Health benefits of combined hormonal contraception

Philip Hannaford

Professor of Primary Care

University of Aberdeen

Disclosure of conflict of interest

I do not have any conflicts of interest to declare

Combined hormonal contraception is popular

Estimated global use

Daily:

- c150 million women
- perhaps 8-9% of all women of reproductive age

Ever:

- 400+ million in high income countries alone

# Combined hormonal contraception is effective: % users experiencing an unplanned pregnancy in the first year

Method	Perfect use	Typical use
No method	85	85
Spermicides	18	28
Fertility awareness methods	0.4 – 5	24
Withdrawal	4	22
Condom (male / female)	2 / 5	18 / 21
Combined hormonal pills, patch, vaginal ring	**0.3**	**9**
Progestogen-only pills	0.3	9
Depo-provera	0.2	6
Copper intrauterine device	0.6	0.8
Levonorgestrel-containing intrauterine device	0.2	0.2
Progestogen-only implants	0.05	0.05
Sterilisation (male / female)	0.1 / 0.5	0.15 / 0.5

WHO Medical eligibility criteria for contraceptive use, 5th edition

Prevention of pregnancy

- Removes the opportunity for pregnancy-related deaths and morbidity
  - especially important in relation to higher-risk pregnancies:
    - < 18 years
    - > 34 years
    - parity > 3
    - closely spaced < 18-23 months
- Removes the need for an unsafe abortion

Contraception saves maternal lives
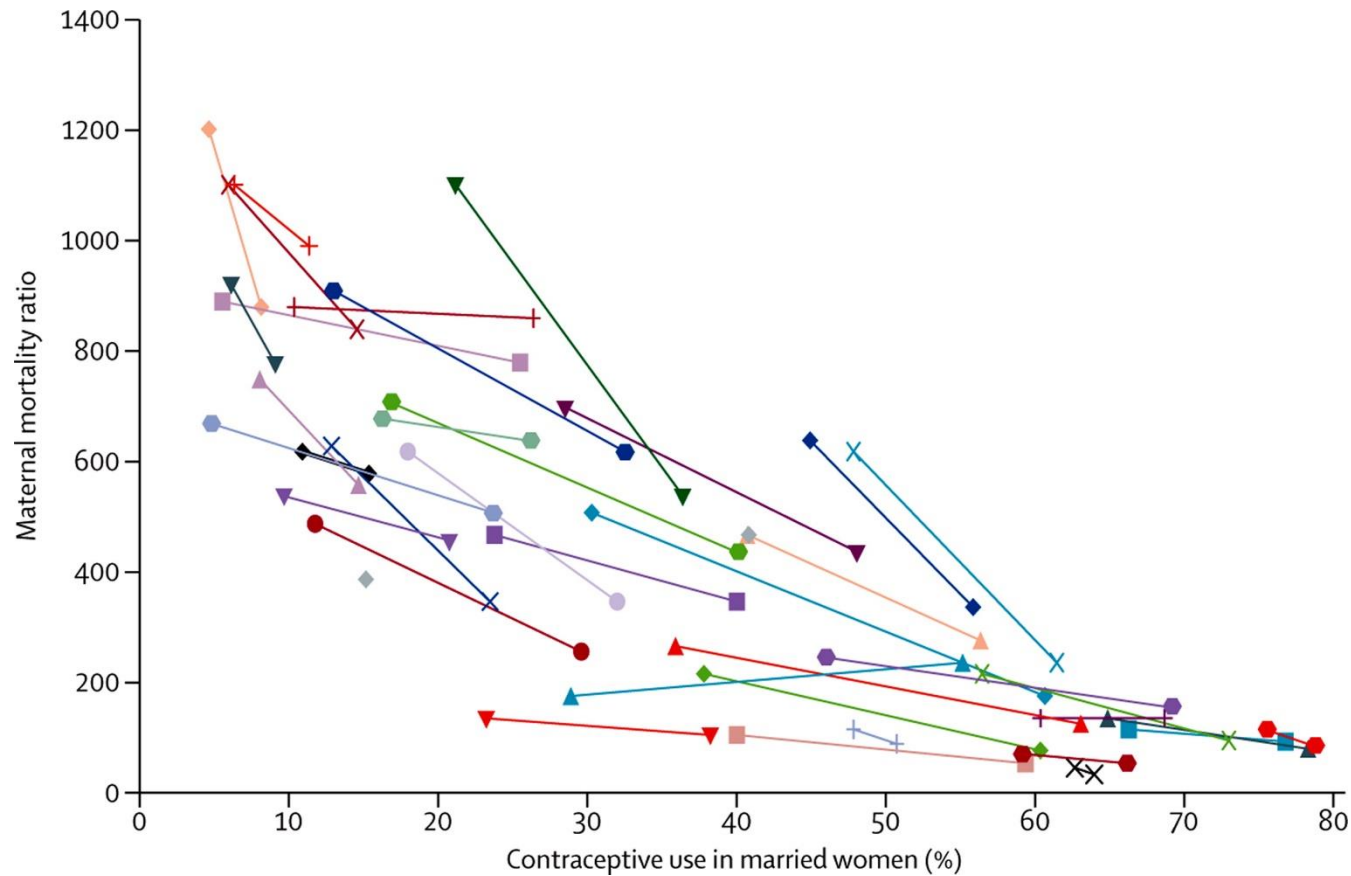
Yearly number of maternal deaths per 100,000 live births (MMR) and contraceptive use in married women in 40 countries over time

Estimated number of maternal deaths averted in 2008 by contraception in selected areas

|	% contraceptive prevalence	maternal deaths	maternal deaths averted (uncertainty range)	% maternal deaths averted
World	64.2	342 203	272 040 (127 937 – 407 134)	44.3
Developed regions	75.0	1 038	1578 (661 – 2 501)	60.3
Developing regions	62.9	341 165	270 461 (127 249 – 404 629)	44.2
Africa	29.1	191 207	92 652 (45 668 – 133 675)	32.7
Asia	67.7	139 369	162 636 (74 860 – 247 736)	53.9

Contraception improves perinatal health
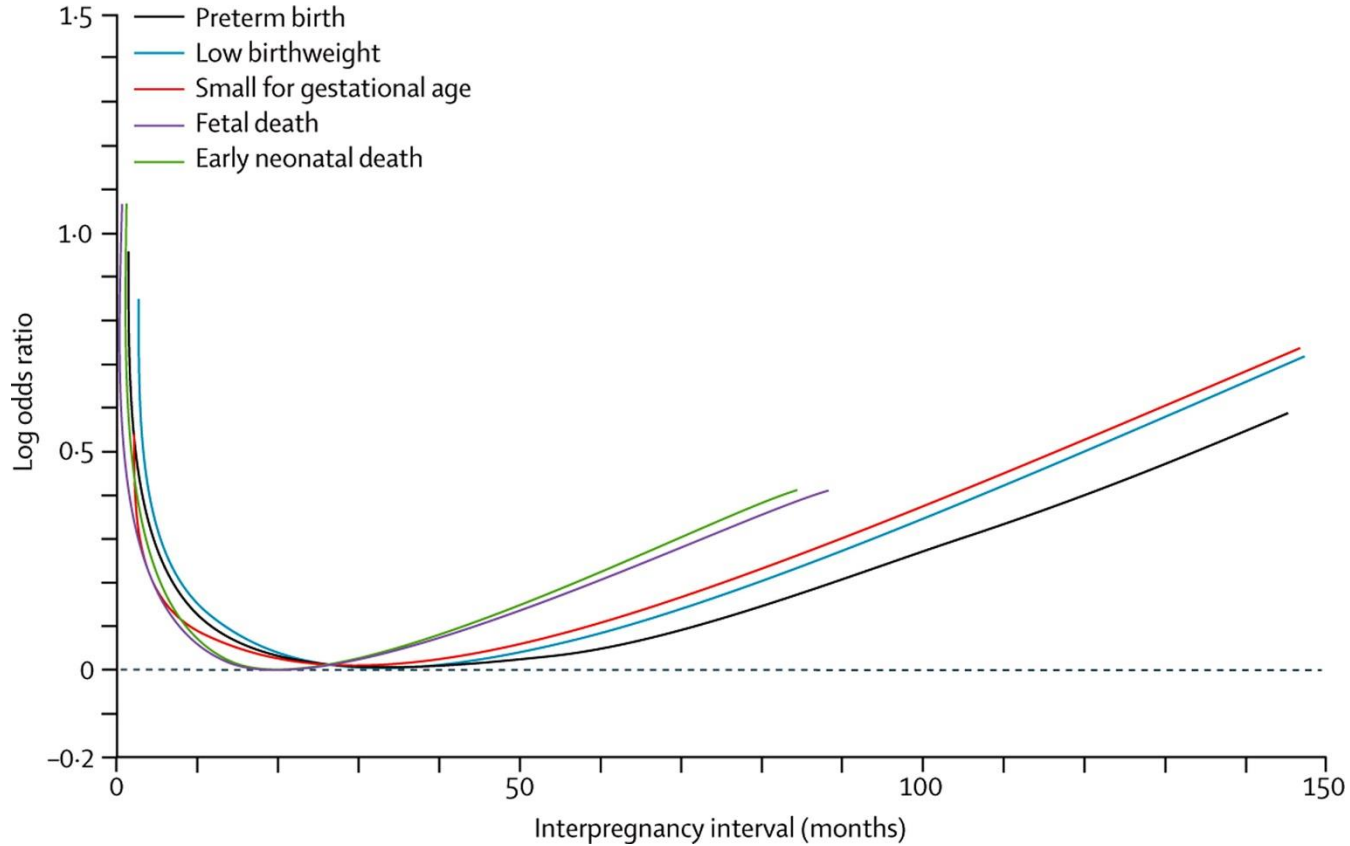
Logs odds ratio of adverse perinatal outcome by interpregnancy interval

Contraception improves infant mortality and health
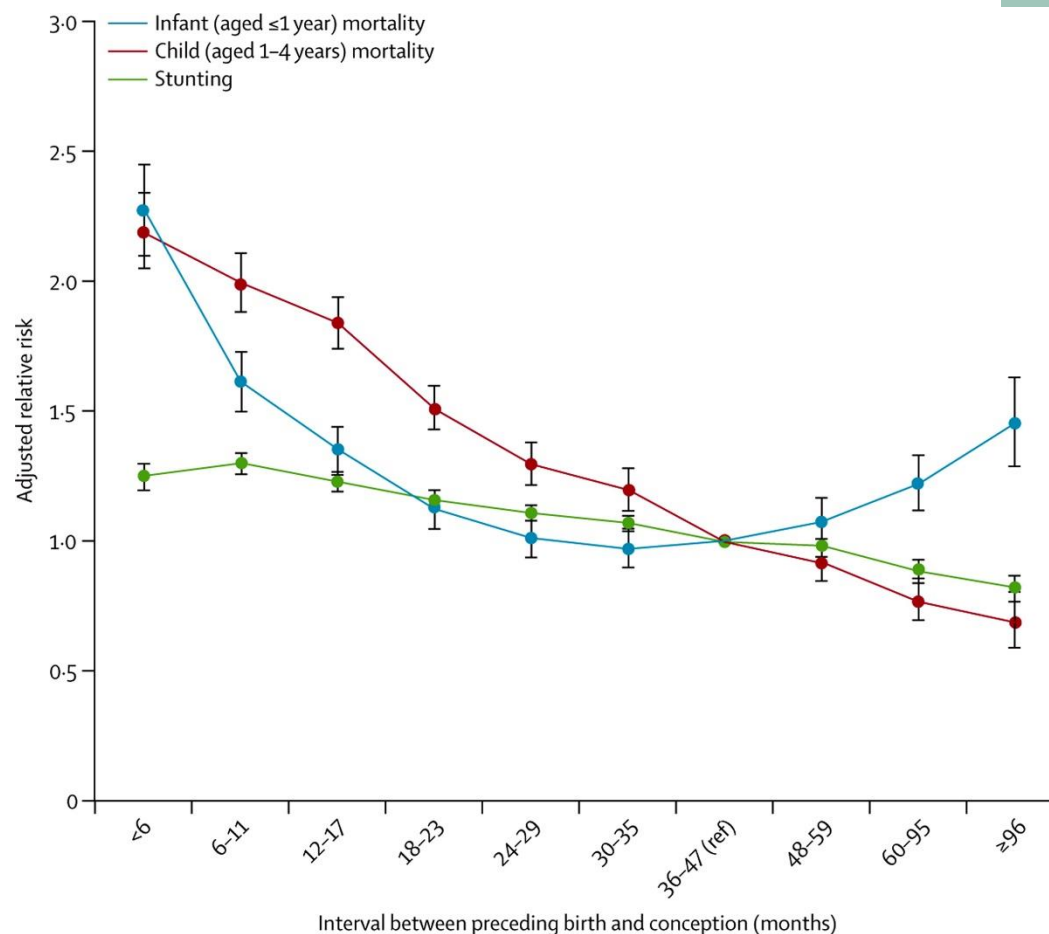
Adjusted relative risk of adverse outcome by interval between preceding birth and conception

Some gynaecological benefits of combined hormonal contraception (1)

- Reduces heavy menstrual bleeding [may help prevent / reduce anaemia] (consistent, good evidence)

- Reduces menstrual pain (more limited evidence)

- *May* reduce premenstrual symptoms / premenstrual dysphoric disorder [PMDD] (limited evidence for drospirenone-containing COCs; sparse and inconclusive evidence for other CHCs)

Some gynaecological benefits of combined hormonal contraception (2)

- Reduces symptoms and risk of recurrence of endometriosis after surgery (good evidence; continuous may be better than cyclical regimen)

- Reduces menstrual irregularity, acne and hirsutism in women with polycystic ovary syndrome (good evidence)

# Skin and bone benefits of combined hormonal contraception

- Reduces acne (limited evidence)

- *May* prevent decline in bone mineral density in perimenopausal women (limited evidence)

- *May* alleviate vasomotor symptoms in perimenopausual women (limited evidence)

Ovarian cancer and COCs: re-analysis 23,257 cases and 87,303 controls from 45 studies

- 45 studies, 21 countries mostly Europe and USA
- Most had at least 100 cases of endometrial cancer
- ~97% eligible study data (3 eligible studies missing)
- Broadly similar information for individuals collated
- Adjusted for study, age at diagnosis, parity and hysterectomy
- Analysis by mid-calendar year of use (grouped as 1960-69, 1970-79, 1980-89) – proxy oestrogen content pills used

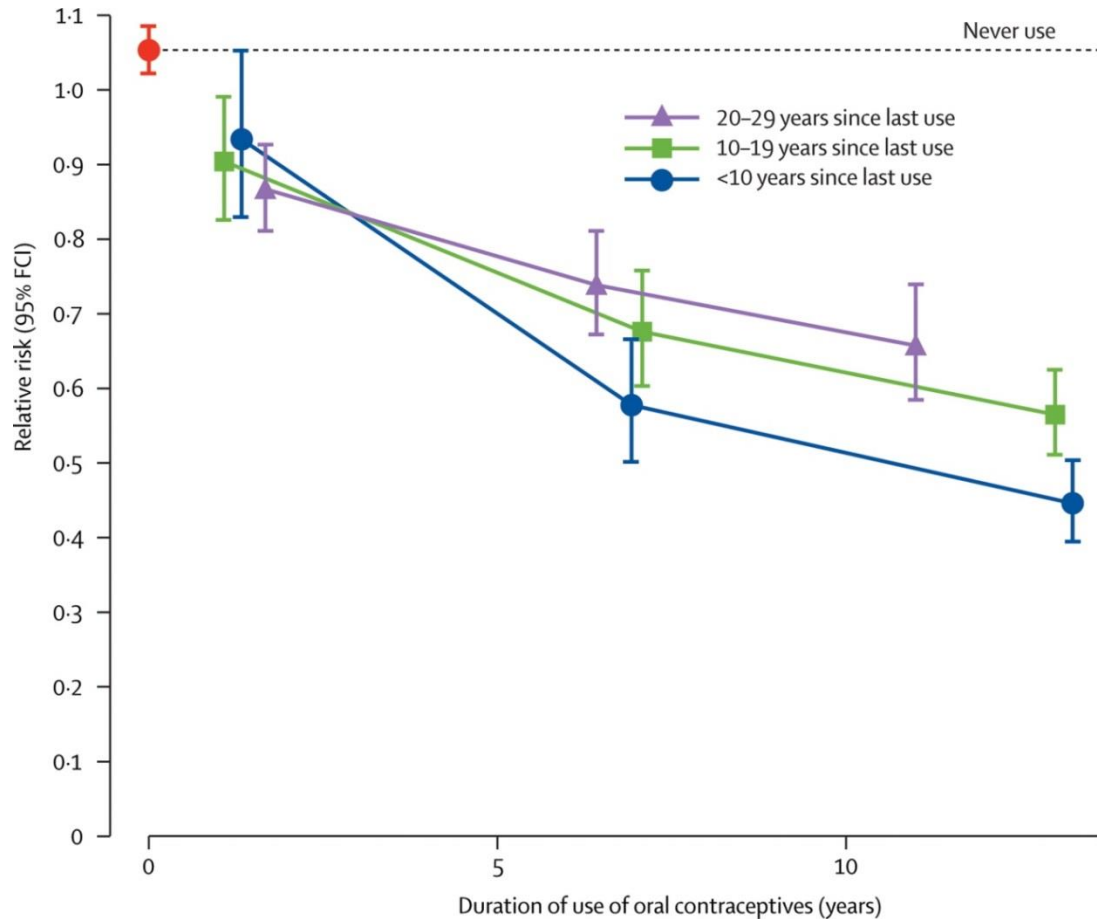# Ovarian cancer and COCs: re-analysis 23,257 cases and 87,303 controls from 45 studies
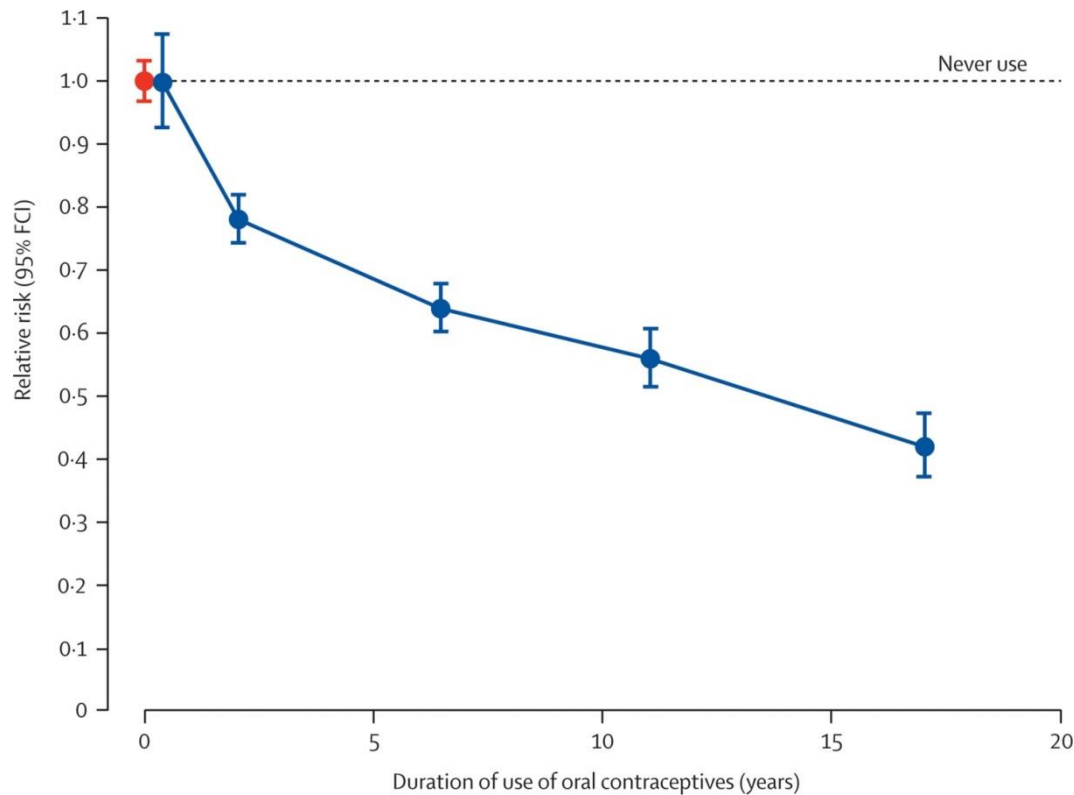
OCs reduce risk
- Ever vs Never
  RR 0.73 (0.70 - 0.76)

Effect increases with duration of use
- Each 5 years of use
  RR decreased
  20% (18% - 23%)

Lancet 2008, 371, 303-314

Ovarian cancer and COCs: re-analysis 23,257 cases and 87,303 controls from 45 studies

Effect persists for at least 30 years after stopping

Nurses Health Study II ovarian cancer risk

Duration of oc use (years)	Cases	Person-years	Hazards ratio (95% confidence interval)
Never	36	321 519	1.0
≤ 0.5	33	165 347	1.82 (1.13 - 2.93)
> 0.5 - 1	25	159 328	1.51 (0.90 - 2.53)
1 - 5	96	679 339	1.33 (0.90 - 1.97)
5 - 10	59	551 456	1.03 (0.67 - 1.56)
10 - 15	26	207 436	1.11 (0.66 - 1.84)
15+	6	94 253	0.43 (1.08 - 1.04)

p-trend 0.006

Cancer Causes Control 2017 28:371-383

Danish Sex Hormone Register Study: ovarian cancer results

	Period of observation	Number cases	Relative Risk * (95% CI)
Any hormonal contraception			
Never	8 150 250	771	1.00
Previous	4 505 157	244	**0.77 (0.66 - 0.91)**
Current & recent	8 839 374	234	**0.58 (0.49 - 0.68)**
Combined oral contraceptives			
Current & recent	7 751 904	175	**0.53 (0.45 - 0.64)**

*adjusted relative risk

BMJ 2018; 362: k3609

Danish Sex Hormone Register Study: ovarian cancer

BMJ 2018; 362: k3609

Danish Sex Hormone Register Study: ovarian cancer results- time since last current use

Any hormonal contraception versus never users:

Years	Period of observation	Number cases	Relative Risk * (95% CI)
1 - 5	2 442 620	110	**0.76 (0.61 - 0.93)**
5 - 10	1 397 257	83	**0.78 (0.61 - 0.99)**
10+	665 281	51	0.80 (0.59 - 1.08)

*adjusted relative risk

Danish Sex Hormone Register Study: ovarian cancer results: use to first switch

Current and recent use versus never users:

Oral combined-20-40 µg EE +	Period of observation	Number cases	Relative Risk * (95% CI)
Norethisterone	116 090	7	1.30 (0.62 – 2.76)
Levonorgestrel	519 113	11	**0.33 (0.18 - 0.61)**
Norgestimate	375 778	11	0.75 (0.41 – 1.37)
Desogestrel	988 952	17	**0.45 (0.27 - 0.73)**
Gestodene	1 887 047	42	**0.57 (0.41 - 0.79)**
Drospirenone	188 928	5	**1.08 (0.44 – 2.64)**
Cyproterone	142 147	0	-

*adjusted relative risk

BMJ 2018; 362: k3609

Public health impact

- Estimated 200,000 cases of ovarian cancer prevented by oral contraceptives in high income countries over past 50 years, and 100,000 deaths
- Numbers will increase substantially in the future

Lancet 2008, 371, 303-314

Endometrial cancer and OCs: re-analysis 27,276 cases and 115,743 controls from 36 studies

- 36 studies, mostly Europe and USA
- Most had at least 200 cases of endometrial cancer
- ~88% eligible data (8 eligible studies missing)
- Broadly similar information for individuals collated
- Adjusted for study, age at diagnosis, parity, body mass index, smoking and use of HRT
- Analysis by mid-calendar year of use (grouped as 1960-69, 1970-79, 1980-89)- proxy for oestrogen content of pills used

Lancet Oncol 2015

Endometrial cancer and OCs: re-analysis 27,276 cases and 115,743 controls from 36 studies

A

Relative risk (y-axis: 0, 0·2, 0·4, 0·6, 0·8, 1·0, 1·2)

Duration of use of oral contraceptives (years) (x-axis: 0, 5, 10, 15)

Legend:
- Never-users*
- Ever-users

Years of use	<1	1–<5	5–<10	10–<15	≥15
Cases/controls	1595/6428	3624/15938	2096/11070	1136/6927	422/3420
RR (99% gsCI)	0·97 (0·88–1·07)	0·81 (0·76–0·86)	0·64 (0·59–0·69)	0·52 (0·47–0·58)	0·32 (0·28–0·38)

OCs reduce risk
- Ever vs Never
  RR 0.69 (0.67 - 0.72)

Effect increases with duration of use
- Each 5 years of use
  RR decreased by
  24% (22% - 27%)

Lancet Oncol 2015

Endometrial cancer and OCs: re-analysis 27,276 cases and 115,743 controls from 36 studies

Effect persists for at least 30 years after stopping
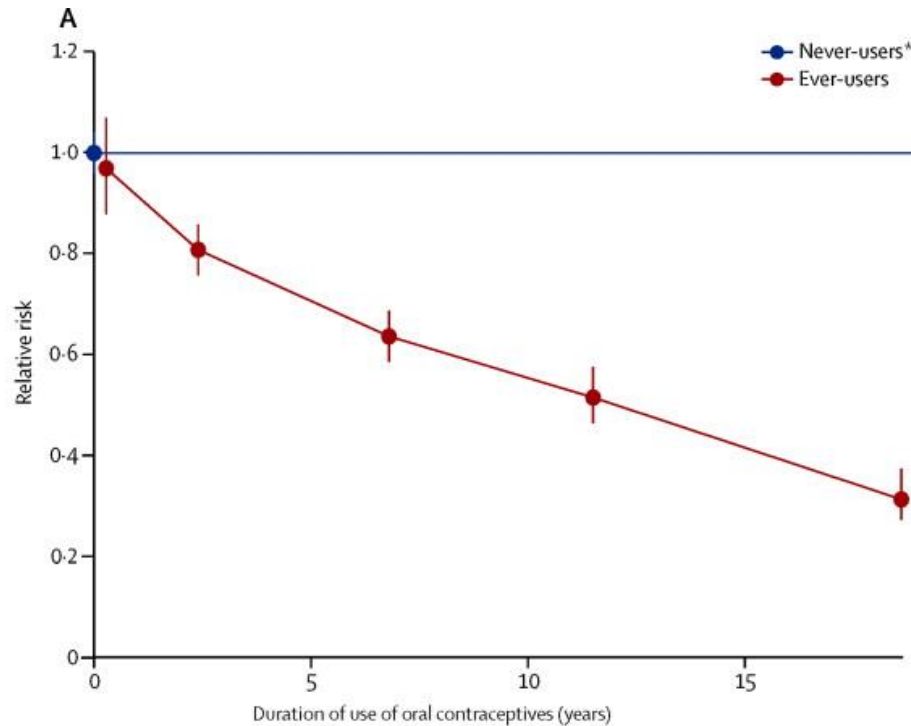
Lancet Oncol 2015
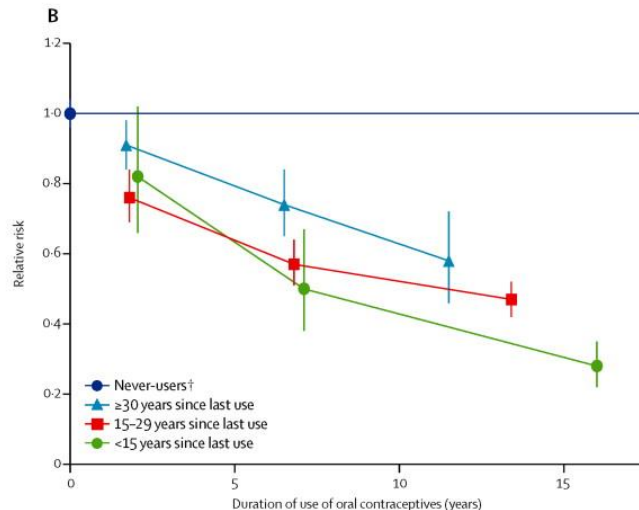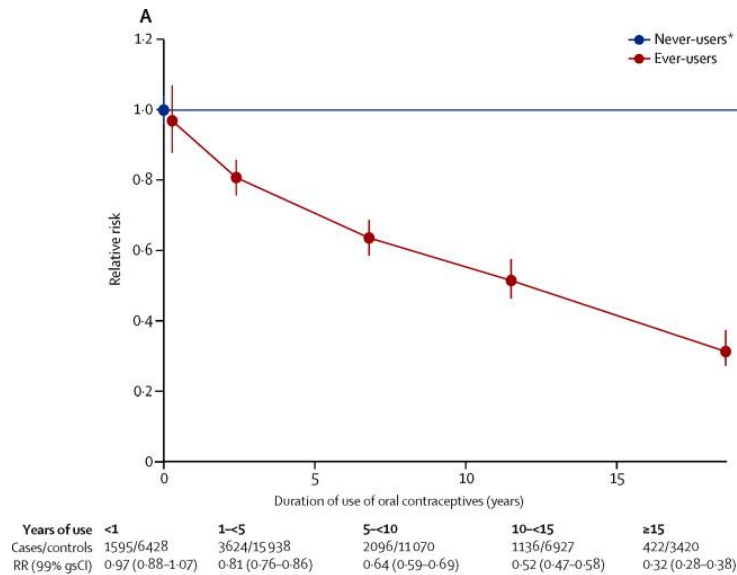
Public health impact

- Estimated 400,000 cases of endometrial cancer prevented by oral contraceptives in high income countries over past 50 years, including 200,000 in past decade (2005-14)
- Numbers will increase substantially in the future

Lancet Oncol 2015

AHRQ meta-analysis- ever versus never oral contraceptive use and colorectal cancer

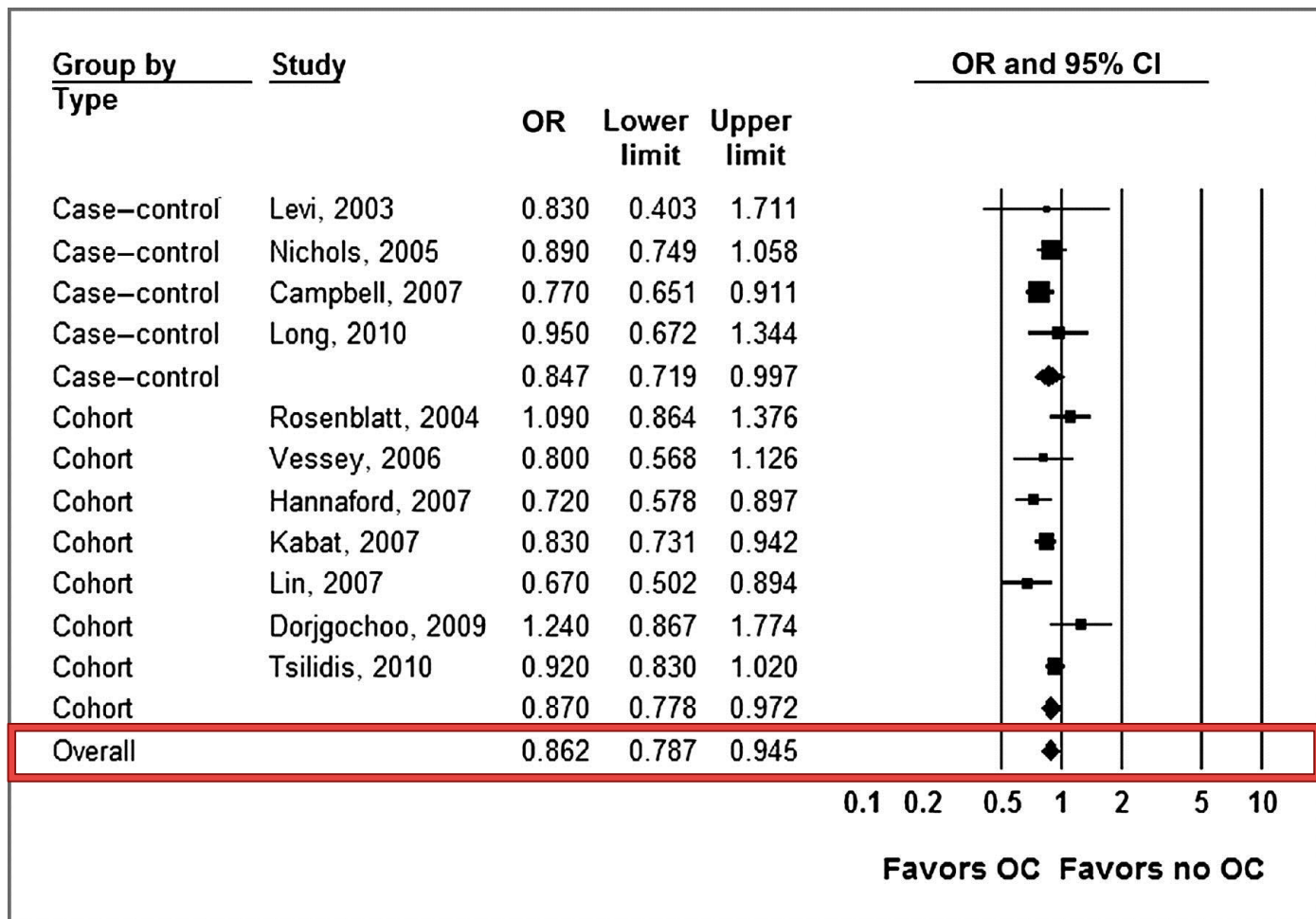| Group by Type	Study	OR	Lower limit	Upper limit	OR and 95% CI
Case–control	Levi, 2003	0.830	0.403	1.711	
Case–control	Nichols, 2005	0.890	0.749	1.058	
Case–control	Campbell, 2007	0.770	0.651	0.911	
Case–control	Long, 2010	0.950	0.672	1.344	
Case–control		0.847	0.719	0.997	
Cohort	Rosenblatt, 2004	1.090	0.864	1.376	
Cohort	Vessey, 2006	0.800	0.568	1.126	
Cohort	Hannaford, 2007	0.720	0.578	0.897	
Cohort	Kabat, 2007	0.830	0.731	0.942	
Cohort	Lin, 2007	0.670	0.502	0.894	
Cohort	Dorjgochoo, 2009	1.240	0.867	1.774	
Cohort	Tsilidis, 2010	0.920	0.830	1.020	
Cohort		0.870	0.778	0.972	
Overall		0.862	0.787	0.945	

0.1 0.2   0.5 1   2   5   10

Favors OC Favors no OC

Public health impact

Unclear but may be be substantial

Combined oral contraception and cancer

↑ Breast
Cervix
(Liver)

Ovary
Endometrium
Colorectum ↓

Mostly during
current & recent use

During current use;
sustained after stopping

So what is the lifetime risk of any
cancer in ever users?

RCGP Oral Contraception Study

Incident cancer to December 2012: Am J Obs Gyne 2017

	n	Ever users Stand rate per 100,000 wy	Never users Stand rate per 100,000 wy	Relative risk (95% CI)
All cancer	7002	542.4	566.1	0.96 (0.91 – 1.01)
Oesphagus / stomach	202	14.5	16.6	0.87 (0.66 – 1.17)
Large bowel / rectum	688	47.9	59.2	0.81 (0.69 – 0.94)
Gallbladder / liver	66	4.7	5.7	0.81 (0.49 – 1.34)
Pancreas	175	13.3	13.5	0.99 (0.73 – 1.35)
Lung	758	59.2	49.2	1.20 (1.02 – 1.41)
Skin: melanoma	251	19.8	18.3	1.08 (0.82 – 1.41)
Skin: other	1305	103.0	93.7	1.10 (0.98 – 1.23)
Breast	2071	160.0	155.2	1.03 (0.94 – 1.13)
Invasive cervix	192	15.5	11.6	1.34 (0.96 – 1.87)
Uterine body	295	19.4	29.6	0.66 (0.52 – 0.83)
Ovary	336	22.1	33.3	0.66 (0.53 – 0.82)
Bladder / kidney	247	17.6	20.3	0.87 (0.67 – 1.13)
CNS / pituitary	83	5.7	7.0	0.83 (0.53 – 1.28)
Thyroid	64	3.5	6.6	0.53 (0.33 – 0.87)
Site unknown	334	23.6	28.2	0.84 (0.67 – 1.05)
Lymphatic / haematopoietic	470	31.9	43.2	0.74 (0.61 – 0.89)
Other cancer	467	35.9	34.4	1.04 (0.86 – 1.27)

Overall cancer in two large cohorts with long term follow-up

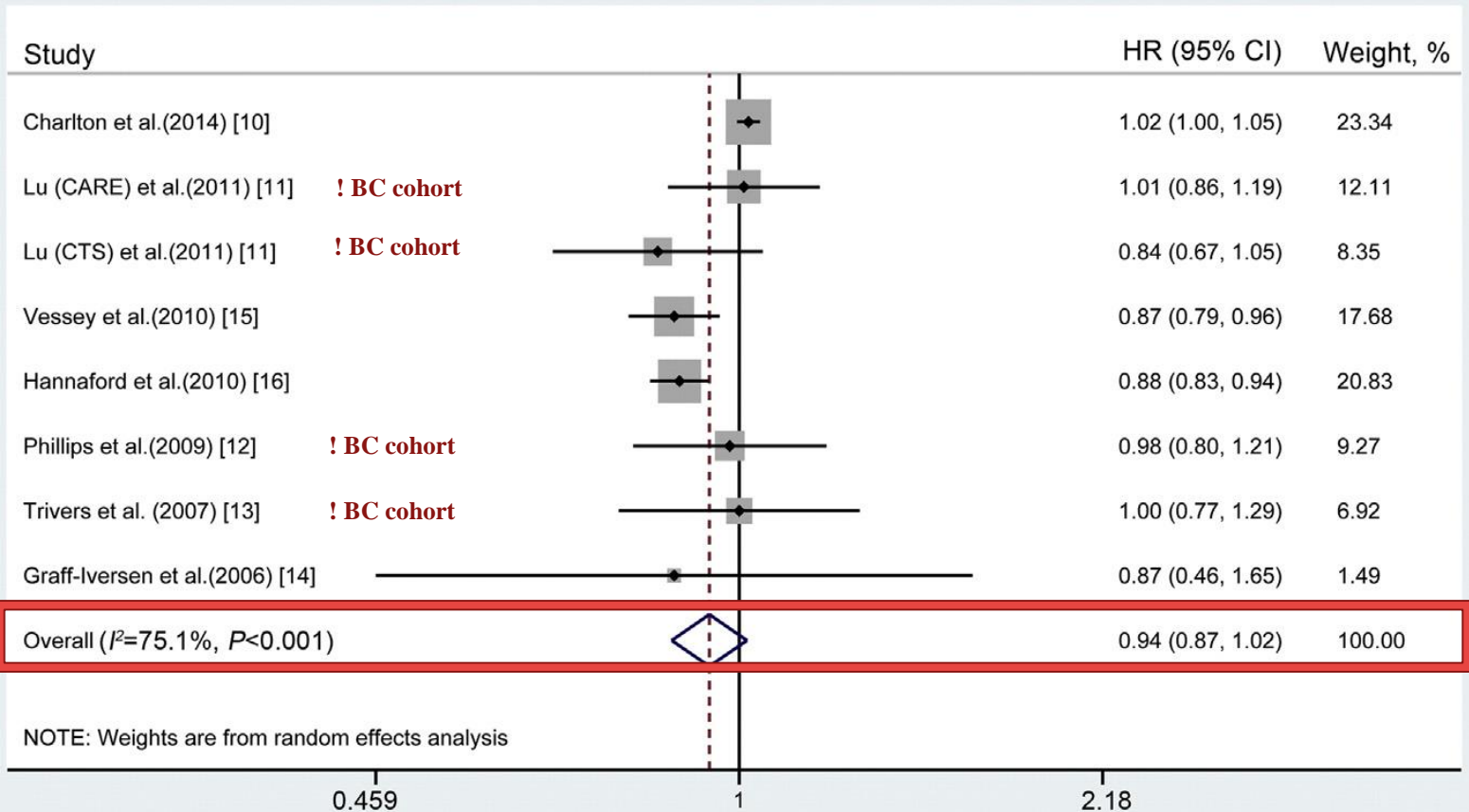| Study	Type event	Average length of follow-up (years)	Number cases	Relative risk ever : never (95% CI)
European Prospective Investigation of Cancer & Nutrition[1]	Deaths	13	5938	Non-smokers at baseline 0.91 (0.85 - 0.98) Smokers at baseline 1.00 (0.90 – 1.12)
Nurses Health Study[2]	Deaths	36	11,781	1.01 (0.97 - 1.05)
RCGP OCS[3]	Incidence	44	7002	0.96 (0.91 - 1.01)

[1] BMC Medicine 2015;13:252   [2] BMJ 2014;349:g6356   [3] Am J Obst Gyne 2017 580.e4

Most recent mortality results from RCGP study

	n	Ever users Standardised rate per 100,000 wy	Never users Standardised rate per 100,000 wy	Relative risk (95% CI)
All causes	4611	366	417	0.88 (0.82-0.93)
- Cancer	2088	165	195	0.85 (0.78-0.93)
- Circulatory disease	1264	99	115	0.86 (0.77-0.96)
- Digestive disease	195	16	17	0.95 (0.71-1.27)
- Accidents & violence	207	19	13	1.49 (1.09-2.05)
- Other causes	851	66	78	0.84 (0.74-0.97)
Woman-years observation		819,175	378,006	

BMJ 2010

Meta-analysis of studies looking at all-cause mortality

Study		HR (95% CI)	Weight, %
Charlton et al.(2014) [10]		1.02 (1.00, 1.05)	23.34
Lu (CARE) et al.(2011) [11]	**! BC cohort**	1.01 (0.86, 1.19)	12.11
Lu (CTS) et al.(2011) [11]	**! BC cohort**	0.84 (0.67, 1.05)	8.35
Vessey et al.(2010) [15]		0.87 (0.79, 0.96)	17.68
Hannaford et al.(2010) [16]		0.88 (0.83, 0.94)	20.83
Phillips et al.(2009) [12]	**! BC cohort**	0.98 (0.80, 1.21)	9.27
Trivers et al. (2007) [13]	**! BC cohort**	1.00 (0.77, 1.29)	6.92
Graff-Iversen et al.(2006) [14]		0.87 (0.46, 1.65)	1.49
Overall (I^2=75.1%, P<0.001)		0.94 (0.87, 1.02)	100.00

NOTE: Weights are from random effects analysis

0.459   1   2.18

Changing all-cause relative risks over time in the three largest cohort studies
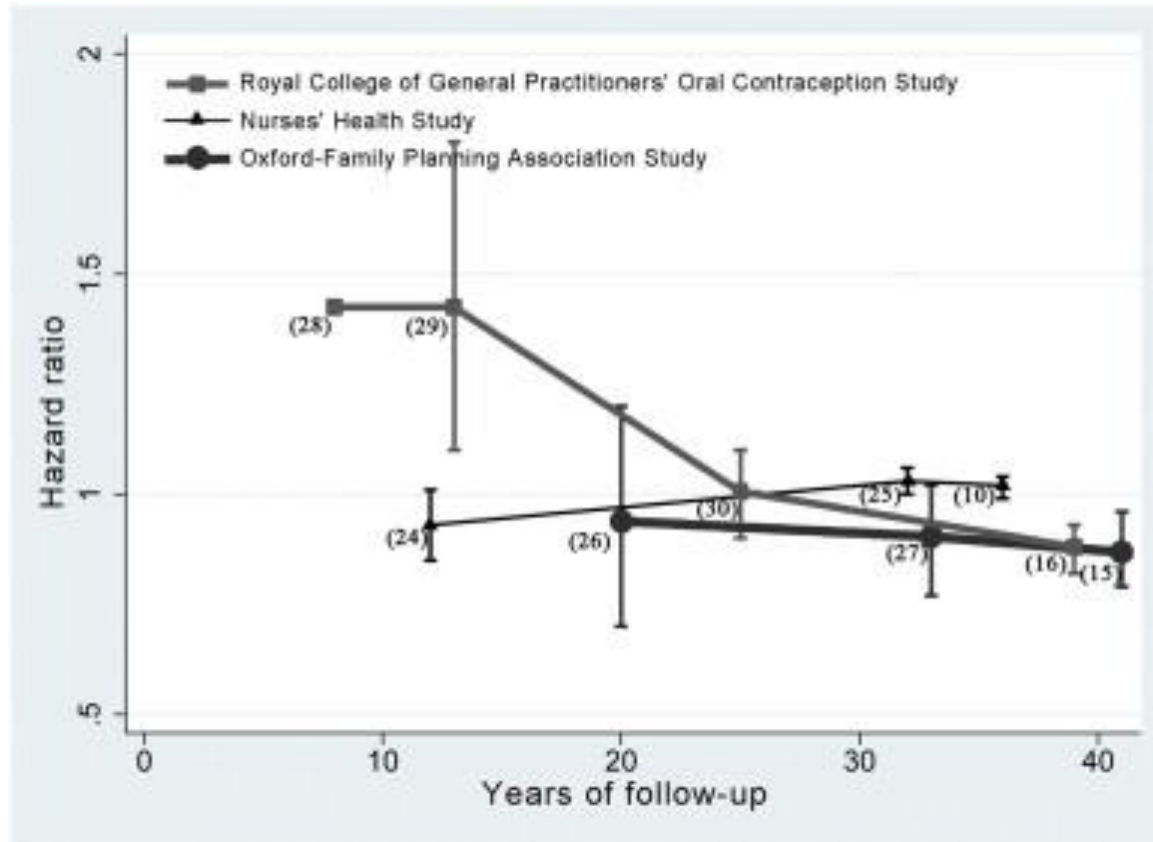
Conclusions

- Combined hormonal contraception is associated with important short- and longer-term contraceptive and non-contraceptive benefits

- For most users the benefits are likely to outweigh the harms

- This said, CHC should be used to prevent pregnancy not disease