ORIGINAL ARTICLE
A common biological basis of obesity and nicotine addiction

TE Thorgeirsson1, DF Gudbjartsson1, P Sulem1, S Besenbacher1,2, U Styrkarsdottir1, G Thorleifsson1, GB Walters1, TAG Consortium9, Oxford-GSK Consortium9, ENGAGE consortium9, H Furberg3, PF Sullivan4, J Marchini5,6, MI McCarthy5,7, V Steinthorsdottir1, U Thorsteinsdottir1,8 and K Stefansson1,8

Smoking influences body weight such that smokers weigh less than non-smokers and smoking cessation often leads to weight increase. The relationship between body weight and smoking is partly explained by the effect of nicotine on appetite and metabolism. However, the brain reward system is involved in the control of the intake of both food and tobacco. We evaluated the effect of single-nucleotide polymorphisms (SNPs) affecting body mass index (BMI) on smoking behavior, and tested the 32 SNPs identified in a meta-analysis for association with two smoking phenotypes, smoking initiation (SI) and the number of cigarettes smoked per day (CPD) in an Icelandic sample (N = 34 216 smokers). Combined according to their effect on BMI, the SNPs correlate with both SI (r = 0.019, P = 0.00054) and CPD (r = 0.032, P = 8.0 × 10⁻⁶). These findings replicate in a second large data set (N = 127 274, thereof 76 242 smokers) for both SI (P = 1.2 × 10⁻⁵) and CPD (P = 9.3 × 10⁻⁵). Notably, the variant most strongly associated with BMI (rs1558902-A in FTO) did not associate with smoking behavior. The association with smoking behavior is not due to the effect of the SNPs on BMI. Our results strongly point to a common biological basis of the regulation of our appetite for tobacco and food, and thus the vulnerability to nicotine addiction and obesity.

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INTRODUCTION
Smoking and obesity are major risk factors for many serious diseases.1,2 Eating and smoking are behavioral traits that are at least in part controlled by the same reward mechanisms.3 Genome-wide association studies (GWAS) have yielded 32 single-nucleotide polymorphisms (SNPs) associated with body mass index (BMI).4 Smoking and SNPs associated with increased smoking quantity have been shown to correlate with lower BMI.5,6 According to the World Health Organization (WHO), more than one billion people smoke and over 400 million people are obese (BMI > 30 kg m⁻²), with both prevalences rising (see url section). Eating can become compulsive, and the neurobiological processes relating to overindulgence in food overlap with those involved in substance abuse and addiction.3 All drugs of abuse have been shown to increase dopamine in the mesolimbic reward system, and studies of both human brain images5 and animal brains6 have revealed that similar neurocircuits are involved in the regulation of rewarding and reinforcement in drug addiction and compulsive eating. Based on the many similarities between hyperphagia and excessive drug use in addiction, it has even been suggested that some forms of obesity should be included as a diagnosis in future editions of the Diagnostic and Statistical Manual of Mental Disorders.8,9 Smoking influences body weight, such that smokers weigh less than non-smokers, and smoking cessation is often accompanied by an increase in weight.5 These effects have been largely attributed to nicotine that increases the metabolic rate and suppresses appetite. Although increased food intake upon smoking cessation is partly explained by a reward substitution mechanism, as food intake is increased to make up for the lack of nicotine, the absence of nicotine has also been shown to increase the reward value of certain foods.10 At the molecular level, these effects are most likely achieved through activation of the nicotinic acetylcholine receptors. The melanocortin (MC) system has a key role in regulating body weight,11 and nicotine was recently shown to interact directly with the MC system in the brain through activation of α₃β₄ nicotinic acetylcholine receptors on pro-opiomelanocortin (POMC) neurons12 in the arcuate nucleus of the hypothalamus. The POMC neurons project to secondary neurons influencing appetite, and nicotine activation leads to the release of melanocortin-4 agonists activating MC4 receptors in the paraventricular nucleus producing appetite suppression, an effect that is absent from POMC KO mice.12

However, the relationship between smoking phenotypes and obesity is more complicated than can be accounted for by the known effects of nicotine on appetite and metabolism. This is evident from the fact that the number of cigarettes smoked per day (CPD) correlates with elevated BMI.13,14 Thus, although smokers weigh less than non-smokers, heavy smokers indeed weigh more than light smokers. BMI and smoking data are widely available from various studies and large sample sizes have been obtained for GWAS of BMI and some smoking phenotypes,15–17 and these studies have uncovered a number of variants associating with obesity (BMI) and with smoking behavior. The variant most strongly correlating with CPD,15–17 rs1051730-A/rs16969968-A, correlates with reduced BMI both in current and former smokers, but does not have an impact on the BMI of never smokers.6 This observation is
consistent with the notion that smoking influences body weight through nicotine’s effects on body and brain, the increase of metabolic rate and suppression of appetite. Here we report how variants correlating with BMI influence smoking behavior.

MATERIALS AND METHODS

Study subjects

Written informed consent was obtained from all subjects. Inclusion in the study required the availability of genotypes from ongoing SNP array typing in Iceland or previous GWAS, 15–17 and the study populations have all been described previously. 15–17 The GWAS of smoking initiation (SI) involved comparison of ever smokers and never smokers, and the studies of smoking quantity probed CPD as a quantitative trait among smokers only. The definitions of smokers and never smokers varied somewhat between studies, 15–17 as questions addressing smoking behavior varied with most studies probing for regular smoking over a certain period of time. Questions probing for smoking quantity also varied between studies, and for analysis of smoking quantity we used CPD data for smokers in categories with each category representing 10 CPD (effect size of 0.1 = 1 CPD). 15–17 CPD at the time of smoking was used for past smokers, and never smokers were excluded from analysis of CPD. All subjects were of European descent. The total sample sizes were \( N = 100,860 \) and \( N = 161,490 \) for CPD and SI, respectively.

Icelandic study design

A generalized form of linear regression was used to test the correlation between quantitative traits (BMI and height) and smoking phenotypes (CPD and SI) in Iceland. The generalized form assumes that the smoking behavior of related individuals is correlated proportional to the kinship between them rather than assuming that the smoking phenotypes of all individuals are independent. Let \( y \) be the vector of smoking behavior measurements, and let \( x \) be the vector of BMI or height measurements. We assume that the expectation of the smoking behavior depends linearly on BMI or height, \( E(y) = x^T \beta \), and that the variance-covariance matrix of the smoking behavior depends only on the pairwise kinship between the study participants, \( \text{Var}(y) = 2\sigma_w^2 \mathbf{K} \), where

\[
\Phi = \left\{ \begin{array}{ll}
\frac{1}{2} & i = j \\
\frac{1}{2}k_{ij} & i \neq j
\end{array} \right.
\]

is based on the kinship between individuals as estimated from the Icelandic genealogical database \( k_{ij} \) and an estimate of the heritability of the trait \( \beta \). Assuming normally distributed errors, the maximum likelihood method gives estimates for \( \beta \), which will asymptotically follow a normal distribution and can be used to estimate the correlation between height and BMI on the one side and CPD and SI on the other.

In order to test the correlation between the set of 32 BMI SNPs or the set of 180 height SNPs and smoking behavior, the same type of analysis was performed replacing the observed BMI and height with the BMI and height predicted based on the sets of 32 and 180 SNPs. We shall describe how this was achieved for BMI, the analysis for height being conceptually identical. For each of the 32 SNPs reported to associate with BMI, let \( f_i \) be its minor allele frequency and \( \gamma_i \) be its published effect on BMI. For an individual with \( g_i \) minor alleles at SNP \( i \), the set of 32 BMI SNPs predict a BMI of

\[
\sum_{i=1}^{32} (g_i - \bar{g})\gamma_i
\]

RESULTS AND DISCUSSION

To study the correlation between obesity variants and smoking phenotypes, we focused on the 32 SNPs associating with BMI

Table 1. Association of BMI, height and SNPs associating with BMI and height with smoking phenotypes in Iceland

<table>
<thead>
<tr>
<th></th>
<th>CPD</th>
<th>Smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>From</td>
<td>N</td>
<td>Correlation (95% CI)</td>
</tr>
<tr>
<td>BMI</td>
<td>33 620</td>
<td>0.095 (0.085, 0.106)</td>
</tr>
<tr>
<td>32 BMI SNPs</td>
<td>24 618</td>
<td>0.032 (0.019, 0.045)</td>
</tr>
<tr>
<td>Height</td>
<td>33 875</td>
<td>-0.004 (-0.015, 0.007)</td>
</tr>
<tr>
<td>180 Height SNPs</td>
<td>24 630</td>
<td>0.001 (-0.011, 0.014)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CI, confidence interval; SNP, single-nucleotide polymorphism.
described in a recent report of a study of 249,796 subjects.4 We weighted the 32 SNPs together based on their published effect on BMI and tested the correlation with both CPD and SI in 49,565 chip-typed Icelanders (Table 1). We also tested the correlation between the actual measured BMI and the smoking phenotypes in a slightly larger set of Icelanders. For comparison, we performed a corresponding study using Icelandic data on human height and 180 SNPs reported to influence human height in a recent study of 183,731 individuals9 (Table 1).

BMI associated with CPD (r = 0.095, P = 2.5 × 10−66) but not SI (r = −0.005, P = 0.29), whereas height did not associate with CPD (r = −0.004, P = 0.46) and showed only weak association with SI (r = −0.012, P = 0.013). The set of 32 BMI SNPs associated with both CPD (r = 0.032, P = 8.0 × 10−7) and SI (r = 0.019, P = 0.00054), whereas the set of 180 height SNPs associated with neither smoking behavior (P = 0.84 and 0.44 for CPD and SI, respectively).

The correlation between the set of 32 BMI SNPs and BMI and the correlation between BMI and CPD predict a correlation between the 32 BMI SNPs and CPD of 0.013, which is significantly lower than the observed correlation of 0.032 between the set of 32 BMI SNPs and CPD (P = 0.0033). The correlation between BMI and SI is negative so that the predicted correlation between the 32 BMI SNPs and SI is also negative and even more significantly different from the observed correlation of 0.019 than from 0. Hence, the observed associations between the BMI variants and the smoking phenotypes are not explained by the direct phenotypic correlations between BMI and smoking behavior.

To investigate the contributions of individual SNPs and to replicate our observations in other populations, we looked up the correlations of each of the 32 SNPs with CPD and SI, using data from our previous studies outside of Iceland15−17 (N = 76,242 for CPD, and N = 127,274 for SI). For these studies, we utilized the fixed-effect additive meta-analysis results for ~2,500,000 SNPs obtained using the inverse-variance method for each of the two smoking phenotypes. Before conducting the meta-analysis, we performed a genonic control correction of each study.18 The combined χ2-test statistics were still somewhat inflated by a factor of λGC = 1.10 (SI) and λGC = 1.06 (CPD). The correlations between the set of 32 BMI SNPs and the two smoking variables were significant in this replication sample with P = 1.2 × 10−5 and 9.3 × 10−5 for SI and CPD, respectively. Combined with Iceland, the association between the 32 BMI SNPs and SI and CPD reached a significance of P = 1.2 × 10−7 and P = 1.6 × 10−9, respectively.

As expected, based on the correlations observed between the combined set of the 32 BMI SNPs (Table 1), we observe congruence in the effects that these SNPs have on BMI and smoking behavior. For most of the SNPs, the allele that associates with increased BMI also associates with both increased probability of SI and higher CPD (Figure 1). We note that the effect sizes are small and although the markers as a group clearly associate with the smoking behaviors, further studies are required to determine unequivocally which of the markers have an impact on smoking behavior. The SNP by far most strongly associated with BMI (rs1558902-A in FTO) represents a notable exception from the trend observed and shows no evidence for association with either CPD or SI.

Considering the 11 BMI SNPs most strongly associated with smoking (P < 0.05), 9 SNPs associate with smoking initiation and 4 with CPD (Supplementary Table 1 and Figure 1). For smoking initiation the most significant associations were to rs10767664-A (effect = 0.050495, P = 1.14 × 10−6) in the Brain Neurotrophin Factor gene (BDNF) and rs2867125-C (effect = 0.0397, P = 0.00021) 45 kb upstream of the Transmembrane protein 18 gene (TMEM18), and for CPD the most significant associations were with rs2867125-C (effect = 0.286, P = 0.000346) (TMEM18) and rs4771122-G (effect = 0.0193, P = 0.00048) in the mitochondrial translational initiation factor 3 gene (MTF3). In addition to rs286125-C (TMEM18), rs2815752-A (NEGR1) is among the top markers (P < 0.05) for both SI (effect = 0.186, P = 0.0244) and CPD (effect = 0.0097, P = 0.0305). A SNP within the BDNF gene has previously been shown to associate with smoking initiation (rs6265-C).16 This SNP is in linkage disequilibrium with the BMI-associated rs10767664 (r2 = 0.85 in Iceland). The association with SI remains significant after removing rs10767664 (P = 1.3 × 10−5).

In summary, we have demonstrated that as a group, the 32 common variants identified in GWAS of BMI also have an impact on the smoking behavior. A variant within the nAChR gene cluster...
at chr5 15q25 (rs1051730-A) was discovered in GWAS of smoking behavior, subsequent to two GWAS of BMI, and subsequently shown to correlate with reduced BMI in smokers without an effect on the BMI of never smokers, thus most likely influencing BMI mainly through its effect on smoking behavior. The variants studied here represent a different class of SNPs affecting both BMI and smoking: They were found in GWAS of BMI and influence BMI in both smokers and never smokers, and the alleles correlating with elevated BMI tend to increase the propensity to smoke and/or associate with increased cigarette intake. We note that, in Iceland, the correlation between the predicted BMI and observed BMI is similar for smokers (0.15, $P = 3.0 \times 10^{-10}$; $N = 20,462$) and never smokers (0.13, $P = 7.2 \times 10^{-31}$; $N = 7910$). The direction of this trend is opposite to what would be expected based on the known effects of nicotine on BMI, and inconsistent with an effect rooted in nicotine-mediated increase of metabolic rate and suppression of appetite. That the majority of variants known to associate with elevation of BMI correlate with smoking behaviors in this manner points to a common biological basis to regulation of the intake of food and tobacco.

CONFLICT OF INTEREST
Authors whose affiliations are listed as Decode genetics/AMGEN are employees of Decode genetics/AMGEN.

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AUTHOR CONTRIBUTIONS
TET, DFG, and KS wrote the manuscript. The study was designed by and the results interpreted by TET, DFG, PS, SB, UT and KS. The meta-analyses of smoking GWAS data were performed by DFG. TET, DFG, PS, SBU, GT, BW and VS worked on data management and analysis. Smoking GWAS consortia were coordinated by HF (TAG), PFS(TAG) JM (OX-GSK) and MIM (ENGAGE). All authors contributed to the final version of the paper.

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TE Thorgerisson et al

Psychology, VU University Amsterdam, Amsterdam, The Netherlands. 1Department of Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands. 12Department of Epidemiology Research, Stenats Serum Institut, Copenhagen, Denmark. 13Estonian Genome Center, University of Tartu, Ria 23b, Tartu 51010, Estonia. 14MBG of University of Tartu and Estonian Biocentre, Ria str 23, Tartu 51010, Estonia. 15Institute of Epidemiology, Helmholtz Zentrum München, Ingolstaedter Landstr. 1, 85764 Munich/Neuherberg, Germany. 16Department of Twin Research and Genetic Epidemiology, King’s College London, St Thomas’ Hospital Campus, London SE17EH, UK. 19Department of Public Health, University of Helsinki, Helsinki, Finland. 30Department of Psychiatry, VU University Medical Center, Amsterdam, The Netherlands. 32Radboud University Nijmegen Medical Centre, Department of Endocrinology, Nijmegen, The Netherlands. 23Radboud University Nijmegen Medical Centre, Department of Toxicology, Nijmegen, The Netherlands. 24Wellcome Trust Sanger Institute, Hinxton, UK. 25Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands. 26Department of Medicine, University of Leipzig, Liebigstr. 18, 04103, Leipzig, Germany. 27Coordination Centre for Clinical Trials, University of Leipzig, Härtelstr. 16–18, 04103, Leipzig, Germany. 28Interdisciplinary Centre for Clinical Research, University of Leipzig,Inselsp. 22, 04103, Leipzig, Germany. 29EMGO Institute/Department of Psychiatry, VU University Medical Center, Amsterdam, The Netherlands. 30Department of Psychiatry, University of Maastricht, Maastricht, The Netherlands. 31Department of Genetics, National Institute of Public Health and Welfare, Helsinki, Finland. 28Finland South and West Study. 29EMGO Institute, Amsterdam, The Netherlands. 30Department of Psychiatry, University of Leicester, LE1 7RH Leicester, UK. 32Radboud University Nijmegen Medical Centre, Department of Urology, Nijmegen, The Netherlands. 33European Bioinformatics Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, CB10 1SD, UK. 34Multidisciplinary Cardiovascular Research Centre (MCRC), Leeds Institute of Genetics, Health and Therapeutics (LIGHT), University of Leeds, Leeds, LS2 9JT, UK. 35Department of Health Sciences and Genetics, Health and Therapeutics (LIGHT), University of Leeds, Leeds, LS2 9JT, UK. 36Department of Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands. 37Vogur SAA Addiction Treatment Center, Reykjavik, Iceland. 38Department of Endocrinology, National Institute of Health and Welfare, Helsinki, Finland. 39Department of Genetics, University of North Carolina, Chapel Hill, North Carolina, USA. 40Department of Internal Medicine, National Institute of Health and Welfare, Helsinki, Finland. 41Institute of Medical Informatics, Biometry and Epidemiology, Ludwig-Maximilians-Universität, Munich, Germany. 42Institute on Aging, Baltimore, Maryland, USA. 43Department of Genetics, University of North Carolina, Chapel Hill, North Carolina, USA. 44Department of Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands. 45Department of Mental Health and Alcohol Abuse Services, National Institute for Health and Welfare, Helsinki, Finland.

The Tobacco and Genetics Consortium (TAG)—Yun Jung Kim1, Jennifer Dackor1, Eric Boerwinkle2, Nora Franceschini2, Diego Ardissono2, Luisa Bernardinelli5, Peter M. Mannucci6,7, Pier M. Zardi7, Ariana Znaor8, Mark Lathrop9,60, Paul Brennan36, Stefania Bandinelli51, Timothy M. Frayling62, Jack M. Guralnick63, Yuri Milaneschi64, John R B Perry65, David Altschuler65–70, Roberto Elosua71, Sek Kathiresan71,56,87, Gavin Lucas72, Oliver Melander37, Christopher J. O’Donnell53, Velkko Salomaa54, Maxime Schwartz55, Benjamin F. Voight56, Brenda W Penninx77,78, Johannes H Smit77,78, Nicole Vogelzangs77,78, Dorret I Boomsma79,7, Eco J C de Geus80, Jacqueline M Vink9, Gonnieke Willemsen37, Stephen J Chinn42, Fanqi Gu76, E. H. Hankinson81, Daniel J. Stamm81, Albert Hofman83, Henning Tiemeier83,84, Andre G Uitterlinden81,85, Cornelia M van Duijn83,86, Stefan Walter83,87, Daniel I Chasman88, Brendan M Everett88,89, Guillaume Paré88, Paul M Ridker88,89, Ming D Li90, Hermine H M Maes91,92, Janet Audrain-McGovern93, Danielle Posthuma94,95, Laura M Thornton96, Cary Lerman93,97, Jaakko Kaprio26,75,98, Jed E Rose99, John P A Ioannidis100–102, Peter Kraft81 and Dan-Yu Lin103.

1Department of Genetics, University of North Carolina, Chapel Hill, North Carolina, USA. 2University of North Carolina Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, North Carolina, USA. 3Human Genetics Center and Institute for Molecular Medicine, University of Texas Health Science Center, Houston, Texas, USA. 4Department of Epidemiology, University of North Carolina, Chapel Hill, North Carolina, USA. 5Division of Cardiology, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy. 6Statistical Laboratory, Centre for Mathematical Sciences, University of Cambridge, Cambridge, UK. 7Department of Applied Health Sciences, University of Pavia, Pavia, Italy. 8Department of Internal Medicine and Medical Specialties, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico, Ospedale Maggiore, Mangiagalli e Regina Elena, University of Milan, Milan, Italy. 9Department of Cardiology, Azienda Ospedaliera Niguarda Ca’ Granda, Milan, Italy. 10HudsonAlpha Institute for Biotechnology, Huntsville, Alabama, USA. 11Cardiovascular Medicine, Stanford University, Stanford, California, USA. 12Stanford Prevention Research Center, Stanford University, Stanford, California, USA. 13Kaiser Permanente Northern California Division of Research, Oakland, California, USA. 14National Institute on Aging, Baltimore, Maryland, USA. 15Medstart Research Institute, National Institute on Aging, Baltimore, Maryland, USA. 16Cardiovascular Health Research Unit, University of Washington, Seattle, Washington, USA. 17Department of Medicine, University of Washington, Seattle, Washington, USA. 18Division of Public Health Sciences, Wake Forest University Health Sciences, Winston-Salem, North Carolina, USA. 19Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, California, USA. 20Department of Biostatistics, University of Washington, Seattle, Washington, USA. 21Department of Epidemiology and Health Services, University of Washington, Seattle, Washington, USA. 22Group Health Research Institute, Seattle, Washington, USA. 23Department of Epidemiology, University of Washington, Washington, USA. 24Department of Clinical Sciences, Diakonhjemmet University Hospital, Oslo, Norway. 25Department of Biostatistics, School of Public Health, University of Michigan, Ann Arbor, Michigan, USA. 26Hjelt Institute, Department of Public Health, University of Helsinki, Helsinki, Finland. 27Diabetes Prevention Unit, National Institute for Health and Welfare, Helsinki, Finland. 28Finland South and West Study. 29EMGO Institute, Amsterdam, The Netherlands. 30Department of Psychiatry, VU University Medical Center, Amsterdam, The Netherlands. 31Center for Population Studies, National Heart, Lung and Blood Institute, Bethesda, Maryland, USA. 32Department of Medicine, Sections of Preventive Medicine and Cardiology, Boston University School of Medicine, Boston, Massachusetts, USA. 33Center for Psychiatric Genetics, NorthShore University HealthSystem

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TE Thorgeirsson et al

Reasearch Center, Verona, Italy. 3Department of Psychiatry, School of Medicine, University of North Carolina, Chapel Hill, North Carolina, USA. 4Genetics Division, GlaxoSmithKline, Upper Merion, Pennsylvania, USA. 5Roche Pharmaceuticals, Nutley, New Jersey, USA. 6Neurosearch Denmark and Department of Psychiatry, University of Toronto, Toronto, Canada. 7Division of Neurosciences and Mental Health, Imperial College London, UK. 8Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA. 9Genetics Division, GlaxoSmithKline, Research Triangle Park, North Carolina, USA. 10University Hospital Center, University of Lausanne, Lausanne, Switzerland. 11Department of Internal Medicine, University of Lausanne, Lausanne, Switzerland. 12Department of Psychiatry, University of Lausanne, Lausanne, Switzerland. 13MRC Epidemiology Unit, Institute of Metabolic Science, Cambridge, UK. 14Wellcome Trust Sanger Institute, Hinxton, UK. 15Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK. 16Center for Human Nutrition, University of Texas Southwestern Medical Center, Dallas, Texas, USA. 17The Heart Research Institute, Sydney, New South Wales, Australia. 18Gladstone Institute of Cardiovascular Disease, University of California, San Francisco, California, USA. 19American Hospital, Istanbul, Turkey. 20Department of Internal Medicine, University of Oulu, Oulu, Finland. 21Division of Cardiology, University of Ottawa Heart Institute, Ottawa, Ontario, Canada. 22Biocenter Oulu, University of Oulu, Oulu, Finland. 23Centre for Addiction and Mental Health, University of Toronto, ON, Canada. 24Medical Research Council Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King’s College London, UK. 25Center for Neuroscience, Division of Medical Sciences, University of Dundee, Dundee, UK. 26Institute of Medicine, University of Bergen, Bergen, Norway. 27Max-Planck Institute of Psychiatry, Munich, Germany. 28Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany. 29Institute of Medical Informatics, Biometry and Epidemiology, Ludwig-Maximilians-University, Munich, Germany. 30Klinikum Grosshadern, Munich, Germany. 31Psychiatrische Klinik und Poliklinik University of Mainz, Germany. 32Division of Genetic Epidemiology, Department of Medical Genetics, Molecular and Clinical Pharmacology, Innsbruck Medical University, Innsbruck, Austria. 33Medical School, University of Split, Split, Croatia. 34Centre for Population Health Sciences, University of Edinburgh, Edinburgh, UK. 35Institute of Genetics and Molecular Medicine, MRC Human Genetics Unit, Edinburgh, UK. 36National Heart and Lung Institute, Imperial College London, UK. 37Division of Epidemiology, Imperial College London, UK. 38Cardiovascular Research Institute, MedStar Health Research Institute, Washington Hospital Center, Washington, District of Columbia, USA. 39Centre for Population Health Sciences, University of Edinburgh, UK. 40The Cardiovascular Institute, University of Pennsylvania, Philadelphia, Pennsylvania, USA. 41The Institute for Translational Medicine and Therapeutics, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA. 42Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, Pennsylvania, USA. 43The Center for Applied Genomics, Children’s Hospital of Philadelphia, Philadelphia, Pennsylvania, USA. 44Institute of Clinical Molecular Biology, Christian-Albrechts-University, Kiel, Germany. 45Istituto di Neurogenetica e Neurofarmacologia, CNR, Monserrato, Cagliari, Italy. 46National Institute on Aging, Baltimore, Maryland, USA. 47Department of Epidemiology, University of Texas MD Anderson Cancer Center, Houston, Texas, USA. 48Department of Mental Health, University of Aberdeen, Aberdeen, UK. 49Department of Psychiatry, University of Halle, Halle, Germany. 50Center for Statistical Genetics, Department of Biostatistics, University of Michigan, Ann Arbor, Michigan, USA. 51Department of Psychiatry and Psychotherapy, University of Greifswald, Greifswald, Germany. 52Interfaculty Institute for Genetics and Functional Genomics, University of Greifswald, Greifswald, Germany. 53Institute of Clinical Chemistry and Laboratory Medicine, University of Greifswald, Greifswald, Germany. 54Department of Social Medicine and Epidemiology, University of Greifswald, Greifswald, Germany. 55Department of Health Sciences, University of Leicester, Leicester, UK. 56Multidisciplinary Cardiovascular Research Centre (MCRC), Leeds Institute of Genetics, Health and Therapeutics (LiGHT), University of Leeds, Leeds, UK. 57Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Leicester, UK. 58Peninsula College of Medicine and Dentistry, Exeter, UK. 59Department of Medical and Molecular Genetics, King’s College London School of Medicine, Guy’s Hospital, London, London. 60Gastroenterology Research Unit, Addenbrooke’s Hospital, Cambridge, UK. 61Gastrointestinal Unit, Molecular Medicine Centre, University of Edinburgh, Western General Hospital, Edinburgh, UK. 62Clinical Pharmacology and Barts and the London Genome Centre, William Harvey Research Institute, Barts and the London School of Medicine, Queen Mary University of London, London, UK. 63Department of Cardiovascular Medicine, University of Oxford, Wellcome Trust Centre for Human Genetics, Oxford, UK. 64BHF Glasgow Cardiovascular Research Centre, Division of Cardiovascular and Medical Sciences, University of Glasgow, Western Infirmary, Glasgow, UK. 65Arthritis Research UK Epidemiology Unit, Musculoskeletal Research Group, University of Manchester, Manchester Academic Health Sciences Centre, Manchester, UK. 66NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester NHS Foundation Trust, Manchester, UK. 67Department of Pathology and Laboratory Medicine, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland. 68Max Planck Institute for Psycholinguistics.

URLS

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