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 × 10⁻⁵). 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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**Keywords:** addiction; body mass index; nicotine dependence; obesity; smoking
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 probing for 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 $g_i$ be the vector of smoking behavior measurements, and let $x_i$ be the vector of BMI or height measurements. We assume that the expectation of the smoking behavior depends linearly on BMI or height, $E(Y) = x_i \beta_i + [b_i]$, and that the variance–covariance matrix of the smoking behavior depends only on the pairwise kinship between the study participants, $Var(y) = 2\sigma^2$.

A generalized form of linear regression was used to test the correlation between additive meta-analysis to combine the results for each SNP. After combining the significance levels of each study population were adjusted individually by 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 ($\lambda_{GC} = 1.10$ for SI and $\lambda_{GC} = 1.06$ 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 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 $\gamma_i$ be its published effect on BMI. We denote the unknown effect of each SNP on smoking behavior being proportional to the SNP’s effect on BMI can be stated as $\gamma_i = k_{\beta_i}$ 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 $\beta_i^2 \sqrt{f_i(1-f_i)}$, 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 weight the smoking behavior $z$-scores of the 32 BMI SNPs together: $z = \frac{\sum_{i=1}^{32} w_i z_i}{\sqrt{\sum_{i=1}^{32} w_i^2}}$. We test this by using the method of genomic control to adjust the significance levels of each study population.

RESULTS AND DISCUSSION

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

<table>
<thead>
<tr>
<th>Table 1. Association of BMI, height and SNPs associating with BMI and height with smoking phenotypes in Iceland</th>
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<tr>
<td><strong>CPD</strong></td>
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<td><strong>From</strong></td>
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<td><strong>BMI</strong></td>
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<td>32 BMI SNPs</td>
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<td>Height</td>
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<td>180 Height SNPs</td>
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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 individuals15–17 (Table 1).

BMI associated with CPD \( (r = 0.095, P = 2.5 \times 10^{-66}) \) 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 \( (r = 0.032, P = 8.0 \times 10^{-7}) \) 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 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 \( \sim 2,500,000 \) 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 \( \chi^2 \)-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 \( 9.3 \times 10^{-5} \), 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 \( \text{(effect) = 0.050495, } P = 1.14 \times 10^{-9} \) \) in the Brain Neurotrophin Factor gene \( (BDNF) \) and rs2867125-C \( \text{(effect) = 0.0397, } P = 0.000021 \) \) 45 kb upstream of the Transmembrane protein 18 gene \( (TMEM18) \), and for CPD the most significant associations were with rs2867125-C \( \text{(effect) = 0.286, } P = 0.000046 \) \) \( (TMEM18) \) and rs4771122-G \( \text{(effect) = 0.0193, } P = 0.000048 \) 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 \( \text{(effect) = 0.186, } P = 0.0244 \) and CPD \( \text{(effect) = 0.0097, } P = 0.0305 \). A SNP within the \( BDNF \) gene has previously been shown to associate with smoking initiation \( (rs6265-C) \). 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 \( (r = 1.3 \times 10^{-5}) \).

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

![Figure 1. Association of obesity variants with smoking initiation (SI) and CPD.](https://example.com/figure1)

**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 \( \beta \)-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).
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.

REFERENCES

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