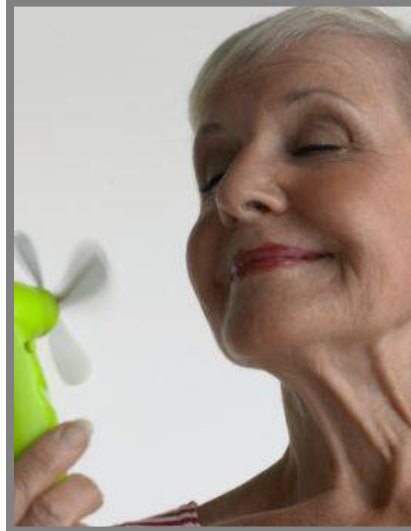


# HRT and Menopause



Mr N Pisal  
Consultant Gynaecologist  
Whittington & Portland Hospital

Menopause  
and HRT



Screening

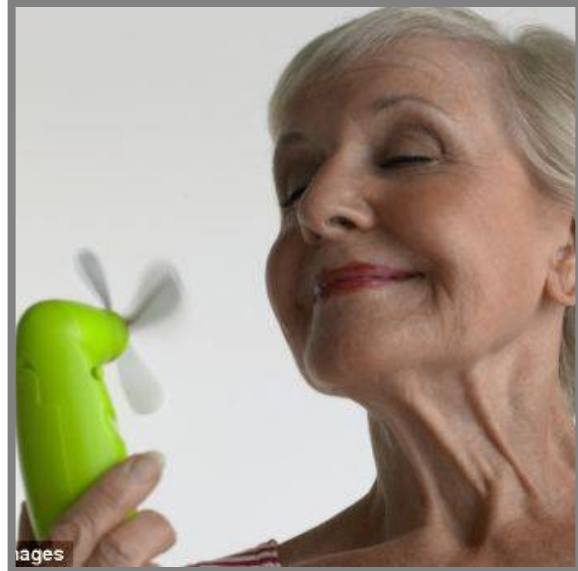


Sexual  
Health



Bone  
Health





## Menopause and HRT



# Menopausal Symptoms

---

- 94% get some symptoms, 25% get severe symptoms
- Hot flushes & sweats
- 74% experience, most common symptom
- Headaches
- Tiredness
- Irritability
- Poor memory
- Sleep disturbance
- Depression, anxiety, Mood swings
- Loss of libido
- Dry skin
- Vaginal atrophy
- Osteoporosis.....



Carol found her own way  
of coping with the hot  
flushes



# HRT

---

- Very effective at treating symptoms of menopause.
- Until recent studies (Women's Health Initiative and Million Women Study), HRT was widely used for long periods





## The world is singing her praises

Adele's 21 has sold 26 million copies, making it the best-selling album in the United States and the world for the second year running (Nic Fildes writes). She is not the only homegrown artist on top of the world. More than half of all albums sold in Britain and one in eight sold globally were by British artists. Simon Cowell's boy band One Direction had two albums in the US top five, while Lenee Sande, Ed Sheeran and Mumford & Sons all enjoyed global success, according to the British Phonographic Industry. Geoff Taylor, who heads the trade body, said: "Music is fundamental to Britain's identity as a nation and the world is singing with us."

# HRT scare prompted by 'flawed' studies

David Derbyshire

Hundreds of thousands of women have suffered needlessly over the past decade because of the HRT scare, a hormone specialist said yesterday.

Helen Buckler, an endocrinologist at the University of Manchester, said that there was an emerging consensus that hormone replacement therapy was safe for most women under 60.

The studies that triggered the scare 11 years ago by claiming a link with breast cancer and heart disease were flawed or not applicable in the UK, she told the Cheltenham Science Festival.

THE TIMES  
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## The girls who are destined to grow up into tomboys

Hannah Devlin Science Editor

Exposure to testosterone in the womb influences whether girls conform to the gender stereotype of playing with dolls or are more likely to seek out "tomboy" activities, scientists have said.

Polly Carmichael, an endocrinologist at Great Ormond Street Hospital, said that there was growing evidence that hormones in early development could have a permanent influence on gender identity and behaviour. The findings challenge the view that giving your child a "gender neutral" upbringing could prevent stereotypes arising in the first place. "There's now good evidence that hormone exposure has an influence," she said.

Dr Carmichael has extensively studied girls born with a syndrome called congenital adrenal hyperplasia (CAH), who have been exposed to a large dose of testosterone in the womb. As a result the children are often born with "male-

like" genitalia, but are now normally assigned a female gender at birth.

She said that girls with the condition provide a natural control group for studying the extent to which biological factors such as genes and hormones influence gender roles, compared with the impact of social factors. "Their behaviour is more boyish in terms of their choice of playmates and self identity," she said.

Dr Carmichael cited one study that showed that girls with CAH were more likely to prefer toys that are usually chosen by boys, such as vehicles and weapons, and have greater interest in rough-and-tumble play.

The same study showed that, while in general, boys and girls of primary school age have 80-90 per cent of playmates of the same sex, girls with CAH do not appear to show a preference for playing with one sex over the other.

The study found that about 50 per cent of their favourite playmates were girls and about 50 per cent were boys.

Her comments come just days after the British Menopause Society published new guidance stating that the benefits of HRT outweighed the risks for women in their 50s. However, Cancer Research UK warned that the treatment remained a risk factor for breast cancer and urged women to reduce the dose and duration of treatment.

HRT is used to ease menopausal symptoms such as hot flashes, night sweats, depression and loss of sex drive. It works by replacing the female sex hormones oestrogen and progesterone that are lost during the menopause.

Fears about the safety of HRT were

raised by studies in 2002 and 2003. The first, the US Women's Health Initiative (WHI), concluded that HRT taken by women in their 50s and 70s increased risks of breast cancer, heart disease and stroke.

The following year the Million Women Study, funded in part by Cancer Research UK, appeared to confirm the cancer link, and about one million women stopped taking HRT as a result. Today, 15 per cent of eligible women use the drug, compared with 30 per cent 10 years ago.

Dr Buckler said that more recent analyses had questioned the findings of

both studies. "The feeling is now that oestrogen may continue to be protective for women immediately post-menopause," she said. "This is coming through as a consensus view."

Last year a series of papers in *Obstetrics and Gynaecology*, the journal of the International Menopause Society, identified problems with the WHI findings. They pointed out that the study was designed to test HRT in women in their sixties and seventies. In Britain the average age of the menopause is 52.

The absolute increase in breast cancer risk was also modest - equivalent of one extra case in 1,000 women taking HRT for a year. Further analysis of the WHI study revealed that the extra health risks applied to older women. The therapy cut the risks of heart disease in younger women.

Dr Buckler said the Million Women study was also flawed. The 13 million women involved were invited to take part when they went for their first mammogram. This meant that women concerned that they were at risk of cancer may have been over-represented in the study, distorting the findings, she said.

Under the Department of Health guidance, amended after the 2002 scare, women are told to take HRT only if they have serious menopausal symptoms, and then for the shortest time possible. Some GPs simply ignore that advice.

The British Menopause Society's new guidance says the benefits outweigh the risks for most women in their 50s and opposes "arbitrary" limits on the duration of HRT.

Cancer Research UK, however, said the incidence of breast cancer had fallen since the drop in HRT use. Jessica Harris, a spokeswoman, said: "There is convincing evidence that women who take HRT have an increased risk of breast cancer, but that risk returns to normal around five years after stopping using it."

Leading article, page 32

## Fizzy drinks leave a bitter aftertaste for the young

Chris Smith Health Correspondent

Teenagers who have a daily can of a sugary drink put themselves at higher risk of heart disease and diabetes even if they are not fat, research has found.

Young people with a can-a-day habit are on the road to serious illness later in life, warned researchers who found that such teenagers had lower levels of good cholesterol and higher levels of harmful fats in their blood. Switching to diet drinks could cut the risk.

Sugary drinks have been linked to obesity and diabetes in adults, but the latest study is the first to show children are at risk.

Gina Ambrosini, of the Medical Research Council Human Nutrition Research Unit at Cambridge University, said: "Our findings suggest drinking a lot of sugary drinks may put young people on a path to the early development of risk factors for diabetes and heart disease."

Her team followed 1,433 Australian



Sugary drinks could cause diabetes

teenagers from the ages of 14 to 17, a third of whom took more than one can a day of drinks with added sugar. Girls in this top third were almost five times as likely to be overweight as those who consumed the least sugary drinks. The findings were less pronounced in boys, although this may be the result of hormonal changes during puberty.

Susan Jebb, head of population health at the Cambridge unit, said it was important for teenagers to change their habits early.



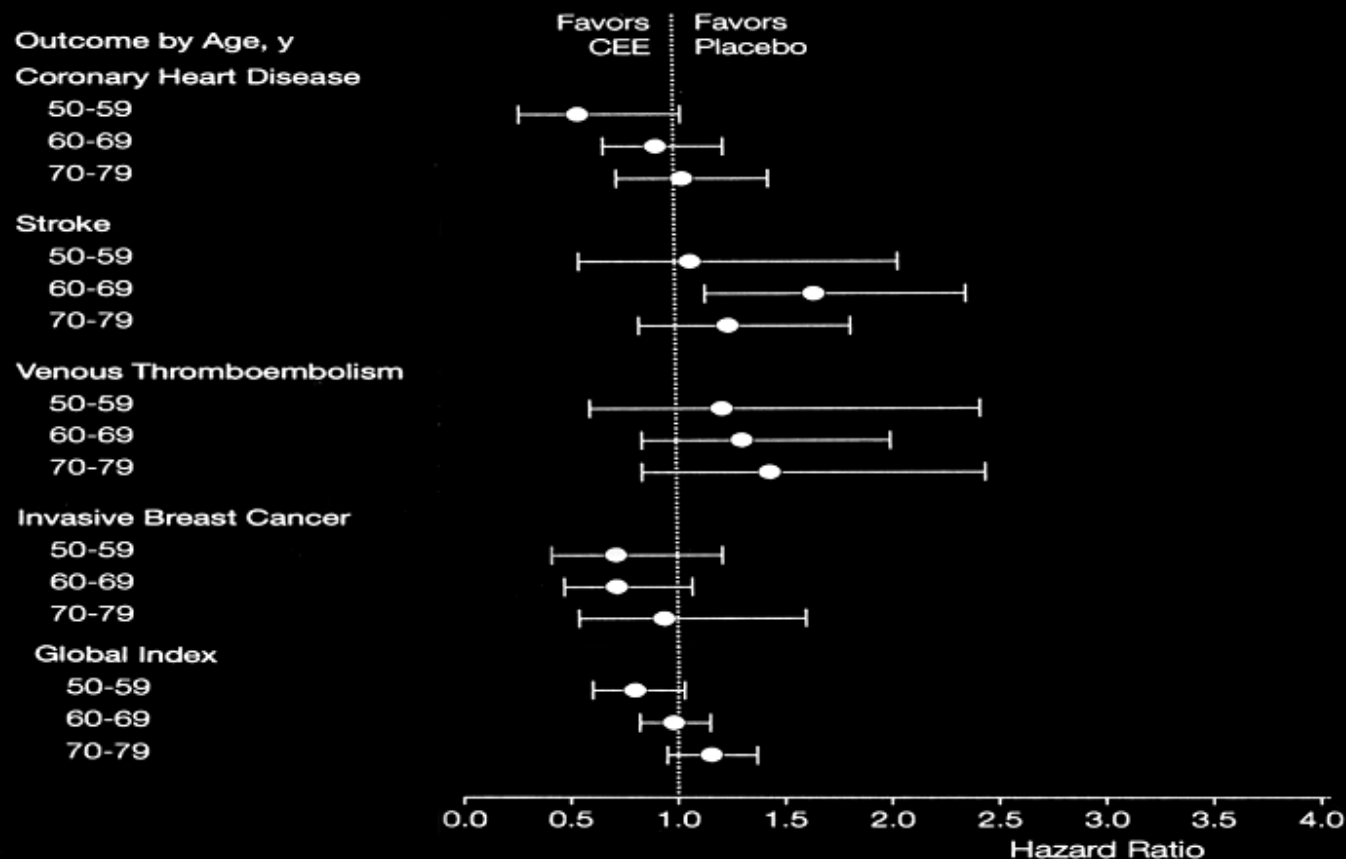
## WHI study (av age 63)

---

	RR (E2 only)	RR (E+P)
CHD	0.91	1.29
Stroke	1.39	1.41
Breast Cancer	0.77	1.26
PE	1.34	2.13
Colorectal Ca	1.08	0.63
Hip Fracture	0.61	0.66



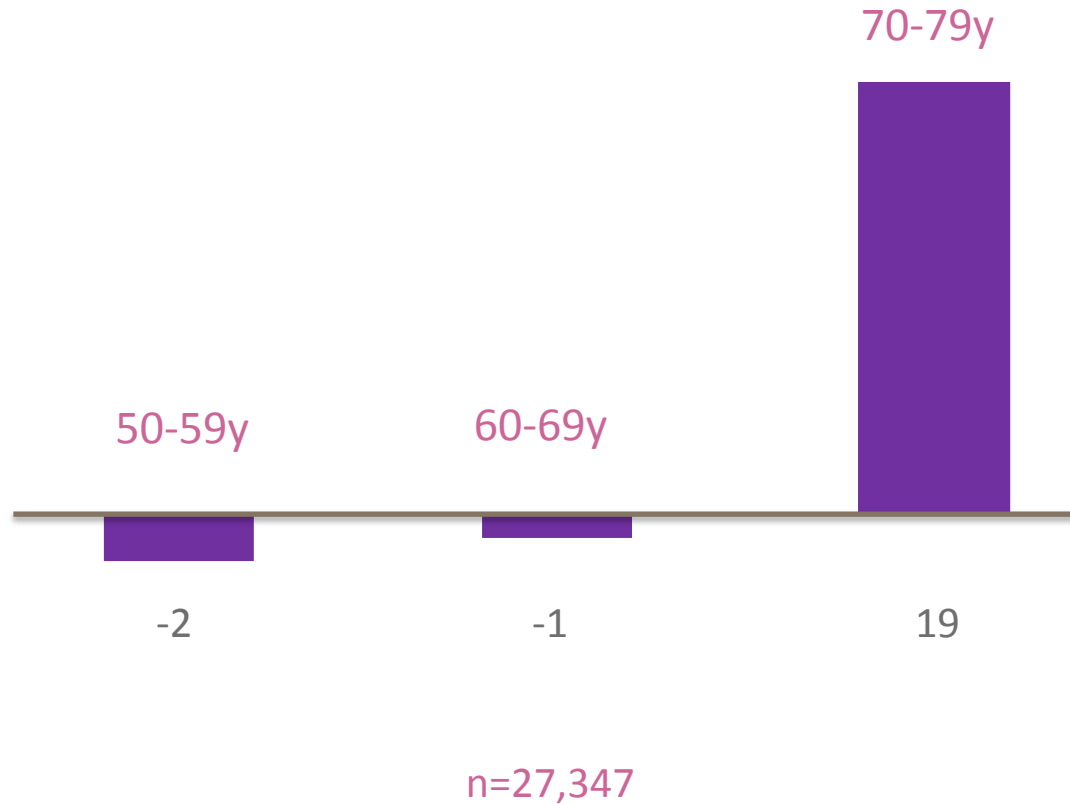
## Selected clinical outcomes by participant age



# WHI studies: Coronary heart disease

## HRT and CHD: absolute risk by age

---



## RESEARCH

## Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial



OPEN ACCESS

Louise Lind Schierbeck *registrar*<sup>1</sup>, Lars Rejnmark *associate professor, consultant*<sup>2</sup>, Charlotte Landbo Tofteng *staff specialist* <sup>1</sup>, Lis Stilgren *consultant*<sup>3</sup>, Pia Eiken *consultant, senior endocrinologist*<sup>4</sup>, Leif Mosekilde *professor, senior consultant*<sup>2</sup>, Lars Køber *professor, consultant*<sup>5</sup>, Jens-Erik Beck Jensen *associate professor, consultant*<sup>1</sup>

<sup>1</sup>Department of Endocrinology, Hvidovre Hospital, Kettegård alle 30, 2650 Hvidovre, Denmark; <sup>2</sup>Department of Medicine and Department of Endocrinology and Internal Medicine, Århus University Hospital, Aarhus, Denmark; <sup>3</sup>Department of Endocrinology, Svendborg Hospital, Svendborg, Denmark; <sup>4</sup>Department of Cardiology, Nephrology, and Endocrinology, Hillerød Hospital, Hillerød, Denmark; <sup>5</sup>Department of Cardiology, Rigshospitalet, Copenhagen, Denmark

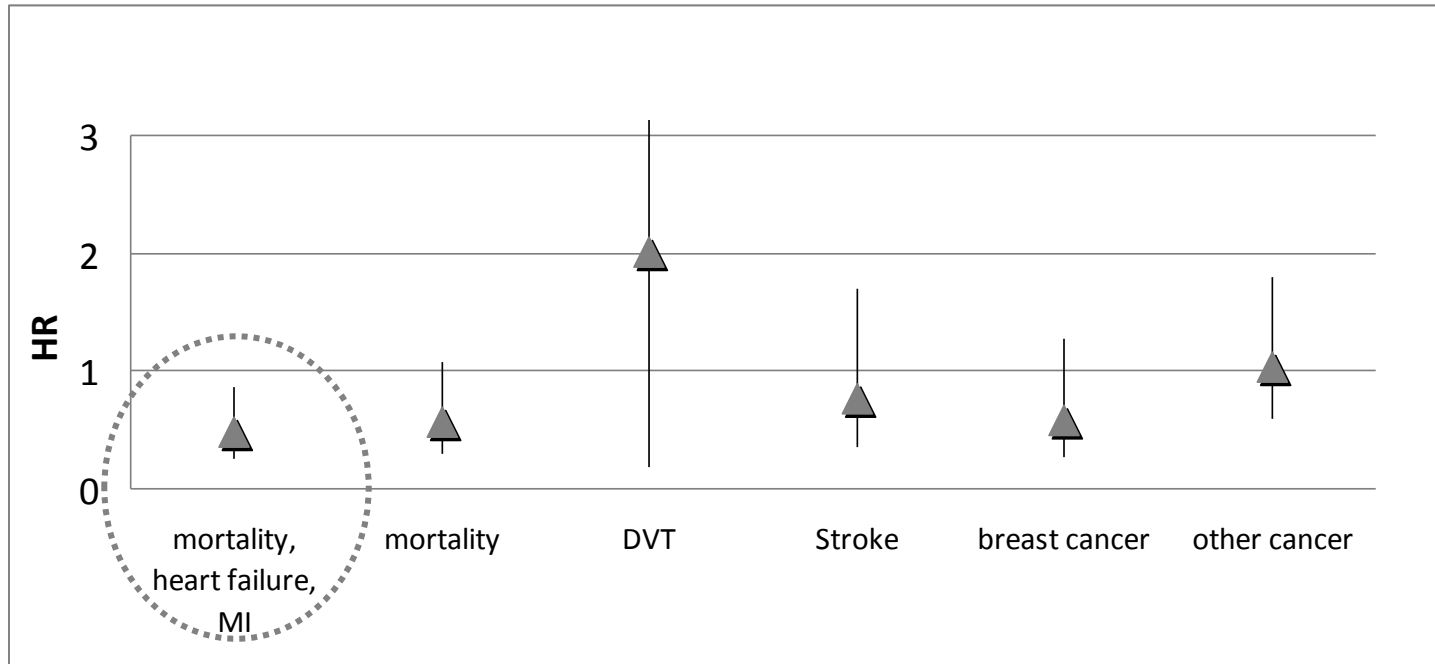
**Main outcome measure** The primary endpoint was a composite of death, admission to hospital for heart failure, and myocardial infarction.

**Results** At inclusion the women on average were aged 50 and had been postmenopausal for seven months. After 10 years of intervention, 16 women in the treatment group experienced the primary composite endpoint compared with 33 in the control group (hazard ratio 0.48, 95% confidence interval 0.26 to 0.87; P=0.015) and 15 died compared with



# The Danish Osteoporosis Prevention Study (DOPS)

Primary endpoint and mortality and major risks for HRT in the total population during randomisation phase (up to year 2002).



BMJ



# HRT and breast cancer risk

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- Combined HRT increased breast cancer risk more than Oestrogen only HRT
- Risk increases with duration of HRT
- Risk seems to go back to normal within 5 y of stopping HRT



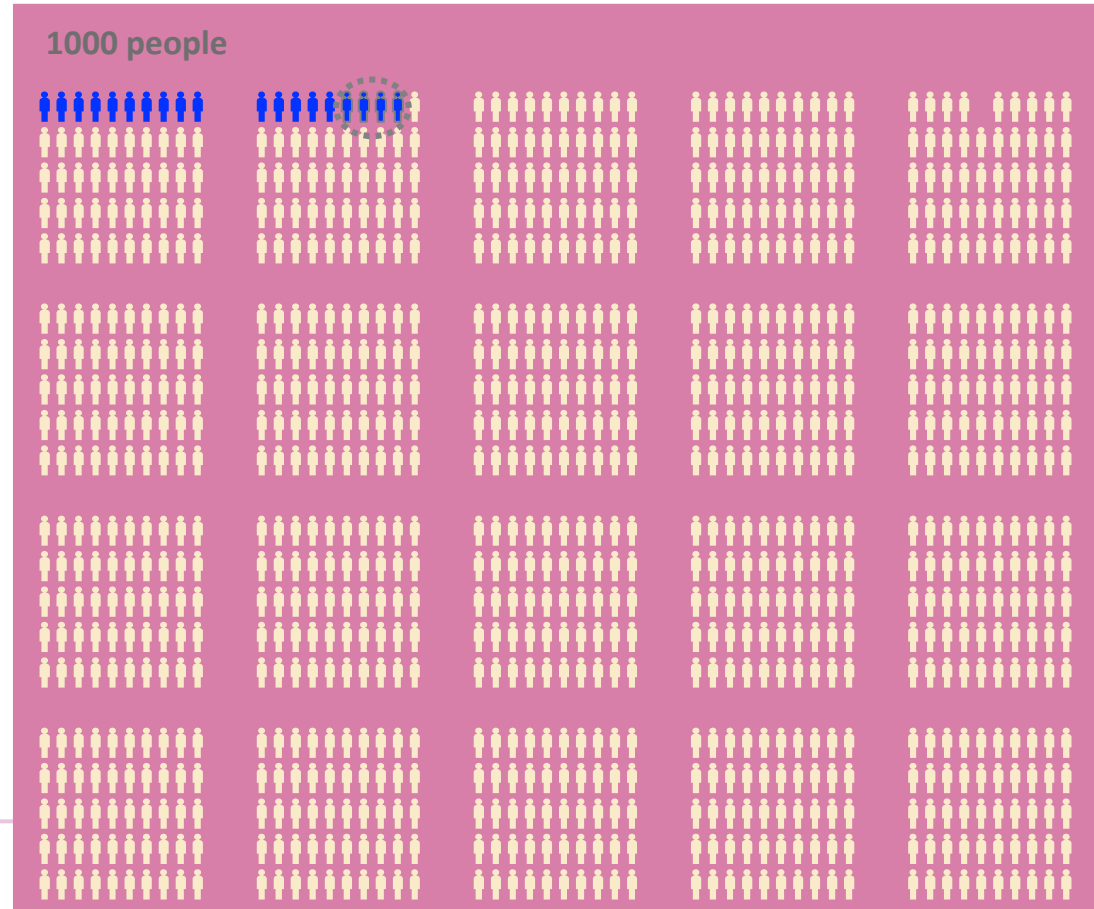
## WHI study (av age 63)

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Colorectal Ca	1.08	0.63
Hip Fracture	0.61	0.66



# Risk for post-menopausal women (mean age 63) developing breast cancer over a five year period (15 out of 1000)



Risk to general population



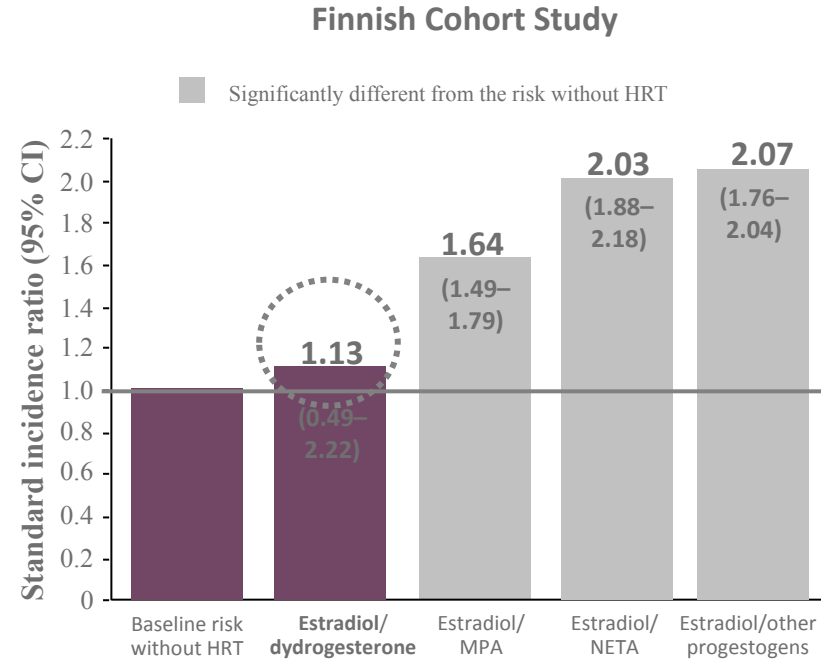
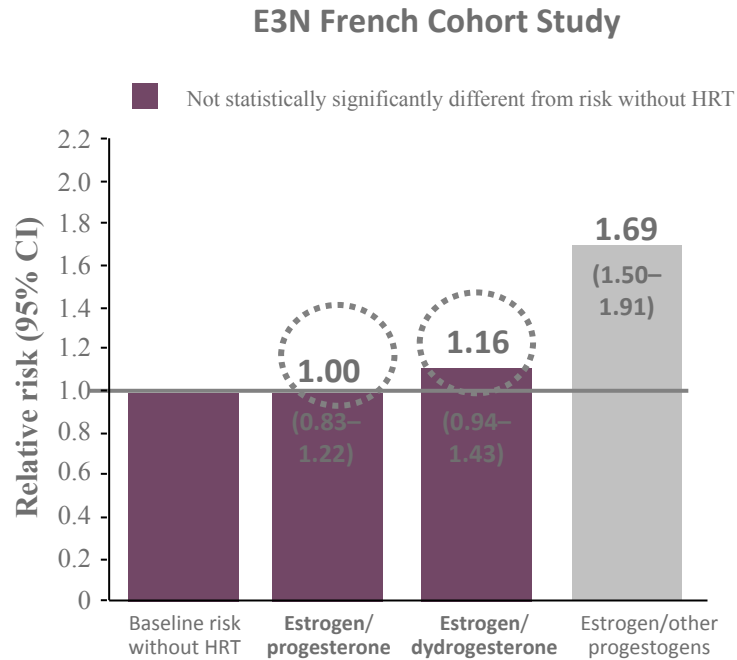
Additional risk for  
cc HRT users:  
4 cases / 1000  
(Not significant in  
latest analysis)

**“Significant reduction  
in breast cancer risk  
in CEE alone study”**

**La Croix AZ et al JAMA  
2011; 305:1305-14**

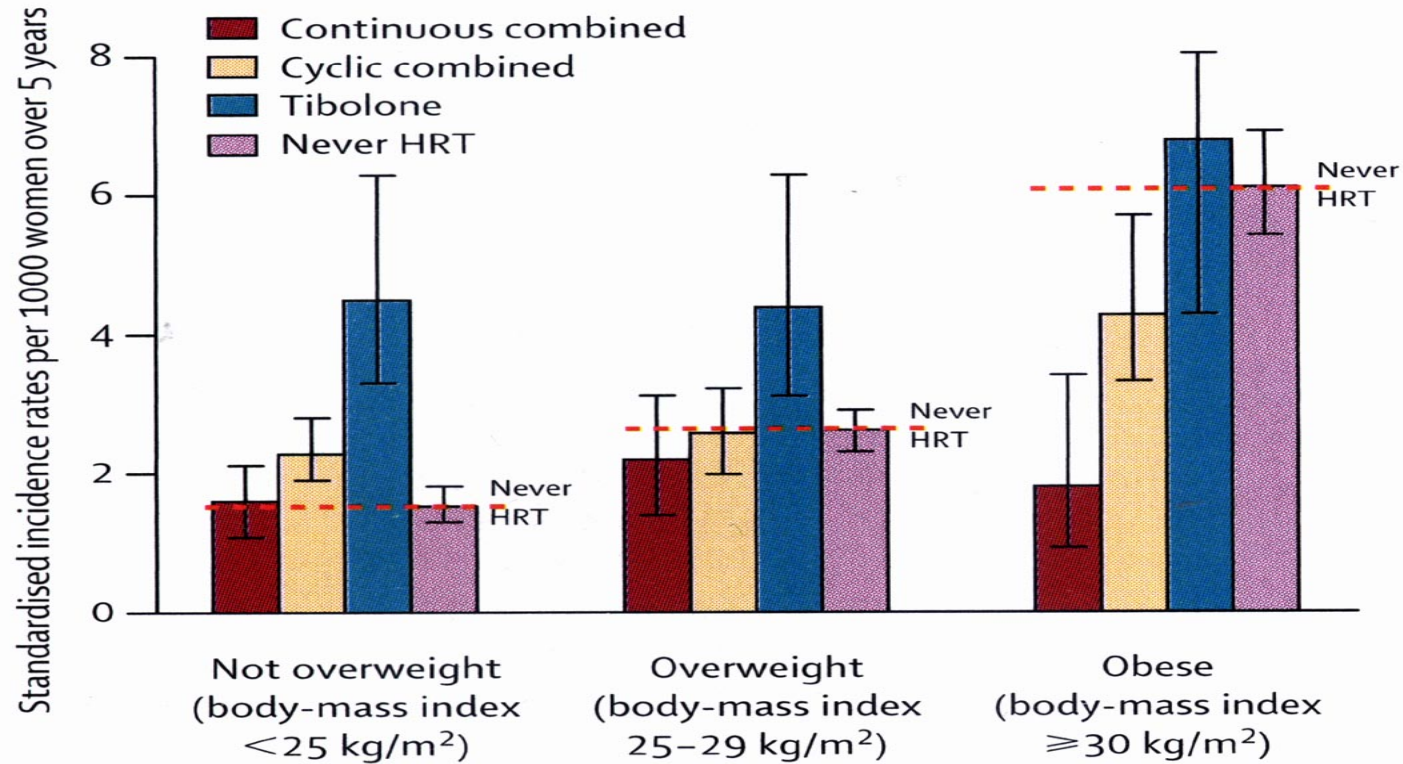


# Breast cancer risk: The progestogen matters!



**“Breast cancer risk was lower with natural progesterone / dydrogesterone”**





**Figure 5: Standardised incidence rates for endometrial cancer per 1000 women in the study cohort over a 5-year period, according to body-mass index and type of HRT last used**



## Risk of VTE with HRT

---

Risk in current users is 3-4 x higher than in non-users  
one case in 5000 users per year

The baseline risk of VTE between the ages of 50 and 70 is higher

Increased risk appears to be concentrated in new users

**VTE risk is not increased with transdermal E (oral 3.5 vs TRD 0.9)**

ESTHER study - Lancet 2003;362:428-432



## HRT and risk of VTE; systematic review and meta-analysis

---

	Pooled O R	Pooled 95% CI
Observational studies Oral oestrogen	2.5	1.9-3.4
Transdermal	1.2	0.9-1.7
Randomised controlled trials Oral oestrogen	2.1	1.4-3.1



## Other benefits of HRT

---

- Urogenital Atrophy<sup>1</sup>
  - Highly effective for vaginal and urinary symptoms
- Cognitive<sup>2</sup>
  - 30% reduction in dementia incidence if HRT started early
- Colon Cancer<sup>3</sup>
  - 44% reduction in CEE + P WHI (RR 0.56 0.38-0.81)



# Ideal HRT regimens

---

- Estradiol gel or patch
  - Estradot patches 25-100mcg
  - Oestrogel 2-4 apps
  - Sandrena gel 0.5-2.0mg/day
- Progesterone/Progestogens
  - Oral: Utrogestan cc100mg, sc200mg 12/28
  - Vaginal: Utrogestan, Crinone 8%, Cyclogest
  - Mirena
- Closest combined oral regimen
  - Femoston range 1:10, 2:10, Conti 1:5, Conti low dose 0.5:2.5



# Mirena: HRT

---

- **Mirena:** HRT / PMS (4yr license)
  - NB: poss prog SEs / bleeding
- “On the way” – “Baby” Mirena 12 & 16 mcg systems (3y & 5y)



# Vaginal Oestrogen

---

- Vaginal symptoms may persist despite HRT
  - Highly effective for local symptoms
  - Vagifem now licensed for indefinite usage
- 
- Creams
    - Ovestin (0.1% estriol) / Gynest (0.01% estriol)
  - Rings
    - Oestradiol: Estring – 2 yr license
  - Vag Tabs
    - Vagifem (10mcg) Total dose = 1.14mg/year



## Key points (HRT)

---

- **Combined HRT** has different profile compared to **oestrogen alone** (lipids, CHD)
- An increase in **breast cancer** risk is related to
  - the duration of use and
  - concurrent use of progestogens.
- **Transdermal oestrogen** have different metabolic profiles and side-effects (VTE risk)
- Mirena or Utrogestan + Transdermal Oestrogen



# Livial

---

- Active ingredient Tibolone
- Mimics action of Oestrogen + Progesterone + Testosterone
- Bleed-free
- Can be used after 54 or 2 years after menopause
- Increases risk of breast cancer (but thought to be less than combined HRT)



## HRT should be part of the overall strategy

---

- Increase weight-bearing exercise
- Calcium + VitD3 supplements (Adcal D3)
- Reduce alcohol intake
- Quit smoking





## Bone Health



# Osteoporosis

---

- Affects two million women in the UK
- 300,000 people in the UK suffer a fragility fracture per year including
  - 76,000 hip fractures
- Numbers increasing



## Risk factors

---

- H/o fracture following a minor fall
- Early menopause (aged less than 45)
- H/o amenorrhoea > 1yr
  
- Smoking + alcohol
- Corticosteroids for three months or more
- Rheumatoid arthritis or coeliac disease
  
- BMI < 19



# DEXA Scan

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- Minimal radiation from a DEXA scan, less than one-tenth the dose of a standard chest X-ray.
- Safe and relatively inexpensive
- Baseline study at 50y of age + repeat every three years



# Prevention of fractures

---

- FRAX tool
  - Early detection and treatment
- Regular weight-bearing exercise
- Adcal D3
- Reduce risk of falling / improve balance etc



# WHI: Grade A evidence of fracture risk reduction with HRT in hip and spine<sup>1</sup>

---

- Regulatory View 2013
  - Minimum effective dosage for shortest duration with annual reappraisal
  - HRT should be used for prevention of **osteoporosis** only in women who are unable to use other medicines that are authorised for this purpose.....
- Menopause/Osteoporosis/Endocrine Society View
  - HRT should be used first line in women younger than 60y for prevention and Rx of osteoporosis

1. T. J. de Villiers and J. C. Stevenson The WHI: the effect of hormone replacement therapy on fracture prevention Climacteric June 2012; 15(3): 263





**Screening after 50**

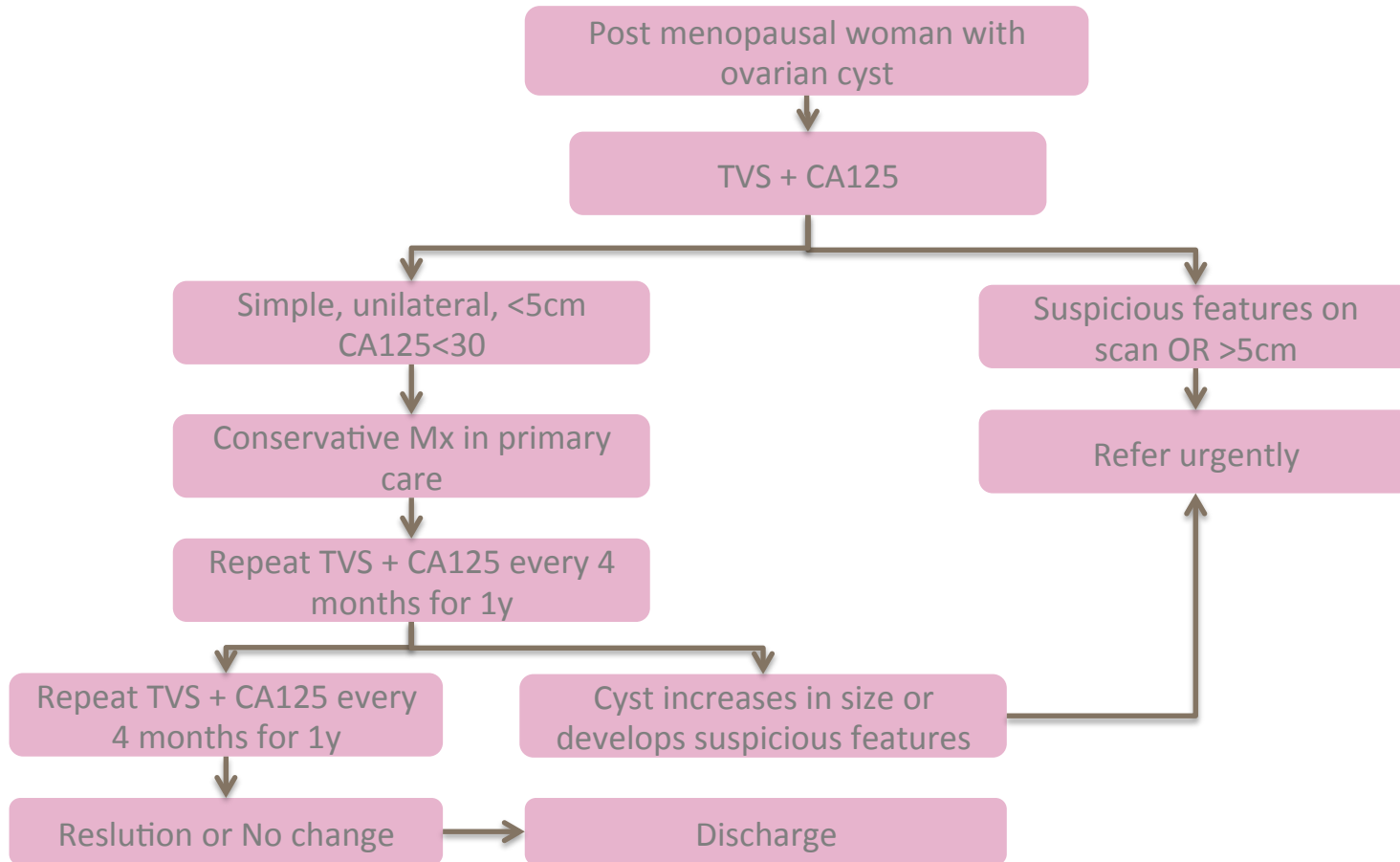


# Ovarian Screening

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- CA125
- TVS
- Only 85% of all and 50% of early ovarian cancers will have raised CA125
- False positives with endometriosis, fibroids etc
- There will be a proportion of interval cancers even if you screen annually
- Screening can be used where risk is increased







## Red Flag Symptoms



# Red Flag Symptoms

---

- Post-menopausal bleeding
- New onset of pelvic or abdominal pain
- Persistent abdominal distension (women often refer to this as 'bloating')
- Feeling full (early satiety) and/or loss of appetite
- Increased urinary urgency and/or frequency.





## Sexual Health and Contraception



- 
- Low libido
  - Vaginal dryness
  - Increased risk of STI



# Sexually transmitted infections double in older population in ten yrs

---

**2 February 2012**

**St BMJ editorial: Sexual health and the older adult**



## Increased risk of STI

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- Less likely to use condoms
- Less likely to be screened
- More likely to start a new relationship
- Atrophic vaginitis: Risk of tears and transmission
- Immune senescence



# HSDD

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- Intrinsa patch 300microgram/24hr
- Twice weekly testosterone patch
- Testim gel (1 pea-sized blob to be applied once a day or once every other day, 1 tube should last for at least 8 days)
- Livial



# Vaginal dryness

---

- Atrophic vaginitis
- Local oestrogen pessaries, cream or ring
- Vagifem 10mcg vaginal tablets or ovestin cream
  - Once at night for two weeks
  - Followed by twice a week for maintenance
- Lubrication such as Sylk / KY



# Vaginal oestrogen

---

- Vaginal symptoms may persist despite HRT
  - Highly effective for local symptoms
  - Vagifem now licensed for indefinite usage
- 
- Creams
    - Ovestin (0.1% estriol) / Gynest (0.01% estriol)
  - Rings
    - Oestradiol: Estring – 2 yr license
  - Vag Tabs
    - Vagifem (10mcg) Total dose = 1.14mg/year



# Summary

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- HRT indicated for menopausal symptoms
- Breast cancer risk seems to be associated with long term use oral progesterone ? could be avoided with Mirena
- Transdermal oestrogen reduces risk of VTE
- Oestrogel: Ability to easily titrate the dose with symptoms
  
- STI on the increase in this age group
- Prevention of osteoporosis
  
- Screening with CA125 + TVS for ovarian cancer, but has limitations



# Thank You



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