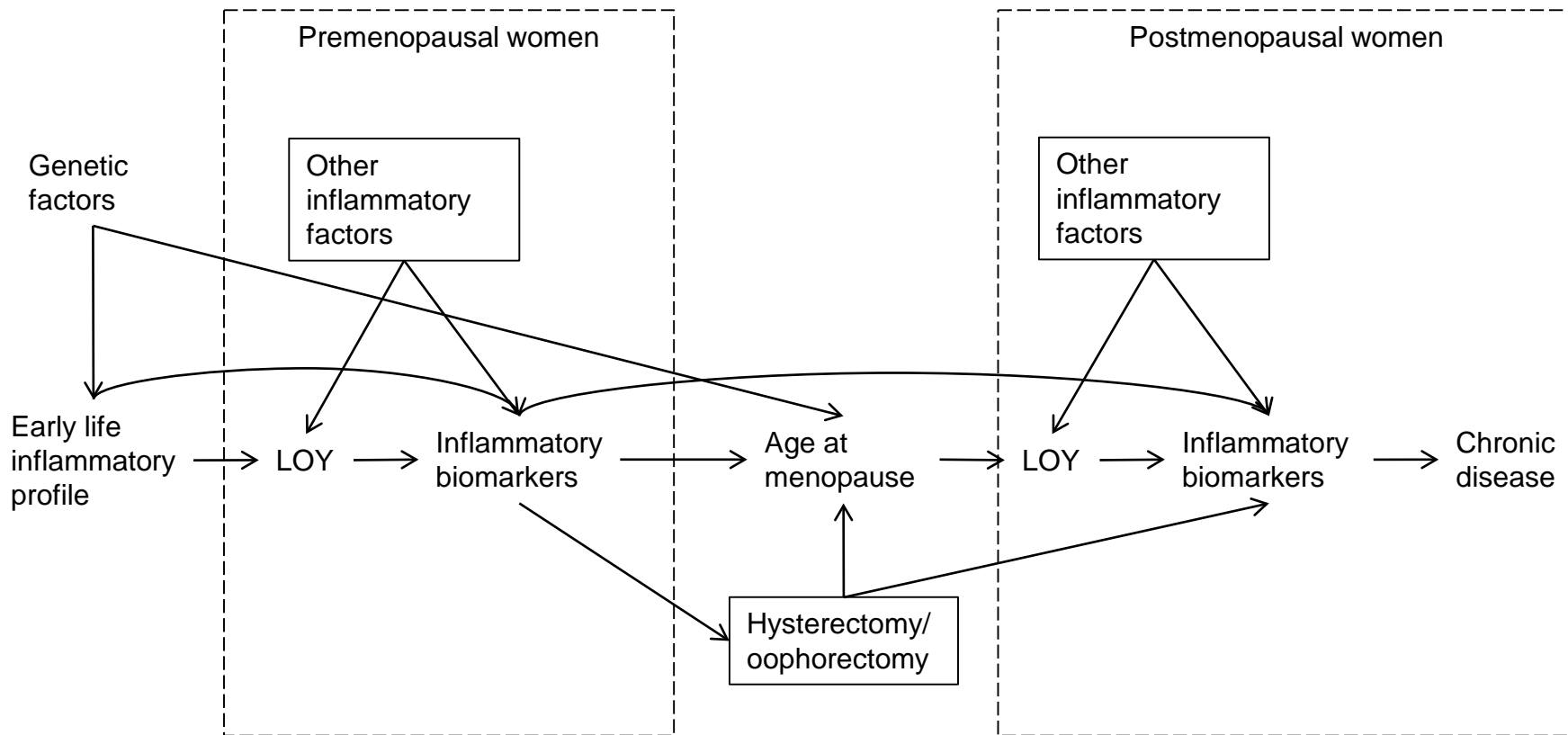**Estimated Number of Lifetime Ovulatory Years and Its Determinants in Relation to Levels of Circulating Inflammatory Biomarkers**

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**Web Material:**

Web Figure 1

Web Tables 1–4

Web Figure 1. Directed acyclic graph of the conceptual framework between LOY and inflammatory biomarkers, highlighting potential complex reciprocal relationships. A solid box indicates conditioning on the factor(s) by either covariate adjustment or restriction.

Web Table 1. Spearman correlations among LOY and its individual components

| | LOY | Age at menopause (or at blood collection) | Duration of OC use | Number of children | Age at menarche |
|---|---|---|---|---|---|
| **Postmenopausal women** | | | | | |
| LOY | 1.00 | 0.64 | -0.69 | -0.21 | -0.22 |
| Age at menopause | | 1.00 | -0.06 | 0.18 | 0.08 |
| Duration of OC use | | | 1.00 | -0.01 | -0.02 |
| Number of children | | | | 1.00 | 0.08 |
| Age at menarche | | | | | 1.00 |
| | | | | | |
| **Premenopausal women** | | | | | |
| LOYs | 1.00 | 0.75 | -0.65 | -0.01 | -0.22 |
| Age at blood collection | | 1.00 | -0.09 | 0.16 | -0.01 |
| Duration of OC use | | | 1.00 | -0.11 | -0.01 |
| Number of children | | | | 1.00 | 0.06 |
| Age at menarche | | | | | 1.00 |

Web Table 2. Associations of inflammatory biomarkers with lifetime ovulatory years and individual components among postmenopausal women who never used HT

| | CRP (mg/L) | IL-6 (pg/mL) | sTNFR2 (pg/mL) |
|---|---|---|---|
| | | Multivariable-adjusted geometric means | |
| **Lifetime ovulatory years[1]** | | | |
| ≤29 years | 2.05 | 1.41 | 2778 |
| 29-33 years | 1.84 | 1.42 | 2757 |
| 34-36 years | 1.82 | 1.30 | 2678 |
| >36 years | 1.66 | 1.19 | 2707 |
| per 5 year | -8.7 (-12.7, -4.5) | -5.5 (-8.8, -2.1) | -0.7 (-1.9, 0.5) |
| p for trend | <0.0001 | 0.002 | 0.27 |
| | | | |
| **Age at menopause[2]** | | | |
| <45 years | 2.11 | 1.48 | 2908 |
| 45-49 years | 1.97 | 1.38 | 2710 |
| 50-54 years | 1.79 | 1.35 | 2679 |
| >54 years | 1.85 | 1.21 | 2587 |
| per 1 year | -1.5 (-2.8, -0.1) | -1.3 (-2.4, -0.2) | -0.5 (-0.9, -0.2) |
| p for trend | 0.03 | 0.02 | 0.004 |
| | | | |
| **Duration of OC use[2]** | | | |
| No use | 1.81 | 1.27 | 2796 |
| < 1.0 years | 1.83 | 1.41 | 2679 |
| 1.0-4.9 years | 1.70 | 1.34 | 2712 |
| 5.0-9.9 years | 1.99 | 1.36 | 2661 |
| ≥ 10 years | 2.35 | 1.37 | 2746 |
| per 1 year | 1.7 (0.3, 3.1) | 0.6 (-0.5, 1.7) | -0.2 (-0.6, 0.2) |
| p for trend | 0.02 | 0.27 | 0.23 |
| | | | |
| **Age at menarche[2]** | | | |
| ≤ 11 years | 1.79 | 1.32 | 2706 |
| 12 years | 2.03 | 1.32 | 2714 |
| 13 years | 1.93 | 1.35 | 2662 |
| 14 years | 1.85 | 1.36 | 2762 |
| ≥ 15 years | 2.03 | 1.41 | 2750 |
| per 1 year | 1.3 (-1.9, 4.6) | 1.5 (-1.0, 4.1) | 0.2 (-0.7, 1.1) |
| p for trend | 0.43 | 0.25 | 0.72 |
| | | | |
| **Parity[2]** | | | |
| Nulliparous | 1.68 | 1.29 | 2645 |
| 1 child | 2.00 | 1.20 | 2692 |
| 2 children | 1.89 | 1.37 | 2741 |

| | | | |
|---|---|---|---|
| 3 children | 1.96 | 1.47 | 2789 |
| 4+ children | 2.14 | 1.43 | 2728 |
| per 1 child | 4.0 (1.4, 6.5) | 2.1 (0.1, 4.2) | 0.0 (-0.7, 0.7) |
| p for trend | 0.003 | 0.04 | 0.96 |

[1]Adjusted for age at blood draw, smoking, BMI, physical activity, aspirin use, NSAIDS use, inflammatory dietary index, and history of diabetes and hypertension,

[2]Plus mutually adjusted for age at menopause, duration of OC use, age at menarche and parity

Web Table 3. Associations of inflammatory biomarkers with measures of OC use among ever users in NHSII

| | CRP (mg/L) | IL-6 (pg/mL) | sTNFR2 (pg/mL) |
|---|---|---|---|
| | Multivariable-adjusted geometric means | | |
| Cumulative estrogen dose[1] | | | |
| 0-20000 | 1.10 | 1.10 | 2344 |
| 20001-50000 | 1.21 | 1.06 | 2339 |
| 50001-90000 | 1.38 | 1.13 | 2410 |
| 90000+ | 1.40 | 1.04 | 2279 |
| p for trend | <0.0001 | 0.32 | 0.35 |
| | | | |
| Cumulative progestin dose[1] | | | |
| 0-300 | 1.15 | 1.09 | 2395 |
| 301-800 | 1.19 | 1.11 | 2341 |
| 800-2000 | 1.27 | 1.10 | 2366 |
| 2000+ | 1.44 | 1.04 | 2322 |
| p for trend | <0.0001 | 0.08 | 0.05 |
| | | | |
| Time since last use[1] | | | |
| >10 years | 1.22 | 1.09 | 2328 |
| 5-10 years | 1.27 | 1.07 | 2340 |
| <5 years | 1.27 | 1.06 | 2347 |
| Current use | 3.19 | 1.10 | 2307 |
| p for trend | 0.15 | 0.43 | 0.77 |
| | | | |
| Age at first use[1] | | | |
| 13-16 years | 1.30 | 1.03 | 2307 |
| 17-20 years | 1.27 | 1.09 | 2327 |
| 21-24 years | 1.32 | 1.09 | 2343 |
| 25+ years | 1.33 | 1.04 | 2390 |
| p for trend | 0.45 | 0.92 | 0.13 |
| | | | |
| Age at last use[1] | | | |
| <20 years | 1.09 | 1.08 | 2417 |
| 20-25 years | 1.16 | 1.11 | 2368 |
| 26-35 years | 1.26 | 1.10 | 2387 |
| 35+ years | 1.51 | 1.09 | 2353 |
| p for trend | <0.0001 | 0.51 | 0.47 |

[1]Adjusted for age at blood draw, menopausal status, smoking, BMI, physical activity, aspirin use, NSAIDS use, inflammatory dietary index, and history of diabetes and hypertension.

Web Table 4. Associations of inflammatory biomarkers with lifetime ovulatory years and individual components among premenopausal women in NHSII exposed to current OC formulations (N=2,371)

| | CRP (mg/L) | IL-6 (pg/mL) | sTNFR2 (pg/mL) |
|---|---|---|---|
| | Multivariable-adjusted geometric means | | |
| Lifetime ovulatory years[1] | | | |
| ≤22 years | 1.11 | 0.92 | 2308 |
| 22-26 years | 0.92 | 0.92 | 2295 |
| 27-30 years | 0.93 | 0.95 | 2282 |
| >30 years | 0.88 | 0.96 | 2396 |
| per 5 year | -10.8 (-14.8, -6.7) | 1.1 (-1.8, 4.1) | 1.3 (0.1, 2.5) |
| p for trend | <0.0001 | 0.45 | 0.04 |
| | | | |
| Duration of OC use[2] | | | |
| No use | 0.88 | 0.93 | 2333 |
| < 1.0 years | 0.86 | 0.96 | 2350 |
| 1.0-4.9 years | 0.89 | 0.95 | 2323 |
| 5.0-9.9 years | 1.02 | 0.95 | 2323 |
| ≥ 10 years | 1.20 | 0.93 | 2249 |
| per 1 year | 2.9 (1.9, 3.9) | -0.3 (-0.9, 0.3) | -0.2 (-0.5, 0.0) |
| p for trend | 0.02 | 0.38 | 0.06 |
| | | | |
| Age at menarche[2] | | | |
| ≤11 years | 0.98 | 0.94 | 2339 |
| 12 years | 0.95 | 0.93 | 2258 |
| 13 years | 1.01 | 0.94 | 2325 |
| 14 years | 0.92 | 0.94 | 2279 |
| ≥ 15 years | 0.95 | 0.97 | 2378 |
| per 1 year | -0.2 (-3.1, 2.7) | 0.7 (-1.2, 2.6) | 0.2 (-0.6, 0.9) |
| p for trend | 0.88 | 0.46 | 0.64 |
| | | | |
| Parity[2] | | | |
| Nulliparous | 0.99 | 1.00 | 2354 |
| 1 child | 1.03 | 0.91 | 2355 |
| 2 children | 0.96 | 0.90 | 2319 |
| 3 children | 0.98 | 0.98 | 2306 |
| 4+ children | 0.85 | 0.94 | 2245 |
| per 1 child | -1.8 (-4.9, 1.4) | -0.8 (-2.8, 1.3) | -0.9 (-1.7, -0.1) |
| p for trend | 0.26 | 0.45 | 0.03 |

[1]Adjusted for age at blood draw, smoking, BMI, physical activity, aspirin use, NSAIDS use, inflammatory dietary index, and history of diabetes and hypertension,

[2]Plus mutually adjusted for duration of OC use, age at menarche and parity