Effectiveness and safety of menopause treatments: Pitfalls of available evidence and future research need.

Bassel H.Al Wattar[1,2], Ewelina Rogozińska[3], Clare Vale[3], David Fisher[3], Irene Petersen[4], Shibani Nicum[5], Daniela Bannington[6], Vikram Talaulikar[7], Nick Freemantle[2].

[1]Beginnings Assisted Conception Unit, Epsom and St Helier University Hospitals, London, UK

[2]Institute for Clinical Trials and Methodology, University College London, London, UK

[3]MRC CTU, Institute for Clinical Trials and Methodology, University College London, London, UK

[4] Primary Care & Population Health, Institute of Epidemiology & Health, University College London Hospitals, London, UK

[5]Research Department of Oncology, Cancer Institute, University College London Hospitals, London, UK

[6] Healthy whole me, London, UK

[7]Reproductive Medicine Unit, Institute for Women's Health, University College London Hospitals, London, UK

Corresponding author: Bassel H. Al Wattar, Beginnings Assisted Conception Unit, Epsom and St Helier University Hospitals, London, UK. Email: b.wattar@nhs.net.

Keywords: menopause, hormonal therapy, evidence synthesis, patient involvement, research priorities.

Funding: None.

Conflict of interest: NF declares grants from several research funders in the United Kingdom in addition to consultation fees from pharmaceutical companies. No direct funds received towards this work. All other authors declare no conflict of interest.

Abstract:

By 2050 more than 1.6 billion women worldwide will be in the post-reproductive age with >75% reporting severe menopausal symptoms. The last few years saw a gradual uplift in public awareness reaffirming the health needs of women with menopause. Still, effective translation of available evidence on menopause treatments is hindered by several methodological limitations and poor research conduct. We argue that a paradigm shift is required in menopause research to address the remaining knowledge gap and guide safe evidence-based care provision. A critical misconception across studies on menopause is the assumption that women represent a homogenous group who respond similarly to a particular therapy irrespective of their exposure and individual risk factors. We highlight potential solutions to optimise the quality of future research in menopause including adopting robust trial methodology, standardise outcome reporting to capture quality of life measures, and improve lay patient and public involvement in future research.

Introduction:

By 2050, it is estimated that 1.6 billion women worldwide will be in the post-reproductive menopause phase of life with >75% reporting severe symptoms (hot flushes, night sweats, brain fog, muscle and joint pain, low mood, irritability, reduced libido, and vulvovaginal dryness) negatively affecting their quality of life (1). Left unmanaged, menopausal symptoms can have a detrimental effect on women's wellbeing, mental health, and their effective participation in society (2,3).

The topic of menopause has been seldom discussed and most women never sought help and took it upon themselves to bare through ''the change'' in silence. The last few years saw a gradual uplift in public awareness reaffirming the health needs of women in post-reproductive years which helped many to break existing taboos and seek the support they need to enjoy healthier more productive lives (4).

As the tide changes, there is a rising risk of overusing some menopausal treatments (especially hormonal ones) outside the boundaries of available evidence (5). Increasing demand is also fuelling questionable clinical practice offering unconventional treatments with a limited body of evidence to back their effectiveness and safety(6).

We argue that a paradigm shift is required in menopause research and evidence synthesis to address the remaining knowledge gap and guide safe evidence-based care provision to affected women. We analyse current pitfalls, propose future solutions, and advocate for the safe evidence-based menopause treatments that directly address the health needs of women with menopause.

State of the art

A third of the female population is currently in the post reproductive years with a rising trend worldwide (8). While common, the management of menopause symptoms receives much less research investment compared to other women's health issues such as pregnancy and childbirth. While a large volume of studies evaluated available treatments for menopausal symptoms (2), several methodological limitations hinder effective translation of this evidence into clinical practice.

The predominant randomised trials involving women with menopause were conducted in 1990s aiming to evaluate the effectiveness and safety of Menopause Hormonal Therapy (MHT) to prevent cardiovascular disease in the post reproductive years with much less focus on optimising women's

quality of life (9). Since then, there has been a gradual increase in the number of published randomised trials and their meta-analyses, evaluating various hormonal, non-hormonal, and non-pharmacological treatments for menopause (Figure 1). Increasing investment in menopause research reflects the rising public awareness demanding better care provision for women in the post reproductive years (10). This includes better appreciation for the role of complementary treatments(11), psychological therapy(12), and support at the workplace (13). Overall, the evidence for the effectiveness and safety of menopause treatments is gradually increasing and is helping to break taboos and establish more specialised services for women in post-reproductive years. Still, evidence translation and translation into clinical practice remain limited with much misinformation and a persistent knowledge gap(14,15). It is therefore important to recognise the methodological limitations and ground clinical practice within its remits.

Suboptimal trial design, conduct and reporting

The early 2000s saw a peak of randomised trials evaluating various menopausal treatments (Figure 1). Majority of these trials were too small to capture important safety outcomes reliably (sample size <500 women), observed a short follow up period (<4 years), and suffered from low external validity (16–18)

To date, a handful of large trials have dominated the discourse on MHT, significantly influencing the findings of published meta-analyses (18) including the Women's Health Initiative (WHI) trials (19,20), the Heart and Estrogen/progestin Replacement Study (HERS)(21), and the Main morbidities recorded in the women's international study of long duration oestrogen after menopause (WISDOM) (22). The publication of the WHI trial led to a rapid decline in the use of MHT worldwide with several health regulators issuing warnings limiting its use in the early 2000s (9).

Unfortunately, most of these large trials suffered from several methodological limitations that significantly impact their external validity and relevance as they evaluated synthetic forms of MHT which are less relevant to contemporary practice, were stopped early, had high loss to follow-up, and failed to adequately account for missing outcomes.

A critical misconception across these trials was the assumption that women in the post-reproductive years are a homogenous group who respond similarly to any hormonal therapy irrespective of their age at time of menopause, cause of menopause (e.g. surgical vs natural), time of starting the treatment since the last period, or the time since the treatment was stopped until the outcome of interest (e.g. cancer) was observed (i.e. recency). Appropriate adjustment for these effect-modifiers proved crucial following the re-analysis of the WHI challenged its conclusion after adjusting for time of starting the treatment since the last period highlighting the potentially beneficial effect of MHT if started within the optimal window of opportunity (23,24). Of course, this post hoc finding requires prospective confirmation.

Early termination and high loss to follow-up substantially affect the internal validity and power of randomised trials in menopause for evaluating key long term safety outcomes (e.g. cardiovascular disease and cancer). For example, to date only four trials (25) evaluated the safety of MHT in women who survived breast cancer. Two of these trials were stopped early for safety reasons and one

suffered from high loss to follow-up which substantially limited the impact of subsequent evidence synthesis (25).

This emphasises the need to adopt a robust trial methodology, with oversight from independent monitoring committees to implement a clear safety and trial continuation criteria. Several decision aid tools could be employed to boost recruitment strategies, minimise risk of failure, and loss to follow up such as Studies Within A Trial (26) and QuinteT Recruitment Intervention (27). There is a need to adopt sophisticated trial analysis methodology that accounts for key participants' characteristics, treatment adherence, and other potential effect modifiers. Investing in long-term follow-ups of randomised cohorts is also important to capture accurately long-term safety outcomes associated with menopause, a practice seldom reported across published trials to date.

Selective outcome reporting and measurement tools

Varied and selective outcome reporting increases bias, research wastage and reduces confidence in synthesised evidence (28). This is particularly relevant in menopause research where early trials were focused on evaluating surrogate outcomes of adverse health conditions (e.g. carotid intima-media thickness as indirect measure of cardiovascular health) often using different measurement instruments (29). While the focus is gradually moving towards evaluating treatments aimed to optimise women's quality of life in the post-reproductive years, there are still no standardised and validated instruments to capture these outcomes(30)(31). Investing resources to develop and validate such tools will help to optimise the quality of future trials particularly as the prospective trial data sharing becomes mainstream to enable robust large scale data pooling and evidence synthesis.

The development and implementation of a core set of minimally reported outcomes is a welcomed solution to mitigate this problem aiming to standardised and harmonise outcome reporting (32). While promising, adoption of this core outcome set remains unclear with no trials reporting its use in published outputs to date. Research funders, publishers, and journal editors have a major role in promoting the adoption of this standardised outcome reporting as well as encouraging open-source data sharing (33,34).

Poor data pooling methodology

Given the highlighted methodological limitations in available trials on menopause treatments, it is not surprising that the majority of their meta-analyses suffered from significant heterogeneity, high risk of bias, and imprecision (2,17,18).

Unfortunately, most of these meta-analyses adopted the same oversimplified assumption that all women with menopause represent a single homogenous group with similar characteristics and treatment response. This is unsurprising a most of these meta-analyses were performed retrospectively using aggregate published data.

Furthermore, there has been a systematic failure to account for key treatment effect-modifiers, independent explanatory variables, and confounders (Table 1) that could significantly influence the effect estimates across evaluated outcomes.

More recent meta-analyses applied meta-regression methodology to explore potential effect modifiers within subgroups and sensitivity analyses. However, such methodology has substantial limitations methodologically given the limited number of studies and the potential for ecological bias. It is also hampered by the varied reporting across primary randomised trials and observational studies (35). Individual patient data meta-analyses will substantially help to resolve this uncertainty across key subgroups of interest; however, they are difficult and laborious to execute (36). For example, a recent individual patient data meta-analysis of 108 647 women evaluated the impact of the type and timing of MHT on the risk of breast cancer among users and past users (37). The analysis suggested a higher risk of breast cancer with the use of combined MHT (oestrogen plus progestogen) after 5 years of use, unfortunately it did not account for the type of progestogen used (bioidentical vs synthetic) which may could also have a significant impact on the risk of cancer (38).

Using a prospective adaptive meta-analysis approach could offer more homogenous evidence synthesis (39), but it requires effective collaboration among trialists to enable effective data sharing. Proactive data sharing coupled with careful consideration for relevant effect modifiers, is therefore key to enable better quality evidence synthesis that could directly inform menopause care provision.

Lay patient and public involvement

Earlier trials evaluating menopause treatment were focused on evaluating objective biological outcomes such as the incidence of cardiovascular or thrombotic events with the use of MHT (9). Gradually, the focus shifted towards patient reported and quality of life outcomes such as control of vasomotor symptoms and cognitive abilities (31,40). While this reflects the increasing public interest in optimising women's quality of life in the post-reproductive years, it also highlights the absences of patient voice in older trials and the narrow focus driven primarily by clinicians.

Several key stakeholders are promoting the culture of effective patient and public involvement in health research including professional health societies (41), governmental bodies (42) and public research funders (43). While promising, this practice is yet to gain momentum in menopause research. In addition to standardising the report of quality-of-life outcome measures in future studies (31), there is a need to actively engage women with menopause in the design, conduct, analysis, interpretation and reporting of future research. This particularly relevant to maximise research impact and address the true health needs of under-represented groups such as ethnic minorities, patients with fluid gender, and those in low income countries with limited access to menopause treatments. These initiatives require institutional support to define the health and research priorities of women with menopause (44), develop a true partnership across relevant stakeholders (45), and specific toolkits to enable research co-production(46).

Conclusion

The use of menopause treatments should be governed and expressed within the limitations of available evidence for their effectiveness and safety. A more nuanced and robust evidence synthesis is needed to acknowledge and account for the varied characteristics of women with menopause, available treatments, and other potential effect modifiers. A proactive collaboration with patients

and the lay public is needed to refine the health research need, increase research impact, and enable more individualised menopause care provision.

Pending future better-quality research, health practitioners should refrain from offering or promoting treatments outside the boundaries of available evidence of safety.

Acknowledgement: None.

Funding: None.

Disclosure: All authors report no conflict of interest.

References:

1. Anagnostis P, Bitzer J, Cano A, Ceausu I, Chedraui P, Durmusoglu F, et al. Menopause symptom management in women with dyslipidemias: an EMAS clinical guide. Maturitas. 2020;135:82–8.
2. Zhang GQ, Chen JL, Luo Y, Mathur MB, Anagnostis P, Nurmatov U, et al. Menopausal hormone therapy and women's health: An umbrella review. Vol. 18, PLoS Medicine. Public Library of Science; 2021.
3. Verdonk P, Bendien E, Appelman Y. Menopause and work: A narrative literature review about menopause, work and health. Work. 2022;(Preprint):1–14.
4. Hogervorst E, Craig J, O'Donnell E. Cognition and mental health in menopause: A review. Best Pract Res Clin Obstet Gynaecol. 2022;81:69–84.
5. National Institute For Health and Care Excellence. Menopause: diagnosis and management. 2019;
6. The Lancet Diabetes & Endocrinology. Menopause: a turning point for women's health. Lancet Diabetes Endocrinol [Internet]. 2022 Jun 1 [cited 2023 Jun 3];10(6):373. Available from: http://www.thelancet.com/article/S2213858722001425/fulltext
7. The British Menopause Society. Joint BMS FSRH RCGP RCOG SfE and RCN Women's Health Forum safety alert. 2023.
8. Menopause [Internet]. [cited 2023 May 8]. Available from: https://www.who.int/news-room/fact-sheets/detail/menopause
9. Cagnacci A, Venier M. The Controversial History of Hormone Replacement Therapy. Medicina (B Aires) [Internet]. 2019 Sep 1 [cited 2023 May 8];55(9). Available from: /pmc/articles/PMC6780820/
10. Hickey M, Hunter MS, Santoro N, Ussher J. Normalising menopause. BMJ [Internet]. 2022 Jun 15 [cited 2023 May 11];377. Available from: https://www.bmj.com/content/377/bmj-2021-069369
11. Guo PP, Li P, Zhang XH, Liu N, Wang J, Chen DD, et al. Complementary and alternative medicine for natural and treatment-induced vasomotor symptoms: An overview of systematic reviews and meta-analyses. Complement Ther Clin Pract. 2019 Aug 1;36:181–94.
12. Hogervorst E, Craig J, O'Donnell E. Cognition and mental health in menopause: A review. Best Pract Res Clin Obstet Gynaecol. 2022 May 1;81:69–84.
13. Jack G, Riach K, Bariola E, Pitts M, Schapper J, Sarrel P. Menopause in the workplace: What employers should be doing. Maturitas. 2016 Mar 1;85:88–95.
14. Temkin SM, Mallen A, Bellavance E, Rubinsak L, Wenham RM. The role of menopausal hormone therapy in women with or at risk of ovarian and breast cancers: Misconceptions and current directions. Cancer [Internet]. 2019 Feb 15 [cited 2023 May 11];125(4):499–514. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/cncr.31911

15. Weiss R. Menopause and social media: Pros and cons for the general public. Maturitas [Internet]. 2023 Mar [cited 2023 May 11];0(0). Available from: http://www.maturitas.org/article/S0378512223000373/fulltext

16. Furness S, Roberts H, Marjoribanks J, Lethaby A. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. Cochrane Database of Systematic Reviews [Internet]. 2012 Aug 15 [cited 2023 May 8];(8). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD000402.pub4/full

17. Sare GM, Gray LJ, Bath PMW. Association between hormone replacement therapy and subsequent arterial and venous vascular events: a meta-analysis. Eur Heart J [Internet]. 2008 Aug 1 [cited 2023 May 8];29(16):2031–41. Available from: https://academic.oup.com/eurheartj/article/29/16/2031/409204

18. Marjoribanks J, Farquhar C, Roberts H, Lethaby A, Lee J. Long-term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database Syst Rev [Internet]. 2017 Jan 17 [cited 2023 May 8];2017(1). Available from: /pmc/articles/PMC6465148/

19. GL A, M L, AR A, T B, SA B, H B, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA [Internet]. 2004 Apr 14 [cited 2023 May 8];291(14):1701–12. Available from: https://pubmed.ncbi.nlm.nih.gov/15082697/

20. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA [Internet]. 2002 Jul 17 [cited 2023 May 8];288(3):321–33. Available from: https://pubmed.ncbi.nlm.nih.gov/12117397/

21. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA [Internet]. 1998 Aug 19 [cited 2023 May 8];280(7):605–13. Available from: https://pubmed.ncbi.nlm.nih.gov/9718051/

22. Vickers MR, MacLennan AH, Lawton B, Ford D, Martin J, Meredith SK, et al. Main morbidities recorded in the women's international study of long duration oestrogen after menopause (WISDOM): a randomised controlled trial of hormone replacement therapy in postmenopausal women. BMJ [Internet]. 2007 Aug 4 [cited 2023 May 8];335(7613):239–44. Available from: https://pubmed.ncbi.nlm.nih.gov/17626056/

23. Stevenson JC, Hodis HN, Pickar JH, Lobo RA. Coronary heart disease and menopause management: the swinging pendulum of HRT. Atherosclerosis [Internet]. 2009 Dec [cited 2023 May 8];207(2):336–40. Available from: https://pubmed.ncbi.nlm.nih.gov/19560146/

24. Hsia J, Langer RD, Manson JAE, Kuller L, Johnson KC, Hendrix SL, et al. Conjugated equine estrogens and coronary heart disease: the Women's Health Initiative. Arch Intern Med [Internet]. 2006 Feb 13 [cited 2023 May 8];166(3):357–65. Available from: https://pubmed.ncbi.nlm.nih.gov/16476878/

25. Poggio F, Del Mastro L, Bruzzone M, Ceppi M, Razeti MG, Fregatti P, et al. Safety of systemic hormone replacement therapy in breast cancer survivors: a systematic review and meta-

analysis. Breast Cancer Res Treat [Internet]. 2022 Jan 1 [cited 2023 May 8];191(2):269–75. Available from: https://pubmed.ncbi.nlm.nih.gov/34731351/

26. Treweek S, Bevan S, Bower P, Campbell M, Christie J, Clarke M, et al. Trial Forge Guidance 1: What is a Study Within A Trial (SWAT)? Trials [Internet]. 2018 Feb 23 [cited 2023 May 8];19(1):1–5. Available from: https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-018-2535-5

27. Donovan JL, Jepson M, Rooshenas L, Paramasivan S, Mills N, Elliott D, et al. Development of a new adapted QuinteT Recruitment Intervention (QRI-Two) for rapid application to RCTs underway with enrolment shortfalls—to identify previously hidden barriers and improve recruitment. Trials [Internet]. 2022 Dec 1 [cited 2023 May 8];23(1):1–14. Available from: https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-022-06187-y

28. Prinsen CAC, Vohra S, Rose MR, Boers M, Tugwell P, Clarke M, et al. How to select outcome measurement instruments for outcomes included in a "Core Outcome Set" - a practical guideline. Trials [Internet]. 2016 Sep 13 [cited 2023 May 8];17(1):1–10. Available from: https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-016-1555-2

29. Grady D, Herrington D, Bittner V, Blumenthal R, Davidson M, Hlatky M, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). JAMA [Internet]. 2002 Jul 3 [cited 2023 May 8];288(1):49–57. Available from: https://pubmed.ncbi.nlm.nih.gov/12090862/

30. Gabes M, Knüttel H, Stute P, Apfelbacher CJ. Measurement properties of patient-reported outcome measures (PROMs) for women with genitourinary syndrome of menopause: A systematic review. Menopause [Internet]. 2019 Nov 1 [cited 2023 May 8];26(11):1342–53. Available from: https://journals.lww.com/menopausejournal/Fulltext/2019/11000/Measurement_properties_of_patient_reported_outcome.18.aspx

31. Utian WH, Woods NF. Impact of hormone therapy on quality of life after menopause. Menopause [Internet]. 2013 Oct [cited 2023 May 8];20(10):1098–105. Available from: https://journals.lww.com/menopausejournal/Fulltext/2013/10000/Impact_of_hormone_therapy_on_quality_of_life_after.19.aspx

32. Lensen S, Archer D, Bell RJ, Carpenter JS, Christmas M, Davis SR, et al. A core outcome set for vasomotor symptoms associated with menopause: the COMMA (Core Outcomes in Menopause) global initiative. Menopause [Internet]. 2021 Aug 26 [cited 2023 Mar 29];28(8):852–8. Available from: https://journals.lww.com/menopausejournal/Fulltext/2021/08000/A_core_outcome_set_for_vasomotor_symptoms.4.aspx

33. Khan K. The CROWN Initiative: journal editors invite researchers to develop core outcomes in women's health. http://dx.doi.org/103109/136971372014930570 [Internet]. 2014 Oct 1 [cited 2023 May 11];17(5):520–1. Available from: https://www.tandfonline.com/doi/abs/10.3109/13697137.2014.930570

34. Chien PFW, Khan KS. Systematic Review Reporting - Writing concisely and precisely. Pak J Med Sci [Internet]. 2023 Mar 1 [cited 2023 May 11];39(2):317. Available from: /pmc/articles/PMC10025746/

35. Godolphin PJ, White IR, Tierney JF, Fisher DJ. Estimating interactions and subgroup-specific treatment effects in meta-analysis without aggregation bias: A within-trial framework. Res Synth Methods. 2022;

36. van Walraven C. Individual patient meta-analysis-rewards and challenges. J Clin Epidemiol [Internet]. 2010 Mar 1 [cited 2023 May 8];63(3):235–7. Available from: http://www.jclinepi.com/article/S0895435609001103/fulltext

37. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. The Lancet. 2019 Sep 28;394(10204):1159–68.

38. Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of breast cancer: nested case-control studies using the QResearch and CPRD databases. BMJ [Internet]. 2020 Oct 28 [cited 2023 Mar 29];371. Available from: https://www.bmj.com/content/371/bmj.m3873

39. Tierney JF, Fisher DJ, Vale CL, Burdett S, Rydzewska LH, Rogozińska E, et al. A framework for prospective, adaptive meta-analysis (FAME) of aggregate data from randomised trials. PLoS Med [Internet]. 2021 May 1 [cited 2023 Mar 29];18(5):e1003629. Available from: https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1003629

40. Cintron D, Lipford M, Larrea-Mantilla L, Spencer-Bonilla G, Lloyd R, Gionfriddo MR, et al. Efficacy of menopausal hormone therapy on sleep quality: systematic review and meta-analysis. Endocrine [Internet]. 2017 Mar 1 [cited 2023 May 8];55(3):702–11. Available from: https://link.springer.com/article/10.1007/s12020-016-1072-9

41. BMS RRFF and F. Challenging the culture on menopause for doctors: BMS, RCOG, RCGP, FSRH, FOM and FPH Position Statement in response to the BMA report. 2020.

42. Department of Health and Social Care. Women's Health Strategy for England. 2022.

43. Russell J, Greenhalgh T, Taylor M. Patient and public involvement in NIHR research 2006–2019: policy intentions, progress and themes. 2019;

44. Graham L, Illingworth BJG, Showell M, Vercoe M, Crosbie EJ, Gingel LJ, et al. Research priority setting in women's health: a systematic review. BJOG [Internet]. 2020 May 1 [cited 2023 May 11];127(6):694–700. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/1471-0528.16150

45. Moss N, Daru J, Lanz D, Thangaratinam S, Khan KS. Involving pregnant women, mothers and members of the public to improve the quality of women's health research. BJOG [Internet]. 2017 Feb 1 [cited 2023 May 11];124(3):362–5. Available from: https://pubmed.ncbi.nlm.nih.gov/27862921/

46. Bagley HJ, Short H, Harman NL, Hickey HR, Gamble CL, Woolfall K, et al. A patient and public involvement (PPI) toolkit for meaningful and flexible involvement in clinical trials – a work in progress. Res Involv Engagem [Internet]. 2016 Apr 27 [cited 2023 May 11];2(1):1–14. Available from: https://researchinvolvement.biomedcentral.com/articles/10.1186/s40900-016-0029-8

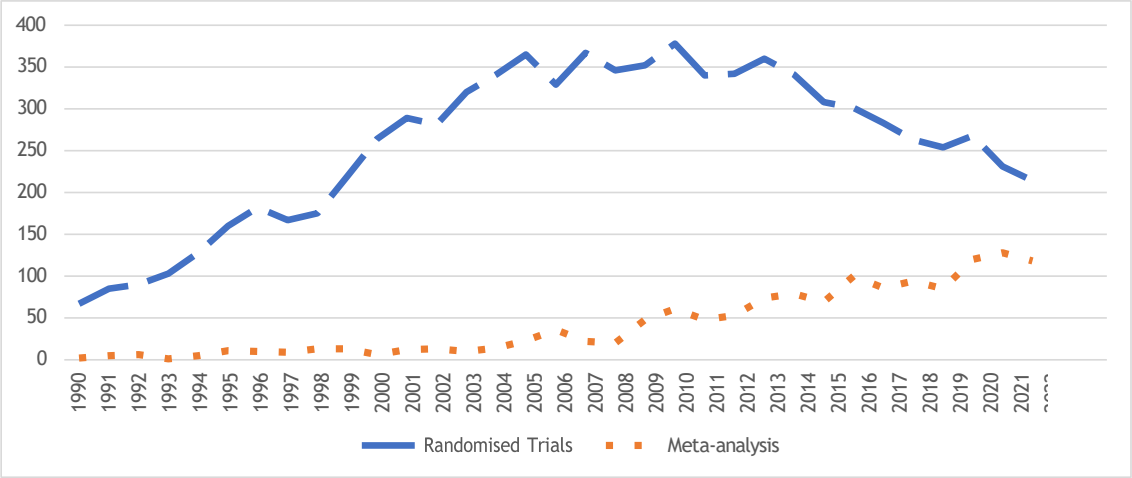

Figure 1: Line chart of the number of randomised trials and meta-analyses published yearly on menopause produced by searching Medline between 1990 and 2022.

Table 1: Key effect modifiers for consideration in future menopause research

Type	Description	Examples
Moderators (Variables that change the size (or direction) of the relationship between		Treatment dose, format, route, composition, duration of use,
Covariates	Variables that explain a part of the variability in the outcome, are not influenced by the intervention, and do not change the relationship between the intervention and the outcome. On their own, covariates predict at least part of the outcome in both the intervention group and the comparison/control group.	Recency (time since the intervention was stopped until the outcome is observed), age at time of starting the intervention, BMI, ethnicity, smoking status, alcohol consumption, socio-economic status and deprivation, morbidity, genetic pre-disposition to develop the outcome of interest.
Confounders	Variables that are related to both the intervention and the outcome, but are not on the causal pathway	Co-morbidities, data missingness, date of study conduct, treatment preference