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Phenotypic and genetic relationship between BMI and cigarette smoking in a sample of UK adults

Amanda G Wills[1,2] and **Christian Hopfer**[1,2]

[1]Division of Substance Dependence, Department of Psychiatry, University of Colorado Anschutz Medical Campus, Mail Stop F570, Building 500, 13001 East 17th Place, Aurora, CO 80045

[2]Institute for Behavioral Genetics, University of Colorado Boulder, 1480 30th Street, Boulder, CO 80301 USA

Abstract

In addition to the health hazards posed individually by cigarette smoking and obesity, the combination of these conditions poses a particular impairment to health. Genetic factors have been shown to influence both traits and, to understand the connection between these conditions, we examined both the observed and genetic relationship between adiposity (an electrical impedance measure of body mass index (BMI)) and cigarettes smoked per day (CPD) in a large sample of current, former, and never smokers in the United Kingdom. In former smokers, BMI was positively associated with cigarettes formerly smoked; further, the genetic factors related to a greater number of cigarettes smoked were also responsible for a higher BMI. In current smokers, there was a positive association between BMI and number of cigarettes smoked, though this relationship did not appear to be influenced by similar genetic factors. We found a positive genetic relationship between smoking in current/former smokers and BMI in never smokers (who would be unmarred by the effects of nicotine). In addition to CPD, in current smokers, we looked at two variables, time from waking to first cigarette and difficulty not smoking for a day, that may align better with cigarette and food 'craving.' However, these smoking measures provided mixed findings with respect to their relationship with BMI. Overall, the positive relationships between the genetic factors that influence CPD in smokers and the genetic factors that influence BMI in former and never smokers point to common biological influences behind smoking and obesity.

Keywords

cigarette smoking; nicotine addiction; BMI; SNP heritability; genetic correlation; UK Biobank

Correspondence should be addressed to: Amanda G. Wills: Division of Substance Dependence, Department of Psychiatry, University of Colorado Anschutz Medical Campus, Mail Stop F570, Building 500, 13001 East 17th Place, Aurora, CO 80045, Amanda.noonan@ucdenver.edu.

1. Introduction

Both cigarette smoking and obesity have major health consequences (Mokdad, Marks, Stroup, & Gerberding, 2004; Peeters et al., 2003; Thompson, Edelsberg, Colditz, Bird, & Oster, 1999). Particularly troublesome is the finding that the combination of obesity and cigarette smoking in individuals (reported to occur in about 5% of the US population (Healton, Vallone, McCausland, Xiao, & Green, 2006)) can synergistically increase risk of mortality (Akbartabartoori, Lean, & Hankey, 2006; Freedman et al., 2006; Peeters et al., 2003; Rupprecht, Donny, & Sved, 2015). Thus, understanding the relationship between these two conditions may lead to insights on how to curb their profound negative impact on public health.

Understanding the relationship between smoking and obesity is complicated by evidence that cigarette smoking has a causal impact on the weight of smokers via the metabolic effects of nicotine, including an increase in energy expenditure and a reduction in appetite (Audrain-McGovern & Benowitz, 2011; Hofstetter, Schutz, Jéquier, & Wahren, 1986). Current smokers tend to be leaner than never or former smokers (Plurphanswat & Rodu, 2014). Thus, a relationship between smoking and obesity may be masked by the metabolic effect of nicotine to reduce body fat. Yet, we do know that within smokers, the greater number of cigarettes smoked per day is related to higher body mass index (BMI) (Chiolero, Jacot-Sadowski, Faeh, Paccaud, & Cornuz, 2007). We also know that even though smokers are leaner than non-smokers, central adiposity tends to be higher in smokers (Kim et al., 2012).

Both smoking and obesity are influenced by genetic factors. Family-based heritability estimates for BMI have ranged from .47 to .90 (Elks et al., 2012); similar estimates for smoking persistence, to include smoking quantity, have generally centered around 50% (Li, Cheng, Ma, & Swan, 2003). Large scale genome-wide analyses have found specific genetic variants that contribute to these traits (Consortium, 2010; Locke et al., 2015). Further, a number of studies have identified genetic variants that are common to both obesity and smoking, such that a specific variant identified to play a role in increased obesity is associated with increased smoking (Thorgeirsson et al., 2013; Wang et al., 2017). Thus, there may be similar neurological processes involved in these two appetitive behaviors, indicating the possible presence of a common propensity toward addictive behaviors that may result in both overeating and nicotine dependence (Rogers, 2017; Volkow, Wang, Tomasi, & Baler, 2013).

Previous analyses have looked at the relationship between BMI and cigarette smoking in current and former smokers (Dare, Mackay, & Pell, 2015). However, the problem in a straightforward analysis within each smoking status group, is that the act of ever smoking may have a direct impact on BMI. The effects of current smoking on body weight have been established in that nicotine is known to affect appetite and metabolism (Audrain-McGovern & Benowitz, 2011; Hofstetter et al., 1986). The analysis of the relationship between previous cigarette smoking and BMI in former smokers is also problematic because the act of smoking cessation has been shown to induce weight gain (Froom, Melamed, & Benbassat, 1998; Krukowski, Bursac, Little, & Klesges, 2016; Tian, Venn, Otahal, & Gall, 2015). Thus,

to understand whether there may be a shared biological underpinning to the propensity toward obesity and cigarette smoking, we would need to compare BMI in never smokers, who would not have been exposed to any effects of nicotine, to smoking quantity in smokers.

While it would not be possible to estimate the observed or phenotypic relationship between smoking and BMI in smokers and never smokers, methods such as Genome-wide Complex Trait Analysis (GCTA) have made it possible to examine shared genetic variation between traits in two different groups of individuals (Lee, Yang, Goddard, Visscher, & Wray, 2012; Yang et al., 2010). Briefly, GCTA uses genome-wide SNP data to estimate the degree to which the conglomerate of common SNPs contributes to the variation of a trait (SNP-based heritability). Further, this method can assess the extent to which the effects of all SNPs on one trait are related to those of another trait (SNP genetic correlation). Because GCTA computes a matrix of pairwise genetic similarity between all ‘unrelated’ individuals in the sample and then compares this genetic similarity to phenotypic similarity, it allows for the comparison between different groups, smokers and never smokers in this case.

Thus, in our analysis we not only examined the phenotypic and genetic correlation between BMI and smoking quantity in current and former smokers, but were also able to include never smokers in our comparisons. Because, as explained above, smoking directly affects body weight, we examined to what degree BMI in never smokers (who would not be influenced by direct effects of nicotine on body weight) is influenced by the same genetic factors that increase quantity of smoking in current and former smokers. Additionally, the vast majority of research asking the question of whether smoking is related to obesity uses smoking quantity as the primary measure, but studies have reported that it may be a poor assessment of cigarette ‘craving’ that might be particularly relevant to overeating and obesity (Donny, Griffin, Shiffman, & Sayette, 2008; Lim et al., 2012). Few studies have examined the association between measures that may be more closely related to smoking dependence and BMI. Thus, in current smokers, we looked at two variables specifically related to smoking dependence: (1) time to first cigarette (Baker et al., 2007) and (2) difficulty of giving up smoking. We also looked at the same genetic correlation between BMI in never smoking and these two more dependence focused variables. These relationships, unmarred by any causal effects of nicotine, provide a unique insight into whether there is a shared genetic predisposition towards two problematic addictions.

2. Methods

2.1 Data: UK Biobank

Participants were volunteers between the ages of 40 and 69 who enrolled in the UK Biobank, a data resource of 500k individuals from the United Kingdom. Recruitment procedures and other details related to this data resource are described at other sources (Allen et al., 2012; Sudlow et al., 2015). We used individuals from the initial release of genetic data including ~50,000 individuals genotyped on the UK BiLEVE array and another ~100,000 participants that were genotyped on the UK Axiom array.

2.1.1 Quality Control.—The Wellcome Trust Centre for Human Genetics conducted prerelease quality control described at http://www.ukbiobank.ac.uk/wpcontent/uploads/2014/04/UKBiobank_genotyping_QC_documentation-web.pdf. Individuals with conflicts between reported and genotypic sex (n = 191) or poor quality genetic samples (n = 1548) were excluded. Also excluded were SNP positions with differing frequencies on the two arrays, batch effects, or deviations from Hardy-Weinburg equilibrium.

Only individuals of Caucasian descent were included and comprised of individuals who self reported as "British" and whose genetic principal components grouped with CEU populations on the HapMap3 reference panel. If individuals self-identified as "Irish" or had "Any other white background" and their first 4 PC scores fell within the range of the UK Biobank's identified Caucasians, they were also included in the analysis.

In addition to the quality control measures carried out by the UK Biobank, SNPs with minor allele frequencies less than 1%, per SNP genotyping call rates less than 95%, deviations from Hardy-Weinburg equilibrium ($p < 0.00001$), that were multi-allelic, or had duplicate positions were removed. Closely related individuals with $\hat{\pi}$ (measure of pairwise genetic relatedness) values >. 05 were excluded due to the possibility of them sharing more similar environments. A total of 120,890 individuals and 535,060 bi-allelic SNPs remained after quality control procedures.

2.2 Measures

Participants answered questions on a touchscreen device. Details for each variable as well as its sample-wide distribution is described at UK Biobank's Data Showcase (http://biobank.ctsu.ox.ac.uk/crystal/) using the noted *Data Field.*

2.2.1 Obesity (BMI).—An electrical impedance measure of BMI (*Data Field 23104*) was used as a continuous measure to assess obesity. As mass was quantified by electrical impedance, it should be noted that this is not conventional BMI, but is highly correlated and used interchangeably with traditional BMI in other analyses using the UK Biobank resource (Heydari, Ayatollahi, & Zare, 2011; Tyrrell et al., 2016; Wade, Carslake, Sattar, Davey Smith, & Timpson, 2018).

2.2.2 CPD.—Current smokers, defined as participants who currently smoked cigarettes on all or most days, were asked "About how many cigarettes do you smoke on average each day?" (*Data Field 3456*) and former smokers, defined as individuals that in the past had smoked cigarettes on all or most days, were asked "About how many cigarettes did you smoke on average each day" (*Data Field 2887*). Individuals who reported more than 100 were asked to confirm by UK Biobank. Further, UK Biobank excluded individuals who reported responses less than 1 or greater than 150. We log transformed this variable. Additionally, never smokers were included in this analysis and were defined as individuals listed as 'Never' smokers by UK Biobank's 'Smoking Status' variable (*Data Field 20116*).

2.2.3 Difficulty not smoking for 1 day (*Data Field 3476*).—The touchscreen prompted current smokers with the question, "How easy or difficult would you find it to go without smoking for a whole day?". Responses ranged from "Very easy" to "Very difficult,"

and we scored these items based on increasing difficulty from 1 to 4. 133 individuals chose not to answer this question, and we set these to missing. Due to restrictions of the software package used for our genetic analysis, this variable was treated as a quantitative, continuous measure instead of as an ordinal measure.

2.2.4 Time from waking to first cigarette (*Data Field 3466*).—

Currently smoking participants were asked "How soon after waking do you smoke your first cigarette of the day?", and were given the options: "Less than 5 minutes", "Between 5–15 minutes", "Between 30 minutes – 1 hour", "Between 1 and 2 hours", and "Longer than 2 hours." Individuals that reported "Do not know" (n = 221) or preferred not to answer (n = 42) were excluded. We rated this item in terms of decreasing time, with the implication that the shorter the duration between waking and first cigarette would indicate a higher addiction liability. Thus, "Longer than 2 hours" was given a score of 1 and "Less than 5 minutes" was given a score of 5. This variable was also treated as quantitative variable due to limitations of the genetic analysis software.

We controlled for gender (*Data Field 31*), birth year (*Data Field 34*), genotype measurement batch (to adjust for selection of smokers in the UK BiLEVE array) (*Data Field 22000*), 15 UK Biobank genetic principal components (to further control for ethnic stratification) (*Data Field 22009*), and socioeconomic deprivation (*Data Field 189*) by using the residuals from models that used these adjusted factors to predict the primary variables. We excluded individuals that were missing genetic data, any of the adjusted factors, or phenotypes of interest.

2.3 Analyses

Variable distributions and phenotypic correlations between BMI, CPD, difficulty not smoking for 1 day (only in current smokers), and time from waking to first cigarette (only in current smokers), were calculated within each smoking status group: never smokers (only BMI), former smokers, and current smokers.

We used Genome-wide Complex Trait Analysis (GCTA) to estimate SNP-based heritability and genetic correlations between BMI, CPD, and the two dependence measures, difficulty not smoking and time from waking to first cigarette. Very briefly, the main concept behind GCTA is to use whole genome SNP data to calculate distal genetic resemblance between 'unrelated' individuals. In contrast to family studies that take advantage of assumed patterns of genetic covariance between individuals of differing genetic relatedness, GCTA constructs a genetic relatedness matrix between all individuals in the sample that gives an estimate of the genetic similarity between any two individuals due to additive genetic effects that are tagged by SNPs. Based upon the degree to which this genetic relatedness corresponds to phenotypic similarity between these individuals, we get an estimate of the degree to which the conglomerate of these SNPs contribute to the variance of a trait. We refer to this as the SNP-based heritability which is distinguishable from family based estimates of heritability, or proportion of trait variance due to additive genetic factors, because it is based solely on the proportion of trait variance that can be attributed to measured SNPs that may not capture the entirety of additive genetic factors contributing to a trait. This method is described in

greater detail at (Yang et al., 2011). Further, this method can be extended to obtain SNP-based genetic correlations between BMI and smoking within smoking status groups (as done with the phenotypic correlation), but also between disparate groups (Lee et al., 2012). For example, we were able to calculate the genetic correlation between BMI in non-smokers and CPD in current smokers.

All analyses and quality control were conducted using PLINK v1.90b3.34 (Chang et al., 2015; Purcell & Chang, 2016), R version R 3.2.1 (Team, 2015), and GCTA version 1.90.0beta (Yang et al., 2011).

3. Results

Descriptive statistics of all study variables are listed in Table I for each smoking status group. Table II lists the phenotypic correlations between BMI and the smoking variable within each smoking status group. For both current and former smokers, higher BMIs are associated with more cigarettes smoked (or previously smoked) per day. Uniquely here, we also looked at the relationship between BMI and smoking dependence related items, difficulty of not smoking and time to first cigarette in current smokers; these items, unlike CPD, were not correlated with BMI.

SNP-based heritability estimates, stratified by smoking status, for BMI, CPD, time to first cigarette, and difficulty not smoking are reported in Table III. These estimates indicate that genetic factors play a role in BMI, CPD, time to first cigarette, and difficulty not smoking.

Genetic correlations between BMI and the smoking phenotypes are listed for all combinations of smoking status groups in Table IV. Largely, the genetic factors that influence BMI in never smokers were positively correlated with the genetic factors influencing smoking phenotypes in both former and current smokers. The exception was with the difficulty of not smoking variable that did not share significant genetic influences with BMI. In former smokers, the same pattern emerged; genetic influences related to more cigarettes smoked per day and smoking sooner after waking were related to higher BMI, while no significant genetic relationship existed between BMI and difficulty of not smoking. Conversely, in current smokers, there was no genetic relationship between BMI and CPD or time from waking to first cigarette. There was however, a statistically significant negative relationship between greater difficulty of not smoking and BMI, such that the genetic influences that predispose to higher BMI are related to those that decrease difficulty of not smoking.

4. Discussion

In this analysis we explored both the observed and genetic relationship between cigarette smoking and BMI in a large sample of individuals in the UK. Our findings largely point to evidence of a relationship that ties increased BMI to an increase in amount of smoking (CPD). Observed correlations demonstrate this relationship in both current and former smokers and replicate findings from an analysis on the relationship between BMI and CPD using a larger version of this sample (Dare et al., 2015). SNP-based heritability estimates confirm the contribution of common genetic variants to BMI, CPD, and the smoking

dependence based measures and are generally consistent in magnitude with other reports in the literature (Hartz et al., 2018; Marioni et al., 2016; Tielbeek et al., 2018; Yang et al., 2015).

Uniquely, we were also able to further disentangle the complexity of the relationship between BMI and smoking by examining the *genetic* correlation between smoking and BMI in disparate sets of individuals. In never and former smokers, the genetic factors responsible for higher BMI were also responsible for greater amounts of smoking in current and former smokers. This points to an underlying link between the mechanisms that predispose one to smoke in higher quantities and have higher BMIs. Unlike the phenotypic correlations described above, these relationships would be less marred, especially in the comparisons that utilize the never smoking group, by the metabolic effects of cigarette smoking that may have a direct impact on BMI. Interestingly, in current smokers, we did not find a shared genetic component between CPD and BMI, despite the phenotypic correlation. We suspect that this may have to do with the aforementioned relationship between nicotine consumption and BMI.

However, the relationship between BMI and the dependence based smoking items, difficulty not smoking and time to first morning cigarette were more mixed. In the sample of current smokers, there were no phenotypic correlations between BMI and these two smoking variables. Though, genetic correlations indicated a positive relationship between genetic factors related to BMI in never and former smokers and time to first morning cigarette in current smokers. Thus, there is an overlap between the genetic predisposition to higher BMI and an earlier time to first morning cigarette. And contrary to the previous finding, in current smokers, the genetic factors related to greater difficulty not smoking for a day were actually related to genetic factors responsible for lower BMI.

The goal in using these two measures, in addition to CPD, was to get information specifically related to cigarette craving that might be less reflected in simply the quantity of cigarettes smoked. The reasoning was that these cigarette smoking items, that are more indicative of nicotine dependence, might connect better with the appetitive and potentially addictive nature of eating (which when done in excess could result in obesity). A positive relationship between BMI and time to morning cigarette was demonstrated in former and never smokers, indicating that there may be an underlying predisposition toward cigarette and food addiction. However, the relationship between difficulty not smoking and BMI was reversed in current smokers. Thus, overall these variables offered mix results in their ability to provide greater insight than simple CPD. This might have been due to the fact that these measures were only available in current smokers (as opposed to both current and former smokers), so sample size may have played a role in the mixed findings.

Further, tied to the issue above that CPD may not be the best measure of smoking behavior in terms of linking it to obesity, BMI may not accurately represent adiposity in general or patterns of food consumption that would be tied to the addictive nature of cigarettes (Nuttall, 2015). In fact, symptoms of food addiction have been found in all BMI categories ranging from obese to underweight, though there is a greater prevalence in obese individuals (Meule, 2011). Also, while CPD is strictly a measure of cigarette consumption, BMI is considered

here the *result* of food consumption, but many other factors could be at play. The relevant example here is cigarette smoking, known to decrease BMI, which we attempted to negate through the use of genetic correlations with a non-smoking sample. Overall, we acknowledge that BMI may only be tangentially related to the construct of food addiction or habitual over-eating that we attempt to link to cigarette addiction. However, the availability of BMI in large datasets and the deep history of this measure as it relates to cigarette smoking solidified our use of it in this study given the above caveats.

Also, though we know that these traits are related, we are blind to the actual genetic factors that are shared. A number of studies have identified specific genetic variants that link smoking and obesity (Freathy et al., 2011; Taylor et al., 2014; Thorgeirsson et al., 2013; Wang et al., 2017). The problem with the above approach is that the top hits for BMI are not necessarily going to be the ones associated with smoking. By looking at the correlation using all SNPs, we get an idea of the total shared liability between smoking and obesity. The downside is that we are unable to pinpoint specific biological pathways that tie these conditions together.

Additionally, there may be gender differences in the relationship between smoking and obesity; specifically, a number of studies have pointed to a stronger relationship in women (Clair et al., 2011; Tuovinen et al., 2016). We did do a gender specific analysis, but for brevity did not report these results. By splitting our sample into males and females, we no longer had enough power to get an accurate estimate of the genetic correlation between smoking and BMI in many cases. Those results that were statistically significant, mirrored those obtained in the combined sample.

Furthermore, it is important to point out that the UK Biobank sample is a volunteer sample that is not representative of the UK as a whole in terms of the prevalence of smoking and other noteworthy traits which could lead to biases in the observed and genetic relationship between traits (Munafò, Tilling, Taylor, Evans, & Davey Smith, 2018). The first data release (used in this analysis) could be particularly problematic in this regard, because it includes individuals genotyped on the UK BiLEVE array that were specifically selected for smoking intensity. Rather than exclude this portion of the sample and reduce sample size, we adjusted for this factor by controlling for genotype batch in our analysis.

4.1 Conclusions

In conclusion, the results here corroborate findings that indicate a common biological underpinning for cigarette smoking and obesity. An underlying genetic predisposition toward the consumption of more cigarettes appears to be linked to the genetic predisposition toward higher BMI. Despite the problematic nature of this inquiry that seeks to understand the relationship beyond the known causal effects of nicotine on BMI, recent methods allowed us to examine these relationships between smokers and non-smokers to reveal a common crux behind these appetitive behaviors. Quantifying the relationship between smoking and obesity is the first step toward understanding the mechanisms that link these two hazards, and if, indeed, we learn that both smoking and obesity are just two manifestations of a single underlying predisposition toward addiction, we have simplified the goal of achieving greater public health.

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Highlights

- Common genetic underpinning between cigarettes smoked per day in smokers and BMI in non-smokers

Table I.

Distribution of raw phenotypes for each smoking status group

	n	Mean (SE)
BMI $_{\text{never smoker}}$	60840	27.17 (.02)
BMI $_{\text{former smoker}}$	38878	28.24 (.02)
BMI $_{\text{current smoker}}$	13857	27.05 (.04)
CPD $_{\text{former smoker}}$	29962	20.76 (.06)
CPD $_{\text{current smoker}}$	10814	17.05 (.08)
Diff[1] $_{\text{current smoker}}$	10836	3.13 (.01)
Wake[2] $_{\text{current smoker}}$	10818	3.49 (.01)

1. Difficulty not smoking for 1 day

2. Time from waking to first cigarette

Table II.

Phenotypic correlations between BMI and smoking phenotypes within each smoking status group

	n	*r*	*p*
$BMI_{\text{former smoker}} - CPD_{\text{former smoker}}$	29403	0.15	< .001
$BMI_{\text{current smoker}} - CPD_{\text{current smoker}}$	10591	0.08	< .001
$BMI_{\text{current smoker}}$ - $Diff^{1}_{\text{current smoker}}$	10613	−0.01	0.21
$BMI_{\text{current smoker}} - Wake^{2}_{\text{current smoker}}$	10596	0.00	.98

1. Difficulty not smoking for 1 day

2. Time from waking to first cigarette

Table III.

SNP-based heritability of each phenotype for each smoking status group

	n	h^2 (SE)	*p*
BMI never smoker	60377	.34 (.01)	< .001
BMI former smoker	38536	.35 (.01)	< .001
BMI current smoker	13713	.31 (.04)	< .001
CPD former smoker	28502	.13 (.02)	< .001
CPD current smoker	11893	.17 (.04)	< .001
Diff[1] current smoker	10719	.07 (.04)	.04
Wake[2] current smoker	10701	.13 (.05)	.004

1. Difficulty not smoking for 1 day

2. Time from waking to first cigarette

Table IV.

SNP Genetic Correlations between BMI and smoking phenotypes for all combinations of smoke status groups

BMI - Smoking	n	*r* (SE)	*p*
BMI $_{\text{never smoker}}$ – CPD $_{\text{former smoker}}$	88879	.38 (.05)	<.001
BMI $_{\text{never smoker}}$ – CPD $_{\text{current smoker}}$	72270	.29 (.07)	<.001
BMI $_{\text{never smoker}}$ – Diff[1] $_{\text{current smoker}}$	71096	−.09 (.10)	.18
BMI $_{\text{never smoker}}$ – Wake[2] $_{\text{current smoker}}$	71078	.16 (.08)	.02
BMI $_{\text{former smoker}}$ - CPD $_{\text{former smoker}}$	67038	.28 (.05)	<.001
BMI $_{\text{former smoker}}$ - CPD $_{\text{current smoker}}$	50429	.29 (.08)	<.001
BMI $_{\text{former smoker}}$ – Diff[1] $_{\text{current smoker}}$	49255	.16 (.13)	.10
BMI $_{\text{former smoker}}$ – Wake[2] $_{\text{current smoker}}$	49237	.23 (.10)	.005
BMI $_{\text{current smoker}}$ – CPD $_{\text{current smoker}}$	25606	−.03 (.12)	.42
BMI $_{\text{current smoker}}$ - Diff[1] $_{\text{current smoker}}$	24432	−.36 (.22)	.03
BMI $_{\text{current smoker}}$ – Wake[2] $_{\text{current smoker}}$	24414	−.002 (.15)	.49

1. Difficulty not smoking for 1 day

2. Time from waking to first cigarette