Summary of evidence for 2019 surveillance of menopause (2015) NICE guideline NG23

Studies identified in searches are summarised from the information presented in their abstracts. We did not specify any age limits on HRT treatment because this information was not consistently reported clearly across the abstracts.

Because of a large volume of evidence, we excluded randomised controlled trials that included less than 100 people.

Feedback from topic experts who advised us on the approach to this surveillance review, was considered alongside the evidence to reach a view on the need to update each section of the guideline.

See the evidence tables for all studies considered in surveillance.

Individualised care

Surveillance proposal

No new information on individualised care was identified at any surveillance review.

Diagnosis of perimenopause and menopause

Surveillance proposal

No new information on diagnosis of perimenopause and menopause was identified at any surveillance review.

Information and advice

Surveillance proposal

No new information on information and advice was identified at any surveillance review.

Managing short-term menopausal symptoms

Surveillance proposal

The section of the guideline on managing short-term menopausal symptoms should not be updated.

Editorial amendments

In recommendation 1.4.25, the cross-reference to section 1.13 of the NICE guideline on early and locally advanced breast cancer should be amended to refer to because the guideline has been updated and the relevant section is now 1.12. The hyperlink should also be updated from the previous guideline so that users go directly to the updated guideline.

Hormone replacement therapy (HRT)

2019 surveillance summary

We identified 16 RCTs and 3 Cochrane reviews that assessed a range of short-term outcomes of HRT.

Vasomotor symptoms

Vasomotor and general menopausal symptoms, including quality of life were assessed in 8 RCTs (1–8) and 2 Cochrane reviews (9,10) (table 1 in the data tables appendix). The included studies assessed a variety of different HRT strategies including oestrogen only and combined HRT in a range of formulations including oral, transdermal and intravaginal preparations.

- HRT compared with placebo consistently improved menopausal symptoms, vasomotor symptoms such as hot flushes and, night sweats, sleep outcomes and quality of life.
- Vasomotor symptoms were worse with tibolone compared with combined HRT.
- There was no difference in hot flushes with bioidentical oestrogen compared with conjugated equine oestrogen.

Vaginal symptoms

Vaginal symptoms and sexual function were assessed in 7 RCTs (11–17) and 1 Cochrane review (18) (table 2 in the data tables appendix). Most studies assessed intravaginal preparations of HRT compared with placebo or another active treatment, usually HRT. HRT improved vaginal symptoms in 7 of the 9 comparisons against placebo and showed no effect in the other two comparisons. All 5 of the comparisons of HRT against another active treatment showed no difference between the groups.

Depression

In 2 RCTs (19,20) HRT was associated with improvements in symptoms of depression compared with placebo (table 3 in the data tables appendix).

Other outcomes

In 2 RCTs (3,21) comparing different preparations of HRT, oestrogen may be more effective than progestogen or conjugated equine oestrogen for improving hormone levels and acceptance by patients. In 1 RCT (17) patients using vaginal oestrogen may be more likely to use the product again when compared with placebo (table 4 in the data tables appendix).

Adverse effects

Adverse effects of HRT were reported in 3 Cochrane reviews (9,10,18) and 1 RCT (3) (table 5 in the data tables appendix). A range of preparations of oestrogen-only HRT, including oral, transdermal, and intranasal showed worse or no effects on adverse events compared with placebo (6 comparisons), or other preparations of HRT (1 comparison). Oestrogen tablets had no effect on endometrial thickness compared with placebo, but an oestrogen ring preparation increased endometrial thickness compared with oestrogen cream. Tibolone was associated with more bleeding than placebo but less than combined HRT.

Intelligence gathering

Vasomotor symptoms

Topic expert feedback noted that the terminology around ‘bioidentical hormones’ is confusing because it can be used to mean chemically identical to the hormones produced by the human body (such preparations are regulated), and preparations of

different hormones in ratios produced in the body (which are not regulated). The study of ‘bioidentical’ oestrogen (9) included regulated products.

Topic experts also suggested that recommendations for women with breast cancer (and other hormone-dependent cancers) should be expanded, for example how treatments for vaginal atrophy might differ for women on tamoxifen and those on aromatase inhibitors.

Impact statement

Vasomotor symptoms

The guideline recommends offering HRT for vasomotor symptoms after discussing the risks and benefits. The new evidence indicating that HRT improves vasomotor symptoms and quality of life is consistent with current recommendations.

The guideline does not currently recommend tibolone because it was associated with reduced quality of life compared with no treatment, and thus was not cost effective. The finding that tibolone was associated with worse vasomotor symptoms compared with conjugated equine oestrogens is therefore consistent with evidence considered during guideline development.

The guideline additionally noted that ‘the efficacy and safety of unregulated compounded bioidentical hormones are unknown’. One study assessed ‘bioidentical’ hormones but referred to regulated products rather than unregulated compounded bioidentical hormones are unknown’. However, new evidence suggested no difference in hot flushes between regulated bioidentical hormones and conjugated equine oestrogens, so no update to consider these treatments separately is necessary.

There is some overlap in recommendations on treatment of menopausal symptoms in women with or at high risk of breast cancer across NICE guidelines, particularly in the guidelines on early and locally advanced breast cancer and familial breast cancer. The guideline on menopause already has cross-references to the breast cancer guidelines. These guidelines have more detailed recommendations for women with or at risk of breast cancer who have treatment-related menopausal

symptoms. We did not find sufficient new evidence to support an update of the menopause guideline in this area.

Vaginal symptoms

The guideline recommends offering vaginal oestrogen to women with urogenital atrophy, including those already on systemic HRT. The new evidence that vaginal oestrogen improves vaginal symptoms and sexual function is consistent with current recommendations.

Depression

The guideline found evidence suggesting that HRT improved symptoms of depression, and recommends considering HRT to alleviate low mood, which is consistent with the new evidence identified in surveillance.

Other outcomes

New evidence indicated that HRT, particularly vaginal oestrogen, was acceptable and satisfactory for patients, and improved hormone levels. The guideline did not address these aspects of HRT use in depth, but the new evidence provides support for the current recommendation to offer intravaginal HRT for women with vaginal symptoms.

New evidence indicated that different hormone preparations may improve levels of follicle stimulating hormone, luteinising hormone and oestrogen. However, these physiological outcomes were not considered by the guideline and the new evidence does not indicate that changes in hormone levels are directly related to changes in symptoms. Therefore, an update to consider these outcomes is not necessary.

Adverse effects

The guideline notes that unscheduled vaginal bleeding is a common side effect of HRT in the first 3 months of treatment. Although study abstracts often did not define what adverse events were included, the new evidence did not highlight any unexpected adverse events. Prescribers should consult the summary of product characteristics for information on possible adverse effects associated with individual HRT products. The guideline should not be updated to consider additional adverse events of HRT at this time.

New evidence is unlikely to change guideline recommendations.

Non-HRT treatments

2019 surveillance summary

We identified 39 RCTs and 1 Cochrane review that assessed treatments other than HRT.

Drug treatments

We identified 11 RCTs of non-HRT drug treatments for menopausal symptoms (table 6 in the data tables appendix). All drugs were compared against placebo, except for 1 study that used a non-active control (vaginal moisturiser).

- In 3 reports from 2 RCTs, (22–24) intravaginal prasterone (dehydroepiandrosterone) was more effective than placebo or across a range of sexual outcomes, including vaginal dryness and dyspareunia, lubrication and orgasm. However, no difference between prasterone and vaginal moisturiser was seen for vaginal dryness or dyspareunia, although prasterone improved sexual health compared with vaginal moisturiser. Prasterone is licensed in the UK for treating vulvar and vaginal atrophy in postmenopausal women having moderate to severe symptoms.
- In 2 RCTs, (25,26) ospemifene improved sexual function, vaginal dryness and dyspareunia.
- In 2 RCTs, of melatonin, one trial suggested this treatment improved ovarian hormone levels, (27) but no effect was seen on low-density lipoprotein (28). No patient-oriented outcomes were reported in the abstracts for these studies.
- In 1 RCT, oxybutynin improved sleep quality and vasomotor symptoms and increased dry mouth (29).
- In 1 RCT, oxytocin vaginal gel improved dyspareunia (30).
- In 2 studies, venlafaxine improved insomnia, sleep quality and quality of life (2,4).

Physical and psychological therapies

We identified 9 RCTs that assessed the effects of physical and psychological treatments for menopause (table 7 in the data tables appendix).

Cognitive behavioural therapy (CBT) was assessed in 3 studies (31–33) with wait list and menopause education acting as controls. Self-managed, therapist-based and telephone-based CBT were associated with improvements in night sweats and insomnia, but inconsistent effects were seen on hot flushes with effects seen in one study (composite outcome of hot flushes and night sweats), but no effect was seen in another study.

New evidence for other physical and psychological therapies indicated that:

- device-guided slow-paced breathing showed inconsistent effects on hot flushes depending on the control group (34).
- exercise interventions had no effect on hot flushes or night sweats but may increase daily step counts and improve symptoms of anxiety or depression (35–37).
- foot reflexology was more effective than control aromatherapy for hot flushes, sweats and night sweats (38).
- health coaching had no effect on depression symptoms (39).
- self-directed learning improved menopausal symptoms (40).

Alternative medicine and complementary therapies

We identified 10 RCTs that assessed a variety of herbal remedies (14,41–51) such as extracts from lavender (and lavender aromatherapy), bitter orange, hops, soy, and homeopathic and ayurvedic preparations compared against mostly placebo controls (table 8 in the data tables appendix).

The trials assessed a range of outcomes including vasomotor symptoms, hot flushes, sleep quality and anxiety and depression. Most studies indicated a significant effect of the herbal remedy; however, the homeopathic remedy had no effect on hot flushes or quality of life compared with placebo.

Chinese herbal medicine

In 1 Cochrane review (52) and 1 RCT (53), Chinese herbal medicine compared with HRT, other drug treatments or placebo, had no effects on menopausal or vasomotor symptoms including hot flushes and night sweats or adverse events (table 9 in the data tables appendix).

Acupuncture

We identified 6 RCTs of acupuncture (table 10 in the data tables appendix) (54–59), 4 of which used a non-sham acupuncture control group (for example, self-care, wait list, or alprazolam).

The studies found improvements in sleep quality, vasomotor symptoms, and oestrogen levels, but no effect on luteinising hormone or follicle stimulating hormone levels. However, these studies may be at risk of bias because the control group was aware that they were not receiving acupuncture.

In 2 RCTs comparing acupuncture with sham acupuncture, inconsistent results were seen for hot flushes. Hot flushes were statistically significantly improved in 1 study, but the result was noted to be less than the minimum clinical difference. There was no effect on hot flushes in the other study. The study finding improved hot flushes also reported improved menopausal symptoms and menopause-related quality of life. However, these measures could be driven by effects on hot flushes to some degree, so they do not indicate a clear clinically important effect.

Intelligence gathering

Topic experts suggested that the guideline could cover more non-hormonal treatments, but the limitations of the evidence base were recognised. Topic experts also highlighted new evidence on CBT, ospemifene and prasterone.

We identified ongoing studies assessing the effects of:

- CBT on vasomotor symptoms of menopause – Can nurse delivered CBT reduce the impact of hot flushes and night sweats in women who have had breast cancer? (ISRCTN12824632).
- complementary therapies, including two doses of standardised black cohosh. The guideline noted ‘there is some evidence that isoflavones or black cohosh may relieve vasomotor symptoms…’ but that ‘multiple preparations are available, and their safety is uncertain, different preparations may vary and interactions with other medicines have been reported’. This ongoing study– Effect of Menopause Relief EP-40 in Women With Menopausal Symptoms (NCT03461380) – may provide further evidence in this area.

We will check the publication status regularly and evaluate the impact of the results on current recommendations as quickly as possible.

Impact statement

Drug treatments

The guideline did not consider melatonin, oxybutynin or oxytocin. The clinical importance of the results reported in the abstracts was unclear and the studies were generally conducted in small numbers of people. Larger studies are needed to clarify the role of these treatments in menopause. Therefore, the guideline should not include these treatments in an update.

The guideline assessed venlafaxine but made no recommendations on this drug. The authors of the study of venlafaxine noted that the effects on sleep were 'modest', and the change in quality of life was small and of borderline statistical significance. Overall, the clinical significance of the findings is unclear. Therefore, there is no clear indication that an update to the guideline to consider venlafaxine is needed.

The guideline did not consider prasterone although it was available as a supplement in some countries when the guideline was developed. A preparation of prasterone is now available (costing £15.94 for 28 pessaries) for treatment of vulvar and vaginal atrophy in postmenopausal women with moderate to severe symptoms in the UK. New evidence suggests that prasterone may reduce vaginal symptoms of menopause and improve sexual function over 3 months of treatment. One of the studies identified in surveillance was also highlighted by topic experts. However, the evidence suggested that prasterone was no more effective than vaginal moisturiser for vaginal dryness and dyspareunia. Further evidence on the effects with prasterone treatment longer than 3 months and longer-term safety data is needed before considering an update of the guideline to evaluate the role of prasterone for treating vaginal symptoms of the menopause.

The guideline assessed ospemifene but made no recommendations on this drug. At the time of guideline development, ospemifene had recently received marketing authorisation in the UK, but its cost was unknown, so it could not be considered alongside vaginal oestrogen in the evidence review. However, it is now available in

the UK (costing £39.50 for 28 tablets) and is licensed for use in postmenopausal women who are not candidates for local vaginal oestrogen therapy.

The evidence on ospemifene reviewed during guideline development included 7 studies, with analyses of the various outcomes including 331 to 1971 women. The quality of these studies ranged from very low to moderate quality. The evidence indicated that ospemifene improved dyspareunia and vaginal dryness. Ospemifene also affected several physiological outcomes, such as reducing parabasal and intermediate cells, increasing superficial cells, and reducing vaginal pH. Ospemifene treatment for up to a year was not associated with endometrial hyperplasia, but endometrial thickness was increased. It was associated with more adverse events than placebo, but women were not more likely to stop treatment over 12 weeks. The new evidence was consistent with these findings and indicated improvements in sexual function. However, the new evidence did not report on adverse events associated with ospemifene. It was not possible to tell from the abstracts whether the effects were clinically meaningful, or durable.

The cost of prasterone is comparable with available intravaginal oestrogen pessaries, and although ospemifene is more expensive, its use is restricted to a smaller group of women for whom intravaginal oestrogen is not suitable. Therefore, we do not expect these treatments to have a substantial impact on NHS resources. Additionally, we are not aware of any new safety issues relating to other treatments for vaginal symptoms of menopause. For these reasons, we decided that an update was not necessary at this time.

New evidence is unlikely to change guideline recommendations.

Physical and psychological therapies

The guideline recommended considering CBT to alleviate low mood or anxiety that arise as a result of the menopause. The new evidence suggests that CBT may be useful for coping with other menopausal symptoms. Additionally, topic experts indicated that an update should look at CBT. However, because of heterogeneity in the type of CBT intervention, and the lack of information on the clinical importance of the effects sizes reported in the abstracts, the evidence base for CBT does not

appear to have advanced sufficiently to indicate a need to update the guideline at this time.

Similarly, the evidence did not show a clear effect of device-guided slow-paced breathing health coaching and exercise interventions and foot reflexology and self-directed learning were each assessed in a single small trial. A larger body of evidence is needed to support considering these treatments in a guideline update.

New evidence is unlikely to change guideline recommendations.

Alternative medicine and complementary remedies

The guideline does not recommend the herbal remedies identified in the new surveillance evidence. However, it recommends explaining to women who wish to try complementary therapies that the quality, purity and constituents of products may be unknown. The new evidence consisted of relatively small RCTs (100–200 participants). Larger studies evaluating complementary therapies in preparations with standardised quality, purity and constituents are needed before considering an update in this area.

New evidence is unlikely to change guideline recommendations.

Chinese herbal medicine

The guideline does not have recommendations on Chinese herbal medicine. The new evidence found no effect of this treatment on any relevant outcomes, indicating that an update in this area is not necessary.

New evidence is unlikely to change guideline recommendations.

Acupuncture

The guideline does not recommend acupuncture and the new evidence, showing little clinically important effect of this treatment, indicates that an update to include acupuncture is not necessary.

New evidence is unlikely to change guideline recommendations.

Long-term benefits and risks of hormone replacement therapy

Surveillance proposal

This section of the guideline on long-term benefits and risks of hormone replacement therapy should not be updated.

2019 surveillance summary

We identified 66 studies looking at long term risks and benefits of HRT, usually compared with an inactive control (mostly placebo). The studies assessed different types of HRT (oestrogen-only, combined, and tibolone) and varying durations of use. Many abstracts did not include specific details about the type or duration of HRT. Additionally, dosage information was not reported in all abstracts so information on dosage was not considered in this surveillance unless the study specifically compared a single regimen at 2 different doses (1 such study identified).

Coronary heart disease

We identified 2 large cohort studies (60,61) that assessed the risk of coronary heart disease with intravaginal HRT use compared with no HRT (table 11 in the data tables appendix). The results were inconsistent, with one study finding no effect and another finding lower risk of coronary heart disease with HRT. One of the studies found lower risk of coronary heart disease mortality.

Stroke

We identified 7 cohort studies (61–67), 1 Cochrane review (68) and one other systematic review (69) that assessed risk of stroke (ischaemic or haemorrhagic) or stroke mortality (table 12 in the data tables appendix). Studies assessed various types and durations of HRT use, and differing lengths of time since stopping HRT.

The studies showed mixed findings:

- 6 analyses suggested increased risk of stroke with
  - Oestrogen-only HRT compared with placebo (68,69).
  - Combined oestrogen (cyclic or continuous) and progestogen HRT compared with placebo or no HRT (65,68).

  - HRT compared with no HRT (63,66).
- 1 analysis suggested increased risk of stroke mortality in the first year after stopping HRT compared with no HRT or current HRT use (67).
- 5 analyses suggested no effect on stroke (mostly haemorrhagic) with combined or oestrogen-only HRT, including analyses of whether HRT was started up to 5 years after menopause or more than 5 years (62,65,66).
- 6 analyses suggested lower risk of stroke with oestrogen-only HRT, intravaginal oestrogen, and combined HRT, compared with no HRT, which was analysed by whether HRT was started up to 5 years after menopause or after 5 years (62,64,65).
- 2 analyses suggested improved stroke mortality with 3–5 years of intravaginal oestrogen and more than a year after stopping HRT (67).

Venous thromboembolism

We identified 2 cohort studies (63,70), 2 Cochrane reviews (10,68), and 1 other systematic review (69) that measured the risk of venous thromboembolism with HRT (table 13 in the data tables appendix). Both oestrogen-only and combined HRT were associated with increased risk of venous thromboembolism. One of the Cochrane reviews (10) suggested no effect of tibolone on risk of venous thromboembolism. However, this result was uncertain, with the confidence intervals indicating that tibolone may be associated with less than half the risk as no HRT but could also nearly double the risk of venous thromboembolism.

Diabetes

We identified one systematic review (69) that suggested a reduced risk of diabetes with either oestrogen-only or combined HRT compared with placebo (table 14 in the data tables appendix).

Other cardiovascular outcomes

We identified 5 cohort studies, 4 RCTs and 2 Cochrane reviews that assessed the effects of HRT on other cardiovascular outcomes (table 15 in the data tables appendix). Preparations of HRT varied across the studies, including oestrogen-only, combined and unspecified HRT. Additionally, studies analysed differing time points, such as stopping in the past year or more than a year ago, having started HRT in the

past 3 years or more than 3 years ago. Results suggested possible inconsistent effects of HRT compared with no HRT including:

- increased risk of acute coronary syndromes (63)
- no effect or increased risk of cardiovascular events or coronary events (10,29,68,71)
- no effect on cerebrovascular events (10) but reduced arterial thromboembolic events (72)
- inconsistent effects on blood pressure (8,73)
- improved blood pressure in one study of combined HRT and increased risk of hypertension in one study of oestrogen alone or combined HRT
- improved blood lipid profile (74).

Cardiovascular mortality (61,67,75–77) showed inconsistent results. Across 9 analyses, 4 suggested a lower risk of cardiovascular mortality and 3 suggested no effect. Analyses suggested increased cardiovascular mortality in the first year after stopping HRT but no effects more than a year after stopping HRT.

A Cochrane review (10) suggested that, compared with combined HRT, tibolone had no effect on cardiovascular, cerebrovascular, or thromboembolic events.

Breast cancer

We identified 10 cohort studies (76,78–86), 2 RCTs, 2 Cochrane reviews (10,68) and 1 other systematic review (69) that addressed the risk of breast cancer (table 16 in the data tables appendix).

Lower risks of breast cancer were seen in 3 studies of oestrogen-only HRT or unspecified HRT (that is, no details about the preparation were reported in the abstract) compared with placebo or no HRT (68,87).

No effect on breast cancer risk was seen in 3 studies of oestrogen-only HRT or unspecified HRT compared with no HRT (79,85,86).

Higher risks of breast cancer were seen in 11 studies of HRT compared with placebo or no HRT including:

- 6 studies of combined HRT (68,69,78,85–87)
- 4 studies of unspecified HRT (76,79,80,84)
- 1 study of intrauterine progestogen (83).

Tibolone showed inconsistent effects on breast cancer with 2 analyses showing no association with breast cancer and 2 suggesting increased risk of breast cancer compared with placebo, no HRT, or combined HRT (10,85).

One study assessed the outcomes for women using HRT who were subsequently diagnosed with breast cancer. HRT was associated with lower breast cancer mortality and recurrence compared with not using HRT at diagnosis (82).

Other cancers

We identified 14 cohort studies (76,80,88–98), 5 RCTs (77,84,99–102), 3 Cochrane reviews (10,68,103) and 1 other systematic review (69) that addressed the risk of cancers other than breast cancer with HRT use compared with an inactive control (table 17 in the data tables appendix).

Overall, studies indicated that HRT use was associated with:

- a generally consistent reduced risk of gastrointestinal cancers, including colorectal cancers.
- an increased risk of ovarian cancer, melanoma and in any cancer
- no effect on risk of non-Hodgkin's lymphoma or lung cancer.

Osteoporosis

We identified 2 cohort studies (104,105), 1 RCT (106), 1 Cochrane review (68) and one other systematic review (69) that addressed outcomes related to osteoporosis (table 18 in the data tables appendix). Overall 9 of 10 analyses showed a lower risk of fracture or increased bone mineral density with HRT use. The remaining analysis suggested no effect.

Dementia

We identified 1 cohort study (107), 4 RCTs (20,108–110), 1 Cochrane review (68) and 1 other systematic review (69) that assessed dementia and cognitive outcomes

(table 19 in the data tables appendix). Overall, results were inconsistent across the 13 analyses:

- 6 analyses suggested worse cognitive outcomes with HRT; however, most analyses were of varying measures of cognitive function rather than diagnosis of dementia
- 6 analyses suggested no effect of HRT; again, most analyses were of varying measures of cognitive function rather than diagnosis of dementia
- 1 analysis suggested reduced risk of Alzheimer's disease with HRT.

Long-term risks not currently covered in the guideline

We identified 4 cohort studies (75,76,82,111), 1 RCT (77), and 1 Cochrane review (10), that measured the effects of HRT use on mortality (1 study specified the outcome as non-breast cancer mortality) (table 20 in the data tables appendix). In 7 analyses, HRT was associated with lower mortality, and 5 analyses found no effect. There was no indication that the results were dependent on population characteristics or type or duration of HRT use.

We identified 11 cohort studies, 4 RCTs, 2 systematic reviews and 3 Cochrane reviews that addressed other outcomes that were not considered in the guideline (table 21 in the data tables appendix). Results indicated:

- HRT was associated with increased risk of faecal incontinence, fibroids, gallbladder disease and gallstones, hearing loss, joint swelling, rheumatoid arthritis, and urinary incontinence (68,69,97,112–116).
- HRT was associated with improvements in albuminuria, anxiety, carpal tunnel syndrome, joint pain, lung function, and tinnitus(20,113,117–120).
- There may be no association between HRT and sudden sensorineural hearing loss (120).
- Inconsistent effects on intraocular pressure were seen, with improvement seen with conjugated equine oestrogen, but no effect seen with combined HRT.(121)

One cohort study (122) compared 2 doses of conjugated equine oestrogen – less than 0.625 mg daily and 0.625 mg daily. Progestogen was also used in both groups. The occurrence of global index events (coronary heart disease, breast cancer, stroke, pulmonary embolism, hip fracture, colorectal cancer, endometrial cancer, or death) was lower with the lower dose. For the higher dose, duration of treatment of 5 or more years was associated with higher rates of global index events than a duration of less than 5 years.

Intelligence gathering

No topic expert feedback was relevant to this section of the guideline.

Impact statement

Coronary heart disease

The guideline considered the effects of HRT on coronary heart disease. Both the guideline and the new evidence found no or reduced risk with oestrogen-only HRT. Therefore, the new evidence is consistent with current recommendations to explain that HRT with oestrogen alone is associated with no, or reduced, risk of coronary heart disease.

Stroke

Evidence identified in developing the guideline found possible increased risk of stroke with combined or oestrogen-only HRT. However, the effects were uncertain. The guideline recommends explaining to women that taking oral (but not transdermal) oestrogen is associated with a small increase in the risk of stroke and that the baseline population risk of stroke in women aged under 60 years is very low.

The new evidence was mixed, with some new evidence indicating an increased risk of stroke with HRT and other studies finding no effect or reduced risk of stroke. Therefore, the uncertain risks of stroke with HRT noted in the guidelines are unlikely to change substantively.

Venous thromboembolism

The guideline recommended explaining to women that oral HRT was associated with an increased risk of venous thromboembolism, but there was no increased risk for

transdermal HRT. The new evidence also indicated an increased risk of venous thromboembolism with HRT, and an uncertain effect of tibolone on venous thromboembolism. Therefore, an update in this area is not necessary because the findings are consistent with the guidelines recommendations on oral HRT, and is is unclear whether tibolone has a different risk profile to oral HRT.

Diabetes

The new evidence of reduced risk of diabetes with HRT is consistent with evidence considered in the guideline. However, in developing the guideline, the protective effects of HRT on type 2 diabetes appeared to last only until HRT was stopped. The recommendations therefore noted there to be no increased risk of type 2 diabetes, rather than a reduced risk of diabetes. The new evidence did not inform whether the effect on diabetes continues after stopping HRT, thus no update in this area is needed.

Other cardiovascular outcomes

The guideline recommended that HRT does not increase cardiovascular disease risk when started in women aged under 60 years and does not affect the risk of dying from cardiovascular disease. The new evidence showed inconsistent effects on other cardiovascular outcomes and cardiovascular mortality. The new evidence is thus unlikely to substantively change the guideline's conclusions about risk of cardiovascular disease and mortality.

Overall impact on cardiovascular outcomes

Overall, the new evidence was generally consistent with the guideline's conclusions about cardiovascular risks associated with HRT use. There was no clear indicator that any additional cardiovascular risks need to be considered by the guideline.

New evidence is unlikely to impact on the guideline.

Breast cancer

The guideline considered the effects of HRT on breast cancer. The effects differed depending on whether HRT use was current or hist orical, duration of treatment, and whether oestrogen-only HRT or combined HRT was used. The guideline recommended explaining to women around the age of menopause that 'HRT with

oestrogen alone is associated with little or no change in the risk of breast cancer' and 'HRT with oestrogen and progestogen can be associated with an increase in the risk of breast cancer'.

Overall the evidence identified in surveillance was consistent with these findings, with oestrogen-only HRT generally showing no or lower risks of breast cancer, and HRT containing progesterone generally showing an increased risk of breast cancer.

Other cancers

The guideline did not address risk of cancers other than breast cancer. Although the new evidence provides additional information on possible risks and benefits of HRT use, they do not substantively change the overall risk–benefit profile of using HRT. The increased risk seen for ovarian cancer is already recognised in the SPCs of hormone replacement therapy products. Evidence suggests a balance between increased risks of some cancers such as melanoma and reduced risks of other cancers such as colorectal cancers. However, the evidence mostly comes from observational studies, and as such, it is not possible to be sure of a cause and effect relationship. The observed cancer rates may be influenced by confounding factors that have not been recognised or measured. Therefore, the guideline should not be updated to address additional cancer risks at this time.

New evidence is unlikely to impact on the guideline.

Osteoporosis

The guideline recommends explaining to women that their risk of fragility fracture is decreased while taking HRT. The new evidence showing reduced risk of fracture with HRT is consistent with this finding.

New evidence is unlikely to impact on the guideline.

Dementia

The guideline recommends explaining to menopausal women that the likelihood of HRT affecting their risk of dementia is unknown. The new evidence showed inconsistent effects on dementia and cognitive function and thus is unlikely to substantially impact on the findings in the guideline.

New evidence is unlikely to impact on the guideline.

Long-term risks not currently covered in the guideline

The guideline did not cover overall mortality and the inconsistency of the new evidence suggests that a guideline update to consider these outcomes is not necessary.

New evidence is unlikely to impact on the guideline.

Other outcomes

The new evidence seems to show inconsistent effects across HRT-related outcomes, such as hearing or joint pain and swelling. The evidence mostly comes from observational studies, and as such, it is not possible to be sure of a cause and effect relationship. The observed effects may be influenced by confounding factors that have not been recognised or measured. Additionally, most of these other outcomes were identified in a single study and we are not aware of clinical or patient concerns on outcomes not covered by current recommendations. Therefore, a guideline update to consider additional outcomes is not necessary at this time.

New evidence is unlikely to impact on the guideline.

Diagnosing and managing premature ovarian insufficiency

Surveillance proposal

No new information on diagnosing and managing premature ovarian insufficiency was identified at any surveillance review.

Research recommendations

What is the safety and effectiveness of alternatives to systemic HRT as treatments for menopausal symptoms in women who have had treatment for breast cancer?

- No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

What is the impact of systemic HRT usage in women with a previous diagnosis of breast cancer for the risk of breast cancer reoccurrence, mortality or tumour aggression?

- No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

How does the preparation of HRT affect the risk of venous thromboembolism (VTE)?

- New research relevant to the risk of venous thromboembolism was identified but does not clearly answer this research recommendation.

What is the difference in the risk of breast cancer in menopausal women on HRT with progesterone, progestogen or selective oestrogen receptor modulators?

- New research relevant to the risk of breast cancer was identified but does not clearly answer this research recommendation.

What is the impact of oestradiol in combination with the levonorgestrel-releasing intrauterine system (LNG-IUS) on the risk of breast cancer and venous thromboembolism (VTE)?

- No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

What are the effects of early HRT use on the risk of dementia?

- New research relevant to the risk of dementia was identified but does not clearly answer this research recommendation.

What are the main clinical manifestations of premature ovarian insufficiency and the short- and long-term impact of the most common therapeutic interventions?

- No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

References

1. Santoro N, Allshouse A, Neal-Perry G, Pal L, Lobo RA, Naftolin F, et al. (2017) Longitudinal changes in menopausal symptoms comparing women randomized to low-dose oral conjugated estrogens or transdermal estradiol plus micronized progesterone versus placebo: the Kronos Early Estrogen Prevention Study. Menopause (New York, N.Y.) 24(3):238–46

2. Ensrud KE, Guthrie KA, Hohensee C, Caan B, Carpenter JS, Freeman EW, et al. (2015) Effects of estradiol and venlafaxine on insomnia symptoms and sleep quality in women with hot flashes. Sleep 38(1):97–108

3. Yu C-G, Zhao S-H, Shi J-Y, Wang W-Z, Chen J-L (2016) A translational study of low-dose estrogen replacement therapy on Kupperman score and levels of hormones in patients with perimenopausal syndrome.

Journal of international translational medicine 4(2):143–6

4. Caan B, LaCroix AZ, Joffe H, Guthrie KA, Larson JC, Carpenter JS, et al. (2015) Effects of estrogen and venlafaxine on menopause-related quality of life in healthy postmenopausal women with hot flashes: a placebo-controlled randomized trial. Menopause (New York, N.Y.) 22(6):607–15

5. Diem SJ, Guthrie KA, Mitchell CM, Reed S., Larson JC, Ensrud KE, et al. (2018) Effects of vaginal estradiol tablets and moisturizer on menopause-specific quality of life and mood in healthy postmenopausal women with vaginal symptoms: A randomized clinical trial. Menopause 25(10):1086–93

6. Constantine GD, Revicki DA, Kagan R, Simon JA, Graham S, Bernick B, et al. (2019) Evaluation of clinical meaningfulness of estrogen plus progesterone oral capsule (TX-001HR) on moderate to severe vasomotor symptoms. Menopause (New York, N.Y.) 26(5):513–9

7. Kagan R, Constantine G, Kaunitz AM, Bernick B, Mirkin S (2018) Improvement in sleep outcomes with a 17beta-estradiol-progesterone oral capsule (TX-001HR) for postmenopausal women. Menopause (New York, N.Y.)

8. Paoletti AM, Cagnacci A, Di Carlo C, Orru MM, Neri M, D'Alterio MN, et al. (2015) Clinical effect of hormonal replacement therapy with estradiol associated with noretisterone or drospirenone. A prospective randomized placebo controlled study. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology 31(5):384–7

9. Gaudard A, Silva de SS, Puga M, Marjoribanks J, da SE, Torloni M (2016) Bioidentical hormones for women with vasomotor symptoms. Cochrane Database of Systematic Reviews (8)

10. Formoso G, Perrone E, Maltoni S, Balduzzi S, Wilkinson J, Basevi V, et

al. (2016) Short?term and long?term effects of tibolone in postmenopausal women. Cochrane Database of Systematic Reviews (10)

11. Constantine GD, Simon JA, Pickar JH, Archer DF, Bernick B, Graham S, et al. (2018) Estradiol vaginal inserts (4 micro g and 10 micro g) for treating moderate to severe vulvar and vaginal atrophy: a review of phase 3 safety, efficacy and pharmacokinetic data. Current Medical Research and Opinion 34(12):2131–6

12. Kroll R, Archer DF, Lin Y, Sniukiene V, Liu JH (2018) A randomized, multicenter, double-blind study to evaluate the safety and efficacy of estradiol vaginal cream 0.003% in postmenopausal women with dyspareunia as the most bothersome symptom. Menopause 25(2):133–8

13. Taylor HS, Tal A, Pal L, Li F, Black DM, Brinton EA, et al. (2017) Effects of Oral vs Transdermal Estrogen Therapy on Sexual Function in Early Postmenopause: Ancillary Study of the Kronos Early Estrogen Prevention Study (KEEPS). JAMA internal medicine 177(10):1471–9

14. Mitchell CM, Reed SD, Diem S, Larson JC, Newton KM, Ensrud KE, et al. (2018) Efficacy of Vaginal Estradiol or Vaginal Moisturizer vs Placebo for Treating Postmenopausal Vulvovaginal Symptoms: A Randomized Clinical Trial. JAMA internal medicine 178(5):681–90

15. Constantine GD, Simon JA, Pickar JH, Archer DF, Kushner H, Bernick B, et al. (2017) The REJOICE trial: a phase 3 randomized, controlled trial evaluating the safety and efficacy of a novel vaginal estradiol soft-gel capsule for symptomatic vulvar and vaginal atrophy. Menopause (New York, N.Y.) 24(4):409–16

16. Archer DF, Kimble TD, Lin FDY, Battucci S, Sniukiene V, Liu JH (2018) A Randomized, Multicenter, Double-Blind, Study to Evaluate the Safety and Efficacy of Estradiol Vaginal Cream 0.003% in Postmenopausal

Women with Vaginal Dryness as the Most Bothersome Symptom. Journal of women's health (2002) 27(3):231–7

17. Rioux JE, Devlin MC, Gelfand MM, Steinberg WM, Hepburn DS (2018) 17beta-estradiol vaginal tablet versus conjugated equine estrogen vaginal cream to relieve menopausal atrophic vaginitis. Menopause 25(11):1208–13

18. Lethaby A, Ayeleke R, Roberts H (2016) Local oestrogen for vaginal atrophy in postmenopausal women. Cochrane Database of Systematic Reviews (8)

19. Gordon JL, Rubinow DR, Eisenlohr-Moul TA, Xia K, Schmidt PJ, Girdler SS (2018) Efficacy of transdermal estradiol and micronized progesterone in the prevention of depressive symptoms in the menopause transition: A randomized clinical trial. JAMA Psychiatry 75(2):149–57

20. Gleason CE, Dowling NM, Wharton W, Manson JE, Miller VM, Atwood CS, et al. (2015) Effects of Hormone Therapy on Cognition and Mood in Recently Postmenopausal Women: Findings from the Randomized, Controlled KEEPS-Cognitive and Affective Study. PLoS medicine 12(6):e1001833–e1001833

21. Kingsberg SA, Kroll R, Goldstein I, Kushner H, Bernick B, Graham S, et al. (2017) Patient acceptability and satisfaction with a low-dose solubilized vaginal estradiol softgel capsule, TX-004HR. Menopause (New York, N.Y.) 24(8):894–9

22. Labrie F, Archer DF, Koltun W, Vachon A, Young D, Frenette L, et al. (2016) Efficacy of intravaginal dehydroepiandrosterone (DHEA) on moderate to severe dyspareunia and vaginal dryness, symptoms of vulvovaginal atrophy, and of the genitourinary syndrome of menopause. Menopause (New York, N.Y.) 23(3):243–56

23. Barton DL, Sloan JA, Shuster LT, Gill P, Griffin P, Flynn K, et al. (2018)

Evaluating the efficacy of vaginal dehydroepiandosterone for vaginal symptoms in postmenopausal cancer survivors: NCCTG N10C1 (Alliance). Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 26(2):643–50

24. Labrie F, Derogatis L, Archer DF, Koltun W, Vachon A, Young D, et al. (2015) Effect of Intravaginal Prasterone on Sexual Dysfunction in Postmenopausal Women with Vulvovaginal Atrophy. The journal of sexual medicine 12(12):2401–12

25. Archer DF, Goldstein SR, Simon JA, Waldbaum AS, Sussman SA, Altomare C, et al. (2019) Efficacy and safety of ospemifene in postmenopausal women with moderate-to-severe vaginal dryness: a phase 3, randomized, double-blind, placebo-controlled, multicenter trial. Menopause (New York, N.Y.)

26. Constantine G, Graham S, Portman DJ, Rosen RC, Kingsberg SA (2015) Female sexual function improved with ospemifene in postmenopausal women with vulvar and vaginal atrophy: results of a randomized, placebo-controlled trial. Climacteric : the journal of the International Menopause Society 18(2):226–32

27. Li Y, Liu H, Sun J, Tian Y, Li C (2016) Effect of melatonin on the peripheral T lymphocyte cell cycle and levels of reactive oxygen species in patients with premature ovarian failure. Experimental and Therapeutic Medicine 12(6):3589–94

28. Parandavar N, Hojat M, Abdali K, Keshtgar S, Emamghoreishi M, Yeganeh BS (2018) The effect of melatonin on the lipid levels in menopausal women: A double-blind, controlled, clinical trial. Journal of education and health promotion 7:144

29. Simon JA, Gaines T, LaGuardia KD, Group E-ROT for VMSS (2016) Extended-release oxybutynin therapy for vasomotor symptoms in women: a randomized clinical trial. Menopause (New York, N.Y.)

23(11):1214–21

30. Torky HA, Taha A, Marie H, El-Desouky E, Raslan O, Moussa AA, et al. (2018) Role of topical oxytocin in improving vaginal atrophy in postmenopausal women: a randomized, controlled trial. Climacteric 21(2):174–8

31. Hardy C, Griffiths A, Norton S, Hunter MS (2018) Self-help cognitive behavior therapy for working women with problematic hot flushes and night sweats (MENOS@Work): a multicenter randomized controlled trial. Menopause (New York, N.Y.) 25(5):508–19

32. Atema V, van Leeuwen M, Kieffer JM, Oldenburg HSA, van Beurden M, Gerritsma MA, et al. (2019) Efficacy of Internet-Based Cognitive Behavioral Therapy for Treatment-Induced Menopausal Symptoms in Breast Cancer Survivors: Results of a Randomized Controlled Trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 37(10):809–22

33. McCurry SM, Guthrie KA, Morin CM, Woods NF, Landis CA, Ensrud KE, et al. (2016) Telephone-Based Cognitive Behavioral Therapy for Insomnia in Perimenopausal and Postmenopausal Women With Vasomotor Symptoms: A MsFLASH Randomized Clinical Trial. JAMA internal medicine 176(7):913–20

34. Huang AJ, Phillips S, Schembri M, Vittinghoff E, Grady D (2015) Device-guided slow-paced respiration for menopausal hot flushes. Obstetrics and gynecology 125(5afarnationalinstituteonaging5r01at005491nccamnationalinstituteonaging1k23ag038335nianationalinstituteonagingnihnationalinstituteonaging):1130–8

35. Daley AJ, Thomas A, Roalfe AK, Stokes-Lampard H, Coleman S, Rees M, et al. (2015) The effectiveness of exercise as treatment for vasomotor menopausal symptoms: randomised controlled trial. BJOG :

an international journal of obstetrics and gynaecology 122(4):565–75

36. Abedi P, Nikkhah P, Najar S (2015) Effect of pedometer-based walking on depression, anxiety and insomnia among postmenopausal women. Climacteric : the journal of the International Menopause Society 18(6):841–5

37. Tadayon M, Abedi P, Farshadbakht F (2016) Impact of pedometer-based walking on menopausal women's sleep quality: a randomized controlled trial. Climacteric : the journal of the International Menopause Society 19(4):364–8

38. Gozuyesil E, Baser M (2016) The effect of foot reflexology applied to women aged between 40 and 60 on vasomotor complaints and quality of life. Complementary therapies in clinical practice 24:78–85

39. Almeida OP, Marsh K, Murray K, Hickey M, Sim M, Ford A, et al. (2016) Reducing depression during the menopausal transition with health coaching: Results from the healthy menopausal transition randomised controlled trial. Maturitas 92:41–8

40. Mirghafourvand M, Sehhatie Shafaie F, Jafari M (2015) Effects of self-directed learning on the early symptoms of menopause. Journal of babol university of medical sciences 17(3):68–75

41. Heudel P-E, Van Praagh-Doreau I, Duvert B, Cauvin I, Hardy-Bessard A-C, Jacquin J-P, et al. (2019) Does a homeopathic medicine reduce hot flushes induced by adjuvant endocrine therapy in localized breast cancer patients? A multicenter randomized placebo-controlled phase III trial. Supportive Care in Cancer 27(5):1879–89

42. Sathyapalan T, Aye M, Rigby AS, Thatcher NJ, Dargham SR, Kilpatrick ES, et al. (2018) Soy isoflavones improve cardiovascular disease risk markers in women during the early menopause. Nutrition, metabolism, and cardiovascular diseases : NMCD 28(7):691–7

43. Gocan A, Imhof M, Schmidt M (2018) Soy germ extract alleviates menopausal hot flushes: Placebo-controlled double-blind trial. European Journal of Clinical Nutrition 72(7):961–70

44. Steels E, Steele M, Harold M, Adams L, Coulson S (2018) A double-blind, randomized, placebo-controlled trial evaluating safety and efficacy of an ayurvedic botanical formulation in reducing menopausal symptoms in otherwise healthy women. Journal of Herbal Medicine 11:30–5

45. Farshbaf-Khalili A, Kamalifard M, Namadian M (2018) Comparison of the effect of lavender and bitter orange on anxiety in postmenopausal women: A triple-blind, randomized, controlled clinical trial. Complementary therapies in clinical practice 31:132–8

46. Kamalifard M, Farshbaf-Khalili A, Namadian M, Ranjbar Y, Herizchi S (2018) Comparison of the effect of lavender and bitter orange on sleep quality in postmenopausal women: A triple-blind, randomized, controlled clinical trial. Women & health 58(8):851–65

47. Dastenaei BM, Safdari F, Jafarzadeh L, Dehkordi ZR, Taghizadeh M, Nikzad M (2017) The effect of evening primrose on hot flashes in menopausal women. Iranian journal of obstetrics, gynecology and infertility 20(10):62–8

48. Steels E, Steele ML, Harold M, Coulson S (2017) Efficacy of a Proprietary Trigonella foenum-graecum L. De-Husked Seed Extract in Reducing Menopausal Symptoms in Otherwise Healthy Women: A Double-Blind, Randomized, Placebo-Controlled Study. Phytotherapy research : PTR 31(9):1316–22

49. Aghamiri V, Mirghafourvand M, Mohammad-Alizadeh-Charandabi S, Nazemiyeh H (2016) The effect of Hop (Humulus lupulus L.) on early menopausal symptoms and hot flashes: A randomized placebo-controlled trial. Complementary therapies in clinical practice 23:130–5

50. Kazemzadeh R, Nikjou R, Rostamnegad M, Norouzi H (2016) Effect of lavender aromatherapy on menopause hot flushing: A crossover randomized clinical trial. Journal of the Chinese Medical Association : JCMA 79(9):489–92

51. Nikjou R, Kazemzadeh R, Asadzadeh F, Fathi R, Mostafazadeh F (2018) The Effect of Lavender Aromatherapy on the Symptoms of Menopause. Journal of the National Medical Association 110(3):265–9

52. Zhu X, Liew Y, Liu Z (2016) Chinese herbal medicine for menopausal symptoms. Cochrane Database of Systematic Reviews (3)

53. Jiang D, Zhou J-H, Zhou J, Gu Y-E, Yang D-X, Weng Q, et al. (2015) Zhi-bai-di-huang-wan, a classic chinese medicinal formula in relieving menopausal symptoms: A multi-centre and controlled trial from UK and China. African Journal of Traditional, Complementary and Alternative Medicines 12(s1):45–51

54. Li O, Wang F (2018) Acupuncture at back-shu points of five zang, Geshu (BL 17) and Shenmen (HT 7) for the treatment of menopausal insomnia. Zhongguo zhen jiu [Chinese acupuncture & moxibustion] 38(5):4672–93

55. Avis NE, Coeytaux RR, Isom S, Prevette K, Morgan T (2016) Acupuncture in Menopause (AIM) study: a pragmatic, randomized controlled trial. Menopause (New York, N.Y.) 23(6):626–37

56. Liu Z, Ai Y, Wang W, Zhou K, He L, Dong G, et al. (2018) Acupuncture for symptoms in menopause transition: a randomized controlled trial. American Journal of Obstetrics and Gynecology 219(4):373

57. Ee C, Xue C, Chondros P, Myers SP, French SD, Teede H, et al. (2016) Acupuncture for Menopausal Hot Flashes: A Randomized Trial. Annals of internal medicine 164(3):146–54

58. Lesi G, Razzini G, Musti MA, Stivanello E, Petrucci C, Benedetti B, et al.

(2016) Acupuncture As an Integrative Approach for the Treatment of Hot Flashes in Women With Breast Cancer: A Prospective Multicenter Randomized Controlled Trial (AcCliMaT). Journal of clinical oncology : official journal of the American Society of Clinical Oncology 34(15):1795–802

59. Peng YY, Jing HT, Luan L, Tu YY (2018) Treatment of Menopausal Syndrome by Combined Electroacupuncture, Acupoint-injection and Fire-needle Therapies. Zhen CI yan jiu = acupuncture research 43(4):260–2

60. Crandall CJ, Hovey KM, Andrews CA, Chlebowski R., Stefanick ML, Lane DS, et al. (2018) Breast cancer, endometrial cancer, and cardiovascular events in participants who used vaginal estrogen in the Women's Health Initiative Observational Study. Menopause 25(1):11–20

61. Mikkola TS, Tuomikoski P, Lyytinen H, Korhonen P, Hoti F, Vattulainen P, et al. (2016) Vaginal estradiol use and the risk for cardiovascular mortality. Human reproduction (Oxford, England) 31(4):804–9

62. Carrasquilla GD, Frumento P, Berglund A, Borgfeldt C, Bottai M, Chiavenna C, et al. (2017) Postmenopausal hormone therapy and risk of stroke: A pooled analysis of data from population-based cohort studies. PLoS medicine 14(11):e1002445

63. Chang W-C, Wang J-H, Ding D-C (2019) Hormone therapy in postmenopausal women associated with risk of stroke and venous thromboembolism: a population-based cohort study in Taiwan. Menopause (New York, N.Y.) 26(2):197–202

64. Chen Y-H, Hsieh T-F, Lee C-C, Wu M-J, Fu Y-C (2015) Estrogen therapy and ischemic stroke in women with diabetes aged over 55 Years: A nation-wide prospective population-based study in Taiwan. PLoS ONE 10(12):144910

65. Lokkegaard E, Nielsen LH, Keiding N (2017) Risk of Stroke With Various Types of Menopausal Hormone Therapies: A National Cohort Study. Stroke 48(8):2266–9

66. Qureshi AI, Malik AA, Saeed O, Defillo A, Sherr GT, Suri MFK (2016) Hormone replacement therapy and the risk of subarachnoid hemorrhage in postmenopausal women. Journal of neurosurgery 124(1):45–50

67. Mikkola TS, Tuomikoski P, Lyytinen H, Korhonen P, Hoti F, Vattulainen P, et al. (2015) Increased Cardiovascular Mortality Risk in Women Discontinuing Postmenopausal Hormone Therapy. The Journal of clinical endocrinology and metabolism 100(12):4588–94

68. Marjoribanks J, Farquhar C, Roberts H, Lethaby A, Lee J (2017) Long?term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database of Systematic Reviews (1)

69. Gartlehner G, Patel S V, Feltner C, Weber RP, Long R, Mullican K, et al. (2017) Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Women: Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA 318(22):2234–49

70. Lee C-H, Cheng C-L, Kao Yang Y-H, Lin L-J (2015) Hormone therapy and risk of venous thromboembolism among postmenopausal women in Taiwan - a 10-year nationwide population-based study. Circulation journal : official journal of the Japanese Circulation Society 79(5):1107–14

71. Huang AJ, Sawaya GF, Vittinghoff E, Lin F, Grady D (2018) Hot flushes, coronary heart disease, and hormone therapy in postmenopausal women. Menopause (New York, N.Y.) 25(11):1286–90

72. Dinger J, Bardenheuer K, Heinemann K (2016) Drospirenone plus estradiol and the risk of serious cardiovascular events in

postmenopausal women. Climacteric : the journal of the International Menopause Society 19(4):349–56

73. Swica Y, Warren MP, Manson JE, Aragaki AK, Bassuk SS, Shimbo D, et al. (2018) Effects of oral conjugated equine estrogens with or without medroxyprogesterone acetate on incident hypertension in the Women's Health Initiative hormone therapy trials. Menopause (New York, N.Y.) 25(7):753–61

74. Ki EY, Hur SY, Park JS, Do Han K, Park YG (2016) Differences in the lipid profile and hormone replacement therapy use in Korean postmenopausal women: the Korea National Health and Nutrition Examination Survey (KNHANES) 2010-2012. Archives of gynecology and obstetrics 294(1):165–73

75. Chen L, Mishra GD, Dobson AJ, Wilson LF, Jones MA (2017) Protective effect of hormone therapy among women with hysterectomy/oophorectomy. Human reproduction (Oxford, England) 32(4):885–92

76. Holm M, Olsen A, Au Yeung SL, Overvad K, Lidegaard O, Kroman N, et al. (2019) Pattern of mortality after menopausal hormone therapy: long-term follow up in a population-based cohort. BJOG : an international journal of obstetrics and gynaecology 126(1):55–63

77. Manson JE, Aragaki AK, Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, et al. (2017) Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality: The Women's Health Initiative Randomized Trials. JAMA 318(10):927–38

78. Brusselaers N, Tamimi RM, Konings P, Rosner B, Adami H-O, Lagergren J (2018) Different menopausal hormone regimens and risk of breast cancer. Annals of oncology : official journal of the European Society for Medical Oncology 29(8):1771–6

79. Ettinger B, Quesenberry C, Schroeder DA, Friedman G (2018) Long-

term postmenopausal estrogen therapy may be associated with increased risk of breast cancer: a cohort study. Menopause (New York, N.Y.) 25(11):1191–4

80. Holm M, Olsen A, Kyrø C, Overvad K, Kroman N, Tjønneland A (2018) The Influence of Menopausal Hormone Therapy and Potential Lifestyle Interactions in Female Cancer Development-a Population-Based Prospective Study. Hormones & cancer 9(4):254–64

81. Liu J-Y, Chen T-J, Hwang S-J (2016) The Risk of Breast Cancer in Women Using Menopausal Hormone Replacement Therapy in Taiwan. International journal of environmental research and public health 13(5)

82. Obi N, Heinz J, Seibold P, Vrieling A, Rudolph A, Chang-Claude J, et al. (2016) Relationship between menopausal hormone therapy and mortality after breast cancer The MARIEplus study, a prospective case cohort. International journal of cancer 138(9):2098–108

83. Siegelmann-Danieli N, Katzir I, Landes JV, Segal Y, Bachar R, Rabinovich HR, et al. (2018) Does levonorgestrel-releasing intrauterine system increase breast cancer risk in peri-menopausal women? An HMO perspective. Breast cancer research and treatment 167(1):257–62

84. Simin J, Tamimi R, Lagergren J, Adami H-O, Brusselaers N (2017) Menopausal hormone therapy and cancer risk: An overestimated risk?. European journal of cancer (Oxford, England : 1990) 84:60–8

85. Suhrke P, Zahl P-H (2015) Breast cancer incidence and menopausal hormone therapy in Norway from 2004 to 2009: a register-based cohort study. Cancer medicine 4(8):1303–8

86. Jones ME, Schoemaker MJ, Wright L, McFadden E, Griffin J, Thomas D, et al. (2016) Menopausal hormone therapy and breast cancer: what is the true size of the increased risk?. British journal of cancer 115(5):607–15

87. Chlebowski RT, Anderson GL, Aragaki AK, Prentice R (2016) Breast Cancer and Menopausal Hormone Therapy by Race/Ethnicity and Body Mass Index. Journal of the National Cancer Institute 108(2)

88. Morch LS, Lidegaard O, Keiding N, Lokkegaard E, Kjaer SK (2016) The influence of hormone therapies on colon and rectal cancer. European journal of epidemiology 31(5):481–9

89. Sadr-Azodi O, Konings P, Brusselaers N (2017) Menopausal hormone therapy and pancreatic cancer risk in women: a population-based matched cohort study. United European gastroenterology journal 5(8):1123–8

90. Zamora-Ros R, Rinaldi S, Biessy C, Tjonneland A, Halkjaer J, Fournier A, et al. (2015) Reproductive and menstrual factors and risk of differentiated thyroid carcinoma: the EPIC study. International journal of cancer 136(5):1218–27

91. Blanks RG, Benson VS, Alison R, Brown A, Reeves GK, Beral V, et al. (2015) Nationwide bowel cancer screening programme in England: cohort study of lifestyle factors affecting participation and outcomes in women. British journal of cancer 112(9):1562–7

92. Botteri E, Støer NC, Sakshaug S, Graff-Iversen S, Vangen S, Hofvind S, et al. (2017) Menopausal hormone therapy and risk of melanoma: Do estrogens and progestins have a different role? International journal of cancer 141(9):1763–70

93. Botteri E, Stoer NC, Sakshaug S, Graff-Iversen S, Vangen S, Hofvind S, et al. (2017) Menopausal hormone therapy and colorectal cancer: a linkage between nationwide registries in Norway. BMJ open 7(11):e017639

94. Brusselaers N, Maret-Ouda J, Konings P, El-Serag HB, Lagergren J (2017) Menopausal hormone therapy and the risk of esophageal and gastric cancer. International journal of cancer 140(7):1693–9

95. Cervenka I, Al Rahmoun M, Mahamat-Saleh Y, Savoye I, Boutron-Ruault MC, Fournier A, et al. (2019) Postmenopausal hormone use and cutaneous melanoma risk: A French prospective cohort study. International journal of cancer

96. Cancer CGOESOO, Beral V, Gaitskell K, Hermon C, Moser K, Reeves G, et al. (2015) Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies. Lancet (London, England) 385(9980):1835–42

97. Kilander C, Lagergren J, Konings P, Sadr-Azodi O, Brusselaers N (2019) Menopausal hormone therapy and biliary tract cancer: a population-based matched cohort study in Sweden. Acta oncologica (Stockholm, Sweden) 58(3):290–5

98. Løkkegaard ECL, Mørch LS (2018) Tibolone and risk of gynecological hormone sensitive cancer. International journal of cancer 142(12):2435–40

99. Chlebowski RT, Wakelee H, Pettinger M, Rohan T, Liu J, Simon M, et al. (2016) Estrogen Plus Progestin and Lung Cancer: Follow-up of the Women's Health Initiative Randomized Trial. Clinical lung cancer 17(1):10–7.e1

100. Eeles RA, Morden JP, Gore M, Mansi J, Glees J, Wenczl M, et al. (2015) Adjuvant Hormone Therapy May Improve Survival in Epithelial Ovarian Cancer: Results of the AHT Randomized Trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 33(35):4138–44

101. Kato I, Chlebowski RT, Hou L, Wactawski-Wende J, Ray RM, Abrams J, et al. (2016) Menopausal estrogen therapy and non-Hodgkin's lymphoma: A post-hoc analysis of women's health initiative randomized clinical trial. International journal of cancer 138(3):604–11

102. Chlebowski RT, Anderson GL, Sarto GE, Haque R, Runowicz CD,

Aragaki AK, et al. (2016) Continuous Combined Estrogen Plus Progestin and Endometrial Cancer: The Women's Health Initiative Randomized Trial. Journal of the National Cancer Institute 108(3)

103. Edey K, Rundle S, Hickey M (2018) Hormone replacement therapy for women previously treated for endometrial cancer. Cochrane Database of Systematic Reviews (5)

104. Kuh D, Muthuri S, Cooper R, Moore A, Mackinnon K, Cooper C, et al. (2016) Menopause, Reproductive Life, Hormone Replacement Therapy, and Bone Phenotype at Age 60-64 Years: A British Birth Cohort. The Journal of clinical endocrinology and metabolism 101(10):3827–37

105. Saarelainen J, Hassi S, Honkanen R, Koivumaa-Honkanen H, Sirola J, Kroger H, et al. (2016) Bone loss and wrist fractures after withdrawal of hormone therapy: The 15-year follow-up of the OSTPRE cohort. Maturitas 85:49–55

106. Watts NB, Cauley JA, Jackson RD, LaCroix AZ, Lewis CE, Manson JE, et al. (2017) No Increase in Fractures After Stopping Hormone Therapy: Results From the Women's Health Initiative. The Journal of clinical endocrinology and metabolism 102(1):302–8

107. Imtiaz B, Tuppurainen M, Rikkonen T, Kivipelto M, Soininen H, Kroger H, et al. (2017) Postmenopausal hormone therapy and Alzheimer disease: A prospective cohort study. Neurology 88(11):1062–8

108. Espeland MA, Rapp SR, Manson JE, Goveas JS, Shumaker SA, Hayden KM, et al. (2017) Long-term Effects on Cognitive Trajectories of Postmenopausal Hormone Therapy in Two Age Groups. The journals of gerontology. Series A, Biological sciences and medical sciences 72(6):838–45

109. Espeland MA, Brinton RD, Manson JE, Yaffe K, Hugenschmidt C, Vaughan L, et al. (2015) Postmenopausal hormone therapy, type 2 diabetes mellitus, and brain volumes. Neurology 85(13):1131–8

110. Henderson VW, St John JA, Hodis HN, McCleary CA, Stanczyk FZ, Shoupe D, et al. (2016) Cognitive effects of estradiol after menopause: A randomized trial of the timing hypothesis. Neurology 87(7):699–708

111. Paganini-Hill A, Corrada MM, Kawas CH (2018) Increased longevity in older users of postmenopausal estrogen therapy: the Leisure World Cohort Study. Menopause (New York, N.Y.) 25(11):1256–61

112. Bengtsson C, Malspeis S, Orellana C, Sparks JA, Costenbader KH, Karlson EW (2017) Association Between Menopausal Factors and the Risk of Seronegative and Seropositive Rheumatoid Arthritis: Results From the Nurses' Health Studies. Arthritis care & research 69(11):1676–84

113. Chlebowski RT, Cirillo DJ, Eaton CB, Stefanick ML, Pettinger M, Carbone LD, et al. (2018) Estrogen alone and joint symptoms in the Women's Health Initiative randomized trial. Menopause (New York, N.Y.) 25(11):1313–20

114. Curhan SG, Eliassen AH, Eavey RD, Wang M, Lin BM, Curhan GC (2017) Menopause and postmenopausal hormone therapy and risk of hearing loss. Menopause (New York, N.Y.) 24(9):1049–56

115. Sommer EM, Balkwill A, Reeves G, Green J, Beral DV, Coffey K, et al. (2015) Effects of obesity and hormone therapy on surgically-confirmed fibroids in postmenopausal women. European journal of epidemiology 30(6):493–9

116. Staller K, Townsend MK, Khalili H, Mehta R, Grodstein F, Whitehead WE, et al. (2017) Menopausal Hormone Therapy Is Associated With Increased Risk of Fecal Incontinence in Women After Menopause. Gastroenterology 152(8):1915–1921e1

117. Kattah AG, Suarez MLG, Milic N, Kantarci K, Zeydan B, Mosley T, et al. (2018) Hormone therapy and urine protein excretion: a multiracial cohort study, systematic review, and meta-analysis. Menopause (New York,

N.Y.) 25(6):625–34

118. Al-Rousan T, Sparks JA, Pettinger M, Chlebowski R, Manson JE, Kauntiz AM, et al. (2018) Menopausal hormone therapy and the incidence of carpal tunnel syndrome in postmenopausal women: Findings from the Women's Health Initiative. PloS one 13(12):e0207509

119. Triebner K, Accordini S, Calciano L, Johannessen A, Benediktsdottir B, Bifulco E, et al. (2019) Exogenous female sex steroids may reduce lung ageing after menopause: A 20-year follow-up study of a general population sample (ECRHS). Maturitas 120:29–34

120. Chen P-J, Chung C-H, Chien W-C, Chen H-C (2019) Hormone therapy is not associated with the risk of sudden sensorineural hearing loss in postmenopausal women: a 10-year nationwide population-based study. Menopause (New York, N.Y.) 26(8):892–8

121. Vajaranant TS, Maki PM, Pasquale LR, Lee A, Kim H, Haan MN (2016) Effects of Hormone Therapy on Intraocular Pressure: The Women's Health Initiative-Sight Exam Study. American journal of ophthalmology 165:115–24

122. Crandall CJ, Hovey KM, Andrews C, Cauley JA, Stefanick M, Shufelt C, et al. (2017) Comparison of clinical outcomes among users of oral and transdermal estrogen therapy in the Women's Health Initiative Observational Study. Menopause (New York, N.Y.) 24(10):1145–53