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Traci L. Leitheiser  
*University of North Dakota*

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# The Impact of Hormone Therapy on Cardiovascular and Bone Health in Women with Premature or Early Menopause

Traci L. Leitheiser, PA-S Contributing Author: Jay Metzger, MPAS

Department of Physician Assistant Studies, University of North Dakota School of Medicine & Health Sciences, Grand Forks, ND 58202-9037



## Abstract

### Objective:

- The Women's Health Initiative (WHI) studies were a catalyst for the dramatic decline in the number of postmenopausal women being prescribed hormone therapy (HT).
- The WHI published the largest randomized, double-blind, placebo-controlled trial regarding the use of HT in postmenopausal women with a mean age of 63 years.
- One group of women thought to benefit from HT but have often been denied HT based on the WHI studies' results is premature and early menopausal women.
- The purpose of this literature review was to compare the WHI studies' results to studies that reviewed coronary heart disease (CHD) benefits, bone health benefits, and risks of HT in premature and early menopause.

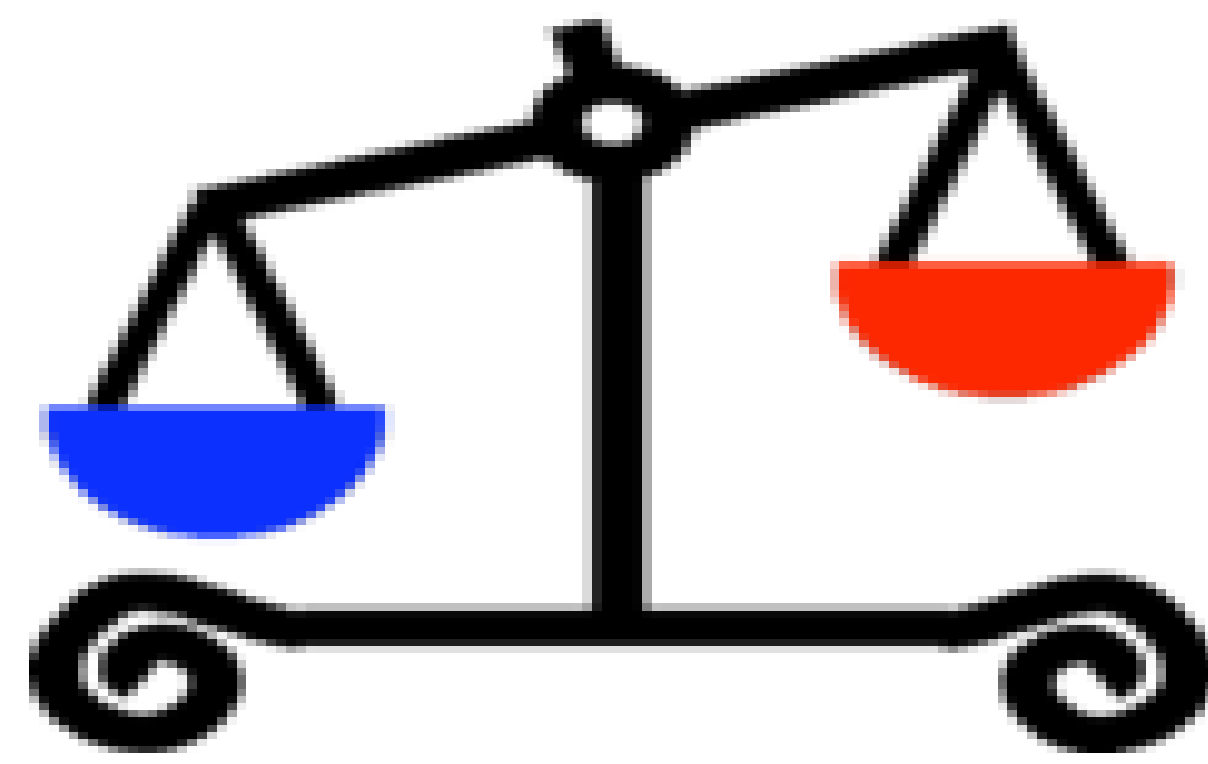
### Methods:

- Articles published in the last 22 years were initially incorporated to include the WHI studies.
- Articles were then further eliminated if they did not discuss CHD or osteoporosis in postmenopausal women less than the age of 45 years.

### Results:

- This literature review recommends individualizing the use of HT in premature and early menopausal women by evaluating their risk factors and performing a thorough review of their family history.
- Further randomized controlled trials and longitudinal studies need to be completed specifically on premature and early menopausal women to confidently substantiate the benefits of HT in the prevention of chronic diseases.

Keywords: Hormone replacement therapy, hormone therapy, menopause, osteoporosis, cardiovascular disease



## Statement of the Problem

- The Women's Health Initiative (WHI) study results significantly impacted the decline in HT prescription practices and usage.
- The harmful effects reported from the WHI study, including risks of CHD, deep venous thrombosis (DVTs), and ischemic strokes, resulted in medical providers questioning the benefits of HT.
- The WHI studies' results have left many postmenopausal women suffering from vasomotor effects, mood swings, sexual dysfunction, sleep disturbances, poor bone health, and an increased risk of cardiovascular disease (CVD).
- Because of the WHI studies, in which participants were approximately twelve years past the mean menopause age, premature and early menopausal women were not treated with HT.
- Premature and early menopausal women are at an increased risk for osteoporosis and cardiovascular disease.
- Medical providers need to be educated about the misconceptions created by the WHI studies.
- Current medical research will guide medical professionals towards individualized care in prescribing HT to women in premature and early menopause.
- Medical providers who provide evidence-based care and complete a thorough medical and family history can safely and confidently prescribe HT.

## Research Question

- First, in contrast to the age included in the WHI trial (mean age 63 years), does the use of hormone therapy versus no hormone therapy in women less than age 45 provide more benefits than risks in the prevention of osteoporosis?
- Second, in contrast to the age included in the WHI trial (mean age 63 years), does the use of hormone therapy versus no hormone therapy in women less than age 45 provide more benefits than risks in the prevention of cardiovascular disease?

## Literature Review

### WHI Studies and Implication of the Results:

- Estrogen plus progestin arm of WHI trial revealed a primary outcome for CHD with a HR of 1.29 and nominal 95% CI [1.02, 1.63] after a mean of 5.2 years (WHI, 2002). (Table 2)
- WHI study's estrogen-only arm revealed a 9% decline in CHD events, with a 25% reduction goal deemed statistically significant (WHISC, 2004).
- The risk of osteoporosis was decreased in both arms of the WHI trials, but authors concluded that the increased risk of ischemic stroke, breast cancer, and DVTs outweighed bone health benefits (WHI, 2002; WHISC, 2004). (Table 2)
- The conclusion of WHI studies was that HT should not be used for the primary prevention of chronic diseases (WHI, 2002; WHISC, 2004).

Baseline Characteristics of Women in the WHI Studies				
Characteristics	CEE-only (N = 6310)	Placebo CEE-only (N = 5429)	CEE + MPA (N = 8506)	Placebo CEE + MPA (N = 8102)
Age at screening-mean (SD), yr.	63.6	63.6	63.2	63.3
Age group 50-59 yr.	30.8	30.8	33.4	33.1
Age group 60-69 yr.	45	45.4	45.3	45.1
Age group 70-79 yr.	24.2	23.8	21.3	21.7
BMI (M, SD)	30.1	30.1	28.5	28.5
Smoking history never used	51.9	50.4	49.6	50
Smoking history past/current	48.1	49.5	50.4	50
Treated for Diabetes	7.7	7.6	4.4	4.4
Treated for HTN	48	47.4	35.7	36.4
↑ Cholesterol Levels	14.5	15.9	12.5	12.9
History of CVD	14.2	14.2	7.1	8.1
Family history of breast cancer	18	17.1	16	15.3

Table 1. By Traci Leitheiser, data from WHI (2002) and WHISC (2004). Notes: Data is presented in percent (percentage) of women unless specified. BMI indicates body mass index; CEE, conjugated equine estrogen; MPA, medroxyprogesterone acetate; CVD, cardiovascular disease; HTN, hypertension. Data rows represent risk factors that the participants in the WHI trials had prior to being placed in the hormone therapy or placebo groups.

### HT Use for Prevention of Osteoporosis in Premature/Early Menopause:

- Even though the USPSTF (2017) granted the use of HT in postmenopausal women a Grade D recommendation, they acknowledged that this recommendation should not be utilized in postmenopausal women less than the age of 45 years.
- Faubion et al. (2015) found further evidence that women who entered menopause between the ages of 40-44 years have a more considerable drop in vertebral bone mineral density (BMD) than women with natural menopause.
- Ran et al. (2017) study results revealed that early menopausal women treated with HT had a statistically significant improvement in L2-L4 BMD ( $p < .01$ ). (Table 2)

### Cardioprotective Benefits of HT in Premature/Early Menopause:

- Faubion et al. (2015) and Rivera et al. (2009) both found a link between CVD and increased mortality among premature and early menopausal women without the use of HT.
- Sullivan, Sarrel, and Nelson (2016) recommend prescribing HT to premature and early menopausal women and recommend continued use until the natural age of menopause.
- The KEEPS study concluded that HT did not significantly improve or harm postmenopausal women (Miller et al., 2019). (Table 2)

## Discussion

### Benefits of HT Use in the Prevention of Osteoporosis:

- One small sample study revealed that bone loss was two times greater in women with bilateral salpingo-oophorectomy (BSO) than women who experience natural menopause.
- Three separate studies recommended individualized HT treatment in premature and early menopausal women and agree that HT improves bone health among this population. (Table 2)
- The WHI studies did not evaluate women less than 45 years old; therefore, the benefit of bone protection could be more significant than the results showed.

### Benefits of HT Use in the Prevention of CHD:

- Harmful effects of HT seem to increase with age, which supports HT's use in premature/early menopausal women to decrease CHD events. (Figure 2)
- Women in the WHI studies being older and having increased risk factors at baseline compared to the KEEPS study women help support that HT is beneficial when started earlier (before age 60), prior to women having increased CVD risk factors. (Table 1)
- When the absolute risk is compared to relative risk, the results of the WHI studies are less significant for harmful effects of ischemic strokes, invasive breast cancer, DVTs, and reveal an improvement in CHD benefit. (Figure 1)

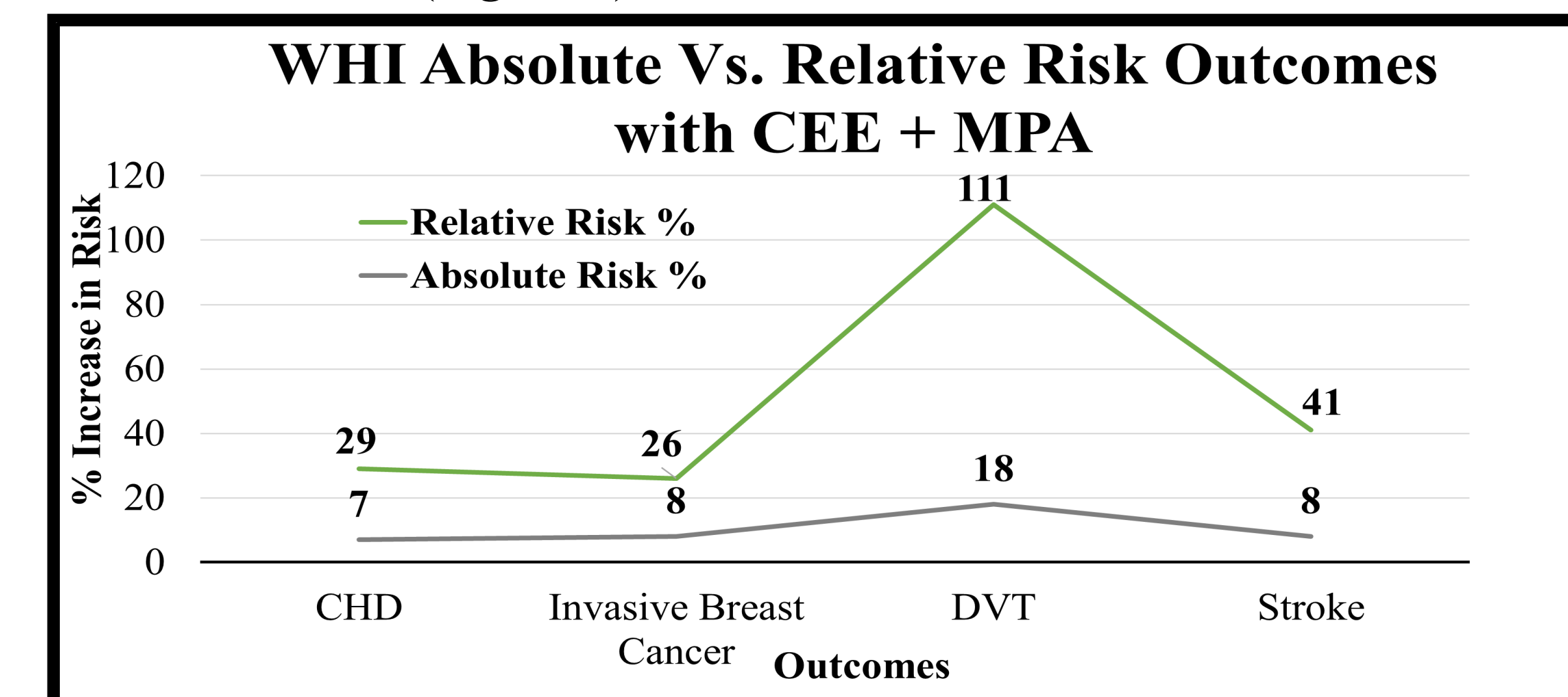


Figure 1. By Traci Leitheiser, data from WHISC (2004). Notes: WHI indicates Women's Health Initiative; CEE, conjugated equine estrogen; CHD, coronary heart disease; MPA, medroxyprogesterone acetate; DVT, deep venous thrombosis.

## Conclusion

- The results of this literature review support the use of HT in premature and early menopause.
- HT should be individualized by reviewing risk factors, past medical and family history.
- The WHI studies should not be used as treatment-based guidelines to treat premature and early menopausal women.
- Premature and early menopausal women should be started on HT at the lowest effective dose and continued until the natural age of menopause.
- More randomized controlled and longitudinal studies focused on premature and early menopausal women are needed to strengthen the evidence for HT use in this population.
- Current providers need to be educated about the WHI studies' limitations to provide high-quality, evidence-based medicine to premature and early menopausal women.

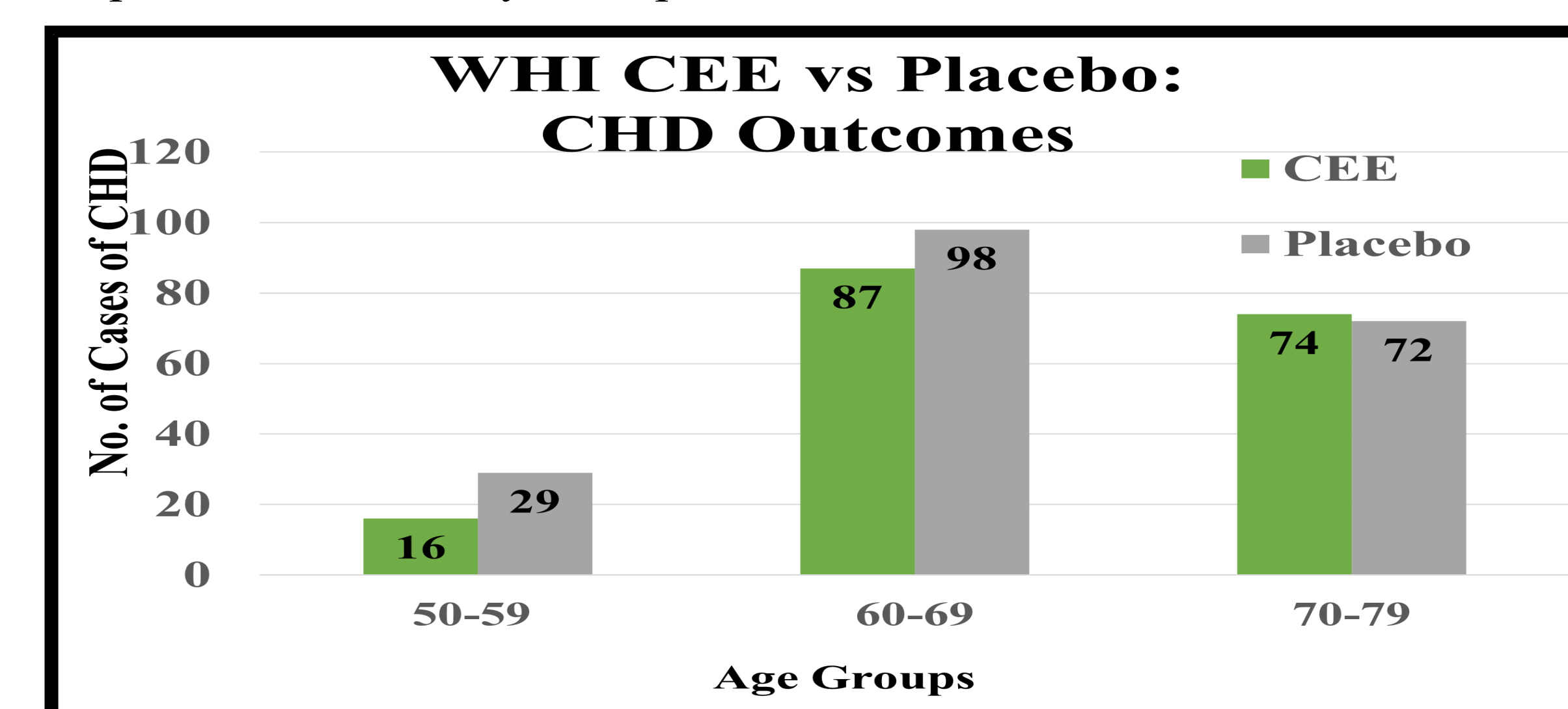


Figure 2. By Traci Leitheiser, data from WHISC (2004). Notes: WHI indicates Women's Health Initiative; CHD, coronary heart disease; CEE, conjugated equine estrogen.

Outcome Data for Reviewed Articles of HT Use					
Author (s)	No. of Women in Study	Follow-up Time (M, Yr.)	Age (M)	CHD Benefits (↑/↓)	Bone Health Benefit (↑/↓)
WHI (2002)	8605	5.2	63.2	↓	↑
WHISC (2004)	5310	6.8	63.6	↑	↑
Hadjidakis et al. (2003)	514	5 yr. periods	38.1-48.1	N/A	↑
Miller et al. (2019)	727	4	52.8	No ↑ or ↓	↑
Ran et al. (2017)	188	5	48.05-51.16	↑	↑
Sullivan et al. (2016)	4748	38	< 45	↑	↑

Table 1. By Traci Leitheiser, data from WHI (2002), WHISC (2004), Hadjidakis et al. (2003), Miller et al. (2019), Ran et al. (2017), and Sullivan et al. (2016). Notes: CHD indicates coronary heart disease; HT, hormone therapy.

## Applicability to Clinical Practice

- The information collected and presented in this literature review will help medical professionals make an evidence-based decision regarding the safety and advantageous use of HT in premature and early menopausal women. (Figure 3)
- The evidence provided in this literature review will allow medical professionals to be confident in their decision to safely prescribe HT to women with premature and early menopause.
- HT is beneficial in improving the vasomotor symptoms of menopause, prevent CHD and osteoporosis, and decrease mortality in premature and early menopausal women.

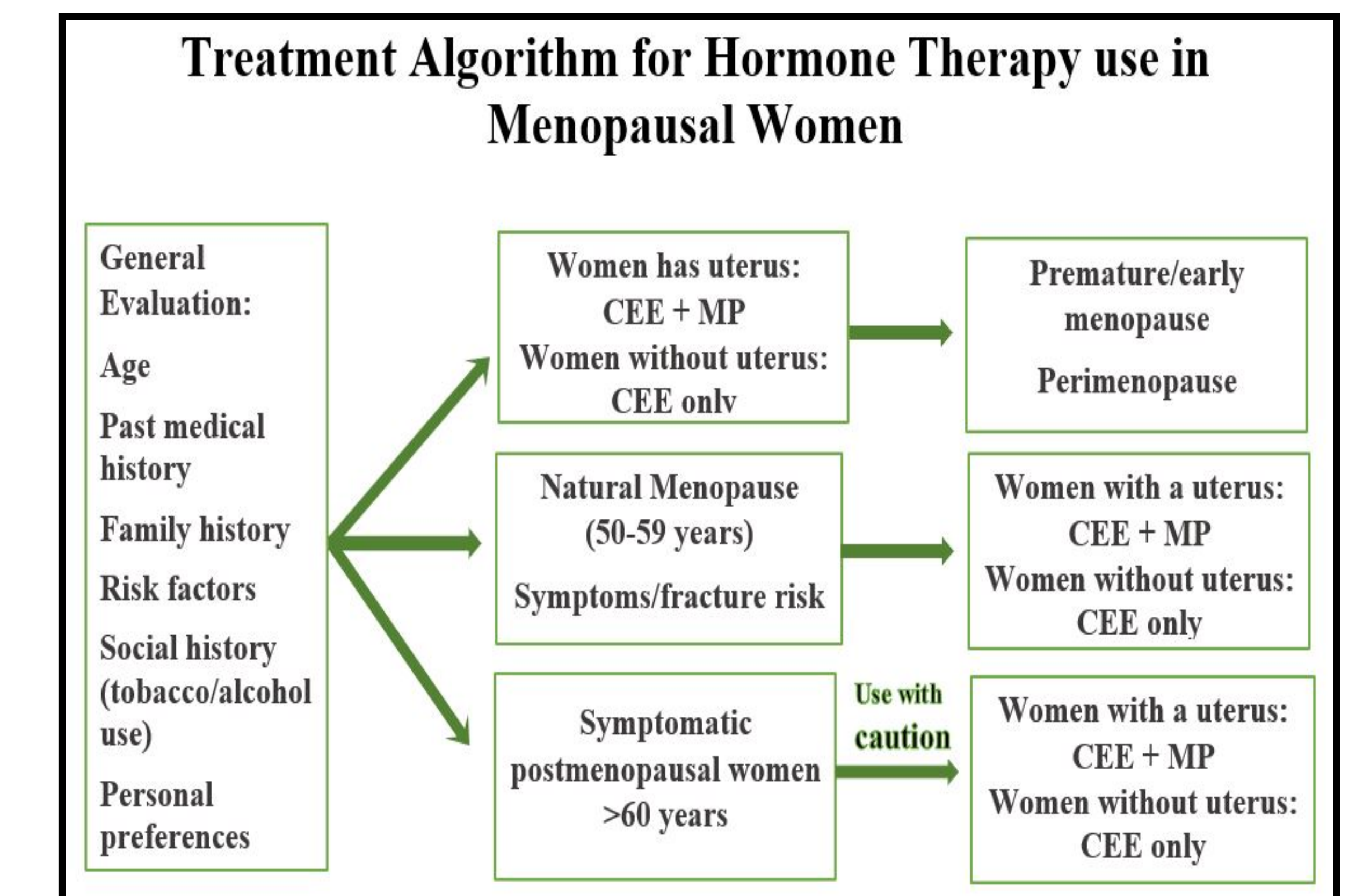


Figure 3. By Traci Leitheiser, data from Faubion et al. (2015), Hadjidakis et al. (2003), Miller et al. (2019), Ran et al. (2017), Rivera et al. (2009), Sullivan et al. (2016), USPSTF (2017), WHI (2002), and WHISC (2004). Notes: CEE indicates conjugated equine estrogen; MP, medroxyprogesterone. Premature/early menopausal women should be treated until the mean age of natural menopause (around the age of 51 years). Hormone therapy appears safe to use up to age 60. F, treating symptomatic women >60 years, weigh risks and benefits and do not use for over 5 years. All age groups should be prescribed the lowest most effective dose of hormone therapy.

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