

Understanding the long-term benefits and risks of HRT

Document produced by Dr Sarah Glynne, GP Menopause Specialist

Understanding the major long-term benefits of HRT

All-cause mortality

Women aged 50–59

7 deaths per 1000 women aged 50–59 each year in the UK¹



2 fewer deaths in women who initiate oral oestrogen and a synthetic progestogen within 10 years of the menopause²



2.5 fewer deaths in women who initiate body-identical oestradiol (oral or transdermal) and a progestogen within 10 years of the menopause*³



Women aged 60–69

16.5 deaths per 1000 women aged 60–69 each year in the UK¹



No reduction in all-cause mortality is seen when older women start oral oestrogen and a synthetic progestogen more than 10 years after menopause²



6.5 fewer deaths in older women who start body-identical oestrogen (oral or transdermal) with a progestogen more than 10 years after menopause*³



*Very few studies have assessed all-cause mortality in women using transdermal oestrogen. To our knowledge, this is the only study that has stratified all-cause mortality in women using transdermal oestrogen by age. No studies, including this one, have evaluated all-cause mortality in women using transdermal oestrogen with body-identical progesterone, which has greater cardiovascular benefits. Randomised clinical trials are needed to quantify the effects of body-identical hormones on all-cause mortality in women.

Coronary heart disease (CHD)

Women aged 50–59

9 cases of CHD per 1000 women aged 50–59 over 5 years⁴



4 fewer cases of CHD (cardiovascular death or non-fatal MI) in women who start HRT within 10 years of the menopause²



Transdermal oestradiol and body-identical progesterone have a superior cardiovascular safety profile and may further reduce cardiovascular mortality in women aged 50–59⁵

Statins have not been shown to prevent CHD or reduce all-cause mortality when used for primary prevention in women⁶

Coronary heart disease (CHD)

Women aged 60–69

18 cases per 1000 women aged 60–69 over 5 years⁴



No change in CHD incidence in women who start HRT more than 10 years after the menopause²



9 fewer deaths in women who start body-identical oestrogen (oestradiol) +/- a progestogen more than 10 years after menopause*³



*Very few studies have assessed CHD risk in women using transdermal oestrogen. To our knowledge, this is the only study that has stratified CHD risk in women using transdermal oestrogen by age. No studies, including this one, have evaluated CHD risk in women using transdermal oestrogen with body-identical progesterone, which has greater cardiovascular benefits. Randomised clinical trials are needed to quantify the effects of body-identical hormones on CHD risk in women.

Diabetes

Women aged 50–59

Globally, 15% of women aged 50–59 are estimated to have diabetes⁷



4.5 fewer cases in women aged 50–59 who take HRT⁸



Women aged 60–69

Globally, 20% of women aged 60–69 are estimated to have diabetes⁷



6 fewer cases in women aged 60–69 who take HRT⁷



HRT also has beneficial effects on glycaemic control in women with established diabetes (reduced insulin resistance, reduced HbA1c)⁹

**Pooled data from 107 clinical trials with 33,315 participants followed for a mean duration of 1.5 years. Limited data suggests that benefits are greater in women who use HRT for more than 1.5 years; in a prospective observational study the risk of new onset diabetes was reduced by 69% in women aged 52 to 62 years who used HRT for between 2.5 and 5 years.¹⁰

Osteoporosis

Women aged 50–59

There are 15 fractures per 1000 women aged 50–59 each year¹¹



7 fewer fractures in women aged 50–59 who use HRT¹²



Women aged 60–69

There are 21 fractures per 1000 women aged 60–69 each year¹¹



5 fewer fractures in women aged 60–69 who take HRT¹²



Dementia

46 cases per 1000 women aged > 65 years¹³



14.5 fewer cases in women who start oestrogen only HRT within 10 years of menopause¹⁴



10 fewer cases in women who start oestrogen and progesterone HRT within 10 years of menopause^{*14}



***Dementia is the leading cause of female death in the UK. The reduction in risk in women using combined HRT (oestrogen plus progesterone) is not statistically significant. However, in clinical studies benefit is likely to have been underestimated because most women received oral oestrogen, typically conjugated equine oestrogen, with or without a synthetic progestin. In the only study that has assessed dementia risk in women treated with body-identical hormones, formulations containing 17 β -oestradiol +/- progesterone were associated with greater reductions in the risk of combined neurodegenerative diseases including Alzheimer's disease.¹⁵ Evidence suggests that the risk of dementia is lower in women who use HRT for more than 10 years.¹⁴⁻¹⁵**

Menopause symptom relief is a key benefit of HRT that is not included here. There is also mounting evidence that HRT may prevent or reduce the risk of other long-term health conditions such as Parkinson's disease, arthritis, lung cancer, and colorectal cancer. The long-term conditions listed above are those for which there is the strongest evidence of benefit. This information is based upon the best currently available evidence.

References

1. Age-specific death rate per 1,000 population in the United Kingdom in 2020, by gender. Available at: <https://www.statista.com/statistics/1125118/death-rate-united-kingdom-uk-by-age/> Accessed 21st November 2022.
2. Boardman HM, Hartley L, Eisinga A, Main C, Roqué i Figuls M, Bonfill Cosp X, Gabriel Sanchez R, Knight B. Hormone therapy for preventing cardiovascular disease in post-menopausal women. Cochrane Database Syst Rev. 2015 Mar 10;(3):CD002229. doi: 10.1002/14651858.CD002229.pub4. PMID: 25754617.
3. Mikkola TS, Tuomikoski P, Lyytinen H, Korhonen P, Hoti F, Vattulainen P, Gissler M, Ylikorkala O. Estradiol-based postmenopausal hormone therapy and risk of cardiovascular and all-cause mortality. Menopause. 2015 Sep;22(9):976-83. doi: 10.1097/GME.0000000000000450. PMID: 25803671
4. Medicines and Healthcare Products Regulatory Agency. Table 2 Detailed summary of relative and absolute risks and benefits during current use from age of menopause and up to age 69, per 1000 women with 5 years of 10 years use of HRT. Available at: <https://assets.publishing.service.gov.uk/media/5d680384ed915d53b8ebdba7/table2.pdf> Accessed 21st November 2022.
5. Mueck AO. Postmenopausal hormone replacement therapy and cardiovascular disease: the value of transdermal estradiol and micronized progesterone. Climacteric. 2012 Apr;15 Suppl 1:11-7. doi: 10.3109/13697137.2012.669624. PMID: 22432811.
6. Hodis HN, Mack WJ. Menopausal Hormone Replacement Therapy and Reduction of All-Cause Mortality and Cardiovascular Disease: It Is About Time and Timing. Cancer J. 2022 May-Jun 01;28(3):208-223. doi: 10.1097/PPO.0000000000000591. PMID: 35594469; PMCID: PMC9178928.
7. International Diabetes Federation. IDF Diabetes Atlas, 9th edn. Brussels, Belgium: International Diabetes Federation, 2019. <http://www.diabetesatlas.org> ; last accessed on June 17 2024.
8. Salpeter SR, Walsh JM, Ormiston TM, Greyber E, Buckley NS, Salpeter EE. Meta-analysis: effect of hormone-replacement therapy on components of the metabolic syndrome in postmenopausal women. Diabetes Obes Metab. 2006 Sep;8(5):538-54. doi: 10.1111/j.1463-1326.2005.00545.x. PMID: 16918589.
9. Mauvais-Jarvis F, Manson JE, Stevenson JC, Fonseca VA. Menopausal Hormone Therapy and Type 2 Diabetes Prevention: Evidence, Mechanisms, and Clinical Implications. Endocr Rev. 2017 Jun 1;38(3):173-188. doi: 10.1210/er.2016-1146. PMID: 28323934; PMCID: PMC5460681.
10. Pentti K, Tuppurainen MT, Honkanen R, Sandini L, Kröger H, Alhava E, Saarikoski S. Hormone therapy protects from diabetes: the Kuopio osteoporosis risk factor and prevention study. Eur J Endocrinol. 2009 Jun;160(6):979-83. doi: 10.1530/EJE-09-0151. Epub 2009 Mar 25. PMID: 19321660.
11. Manson JE, Chlebowski RT, Stefanick ML, Aragaki AK, Rossouw JE, Prentice RL, Anderson G, Howard BV, Thomson CA, LaCroix AZ, Wactawski-Wende J, Jackson RD, Limacher M, Margolis KL, Wassertheil-Smoller S, Beresford SA, Cauley JA, Eaton CB, Gass M, Hsia J, Johnson KC, Kooperberg C, Kuller LH, Lewis CE, Liu S, Martin LW, Ockene JK, O'Sullivan MJ, Powell LH, Simon MS, Van Horn L, Vitolins MZ, Wallace RB. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. JAMA. 2013 Oct 2;310(13):1353-68. doi: 10.1001/jama.2013.278040. PMID: 24084921; PMCID: PMC3963523.
12. Zhu L, Jiang X, Sun Y, Shu W. Effect of hormone therapy on the risk of bone fractures: a systematic review and meta-analysis of randomized controlled trials. Menopause. 2016 Apr;23(4):461-70. doi: 10.1097/GME.0000000000000519. PMID: 26529613
13. Wittenberg R, Hu B, Barraza-Araiza L, Rehili A. Projections of older people with dementia and costs of dementia care in the United Kingdom, 2019-2040. CPEC Working Paper 5. Care Policy and Evaluation Centre, London School of Economics and Political Science. November 2019. Available at: https://www.alzheimers.org.uk/sites/default/files/2019-11/cpec_report_november_2019.pdf
14. Nerattini M, Jett S, Andy C, Carlton C, Zarate C, Boneu C, Battista M, Pahljani S, Loeb-Zeitlin S, Havryulik Y, Williams S, Christos P, Fink M, Brinton RD, Mosconi L. Systematic review and meta-analysis of the effects of menopause hormone therapy on risk of Alzheimer's disease and dementia. Front Aging Neurosci. 2023 Oct 23;15:1260427.
15. Kim YJ, Soto M, Branigan GL, Rodgers K, Brinton RD. Association between menopausal hormone therapy and risk of neurodegenerative diseases: Implications for precision hormone therapy. Alzheimers Dement (N Y). 2021 May 13;7(1):e12174. doi: 10.1002/trc2.12174. PMID: 34027024; PMCID: PMC8118114.

Understanding the risks of HRT

Breast cancer

23 cases of breast cancer in women aged 50–59 per 1,000 women over five years¹



An additional 4 cases in women who use combined HRT consisting of oral oestrogen with a synthetic progestogen¹



4 fewer cases in women who use oral oestrogen alone¹



No additional cases in women who use oestrogen with body-identical progesterone for up to 5 years^{2,3*}



*It is not currently possible to quantify breast cancer risk in women who use body-identical progesterone for more than 5 years due to a lack of long-term safety data.

Venous thrombo-embolism (VTE) Women aged 50–59

5 cases of VTE per 1000 women aged 50–59 over 5 years⁴



An additional 1.5 cases in women who use oral oestrogen only for 5 years⁴



An additional 7 cases who use combined HRT consisting of an oral oestrogen with a synthetic progestogen for 5 years⁴



No evidence of increased risk in women aged 50–59 who use transdermal oestrogen with or without body-identical progesterone or dydrogesterone^{5–7}



Venous thrombo-embolism (VTE) Women aged 60–69

8 cases of VTE per 1000 women aged 60–69 over 5 years⁴



An additional 2.5 cases in women who use oral oestrogen only for 5 years⁴



An additional 10 cases who use combined HRT consisting of an oral oestrogen with a synthetic progestogen for 5 years⁴



No evidence of increased risk in women aged 60–69 who use transdermal oestrogen with or without body-identical progesterone or dydrogesterone^{5–7}



Stroke

Women aged 50–59

4 cases of stroke per 1000 women aged 50–59 each year ⁴



No additional cases in women aged 50–59 who initiate HRT within 10 years of the menopause ^{8–10*}



*This is true for all types and combinations of HRT. In the Women's Health Initiative (WHI) study there was no increased risk of stroke in women aged 50–59 who used an oral oestrogen combined with a synthetic progestogen.⁸ Observational studies have reported no increased risk of stroke in women aged 50–59 using transdermal oestrogen with or without a progestogen.^{9–10} The event rate in women aged 50–59 in clinical studies is low. Stroke risk in younger women is linked to thromboembolic risk.¹¹ Transdermal oestrogen and body-identical progesterone are not associated with an increased risk of thrombosis and are the safest options.⁷

Stroke

Women aged 60–69

9 cases of stroke per 1000 women aged 60–69 each year ⁴



4.5 additional cases per 1000 women aged 60–69 who start HRT more than 10 years after the menopause and use an oral oestrogen alongside a progestogen ⁸



No additional cases in women aged 60–69 using transdermal oestrogen +/- progestogen ^{10, 12*}



*A single observational study has reported a small increased risk of stroke in older women who used higher doses of transdermal oestrogen (> 50mcg patch twice weekly; +2 additional cases per 1000 women per year) ¹². The event rate was very low – just 103 of 15,710 cases of stroke occurred in women using transdermal oestrogen, and the authors did not report the duration of use, age of initiation or type of progestogen. More research is needed to explore stroke risk associated with body-identical hormones in older women.

These figures are based on the best currently available evidence. Mounting observational study data suggests that body-identical hormones are safer and associated with fewer risks, but randomised clinical trials are needed to confirm and quantify these findings. For more information and evidence-based support for your perimenopause and menopause, download the free balance app available on the App Store or Google Play.

References

1. Women's Health Concern. Understanding the risks of breast cancer. Available at: <https://thebms.org.uk/wp-content/uploads/2016/04/WHC-UnderstandingRisksOfBreastCancer-MARCH2017.pdf> Accessed 21st November 2022.
2. Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. *Breast Cancer Res Treat.* 2008 Jan;107(1):103–11. doi: 10.1007/s10549-007-9523-x. Epub 2007 Feb 27. Erratum in: *Breast Cancer Res Treat.* 2008 Jan;107(2):307–8. PMID: 17333341; PMCID: PMC2211383.
3. Abenham HA, Suissa S, Azoulay L, Spence AR, Czuzoj-Shulman N, Tulandi T. Menopausal Hormone Therapy Formulation and Breast Cancer Risk. *Obstet Gynecol.* 2022 Jun 1;139(6):1103–1110. doi: 10.1097/AOG.0000000000004723. Epub 2022 May 3. PMID: 35675607.
4. Medicines and Healthcare Products Regulatory Agency. Table 2 Detailed summary of relative and absolute risks and benefits during current use from age of menopause and up to age 69, per 1000 women with 5 years of 10 years use of HRT. Available at: <https://assets.publishing.service.gov.uk/media/5d680384ed915d53b8ebdba7/table2.pdf> Accessed 21st November 2022.
5. Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. *BMJ.* 2019 Jan 15;364:l162. doi: 10.1136/bmj.l162. Erratum for: *BMJ.* 2019 Jan 9;364:k4810. PMID: 30647094; PMCID: PMC6333215.
6. Canonico M, Plu-Bureau G, Lowe GD, Scarabin PY. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. *BMJ.* 2008 May 31;336(7655):1227–31. doi: 10.1136/bmj.39555.441944.BE. Epub 2008 May 20. PMID: 18495631; PMCID: PMC2405857.
7. Scarabin PY. Progestogens and venous thromboembolism in menopausal women: an updated oral versus transdermal estrogen meta-analysis. *Climacteric.* 2018 Aug;21(4):341–345. doi: 10.1080/13697137.2018.1446931. Epub 2018 Mar 23. PMID: 29570359.
8. Rossouw JE, Prentice RL, Manson JE, Wu L, Barad D, Barnabei VM, Ko M, LaCroix AZ, Margolis KL, Stefanick ML. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA.* 2007 Apr 4;297(13):1465–77. doi: 10.1001/jama.297.13.1465. Erratum in: *JAMA.* 2008 Mar 26;299(12):1426. PMID: 17405972.
9. Canonico M, Carcaillon L, Plu-Bureau G, Oger E, Singh-Manoux A, Tubert-Bitter P, Elbaz A, Scarabin PY. Postmenopausal Hormone Therapy and Risk of Stroke: Impact of the Route of Estrogen Administration and Type of Progestogen. *Stroke.* 2016 Jul;47(7):1734–41. doi: 10.1161/STROKEAHA.116.013052. Epub 2016 Jun 2. PMID: 27256671; PMCID: PMC4927222.
10. Løkkegaard E, Nielsen LH, Keiding N. Risk of Stroke With Various Types of Menopausal Hormone Therapies: A National Cohort Study. *Stroke.* 2017 Aug;48(8):2266–2269. doi: 10.1161/STROKEAHA.117.017132. Epub 2017 Jun 16. Erratum in: *Stroke.* 2018 Mar;49(3):e142. PMID: 28626058.
11. Lobo RA, Clarkson TB. Different mechanisms for benefit and risk of coronary heart disease and stroke in early postmenopausal women: a hypothetical explanation. *Menopause.* 2011 Feb;18(2):237–40. PMID: 21341399.
12. Renoux C, Dell'aniello S, Garbe E, Suissa S. Transdermal and oral hormone replacement therapy and the risk of stroke: a nested case-control study. *BMJ.* 2010 Jun 3;340:c2519. doi: 10.1136/bmj.c2519. PMID: 20525678.

newson

education



Confidence in Menopause

Confidence in Menopause is a CPD-accredited online course designed to increase your knowledge of, and confidence in, managing all aspects of perimenopause and menopause.

The course features study-based modules to reflect the breadth of menopause care, including patients presenting with physical and psychological symptoms of menopause, and patients with a history of other health conditions such as migraine, endometriosis and breast cancer.



newson.health



Newson Health

