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**Supplement Figure 1.** Euler diagram summarizing PUFA SNP selection

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**Supplement Figure 2.** Restricted cubic spline model with 5 knots (5th, 25th, 50th, 75th, and 95th percentiles) for the relation between weighted polygenic risk score (wPRS) and prostate cancer risk for LA (plot generated using macro developed by Desquilbet 2010)



**Supplement Figure 3.** Restricted cubic spline model with 5 knots (5th, 25th, 50th, 75th, and 95th percentiles) for the relation between weighted polygenic risk score (wPRS) and prostate cancer risk for AA (plot generated using macro developed by Desquilbet 2010)



**Supplement Figure 4.** Restricted cubic spline model with 5 knots (5th, 25th, 50th, 75th, and 95th percentiles) for the relation between weighted polygenic risk score (wPRS) and prostate cancer risk for EPA (plot generated using macro developed by Desquilbet 2010)



**Supplement Figure 5.** Restricted cubic spline model with 5 knots (5th, 25th, 50th, 75th, and 95th percentiles) for the relation between weighted polygenic risk score (wPRS) and prostate cancer risk for DPA (plot generated using macro developed by Desquilbet 2010)



**Supplement Figure 6.** Meta-analysis of PRACTICAL studies for the association between one standard deviation increase in LA wPRS and prostate cancer risk

**Supplement Figure 7.** Meta-analysis of PRACTICAL studies for the association between one standard deviation increase in AA wPRS and prostate cancer risk

**Supplement Figure 8.** Meta-analysis of PRACTICAL studies for the association between one standard deviation increase in ALA wPRS and prostate cancer risk

**Supplement Figure 9.** Meta-analysis of PRACTICAL studies for the association between one standard deviation increase in EPA wPRS and prostate cancer risk

**Supplement Figure 10.** Meta-analysis of PRACTICAL studies for the association between one standard deviation increase in DPA wPRS and prostate cancer risk

**Supplement Figure 11.** Meta-analysis of PRACTICAL studies for the association between one standard deviation increase in DHA wPRS and prostate cancer risk

**Supplement Table 1**. Sensitivity analyses using different covariate adjustments for the association between PUFA-specific weighted-polygenic risk scores (wPRSs) and prostate cancer risk using individual-level data from the PRACTICAL consortium

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Model** | **N****Case/Control** |  | **ω-6** |  | **ω-3** |
| **Linoleic****acid****(LA)** |  | **Arachidonic****acid****(AA)** |  | **α-linolenic****acid****(ALA)** |  | **Eicosapentaenoic****acid****(EPA)** |  | **Docosapentaenoic****acid****(DPA)** |  | **Docosahexaenoic****acid****(DHA)** |
| **OR­** | **95% CI** |  | **OR­** | **95% CI** |  | **OR­** | **95% CI** |  | **OR­** | **95% CI** |  | **OR­** | **95% CI** |  | **OR­** | **95% CI** |
| Unadjusted | 22721/23,034 |  | 1.01 | 0.99, 1.03 |  | 1.00 | 0.98, 1.02 |  | 1.00 | 0.98, 1.02 |  | 1.00 | 0.98, 1.02 |  | 1.01 | 0.99, 1.02 |  | 1.00 | 0.99, 1.02 |
| Model 1 | 22,721/23,034 |  | 1.00 | 0.98, 1.02 |  | 1.01 | 0.99, 1.03 |  | 0.99 | 0.97, 1.01 |  | 1.01 | 0.99, 1.03 |  | 1.01 | 0.99, 1.03 |  | 1.00 | 0.98, 1.02 |
| Model 2 | 3,441/2,496 |  | 0.99 | 0.94, 1.05 |  | 1.01 | 0.95, 1.07 |  | 0.99 | 0.94, 1.05 |  | 0.99 | 0.94, 1.05 |  | 0.99 | 0.94, 1.05 |  | 0.97 | 0.92, 1.03 |

Note:

Model 1: ORs and 95% CIs adjusted for age, eight principal components for European ancestry, and PRACTICAL study site.

Model 2: ORs and 95% CIs adjusted for age, eight principal components for European ancestry, PRACTICAL study site, and physical activity.

**Supplement Table 2.** Egger regression to assess the potential effect of pleiotropy and invalid instrument on the two-sample Mendelian randomization estimate using summary statistics

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **PUFA** |  | **Two-sample Mendelian randomization****estimate using summary statisticsa** |  | **Intercept from****Egger regressionb** |
|  | **OR­c** | **95% CI** | ***p* value** |  | **β0** | ***p* value** |
| ω-6 PUFAs |  |  |  |  |  |  |  |
| LA |  | 0.99 | 0.97, 1.02 | 0.72 |  | 0.00587 | 0.34 |
| AA |  | 1.01 | 0.99, 1.02 | 0.55 |  | -0.00603 | 0.74 |
| ω-3 PUFAs |  |  |  |  |  |  |  |
| ALA |  | 0.99 | 0.98, 1.01 | 0.53 |  | -0.00899 | 0.53 |
| EPA |  | 1.01 | 0.99, 1.03 | 0.44 |  | -0.00399 | 0.88 |
| DPA |  | 1.01 | 0.99, 1.03 | 0.32 |  | 0.01304 | <0.0001 |
| DHA |  | 1.00 | 0.98, 1.02 | 0.96 |  | 0.00066 | 0.96 |

Note:

a Two-sample Mendelian randomization estimate calculated using summary statistics (Burgess *et al*, 2013), as follows:

$\hat{β}\_{IVW}= \frac{\sum\_{i=1}^{g}X\_{g}Y\_{g}σ\_{Yg}^{-2}}{\sum\_{i=1}^{g}X\_{g}^{2}σ\_{Yg}^{-2}}$ , $se\left(\hat{β}\_{IVW}\right)=\sqrt{\frac{1}{\sum\_{i=1}^{g}X\_{g}^{2}σ\_{Yg}^{-2}}}$ ,

where Xg summary estimate for each variant (g) included in the genetic instrument with levels of PUFA (X) obtained from the published GWAS, and Yg and σYg estimates were obtained from the PRACTICAL consortium for each variant in relation to prostate cancer risk (Y).

b Estimate of the average pleiotropic effect across genetic variants (Bowden *et al*, 2015).

c Odds ratios and 95% CI were calculated using $\hat{β}\_{IVW}$ and $se\left(\hat{β}\_{IVW}\right)$, and represent effects for an increase of 1.20 (for LA), 1.13 (for AA), 0.01 (for ALA), 0.06 (for EPA), 0.06 (for DPA), 0.08 (for DHA) in percent of total fatty acids (representing one standard deviation increase in weighted-polygenic risk score from individual-level data).

**Supplement Table 3.** Association between PUFAs on prostate cancer risk after accounting for potential pleiotropy of variants used in the genetic instruments on other PUFA subtypes via the weighted regression-based method using summary statistics for all nine GWAS-identified variants

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Outcomea** | **Predictorb** | **Covariateb** |  | **Weighted regression-based****method** |
|  | **ORc** | **95% CI** | ***p* value** |
|  |
| βPC | βLA | -- |  | 0.99 | 0.98, 1.01 | 0.39 |
|  |  | βAA |  | 0.97 | 0.93, 1.02 | 0.30 |
|  |  | βALA, βEPA, βDPA, βDHA |  | 0.98 | 0.93, 1.04 | 0.53 |
|  |  | βAA, βALA, βEPA, βDPA, βDHA |  | 0.96 | 0.90, 1.03 | 0.25 |
|  |  |  |  |  |  |  |
| βPC | βAA | -- |  | 1.00 | 0.99, 1.02 | 0.57 |
|  |  | βLA |  | 0.98 | 0.95, 1.02 | 0.43 |
|  |  | βALA, βEPA, βDPA, βDHA |  | 1.04 | 0.83, 1.30 | 0.75 |
|  |  | βLA, βALA, βEPA, βDPA, βDHA |  | 0.88 | 0.60, 1.29 | 0.50 |
|  |  |  |  |  |  |  |
| βPC | βALA | -- |  | 1.00 | 0.99, 1.01 | 0.71 |
|  |  | βLA, βAA |  | 1.02 | 0.95, 1.09 | 0.65 |
|  |  | βEPA, βDPA, βDHA |  | 1.03 | 0.96, 1.10 | 0.37 |
|  |  | βLA, βAA, βEPA, βDPA, βDHA |  | 0.97 | 0.77, 1.21 | 0.76 |
|  |  |  |  |  |  |  |
| βPC | βEPA | -- |  | 1.00 | 0.99, 1.02 | 0.43 |
|  |  | βLA, βAA |  | 1.01 | 0.98, 1.04 | 0.46 |
|  |  | βALA, βDPA, βDHA |  | 1.05 | 0.86, 1.28 | 0.61 |
|  |  | βLA, βAA, βALA, βDPA, βDHA |  | 1.10 | 0.88, 1.36 | 0.41 |
|  |  |  |  |  |  |  |
| βPC | βDPA | -- |  | 1.01 | 0.99, 1.02 | 0.40 |
|  |  | βLA, βAA |  | 1.01 | 0.98, 1.03 | 0.54 |
|  |  | βALA, βEPA, βDHA |  | 0.98 | 0.83, 1.16 | 0.79 |
|  |  | βLA, βAA, βALA, βEPA, βDHA |  | 0.96 | 0.76, 1.22 | 0.76 |
|  |  |  |  |  |  |  |
| βPC | βDHA | -- |  | 1.00 | 0.99, 1.01 | 0.87 |
|  |  | βLA, βAA |  | 1.00 | 0.99, 1.01 | 0.64 |
|  |  | βALA, βEPA, βDPA |  | 1.01 | 0.99, 1.03 | 0.44 |
|  |  | βLA, βAA, βALA, βEPA, βDPA |  | 1.01 | 0.98, 1.04 | 0.61 |

Note:

aThe effect of the instrumental variable on prostate cancer risk (i.e., βPC).

bThe effect of the instrumental variable on levels of plasma phospholipid PUFA levels (i.e., βLA, βAA, etc.).

cThe association between the instrumental variable’s effect (one standard deviation increase) on phospholipid PUFA levels with the same instrumental variable’s effect on prostate cancer risk using weighted regression-based method (Burgess *et al*, 2015; Burgess & Thompson, 2015).