Genotyping and genotype risk scores

Genotyping of FOS and CARDIA samples was performed on the Affymetrix GeneChip® Human Mapping 500K Array and the Genome-Wide Human SNP Array 6.0 (Affymetrix, Inc., Santa Clara, CA, USA), respectively. Details about the imputation of CARDIA samples have been published previously(1; 2). Imputation in FOS was performed with MACH 1.0 with HapMap II release 22 CEU as the reference population.

Statistical analyses

We used similar statistical methods to model T2D risk as in our previous FOS and CARDIA analyses(4-6). In FOS, models for incident T2D were constructed using pooled logistic regression models with generalized estimating equations to account for familial relatedness. We pooled observations into four examination periods (examinations 1 and 2, 3 and 4, 5 and 6, and 7 and 8) to determine the 8-to-10-year risk of diabetes over 34 years of person-time(5). Only person-periods without diabetes at the beginning of the observation period were eligible for inclusion in the analyses. In CARDIA, we used Cox proportional-hazards regression to model the time to incident T2D, calculated from the date of the baseline examination to the date of the first follow-up examination meeting our criteria for incident T2D (cases) or to the date of the last CARDIA examination for each participant without incident T2D (censored individuals).

In each study, we constructed regression models for incident T2D as a function of GRS, sex, and age (demographic model) and GRS, sex, age, and risk factors routinely measured in clinical

practice (clinical model: parental history of diabetes (yes vs. no), BMI, systolic blood pressure, fasting plasma glucose, and log-transformed HDL cholesterol and triglyceride levels). We chose these risk factors based on their association with incident T2D in prior studies(8) and used values from the baseline examination for each included person-period. As in our previously analyses(4; 6), we used C statistics and continuous net reclassification improvement (NRI) indices to compare prediction models in logistic and Cox regression(9-12). Unlike categorical NRI indices, continuous NRI do not require discrete risk categories but instead use the proportions of cases correctly assigned a higher model probability and non-cases correctly assigned a lower model probability by a second model compared to with the first(9). Continuous NRI values of 0.2 indicate weak reclassification improvement, while values of 0.4 indicate a moderate effect(13). C statistics and NRI were calculated at 25 years of follow-up in CARDIA, and analyses were performed in whites and blacks separately, using race-specific GRS as described above.

References

1. Lettre G, Palmer CD, Young T, Ejebe KG, Allayee H, Benjamin EJ, Bennett F, Bowden DW, Chakravarti A, Dreisbach A, Farlow DN, Folsom AR, Fornage M, Forrester T, Fox E, Haiman CA, Hartiala J, Harris TB, Hazen SL, Heckbert SR, Henderson BE, Hirschhorn JN, Keating BJ, Kritchevsky SB, Larkin E, Li M, Rudock ME, McKenzie CA, Meigs JB, Meng YA, Mosley TH, Newman AB, Newton-Cheh CH, Paltoo DN, Papanicolaou GJ, Patterson N, Post WS, Psaty BM, Qasim AN, Qu L, Rader DJ, Redline S, Reilly MP, Reiner AP, Rich SS, Rotter JI, Liu Y, Shrader P, Siscovick DS, Tang WH, Taylor HA, Tracy RP, Vasan RS, Waters KM, Wilks R, Wilson JG, Fabsitz RR, Gabriel SB, Kathiresan S, Boerwinkle E: Genome-wide association study of coronary heart disease and its risk factors in 8,090 African Americans: the NHLBI CARe Project. PLoS genetics 2011;7:e1001300

2. Lemaitre RN, Tanaka T, Tang W, Manichaikul A, Foy M, Kabagambe EK, Nettleton JA, King IB, Weng LC, Bhattacharya S, Bandinelli S, Bis JC, Rich SS, Jacobs DR, Jr., Cherubini A, McKnight B, Liang S, Gu X, Rice K, Laurie CC, Lumley T, Browning BL, Psaty BM, Chen YD, Friedlander Y, Djousse L, Wu JH, Siscovick DS, Uitterlinden AG, Arnett DK, Ferrucci L, Fornage M, Tsai MY, Mozaffarian D, Steffen LM: Genetic loci associated with plasma phospholipid n-3 fatty acids: a meta-analysis of genome-wide association studies from the CHARGE Consortium. PLoS genetics 2011;7:e1002193

3. Gabriel SB, Schaffner SF, Nguyen H, Moore JM, Roy J, Blumenstiel B, Higgins J, DeFelice M, Lochner A, Faggart M, Liu-Cordero SN, Rotimi C, Adeyemo A, Cooper R, Ward R, Lander ES, Daly MJ, Altshuler D: The structure of haplotype blocks in the human genome. Science 2002;296:2225-2229

4. Meigs JB, Shrader P, Sullivan LM, McAteer JB, Fox CS, Dupuis J, Manning AK, Florez JC, Wilson PW, D'Agostino RB, Sr., Cupples LA: Genotype score in addition to common risk factors for prediction of type 2 diabetes. New England Journal of Medicine 2008;359:2208-2219

5. de Miguel-Yanes JM, Shrader P, Pencina MJ, Fox CS, Manning AK, Grant RW, Dupuis Je, Florez JC, D'Agostino RB, Cupples LA, Meigs JB, the MI, the DI: Genetic risk reclassification for type 2 diabetes by age below or above 50 years using 40 type 2 diabetes risk single nucleotide polymorphisms. Diabetes Care 2011;34:121-125

6. Vassy JL, Durant NH, Kabagambe EK, Carnethon MR, Rasmussen-Torvik LJ, Fornage M, Lewis CE, Siscovick DS, Meigs JB: A genotype risk score predicts type 2 diabetes from young adulthood: the CARDIA study. Diabetologia 2012;55:2604-2612

7. Morris AP, Voight BF, Teslovich TM, Ferreira T, Segre AV, Steinthorsdottir V, Strawbridge RJ, Khan H, Grallert H, Mahajan A, Prokopenko I, Kang HM, Dina C, Esko T, Fraser RM, Kanoni S, Kumar A, Lagou V, Langenberg C, Luan J, Lindgren CM, Muller-Nurasyid M, Pechlivanis S, Rayner NW, Scott LJ, Wiltshire S, Yengo L, Kinnunen L, Rossin EJ, Raychaudhuri S, Johnson AD, Dimas AS, Loos RJ, Vedantam S, Chen H, Florez JC, Fox C, Liu CT, Rybin D, Couper DJ, Kao WH, Li M, Cornelis MC, Kraft P, Sun Q, van Dam RM, Stringham HM, Chines PS, Fischer K, Fontanillas P, Holmen OL, Hunt SE, Jackson AU, Kong A, Lawrence R, Meyer J, Perry JR, Platou CG, Potter S, Rehnberg E, Robertson N, Sivapalaratnam S, Stancakova A, Stirrups K, Thorleifsson G, Tikkanen E, Wood AR, Almgren P, Atalay M, Benediktsson R, Bonnycastle LL, Burtt N, Carey J, Charpentier G, Crenshaw AT, Doney AS, Dorkhan M, Edkins S, Emilsson V, Eury E, Forsen T, Gertow K, Gigante B, Grant GB, Groves CJ, Guiducci C, Herder C, Hreidarsson AB, Hui J, James A, Jonsson A, Rathmann W, Klopp N, Kravic J, Krjutskov K, Langford C, Leander K, Lindholm E, Lobbens S, Mannisto

S, Mirza G, Muhleisen TW, Musk B, Parkin M, Rallidis L, Saramies J, Sennblad B, Shah S, Sigurethsson G, Silveira A, Steinbach G, Thorand B, Trakalo J, Veglia F, Wennauer R, Winckler W, Zabaneh D, Campbell H, van Duijn C, Uitterlinden AG, Hofman A, Sijbrands E, Abecasis GR, Owen KR, Zeggini E, Trip MD, Forouhi NG, Syvanen AC, Eriksson JG, Peltonen L, Nothen MM, Balkau B, Palmer CN, Lyssenko V, Tuomi T, Isomaa B, Hunter DJ, Qi L, Shuldiner AR, Roden M, Barroso I, Wilsgaard T, Beilby J, Hovingh K, Price JF, Wilson JF, Rauramaa R, Lakka TA, Lind L, Dedoussis G, Njolstad I, Pedersen NL, Khaw KT, Wareham NJ, Keinanen-Kiukaanniemi SM, Saaristo TE, Korpi-Hyovalti E, Saltevo J, Laakso M, Kuusisto J, Metspalu A, Collins FS, Mohlke KL, Bergman RN, Tuomilehto J, Boehm BO, Gieger C, Hveem K, Cauchi S, Froguel P, Baldassarre D, Tremoli E, Humphries SE, Saleheen D, Danesh J, Ingelsson E, Ripatti S, Salomaa V, Erbel R, Jockel KH, Moebus S, Peters A, Illig T, de Faire U, Hamsten A, Morris AD, Donnelly PJ, Frayling TM, Hattersley AT, Boerwinkle E, Melander O, Kathiresan S, Nilsson PM, Deloukas P, Thorsteinsdottir U, Groop LC, Stefansson K, Hu F, Pankow JS, Dupuis J, Meigs JB, Altshuler D, Boehnke M, McCarthy MI: Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. Nature Genetics 2012;44:981-990

8. Wilson PWF, Meigs JB, Sullivan L, Fox CS, Nathan DM, D'Agostino RB, Sr.: Prediction of incident diabetes mellitus in middle-aged adults: the Framingham Offspring Study. Archives of Internal Medicine 2007;167:1068-1074

9. Pencina MJ, D'Agostino RB, Sr., Steyerberg EW: Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. Stat Med 2011;30:11-21

10. Pencina MJ, D'Agostino RB, Sr., D'Agostino RB, Jr., Vasan RS: Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157-172

11. DeLong ER, DeLong DM, Clarke-Pearson DL: Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837-845

12. Pencina MJ, D'Agostino RB: Overall C as a measure of discrimination in survival analysis: model specific population value and confidence interval estimation. Stat Med 2004;23:2109-2123

13. Pencina MJ, D'Agostino RB, Sr., Demler OV: Novel metrics for evaluating improvement in discrimination: net reclassification and integrated discrimination improvement for normal variables and nested models. Stat Med 2012;31:101-113