Body mass index change in gastrointestinal cancer and chronic obstructive pulmonary disease is associated with Dedicator of Cytokinesis 1

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Citation

Published Version
doi:10.1002/jcsm.12171

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Body mass index change in gastrointestinal cancer and chronic obstructive pulmonary disease is associated with Dedicator of Cytokinesis 1

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Abstract

Background There have been a number of candidate gene association studies of cancer cachexia-related traits, but no genome-wide association study (GWAS) has been published to date. Cachexia presents in patients with a number of complex traits, including both cancer and COPD. The objective of the current investigation was to search for a shared genetic aetiology for change in body mass index (ΔBMI) among cancer and COPD by using GWAS data in the Framingham Heart Study.

Methods A linear mixed effects model accounting for age, sex, and change in smoking status was used to calculate ΔBMI in participants over 40 years of age with three consecutive BMI time points (n = 4162). Four GWAS of ΔBMI using generalized estimating equations were performed among 1085 participants with a cancer diagnosis, 204 with gastrointestinal (GI) cancer, 112 with lung cancer, and 237 with COPD to test for association with 418 365 single-nucleotide polymorphisms (SNPs).

Results Two SNPs reached a level of genome-wide significance (P < 5 × 10⁻⁸) with ΔBMI: (i) rs41526344 within the CNTN4 gene, among COPD cases (β = 0.13, P = 4.3 × 10⁻⁸); and (ii) rs4751240 in the gene Dedicator of Cytokinesis 1 (DOCK1) among GI cancer cases (β = 0.10, P = 1.9 × 10⁻⁸). The DOCK1 SNP association replicated in the ΔBMI GWAS among COPD cases (βmeta-analysis = 0.10, Pmeta-analysis = 9.3 × 10⁻⁷). The DOCK1 gene codes for the dedicator of cytokinesis 1 protein, which has a role in myoblast fusion.

Conclusions In sum, one statistically significant common variant in the DOCK1 gene was associated with ΔBMI in GI cancer and COPD cases providing support for at least partially shared aetiology of ΔBMI in complex diseases.

Keywords GWAS; COPD; Cancer; Longitudinal; BMI; Cachexia

Received: 28 June 2016; Revised: 26 September 2016; Accepted: 2 November 2016

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Introduction

Despite the success of genome-wide association studies (GWASes) at identifying thousands of associations with hundreds of complex diseases and traits,¹ there has been no published GWAS investigating a cancer cachexia-related trait. Although there have been a number of published candidate-gene association studies investigating cancer...
cachexia-related traits (reviewed in Refs2,3), candidate-gene association studies are limited to known biology and do not take advantage of the agnostic, hypothesis-free approach of genome scans. Thus, the cancer cachexia community would benefit from GWASes in order to discover new genes and pathways involved in the aetiology of cachexia.

Body mass index (BMI) is a highly heritable cross-sectional measure that is frequently employed to monitor changes in body composition in epidemiological studies. Over 100 genetic loci have been associated with BMI.4,5 Changes in BMI (ΔBMI) have also been shown to be heritable with estimates ranging from 0.14 to 0.86.6,7 At one end of the BMI spectrum, obesity is a known risk factor for a number of complex diseases. At the other end of the spectrum, patients who lose weight are also at increased risk of mortality, which is the impetus for investigating muscle wasting and cachexia.8 Cachexia can be characterized in part as a rapid change in weight, including loss of fat-free muscle, as part of the pathology of an illness.8 Cachexia is often thought of with respect to cancer; however, it occurs in patients suffering from many chronic, complex diseases, including chronic obstructive pulmonary disease (COPD), congestive heart failure, AIDS, and cystic fibrosis, among others.8,9 In fact, the number of COPD patients with cachexia was recently estimated to be 1.4 times higher than the number of cancer patients with cachexia.10 Regardless of the primary complex disease diagnosis, cachexia is associated with poor prognosis and an increased burden on the healthcare system.8,11

In the current report, we begin to fill the gap in reported GWASes investigating cachexia-related traits. We analysed genetic data available via public access (dbGaP) from the Framingham Heart Study (FHS).12 In the current manuscript, we integrated data from GWAS of ΔBMI in cancer and COPD cases to search for overlapping genetic variants.

Materials and methods

Study population

Ethics approval was obtained for the proposed analyses from the Brigham and Women’s Hospital Institutional Review Board and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Phenotype and genotype data from FHS were used in the analyses. The FHS is a longitudinal population-based study of individuals from Framingham, MA.12 FHS genotype and phenotype data were downloaded through authorized accession obtained from National Institutes of Health Data Access Committee of dbGaP phs000007.v16.p6. Genotype data from the Affymetrix 500 k mapping array plus the Affymetrix 50 k supplemental array (phs000342.v4.p6) were used in the analyses.

Generating change in body mass index phenotype in cancer and chronic obstructive pulmonary disease cases

Figure 1A depicts a flowchart illustrating the number of subjects included in the analyses with genotype, ΔBMI, and additional phenotype (cancer and/or COPD diagnoses). Using the FHS data, ΔBMI was calculated by using the last three consecutive time points (~2–4 years apart) for individuals over 40 years of age who participated in the Original and Offspring Cohorts by using a random slope and intercept linear mixed effects model accounting for age, sex, and change in smoking status as fixed effects. COPD diagnosis was generated by using spirometry13 reported at visits 16, 17, and 19 in the FHS Original Cohort and

Figure 1 (A) Flowchart of number of subjects included in analyses with genotype, change in body mass index and additional phenotype data. (B) Venn diagram representing overlap between all subjects with change in body mass index, cancer, and chronic obstructive pulmonary disease diagnoses. Counts are based on the number of participants with genotype data and change in body mass index variable.
visits 5, 6, 7, and 8 in the FHS Offspring Cohort. An individual was coded as having COPD if they had at least two moderately obstructed (or worse) spirometry tests (FEV₁ < 80% and FEV₁/FVC < 0.7) that did not improve at a later visit (n = 344). An individual was coded as having any cancer if they reported a cancer diagnosis as coded with SEER ICD-O topography (TOPO) codes at any time during the study (n = 1085). Please see Table S1 for specific details on the TOPO codes used. Overall, 4162 participants had information to calculate ΔBMI and genotype data. Of these, 1085 had a cancer diagnosis, 344 had COPD based on lung function, 204 had a GI cancer diagnosis, and 112 had a lung cancer diagnosis. A total of 237 COPD cases did not also have a concurrent cancer diagnosis based on TOPO codes.

### Genome-wide association studies of change in body mass index

Genotyping quality control procedures were used to ensure high-quality data for association testing. The Affymetrix 500k and 50k data were cleaned separately and then combined prior to association testing. Briefly, DNA samples were excluded if missing more than 3% of genotypes, if reported familial relationships did not agree with those estimated from the genotypes, exhibited excess heterozygosity or homozygosity, or were outliers by using principal components analysis to detect population substructure. Single-nucleotide polymorphisms (SNPs) that failed genotyping in more than 5% of the samples or with Hardy–Weinberg equilibrium P-values less than 1 × 10⁻⁷ were removed. SNP analyses were restricted to autosomal variants with minor allele frequencies greater than 5%. A total of 4 GWAS (within COPD, all cancer, lung cancer, and GI cancer subjects) were performed by using generalized estimating equations accounting for family structure in FHS to test for association between 418,365 SNPs and ΔBMI by using the R library GWAF. All GWAS findings were further adjusted by using genomic control to control for population substructure. Meta-analyses were performed between independent samples from FHS cancer cases and FHS COPD cases without cancer, assuming a fixed effects model by using metal software. Meta-analysis results with P_heterozygosity < 0.1 were excluded. Regional association plots were generated by using LocusZoom. HaploReg v4.1 was used to assess the relationship between significant GWAS SNPs and epigenomic annotations in cell types from the Roadmap Epigenomics and ENCODE projects. The results with P < 5 × 10⁻⁸ were considered statistically/genome-wide significant (GWS) accounting both for the number of variants tested and the linkage disequilibrium (LD) structure of the genome.

### Results

#### Cancer and chronic obstructive pulmonary disease population characteristics

Only subjects over the age of 40 with at least 3 consecutive BMI measurements in FHS were considered for the analyses. There was some overlap in cancer and COPD diagnoses in the population (Figure 1B). Among FHS participants who had a COPD diagnosis, 107 (31.1%) also reported a cancer diagnosis of which 18 (5.2%) had GI cancer and 26 (7.6%) had lung cancer. In the current genetic analysis, COPD cases with a cancer diagnosis were excluded from the COPD ΔBMI GWAS to create an independent case population for meta-analyses.

Table 1 summarizes the characteristics of cancer and COPD cases from the FHS included in the analyses. A total of 4162 FHS participants over the age of 40 at baseline BMI measurement had three consecutive time points available to generate ΔBMI. Among these FHS participants, 237 had COPD based on spirometry without concurrent reported cancer diagnoses, 1085 had some type of cancer (except non-melanoma skin cancer), 204 had GI cancer, and 112 had lung cancer (Figure 1). The percentage of men was comparable between the COPD cases and the

### Table 1 Characteristics of cancer and chronic obstructive pulmonary disease cases in Framingham Heart Study used in analyses

<table>
<thead>
<tr>
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<th>Framingham Heart Study (FHS)</th>
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<tbody>
<tr>
<td></td>
<td>All</td>
</tr>
<tr>
<td>n</td>
<td>4162</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>45.2</td>
</tr>
<tr>
<td>Median initial BMI (IQR)</td>
<td>26.8 (6.0)</td>
</tr>
<tr>
<td>Median initial age (IQR)</td>
<td>62 (19)</td>
</tr>
<tr>
<td>Median follow-up time (IQR)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Median ΔBMI (IQR)</td>
<td>0.01 (0.2)</td>
</tr>
</tbody>
</table>

ΔBMI, change in body mass index; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; IQR, interquartile range.

*COPD cases without any cancer. Chronic obstructive pulmonary disease in FHS was coded by using lung function testing. Initial age and BMI in FHS are based on the first of three consecutive time points an individual participated in FHS.*
total subset with ΔBMI, whereas there were more men with a cancer diagnosis in the FHS data than total subset with ΔBMI (Table 1). The lung cancer population had the highest percentage of men (57.1%). Baseline BMI was comparable between the total FHS with ΔBMI, COPD, and cancer subsets. The FHS participants with a cancer diagnosis were older (median: 66 years) than those with COPD without cancer (median: 61 years) and the collective FHS population with ΔBMI (median: 62 years). The GI cancer case subset had the oldest median baseline age of 69 years (Table 1). The follow-up time was comparable among the COPD, cancer, and total populations with ΔBMI (follow-up time range: 7–9 years). Overall, most participants’ BMI increased slightly (median ΔBMI: 0.01) during the interval used to evaluate BMI. On average, the COPD population’s BMI increased the most (median ΔBMI: 0.03), and the GI cancer population was the only population that lost BMI overall (median ΔBMI: −0.02).

**Genome-wide association studies of change in body mass index in cancer and chronic obstructive pulmonary disease cases**

The quantile–quantile and Manhattan plots summarizing the results from the individual ΔBMI GWASes among cancer and COPD cases are presented in Figures S1–S4. All SNP results with suggestive associations ($P < 5 \times 10^{-5}$) are presented in Tables S2–S5. No SNP reached a level of GWS ($P < 5 \times 10^{-8}$) in the GWAS of ΔBMI among all cancer cases (Figure S1). However, two SNPs achieved GWS with ΔBMI separately among COPD or GI cancer cases. More specifically, rs41526344, within the CNTN4 gene, was significantly associated with ΔBMI among COPD cases ($P = 4.3 \times 10^{-8}$). CNTN4 codes for contactin 4, a neuronal network axon-associated cell adhesion molecule implicated in the genetics of neuropsychiatric disorders.21 Further, rs4751240 was significantly associated with ΔBMI among GI cancer cases ($P = 0.13, P = 4.3 \times 10^{-8}$). CNTN4 is located near the tumour suppressor Nkx2-8.22,23 We also identified an association in the meta-analysis of ΔBMI between lung cancer and COPD cases near the FAM73B gene (rs7042889, $P_{\text{meta-analysis}} = 1.4 \times 10^{-7}$; Table S10). The haplotype analysis revealed that rs7042889 is in high LD with eight SNPs that alter regulatory motifs, including rs7873667 which alters a number of motifs including several forkhead box (Fox) motifs (Table S10).

**Discussion**

In summary, we report findings from the first GWAS of a cachexia-related trait, ΔBMI, among cancer and COPD cases. We found one SNP, rs41526344, significantly associated with ΔBMI among COPD cases in the CNTN4 gene but were unable to replicate it. The DOCK1 SNP rs4751240 was significantly associated with ΔBMI among GI cancer cases and replicated among COPD cases. We also identified a nearly significant...
association with rs7042889 in the meta-analysis of ΔBMI between lung cancer and COPD cases near the FAM73B gene.

The rs4751240 SNP in the DOCK1 gene achieved a level of GWS \((P < 5 \times 10^{-8})\) in the analysis of ΔBMI among GI cancer cases and replicated nominally in the analyses among COPD cases. DOCK1 is a guanine nucleotide exchange factor, catalysing the exchange of GDP to GTP to activate Rho proteins.24 In mouse models, knockout of DOCK1 is embryonic lethal with a dramatic reduction of skeletal muscle tissues attributed to a deficiency in myoblast fusion.22 Myoblast fusion is also critical for satellite cell-mediated muscle regeneration in adults.25 As cachexia can be the result of both

Figure 2 Regional association plots of the top regions identified in the meta-analysis between cancer and chronic obstructive pulmonary disease cases: (A) The region on chromosome 3 where the top variant from the meta-analysis investigating change in body mass index among any cancer and chronic obstructive pulmonary disease cases rs188981 \((\beta: -0.025, P = 6.0 \times 10^{-8})\) is located in an intergenic region between the genes SUCNR1 and MBLN1. (B) Displays the DOCK1 region on chromosome 9, where the top variant rs4751240 \((\beta = 0.1, P = 9.3 \times 10^{-10})\) in the meta-analysis between investigating change in body mass index among gastrointestinal cancer and chronic obstructive pulmonary disease cases is located.

Figure 3 Boxplot of change in body mass index stratified by DOCK1 SNP rs4751240 genotype between (A) gastrointestinal cancer cases and (B) and chronic obstructive pulmonary disease cases.
increased muscle breakdown and decreased muscle production, genetic variation in DOCK1 may influence muscle regeneration. The DOCK1 SNP, rs4751240, is an intronic variant. SNPs in non-coding regions of the genome may directly alter or may be in LD with genetic variants that alter regulatory regions such as transcription factor or enhancer binding sites and in turn have an effect on gene expression and protein abundance. The rs4751240 SNP is within a motif for the tumour suppressor Nxx2-8, whose mechanism of tumour suppression is by up-regulating FOXO3a protein encoded by the FOXO3 gene. The Fox class O (FoxO) transcription factor family members FOXO1 and FOXO3 are well known to play a role in energy metabolism, protein breakdown, regulation of muscle mass, and adaptation to exercise. All FoxOs are activated in response to insulin stimulation and/or oxidative stress by phosphorylation at three evolutionarily conserved sites. Interestingly, the top SNP associated with ΔBMI in the meta-analysis of lung cancer and COPD cases is in high LD with rs78736677 (Table S10) that disrupts several Fox transcription factors, including FoxO. In a recent mega-GWAS, rs9400239 in FOXO3 was significantly associated with cross-sectional BMI (β = 0.0019, P = 1.61 × 10⁻⁸) in individuals of European ancestry, further supporting the role of this pathway in determining BMI.⁴

The top finding in the meta-analysis of ΔBMI between all cancer and COPD cases is intergenic to SUCNR1 and MBLN1. SUCNR1 codes for the succinate receptor 1 gene, which is a G-protein coupled receptor for succinate, an intermediate of the citric acid cycle. MBLN1 codes for the muscleblind-like splicing regulator 1, which plays a role in myotonic dystrophy and knockout of the gene in the mouse leads to muscle abnormalities and cataracts. This result, however, fails to achieve a level of genome-wide significance. The power of the analysis may be limited both by the sample size and heterogeneity of ΔBMI trajectories among different types of cancer. The analyses that were performed among different cancer types further reduced the sample size but may have increased the homogeneity of the ΔBMI trajectory, thereby increasing the power to detect the significant association in the GI cancer group.

We identified one variant, rs41526344, significantly associated with ΔBMI among COPD cases in the CNTN4 gene, coding for contactin-4. Contactins are a family of neural immunoglobulin cell adhesion molecules (IgCAMs) with six N-terminal immunoglobulin repeats followed by four fibronectin type III repeats. The prototypical contactin is contactin-1 with shared amino acid identity ranging from 33 to 52% identity with contactin-4 depending on the domain. Genetic variations in CNTN4, CNTN5, and CNTN6 have been associated with autism spectrum disorders. Increased signal transduction via the mTOR signal transduction pathway is one mechanism common to many autism spectrum disorder genes including contactins. Interestingly, decreased mTOR signalling is observed during fasting and disease as muscle growth and atrophy depends on the mTOR pathway. Further, mutations in CNTN1 cause a familial form of the lethal congenital myopathy, a disease whose hallmark is low muscle tone. In the current study, we identified a significant association with a CNTN4 SNP with ΔBMI among COPD cases; however, we were not able to replicate the findings among cancer cases.

There have been a number of candidate gene association studies investigating the genetics of cancer cachexia-related traits such as low BMI, low FFMI, weight loss, and muscle strength, but no GWAS has been reported to our knowledge. Systematic reviews of the genetics of cancer cachexia highlighted genes involved in inflammatory response regulation, homeostasis, pathways directing muscle and fat metabolism, and appetite regulation. Among COPD cases, muscle quadriceps muscle strength and low FFMI candidate gene studies have reported associations with the Angiotensin Converting Enzyme gene, Bradykinin Receptor gene, ILβ, IL6, TNFα, and vitamin D receptor. Wan and colleagues from our research group reported GWAS findings investigating two continuous outcomes, BMI and FFMI, in COPD cases. They found several SNPs tagging the fat-mass and obesity (FTO) gene significantly associated (meta-analysis: P < 5 × 10⁻⁷) with reduced BMI and FFMI in COPD cases. Single-nucleotide polymorphisms in the FTO gene have been repeatedly associated with BMI and diabetes. It is interesting to note that we did not find statistically significant associations with any known cachexia candidate genes. This may indicate that the genetic aetiology of longitudinal BMI is different than cross-sectional BMI; however, larger sample sizes will be required to clarify this issue. The current report begins to fill the void of reported GWASes investigating cachexia-related traits and provides a foundation for expanding this work to larger case populations with more extensive phenotyping for monitoring cachexia.

In the current report, we took advantage of a publicly available dataset to test the hypothesis that a shared genetic aetiology exists for ΔBMI among cancer and COPD cases. We considered SNPs with P < 5 × 10⁻⁸, the generally accepted threshold for statistical significance in GWAS, as statistically significant because it has been shown to account both for the number of variants tested and the LD structure of the genome. Further, the Bonferroni adjusted threshold for 418 365 SNPs tested in four GWASes is α = 3.0 × 10⁻⁸, and the finding with DOCK1 among GI cancer cases is also below this more conservative level of statistical significance (P = 1.9 × 10⁻⁸). We do acknowledge that the sample sizes became relatively small when we examined individual groups of cancer patients. Despite this limitation, the rs4751240 finding in DOCK1 did reach a level of genome-wide significance among GI cancer cases, and we were able to replicate the finding among COPD cases contributing to a meta-analysis of P = 9.3 × 10⁻¹⁰. This finding supports the hypothesis that a shared genetic aetiology exists for ΔBMI among GI cancer and COPD cases and also underscores the need for further...
investigations into larger cancer and COPD populations to increase the power to detect additional signals. Further, our investigation was underpowered for additional genetic analyses such as epistasis. In future investigations, we plan to investigate the role of epistasis in cachexia by, for example, testing for significant genetic interactions between the DOCK1 SNP identified in the current analyses and variants in other candidate genes whose role in cachexia has been implicated.

Further limitations of the analyses include an inability to address the temporal relationship between disease diagnoses and ΔBMI in our analyses. It is possible, for example, that an individual received a cancer diagnosis many years before the initial BMI time point used to generate the ΔBMI phenotype in FHS. We performed our analyses in a longitudinal, population-based cohort and screened for participants over the age of 40 and only considered the last three consecutive BMI measurements reported among cancer and COPD cases. The median age for the first BMI measurement included in the GI cancer analysis was 69 with a median follow-up period of 7 years (Table 1). With the focus on the last three consecutive time points with BMI data available in FHS combined with the advanced age of the population under investigation, the majority of cancer diagnoses would most likely have been made either prior or during the window we investigated ΔBMI. Although timing of diagnosis of cancer relative to ΔBMI is important, even more important issues are the stage, extent, and treatment of the cancer, including consideration of course of chemotherapy and any resultant toxicity, relative to ΔBMI. We plan to pursue these more detailed characterizations in future studies. Cancers are likely present for years before diagnoses are made, and the pre-diagnosis duration is typically unknown. We think that the fact that we have found interesting genetic association results with these limitations argues that there are likely important signals to find.

The current report has many limitations. We mined a publicly available study, the FHS, to investigate ΔBMI among COPD and cancer cases. The FHS participants had BMI measured every 2–4 years. The ideal study design would ascertain patients for longitudinal assessments of cachexia, including measuring BMI and/or more precise measurements of muscle mass every 3–6 months in addition to other characteristics established in the cachexia consensus definition. Further, our sample sizes became small when we restricted analyses to cancer and COPD subsets of the population. As we used a hypothesis-free approach to search for genetic variants associated with ΔBMI among cancer and COPD cases, replicating the finding in independent populations ascertained for cachexia will be a crucial next step.

The current analysis demonstrates evidence for the involvement of the DOCK1 gene with ΔBMI among both GI cancer and COPD cases. The current investigation has highlighted genes known for their involvement in energy metabolism and muscle maintenance as associated with ΔBMI. Future directions will include collection and analysis of gene expression data to identify expression biomarkers associated with ΔBMI among COPD and cancer cases in addition to more information on cancer diagnosis, stage, extent, and treatment. Our future efforts will be directed at analysing additional longitudinal data characterizing both genetic and gene expression to gain further insight on biomarkers that can be used to monitor the development and prognosis of cachexia.

Acknowledgements

The authors certify that they comply with the ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2015. A portion of the results of this manuscript have been published in the form of an abstract: the American Society of Human Genetics Conference, Baltimore, MD, 2015. The FHS is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with Boston University (contract no. N01-HC-25195). This manuscript does not necessarily reflect the opinions or views of the FHS, Boston University, or NHLBI. SHARe Illumina genotyping was provided under an agreement between Illumina and Boston University.

This study was funded by the National Institutes of Health—National Heart, Lung, and Blood Institute (N02-HL-64278, N01 HC 25195, P01 HL105339, R01 HL111759, R01 HL113264, K99 HL121087); Parker B Francis Foundation.

Online supplementary material

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:

**Figure S1.** Quantile-Quantile and Manhattan plots of GWAS results of the FHS ΔBMI phenotype in any cancer cases

**Figure S2.** Quantile-Quantile and Manhattan plots of GWAS results of the FHS ΔBMI phenotype in COPD cases

**Figure S3.** Quantile-Quantile and Manhattan plots of GWAS results of the FHS ΔBMI phenotype in GI cancer cases

**Figure S4.** Quantile-Quantile and Manhattan plots of GWAS results of the FHS ΔBMI phenotype in lung cancer cases

**Table S1.** ICD-O TOPO codes used to classify cancer cases.

**Table S2.** Suggestive results (P < 5x10^-5) from the GWAS of ΔBMI in any cancer cases

**Table S3.** Suggestive results (P < 5x10^-5) from the GWAS of ΔBMI in GI cancer cases

**Table S4.** Suggestive results (P < 5x10^-5) from the GWAS of ΔBMI in COPD cases

**Table S5.** Suggestive results (P < 5x10^-5) from the GWAS of ΔBMI in lung cancer cases

**Table S6.** Suggestive results (P < 5x10^-5) from the GWAS of ΔBMI in breast cancer cases
Table S7. Suggestive results (P < 5x10^{-5}) from the GWAS of ΔBMI in prostate cancer cases

Table S8. Suggestive results (P < 5x10^{-5}) from the meta-analysis GWAS of ΔBMI in any cancer cases with GWAS of ΔBMI COPD cases.

Table S9. Suggestive results (P < 5x10^{-5}) from the meta-analysis GWAS of ΔBMI in GI cancer cases with GWAS of ΔBMI COPD cases.

Table S10. Suggestive results (P < 5x10^{-5}) from the meta-analysis GWAS of ΔBMI in lung cancer cases with GWAS of ΔBMI COPD cases.

Conflict of Interest

M.-L.N. McDonald declares that she has no conflict of interest. S. Won declares that he has no conflict of interest. M. Mattheisen declares that he has no conflict of interest. P.J. Castaldi declares that he has no conflict of interest. M. H. Cho declares that he has no conflict of interest. E. Rutten declares that she has no conflict of interest. M. Hardin declares that she has no conflict of interest. W.-K. Yip declares that he has no conflict of interest. C.P. Hersh declares that he has no conflict of interest. E.K. Silverman has received honoraria and consulting fees from Merck, grant support and consulting fees from GlaxoSmithKline, and honoraria and travel support from Novartis in the past 3 years.

References


