Supplementary materials for the manuscript *Multi-trait Genetic Association Analysis identifies 50 new risk loci for gastroesophageal reflux, seven new loci for Barrett's esophagus and provides insights into clinical heterogeneity in reflux diagnosis*

Table of Contents

Online methods

S1. Selection of proxy traits for the multi-trait GWAS analysis

GERD. To improve power to identify GERD loci, we selected traits genetically correlated with GERD based on availability of very large sample sizes in the respective trait GWASs (N > 100,000) and the strength of the estimated genetic correlation, rg. We considered the traits which were found to be correlated with GERD in An et al [1]; for our MTAG analysis our power derives from traits which have both large sample sizes and at least moderate correlation with GERD. We hence selected genetically correlated traits with very strong evidence of statistical association where (abs(rg) > 0.3 with rg p-value <1e-20). Using these criteria, we selected body mass index (BMI), Major Depressive Disorder (MDD) and educational attainment (EDU) to be incorporated alongside GERD in the multi-trait GWAS (Figure 1).
[GERD multi trait model includes: GERD, BMI, MDD, EDU]

Barrett's Esophagus (BE). Given the high correlation between GERD and BE (rg =0.5) [1], we also performed a multi-trait analysis with BE added to the model.
[BE multi trait model includes: BE, GERD, BMI, MDD, EDU]

S2. Phenotypic definition for GERD and BE used in the main analysis

GERD. We used the summary statistics obtained from our most recent GERD GWAS meta-analysis[1] combining data from the UK Biobank (UKB) and QSkin[2] studies (excluding the 23andMe cohort), including up to 78,707 cases and 288,734 individuals with no history of GERD-related diagnosis or no use of GERD-related medication as controls. Data on GERD was retrieved across several data fields in the UKBB: self-report (Field ID: 20002), ICD-10 diagnosis (FID: 41202, 41204), ICD-9 diagnosis (FID: 41203, 41205), operative procedures (FID: 41200, 41210) and use of GERD-related medications (See Supplementary Table 3 from An et al.[1]). Presence of any GERD diagnosis on any of the above data-fields (including GERD medications) were regarded as an indicator for GERD. Individuals that did not have any history or occurring conditions of disorders in their upper digestive system were defined as controls. GERD cases were defined based on a combination of the use of GERD medication, self-reported GERD symptoms such as heartburn, and hospital records (ICD-10), although we have previously shown very strong genetic similarity (i.e. rg>0.9) between these broad GERD definitions and clinically diagnosed GERD[1]. The precise definition for GERD used both UK Biobank and QSKIN separately was provided in **Online methods S3**.

BE. We similarly used the summary statistics obtained from the largest BE GWAS meta-analysis combining data from the UKB and the esophageal cancer consortium (See Online methods S3.6 for description of this dataset). In the UKB, BE cases were determined through ICD10 codes (K22.7); for the other studies diagnosis of BE were obtained through clinically verified. However, despite differences in case definition for BE, both datasets had compatible genetic architecture with very high genetic correlations (rg=0.8).

S3. Description of studies and/or data sources (including replication datasets)

The brief description for each input GWAS in the multi-trait GWAS analysis and the equivalent effect sample size is shown in **Supplementary Table ST1**.

S3.1 GERD GWAS meta-analysis combining UKB and QSKIN

GERD in the UK Biobank study The UK Biobank is a large-scale population-based cohort consisting of more than half a million middle aged participants recruited from the United Kingdom. Participants reported information ranging from self-reported lifestyle, anthropometric measurements, mental health, up to clinical diagnosis of diseases obtained through linkage with national registries and hospital records. Detailed description of the genotyping and genetic imputation of the UK Biobank participants have been previously provided[3]. We defined GERD cases with a mixture of self-reported GERD symptoms, ICD-10 diagnosis and GERD related medication as outlined above.

GERD in the QSKIN study The QSkin cohort[2] is a population-based cohort study conducted by the QIMR Berghofer Medical Research Institute to investigate risk factors for skin cancers and other complex diseases in Queensland, Australia. Ethics approval was granted by the Human Research Ethics Committee of the QIMR Berghofer Medical Research Institute. QSkin participants provided written consent to participate in the study. In QSkin, GERD cases were defined as individuals who self-reported heartburn and took one or more types of GERD-related medications, identified through medical linkage with the Australian PBS database that captures the use of all prescription medicines. Individuals with conflicting self-reported GERD and inference of GERD through medical linkage were removed from the analysis. The summary GWAS results for 2,987 GERD cases and 10,169 controls were then meta-analysed with the UK Biobank GERD GWAS, as described in An et al.[1]

S3.2 BMI GWAS from meta-analysis of UK Biobank and the GIANT consortium

The GIANT consortium consists of numerous large scale studies around the world involved in genetic analyses on anthropometric phenotypes. Detailed information about the phenotypes and genetic data gathered from these studies have been previously reported. For our multi-trait analysis, we obtained the summary level data for the European BMI GWAS meta-analysis (n=681,275) combining data from the UK Biobank and GIANT consortium through the GIANT online repository (https://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files), as published in Yengo et al.[4]

S3.3 Major Depressive Disorder GWAS from PGC and UK Biobank GWA meta-analysis

The Psychiatric Genomics Consortium (PGC) is the world's largest consortium for the genetic analysis of psychiatric and behavioural phenotypes. The major depressive disorder (MDD) GWAS summary statistics used in the present analysis (cases=170,756; controls=329,443) was a GWA meta-analysis of the MDD genetic estimates between UK Biobank, 23andMe and participating studies from the PGC evaluated among individuals of European ancestry, with details on the genetic and phenotypic QC described in Howard et al. 2019.[5] We obtained the version of the MDD summary statistics excluding the 23andMe cohort (to prevent biased estimates in the replication analysis) directly through the PGC online repository accessible here via https://www.med.unc.edu/pgc/download-results/mdd/.

S3.4 Education Attainment GWAS from SSGAC

The Social Science Genetic Association Consortium (SSGAC) is a collective platform for both medical researchers and social scientists to coordinate genetic association studies for social science outcomes. We obtained the summary statistics for the largest European education attainment GWAS

(Lee et al. 2018[6]) to date (n=766,345) from the SSGAC public data repository (https://www.thessgac.org/data). The education attainment GWAS was conducted on 1.1 million participants of European ancestry. Specific detail on phenotype definitions adopted for each participating study, genetic QC and study characteristics were previously reported.

S3.5 Risk of Barrett's Esophagus and Esophageal Adenocarcinoma from GWAS meta-analysis combining UK Biobank, BEACON, Bonn, Cambridge and Oxford studies

Summary The BE GWAS summary statistics adopted for the multi-trait GWAS (MTAG) analysis were drawn from a GWAS-meta-analysis combining UKB with a broader collective, including Barrett's and Esophageal Adenocarcinoma Consortium (BEACON), Bonn, Cambridge and Oxford studies, totalling 9,680 cases[1]. Clinical diagnosis for BE cases from UKB were derived through hospital records (ICD-10), while BE cases from other studies were pathologically verified[7]. Both the GWAS estimates for BE in the esophageal cancer collective (BEACON, Bonn, Cambridge and Oxford) and BE from the UKB were combined using fixed effect meta-analysis models (METAL software[8]). These GWAS results were previously reported in the An et al. [1] GWAS article. Descriptions of the individual BE GWASs are provided below.

BE in BEACON, Bonn, Cambridge and Oxford studies. The largest GWAS meta-analysis to date for histologically verified Barrett's Esophagus and esophageal adenocarcinoma susceptibility was previously published in the Gharahkhani et al. 2016 study.[7] These genetic estimates combine GWAS findings from participating studies from the BEACON consortium, the Bonn study from Germany, and the Cambridge and Oxford studies from the UK. Precise breakdown of the baseline characteristics, phenotypic definitions adopted, genetic QC and number of cases for each study had been previously reported.[7] Participants involved in these GWAS studies did not overlap with those that participated in the primary GERD GWAS (UKB + QSkin). All participants provided informed consent, and ethics approval was granted from the relevant human research ethics committee of each participating institution.[7] Summary statistics for BE, EA and the combined BE+EA phenotype (BE/EA) were obtained through a written request to the BEACON working group and group authors for the Bonn, Cambridge and Oxford studies. Note that the BE/EA results were only used for the genetic prediction analysis from GERD subgroup analyses (see Online methods S6.2). The BE MTAG analysis (only BE were used) only used the GWAS meta-analysis between the UKB BE GWAS and the Gharahkhani et al. BE GWAS [7], alongside GWAS estimates from other proxy traits (GERD, BMI, MDD, EDU; see Online methods S4).

BE in UK Biobank Clinical diagnosis for BE cases from UKB were derived through hospital records (ICD-10). The relevant datafield to extract these information were the UKBB field ID 41202 and 41204 (field for ICD10 main and secondary diagnosis) using ICD-10 code: K227 (corresponding to K22.7). EA was defined in a similar fashion using ICD10 definitions (using all code with prefix matching "C15"); however, **for our MTAG analyses on BE, we did not include patients diagnosed with EA as cases nor controls**.The number of BE cases in the UKB dataset at the time of the analysis was 2831. The GWAS for BE in the UKB was performed using 250,910 healthy controls (i.e. people who did not self-report nor have medical history indicative of any disorder in their upper digestive system) and 2831 BE cases.

S4 Multi-trait GWAS analysis for GERD and BE

The Multi-Trait Analysis of GWAS (MTAG) framework is a method for combining GWAS summary statistics[9]. It performs a generalized multi-trait GWAS meta-analysis for different traits and accounts for sample overlap and incomplete genetic correlation. We performed a MTAG on GERD, leveraging the (genetic) correlation structure with BMI, MDD and EDU (**Figure 1**). Briefly, MTAG first estimates the pairwise genetic correlation between each trait against GERD using LD-score regression[10], then uses these estimates to calibrate the variance-covariance matrix of the random effect component in the model while adequately adjusting for structural variation (sample overlap and population stratification), and then performs a random-effect meta-analysis to generate the (meta-analysed) SNP-level summary statistics [9]. A key feature is that MTAG produces genome-wide results separately for each input trait. That is, if one is interested in GERD then one can generate GERD-specific odds ratios and p-values which should be comparable with standard GWAS results; in practice we replicate the MTAG results in a standard GERD and BE GWAS in an independent dataset.

The MTAG analyses were performed using the MTAG software[9] written in Python, available for download at https://github.com/JonJala/mtag. The LD reference panels were obtained from the recommended source outlined in the ldsc package. We first estimated the genetic correlation between GERD and the aforementioned traits to evaluate the relative increase in power for loci detection for GERD in the multi-trait GWAS framework. The pairwise genetic correlations between GERD and BMI, MDD and EDU were evaluated using bivariate LD-score regression[10] models. For all LD-score analyses, only the EUR LD reference panel was used. Specifically, for binary traits, the population and sample prevalence of the trait were calculated and provided to LDSC prior to the regression procedure. The estimated increase in effective sample size for the MTAG output was derived based on the increase of chi-square statistics.[9] We applied all the parameters at default settings, apart from adding the --fdr flag to compute max FDR calculations. The inflation of test statistics in the MTAG output for GERD was used to derive the predicted increase in sample size. The same analysis pipeline was adopted for the MTAG BE analysis (traits included: BE, GERD, BMI, MDD, EDU).

We subsequently ran MTAG with BE added (model includes GERD, BE, BMI, MDD, EDU; **Figure 1**), with loci significantly associated with BE taken forward for replication in an independent BE sample.

S4.1 Identifying MTAG candidate loci for GERD and BE

For each MTAG analysis, genetic associations with a P-value$<5x10^{-8}$ were then clumped for linkage disequilibrium (LD) (r2 threshold=0.1) to select 1 peak SNP per independent locus using the FUMA platform[11]; each represents a statistically independent genome-wide locus for GERD/BE. The LocusZoom[12] software was used to generate regional locus plots (also known as LocusZoom plots) illustrating the LD pattern around the novel GERD/BE susceptibility loci discovered from the GERD/BE MTAG analysis. LocusZoom plots can help illustrate patterns of LD within the locus region and assist in determining the putatively causal variant in each region and/or secondary associations. We manually extract the LocusZoom plots for the region corresponding to each of the novel GERD/BE genome-wide loci via querying the region page in LocusZoom.

Note that we did not incorporate BE into the initial GERD MTAG model to allow us to independently validate the association of GERD SNPs on BE/EA in downstream analyses (see below). Given the weaker genetic correlations between BE and MDD/EDU, for the model including BE we performed sensitivity analysis with MDD and EDU dropped from the MTAG model.

S4.2 Replication analysis from 23andMe

23andMe summary statistics Detailed information on the 23andMe research team can be found in https://research.23andme.com/research/. The GWAS summary statistics derived from 23andMe samples can only be made available through direct request (dataset-request@23andMe.com).

23andMe replication procedure-GERD We sought replication of the peak SNP from each of the novel GERD MTAG loci using data from 23andMe. Informed consent from all 23andMe participants was obtained under a research protocol that was approved by the AAHRPP-accredited institutional review board, Ethical and Independent Review Services, USA. In 23andMe, participants were classified as GERD cases if they reported having ever been diagnosed with heartburn, acid reflux, or acid reflux disease, or were treated with GERD/heartburn-related medications.[13] Controls were selected based on individuals that did not have any history of (or any symptoms of) heartburn, acid reflux, or used any heartburn-related medications. Following removal of close relatives, association analysis of the 23andMe data (462,753 cases; 1,127,474 controls) was conducted using logistic regression models, with age, sex and the first five principal components as covariates. The P-values from the logistic regression were adjusted for the estimated LD-score intercept.

23andMe replication procedure-BE We sought replication of the peak SNP from each of the novel BE MTAG loci using data from 23andMe. Informed consent from all 23andMe participants was obtained under a research protocol that was approved by the AAHRPP-accredited institutional review board, Ethical and Independent Review Services, USA. In 23andMe, participants were classified as BE cases if they reported having ever been diagnosed with BE. Controls were selected based on individuals that did not report any history of BE diagnosis. Following removal of close relatives, association analysis of the 23andMe data (24,099 BE cases; 1,484,025 self-identified to not have BE) was conducted using logistic regression models, with age, sex and the first five principal components as covariates. The P-values from the logistic regression were adjusted for the estimated LD-score intercept.

S4.3 Sensitivity analyses on alternative GERD and BE definitions in MTAG model

Whilst broad phenotype combining multiple case definitions for GERD is more efficient in gene-mapping studies compared to highly refined GERD phenotypes, vaguely defined phenotypes can potentially contribute to genetic heterogeneity in the resultant MTAG output, further confounding downstream genetic inferences. Despite previously showing that the overall genetic architecture for GERD obtained using different case definitions were broadly compatible, we intend to address whether the resultant MTAG loci had consistent effect sizes across different case definitions. Here we repeated our MTAG model for GERD using (i) a UKB GWAS for GERD with cases derived solely from medication data (i.e. PPI use), (ii) self-report and (iii) with cases derived solely from ICD-10 codes; and compared the distribution of GERD SNP effect sizes against those derived from alternative MTAG models in (i), (ii) and (ii).

For BE, we performed a sensitivity MTAG analysis using only pathologically confirmed BE cases in our primary BE GWAS in the multi-trait framework. We similarly plotted the SNP effect sizes of the BE loci for the original model (using meta-BE combining ICD-10 BE and pathologically confirmed BE) against the revised model (using only pathologically confirmed BE) and estimated the correlation coefficient between the two.

S5 Post-GWAS analyses

We conducted a series of post-GWAS analyses including transcriptomic, tissue-enrichment and PheWAS analyses to unravel biological insights of the GWAS findings from the MTAG analyses.

S5.1 Transcriptome-wide association study for the MTAG GERD and BE GWAS

We followed up our GERD/BE MTAG with a transcriptome-wide association study (TWAS) analysis using metaXcan,[14] a summary statistics-based test which evaluates the association between genetically predicted expression levels and GERD based on eQTL data from a nominated tissue type. We tested three esophageal-related tissue types (esophageal mucosa, esophageal muscularis, gastroesophageal junction separately), correcting for the total number of genes tested across all 3 tissues and 2 traits (i.e. Bonferroni corrected $P=1.2x10^{-6}$, derived from 0.05 divided by 2*20,914 tests, where 20,914 is the number of genes tested across all tissues of interest, for GERD and for BE). We also implemented multiXcan[15] (an extended version of metaXcan) which re-weights the eQTL-gene association across all 44 human tissue types for more accurate calibration of effect sizes. Since multiXcan generates one weighted result per gene, the significance threshold for the multiXcan TWAS analysis was set at $P=1.43x10^{-6}$ after Bonferroni correction for 2*17,500 tests.[15]

S5.2 Tissue enrichment analysis using MAGMA

We performed a tissue enrichment analysis based on the mapped genes inferred through location proximity and eQTL information from the GTEx[16] v8 human tissue datasets using FUMA.[11] The tissue enrichment analysis was performed via MAGMA[17] as implemented directly in the FUMA platform. The FUMA platform can be accessed via https://fuma.ctglab.nl/. For the post-GWAS analysis on the entire MTAG GERD/BE genetic summary statistics, we uploaded the summary statistics to the FUMA platform and performed LD-pruning (to obtain a set of independent genome wide significant SNPs), Gene mapping and the genome-wide MAGMA analysis through the SNP2GENE and GENE2FUNC feature.

S5.3 PheWAS analysis to evaluate pleiotropic associations between novel loci and other complex traits

We conducted a Phenome-wide association study (PheWAS) to investigate the pleiotropy between novel loci and other complex traits using the Genetics OpenTarget platform (https://genetics.opentargets.org/). This was done by manually querying each of the novel GERD SNPs by RSID on the platform and retrieving SNP association with other complex traits/diseases.

S6 Evaluation of GERD genetic subgroups based on relative contribution from MDD and BMI genetic signals

Our multitrait analysis identifies novel GERD loci by leveraging the correlation between different traits but in practice the signals at some loci are driven by the effect of a SNP on psychological factors such as MDD, whilst others are driven by effects on traits such as obesity. We hence employed a simple heuristic to categorize loci associated with GERD into either i) obesity-driven GERD loci or ii) psychology-driven GERD loci or iii) loci where the situation is unclear, based on the genetic evidence of association (chi-squared statistics) with BMI (for category i) or MDD (for category ii).

Description of model. The MTAG analysis leverages genetically correlated traits to perform a cross-trait random effect meta-analysis of genetic associations for each queried trait separately. Because the MTAG-derived betas follow the same variance-covariance matrix incorporating GWAS estimation errors (and correlated errors due to overlapping samples between traits) for each SNP, patterns of heterogeneity in effect sizes can be tested by stratifying each genetic loci based on their pattern of pleiotropy (shared influence) with BMI or MDD. We can then systematically group each genetic loci based on whether its association was consistent with an influence from/with BMI (MDD vice versa), where we can define the membership for loci i as $G(i)$, we have that

Here $Z_{i,BMI}$ and $Z_{i,MDD}$ refers to the absolute z-score for loci i on BMI and MDD respectively. nF, F, U represents the obesity-driven GERD, depression-driven GERD and indeterminate subgroup for loci not fulfilling either criteria. The θ parameter is the only tuning parameter to quantify the minimal Z-score to declare evidence for an association with BMI/MDD. We set θ to be $Z = 3.45$ (or equivalently, a chi-squared value of 11.9) derived based on the equivalent z-score for a Bonferroni corrected p-value of 0.05/88. Our pragmatic classification results based on various threshold of θ were supplied in Supplementary Table (see eMethods - Supplementary Method 1), all of which made no drastic difference to the main findings.

$$G(i) = \begin{cases} nF, & z_{i,BMI} > z_{i,MDD} \cap z_{i,BMI} > \theta \\ F, & z_{i,BMI} < z_{i,MDD} \cap z_{i,MDD} > \theta \\ U, & otherwise. \end{cases}$$

To categorize a SNP as obesity-driven, we stipulated that the SNP must show strong evidence for an association (univariate chi-squared test statistic >11.9) with BMI that is greater than the association with MDD. In contrast, SNPs with MDD chi-squared values > 11.9 and with chi-squared values on MDD > BMI were categorised as depression-driven GERD SNPs. A chi-squared test statistic of 11.9 was derived from P=0.05 after bonferroni correction for 88 SNPs. The remaining SNPs were left unlabelled. We then tested whether the loci in categories (i) and (ii) have different properties in terms of

(A) their differential gene expression in various tissue types
(B) their genetic association with BE and EA risk.

S6.1 Evaluating the predicted gene expression in different tissue types

For (A), we evaluated whether the categories exhibit different patterns of tissue enrichment using MAGMA in 44 distinct human tissue types from GTEx[16]. We queried the lists of mapped GERD genes identified through through location proximity and eQTL information for subgroup (i) and (ii) separately via the *gene2func* feature in FUMA.[17]

Procedure. Upon categorising each of the 88 GERD SNPs, we retrieved all the genes associated with each of the SNP members in each subgroup and compiled two lists of genes for the non-functional and functional GERD subgroup separately. SNPs that fall in intronic regions or cannot be mapped in eQTL databases were subsequently dropped from the enrichment tests. We then inserted these gene lists (each in turn) into FUMA, and then performed the MAGMA gene-tissue enrichment analyses via

the *gene2func* feature in FUMA. We adopted all the recommended default settings and selected "all" genes for the background gene set in the MAGMA analysis.

S6.2 Estimation of GERD effect sizes on Barrett's Esophagus and esophageal adenocarcinoma (BE/EA)

For (B), we tested whether collectively the loci within each category (i-iii) are associated with risk of BE/EA; to assess this, for the SNPs in each category, we fitted a inverse-variance weighted regression model for the genetic effect size on GERD against BE/EA. As compared to the conventional unweighted regression approach, the inverse-variance weighted regression model makes different assumptions about the contribution of different GERD SNPs in predicting GERD relative to its effect size and precision. The BE/EA effect sizes were derived from a set of 6,167 BE cases, 4,112 EA cases and 17,159 controls (Gharahkhani et al.[7]) essentially independent of those used to derive the GERD effect sizes (a very small number of individuals may overlap). To increase power, for our primary analysis we combined BE and EA as a single disease phenotype (BE/EA) given BE's status as a premalignant precursor for EA and given their very high genetic correlation[7,18].

For each category (obesity-driven GERD loci only, psychology-driven GERD only, as well as all GERD loci), we also tested for genetic heterogeneity in the effect sizes on BE/EA through the Cochran Q test statistics[19]. Given obesity is associated with greater risk of EA[20], we also performed sensitivity analysis adjusting for BMI in the genetic association between obesity-driven GERD and BE/EA. This multivariable model [21] is implemented by jointly fitting the BMI effect size along with the GERD log(OR) estimates in the regression against BE/EA.

S7 Patient and Public Involvement statement

This study uses GWAS summary data and does not directly involve the use of patient level data or public involvement. The involvement of 23andMe participants and information on data consent for 23andMe data is described as follows. Informed consent from all 23andMe participants was obtained under a research protocol that was approved by the AAHRPP-accredited institutional review board, Ethical and Independent Review Services, USA. Study participants were not involved in the study design or interpretation.

Supplementary Tables

Note: See separate attachment for the Supplementary Table file containing Supplementary Table ST1-ST18.

Supplementary Figure captions

Note: All supplementary figures are attached as separate files

Supplementary Figure 1. The Quantile-to-Quantile plot for the MTAG GERD GWAS. The red dotted line represents the line at y=x under the null. The x- and y-axis refers to the expected and the observed negative log10 p-value of the association between each individual SNP and GERD susceptibility.

Supplementary Figure 2. Regional LocusZoom plot for all genome-wide GERD loci (n=88) identified in the GERD MTAG analysis

Supplementary Figure 3. Regional LocusZoom plot for the seven novel BE loci identified in the BE MTAG analysis with strong evidence of replication in the independent 23andMe cohort.

Supplementary Figure 4. Comparison of MTAG GERD genome-wide significant loci effect sizes using alternative case definitions for GERD.

Supplementary Figure 5. Comparison of MTAG BE genome-wide significant loci effect sizes between ICD-10 defined BE and pathologically verified BE cases.

Supplementary Figure 6. Venn diagram illustrating the number of genes identified to be associated with GERD and BE susceptibility using multiXcan

Supplementary Figure 7. Regulation of differential gene expression for complete MTAG GERD genes (n=267 input genes) identified in FUMA on 53 human tissues evaluated via MAGMA.

Supplementary Figure 8. GWAS catalog lookup on GERD-associated genes in FUMA. The enrichment p-value are coded in -log10(p-value) where larger values infer stronger evidence for a significant association. For each gene entry along the x-axis, a yellow block is present if the gene have been previously reported to be associated with the relevant disease/trait of interest (in the y-axis).

Supplementary Figure 9. PheWAS plot illustrating the association between each of the seven novel BE loci identified in the BE MTAG analysis against a range of complex traits from the OpenTarget platform. Each point represent the -log10 p-value of the association between the putative trait of interest and the BE-associated variant.

Supplementary Figure 10. Regulation of differential gene expression for obesity-driven GERD genes on 53 human tissues evaluated via MAGMA. Tissue expression data extracted from the GTEx v8 database.

Supplementary Figure 11. Regulation of differential gene expression for depression-driven GERD genes on 53 human tissues evaluated via MAGMA. Tissue expression data extracted from the GTEx v8 database.

Supplementary Figure 12. Gene expression heatmap showing the average expression per label (log2 transformed) across 53 human tissues for obesity-driven GERD genes. Tissue expression data extracted from the GTEx v8 database.

Supplementary Figure 13. Gene expression heatmap showing the average expression per label (log2 transformed) across 53 human tissues for depression-driven GERD genes. Tissue expression data extracted from the GTEx v8 database.

Supplementary Figure 14. Estimation of the genetic association between GERD and risk of Barrett's Esophagus only, stratified by genetic GERD subtypes. Each of the slopes represent the estimated magnitude of association between per unit increase in log(OR) of GERD on log(OR) of BE, for all GERD loci (in blue; with the 95% confidence interval bound shaded), all functional GERD loci (in green), all non-functional GERD loci (in orange) using an inverse variance weighted regression model. Points labelled unclear are those in the indeterminate subset.

Supplementary Figure 15. Estimation of the genetic association between GERD and risk of Esophageal Adenocarcinoma only, stratified by genetic GERD subtypes. Each of the slopes represent the estimated magnitude of association between per unit increase in log(OR) of GERD on log(OR) of EA, for all GERD loci (in blue; with the 95% confidence interval bound shaded), all functional GERD loci (in green), all non-functional GERD loci (in orange) using an inverse variance weighted regression model. Points labelled unclear are those in the indeterminate subset.

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