Primary Dysmenorrhea
Evidence based management guidelines

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What is it

Recurrent lower abdominal cramping during cycle

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Classification

Primary dysmenorrhoea

Secondary dysmenorrhoea

- Endometriosis
- Adenomyosis
- Leiomyomas

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Why is it important

It causes

- Pain in young women
- Absenteeism

High prevalence

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Epidemiology

PD

- 25% of all women
- 90% of adolescents

Absenteeism

- Up to three days
  per cycle in 15%

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Epidemiology

More in:

- In smokers
- Early age menarche
- Longer cycles

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Pathophysiology

True aetiology uncertain

Most plausible

↑ endometrial prostaglandin production → ↑ myometrial contractions & vasoconstriction → uterine ischemia → pain

8 to 72 hours

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Diagnosis

History

Clinical findings

Differential diagnosis

Special investigations

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Differential diagnosis

Causes of pelvic pain

Investigate appropriately according to findings obtained in history

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Pain syndrome

PD not regarded as chronic pain syndrome

Many shared features

- ↓QOL
- ↓hypothalamic-pituitary axis
- Alterations central processing noxious stimuli

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Management

PD

- Symptom relief
- Grading of disease
- Counselling
- Appropriate follow-up and support

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Management

SD

Treat underlying cause

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Quality of evidence

Most

Moderate, low, or very low grade

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Level of evidence (LOE)	Description
Level I	Evidence from a systematic review or meta-analysis of all relevant RCTs (randomized controlled trial) or evidence-based clinical practice guidelines based on systematic reviews of RCTs or three or more RCTs of good quality that have similar results.
Level II	Evidence obtained from at least one well-designed RCT (e.g. large multi-site RCT).
Level III	Evidence obtained from well-designed controlled trials without randomization (i.e. quasi-experimental).
Level IV	Evidence from well-designed case-control or cohort studies.
Level V	Evidence from systematic reviews of descriptive and qualitative studies (meta-synthesis).
Level VI	Evidence from a single descriptive or qualitative study.
Level VII	Evidence from the opinion of authorities and/or reports of expert committees.

NSAIDs

vs placebo

73 RCTs

OR 4.5, 95% CI 3.85 to 5.27 pain relief

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NSAIDs

vs paracetamol

OR 1.90, 95% CI 1.05 to 3.44 pain relief

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NSAIDs

vs Aspirin

1 RCT 34 women

NSAIDs better RR 2.29 95% CI 1.09 to 4.79

pain relief

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NSAIDs

vs NSAIDs

Insufficient evidence

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NSAIDs

Effective:

Pain relief

Restriction of daily activities

(RR 0.65 95% CI 0.51 to 0.83)

Absence from school

(RR 0.46 95% CI 0.34 to 0.61)

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NSAIDs

Beware: significant risk of adverse effects

vs placebo:

GIT ulceration, bleeding (traditional NSAIDs)

↑ CVS risk (some COX-2)

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Aspirin

vs placebo

Systematic review 8 RCTs

RR 1.60 95% CI 1.12 to 2.29 pain relief

2 other systematic reviews 4 RCTs → NS

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Aspirin

Daily activities and absenteeism

Data: NS

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Aspirin

Adverse effects

Compared with placebo: NS

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Paracetamol

vs placebo

Very low quality evidence: NS

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COC

Frequently used

Limited evidence

- 497 women in review 6 RCTs

Daily activities

- No data

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COC

vs placebo

Effective

OR 2.01 95% CI 1.32 to 3.08

Adverse effects: NS

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COC

vs NSAIDs

No data

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Herbal and dietary therapies

Magnesium

Vitamin B12

- Might be beneficial
- Evidence weak
- Small numbers
  - Dosage: unknown

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Herbal and dietary therapies

Other herbal and dietary therapies

Insufficient data

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Behavioural interventions

Might be beneficial for pain relief

- Pain management training
- Relaxation

Interpret with caution; poor quality data

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Exercise

Might be beneficial pain relief

Interpret with caution: 1 single RCT

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Transcutaneous electrical nerve stimulation

7 RCTs

High frequency TENS

More effective than placebo pain relief

OR 7.2 95% CI 3.1 to 16.5

TENS

Absenteeism

Data: NS

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TENS

Low frequency

Data pain relief: NS

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TENS

vs NSAIDs

low quality evidence (32 women) favours NSAID

OR 0.26 95% CI 0.09 to 0.75

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Chinese Herbal Medicine

vs placebo

Results unclear

Data could not be combined

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Topical Heat

Abdominal heated patch (38.9C)

vs unheated

- Effective for pain relief

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Topical Heat

vs NSAIDs

Low quality evidence: NS

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Topical Heat

vs paracetamol

Topical heat more effective

Mean pain score 2.48 compared to 2.17 (p = 0.015)

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Acupuncture

Pain relief:

Better than placebo, NSAIDs &

Chinese herbs

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Acupressure

Better than placebo for pain relief and menstrual symptoms

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Acupuncture and acupressure

Further well designed RCTs needed

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Interventions not effective

β_2 – agonists

Spinal manipulation by physiotherapists and chiropractors

Surgical intervention of nerve pathways

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Now

So what?

Implication for practice

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What are we trying to achieve

Pain relief

Less absenteeism

Exclude pathology

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Treatment options

Some options

- achieve both
- achieve one
- are counterproductive
- are not practically feasible

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Most practical

COC

- Additional advantages

NSAIDs prn

Maybe heat patch

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COC

Without placebo

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Women were not designed to menstruate

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Women were not designed to menstruate

Placebo: since 1950

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The opportunity

Adolescents seldom get sick

Opportunity

- Counsel regarding safe sex
- and contraception, HPV vaccine
- Etc

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Conclusion

Common condition

Many women do not seek help → normal plight of being female

When obtaining history: ask about PD

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Conclusion

When treating PD

- Use the opportunities it created

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Contraception in perimenopausal women

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Introduction

Population with specific needs and challenges

Which methods are safe

When and how to stop

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Fertility

Women >40 years → ↓natural ability to fall pregnant

- Conception rate 12/1000 compared to 110/1000 in women 20 - 25 years

Still require effective and safe contraception

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Perimenopausal women

Generally: ↓ in frequency of intercourse

Some are in new relationships often resulting in ↑ in coital frequency

Older women may abandon contraception

When unintended pregnancy → 35% will have TOP

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Contraceptive methods

No method is contra-indicated on age alone

Less effective methods can be used effectively at this age in combination with a natural decline in ability to fall pregnant

Risk of contraception to be weighed against risk of unintended pregnancy

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Combined oral contraceptives (COCs)

Can safely be used up to menopause in:

- Non-smokers
- No risk factors for cardiovascular disease
- No risk factors for arterial or venous disease
  - Not: Obesity, smoking, hypertension, DM, migraine

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Some Risks of COCs

VTE

Absolute risk remains small

18 events per 100 000 users 40 – 44 year old – 2 x of 20 -24 years

Risk highest in first year and may decrease with prolonged use

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Some Risks of COCs

Breast cancer

- Risk very small and is age related
- RR 1.24 and normalises after 10 years of stopping

Cervical cancer

- Risk ↑ with duration of use
- RR 4.03 after 10 years → screen!

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Benefits

Reduced risk of

- Ovarian cancer – RR 0.42 after 15 years use & protection lasts for 30 years
- Endometrial Ca – 40% risk ↓ lasting 15 years

Beneficial effect on BMD

Cycle and perimenopausal symptom control

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COCs

Any monophasic 30 µg EE

21/7, 24/4, continuous regimen or tailored extended use

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Progestogen only methods

Reliable but not very popular

Can cause irregular and unpredictable bleeding

Breast cancer risk ↓ than COCs

Long term DMPA → reversible ↓ BMD

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Levonorgestrel releasing intrauterine system (LNG-IUS)(Mirena®)

Very effective and safe

Licensed for 5 years, very safe for 7 years in women >37 years

Effective in treating HMB

Endometrial protection when HT required

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Copper IUD

Optimal for older women with normal cycles

Safe and effective

Irregular HMB needs to be investigated

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Barrier methods and spermicides

Condoms more effective in this age group compared to younger women

Can be problematic in males experiencing erectile dysfunction when using condoms

Male and female condoms same efficacy

Spermicides should not be used alone

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Other methods

Fertility awareness based methods → less reliable

Coitus interruptus not recommended

Emergency contraception is safe

- Levonorgestrel-only emergency pills should be used
- Single dose 1.5 mg up to 5 days after event
- IUD

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Permanent measures

Often used in women > 40 yrs

Very effective

Laparoscopic procedure Filschie clip consider salpingectomy → reduces ovarian cancer risk

Hysteroscopic tubal occlusion – no more

Vasectomy

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Natural FP

For those who cannot use available options

For those who chose to use it

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NFP

Limited knowledge

Women seldom counselled about this

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Physiology

Six fertility days per cycle

Sperm survives 5 days in female genital tract

Oocyte life span about 24 hours

Best chance – intercourse before ovulation

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Physiology

Ovulation occurs in mid-cycle in 30% of cycles and within 4 days before or after the midpoint in 95% of cycles

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Physiology

Cervical secretions

- Initially absent in the first 3 to 4 days of cycle
- Before and immediately after ovulation secretions more in volume and clear in appearance
- Disappear until after the next menstruation

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Physiology

The probability of conception is very low (near zero) when intercourse occurs on days with no secretion and is about 30% when intercourse occurs on days with the most fertile type mucus

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Concept

Identification of fertile days

- Cycle length
- Clinical indicators of ovulation:
  - cervical secretions
  - basal body temperature

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Concept

Avoid intercourse or use barrier on fertile days

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Classification

Fertility awareness based methods

- Standard Days Method®
- TwoDay method®
- Ovulation method
- Symptothermal method
- Other

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Standard Days Method

For women with cycles between 26 and 32 days

Unprotected intercourse should be avoided from day 8 to day 19

Pregnancy rate: <5 per 100 women years over 13 cycles with correct use and 12 with typical use

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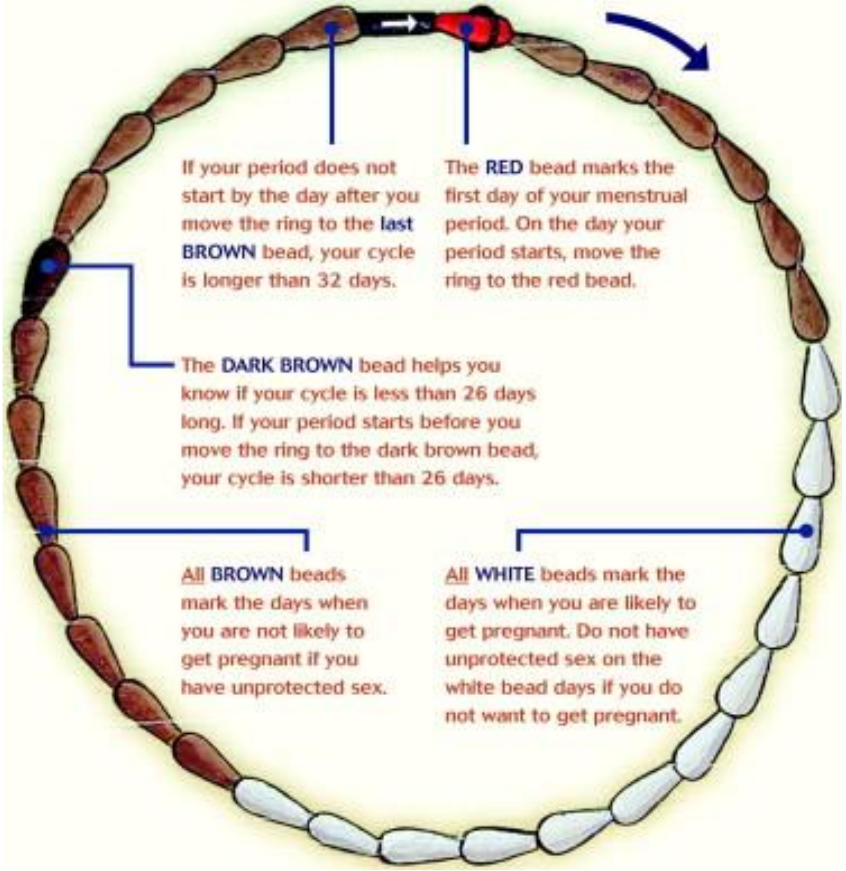
Cycle Beads



Two Day Method

Unprotected intercourse is avoided on any day with vaginal secretion as well as the following day

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Two Day Method

The mean length of the fertile period according to this method, where the presence of secretions is important and the characteristics are ignored, is 13 days

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Two Day Method

Correct use pregnancy rate studied over 13 cycles

is 3 pregnancies per 100 women years and <14 for

typical use

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Symptothermal Method

Vaginal secretions is combined with measurements of basal body temperature

Onset of secretions indicate the beginning of the fertile period

Rise in basal body temperature signals the end

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Symptothermal Method

Temperature readings and information on secretions are recorded on a chart

Unprotected intercourse avoided

- on days with secretions
- days after intercourse on pre-ovulatory days as semen can be confused with secretions

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Symptothermal Method

Unprotected intercourse avoided

until there is a rise in basal body temperature for three consecutive days after 6 days of lower temperature, or 4 days after the last wet secretions

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Symptothermal Method

Correct use has a pregnancy rate of 2 per 100 women years and typical use between 13 and 20

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When to stop contracetion

Women up to 50:

2 years after last spontaneous menstrual period

Women > 50:

1 year after last spontaneous menstrual period

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When to stop

In COC users

Age 50 → switch to POP or non-hormonal → continue until 1 year after last spontaneous menstrual period, or 2 measurements of FSH ≥ 30 IU/l 6 to 8 weeks apart

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When to stop

POP users

FSH levels → if elevated twice → discontinue after using for another year

Or

Continue use until 55 years of age and then stop

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When to stop

DMPA

Use after 45 yrs → counsel about risk of ↓ BMD → allow to continue until age 50 yrs if no osteoporosis risk factors

Women with osteoporosis risk factors after age 40 yrs should consider alternative methods

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When to stop

LNG-IUS and amenorrhoea

FSH levels → if elevated twice → discontinue after using for another year

Or

Continue use until 55 years of age and then stop

Endometrial protection in HT users

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Conclusion

Peri-menopausal women require contraception

All options are available

Counsel and individualise

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Menopausal Hormone Therapy and Breast Cancer Risk

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Outline

1. Menopausal hormone therapy

    Consensus statement

2. MHT and breast cancer risk

3. Communicating risk

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Menopausal hormone therapy

Who needs hormone therapy?

Symptomatic peri- and post-menopausal women in whom treatment is not contra-indicated

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What are the concerns

Concerns patients have

Concerns doctors have

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What are the concerns patients have?

Weight gain

Cancer risk and all the bad things they hear or read in the lay press

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HT and weight gain

What is the evidence?

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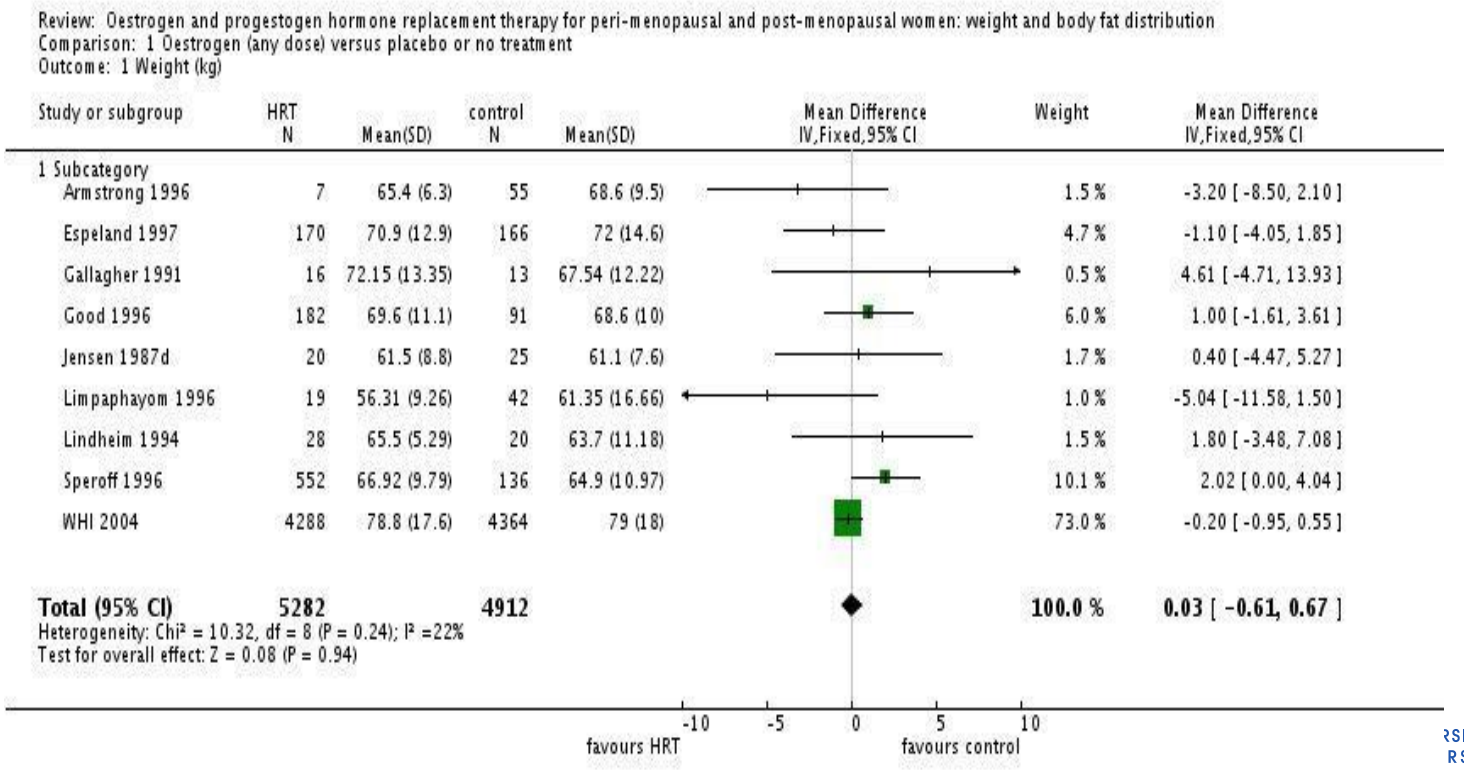
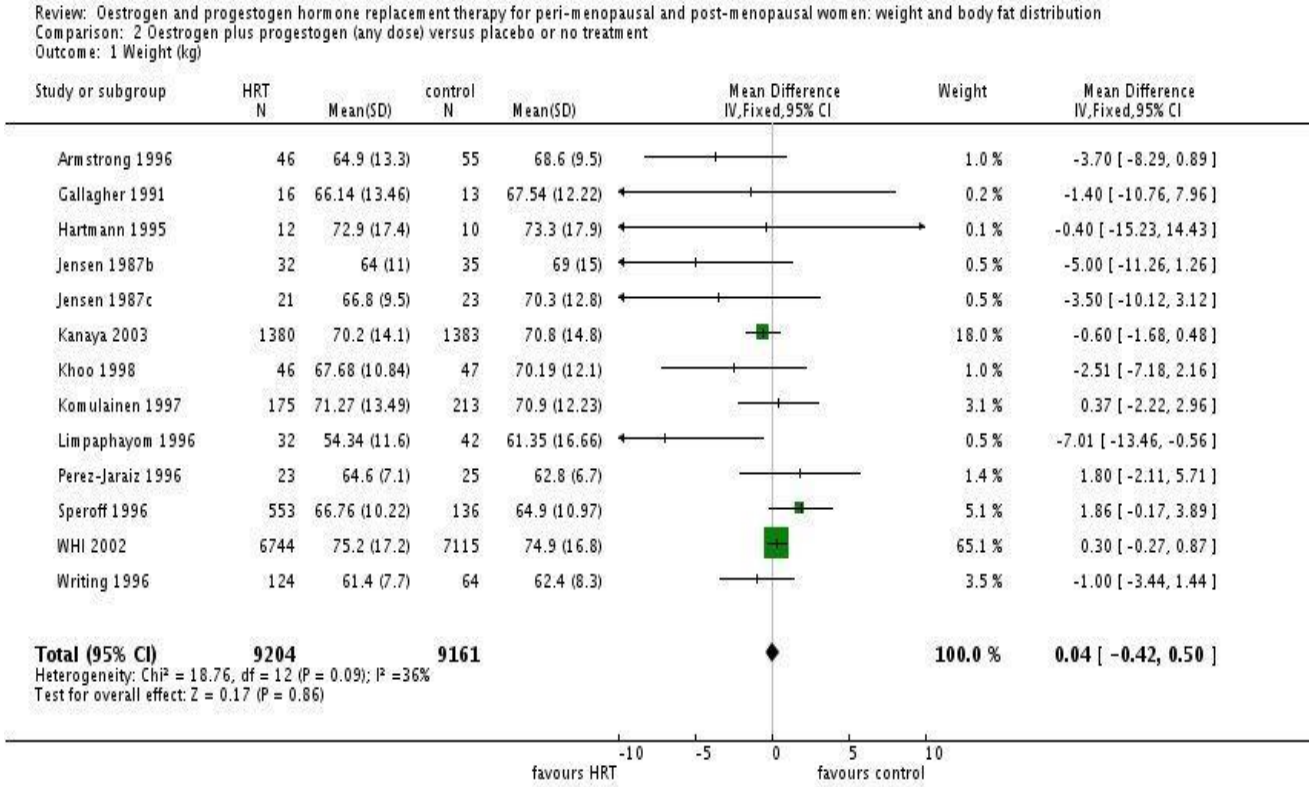
Weight gain: kg (E)



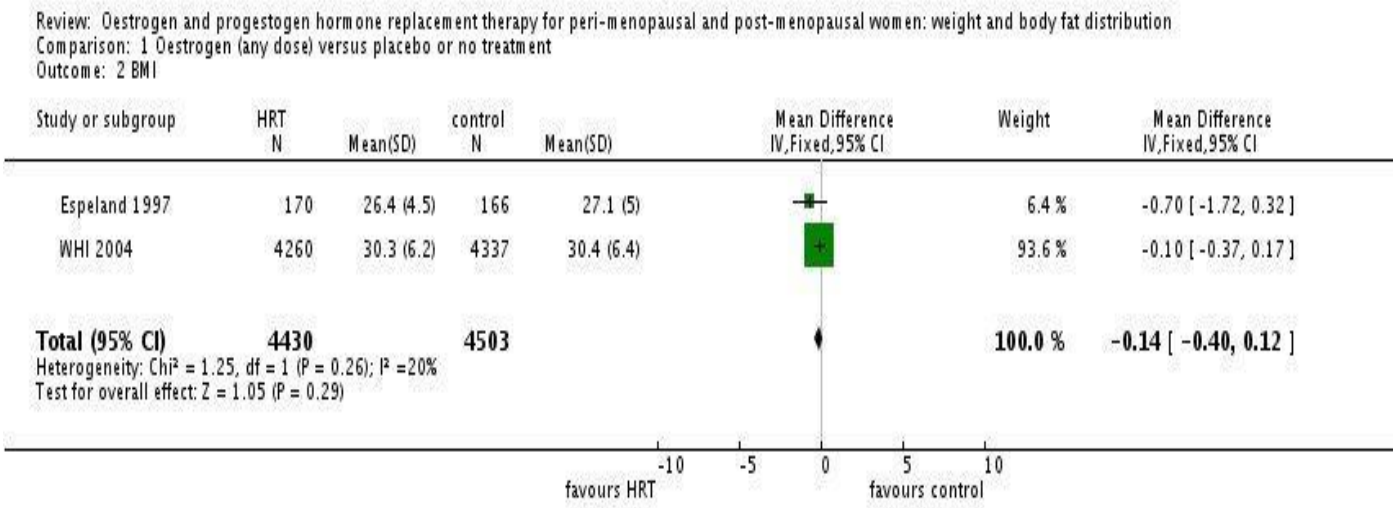
Cochrane database of Systematic Reviews 1999 Issue 3

Weight gain: kg (E+P)



Cochrane database of Systematic Reviews 1999 Issue 3

Weight gain: BMI (E)

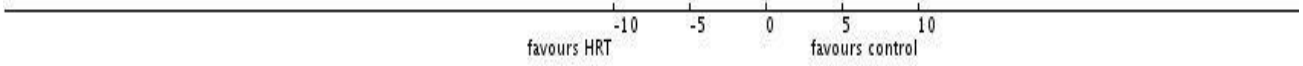


Weight gain: BMI (E+P)

Review: Oestrogen and progestogen hormone replacement therapy for peri-menopausal and post-menopausal women: weight and body fat distribution
Comparison: 2 Oestrogen plus progestogen (any dose) versus placebo or no treatment
Outcome: 2 BMI

Study or subgroup	HRT N	HRT Mean(SD)	control N	control Mean(SD)	Weight	Mean Difference IV,Fixed,95% CI
Hartmann 1995	12	28.1 (5.1)	10	28.2 (4.9)	0.2 %	-0.10 [-4.29, 4.09]
Kanaya 2003	1380	27.7 (5.3)	1383	28 (5.4)	18.0 %	-0.30 [-0.70, 0.10]
Komulainen 1997	175	27.51 (4.77)	213	27.73 (4.77)	3.2 %	-0.22 [-1.17, 0.73]
Mijatovic 1998	14	26 (3.9)	13	26 (4.6)	0.3 %	0.0 [-3.23, 3.23]
Myrup 1992	11	23.7 (2.7)	24	26.5 (6)	0.3 %	-2.80 [-5.68, 0.08]
Tonstad 1995	39	23.6 (2.8)	29	24.3 (2.7)	1.7 %	-0.70 [-2.02, 0.62]
Walsh 1998	70	25.63 (3.21)	85	26.12 (3.63)	2.5 %	-0.49 [-1.57, 0.59]
WHI 2002	6704	28.8 (6)	7080	28.8 (5.9)	72.7 %	0.0 [-0.20, 0.20]
Wimalawansa 1995	12	25.3 (2.94)	9	24.9 (2.97)	0.4 %	0.40 [-2.16, 2.96]
Wimalawansa 1998	15	25 (3.17)	14	26 (2.2)	0.7 %	-1.00 [-2.98, 0.98]
Total (95% CI)	**8432**		**8860**		**100.0 %**	**-0.10 [-0.27, 0.07]**

Heterogeneity: Chi² = 7.62, df = 9 (P = 0.57); I² =0.0%
Test for overall effect: Z = 1.16 (P = 0.25)



Cochrane database of Systematic Reviews 1999 Issue 3

HRT and weight gain

The evidence show no increase in weight gain

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HT and weight gain

Hormone preparations have zero kilojoules

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WHI trial

BBC NEWS

You are in: Health

News Front Page
World
UK
England
N Ireland
Scotland
Wales
Politics
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Science/Nature
Technology
Health
Medical notes
Education

Talking Point

Country Profiles
In Depth

Programmes

Wednesday, 10 July, 2002, 11:29 GMT 12:29 UK

HRT linked to breast cancer

The study examined estrogen and progestin

Women who take hormone replacement therapy may be at increased risk of breast cancer, heart disease and stroke, a study suggests.

WHI 2002

Labelled HRT as dangerous based on increaed breast cancer risk

- This was reported as a 26% increase in breast cancer risk

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WHI 2002

Labelled HRT as dangerous based on increaed breast cancer risk

An absolute inreased risk of 8 additional invasive breast cancers per 10 000 users of E+P per year

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WHI study

Prospective study to evaluate the effectiveness of HRT in ***preventing CHD*** in asymptomatic post-menopausal women

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WHI study

Prospective study to evaluate the effectiveness of HRT in ***preventing CHD*** in asymptomatic post-menopausal women

- Mean age of population studied 63
- Hypertension and obesity in significant numbers

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WHI study

Don’t prescribe HRT to asymptomatic 63 year old (obese and hypertensive) ***solely to prevent CHD***, because it does not prevent CHD in this population

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The concerns doctors have regarding HRT risk

VTE /CVI

Cardiovascular disease

Breast cancer

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CLIMACTERIC 2013;16:203–204

Global Consensus Statement on Menopausal Hormone Therapy

T. J. de Villiers, M. L. S. Gass[*], *C. J. Haines*[†], *J. E. Hall*[‡], *R. A. Lobo*[**], *D. D. Pierroz*[††] *and M. Rees*[‡‡]

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The following Consensus Statement is endorsed by The American Society for Reproductive Medicine, The Asia Pacific Menopause Federation, The Endocrine Society, The European Menopause and Andropause Society, The International Menopause Society, The International Osteoporosis Foundation and The North American Menopause Society.

CLIMACTERIC, 2016
VOL. 19, NO. 4, 313–315
http://dx.doi.org/10.1080/13697137.2016.1196047

Taylor & Francis
Taylor & Francis Group

Revised Global Consensus Statement on Menopausal Hormone Therapy

T. J. de Villiers[a], J. E. Hall[b], J. V. Pinkerton[c], S. Cerdas Pérez[d], M. Rees[e], C. Yang[f] and D. D. Pierroz[g]

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The following Consensus Statement is endorsed by The International Menopause Society, The North American Menopause Society, The Endocrine Society, The European Menopause and Andropause Society, The Asia Pacific Menopause Federation, The International Osteoporosis Foundation and The Federation of Latin American Menopause Societies.

Global consensus statement 1

Menopausal Hormone Therapy (MHT) including tibolone is the most effective treatment for vasomotor symptoms

- < 60 years of age or within 10 years after onset of menopause

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How effective are hormones in treating menopausal symptoms

Oestrogen is highly effective

Nothing else comes close to it

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Hot flushes: frequency/week

Review: Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes
Comparison: 2 Any HRT versus placebo: vasomotor outcomes at end of study
Outcome: 1 Hot flush frequency/week

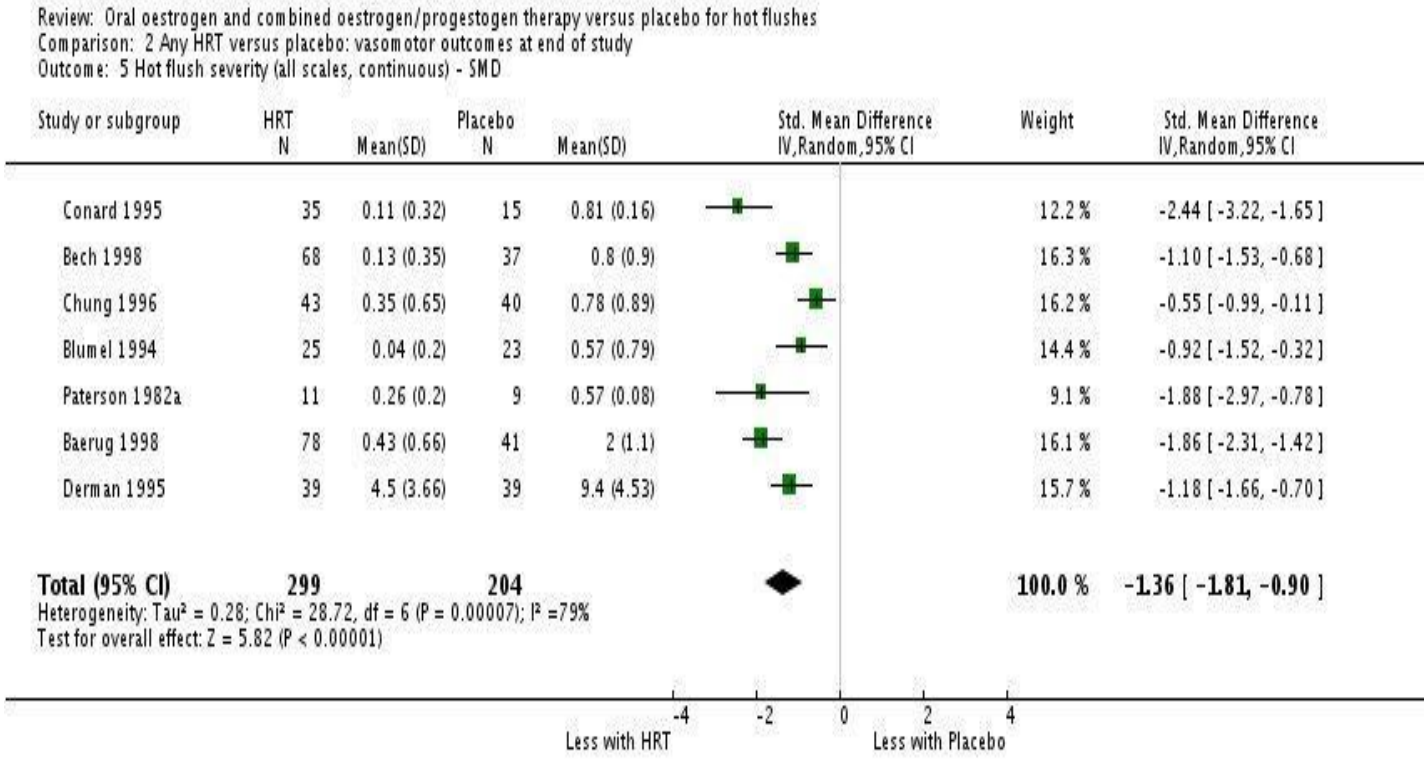
Study or subgroup	HRT N	HRT Mean(SD)	Placebo N	Placebo Mean(SD)	Weight	Mean Difference IV,Random,95% CI
Baerug 1998	73	3.7 (6.85)	33	33.5 (31)	10.7 %	-29.80 [-40.49, -19.11]
Conard 1995	35	0.98 (2.87)	15	32.2 (35.56)	5.6 %	-31.22 [-49.24, -13.20]
Coope 1975	15	2.87 (6.35)	15	21.93 (26.8)	7.9 %	-19.06 [-33.00, -5.12]
Coope 1981	29	4.9 (14.4)	26	16.3 (26.9)	9.8 %	-11.40 [-22.99, 0.19]
Derman 1995	34	0.85 (16.6)	36	12.64 (16.6)	14.0 %	-11.79 [-19.57, -4.01]
Notelovitz 2000a	225	13 (24)	55	28 (29)	13.4 %	-15.00 [-23.28, -6.72]
Symons 2000 Study 1	149	7.6 (13.9)	38	25 (29)	12.0 %	-17.40 [-26.89, -7.91]
Symons 2000 Study 2	199	14.1 (26.2)	67	39.4 (32.7)	13.0 %	-25.30 [-33.93, -16.67]
Viklylaeva 1997	32	13.84 (15.3)	28	23.68 (16.5)	13.6 %	-9.84 [-17.93, -1.75]
Total (95% CI)	**791**		**313**		**100.0 %**	**-17.92 [-22.86, -12.99]**

Heterogeneity: Tau² = 29.47; Chi² = 17.38, df = 8 (P = 0.03); I² =54%
Test for overall effect: Z = 7.12 (P < 0.00001)

-100 -50 0 50 100
Less with HRT
Less with Placebo

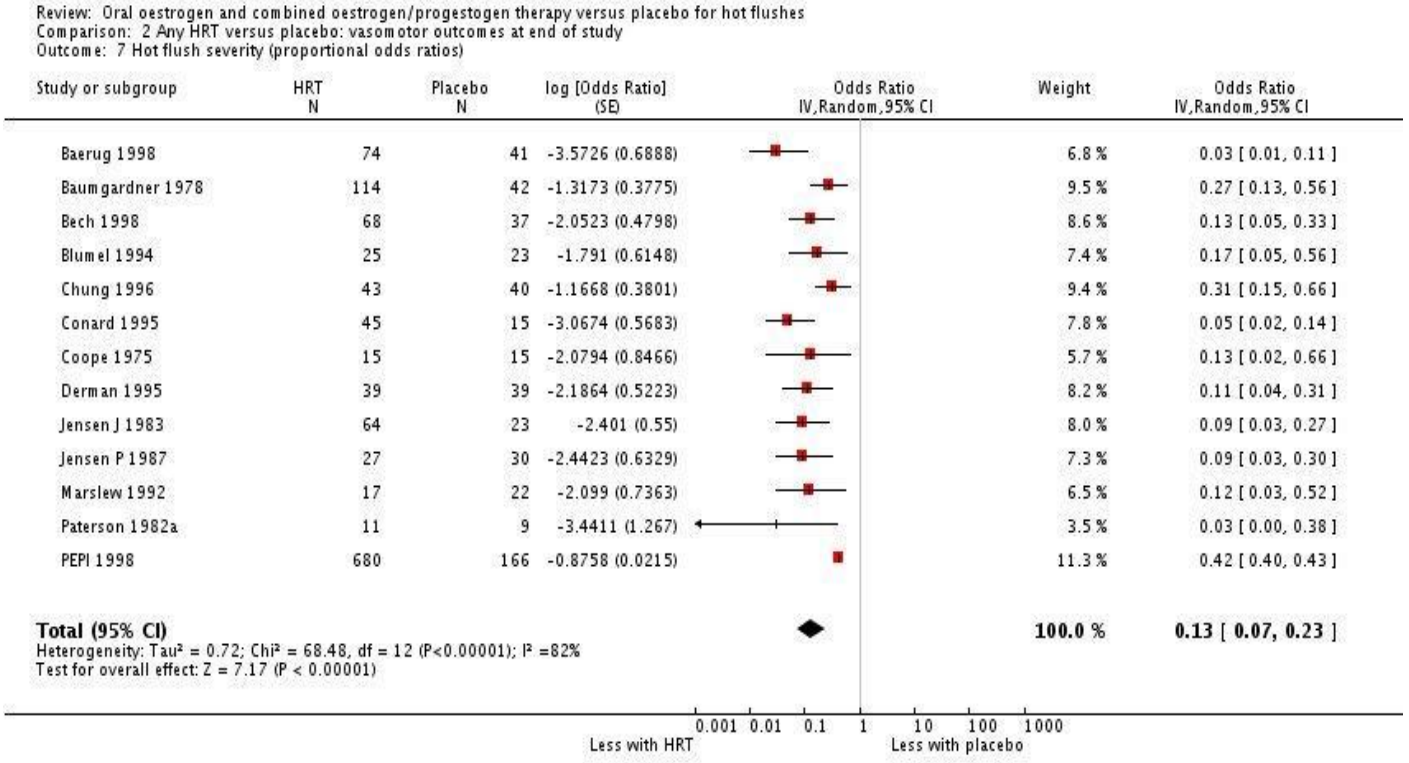
Cochrane database of Systematic Reviews 2009 Issue 1

Hot flushes: severity



Cochrane database of Systematic Reviews 2009 Issue 1

Hot flushes: severity (odds ratio)



Cochrane database of Systematic Reviews 2009 Issue 1

Global consensus statement 2

MHT including tibolone is effective and appropriate for the prevention

- bone loss
- osteoporosis-related fractures in at-risk women before age 60 years or within 10 years after menopause

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Global consensus statement 3

RCTs and observational data provide evidence that standard-dose oestrogen-alone MHT may decrease CHD and all-cause mortality in women < 60 years of age and within 10 years of menopause

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Global consensus statement 3

Data on oestrogen plus progestogen MHT in this population show a similar trend for mortality but in most RCTs no significant increase or decrease in coronary heart disease has been found

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Global consensus statement 4

Local low-dose oestrogen therapy is preferred for women whose symptoms are limited to vaginal dryness or associated discomfort with intercourse

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Global consensus statement 4

MHT including tibolone is effective in the treatment of vulvovaginal atrophy - component of the genitourinary syndrome of menopause (GSM)

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Global consensus statement 5

Oestrogen as a single systemic agent is appropriate in women after hysterectomy but additional progestogen is required in the presence of a uterus (probably also for women who had endometriosis)

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Global consensus statement 6

The option of MHT is an individual decision in terms of quality of life and health priorities as well as personal risk factors such as age, time since menopause and the risk of venous thromboembolism, stroke, ischemic heart disease and breast cancer

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Global consensus statement 7

The risk of VTE and ischemic stroke increases with oral MHT but the absolute risk is rare below age 60 years

Observational studies point to a lower risk with transdermal therapy

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VTE and hormone therapy

Transdermal oestrogen not associated with increased risk (observational data)

Absolute risk remains small

Don’t stop and start

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Stroke risk and hormone therapy

Increased risk regardless of age and years since onset of menopause

Absolute excess risk of stroke in women 50-59 years minimal

- 2 additional cases per 10 000 person years
- 8 additional cases per 10 000 person years in WHI

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Global consensus statement 8

The risk of breast cancer in women over 50 years associated with MHT is a complex issue

- Decreased risk for E alone
- Possible increased risk with E + P

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Global consensus statement 8

The risk of breast cancer attributable to MHT is rare

- Incidence of <1.0 per 1000 women per year of use
- Similar or lower than the increased risk associated with common factors such as sedentary lifestyle, obesity and alcohol consumption
- The risk may decrease after treatment is stopped, but data are inconsistent

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Global consensus statement 9

The dose and duration of MHT should be consistent with treatment goals and safety issues and should be individualised

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Global consensus statement 10

The use of custom-compounded bio-identical hormone therapy is not recommended

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Global consensus statement 11

Current safety data do not support the use of MHT in breast cancer survivors

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MHT and Breast Cancer Risk

Breast cancer risk

Varies substantially between women

Those with low baseline risk will experience less excess risk

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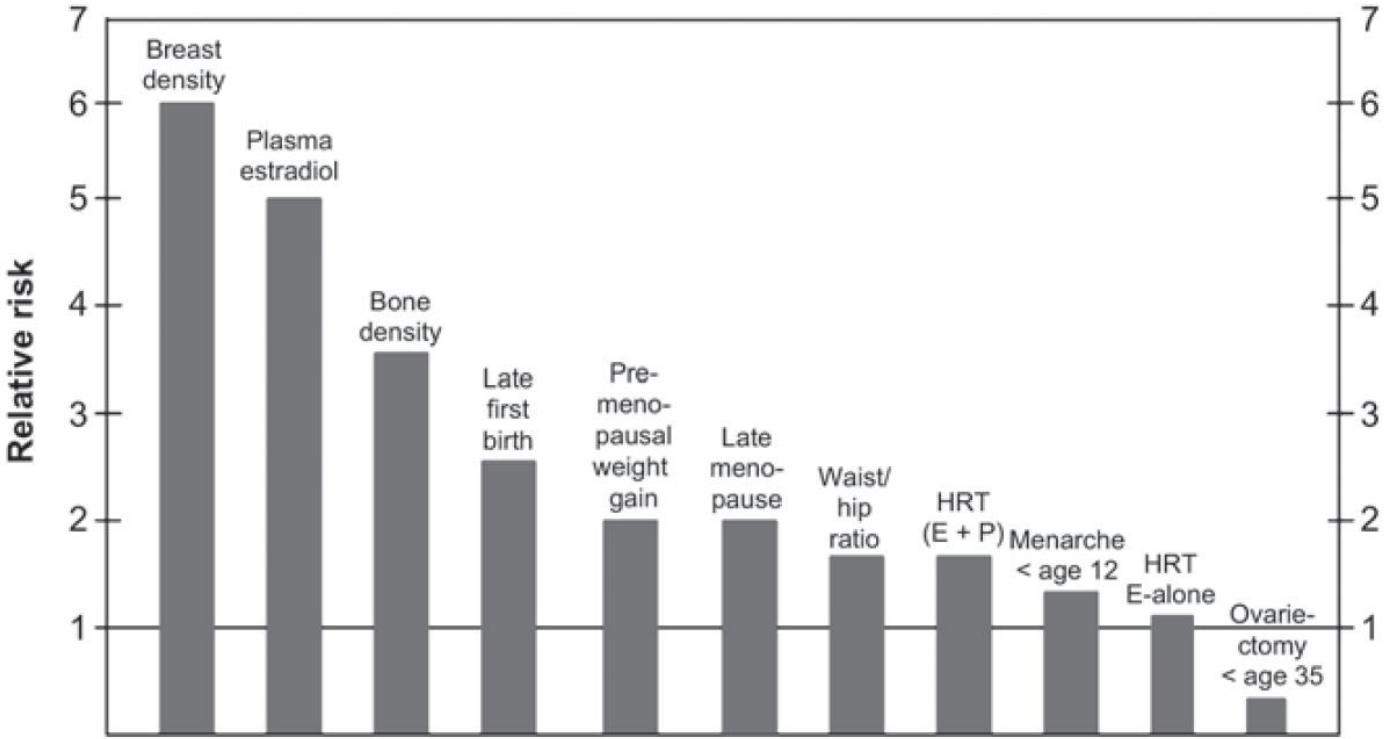
Reproductive breast cancer risk factors



Age Specific Probabilities of Developing Breast Cancer

Current age	Probability of Breast Cancer in next 10 years	Incidence 1 in
20	0.05%	2,152
30	0.40%	251
40	1.45%	69
50	2.78%	36
60	3.81%	26
70	4.31%	23

Breast cancer risk and age

	Probability	
Birth to age 49	1.9	1 in 53
Age 50 – 69	2.3	1 in 44
Age 60 – 69	3.5	1 in 29
Age 70 and older	6.7	1 in 15
Lifetime risk	12.3	1 in 8

Breast cancer risk

Factor	RR	95% CI
>10 kg weight gain since menopause	1.18	1.03 – 1.35
Female air hostess night shift	1.51	1.36 – 1.68
Female night shift worker	1.44	1.26 – 1.65
Physical activity	0.88	0.85 – 0.90

Table 1 Risk factors reported to be associated with the development of breast cancer

	Relative risk	*95% confidence interval*	*Reference*
Dietary fiber intake	0.31	0.20–0.47	27
Significant weight gain from age 21 to present	0.52	0.32–0.83	28, 29
Garlic and onions 7–10 times/week	0.52	0.34–0.78	30
High level of stress	0.60	0.37–0.97	31
Grapefruit	0.60	0.37–0.98	32
Fish oil	0.68	0.50–0.92	33
Large body build at menarche	0.69	0.49–0.96	28, 29
Conjugated equine estrogen	0.77	0.59–1.01	34
Aspirin	0.80	0.71–0.90	35
Coffee consumption >5 cups/day	0.80	0.64–0.99	36
Above average weight at 12 years	0.85	0.74–0.98	37
Low income	0.85	0.84–0.87	38
Cigarette smoking	1.06	1.01–1.10	39
Birth weight	1.09	2.00–17.00	40
Fish intake	1.14	1.03–1.26	41
Birth length >51 cm	1.17	1.02–1.35	42
Use of antihypertensive medicine >5 years	1.18	1.02–1.36	43
Exposure to light at night	1.22	1.12–1.31	44
Cigarette smoking	1.24	1.06–1.44	45
Premarin/progestin	1.24	1.01–1.54	46
Premarin/progestin	1.26	1.00–1.59	47
Alcohol	1.26	1.06–1.44	45
French fries (1 additional serving/week)	1.27	1.12–1.44	48
Physical abuse in adulthood	1.28	1.07–1.52	49
Grapefruit	1.3	1.06–1.58	50
Digoxin (current users)	1.39	1.32–1.46	51
Night shift work	1.51	1.36–1.68	52, 53
>15 kg weight gain during pregnancy	1.61	1.03–2.52	54
Cigarettes at least 10/day	1.7	1.20–2.43	55
Flight attendant (Finnish)	1.87	1.15–2.23	56, 57
Father ≥ 40 years old (premenopausal breast cancer)	1.9	1.12–3.26	58
Dutch famine	2.01	0.92–4.41	59
Placental weight	2.05	1.15–3.64	60
Antibiotic use	2.07	1.48–2.89	61
Increased carbohydrate intake	2.22	1.63–3.04	62
Left-handedness (premenopausal)	2.41	1.35–4.30	63
Intercristal width* of >30 cm in a mother who was born >40 weeks' gestation	3.7	2.1–6.8	64
Flight attendant (Icelandic)	4.1	1.70–8.50	65
Betel quid chewing	4.78	2.87–8.00	66
Electric blanket use	4.9	1.50–15.6	67
Vitamin D deficiency	5.83	2.31–14.7	68, 69
Intercristal width* of >30 cm in a mother who had given birth previously	7.2	3.4–15.4	64
Tobacco smoking and lung cancer	26.07	6.58–103.3	70

*, The intercristal width is the maximal width between the iliac crests

Perspective

None of these consistently shown to be risk factors

Post-hoc statistical manipulation such as data mining or retrospective sub-stratification to find publishable “statistical” result

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WHI follow-up data

Daily Mail

MONDAY, APRIL 9, 2007 www.dailymail.co.uk 45p

Now experts say hormone therapy can CUT heart attack danger

U-TURN ON THE RISKS OF HRT

By Jenny Hope
Medical Correspondent

MILLIONS of women may have been scared into abandoning HRT unnecessarily, it was revealed yesterday.

A U.S. report which linked the treatment to heart disease and strokes has been shown to be dramatically flawed.

A detailed new look at its research results revealed that hormone replacement therapy may actually protect many patients against such illnesses.

British experts said the revised analysis of the Women's Health Initiative Study virtually reversed the 2002 warning that led millions of women to stop HRT or not start it.

It has discovered that any extra risks may apply only to older patients – with HRT actually boosting the health of the women in their 50s who are most likely to use it to fight symptoms of the menopause. Their risk of stroke is no higher and their risk of dying prematurely is actually 30 per cent lower.

Dr John Stevenson, an HRT expert from London's Royal Brompton Hospital, launched a furious attack on the original researchers and warned that women who stopped taking hormones would go on to suffer heart attacks and other illnesses they 'didn't deserve'.

He said: "This is a U-turn of dramatic proportions. These conclusions are at complete variance with the widely-publicised 2002 results on which our guidance on prescribing is based.

"We are astonished that a study which made such a claim for the dangers of HRT is now showing just the opposite. It is an affront to science, adding insult to injury for the thousands

Turn to Page 4

Faye Turney, interviewed by Sir Trevor McDonald, has sold her story for at least £100,000

Should hostage Britons be allowed to turn captivity into cash?

SEE PAGES 6-7

WHI secondary analysis 2007

Women who began HRT within the first 10 years following the menopause actually reduced their risk of coronary heart disease (HR of 0.76)

WHI secondary analysis 2007

The data also showed that hormone users aged 50 – 59 had a 30% lower risk of ***all cause mortality*** than those in placebo group

WHI longer follow-up

11-year follow-up study

Women randomised to CEE/MPA ***without prior exposure to HRT*** had no increase in breast cancer incidence relative to women randomised to placebo (HR 1.16; 95% CI 0.98 – 1.37)

WHI longer follow-up

CEE alone

Reduced breast cancer incidence (HR 0.82; 95% CI 0.65 – 1.04) (NS)

In adherent women

Statistically significant reduction in breast cancer incidence (HR 0.67; 95% CI 0.47 – 0.97)

WHI longer follow-up

After 12.6 years

Significant persistence in the reduction in breast cancer incidence in the group of women randomised to CEE regardless of adherence

(HR 0.77; 95% CI 0.62 – 0.95)

From WHI

Data from the WHI clearly show

over 11 years, there is ***no increased risk*** of breast cancer in

HRT-naïve women who received CEE/MPA

From WHI

Data from the WHI clearly show

over 11 years, there is ***no increased risk*** of breast cancer in HRT-naïve women who received CEE/MPA

a ***decreased risk*** of breast cancer in those women who received CEE alone

From WHI

Furthermore, for all women in the WHI CEE/MPA trial, there was no increased risk for breast cancer in the first 5 years

HRT and breast cancer risk

It remains unproven as to whether

or not HRT increases the risk of breast cancer

Even if it does the magnitude of that risk is very small and

less than many common lifestyle factors

Breast Cancer Risk and HRT results from the reanalysis of epidemiological studies by the Collaborative Group on Hormonal Factors in Breast Cancer (1997) and the Canadian Consensus on Menopause and Osteoporosis

Risk Factor	Breast Cancers diagnosed over the 20 year from ages 50 to 70	Extra Breast Cancers
Never used HRT	45/1000	–
> 5 years' HRT use	47/1000	2/1000
>10 years' HRT use	51/1000	6/1000
>15 years' HRT use	57/1000	12/1000
Late menopause (age 60)	59/1000	14/1000
Alcohol (2 drinks/day)	72/1000	27/1000
No daily exercise	72/1000	27/1000
Weight gain (>20 kg)	90/1000	45/1000

**Data from V. Beral and the Collaborative Group on Hormonal Factors in Breast Cancer[21] Table was adapted from Table 1, Belisle and Durzke. Hormone Replacement Therapy and Cancer[22] and appears by permission of the Society of Obstetricians and Gynaecologists of Canada.*

WHI in context

Therapy	Event	RR (95% CI	Additional cases per 10 000/year
CEE/MPA	Breast cancer death	1.96 (1.00 – 4.04)	1.30
Raloxifene	Fatal stroke	1.49 (1.00 – 2.24)	20
Aspirin	Sudden death	1.96 (0.91 – 4.23)	5
Fenobarb	Total mortality	1.11 (0.95 – 1.29)	13
ß-carotene	Total mortality	1.17 (1.03 – 1.33)	25
Ca supplement	Total mortality	1.09 (0.96 -1.23)	8

HRT and breast cancer mortality

HRT and breast cancer mortality

Most randomised controlled trials and observational study data indicate that HRT is associated with either a null or reduced overall breast cancer mortality

HRT as a risk factor for death from breast cancer

Women using MHT at the time of diagnosis of breast cancer have improved survival rates

Paradox: possible slightly increased risk and better outcome

earlier diagnosis, localised, smaller, better differentiated

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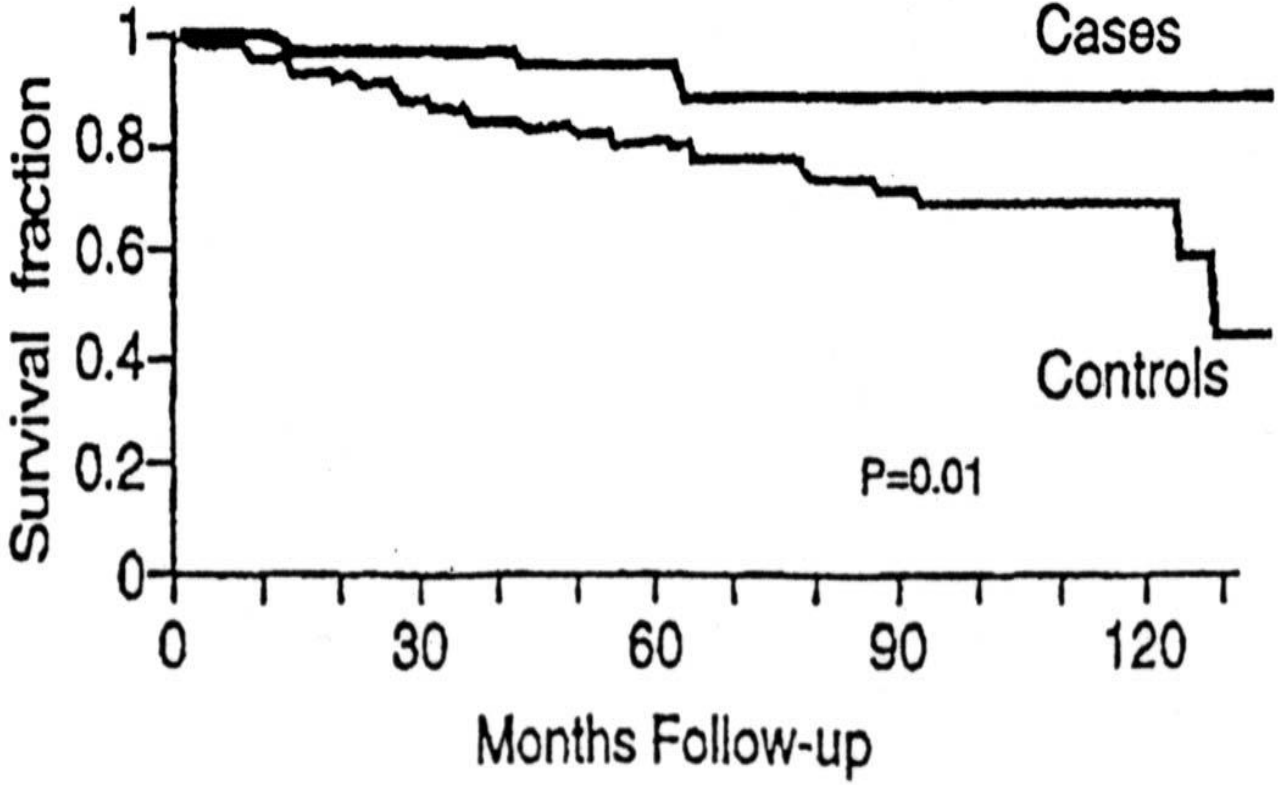
Survival in breast cancer: users vs non users



In a nutshell

HRT does not cause breast cancer

E & P might have a zero to small risk

E reduces risk

Better survival in HRT users

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Causing disease

RR of lung cancer in male smoker vs non smoker is 26.07

RR of cervical cancer if HPV 16 positive vs HPV 16 negative is 435

HR breast cancer WHI 2002 was 1.26

(95% CI 1.00 – 1.59)

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In perspective

RR

HR breast cancer WHI 2002 was 1.26 (95% CI 1.00 – 1.59)

AR

4 per 1000 women taking E+P for 5 years

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Millions of women stopped their

HRT following this non-significant statistic

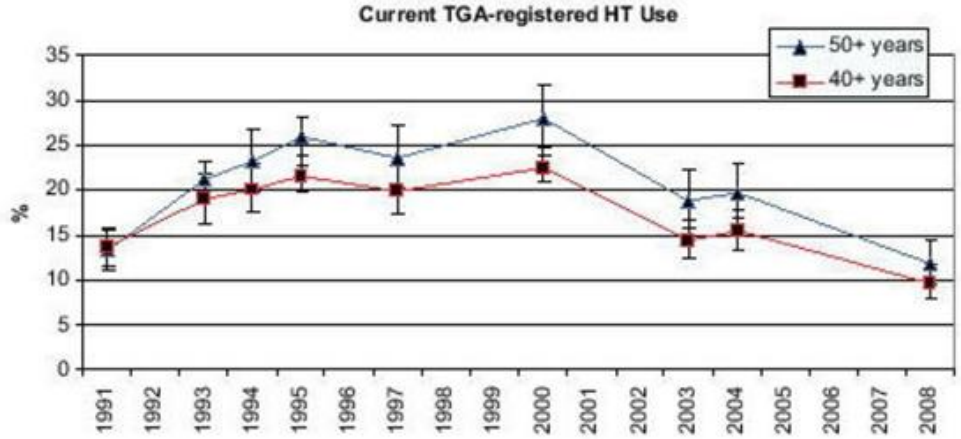

Figure 1 Current hormone therapy (HT) use by age group, women aged ≥40 years and women aged ≥50 years, over time (South Australian Health Omnibus Surveys 1991–2008)[15]. TGA, Therapeutic Goods Administration

How do you communicate risk?

P value?

Comparative data?

- Compared to average of population?
- Compared to other conditions?

How do you frame it?

- Positively?
- Negatively?

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How do you communicate risk?

What terminology do you use or should you use?

- Relative risk? Relative risk reduction?
- Odds Ratio? Hazard ratio?
- Absolute risk? Absolute risk reduction?
- Numbers needed to treat? Numbers needed to harm?
- Common? Rare? Very rare?

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The problem

Doctors struggle to understand risk

Patients don’t understand it

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How should you communicate risk?

For the most part, there is confusion and continious debate between clinicians about how best to translate concepts of epidemiological risk into clinical risk

The language statisticians use…

Relative Risk

The incidence in exposed individuals divided by the incidence in unexposed individuals

Odds Ratio

The odds that an individual with a specific condition has been exposed to a risk factor divided by the odds that a control has been exposed

The odds ratio is used in case-control studies

The odds ratio provides a reasonable estimate of the relative risk for uncommon conditions

Hazard Ratio

Ratio of instantaneous risk in two experimental arms

It represents **point estimate at any given point of time,** it is not cumulative estimate like relative risk and odds ratio

Interpretation remains same as Odds ratio, keeping in mind the time factor

The RR and OR are interpreted relative to the number one

An OR of 0.6, for example, suggests that patients exposed to a variable of interest were 40% less likely to develop a specific outcome compared to the control group

An OR of 1.5 suggests that the risk was increased by 50%

Risk reduction can be presented using:

relative risk reduction (RRR)

absolute risk reduction (ARR), or

numbers needed to treat (NNT)

Relative, absolute and excess risk

Risk of dying in a plane crash = 1 in 10 million

With five plane flights: risk = 5 in 10 million

The RR = 5.0 (500% increase)

Absolute excess for five fligts is 4 in 10 million

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The RRR is the reduction of risk in the intervention group relative to the risk in the control group

For a risk of 20% in the control group and a risk of 10% in the intervention group, the RRR would be 50%

The ARR is the difference in risks between two groups

For a risk of 20% in the control group and a risk of 10% in the intervention group the ARR would be 10%

In a clinical trial of a drug to prevent migraines, 2 of 100 people taking the drug experience a migraine (2%), compared with 4 of 100 people taking a placebo (4%)

The ***absolute risk reduction*** is 2%, because 4% − 2% = 2%
That is, there were 2% fewer migraines in people taking the drug

In a clinical trial of a drug to prevent migraines, 2 of 100 people taking the drug experience a migraine (2%), compared with 4 of 100 people taking a placebo (4%)

The ***relative risk reduction*** is 50%, because 4% of people taking placebo had a migraine, but only 2% of those taking the drug

The NNT is the number of patients who need to be treated (or screened) to prevent one additional adverse outcome

For a risk of 20% in the control group and a risk of 10% in the intervention group NNT = 10

Ms Jones

Just turned 50, fit and healthy

- Fam hist = neg; Men at 14; 1st child at 26

Wants mammography screening

- Her sister thinks it can only be a good thing; Ms Jones is sceptical – concerned about false alarms

She wants to know about benefits and harms

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Mammography data

USPSTF review → 15% decrease RR in mortality

Meta analysis including the Age trial → 16% RR reduction in mortality

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Ms Jones could be presented with the following statements:

RRR:

Early detection with mammography reduces the risk of dying from breast cancer by 15%

ARR:

Early detection with mammography reduces the risk of dying from breast cancer by 0.05%

NNT:

2000 women need to have regular mammograms for more than 10 years to prolong one life

Some risk communication suggestions

A recent review of evidence suggested that using RRR makes treatment benefits and changes in risk seem larger than they are

Information on risk reduction be consistently presented using ARR

A Cochrane review of 22 randomised controlled trials suggests that, compared with general risk information, personalised risk communication (whether written, spoken, or visually presented) in the context of screening tests can lead to more accurate risk perception, improved knowledge, and increased uptake of screening tests

The risk of breast cancer can be presented as a general population based risk estimate (generalised risk information) or on the basis of the individual's own risk factors (personalised risk information)

Breast Cancer Risk Assessment Tool

An interactive tool to help estimate a woman's risk of developing breast cancer

Last modified date: 05/16/2011

- Get Started with the Risk Tool
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Breast Cancer: Prevention, Genetics, Causes

Current Clinical Trials: Breast Cancer *In Situ:* Treatment

Current Clinical Trials: Breast Cancer Prevention

Current Clinical Trials: Breast Cancer Screening

Breast Cancer Risk in American Women

The Breast Cancer Risk Assessment Tool is an interactive tool designed by scientists at the National Cancer Institute (NCI) and the National Surgical Adjuvant Breast and Bowel Project (NSABP) to estimate a woman's risk of developing invasive breast cancer. See About the Tool for more information.

The Breast Cancer Risk Assessment Tool may be updated periodically as new data or research becomes available.

Risk Tool

(Click a question number for a brief explanation, or read all explanations.)

1. Does the woman have a medical history of any breast cancer or of ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS) or has she received previous radiation therapy to the chest for treatment of Hodgkin lymphoma? — Select

2. Does the woman have a mutation in either the *BRCA1* or *BRCA2* gene, or a diagnosis of a genetic syndrome that may be associated with elevated risk of breast cancer? — Select

3. What is the woman's age?
   This tool only calculates risk for women 35 years of age or older. — Select

4. What was the woman's age at the time of her first menstrual period? — Select

Risk Tool

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This tool only calculates risk for women 35 years of age or older. — Select

4. What was the woman's age at the time of her first menstrual period? — Select

5. What was the woman's age at the time of her first live birth of a child? — Select

6. How many of the woman's first-degree relatives - mother, sisters, daughters - have had breast cancer? — Select

7. Has the woman ever had a breast biopsy? — Select

   7a. How many breast biopsies (positive or negative) has the woman had? — Select

   7b. Has the woman had at least one breast biopsy with atypical hyperplasia? — Select

8. What is the woman's race/ethnicity? — Select

   8a. What is the sub race/ethnicity? — Select

Calculate Risk >

5 Year Risk of Developing Breast Cancer

- This woman (age 53): 1.2%
- Average woman (age 53): 1.4%

Explanation

Based on the information provided (see below), the woman's estimated risk for developing invasive breast cancer over the next 5 years is 1.2% compared to a risk of 1.4% for a woman of the same age and race/ethnicity from the general U.S. population. This calculation also means that the woman's risk of NOT getting breast cancer over the next 5 years is 98.8%.

Lifetime Risk of Developing Breast Cancer

- This woman (to age 90): 9.4%
- Average woman (to age 90): 10.6%

Explanation

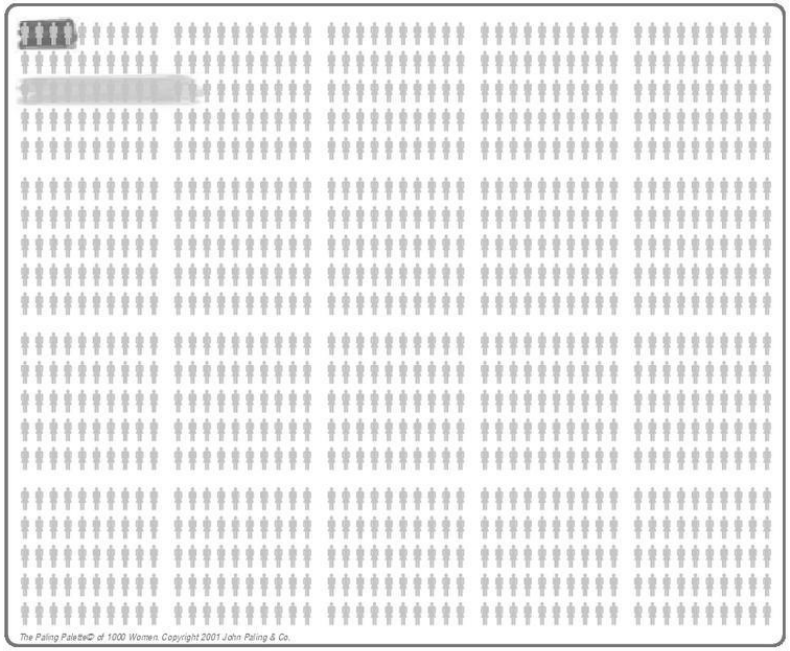
Based on the information provided (see below), the woman's estimated risk for developing invasive breast cancer over her lifetime (to age 90) is 9.4% compared to a risk of 10.6% for a woman of the same age and race/ethnicity from the general U.S. population.

There is growing evidence to support the use of pictographs to present natural frequencies, with evidence suggesting that these are well understood and that they effectively support communication about individual statistics

One Thousand People
– Pictures to Help You

See Your Odds

We can only show you averages. It is impossible to predict whether your results will be positive or negative.



Odds for a 39 year old woman of producing a child with Downs Syndrome or other chromosome abnormality 12 out of 1000

Odds of a woman having a miscarriage as a result of amniocentesis (4 out of 1,000)

Data from Hook EB, Cross PK and Schreinemachers DM. Chromosome abnormality rates at amniocentesis and in live born infants. JAMA 249(15):2034-8

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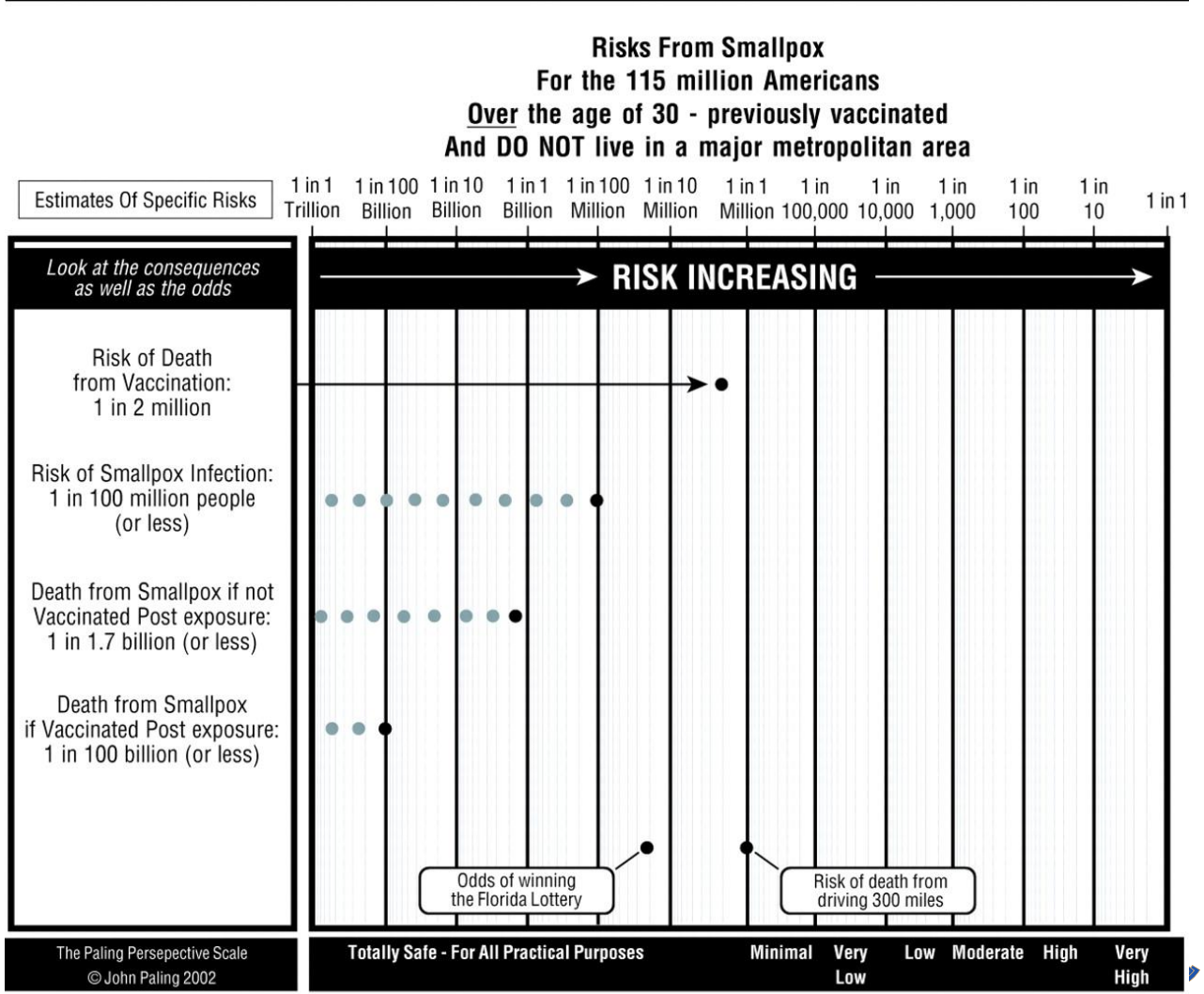
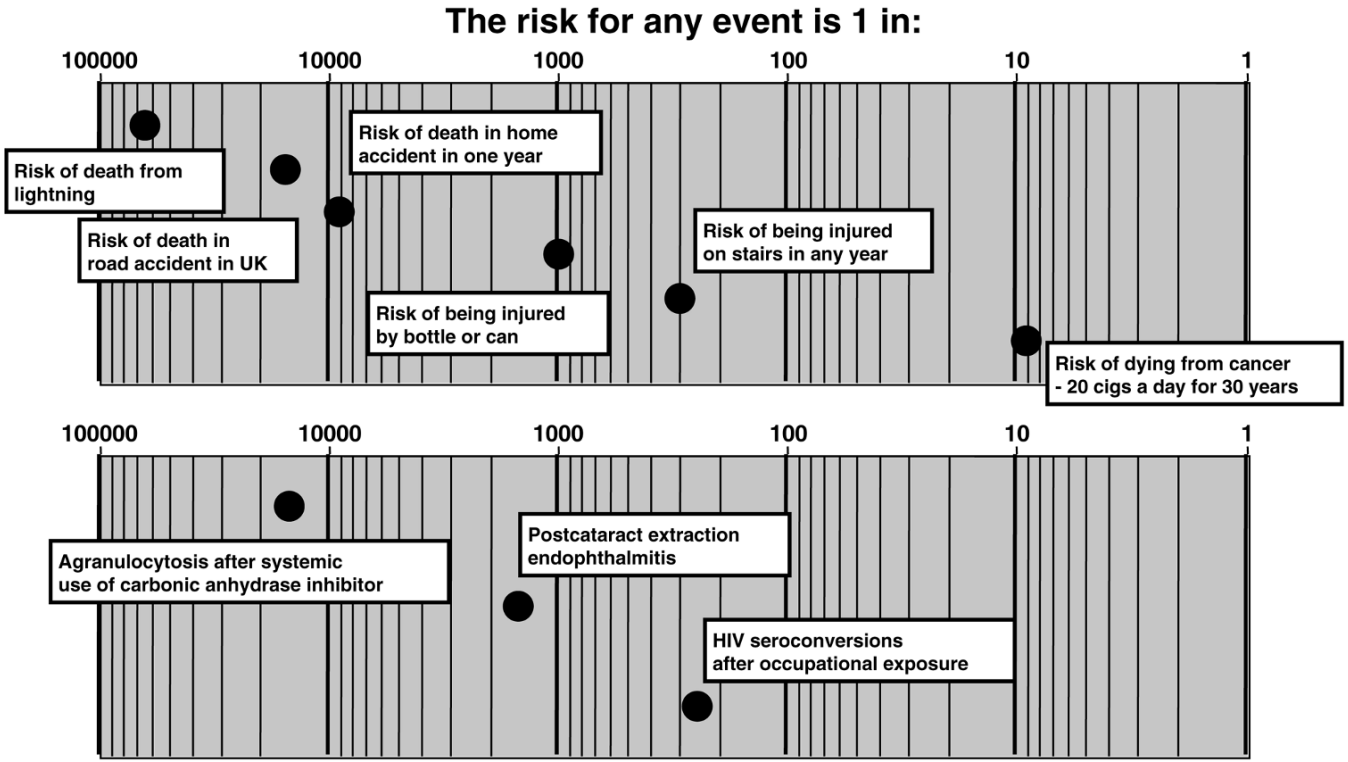
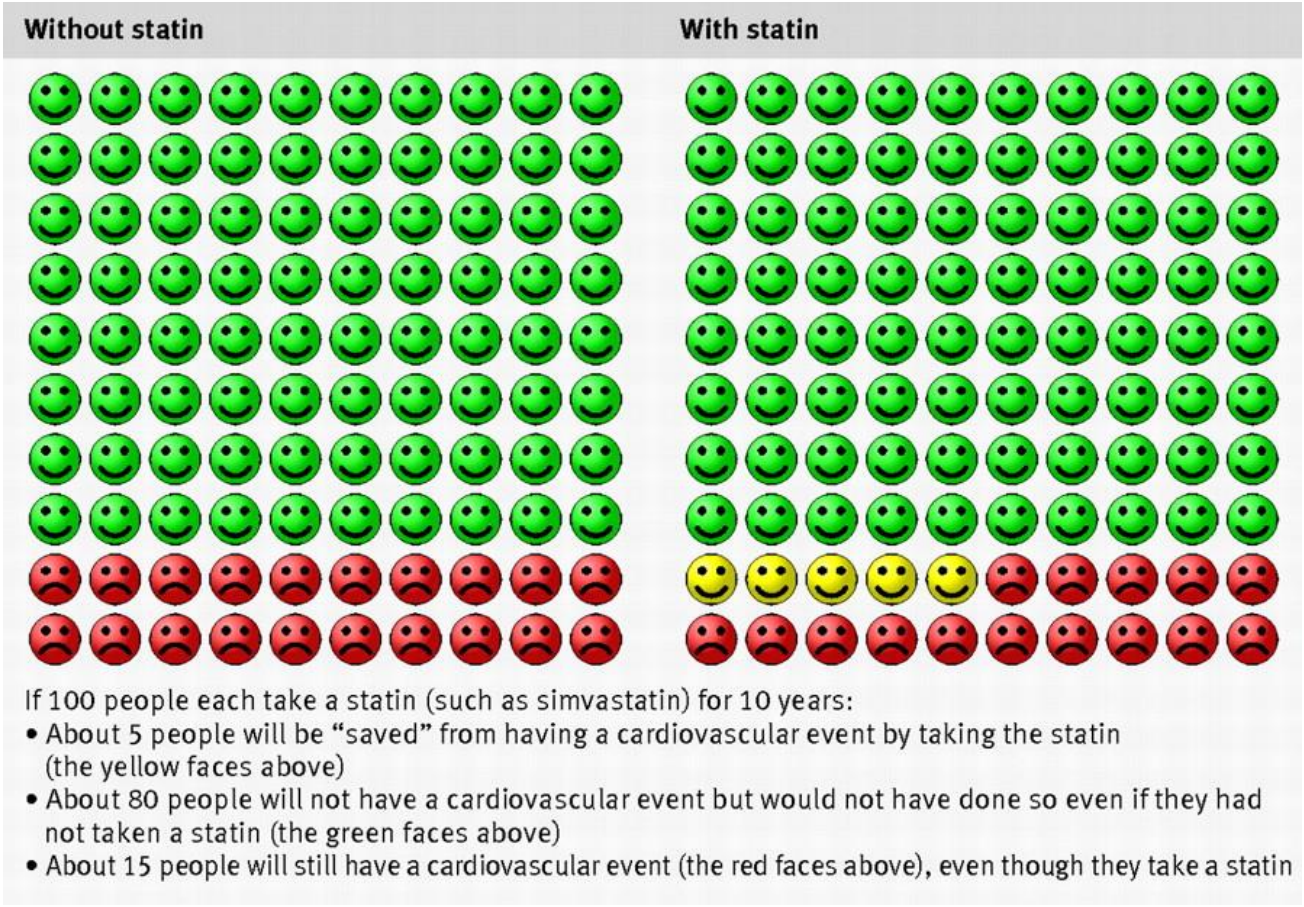

Risks From Smallpox
For the 115 million Americans
Over the age of 30 - previously vaccinated
And DO NOT live in a major metropolitan area
Estimates Of Specific Risks
1 in 1 Trillion
1 in 100 Billion
1 in 10 Billion
1 in 1 Billion
1 in 100 Million
1 in 10 Million
1 in 1 Million
1 in 100,000
1 in 10,000
1 in 1,000
1 in 100
1 in 10
1 in 1
Look at the consequences as well as the odds
RISK INCREASING
Risk of Death from Vaccination: 1 in 2 million
Risk of Smallpox Infection: 1 in 100 million people (or less)
Death from Smallpox if not Vaccinated Post exposure: 1 in 1.7 billion (or less)
Death from Smallpox if Vaccinated Post exposure: 1 in 100 billion (or less)
Odds of winning the Florida Lottery
Risk of death from driving 300 miles
The Paling Persepective Scale
© John Paling 2002
Totally Safe - For All Practical Purposes
Minimal
Very Low
Low
Moderate
High
Very High





Haroon Ahmed et al. BMJ 2012;344:bmj.e3996

How to communicate risk?

Use absolute risk

Be careful with comparative risks

Provide risk as well as benefit

- “Transaction” where patients “buy” benefits with a “currency” called risk

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More than one paradox in MHT

Paradox 1

Women produce hormones for the best part of 40 years, no problem

When they stop producing their own, it all of a sudden becomes “dangerous” to prescribe hormones

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Paradox 2

Having to convince women that an intervention associated with a 30 to 40% reduction in all cause mortality, is safe and will not kill them

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Thank you

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