INTRODUCTION

Smoking and obesity are major risk factors for many serious diseases. Eating and smoking are behavioral traits that are at least in part controlled by the same reward mechanisms. Genome-wide association studies (GWAS) have yielded 32 single-nucleotide polymorphisms (SNPs) associated with body mass index (BMI). Smoking and SNPs associated with increased smoking quantity have been shown to correlate with lower BMI. 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. All drugs of abuse have been shown to increase dopamine in the mesolimbic reward system, and studies of both human brain images and animal brains 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.

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 ($r = 0.032$, $P = 8.0 \times 10^{-5}$). 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.

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

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**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 Consortium5, ENGAGE consortium5, 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 ($r = 0.032$, $P = 8.0 \times 10^{-5}$). 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.

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

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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

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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, and the study populations have all been described previously. 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, 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 for SI and 0.021 for 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 each SNP with smoking behavior, we weighted the smoking phenotypes of all individuals by the published effect on BMI. We denote the unknown effect of each SNP on smoking behavior with \( \beta \), and its minor allele frequency with \( \gamma \). We report a correlation between the 32 BMI SNPs and smoking behavior.

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 \( \rho_{BMISNPs,BMI} \), and the variance of the estimator with \( \text{Var}(\rho_{BMISNPs,BMI}) \), similarly for the correlation between BMI and CPD. Then, \( \rho_{BMISNPs,BMI,CPD} \) is an estimator of the correlation between the 32 BMI SNPs and CPD, assuming conditional independence, and

\[
\text{Var}(\rho_{BMISNPs,BMI,CPD}) \approx \text{Var}(\rho_{BMISNPs,BMI}) + \text{Var}(\rho_{BMI,CPD}) - \rho_{BMISNPs,BMI} \cdot \rho_{BMI,CPD}
\]

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 BMI 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. The significance levels of each study population were adjusted individually using the method of genomic control. 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.

RESULTS AND DISCUSSION

To study the correlation between obesity variants and smoking phenotypes, we focused on the 32 SNPs associating with BMI and 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 \( g_i \) be its published effect on BMI. We denote the unknown effect of each SNP on smoking behavior with \( \beta_i \), and our assumption about the SNP’s effect on smoking behavior being proportional to the SNP’s effect on BMI can be stated as \( \beta_i = k g_i \) for some constant \( k \).

The expected z-score associated with each SNP is

\[
z_i = \sqrt{\sum w_i \frac{z_i}{\text{Var}(z_i)}}
\]

where

\[
\text{Var}(z_i) = \frac{1}{\sum w_i} \sum w_i \text{Var}(z_i)
\]

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

|          | CPD |          | Smoking |
|----------|-----|----------|---------|
|          | From | N      | Correlation (95% CI) | P     |          | N      | Correlation (95% CI) | P     |
| BMI      |       | 33620  | 0.095 (0.085, 0.106) | 2.5 x 10^-68 | 49565  | -0.005 (-0.014, 0.004) | 0.29  |
| 32 BMI SNPs | 24618 | 0.032 (0.019, 0.045) | 8.0 x 10^-7 | 34216  | 0.019 (0.008, 0.030) | 0.00054 |
| Height   | 33875 | -0.004 (-0.015, 0.007) | 0.46 | 49931  | -0.012 (-0.021, -0.002) | 0.013 |
| 180 Height SNPs | 24630 | 0.001 (-0.011, 0.014) | 0.84 | 34231  | 0.004 (-0.007, 0.015) | 0.44 |

Abbreviations: BMI, body mass index; CI, confidence interval; SNP, single-nucleotide polymorphism.

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described in a recent report of a study of 249,796 subjects. 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 individuals. The correlation of each of the 32 SNPs with CPD and SI, using data obtained using the inverse-variance method for each of the two smoking behaviors. A variant within the TMEM18 gene (rs6265C) 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 (rs6265C). 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 × 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 chr15q25 (rs1051730-A) was discovered in GWAS of smoking behavior, 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, \(P = 3.0 \times 10^{-21}\), \(N = 20,462\)) 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.

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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, SBUS, 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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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 (references 15–17). The ENGAGE Consortium—Ida Surakka,8,9 Jacqueline M Vink10, Najaf Amin11, Frank Geller12, Thoerunn Rafnar,13 Tönu Esko13,14, Stefan Walter15, Christian Gieger15, Rajesh Rawal15, Massimo Mangino16, Inga Prokopenko5,6 Reekid Mägi5,6,13 Kaisu Kesiktalo19, Iris H. Gudjonsdottir1, Solveig Grettardottir1, Heirinn Stefnasson1, Yuri S Aulchenko1, Mari Nellis12,14 Katja K Aben17,21, Martin den Heijer21,23,24, Nicole Soranzo16,24, Ana M Valdes16, Claire Steves16, André G Uitterlinden1,25, Albert Hofman24,25, Anna-Liisa Hartikainen30, Anneli Pouta31, Jaana Laitinen12, Matti Isohanni32, Shen Huei-Yi33, Maxine Allen5, Maria Krestyaninova33, Alistair S Hall34, John R Thompson35, Hogni Oskarsson6, Thorarin Tyrfingsson37, Lambertus A Kiemeneij21,22,38 Marjo-Riitta Järvelin11,39,40,41, Veikko Salomaa6, Michael Stumvoll26,27, Tom D Spector16, Hu-Erich Wichmann15,42,43, Andres Metspalu13,14, Niles J Samarini44, Brenda W Pennink35, Ben A Oostra36, Dorret I Boomsma15, Henning Tiemeier11, Cornelis M van Duijn11, Jaakkko Kaprio6,19,46, Jeffrey R Gulcher1

1 Decode genetics/AMGEN, Sturlugata 8, Reykjavik, Iceland.
2 Wellcome Trust Center of Human Genetics, Oxford, UK.
3 Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, UK.
4 Institute for Molecular Genetics Finland, FIMM, University of Helsinki, Finland.
5 National Institute for Health and Welfare, Helsinki, Finland.
6 Department of Biological
Common biological basis of obesity and nicotine addiction

TE Thorgeirsson et al

Psychology, VU University Amsterdam, Amsterdam, The Netherlands. 15 Department of Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands. 16 Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark. 17 Estonian Genome Center, University of Tartu, Ria 23b, Tartu 51010, Estonia. 18 MBG of University of Tartu and Estonian Biocentre, Ria str 23, Tartu 51010, Estonia. 19 Institute of Epidemiology, Helmholtz Zentrum München, Ingolstaedter Landstr. 1, 85764 Munich/Neuherberg, Germany. 20 Department of Twin Research and Genetic Epidemiology, King’s College London, St Thomas’ Hospital Campus, London SE17EH, UK. 21 Department of Public Health, University of Helsinki, Helsinki, Finland. 22 Radboud University Nijmegen Medical Centre, Department Of Epidemiology, Biostatistics and HTA, Nijmegen, The Netherlands. 23 Comprehensive Cancer Centre East, Nijmegen, The Netherlands. 24 Radboud University Nijmegen Medical Centre, Department of Endocrinology, Nijmegen, The Netherlands. 25 Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands. 26 Department of Medicine, University of Leipzig, Liebigstr. 18, 04103, Leipzig, Germany. 27 Coordination Centre for Clinical Trials, University of Leipzig, Härtelstr. 16–18, 04103, Leipzig, Germany. 28 Interdisciplinary Centre for Clinical Research, University of Leipzig, Inselsstr. 22, 04103, Leipzig, Germany. 29 EMGO Institute/Department of Psychiatry, VU University Medical Center, Amsterdam, The Netherlands. 30 Department of Psychiatry, University of Mainz, Mainz, Germany. 31 Institute of Clinical Medicine, University of Oulu, Oulu, Finland. 32 Life course and service Department, National Institute of Health and Welfare, Oulu, Finland. 33 Finnish Institute of Occupational Health, Oulu, Finland. 34 European Bioinformatics Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, CB10 1 SD, UK. 35 Multidisciplinary Cardiovascular Research Centre (MCRC), Leeds Institute of Genetics, Health and Therapeutics (LIGHT), University of Leeds, Leeds, LS2 9JT, UK. 36 Department of Health Sciences and Genetics, University of Leicester, LE1 7RH Leicester, UK. 37 Therapeia, 101 Reykjavik, Iceland. 38 Vogur SAA Addiction Treatment Center, Reykjavik, Iceland. 39 Radboud University Nijmegen Medical Centre, Department of Urology, Nijmegen, The Netherlands. 40 Department of Epidemiology and Public Health, Imperial College, Faculty of Medicine, London, UK. 41 Institute of Health Sciences, University of Oulu, Oulu, Finland. 42 Biocenter Oulu, University of Oulu, Oulu, Finland. 43 Institute of Medical Informatics, Biometry and Epidemiology, Ludwig-Maximilians-Universität, Munich, Germany. 44 Klinikum Grosshadern, Munich, Germany. 45 Department of Cardiovascular Sciences, University of Leicester, Clinical Sciences Wing, Glenfield Hospital, Groby Road, Leicester, LE3 9QP, UK. 46 Department of Clinical Genetics, Erasmus University Medical Center, Rotterdam, The Netherlands. 47 Department of Mental Health and Alcohol Abuse Services, National Institute for Health and Welfare, Helsinki, Finland.

The Tobacco and Genetics Consortium (TAG)—Yung Jun Kim1, Jennifer Dackor2, Eric Boerwinkle3, Nora Franceschini4, Diego Ardissino5, Luisa Bernardinelli6,7, Piera A Merlini9, Devin Absher10, Themistocles L Assimes11, Ardissino5, Luisa Bernardinelli6,7, Pier M Mannucci8, Francesco Reykjavik, Iceland. 38 Radboud University Nijmegen Medical Centre, Department of Cardiology, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy. 44 Statistical Laboratory, Centre for Mathematical Sciences, University of Cambridge, Cambridge, UK. 45 Department of Applied Health Sciences, University of Pavia, Pavia, Italy. 46 Department of Internal Medicine and Medical Specialties, Fondazione Istituto di Ricerco e Cura a Carattere Scientifico, Ospedale Maggiore, Mangiagalli e Regina Elena, University of Milan, Milan, Italy. 47 Department of Cardiology, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy. 48 Statistical Laboratory, Centre for Mathematical Sciences, University of Cambridge, Cambridge, UK. 49 Department of Health Sciences and Genetics, University of Leicester, Clinical Sciences Wing, Glenfield Hospital, Groby Road, Leicester, LE3 9QP, UK. 50 Department of Clinical Genetics, Erasmus University Medical Center, Rotterdam, The Netherlands. 51 Department of Mental Health and Alcohol Abuse Services, National Institute for Health and Welfare, Helsinki, Finland.

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