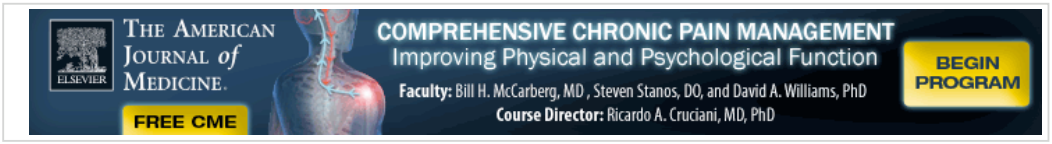

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Bayesian Meta-analysis of Hormone Therapy and Mortality in Younger Postmenopausal Women

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Article Outline

Abstract

Background

There is uncertainty over the risks and benefits of hormone therapy. We performed a Bayesian meta-analysis to evaluate the effect of hormone therapy on total mortality in younger postmenopausal women. This analysis synthesizes evidence from different sources, taking into account varying views on the issue.

Methods

A comprehensive search from 1966 through January 2008 identified randomized controlled trials of at least 6 month's duration that evaluated hormone therapy in women with mean age <60 years and reported at least one death, and prospective observational cohort studies that evaluated the relative risk of mortality associated with hormone therapy after adjustment for confounding variables.

Results

The results were synthesized using a hierarchical random-effects Bayesian meta-analysis. The pooled results from 19 randomized trials, with 16,000 women (mean age 55 years) followed for 83,000 patient-years, showed a mortality relative risk of 0.73 (95% credible interval 0.52-0.96). When data from 8 observational studies were added to the analysis, the resultant relative risk was 0.72 (credible interval 0.62-0.82). The posterior probability that hormone therapy reduces total mortality in younger women is almost 1.

Conclusions

The synthesis of data using Bayesian meta-analysis indicates a reduction in mortality in younger postmenopausal women taking hormone therapy compared with no treatment. This finding should be interpreted taking into account the potential benefits and harms of hormone therapy.

Keywords: Bayesian meta-analysis, Hormone therapy, Menopause, Mortality

Hormone therapy to treat menopausal estrogen deficiency has been in widespread use for over 60 years.[1] Long-term treatment was assumed to prevent the atherosclerosis, osteoporosis, and increase in mortality seen following the menopausal transition.[1], [2], [3] Since 1983, several observational studies consistently showed that hormone users, many of whom started treatment shortly after menopause, had a significant reduction in total mortality compared with nonusers, even after adjustment for confounding factors.[4], [5], [6], [7], [8] The available evidence supported the routine use of hormone therapy to increase longevity in postmenopausal women.[9]

Clinical Significance

The publication of the Women's Health Initiative (WHI) in 2002 seemed to contradict these assumptions.[10] For women of mean age 63 years, estrogen-progestin treatment increased the risk for composite outcomes, termed the global index, by 13% compared with placebo, without increasing mortality. In the confusion that ensued after this publication, it was possible to make 2 erroneous assumptions: that hormone therapy had similar effects in younger and older women, and that the increased global index translated into an increased risk for death. In 2004, a meta-analysis of randomized trials showed that hormone therapy reduced total mortality by 40% in trials of younger women but not in older women.[11] In the wake of the WHI trial, this reduction in mortality was considered to be “implausible” and “difficult to reconcile.”[12] In 2006, another meta-analysis of randomized trials found a 32% reduction in coronary heart disease events in younger women.[13] It was not until 2007 that age-specific mortality data from both arms of the WHI trial were provided, which showed a 30% mortality reduction in women under 60 years of age.[14] A recent cost-effectiveness analysis found that hormone therapy given to younger postmenopausal women for 5-30 years results in a small increase in life expectancy and a substantial increase in quality-adjusted life-years.[15]

To make sense of the accumulated evidence, we performed a Bayesian meta-analysis of hormone therapy and mortality in younger postmenopausal women, which serves to update the previous meta-analysis[11] by including age-specific data from the WHI trials. We focused on mortality because it is the clinical outcome that balances the benefits and harms of treatment, and because conflicting conclusions have emerged about its risk. We believe that a Bayesian meta-analysis is appropriate because it allows us to directly incorporate previous assessments from observational studies into the pooled trial data, and can determine the probability of the hypothesis that hormone therapy reduces mortality in younger women. In addition, Bayesian analysis allows us to quantify the effect that prior beliefs—such as those coming from incorrect assumptions made after the WHI trial—can have on our understanding of the evidence.

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Methods

Study Design

The MEDLINE, EMBASE, CINAHL, and Cochrane databases were searched comprehensively to identify studies in any language published between 1966 and January 2008 that evaluated hormone therapy, defined as the oral or transdermal use of estrogen or estrogen-progestin therapy, in postmenopausal women. Women were considered to be postmenopausal after 12 consecutive months of amenorrhea. The search was augmented by scanning selected journals and references of identified articles.

Two investigators independently evaluated studies for inclusion. Observational studies were included if they were prospective cohort studies of postmenopausal women that evaluated the relative risk of mortality associated with hormone use and used multivariate analysis to adjust for standard confounding factors. Randomized trials were included if they evaluated women with mean age of <60 years at start of trial, compared hormone therapy with placebo or no treatment for at least 6 month's duration, and reported at least one death. Attempts were made to contact the investigators to obtain information concerning deaths during the trial.

Two independent reviewers extracted data, reconciling differences by consensus. For observational studies, the outcome measured was adjusted relative risk or hazard ratio for total mortality. For studies in which more than one multivariate analysis was reported, the estimate for long-term use was chosen, if available. For randomized trials, the outcome measured was total deaths in the treatment and control groups.

Statistical Analysis

To capture variability from all sources, to make the probability statement for the treatment effect and to incorporate the prior beliefs and external information, we synthesized the results from the randomized controlled trials using a hierarchical Bayesian random-effects model.[16], [17], [18], [19], [20] Details of the Bayesian analysis can be found in the Appendix (available online).

To synthesize trial data in conjunction with observational data, we applied 3 different prior distributions to the model: a “non-informative” prior distribution,[21] an “informative” prior distribution generated from the observational studies,[22] and a “sceptical” prior distribution using observational data.[17], [23], [24] In addition, to assess the effect of incorrect assumptions, we generated an “erroneous” prior distribution using the global index from the WHI trial to approximate an increased relative risk of death in younger women when, in fact, no increase in mortality was seen.[10]

For the “non-informative” prior distribution, we set a relative risk of 1.0 with a large variance, so that the pooled trial data dominated the posterior distribution. This result is similar to that obtained from a traditional non-Bayesian meta-analysis. For the “informative” prior distribution, we applied the same random-effects model to the pooled observational studies; randomized trial data were then added via the Bayes rule to produce posterior distributions. The “sceptical” prior distribution used the assumption that most clinically important interventions reduce the relative risk of major outcomes by 10%-20%.[24] We assigned a highly skeptical prior distribution to our model that allowed only a 5% chance to observe a large benefit, such as the 30% risk reduction taken from observational studies.

The treatment effects were obtained from the posterior distributions of the Bayesian analysis and are reported as relative risk with 95% associated credible interval (CrI), which is a Bayesian analog of the 95% confidence interval from traditional meta-analyses. The results are presented in a forest plot, which displays the relative risk for both the individual trials and also the pooled results. The posterior probability of a mortality benefit with hormone therapy, that is, a relative risk of <1, also was reported. The analysis was performed using the software WinBUGS 1.4 (MRC Biostatistics Unit, Cambridge, UK), which

generates inferences using the Gibbs sampler (Appendix [available online]).

Role of Funding Source

Funding for this analysis came from salary support for S. Salpeter, J. Cheng, and L. Thabane and from a Podell Emeriti Award for E. Salpeter. The institutions had no role in the design, conduct, or reporting of the study. No sponsorship from the institutions or the pharmaceutical industry was provided to conduct this analysis.

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Results

The database search identified approximately 4000 articles, of which 398 were potentially relevant studies. Of these, 8 observational studies[5, 6, 7, 8, 25, 26, 27, 28] and 19 randomized controlled trials[10, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46] met the inclusion criteria (Table 1 [available online], Figure 1). A previous meta-analysis provided information on 17 of the randomized trials.[11] A subsequent publication[14] provided age-specific mortality data for the 2 WHI trials.[10, 46] In the observational cohorts, a total of 212,171 women were followed for a mean of 13.8 years (range, 6-22 years). In the randomized trials, there were 8689 women in the treatment groups and 7594 women in the control groups, with a mean age of 54.5 years followed for 5.1 years (range, 1-6.8 years). Interventions included conjugated equine estrogen, oral esterified estrogen, or transdermal estrogen, alone or in combination with a progestin, given on a continuous or cyclic basis.

Table 1. Characteristics of Included Randomized Trials

Study*, Year, Reference	Design, Duration	Number (n) in Treatment	Number (n) in Control	Dropout in Treatment	Dropout in Control	Mean Age (Years) in Treatment	Mean Age (Years) in Control	Intervention	Outcomes	Comments
Angerer, 2000[29]	Double blind, 1 year	215	66	28%	29%	59.0	59.5	Estradiol plus gestodone vs placebo	Carotid artery dispensability	
Arrenbrecht, 2002[30]	Double blind, 2 years	108	53	24%	24%	50.5	50.5	TD estradiol vs placebo	Bone mineral density	
Giske, 2002[31]	Double blind, 2 years	123	43	11.4%	30.2%	49.1	49.6	Estradiol vs placebo	Bone mineral density	
Guidozzi, 1999[32]	Open label, 4 years	62	68	4%	4%	51	51	CEE plus MPA vs placebo	Survival	
Hall, 1994[33]	Open label, 2 years	100	100	37%	16%	55.8	56.1	TD estradiol vs placebo	Bone mineral density	
Hall, 1998[34]	Single blind, 1 year	40	20	20%	30%	58.6	61.3	TD estradiol plus MPA vs placebo	Angina	
Komulainen, 1999[35]	Open label, 5 years	115	115	5.2%	5.2%	52.9	52.6	Estradiol plus cyproterone acetate vs placebo	Bone mineral density	Vitamin D also studied
Kyllonen, 1998[36]	Double blind, 2 years	52	26	22%	22%	52.6	52.6	Estradiol plus cyclic MPA vs placebo	Lumbar spine mobility	
Lindsay, 1976[37]	Double blind, 5 years	63	57	6.3%	5.3%	44-50	44-50	Mestranol vs placebo	Bone mineral content	
MacDonald, 1994[38]	Double blind, 1 year	40	22	22.5%	40.9%	53	55	TD estradiol with or without cyclic norethisterone vs placebo	Bone mineral density and rheumatoid arthritis disease activity	
Mijatovic, 1998[39]	Double blind, 2 years	13	13	5%	6.7%	55.7	54.9	CEE vs placebo	Homocysteine levels	Raloxifene also studied
Mosekilde, 2002[40]	Open label, 5 years	502	504	9.6%	9.1%	49.5	50.0	Estradiol plus cyclic norethisterone vs placebo	Bone mineral density and forearm fracture	
Nachtigall,	Double	84		3.6%		55.3		CEE plus MPA vs	Medical illness	

Study*, Year, Reference	Design, Duration	Number (n) in Treatment	Number (n) in Control	Dropout in Treatment	Dropout in Control	Mean Age (Years) in Treatment	Mean Age (Years) in Control	Intervention	Outcomes	Comments
1979[41]	blind, 10 years	84		8.3%		54.9		placebo	or death	
PEPI trial Writing Group, 1995[42]	Double blind, 3 years	701	174	16%	32.8%	56.1	56.1	CEE plus MPA or cyclic MPA or cyclic micronized progesterone vs placebo	Lipids, fibrinogen, blood pressure and insulin	
Perez-Jaraiz, 1996[43]	Open-label, 1 year	26	52	5.8%	5.8%	48	50	TD estradiol plus cyclic MPA vs calcium	Bone mineral density	Calcitonin also studied
Ravn, 1999[44]	Open label, 4 years	110	109	25.5%	26.7%	55	55	CEE plus MPA or estradiol plus cyclic norethisterone vs placebo	Bone mineral density	Alendronate also studied
Watts, 2000[45]	Double blind, 2 years	303	103	10%	10%	51.8	51.3	CEE vs placebo	Bone mineral density	
WHI Writing Group, 2002[10]	Double blind, 5.2 years	4476	4356	6.3%	6.1%	50-59	50-59	CEE plus MPA vs placebo	Disease events and mortality	Data for 50-59 years[14]
WHI Writing Group, 2004[46]	Double blind, 6.8 years	1637	673	4.9%	5.5%	50-59	50-59	CEE vs placebo	Disease events and mortality	Data for 50-59 years[14]

CEE = conjugated equine estrogen; MPA = medroxyprogesterone acetate; TD = transdermal; WHI = Women's Health Initiative.

*Most studies are identified by the first author's surname.

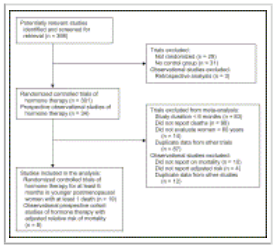

Figure 1.
Flow chart of search for trials and observational studies.

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Using a “non-informative” prior distribution to pool data from 19 randomized trials, the mortality relative risk (RR) was 0.73 (95% CrI, 0.52-0.96), and the posterior probability of a mortality benefit was 0.985 (Table 2, Figure 2). There were a total of 156 deaths in 8689 participants in the hormone therapy group (1.80%) and 211 deaths in 7594 participants in the control group (2.64%) over the course of 5.1 years, indicating an absolute risk reduction of 0.84%.

Table 2. Table of Results

Source of Assumptions	Prior Distribution	Relative Risk (95% Credible Interval)	Probability of Relative Risk <1	Between-study Variance on Log-relative Risk Scale
External information:	Non-informative prior distribution	0.73 (0.52-0.96)	0.985	0.067
Synthesis of randomized trial data with observational studies	Informative prior distribution*	0.72 (0.62-0.82)	1.000	0.024
	Sceptical prior distribution†	0.83 (0.68-1.00)	0.975	0.026
Prior beliefs:	Erroneous prior distribution‡	1.09 (0.97-1.23)	0.077	0.308

Source of Assumptions	Prior Distribution	Relative Risk (95% Credible Interval)	Probability of Relative Risk <1	Between-study Variance on Log-relative Risk Scale
Erroneous assumptions				

✻The Bayesian estimates obtained from 8 observational studies are: log-relative risk = −0.35 (−0.53, −0.16); SD of log-relative risk = 0.092, therefore variance = 0.008 and precision = 125; between-study SD = 0.17.

†Mean = 0; variance = (0.008*sqrt[8]) such that the prior probability that the true relative risk is >0 is 0.05; between-study SD is adopted from the Bayesian estimate from observational studies.

‡Mean = 0.13; variance = (0.06*0.06); precision = 278; between-study SD = 0.4. These estimates were derived using the Bayesian random-effects model, and were based on an erroneous interpretation of the Women's Health Initiative (probabilities of global index: treatment group = 571/8506, placebo = 623/8102).

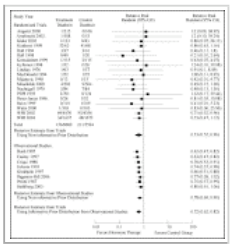

Figure 2.
Bayesian meta-analysis: effect of hormone therapy on mortality in younger postmenopausal women.

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Using an “informative” prior distribution, the 8 observational studies were pooled to obtain a RR of 0.78 (CrI, 0.69-0.90). When trial data were added, the RR was 0.72 (CrI, 0.62-0.82), with the posterior probability of a mortality benefit of 1.0 (Table 2, Figure 2).

Using a “sceptical” prior distribution, the RR was 0.83 (CrI, 0.68-1.00), with the posterior probability of a mortality benefit of 0.975 (Table 2, Figure 2). When an “erroneous” prior distribution was used, based on a belief that hormone therapy increased mortality, the resultant RR was 1.09 (CrI, 0.97-1.23). Using this assumption, the posterior probability that hormone therapy reduced mortality was 0.077 (Table 2).

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Discussion

This Bayesian meta-analysis synthesized the available data in order to understand the effect of hormone therapy on mortality in younger postmenopausal women. We focused our investigation on mortality because it is an important clinical outcome, one that balances the benefits and harms of treatment. In addition, mortality is an area where the evidence seems uncertain, leading to the current controversies about hormone therapy. We used a Bayesian approach, which pools data from different sources, taking into account varying views on the issue.

Using pooled data from 8 observational studies, which followed 200,000 women for an average of 14 years, the mortality relative risk was 0.78. Pooled data from 19 randomized controlled trials, which followed younger postmenopausal women for over 83,000 patient-years, showed a similar mortality relative risk of 0.73. These results are similar to that found in the WHI trials, which showed a mortality hazard ratio of 0.7 in this younger age group.[14] In this analysis, when randomized trial data were added to observational studies using an “informative” prior distribution, the resultant mortality relative risk was 0.72. The mortality reduction was 20%-30% over the course of 5 years' treatment, with an absolute risk reduction of close to 1%.

Bayesian analysis has the ability to determine the level of certainty about our conclusions. When randomized trial data are pooled using a “non-informative” prior distribution so the treatment effect is similar to that obtained using traditional meta-analysis, the posterior probability that hormone therapy provides a mortality benefit in younger women is 0.985. When an “informative” observational prior distribution is used, the posterior probability of a mortality benefit is essentially 1. When greater uncertainty is placed on the results from observational studies with a “sceptical” prior distribution, the results still remain robust, with a posterior probability of a mortality reduction of 0.975. Overall, our analysis shows that there is convergence of evidence from different sources.

From this synthesis of the data, we can see that the results from observational studies and randomized trials are remarkably similar, both showing reductions in total mortality of approximately 25%. We also can see that the age-specific results from the WHI are similar to those of other trials in younger women. A meta-analysis of randomized trials that was published before the availability of WHI data found a 39% reduction in total mortality in younger women,[11] whereas the WHI trials found a 30% reduction in this age group.[14] It is important to note that there still is substantial uncertainty in prevailing beliefs about a mortality benefit in early postmenopausal women.[47], [48] This might be because age-specific mortality data for the WHI were not available until 2007,[14] 5 years after the original publication.[10] The authors initially reported that mortality was not increased for all ages combined (hazard ratio 0.98), but that the “global index” of composite outcomes was increased by 13%.[10] Now it seems plausible that misconceptions may have occurred in the interpretation of the available data, with a tendency of over-interpreting the results toward greater harm than benefit and assuming that hormone therapy had similar effects in younger and older women.[47], [48] Quite possibly, many concluded after the first WHI publication that observational data had been misleading

because there was not adequate adjustment for socioeconomic status, and that hormone therapy in fact increases mortality in all ages.

In this Bayesian analysis, we see that if one assumed that hormone therapy had similar effects in younger and older women and that the global index from the WHI translated into an increased risk for death, there would now be a great deal of uncertainty in interpreting the available age-specific mortality data. In fact, when using an "erroneous" prior distribution—which assumed an increased mortality in younger women—the addition of randomized trial data resulted in a posterior probability of 0.077 that hormone therapy reduces mortality in younger women. Thus, the "erroneous" prior distribution dominated the empirical evidence from field trials. This may explain why there is such difficulty at present accepting the conclusion that hormone therapy has a mortality benefit in this age group.

This meta-analysis has several potential limitations. Standard meta-analytic results are uncertain when the number of events per study is small, as is the case with mortality. In addition, there was wide variability in the 19 trials, such as the size of the trial, medications used, populations of women studied, and method of administration. We included both blinded and open-label trials with a wide range of methodological quality. Random-effects Bayesian meta-analysis is a useful approach when pooling heterogeneous studies, as it accounts for the possibility of between-trial variations. Despite these differences, little inter-study heterogeneity was seen in the results. Another limitation is that the 8 observational studies used varying methods in the adjustment for confounding variables, such as age, comorbid illnesses, and socioeconomic status. However, the results for trial data were remarkably similar to those of observational data, which indicate that most sources of bias were accounted for.

Estimates for relative risks were pooled from data on estrogen therapy and estrogen-progestin therapy, despite the fact that there are differences between these 2 types of treatment. However, evidence from the WHI trial indicates that similar mortality reductions are seen in younger women with single or combined treatment.[14] This analysis was based only on published data, and therefore may be subject to publication bias. However, funnel plots of effect size versus standard error did not show evidence of bias. Furthermore, most trials did not report mortality as a primary or secondary outcome, so it is unlikely that deaths in those trials would have affected the decision to publish.

There are advantages and disadvantages of using Bayesian meta-analysis. Bayesian analysis allows us to compile all of the available data together, synthesize them into a coherent summary, and calculate the posterior probability of a given hypothesis. It can incorporate external information such as observational studies into pooled trial data to obtain a more precise estimate of treatment effect. In addition, it can illustrate how previously held assumptions—quantified in a form of prior distribution—can affect our understanding of the results. A disadvantage of this technique is that the results of the meta-analysis are dependent on the choice of prior distributions used. We performed the analysis using "informative," "non-informative," and "sceptical" prior distributions to assess how sensitive the results were to the prior assumptions used, and the results remained robust, showing strong beneficial mortality effect in each analysis.

It is clear that these findings need to be interpreted in the light of potential benefits and harms of hormone therapy. The available evidence indicates that hormone therapy in younger postmenopausal women increases the risk of breast cancer and pulmonary embolism, and reduces the risk of cardiovascular events, colon cancer, and hip fracture.[13], [14], [49], [50], [51], [52], [53] The cardiovascular benefit is a result of a small absolute increase in stroke and a greater reduction in coronary heart disease events.[14], [51], [54] The total mortality benefit for younger women seen in the randomized trials and observational studies indicates that the reduction in deaths from coronary heart disease, fracture, and colon cancer outweighed the increase in deaths from breast cancer, stroke, and pulmonary embolism. In addition to this mortality benefit, hormone therapy in younger women provides an improvement in quality-of-life measures, at least in the first few years of treatment.[55], [56], [57], [58], [59]

The past 6 years have seen marked fluctuations in our understanding of the effects of hormone therapy in young postmenopausal women. Guidelines published after the first WHI report concluded that hormone therapy had greater harms than benefits in women of all ages and should be used only for short durations in women with severe menopausal symptoms.[60], [61], [62] After age-specific data from the WHI surfaced, position statements from 2007 concluded that the initiation of hormone therapy in younger women may in fact reduce cardiovascular morbidity and mortality, but no mention was made of an overall reduction in mortality.[63], [64] It is our hope that this Bayesian meta-analysis will help to clarify the role of hormone therapy in younger women. The aim is to optimize the synthesis of evidence from different sources while taking into account varying views on the subject. These issues have bearing on development of guidelines to inform policy and practice.

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Supplementary data

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