**The PRACTICAL CONSORTIUM (in addition to those named in the author list)**

Information of the consortium can be found at <http://practical.ccge.medschl.cam.ac.uk/>.

Additional members from the consortium are: Margaret Cook 1, Angela Morgan 2, Artitaya Lophatananon 3,4, Cyril Fisher 2, Daniel Leongamornlert 2, Edward J. Saunders 2, Emma J. Sawyer 2, Koveela Govindasami 2, Malgorzata Tymrakiewicz 2, Michelle Guy 2, Naomi Livni 2, Rosemary Wilkinson 2, Sara Jugurnauth-Little 2, Steve Hazel 2, Tokhir Dadaev 2, Melissa C. Southey 5, Liesel M. Fitzgerald 6, John Pedersen 7, John Hopper 8, Robert MacInnis 6,8, Robert Szulkin 9, Ami Karlsson 9, Carin Cavalli-Bjoerkman 9, Jan-Erik Johansson 9, Jan Adolfson 9, Markus Aly 9,10, Michael Broms 9, Paer Stattin 9, Brian E. Henderson 11, Fredrick Schumacher 11, Anssi Auvinen 12, Kimmo Taari 13, Liisa Maeaettaenen 14, Paula Kujala 15, Teemu Murtola 16,17, Teuvo LJ Tammela 17, Tiina Wahlfors 18, Andreas Roder 19, Peter Iversen 19, Peter Klarskov 20, Sune F. Nielsen 21,22, Tim J. Key 23, Hans Wallinder 24, Sven Gustafsson 24, David Neal 25, Freddie Hamdy 26, Angela Cox 27, Anne George 28, Athene Lane 28, Gemma Marsden 26, Michael Davis 25, Paul Brown 25, Paul Pharoah 29, Lisa B. Signorello 31,30, Shannon K. McDonnell 32, Daniel J. Schaid 32, Liang Wang 32, Lori Tillmans 32, Shaun Riska 32, Antje Rinckleb 33, Kathleen Herkommer 34, Manuel Luedeke 33, Walther Vogel 35, Dominika Wokozorczyk 36, Jan Lubiski 36, Wojciech Kluzniak 36, Kai-Uwe Saum37, Christa Stegmaier 38, Babu Zachariah 39, Hui-Yi Lin 40, Hyun Park 39, James Haley 39, Julio Pow-Sang 39, Maria Rincon 39, Selina Radlein 39, Thomas Sellers 39, Chavdar Slavov 41, Aleksandrina Vlahova 42, Atanaska Mitkova 43, Darina Kachakova 43, Elenko Popov 41, Svetlana Christova 42, Tihomir Dikov 42, Vanio Mitev 43, Allison Eckert 44, APCB BioResource 44,45, Amanda Spurdle 46, Angus Collins 44, Glenn Wood 44, Greg Malone 44, Judith A. Clements 44, Kimberly Alexander 44, Kris Kerr 44, Mary-Anne Kedda 44, Megan Turner 44, Pamela Saunders 44, Peter Heathcote 44, Srilakshmi Srinivasan 44, Tracy Omara 44, Trina Yeadon 44, Joana Santos 47, Carmen Jerónimo47, Paula Paulo 47, Pedro Pinto 47, Rui Henrique 47, Sofia Maia 47, Agnieszka Michael 48, Andrzej Kierzek 48, Huihai Wu 48, Suzanne Kolb49.

1 Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Strangeways Research Laboratory, 2 Worts’ Causeway, Cambridge CB1 8RN, UK, 2 The Institute of Cancer Research, 15 Cotswold Rd, Sutton, London, SM2 5NG, UK, 3 Institute of Population Health, University of Manchester, Oxford Rd, Manchester, M13 9PL, UK, 4 Warwick Medical School, University of Warwick, Coventry, CV4 7AL, UK, 5 Genetic Epidemiology Laboratory, Department of Pathology, The University of Melbourne, Grattan Street, Parkville, Victoria 3010, Australia, 6 Cancer Epidemiology Centre, The Cancer Council Victoria, 615 St Kilda Road, Melbourne, Victoria, 3004, Australia, 7 Tissupath Pty Ltd., Melbourne,Victoria 3122, Australia, 8 Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Victoria 3010, Australia, 9 Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, SE-171 77, Sweden, 10 Department of Clinical Sciences at Danderyds Hospital, Stockholm, Sweden, 11 Department of Preventive Medicine, Keck School of Medicine, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, California, USA, 12 Department of Epidemiology, School of Health Sciences, University of Tampere, Tampere, Finland, 13 Department of Urology, Helsinki University Central Hospital and University of Helsinki, Helsinki, Finland, 14 Finnish Cancer Registry, Helsinki, Finland, 15 Fimlab Laboratories, Tampere University Hospital, Tampere, Finland, 16 School of Medicine, University of Tampere, Tampere, Finland, 17 Department of Urology, Tampere University Hospital and Medical School, University of Tampere, Finland, 18 BioMediTech, University of Tampere and FimLab Laboratories, Tampere, Finland, 19 Copenhagen Prostate Cancer Center, Department of Urology, Rigshospitalet, Copenhagen University Hospital, Tagensvej 20, 7521, DK-2200 Copenhagen, Denmark, 20 Department of Urology, Herlev Hospital, Copenhagen University Hospital, Herlev Ringvej 75, DK-230 Herlev, Denmark, 21 Department of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital, Herlev Ringvej 75, DK-230 Herlev, Denmark, 22 Faculty of Health and Medical Sciences, University of Copenhagen, 23 Cancer Epidemiology Unit, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK, 24 Department of Epidemiology and Biostatistics, School of Public Health, Imperial College, London, UK, 25 Surgical Oncology (Uro-Oncology: S4), University of Cambridge, Box 279, Addenbrooke’s Hospital, Hills Road, Cambridge, UK and Cancer Research UK Cambridge Research Institute, Li Ka Shing Centre, Cambridge, UK, 26 Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK, Faculty of Medical Science, University of Oxford, John Radcliffe Hospital, Oxford, UK, 27 CR-UK/YCR Sheffield Cancer Research Centre, University of Sheffield, Sheffield, UK, 28 University of Cambridge, Department of Oncology, Box 279, Addenbrooke's Hospital, Hills Road Cambridge CB2 0QQ, UK, 29 Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge, Strangeways Research Laboratory, Worts Causeway, Cambridge, UK, 30 International Epidemiology Institute, 1555 Research Blvd., Suite 550, Rockville, MD 20850, USA, 31 Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA, 32 Mayo Clinic, Rochester, Minnesota, USA, 33 Department of Urology, University Hospital Ulm, Germany, 34 Department of Urology, Klinikum rechts der Isar der Technischen Universitaet Muenchen, Munich, Germany, 35 Institute of Human Genetics, University Hospital Ulm, Germany, 36 International Hereditary Cancer Center, Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland, 37 Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), 69120 Heidelberg, Germany, 38 Saarland Cancer Registry, 66119 Saarbruecken, Germany, 39 Department of Cancer Epidemiology, Moffitt Cancer Center, 12902 Magnolia Drive, Tampa, FL 33612, USA, 40 Biostatistics Program, Moffitt Cancer Center, 12902 Magnolia Drive, Tampa, FL 33612, USA, 41 Department of Urology and Alexandrovska University Hospital, Medical University, Sofia, Bulgaria, 42 Department of General and Clinical Pathology, Medical University, Sofia, Bulgaria, 43 Department of Medical Chemistry and Biochemistry, Molecular Medicine Center, Medical University, Sofia, 2 Zdrave Str., 1431 Sofia, Bulgaria, 44 Australian Prostate Cancer Research Centre-Qld, Institute of Health and Biomedical Innovation and School of Biomedical Science, Queensland University of Technology, Brisbane, Australia, 45 Australian Prostate Cancer BioResource, Brisbane, QLD, 46 Molecular Cancer Epidemiology Laboratory, Queensland Institute of Medical Research, Brisbane, Australia, 47 Department of Genetics, Portuguese Oncology Institute, Porto, Portugal, 48 The University of Surrey, Guildford, Surrey, GU2 7XH, UK, 49 Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington, 98109-1024, USA

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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)

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**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)

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**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)

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**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)

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**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:

, ,

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 and , 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).