**e-Tables**

**e-Table 1: Disease risk input data**

|  |  |  |
| --- | --- | --- |
| **Disease conditions stratified by age group (years)** | **Hazard Ratio** | **Data Sources** |
| **Breast Cancer** |  |  |
| 50-59 | 0.76 | [[1]](#footnote-1)Manson JE, et. al. (2013) |
| 60-69 | 0.78 | 1Manson JE, et. al. (2013) |
| 70-79 | 0.85 | 1Manson JE, et. al. (2013) |
| All | 0.79 | 1Manson JE, et. al. (2013) |
| CHD |  |  |
| 50-59 | 0.65 | 1Manson JE, et. al. (2013) |
| 60-69 | 1.00 | 1Manson JE, et. al. (2013) |
| 70-79 | 1.01 | 1Manson JE, et. al. (2013) |
| All | 0.94 | 1Manson JE, et. al. (2013) |
| Stroke |  |  |
| 50-59 | 0.96 | 1Manson JE, et. al. (2013) |
| 60-69 | 1.25 | 1Manson JE, et. al. (2013) |
| 70-79 | 1.12 | 1Manson JE, et. al. (2013) |
| All | 1.15 | 1Manson JE, et. al. (2013) |
| Pulmonary Embolism |  |  |
| 50-59 | 1.06 | 1Manson JE, et. al. (2013) |
| 60-69 | 1.45 | 1Manson JE, et. al. (2013) |
| 70-79 | 0.82 | 1Manson JE, et. al. (2013) |
| All | 1.15 | 1Manson JE, et. al. (2013) |
| Colorectal Cancer |  |  |
| 50-59 | 0.76 | 1Manson JE, et. al. (2013) |
| 60-69 | 1.04 | 1Manson JE, et. al. (2013) |
| 70-79 | 1.61 | 1Manson JE, et. al. (2013) |
| All | 1.13 | 1Manson JE, et. al. (2013) |
| Hip Fracture |  |  |
| 50-59 | 0.88 | 1Manson JE, et. al. (2013) |
| 60-69 | 0.95 | 1Manson JE, et. al. (2013) |
| 70-79 | 0.89 | 1Manson JE, et. al. (2013) |
| All | 0.91 | 1Manson JE, et. al. (2013) |
| Global Index |  |  |
| 50-59 | 0.82 | 1Manson JE, et. al. (2013) |
| 60-69 | 1.03 | 1Manson JE, et. al. (2013) |
| 70-79 | 1.10 | 1Manson JE, et. al. (2013) |
| All | 1.02 | 1Manson JE, et. al. (2013) |

**e-Table 2: Medical expenditure input data**

|  |  |  |
| --- | --- | --- |
| **Disease condition** | **Expenditure ($)** | **Data source** |
| Base-case analysis | | |
| Breast Cancer | 6027.91 | MEPS |
| CHD | 4415.65 | MEPS |
| Stroke | 5761.94 | MEPS |
| Pulmonary Embolism | 4257.01 | MEPS |
| Colorectal Cancer | 13618.06 | MEPS |
| Hip Fracture | 15812.83 | MEPS |
| Global Index | 8315.01 | MEPS |
| Sensitivity analysisa | | |
| Breast Cancer | 5299.88 | [[2]](#footnote-2)Shreibati JB, et. al. (2018) |
| CHD | 1336.91 | 1Shreibati JB, et. al. (2018) |
| Stroke | 2809.64 | 1Shreibati JB, et. al. (2018) |
| Pulmonary Embolism | 1089.45 | 1Shreibati JB, et. al. (2018) |
| Colorectal Cancer | 4526.06 | 1Shreibati JB, et. al. (2018) |
| Hip Fracture | 2316.45 | 1Shreibati JB, et. al. (2018) |
| Global Index | 2632.56 | 1Shreibati JB, et. al. (2018) |

aThe base-case analysis was repeated using medical expenditure data from WHI participants with Medicare fee-for-service benefits. This expenditure data (1998 – 2012) comes directly from WHI participants based on healthcare spending Medicare Carrier, Hospice, Home Health and Durable Medical Equipment claims.

**e-Table 3: Differences in medical expenditures (using Medicare data) for treating disease conditions between real and hypothetical non-WHI scenarios over a 13-year cumulative period (2003-2015): *Only Women with Hysterectomy***

|  |  |  |  |
| --- | --- | --- | --- |
| **Disease conditions stratified by age groups (years)** | **Counts of disease attributable to ET (rates in ET group minus rate in placebo)** | **aCumulative medical expenditure differences between real and hypothetical non-WHI scenarios ($millions)** | |
| **Annual** | **13-Year (95%LCL,95%UCL)** |
| **Breast Cancer** |  |  |  |
| **5**0-59 | -10109 | -53 | -696 |
| 60-69 | -15426 | -82 | -1063 |
| 70-79 | -6181 | -33 | -426 |
| **Coronary heart disease (CHD)** |  |  |  |
| 50-59 | -15887 | -21 | -276 |
| 60-69 | 0 | 0 | 0 |
| 70-79 | 0 | 0 | 0 |
| **Stroke** |  |  |  |
| 50-59 | -2888 | -8 | -105 |
| 60-69 | 17355 | 49 | 634 |
| 70-79 | 8651 | 24 | 316 |
| **Pulmonary Embolism** |  |  |  |
| 50-59 | 1446 | 2 | 20 |
| 60-69 | 11569 | 13 | 164 |
| 70-79 | -6179 | -7 | -87 |
| **Colorectal Cancer** |  |  |  |
| 50-59 | -4333 | -20 | -255 |
| 60-69 | 0 | 0 | 0 |
| 70-79 | 13599 | 62 | 800 |
| **Hip Fracture** |  |  |  |
| 50-59 | -1447 | -3 | -43 |
| 60-69 | 0 | 0 | 0 |
| 70-79 | -8653 | -20 | -260 |
| **Global Index** |  |  |  |
| 50-59 | -37549 | -99 | -1285 |
| 60-69 | 13495 | 36 | 462 |
| 70-79 | 40792 | 107 | 1396 |

The unit expenditure per disease based on Medicare data are: $5299.88, breast cancer; $1336.91, CHD; $2809.64, stroke; $1089.45, PE; $4526.06, colorectal cancer; $2316.45, hip fracture; $2632.56, global index

aThe annual expenditures accrued during each year of the observation period, 2003-2015, were summed up to generate 13-year cumulative expenditures associated with treating chronic condition. A positive difference in the medical expenditures corresponds to excess cost of treatment of excess diseases. Conversely, negative differences correspond to monetary savings in medical expenditures for diseases averted.

**e-Table 4: Differences in medical expenditures (using Medicare data) for treating disease conditions between real and hypothetical non-WHI scenarios over a 13-year cumulative period (2003-2015) compared to a pre-WHI period from 1996-2001: *Only Women with Hysterectomy***

|  |  |  |  |
| --- | --- | --- | --- |
| **Disease conditions stratified by age groups (years)** | **Counts of disease attributable to ET (rates in ET group minus rate in placebo)** | **aCumulative medical expenditure differences between real and hypothetical non-WHI scenarios ($millions)** | |
| **Annual** | **13-Year (95%LCL,95%UCL)** |
| **Breast Cancer** |  |  |  |
| **5**0-59 | -12614 | -76 | -988 |
| 60-69 | -20277 | -122 | -1589 |
| 70-79 | -8203 | -49 | -643 |
| **Coronary heart disease (CHD)** |  |  |  |
| 50-59 | -19820 | -87 | -1138 |
| 60-69 | 0 | 0 | 0 |
| 70-79 | 0 | 0 | 0 |
| **Stroke** |  |  |  |
| 50-59 | -3602 | -21 | -270 |
| 60-69 | 22814 | 131 | 1709 |
| 70-79 | 11484 | 66 | 860 |
| **Pulmonary Embolism** |  |  |  |
| 50-59 | 1806 | 8 | 100 |
| 60-69 | 15210 | 65 | 842 |
| 70-79 | -8201 | -35 | -454 |
| **Colorectal Cancer** |  |  |  |
| 50-59 | -5406 | -74 | -957 |
| 60-69 | 0 | 0 | 0 |
| 70-79 | 18051 | 246 | 3196 |
| **Hip Fracture** |  |  |  |
| 50-59 | -1803 | -28 | -371 |
| 60-69 | 0 | 0 | 0 |
| 70-79 | -11485 | -182 | -2361 |
| **Global Index** |  |  |  |
| 50-59 | -46850 | -389 | -5064 |
| 60-69 | 17742 | 148 | 1918 |
| 70-79 | 54149 | 450 | 5853 |

The unit expenditure per disease based on Medicare data are: $5299.88, breast cancer; $1336.91, CHD; $2809.64, stroke; $1089.45, PE; $4526.06, colorectal cancer; $2316.45, hip fracture; $2632.56, global index

aThe annual expenditures accrued during each year of the observation period, 2003-2015, were summed up to generate 13-year cumulative expenditures associated with treating chronic condition. A positive difference in the medical expenditures corresponds to excess cost of treatment of excess diseases. Conversely, negative differences correspond to monetary savings in medical expenditures for diseases averted.

**e-Table 5a: Differences in medical expenditures for treating disease conditions between real and hypothetical non-WHI scenarios over a 13-year cumulative period (2003-2015): *Only Women with Hysterectomy using LCL of Hazard Ratio***

|  |  |  |  |
| --- | --- | --- | --- |
| **Disease conditions stratified by age groups (years)** | **Counts of disease attributable to ET (rates in ET group minus rate in placebo)** | **aCumulative medical expenditure differences between real and hypothetical non-WHI scenarios ($millions)** | |
| **Annual** | **13-Year (95%LCL,95%UCL)** |
| **Breast Cancer** |  |  |  |
| **5**0-59 | -24552 | -148 | -1924 |
| 60-69 | -32776 | -198 | -2574 |
| 70-79 | -23486 | -142 | -1846 |
| **Coronary heart disease (CHD)** |  |  |  |
| 50-59 | -30329 | -134 | -1742 |
| 60-69 | -26992 | -119 | -1547 |
| 70-79 | -29667 | -131 | -1703 |
| **Stroke** |  |  |  |
| 50-59 | -14442 | -83 | -1079 |
| 60-69 | -3856 | -22 | -286 |
| 70-79 | -17306 | -100 | -1300 |
| **Pulmonary Embolism** |  |  |  |
| 50-59 | -7221 | -31 | -403 |
| 60-69 | -1928 | -8 | -104 |
| 70-79 | -19778 | -84 | -1092 |
| **Colorectal Cancer** |  |  |  |
| 50-59 | -12998 | -177 | -2301 |
| 60-69 | -13496 | -184 | -2392 |
| 70-79 | 0 | 0 | 0 |
| **Hip Fracture** |  |  |  |
| 50-59 | -7221 | -114 | -1482 |
| 60-69 | -13496 | -213 | -2769 |
| 70-79 | -32139 | -508 | -6604 |
| **Global Index** |  |  |  |
| 50-59 | -69324 | -576 | -7488 |
| 60-69 | -25064 | -208 | -2704 |
| 70-79 | -19778 | -164 | -2132 |

The unit expenditure per disease based on MEPS (2003-2015) data are: $6027.91, breast cancer; $4415.65, CHD; $5761.94, stroke; $4257.01, PE; $13618.06, colorectal cancer; $15812.83, hip fracture; $8315.01, global index. The unit expenditure for the global index was calculated as the arithmetic average of the 6 comprising diseases.

aThe annual expenditures accrued during each year of the observation period, 2003-2015, were summed up to generate 13-year cumulative expenditures associated with treating chronic condition. A positive difference in the medical expenditures corresponds to excess cost of treatment of excess diseases. Conversely, negative differences correspond to monetary savings in medical expenditures for diseases averted.

**e-Table 5b: Differences in medical expenditures for treating disease conditions between real and hypothetical non-WHI scenarios over a 13-year cumulative period (2003-2015): *Only Women with Hysterectomy using UCL of Hazard Ratio***

|  |  |  |  |
| --- | --- | --- | --- |
| **Disease conditions stratified by age groups (years)** | **Counts of disease attributable to ET (rates in ET group minus rate in placebo)** | **aCumulative medical expenditure differences between real ($millions)** | |
| **Annual** | **13-Year** |
| **Breast Cancer** |  |  |  |
| **5**0-59 | 4333 | 26 | 338 |
| 60-69 | 1928 | 12 | 156 |
| 70-79 | 11125 | 67 | 871 |
| **Coronary heart disease (CHD)** |  |  |  |
| 50-59 | -1444 | -6 | -78 |
| 60-69 | 26992 | 119 | 1547 |
| 70-79 | 29667 | 131 | 1703 |
| **Stroke** |  |  |  |
| 50-59 | 8665 | 50 | 650 |
| 60-69 | 38560 | 222 | 2886 |
| 70-79 | 34611 | 199 | 2587 |
| **Pulmonary Embolism** |  |  |  |
| 50-59 | 10110 | 43 | 559 |
| 60-69 | 25064 | 107 | 1391 |
| 70-79 | 7417 | 32 | 416 |
| **Colorectal Cancer** |  |  |  |
| 50-59 | 4333 | 59 | 767 |
| 60-69 | 13496 | 184 | 2392 |
| 70-79 | 27194 | 370 | 4810 |
| **Hip Fracture** |  |  |  |
| 50-59 | 4333 | 69 | 897 |
| 60-69 | 13496 | 213 | 2769 |
| 70-79 | 14833 | 235 | 3055 |
| **Global Index** |  |  |  |
| 50-59 | -5777 | -48 | -624 |
| 60-69 | 52056 | 433 | 5629 |
| 70-79 | 101361 | 843 | 10959 |

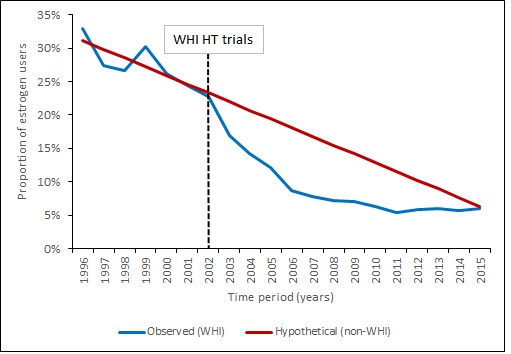
The unit expenditure per disease based on MEPS (2003-2015) data are: $6027.91, breast cancer; $4415.65, CHD; $5761.94, stroke; $4257.01, PE; $13618.06, colorectal cancer; $15812.83, hip fracture; $8315.01, global index. The unit expenditure for the global index was calculated as the arithmetic average of the 6 comprising diseases.

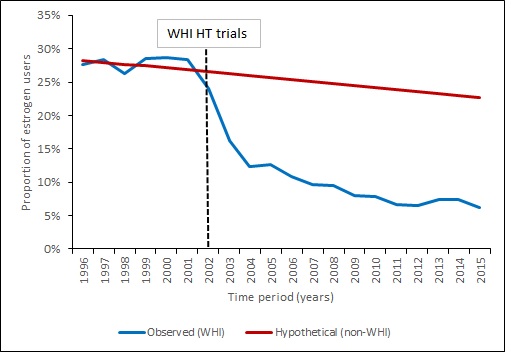
aThe annual expenditures accrued during each year of the observation period, 2003-2015, were summed up to generate 13-year cumulative expenditures associated with treating chronic condition. A positive difference in the medical expenditures corresponds to excess cost of treatment of excess diseases. Conversely, negative differences correspond to monetary savings in medical expenditures for diseases averted.

**e-Figures**

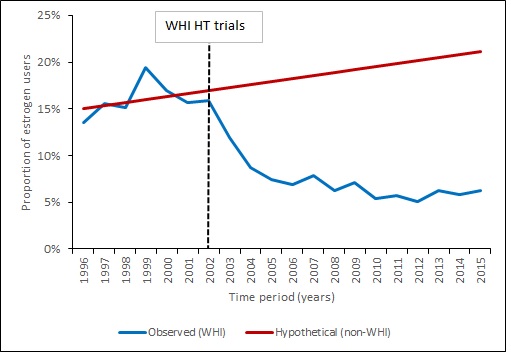
**e-Figure 1: Temporal trends of prevalence of estrogen-alone utilization before and after publication of the WHI ET results in the overall population of women**

**e-Figure 1a**: **Trends of prevalence in 50-59 year olds overall**



**e-Figure 1b**: **Trends of prevalence in 60-69 year olds overall**

**e-Figure 1c**: **Trends of prevalence in 70-79 year olds overall**



**e-Figure 2**: **Trends in excess global disease index attributable to estrogen therapy between observed and hypothetical non-WHI scenarios stratified by age groups among women with a history of hysterectomy**

**e-Figure 2a: Trends of attributable global disease index among 50-59 year group among women with a history of hysterectomy**

**WHI HT trials**

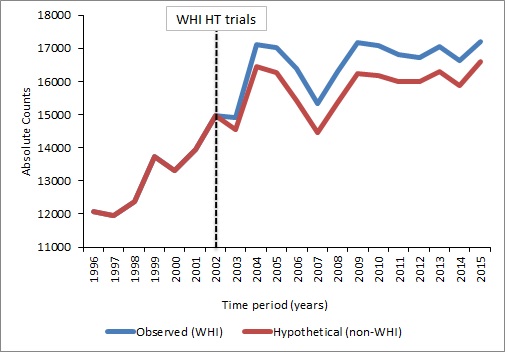
**e-Figure 2b**: **Trends of attributable global disease index among 60-69 year group among women with a history of hysterectomy**

**WHI HT trials**

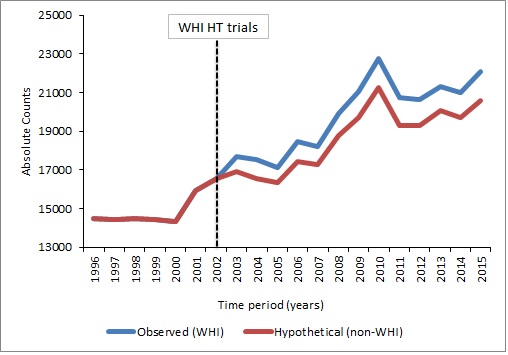
**e-Figure 2c**: **Trends of attributable global disease index among 70-79 year group among women with a history of hysterectomy**

**e-Figure 3: Trends in excess individual chronic diseases attributable to estrogen therapy between observed and hypothetical non-WHI scenarios stratified by age groups**

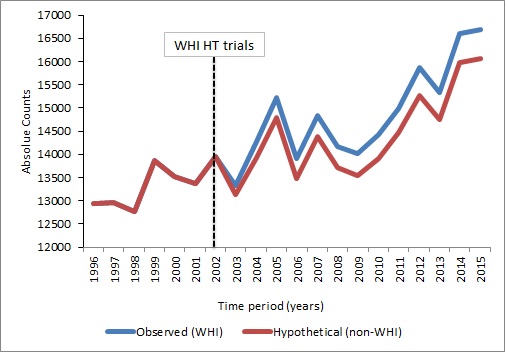
**e-Figure 3a**: Trends of attributable breast cancer among 50-59 year group with history of hysterectomy



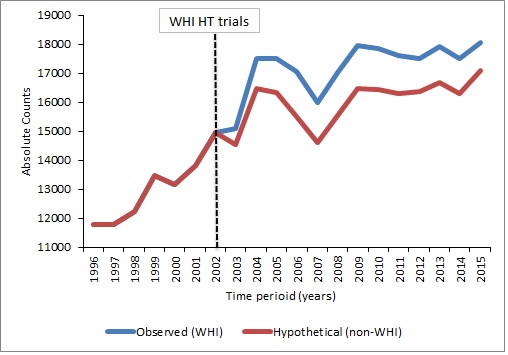
**e-Figure 3b**: Trends of attributable breast cancer among 60-69 year group with history of hysterectomy



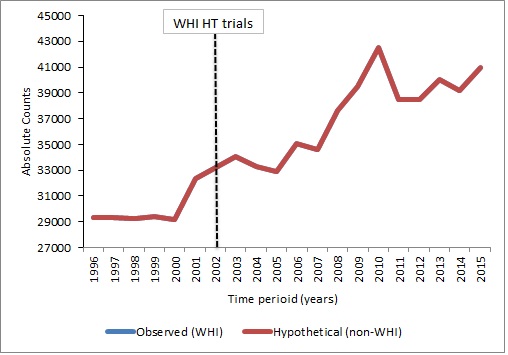
**e-Figure 3c**: Trends of attributable breast cancer among 70-79 year group with history of hysterectomy



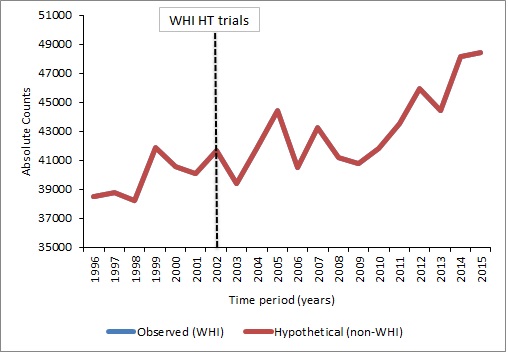
**e-Figure 3d**: Trends of attributable CHD among 50-59 year group with history of hysterectomy



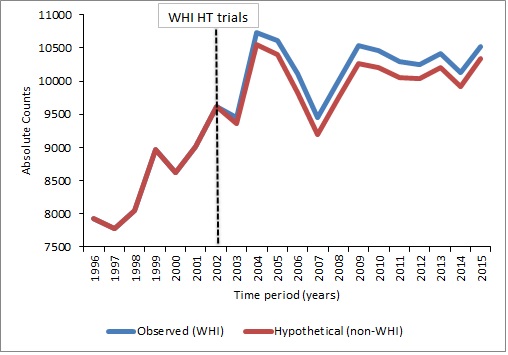
**e-Figure 3e**: Trends of attributable CHD among 60-69 year group with history of hysterectomy



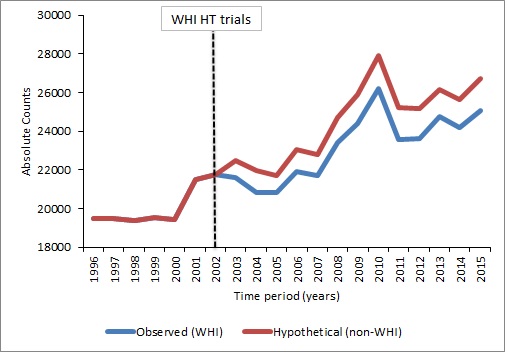
**e-Figure 3f**: Trends of attributable CHD among 70-79 year group with history of hysterectomy



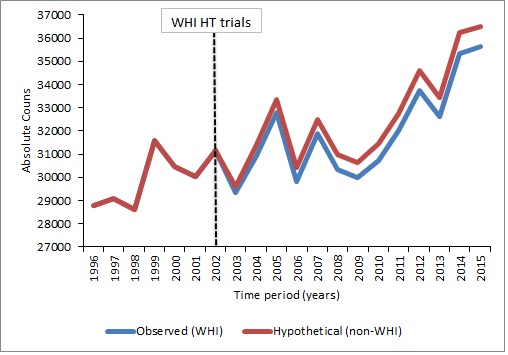
**e-Figure 3g**: Trends of attributable stroke among 50-59 year group with history of hysterectomy



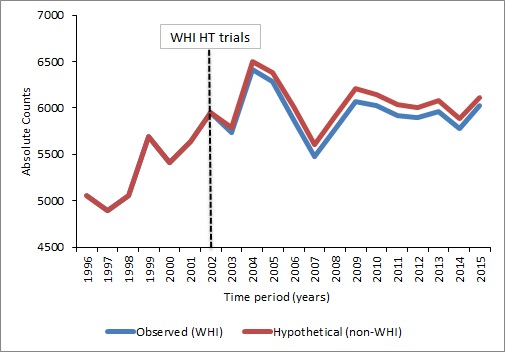
**e-Figure 3h**: Trends of attributable stroke among 60-69 year group with history of hysterectomy



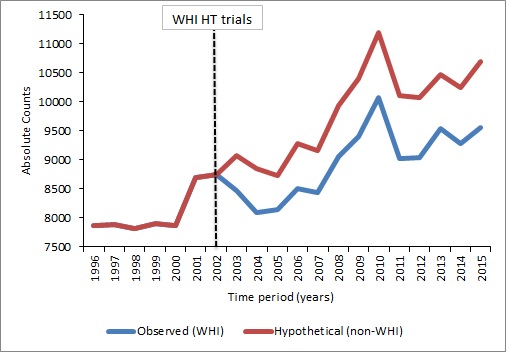
**e-Figure 3i**: Trends of attributable stroke among 70-79 year group with history of hysterectomy



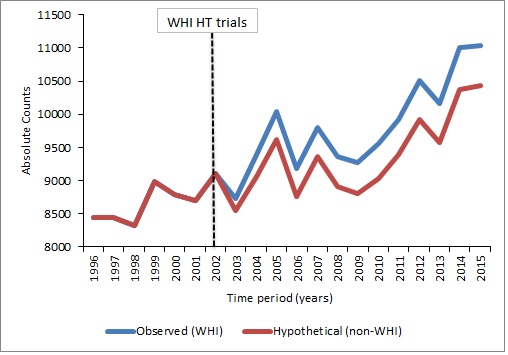
**e-Figure 3j**: Trends of attributable pulmonary embolism among 50-59 year group with history of hysterectomy



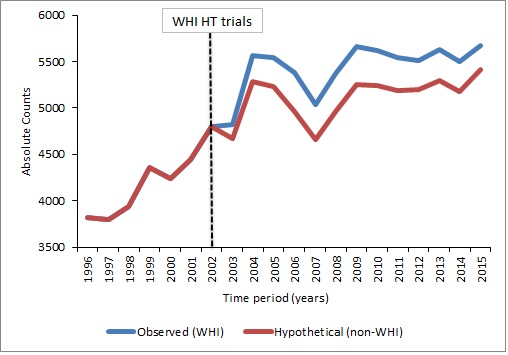
**e-Figure 3k**: Trends of attributable pulmonary embolism among 60-69 year group with history of hysterectomy



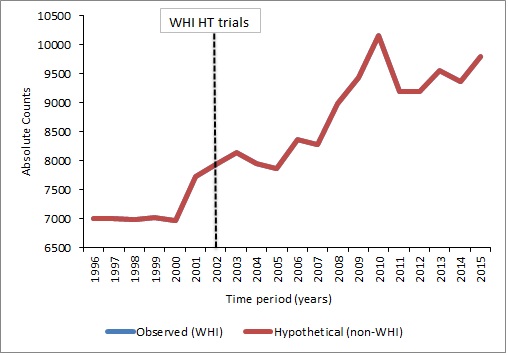
**e-Figure 3l**: Trends of attributable pulmonary embolism among 70-79 year group with history of hysterectomy



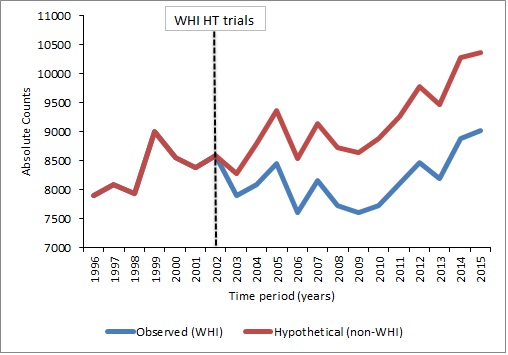
**e-Figure 3m**: Trends of attributable colorectal cancer among 50-59 year group with history of hysterectomy



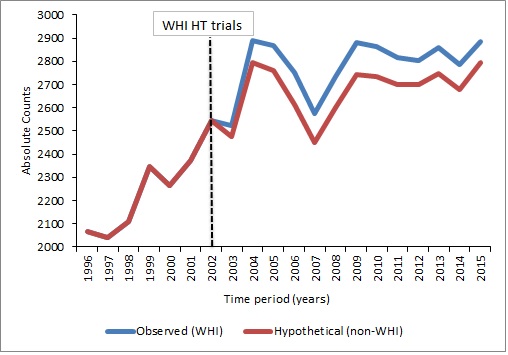
**e-Figure 3n**: Trends of attributable colorectal cancer among 60-69 year group with history of hysterectomy



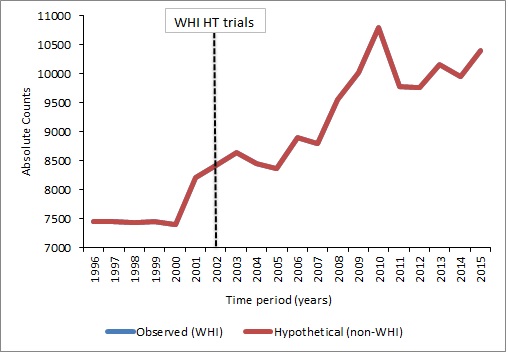
**e-Figure 3o**: Trends of attributable colorectal cancer among 70-79 year group with history of hysterectomy



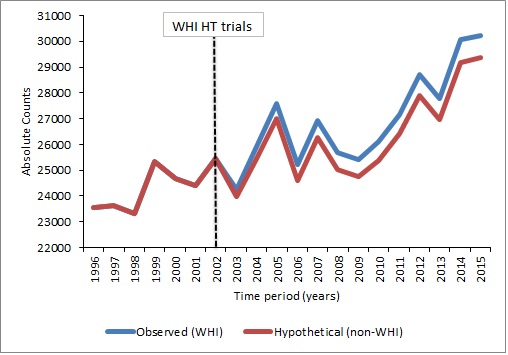
**e-Figure 3p**: Trends of attributable hip fracture among 50-59 year group with history of hysterectomy



**e-Figure 3q**: Trends of attributable hip fracture among 60-69 year group with history of hysterectomy

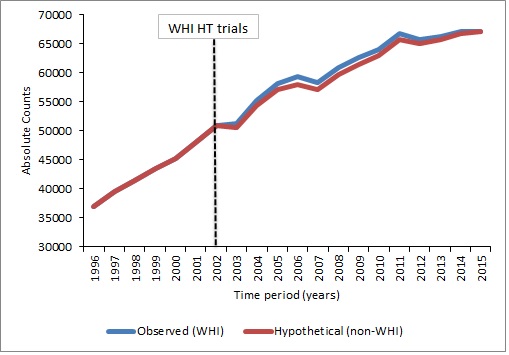


**e-Figure 3r**: Trends of attributable hip fracture among 70-79 year group with history of hysterectomy

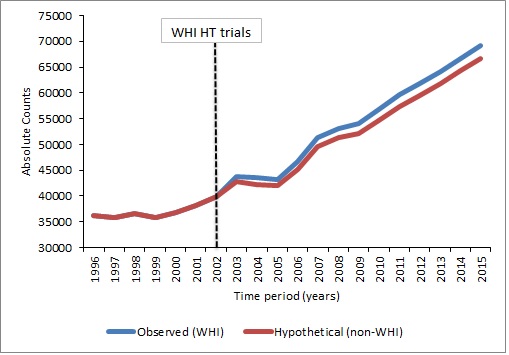


**e-Figure 4:** **Trends in excess individual chronic diseases attributable to estrogen therapy between observed and hypothetical non-WHI scenarios stratified by age groups: *Overall women with or without hysterectomy.***

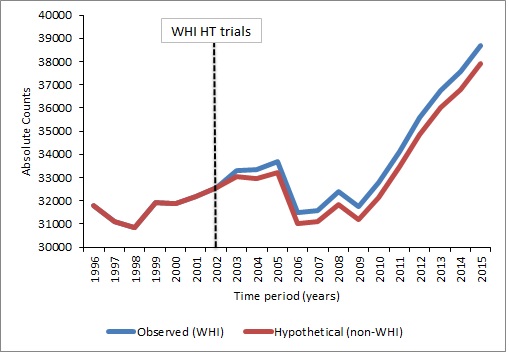
**e-Figure 4a**: Trends of attributable breast cancer among 50-59 year group overall



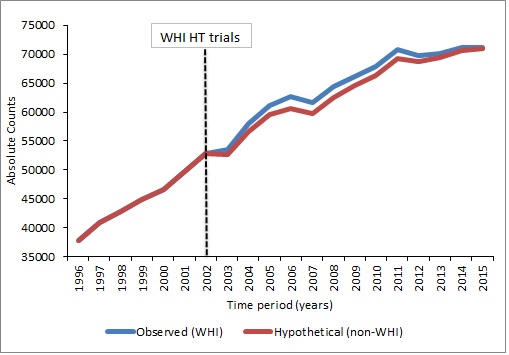
**e-Figure 4b**: Trends of attributable breast cancer among 60-69 year group overall



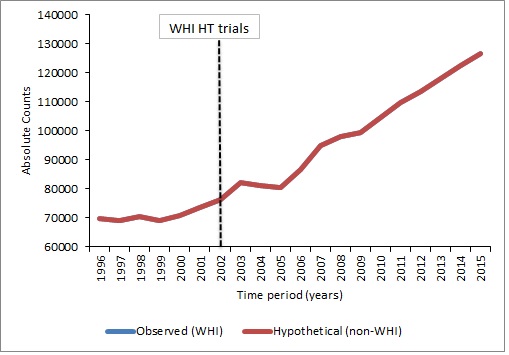
**e-Figure 4c**: Trends of attributable breast cancer among 70-79 year group overall



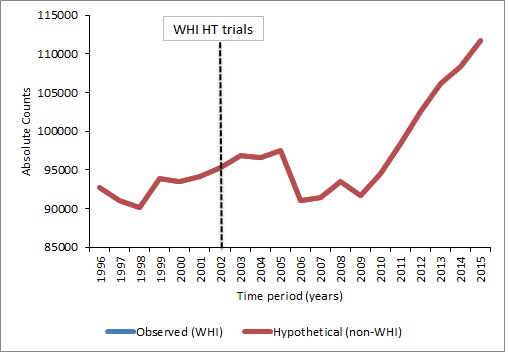
**e-Figure 4d**: Trends of attributable CHD among 50-59 year group overall



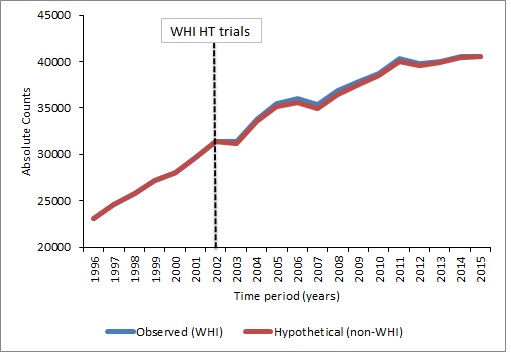
**e-Figure 4e**: Trends of attributable CHD among 60-69 year group overall



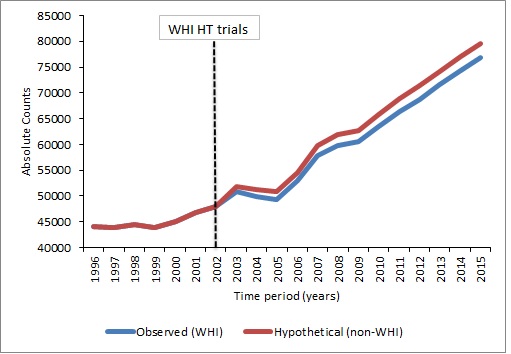
**e-Figure 4f**: Trends of attributable CHD among 70-79 year group overall



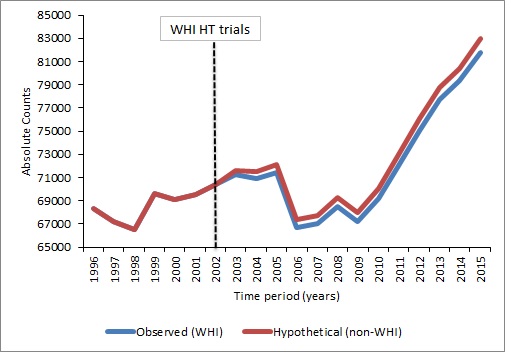
**e-Figure 4g**: Trends of attributable stroke among 50-59 year group overall



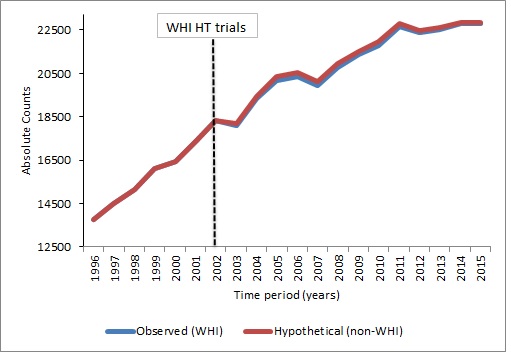
**e-Figure 4h**: Trends of attributable stroke among 60-69 year group overall



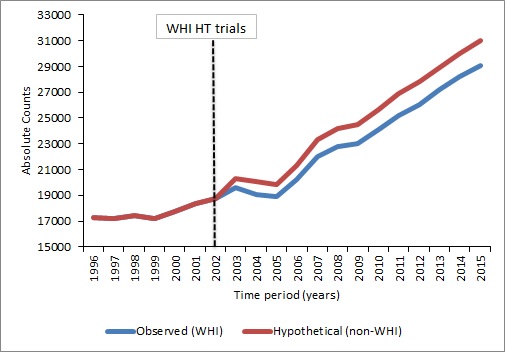
**e-Figure 4i**: Trends of attributable stroke among 70-79 year group overall



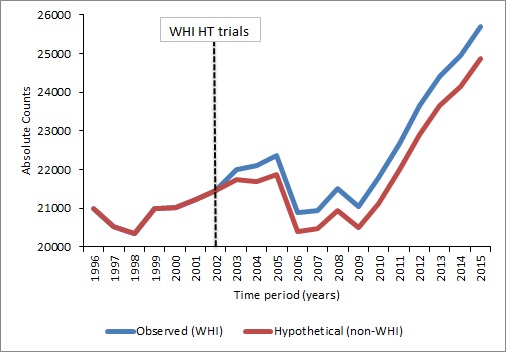
**e-Figure 4j**: Trends of attributable pulmonary embolism among 50-59 year group overall



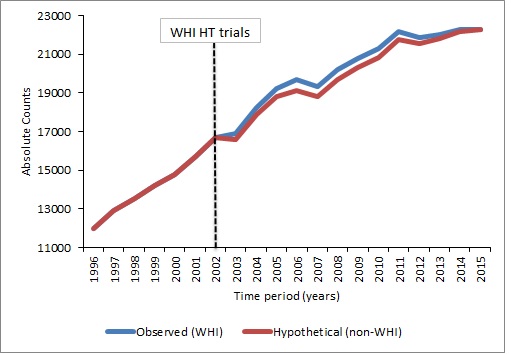
**e-Figure 4k**: Trends of attributable pulmonary embolism among 60-69 year group overall



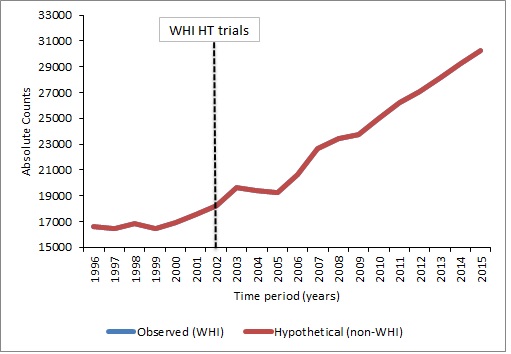
**e-Figure 4l**: Trends of attributable pulmonary embolism among 70-79 year group overall



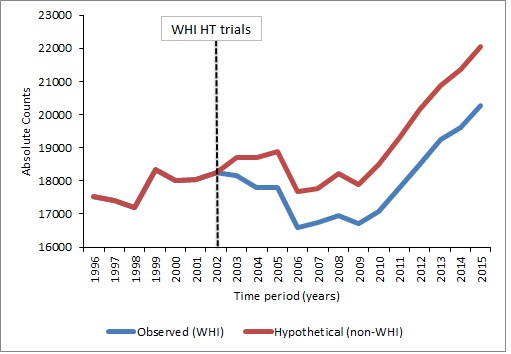
**e-Figure 4m**: Trends of attributable colorectal cancer among 50-59 year group overall



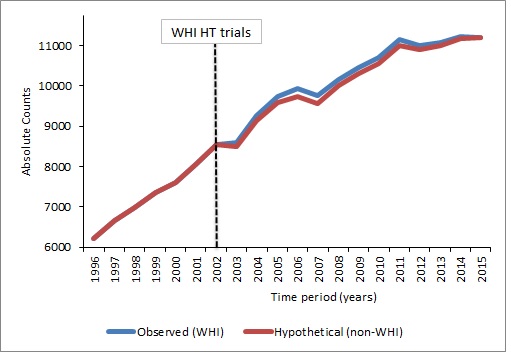
**e-Figure 4n**: Trends of attributable colorectal cancer among 60-69 year group overall



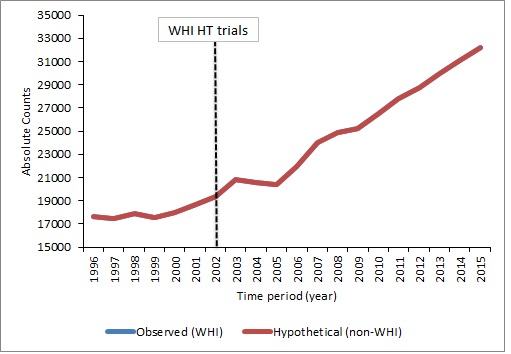
**e-Figure 4o**: Trends of attributable colorectal cancer among 70-79 year group overall



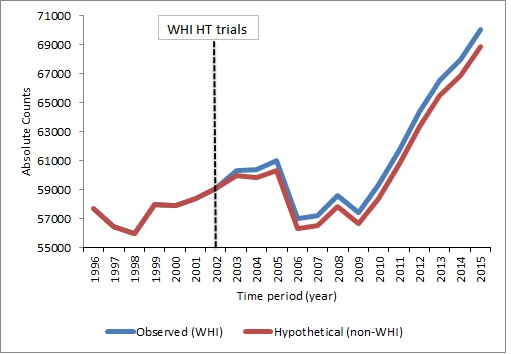
**e-Figure 4p**: Trends of attributable hip fracture among 50-59 year group overall



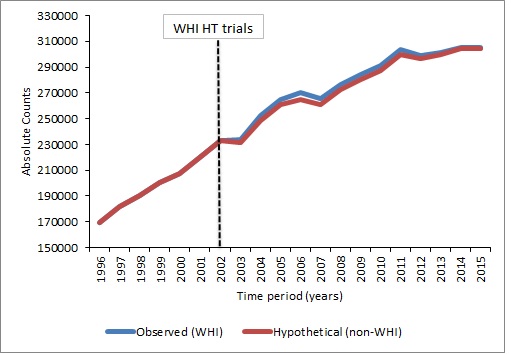
**e-Figure 4q**: Trends of attributable hip fracture among 60-69 year group overall



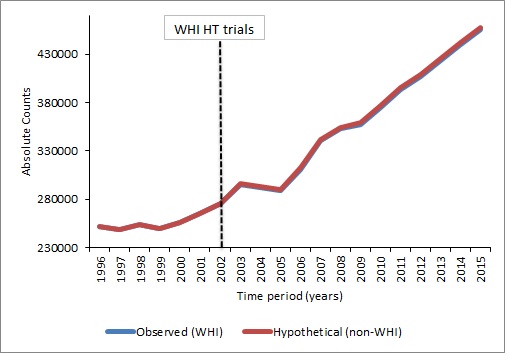
**e-Figure 4r**: Trends of attributable hip fracture among 70-79 year group overall



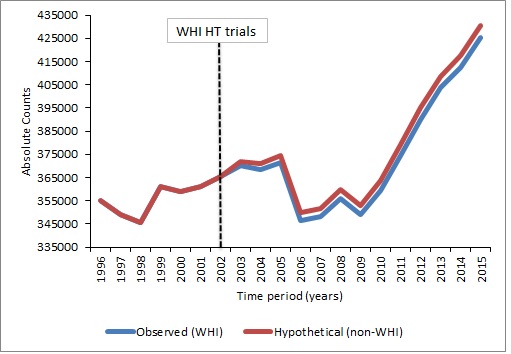
**e-Figure 4s**: Trends of attributable global index among 50-59 year group overall



**e-Figure 4t**: Trends of attributable global index among 60-69 year group overall

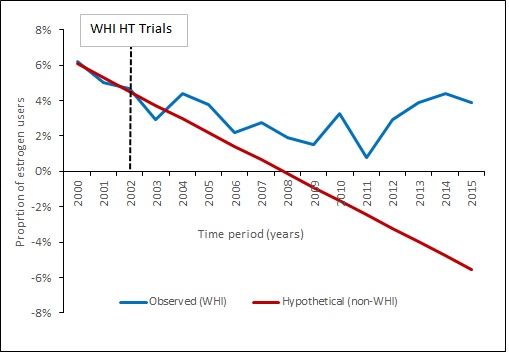


**e-Figure 4u**: Trends of attributable global index among 70-79 year group overall

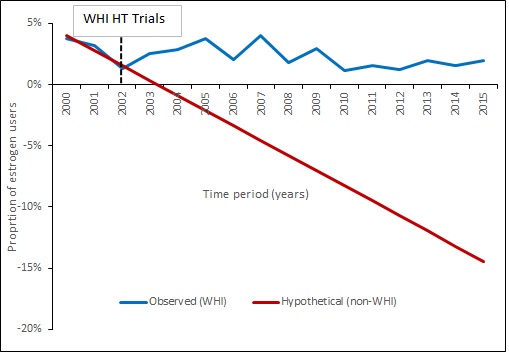


**e-Figure 5: Temporal trends of incidence (new users) of estrogen-alone utilization before and after publication of the WHI ET results, overall and among women with a history of hysterectomy**

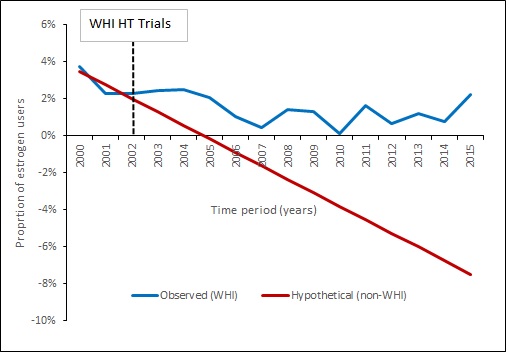
**e-Figure 5a**: Temporal trends of new-user 50-59 year-old women with a history of hysterectomy before and after publication of the WHI ET results



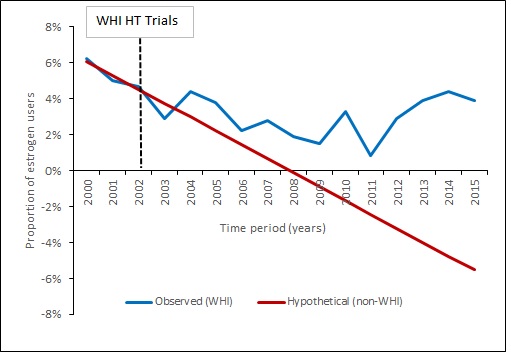
**e-Figure 5b**: Temporal trends of new-user 60-69 year-old women with a history of hysterectomy before and after publication of the WHI ET results



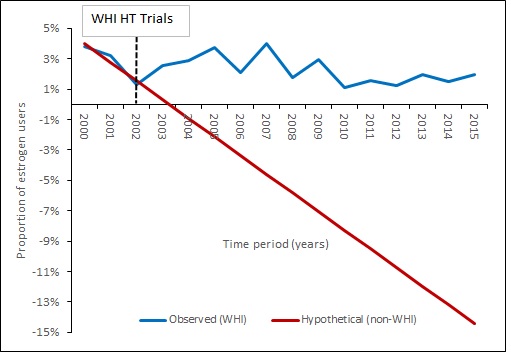
**e-Figure 5c**: Temporal trends of new-user 70-79 year-old women with a history of hysterectomy before and after publication of the WHI ET results



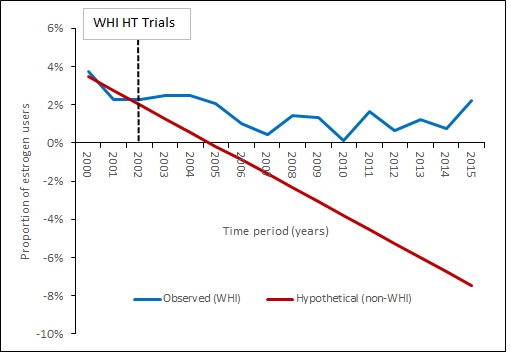
**e-Figure 5d**: Temporal trends of new-user 50-59 year-old women overall before and after publication of the WHI ET results



**e-Figure 5e**: Temporal trends of new-user 60-69 year-old women overall before and after publication of the WHI ET results



**e-Figure 5f:** Temporal trends of new-user 70-79 year-old women overall before and after publication of the WHI ET results



1. 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;310(13):1353-68. Epub 2013/10/03. doi: 10.1001/jama.2013.278040. PubMed PMID: 24084921; PMCID: PMC3963523. [↑](#footnote-ref-1)
2. Shreibati JB, Manson JE, Margolis KL, Chlebowski RT, Stefanick ML, Hlatky MA. Impact of hormone therapy on Medicare spending in the Women's Health Initiative randomized clinical trials. Am Heart J. 2018;198:108-

   14. Epub [↑](#footnote-ref-2)