

ORIGINAL ARTICLE

A common biological basis of obesity and nicotine addiction

TE Thorgeirsson¹, DF Gudbjartsson¹, P Sulem¹, S Besenbacher^{1,2}, U Styrkarsdottir¹, G Thorleifsson¹, GB Walters¹, TAG Consortium⁹, Oxford-GSK Consortium⁹, ENGAGE consortium⁹, H Furberg³, PF Sullivan⁴, J Marchini^{5,6}, MI McCarthy^{5,7}, V Steinthorsdottir¹, U Thorsteinsdottir^{1,8} and K Stefansson^{1,8}

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 ($r = 0.032$, $P = 8.0 \times 10^{-7}$). These findings replicate in a second large data set ($N = 127\,274$, thereof 76 242 smokers) for both SI ($P = 1.2 \times 10^{-5}$) and CPD ($P = 9.3 \times 10^{-5}$). 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.

Translational Psychiatry (2013) 3, e308; doi:10.1038/tp.2013.81; published online 1 October 2013

Keywords: addiction; body mass index; nicotine dependence; obesity; smoking

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 $> 30 \text{ kg m}^{-2}$), 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 images³ and animal brains⁷ 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 $\alpha_3\beta_4$ 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 BMI⁴ 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

¹Decode genetics/AMGEN, Sturlugata 8, Reykjavik, Iceland; ²Bioinformatics Research Centre, Aarhus University, Aarhus, Denmark; ³Department of Epidemiology, Memorial Sloan Kettering Cancer Center, NY, USA; ⁴Departments of Genetics and Psychiatry, CB# 7264, 5097 Genomic Medicine, NC, USA; ⁵Wellcome Trust Centre of Human Genetics, Oxford, UK; ⁶Department of Statistics, University of Oxford, Oxford, UK; ⁷Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, UK and ⁸Faculty of Medicine, University of Iceland, Reykjavik, Iceland. Correspondence: Dr TE Thorgeirsson or Dr K Stefansson, Decode genetics/AMGEN, Sturlugata 8, 101 Reykjavik, Iceland. E-mail: kstefans@decode.is or thorgeir@decode.is

⁹The collaborators from these consortia are listed in a section entitled CONSORTIA.

Received 19 July 2013; accepted 22 July 2013

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, $Ey = \alpha + \beta x$, and that the variance-covariance matrix of the smoking behavior depends only on the pairwise kinship between the study participants, $Var(y) = 2\sigma^2\Phi$, where

$$\Phi_{ij} = \begin{cases} \frac{1}{2}, & i = j \\ 2\rho k_{ij}, & i \neq j \end{cases}$$

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 (ρ). Assuming normally distributed errors, the maximum likelihood method gives estimates for β , 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 γ_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

$$\sum_{i=1}^{32} (g_i - 2f_i)\gamma_i$$

Conditional independence

We observe a correlation between the 32 BMI SNPs and smoking behavior. The 32 BMI SNPs associate with BMI and BMI associates with CPD. The question then arises of whether the correlation between the 32 BMI SNPs and CPD is all going through BMI. In other words, are the 32 BMI SNPs and CPD correlated conditional on BMI? Assuming that the 32 BMI SNPs and CPD are independent conditional on BMI, then the correlation between the 32 BMI SNPs and CPD will be the product of the correlation between the 32 BMI SNPs and BMI and the correlation between BMI and CPD. Denoting the estimator for the correlation between the 32 BMI SNPs and BMI with $c_{\text{BMISNPs,BMI}}$, and the variance of the estimator with $\text{Var}(c_{\text{BMISNPs,BMI}})$, and similarly for the correlation between BMI and CPD. Then, $c_{\text{BMISNPs,BMI}}c_{\text{BMI,CPD}}$ is an estimator of the correlation between the 32 BMI SNPs and CPD, assuming conditional independence, and $\text{Var}(c_{\text{BMISNPs,BMI}})\text{Var}(c_{\text{BMI,CPD}}) + \text{Var}(c_{\text{BMISNPs,BMI}})^2c_{\text{BMI,CPD}}^2 + c_{\text{BMISNPs,BMI}}^2\text{Var}(c_{\text{BMI,CPD}})$ gives an estimate of the variance of the estimator. A standard test for the mean of two samples can now be applied to test the difference between the observed correlation between the 32 BMI SNPs and CPD and the correlation predicted based on the 32 BMI SNPs and CPD being independent conditional on BMI.

Replication outside of Iceland

The non-Icelandic studies shared only summary results from the genome-wide smoking behavior association scans in the form of effect sizes, P -values and allele frequencies. The ~ 2.5 million SNPs from the HapMap dataset were imputed and tested for association within each study population.^{15–17} The significance levels of each study population were adjusted individually using the method of genomic control.¹⁸ We used standard fixed-effects additive meta-analysis to combine the results for each SNP. After combining the results from all the populations, we again applied the method of genomic control and adjusted both smoking phenotypes accordingly ($\lambda_{\text{GC}} = 1.10$ and $\lambda_{\text{GC}} = 1.06$ for SI and CPD, respectively).

As data were not available on the individual level, we could not predict SI and CPD on the individual level as was done in Iceland. In order to test for the association of the 32 SNPs associating with BMI and the 180 SNPs associating with height with smoking behavior, we weighted the combined significance over all the populations of each SNP by the expected z -score associated with the SNP, assuming that the effect on smoking behavior was proportional to the effect on BMI or height as follows. Again let us take BMI as an example. For each of the 32 SNPs reported to associate with BMI, let f_i be its minor allele frequency and γ_i be its published effect on BMI. We denote the unknown effect of each SNP on smoking behavior with β_i and our assumption about the SNP's effect on smoking behavior being proportional to the SNP's effect on BMI can be stated as $\beta_i = k\gamma_i$ for some constant k . Quantifying the significance of the association of each SNP with smoking behavior by its z -score z_i , maximal power is achieved by weighing the SNPs according to the expected z -score. The expected z -score for the i th SNP is proportional to $\beta_i\sqrt{f_i(1-f_i)}$, which we assume is proportional to $\gamma_i\sqrt{2f_i(1-f_i)}$, which we will refer to as w_i and use to weigh the smoking behavior z -scores of the 32 BMI SNPs

$$\text{together: } z = \frac{\sum_{i=1}^{32} w_i z_i}{\sqrt{\sum_{i=1}^{32} w_i^2}}$$

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

From	CPD			Smoking		
	N	Correlation (95% CI)	P	N	Correlation (95% CI)	P
BMI	33 620	0.095 (0.085, 0.106)	2.5×10^{-68}	49 565	-0.005 (-0.014, 0.004)	0.29
32 BMI SNPs	24 618	0.032 (0.019, 0.045)	8.0×10^{-7}	34 216	0.019 (0.008, 0.030)	0.00054
Height	33 875	-0.004 (-0.015, 0.007)	0.46	49 931	-0.012 (-0.021, -0.002)	0.013
180 Height SNPs	24 630	0.001 (-0.011, 0.014)	0.84	34 231	0.004 (-0.007, 0.015)	0.44

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 individuals¹⁹ (Table 1).

BMI associated with CPD ($r=0.095$, $P=2.5 \times 10^{-68}$) 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 ($r=0.032$, $P=8.0 \times 10^{-7}$) 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 Iceland^{15–17} ($N=76\,242$ for CPD, and $N=127\,274$ for SI). For these studies, we utilized the fixed-effect additive meta-analysis results for $\sim 2\,500\,000$ SNPs obtained using the inverse-variance method for each of the two smoking phenotypes. Before conducting the meta-analysis, we performed a genomic control correction of each study.¹⁸ The combined χ^2 -test statistics were still somewhat inflated by a factor of $\lambda_{GC}=1.10$ (SI) and $\lambda_{GC}=1.06$ (CPD). The correlations between the set of 32 BMI SNPs and the two smoking variables were significant in this replication sample with $P=1.2 \times 10^{-5}$ 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 $P=1.2 \times 10^{-7}$ and $P=1.6 \times 10^{-9}$, 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, $P=1.14 \times 10^{-6}$) in the Brain Neurotrophin Factor gene (*BDNF*) and rs2867125-C (effect = 0.0397, $P=0.000021$) 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 (*MTIF3*). In addition to

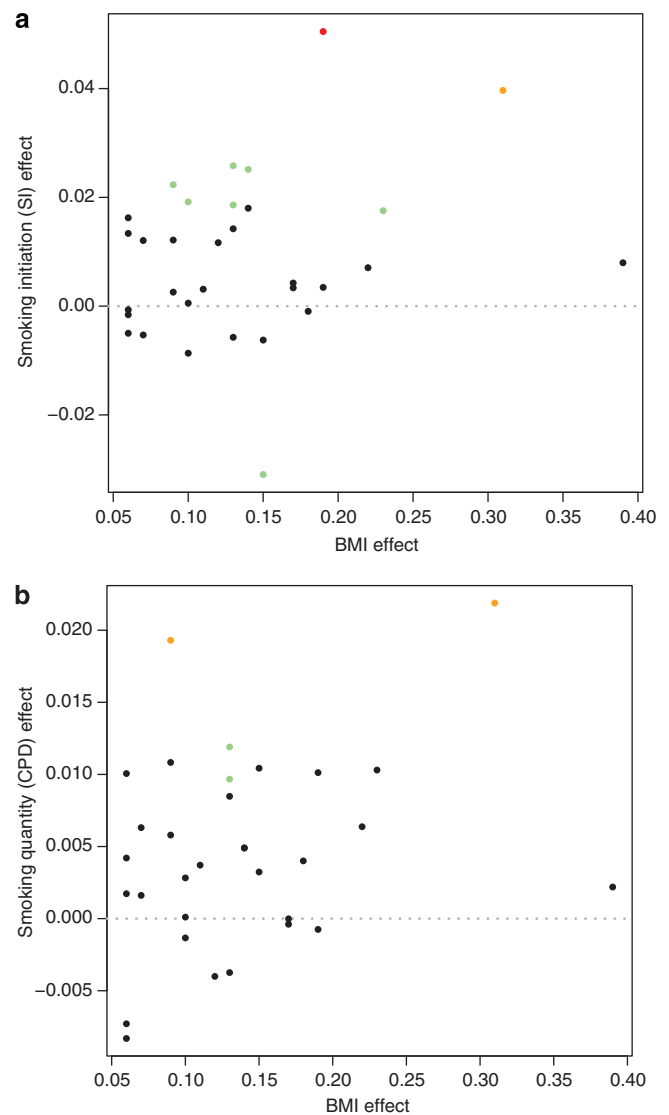


Figure 1. Association of obesity variants with smoking initiation (SI) and CPD. The effects on smoking behaviors are depicted vs the effects on BMI from a large meta-analysis.⁴ (a) The effect on smoking initiation vs the effect on BMI. (b) The effect on CPD vs the effect on BMI. The BMI effect is in standard units, and the effects on SI and CPD were obtained using a standard fixed-effects additive meta-analysis to combine the results for each SNP from Iceland with additional data from three large GWAS.^{15–17} The effects on SI are the β -values from logistic regression treating ever smoking as the response and the allele counts as covariates, and the GWAS of CPD used smoking quantity in categories with each category representing 10 CPD (effect size of 0.1 = 1 CPD). The dots representing each data point are color coded to indicate the p -value obtained as red ($P<0.0001$), yellow ($P<0.001$), green ($P<0.05$) and black ($P\geq 0.05$) and the input data are provided in (Supplementary Table 1).

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 ($r^2=0.85$ in Iceland). The association with SI remains significant after removing rs10767664 ($P=1.3 \times 10^{-5}$).

In summary, we have demonstrated that as a group, the 32 common variants identified in GWAS of BMI⁴ 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^{20,21} and subsequently shown to correlate with reduced BMI in smokers without an effect on the BMI of never smokers,⁶ 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, $P=3.0 \times 10^{-97}$, $N=20462$) and never smokers (0.13, $P=7.2 \times 10^{-33}$, $N=7910$). 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.

ACKNOWLEDGMENTS

We thank the participants in the genetic studies whose contributions made this work possible. This work was supported in part by NIH (R01-DA017932 and R01-DA022522) and the European Commission's Sixth Framework Programme, Integrated Project GENADDICT (LSHM-CT-2004-005166). The ENGAGE smoking consortium was formed through a component of the Integrated Project ENGAGE, supported by the European Commission's Seventh Framework Program, grant agreement HEALTH-F4-2007-201413. SB was funded by the FP7-PEOPLE-2009-IAPP 251592 grant (NextGene).

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, SB,US, 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.

REFERENCES

- Haslam DW, James WP. Obesity. *Lancet* 2005; **366**: 1197–1209.
- Jha P. Avoidable global cancer deaths and total deaths from smoking. *Nat Rev Cancer* 2009; **9**: 655–664.

Supplementary Information accompanies the paper on the Translational Psychiatry website (<http://www.nature.com/tp>)

CONSORTIA

The data utilized came from three large GWAS done by the ENGAGE, TAG, and OX-GSK consortia (references 15–17). The additional collaborators from these three consortia are listed below.

ENGAGE Consortium—Ida Surakka^{8,9}, Jacqueline M Vink¹⁰, Najaf Amin¹¹, Frank Geller¹², Thorunn Rafnar¹, Tõnu Esko^{13,14}, Stefan Walter¹¹, Christian Gieger¹⁵, Rajesh Rawal¹⁵, Massimo Mangino¹⁶, Inga Prokopenko^{5,6}, Reedik Mägi^{5,6,13}, Kaisu Kesitalo¹⁹, Iris H. Gudjonsdottir¹, Solveig Gretarsdottir¹, Hreinn Stefansson¹, Yurii S Aulchenko¹¹, Mari Nelis^{13,14}, Katja K Aben^{21,22}, Martin den Heijer^{21,23}, Nicole Soranzo^{16,24}, Ana M Valdes¹⁶, Claire Steves¹⁶, André G Uitterlinden^{11,25}, Albert Hofman⁶, Anke Tönjes^{26,27}, Peter Kovacs²⁸, Jouke Jan Hottenga¹⁰, Goncke Willemsen¹⁰, Nicole Vogelzangs²⁹, Angela Döring¹⁵, Norbert Dahmen³⁰, Barbara Nitz¹⁵, Samuli Ripatti^{8,9}, Markus Perola^{9,13}, Johannes Kettunen²⁴,

- Volkow ND, Wang GJ, Fowler JS, Telang F. Overlapping neuronal circuits in addiction and obesity: evidence of systems pathology. *Philos Trans R Soc Lond B Biol Sci* 2008; **363**: 3191–3200.
- Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU *et al*. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet* 2010; **42**: 937–948.
- Audrain-McGovern J, Benowitz NL. Cigarette smoking, nicotine, and body weight. *Clin Pharmacol Ther* 2011; **90**: 164–168.
- Freathy RM, Kazeem GR, Morris RW, Johnson PC, Paternoster L, Ebrahim S *et al*. Genetic variation at CHRNA5-CHRNA3-CHRNA4 interacts with smoking status to influence body mass index. *Int J Epidemiol* 2011; **40**: 1617–1628.
- Kenny PJ. Reward mechanisms in obesity: new insights and future directions. *Neuron* 2011; **69**: 664–679.
- Volkow ND, O'Brien CP. Issues for DSM-V: should obesity be included as a brain disorder? *Am J Psychiatry* 2007; **164**: 708–710.
- Devlin MJ. Is there a place for obesity in DSM-V? *Int J Eat Disord* 2007; **40**: S83–S88.
- Lerman C, Berrettini W, Pinto A, Patterson F, Crystal-Mansour S, Wileyto EP *et al*. Changes in food reward following smoking cessation: a pharmacogenetic investigation. *Psychopharmacology* 2004; **174**: 571–577.
- Schwartz MW, Woods SC, Porte Jr. D, Seeley RJ, Baskin DG. Central nervous system control of food intake. *Nature* 2000; **404**: 661–671.
- Mineur YS, Abizaid A, Rao Y, Salas R, DiLeone RJ, Gundisch D *et al*. Nicotine decreases food intake through activation of POMC neurons. *Science* 2011; **332**: 1330–1332.
- Bamia C, Trichopoulos A, Lenas D, Trichopoulos D. Tobacco smoking in relation to body fat mass and distribution in a general population sample. *Int J Obes Relat Metab Disord* 2004; **28**: 1091–1096.
- Chiolero A, Jacot-Sadowski I, Faeh D, Paccaud F, Cornuz J. Association of cigarettes smoked daily with obesity in a general adult population. *Obesity* 2007; **15**: 1311–1318.
- Thorgeirsson TE, Gudbjartsson DF, Surakka I, Vink JM, Amin N, Geller F *et al*. Sequence variants at CHRNA3-CHRNA6 and CYP2A6 affect smoking behavior. *Nat Genet* 2010; **42**: 448–453.
- The-Tobacco-and-Genetics-Consortium. Genome-wide meta-analyses identify multiple loci associated with smoking behavior. *Nat Genet* 2010; **42**: 441–447.
- Liu JZ, Tozzi F, Waterworth DM, Pillai SG, Muglia P, Middleton L *et al*. Meta-analysis and imputation refines the association of 15q25 with smoking quantity. *Nat Genet* 2010; **42**: 436–440.
- Devlin B, Roeder K. Genomic control for association studies. *Biometrics* 1999; **55**: 997–1004.
- Lango Allen H, Estrada K, Lettre G, Berndt SI, Weedon MN, Rivadeneira F *et al*. Hundreds of variants clustered in genomic loci and biological pathways affect human height. *Nature* 2010; **467**: 832–838.
- Thorgeirsson TE, Geller F, Sulem P, Rafnar T, Wiste A, Magnusson KP *et al*. A variant associated with nicotine dependence, lung cancer and peripheral arterial disease. *Nature* 2008; **452**: 638–642.
- Saccone SF, Hinrichs AL, Saccone NL, Chase GA, Konvicka K, Madden PA *et al*. Cholinergic nicotinic receptor genes implicated in a nicotine dependence association study targeting 348 candidate genes with 3713 SNPs. *Hum Mol Genet* 2007; **16**: 36–49.



This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivs 3.0 Unported License. To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc-nd/3.0/>

Anna-Liisa Hartikainen³⁰, Anneli Pouta³¹, Jaana Laitinen³², Matti Isohanni³⁰, Shen Huei-Yi^{8,9}, Maxine Allen⁵, Maria Krestyaninova³³, Alistair S Hall³⁴, John R Thompson³⁵, Hogni Oskarsson³⁶, Thorarinn Tyrfinngsson³⁷, Lambertus A Kiemeny^{21,22,38}, Marjo-Riitta Järvelin^{31,39,40,41}, Veikko Salomaa⁹, Michael Stumvoll²⁶, Tim D Spector¹⁶, H-Erich Wichmann^{15,42,43}, Andres Metspalu^{13,14}, Nilesh J Samani⁴⁴, Brenda W Penninx²⁹, Ben A Oostra⁴⁵, Dorret I Boomsma¹⁰, Henning Tiemeier¹¹, Cornelia M van Duijn¹¹, Jaakko Kaprio^{8,19,46}, Jeffrey R Gulcher¹

¹Decode genetics/AMGEN, Sturlugata 8, Reykjavik, Iceland. ⁵Wellcome Trust Center of Human Genetics, Oxford, UK ⁶Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, UK. ⁸Institute for Molecular Genetics Finland, FIMM, University of Helsinki, Finland. ⁹National Institute for Health and Welfare, Helsinki, Finland. ¹⁰Department of Biological

Psychology, VU University Amsterdam, Amsterdam, The Netherlands. ¹¹Department of Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands. ¹²Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark. ¹³Estonian Genome Center, University of Tartu, Riia 23b, Tartu 51010, Estonia. ¹⁴IMCB of University of Tartu and Estonian Biocentre, Riia 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. ²¹Radboud University Nijmegen Medical Centre, Department of Epidemiology, Biostatistics and HTA, Nijmegen, The Netherlands. ²²Comprehensive Cancer Centre East, Nijmegen, The Netherlands. ²³Radboud University Nijmegen Medical Centre, Department of Endocrinology, 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, Inselstr. 22, 04103, Leipzig, Germany. ²⁹EMGO Institute/Department of Psychiatry, VU University Medical Center, Amsterdam, The Netherlands. ³⁰Department of Psychiatry, University of Mainz, Mainz, Germany. ³⁰Institute of Clinical Medicine, University of Oulu, Oulu, Finland. ³¹Lifecourse and service Department, National Institute of Health and Welfare, Oulu, Finland. ³²Finnish Institute of Occupational Health, Oulu, Finland. 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, University of Leicester, LE1 7RH Leicester, UK. ³⁶Therapeia, 101 Reykjavik, Iceland. ³⁷Vogur SAA Addiction Treatment Center, Reykjavik, Iceland. ³⁸Radboud University Nijmegen Medical Center, Department of Urology, Nijmegen, The Netherlands. ³⁹Department of Epidemiology and Public Health, Imperial College, Faculty of Medicine, London, UK. ⁴⁰Institute of Health Sciences, University of Oulu, Oulu, Finland. ⁴¹Biocenter Oulu, University of Oulu, Oulu, Finland. ⁴²Institute of Medical Informatics, Biometry and Epidemiology, Ludwig-Maximilians-Universität, Munich, Germany. ⁴³Klinikum Grosshadern, Munich, Germany. ⁴⁴Department of Cardiovascular Sciences, University of Leicester, Clinical Sciences Wing, Glenfield Hospital, Groby Road, Leicester, LE3 9QP, UK. ⁴⁵Department of Clinical Genetics, Erasmus University Medical Center, Rotterdam, The Netherlands. ⁴⁶Department 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 Boerwinkle³, Nora Franceschini⁴, Diego Ardisson⁵, Luisa Bernardinelli^{6,7}, Pier M Mannucci⁸, Francesco Mauri⁹, Piera A Merlini⁹, Devin Absher¹⁰, Themistocles L Assimes¹¹, Stephen P Fortmann¹², Carlos Iribarren¹³, Joshua W Knowles¹¹, Thomas Quertermous¹¹, Luigi Ferrucci¹⁴, Toshiko Tanaka¹⁵, Joshua C Bis^{16,17}, Curt D Furberg¹⁸, Talin Haritunians¹⁹, Barbara McKnight^{16,20}, Bruce M Psaty^{16,17,21,22}, Kent D Taylor¹⁹, Evan L Thacker^{16,23}, Peter Almgren²⁴, Leif Groop²⁴, Claes Ladenvall²⁴, Michael Boehnke²⁵, Anne U Jackson²⁵, Karen L Mohlke^{1,2}, Heather M Stringham²⁵, Jaakko Tuomilehto^{26–28}, Emelia J Benjamin^{29,30}, Shih-Jen Hwang³¹, Daniel Levy³², Sarah Rosner Preis³¹, Ramachandran S Vasani^{29,32}, Jubao Duan³³, Pablo V Gejman³³, Douglas F Levinson³⁴, Alan R Sanders³³, Jianxin Shi³⁵, Esther H Lips³⁶, James D McKay³⁶, Antonio Agudo³⁷, Luigi Barzan³⁸, Vladimir Bencko³⁹, Simone Benhamou^{40,41}, Xavier Castellsagué³⁷, Cristina Canova⁴², David I Conway⁴³, Eleonora Fabianova⁴⁴, Lenka

Foretova⁴⁵, Vladimir Janout⁴⁶, Claire M Healy⁴⁷, Ivana Holcátová³⁹, Kristina Kjaerheim⁴⁸, Pagona Lagiou⁴⁹, Jolanta Lissowska⁵⁰, Ray Lowry⁵¹, Tatiana V Macfarlane⁵², Dana Mates⁵³, Lorenzo Richiardi⁵⁴, Peter Rudnai⁵⁵, Neonilia Szeszenia-Dabrowska⁵⁶, David Zaridze⁵⁷, Ariana Znaor⁵⁸, Mark Lathrop^{59,60}, Paul Brennan³⁶, Stefania Bandinelli⁶¹, Timothy M Frayling⁶², Jack M Guralnik⁶³, Yuri Milanese⁶⁴, John R B Perry⁶², David Altshuler^{65–70}, Roberto Elosua⁷¹, Sek Kathiresan^{65,68,72}, Gavin Lucas⁷¹, Olle Melander⁷³, Christopher J O'Donnell⁷⁴, Veikko Salomaa⁷⁵, Stephen M Schwartz¹⁶, Benjamin F Voight⁷⁶, Brenda W Penninx^{77,78}, Johannes H Smit^{77,78}, Nicole Vogelzang^{77,78}, Dorret I Boomsma⁷⁹, Eco J C de Geus⁷⁹, Jacqueline M Vink⁷⁹, Gonneke Willemsen⁷⁹, Stephen J Chanock⁸⁰, Fangyi Gu⁸¹, Susan E Hankinson⁸², David J Hunter⁸¹, Albert Hofman⁸³, Henning Tiemeier^{83,84}, Andre G Uitterlinden^{83,85}, Cornelia M van Duijn^{83,86}, Stefan Walter^{83,87}, Daniel I Chasman⁸⁸, Brendan M Everett^{88,89}, Guillaume Pare⁸⁸, Paul M Ridker^{88,89}, Ming D Li⁹⁰, Hermine H Maes^{91,92}, Janet Audrain-McGovern⁹³, Danielle Posthuma^{94,95}, Laura M Thornton⁹⁶, Caryn Lerman^{93,97}, Jaakko Kaprio^{26,75,98}, Jed E Rose⁹⁹, John P A Ioannidis^{100–102}, 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. ¹⁵Medstar 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, Seattle, Washington, USA. ²⁴Department of Clinical Sciences, Diabetes and Endocrinology Unit, Lund University, Malmö, Sweden. 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 Ostrobothnia Central Hospital, Seinäjoki, Finland. ²⁹Boston University School of Medicine, Boston, Massachusetts, USA. ³⁰Boston University School of Public Health, Boston, Massachusetts, USA. 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

Research Institute, Evanston, Illinois, USA. ³⁴Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, California, USA. ³⁵Biostatistics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland, USA. ³⁶International Agency for Research on Cancer (IARC), Lyon, France. ³⁷Institut Català d'Oncologia, Barcelona, Spain. ³⁸General Hospital, Pordenone, Italy. ³⁹Institute of Hygiene and Epidemiology, First Faculty of Medicine, Charles University, Prague, Czech Republic. ⁴⁰Institut National de la santé et de la Recherche Médicale (INSERM) U794, Paris, France. ⁴¹Institut Gustave Roussy, Villejuif, France. ⁴²Department of Environmental Medicine and Public Health, University of Padua, Padua, Italy. ⁴³University of Glasgow Medical Faculty Dental School, Glasgow, UK. ⁴⁴Specialized Institute of Hygiene and Epidemiology, Banská Bystrica, Slovakia. ⁴⁵Department of Cancer Epidemiology and Genetics, Masaryk Memorial Cancer Institute, Brno, Czech Republic. ⁴⁶Palacky University, Olomouc, Czech Republic. ⁴⁷Trinity College School of Dental Science, Dublin, Ireland. ⁴⁸Cancer Registry of Norway, Oslo, Norway. ⁴⁹University of Athens School of Medicine, Athens, Greece. ⁵⁰Department of Cancer Epidemiology and Prevention, Maria Skłodowska-Curie Cancer Center and Institute of Oncology, Warsaw, Poland. ⁵¹University of Newcastle Dental School, Newcastle, UK. ⁵²University of Aberdeen School of Medicine, Aberdeen, UK. ⁵³Institute of Public Health, Bucharest, Romania. ⁵⁴Center for Experimental Research and Medical Studies, University of Turin, Turin, Italy. ⁵⁵National Institute of Environmental Health, Budapest, Hungary. ⁵⁶Department of Epidemiology, Institute of Occupational Medicine, Lodz, Poland. ⁵⁷Institute of Carcinogenesis, Cancer Research Centre, Moscow, Russia. ⁵⁸Croatian National Cancer Registry, Zagreb, Croatia. ⁵⁹Centre National de Genotypage, Institut Genomique, Commissariat à l'énergie Atomique, Evry, France. ⁶⁰Fondation Jean Dausset-Centre d'Étude du Polymorphisme Humain (CEPH), Paris, France. ⁶¹Geriatric Unit, Azienda Sanitaria di Firenze, Florence, Italy. ⁶²Genetics of Complex Traits, Peninsula Medical School, The University of Exeter, Exeter, UK. ⁶³Laboratory of Epidemiology, Demography and Biometry, National Institute on Aging, Bethesda, Maryland, USA. ⁶⁴Tuscany Health Regional Agency, Florence, Italy. ⁶⁵Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, Massachusetts, USA. ⁶⁶Department of Molecular Biology, Massachusetts General Hospital, Boston, Massachusetts, USA. ⁶⁷Diabetes Unit, Massachusetts General Hospital, Boston, Massachusetts, USA. ⁶⁸Center for Human Genetics Research, Massachusetts General Hospital, Boston, Massachusetts, USA. ⁶⁹Department of Genetics, Harvard Medical School, Boston, Massachusetts, USA. ⁷⁰Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA. ⁷¹Cardiovascular Epidemiology and Genetics, Institut Municipal d'Investigació Mèdica, Barcelona, Spain. ⁷²Harvard Medical School, Boston, Massachusetts, USA. ⁷³Department of Clinical Sciences, Hypertension and Cardiovascular Diseases, University Hospital Malmö, Lund University, Malmö, Sweden. ⁷⁴National Heart, Lung, and Blood Institute's Framingham Heart Study, Framingham, Massachusetts, USA. ⁷⁵National Institute for Health and Welfare (THL), Helsinki, Finland. ⁷⁶Program in Medical and Population Genetics, Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, Massachusetts, USA. ⁷⁷EMGO Institute, Vrije Universiteit (VU) Medical Center, Amsterdam, The Netherlands. ⁷⁸Department of Psychiatry, VU University Medical Center, Amsterdam, The Netherlands. ⁷⁹Biological Psychology, VU University Amsterdam, Amsterdam, The Netherlands. ⁸⁰Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland, USA. ⁸¹Program in Molecular and Genetic Epidemiology, Department of Epidemiology, Harvard University, Boston, Massachusetts, USA. ⁸²Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA. ⁸³Department of Epidemiology, Erasmus Medical Center, Member of the Netherlands Consortium on Healthy Aging,

Rotterdam, The Netherlands. ⁸⁴Department of Child and Adolescent Psychiatry, Erasmus Medical Center, Rotterdam, The Netherlands. ⁸⁵Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands. ⁸⁶Centre for Medical Systems Biology, Erasmus Medical Center, Rotterdam, The Netherlands. ⁸⁷Department of Public Health, Erasmus Medical Center, Rotterdam, The Netherlands. ⁸⁸Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA. ⁸⁹Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA. ⁹⁰Department of Psychiatry and Neurobehavioral Sciences, University of Virginia, Charlottesville, Virginia, USA. ⁹¹Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, Virginia, USA. ⁹²Massey Cancer Center, Virginia Commonwealth University, Richmond, Virginia, USA. ⁹³Department of Psychiatry, University of Pennsylvania, Philadelphia, Pennsylvania, USA. ⁹⁴Department of Functional Genomics, VU Amsterdam, Amsterdam, The Netherlands. ⁹⁵Department of Medical Genomics, VU University Medical Center Amsterdam, Amsterdam, The Netherlands. ⁹⁶Department of Psychiatry, University of North Carolina, Chapel Hill, North Carolina, USA. ⁹⁷Abramson Cancer Center, University of Pennsylvania, Philadelphia, Pennsylvania, USA. ⁹⁸Institute for Molecular Medicine, University of Helsinki, Helsinki, Finland. ⁹⁹Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, North Carolina, USA. ¹⁰⁰Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece. ¹⁰¹Tufts Clinical and Translational Science Institute, Tufts University School of Medicine, Boston, Massachusetts, USA. ¹⁰²Center for Genetic Epidemiology and Modeling, Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston, Massachusetts, USA. ¹⁰³Department of Biostatistics, University of North Carolina, Chapel Hill, North Carolina, USA.

Oxford-GSK Consortium—Jason S Liu¹, Federica Tozzi^{2,3}, Dawn M Waterworth⁴, Sreekumar G Pillai⁵, Pierandrea Muglia⁶, Lefkos Middleton⁷, Wade Berrettini⁸, Christopher W Knouff⁹, Xin Yuan⁴, Gérard Waeber^{10,11}, Peter Vollenweider^{10,11}, Martin Preisig^{10,12}, Nicholas J Wareham¹³, Jing Hua Zhao¹³, Ruth JF Loos¹³, Inês Barroso¹⁴, Kay-Tee Khaw¹⁵, Scott Grundy¹⁶, Philip Barter¹⁷, Robert Mahley^{18,19}, Antero Kesaniemi²⁰, Ruth McPherson^{21,22}, John Vincent²³, John Strauss²³, James Kennedy²³, Anne Farmer²⁴, Peter McGuffin²⁴, Richard Day²⁵, Keith Matthews²⁶, Per Bakke²⁶, Amund Gulsvik²⁶, Susanne Lucae²⁷, Marcus Ising²⁷, Tanja Brueckl²⁷, Sonja Horstmann²⁷, Joachim Heinrich^{28,29,30}, Rajesh Rawal²⁸, Norbert Dahmen³¹, Claudia Lamina^{28,32}, Ozren Polasek³³, Lina Zgaga³⁴, Jennifer Huffman³⁵, Susan Campbell³⁵, Jaspal Kooner³⁶, John C Chambers³⁷, Mary Susan Burnett³⁸, Joe Devaney³⁸, Augusto D Pichard³⁸, Kenneth M Kent³⁸, Lowell Satler³⁸, Joseph M Lindsay³⁸, Ron Waksman³⁸, Stephen Epstein³⁸, Jim F Wilson³⁹, Sarah H Wild³⁹, Harry Campbell³⁹, Veronique Vitart³, Muredach P Reilly^{40,41}, Mingyao Li⁴², Liming Qu⁴², Robert Wilensky⁴⁰, William Matthai⁴⁰, Hakon H Hakonarson⁴³, Daniel J Rader^{40,41}, Andre Franke⁴⁴, Michael Wittig⁴⁴, Arne Schäfer⁴⁴, Manuela Uda⁴⁵, Antonio Terracciano⁴⁶, Xiangjun Xiao⁴⁷, Fabio Busonero⁴⁵, Paul Scheet⁴⁷, David Schlessinger⁴⁶, David St Clair⁴⁸, Dan Rujescu⁴⁹, Gonçalo R Abecasis⁵⁰, Hans Jürgen Grabe⁵¹, Alexander Teumer⁵², Henry Völzke⁵³, Astrid Petersmann⁵⁴, Ulrich John⁵⁵, Igor Rudan³⁹, Caroline Hayward³⁵, Alan F Wright³⁵, Ivana Kolcic³³, Benjamin J Wright⁵⁶, John R Thompson⁵⁶, Anthony J Balmforth⁵⁷, Alistair S Hall⁵⁷, Nilesh J Samani⁵⁸, Carl A Anderson¹⁴, Tariq Ahmed⁵⁹, Christopher G Mathew⁶⁰, Miles Parkes⁶¹, Jack Satsangi⁶², Mark Caulfield⁶³, Patricia B Munroe⁶³, Martin Farrall⁶⁴, Anna Dominiczak⁶⁵, Jane Worthington^{66,67}, Wendy Thomson^{66,67}, Steve Eyre^{66,67}, Anne Barton^{66,67}, Vincent Mooser⁶⁸, Clyde Franks⁶⁹.

¹Department of Statistics, University of Oxford, 1 South Parks Road, Oxford OX1 3TG, UK. ²Clinical Sciences-Aptuit Medicines

Research 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-Universität, 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 for Community Medicine, University of Greifswald, Greifswald, Germany. ⁵⁴Institute of Clinical Chemistry and Laboratory Medicine, University of Greifswald, Greifswald, Germany. ⁵⁵Department of Social Medicine and Epidemiology, University of Greifswald, Greifswald, Germany. ⁵⁶Department of Health Sciences, University of Leicester, Leicester, UK. ⁵⁷Multidisciplinary Cardiovascular Research Centre (MCRC), Leeds Institute of Genetics, Health and Therapeutics (LIGHT), University of Leeds, Leeds, UK. ⁵⁸Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Leicester, UK. ⁵⁹Peninsula College of Medicine and Dentistry, Exeter, UK. ⁶⁰Department of Medical and Molecular Genetics, King's College London School of Medicine, Guy's Hospital, London, UK. ⁶¹Gastroenterology Research Unit, Addenbrooke's Hospital, Cambridge, UK. ⁶²Gastrointestinal Unit, Molecular Medicine Centre, University of Edinburgh, Western General Hospital, Edinburgh, UK. ⁶³Clinical 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. ⁶⁴Department of Cardiovascular Medicine, University of Oxford, Wellcome Trust Centre for Human Genetics, Oxford, UK. ⁶⁵BHF Glasgow Cardiovascular Research Centre, Division of Cardiovascular and Medical Sciences, University of Glasgow, Western Infirmary, Glasgow, UK. ⁶⁶Arthritis Research UK Epidemiology Unit, Musculoskeletal Research Group, University of Manchester, Manchester Academic Health Sciences Centre, Manchester, UK. ⁶⁷NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester NHS Foundation Trust, Manchester, UK. ⁶⁸Department of Pathology and Laboratory Medicine, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland. ⁶⁹Max Planck Institute for Psycholinguistics.

URLS

http://www.who.int/tobacco/mpower/mpower_report_full_2008.pdf
<http://www.who.int/mediacentre/factsheets/fs311/en/index.html>