

3.1.3 OTHER HEALTH BENEFITS

Colorectal cancer

Summary

Currently available evidence is ambiguous with respect to the effect of HRT use upon colorectal cancer. Whilst evidence from observational studies suggests a risk reduction for both colon and rectal cancer incidence, this benefit was not statistically confirmed in the two recent large randomised controlled trials. However, both of these RCTs were conducted in an older patient population (~25% of the women had used HRT prior to baseline in the two studies). On balance, a tendency toward a decreased risk is apparent. There is insufficient information to determine differential effects of type, duration or recency of therapy on colorectal cancer risk.

Existing systematic reviews

Overall, five existing systematic reviews were identified which examined the association between HRT and colorectal cancer. All reviews included predominantly observational studies and therefore represent only level II evidence. The characteristics and quality of the included systematic reviews are summarised in Table 41. For further details see Appendix B (Section 9.1.3).

TABLE 41 HRT: COLORECTAL CANCER – EXISTING SYSTEMATIC REVIEWS

Study	Study type (number of included studies) Study quality	Population	Intervention	Comparator	Outcomes
Level III-2 evidence					
Fernandez <i>et al.</i> (2000)	Systematic review of observational studies (19) <i>Poor</i>	Not specifically defined	HRT Mode of administration and dose not specified	No HRT	Incidence (colon or rectal cancer)
Crandall (1999)	Systematic review of observational studies (30 including 1 RCT and 3 meta-analyses) <i>Poor</i>	Postmenopausal women	HRT Mode of administration and dose not specified	Not specified but assumed to be no HRT	Incidence (colon cancer only)
Grodstein <i>et al.</i> (1999)	Systematic review of observational studies (18 including 1 RCT) <i>Poor</i>	Postmenopausal women (some studies included premenopausal women)	HRT Mode of administration and dose not specified	No HRT	Incidence (colon or rectal cancer)
Nanda <i>et al.</i> (1999)	Systematic review of observational studies (25 including 1 RCT) <i>Fair</i>	Postmenopausal women	HRT Mode of administration and dose not specified	No HRT	Incidence Mortality (colon or rectal cancer)
Hebert-Croteau (1998)	Systematic review of observational studies (19 including 1 RCT) <i>Fair</i>	Postmenopausal women	HRT Mode of administration and dose not specified	No HRT	Incidence (colon cancer only)

See Section 9.1.3.

Abbreviations: RCT, randomised controlled trial.

Three of the most recent systematic reviews (Fernandez *et al.*, 2000; Crandall, 1999; Grodstein *et al.*, 1999) were considered to be of poor methodological quality for the following reasons: (i) a limited literature search was performed, (ii) there was no formal attempt to assess the quality of each of the included studies and (iii) little information was provided regarding the characteristics of each included study. There is the potential for significant bias in these reviews and as such they were not considered further.

The search also identified two systematic reviews of predominantly observational studies which were considered to be of fair methodological quality (Nanda *et al.*, 1999; Hebert-Croteau, 1998). The main results of these reviews are summarised in Table 42 and Figure 14.

While the results of the many studies included in the systematic reviews were somewhat variable, both systematic reviews concluded that the available evidence suggests that recent use of HRT is associated with a decreased risk of colon cancer. In addition, the Nanda *et al.* (1999) review examined the association between colon cancer mortality and HRT and suggested that the risk of death due to colon cancer is significantly reduced in women who use HRT. However, it should be noted that the healthy user and surveillance biases associated with observational studies may have contributed to this result. There was no association shown between the ever-use of HRT and rectal or colorectal cancer in the review by Nanda *et al.* (1999).

TABLE 42 HRT: COLORECTAL CANCER – RESULTS OF EXISTING SYSTEMATIC REVIEWS

Study	Type	Number of studies	Relative risk (95% CI)
Incidence			
<i>Nanda 1999</i>			
Ever-use	Colorectal	17	0.89 (0.76, 1.05)
Ever-use	Rectal	11	0.97 (0.85, 1.11)
Ever-use ^a	Colon	15	0.92 (0.79, 1.08)
Ever-use ^b	Colon	14	0.88 (0.80, 0.97)
<i>Duration of use</i>			
< 5 years	Colon	4	1.03 (0.74, 1.44)
≥ 5 years	Colon	4	0.89 (0.70, 1.14)
Recent use	Colon	7	0.67 (0.59, 0.77)
Past use	Colon		0.93 (0.82, 1.06)
<i>Hebert-Croteau 1998</i>			
Ever-use	Colon	19	0.85 (0.73, 0.99)
<i>Duration of use</i>			
< 5 years	Colon	5	0.88 (0.64, 1.21)
≥ 5 years	Colon	7	0.73 (0.53, 1.02)
Recent use	Colon	6	0.69 (0.52, 0.91)
Past use	Colon	6	0.78 (0.69, 0.88)
Mortality			
<i>Nanda 1999</i>			
Ever-use	Colon	3	0.72 (0.64, 0.81)

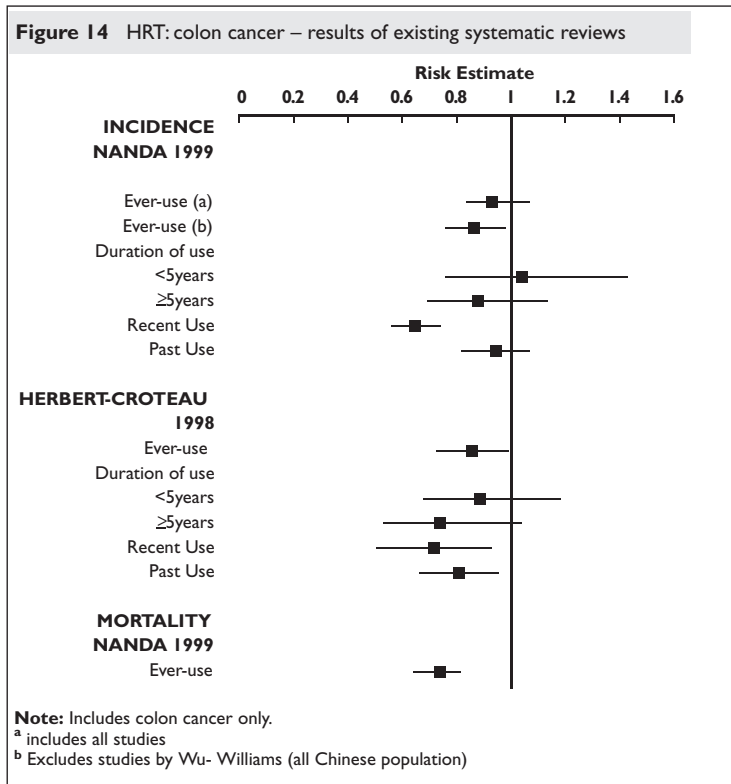
Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: CI, confidence interval.

^a Includes all studies

^b Excludes study by Wu-Williams (all Chinese population)

^c All relative risks shown here from Hebert-Croteau based on analyses of all study types using the random effects model. For analyses restricted to particular study types see the original paper.



Original studies

There is existing evidence regarding the association between HRT and colorectal cancer. The two most recent, fair quality reviews include studies published up to 1999. Therefore, a search for original studies was conducted for the years 1999-2003 to update the systematic reviews. The search identified two RCTs (Rossouw, 2002; Hulley *et al.*, 1998; Hulley *et al.* 2002), both considered to be of good methodological quality. In addition there was one case-control study (Fernandez *et al.*, 2003) which was considered to be of fair methodological quality. For details of the characteristics and quality of each of the included studies see Table 43. For further details see Appendix B (Section 9.1.3).

TABLE 43 HRT: COLORECTAL CANCER – ORIGINAL STUDIES

Study	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Level II evidence					
Rossouw <i>et al.</i> (2002)	Double-blind RCT WHI Mean follow-up 5.2 years <i>Good</i>	Postmenopausal women aged 50-79 with intact uterus Mean age 63 years N=16,608	EPRT Oral CEE 0.625 mg and MPA 2.5 mg N=8506	Placebo n=8102	Incidence
Hulley <i>et al.</i> (1998); Hulley <i>et al.</i> (2002)	Double-blind RCT HERS and HERS II Mean follow-up 6.8 years <i>Good</i>	Postmenopausal women with existing CHD < 80 years with intact uterus Mean age 67 years N=2763	EPRT Oral CEE 0.625 mg and MPA.5 mg HERS N=1380 HERS II N=1156	Placebo HERS N=1156 HERS II N=1165	Incidence
Level III-2 evidence					
Fernandez <i>et al.</i> (2003)	Case-control (hospital-based) <i>Fair</i>	Postmenopausal women N=8350	HRT Mode of administration and dose not specified N=613	No HRT N=7737	Incidence

See Section 9.1.3.

Abbreviations: CEE, conjugated equine oestrogen; CHD, coronary heart disease; EPRT, oestrogen + progestogen; HERS, Heart and Estrogen/progestin Replacement Study; HRT, oestrogen ± progestogen; MPA, medroxyprogesterone acetate; RCT, randomised controlled trial; WHI, Women's Health Initiative;

The results of the two RCTs are summarised in Table 44 and Figure 15. Although both studies showed a tendency toward a decreased risk of colorectal or colon cancer associated with use of EPRT, neither reach statistical significance.

TABLE 44 HRT: COLORECTAL CANCER – RCT RESULTS

Author	Type of cancer	HRT (n/N)	No HRT (n/N)	Type of risk measure	Risk estimate
Rossouw (2002) ^a	Colorectal	45/8506	67/8102	HR	0.63 (0.32, 1.24) ^b
Hulley (2002) ^c	Colon	2.0/1000 py	2.9/1000 py	HR	0.69 (0.32, 1.49)
Hulley (2002) ^{de}	Colon	2.5/1000 py	3.1/1000 py	HR	0.82 (0.46, 1.47)

Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: HR, hazard ratio; py, person years.

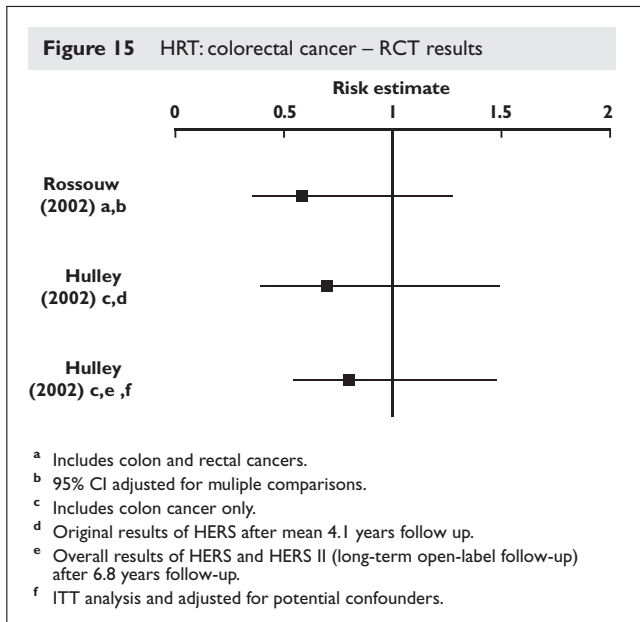
^a Includes colon and rectal cancers

^b 95% CI adjusted for multiple comparisons.

^c Original results of HERS after mean 4.1 years follow-up

^d Overall results of HERS and HERS II (long-term open-label follow-up) after 6.8 years follow-up

^e ITT analysis adjusted for potential confounders.



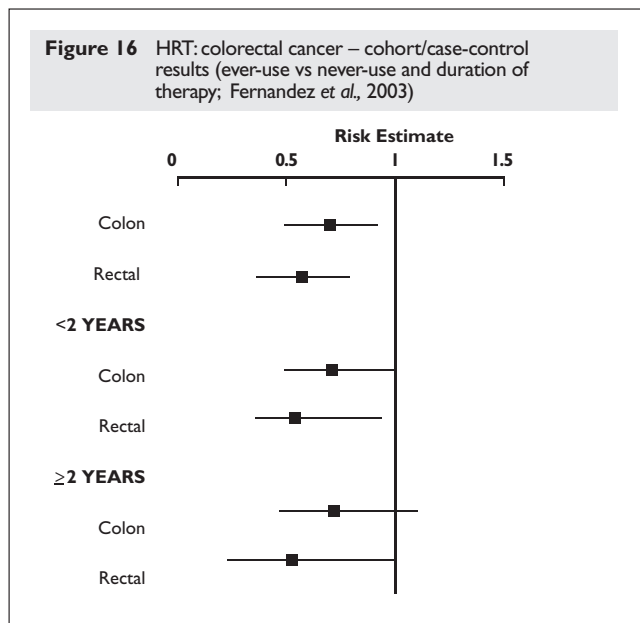
Only one original level III-2 study was identified which has been published since the Nanda and Hebert-Croteau reviews. This case-control study by Fernandez *et al.* (2003) examined the risk of developing different types of cancer (including colon and rectal) in association with any HRT use (ie, including both ERT and EPRT). This study was considered to be of fair methodological quality.

The results suggest that ever-use of any HRT therapy is associated with a decreased risk of colon and rectal cancer; results were either statistically significant or approached statistical significance. However, these results should be viewed with caution considering the problems associated with bias in observational studies of HRT use. The results are summarised in Table 45 and Figure 16.

TABLE 45 HRT: COLORECTAL CANCER – CASE-CONTROL RESULTS (EVER-USE VS NEVER-USE AND DURATION OF THERAPY; FERNANDEZ *ET AL.*, 2003)

Type of cancer	HRT (case/control)	No HRT (case/control)	Type of risk measure	Risk estimate
Colon	54/537	832/6439	OR	<i>0.7 (0.5, 0.9)</i>
Rectal	22/537	466/6439	OR	<i>0.5 (0.3, 0.8)</i>
< 2 years				
Colon	33/344	832/6439	OR	0.7 (0.5, 1.0)
Rectal	15/344	466/6439	OR	<i>0.5 (0.3, 0.9)</i>
≥ 2 years				
Colon	20/180	832/6439	OR	0.7 (0.4, 1.1)
Rectal	7/180	466/6439	OR	<i>0.5 (0.2, 1.0)</i>

Note: Risk estimates in italics are considered statistically significant as they do not include one. Abbreviations: OR, odds ratio.



Osteoporotic fracture

Summary

Good quality level I and level III-2 evidence suggests a reduced risk of fracture with HRT. Specifically, the observational evidence indicates a reduced risk that is consistent across anatomical locations. Whilst the evidence suggests that treatments with progestogen confer a greater protection, a direct comparison may not be appropriate due to the different populations of women involved. The only study (level III-2 evidence) to report fracture risk by duration of HRT use, found a benefit in > 2 years of use only.

Data from recent large RCTs (level II evidence) comparing combined HRT with placebo is inconsistent. The WHI study showed a significant reduction in 'other osteoporotic fractures' but the results for hip and vertebral fracture failed to reach statistical significance when fully adjusted. However, a more recent updated analysis of this trial suggested that HRT conferred a benefit in reducing hip, vertebral and peripheral fractures. This result is in contrast to the HERS study which showed no protective effect against fractures at any location.

Any protective benefit that is present appears to be conditional upon continued use. Evidence from past-users, shows that risk reduction is not maintained beyond 5 years after cessation of HRT.

Low potency oral and vaginal HRT appear not to offer a protective effect.

Existing systematic reviews

Five systematic reviews were identified by the literature search. Three of these were limited to RCTs and therefore constituted level I evidence. The recent review conducted by Nelson (2002) encompassed both RCTs and cohort studies and therefore can be considered a combination of level I and level III-2 evidence. Whilst these reviews also reported BMD, the current review only presents the results for fracture as the most patient relevant outcome. One of the reviews (Kanis *et al.*, 2002) included only RCTs conducted in osteopaenic or osteoporotic women. The main characteristics and quality of these reviews are summarised in Table 46. For further details see Appendix B (Section 9.1.3).

TABLE 46 HRT: OSTEOPOROTIC FRACTURE – EXISTING SYSTEMATIC REVIEWS

Study	Study type Study quality	Population No. of studies	Intervention	Comparator	Outcomes
Level I evidence					
Kanis <i>et al.</i> (2002)	Systematic review of RCTs <i>Good</i>	Osteopaenic or osteoporotic women (specifically postmenopausal in 3 of 4 included studies)	ERT or EPRT Any mode of administration or dose	Placebo (with or without calcium or vitamin D)	Fracture
Wells <i>et al.</i> (2002)	Systematic review of RCTs <i>Good</i>	Postmenopausal women	ERT or EPRT Any mode of administration or dose	Placebo (with or without calcium or vitamin D)	Radiologically confirmed fracture (vertebra, wrist, hip)
Torgerson & Bell-Syer (2001)	Systematic review of RCTs <i>Good</i>	Postmenopausal women	ERT or EPRT Any mode of administration or dose	Placebo, no HRT, calcium or vitamin D	Non-vertebral fracture
O'Connell <i>et al.</i> (1998)	Systematic review of RCTs <i>Good</i>	Peri or postmenopausal women	ERT or EPRT Any mode of administration or dose	Placebo, no HRT or active comparator	Fracture
Level I/III-2 evidence					
Nelson (2002)	Systematic review of RCTs and cohort studies <i>Good</i>	Postmenopausal women without secondary causes of osteoporosis	HRT Any mode of administration or dose	No HRT	Radiologically confirmed fracture
Hailey <i>et al.</i> (1998)	Unclear: Studies not listed <i>Fair</i>	Postmenopausal women with or without previous fracture	HRT Any mode of administration Any dose	Not stated	Fracture

See Section 9.1.3.

Abbreviations: BMD, bone mineral density; ERT, oestrogen-only therapy; EPRT, oestrogen + progestogen; HRT, oestrogen ± progestogen; RCT, randomised controlled trial;

The systematic reviews of RCTs conducted by Kanis *et al.* (2002), Wells *et al.* (2002), Torgerson *et al.* (2001) and O'Connell *et al.* (1998) were considered to be of good methodological quality. The search also identified two systematic reviews which included results from observational studies. The most recent of these by Nelson (2002) was considered to be a high quality review, however the earlier review by Hailey *et al.* (1998) was only considered to be of fair quality due to poor reporting.

The main results of each of the systematic reviews of observational studies are summarised in Table 47.

TABLE 47 HRT: OSTEOPOROTIC FRACTURE – RESULTS OF EXISTING SYSTEMATIC REVIEWS

Study	Number of included studies	Results and conclusion
Kanis (2002)	4 RCTs with fracture data	<p><i>Non-vertebral fracture</i></p> <p>The authors conclude that there was no evidence that oestrogens decreased the risk of non-vertebral osteoporotic fractures. However they state that the number of patients was too small to provide conclusive data.</p> <p><i>Vertebral fracture</i></p> <p>With respect to vertebral fractures, there appeared to be "a trend for oestrogens to decrease the risk of fracture". In one of the studies not reporting fracture incidence results suitable for inclusion in the meta-analysis, the number of new vertebral fractures was almost identical between groups, but in another the rate was reduced. In yet another study there was a trend only.</p>
Wells (2002)	7 RCTs with fracture data (57 overall including BMD)	<p><i>Vertebral and non-vertebral fracture</i></p> <p>For vertebral fracture the pooled RR was 0.66 (0.41, 1.07). For non-vertebral fracture the RR was 0.87 (0.71, 1.08). Concluded that there was a non-significant trend towards reduced fracture in women on HRT. Note that this review excluded 8 studies included in the Torgerson review as they considered them to be of poor methodological quality.</p>
Torgerson (2001)	22 RCTs	<p><i>Non-vertebral fracture</i></p> <p>Pooled analysis showed HRT was associated with a 27% reduction in fracture risk (RR 0.73; 0.56, 0.94). Effect was greater in younger women (< 60 years: RR 0.67; 0.46, 0.98) compared with older women (≥ 6- years: RR 0.88; 0.71, 1.08). Reduction in risk was more marked for hip and wrist fractures alone. The authors concluded that there was a significant reduction in non-vertebral fractures in women on HRT; however this may be attenuated in older women.</p>
O'Connell (1998)	2 RCTs with fracture data (37 studies overall including BMD)	<p><i>Vertebral or non-vertebral fracture</i></p> <p>Only two RCTs reporting fracture data were identified. One small trial reported no significant difference in fracture rates after one year between the HRT and placebo arms (RR 0.63; 0.28, 1.43). The other study had long-term follow-up (10 years) however they only reported total fractures and not new fractures. The authors of this review conclude that the available evidence provides "inadequate evidence on the effects of treatment on fracture risk."</p>
Nelson (2002)	12 studies reporting fracture (1 meta-analysis, 5 RCTs and 6 cohort studies)	<p><i>Vertebral and non-vertebral fracture</i></p> <p>The authors note that the included RCTs have methodological limitations. In the good-quality cohort studies, risk reductions of 20%-30% were seen for hip fracture. Risks were also reduced for other types of fracture. However, they note that even good quality cohort studies are subject to healthy-user bias, which may confound results. They conclude that the evidence supports a benefit for oestrogen in reducing fracture, however the fracture data is based on one arm of a RCT and cohort studies.</p>
Hailey (1998)	Unclear	<p><i>Vertebral and non-vertebral fracture</i></p> <p>The authors conclude that there is (i) <i>fair</i> evidence that ever-use of HRT results in a decreased risk of all types of fracture; (ii) <i>fair</i> evidence that long-term use of HRT has a protective effect for fractures; (iii) <i>fair</i> evidence that HRT do not decrease hip fracture at older ages; and (iv) <i>fair</i> evidence that a longer duration since using therapy reduces the protective effect of HRT on fracture. Fair evidence is defined as evidence derived from cohort and/or case-control studies.</p>

Abbreviations: BMD, bone mineral density; RCT, randomised controlled trial; RR, relative risk.

As a whole, the results appear to indicate that the use of HRT may confer some benefit with regards to

decreasing fracture incidence. However, it should be noted that both of the most recent level I reviews by Kanis *et al.* (2002) and Wells *et al.* (2002) showed non-significant results. These contrast with those of the Torgerson *et al.* (2002) review, possibly due to the more restricted inclusion of higher quality trials. Healthy user bias and surveillance bias associated with observational studies may have contributed to the favourable association of HRT and fracture reduction in the Level III-2 reviews. This is particularly problematic for the outcome of fracture where known confounders (such as nutrition and physical activity) are difficult to quantify and therefore accurately adjust for.

Original studies

There are a number of existing systematic reviews which review the evidence regarding the association between HRT and fracture. The reviews by Kanis *et al.* (2002), Wells *et al.* (2002) and Nelson *et al.* (2002) provide the most up-to-date, good quality level I and level I/III-2 evidence with the literature searched to 2000, 1999 and 2001 respectively. All relevant original studies published subsequent to 1999 that were not included in these recent systematic reviews are listed in Table 48. For further details see Appendix B (Section 9.1.3).

TABLE 48 HRT: OSTEOPOROTIC FRACTURE – ORIGINAL STUDIES

Study	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Level II evidence					
Cherry (2002)	RCT ESPRIT study <i>Poor</i>	Postmenopausal women aged 50-69 with previous MI Mean age 63 N=1017	Oestradiol valerate 2 mg	Placebo	Fracture reported in questionnaire completed by GP
Rossouw <i>et al.</i> (2002)	RCT WHI study <i>Fair</i>	Postmenopausal women aged 50-79 Mean age 63.3 N=16,608	Oral conjugated equine oestrogen 0.625 mg and medroxyprogesterone 2.5 mg	Placebo	Radiologically confirmed fracture
Hulley <i>et al.</i> (1998)	RCT HERS I <i>Fair</i>	Postmenopausal women < 80 years with existing CHD Mean age 66.7 N=2763	Oral conjugated equine oestrogen 0.625 mg and medroxyprogesterone 2.5 mg	Placebo	Radiologically confirmed fracture
Hulley <i>et al.</i> (2002)	Open label extension of RCT HERS II <i>Fair</i>	Women surviving HERS I who consented to follow-up Mean age 71 N=2321	Oral conjugated equine oestrogen 0.625 mg and medroxyprogesterone 2.5 mg	Placebo	Radiologically confirmed fracture

Study	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Level III-2 evidence					
Randell <i>et al.</i> (2002)	Cohort <i>Fair</i>	Postmenopausal women with an intact uterus aged 47-56 Mean age 53 N=7217	Any HRT Any mode of administration or dose	No HRT	Radiologically confirmed fracture
Wu <i>et al.</i> (2002)	Cohort <i>Poor</i>	Postmenopausal Mean age 59 N=104	Any HRT Any mode of administration or dose	No HRT	Reported fractures were radiologically confirmed
Mallmin <i>et al.</i> (1994)	Case-control (population-based) <i>Fair</i>	Subgroup postmenopausal women included in analysis Mean age~63 N=485	Any HRT Any mode of administration or dose	No HRT	Radiologically confirmed wrist fracture
Michaelsson <i>et al.</i> (1998); Michaelsson <i>et al.</i> (2002)	Case control (population-based) <i>Good</i>	Women without normal menses (peri or postmenopausal) Mean age 71 N=4589	Various HRT reported Various modes reported Medium potency or low potency	No HRT	Hip fracture from hospital records

See Section 9.1.3.

Abbreviations: CHD, coronary heart disease; ESPRIT, oEstrogen in the Prevention of ReInfarction Trial; GP, general practitioner; HERS, Heart and Estrogen/progestin Replacement Study; MI, myocardial infarction; RCT, randomised controlled trial; WHI, Women's Health Initiative.

The search identified three additional RCTs (Rossouw *et al.*, 2002; Cherry, 2002; Hulley *et al.*, 1998; Hulley *et al.*, 2002), The study conducted by the ESPRIT team (Cherry, 2002) was of poorer methodological quality with respect to the fracture outcome, as potential confounders of bone metabolism were not measured at baseline, nor controlled throughout the study. Furthermore, it was conducted in a population of patients who had survived an acute myocardial infarction, was of only two years duration and had a smaller sample size than the other two RCTs. Therefore, it will not be considered further here (see Appendix B). The HERS and HERS II study (Hulley *et al.*, 1998; Hulley *et al.*, 2002) were also conducted in a population with coronary disease.

In addition to the RCTs, there were two cohort studies (Randell *et al.*, 2002; Wu *et al.*, 2002) however the study undertaken by Wu *et al.*, 2002 will not be considered further due to selection bias introduced when women with a known low BMD were encouraged to participate in the HRT treatment arm. Two case-control studies were identified that were not included in the systematic reviews (Michaelsson *et al.*, 1998, 2002; Mallmin *et al.*, 1994).

The results of the included placebo-controlled RCTs are summarised in Table 49 and Figure 17, with different fracture locations shown as reported in the publications.

TABLE 49 HRT: OSTEOPOROTIC FRACTURE – RCT RESULTS

Author	HRT (n/N)	No HRT (n/N)	Type of measure	Risk estimate
<i>Any fracture</i>				
Hulley (1998) ^a	26.7/1000 py	28/1000 py	HR	0.96 (0.76, 1.20)
Hulley (2002) ^{b,c}	29.7/1000 py	28.4/1000 py	HR	1.07 (0.89, 1.29)
Rossouw (2002)	650/8506	788/8102	HR	0.76 (0.63, 0.92)
<i>Hip fracture</i>				
Hulley (2002) ^{b,c}	nr	nr	HR	1.61 (0.97, 2.66)
Rossouw (2002)	44/8506	62/8102	HR	0.66 (0.33, 1.33)
<i>Wrist fracture</i>				
Hulley (2002) ^{b,c}	nr	nr	HR	1.00 (0.65, 1.53)
<i>Vertebral fracture</i>				
Hulley (2002) ^{b,c}	nr	nr	HR	0.89 (0.53, 1.50)
Rossouw (2002)	41/8506	60/8102	HR	0.66 (0.32, 1.34)
<i>Other osteoporotic fracture</i>				
Rossouw (2002)	579/8506	701/8102	HR	0.77 (0.60, 0.94)

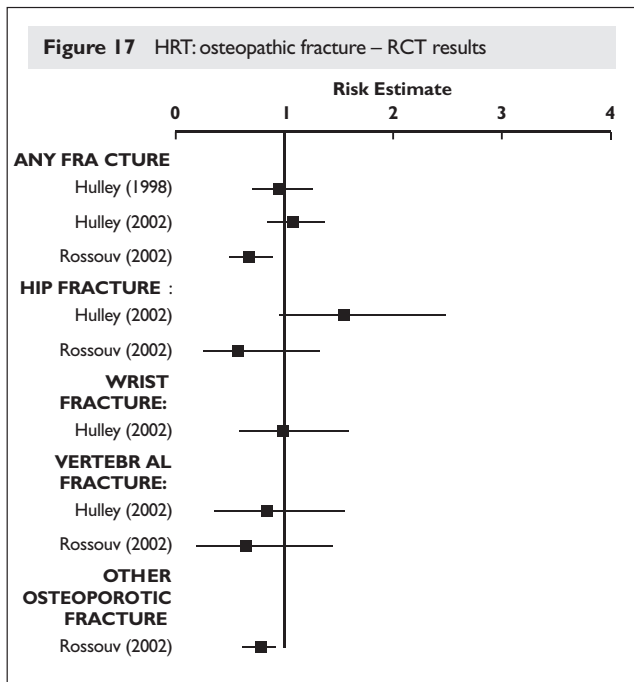
Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: HR, hazard ratio; nr, not reported; py, person-years.

^a Original results of HERS after mean 4.1 years follow-up

^b Overall results of HERS and HERS II (long-term open-label follow-up) after 6.8 years follow-up

^c Hazard ratio adjusted for confounding factors



The results of the additional RCTs fail to show a consistent impact of HRT upon the risk of fracture. The only statistically significant risk reduction was observed in the WHI study (Rossouw *et al.*, 2002) with respect to ‘other osteoporotic fractures’ which contributed the bulk of ‘any fracture’. It is important to note that whilst a RCT, the fracture results in this study were not adjusted for potential fracture-relevant confounding factors that may have been different between groups at baseline.

Since the literature search conducted for this review an updated analysis of fracture data from the WHI study has been published. The results of this analysis suggest that HRT reduced fracture risk at all locations examined (ie, hip, vertebral and lower arm/wrist). For details see Addendum A.

The results of the included cohort and case-control studies, for the comparison of ever-use versus never-use, are presented in Table 50 and Figure 18.

TABLE 50 HRT: OSTEOPOROTIC FRACTURE – COHORT/CASE-CONTROL RESULTS (EVER-USE VS NEVER-USE)

Author	Type of study	Type of HRT used	HRT (n/N or case/control)	No HRT (n/N or case/control)	Type of risk measure	Risk estimate
<i>Any fracture</i>						
Randell et al. (2002) ^a	Cohort	HRT (4.5/previous 5 years)	94/1335	352/3335	RR	<i>0.62 (0.48, 0.79)</i>
Randell et al. (2002) ^a	Cohort	HRT (> 6 months/previous 5 years)	103/1335	352/3335	RR	<i>0.71 (0.56, 0.91)</i>
<i>Hip fracture</i>						
Michaelsson et al. (1998) ^b	Case-control	HRT any admin	120/456	956/2073	OR	<i>0.58 (0.46, 0.75)</i>
Michaelsson et al. (1998) ^b	Case-control	ERT any admin	81/229	956/2073	OR	<i>0.69 (0.52, 0.93)</i>
Michaelsson et al. (1998) ^b	Case-control	EPRT any admin	56/274	956/2073	OR	<i>0.46 (0.32, 0.66)</i>
Michaelsson et al. (1998) ^b	Case-control	HRT oral	97/389	956/2073	OR	<i>0.54 (0.41, 0.71)</i>
Michaelsson et al. (1998) ^b	Case-control	HRT transdermal	23/94	956/2073	OR	<i>0.62 (0.36, 1.06)</i>
Michaelsson et al. (2002) ^c	Case-control	HRT low potency oral or vaginal	221/641	956/2073	OR	<i>0.88 (0.73, 1.05)</i>
Michaelsson et al. (2002) ^c	Case-control	HRT low potency oral only	116/273	956/2073	OR	<i>1.02 (0.80, 1.30)</i>
Michaelsson et al. (2002) ^c	Case-control	ERT low potency vaginal only	84/298	956/2073	OR	<i>0.75 (0.57, 0.98)</i>
Michaelsson et al. (2002) ^c	Case-control	ERT low potency oral and vaginal	17/65	956/2073	OR	<i>0.67 (0.39, 1.17)</i>
<i>Wrist fracture</i>						
Randell et al. (2002) ^a	Cohort	HRT (4.5/previous 5 years)	22/1335	145/3335	RR	<i>0.41 (0.26, 0.67)</i>
Randell et al. (2002) ^a	Cohort	HRT (> 6 months/previous 5 years)	36/1335	145/3335	RR	<i>0.66 (0.45, 0.98)</i>
Mallim et al. (1994)	Case-control	HRT <2 years ever use	nr	nr	OR	<i>1.14 (0.57, 2.26)</i>
Mallim et al. (1994)	Case-control	HRT >2 years ever use	nr	nr	OR	<i>0.44 (0.22, 0.89)</i>
<i>Other fracture</i>						
Randell et al. (2002) ^a	Cohort	HRT (4.5/previous 5 years)	72/1335	207/3335	RR	<i>0.74 (0.55, 0.98)</i>
Randell et al. (2002) ^a	Cohort	HRT (> 6 months/previous 5 years)	67/1335	207/3335	RR	<i>0.72 (0.53, 0.97)</i>

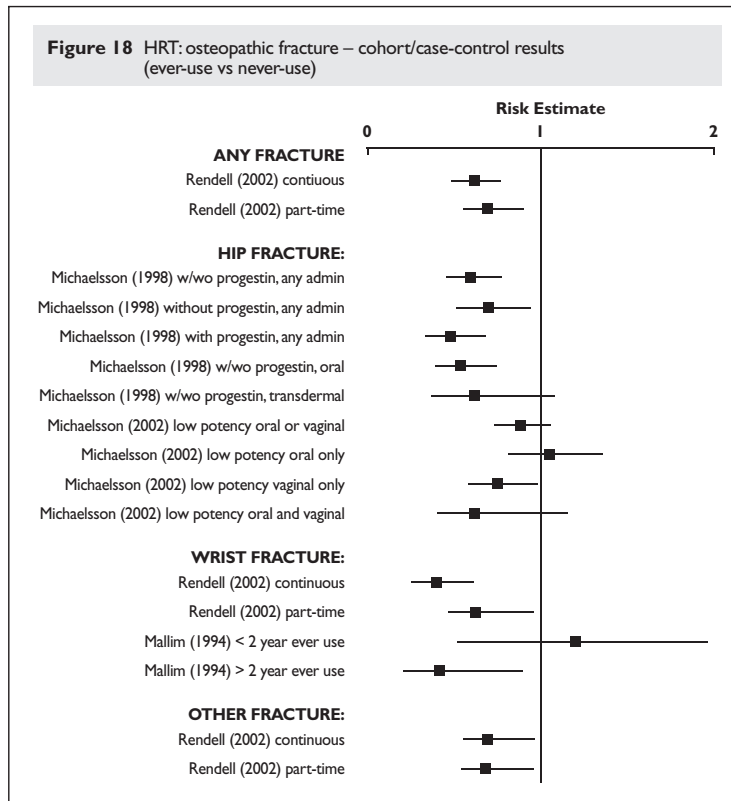
Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: ERT, oestrogen-only therapy; EPRT, oestrogen + progestogen; HRT, oestrogen ± progestogen; nr, not reported; OR, odds ratio; RR, relative risk.

^a Adjusted for age, time since menopause, BMI, health disorders and previous fractures

^b Adjusted for age and indication for HRT being osteoporosis

^c Adjusted for age, current weight, physical activity, smoking, parity, menopausal age, climacteric symptoms and oral contraceptive use.



In general, the cohort and case-control studies provide greater support for a risk reduction in fracture incidence with HRT use, and these observed effects appear to be relatively consistent across various anatomical locations. The notable exception is the use of low potency HRT, which appears to confer little benefit. Furthermore, the Mallmin *et al.* (1994) study showed a risk reduction only with therapy of greater than two years duration.

The results of Michaelsson *et al.* (1998) suggest that formulations with progestogen may provide a somewhat greater benefit. In contrast to oral HRT, the risk reduction with transdermal HRT failed to reach statistical significance. It is possible that this may have been influenced by the smaller sample of women using this mode of administration, as the odds ratio of 0.62 was only marginally less than that obtained for oral HRT (0.54).

The studies that presented results for current use versus never use are summarised in Table 51 and Figure 19.

TABLE 51 HRT: OSTEOPOROTIC FRACTURE – CASE-CONTROL RESULTS (CURRENT USE VS NEVER USE)

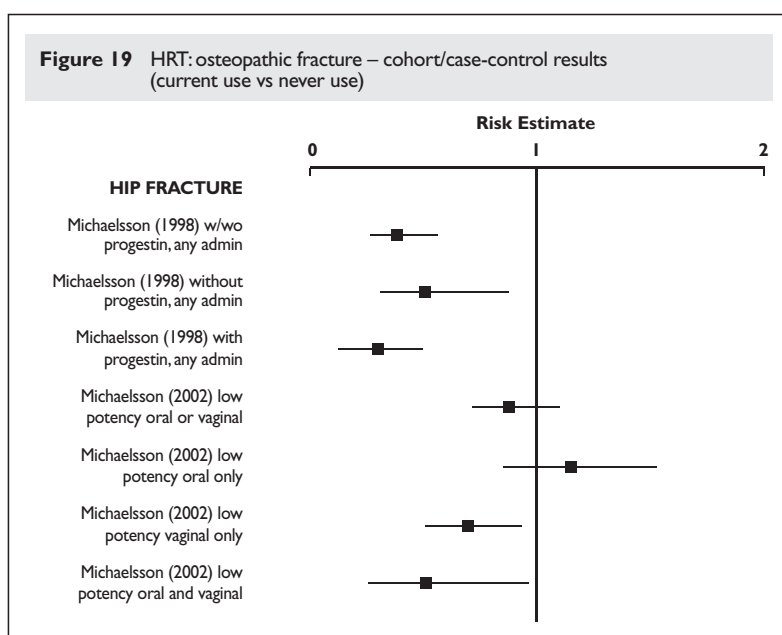
Author	Type of study	Type of HRT used	HRT (case/control)	No HRT (case/control)	Type of risk measure	Risk estimate
<i>Hip fracture</i>						
Michaelsson et al. (1998) ^a	Case-control	HRT any admin	40/239	956/2073	OR	0.36 (0.24, 0.53)
Michaelsson et al. (1998) ^a	Case-control	ERT, any admin	16/62	956/2073	OR	0.48 (0.26, 0.87)
Michaelsson et al. (1998) ^a	Case-control	EPRT, any admin	24/17	956/2073	OR	0.29 (0.17, 0.48)
Michaelsson et al. (2002) ^b	Case-control	low potency oral or vaginal	164/487	956/2073	OR	0.86 (0.70, 1.06)
Michaelsson et al. (2002) ^b	Case-control	low potency oral only	94/203	956/2073	OR	1.11 (0.85, 1.46)
Michaelsson et al. (2002) ^b	Case-control	low potency vaginal only	55/222	956/2073	OR	0.67 (0.49, 0.92)
Michaelsson et al. (2002) ^b	Case-control	low potency oral and vaginal	11/57	956/2073	OR	0.50 (0.25, 0.96)

Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: ERT, oestrogen-only therapy; EPRT, oestrogen + progestogen; HRT, oestrogen ± progestogen; OR, odds ratio.

^a Adjusted for age and indication for HRT being osteoporosis

^b Adjusted for age, current weight, physical activity, smoking, parity, menopausal age, climacteric symptoms and oral contraceptive use.



When current HRT use was compared with never-use, the results concur with those of ever-use vs never-use of HRT.

Table 52 and Figure 20 summarise the results relating to past use of HRT.

TABLE 52 HRT: OSTEOPOROTIC FRACTURE – COHORT/CASE-CONTROL RESULTS (PAST USE VS NEVER USE)

Author	Type of study	Type of HRT use	HRT (case/control)	No HRT (case/control)	Type of risk measure	Risk estimate
<i>Any fracture</i>						
Randell et al. (2002) ^a	Cohort	past use only	130/1212	352/3335	RR	1.02 (0.82, 1.26)
<i>Hip fracture</i>						
Michaelsson et al. (1998) ^b	Case-control	HRT, any admin	80/217	956/2073	OR	0.76 (0.57, 1.01)
Michaelsson et al. (1998) ^b	Case-control	ERT, any admin	65/167	956/2073	OR	0.76 (0.56, 1.04)
Michaelsson et al. (1998) ^b	Case-control	EPRT, any admin	32/9	956/2073	OR	0.71 (0.46, 1.12)
Michaelsson et al. (2002) ^c	Case-control	low potency oral or vaginal	57/154	956/2073	OR	0.93 (0.67, 1.29)
Michaelsson et al. (2002) ^c	Case-control	low potency oral only	22/70	956/2073	OR	0.76 (0.46, 1.27)
Michaelsson et al. (2002) ^c	Case-control	low potency vaginal only	29/76	956/2073	OR	0.97 (0.61, 1.54)
Michaelsson et al. (2002) ^c	Case-control	low potency oral and vaginal	6/8	956/2073	OR	1.90 (0.65, 5.61)
<i>Wrist fracture</i>						
Randell et al. (2002) ^a	Cohort	past use only	65/1212	145/3335	RR	1.44 (1.06, 1.95)
<i>Other fracture</i>						
Randell et al. (2002) ^a	Cohort	past use only	65/1212	207/3335	RR	0.75 (0.55, 1.02)

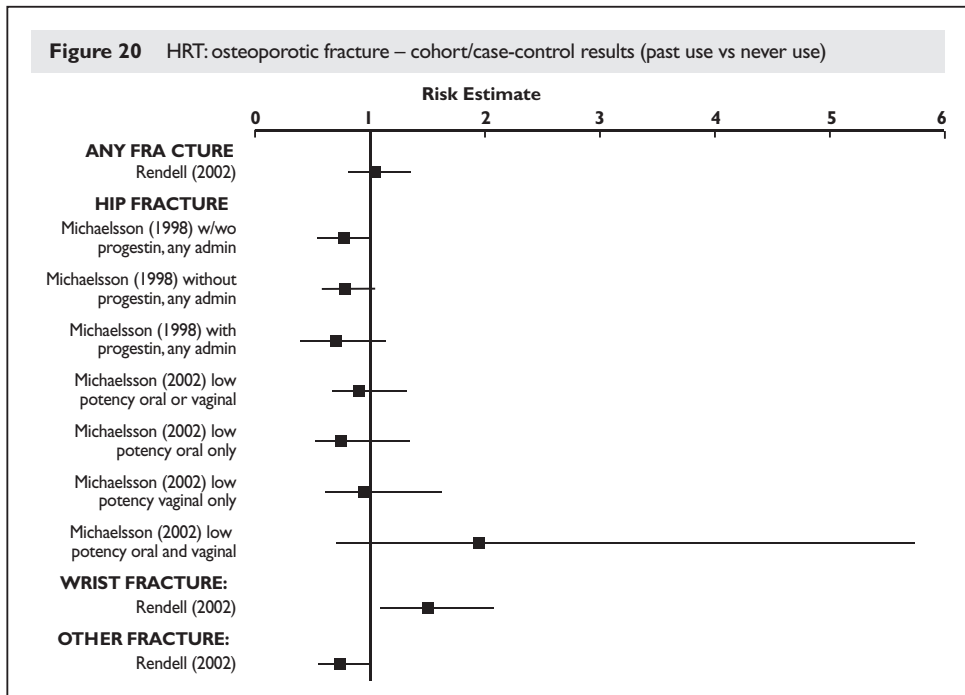
Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: ERT, oestrogen-only therapy; EPRT, oestrogen + progestogen therapy; HRT, oestrogen ± progestogen therapy; OR, odds ratio; RR, relative risk.

a Adjusted for age, time since menopause, BMI, health disorders and previous fractures

b Adjusted for age and indication for HRT being osteoporosis

c Adjusted for age, current weight, physical activity, smoking, parity, menopausal age, climacteric symptoms and oral contraceptive use.



The results observed in past users indicate that any risk reduction is transient in nature. No subgroup of past-users showed a statistically significant risk reduction in fracture relative to never-users. These results are reinforced by the recency of use data shown in Table 53 and Figure 21. Data relating to the effect of recency of use was only available from the Michaelsson (1998) study. This study reported the recency of cessation of HRT use (< 1 year, 1–5 years, > 5 years) with a breakdown by duration of use within each of these categories.

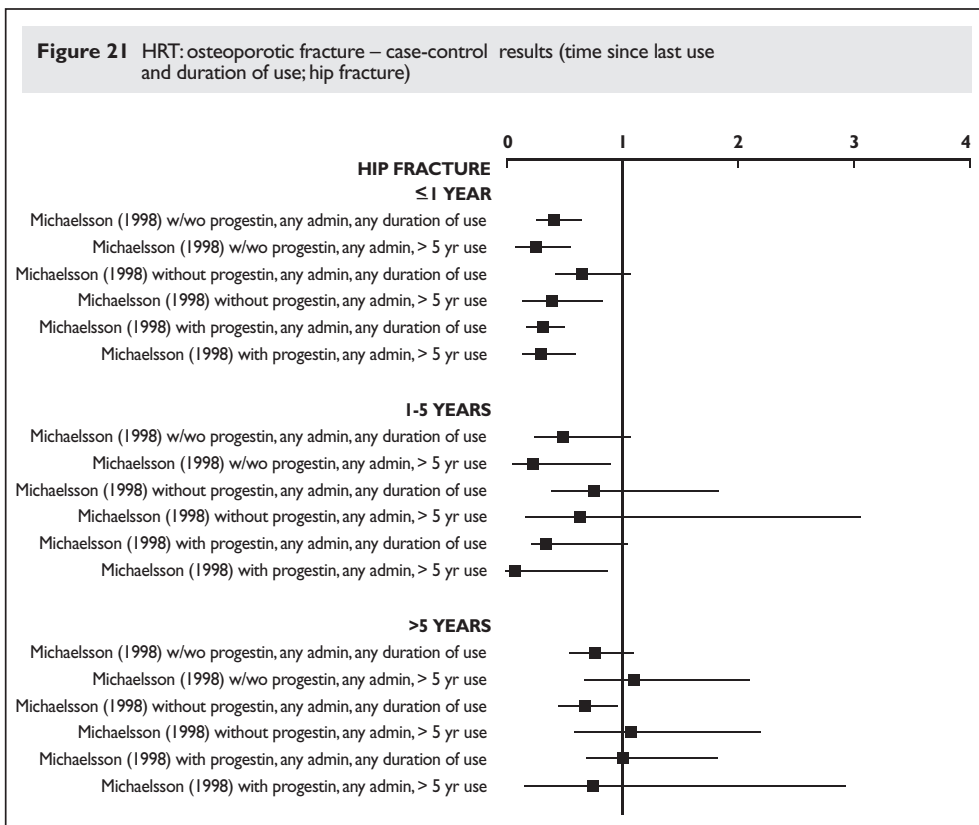
TABLE 53 HRT: OSTEOPOROTIC FRACTURE – CASE-CONTROL RESULTS (TIME SINCE LAST USE AND DURATION OF USE; HIP FRACTURE)

Author	Type of study	Type and duration of HRT use	HRT (case/control)	No HRT (case/control)	Type of risk measure	Risk estimate
≤ 1 year ago						
Michaelsson et al. (1998) ^a	case-control	HRT, any admin, any duration of use	47/260	956/2073	OR	<i>0.38 (0.26, 0.56)</i>
Michaelsson et al. (1998) ^a	case-control	HRT, any admin, > 5 yr use	14/97	956/2073	OR	<i>0.28 (0.16, 0.51)</i>
Michaelsson et al. (1998) ^a	case-control	ERT, any admin, any duration of use	21/70	956/2073	OR	<i>0.61 (0.35, 1.04)</i>
Michaelsson et al. (1998) ^a	case-control	ERT, any admin, > 5 yr use	8/36	956/2073	OR	<i>0.35 (0.15, 0.82)</i>
Michaelsson et al. (1998) ^a	case-control	EPRT, any admin, any duration of use	28/198	956/2073	OR	<i>0.28 (0.17, 0.47)</i>
Michaelsson et al. (1998) ^a	case-control	EPRT, any admin, > 5 yr use	9/66	956/2073	OR	<i>0.24 (0.11, 0.52)</i>
1–5 years ago						
Michaelsson et al. (1998) ^a	case-control	HRT, any admin, any duration of use	11/45	956/2073	OR	<i>0.52 (0.26, 1.04)</i>
Michaelsson et al. (1998) ^a	case-control	HRT, any admin, > 5 yr use	3/18	956/2073	OR	<i>0.27 (0.08, 0.94)</i>
Michaelsson et al. (1998) ^a	case-control	ERT, any admin, any duration of use	9/23	956/2073	OR	<i>0.82 (0.37, 1.84)</i>
Michaelsson et al. (1998) ^a	case-control	ERT, any admin, > 5 yr use	3/6	956/2073	OR	<i>0.65 (0.14, 3.05)</i>
Michaelsson et al. (1998) ^a	case-control	EPRT, any admin, any duration of use	7/31	956/2073	OR	<i>0.42 (0.17, 1.04)</i>
Michaelsson et al. (1998) ^a	case-control	EPRT, any admin, > 5 yr use	1/12	956/2073	OR	<i>0.10 (0.01, 0.87)</i>
> 5 years ago						
Michaelsson et al. (1998) ^a	case-control	HRT, any admin, any duration of use	46/125	956/2073	OR	<i>0.75 (0.52, 1.07)</i>
Michaelsson et al. (1998) ^a	case-control	HRT, any admin, > 5 yr use	15/28	956/2073	OR	<i>1.07 (0.57, 2.03)</i>
Michaelsson et al. (1998) ^a	case-control	ERT, any admin, any duration of use	38/115	956/2073	OR	<i>0.65 (0.44, 0.96)</i>
Michaelsson et al. (1998) ^a	case-control	ERT, any admin, > 5 yr use	12/22	956/2073	OR	<i>1.06 (0.52, 2.19)</i>
Michaelsson et al. (1998) ^a	case-control	EPRT, any admin, any duration of use	17/38	956/2073	OR	<i>1.00 (0.55, 1.82)</i>
Michaelsson et al. (1998) ^a	case-control	EPRT, any admin, > 5 yr use	3/8	956/2073	OR	<i>0.74 (0.19, 2.93)</i>

Note: Risk estimates in italics are considered statistically significant as they do not include one.

Abbreviations: ERT, oestrogen-only therapy; EPRT, oestrogen + progestogen therapy; HRT, oestrogen ± progestogen therapy; OR, odds ratio.

^a Adjusted for age and indication for HRT being osteoporosis.



The results demonstrate a diminishing reduction in risk as time passes beyond the cessation of HRT; after five years no benefit remains. Furthermore, this loss of effect is not prevented by having used HRT for longer than five years duration.

Cognition/dementia

Summary

Women in general

Interpretation of the evidence related to the effect of HRT upon cognition is difficult as studies enrol different subjects and use a wide variety of tests to measure cognitive outcomes. On balance, the evidence from existing systematic reviews and subsequent original studies fails to show a consistent benefit of HRT upon cognition. Nevertheless, there are certainly isolated studies that show a positive effect in some cognitive domains. There is level III evidence which suggests no change or a decreased risk of dementia associated with use of HRT.

Women with dementia

Overall, there is a paucity of good quality evidence regarding the association between HRT and cognitive function in women with dementia. The highest quality systematic review concluded that HRT is not indicated for cognitive improvement or maintenance in women with dementia.

Within the included studies, the methods and instruments used to measure cognition and dementia were highly variable. For this reason, it would be misleading to tabulate the results in a manner comparable to the other outcomes. Therefore, the results for cognition/dementia are presented in a narrative fashion.

It should be noted that since the literature search conducted for this review an updated analysis of cognition data from the WHI study has been published. For details see Addendum A. The conclusions from the WHI publications contradict the evidence identified in the literature search.

Cognition in women without dementia

Existing systematic reviews

Our search identified four existing systematic reviews of the effect of ERT or HRT on cognition in postmenopausal women without dementia: one systematic review limited to RCTs which was considered to be of good methodological quality (Hogervorst *et al.*, 2002; level I evidence); and three systematic reviews which included RCTs and observational studies, with one review of good methodological quality (LeBlanc *et al.*, 2002; level III-2 evidence) and two reviews of fair methodological quality (Yaffe *et al.*, 1998; Haskell *et al.*, 1997; level III-2 evidence). The characteristics and quality of the included systematic reviews are summarised in Table 54. For further details see Appendix B (Section 9.1.3).

TABLE 54 HRT: COGNITION IN WOMEN WITHOUT DEMENTIA – EXISTING SYSTEMATIC REVIEWS

Study	Study type (No. of studies) Study quality	Population	Intervention	Comparator	Outcomes
Level I evidence					
Hogervorst <i>et al.</i> (2002a)	Systematic review of RCTs (9) Good	Healthy women with natural or surgical menopause	Oestrogen, alone or together with progestogen/progesterone Any mode of administration Any dose	Placebo	Tests of cognitive function ^a
Level III-2 evidence					
Leblanc <i>et al.</i> (2001); Leblanc <i>et al.</i> (2002)	Systematic review (9 RCTs and 8 cohort studies) Good	Postmenopausal women without existing dementia (type not defined)	Hormone replacement therapy Mode of administration not specified Any dose	No HRT	Tests of cognitive function ^a Dementia
Yaffe <i>et al.</i> (1998)	Systematic review (7 RCTs, 1 non-RCT, 1 cohort, 1 case series and 3 cross-sectional) Fair	Non-demented postmenopausal women (dementia type not defined)	Oestrogen-containing therapy Mode of administration not specified Any dose	No HRT	Tests of cognitive function ^a Dementia
Haskell <i>et al.</i> (1997)	Systematic review (7 RCTs and 2 non-RCTs) Fair	Women without dementia (type not defined)	Hormone replacement therapy including oestrogen Mode of administration not specified Any dose	No HRT	Tests of cognitive function ^a

See Section 9.1.3.

Abbreviations: RCT, randomised controlled trial.

^a See Appendix C (Section 10) for further details of the cognitive tests used by the studies included in the reviews.

The main results of each of the systematic reviews are summarised in Table 55. As stated by all of the authors, interpretation of the evidence related to the association between oestrogen therapy and cognition is difficult because the studies enrol different subjects and use a wide variety of tests to cognitive outcomes. Furthermore, many of the studies do not use validated cognitive tests. The range of cognitive tests used by studies included in each of these reviews is summarised in Appendix C. Only one of the four reviews (Hogervorst *et al.*, 2002) attempted to combine quantitatively test outcomes. This Cochrane review calculated the weighted mean difference for 19 outcomes based on data from 1 – 5 studies per outcome. The reviews by LeBlanc, Hogervorst and Haskell qualitatively combined cognitive test results according to the cognitive function they measured (eg, memory, speed, attention, abstract reasoning). Although cross-sectional studies suggest that HRT affects memory, especially verbal memory, results from RCTs are conflicting.

Two of the reviews, Hogervorst *et al.* (2002) and Haskell *et al.* (1997) concluded that there was little evidence regarding the effect of HRT or ERT on overall cognitive function. Meta-analyses by Hogervorst showed a positive effect of 10 mg of estradiol bolus injections intramuscularly monthly in relatively young surgically menopausal women on a test of immediate recall, a test of abstract reasoning and a test of speed and accuracy. However, most studies found no evidence of an effect on verbal or visual memory, mental rotations, speed or accuracy measures. There was little evidence that Premarin had positive effects on cognitive function.

On the other hand, both LeBlanc *et al.* (2002) and Yaffe *et al.* (1998) concluded that there is evidence that oestrogen therapy improves cognitive performance in recently menopausal (ie, symptomatic) women, but that there is no evidence of a beneficial effect in asymptomatic women. The review by LeBlanc also observed that there was insufficient evidence about the effects of the addition of progestogens to oestrogen, and that the included studies were too dissimilar in design to make any conclusions regarding which formulations or dosage or oestrogen may be more beneficial for cognition in symptomatic women.

TABLE 55 HRT: COGNITION IN WOMEN WITHOUT DEMENTIA – RESULTS OF EXISTING SYSTEMATIC REVIEWS

Study	Number of included studies	Results and conclusion
Hogervorst (2002a)	15 studies (15 RCTs)	There were some small effects on verbal memory functions (immediate recall), on a test of abstract reasoning and a test of speed and accuracy in relatively young (47 years) surgically menopausal women. However, given that these results from were from small studies by the same author it is difficult to know if the results are applicable to other types of HRT in different patients groups. Statistically significant results are as follows: the standardised mean difference for (i) the Paired Associates test was 1.020 (0.187, 1.853; based on 2 studies); for (ii) the Paired Associates learning test was 0.661 (0.017, 1.305; based on 3 studies); for (iii) Abstract reasoning was 6.800 (5.525, 8.075; based on 1 study); for (iv) clerical speed and accuracy was 6.000 (4.716, 7.284; based on 1 study). Based on the available evidence the authors concluded that HRT cannot be recommended for overall cognitive improvement or maintenance.
Leblanc (2002)	17 studies (9 RCTs and 8 cohort studies)	The authors reported that it is difficult to compare studies about HRT and cognitive function and report overall conclusions because the studies enlist different patient populations and report different cognitive test outcomes. No deleterious effects of oestrogen on cognition have been reported. HRT does not appear to enhance performance on formal cognitive testing for asymptomatic women, although some studies have found that symptomatic women have improved cognitive performance with HRT, especially in tests of verbal memory and vigilance. There is insufficient evidence about whether progestogens attenuate these cognitive effects. Because of the heterogeneous study designs, no conclusions can be drawn about whether specific oestrogen formulations or dosages might be more beneficial. Duration of use did not appear to be related to cognitive performance.
Yaffe (1998)	13 studies (7 RCTs, 1 non-RCT, 1 cohort, 1 nested case-control, 3 cross-sectional)	The authors found that studies conducted in women had substantial methodological problems and have produced conflicting results. The largest and best quality observational study of the effect of oestrogen use on cognition in non-demented women showed no benefit, while the results of 8 small trials are inconclusive. The authors concluded that there is evidence that oestrogen therapy improves cognitive performance in recently menopausal women, but no evidence of a beneficial effect in asymptomatic women.
Haskell (1997)	9 studies (7 RCTs, and 2 non-RCTs)	These authors noted the diversity in baseline conditions of the subjects and the failure of the identified studies to define suitably valid and reliable measures of outcome. Of the 10 RCTs, only 5 directly assessed memory functions using performance tests that were able to separate memory from other domains of cognitive functioning, and only 3 of these reported favourable effects of oestrogen. Only one of the studies that used performance measures of cognition statistically controlled for potential confounders (ie, depression and vasomotor symptoms). The authors concluded that the available clinical trials provide insufficient evidence to support the conclusion that HRT improves cognitive function.

Abbreviations: RCT, randomised controlled trial.

Original studies

The good quality reviews by Hogervorst *et al.* (2002) and Le Blanc *et al.* (2002) were comprehensive and provided detailed analysis of the evidence regarding the association between oestrogen and cognitive function in women without dementia. Consequently, the search for additional original studies was conducted for the years 2000-2003 to supplement and update the evidence provided by these two systematic reviews. The search identified one RCT and four cohort studies. The RCT (Hays *et al.*, 2003) was considered to be fair quality, while three of the cohort studies were considered to be good quality (Carlson *et al.*, 2001; De Moraes *et al.*, 2001; Rice *et al.*, 2000), and one was considered to be fair quality (Lokkegaard *et al.*, 2002). For details of the characteristics and quality of these studies see Table 56. For further details see Appendix B (Section 9.1.3).

TABLE 56 HRT: COGNITION IN WOMEN WITHOUT DEMENTIA – ORIGINAL STUDIES

Study	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Level II evidence					
Hays <i>et al.</i> (2003)	RCT Follow-up 5.2 years Fair	Women without dementia (type not defined) Mean age 63 y N=5402	Oral 0.625mg CEE + 2.5mg MPA	Matching placebo	MMSE only
Level III-2 evidence					
Lokkegaard <i>et al.</i> (2002)	Cohort Follow-up 11 years Fair	Women without dementia (type not defined) Age < 60 y N=226	HRT Mode of administration not specified Any dose	Never-use HRT	Tests of cognitive function
Carlson <i>et al.</i> (2001)	Cohort Follow-up 3 years Good	Women without dementia (type not defined) Age 72–77 y N=1800	HRT Mode of administration not specified Any dose	Never-use HRT	Tests of cognitive function
De Moraes <i>et al.</i> (2001)	Cohort Good	Women without dementia (type not defined) Mean age 57 y N=2859	Current-use of oestrogen alone or in combination with progestogen Mode of administration not specified Any dose	Never-use HRT	Tests of cognitive function
Rice <i>et al.</i> (2000)	Cohort Good	Women without dementia Age 71–75 y N=837	Oestrogen with or without progestogen Mode of administration not specified Any dose	Never-use HRT	Tests of cognitive function

See Section 9.1.3.

Abbreviations: MMSE, Mini Mental State Examination; RCT, randomised controlled trial.

The results of the five original studies regarding cognition in women without dementia are presented in Table 57. Two of the original studies (Hays *et al.*, 2003; De Moraes *et al.*, 2001) found no association between HRT use and cognitive functioning. The study by De Moraes also found no association between duration of use and patterns of cognitive change. However, the tests used in these two studies may mean that neither study was sensitive to changes in particular cognitive domains: the RCT by Hays *et al.* (2003) used a global cognitive test (MMSE) only, while the cohort study by De Moraes *et al.* (2001) was restricted to three domain-specific tests.

The remaining three studies found evidence of a modest beneficial association between HRT use and cognitive function. Both Lokkegaard *et al.* (2002) and Carlson *et al.* (2001) found that current users of HRT showed less pronounced decline in cognitive performance compared to never-users. The study by Rice *et al.* (2000) found an improvement in some cognitive domains for users of unopposed ERT versus never users. However, this study also found that the beneficial effect of oestrogen appeared to be ameliorated by the addition of MPA.

TABLE 57 HRT: COGNITION IN WOMEN WITHOUT DEMENTIA – RESULTS OF ORIGINAL STUDIES

Study	Results and conclusion
Level II evidence	
Hays (2003)	The change in MMSE over one year from baseline with HRT minus placebo was 0.1 ± 0.2 (mean \pm SD; $P=0.40$; $N=5047$). The change in MMSE over three years from baseline with HRT minus placebo was 0.2 ± 0.6 (mean \pm SD; $P=0.79$; $N=399$). The authors concluded that randomisation to oestrogen plus progestogen in the WHI study resulted in no significant effects on 'mental health'.
Level III-2 evidence	
Lokkegaard (2002)	Although they found evidence that HRT influences aging-related changes in concentration and visuomotor function, the authors were unable to confirm that HRT enhances memory function. Current users of HRT at follow-up showed less pronounced decline in cognitive performance compared to never users in 1/6 domains for concentration ability (OR 0.90, 95% CI 0.82-0.98), in 2/8 domains for visuomotor function (OR 0.85; 0.73-0.99 for Figure Drawing Dominant hand time, and OR of 0.86; 0.73-0.99 for Pen-to-point dominant hand std dev., in 0/6 domains for learning and memory, 0/2 domains for visuo-spatial function, 0/4 domains of attention and perception, and 0/2 domains of vigilance. Furthermore, women who chose to start HRT after baseline had better cognitive performance prior to treatment. This highlights the importance of considering 'health user bias' when interpreting the results of observational studies.
Carlson (2001)	The authors concluded that in their population cohort of older women, lifetime HRT exposure was associated with improved global cognition and attenuated the decline over the 3 year interval (attenuation of 1.50 points at the mean age of 76 years). This was considered to be clinically significant as well as statistically significant. Improvements were greatest in women ≥ 85 years. Data on the incidence of dementia during the observation period are to be published in a separate report.
De Moraes (2001)	The authors report mean cognitive score difference between visits 2 and 4 by (1) menopausal status and use of ERT, stratified by median age at visit 2, and (2) duration of use of ERT in menopausal women who are current users, stratified by median age at visit 2. With one exception, which may be chance finding due to multiple testing (there was a significantly larger word fluency score decline among naturally postmenopausal women ≤ 56 years who had used ERT for 11-44 years), no associations were observed between ERT use or duration and 6-year changes in cognitive functioning. Thus was true for older (>56 years) and younger (≤ 56 years) women in this cohort. The authors concluded that for women aged 44 – 67, use of ERT is not associated with age-related cognitive declines.
Rice (2000)	Women who had never used postmenopausal HRT improved slightly on the CASI scale. For past users versus never users there was a statistically significant difference (improvement) for 1/5 domains (abstract reasoning) but not for the global score. For Current unopposed ERT users versus Never users there was a statistically significant difference (improvement) for 2/5 domains (abstract reasoning, category fluency) and for the global score. For current combined HRT users versus never users there was a statistically significant difference (worsening) for 1/5 domains (mental tracking) and for the global score. The improvement observed in past users was intermediate between changes for never users and current unopposed ERT users, and was not statistically significantly different than that for never users. Also, past users were more educated and more likely to speak English at the interview than never users. The findings support a modest beneficial association between current ERT and rate of cognitive change, but the study also observed a modest detrimental effect of HRT use on rate of cognitive changes (ie, the beneficial effect of oestrogen on cognitive changes appeared to be opposed by MPA). Also women with surgical menopause showed less of a benefit than women with natural menopause.

Abbreviations: ERT, oestrogen-only therapy; MMSE, Modified Mini Mental State Examination; MPA, medroxyprogesterone acetate; OR, odds ratio; SD, standard deviation; WHI, Women's Health Initiative.

Cognition in women with dementia

Existing systematic reviews

Our search identified three existing systematic reviews of the effect of ERT or HRT on cognition in postmenopausal women with dementia: one systematic review of RCTs rated as good quality (Hogervorst *et al.*, 2003), and two systematic reviews of RCTs and observational studies rated as fair quality (Haskell *et al.*, 1997; Yaffe *et al.*, 1998). The characteristics and quality of the included systematic reviews are summarised in Table 58. For further details see Appendix B (Section 9.1.3).

TABLE 58 HRT: COGNITION IN WOMEN WITH DEMENTIA – EXISTING SYSTEMATIC REVIEWS

Study	Study type (No. of included studies) Study quality	Population N	Intervention N	Comparator N	Outcomes
Level I evidence					
Hogervorst <i>et al.</i> (2002b)	Systematic review (5 RCTs) Good	Women with AD	Oestrogen, alone or together with progestogen/progesterone Any mode of administration Any dose	Placebo	Tests of cognitive function ^a
Level III-2 evidence					
Yaffe <i>et al.</i> (1998)	Systematic review (1 RCT, 1 non-RCT and 2 uncontrolled trials) Fair	Women with AD (4 studies)	Oestrogen-containing therapy Mode of administration not specified Any dose	No HRT	Tests of cognitive function ^a Dementia
Haskell <i>et al.</i> (1997)	Systematic review of RCTs and observational studies Fair	Women with AD (1 study)	Hormone replacement therapy including oestrogen Mode of administration not specified Any dose	No HRT	Tests of cognitive function ^a

See Section 9.1.3.

Abbreviations: AD, Alzheimer's disease; RCT, randomised controlled trial.

^a See Appendix C (Section 10) for further details of the cognitive tests used by the studies included in the reviews.

The results of the existing systematic reviews of the effects of oestrogen on cognition in women with dementia are presented in Table 59. Overall, there is a paucity of good quality evidence regarding the association between oestrogen therapy and cognitive function in women with dementia. The highest quality review by Hogervorst *et al.* (2003) concluded that based on the current evidence ERT or HRT is not indicated for cognitive improvement or maintenance in women with AD. The remaining two reviews (Haskell *et al.*, 1997; Yaffe *et al.*, 1998) reported evidence of improvement on some but not all dementia scales. However both of these reviews were based on small studies with a number of methodological problems.

TABLE 59 HRT: COGNITION IN WOMEN WITH DEMENTIA – RESULTS OF EXISTING SYSTEMATIC REVIEWS

Study	Number of included studies	Results and conclusion
Level I evidence		
Hogervorst (2002b)	7 studies (all RCTs)	The authors conclude that “currently, HRT or ERT for cognitive improvement or maintenance is not indicated for women with AD”. There was a small but not clinically relevant positive effect from low dosage oestrogens (CEE, 0.625 mg/day) on the MMSE after 2 months (WMD=1.28; 0.26-2.30). But this effect disappeared after 3, 6 and 12 months of treatment. There were short-term effects of 1.25 mg/day CEE on tests of concentration (the Trail marking test-B: WMD=-40.99; -79.29 to -2.51) and executive function (Digit Span backward: WMD=0.67; -0.01 to 1.34). With regard to memory, only cued delayed recall of a word list was positively affected by 2 months of oestradiol (WMD=6.50; 4.04 to 8.96). No effects were seen on other word lists, Paragraph Recall or Paired Associate Learning. After correction for multiple testing, only the short-term positive treatment of oestradiol on memory remained.
Level III-2 evidence		
Haskell <i>et al.</i> (1997)	1 study (non-RCT)	The authors observed “some ameliorative effects of oestrogen on the CNS of patients with AD”, ie, greater improvement on one dementia scale but not on two others in the oestrogen-treated group compared to the placebo-treated group. However; these results should be interpreted with caution because of the small sample size (N=7 in each arm).
Yaffe <i>et al.</i> (1998)	4 studies (1 RCT, 1 non-RCT and 2 uncontrolled trials)	Each of the four studies in women with dementia found improvement in some but not all measures of dementia severity after treatment with oestrogen therapy. However; all of the studies were limited by small sample size, short duration of therapy (3 to 6 weeks) and the inclusion of subjects with a wide range of dementia severity.

Abbreviations: AD, Alzheimer’s disease; CNS, central nervous system; MMSE, Modified Mini Mental State Examination; RCT, randomised controlled trial; WMD, weighted mean difference.

Original studies

No relevant studies have been published since the literature search performed for the existing systematic review with regards to cognition in women with dementia.

Dementia

Existing systematic reviews

Our search identified two existing systematic reviews of the association between HRT and risk of dementia: Le Blanc *et al.*(2002) and Yaffe *et al.*(1998). Both reviews were based on RCTs and observational studies, and the review by Le Blanc was rated as good quality while the review by Yaffe was rated as fair quality. The characteristics and quality of the included systematic reviews are summarised in Table 60. For further details see Appendix B (Section 9.1.3).

TABLE 60 HRT: DEMENTIA – EXISTING SYSTEMATIC REVIEWS

Study	Study type (No. of included studies) Study quality	Population	Intervention	Comparator	Outcomes
Level III-2 evidence					
Leblanc <i>et al.</i> (2001); Leblanc <i>et al.</i> (2002)	Systematic review of RCTs and observational studies (12) Good	Women without dementia at baseline	Hormone replacement therapy Mode of administration not specified Any dose	No HRT	Tests of cognitive function Dementia (any type)
Yaffe <i>et al.</i> (1998)	Systematic review of RCTs and observational studies (10) Fair	Women without dementia (assessment of dementia varied widely between studies)	Oestrogen-containing therapy Mode of administration not specified Any dose	No HRT	Tests of cognitive function Dementia (any type)

See Section 9.1.3.

Abbreviations: RCT, randomised controlled trial.

Results from the existing systematic reviews of the association between HRT and risk of dementia are presented in Table 61. The two existing systematic reviews by Le Blanc *et al.* (2002) and Yaffe *et al.* (1998) were based on almost the same studies, and both reviews found that HRT users had a significantly decreased risk of dementia compared to never users. However the authors of both reviews noted that studies in this area have substantial methodological problems. No conclusions can be drawn regarding the addition of progestogen to oestrogen, or the relative effectiveness of specific dosages or formulations of oestrogen.

TABLE 61 HRT: DEMENTIA – RESULTS OF EXISTING SYSTEMATIC REVIEWS

Study	Number of included studies	Results and conclusion
Level III-2 evidence		
Leblanc (2002)	12 studies (2 cohort and 10 case-control studies)	The summary RR for AD was 0.66 (0.53-0.82), and the estimate did not change substantially when restricted to case-control studies (RR, 0.71; 0.56-0.91) or to cohort studies (RR, 0.50; 0.30-0.80), or when poor quality studies were excluded (RR, 0.64; 0.32-1.06) – although excluding poor quality studies made the result non significant. Whether oestrogen is associated with a decreased risk of other forms of dementia is unknown. No conclusions can be drawn about progestogens or whether specific dosages or formulations of oestrogens are more protective. Although the meta-analysis suggests that HRT users have a 34% decreased risk of AD, there are limitations in the studies on which this estimate is based: use of proxy respondents, poor recall in women with undiagnosed mild memory changes, women with dementia less likely to receive HRT, and health user bias. Concluded that only RCTs can determine conclusively whether HRT use prevents AD.
Yaffe (1998)	10 studies (2 cohort studies, 8 case-control studies)	The authors conclude that the studies in this area have "substantial methodological problems and have produced conflicting results" and that "given the known risks of estrogen therapy we do not recommend estrogen for the prevention or treatment of AD or other dementias until adequate trials have been completed". Meta-analysis of the observational studies of oestrogen and dementia outcome "AD and other dementia types" derived a summary OR of 0.71 (0.53-0.96). For studies which used the NINCDS-ADRA diagnostic criteria, the pooled OR was 0.69 (0.48-1.01).

Abbreviations: AS, Alzheimer's disease; RR, relative risk.

Original studies

The comprehensive, good quality systematic review by Le Blanc *et al.* (2002) of evidence regarding the association between oestrogen and the risk of dementia was based on a literature review conducted up to December 2000. Consequently, the search for additional original studies was conducted for the years 2000-2003 to supplement and update the evidence provided by this systematic review. The search identified one original nested case-control study of fair quality (Seshadri *et al.*, 2002). For details of the characteristics and quality of this study see Table 62. For further details see Appendix B (Section 9.1.3).

TABLE 62 HRT: DEMENTIA – ORIGINAL STUDIES

Study	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Level III-2 evidence					
Seshadri <i>et al.</i> (2001)	Nested case-control (population-based) <i>Fair</i>	Cases with AD/ controls without AD N=280	Oral or transdermal oestrogen with or without progestogen Any dose	Never-use HRT	AD

See Section 9.1.3.

Abbreviations: AD, Alzheimer's disease.

The results of the additional study by Seshadri *et al.* (2001) on the association between HRT and risk of dementia are presented in Table 63. These authors concluded that the use of ERT or combined HRT in women after the onset of menopause was not associated with a reduced risk of developing AD. However, the results should be interpreted with caution as 'non-users' included subjects who had taken HRT for less than one year, and the menopausal status of the controls was not matched to the cases.

TABLE 63 HRT DEMENTIA – RESULTS OF ORIGINAL STUDIES

Study	Results and conclusion
Level III-2 evidence	
Seshadri (2001)	Among the 59 newly diagnosed cases of AD, 15 (25%) were current oestrogen users, while among the controls, 53 (24%) were current users. The adjusted OR comparing all current oestrogen users with non-users was 1.18 (0.59-2.37). In oestrogen users who took the therapy for ≥ 5 years compared with non-users, the OR was 1.05 (0.32-3.44). OR were similar for unopposed oestrogen users and combined oestrogen-progestogen users. The authors concluded that the use of HRT in women after the onset of menopause was not associated with a reduced risk of developing AD.

Abbreviations: AD, Alzheimer's disease; OR, odds ratio.