**Legends**

**Supplementary Table 1.** Crude and adjusted Cox regression models stratified by age regarding the association of sex steroid treatment with death due to COVID-19, as well as all secondary outcomes.

**Supplementary Table 2.** Crude and adjusted Cox regression models regarding the association of systemic estrogen treatment with/without progestogens in relation to death due to COVID-19, laboratory-confirmed SARS-CoV-2 infection, outpatient visits/inpatient hospitalizations with/without ICU admission or hospitalization requiring ICU admission.

**Supplementary Table 3.** Crude and adjusted Cox regression models evaluating the effect of cessation of sex steroid treatment in relation to death due to COVID-19 (i.e. restricting the analyses among those with ongoing treatment as opposed to ever treatment), as well as all secondary outcomes.

**Supplementary Table 4.** Crude and adjusted Cox regression models regarding the association of sex steroid treatment in relation to all-cause mortality.

**Supplementary Table 5.** Crude and adjusted Cox regression models stratified by timing in the COVID-19 pandemic outbreak in relation to the first (1st January 2020 - 31st August 2020) or second wave of COVID-19 pandemic (1st September 2020 - 31st December 2020).

**Supplementary Table 1.** Crude and adjusted Cox regression models stratified by age regarding the association of sex steroid treatment with death due to COVID-19

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | | | | | |
|  |  | **Exposed group** | | **Comparison group** | |  |  | |
| **Exposure** | **Age (years)** | **n total** | **n events (%)** | **n total** | **n events (%)** | **Crude HR (95% CI)** | **Adjusted HR (95% CI)\*** | |
| Local estrogens alone | 53-62 | 2577 | 0 (0.00) | 12885 | 0 (0.00) | NE | NE | |
| 63-72 | 2976 | 5 (0.17) | 14880 | 6 (0.04) | 4.17(1.27 - 13.65) | 4.33(1.31 - 14.30) | |
| >73 | 4428 | 45 (1.02) | 22124 | 108 (0.49) | 2.08(1.47 - 2.95) | 1.87(1.32 - 2.65) | |
| Systemic estrogens without progestogens | 53-62 | 2715 | 0 (0.00) | 13576 | 0 (0.00) | NE | NE | |
| 63-72 | 308 | 0 (0.00) | 1540 | 0 (0.00) | NE | NE | |
| >73 | 166 | 5 (3.01) | 830 | 4 (0.48) | 6.25(1.68 - 23.27) | 4.73(1.22 - 18.32) | |
| Systemic estrogens and progestogens | 53-62 | 7508 | 0 (0.00) | 37535 | 1 (0.00) | NE | NE | |
| 63-72 | 654 | 0 (0.00) | 3270 | 1 (0.03) | NE | NE | |
| >73 | 190 | 0 (0.00) | 950 | 2 (0.21) | NE | NE | |
| Progestogens alone | 53-62 | 8803 | 0 (0.00) | 44016 | 1 (0.00) | NE | NE | |
| 63-72 | 316 | 0 (0.00) | 1580 | 0 (0.00) | NE | NE | |
| >73 | 204 | 2 (0.98) | 1020 | 6 (0.59) | 1.67(0.34 - 8.26) | 2.03(0.40 - 10.43) | |
| Tibolone alone | 53-62 | 699 | 0 (0.00) | 3495 | 0 (0.00) | NE | NE | |
| 63-72 | 175 | 0 (0.00) | 875 | 0 (0.00) | NE | NE | |
| >73 | 49 | 0 (0.00) | 245 | 0 (0.00) | NE | NE | |

Abbreviations: HR, hazard ratio; CI: confidence intervals; NE: not estimated.

\*Models adjusted for age, civil status, income, education, obesity, alcohol dependence syndrome, and Charlson Comorbidity Index(CCI).

**Supplementary Table 1(continuing).** Crude and adjusted Cox regression models regarding the association of sex steroid treatment with outpatient visits, inpatient hospitalizations with or without the need for ICU admission, and hospitalizations requiring ICU admission due to COVID-19

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Laboratory confirmed Sars-CoV2** | | | | | | | **Outpatient visits /Inpatient hospitalizations with/without ICU admission** | | | | | | | | | **Hospitalization requiring ICU admission** | | | | | | |
|  |  | **Exposed** | | **Controls** | |  |  | | **Exposed** | | **Controls** | | |  |  | | **Exposed** | | | | **Controls** | |  |  |
| **Exposure** | **Age** | **n total** | **n events (%)** | **n total** | **n events (%)** | **Crude HR (95% CI)** | **Adjusted HR (95% CI)** | **n total** | | **n events (%)** | | **n total** | **n events (%)** | **Crude HR (95% CI)** | | **Adjusted HR (95% CI)** | **n total** | | **n events (%)** | **n total** | | **n events (%)** | **Crude HR (95% CI)** | **Adjusted HR (95% CI)** |
| Local estrogens only | 53-62 | 2577 | 443 (4.43) | 12885 | 2077 (4.16) | 1.05(0.93 - 1.18) | 1.07(0.95 - 1.20) | 2577 | | 68 (0.68) | | 12885 | 353 (0.71) | 1.13(0.67 - 1.92) | | 1.13(0.67 - 1.92) | 2577 | | 3 (0.12) | 12885 | | 6 (0.05) | 2.50(0.63 - 10.00) | 2.50(0.62 - 10.00) |
| 63-72 | 2976 | 271 (2.71) | 14880 | 1158 (2.32) | 1.18(1.01 - 1.37) | 1.17(1.00 - 1.36) | 2976 | | 97 (0.97) | | 14880 | 311 (0.62) | 2.21(1.41 - 3.48) | | 2.21(1.41 - 3.48) | 2976 | | 3 (0.10) | 14880 | | 12 (0.08) | 1.25(0.35 - 4.43) | 1.31(0.37 - 4.65) |
| >73 | 4428 | 330 (3.30) | 22124 | 1316 (2.64) | 1.25(1.09 - 1.43) | 1.19(1.04 - 1.37) | 4428 | | 219 (2.19) | | 22124 | 858 (1.72) | 1.60(1.18 - 2.19) | | 1.60(1.18 - 2.19) | 4428 | | 5 (0.11) | 22124 | | 10 (0.05) | 2.50(0.85 - 7.31) | 2.48(0.85 - 7.28) |
| Systemic estrogens without progestogens | 53-62 | 2715 | 392 (12.3) | 13576 | 2076 (13.02) | 0.93(0.83 - 1.04) | 0.94(0.84 - 1.06) | 2715 | | 64 (2.00) | | 13576 | 300 (1.88) | 0.92(0.55 - 1.54) | | 0.92(0.55 - 1.54) | 2715 | | 0 (0.00) | 13576 | | 9 (0.07) | NE | NE |
| 63-72 | 308 | 20 (0.64) | 1540 | 100 (0.62) | 0.99(0.60 - 1.64) | 1.01(0.61 - 1.69) | 308 | | 3 (0.09) | | 1540 | 30 (0.19) | NE | | NE | 308 | | 0 (0.00) | 1540 | | 2 (0.13) | NE | NE |
| >73 | 166 | 11 (0.35) | 830 | 35 (0.22) | 1.47(0.73 - 2.98) | 1.38(0.67 - 2.82) | 166 | | 6 (0.17) | | 830 | 19 (0.12) | 0.83(0.10 - 6.92) | | 0.83(0.10 - 6.92) | 166 | | 0 (0.00) | 830 | | 0 (0.00) | NE | NE |
| Systemic estrogens and progestogens | 53-62 | 7508 | 1141 (13.66) | 37535 | 5360 (12.84) | 1.08(1.01 - 1.15) | 1.07(1.00 - 1.15) | 7508 | | 111 (1.33) | | 37535 | 691 (1.65) | 0.72(0.51 - 1.03) | | 0.72(0.51 - 1.03) | 7508 | | 2 (0.03) | 37535 | | 11 (0.03) | 0.91(0.20 - 4.10) | 0.98(0.22 - 4.44) |
| 63-72 | 654 | 47 (0.57) | 3270 | 223 (0.54) | 1.08(0.78 - 1.49) | 1.11(0.80 - 1.54) | 654 | | 12 (0.14) | | 3270 | 57 (0.14) | 1.14(0.43 - 3.00) | | 1.14(0.43 - 3.00) | 654 | | 1 (0.15) | 3270 | | 2 (0.06) | 2.50(0.23 - 27.55) | 2.65(0.24 - 29.28) |
| >73 | 190 | 8 (0.09) | 950 | 31 (0.08) | 1.17(0.51 - 2.66) | 1.18(0.51 - 2.71) | 190 | | 0 (0.00) | | 950 | 28 (0.07) | NE | | NE | 190 | | 0 (0.00) | 950 | | 0 (0.00) | NE | NE |
| Progestogens only | 53-62 | 8803 | 1344 (14.41) | 44016 | 6440 (13.81) | 1.04(0.98 - 1.11) | 1.03(0.97 - 1.10) | 8803 | | 154 (1.65) | | 44016 | 867 (1.86) | 0.74(0.54 - 1.01) | | 0.74(0.54 - 1.01) | 8803 | | 1 (0.01) | 44016 | | 32 (0.07) | 0.16(0.02 - 1.14) | 0.16(0.02 - 1.17) |
| 63-72 | 316 | 15 (0.16) | 1580 | 108 (0.23) | 0.70(0.40 - 1.23) | 0.68(0.38 - 1.23) | 316 | | 0 (0.00) | | 1580 | 13 (0.03) | NE | | NE | 316 | | 0 (0.00) | 1580 | | 1 (0.06) | NE | NE |
| >73 | 204 | 14 (0.15) | 1020 | 53 (0.11) | 1.43(0.79 - 2.59) | 1.48(0.77 - 2.84) | 204 | | 14 (0.16) | | 1020 | 32 (0.07) | 2.50(0.75 - 8.30) | | 2.50(0.75 - 8.30) | 204 | | 0 (0.00) | 1020 | | 0 (0.00) | NE | NE |
| Tibolone only | 53-62 | 699 | 119 (12.90) | 3495 | 509 (11.03) | 1.20(0.97 - 1.47) | 1.19(0.97 - 1.47) | 699 | | 17 (1.87) | | 3495 | 80 (1.73) | 0.77(0.27 - 2.21) | | 0.77(0.27 - 2.21) | 699 | | 0 (0.00) | 3495 | | 3 (0.09) | NE | NE |
| 63-72 | 175 | 24 (2.58) | 875 | 72 (1.56) | 1.80(1.12 - 2.89) | 1.82(1.12 - 2.95) | 175 | | 3 (0.31) | | 875 | 9 (0.19) | 1.25(0.14 - 11.18) | | 1.25(0.14 - 11.18) | 175 | | 0 (0.00) | 875 | | 1 (0.11) | NE | NE |
| >73 | 49 | 1 (0.12) | 245 | 8 (0.17) | 0.63(0.08 - 5.00) | 0.70(0.09 - 5.72) | 49 | | 3 (0.31) | | 245 | 6 (0.12) | 2.50(0.23 - 27.57) | | 2.50(0.23 - 27.57) | 49 | | 0 (0.00) | 245 | | 0 (0.00) | NE | NE |

Abbreviations: HR, hazard ratio; CI, confidence intervals; ICU, intensive care unit; NE: not estimated

\*Models adjusted for occupation, family type, education, obesity, alcohol dependence syndrome, and Charlson Comorbidity Index

**Supplementary Table 2.** Crude and adjusted Cox regression models regarding the association of systemic estrogen treatment with/without progestogens in relation to death due to COVID-19, laboratory-confirmed SARS-CoV-2 infection, outpatient visits/inpatient hospitalizations with/without ICU admission or hospitalization requiring ICU admission.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | | | | | | |
|  | **Exposed** | | | **Unexposed** | |  |  | |
| **Exposure** | | **n total** | **n events (%)** | **n total** | **n events (%)** | **Crude HR (95% CI)** | **Adjusted HR (95% CI)\*** | |
| Systemic estrogens with/without progestogens | | 11541 | 5 | 57701 | 8 | 3.13 (1.02-9.55) | 4.22 (1.37-13.05) | |

Abbreviations: HR, hazard ratio; CI: confidence intervals

\*Models adjusted for age, civil status, income, education, obesity, alcohol dependence syndrome, and Charlson Comorbidity Index(CCI).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Laboratory confirmed SARS-CoV-2 infection** | | | | | | | | | **Outpatient visits /Inpatient hospitalizations with/without ICU admission** | | | | | | | | | | **Hospitalization requiring ICU admission** | | | | | | | | | |
|  | **Exposed** | | **Unexposed** | | |  | |  | | **Exposed** | | | **Unexposed** | | |  | |  | | **Exposed** | | | **Unexposed** | | |  | |  | |
| **Exposure** | **n total** | **n events (%)** | **n total** | **n events (%)** | **Crude HR (95% CI)** | | **Adjusted HR (95% CI)** | | **n total** | | **n events (%)** | **n total** | | **n events (%)** | **Crude HR (95% CI)** | | **Adjusted HR (95% CI)** | | **n total** | | **n events (%)** | **n total** | | **n events (%)** | **Crude HR (95% CI)** | | **Adjusted HR (95% CI)** | |
| Systemic estrogens with/without progestogens | 11541 | 1620 | 57701 | 7826 | 1.04 (0.98-1.01) | | 1.04 (0.98-1.10) | | 11541 | | 195 | 57701 | | 1126 | 0.86 (0.74-1.00) | | 0.90 (0.75-1.05) | | 11541 | | 3 | 57701 | | 24 | 0.63 (0.19-2.08) | | 0.65 (0.19-2.16) | |
|  |  |  |  |  |  | |  | |  | |  |  | |  |  | |  | |  | |  |  | |  |  | |  | |

Abbreviations: HR, hazard ratio; CI, confidence intervals; ICU, intensive care unit

\*Models adjusted for age, civil status, income, education, obesity, alcohol dependence syndrome, and Charlson Comorbidity Index(CCI).

**Supplementary Table 3.** Crude and adjusted Cox regression models evaluating the effect of treatment cessation in relation to death due to COVID-19 (i.e. restricting the analyses among those with ongoing treatment as opposed to ever treatment).

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | | | | | | |
|  | **Exposed** | | | **Unexposed** | |  |  | |
| **Exposure** | **Person time (in years)** | | **n events (%)** | **Person time (in years)** | **n events (%)** | **Crude HR (95% CI)** | **Adjusted HR (95% CI)\*** | |
| Local estrogens alone | | 3964 | 21 | 19813 | 55 | 1.55 (0.94-2.56) | 1.71 (1.03-2.82) | |
| Systemic estrogens without progestogens | | 1240 | 2 | 6200 | 0 | NE | NE | |
| Systemic estrogens and progestogens | | 3248 | 0 | 16236 | 0 | NE | NE | |
| Progestogens alone | | 4636 | 1 | 23180 | 2 | 0.96 (0.09-10.57) | 0.65 (0.05-7.83) | |
| Tibolone alone | | 359 | 0 | 1794 | 0 | NE | NE | |

Abbreviations: HR, hazard ratio; CI: confidence intervals; NE: not estimated.

\*Models adjusted for occupation, family type, education, obesity, alcohol dependence syndrome, and Charlson Comorbidity Index

**Supplementary Table 3(continuing).** Crude and adjusted Cox regression models evaluating the effect of treatment cessation in relation to outpatient visits, inpatient hospitalizations with or without the need for ICU admission, and hospitalizations requiring ICU admission due to COVID-19 (i.e. restricting the analyses among those with ongoing treatment as opposed to ever treatment).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Laboratory confirmed Sars-CoV2** | | | | | | | | | **Outpatient visits /Inpatient hospitalizations with/without ICU admission** | | | | | | | | | | **Hospitalization requiring ICU admission** | | | | | | | | | |
|  | **Exposed** | | **Controls** | | |  | |  | | **Exposed** | | | **Controls** | | |  | |  | | **Exposed** | | | **Controls** | | |  | |  | |
| **Exposure** | **Person time (in years)** | **n events (%)** | **Person time (in years)** | **n events (%)** | **Crude HR (95% CI)** | | **Adjusted HR (95% CI)** | | **Person time (in years)** | | **n events (%)** | **Person time (in years)** | | **n events (%)** | **Crude HR (95% CI)** | | **Adjusted HR (95% CI)** | | **Person time (in years)** | | **n events (%)** | **Person time (in years)** | | **n events (%)** | **Crude HR (95% CI)** | | **Adjusted HR (95% CI)** | |
| local estrogens only | 3962 | 192 | 19814 | 513 | 1.51 (1.28-1.78) | | 1.50 (1.26-1.75 | | 3962 | | 135 | 19812 | | 510 | 1.07 (0.89-1.30) | | 1.12 (0.93-1.36) | | 397 | | 5 | 19811 | | 6 | 3.29 (1.00-10.78) | | 3.07 (0.90-10.40) | |
| systemic estrogens without progestogens | 1238 | 128 | 6201 | 130 | 0.91 (0.71-1.16) | | 0.93 (0.73-1.19) | | 1242 | | 45 | 6201 | | 21 | 1.97 (1.17-3.30) | | 1.99 (1.18-3.35) | | 1241 | | 0 | 6212 | | 2 | NE | | NE | |
| estrogens and progestogens | 3247 | 365 | 16252 | 794 | 1.08 (0.95-1.22) | | 1.07 (0.94-1.21) | | 3249 | | 73 | 16233 | | 188 | 089 (0.68-1.17) | | 0.91(0.69-1.19) | | 3248 | | 2 | 16242 | | 2 | 2.36 (0.33-16.76) | | 2.35 (0.33-16.83) | |
| progestogens only | 4629 | 1035 | 23178 | 1996 | 0.96 (0.89-1.04) | | 0.97 (0.90-1.04) | | 4635 | | 148 | 23178 | | 279 | 0.99 (0.81-1.21) | | 1.00 (0.82-1.22) | | 4634 | | 1 | 23178 | | 12 | 0.16 (0.02-1.20) | | 0.15 (0.02 (1.16) | |
| Tibolone only | 358 | 45 | 1793 | 14 | 0.90 (0.49-1.63) | | 0.83 (0.45-1.53) | | 355 | | 14 | 1791 | | 3 | 1.31 (0.38-4.58) | | 1.44 (0.41-5.09) | | 359 | | 0 | 1787 | | 1 | NE | | NE | |

Abbreviations: HR, hazard ratio; CI, confidence intervals; ICU, intensive care unit; NE: not estimated.

\*Models adjusted for occupation, family type, education, obesity, alcohol dependence syndrome, and Charlson Comorbidity Index

**Supplementary Table 4.** Crude and adjusted Cox regression models regarding the association of sex steroid treatment with death.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | | | | | |
|  | **Exposed** | | **Unexposed** | |  |  | |
| **Exposure** | **n total** | **n events (%)** | **n total** | **n events (%)** | **Crude HR (95% CI)** | **Adjusted HR (95% CI)\*** | |
| Local estrogens only | 9981 | 465(4.7) | 49889 | 2316 (4.6) | 1.00(0.91 - 1.11) | 1.00(0.90 - 1.10) | |
| Systemic estrogens without progestogens | 3189 | 20 (0.6) | 15946 | 100 (0.6) | 1.00(0.62 - 1.62) | 0.99(0.61 - 1.60) | |
| Systemic estrogens and progestogens | 8352 | 6 (0.1) | 41755 | 30 (0.1) | 1.00(0.42 - 2.40) | 1.09(0.45 - 2.63) | |
| Progestogens only | 9323 | 46 (0.5) | 46616 | 230 (0.5) | 1.00(0.73 - 1.37) | 1.30(0.95 - 1.79) | |
| Tibolone only | 923 | 0 (0.0) | 4615 | 0 (0.0) | NE | NE | |

Abbreviations: HR, hazard ratio; CI: confidence intervals; NE: not estimated.

\*Models adjusted for age, civil status, income, education, obesity, alcohol dependence syndrome, and Charlson Comorbidity Index(CCI).

**Supplementary Table 5.** Crude and adjusted Cox regression models stratified by timing in the COVID-19 pandemic outbreak in relation to the first (1st January 2020 - 31st August 2020) or second wave of COVID-19 pandemic (1st September 2020 - 31st December 2020).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Death due to COVID-19** |  |  |  |  |
|  | **Exposed** | **Unexposed** |  |  |
| **Local estrogens only** | **n events** | **n events** | **Crude HR (95% CI)** | **Adjusted HR (95% CI)** |
| Wave 1 | 30 | 63 | 2.38(1.54 - 3.68) | 2.12(1.37 – 3.28) |
| Wave 2 | 20 | 51 | 1.96(1.17 - 3.29) | 1.88 (1.12 – 3.17) |
| **Systemic estrogens without progestogens** |  |  |  |  |
| Wave 1 | 4 | 2 | 10.00(1.83 – 54.60) | 9.51 (1.58 – 57.18) |
| Wave 2 | 1 | 2 | 2.50 (0.23-27.60) | 2.07 (0.18-23.39) |
| **Estrogens and progestogens** |  |  |  |  |
| Wave 1 | 0 | 2 | NE | NE |
| Wave 2 | 0 | 2 | NE | NE |
| **Progestogens only** |  |  |  |  |
| Wave 1 | 2 | 4 | 2.50 (0.46 – 13.65) | 5.46 (0.91 – 32.83) |
| Wave 2 | 0 | 3 | NE | NE |
| **Tibolone only** |  |  |  |  |
| Wave 1 | 0 | 0 | NE | NE |
| Wave 2 | 0 | 0 | NE | NE |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Laboratory confirmed Sars-CoV2** |  |  |  |  |
|  | **Exposed** | **Unexposed** |  |  |
| **Local estrogens only** | **n events** | **n events** | **Crude HR (95% CI)** | **Adjusted HR (95% CI)** |
| Wave 1 | 313 | 1274 | 1.15 (1.02 - 1.30) | 1.10 (0.97 - 1.25) |
| Wave 2 | 734 | 3285 | 1.15 (1.06 - 1.25) | 1.14 (1.05 - 1.24) |
| **Systemic estrogens without progestogens** |  |  |  |  |
| Wave 1 | 78 | 388 | 0.99 (0.78 - 1.27) | 1.02 (0.80 - 1.30) |
| Wave 2 | 346 | 1824 | 0.95 (0.85 - 1.07) | 0.96 (0.86 - 1.08) |
| **Estrogens and progestogens** |  |  |  |  |
| Wave 1 | 165 | 949 | 0.87 (0.74 - 1.02) | 0.90 (0.76 - 1.07) |
| Wave 2 | 1031 | 4668 | 1.10 (1.03 - 1.18) | 1.10 (1.03 - 1.18) |
| **Progestogens only** |  |  |  |  |
| Wave 1 | 224 | 1067 | 1.04 (0.90 - 1.20) | 1.04 (0.90 - 1.20) |
| Wave 2 | 1150 | 5542 | 1.04 (0.98 - 1.11) | 1.03 (0.97 - 1.10) |
| **Tibolone only** |  |  |  |  |
| Wave 1 | 26 | 98 | 1.33 (0.86 - 2.05) | 1.30 (0.84 - 2.01) |
| Wave 2 | 118 | 491 | 1.21 (0.99 - 1.48) | 1.21 (0.99 - 1.48) |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Outpatient visits /Inpatient hospitalizations with/without ICU admission** |  |  |  |  |
|  | **Exposed** | **Unexposed** |  |  |
| **Local estrogens only** | **n events** | **n events** | **Crude HR (95% CI)** | **Adjusted HR (95% CI)** |
| Wave 1 | 221 | 915 | 1.26 (1.09 - 1.46) | 1.21 (1.04 - 1.40) |
| Wave 2 | 164 | 612 | 1.42 (1.20 - 1.69) | 1.40 (1.17 - 1.66) |
| **Systemic estrogens without progestogens** |  |  |  |  |
| Wave 1 | 51 | 215 | 1.20 (0.89 - 1.63) | 1.23 (0.90 - 1.67) |
| Wave 2 | 21 | 136 | 0.80 (0.50 - 1.26) | 0.82 (0.52 - 1.30) |
| **Estrogens and progestogens** |  |  |  |  |
| Wave 1 | 74 | 494 | 0.75 (0.59 - 0.96) | 0.82 (0.64 - 1.04) |
| Wave 2 | 49 | 283 | 0.86 (0.64 - 1.17) | 0.96 (0.71 - 1.31) |
| **Progestogens only** |  |  |  |  |
| Wave 1 | 108 | 570 | 0.95 (0.77 - 1.17) | 0.96 (0.78 - 1.18) |
| Wave 2 | 61 | 351 | 0.90 (0.68 - 1.18) | 0.92 (0.70 - 1.21) |
| **Tibolone only** |  |  |  |  |
| Wave 1 | 14 | 57 | 1.23 (0.69 - 2.21) | 1.28 (0.71 - 2.30) |
| Wave 2 | 9 | 37 | 1.22 (0.59 - 2.52) | 1.33 (0.64 - 2.77) |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Hospitalization requiring ICU admission** |  |  |  |  |
|  | **Exposed** | **Unexposed** |  |  |
| **Local estrogens only** | **n events** | **n events** | **Crude HR (95% CI)** | **Adjusted HR (95% CI)** |
| Wave 1 | 7 | 14 | 2.50 (1.01 - 6.19) | 2.36 (0.95 - 5.87) |
| Wave 2 | 4 | 14 | 1.43 (0.47 - 4.34) | 1.51 (0.49 - 4.59) |
| **Systemic estrogens without progestogens** |  |  |  |  |
| Wave 1 | 0 | 6 | NE | NE |
| Wave 2 | 0 | 5 | NE | NE |
| **Estrogens and progestogens** |  |  |  |  |
| Wave 1 | 1 | 2 | 2.50 (0.23 - 27.57) | 2.05 (0.18 - 22.76) |
| Wave 2 | 2 | 11 | 0.91 (0.20 - 4.10) | 1.04 (0.23 - 4.75) |
| **Progestogens only** |  |  |  |  |
| Wave 1 | 0 | 15 | NE | NE |
| Wave 2 | 1 | 18 | 0.28 (0.04 - 2.08) | 0.29 (0.04 - 2.19) |
| **Tibolone only** |  |  |  |  |
| Wave 1 | 0 | 0 | NE | NE |
| Wave 2 | 0 | 4 | NE | NE |

\*Models adjusted for age, civil status, income, education, obesity, alcohol dependence syndrome, and Charlson Comorbidity Index(CCI).

NE: not estimated.