Shared Genetic Etiology of Obesity-Related Traits and Barrett's Esophagus/Adenocarcinoma: Insights from Genome-Wide Association Studies

Anne C. Böhmer[1,2], Julian Hecker[3], Julia Schröder[1,2], Puya Gharahkhani[4], Andrea May[5], Christian Gerges[6], Mario Anders[7,8], Jessica Becker[1,2], Timo Hess[9], Nicole Kreuser[10], René Thieme[10], Tania Noder[7], Marino Venerito[11], Lothar Veits[12], Thomas Schmidt[13], Claudia Fuchs[14], Jakob R. Izbicki[15], Arnulf H. Hölscher[14], Arne Dietrich[10], Yusef Moulla[10], Orestis Lyros[10], Hauke Lang[16], Dietmar Lorenz[17], Brigitte Schumacher[18], Rupert Mayershofer[19], Yogesh Vashist[15,20], Katja Ott[13,21], Michael Vieth[12], Josef Weismüller[22], Susanne Moebus[23], Michael Knapp[24], Horst Neuhaus[6], Thomas Rösch[7], Christian Ell[5], Markus M. Nöthen[1,2], David C. Whiteman[25], Ian Tomlinson[26], Janusz Jankowski[27,28], Rebecca C. Fitzgerald[29], Claire Palles[26], Thomas L. Vaughan[30], Ines Gockel[10], Aaron P. Thrift[31,32], Heide Fier[3], and Johannes Schumacher[1,9]

ABSTRACT

Background: Obesity is a major risk factor for esophageal adenocarcinoma (EA) and its precursor Barrett's esophagus (BE). Research suggests that individuals with high genetic risk to obesity have a higher BE/EA risk. To facilitate understanding of biological factors that lead to progression from BE to EA, the present study investigated the shared genetic background of BE/EA and obesity-related traits.

Methods: Cross-trait linkage disequilibrium score regression was applied to summary statistics from genome-wide association meta-analyses on BE/EA and on obesity traits. Body mass index (BMI) was used as a proxy for general obesity, and waist-to-hip ratio (WHR) for abdominal obesity. For single marker analyses, all genome-wide significant risk alleles for BMI and WHR were compared with summary statistics of the BE/EA meta-analyses.

Results: Sex-combined analyses revealed a significant genetic correlation between BMI and BE/EA ($r_g = 0.13$, $P = 2 \times 10^{-04}$) and a r_g of 0.12 between WHR and BE/EA ($P = 1 \times 10^{-02}$). Sex-specific analyses revealed a pronounced genetic correlation between BMI and EA in females ($r_g = 0.17$, $P = 1.2 \times 10^{-03}$), and WHR and EA in males ($r_g = 0.18$, $P = 1.51 \times 10^{-02}$). On the single marker level, significant enrichment of concordant effects was observed for BMI and BE/EA risk variants ($P = 8.45 \times 10^{-03}$) and WHR and BE/EA risk variants ($P = 2 \times 10^{-02}$).

Conclusions: Our study provides evidence for sex-specific genetic correlations that might reflect specific biological mechanisms. The data demonstrate that shared genetic factors are particularly relevant in progression from BE to EA.

Impact: Our study quantifies the genetic correlation between BE/EA and obesity. Further research is now warranted to elucidate these effects and to understand the shared pathophysiology.

[1]Institute of Human Genetics, University of Bonn, Bonn, Germany. [2]Department of Genomics, Life and Brain Center, University of Bonn, Bonn, Germany. [3]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, Massachusetts. [4]Statistical Genetics, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia. [5]Department of Medicine II, Sana Klinikum, Offenbach, Germany. [6]Department of Internal Medicine II, Evangelisches Krankenhaus, Düsseldorf, Germany. [7]Department of Interdisciplinary Endoscopy, University Hospital Hamburg-Eppendorf, Hamburg, Germany. [8]Department of Gastroenterology and Interdisciplinary Endoscopy, Vivantes Wenckebach-Klinikum, Berlin, Germany. [9]Center for Human Genetics, University Hospital Marburg, Marburg, Germany. [10]Department of Visceral, Transplant, Thoracic and Vascular Surgery, University Hospital of Leipzig, Leipzig, Germany. [11]Department of Gastroenterology, Hepatology and Infectious Diseases, Otto-von-Guericke University Hospital, Magdeburg, Germany. [12]Institute of Pathology, Klinikum Bayreuth, Bayreuth, Germany. [13]Department of General, Visceral and Transplantation Surgery, University of Heidelberg, Heidelberg, Germany. [14]Department of General, Visceral and Cancer Surgery, University of Cologne, Cologne, Germany. [15]Department of General, Visceral and Thoracic Surgery, University Medical Center Hamburg-Eppendorf, University of Hamburg, Hamburg, Germany. [16]Department of General, Visceral and Transplant Surgery, University Medical Center, University of Mainz, Mainz, Germany. [17]Department of General, Visceral and Thoracic Surgery, Klinikum Darmstadt, Darmstadt, Germany. [18]Department of Internal Medicine and Gastroenterology, Elisabeth Hospital, Essen, Germany. [19]Gastroenterologie am Burgweiher, Bonn, Germany. [20]Kantonsspital Aarau, Aarau, Switzerland. [21]Department of General, Visceral and Thorax Surgery, RoMed Klinikum Rosenheim, Rosenheim, Germany. [22]Gastroenterologische Gemeinschaftspraxis, Koblenz, Germany. [23]Centre of Urban Epidemiology, Institute of Medical Informatics, Biometry and Epidemiology, University of Essen, Essen, Germany. [24]Institute for Medical Biometry, Informatics, and Epidemiology, University of Bonn, Bonn, Germany. [25]Cancer Control, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia. [26]Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, United Kingdom. [27]University of Central Lancashire, Westlakes Science and Technology Park, Moor Row, United Kingdom. [28]Warwick Medical School, University of Warwick, Warwick, United Kingdom. [29]Medical Research Council (MRC) Cancer Unit, Hutchison-MRC Research Centre and University of Cambridge, Cambridge, United Kingdom. [30]Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington. [31]Dan L. Duncan Comprehensive Cancer Center, Baylor College of Medicine, Houston, Texas. [32]Section of Epidemiology and Population Sciences, Department of Medicine, Baylor College of Medicine, Houston, Texas.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

A.C. Böhmer, J. Hecker, H. Fier, and J. Schumacher contributed equally to this article.

Corresponding Author: Anne C. Böhmer, Institute of Human Genetics, University of Bonn, Venusberg-Campus 1, 53111 Bonn, Germany. Phone: 49-228-6885-444; Fax: 49-228-6885-401; E-mail: aboehmer@uni-bonn.de

Cancer Epidemiol Biomarkers Prev 2020;29:427–33

doi: 10.1158/1055-9965.EPI-19-0374

Introduction

Over the past four decades, the incidence of esophageal adenocarcinoma (EA) has shown a continuous increase in developed nations (1). In 2012, the global incidence rate was estimated at 0.7 per 100,000 person-years, with a male predominance in incidence (2, 3). Without early detection, EA has a mortality rate of >85% (1). EA is typically preceded by the precancerous condition Barrett's esophagus (BE), which is characterized by the replacement of normal stratified squamous epithelium of the distal esophagus by metaplastic columnar epithelium. It has been proposed that BE develops in response to an adaption to the harsh and acidic esophageal environment of chronic gastroesophageal reflux disease (1). BE and EA are multifactorial disorders. Genome-wide association studies (GWAS) of BE and EA have successfully identified disease-associated single-nucleotide polymorphisms (SNPs) and contributory biological pathways (4). Further genetic studies revealed that BE and EA share polygenic effects that contribute to risk of both diseases: Ek and colleagues showed that both disorders have heritable components with substantial overlap in the set of genes contributing to risk of each condition ($r_g = 1.0$; ref. 5). Further evidence is provided by the today's largest GWAS meta-analysis (4). Here, all genome-wide significant loci from a separate BE and EA meta-analysis were also identified in a combined BE/EA meta-analysis except for one locus on chromosome 3q27, which was significant in EA only. By contrast, all risk loci identified for BE were also associated with EA.

Epidemiologic studies estimated that prevalence of BE in developed nations is up to 5.6% (6), and research suggests that progression to EA occurs in around 0.12% to 0.5% of BE patients per year (7). The low progression rate complicates the clinical management of BE with the challenge of underdiagnosis of a serious disease and overdiagnosis of early benign esophageal changes. Therefore, there is a need for improved surveillance and intervention strategies for prevention of EA.

A number of studies have reported a positive association between EA and high body mass index (BMI; ref. 8). An investigation of 12 epidemiologic studies revealed that BMI is directly associated with the risk of EA (9). Of note, the association between obesity and EA seems to be stronger than that for other types of obesity-related cancers (8). In contrast, studies of obesity-related traits and BE risk have generated nonreplicable results (10, 11). Although BMI is used as a marker of overall obesity in epidemiologic studies, this anthropometric marker does not indicate body fat distribution. Abdominal obesity or visceral fat is more often observed in men (12). There is evidence that abdominal obesity is much more strongly associated with EA than BMI alone, possibly contributing to the striking imbalance of disease occurrence between the sexes with a strong male predominance of EA (7:1 male-to-female ratio; ref. 8). Previous authors have suggested that waist circumference or waist-to-hip ratio (WHR), as proxies for body fat distribution, might be used as predictors of obesity-related diseases, including BE and EA (8, 13). A study by Steffens and colleagues analyzed a European prospective cohort (EPIC study) and showed that abdominal obesity, rather than general obesity, contributes to EA risk (14).

The use of genetic data and the application of novel bioinformatic methods have led to new insights into the relationship between obesity and BE/EA. Using a case–control approach, Thrift and colleagues demonstrated that obesity was a risk factor for BE and EA, independent of other confounding factors (15). This study applied the Mendelian randomization (MR) approach to show the causal nature of the observed association between obesity and BE/EA. In their study, Thrift and colleagues derived a genetic risk score in 29 BMI-associated SNPs and revealed that individuals with a high genetic susceptibility to obesity have higher risks of BE and EA than individuals with low genetic obesity risk. The MR approach incorporates genetic information of single genetic variants; the present study expands the analyses to a genome-wide level in order to elucidate the overall shared genetic background between BE and EA and obesity-related traits. For this, we used cross-trait linkage disequilibrium (LD) score regression (LDSR), a method that estimates genetic correlation on a genome-wide level by using GWAS summary statistics (16).

In order to better understand the relation of BE and EA with obesity, the present study aimed at quantifying and elucidating the shared genetic background of these traits. This might help to get a better understanding of the biological factors that lead to progression from BE and EA within the context of obesity.

Materials and Methods

Description of GWAS data sets

Data on BE and EA were obtained from a previous GWAS meta-analysis (4). This meta-analysis combined data sets from four GWAS cohorts: (i) the BEACON cohort (2,406 BE cases, 1,508 EA cases, and 6,718 controls); (ii) the Bonn cohort (1,037 BE cases, 1,609 EA cases, and 3,537 controls); (iii) the Cambridge cohort (873 BE cases, 995 EA cases, and 3,408 controls); and (iv) the Oxford cohort (1,851 BE cases and 3,496 controls). All BE patients had a histopathologic diagnosis of intestinal metaplasia in the distal esophagus. All EA patients had a histopathologic diagnosis of adenocarcinoma in the distal esophagus. Informed consent was obtained in the four studies from all participants and ethics approval was obtained from the ethics boards of every participating institution. The studies were conducted in accordance with guidelines of the Declaration of Helsinki, and the studies were approved by an institutional review board. In total, the GWAS meta-analysis sample comprised 6,167 BE cases (1,508 females and 4,659 males); 4,112 EA cases (526 females and 3,586 males); and 17,159 controls (7,970 females and 9,189 males). All cases and controls were of European ancestry. Genotyping was performed using high-dense Illumina SNP arrays. This resulted in 11,951,684 genotyped or imputed SNPs for each participant (4). Association data were available for three different analyses: (i) BE, (ii) EA, and (iii) BE/EA combined.

Genetic data for BMI and WHR were retrieved from the GWAS meta-analyses performed by the Genetic Investigation of ANthropometric Traits (GIANT) consortium for: (i) BMI (17) and (ii) WHR (18). Association data were available from 2,554,623 SNPs for 322,154 individuals in the BMI study (17), and 2,542,447 SNPs for 210,088 individuals in the WHR study (18). For GIANT data, association data for both sex-specific and sex-combined analyses were available. Only GIANT data from individuals of European descent were integrated into the present analyses.

LD score regression genetic correlation analyses

To estimate genetic correlations between obesity-related traits and Barrett's phenotypes (i.e., BE, EA, and BE/EA combined), LD score regression (LDSC) analyses were conducted (16). Using the default parameters of the LDSC software (19), quality control (QC) was performed for the genome-wide summary statistics of the Barrett's phenotypes, BMI, and WHR data sets. For the BMI and WHR data sets, QC was performed for both sex-specific and sex-combined data. Supplementary Table S1 lists the number of overlapping SNPs in each analysis post-QC. Genetic correlations were estimated for nine pairwise combinations (see **Table 1**), as based on the available,

Table 1. Pairwise genetic correlation, as calculated by LDSC.

		BE r_g (se) and *P* value	EA r_g (se) and *P* value	BE/EA r_g (se) and *P* value
BMI	Male	**0.14 (0.04), 1.00 × 10^{-03}***	0.09 (0.05), 0.10	**0.08 (0.04), 6.44 × 10^{-02}**
	Female	0.06 (0.05), 0.22	**0.17 (0.05), 1.20 × 10^{-03}***	**0.16 (0.04), 5.02 × 10^{-05}***
	Sex-combined	**0.11 (0.04), 5.50 × 10^{-03}**	**0.15 (0.04), 1.00 × 10^{-03}***	**0.13 (0.04), 2.00 × 10^{-04}***
WHR	Male	0.06 (0.07), 0.42	**0.18 (0.07), 1.51 × 10^{-02}**	0.11 (0.06), 0.06
	Female	0.05 (0.06), 0.41	0.09 (0.07), 0.20	0.08 (0.06), 0.15
	Sex-combined	0.07 (0.05), 0.18	**0.16 (0.06), 8.20 × 10^{-03}**	**0.12 (0.05), 1.34 × 10^{-02}**
$WHR_{adj}BMI$	Male	0.003 (0.08), 1	0.11 (0.08), 0.17	0.05 (0.07), 0.48
	Female	0.01 (0.07), 0.86	0.01 (0.08), 0.85	0.02 (0.06), 0.72
	Sex-combined	0.03 (0.05), 0.58	0.08 (0.07), 0.23	0.06 (0.05), 0.27

Note: Significant *P* values are highlighted in bold. Asterisk indicates *P* values significant after Bonferroni correction for multiple testing (27 tests).
Abbreviations: r_g, genetic correlation; SE, standard error; $WHR_{adj}BMI$, waist-to-hip ratio adjusted for BMI.

precomputed LD scores for the European population. These LD scores are provided by the developers of the LDSC software.

Enrichment of concordant effects

Risk alleles for all genome-wide significant variants in the BMI and WHR GWAS studies were compared with those reported in the BE/EA GWAS meta-analysis. Data on genome-wide significant SNPs (hereafter referred to as index SNPs) for BMI and WHR were obtained from the supplementary material of the BMI (17) and WHR GWAS (18). All index SNPs identified in Europeans in the sex-combined and sex-specific analyses were included. Association data on index SNPs for the three Barrett's phenotypes were retrieved from the GWAS meta-analyses (4). The direction of effect of the risk allele for the BMI and WHR index SNPs was then compared with the effect directions observed in the meta-analysis data for the Barrett's phenotypes. If both alleles revealed the same risk allele, this was referred to as concordant effects. Enrichment analysis of concordant effects was performed using a one-sided binomial test of the number of concordant effects versus a null expectation of $P = 0.5$. Enrichment of concordant and nominally significant ($P < 0.05$) index SNPs were tested using a second one-sided binomial test with a null expectation of $P = 0.05$.

Results

Shared genetic etiology for obesity-related traits and BE/EA

Results concerning the shared genetic correlation between obesity-related traits and Barret's phenotypes are summarized in **Table 1**.

For BMI, the male-only analysis revealed a significant genetic correlation of $r_g = 0.14$ with BE (SE = 0.04, $P = 1 \times 10^{-03}$), whereas the genetic correlation with EA was much weaker and not significant ($r_g = 0.09$, SE = 0.05, $P = 0.10$). The genetic correlation with male BMI and the combined BE/EA data revealed $r_g = 0.08$ (SE = 0.04, $P = 6.4 \times 10^{-02}$).

The opposite effect was observed in females. Here, a genetic correlation of $r_g = 0.17$ was observed between BMI and EA (SE = 0.05, $P = 1.2 \times 10^{-03}$), and a much weaker and nonsignificant genetic correlation was found between BMI and BE ($r_g = 0.06$, SE = 0.05, $P = 0.22$). The genetic correlation with female BMI and combined BE/EA data was $r_g = 0.16$ (SE = 0.04, $P = 5.02 \times 10^{-05}$).

For WHR, the male-only analysis revealed a genetic correlation of $r_g = 0.18$ with EA (SE = 0.07, $P = 1.51 \times 10^{-02}$), whereas the genetic correlation with BE was much weaker and not significant. The genetic correlation with male WHR and combined BE/EA was $r_g = 0.11$, but not significant. In females, no significant genetic correlation with WHR was observed for either BE, EA or BE/EA (**Table 1**).

Following adjustment of WHR for BMI, no significant genetic correlation was observed for males or females.

Enrichment of concordant effects

Results for the enrichment of concordant effects of the first and second binominal test are shown in **Table 2**. Comparisons of sex-specific findings were hampered by variations in the number of index SNPs between males and females. However, the sex-combined analysis revealed a significant enrichment of index SNPs with concordant and significant effects in (i) BMI and EA ($P = 7.51 \times 10^{-03}$) and (ii) BMI and BE/EA ($P = 8.45 \times 10^{-03}$). In addition, a nominally significant enrichment of index SNPs with the same allelic direction and significance was observed for WHR and BE/EA ($P = 0.02$). All index SNPs with concordant and significant effects as well as their association *P* values for obesity and Barrett phenotypes are listed in **Table 3**.

Discussion

Epidemiologic studies have implicated obesity as a risk factor for both EA and its precursor BE. Modern genetic approaches enable analysis of their shared etiology on a genetic level using large-scale GWAS data sets. In the present study, LDSC was used to estimate the genetic correlation between Barrett's phenotypes (BE, EA, and BE/EA) and obesity. The analyses were performed using the largest available GWAS data sets for Barrett's phenotypes, obesity, and body fat distribution to date (4, 17, 18). The analyses differentiated between genetic risk for increased BMI, as a proxy for general obesity, and the genetic risk for increased WHR, as a proxy for abdominal obesity.

The present analyses revealed that obesity-related traits and Barrett's phenotypes share a substantial proportion of their genetic etiology. This is consistent with the results of the study performed by Thrift and colleagues, which indicated that obesity is an independent risk factor for BE and EA (15). A recent study by Lindström and colleagues analyzed the pairwise genetic correlations between different types of cancer and noncancer traits, including BMI (20). Two cancer types (breast and prostate cancer) showed negative genetic correlations with BMI. Positive genetic correlation with BMI were observed for lung cancer ($r_g = 0.116$), pancreatic cancer ($r_g = 0.243$), and colorectal cancer ($r_g = 0.157$). In this present study, we observed a comparable strong genetic correlation between EA and

Table 2. Results of enrichment for concordant effects analysis.

			BE				EA				BE/EA			
		Index SNPs, *n*	Same direction	P_{binom} [a]	Same direction, $P < 0.05$	P_{binom} [b]	Same direction	P_{binom} [a]	Same direction, $P < 0.05$	P_{binom} [b]	Same direction	P_{binom} [a]	Same direction and $P < 0.05$	P_{binom} [b]
BMI	Male	30	16	0.43	1	0.56	17	0.29	4	**8.80×10^{-03}**	16	0.43	6	**$8.09 \times 10^{-05*}$**
	Female	38	26	**0.02**	2	0.38	25	**0.04**	4	**0.03**	30	**$2.3 \times 10^{-04*}$**	5	**0.02**
	Sex-combined	77	45	0.09	4	0.18	46	0.06	7	**7.51×10^{-03}**	47	0.03	7	**8.45×10^{-03}**
WHR	Male	2	1	0.75	0	1	1	0.72	1	**0.05**	1	0.75	0	1
	Female	30	16	0.43	2	0.19	14	0.71	2	0.15	16	0.43	3	**0.02**
	Sex-combined	26	13	0.58	2	0.14	12	0.72	1	0.46	13	0.58	3	**0.02**

Note: Genome-wide significant SNPs in BMI and WHR studies are referred to as index SNPs. Significance was evaluated using a Bonferroni-corrected threshold of $P = 0.002$ (0.05/18 traits tested). *P* values highlighted in bold are nominally significant. Asterisk indicates *P* values below the threshold for multiple testing.

[a] P_{binom}: first one-sided binomial test of the number of concordant effects versus a null expectation of $P = 0.5$.

[b] P_{binom}: second one-sided binomial test of the number of concordant and nominally significant ($P < 0.05$) SNP effects with a null expectation of $P = 0.05$.

BMI. The study by Lindström and colleagues did not investigate genetic correlations with WHR and sex-specific effects.

The analyses generated two additional findings. First, the genetic correlation between obesity-related traits and EA seems to be stronger than the genetic correlation between obesity-related traits and BE. Although the observed difference is only moderate and not statistically significant, this finding suggests that the underlying biological factors have a stronger impact on the development of EA than on BE.

This hypothesis is consistent with data from previous epidemiologic studies, which demonstrated consistent positive associations for both BMI and abdominal obesity, and EA (9, 21, 22). For BE, previous studies revealed general associations with abdominal obesity, however, not with BMI (10, 11, 23). On the translational level, the present genetic data emphasize that the management and regulation of obesity, for example via modifications to diet and life style, might have a protective impact in terms of EA development, and that the surveillance of obese BE patients might be an important aspect in terms of EA prevention.

Second, the results indicate sex-specific differences in EA development. The genetic correlation between EA and general obesity—as measured according to BMI—was strongest in women, whereas the genetic correlation with abdominal obesity—as measured according to WHR—was strongest in men. This finding is consistent with previously hypothesized mechanisms (1). The accumulation of abdominal fat, which occurs more frequently in men, might increase intra-abdominal pressure, which in turn promotes gastroesophageal reflux. In contrast, systemic inflammatory processes within adipose tissue in general might be a more important etiologic factor in women. However, we also observed a strong genetic correlation between BMI and BE in men, but not in women.

Interestingly, the to-date largest epidemiologic study that investigates obesity traits and risk of BE reported waist circumference, but not BMI, as a risk factor for BE (10). Contrarily, the present study finds a correlation between BE and BMI, but not WHR. However, these are not necessarily conflicting results. Here, we have studied the relation between the Barrett's phenotypes and obesity-related traits on a genetic level, whereas Kubo and colleagues investigated the relationship on a phenotypic level.

As limitation we note that the underlying sample sizes of the EA, BE, and BE/EA summary statistics are only moderate and our results are not validated based on an external data set. In addition, the genetic correlation between two traits does not allow drawing conclusions in terms of causality. As shown in Bulik-Sullivan and colleagues (19), genetic correlations estimated from summary statistics could be the result of a direct effect between both traits or implied by an indirect effect that is mediated by a third trait.

On the single marker level, the present analyses revealed a significant enrichment of obesity-associated SNPs for EA but not for BE. Although the associated variants require further replication in independent EA samples, elucidation of the underlying pathomechanisms and implicated genes might facilitate understanding of the biological factors that lead to EA progression within the context of obesity. For example, the most strongly associated locus in a previous GWAS of BMI was *FTO* (17). In the present study, the *FTO* locus showed association signals for BMI and EA in both sexes, but no concordance for BMI and BE (**Table 3**). Functional follow-up studies indicated a potential mechanism for the genetic association between *FTO* and obesity, involving regulatory dysfunction of *IRX3* and *IRX5* expression during early adipocyte differentiation (24). Although the biological mechanisms that link obesity and cancer remain largely unknown, consensus is growing, that dysregulation of adipocyte function is a major contributor (25, 26).

Table 3. Overview of BMI and WHR index SNPs that showed significant BE/EA associations with the same effect alleles.

Gender	Phenotype	SNP	Chr	Pos (hg19)	Nearest gene	Effect allele	Other allele	P_obesity	P_Barrett-phenotype
Male BMI	BE	rs2820292	1	201,784,287	*NAV1*	C	A	2.26E−08	2.60E−03
	EA	rs13021737	2	632,348	*TMEM18*	G	A	3.86E−22	1.60E−02
		rs1516725	3	185,824,004	*ETV5*	C	T	1.05E−12	1.06E−02
		rs12429545	13	54,102,206	*OLFM4*	A	G	1.51E−08	2.07E−05
		rs1558902	16	53,803,574	*FTO*	A	T	1.04E−93	1.33E−03
	BE/EA	rs2820292	1	201,784,287	*NAV1*	C	A	2.26E−08	9.17E−03
		rs1516725	3	185,824,004	*ETV5*	C	T	1.05E−12	2.32E−02
		rs12429545	13	54,102,206	*OLFM4*	A	G	1.51E−08	2.70E−04
		rs16951275	15	68,077,168	*MAP2K5*	T	C	8.53E−11	4.43E−02
		rs1558902	16	53,803,574	*FTO*	A	T	1.04E−93	2.39E−03
		rs2287019	19	46,202,172	*QPCTL*	C	T	2.69E−12	1.85E−02
Female BMI	BE	rs205262	6	34,563,164	*C6orf106*	G	A	2.04E−09	2.86E−02
		rs7141420	14	79,899,454	*NRXN3*	T	C	1.45E−11	1.23E−02
	EA	rs13021737	2	632,348	*TMEM18*	G	A	6.99E−40	1.60E−02
		rs1516725	3	185,824,004	*ETV5*	C	T	1.91E−15	1.06E−02
		rs1558902	16	53,803,574	*FTO*	A	T	4.03E−84	1.33E−03
		rs1808579	18	21,104,888	*C18orf8*	C	T	1.23E−08	1.64E−02
	BE/EA	rs1516725	3	185,824,004	*ETV5*	C	T	1.91E−15	2.32E−02
		rs6465468	7	95,169,514	*ASB4*	T	G	4.98E−08	3.79E−02
		rs16951275	15	68,077,168	*MAP2K5*	T	C	2.96E−10	4.43E−02
		rs1558902	16	53,803,574	*FTO*	A	T	4.03E−84	2.39E−03
		rs2287019	19	46,202,172	*QPCTL*	C	T	8.60E−10	1.85E−02
Combined BMI	BE	rs2820292	1	201,784,287	*NAV1*	C	A	1.83E−10	2.60E−03
		rs205262	6	34,563,164	*C6orf106*	G	A	1.75E−10	2.86E−02
		rs7141420	14	79,899,454	*NRXN3*	T	C	1.23E−14	1.23E−02
		rs17724992	19	18,454,825	*PGPEP1*	A	G	3.42E−08	3.11E−03
Combined BMI	EA	rs13021737	2	632,348	*TMEM18*	G	A	1.11E−50	1.60E−02
		rs1516725	3	185,824,004	*ETV5*	C	T	1.89E−22	1.06E−02
		rs2245368	7	76,608,143	*PMS2L11*	C	T	3.19E−08	1.71E−02
		rs12429545	13	54,102,206	*OLFM4*	A	G	1.09E−12	2.07E−05
		rs1558902	16	53,803,574	*FTO*	A	T	7.51E−153	1.33E−03
		rs1000940	17	5,283,252	*RABEP1*	G	A	1.28E−08	6.60E−03
		rs1808579	18	21,104,888	*C18orf8*	C	T	4.17E−08	1.64E−02
	BE/EA	rs2820292	1	201,784,287	*NAV1*	C	A	1.83E−10	9.17E−03
		rs2121279	2	143,043,285	*LRP1B*	T	C	2.31E−08	2.06E−02
		rs1516725	3	185,824,004	*ETV5*	C	T	1.89E−22	2.32E−02
		rs12429545	13	54,102,206	*OLFM4*	A	G	1.09E−12	2.70E−04
		rs16951275	15	68,077,168	*MAP2K5*	T	C	1.91E−17	4.43E−02
		rs1558902	16	53,803,574	*FTO*	A	T	7.51E−153	2.39E−03
		rs2287019	19	46,202,172	*QPCTL*	C	T	4.59E−18	1.85E−02
Male WHR	BE	No SNPs with same allelic effect direction and with $P < 0.05$ in BE/EA							
	EA	rs1936805	6	127,452,116	*RSPO3*	T	C	5.401E−10	4.79E−02
	BE/EA	No SNPs with same allelic effect direction and with $P < 0.05$ in BE/EA							
Female WHR	BE	rs10919388	1	170,372,503	*GORAB*	C	A	1.13E−08	8.96E−04
		rs2645294	1	119,574,587	*TBX15-WARS2*	T	C	1.28E−09	4.10E−02
	EA	rs10919388	1	170,372,503	*GORAB*	C	A	1.13E−08	4.88E−02
		rs1106529	1	119,531,497	*TBX15*	A	G	1.91E−09	2.55E−02
	BE/EA	rs10919388	1	170,372,503	*GORAB*	C	A	1.13E−08	8.96E−04
		rs2645294	1	119,574,587	*TBX15-WARS2*	T	C	1.28E−09	1.50E−02
		rs1106529	1	119,531,497	*TBX15*	A	G	1.91E−09	2.56E−02
Combined WHR	BE	rs2645294	1	119,574,587	*TBX15-WARS2*	T	C	3.41E−12	4.10E−02
		rs2071449	12	54,428,011	*HOXC4-HOXC6*	A	C	3.85E−12	1.33E−02
	EA	rs1106529	1	119,531,497	*TBX15*	A	G	2.94E−12	2.55E−02
Combined WHR	BE/EA	rs1106529	1	119,531,497	*TBX15*	A	G	2.94E−12	2.56E−02
		rs2645294	1	119,574,587	*TBX15-WARS2*	T	C	3.41E−12	1.50E−02
		rs2071449	12	54,428,011	*HOXC4-HOXC6*	A	C	3.85E−12	1.97E−02

Note: P_obesity is the association *P* value extracted from the GWAS data by Locke and colleagues (17) for the BMI trait and by Shungin and colleagues (18) for WHR trait. P_Barrett-phenotype is the association *P* value for BE, EA, and BE/EA extracted from the meta-analysis by Gharahkhani and colleagues (4).

In conclusion, to our knowledge, the present study is the first systematic genome-wide investigation of the shared genetic etiology of Barrett's phenotypes and obesity-related traits. The data suggest, and for the first time quantify, shared genetic factors that are particularly relevant in terms of progression from BE to EA, and that dietary and lifestyle interventions may therefore be beneficial for BE patients. The data also indicate sex differences in terms of the mechanisms that underlie the association between obesity-related traits and progression from BE to EA. Further research is warranted to elucidate the mechanisms and biological factors that underlie the potential pleiotropic effects.

Disclosure of Potential Conflicts of Interest

R.C. Fitzgerald is an advisor for Medtronic. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: A.C. Böhmer, J. Hecker, J.R. Izbicki, B. Schumacher, Y. Vashist, D.C. Whiteman, I. Gockel, J. Schumacher

Development of methodology: A.C. Böhmer, B. Schumacher, D.C. Whiteman

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A.C. Böhmer, A. May, C. Gerges, M. Anders, J. Becker, T. Hess, R. Thieme, T. Noder, M. Venerito, T. Schmidt, C. Fuchs, A.H. Hölscher, A. Dietrich, Y. Moulla, O. Lyros, H. Lang, D. Lorenz, B. Schumacher, R. Mayershofer, Y. Vashist, K. Ott, M. Vieth, J. Weismüller, S. Moebus, H. Neuhaus, T. Rösch, C. Ell, M.M. Nöthen, D.C. Whiteman, I. Tomlinson, R.C. Fitzgerald, C. Palles, T.L. Vaughan, I. Gockel

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.C. Böhmer, J. Hecker, J. Schröder, P. Gharahkhani, T. Hess, T. Schmidt, A. Dietrich, Y. Vashist, M. Vieth, M. Knapp, J. Jankowski, I. Gockel, A.P. Thrift, H. Fier, J. Schumacher

Writing, review, and/or revision of the manuscript: A.C. Böhmer, J. Hecker, J. Schröder, P. Gharahkhani, C. Gerges, M. Venerito, T. Schmidt, A. Dietrich, O. Lyros, H. Lang, B. Schumacher, Y. Vashist, K. Ott, M. Vieth, J. Weismüller, H. Neuhaus, M.M. Nöthen, D.C. Whiteman, J. Jankowski, R.C. Fitzgerald, T.L. Vaughan, I. Gockel, A.P. Thrift, J. Schumacher

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): N. Kreuser, R. Thieme, M. Venerito, L. Veits, C. Fuchs, J.R. Izbicki, B. Schumacher, Y. Vashist, K. Ott, M. Vieth, S. Moebus, M.M. Nöthen, I. Gockel

Study supervision: A.C. Böhmer, J.R. Izbicki, B. Schumacher, D.C. Whiteman, J. Jankowski, I. Gockel, J. Schumacher

Acknowledgments

The authors thank all affected individuals and their families, and all controls, for their participation. The authors acknowledge the contribution of all centers and hospitals for sample collection. A full list of centers and hospitals from the United Kingdom is provided in the Supplementary Material. The authors thank Stuart MacGregor for contributing to this work and insightful comments. This work was supported by the BONFOR-program of the Medical Faculty, University of Bonn (grant number O-149.0121). A.C. Böhmer is supported by the DietBodyBrain (DietBB) Competence Cluster in Nutrition Research, which is funded by the German Federal Ministry of Education and Research (grant number 01EA1809B). J. Hecker and H. Fier received support from the Cure Alzheimer's Fund; the National Institute of Mental Health (grant numbers R01MH081862 and R01MH087590); the National Human Genome Research Institute (grant number R01HG008976); and the National Heart, Lung, and Blood Institute (grant numbers U01HL089856, U01HL089897, P01HL120839, and P01HL132825). J. Schumacher received support for this work from the Else Kröner Fresenius Foundation (grant number 2013_A118). The laboratory of R.C. Fitzgerald is funded by a Core Programme Grant from the Medical Research Council (grant number RG84369). The authors thank the Human Research Tissue Bank, which is supported by the UK National Institute for Health Research (NIHR) Cambridge Biomedical Research Centre, from Addenbrooke's Hospital. Additional infrastructure support was provided from the Cancer Research UK–funded Experimental Cancer Medicine Centre.

The MD Anderson controls were drawn from dbGaP (study accession: phs000187.v1.p1). Genotyping of these controls was done through The University of Texas MD Anderson Cancer Center (UTMDACC) and the Johns Hopkins University Center for Inherited Disease Research (CIDR). We acknowledge the principal investigators of this study: Christopher Amos, Qingyi Wei, and Jeffrey E. Lee. Controls from the Genome-Wide Association Study of Parkinson Disease were obtained from dbGaP (study accession: phs000196.v2.p1). This work, in part, used data from the National Institute of Neurological Disorders and Stroke (NINDS) dbGaP database from the CIDR:NeuroGenetics Research Consortium Parkinson's disease study. We acknowledge the principal investigators and coinvestigators of this study: Haydeh Payami, John Nutt, Cyrus Zabetian, Stewart Factor, Eric Molho, and Donald Higgins. Controls from the Chronic Renal Insufficiency Cohort (CRIC) were drawn from dbGaP (study accession: phs000524.v1.p1). The CRIC study was done by the CRIC investigators and supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Data and samples from CRIC reported here were supplied by NIDDK Central Repositories. This report was not prepared in collaboration with investigators of the CRIC study and does not necessarily reflect the opinions or views of the CRIC study, the NIDDK Central Repositories, or the NIDDK. We acknowledge the principal investigators and the project officer of this study: Harold I. Feldman, Raymond R. Townsend, Lawrence J. Appel, Mahboob Rahman, Akinlolu Ojo, James P. Lash, Jiang He, Alan S. Go, and John W. Kusek.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received April 8, 2019; revised July 9, 2019; accepted November 15, 2019; published first November 20, 2019.

References

1. Reid BJ, Li X, Galipeau PC, Vaughan TL. Barrett's oesophagus and oesophageal adenocarcinoma: time for a new synthesis. Nat Rev Cancer 2010;10:87–101.
2. Coleman HG, Xie SH, Lagergren J. The epidemiology of esophageal adenocarcinoma. Gastroenterology 2018;154:390–405.
3. Arnold M, Soerjomataram I, Ferlay J, Forman D. Global incidence of oesophageal cancer by histological subtype in 2012. Gut 2015;64:381–7.
4. Gharahkhani P, Fitzgerald RC, Vaughan TL, Palles C, Gockel I, Tomlinson I, et al. Genome-wide association studies in oesophageal adenocarcinoma and Barrett's oesophagus: a large-scale meta-analysis. Lancet Oncol 2016;17:1363–73.
5. Ek WE, Levine DM, D'Amato M, Pedersen NL, Magnusson PK, Bresso F, et al. Germline genetic contributions to risk for esophageal adenocarcinoma, Barrett's esophagus, and gastroesophageal reflux. J Natl Cancer Inst 2013;105:1711–8.
6. Spechler SJ, Souza RF. Barrett's esophagus. N Engl J Med 2014;371:836–45.
7. Hvid-Jensen F, Pedersen L, Drewes AM, Sorensen HT, Funch-Jensen P. Incidence of adenocarcinoma among patients with Barrett's esophagus. N Engl J Med 2011;365:1375–83.
8. Lagergren J. Influence of obesity on the risk of esophageal disorders. Nat Rev Gastroenterol Hepatol 2011;8:340–7.
9. Hoyo C, Cook MB, Kamangar F, Freedman ND, Whiteman DC, Bernstein L, et al. Body mass index in relation to oesophageal and oesophagogastric junction adenocarcinomas: a pooled analysis from the International BEACON Consortium. Int J Epidemiol 2012;41:1706–18.
10. Kubo A, Cook MB, Shaheen NJ, Vaughan TL, Whiteman DC, Murray L, et al. Sex-specific associations between body mass index, waist circumference and the risk of Barrett's oesophagus: a pooled analysis from the international BEACON consortium. Gut 2013;62:1684–91.
11. Corley DA, Kubo A, Levin TR, Block G, Habel L, Zhao W, et al. Abdominal obesity and body mass index as risk factors for Barrett's esophagus. Gastroenterology 2007;133:34–41; quiz 311.
12. Karastergiou K, Smith SR, Greenberg AS, Fried SK. Sex differences in human adipose tissues – the biology of pear shape. Biol Sex Differ 2012;3:13.

13. Pischon T, Boeing H, Hoffmann K, Bergmann M, Schulze MB, Overvad K, et al. General and abdominal adiposity and risk of death in Europe. N Engl J Med 2008; 359:2105–20.
14. Steffen A, Huerta JM, Weiderpass E, Bueno-de-Mesquita HB, May AM, Siersema PD, et al. General and abdominal obesity and risk of esophageal and gastric adenocarcinoma in the European prospective investigation into cancer and nutrition. Int J Cancer 2015;137:646–57.
15. Thrift AP, Shaheen NJ, Gammon MD, Bernstein L, Reid BJ, Onstad L, et al. Obesity and risk of esophageal adenocarcinoma and Barrett's esophagus: a Mendelian randomization study. J Natl Cancer Inst 2014;106. doi: 10.1093/jnci/dju252.
16. Bulik-Sullivan B, Finucane HK, Anttila V, Gusev A, Day FR, Loh PR, et al. An atlas of genetic correlations across human diseases and traits. Nat Genet 2015;47: 1236–41.
17. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, et al. Genetic studies of body mass index yield new insights for obesity biology. Nature 2015;518: 197–206.
18. Shungin D, Winkler TW, Croteau-Chonka DC, Ferreira T, Locke AE, Magi R, et al. New genetic loci link adipose and insulin biology to body fat distribution. Nature 2015;518:187–96.
19. Bulik-Sullivan BK, Loh PR, Finucane HK, Ripke S, Yang J; Schizophrenia Working Group of the Psychiatric Genomics Consortium, et al. LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. Nat Genet 2015;47:291–5.
20. Lindström S, Finucane H, Bulik-Sullivan B, Schumacher FR, Amos CI, Hung RJ, et al. Quantifying the genetic correlation between multiple cancer types. Cancer Epidemiol Biomarkers Prev 2017;26:1427–35.
21. Corley DA, Kubo A, Zhao W. Abdominal obesity and the risk of esophageal and gastric cardia carcinomas. Cancer Epidemiol Biomarkers Prev 2008;17:352–8.
22. Kubo A, Corley DA. Body mass index and adenocarcinomas of the esophagus or gastric cardia: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2006;15:872–8.
23. Edelstein ZR, Farrow DC, Bronner MP, Rosen SN, Vaughan TL. Central adiposity and risk of Barrett's esophagus. Gastroenterology 2007;133:403–11.
24. Claussnitzer M, Dankel SN, Kim KH, Quon G, Meuleman W, Haugen C, et al. FTO obesity variant circuitry and adipocyte browning in humans. N Engl J Med 2015;373:895–907.
25. Greenberg AS, Obin MS. Obesity and the role of adipose tissue in inflammation and metabolism. Am J Clin Nutr 2006;83:461S–5S.
26. Calle EE, Thun MJ. Obesity and cancer. Oncogene 2004;23:6365–78.