Article:
Liyanage, UE, Law, MH, Ong, JS et al. (7 more authors) (2018) Polyunsaturated fatty acids and risk of melanoma: A Mendelian randomisation analysis. International Journal of Cancer, 143 (3). pp. 508-514. ISSN 0020-7136

https://doi.org/10.1002/ijc.31334

Title:
Polyunsaturated fatty acids and risk of melanoma: A Mendelian randomisation analysis

Supplementary information

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Acknowledgements

We acknowledge Australian National Health and Medical Research Council funding (1123248). Stuart Macgregor is supported by an Australian Research Council Fellowship.

Contributing studies to melanoma GWAS:

GenoMEL
The GenoMEL study (http://www.genomel.org/) was funded by the European Commission under the 6th Framework Programme (contract no. LSHC-CT-2006-018702), by Cancer Research UK Programme Awards (C588/A4994 and C588/A10589), by a Cancer Research UK Project Grant (C8216/A6129) and by a grant from the US National Institutes of Health (NIH; CA83115). This research was also supported by the intramural Research Program of the NIH, National Cancer Institute (NCI), Division of Cancer Epidemiology and Genetics.
This study makes use of data generated by the Wellcome Trust Case Control Consortium (http://www.wtccc.org.uk/). A full list of the investigators who contributed to the generation of the data is available from their website (see URLs). Funding for the project was provided by the Wellcome Trust under award 076113.
Genotyping for the CIDRUK samples were provided by the Center for Inherited Disease Research (CIDR). CIDR is fully funded through a federal contract from the National Institutes of Health to The Johns Hopkins University, contract number HHSN268201200008I.
Funding specific to particular centers is given below:
Stockholm: Swedish Cancer Society, Karolinska Institutet Research Funds, Radiumhemmet Research Funds, Stockholm County Council Research Funding (ALF).
Lund: Funding to be acknowledged; Swedish Cancer Society, Gunnar Nilsson Foundation, and European Research Council Advanced Grant (ERC-2011–294576).
Genoa: Italian Ministry of Education, University and Research PRIN 2008, IMI and Mara Naum foundation. Italian association for cancer research (AIRC) IG 2014 (15460) to PG; IRCCS AOU San Martino-IST Istituto Nazionale per la Ricerca sul Cancro, 5% per la ricerca corrente, to PG and GBS.
Leiden: Grant provided by European Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) −Netherlands hub (CO18).
Spain: The research at the Melanoma Unit in Barcelona is or was partially funded by Grants from Fondo de Investigaciones Sanitarias P.I. 09/01393 & 12/00840, Spain; by the CIBER de Enfermedades Raras of the Instituto de Salud Carlos III, Spain; by the AGAUR 2009 SGR 1337 and AGAUR 2014_SGR_603 of the Catalan Government, Spain; by a grant from "Fundació La Marató de TV3, 201331-30", Catalonia, Spain; by the European Commission under the 6th Framework Programme, Contract no: LSHC-CT-2006-018702 (GenoMEL) and by the National Cancer Institute (NCI) of the US National Institute of Health (NIH) (CA83115).
Norway: Grants from the Comprehensive Cancer Center, Oslo University Hospital (SE0728) and the Norwegian Cancer Society (71512-PR-2006-0356).

AMFS
The AMFS was supported by the National Health and Medical Research Council of Australia

(NHMRC) (project grants 566946, 107359, 211172 and program grant number 402761 to GJM and RFK); the Cancer Council New South Wales (project grant 77/00, 06/10), the Cancer Council Victoria and the Cancer Council Queensland (project grant 371); and the US National Institutes of Health (NIH RO1 grant CA-83115-01A2 and 2R01CA083115-11A1 to the international Melanoma Genetics Consortium - GenoMEL). Anne E. Cust is supported by fellowships from the Cancer Institute NSW and the NHMRC. We gratefully acknowledge all of the participants, and the work and dedication of the research coordinators, interviewers, examiners and data management staff.

WAMHS
The WAMHS gratefully acknowledges all study participants for their time and contributions, and the Western Australian DNA Bank and the Ark at The University of Western Australia for bio specimen and bioinformatics related support. The Western Australian Cancer Registry, the WAMHS study team and the WAMHS Management Committee are also gratefully acknowledged for their assistance, as well as the Scott Kirkbride Melanoma Research Centre for funding received to establish the WAMHS resource and related salaries and PhD stipends. The Cancer Council Western Australia is also acknowledged for current salary support for Sarah Ward (Capacity Building and Collaboration grant).
Genotyping services were provided by the Center for Inherited Disease Research (CIDR).
CIDR is fully funded through a federal contract from the National Institutes of Health to The Johns Hopkins University, contract number HHSN268201200008I'

Q-MEGA cases and QTWINs controls (used in Q-MEGA_610k set)
Acknowledgement/grants: Q-MEGA and QTWIN thanks A. Baxter, M. de Nooyer, I. Gardner, D. Statham, B. Haddon, M.J. Wright, J. Palmer, J. Symmons, B. Castellano, L. Bardsley, S. Smith, D. Smyth, L. Wallace, M.J. Campbell, A. Caracella, M. Kvaskoff, O. Zheng, B. Chapman and H. Beeby for their input in project management, sample processing and database development. We are grateful to the many research assistants and interviewers for assistance with the studies contributing to the QMEGA and QTWIN collections The Q-MEGA/QTWIN study was supported by the Melanoma Research Alliance, the NIH NCI (CA88363, CA83115, CA122838, CA87969, CA055075, CA100264, CA133996 and CA49449), the National Health and Medical Research Council of Australia (NHMRC) (200071, 241944, 339462, 380385, 389927,389875, 389891, 389892,389938, 443036, 442915, 442981, 496610, 496675, 496739, 552485, 552498), the Cancer Councils New South Wales, Victoria and Queensland, the Cancer Institute New South Wales, the Cooperative Research Centre for Discovery of Genes for Common Human Diseases (CRC), Cerylid Biosciences (Melbourne), the Australian Cancer Research Foundation, The Wellcome Trust (WT084766/Z/08/Z) and donations from Neville and Shirley Hawkins. Stuart MacGregor acknowledges fellowship support from the Australian National Health and Medical Research Council and from the Australian Research Council.

Endometriosis
Contributors to the Endometriosis collection: Anjali K. Henders, S.H. Kennedy, S. Macgregor, N.G. Martin, S. Missmer, G.W. Montgomery, D.R. Nyholt, J.N. Painter, S.A. Treloar, L. Wallace, K.T. Zondervan. Acknowledgements: We acknowledge all the participants in the QIMR and endometriosis studies. We thank Anjali Henders, Leanne

Wallace, and Lisa Bardsley for project management, sample processing and database development. We thank Endometriosis Associations for supporting study recruitment and S. Nicolaides and the Queensland Medical Laboratory for assistance with blood collection including pro bono collection and delivery of blood samples. Funding: This work was supported by the Cooperative Research Centre (CRC) for Discovery of Genes for Common Nature Genetics: doi:10.1038/ng.3373Law et al., Supplementary Note Human Diseases, Cerylid Biosciences (Melbourne), The Wellcome Trust and donations from Neville and Shirley Hawkins. Endometriosis sample genotyping was funded by a grant from the Wellcome Trust (WT084766/Z/08/Z) and NHMRC (496610). G.W.M. is supported by the NHMRC Fellowships scheme. D.R.N. was supported by the NHMRC Fellowship (613674) and Australian Research Council (ARC) Future Fellowship (FT0991022) schemes.

Study of Digestive Health
Controls for use with the Q-MEGA_omni dataset were derived from the Study of Digestive Health group (SDH). The SDH was supported by grant number 5 RO1 CA 001833-02 from the National Cancer Institute. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute. We gratefully acknowledge the cooperation of the following institutions: Sullivan and Nicolaides Pathology (Brisbane); Queensland Medical Laboratory (Brisbane); Queensland Health Pathology Services (Brisbane); Institute of Medical and Veterinary Science (Adelaide); SouthPath (Adelaide). We also acknowledge the contribution of the study nurses and research assistants and would like to thank all of the people who participated in the study. DCW was supported by an NHMRC Research Fellowship (APP1058522).

Australian & New Zealand Registry of Advanced Glaucoma (ANZRAG) Support for recruitment of ANZRAG was provided by the Royal Australian and New Zealand College of Ophthalmology (RANZCO) Eye Foundation. Genotyping was funded by the National Health and Medical Research Council of Australia (#535074 and #1023911). This work was also supported by funding from the Bright Focus Foundation and a Ramaciotti Establishment Grant. The authors acknowledge the support of Ms. Bronwyn Usher-Ridge in patient recruitment and data collection, and Dr Patrick Danoy and Dr Johanna Hadler for genotyping.

Inflammatory Bowel Disease (IBD)
The authors express their thanks to Sullivan and Nicolaides Pathology, Queensland Medical Laboratories and the Queensland Health Pathology Service for identifying participants for this study. They are also grateful to Peter Schultz, Lauren Aoude, Loralie Parsonson, Stephen Walsh, Mitchell Stark, John Cardinal and Herlina Handoko for technical support.

This research was supported by grant number CA 001833-03 from the United States National Cancer Institute. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute. PMW and DCW are Senior Research Fellows of the National Health and Medical Research Council of Australia.
NP is supported by a PhD scholarship from the National Health and Medical Research Council of Australia. The funding bodies played no role in the design or conduct of the study, the collection, management, analysis, or interpretation of the data, or the preparation, review or approval of the manuscript.

M.D. Anderson
Funding was provided by NCI grant P50CA093459, as well as by philanthropic contributions to the University of Texas MD Anderson Cancer Center Moon Shots Program, the Miriam and Jim Mulva Melanoma Research Fund and the Marit Peterson Fund for Melanoma Research. The authors thank the John Hopkins University Center for Inherited Disease Research for conducting high-throughput genotyping and University of Washington for the performance of quality control of the high-density SNP data.

MELARISK, Paris, France
Grants from Institut National du Cancer (INCa-PL016 and INCa_5982) to F. Demenais, Ligue Nationale Contre Le Cancer (PRE 09/FD to F. Demenais and doctoral fellowship to M. Brossard), Fondation pour la Recherche Medicale (FDT20130928343), Programme Hospitalier de Recherche Clinique (AOM-07-195) to M.-F. Avril and F. Demenais. Ministère de l'Enseignement Supérieur et de la Recherche and Institut National du Cancer (INCa) to M. Lathrop. The authors thank the Epidemiological Study on the Genetics and Environment of Asthma (EGEA) cooperative group for giving access to data of the EGEA study (https://egeanet.vjf.inserm.fr). We acknowledge that the biological specimens of the French MELARISK study were obtained from the Institut Gustave Roussy and Fondation Jean Dausset–CEPH Biobanks.

Essen-Heidelberg
The study was supported by a grant from Deutsche Forshungsgemeinschaft (GZ: SCHA 422/11-1)
Harvard
Funding was provided by NIH grant R03CA167741.
Cambridge: SEARCH/MAPLES
We would like to thank Don Conroy, Craig Luccarini and Rebecca Mayes for their technical assistance. Funding: A.M. Dunning received funding from Cancer Research UK (Grant Numbers, C8197/A10123, C8197/A10865) and K.A. Pooley from Cancer Research UK (Grant Number C1287/A9540) and The Isaac Newton Trust.

Supplementary Tables

Supplementary Table 1: Association of PUFA MR SNPs with height

SNP	EA/NEA	EAF	B	SE	*P*	N
rs10740118	C/G	0.47	0.010	0.0030	1.1×10^{-3}	253,207
rs174538	A/G	0.33	-0.011	0.0032	7.5×10^{-4}	253,167
rs174547	T/C	0.63	0.013	0.0031	4.7×10^{-5}	253,196
rs16966952	A/G	0.25	-0.013	0.0033	1.1×10^{-4}	236,235
rs780094	T/C	0.38	-0.021	0.0030	5.7×10^{-12}	253,130
rs3734398	T/C	0.56	-0.0012	0.0029	0.68	252,890
rs2236212	C/G	0.43	0.0007	0.0029	0.81	253,040
rs3798713	C/G	0.43	0.0006	0.0029	0.83	253,019

EA - Effect allele, NEA - Non effect allele, EAF - Effect allele frequency, SE - Standard error, *P* - *P* value, N - Sample size, β - Magnitude of association between the SNP and the trait (unit – 1 standard deviation change). Data extracted on 05/12/2016 from https://www.broadinstitute.org/collaboration/giant/images/0/01/GIANT_HEIGHT_Wood_et_al_2014_publicrelease_HapMapCeuFreq.txt.gz[1].

Supplementary Table 2: Association of PUFA MR SNPs with BMI

SNP	EA/NEA	EAF	β	SE	*P*	N
rs10740118	G/C	0.53	0.0144	0.0036	6.3×10^{-5}	236,158
rs174538	A/G	0.34	0.0009	0.0033	0.79	339,082
rs174547	C/T	0.37	0.0023	0.0032	0.46	339,131
rs16966952	A/G	0.27	-0.0124	0.0041	3×10^{-2}	218,552
rs780094	T/C	0.38	-0.0121	0.003	7.0×10^{-5}	339,056
rs3734398	T/C	0.57	-0.0009	0.0036	0.80	235,897
rs2236212	G/C	0.57	-0.001	0.0036	0.78	235,982
rs3798713	G/C	0.57	-0.0009	0.0036	0.80	236,012

EA - Effect allele, NEA - Non effect allele, EAF - Effect allele frequency, SE - Standard error, *P* - *P* value, N - Sample size, β - Magnitude of association between the SNP and the trait (unit – kg/m^2). Data extracted on 05/12/2016 from https://www.broadinstitute.org/collaboration/giant/images/f/f0/All_ancestries_SNP_gwas_mc_merge_nogc.tbl.uniq.gz[2].

Supplementary Table 3: Association of PUFA MR SNPs with educational attainment

SNP	EA/NEA	EAF	β	SE	*P*	N
rs10740118	C/G	0.48	1.043	0.01	1.21×10^{-5}	293,723
rs174538	A/G	0.32	1.005	0.01	0.64	293,723
rs174547	T/C	0.63	0.993	0.01	0.51	293,723
rs16966952	A/G	0.26	1.011	0.011	0.33	293,723
rs780094	T/C	0.39	0.988	0.01	0.23	293,723
rs3734398	T/C	0.54	0.997	0.01	0.77	293,723
rs2236212	C/G	0.45	1.003	0.01	0.74	293,723
rs3798713	C/G	0.45	1.004	0.01	0.68	293,723

EA - Effect allele, NEA - Non effect allele, EAF - Effect allele frequency, SE - Standard error, *P* - *P* value, N - Sample size, β - Magnitude of association between the SNP and the trait (unit - individual's years of schooling according to International Standard Classification of Education (ISCED 1997). Data extracted on 05/12/2016 from https://www.thessgac.org/data [3].

Supplementary Table 4: Association of PUFA MR SNPs with waist circumference

SNP	EA/NEA	EAF	β	SE	P	N
rs10740118	G/C	0.53	0.012	4.3×10^{-3}	7×10^{-02}	153,935
rs174538	A/G	0.34	0.0028	3.6×10^{-3}	0.44	244,354
rs174547	C/T	0.37	0.0024	3.5×10^{-3}	0.49	244,381
rs16966952	A/G	0.27	-0.019	0.0048	6.9×10^{-05}	140,000
rs780094	T/C	0.38	-0.0086	3.4×10^{-3}	0.011	244,317
rs3734398	T/C	0.57	0.0021	4.3×10^{-3}	0.63	153,779
rs2236212	G/C	0.57	0.0027	4.3×10^{-3}	0.53	153,863
rs3798713	G/C	0.57	0.0029	4.3×10^{-3}	0.5	153,885

EA - Effect allele, NEA - Non effect allele, EAF - Effect allele frequency, SE - Standard error, P - P value, N - Sample size, β - Magnitude of association between the SNP and the trait (unit – 1 standard deviation change). Data extracted on 05/12/2016 from http://portals.broadinstitute.org/collaboration/giant/images/e/ea/GIANT_2015_WC_COMBINED_AllAncestries.txt.gz[4].

Supplementary Table 5: Association of PUFA MR SNPs with fasting blood sugar

SNP	EA/NEA	MAF	β	SE	P	N
rs10740118	C/G	0.42	-0.0041	0.0037	0.27	46186
rs174538	A/G	0.32	-0.18	0.0039	4.7×10^{-06}	46186
rs174547	T/C	0.34	0.021	0.038	1.7×10^{-08}	46186
rs16966952	A/G	0.28	-0.001	0.004	0.80	46186
rs780094	T/C	0.39	-0.026	0.037	2.5×10^{-12}	46186
rs3734398	T/C	0.45	-0.0005	0.037	0.90	46186
rs2236212	C/G	0.45	0.0006	0.037	0.87	46186
rs3798713	C/G	0.43	0.0005	0.037	0.89	46186

EA - Effect allele, NEA - Non effect allele, EAF - Effect allele frequency, SE - Standard error, P - P value, N - Sample size, β - Magnitude of association between the SNP and the trait (unit - mmol/l) . Data extracted on 05/12/2016 from https://www.magicinvestigators.org/downloads/ ftp://ftp.sanger.ac.uk/pub/magic/MAGIC_FastingGlucose.txt[5]

Supplementary Table 6: Effect estimates of PUFA for genome wide significant genetic variants reported by the CHARGE consortium[6, 7]

	SNP	EA /NEA	EAF	*P*- value	β	S.E.	%VE per allele	% VE per IV	F - statistic per IV
	Linoleic acid (LA,18:2n6)								
10	rs10740118	C/G	0.56	8.1×10^{-9}	-0.248	0.043	0.2–0.7		
11	rs174547	C/T	0.32	5.0×10^{-274}	1.474	0.042	7.6–18.1	8.3–21.3	1104–3533
16	rs16966952	A/G	0.31	1.2×10^{-15}	0.351	0.044	0.5–2.5		
	Arachidonic acid (AA, 20:4n6)								
11	rs174547	C/T	0.68	3×10^{-971}	-1.691	0.025	32.63	33.07	11302
16	rs16966952	A/G	0.31	2.4×10^{-10}	-0.199	0.031	0.44		
	α-Linolenic acid (ALA, 18:3n3)								
11	rs174547	C/T	0.33	3.5×10^{-64}	0.016	0.001	1.03	1.03	476
	Eicosapentaenoic acid (EPA, 20:5n3)								
6	rs3798713	C/G	0.43	1.9×10^{-12}	0.035	0.005	0.36	2.05	479
11	rs174538	G/A	0.72	5.4×10^{-58}	0.083	0.005	1.69		
	Docosapentaenoic acid (DPA, 20:5n3)								
2	rs780094	T/C	0.41	9.0×10^{-09}	0.017	0.003	0.46		
6	rs3734398	C/T	0.43	9.6×10^{-44}	0.040	0.003	2.74	11.58	1997
11	rs174547	T/C	0.67	3.8×10^{-154}	0.075	0.003	8.38		
	Docosahexaenoic acid (DHA, 22:6n3)								
6	rs2236212	G/C	0.57	1.3×10^{-15}	0.113	0.014	0.65	0.65	299

Chr - Chromosome, SNP - Single nucleotide polymorphism, EA - Effect Allele, NEA - Non effect allele, EAF - Effect allele frequency, β - Magnitude of association between SNP and PUFA, S.E. - standard error of the magnitude of association between SNP and PUFA, % VE per allele - Variation explained per allele, IV - Instrumental variable

Supplementary Table 7: **Mendelian randomisation results: LA concentration and melanoma**

SNP	Gene/GRCh19 position	CHR	EA/ NEA	R^2	β LA	σ LA	β melanoma	σ melanoma	EAF	β IVW	σ IVW
rs10740118	65101207	10	C/G	0.2-0.7%	-0.248	0.043	-0.0104	0.017	0.56	0.042	0.071
rs174547	*FADS1*	11	C/T	7.6-18.1%	1.474	0.042	-0.0271	0.018	0.32	-0.018	0.012
rs16966952	15135943	16	A/G	0.5-2.5%	0.351	0.044	-0.0030	0.018	0.31	- 0.009	0.053
Combined				8.3-21.3%						-0.016	0.011

Supplementary Table 8: **Mendelian randomisation results: AA concentration and melanoma**

SNP	Gene/GRCh19 position	CHR	EA/NEA	R^2	β AA	σ AA	β melanoma	σ melanoma	EAF	β IVW	σ IVW
rs174547	*FADS1*	11	C/T	32.63%	-1.691	0.025	-0.0271	0.018	0.68	0.016	0.011
rs16966952	15135943	16	A/G	0.44%	-0.199	0.031	-0.0030	0.019	0.31	0.015	0.095
Combined				33.07%						0.016	0.011

Supplementary Table 9: **Mendelian randomisation results: ALA concentration and melanoma**

SNP	Gene	CHR	EA/NEA	R^2	β ALA	σ ALA	β melanoma	σ melanoma	EAF	β IVW	σ IVW
rs174547	*FADS1*	11	C/T	1.03%	0.016	0.001	-0.0271	0.018	0.33	-1.69	1.13

Supplementary Table 10: **Mendelian randomisation results: EPA concentration and melanoma**

SNP	Gene/GRCh19 position	CHR	EA/NEA	R^2	β EPA	σ EPA	β melanoma	σ melanoma	EAF	β IVW	σ IVW
Rs3798713	11008622	6	C/G	0.36%	0.035	0.005	-0.0150	0.017	0.43	-0.43	0.49
Rs174538	61560081	11	A/G	1.69%	-0.083	0.005	-0.0341	0.019	0.72	0.41	0.23
Combined				2.05%						-0.27	0.21

Supplementary Table 11: **Mendelian randomisation results: DPA concentration and melanoma**

SNP	Gene	CHR	EA/NEA	R^2	β DPA	σ DPA	β melanoma	σ melanoma	EAF	β IVW	σ IVW
rs174547	*FADS1*	11	T/C	8.4%	0.075	0.0028	0.027	0.018	0.67	0.36	0.24
rs3734398	*ELOVL2*	6	C/T	2.8%	0.040	0.0029	-0.017	0.017	0.43	-0.42	0.43
Combined				11.2%						0.17	0.21

Supplementary Table 12: **Mendelian randomisation results: DHA concentration and melanoma**

SNP	Gene/GRCh19 position	CHR	EA/NEA	R^2	β DHA	σ DHA	β melanoma	σ melanoma	EAF	β IVW	σ IVW
Rs2236212	10995015	6	C/G	0.65%	0.113	0.014	-0.0188	0.017	0.57	-0.17	0.15

Supplementary Table 13: Effect estimates of melanoma for genetic variants used as IVs in the analysis reported by the Melanoma consortium

Chr	SNP	EA/NEA	EAF	*P*-value	β	S.E.
Linoleic acid (LA,18:2n6)						
10	rs10740118	C/G	0.58	0.5541	-0.0104	0.0175
11	rs174547	C/T	0.34	0.1399	-0.0271	0.0183
16	rs16966952	A/G	0.31	0.8708	-0.0030	0.0185
Arachidonic acid (AA, 20:4n6)						
11	rs174547	C/T	0.66	0.1399	-0.0271	0.0183
16	rs16966952	A/G	0.31	0.8708	-0.0030	0.0185
α -Linolenic acid (ALA, 18:3n3)						
11	rs174547	C/T	0.34	0.1399	-0.0271	0.0183
Eicosapentaenoic acid (EPA, 20:5n3)						
6	rs3798713	C/G	0.43	0.3901	-0.0150	0.0174
11	rs174538	A/G	0.69	7.016×10^{-2}	-0.0341	0.0188
Docosapentaenoic acid (DPA, 20:5n3)						
2	rs780094	C/T	0.41	1.323×10^{-2}	-0.0435	0.0175
6	rs3734398	C/T	0.43	0.3351	-0.0168	0.0174
11	rs174547	T/C	0.66	0.1399	0.0271	0.0183
Docosahexaenoic acid (DHA, 22:6n3)						
6	rs2236212	C/G	0.58	0.283	-0.0188	0.0174

Chr - Chromosome, SNP - Single nucleotide polymorphism, EA - Effect Allele, NEA - Non effect allele, EAF - Effect allele frequency, β - Magnitude of association between SNP and melanoma, S.E. – Standard error of magnitude of association between SNP and melanoma

Supplementary Figures 1: Scatter plots illustrating correlation between PUFAs and potential confounding trait (height) and vice-versa

Height data source - https://www.ncbi.nlm.nih.gov/pubmed/25282103 - Wood *et.al,*[1]

DPA, EPA, ALA, DHA data source - http://www.chargeconsortium.com - Lemaitre *et. al,*[6]

LA, AA data source - http://www.chargeconsortium.com – Guan *et.al,*[7]

r^2 - coefficient of determination (strength of the linear relationship between traits)
P- *P* value
Trend line - regression line

Figure 01- Scatter plot showing the correlation between DPA and height using genome-wide significant DPA SNPs

X axis - effect size on DPA
Y axis - effect size on height

Figure 02- Scatter plot showing the correlation between height and DPA using genome-wide significant height SNPs

X axis - effect size on height
Y axis - effect size on DPA

Figure 03- Scatter plot showing the correlation between EPA and height using genome-wide significant EPA SNPs

X axis - effect size on EPA
Y axis - effect size on height

Figure 04- Scatter plot showing the correlation between height and EPA using genome-wide significant height SNPs

X axis - effect size on height
Y axis - effect size on EPA

Figure 05- Scatter plot showing the correlation between ALA and height using genome-wide significant ALA SNPs
X axis - effect size on ALA
Y axis - effect size on height

Figure 06- Scatter plot showing the correlation between height and ALA using genome-wide significant height SNPs

X axis - effect size on height

Y axis - effect size on ALA

Figure 07- Scatter plot showing the correlation between DHA and height using genome-wide significant DHA SNPs

X axis - effect size on DHA
Y axis - effect size on height

Figure 08- Scatter plot showing the correlation between height and DHA using genome-wide significant height SNPs
X axis - effect size on height
Y axis - effect size on DHA

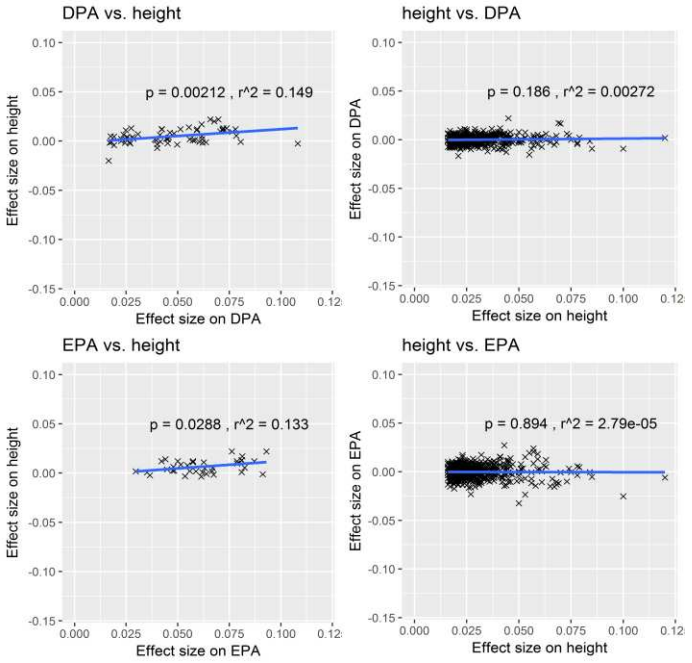
Figure 09- Scatter plot showing the correlation between LA and height using genome-wide significant LA SNPs
X axis - effect size on LA
Y axis - effect size on height

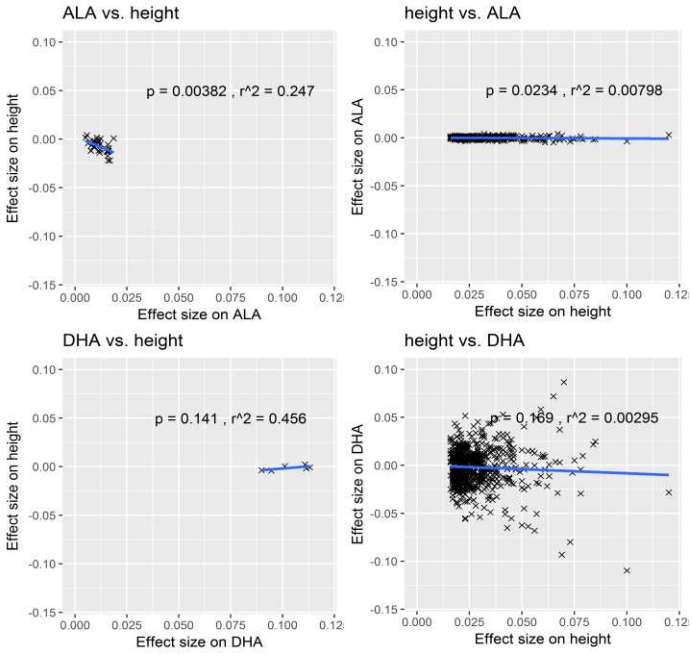
Figure 10- Scatter plot showing the correlation between height and LA using genome-wide significant height SNPs
X axis - effect size on height
Y axis - effect size on LA

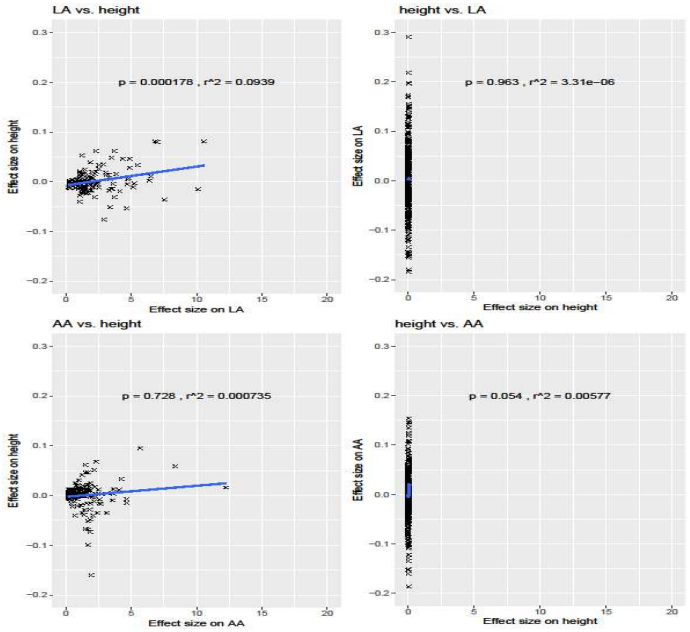
Figure 11- Scatter plot showing the correlation between AA and height using genome-wide significant AA SNPs
X axis - effect size on AA
Y axis - effect size on height

Figure 12- Scatter plot showing the correlation between height and AA using genome-wide significant height SNPs
X axis - effect size on height
Y axis - effect size on AA

(These plots are uploaded as separate tiff files)


DPA vs. height
p = 0.00212 , r^2 = 0.149
Effect size on height
Effect size on DPA
height vs. DPA
p = 0.186 , r^2 = 0.00272
Effect size on DPA
Effect size on height
EPA vs. height
p = 0.0288 , r^2 = 0.133
Effect size on height
Effect size on EPA
height vs. EPA
p = 0.894 , r^2 = 2.79e-05
Effect size on EPA
Effect size on height


ALA vs. height
p = 0.00382 , r^2 = 0.247
Effect size on height
Effect size on ALA
height vs. ALA
p = 0.0234 , r^2 = 0.00798
Effect size on ALA
Effect size on height
DHA vs. height
p = 0.141 , r^2 = 0.456
Effect size on height
Effect size on DHA
height vs. DHA
p = 0.169 , r^2 = 0.00295
Effect size on DHA
Effect size on height



Supplementary Figure 13 - Two sample MR report for Fasting blood sugar versus Melanoma

Two sample MR analysis performed for Fasting blood sugar mmol/L (Scott RA *et.al*,)[8] against Melanoma (Law *et. al*,)[9] using MR-Base [10].

nsnp - number of SNPs = 9, β - beta (effect estimates of causality of melanoma from FBS analysed using different MR methods) , se - standard error, *P*-value – Significance of the causality of melanoma from FBS using different MR methods

MR Egger - A more reliable method than IVW method of MR to detect causality when using invalid instruments [11]

Weighted median - A robust method when some of the IVs are invalid (50%)[12]

Method	β	se	*P*-value
Fixed effects meta-analysis (simple SE)	0.204	0.158	0.196
Fixed effects meta-analysis (delta method)	0.200	0.160	0.210
Random effects meta-analysis (delta method)	0.260	0.262	0.320

Method	β	se	*P*-value
Maximum likelihood	0.210	0.160	0.190
MR Egger	-0.042	0.594	0.946
Weighted median	0.122	0.210	0.558
Inverse variance weighted	0.204	0.237	0.388

Supplementary Figure 14 - Two sample MR report for BMI versus Melanoma

Two sample MR report, performed for Body mass index (kg/m^2) (Locke AE *et.al*,)[2] against Melanoma (Law *et.al,*)[9] using MR-Base [10].

nsnp - number of SNPs = 86, β - beta (effect estimates of causality of melanoma from FBS analysed using different MR methods), se - standard error, *P*-value – Significance of the causality of melanoma from FBS using different MR methods

MR Egger - A more reliable method than IVW method of MR to detect causality when using invalid instruments [11]

Weighted median - A robust method when some of the IVs are invalid (50%)[12]

Method	β	se	*P*-value
Fixed effects meta-analysis (simple SE)	0.032	0.078	0.687
Fixed effects meta-analysis (delta method)	0.032	0.079	0.679
Random effects meta-analysis (delta method)	0.033	0.079	0.679
Maximum likelihood	0.032	0.079	0.682
MR Egger	0.229	0.194	0.242
Weighted median	0.023	0.125	0.856
Inverse variance weighted	0.032	0.080	0.693

Supplementary Figure 15 - Two sample MR report for height versus Melanoma

Two sample MR analysis performed for height (m) (Liu F *et.al*,) [13] against Melanoma (Law *et.al,*) [9] using MR-Base [10]

nsnp - number of SNPs = 534, β - beta (effect estimates of causality of melanoma from FBS analysed using different MR methods), se - standard error, *P*-value - Significance of the causality of melanoma from FBS using different MR methods

MR Egger - A more reliable method than IVW method of MR to detect causality when using invalid instruments [11]

Weighted median - A robust method when some of the IVs are invalid (50%)[12]

Method	β	se	*P*-value
Fixed effects meta-analysis (simple SE)	0.078	0.032	0.013
Fixed effects meta-analysis (delta method)	0.075	0.032	0.018
Random effects meta-analysis (delta method)	0.079	0.034	0.019
Maximum likelihood	0.079	0.032	0.014
MR Egger	0.028	0.091	0.761
Weighted median	0.115	0.053	0.031
Inverse variance weighted	0.079	0.034	0.020

Supplementary Notes

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