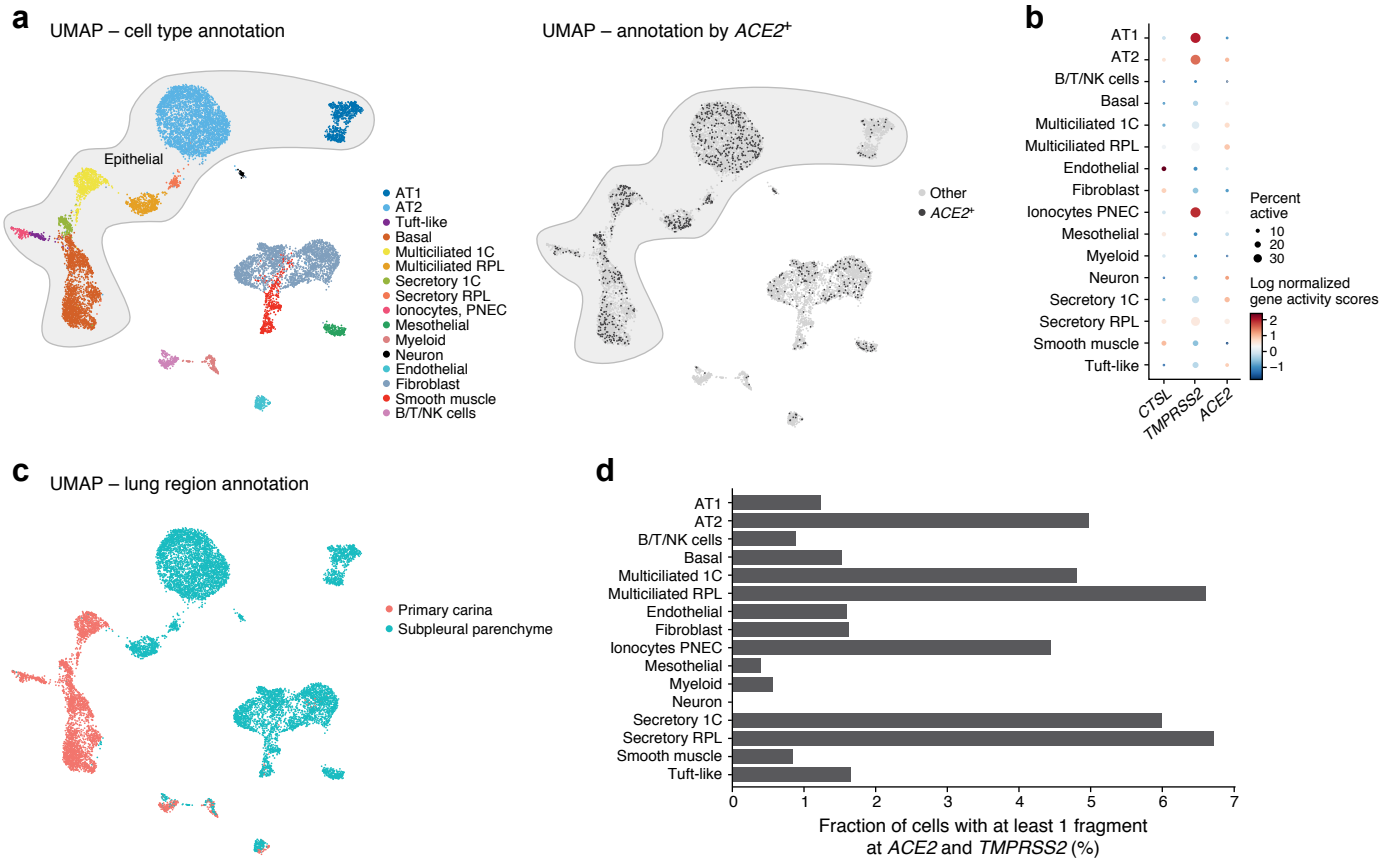
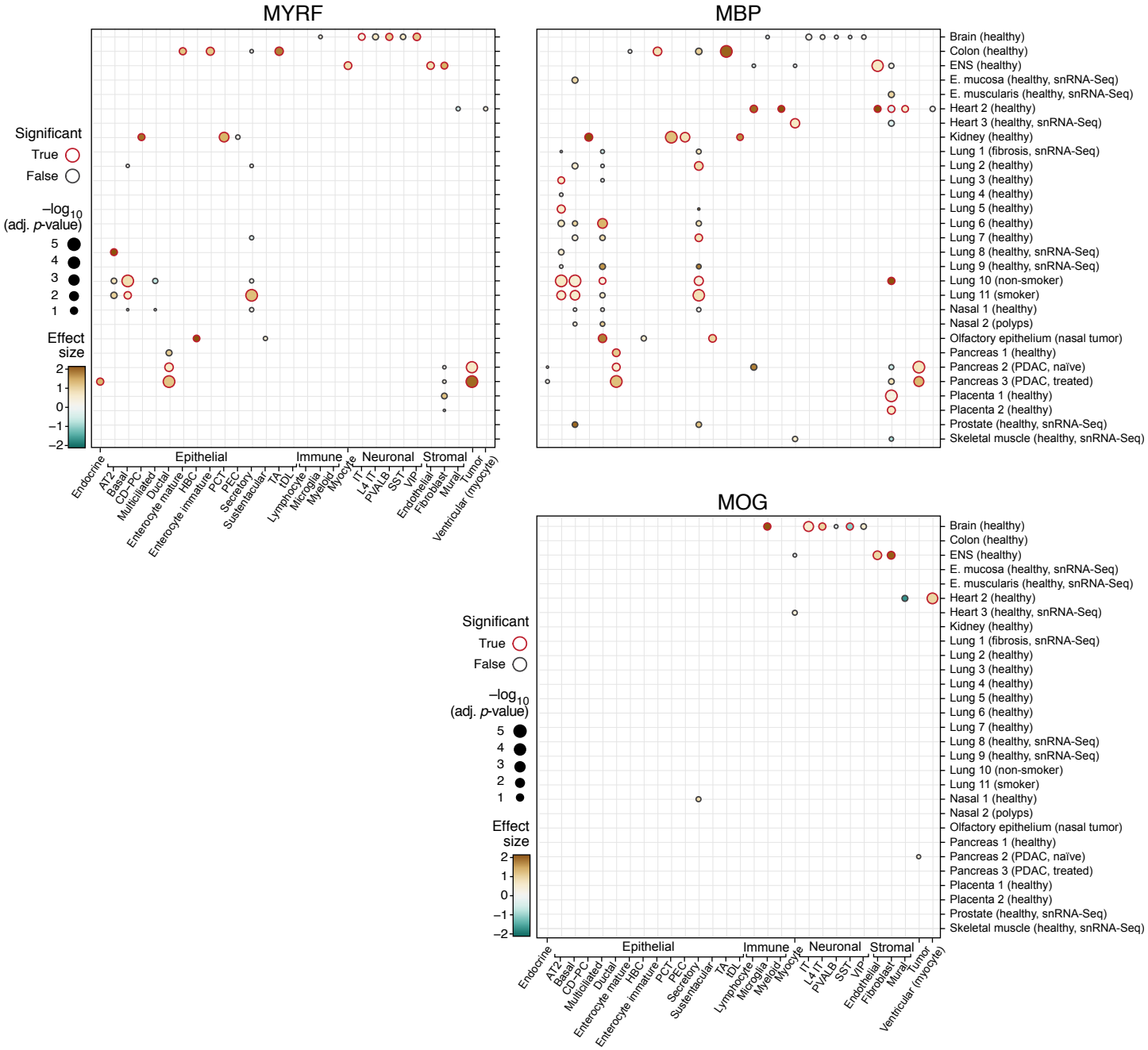
Supplementary Figure 1



Supplementary Fig. 1. Open chromatin at the *ACE2* and *TMPRSS2* loci in AT2, ciliated and secretory cells in the lung and airways

(a,c) Single-cell ATAC-seq of lung samples from primary carina (1C) and subpleural parenchyme (RPL) (*n*=1 patient, *k*=3 samples, 3,366 cells from 1C, 8,340 cells from RPL). Uniform Manifold Approximation and Projection (UMAP) embedding of scATAC-seq profiles (dots) colored by (a, left) cell types, (a, right) cells with at least 1 fragment (indicating accessibility, open chromatin) mapping to the *ACE2* gene locus (defined as -2kb upstream the Transcription Start Site to Transcription End Site), grey shaded area indicates epithelial cell types., or by sample location (c). (b) Inferred gene activity of *ACE2, TMPRSS2, CTSL* across cell types. Log normalized mean "scATAC activity score" (quantified from accessibility, open chromatin) (dot color) and proportion of cells with active scores (dot size) for *ACE2, TMPRSS2,* and *CTSL* (columns) across different cell types (rows) from the primary carina (1C) and subpleural parenchyme (RPL). (d) Some AT2, ciliated and secretory cells have accessible chromatin at both *ACE2* and *TMPRSS2* loci. Proportion of cells (*x* axis) in each cell type (*y* axis) with accessible chromatin (at least 1 fragment) at both the *ACE2* and *TMPRSS2* loci (defined as -2kb upstream of the Transcription Start Site to Transcription End Site).

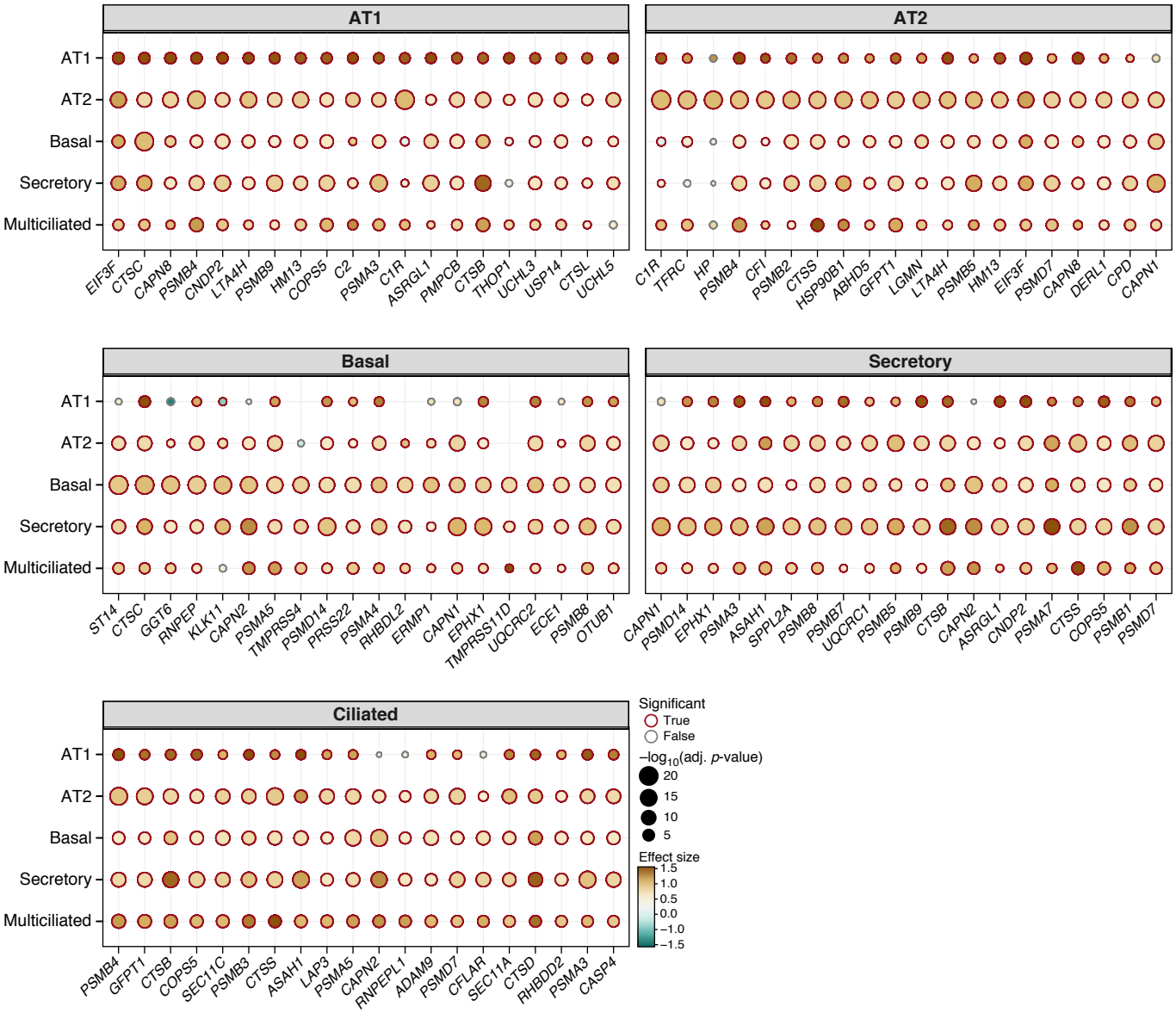
Supplementary Figure 2



Supplementary Fig. 2. Co-expression of *ACE2* and *MYRF, MBP, MOG*.

Co-expression of *ACE2* and *MYRF, MBP*, *MOG* in select single-cell datasets. P-values and significance (FDR 10%) derived from the logistic mixed-effects model.

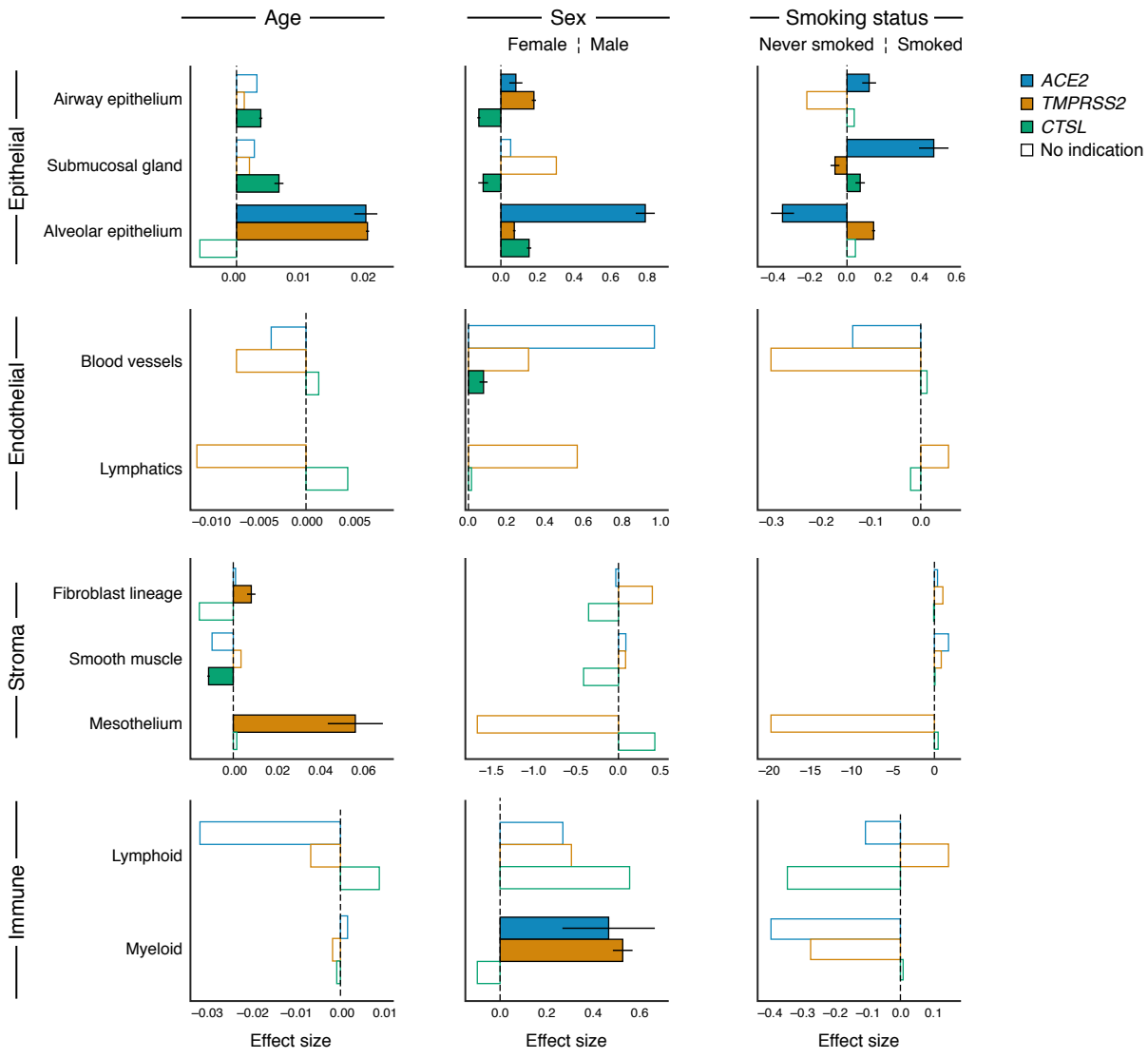
Supplementary Figure 3



Supplementary Fig. 3. *ACE2*-protease co-expression of the top 20 most significantly co-expressed human proteases in key lung epithelial cell types.

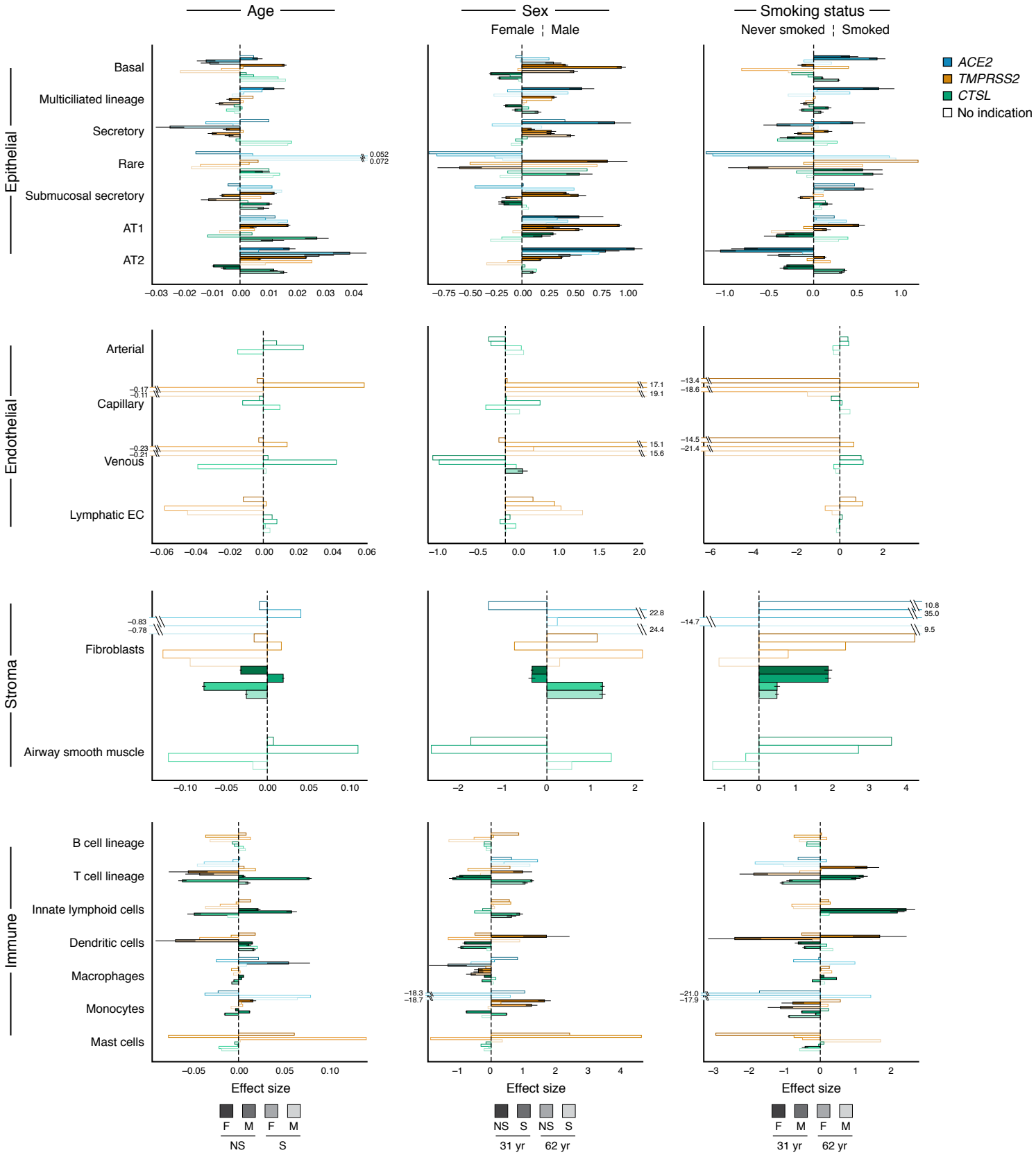
Significance (dot size) and effect size (dot color) of co-expression of each protease (columns) with *ACE2* in each cell subset (rows).

Supplementary Figure 4



Supplementary Fig. 4. Age, sex, and smoking status associations with expression of *ACE2*, *TMPRSS2*, and *CTSL* across level 2 cell type annotations modeled without interaction terms. Age, sex, and smoking assocations with expression of *ACE2* (blue), *TMPRSS2* (yellow), and *CTSL* (green) modeled without interaction terms on 985,420 cells from 164 donors. Level 2 cell types are shown on the y-axes, and are subdivided by level 1 cell type annotations (top to bottom: epithelial, endothelial, stromal and immune cells). The effect size (x axis) is given as a log fold change (sex, smoking status) or the slope of log expression per year (age). Positive effect sizes indicate increases with age, in males, and in smokers. As the age effect size is given per year, it is not directly comparable to the sex and smoking status effect sizes. Colored bars: associations with an FDR-corrected p-value<0.05 (one-sided Wald test on regression model coefficients), consistent effect direction in pseudo-bulk analysis, and consistent results using the model with interaction terms (**Methods**). White bars: associations that do not pass all of the three above-mentioned evaluation criteria. Error bars: standard errors around coefficient estimates. Error bars are only shown for colored bars (indications or robust trends) to limit figure size. Only cell types with at least 1000 cells across donors are included. Number of cells and donors per cell type: Airway epithelium: 218787, 161, Submucosal gland: 33661, 45, Alveolar Epithelium: 185485, 106, Blood vessels: 42519, 79, Lymphatics: 5055, 76, Fibroblast lineage: 53166, 94, Smooth muscle: 16272, 61, Mesothelium: 2490, 29, Lymphoid: 132777, 134, Myeloid: 246957 cells, 121 donors.

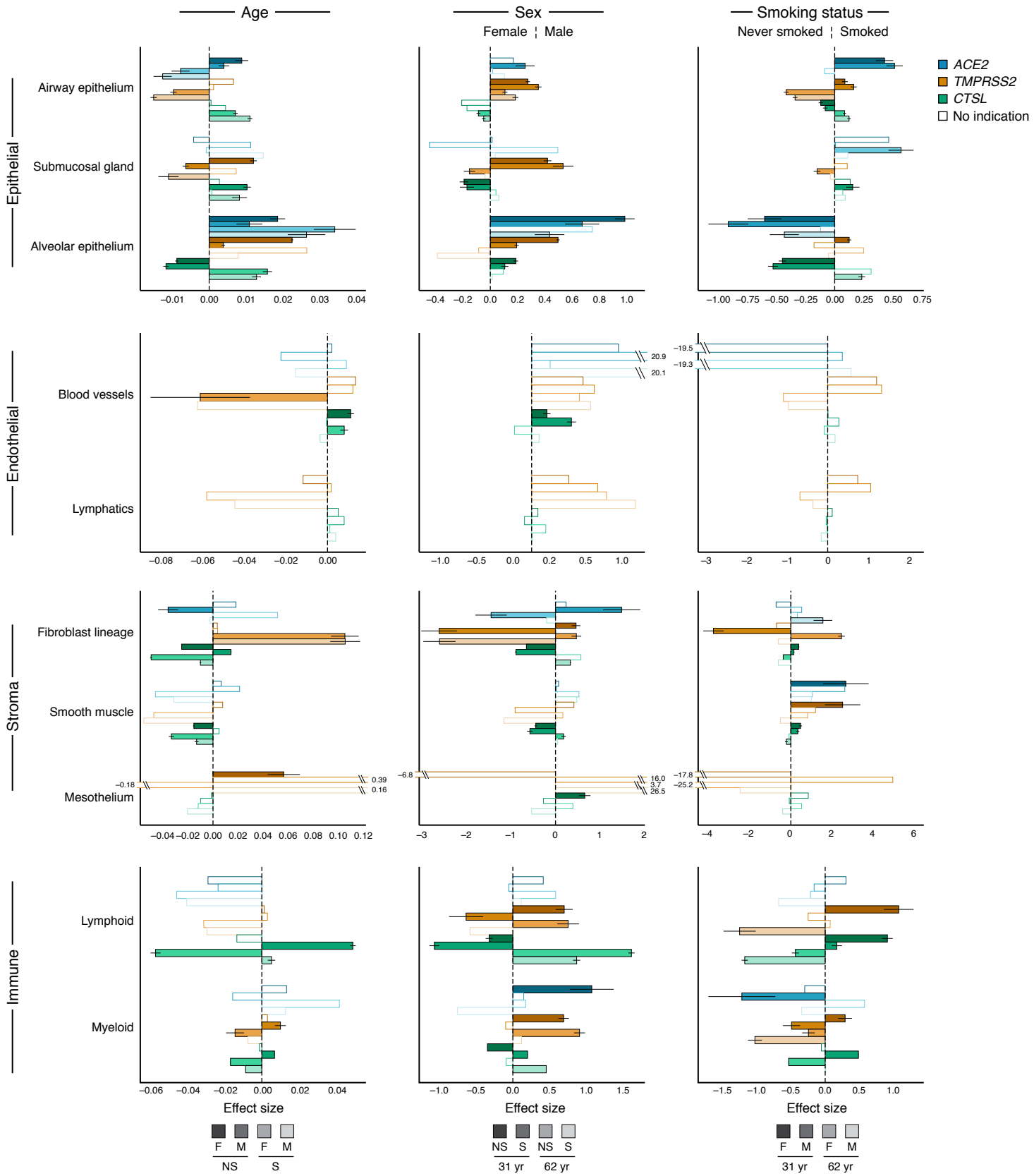
Supplementary Figure 5



Supplementary Fig. 5. Age, sex, and smoking status associations with expression of *ACE2*, *TMPRSS2*, and *CTSL* across level 3 cell type annotations modeled with interaction terms.

Age, sex, and smoking assocations with expression of *ACE2* (blue), *TMPRSS2* (yellow), and *CTSL* (green) modeled with interaction terms on 985,420 cells from 164 donors. Level 3 cell types are shown on the y-axes, and are subdivided by level 1 cell type annotations (top to bottom: epithelial, endothelial, stromal and immune cells). The effect size (x axis) is given as a log fold change (sex, smoking status) or the slope of log expression per year (age). Positive effect sizes indicate increases with age, in males, and in smokers. As the age effect size is given per year, it is not directly comparable to the sex and smoking status effect sizes. Colored bars: associations with an FDR-corrected p-value<0.05 (one-sided Wald test on regression model coefficients) and a consistent effect direction in pseudo-bulk analysis (**Methods**). White bars: associations that do not pass the two above-mentioned evaluation criteria. Error bars: standard errors around coefficient estimates. Error bars are only shown for colored bars (indications or robust trends) to limit figure size. Only cell types with at least 1000 cells across donors are included. Number of cells and donors per cell type: Basal: 155877, 105, Multiciliated lineage: 37530, 157, Secretory: 22306, 140, Rare: 2676, 71, Submucosal secretory: 33661, 45, AT1: 29973, 101, AT2: 155512, 104, Arterial: 3497, 37, Capillary: 15745, 34, Venous: 7173, 33, Lymphatic EC: 5055, 76, Fibroblasts: 9112, 51, Airway smooth muscle: 1077, 13, B cell lineage: 11761, 90, T cell lineage: 52139, 97, Innate lymphoid cells: 29836, 56, Dendritic cells: 9017, 90, Macrophages: 156964, 89, Monocytes: 42703, 96, Mast cells: 13581 cells, 88 donors. AT1, 2: alveolar type 1, 2. EC: endothelial cell.

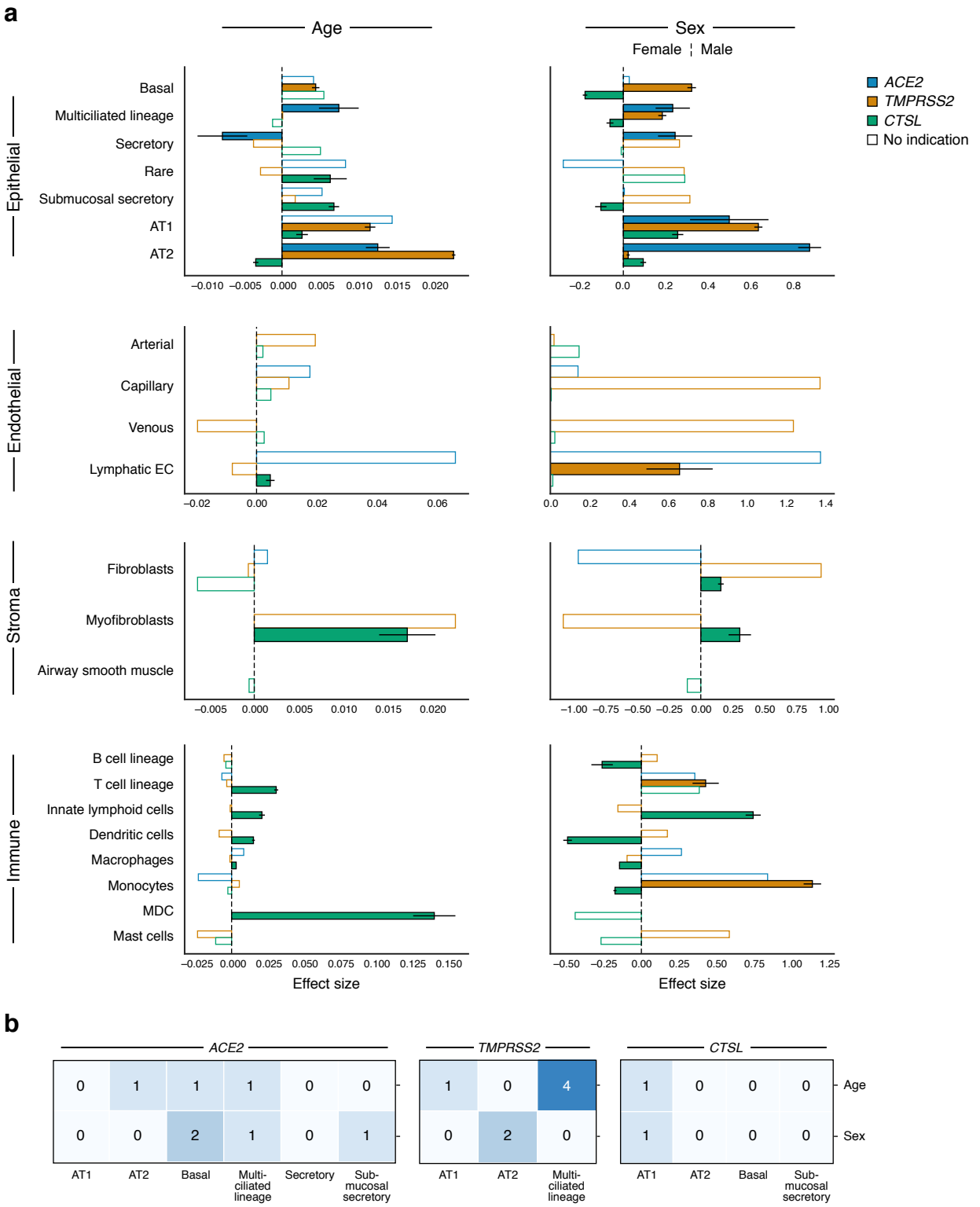
Supplementary Figure 6



Supplementary Fig. 6. Age, sex, and smoking status associations with expression of *ACE2*, *TMPRSS2*, and *CTSL* across level 2 cell type annotations modeled with interaction terms.

Age, sex, and smoking associations with expression of *ACE2* (blue), *TMPRSS2* (yellow), and *CTSL* (green) modeled with interaction terms on 985,420 cells from 164 donors. Level 2 cell types are shown on the y-axes, and are subdivided by level 1 cell type annotations (top to bottom: epithelial, endothelial, stromal and immune cells). The effect size (x axis) is given as a log fold change (sex, smoking status) or the slope of log expression per year (age). Positive effect sizes indicate increases with age, in males, and in smokers. As the age effect size is given per year, it is not directly comparable to the sex and smoking status effect sizes. Colored bars: associations with an FDR-corrected p-value<0.05 (one-sided Wald test on regression model coefficients) and a consistent effect direction in pseudo-bulk analysis (**Methods**). White bars: associations that do not pass the two above-mentioned evaluation criteria. Error bars: standard errors around coefficient estimates. Error bars are only shown for colored bars (indications or robust trends) to limit figure size. Only cell types with at least 1000 cells across donors are included. Number of cells and donors per cell type: Airway epithelium: 218787, 161, Submucosal gland: 33661, 45, Alveolar Epithelium: 185485, 106, Blood vessels: 42519, 79, Lymphatics: 5055, 76, Fibroblast lineage: 53166, 94, Smooth muscle: 16272, 61, Mesothelium: 2490, 29, Lymphoid: 132777, 134, Myeloid: 246957 cells, 121 donors.

Supplementary Figure 7

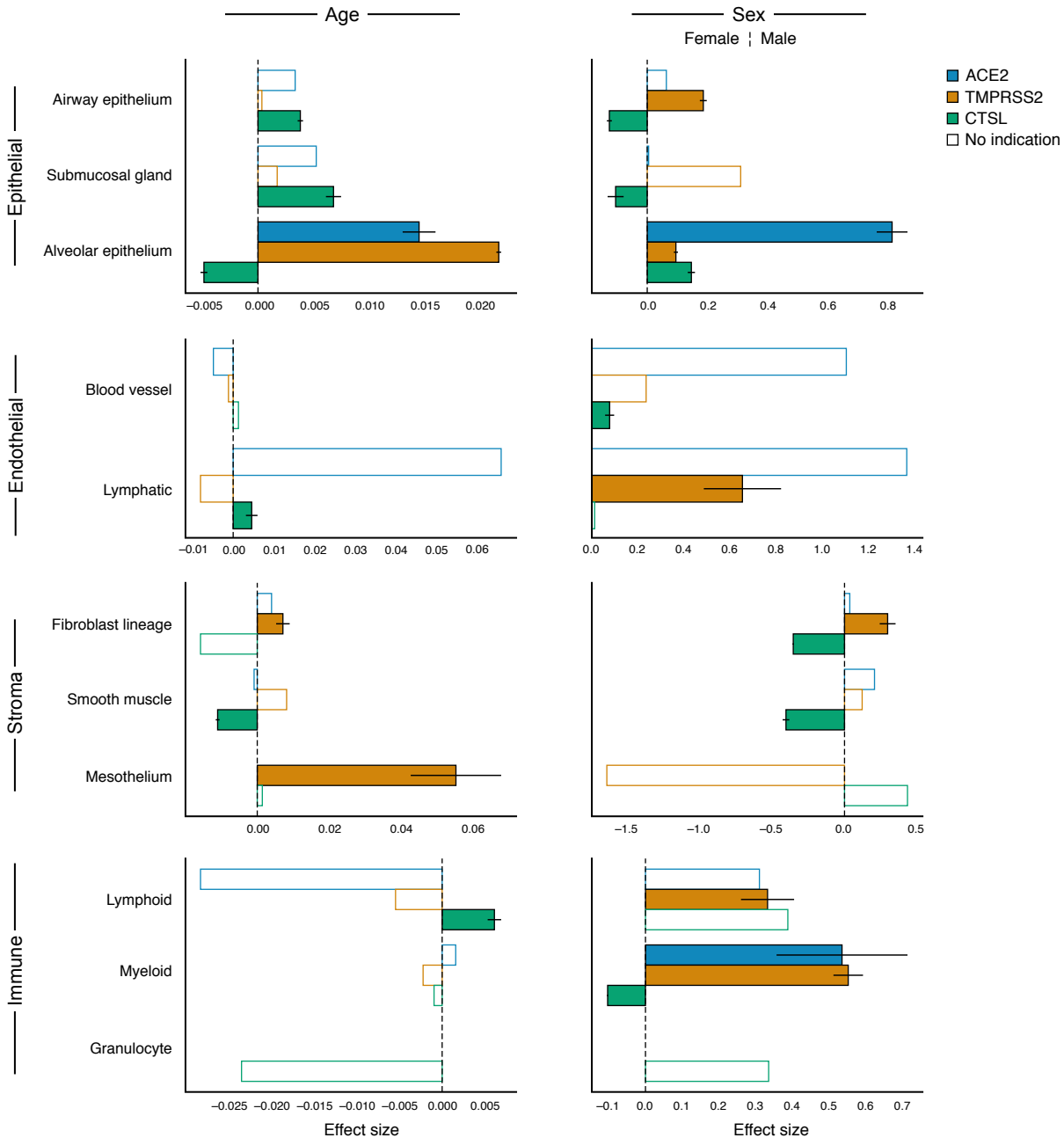


Supplementary Fig. 7. Age and sex associations with expression of *ACE2*, *TMPRSS2*, and *CTSL* across level 3 cell type annotations modeled without interaction terms.

(**a**) Age and sex assocations with expression of *ACE2* (blue), *TMPRSS2* (yellow), and *CTSL* (green) modeled without interaction terms on 1,096,604 cells from 185 donors. Level 3 cell types are shown on the y-axes, and are subdivided by level 1 cell type annotations (top to bottom: epithelial, endothelial, stromal and immune cells). The effect size (x axis) is given as a log fold change (sex) or the slope of log expression per year (age). Positive effect sizes indicate increases with age and in males. As the age effect size is given per year, it is not directly comparable to the sex effect size. Colored bars: associations with an FDR-corrected p-value<0.05 (one-sided Wald test on regression model coefficients), consistent effect direction in pseudo-bulk analysis, and consistent results using the model with interaction terms (**Methods**). White bars: associations that do not pass all of the three above-mentioned evaluation criteria. Error bars: standard errors around coefficient estimates. Error bars are only shown for colored bars (indications or robust trends) to limit figure size. Only cell types with at least 1000 cells across donors are included. Number of cells and donors per cell type: Basal: 156378, 110, Multiciliated lineage: 41999, 170, Secretory: 26025, 154, Rare: 2676, 71, Submucosal secretory: 33661, 45, AT1: 40043, 115, AT2: 182124, 118, Arterial: 4355, 42, Capillary: 18999, 43, Venous: 7893, 38, Lymphatic EC: 6149, 89, Fibroblasts: 9996, 54, Myofibroblasts: 2193, 44, Airway smooth muscle: 1077, 13, B cell lineage: 12453, 105, T cell lineage: 59841, 118, Innate lymphoid cells: 31106, 71, Dendritic cells: 9526, 101, Macrophages: 188971, 110, Monocytes: 43493, 107, MDC: 1514, 6, Mast cells: 15271 cells, 107 donors.(**b**) Robustness of associations to holding out a dataset. The values show the number of held-out datasets that result in loss of association between a given covariate (rows) and *ACE2,*

TMPRSS2, or *CTSL* expression in a given cell type (columns). Robust trends are determined by significant effects that are robust to holding out any dataset (0 values). From left to right: results for *ACE2, TMPRSS2,* and *CTSL.* AT1, 2: alveolar type 1, 2. EC: endothelial cell. MDC: monocyte derived cell.

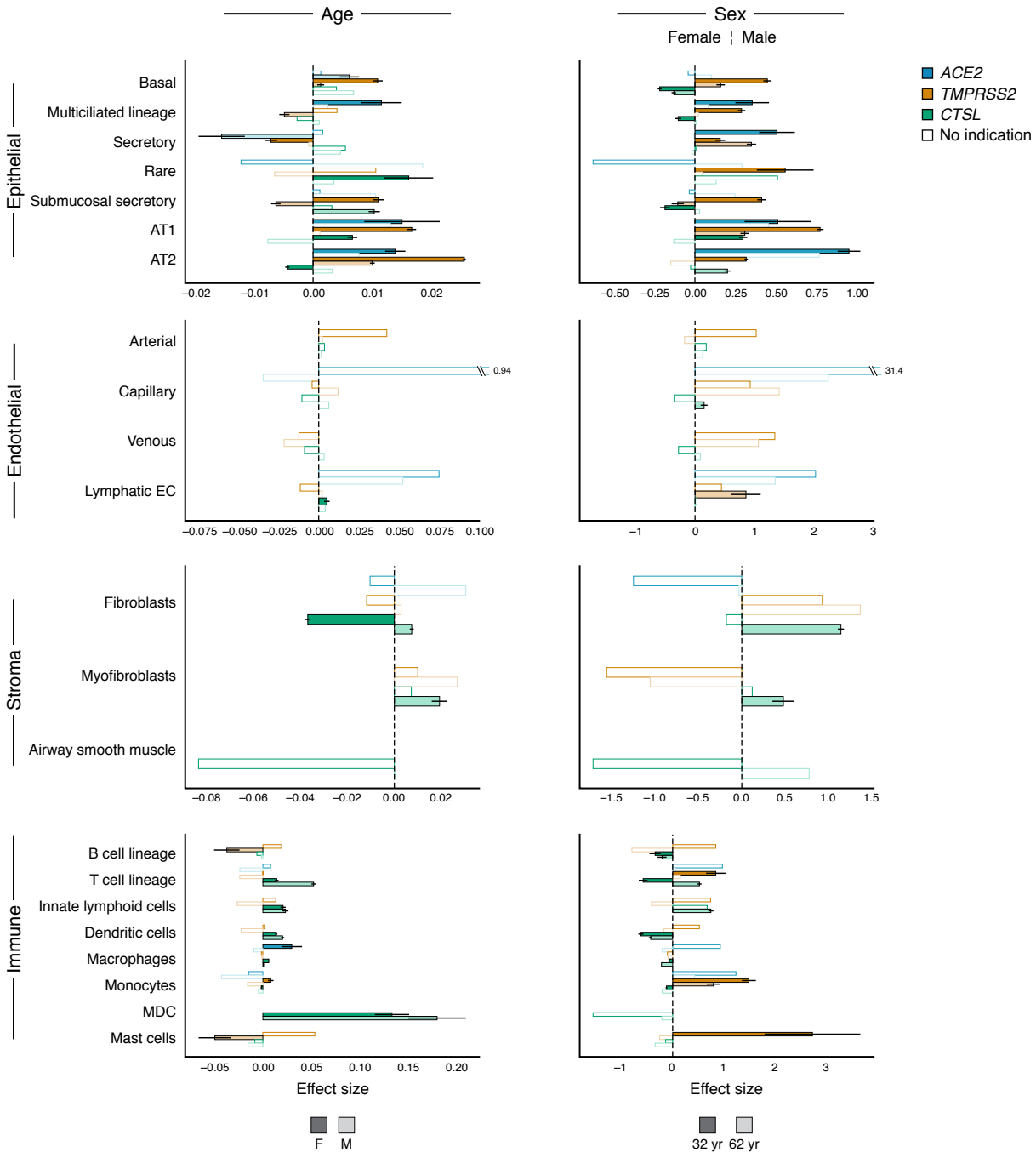
Supplementary Figure 8



Supplementary Fig. 8. Age and sex associations with expression of *ACE2*, *TMPRSS2*, and *CTSL* across level 2 cell type annotations modeled without interaction terms.

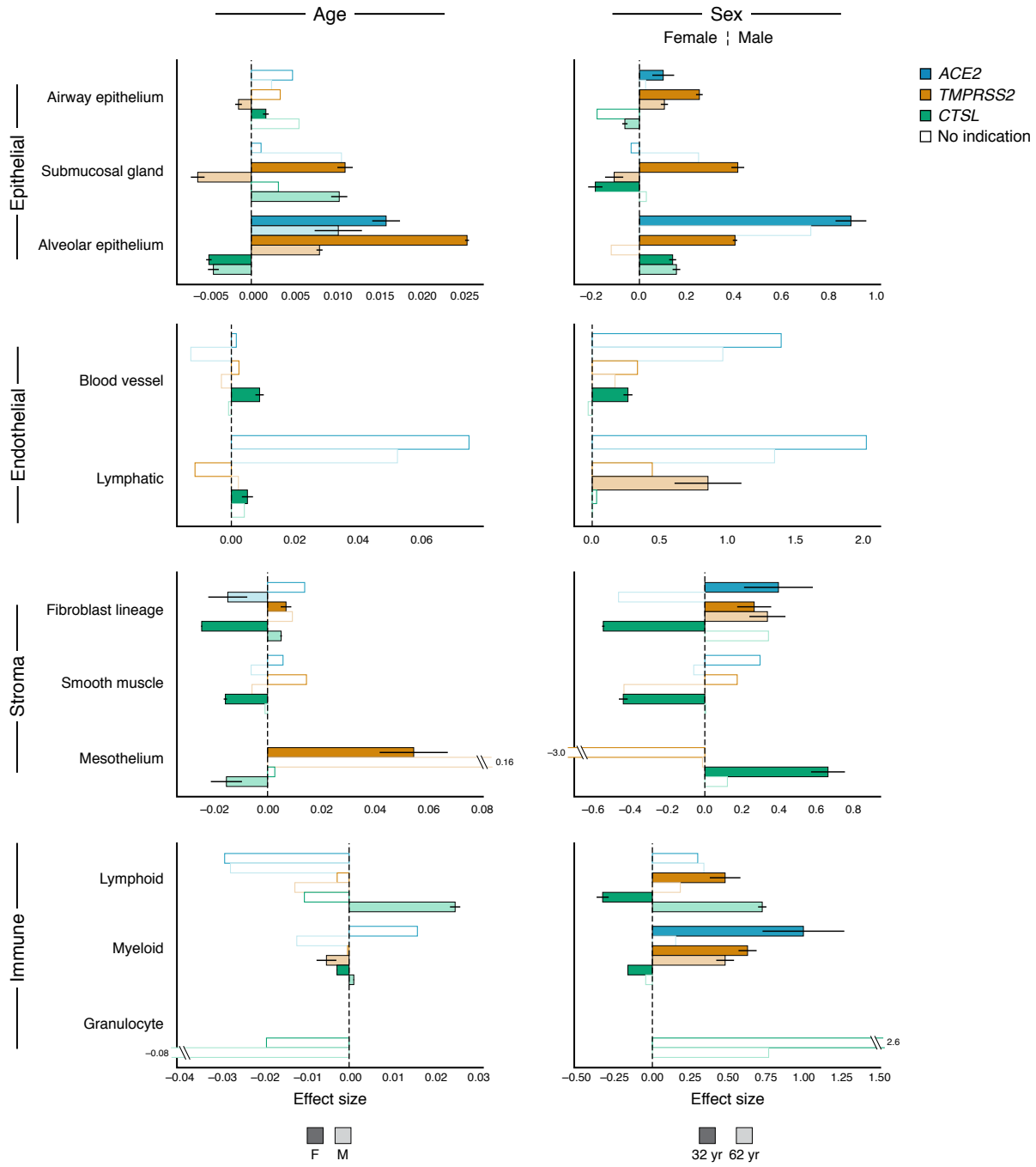
Age and sex assocations with expression of *ACE2* (blue), *TMPRSS2* (yellow), and *CTSL* (green) modeled without interaction terms on 1,096,604 cells from 185 donors. Level 2 cell types are shown on the y-axes, and are subdivided by level 1 cell type annotations (top to bottom: epithelial, endothelial, stromal and immune cells). The effect size (x axis) is given as a log fold change (sex) or the slope of log expression per year (age). Positive effect sizes indicate increases with age and in males. As the age effect size is given per year, it is not directly comparable to the sex effect size. Colored bars: associations with an FDR-corrected p-value<0.05 (one-sided Wald test on regression model coefficients), consistent effect direction in pseudo-bulk analysis, and consistent results using the model with interaction terms (**Methods**). White bars: associations that do not pass all of the three above-mentioned evaluation criteria. Error bars: standard errors around coefficient estimates. Error bars are only shown for colored bars (indications or robust trends) to limit figure size. Only cell types with at least 1000 cells across donors are included. Number of cells and donors per cell type: Airway epithelium: 227572, 181, Submucosal gland: 33661, 45, Alveolar epithelium: 222167, 120, Blood vessel: 51640, 92, Lymphatic: 6149, 89, Fibroblast lineage: 58621, 108, Smooth muscle: 16493, 66, Mesothelium: 2500, 31, Lymphoid: 142441, 155, Myeloid: 283467, 142, Granulocyte: 1141 cells, 14 donors.

Supplementary Figure 9



Supplementary Fig. 9. Age and sex associations with expression of *ACE2*, *TMPRSS2*, and *CTSL* across level 3 cell type annotations modeled with interaction terms. Age and sex assocations with expression of *ACE2* (blue), *TMPRSS2* (yellow), and *CTSL* (green) modeled with interaction terms on 1,096,604 cells from 185 donors. Level 3 cell types are shown on the y-axes, and are subdivided by level 1 cell type annotations (top to bottom: epithelial, endothelial, stromal and immune cells). The effect size (x axis) is given as a log fold change (sex) or the slope of log expression per year (age). Positive effect sizes indicate increases with age and in males. As the age effect size is given per year, it is not directly comparable to the sex effect size. Colored bars: associations with an FDR-corrected p-value<0.05 (one-sided Wald test on regression model coefficients) and a consistent effect direction in pseudo-bulk analysis (**Methods**). White bars: associations that do not pass the two above-mentioned evaluation criteria. Error bars: standard errors around coefficient estimates. Error bars are only shown for colored bars (indications or robust trends) to limit figure size. Only cell types with at least 1000 cells across donors are included. Number of cells and donors per cell type: Basal: 156378, 110, Multiciliated lineage: 41999, 170, Secretory: 26025, 154, Rare: 2676, 71, Submucosal secretory: 33661, 45, AT1: 40043, 115, AT2: 182124, 118, Arterial: 4355, 42, Capillary: 18999, 43, Venous: 7893, 38, Lymphatic EC: 6149, 89, Fibroblasts: 9996, 54, Myofibroblasts: 2193, 44, Airway smooth muscle: 1077, 13, B cell lineage: 12453, 105, T cell lineage: 59841, 118, Innate lymphoid cells: 31106, 71, Dendritic cells: 9526, 101, Macrophages: 188971, 110, Monocytes: 43493, 107, MDC: 1514, 6, Mast cells: 15271 cells, 107 donors. AT1, 2: alveolar type 1, 2. EC: endothelial cell. MDC: monocyte derived cell.

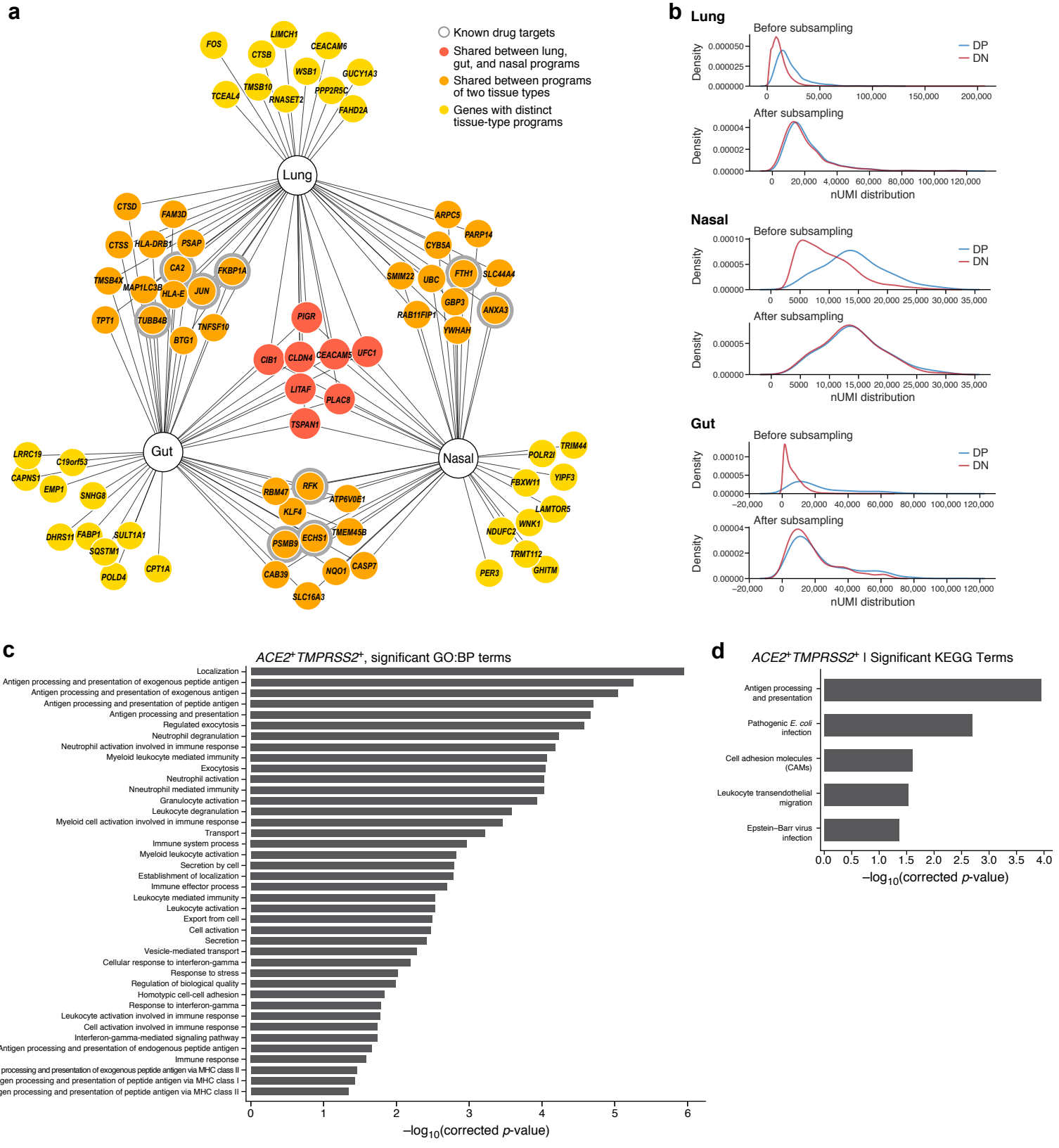
Supplementary Figure 10



Supplementary Fig. 10. Age and sex associations with expression of *ACE2*, *TMPRSS2*, and *CTSL* across level 2 cell type annotations modeled with interaction terms.

Age and sex assocations with expression of *ACE2* (blue), *TMPRSS2* (yellow), and *CTSL* (green) modeled with interaction terms on 1,096,604 cells from 185 donors. Level 2 cell types are shown on the y-axes, and are subdivided by level 1 cell type annotations (top to bottom: epithelial, endothelial, stromal and immune cells). The effect size (x axis) is given as a log fold change (sex) or the slope of log expression per year (age). Positive effect sizes indicate increases with age and in males. As the age effect size is given per year, it is not directly comparable to the sex effect size. Colored bars: associations with an FDR-corrected p-value<0.05 (one-sided Wald test on regression model coefficients) and a consistent effect direction in pseudo-bulk analysis (**Methods**). White bars: associations that do not pass the two above-mentioned evaluation criteria. Error bars: standard errors around coefficient estimates. Error bars are only shown for colored bars (indications or robust trends) to limit figure size. Only cell types with at least 1000 cells across donors are included. Number of cells and donors per cell type: Airway epithelium: 227572, 181, Submucosal gland: 33661, 45, Alveolar epithelium: 222167, 120, Blood vessel: 51640, 92, Lymphatic: 6149, 89, Fibroblast lineage: 58621, 108, Smooth muscle: 16493, 66, Mesothelium: 2500, 31, Lymphoid: 142441, 155, Myeloid: 283467, 142, Granulocyte: 1141 cells, 14 donors.

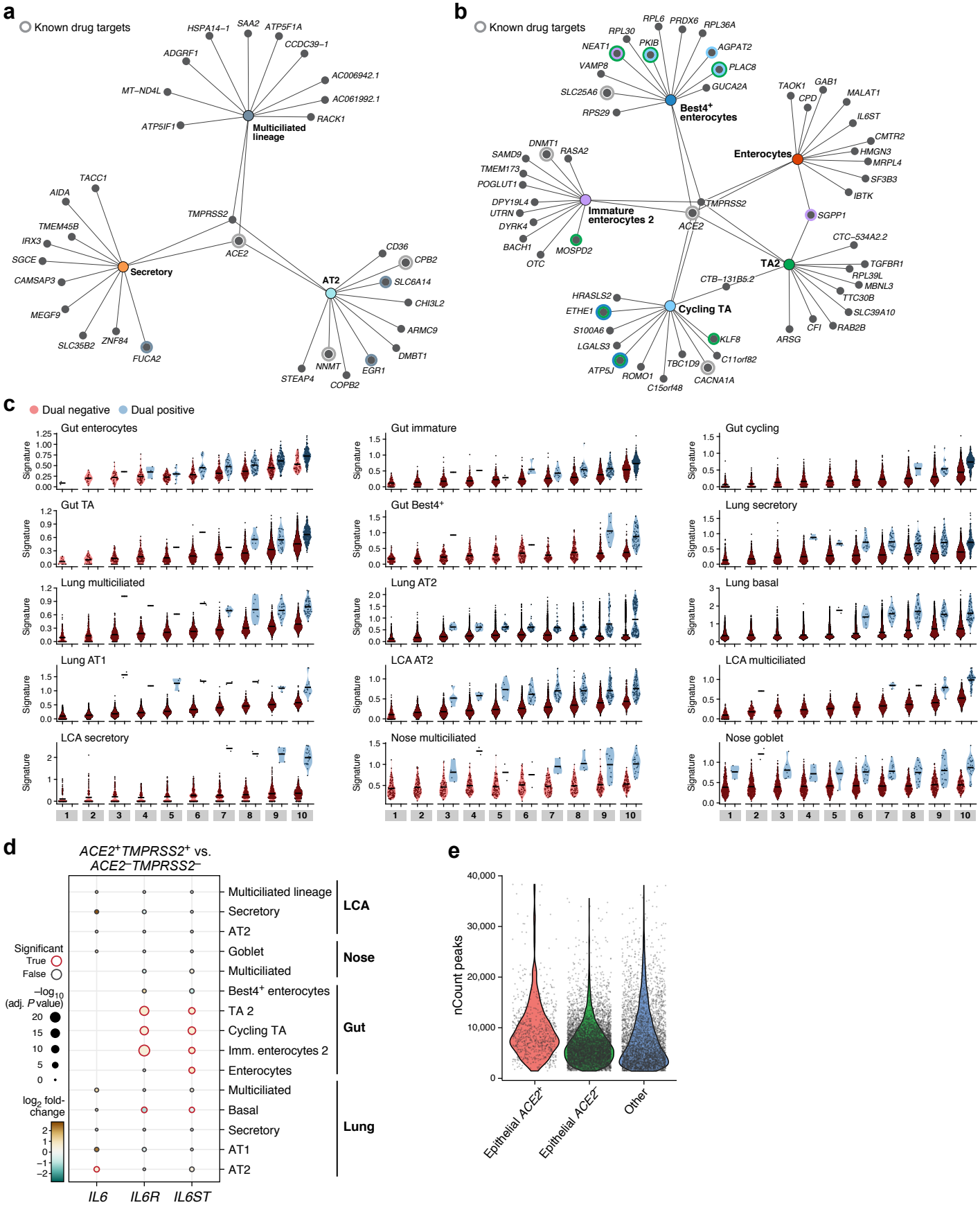
Supplementary Figure 11



Supplementary Fig. 11. Tissue programs for double positive cells

(**a**) Selected tissue program genes. Node: gene; Edge: program membership. Genes are selected heuristically for visualization, derived from the positive feature importance values of a random forest classifier without nUMI distribution matching (Methods).). (**b**) Stratified subsampling to match nUMI distributions. (**c,d**) Enrichment (-log10(adj P-value), x axis) of GO Biological Process (c) and KEGG pathway (d) gene sets (y axis) in the full tissue programs without nUMI distribution matching.

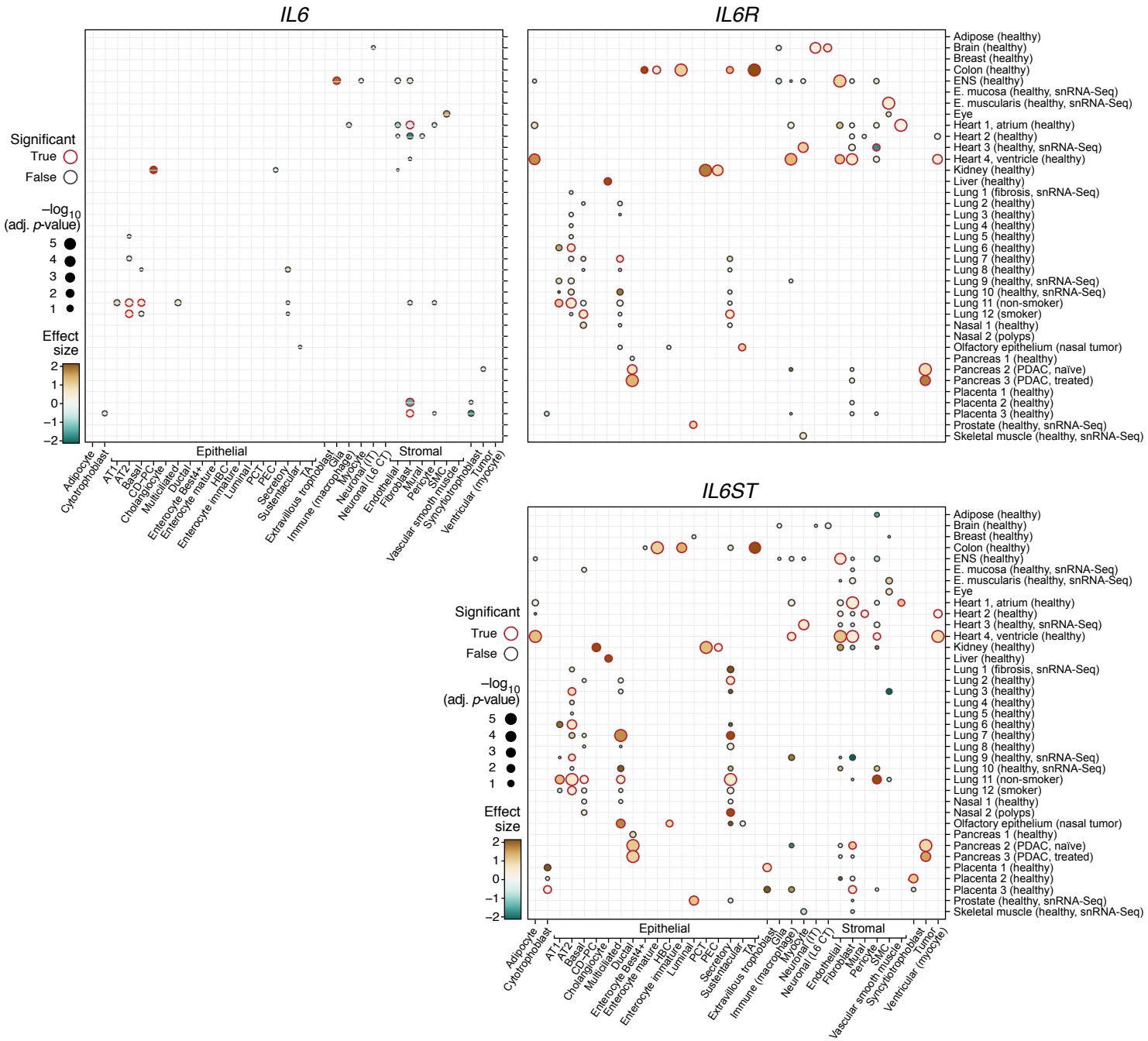
Supplementary Figure 12



Supplementary Fig. 12. Cell programs for double positive cells

(**a,b**) Top 12 genes from each cell program recovered for different lung (**a**) or gut (**b**) epithelial cell-type (nodes, colors). Colored concentric circles: overlap with a gene in the top 250 significant genes in other cell types. *ACE2* and *TMPRSS2* are included even if not among the top 12. (**c**) Comparison of signature scores of cell programs between DP and DN cells for each cell type stratified by gene complexity bin. Cells were partitioned into 10 gene complexity bins for every cell type. (**d,e**) *IL6* and its receptor's expression in specific cell types in lung and heart. (**d**) Significance (dot size, -log10(adj P-value by) and fold change (dot color) of differential expression between DP and DN cells within different types (rows) for *IL6* and its receptors *IL6R* and *IL6ST* (columns) across tissues. (**e)** Distribution of number of counts in peaks (y axis) in $ACE2^{+}$ epithelial cells (having at least 1 fragment in the *ACE2* gene locus) and $ACE2^{-}$ cells.

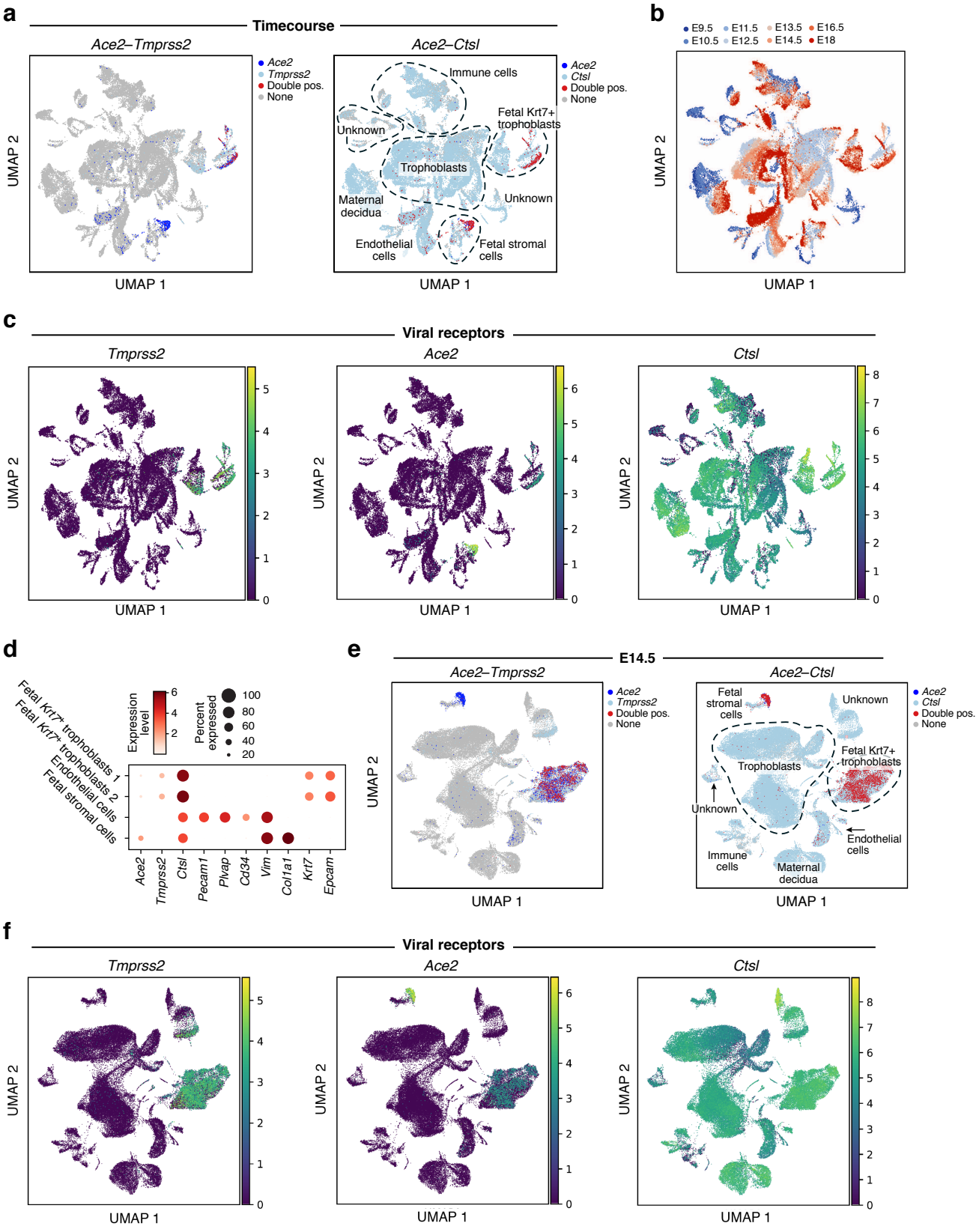
Supplementary Figure 13



Supplementary Fig. 13. Co-expression of *ACE2* and *IL6*, *IL6R*, *IL6ST*.

Co-expression of *ACE2* and *IL6*, *IL6R*, *IL6ST* in select single-cell datasets. P-values and significance (FDR 10%) derived from the logistic mixed-effects model.

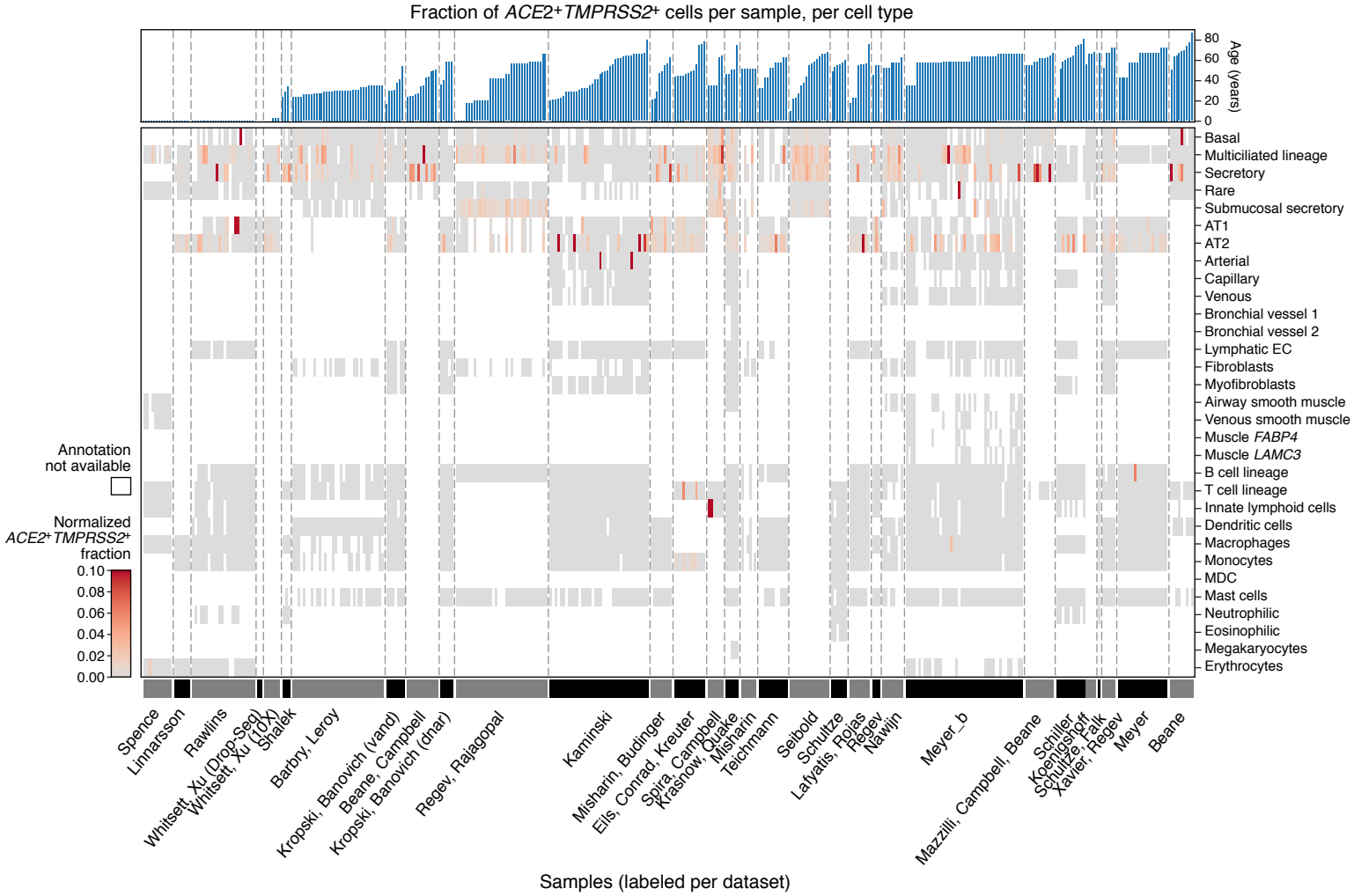
Supplementary Figure 14



Supplementary Fig. 14. Expression of *Ace2*, *Tmprss2* and *Ctsl* in mouse placenta.

UMAP embedding of placenta cells from embryonic days 9.5 to 18 (a-c) or embryonic day 14.5 (e,f) colored by *Ace2, Tmprss2* and *Ctsl* single and double positive cells (a,d), time point (b) or gene expression (c,e, ln(TP100k+1)). (d) Dotplot that shows the expression of marker genes and entry factors in cell types of interest.

Supplementary Figure 15



Supplementary Fig. 15. Variation in fraction of *ACE2*$^{+}$*TMPRSS2*$^{+}$ cells

The normalized fraction of *ACE2*$^{+}$*TMPRSS2*$^{+}$ cells in 377 lung and nasal samples from 228 donors, subdivided by level 3 cell type. Samples are grouped by dataset and ordered by donor age within each dataset (blue bars at the top). Datasets are ordered by mean age of donors. White patches indicate that the cell type annotation was not observed in the sample's annotations, either due to coarseness of annotation, or absence of cell type in the sample. Only level 3 cell types are shown, and only those cell types that were annotated in at least 3 different samples. The color bar maximum is set to 0.1, so that lower fractions can be visually distinguished. AT1, 2: alveolar type 1, 2. EC: endothelial cell. MDC: monocyte derived cell.