Addictive Behaviors 89 (2019) 98–103

Contents lists available at ScienceDirect

Addictive Behaviors

journal homepage: www.elsevier.com/locate/addictbeh

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

Amanda G. Wills[a,b,*], Christian Hopfer[a,b]

[a] 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, USA

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

HIGHLIGHTS

- Higher numbers of cigarettes smoked per day are associated with greater BMI in current and former smokers.
- There is evidence for a common genetic underpinning between cigarettes smoked per day in smokers and BMI in non-smokers
- The relationship between smoking dependence based measures (that may be related to an underlying propensity toward addiction) and BMI is less clear.

ARTICLE INFO

Keywords:
Cigarette smoking
Nicotine addiction
BMI
SNP heritability
Genetic correlation
UK Biobank

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.

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

* Corresponding author at: 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, USA.
E-mail address: Amanda.noonan@ucdenver.edu (A.G. Wills).

https://doi.org/10.1016/j.addbeh.2018.09.025
Received 17 May 2018; Received in revised form 1 August 2018; Accepted 24 September 2018
Available online 25 September 2018
0306-4603/

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 0.47 to 0.90 (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 toward 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 500 k 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 pre-release quality control described at http://www.ukbiobank.ac.uk/wp-content/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 < 1%, per SNP genotyping call rates < 95%, deviations from Hardy-Weinburg equilibrium ($p < .00001$), that were multi-allelic, or had duplicate positions were removed. Closely related individuals with $\hat{\pi}$ (measure of pairwise genetic relatedness) values > 0.05 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