Clinical Trial
Update 2015

Dr Sonia Davison
MBBS FRACP PhD
Women’s Health Research Program
Monash University
Jean Hailes for Women’s Health
Criteria for Inclusion

- Area of relevance / interest
- Big / novel study
- Big news for 2015
- Robust methodology
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALP</td>
<td>alkaline phosphatase</td>
</tr>
<tr>
<td>AMI</td>
<td>acute myocardial infarction</td>
</tr>
<tr>
<td>bd</td>
<td>twice daily administration</td>
</tr>
<tr>
<td>BMD</td>
<td>bone mineral density</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>BSO</td>
<td>bilateral salpingo-oophorectomy</td>
</tr>
<tr>
<td>CEE</td>
<td>conjugated equine oestrogens</td>
</tr>
<tr>
<td>CHD</td>
<td>coronary heart disease</td>
</tr>
<tr>
<td>Cl</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CO₂</td>
<td>carbon dioxide</td>
</tr>
<tr>
<td>CVA</td>
<td>stroke</td>
</tr>
<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
</tr>
<tr>
<td>DHEA</td>
<td>dehydroepiandrosterone</td>
</tr>
<tr>
<td>F/U</td>
<td>follow-up</td>
</tr>
<tr>
<td>gp</td>
<td>group</td>
</tr>
<tr>
<td>HR</td>
<td>hazard ratio</td>
</tr>
<tr>
<td>hrs</td>
<td>hours</td>
</tr>
<tr>
<td>HRT</td>
<td>PM hormone therapy men</td>
</tr>
<tr>
<td>MPA</td>
<td>medroxyprogesterone acetate</td>
</tr>
<tr>
<td>n</td>
<td>number</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>P1NP</td>
<td>bone turnover marker</td>
</tr>
<tr>
<td>PreM</td>
<td>premenopausal</td>
</tr>
<tr>
<td>PM</td>
<td>postmenopausal</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>PV</td>
<td>vaginal administration</td>
</tr>
<tr>
<td>QOL</td>
<td>quality of life</td>
</tr>
<tr>
<td>RCT</td>
<td>randomised controlled trial</td>
</tr>
<tr>
<td>Rx</td>
<td>treatment</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>VMS</td>
<td>vasomotor symptoms</td>
</tr>
<tr>
<td>WHI</td>
<td>Women’s Health Initiative study</td>
</tr>
<tr>
<td>wks</td>
<td>weeks</td>
</tr>
<tr>
<td>yr</td>
<td>year</td>
</tr>
<tr>
<td>women</td>
<td></td>
</tr>
</tbody>
</table>
Levels of evidence

Oxford Centre for Evidence-based medicine:

1a – systematic review of RCTs
1b – large individual RCT (with narrow confidence interval)
2a – systematic review of cohort studies
2b – individual cohort study (or low quality RCT, e.g. <80% follow-up)
2c – ecological studies
3a – systematic review of case-control studies
3b – individual case-control study
4 – case-series
5 – expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”
Estradiol-based postmenopausal hormone therapy and risk of cardiovascular and all-cause mortality.

489,105 PM ; HRT use from 1994-2009

Main oestrogen = oestradiol (oral or transdermal)
Mean age of initiation 52.2 yrs
• Oestrogen only – mean 3.9 yrs
• Oestrogen / progestogen – mean 4.5 yrs
‌ Use of any HRT (per 10,000 F/U yrs):
  ↓ 2-19 CHD deaths (18% ↓ in risk)
  ↓ 1-9 CVA deaths (18% ↓ in risk)
  ↓ 12-78 deaths from all cause mortality (12% ↓ in risk)
‌ No difference to findings if HRT initiated <60 or >60 yrs of age

Mikkola TS et al Menopause 2015. 22(9):976-83
Estradiol-based postmenopausal hormone therapy and risk of cardiovascular and all-cause mortality.

Mikkola TS et al Menopause 2015. 22(9):976-83
Does menopausal hormone therapy reduce myocardial infarction risk if initiated early after menopause? A population-based case-control study.

Stockholm Heart Epidemiology Program
347 PM, 40-62 yrs, past AMI
- 499 age-matched controls
- 292 ever-users of HRT (29% cases / 38% controls)

<table>
<thead>
<tr>
<th>Compared to never use of HRT:</th>
<th>Risk of AMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early initiation HRT (&lt;60 yrs or within 10 yrs of menopause)</td>
<td>≣</td>
</tr>
<tr>
<td>Late initiation HRT</td>
<td>≣</td>
</tr>
<tr>
<td>HRT use ≥5yrs</td>
<td>≣</td>
</tr>
<tr>
<td>HRT use &lt;5yrs</td>
<td>≣</td>
</tr>
</tbody>
</table>

Carrasquilla GD et al Menopause 2015;22(6);598-606
Hormone therapy after uterine cervical cancer treatment: a Swedish population-based study.

837 ♀, <45yrs at diagnosis of cervical cancer

- 257 ♀ (31%) BSO and / or radiotherapy
  - 67% had at least one script for HRT dispensed
  - Gradual ↓ in use up to 5yrs, to 39%
  - <40 yrs: HRT use 79% at 1yr; 45% after 5yrs

Everhof ÅH et al Menopause 2015; 22 (6); 633-9
Hormone therapy and risk of cardiovascular outcomes and mortality in women treated with statins.

40,958 ♀, 40-74 yrs

Prescribed statin between 2006-7
- F/U mean 4 yrs
- Statin use: 70% for primary prevention
- 7% users on HRT (2862 ♀); mean 61 yrs
  - 53% 50-64yrs
  - 31% 65-74yrs

<table>
<thead>
<tr>
<th></th>
<th>HRT users</th>
<th>Non-HRT users</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD deaths per 10,000 person yrs</td>
<td>N =5; HR 0.38 (95% CI 0.12-1.19)</td>
<td>N = 18</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>N =33; HR 0.53 (95% CI 0.34-0.81)</td>
<td>N = 87</td>
</tr>
</tbody>
</table>

Berglind IA et al. Menopause 2015; 22(4):369-76
Menopause
Symptoms of depressed mood, disturbed sleep, and sexual problems in midlife women: cross-sectional data from the Study of Women's Health Across the Nation.

1716♀, mean 49.8yrs

- Depressed mood 17%
- Sleep problem 37%
- Any sexual problem 42%

All 3 problems: 5% (n=90)
- Lower household income
- Less educated
- Surgical menopause or late perimenopause
- General health = poor or fair
- More stressful life events
- Lower social support
VMS
Moderate to severe vasomotor and sexual symptoms remain problematic for women aged 60 to 65 years.

**2020 PM ‍♀️, 40-65 yrs**

**Mod-severe VMS:**
- 2.8% pre-menopausal
- 17.1% peri-menopausal
- 15.1% PM, 55-59yrs
- 6.5% PM, 60-65yrs

**Prescription therapy for menopausal symptoms:**
- 135 ‍♀️ (6.6%)
  - 120 HRT (5.9%)
  - 15 non-hormonal (0.7%)

**Risk factors for moderate to severe vasomotor symptoms:**
- Smoking, OR 1.6 (95% CI 1.1-2.3)
- BMI 25-29.9kg/m², OR 1.7 (95% CI 1.1-2.5)
- Tertiary education, OR 0.7 (95% CI 0.5-0.9)

*Gartoulla P et al Menopause 2015; 22(7):694-701*
Decreasing menopausal symptoms in women undertaking a web-based multi-modal lifestyle intervention: The Women's Wellness Program.

225 ♀, 40-65yrs (mean 50.9yrs)

- 12 week intervention (on-line independent / nurse consultant / on-line virtual nurse consultation)
- Healthy lifestyle behaviours (exercise / smoking / healthy eating etc)

All methods of intervention delivery:
- ↓ anxiety
- ↓ depression
- ↓ VMS
- ↓ sexual dysfunction

(benefits more pronounced in one-on-one group); all p<0.05

Anderson D et al Maturitas 2015; 81(1); 69-75
Does quitting smoking decrease the risk of midlife hot flashes? A longitudinal analysis.

761PM ♀, 45-54 yrs
F/U 7 yrs

- Former-smokers vs. smokers:
  - ↓ number / severity / frequency of flushes
    (OR 0.55 to 0.80)
- Non-smokers vs. Former and current smokers:
  - ↓ severity / frequency of flushes
  - ↓ symptoms in women who ceased smoking >5yrs ago
    (OR 0.36 to 0.63)
Facilitating lifestyle changes to manage menopausal symptoms in women with breast cancer: a randomized controlled pilot trial of The Pink Women's Wellness Program.

55 ♀, 45-60yrs

- breast cancer
- 1 mod-severe menopausal symptom
- Intervention or control gp – 12 wks
- Intervention = clinical consultations and health education program

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatic symptoms</td>
<td>↓</td>
<td>⇨</td>
</tr>
<tr>
<td>VMS</td>
<td>↓</td>
<td>⇨</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>↓</td>
<td>⇨</td>
</tr>
<tr>
<td>Physical and functional wellbeing</td>
<td>↑</td>
<td>⇨</td>
</tr>
</tbody>
</table>
Cancer
Dietary patterns and breast cancer risk: a study in 2 cohorts.

4400 ♂

Canadian Study of Diet, Lifestyle and Health and National Breast Screening study

• 1097 breast cancer / 3320 controls
• Average ages for groups 58-67 yrs

<table>
<thead>
<tr>
<th>Diet</th>
<th>Risk of breast cancer HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy (vegetables and legumes)</td>
<td>0.73 (0.58-0.91)</td>
</tr>
<tr>
<td>Ethnic (rice, spinach, fish, tofu, liver, eggs, salted and dried meat)</td>
<td>No relationship</td>
</tr>
<tr>
<td>Meat and potatoes (red meat and potatoes)</td>
<td>Trend only: 1.26 (0.92-1.73)</td>
</tr>
</tbody>
</table>
Oral bisphosphonate use and risk of postmenopausal endometrial cancer.

89,000 ♂; 50-79 yrs in WHI

- 39,000 in RCT / 50,000 in observational study
- Median 12.5 yr F/U
- Bisphosphonate – alendronate 90%
- 1123 cases of endometrial cancer

- Ever use of bisphosphonates in 10% of ♂:
  - endometrial carcinoma (HR 0.80; 95% CI 0.64-1.00; p=0.05)

Hormone therapy and young-onset breast cancer

3000 

- Two Sister Study: breast cancer diagnosis <50yrs vs. controls
  - Recruited 2008-2010
  - Mean age 47.3 yrs

<table>
<thead>
<tr>
<th>HRT use</th>
<th>Breast cancer n = 1419</th>
<th>Controls n = 1665</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ever use of HRT</td>
<td>7 %</td>
<td>11%</td>
</tr>
</tbody>
</table>

- Oestrogen + progestogen HRT: ↔ Breast cancer risk
- Oestrogen only HRT: ↓ Breast cancer risk; OR 0.58 (95% CI 0.34-0.99)

Bone
A randomized, double-blind, placebo-controlled study to evaluate the effects of alendronate on bone mineral density and bone remodelling in perimenopausal women with low bone mineral density.

40 ♂, perimenopausal

- Mean age 49.3yrs
- T score <-1.0 at lumbar spine / femoral neck or total hip
  - Alendronate 70mg wkly vs. Placebo (+2800 IU vitamin D3)
  - 12 months

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Alendronate</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine BMD</td>
<td>↑ 3.7%</td>
<td>↓ 3.3%</td>
</tr>
<tr>
<td>Femoral neck BMD</td>
<td>↑ 2.1%</td>
<td>↓ 1.9%</td>
</tr>
<tr>
<td>ALP</td>
<td>↓ 38%</td>
<td>↑ 3%</td>
</tr>
<tr>
<td>P1NP</td>
<td>↓ 27%</td>
<td>↑ 21%</td>
</tr>
</tbody>
</table>

P<0.05 for all differences

Long-term follow-up of bone density in women with primary ovarian insufficiency.

72 PM ; mean 34.1 yrs (SD 6.7), F/U 8yrs

- **BMD at baseline:**
  - Lumbar spine T score mean -1.03 (SD 1.39)
    - 18% - osteoporosis
    - 28% - osteopaenia
  - Femoral neck T score mean -0.29 (SD 1.09)
    - 1.4% - osteoporosis
    - 23% - osteopaenia

- Hormone treatments:
  - CEE + MPA
  - 17β oestradiol +norethisterone
  - ethinyl oestradiol + levonorgestrel

- **No change** in overall BMD after 8 yrs F/U

Benetti-Pinto CL et al Menopause. 2015 22(9):946-9
Indirect comparison of teriparatide, denosumab, and oral bisphosphonates for the prevention of vertebral and nonvertebral fractures in postmenopausal women with osteoporosis.

**LEVEL 1**

Meta-analysis

15 studies, 1-4 yrs duration

- **Vertebral fracture ↓**: Teriparatide + denosumab > alendronate + risedronate
- **Non-vertebral fracture ↓**: All agents effective
- **Hip fracture ↓**: denosumab, alendronate, risedronate
- **Upper arm fracture ↓**: risedronate

Zhang L et al Menopause. 2015;22(9): 1021-5
Indirect comparison of teriparatide, denosumab, and oral bisphosphonates for the prevention of vertebral and nonvertebral fractures in postmenopausal women with osteoporosis.

**FIG. 2.** Efficacy of interventions, versus placebo, for reducing vertebral fracture. RR, risk ratio.

Zhang L et al Menopause. 2015;22(9): 1021-5
Genito-urinary
Sexual function after fractional microablative CO\(_2\) laser in women with vulvovaginal atrophy.

77 PM †, mean 60.6 ± 6.2 yrs

- 3 fractional microablative CO\(_2\) laser Rx in 12 wks

Theory: connective tissue remodelling with production of new collagen and elastic fibres

Results:

- ↑ sexual function scores (p<0.01)
- ↑ satisfaction with sexual life (p<0.01)
- 85% of † not sexually active at baseline resumed sexual function at 12 wks
- Improved physical and mental domains of QOL evaluations (p<0.01)

Prasterone has parallel beneficial effects on the main symptoms of vulvovaginal atrophy: 52-week open-label study.

521 ♀, 43-75 yrs (median 58yrs)

- Open-label
- Prasterone (DHEA) 0.5% (6.5mg) daily PV for 12 months
- Changes from baseline to 12 months:
  - Parabasal cells 55% to 13%
  - Superficial cells 2% to 9.4%
  - Vaginal pH 6.2 to 5.1
  - Dyspareunia ↓ 66%
  - Vaginal secretions / epithelial integrity / thickness

all p<0.001

Brain
Grandparenting predicts late-life cognition: Results from the Women's Healthy Ageing Project.

Mean age 69.6yrs
Average 12.9yrs education
87% had grandchildren
72% minded grandchildren (average 3.2 children)
  0.9yrs younger
  More likely to have ≥12 yrs education
  Higher scores in **executive function**
  Higher performance in those minding children 1 day per wk vs. >1 day per wk

P<0.05 for difference between groups

Burn K, Szoeke C. Maturitas 2015; 81(2); 317-22
Effects of a soy-based dietary supplement compared with low-dose hormone therapy on the urogenital system: a randomized, double-blind, controlled clinical trial.

60 PM ♀; 40-60 yrs

- 3 groups, 16 wks Rx:
  - Soy dietary supplement (90mg isoflavone)
  - Low dose HRT (1mg oestradiol + 0.5mg norethisterone)
  - Placebo

- Vaginal dryness ↓:
  - soy and HRT gps (p=0.04)

- Vaginal pH ↓ / maturation value ↑:
  - HRT gp only (p<0.01)

- No change in endometrial thickness for any gp

Carmignani LO et al Menopause 2015; 22(7):741-9
Metabolism
Metformin for overweight women at midlife: a double-blind, randomized, controlled trial.

118 ♂, 35-65yrs (mean 53yrs)
BMI 30-40kg/m2 or waist circumference >88cm
Metformin 850mg bd or placebo – 26 wks

- ↓ HbA1C (-0.1%)
- ↓ Fasting insulin (-1.0pmol/L)
- ↓ BMI (mean change 1kg/m2; 95% CI 1.37 to -0.62) (all P<0.05)
- ↔ Waist circumference / fasting glucose / lipid profile

Worsley R et al Climacteric 2015; 18(2); 270-7
And finally...
Effects of caffeine on the human circadian clock in vivo and in vitro.

5 subjects: 3 ♀ , 2 ♂
Mean age 24 yrs
Double-blind placebo controlled study, 49 days
• Dim light / dim light with caffeine / bright light / bright light with caffeine – prior to bedtime
• Caffeine dose equivalent to double espresso 3 hrs before bedtime
• Background: caffeine alters circadian clock in red bread mould, green algae, fruit flies and sea snails

Results:
• Caffeine - 40 minute delay of circadian melatonin rhythm – half the effect of being exposed to bright light
• Caffeine increased cyclic AMP levels – a core component of the cellular circadian clock
Clinical Trial Update 2015

Dr Sonia Davison
MBBS FRACP PhD
Women’s Health Research Program
Monash University
Jean Hailes for Women’s Health