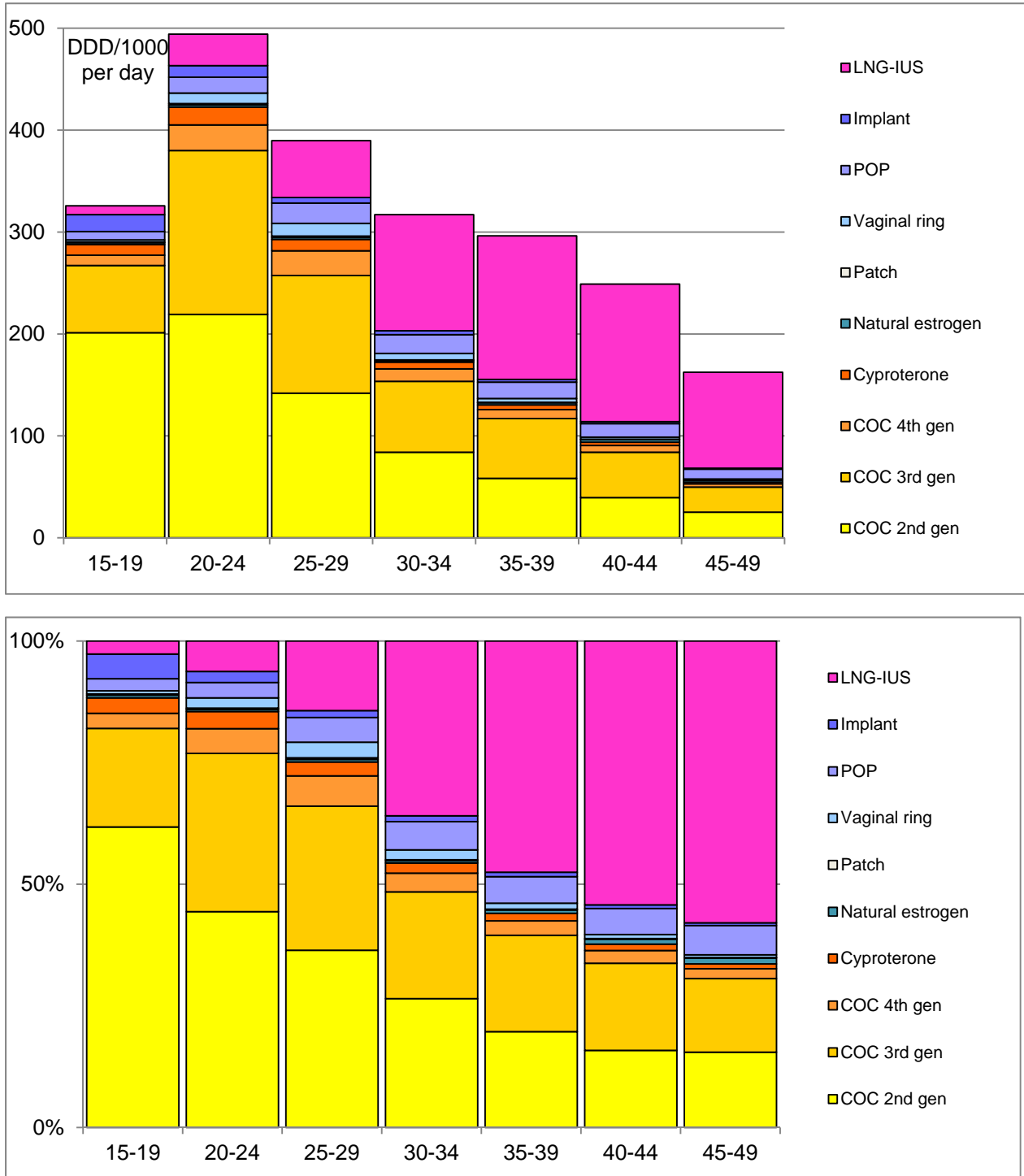
This supplementary material has been provided by the authors to give readers additional information about their work.

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

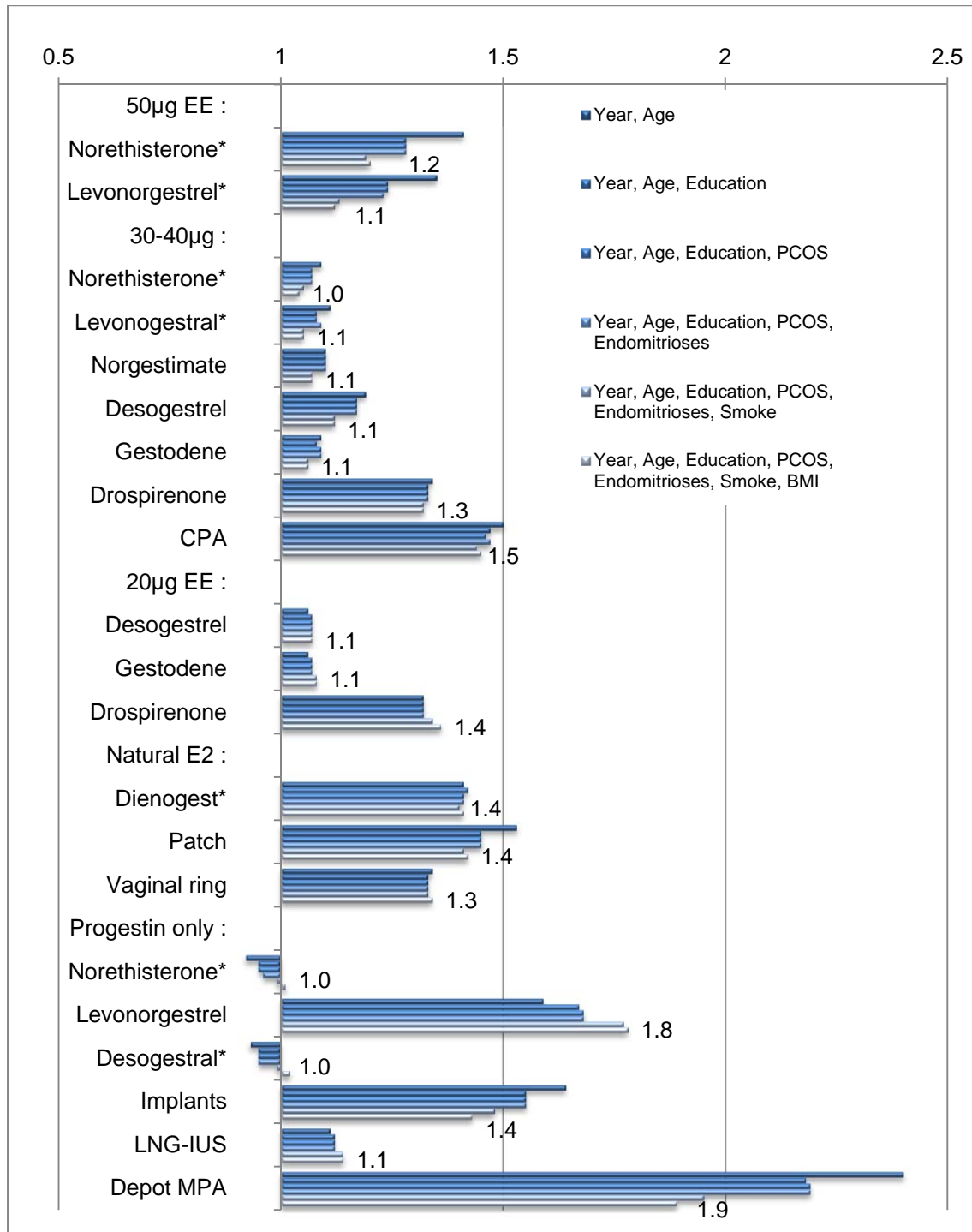
Upper: Defined daily doses per 1000 per day, lower: Per cent distribution among users.



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	<i>G03AA03, G03AA05</i>
Levonorgestrel	<i>G03AA07,</i>
30-40 µg EE	
Norethisterone	<i>G03AA01, G03AA05, G03AB04</i>
Levonorgestrel	<i>G03AA07, G03AB03</i>
Norgestimate	<i>G03AA11</i>
Desogestrel	<i>G03AA09, G03AB05</i>
Gestodene	<i>G03AA10, G03AB06</i>
Drospirenone	<i>G03AA12</i>
CPA	<i>G03HB01</i>
20 µg EE	
Desogestrel	<i>G03AA09, G03AB05</i>
Gestodene	<i>G03AA10</i>
Drospirenone	<i>G03AA12</i>
Natural estrogen	
Dienogest	<i>G03AB</i>
NOMAC	<i>G03AA14</i>
Non-oral	
Patch	<i>G03AA13</i>
Vaginal ring	<i>G02BB01</i>
Progestin-only products	
Oral	
Norethisterone	<i>G03AC01, G03AC02,</i>
Levonorgestrel	<i>G03AC03,</i>
Desogestrel	<i>G03AC09</i>
Non-oral	
Implant	<i>G03AC08</i>
LNG-IUS	<i>G02BA03</i>
MPA depot	<i>G03DA02</i>

[§]) 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
N06AA02	Imipramine	Old	N06AF02	Nialamide	Old
N06AA03	Imipramine oxide	Old	N06AF03	Phenelzine	Old
N06AA04	Clomipramine	Old	N06AF04	Tranlycypromine	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	Oxatriptan	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	<i>Bupropion</i> *	Not included
	N06AB02	Zimelidine	SSRI	N06AX13	Medifoxamine
N06AB03	Fluoxetine	SSRI	N06AX14	Tianeptine	Old
N06AB04	Citalopram	SSRI	N06AX15	Pivagabine	Old
N06AB05	Paroxetine	SSRI	N06AX16	Venlafaxine	New non-SSRI
N06AB06	Sertraline	SSRI	N06AX17	Milnacipran	Old
N06AB07	Alaproclate	SSRI	N06AX18	Reboxetine	New non-SSRI
N06AB08	Fluvoxamine	SSRI	N06AX19	Gepirone	Old
N06AB09	Etoperidone	SSRI	N06AX21	Duloxetine	New non-SSRI
N06AB10	Escitalopram	SSRI	N06AX22	Agomelatine	New non-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 Hormonal contraception [§]	Person Years	First use of antidepressants (AD)			
		Events AD	RR	95% CL 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		
	Person	Events	Rate ratio*	Person	Events	Rate ratio*
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 hormonal contraception§	15-19			20-30		
	Person years	Events DD	Rate ratio* [95% CL]	Person Years	Events AD	Rate ratio* [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 studies¹⁻¹² 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 changes 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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