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 hormone replacement therapy (HRT) 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.

Individualised care

Surveillance proposal

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

Diagnosis of perimenopause and menopause

Surveillance proposal

The section of the guideline on diagnosis of perimenopause and menopause should not be updated.

2019 surveillance summary

We identified one study (de Kat et al. 2019) that assessed the diagnostic accuracy of anti-Mullerian hormone measurement (n=2,434). It found that anti-Mullerian hormone measurements in premenopausal women had C-statistic values (equivalent to AUC) of 0.64 to 0.69. The authors concluded that this strategy 'does not improve prediction of menopause'.

Intelligence gathering

At consultation, a stakeholder highlighted the study by de Kat et al. (2019). It was suggested as indicating a need to update this section of the guideline, but the results did not support that conclusion.

Impact statement

The finding that anti-Mullerian hormone measurements does not improve prediction of menopause is consistent with current recommendations that state:

- do not use anti-Müllerian hormone testing to diagnose perimenopause or menopause
- do not use anti-Müllerian hormone testing routinely to diagnose premature ovarian sufficiency.

New evidence is unlikely to impact on the guideline.

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 be updated.

Hormone replacement therapy (HRT)

2019 surveillance summary

Vasomotor symptoms

Vasomotor and general menopausal symptoms, including quality of life were assessed in 8 RCTs (Caan et al. 2015, Ensrud et al. 2015, Paoletti et al.

2015, Yu et al. 2016, Santoro et al. 2017, Diem et al. 2018, Kagan et al. 2018, Constantine et al. 2019) and 2 Cochrane reviews (Formoso et al. 2016, Gaudard et al. 2016) (table 1). 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.

Table 1 Vasomotor and general menopausal symptoms

Reference	Study type	Sample size	Number of studies	Duration (months)	Population	Intervention	Comparator	Outcome	Result
Gaudard et al. (2016)	SR-C	793	4	–	Women with menopausal symptoms	HRT (oestrogen patch)	Placebo	Hot flushes	Improved with intervention
Gaudard et al. (2016)	SR-C	–	3	–	Women with menopausal symptoms	HRT (oestrogen gel)	Placebo	Hot flushes	Improved with intervention
Gaudard et al. (2016)	SR-C	356	2	–	Women with menopausal symptoms	HRT (oestrogen, oral)	Placebo	Hot flushes	Improved with intervention
Gaudard et al. (2016)	SR-C	–	1	–	Women with menopausal symptoms	HRT (oestrogen topical emulsion)	Placebo	Hot flushes	Improved with intervention
Gaudard et al. (2016)	SR-C	458	1	–	Women with menopausal symptoms	HRT (oestrogen intranasal)	Placebo	Hot flushes	Improved with intervention
Santoro et al. (2017)	RCT	727	–	48	Postmenopausal women	HRT (conjugated oestrogen plus progestogen)	Placebo	Hot flushes	Improved with intervention
Santoro et al. (2017)	RCT	727	–	48	Postmenopausal women	HRT (oestrogen, transdermal)	Placebo	Hot flushes	Improved with intervention

Gaudard et al. (2016)	SR-C	–	–	–	Women with menopausal symptoms	HRT (oestrogen, bioidentical oral)	HRT (conjugated equine oestrogen)	Hot flushes	No effect of intervention
Ensrud et al. (2015)	RCT	339	–	2	Women with hot flushes	HRT (oestrogen only)	Placebo	Insomnia	Improved with intervention
Santoro et al. (2017)	RCT	727	–	48	Postmenopausal women	HRT (conjugated oestrogen plus progestogen)	Placebo	Insomnia	Improved with intervention
Santoro et al. (2017)	RCT	727	–	48	Postmenopausal women	HRT (oestrogen, transdermal)	Placebo	Insomnia	Improved with intervention
Yu, C-G; et al. (2016)	RCT	100	–	3	Women with menopausal symptoms	HRT (oestrogen)	HRT (progestogen)	Menopause symptoms	Improved with intervention
Santoro et al. (2017)	RCT	727	–	48	Postmenopausal women	HRT (conjugated oestrogen plus progestogen)	Placebo	Night sweats	Improved with intervention
Santoro et al. (2017)	RCT	727	–	48	Postmenopausal women	HRT (oestrogen, transdermal)	Placebo	Night sweats	Improved with intervention
Caan et al. (2015)	RCT	339	–	2	Women with vasomotor symptoms	HRT (oestrogen, low-dose)	Placebo	Quality of life	Improved with intervention
Diem et al. (2018)	RCT	302	–	3	Postmenopausal women with vulvovaginal symptoms	HRT (vaginal oestrogen) plus placebo gel	Placebo vaginal tablet and gel	Quality of life (menopause related)	Improved with intervention
Constantine et al. (2019)	RCT	726	–	3	Postmenopausal women	HRT (oestrogen plus progestogen)	Placebo	Quality of life (menopause related)	Improved with intervention
Ensrud et al. (2015)	RCT	339	–	2	Women with hot flushes	HRT (oestrogen only)	Placebo	Sleep quality	Improved with intervention
Kagan et al. (2018)	RCT	1,835	–	3	Postmenopausal women	HRT (oestrogen plus progestogen)	Placebo	Sleep score	Improved with intervention
Formoso et al. (2016)	SR-C	1,657	7	–	Women with menopausal symptoms	HRT (tibolone)	Placebo	Vasomotor symptoms	Improved with intervention
Constantine et al. (2019)	RCT	726	–	3	Postmenopausal women	Oestrogen plus progestogen (oral capsule)	Placebo	Vasomotor symptoms	Improved with intervention

Paoletti et al. (2015)	RCT	100	–	12	Postmenopausal women with vasomotor symptoms	HRT (oestrogen plus progestogen)	Placebo	Vasomotor symptoms	Improved with intervention
Formoso et al. (2016)	SR-C	1,336	9	–	Women with menopausal symptoms	HRT (tibolone)	HRT (combined)	Vasomotor symptoms	Worse with intervention

Vaginal symptoms

Vaginal symptoms and sexual function were assessed in 7 RCTs (Constantine et al. 2017, 2018, Taylor et al. 2017, Kroll et al. 2018, Mitchell et al. 2018, Rioux et al. 2018, Archer et al. 2019) and 1 Cochrane review (Lethaby et al. 2016) (table 2). 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.

The study by Archer et al. (2019) indicated that a similar proportion of people taking ospemifene (35%) and placebo (33%) had adverse events during the 12-week study. The authors did not report statistical analysis of adverse events, most of which were numerically similar between groups. However, women taking ospemifene reported hot flushes more often (6%) than those taking placebo (3%).

Table 2 Vaginal symptoms

Reference	Study type	Sample size	Number of studies	Duration (months)	Population	Intervention	Comparator	Outcome	Result
Lethaby et al. (2016)	SR-C	67	1	–	Women with vaginal atrophy after the menopause	HRT (oestrogen ring)	Placebo	Symptoms of vaginal atrophy	Improved with intervention
Lethaby et al. (2016)	SR-C	198	2	–	Women with vaginal atrophy after the menopause	HRT (oestrogen cream)	Placebo	Symptoms of vaginal atrophy	Improved with intervention

Lethaby et al. (2016)	SR-C	50	1	–	Women with vaginal atrophy after the menopause	HRT (oestrogen cream)	Isoflavone gel	Symptoms of vaginal atrophy	No effect of intervention
Lethaby et al. (2016)	SR-C	341	2	–	Women with vaginal atrophy after the menopause	HRT (oestrogen ring)	HRT (oestrogen cream)	Symptoms of vaginal atrophy	No effect of intervention
Lethaby et al. (2016)	SR-C	208	2	–	Women with vaginal atrophy after the menopause	HRT (oestrogen tablet)	HRT (oestrogen cream)	Symptoms of vaginal atrophy	No effect of intervention
Lethaby et al. (2016)	SR-C	567	3	–	Women with vaginal atrophy after the menopause	HRT (oestrogen ring)	HRT (oestrogen tablet)	Symptoms of vaginal atrophy	No effect of intervention
Lethaby et al. (2016)	SR-C	1,638	2	–	Women with vaginal atrophy after the menopause	HRT (oestrogen tablet)	Placebo	Symptoms of vaginal atrophy	No effect of intervention
Constantine et al. (2018)	RCT	561	–	3	Postmenopausal women with vulvovaginal atrophy	HRT (oestrogen, intravaginal)	Placebo	Dyspareunia	Improved with intervention
Kroll et al. (2018)	RCT	550	–	3	Postmenopausal women with vulvovaginal atrophy	HRT (oestrogen intravaginal)	Placebo	Dyspareunia	Improved with intervention
Taylor et al. (2017)	RCT	670	–	48	Postmenopausal women	HRT (oestrogen plus progestogen)	Placebo	Sexual function	Improved with intervention
Mitchell et al. (2018)	RCT	302	–	3	Postmenopausal women with moderate to severe vulvovaginal symptoms	HRT (vaginal oestrogen tablet plus placebo gel)	Placebo tablet plus placebo gel	Sexual function	No effect of intervention
Taylor et al. (2017)	RCT	670	–	48	Postmenopausal women	HRT (conjugated equine oestrogens plus progestogen)	Placebo	Sexual function	No effect of intervention
Constantine et al. (2017)	RCT	764	–	3	Postmenopausal women	HRT (vaginal oestrogen gel capsule)	Placebo	Dyspareunia plus measures of superficial and parabasal cells, and vaginal pH	Improved with intervention

Archer et al. (2018)	RCT	576	–	3	Postmenopausal women with vaginal atrophy	HRT (oestrogen vaginal cream)	Placebo	Vaginal dryness	Improved with intervention
Rioux J.E.; et al. (2018)	RCT	159	–	6	Women with menopausal symptoms	HRT (oestrogen, intravaginal, 25 mg)	HRT (conjugated equine oestrogen, intravaginal, 1.25 mg)	Vaginal symptoms	No effect of intervention

Depression

In 2 RCTs (Gleason et al. 2015, Gordon et al. 2018) HRT was associated with improvements in symptoms of depression compared with placebo (table 3).

Table 3 Depression

Reference	Study type	Sample size	Number of studies	Population	Intervention	Comparator	Outcome	Result
Gordon et al. (2018)	RCT	172	–	Postmenopausal women	HRT (oestrogen, transdermal, plus progestogen, oral)	Placebo	Depression score	Improved with intervention
Gleason et al. (2015)	RCT	693	–	Postmenopausal women	HRT (conjugated equine oestrogen, oral, plus progestogen)	Placebo	Depression symptoms	Improved with intervention

Other outcomes

In 2 RCTs (Yu et al. 2016, Kingsberg et al. 2017) 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 (Rioux et al. 2018) patients using vaginal oestrogen may be more likely to use the product again when compared with placebo (table 4).

Table 4 Other outcomes

Reference	Study type	Sample size	Number of studies	Duration (months)	Population	Intervention	Comparator	Outcome	Result

Rioux J.E.; et al. (2018)	RCT	159	–	6	Women with menopausal symptoms	HRT (oestrogen, intravaginal)	HRT (conjugated equine oestrogen, intravaginal)	Follicle stimulating hormone level	Improved with intervention
Kingsberg et al. (2017)	RCT	764	–	–	Postmenopausal women with vulval and vaginal atrophy	HRT (oestrogen vaginal capsule)	Placebo	Intention to use product again	Improved with intervention
Yu, C-G; et al. (2016)	RCT	100	–	3	Women with menopausal symptoms	HRT (oestrogen)	HRT (progestogen)	Luteinising hormone and follicle stimulating hormone levels	Improved with intervention
Rioux J.E.; et al. (2018)	RCT	159	–	6	Women with menopausal symptoms	HRT (oestrogen, intravaginal)	HRT (conjugated equine oestrogen, intravaginal)	Oestrogen level	Improved with intervention
Yu, C-G; et al. (2016)	RCT	100	–	3	Women with menopausal symptoms	HRT (oestrogen)	HRT (progestogen)	Oestrogen level	Improved with intervention
Rioux J.E.; et al. (2018)	RCT	159	–	6	Women with menopausal symptoms	HRT (oestrogen, intravaginal)	HRT (conjugated equine oestrogen, intravaginal)	Patient acceptance	Improved with intervention
Kingsberg et al. (2017)	RCT	764	–	–	Postmenopausal women with vulval and vaginal atrophy	HRT (oestrogen vaginal capsule)	Placebo	Satisfaction with treatment	Improved with intervention

Adverse effects

Adverse effects of HRT were reported in 3 Cochrane reviews (Formoso et al. 2016, Gaudard et al. 2016, Lethaby et al. 2016) and 1 RCT (Yu et al. 2016) (table 5). 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.

Table 5 Adverse effects

Reference	Study type	Sample size	Number of studies	Duration (months)	Population	Intervention	Comparator	Outcome	Result
Gaudard et al. (2016)	SR-C	103	1	–	Women with menopausal symptoms	HRT (oestrogen, oral)	HRT (conjugated equine oestrogen)	Adverse events	No effect of intervention
Gaudard et al. (2016)	SR-C	433	3	–	Women with menopausal symptoms	HRT (oestrogen, oral)	Placebo	Adverse events	No effect of intervention
Gaudard et al. (2016)	SR-C	200	1	–	Women with menopausal symptoms	HRT (oestrogen topical emulsion)	Placebo	Adverse events	No effect of intervention
Gaudard et al. (2016)	SR-C	1,822	9	–	Women with menopausal symptoms	HRT (oestrogen patch)	Placebo	Adverse events	Worse with intervention
Gaudard et al. (2016)	SR-C	1,086	3	–	Women with menopausal symptoms	HRT (oestrogen gel)	Placebo	Adverse events	Worse with intervention
Gaudard et al. (2016)	SR-C	458	1	–	Women with menopausal symptoms	HRT (oestrogen intranasal)	Placebo	Adverse events	Worse with intervention
Formoso et al. (2016)	SR-C	6,438	16	–	Women with menopausal symptoms	HRT (tibolone)	HRT (combined)	Bleeding	Improved with intervention
Formoso et al. (2016)	SR-C	7,814	9	–	Women with menopausal symptoms	HRT (tibolone)	Placebo	Bleeding	Worse with intervention
Lethaby et al. (2016)	SR-C	151	2	–	Women with vaginal atrophy after the menopause	HRT (oestrogen tablet)	Placebo	Endometrial thickness	No effect of intervention
Lethaby et al. (2016)	SR-C	273	2	–	Women with vaginal atrophy after the menopause	HRT (oestrogen ring)	HRT (oestrogen cream)	Endometrial thickness	Worse with intervention
Yu, C-G; et al. (2016)	RCT	100	–	3	Women with menopausal symptoms	HRT (oestrogen)	HRT (progestogen)	Adverse events, uterine volume and endometrial thickness	No effect of intervention

Intelligence gathering

Vasomotor symptoms

Topic expert feedback noted that the terminology around 'bioidentical hormones' is confusing because it can be used not only to mean regulated products that are chemically identical to the hormones produced by the human body, but also preparations of different hormones that are mixed in compounding pharmacies to match ratios produced in the body (these preparations are not regulated). The study of 'bioidentical' oestrogen (Gaudard et al. 2016) 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. 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. Additionally, the current recommendation, ‘Explain to women that the efficacy and safety of unregulated compounded bioidentical hormones are unknown.’, uses sufficiently precise wording, so no update 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

Drug treatments

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

- In 3 reports from 2 RCTs, (Labrie et al. 2015, 2016, Barton et al. 2018) 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, (Constantine et al. 2015, Archer et al. 2019) ospemifene improved sexual function, vaginal dryness and dyspareunia.

- In 2 RCTs, of melatonin, one trial suggested this treatment improved ovarian hormone levels, (Li et al. 2016) but no effect was seen on low-density lipoprotein (Parandavar et al. 2018). 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 (Simon et al. 2016).
- In 1 RCT, oxytocin vaginal gel improved dyspareunia (Torky et al. 2018).
- In 2 studies, venlafaxine improved insomnia, sleep quality and quality of life (Caan et al. 2015, Ensrud et al. 2015).

Table 6 Non-HRT drug treatments

Reference	Study type	Sample size	Duration (months)	Population	Intervention	Comparator	Outcome	Result
Labrie, Fernand; et al. (2015)	RCT	482	3	Postmenopausal women with vaginal atrophy	Prasterone (dehydroepiandrosterone, intravaginal)	Placebo	Dyspareunia	Improved with intervention
Labrie, Fernand; et al. (2016)	RCT	482	3	Women with vulvovaginal atrophy	Prasterone (dehydroepiandrosterone, intravaginal)	Placebo	Dyspareunia	Improved with intervention
Labrie, Fernand; et al. (2015)	RCT	482	3	Postmenopausal women with vaginal atrophy	Prasterone (dehydroepiandrosterone, intravaginal)	Placebo	Lubrication	Improved with intervention
Labrie, Fernand; et al. (2015)	RCT	482	3	Postmenopausal women with vaginal atrophy	Prasterone (dehydroepiandrosterone, intravaginal)	Placebo	Orgasm	Improved with intervention
Labrie, Fernand; et al. (2015)	RCT	482	3	Postmenopausal women with vaginal atrophy	Prasterone (dehydroepiandrosterone, intravaginal)	Placebo	Satisfaction	Improved with intervention
Labrie, Fernand; et al. (2015)	RCT	482	3	Postmenopausal women with vaginal atrophy	Prasterone (dehydroepiandrosterone, intravaginal)	Placebo	Sexual desire	Improved with intervention
Barton, Debra L; et al. (2018)	RCT	464	3	Postmenopausal women with a history of breast or gynaecological cancer	Prasterone (dehydroepiandrosterone, intravaginal)	Intravaginal moisturiser	Sexual health	Improved with intervention
Labrie, Fernand; et al. (2016)	RCT	482	3	Women with vulvovaginal atrophy	Prasterone (dehydroepiandrosterone, intravaginal)	Placebo	Vaginal dryness	Improved with intervention
Labrie, Fernand; et al. (2016)	RCT	482	3	Women with vulvovaginal atrophy	Dehydroepiandrosterone (intravaginal)	Placebo	Parabasal cells	Improved with intervention
Labrie, Fernand; et al. (2016)	RCT	482	3	Women with vulvovaginal atrophy	Dehydroepiandrosterone (intravaginal)	Placebo	Superficial cells	Improved with intervention
Labrie, Fernand; et al. (2016)	RCT	482	3	Women with vulvovaginal atrophy	Dehydroepiandrosterone (intravaginal)	Placebo	Vaginal pH	Improved with intervention
Barton, Debra L; et al. (2018)	RCT	464	3	Postmenopausal women with a history of breast or gynaecological cancer	Dehydroepiandrosterone (intravaginal)	Intravaginal moisturiser	Vaginal dyness of dyspareunia	No effect of intervention
Barton, Debra L; et al. (2018)	RCT	464	3	Postmenopausal women with a history of breast or gynaecological cancer	Prasterone (dehydroepiandrosterone, intravaginal)	Intravaginal moisturiser	Vaginal dryness or dyspareunia	No effect of intervention

Parandavar, Nehleh; et al. (2018)	RCT	240	3	Postmenopausal women	Melatonin	Placebo	Low-density lipoprotein cholesterol	No effect of intervention
Li Y.; et al. (2016)	RCT	128	6	Women with premature ovarian failure	Melatonin	Placebo	Luteinising and follicle stimulating hormone levels	Improved with intervention
Li Y.; et al. (2016)	RCT	128	6	Women with premature ovarian failure	Melatonin	Placebo	Ovarian hormone secretion	Improved with intervention
Parandavar, Nehleh; et al. (2018)	RCT	240	3	Postmenopausal women	Melatonin	Placebo	Triglycerides	No effect of intervention
Archer, David F; et al. (2019)	RCT	631	3	Postmenopausal women with vaginal dryness	Ospemifene	Placebo	Dyspareunia	Improved with intervention
Constantine, G; et al. (2015)	RCT	919	3	Postmenopausal women with vulvar and vaginal atrophy	Ospemifene	Placebo	Sexual function	Improved with intervention
Archer, David F; et al. (2019)	RCT	631	3	Postmenopausal women with vaginal dryness	Ospemifene	Placebo	Sexual function	Improved with intervention
Archer, David F; et al. (2019)	RCT	631	3	Postmenopausal women with vaginal dryness	Ospemifene	Placebo	Vaginal dryness	Improved with intervention
Archer, David F; et al. (2019)	RCT	631	3	Postmenopausal women with vaginal dryness	Ospemifene	Placebo	Parabasal and superficial cells, vaginal pH, and severity of vaginal dryness	Improved with intervention
Simon, James A; et al. (2016)	RCT	148	–	Postmenopausal women	Oxybutynin	Placebo	Vasomotor symptoms	Improved with intervention
Simon, James A; et al. (2016)	RCT	148	3	Postmenopausal women	Oxybutynin	Placebo	Dry mouth	Worse with intervention
Simon, James A; et al. (2016)	RCT	148	–	Postmenopausal women	Oxybutynin	Placebo	Sleep quality	Improved with intervention
Torky H.A.; et al. (2018)	RCT	140	1	Postmenopausal women with vulvovaginal atrophy	Oxytocin intravaginal gel	Placebo	Dyspareunia	Improved with intervention
Ensrud, Kristine E; et al. (2015)	RCT	339	2	Women with hot flushes	Venlafaxine	Placebo	Insomnia	Improved with intervention
Caan, Bette; et al. (2015)	RCT	339	2	Women with vasomotor symptoms	Venlafaxine	Placebo	Quality of life	Improved with intervention

Ensrud, Kristine E; et al. (2015)	RCT	339	2	Women with hot flushes	Venlafaxine	Placebo	Sleep quality	Improved with intervention
Islam et al. (2019)	SR	8,480 (36 studies	–	Postmenopausal women	Testosterone	Placebo or HRT	Satisfactory sexual event frequency	Improved with intervention
Islam et al. (2019)	SR	8,480 (36 studies	–	Postmenopausal women	Testosterone	Placebo or HRT	Sexual desire	Improved with intervention
Islam et al. (2019)	SR	8,480 (36 studies	–	Postmenopausal women	Testosterone	Placebo or HRT	Arousal	Improved with intervention
Islam et al. (2019)	SR	8,480 (36 studies	–	Postmenopausal women	Testosterone	Placebo or HRT	Responsiveness	Improved with intervention
Islam et al. (2019)	SR	8,480 (36 studies	–	Postmenopausal women	Testosterone	Placebo or HRT	Orgasm	Improved with intervention

Physical and psychological therapies

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

Cognitive behavioural therapy (CBT) was assessed in 3 studies (McCurry et al. 2016, Hardy et al. 2018, Atema et al. 2019) 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 (Huang et al. 2015).
- exercise interventions had no effect on hot flushes or night sweats but may increase daily step counts and improve symptoms of anxiety or depression (Abedi et al. 2015, Daley et al. 2015, Tadayon et al. 2016).
- foot reflexology was more effective than control aromatherapy for hot flushes, sweats and night sweats (Gozuyesil and Baser 2016).

- health coaching had no effect on depression symptoms (Almeida et al. 2016).
- self-directed learning improved menopausal symptoms (Mirghafourvand et al. 2015).

Table 7 Physical and psychological treatments

Reference	Study type	Sample size	Number of studies	Duration (months)	Population	Intervention	Comparator	Outcome	Result
Hardy, Claire; et al. (2018)	RCT	124	–	2	Women with vasomotor symptoms	CBT, self-help	Wait list control	Hot flushes or night sweats	Improved with intervention
Atema et al. (2019)	RCT	254	–	2	Women with a history of breast cancer and menopausal symptoms	CBT, self-managed	Wait list control	Impact of hot flushes and night sweats	Improved with intervention
Atema et al. (2019)	RCT	254	–	2	Women with a history of breast cancer and menopausal symptoms	CBT, self-managed	Wait list control	Sleep quality	Improved with intervention
McCurry, Susan M; et al. (2016)	RCT	106	–	2	Menopausal women with insomnia	CBT, telephone-based	Menopause education control	Hot flushes	No effect of intervention
McCurry, Susan M; et al. (2016)	RCT	106	–	2	Menopausal women with insomnia	CBT, telephone-based	Menopause education control	Insomnia	Improved with intervention
McCurry, Susan M; et al. (2016)	RCT	106	–	2	Menopausal women with insomnia	CBT, telephone-based	Menopause education control	Sleep quality	Improved with intervention
Atema et al. (2019)	RCT	254	–	2	Women with a history of breast cancer and menopausal symptoms	CBT, therapist-guided	Wait list control	Impact of hot flushes and night sweats	Improved with intervention
Atema et al. (2019)	RCT	254	–	2	Women with a history of breast cancer and menopausal symptoms	CBT, therapist-guided	Wait list control	Sleep quality	Improved with intervention
Huang, Alison J; et al. (2015)	RCT	123	–	3	Women with vasomotor symptoms	Device-guided slow-paced breathing	Control device	Hot flush frequency	Improved with intervention
Huang, Alison J; et al. (2015)	RCT	123	–	3	Women with vasomotor symptoms	Device-guided slow-paced breathing	Control device	Hot flushes	Improved with intervention

Huang, AJ; et al. (2015)	RCT	123	–	3	Women with vasomotor symptoms	Device-guided slow-paced breathing	Non-rhythmic music	Hot flushes	No effect of intervention
Daley, A J; et al. (2015)	RCT	261	–	6	Women with vasomotor symptoms	Exercise intervention (2 consultations with physical activity facilitator)	Control	Hot flushes or night sweats	No effect of intervention
Daley, A J; et al. (2015)	RCT	261	–	6	Women with vasomotor symptoms	Exercise intervention (menopause information DVD and written information to encourage physical activity)	Control	Hot flushes or night sweats	No effect of intervention
Abedi, P; et al. (2015)	RCT	106	–	3	Postmenopausal women	Exercise intervention (pedometer-monitored walking)	Unspecified control	Anxiety and insomnia	Improved with intervention
Abedi, P; et al. (2015)	RCT	106	–	3	Postmenopausal women	Exercise intervention (pedometer-monitored walking)	Unspecified control	Depression	Improved with intervention
Tadayon, M; et al. (2016)	RCT	112	–	3	Postmenopausal women	Exercise intervention (pedometer-monitored walking)	Usual care	Sleep quality	Improved with intervention
Abedi, P; et al. (2015)	RCT	106	–	3	Postmenopausal women	Exercise intervention (pedometer-monitored walking)	Unspecified control	Step count increase	Improved with intervention
Gozuyesil, Ebru; Baser, Muruvvet (2016)	RCT	120	–	–	Women with vasomotor symptoms	Foot reflexology	Control aromatherapy	Hot flushes, sweats and night sweats	Improved with intervention
Almeida, Osvaldo P; et al. (2016)	RCT	351	–	12	Menopausal women	Health coaching	Usual care	Depression symptoms	No effect of intervention
Mirghafourvand, M; et al. (2015)	RCT	124	–	2	Women with menopausal symptoms	Self-directed learning	Control (no learning)	Hot flushes	Improved with intervention
Mirghafourvand, M; et al. (2015)	RCT	124	–	2	Women with menopausal symptoms	Self-directed learning	Control (no learning)	Menopausal symptoms	Improved with intervention

Alternative medicine and complementary therapies

We identified 10 RCTs that assessed a variety of herbal remedies (Aghamiri et al. 2016, Kazemzadeh et al. 2016, Dastenaei et al. 2017, Steels et al. 2017, 2018, Farshbaf-Khalili et al. 2018, Gocan et al. 2018, Kamalifard et al. 2018, Mitchell et al. 2018, Nikjou et al. 2018, Sathyapalan et al. 2018, Heudel et al. 2019) such as extracts from lavender (and lavender aromatherapy), bitter orange, hops, soy, and homeopathic and ayurvedic preparations compared against mostly placebo controls (table 8).

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.

Table 8 Alternative and complementary medicine

Reference	Study type	Sample size	Number of studies	Duration (months)	Population	Intervention	Comparator	Outcome	Result
Heudel P.-E.; et al. (2019)	RCT	299	–	1	Women with breast cancer (non-metastatic, localised, ECOG=PS<=1)	Actheane (homeopathic medicine complex)	Placebo	Hot flushes	No effect of intervention
Heudel P.-E.; et al. (2019)	RCT	299	–	1	Women with breast cancer and vasomotor symptoms	Actheane (homeopathic medicine complex)	Placebo	Quality of life	No effect of intervention
Steels E.; et al. (2018)	RCT	117	–	3	Women with menopausal symptoms	Ayurvedic herbal remedy	Placebo	Vasomotor symptoms	Improved with intervention
Steels E.; et al. (2018)	RCT	117	–	3	Women with menopausal symptoms	Ayurvedic herbal remedy	Placebo	Quality of life (menopause related)	Improved with intervention
Farshbaf-Khalili, Azizeh; et al. (2018)	RCT	156	–	2	Postmenopausal women	Bitter orange capsule	Placebo	Anxiety	Improved with intervention
Kamalifard M.; et al. (2017)	RCT	156	–	2	Women with menopausal symptoms	Bitter orange capsule	Placebo	Depression	Improved with intervention

Kamalifard, Mahin; et al. (2019)	RCT	157	–	3	Postmenopausal women	Bitter orange capsule	Placebo	Sleep quality	Improved with intervention
Dastenaei, BM; et al. (2017)	RCT	100	–	1	Postmenopausal women	Evening primrose oil	Placebo	Hot flushes	Improved with intervention
Steels, E; et al. (2017)	RCT	115	–	3	Women with menopausal symptoms	Fenugreek seed extract	Placebo	Hot flushes	Improved with intervention
Steels, E; et al. (2017)	RCT	115	–	3	Women with menopausal symptoms	Fenugreek seed extract	Placebo	Menopausal symptoms	Improved with intervention
Aghamiri, Vida; et al. (2016)	RCT	120	–	3	Women with symptoms of menopause	Hop extract	Placebo	Hot flushes	Improved with intervention
Aghamiri, Vida; et al. (2016)	RCT	120	–	3	Women with symptoms of menopause	Hop extract	Placebo	Menopausal symptoms	Improved with intervention
Kazemzadeh, Rafat; et al. (2016)	RCT	100	–	3	Women with menopausal symptoms	Lavender aromatherapy	Control aromatherapy	Hot flushes	Improved with intervention
Nikjou R.; et al. (2018)	RCT	100	–	–	Women with menopausal symptoms	Lavender aromatherapy	Diluted milk control	Menopausal symptoms	Improved with intervention
Farshbaf-Khalili, Azizeh; et al. (2018)	RCT	157	–	3	Postmenopausal women	Lavender capsule	Placebo	Anxiety	Improved with intervention
Farshbaf-Khalili, Azizeh; et al. (2018)	RCT	157	–	3	Postmenopausal women	Lavender capsule	Bitter orange capsule	Anxiety	No effect of intervention
Kamalifard M.; et al. (2017)	RCT	156	–	2	Women with menopausal symptoms	Lavender capsule	Placebo	Depression	Improved with intervention
Kamalifard, Mahin; et al. (2018)	RCT	156	–	2	Postmenopausal women	Lavender capsule	Placebo	Sleep quality	Improved with intervention
Sathyapalan, T; et al. (2018)	RCT	200	–	6	Women in early menopause	Protein bar with isoflavones	Protein bar without isoflavones	Cardiovascular risk factors	Improved with intervention
Gocan A.; et al. (2018)	RCT	180	–	3	Women with hot flushes	Soy germ extract	Placebo	Hot flushes	Improved with intervention
Mitchell, Caroline M; et al. (2018)	RCT	302	–	3	Postmenopausal women with moderate to severe vulvovaginal symptoms	Vaginal moisturiser plus placebo vaginal tablet	Placebo tablet plus placebo gel	Sexual function	No effect of intervention

Chinese herbal medicine

In 1 Cochrane review (Zhu et al. 2016) and 1 RCT (Jiang et al. 2015), 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).

Table 9 Chinese herbal medicine

Reference	Study type	Sample size	Number of studies	Duration (months)	Population	Intervention	Comparator	Outcome	Result
Zhu, X; et al. (2016)	SR-C	705	7	–	Women with menopausal symptoms	Chinese herbal medicine	Placebo	Adverse events	No effect of intervention
Zhu, X; et al. (2016)	SR-C	864	2	–	Women with menopausal symptoms	Chinese herbal medicine	HRT	Adverse events	No effect of intervention
Zhu, X; et al. (2016)	SR-C	139	2	–	Women with menopausal symptoms	Chinese herbal medicine	Other drug treatments (such as fluoxetine)	Adverse events	No effect of intervention
Zhu, X; et al. (2016)	SR-C	199	2	–	Women with menopausal symptoms	Chinese herbal medicine	Placebo	Hot flushes	No effect of intervention
Jiang D.; et al. (2015)	RCT	224	–	3	Women with menopausal symptoms	Chinese herbal medicine	Placebo	Menopausal symptoms	No effect of intervention
Zhu, X; et al. (2016)	SR-C	64	1	–	Women with menopausal symptoms	Chinese herbal medicine	Placebo	Night sweats	No effect of intervention
Zhu, X; et al. (2016)	SR-C	256	3	–	Women with menopausal symptoms	Chinese herbal medicine	Placebo	Vasomotor symptoms	No effect of intervention
Zhu, X; et al. (2016)	SR-C	127	2	–	Women with menopausal symptoms	Chinese herbal medicine	HRT	Vasomotor symptoms	No effect of intervention

Acupuncture

We identified 6 RCTs of acupuncture (table 10) (Avis et al. 2016, Ee et al. 2016, Lesi et al. 2016, Li and Wang 2018, Liu et al. 2018, Peng et al. 2018), 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.

Table 10 Acupuncture

Reference	Study type	Sample size	Number of studies	Duration (months)	Population	Intervention	Comparator	Outcome	Result
Li, O; Wang, F (2018)	RCT	128	–	2	Women with menopausal insomnia	Acupuncture	Alprazolam	Oestrogen levels	Improved with intervention
Avis, Nancy E; et al. (2016)	RCT	209	–	6	Women with vasomotor symptoms	Acupuncture	Waitlist control	Vasomotor symptoms	Improved with intervention
Li, O; Wang, F (2018)	RCT	128	–	2	Women with menopausal insomnia	Acupuncture	Alprazolam	Sleep quality	Improved with intervention
Li, O; Wang, F (2018)	RCT	128	–	2	Women with menopausal insomnia	Acupuncture	Alprazolam	Luteinising hormone and follicle stimulating hormone levels	No effect of intervention

Liu Z.; et al. (2018)	RCT	360	–	8	Women with menopausal symptoms	Acupuncture	Sham acupuncture	Hot flushes	Improved with intervention
Liu Z.; et al. (2018)	RCT	360	–	8	Women with menopausal symptoms	Acupuncture	Sham acupuncture	Menopausal symptoms	Improved with intervention
Liu Z.; et al. (2018)	RCT	360	–	8	Women with menopausal symptoms	Acupuncture	Sham acupuncture	Quality of life (menopause related)	Improved with intervention
Ee, Carolyn; et al. (2016)	RCT	327	–	2	Women with vasomotor symptoms	Acupuncture	Sham acupuncture	Hot flushes	No effect of intervention
Lesi, Grazia; et al. (2016)	RCT	190	–	3	Women with breast cancer and vasomotor symptoms	Acupuncture plus enhanced self-care	Self-care	Hot flushes	Improved with intervention
Peng, YY; et al. (2018)	RCT	100	–	3	Women with menopausal symptoms	Acupuncture therapies (electroacupuncture, plus acupoint injection, plus fire needle treatment)	Control (no intervention)	Menopausal symptoms	Improved with intervention

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.

In consultation, a stakeholder highlighted a systematic review (Islam et al. 2019) showing that testosterone improved measures of sexual function in postmenopausal women.

Impact statement

Melatonin, oxybutynin and oxytocin

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.

Venlafaxine

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.

Testosterone

Evidence indicating that testosterone improves sexual function in postmenopausal women is consistent with the current recommendation to consider testosterone supplementation for menopausal women with low sexual desire if HRT alone is not effective.

Ospemifene and prasterone

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.

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 identified through the surveillance review was consistent with these findings and indicated improvements in sexual function.

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. However, several stakeholders suggested that these

treatments should be assessed in an update, so we decided that an update to the guideline should cover urogenital atrophy, including ospemifene and prasterone.

New evidence identified that may change current 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 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 (Mikkola et al. 2016, Crandall et al. 2018) that assessed the risk of coronary heart disease with intravaginal HRT use compared with no HRT (table 11). 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.

Table 11 Coronary heart disease

Reference	Study type	Sample size	Number of studies	Population	Intervention	Comparator	Outcome	Result
Crandall et al. (2018)	Cohort	45,663	–	Postmenopausal women without hysterectomy	HRT (oestrogen, intravaginal)	No HRT	Coronary heart disease	Improved with intervention
Crandall et al. (2019)	Cohort	45,664	–	Postmenopausal women with previous hysterectomy	HRT (oestrogen, intravaginal)	No HRT	Coronary heart disease	No effect of intervention
Mikkola et al. (2016)	Cohort	195,756	–	Postmenopausal women	HRT (oestrogen, intravaginal, 3–5 year duration)	no HRT	Coronary heart disease (mortality)	Improved with intervention

Stroke

We identified 7 cohort studies (Chen et al. 2015, Mikkola et al. 2015, 2016, Qureshi et al. 2016, Carrasquilla et al. 2017, Lokkegaard et al. 2017, Chang et al. 2019), 1 Cochrane review (Marjoribanks et al. 2017) and one other systematic review (Gartlehner et al. 2017) that assessed risk of stroke (ischaemic or haemorrhagic) or stroke mortality (table 12). 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 (Gartlehner et al. 2017, Marjoribanks et al. 2017).

  - Combined oestrogen (cyclic or continuous) and progestogen HRT compared with placebo or no HRT (Lokkegaard et al. 2017, Marjoribanks et al. 2017).
  - HRT compared with no HRT (Qureshi et al. 2016, Chang et al. 2019).
- 1 analysis suggested increased risk of stroke mortality in the first year after stopping HRT compared with no HRT or current HRT use (Mikkola et al. 2015).
- 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 (Qureshi et al. 2016, Carrasquilla et al. 2017, Lokkegaard et al. 2017).
- 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 (Chen et al. 2015, Carrasquilla et al. 2017, Lokkegaard et al. 2017).
- 2 analyses suggested improved stroke mortality with 3–5 years of intravaginal oestrogen and more than a year after stopping HRT (Mikkola et al. 2015).

Table 12 Stroke

Reference	Study type	Sample size	Number of studies	Population	Intervention	Comparator	Outcome	Result
Mikkola et al. (2015)	Cohort	332,202	–	Postmenopausal women	HRT (stopped more than a year ago)	No HRT	Mortality, stroke	Improved with intervention
Mikkola et al. (2016)	Cohort	195,756	–	Postmenopausal women	HRT (oestrogen, intravaginal, 3–5 year duration)	no HRT	Mortality, stroke	Improved with intervention
Mikkola et al. (2015)	Cohort	332,202	–	Postmenopausal women	HRT (stopped up to a year ago)	No HRT	Mortality, stroke	Worse with intervention
Mikkola et al. (2015)	Cohort	332,202	–	Postmenopausal women	HRT (stopped up	HRT (current use)	Mortality, stroke	Worse with intervention

					to a year ago)			
Carrasquilla et al. (2017)	Cohort	88,914	–	Postmenopausal women	HRT (started within 5 years of menopause)	No HRT	Stroke	Improved with intervention
Carrasquilla et al. (2017)	Cohort	88,914	–	Postmenopausal women	HRT (conjugated equine oestrogen started later than 5 years after menopause)	No HRT	Stroke	Improved with intervention
Carrasquilla et al. (2017)	Cohort	88,914	–	Postmenopausal women	HRT (combined HRT started later than 5 years after menopause)	No HRT	Stroke	Improved with intervention
Lokkegaard et al. (2017)	Cohort	980,003	–	Postmenopausal women	HRT (oestrogen, intravaginal)	No HRT	Stroke	Improved with intervention
Lokkegaard et al. (2017)	Cohort	980,003	–	Postmenopausal women	HRT (transdermal)	No HRT	Stroke	No effect of intervention
Marjoribanks et al. (2017)	SR-C	–	–	Postmenopausal women	HRT (combined, continuous)	Placebo	Stroke	Worse with intervention
Marjoribanks et al. (2017)	SR-C	–	–	Postmenopausal women	HRT (oestrogen only)	Placebo	Stroke	Worse with intervention
Gartlehner et al. (2017)	SR	40,058	18	Postmenopausal women	HRT (oestrogen only)	Placebo	Stroke	Worse with intervention
Gartlehner et al. (2017)	SR	40,058	18	Postmenopausal women	HRT (oestrogen plus progestogen)	Placebo	Stroke	Worse with intervention
Lokkegaard et al. (2017)	Cohort	980,003	–	Postmenopausal women	HRT (current use)	No HRT	Stroke	Worse with intervention
Lokkegaard et al. (2017)	Cohort	980,003	–	Postmenopausal women	HRT (continuous oestrogen plus progestogen)	No HRT	Stroke	Worse with intervention
Lokkegaard et al. (2017)	Cohort	980,003	–	Postmenopausal women	HRT (cyclic oestrogen plus progestogen)	No HRT	Stroke	Worse with intervention
Lokkegaard et al. (2017)	Cohort	980,003	–	Postmenopausal women	HRT (oestrogen only)	No HRT	Stroke	Worse with intervention

Chen et al. (2015)	Cohort	1,284	–	Postmenopausal women with diabetes	HRT (conjugated equine oestrogen)	No HRT	Stroke (ischaemic)	Improved with intervention
Chang et al. (2019)	Cohort	4,982	–	Postmenopausal women	HRT	No HRT	Stroke (ischaemic)	Worse with intervention
Carrasquilla et al. (2017)	Cohort	88,914	–	Postmenopausal women	HRT (conjugated equine oestrogen started later than 5 years after menopause)	No HRT	Stroke, haemorrhagic	Improved with intervention
Carrasquilla et al. (2017)	Cohort	88,914	–	Postmenopausal women	HRT (started within 5 years of menopause)	No HRT	Stroke, haemorrhagic	No effect of intervention
Carrasquilla et al. (2017)	Cohort	88,914	–	Postmenopausal women	HRT (combined HRT started later than 5 years after menopause)	No HRT	Stroke, haemorrhagic	No effect of intervention
Qureshi et al. (2016)	Cohort	93,676	–	Postmenopausal women	HRT (oestrogen only, current use)	No HRT	Subarachnoid haemorrhage	No effect of intervention
Qureshi et al. (2016)	Cohort	93,676	–	Postmenopausal women	HRT (oestrogen plus progestogen, current use)	No HRT	Subarachnoid haemorrhage	No effect of intervention
Qureshi et al. (2016)	Cohort	93,676	–	Postmenopausal women	HRT (current use)	No HRT	Subarachnoid haemorrhage	Worse with intervention

Venous thromboembolism

We identified 2 cohort studies (Lee et al. 2015, Chang et al. 2019), 2 Cochrane reviews (Formoso et al. 2016, Marjoribanks et al. 2017), and 1 other systematic review (Gartlehner et al. 2017) that measured the risk of venous thromboembolism with HRT (table 13). Both oestrogen-only and combined HRT were associated with increased risk of venous thromboembolism. One of the Cochrane reviews (Formoso et al. 2016) 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.

Table 13 Venous thromboembolism

Reference	Study type	Sample size	Number of studies	Population	Intervention	Comparator	Outcome	Result
Formoso et al. (2016)	SR-C	4529	4	Women with menopausal symptoms	HRT (tibolone)	HRT (combined)	Venous thromboembolism	No effect of intervention
Formoso et al. (2016)	SR-C	9,176	–	Women with menopausal symptoms	HRT (tibolone)	Placebo	Venous thromboembolism	No effect of intervention
Marjoribanks et al. (2017)	SR-C	–	–	Postmenopausal women	HRT (combined, continuous)	Placebo	Venous thromboembolism	Worse with intervention
Marjoribanks et al. (2017)	SR-C	–	–	Postmenopausal women with cardiovascular disease	HRT (combined, continuous)	Placebo	Venous thromboembolism	Worse with intervention
Marjoribanks et al. (2017)	SR-C	–	–	Postmenopausal women	HRT (oestrogen only)	Placebo	Venous thromboembolism	Worse with intervention
Marjoribanks et al. (2017)	SR-C	–	–	Postmenopausal women	HRT (oestrogen only)	Placebo	Venous thromboembolism	Worse with intervention
Gartlehner et al. (2017)	SR	40,058	18	Postmenopausal women	HRT (oestrogen only)	Placebo	Venous thromboembolism	Worse with intervention
Gartlehner et al. (2017)	SR	40,058	18	Postmenopausal women	HRT (oestrogen plus progestogen)	Placebo	Venous thromboembolism	Worse with intervention
Chang et al. (2019)	Cohort	4,982	–	Postmenopausal women	HRT	No HRT	Venous thromboembolism	Worse with intervention
Lee et al. (2015)	Cohort	924,557	–	Postmenopausal women	HRT	No HRT	Venous thromboembolism	Worse with intervention

Diabetes

We identified one systematic review (Gartlehner et al. 2017) that suggested a reduced risk of diabetes with either oestrogen-only or combined HRT compared with placebo (table 14).

Table 14 Diabetes

Reference	Study type	Sample size	Number of studies	Population	Intervention	Comparator	Outcome	Result
Gartlehner et al. (2017)	SR	40,058	18	Postmenopausal women	HRT (oestrogen only)	Placebo	Diabetes	Improved with intervention
Gartlehner et al. (2017)	SR	40,058	18	Postmenopausal women	HRT (oestrogen plus progestogen)	Placebo	Diabetes	Improved with intervention

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). 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 (Chang et al. 2019)
- no effect or increased risk of cardiovascular events or coronary events (Formoso et al. 2016, Simon et al. 2016, Marjoribanks et al. 2017, Huang et al. 2018)
- no effect on cerebrovascular events (Formoso et al. 2016) but reduced arterial thromboembolic events (Dinger et al. 2016)
- inconsistent effects on blood pressure (Paoletti et al. 2015, Swica et al. 2018)
- 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 (Ki et al. 2016).

Cardiovascular mortality (Mikkola et al. 2015, 2016, Chen et al. 2017, Manson et al. 2017, Holm et al. 2019) 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 (Formoso et al. 2016) suggested that, compared with combined HRT, tibolone had no effect on cardiovascular, cerebrovascular, or thromboembolic events.

Table 15 Other cardiovascular outcomes

Reference	Study type	Sample size	Number of studies	Population	Intervention	Comparator	Outcome	Result
Chang et al. (2019)	Cohort	4,982	–	Postmenopausal women	HRT	No HRT	Acute coronary syndrome	Worse with intervention
Dinger, J; et al. (2016)	Cohort	30,597	–	Postmenopausal women	HRT (oestrogen plus progestogen, drospirenone)	HRT (oestrogen plus non-drospirenone progestogen)	Arterial thromboembolic events	Improved with intervention
Paoletti et al. (2016)	RCT	101	–	Postmenopausal women with vasomotor symptoms	HRT (oestrogen plus progestogen)	Placebo	Blood pressure	Improved with intervention
Formoso et al. (2016)	SR-C	8,401	4	Women with menopausal symptoms	HRT (tibolone)	Placebo	Cardiovascular events	No effect of intervention
Formoso et al. (2016)	SR-C	3,794	2	Women with menopausal symptoms	HRT (tibolone)	HRT (combined)	Cardiovascular events	No effect of intervention
Huang et al. (2018)	RCT	2,763	–	Postmenopausal women with congestive heart disease who did not have hot flushes at baseline	HRT (conjugated equine oestrogens plus progestogen)	Placebo	Cardiovascular events	No effect of intervention
Huang et al. (2018)	RCT	2,763	–	Postmenopausal women with congestive heart disease who had hot flushes at baseline	HRT (conjugated equine oestrogens plus progestogen)	Placebo	Cardiovascular events	Worse with intervention
Simon et al. (2016)	Cohort	–	–	Women with menopausal symptoms	HRT (oestrogen, transdermal)	HRT (oestrogen, oral)	Cardiovascular events	No effect of intervention
Formoso et al. (2016)	SR-C	7,930	4	Women with menopausal symptoms	HRT (tibolone)	Placebo	Cerebrovascular events	No effect of intervention
Formoso et al. (2016)	SR-C	4,562	4	Women with menopausal symptoms	HRT (tibolone)	HRT (combined)	Cerebrovascular events	No effect of intervention

Marjoribanks et al. (2017)	SR-C	–	–	Postmenopausal women	HRT (oestrogen only)	Placebo	Coronary event	No effect of intervention
Marjoribanks et al. (2017)	SR-C	–	–	Postmenopausal women	HRT (combined, continuous)	Placebo	Coronary event	Worse with intervention
Swica et al. (2018)	RCT	27,347	–	Postmenopausal women without history of hysterectomy who did not have hypertension at baseline	HRT (conjugated equine oestrogens plus progestogen)	Placebo	Hypertension (diagnosis)	Worse with intervention
Swica et al. (2018)	RCT	27,347	–	Postmenopausal women with history of hysterectomy who did not have hypertension at baseline	HRT (conjugated equine oestrogens)	Placebo	Hypertension (diagnosis)	Worse with intervention
Ki et al. (2016)	Cohort	2,232	–	Postmenopausal women	HRT	No HRT	Low-density lipoprotein	Improved with intervention
Mikkola et al. (2015)	Cohort	332 202	–	Postmenopausal women	HRT (stopped up to a year ago)	HRT (current use)	Mortality, cardiac	Worse with intervention
Chen et al. (2017)	Cohort	13,715	–	Postmenopausal women	HRT (started 3 or more years ago)	No HRT	Mortality, cardiovascular	Improved with intervention
Chen et al. (2017)	Cohort	13,715	–	Postmenopausal women	HRT (started after hysterectomy or oophorectomy, in past 3 years)	No HRT	Mortality, cardiovascular	Improved with intervention
Chen et al. (2017)	Cohort	13,715	–	Postmenopausal women	HRT (started after hysterectomy or oophorectomy, more than 3 years ago)	No HRT	Mortality, cardiovascular	Improved with intervention
Holm et al. (2019)	Cohort	29,243	–	Women aged 50–64 years	HRT (after 5 years of follow-up)	No HRT	Mortality, cardiovascular	Improved with intervention
Mikkola et al. (2015)	Cohort	332 202	–	Postmenopausal women	HRT (stopped more than a year ago)	No HRT	Mortality, cardiovascular	Improved with intervention
Manson et al. (2017)	RCT	27,347	–	Postmenopausal women	HRT (conjugated equine oestrogen alone or with progestogen)	Placebo	Mortality, cardiovascular	No effect of intervention

Chen et al. (2017)	Cohort	13,715	–	Postmenopausal women	HRT (started in past 3 years)	No HRT	Mortality, cardiovascular	No effect of intervention
Chen et al. (2017)	Cohort	13,715	–	Postmenopausal women	HRT (started after natural menopause)	No HRT	Mortality, cardiovascular	No effect of intervention
Mikkola et al. (2015)	Cohort	332 202	–	Postmenopausal women	HRT (stopped up to a year ago)	No HRT	Mortality, cardiovascular	Worse with intervention
Ki et al. (2016)	Cohort	2,232	–	Postmenopausal women	HRT	No HRT	Non-high-density lipoprotein	Improved with intervention
Ki et al. (2016)	Cohort	2,232	–	Postmenopausal women	HRT	No HRT	Total cholesterol to high-density lipoprotein ratio	Improved with intervention
Ki et al. (2016)	Cohort	2,232	–	Postmenopausal women	HRT	No HRT	Triglycerides	Improved with intervention

Breast cancer

We identified 10 cohort studies (Suhrke and Zahl 2015, Jones et al. 2016, Liu et al. 2016, Obi et al. 2016, Simin et al. 2017, Brusselaers et al. 2018, Ettinger et al. 2018, Holm et al. 2018, 2019, Siegelmann-Danieli et al. 2018), 2 RCTs (Chlebowski et al. 2016, Chlebowski et al. 2017), 2 Cochrane reviews (Formoso et al. 2016, Marjoribanks et al. 2017) and 1 other systematic review (Gartlehner et al. 2017) that addressed the risk of breast cancer (table 16).

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 (Chlebowski et al. 2016a, Marjoribanks et al. 2017).

No effect on breast cancer risk was seen in 3 studies of oestrogen-only HRT or unspecified HRT compared with no HRT (Suhrke and Zahl 2015, Jones et al. 2016, Ettinger et al. 2018).

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

- 6 studies of combined HRT (Suhrke and Zahl 2015, Chlebowski et al. 2016a, Jones et al. 2016, Gartlehner et al. 2017, Marjoribanks et al. 2017, Brusselaers et al. 2018)

- 4 studies of unspecified HRT (Simin et al. 2017, Ettinger et al. 2018, Holm et al. 2018, 2019)
- 1 study of intrauterine progestogen (Siegelmann-Danieli et al. 2018).

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 (Suhrke and Zahl 2015, Formoso et al. 2016).

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 (Obi et al. 2016).

Table 16 Long-term HRT breast cancer outcomes

Reference	Study type	Sample size	Number of studies	Duration (months)	Population	Intervention	Comparator	Outcome	Result
Marjoribanks et al. (2017)	SR-C	–	–	84	Postmenopausal women	HRT (oestrogen only)	Placebo	Cancer, breast	Improved with intervention
Formoso et al. (2016)	SR-C	5,500	4	–	Women with menopausal symptoms and no history of breast cancer	HRT (tibolone)	Placebo	Cancer, breast	No effect of intervention
Formoso et al. (2016)	SR-C	4,835	5	–	Women with menopausal symptoms	HRT (tibolone)	HRT (combined)	Cancer, breast	No effect of intervention
Marjoribanks et al. (2017)	SR-C	–	–	67	Postmenopausal women	HRT (combined, continuous)	Placebo	Cancer, breast	Worse with intervention
Formoso et al. (2016)	SR-C	3,165	2	–	Women with menopausal symptoms and a history of breast cancer	HRT (tibolone)	Placebo	Cancer, breast	Worse with intervention
Gartlehner et al. (2017)	SR	40,058	18	–	Postmenopausal women	HRT (oestrogen plus progestogen)	Placebo	Cancer, breast (invasive)	Worse with intervention
Chlebowski et al. (2016)	RCT	27,344	–	–	Postmenopausal women	HRT (oestrogen only)	No HRT	Cancer, breast	Improved with intervention

Chlebowski et al. (2017)	RCT	1,616	–	86	Postmenopausal women with more than 80% African ancestry who have had hysterectomy	HRT	Placebo	Cancer, breast	Improved with intervention
Chlebowski et al. (2016)	RCT	27,344	–	–	Postmenopausal women	HRT (oestrogen plus progestogen)	No HRT	Cancer, breast	Worse with intervention
Liu et al. (2016)	Cohort	22,929	–	–	Postmenopausal women	HRT (4-year duration)	No HRT	Cancer, breast	Improved with intervention
Liu et al. (2016)	Cohort	22,929	–	–	Postmenopausal women	HRT (8-year duration)	No HRT	Cancer, breast	Improved with intervention
Suhrke and Zahl (2015)	Cohort	449,717	–	60	Postmenopausal women	HRT (oestrogen only, at least 1-year duration)	No HRT	Cancer, breast	No effect of intervention
Ettinger et al. (2019)	Cohort	455	–	–	Postmenopausal women	HRT (long-term use)	No HRT use	Cancer, breast	No effect of intervention
Jones et al. (2016)	Cohort	58,148	–	65	Postmenopausal women	HRT (oestrogen only)	No HRT	Cancer, breast	No effect of intervention
Suhrke and Zahl (2015)	Cohort	449,717	–	60	Postmenopausal women	HRT (oestrogen plus progestogen, at least 1-year duration)	No HRT	Cancer, breast	Worse with intervention
Suhrke and Zahl (2015)	Cohort	449,717	–	60	Postmenopausal women	HRT (tibolone, at least 1-year duration)	No HRT	Cancer, breast	Worse with intervention
Brusselaers et al. (2018)	Cohort	1,160,351	–	–	Postmenopausal women	HRT (oestrogen only, current use)	No HRT	Cancer, breast	Worse with intervention
Brusselaers et al. (2018)	Cohort	1,160,351	–	–	Postmenopausal women	HRT (oestrogen plus progestogen, current use)	No HRT	Cancer, breast	Worse with intervention
Ettinger et al. (2018)	Cohort	454	–	–	Postmenopausal women	HRT (long-term use)	No HRT use	Cancer, breast	Worse with intervention
Jones et al. (2016)	Cohort	58,148	–	65	Postmenopausal women	HRT (oestrogen plus progestogen, current use)	No HRT	Cancer, breast	Worse with intervention

Holm et al. (2018)	Cohort	29,152	–	–	Postmenopausal women	HRT	No HRT	Cancer, breast	Worse with intervention
Siegelmann-Danieli et al. (2018)	Cohort	40,678	–	–	Perimenopausal women	HRT (progestogen, intrauterine)	Control	Cancer, breast (invasive)	Worse with intervention
Obi et al. (2016)	Cohort	3,321	–	–	Postmenopausal women diagnosed with breast cancer	HRT (current use at breast cancer diagnosis)	No current HRT use at time of breast cancer diagnosis	Cancer, breast (mortality)	Improved with intervention
Obi et al. (2016)	Cohort	3,321	–	–	Postmenopausal women diagnosed with breast cancer (low grade)	HRT (current use at breast cancer diagnosis)	No current HRT use at time of breast cancer diagnosis	Cancer, breast (mortality)	Improved with intervention
Holm et al. (2019)	Cohort	29,243	–	–	Women aged 50–64 years	HRT (after 15 years of follow-up)	No HRT	Cancer, breast (mortality)	Worse with intervention
Obi et al. (2016)	Cohort	3,321	–	–	Postmenopausal women diagnosed with breast cancer	HRT (current use at breast cancer diagnosis)	No current HRT use at time of breast cancer diagnosis	Cancer, breast (recurrence)	Improved with intervention
Simin et al. (2017)	Cohort	290,186	–	–	Women aged 40 years or older	HRT	No HRT	Cancer, breast, endometrial or ovarian	Worse with intervention

Cancers other than breast cancer

We identified 14 cohort studies (Blanks et al. 2015, Zamora-Ros et al. 2015, Cancer et al. 2015, Morch et al. 2016, Botteri et al. 2017a, Sadr-Azodi et al. 2017, Botteri et al. 2017b, Brusselaers et al. 2017, Holm et al. 2018, 2019, Løkkegaard and Mørch 2018, Cervenka et al. 2019, Kilander et al. 2019), 5 RCTs (Eeles et al. 2015, Chlebowski et al. 2016b, 2016c, Kato et al. 2016, Manson et al. 2017, Simin et al. 2017), 3 Cochrane reviews (Formoso et al. 2016, Marjoribanks et al. 2017, Edey et al. 2018) and 1 other systematic review (Gartlehner et al. 2017) that addressed the risk of cancers other than breast cancer with HRT use compared with an inactive control (table 17).

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.

Table 16 Long-term HRT breast cancer outcomes

Reference	Study type	Sample size	Number of studies	Duration (months)	Population	Intervention	Comparator	Outcome	Result
Marjoribanks et al. (2017)	SR-C	–	–	84	Postmenopausal women	HRT (oestrogen only)	Placebo	Cancer, breast	Improved with intervention
Formoso et al. (2016)	SR-C	5,500	4	–	Women with menopausal symptoms and no history of breast cancer	HRT (tibolone)	Placebo	Cancer, breast	No effect of intervention
Formoso et al. (2016)	SR-C	4,835	5	–	Women with menopausal symptoms	HRT (tibolone)	HRT (combined)	Cancer, breast	No effect of intervention
Marjoribanks et al. (2017)	SR-C	–	–	67	Postmenopausal women	HRT (combined, continuous)	Placebo	Cancer, breast	Worse with intervention
Formoso et al. (2016)	SR-C	3,165	2	–	Women with menopausal symptoms and a history of breast cancer	HRT (tibolone)	Placebo	Cancer, breast	Worse with intervention
Gartlehner et al. (2017)	SR	40,058	18	–	Postmenopausal women	HRT (oestrogen plus progestogen)	Placebo	Cancer, breast (invasive)	Worse with intervention
Chlebowski et al. (2016)	RCT	27,344	–	–	Postmenopausal women	HRT (oestrogen only)	No HRT	Cancer, breast	Improved with intervention
Chlebowski et al. (2017)	RCT	1,616	–	86	Postmenopausal women with more than 80% African ancestry who have had hysterectomy	HRT	Placebo	Cancer, breast	Improved with intervention
Chlebowski et al. (2016)	RCT	27,344	–	–	Postmenopausal women	HRT (oestrogen plus progestogen)	No HRT	Cancer, breast	Worse with intervention
Liu et al. (2016)	Cohort	22,929	–	–	Postmenopausal women	HRT (4-year duration)	No HRT	Cancer, breast	Improved with intervention
Liu et al. (2016)	Cohort	22,929	–	–	Postmenopausal women	HRT (8-year duration)	No HRT	Cancer, breast	Improved with intervention

Suhrke and Zahl (2015)	Cohort	449,717	–	60	Postmenopausal women	HRT (oestrogen only, at least 1-year duration)	No HRT	Cancer, breast	No effect of intervention
Ettinger et al. (2019)	Cohort	455	–	–	Postmenopausal women	HRT (long-term use)	No HRT use	Cancer, breast	No effect of intervention
Jones et al. (2016)	Cohort	58,148	–	65	Postmenopausal women	HRT (oestrogen only)	No HRT	Cancer, breast	No effect of intervention
Suhrke and Zahl (2015)	Cohort	449,717	–	60	Postmenopausal women	HRT (oestrogen plus progestogen, at least 1-year duration)	No HRT	Cancer, breast	Worse with intervention
Suhrke and Zahl (2015)	Cohort	449,717	–	60	Postmenopausal women	HRT (tibolone, at least 1-year duration)	No HRT	Cancer, breast	Worse with intervention
Brusselaers et al. (2018)	Cohort	1,160,351	–	–	Postmenopausal women	HRT (oestrogen only, current use)	No HRT	Cancer, breast	Worse with intervention
Brusselaers et al. (2018)	Cohort	1,160,351	–	–	Postmenopausal women	HRT (oestrogen plus progestogen, current use)	No HRT	Cancer, breast	Worse with intervention
Ettinger et al. (2018)	Cohort	454	–	–	Postmenopausal women	HRT (long-term use)	No HRT use	Cancer, breast	Worse with intervention
Jones et al. (2016)	Cohort	58,148	–	65	Postmenopausal women	HRT (oestrogen plus progestogen, current use)	No HRT	Cancer, breast	Worse with intervention
Holm et al. (2018)	Cohort	29,152	–	–	Postmenopausal women	HRT	No HRT	Cancer, breast	Worse with intervention
Siegelmann-Danieli et al. (2018)	Cohort	40,678	–	–	Perimenopausal women	HRT (progestogen, intrauterine)	Control	Cancer, breast (invasive)	Worse with intervention
Obi et al. (2016)	Cohort	3,321	–	–	Postmenopausal women diagnosed with breast cancer	HRT (current use at breast cancer diagnosis)	No current HRT use at time of breast cancer diagnosis	Cancer, breast (mortality)	Improved with intervention
Obi et al. (2016)	Cohort	3,321	–	–	Postmenopausal women diagnosed with breast cancer (low grade)	HRT (current use at breast cancer diagnosis)	No current HRT use at time of breast	Cancer, breast (mortality)	Improved with intervention

							cancer diagnosis		
Holm et al. (2019)	Cohort	29,243	–	–	Women aged 50–64 years	HRT (after 15 years of follow-up)	No HRT	Cancer, breast (mortality)	Worse with intervention
Obi et al. (2016)	Cohort	3,321	–	–	Postmenopausal women diagnosed with breast cancer	HRT (current use at breast cancer diagnosis)	No current HRT use at time of breast cancer diagnosis	Cancer, breast (recurrence)	Improved with intervention
Simin et al. (2017)	Cohort	290,186	–	–	Women aged 40 years or older	HRT	No HRT	Cancer, breast, endometrial or ovarian	Worse with intervention

Osteoporosis

We identified 2 cohort studies (Kuh et al. 2016, Saarelainen et al. 2016), 1 RCT (Watts et al. 2017), 1 Cochrane review (Marjoribanks et al. 2017) and one other systematic review (Gartlehner et al. 2017) that addressed outcomes related to osteoporosis (table 18). 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.

Table 18 Osteoporosis

Reference	Study type	Sample size	Number of studies	Population	Intervention	Comparator	Outcome	Result
Kuh et al. (2016)	Cohort	848	–	Postmenopausal women	HRT	No HRT	Bone mineral density	Improved with intervention
Marjoribanks et al. (2017)	SR-C	–	–	Postmenopausal women	HRT (combined, continuous)	Placebo	Fracture	Improved with intervention
Marjoribanks et al. (2017)	SR-C	–	–	Postmenopausal women	HRT (oestrogen only)	Placebo	Fracture	Improved with intervention
Gartlehner et al. (2017)	SR	40,058	18	Postmenopausal women	HRT (oestrogen only)	Placebo	Fracture	Improved with intervention
Gartlehner et al. (2017)	SR	40,058	18	Postmenopausal women	HRT (oestrogen plus progestogen)	Placebo	Fracture	Improved with intervention

Watts et al. (2017)	RCT	15,187	–	Women with hysterectomy	HRT (conjugated equine oestrogen)	Placebo	Fracture	Improved with intervention
Watts et al. (2017)	RCT	15,187	–	Women with menopausal symptoms	HRT (oestrogen plus progestogen)	Placebo	Fracture	No effect of intervention
Marjoribanks et al. (2017)	SR-C	–	–	Postmenopausal women	HRT (oestrogen only)	Placebo	Fracture (clinical)	Improved with intervention
Saarelainen et al. (2016)	Cohort	5,119	–	Postmenopausal women	HRT (10 year duration)	No HRT	Fracture, wrist	Improved with intervention
Saarelainen et al. (2016)	Cohort	5,119	–	Postmenopausal women	HRT (15 year duration)	No HRT	Fracture, wrist	Improved with intervention

Dementia

We identified 1 cohort study (Imtiaz et al. 2017), 4 RCTs (Espeland et al. 2015, 2017, Gleason et al. 2015, Henderson et al. 2016), 1 Cochrane review (Marjoribanks et al. 2017) and 1 other systematic review (Gartlehner et al. 2017) that assessed dementia and cognitive outcomes (table 19). 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.

Table 19 Dementia

Reference	Study type	Sample size	Number of studies	Population	Intervention	Comparator	Outcome	Result
Imtiaz et al. (2017)	Cohort	8,195	–	Postmenopausal women	HRT (long-term use)	No HRT	Alzheimer's disease	Improved with intervention
Imtiaz et al. (2017)	Cohort	8,195	–	Postmenopausal women	HRT	No HRT	Alzheimer's disease	No effect of intervention
Espeland et al. (2017)	RCT	4,256	–	Women with menopausal symptoms aged 50–54 years	HRT (conjugated equine oestrogens, plus progestogen for women without hysterectomy)	Placebo	Cognitive function	No effect of intervention
Espeland et al. (2017)	RCT	4,256	–	Women with menopausal symptoms aged 65–79 years	HRT (conjugated equine oestrogens, plus progestogen for women without hysterectomy)	Placebo	Cognitive function	Worse with intervention
Gleason et al. (2015)	RCT	693	–	Postmenopausal women	HRT (conjugated equine oestrogen, oral, plus progestogen)	Placebo	Cognitive outcomes	No effect of intervention
Gleason et al. (2015)	RCT	693	–	Postmenopausal women	HRT (oestrogen, transdermal)	Placebo	Cognitive outcomes	No effect of intervention
Marjoribanks et al. (2017)	SR-C	–	–	Postmenopausal women	HRT (combined, continuous)	Placebo	Dementia	Worse with intervention
Gartlehner et al. (2017)	SR	40,058	18	Postmenopausal women	HRT (oestrogen plus progestogen)	Placebo	Dementia (probable)	Worse with intervention
Espeland et al. (2017)	RCT	4,256	–	Women with menopausal symptoms aged 65–79 years	HRT (conjugated equine oestrogens, plus progestogen for women without hysterectomy)	Placebo	Executive function	Worse with intervention
Henderson et al. (2016)	RCT	567	–	Postmenopausal women	HRT (oestrogen,	Placebo	Memory, verbal	No effect of intervention

					oral, plus progestogen in women without hysterectomy)			
Espeland et al. (2017)	RCT	4,256	–	Women with menopausal symptoms aged 65–79 years	HRT (conjugated equine oestrogens, plus progestogen for women without hysterectomy)	Placebo	Memory, working	Worse with intervention
Espeland et al. (2015)	RCT	1,402	–	Postmenopausal women without diabetes	HRT (conjugated equine oestrogen plus progestogen)	Placebo	Total brain volume	No effect of intervention
Espeland et al. (2015)	RCT	1,402	–	Postmenopausal women with diabetes	HRT (conjugated equine oestrogen plus progestogen)	Placebo	Total brain volume	Worse with intervention

Long-term risks not currently covered in the guideline

We identified 4 cohort studies (Obi et al. 2016, Chen et al. 2017, Paganini-Hill et al. 2018, Holm et al. 2019), 1 RCT (Manson et al. 2017), and 1 Cochrane review (Formoso et al. 2016), that measured the effects of HRT use on mortality (1 study specified the outcome as non-breast cancer mortality) (table 20). 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). 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 (Sommer et al. 2015, Bengtsson et al. 2017,

Curhan et al. 2017, Gartlehner et al. 2017, Marjoribanks et al. 2017, Staller et al. 2017, Chlebowski et al. 2018, Kilander et al. 2019).

- HRT was associated with improvements in albuminuria, anxiety, carpal tunnel syndrome, joint pain, lung function, and tinnitus (Gleason et al. 2015, Al-Rousan et al. 2018, Chlebowski et al. 2018, Kattah et al. 2018, Chen et al. 2019, Triebner et al. 2019).
- There may be no association between HRT and sudden sensorineural hearing loss (Chen et al. 2019).

- Inconsistent effects on intraocular pressure were seen, with improvement seen with conjugated equine oestrogen, but no effect seen with combined HRT (Vajaranant et al. 2016).

One cohort study (Crandall et al. 2017) 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.

Table 20 Mortality

Reference	Study type	Sample size	Number of studies	Population	Intervention	Comparator	Outcome	Result
Chen et al. (2017)	Cohort	13,715	–	Postmenopausal women	HRT (started 3 or more years ago)	No HRT	Mortality	Improved with intervention
Chen et al. (2017)	Cohort	13,715	–	Postmenopausal women	HRT (started in past 3 years)	No HRT	Mortality	Improved with intervention
Chen et al. (2017)	Cohort	13,715	–	Postmenopausal women	HRT (started after hysterectomy or oophorectomy, in past 3 years)	No HRT	Mortality	Improved with intervention
Chen et al. (2017)	Cohort	13,715	–	Postmenopausal women	HRT (started after hysterectomy	No HRT	Mortality	Improved with intervention

					or oophorectomy, more than 3 years ago)			
Paganini-Hill et al. (2018)	Cohort	8,801	–	Postmenopausal women	HRT	No HRT use	Mortality	Improved with intervention
Formoso et al. (2016)	SR-C	8,242	4	Women with menopausal symptoms	HRT (tibolone)	Placebo	Mortality	No effect of intervention
Manson et al. (2017)	RCT	27,347	–	Postmenopausal women	HRT (conjugated equine oestrogen alone or with progestogen)	Placebo	Mortality	No effect of intervention
Manson et al. (2017)	RCT	27,347	–	Postmenopausal women	HRT (conjugated equine oestrogen)	Placebo	Mortality	No effect of intervention
Manson et al. (2017)	RCT	27,347	–	Postmenopausal women	HRT (conjugated equine oestrogen plus progestogen)	Placebo	Mortality	No effect of intervention
Chen et al. (2017)	Cohort	13,715	–	Postmenopausal women	HRT (started after natural menopause)	No HRT	Mortality	No effect of intervention
Holm et al. (2019)	Cohort	29,243	–	Women aged 50–64 years	HRT	No HRT	Mortality	No effect of intervention
Obi et al. (2016)	Cohort	3,321	–	Postmenopausal women diagnosed with breast cancer	HRT (current use at breast cancer diagnosis)	No current HRT use at time of breast cancer diagnosis	Mortality (all cause)	Improved with intervention
Obi et al. (2016)	Cohort	3,321	–	Postmenopausal women diagnosed with breast cancer	HRT (current use at breast cancer diagnosis)	No current HRT use at time of breast cancer diagnosis	Mortality (not breast cancer related)	Improved with intervention

Table 21 Other long-term risks associated with HRT

Reference	Study type	Sample size	Number of studies	Population	Intervention	Comparator	Outcome	Result
Kattah et al. (2018)	SR	–	12	Postmenopausal women	HRT	No HRT	Albuminuria	Improved with intervention
Kattah et al. (2018)	Cohort	2,217	–	Postmenopausal women	HRT	No HRT	Albuminuria	Improved with intervention
Gleason et al. (2015)	RCT	693	–	Postmenopausal women	HRT (conjugated equine oestrogen, oral, plus progestogen)	Placebo	Anxiety	Improved with intervention
Al-Rousan et al. (2018)	Cohort	16,053	–	Postmenopausal women with hysterectomy	HRT (conjugated equine oestrogen)	Placebo	Carpal tunnel syndrome	Improved with intervention
Al-Rousan et al. (2018)	Cohort	16,053	–	Postmenopausal women without hysterectomy	HRT (conjugated equine oestrogen plus progestogen)	Placebo	Carpal tunnel syndrome	Improved with intervention
Staller et al. (2017)	Cohort	55,828	–	Postmenopausal women	HRT (past use)	No HRT	Faecal incontinence	Worse with intervention
Staller et al. (2017)	Cohort	55,828	–	Postmenopausal women	HRT (current use)	No HRT	Faecal incontinence	Worse with intervention
Sommer et al. (2015)	Cohort	610,604	–	Postmenopausal women (without hysterectomy or history of fibroids)	HRT	No HRT	Fibroids	Worse with intervention
Marjoribanks et al. (2017)	SR-C	–	–	Postmenopausal women	HRT (combined, continuous)	Placebo	Gallbladder disease	Worse with intervention
Marjoribanks et al. (2017)	SR-C	–	–	Postmenopausal women	HRT (oestrogen only)	Placebo	Gallbladder disease	Worse with intervention
Gartlehner et al. (2017)	SR	40,058	18	Postmenopausal women	HRT (oestrogen only)	Placebo	Gallbladder disease	Worse with intervention
Gartlehner et al. (2017)	SR	40,058	18	Postmenopausal women	HRT (oestrogen plus progestogen)	Placebo	Gallbladder disease	Worse with intervention
Kilander et al. (2019)	Cohort	1,160,351	–	Postmenopausal women	HRT	No HRT use	Gallstone disease	Worse with intervention

Crandall, Carolyn J; et al. (2017)	Cohort	45,112	–	Postmenopausal women	HRT (conjugated equine oestrogen, less than 0.625 mg/day, plus progestogen)	HRT (conjugated equine oestrogen, 0.625 mg/day, plus progestogen)	Global index event (coronary heart disease, breast cancer, stroke, pulmonary embolism, hip fracture, colorectal cancer, endometrial cancer, or death)	Improved with intervention
Crandall, Carolyn J; et al. (2017)	Cohort	45,112	–	Postmenopausal women	HRT (conjugated equine oestrogen, 0.625 mg/day, plus progestogen for at least 5 years)	HRT (conjugated equine oestrogen, 0.625 mg/day, plus progestogen for less than 5 years)	Global index event (coronary heart disease, breast cancer, stroke, pulmonary embolism, hip fracture, colorectal cancer, endometrial cancer, or death)	Worse with intervention
Curhan et al. (2017)	Cohort	80,972	–	Postmenopausal women	HRT (5 to 10 year duration of oestrogen-only or oestrogen plus progestogen)	No HRT	Hearing loss	Worse with intervention
Curhan et al. (2018)	Cohort	80,973	–	Postmenopausal women	HRT (more than 10 year duration of oestrogen-only or oestrogen plus progestogen)	No HRT	Hearing loss	Worse with intervention
Vajaranant et al. (2016)	RCT	1,668	–	Postmenopausal women	HRT (conjugated equine oestrogen in women with hysterectomy)	Placebo	Intraocular pressure	Improved with intervention
Vajaranant et al. (2016)	RCT	2,679	–	Postmenopausal women	HRT (oestrogen plus progestogen	Placebo	Intraocular pressure	No effect of intervention

					in women without hysterectomy)			
Chlebowski et al. (2018)	RCT	10,739	–	Postmenopausal women with hysterectomy	HRT (conjugated equine oestrogens)	Placebo	Joint pain (frequency)	Improved with intervention
Chlebowski et al. (2018)	RCT	10,739	–	Postmenopausal women with hysterectomy	HRT (conjugated equine oestrogens)	Placebo	Joint swelling (frequency)	Worse with intervention
Triebner et al. (2019)	Cohort	658	–	Postmenopausal women	HRT (6–10 years of use)	No HRT	Lung function (FEV1)	Improved with intervention
Triebner et al. (2019)	Cohort	658	–	Postmenopausal women	HRT (more than 10 years of use)	No HRT	Lung function (FEV1)	Improved with intervention
Bengtsson et al. (2017)	Cohort	237,130	–	Postmenopausal women	HRT (use for 8 years or more)	No HRT or less than 8 years of HRT	Rheumatoid arthritis (seropositive)	Worse with intervention
Chen et al. (2019)	Cohort	13,112	–	Postmenopausal women	HRT	No HRT use	Sudden sensorineural hearing loss	No effect of intervention
Chen et al. (2018)	Cohort	55,680	–	Postmenopausal women	HRT	No HRT	Tinnitus	Improved with intervention
Gartlehner et al. (2017)	SR	40,058	18	Postmenopausal women	HRT (oestrogen only)	Placebo	Urinary incontinence	Worse with intervention
Gartlehner et al. (2017)	SR	40,058	18	Postmenopausal women	HRT (oestrogen plus progestogen)	Placebo	Urinary incontinence	Worse with intervention

Intelligence gathering

While consulting on the decision not to update this guideline, a new report on the risk of breast cancer associated with HRT use was published (CGHF-BC 2019). accompanied by an MHRA drug safety update on HRT based on the results of this study. This drug safety update reiterated advice that is already included in the summary of product characteristics, namely 'only prescribe HRT to relieve post-menopausal symptoms that are adversely affecting quality of life and regularly review patients using HRT to ensure it is used for the shortest time and at the lowest dose.' We expect prescribers to follow NICE guidance in conjunction with the SPC for any treatments.

CGHF-BC 2019 performed detailed and complex analyses. The results cannot be easily compared directly with the risk data considered when developing the guideline. CGHF-BC 2019 data on risk of breast cancer was reported over different treatment and follow-up periods than is detailed currently in the guideline.

For up to 5 years' use of HRT and follow up of 5–10 years, the CGHF-BC 2019 risks of breast cancer were similar to that detailed in the guideline.

For example, for oestrogen plus progesterone HRT, the guideline notes that observational data indicates up to 5 years of use would lead to an estimated 12 more (6 to 19) cases of breast cancer per 1000 women over 7.5 years. This contrasts with the slightly lower risk estimate of 8 extra cases per 1000 women over 5 years (with 5 years of HRT use) and the slightly higher estimate of 17 extra cases per 1000 women over 20 years (with 5 years of HRT use) reported by the MHRA.

For oestrogen only HRT, the guideline notes that observational data indicates that up to 5 years of use would lead to an estimated 4 more (1 to 9) cases of breast cancer per 1000 women over 7.5 years. This contrasts with the slightly lower risk estimate of 3 extra cases per 1000 women over 5 years (with 5 years of HRT use) and the slightly higher estimate of 5 extra cases per 1000 women over 20 years (with 5 years of HRT use) reported by the MHRA. Therefore, overall the risk of breast cancer reported by both sources are broadly similar. For 10 years of HRT use, the additional risk of breast cancer was also broadly similar over the same periods.

However, the drug safety update highlighted that 'some excess risk of breast cancer with systemic HRT persists for more than 10 years after stopping; the total increased risk of breast cancer associated with HRT is therefore higher than previous estimates'. The MHRA drug safety update, based on the results of CGHF-BC 2019 therefore, suggests that risk data in the guideline, particularly that for people who have stopped taking HRT, are out of date and an update is necessary.

However, CGHF-BC 2019 conducted a case-control analysis of individual participant data from 568,859 women. The review protocols from the guideline excluded this study design. Many of the studies informing the CGHF-BC 2019 paper were excluded from the guideline. Similarly, many of the studies informing the guideline were excluded from the CGHF-BC 2019 dataset. Additionally, in surveillance we identified 10 new cohort studies that measured the effects of HRT on breast cancer, only 1 of which was included in CGHF-BC 2019. Notably, one analysis of more than 1 million women (Brusselaers 2019) was not included in CGHF-BC 2019.

When looking at results across all studies there are inconsistencies in the direction and size of effects of different types and durations of HRT on rates of breast cancer. For example, the size of the effects of HRT on breast cancer reported in Brussellaers 2019 (more than 1 million women) were consistently smaller than the effects reported in CGHF-BC 2019 (more than half a million women).

Impact statement

Breast cancer

The guideline considered the effects of HRT on breast cancer. The effects differed depending on whether HRT use was current or historical, 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 HRT containing progesterone generally showing an increased risk of breast cancer and oestrogen-only HRT generally showing an increased risk of breast cancer although the size of this risk was generally lower than for combined HRT.

An MHRA drug safety update based on data from CGHF-BC 2019 suggested that ‘some excess risk of breast cancer with systemic HRT persists for more

than 10 years after stopping; the total increased risk of breast cancer associated with HRT is therefore higher than previous estimates'. This means that the risk data in the guideline, particularly that for people who have stopped taking HRT should be reconsidered.

Surveillance also identified other studies reporting on the risk of breast cancer with HRT, and overall the evidence showed enough inconsistency in size and occasionally direction of effects. An update to the guideline is necessary to consider all data on the risk of breast cancer associated with HRT.

However, if the update process results in the inclusion of case-control studies for breast cancer, then all other risks and benefits of HRT should be reconsidered using the same revised methods. While the update is in process, we will remove the risk table for breast cancer and cross-refer to the MHRA risk table until the update publishes.

New evidence identified that may change current recommendations.

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.

New evidence is unlikely to impact on the guideline.

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.

New evidence is unlikely to impact on the guideline.

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 guideline's recommendations on oral HRT, and it is unclear whether tibolone has a different risk profile to oral HRT.

New evidence is unlikely to impact on the guideline.

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.

New evidence is unlikely to impact on the guideline.

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.

New evidence is unlikely to impact on the guideline.

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.

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. We expect prescribers to follow NICE guidance in conjunction with the SPC for any treatments. 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.

Overall impact on the guideline

We identified a need to update the risks of breast cancer associated with HRT use, but data on the other long-term benefits and risks including coronary heart disease, stroke, venous thromboembolism, diabetes, osteoporosis and dementia did not indicate that they need to be updated.

Diagnosing and managing premature ovarian insufficiency

Surveillance proposal

This section of the guideline on diagnosing and managing premature ovarian insufficiency should not be updated.

2019 surveillance summary

We identified one study Cartwright et al. (2016) (n=36) assessing the effects of HRT compared with the combined contraceptive pill and no treatment in women with spontaneous premature ovarian sufficiency. Results showed a significant increase in bone lumbar spine bone mineral density after 2 years with HRT compared with the combined contraceptive pill.

Intelligence gathering

In consultation, the study by Cartwright et al. (2016) was highlighted by a stakeholder.

Impact statement

Because the baseline bone mineral density of participants was not reported in the abstract, it is not possible to tell whether the small increase in bone mineral density is clinically important. Additionally, the abstract did not report analysis of each treatment compared with no treatment and did not report on effects on menopausal symptoms. Overall, this study contributes little to answering the question of whether HRT or the combined contraceptive is more effective in women with premature ovarian sufficiency. Therefore, no update is necessary.

New evidence is unlikely to impact on the guideline.

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.

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