# SUPPLEMENTARY INFORMATION

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**Supplemental Table 1. Principal investigators at the 17 participating sites in MARC-35**

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|---|---|
| Amy D. Thompson, MD | Alfred I. duPont Hospital for Children, Wilmington, DE |
| Federico R. Laham, MD, MS | Arnold Palmer Hospital for Children, Orlando, FL |
| Jonathan M. Mansbach, MD, MPH | Boston Children's Hospital, Boston, MA |
| Vincent J. Wang, MD, MHA and Susan Wu, MD | Children's Hospital of Los Angeles, Los Angeles, CA |
| Michelle B. Dunn, MD and Jonathan M. Spergel, MD, PhD | Children's Hospital of Philadelphia, Philadelphia, PA |
| Juan C. Celedón, MD, DrPH | Children's Hospital of Pittsburgh, Pittsburgh, PA |
| Michael R. Gomez, MD, MS-HCA and Nancy Inhofe, MD | The Children's Hospital at St. Francis, Tulsa, OK |
| Brian M. Pate, MD and Henry T. Puls, MD | The Children's Mercy Hospital & Clinics, Kansas City, MO |
| Stephen J. Teach, MD, MPH | Children's National Medical Center, Washington, D.C. |
| Richard T. Strait, MD and Stephen C. Porter, MD, MSc, MPH | Cincinnati Children's Hospital and Medical Center, Cincinnati, OH |
| Ilana Y. Waynik, MD | Connecticut Children's Medical Center, Hartford, CT |
| Sujit Iyer, MD | Dell Children's Medical Center of Central Texas, Austin, TX |
| Michelle D. Stevenson, MD, MS | Norton Children's Hospital, Louisville, KY |
| Wayne G. Shreffler, MD, PhD and Ari R. Cohen, MD | Massachusetts General Hospital, Boston, MA |
| Anne K. Beasley, MD and Cindy S. Bauer, MD | Phoenix Children's Hospital, Phoenix, AZ |
| Thida Ong, MD and Markus Boos, MD, PhD | Seattle Children's Hospital, Seattle, WA |
| Charles G. Macias, MD, MPH | Texas Children's Hospital, Houston, TX |

**Supplemental Table 2. Comparisons between analytic and non-analytic cohorts in the MARC-35 cohort**

| Variables | Analytic cohort (n=244) | Non-analytic cohort (n=772) | P-value |
|---|---|---|---|
| **Baseline characteristics** | | | |
| Age (month), median (IQR) | 3 (2-6) | 3 (2-6) | 0.75 |
| Female sex | 98 (40) | 308 (40) | 0.99 |
| Race/ethnicity | | | 0.99 |
| Non-Hispanic white | 102 (42) | 328 (42) | |
| Non-Hispanic black | 57 (23) | 182 (24) | |
| Hispanic | 76 (31) | 232 (30) | |
| Others | 9 (4) | 30 (4) | |
| Parental history of asthma | 76 (31) | 269 (35) | 0.31 |
| Maternal smoking during pregnancy | 34 (14) | 113 (15) | 0.86 |
| C-section delivery | 84 (34) | 264 (34) | 0.99 |
| Prematurity (32-36.9 weeks of gestation) | 47 (19) | 139 (18) | 0.73 |
| Mostly breastfed for the first 3 month of age | 115 (47) | 357 (46) | 0.48 |
| Ever attended daycare | 71 (29) | 163 (21) | 0.01 |
| Previous breathing problems before the index hospitalization | | | 0.21 |
| 1 episode | 30 (12) | 130 (17) | |
| > 2 episodes | 10 (4) | 36 (5) | |
| History of eczema | 31 (13) | 118 (15) | 0.37 |
| Corticosteroid use before the index hospitalization | 18 (7) | 72 (9) | 0.42 |
| Lifetime history of systemic antibiotic use | 79 (32) | 239 (31) | 0.74 |
| **Clinical presentation** | | | |
| Body weight at presentation (kg), median (IQR) | 6.1 (4.6-8.0) | 6.1 (4.7-7.7) | 0.93 |
| Respiratory rate at presentation (per minute), median (IQR) | 48 (40-60) | 48 (40-60) | 0.95 |
| Oxygen saturation at presentation | | | 0.13 |
| <90% | 18 (7) | 73 (9) | |
| 90-93% | 29 (12) | 126 (16) | |
| ≥94% | 190 (78) | 559 (72) | |
| **Respiratory virus** | | | |
| Any RSV | 222 (91) | 599 (78) | <0.001 |
| Any rhinovirus | 51 (21) | 163 (21) | 0.99 |
| Other coinfection pathogens* | 47 (19) | 190 (25) | 0.10 |
| **Clinical outcomes** | | | |
| Positive pressure ventilation during hospitalization‡ | 18 (7) | 37 (5) | 0.16 |
| Intensive care use during hospitalization§ | 42 (17) | 121 (16) | 0.64 |
| Hospital length of stay (day), median (IQR) | 2 (1-3) | 2 (1-3) | 0.22 |

Abbreviations: IQR, interquartile range; RSV, respiratory syncytial virus.

Data are n (%) of infants unless otherwise indicated. Percentages may not equal 100 because of rounding and missingness. Chi-square tests were used to compare proportions for categorical variables (such as sex), and Mann–Whitney *U* tests to compare median for continuous variables (such as age).

[*] Defined as an infant having a cough that wakes him or her at night or causes emesis, or when the child has wheezing or shortness of breath without cough.
[†] Adenovirus, bocavirus, *Bordetella pertussis*, enterovirus, human coronavirus NL63, OC43, 229E, or HKU1, human metapneumovirus, influenza A or B virus, *Mycoplasma pneumoniae*, and parainfluenza virus 1-3.
[‡] Defined as use of invasive and/or non-invasive mechanical ventilation (e.g., continuous positive airway pressure ventilation).
[§] Defined as use of positive pressure ventilation and/or intensive care unit admission.

**Supplemental Table 3. Pathway enrichment analysis of each module of weighted gene co-expression network analysis in host response**

| Host response module | Number of assigned genes | GO ID | Category | Pathway[*] | FDR[†] | Correlation coefficient[‡] (P-value) | |
|---|---|---|---|---|---|---|---|
| | | | | | | PPV | Intensive care treatment |
| **T cell regulation** | 96 | GO:0002250 | BP | Adaptive immune response | <0.001 | -0.24 (<0.001) | -0.23 (<0.001) |
| | | GO:0042110 | BP | T cell activation | <0.001 | | |
| | | GO:0051249 | BP | Regulation of lymphocyte activation | <0.001 | | |
| | | GO:0050851 | BP | Antigen receptor-mediated signaling pathway | <0.001 | | |
| | | GO:0050863 | BP | Regulation of T cell activation | <0.001 | | |
| | | GO:0030098 | BP | Lymphocyte differentiation | <0.001 | | |
| | | GO:0030217 | BP | T cell differentiation | <0.001 | | |
| | | GO:0050852 | BP | T cell receptor signaling pathway | <0.001 | | |
| | | GO:0050870 | BP | Positive regulation of T cell activation | <0.001 | | |
| | | GO:0045580 | BP | Regulation of T cell differentiation | <0.001 | | |
| | | GO:0002429 | BP | Immune response-activating cell surface receptor signaling pathway | <0.001 | | |
| | | GO:0002757 | BP | Immune response-activating signal transduction | <0.001 | | |
| | | GO:0045619 | BP | Regulation of lymphocyte differentiation | <0.001 | | |
| | | GO:0002768 | BP | Immune response-regulating cell surface receptor signaling pathway | <0.001 | | |
| | | GO:0002764 | BP | Immune response-regulating signaling pathway | <0.001 | | |
| | | GO:0002253 | BP | Activation of immune response | <0.001 | | |
| | | GO:0051251 | BP | Positive regulation of lymphocyte activation | <0.001 | | |

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|---|---|---|---|---|---|---|---|
| | | GO:1903039 | BP | Positive regulation of leukocyte cell-cell adhesion | <0.001 | | |
| | | GO:0050671 | BP | Positive regulation of lymphocyte proliferation | <0.001 | | |
| | | GO:0046651 | BP | Lymphocyte proliferation | <0.001 | | |
| **Neutrophil/IL-1** | 156 | GO:0071347 | BP | Cellular response to interleukin-1 | <0.001 | 0.23 (<0.001) | 0.26 (<0.001) |
| | | GO:0070555 | BP | Response to interleukin-1 | <0.001 | | |
| | | GO:0030593 | BP | Neutrophil chemotaxis | <0.001 | | |
| | | GO:0097530 | BP | Granulocyte migration | <0.001 | | |
| | | GO:1990266 | BP | Neutrophil migration | <0.001 | | |
| | | GO:0002819 | BP | Regulation of adaptive immune response | <0.001 | | |
| | | GO:0071621 | BP | Granulocyte chemotaxis | <0.001 | | |
| | | GO:0046456 | BP | Icosanoid biosynthetic process | <0.001 | | |
| | | GO:0060759 | BP | Regulation of response to cytokine stimulus | <0.001 | | |
| | | GO:0030728 | BP | Ovulation | <0.001 | | |
| | | GO:0006636 | BP | Unsaturated fatty acid biosynthetic process | <0.001 | | |
| | | GO:0033089 | BP | Positive regulation of T cell differentiation in thymus | <0.001 | | |
| | | GO:0032006 | BP | Regulation of tor signaling | <0.001 | | |
| | | GO:0006089 | BP | Lactate metabolic process | <0.001 | | |
| | | GO:0071634 | BP | Regulation of transforming growth factor beta production | <0.001 | | |
| | | GO:0071604 | BP | Transforming growth factor beta production | <0.001 | | |
| | | GO:0070821 | CC | Tertiary granule membrane | <0.001 | | |
| | | GO:0070820 | CC | Tertiary granule | <0.001 | | |
| | | GO:0004896 | MF | Cytokine receptor activity | <0.001 | | |
| | | GO:0140375 | MF | Immune receptor activity | <0.001 | | |

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|---|---|---|---|---|---|---|---|
| **GPCR** | 60 | GO:0035256 | MF | G protein-coupled glutamate receptor binding | 0.002 | -0.21 (0.001) | -0.20 (<0.001) |
|  |  | GO:0071889 | MF | 14-3-3 protein binding | 0.007 |  |  |
|  |  | GO:0004864 | MF | Protein phosphatase inhibitor activity | 0.008 |  |  |
| **Type I IFN** | 73 | GO:0032606 | BP | Type I interferon production | <0.001 | -0.21 (0.001) | -0.21 (0.001) |
|  |  | GO:0032479 | BP | Regulation of type I interferon production | <0.001 |  |  |
|  |  | GO:0060337 | BP | Type I interferon signaling pathway | <0.001 |  |  |
|  |  | GO:0071357 | BP | Cellular response to type I interferon | <0.001 |  |  |
|  |  | GO:0034340 | BP | Response to type I interferon | <0.001 |  |  |
|  |  | GO:0051607 | BP | Defense response to virus | <0.001 |  |  |
|  |  | GO:0009615 | BP | Response to virus | <0.001 |  |  |
|  |  | GO:0034341 | BP | Response to interferon-gamma | <0.001 |  |  |
|  |  | GO:0060333 | BP | Interferon-gamma-mediated signaling pathway | <0.001 |  |  |
|  |  | GO:0071346 | BP | Cellular response to interferon-gamma | <0.001 |  |  |
|  |  | GO:1903900 | BP | Regulation of viral life cycle | <0.001 |  |  |
|  |  | GO:1903901 | BP | Negative regulation of viral life cycle | <0.001 |  |  |
|  |  | GO:0048525 | BP | Negative regulation of viral process | <0.001 |  |  |
|  |  | GO:0050792 | BP | Regulation of viral process | <0.001 |  |  |
|  |  | GO:0035455 | BP | Response to interferon-alpha | <0.001 |  |  |
|  |  | GO:0045069 | BP | Regulation of viral genome replication | <0.001 |  |  |
|  |  | GO:0045071 | BP | Negative regulation of viral genome replication | <0.001 |  |  |
|  |  | GO:0019079 | BP | Viral genome replication | <0.001 |  |  |
|  |  | GO:0046596 | BP | Regulation of viral entry into host cell | <0.001 |  |  |

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|---|---|---|---|---|---|---|---|
|  |  | GO:1902187 | BP | Negative regulation of viral release from host cell | <0.001 |  |  |
| **HR-1** | 194 | GO:0030863 | CC | Cortical cytoskeleton | 0.001 | -0.21 (0.001) | -0.17 (0.006) |
|  |  | GO:0000313 | CC | Organellar ribosome | 0.001 |  |  |
|  |  | GO:0005761 | CC | Mitochondrial ribosome | 0.001 |  |  |
|  |  | GO:0005884 | CC | Actin filament | 0.004 |  |  |
|  |  | GO:0030864 | CC | Cortical actin cytoskeleton | 0.004 |  |  |
|  |  | GO:0000315 | CC | Organellar large ribosomal subunit | 0.006 |  |  |
|  |  | GO:0005762 | CC | Mitochondrial large ribosomal subunit | 0.006 |  |  |
|  |  | GO:0097197 | CC | Tetraspanin-enriched microdomain | 0.007 |  |  |
|  |  | GO:0031941 | CC | Filamentous actin | 0.007 |  |  |
|  |  | GO:0001725 | CC | Stress fiber | 0.007 |  |  |
|  |  | GO:0097517 | CC | Contractile actin filament bundle | 0.007 |  |  |
|  |  | GO:0031094 | CC | Platelet dense tubular network | 0.007 |  |  |
|  |  | GO:0032432 | CC | Actin filament bundle | 0.009 |  |  |
|  |  | GO:0042641 | CC | Actomyosin | 0.009 |  |  |
|  |  | GO:0016327 | CC | Apicolateral plasma membrane | 0.02 |  |  |
| **ATP synthesis** | 57 | GO:0005753 | CC | Mitochondrial proton-transporting ATP synthase complex | 0.01 | 0.20 (0.002) | 0.17 (0.008) |
|  |  | GO:0045259 | CC | Proton-transporting ATP synthase complex | 0.01 |  |  |
|  |  | GO:0046933 | MF | Proton-transporting ATP synthase activity, rotational mechanism | 0.01 |  |  |
|  |  | GO:0015252 | MF | Proton channel activity | 0.01 |  |  |
| **HR-2** | 135 | GO:0043001 | BP | Golgi to plasma membrane protein transport | 0.002 | -0.19 (0.003) | -0.18 (0.004) |
|  |  | GO:0002523 | BP | Leukocyte migration involved in inflammatory response | 0.002 |  |  |
|  |  | GO:0051693 | BP | Actin filament capping | 0.002 |  |  |

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|---|---|---|---|---|---|---|---|
|  |  | GO:0030835 | BP | Negative regulation of actin filament depolymerization | 0.002 |  |  |
|  |  | GO:1901879 | BP | Regulation of protein depolymerization | 0.002 |  |  |
|  |  | GO:0030834 | BP | Regulation of actin filament depolymerization | 0.003 |  |  |
|  |  | GO:0030042 | BP | Actin filament depolymerization | 0.003 |  |  |
|  |  | GO:0006893 | BP | Golgi to plasma membrane transport | 0.003 |  |  |
|  |  | GO:0061951 | BP | Establishment of protein localization to plasma membrane | 0.003 |  |  |
|  |  | GO:0030837 | BP | Negative regulation of actin filament polymerization | 0.003 |  |  |
|  |  | GO:0098840 | BP | Protein transport along microtubule | 0.003 |  |  |
|  |  | GO:0099118 | BP | Microtubule-based protein transport | 0.003 |  |  |
|  |  | GO:0010644 | BP | Cell communication by electrical coupling | 0.003 |  |  |
|  |  | GO:1901880 | BP | Negative regulation of protein depolymerization | 0.003 |  |  |
|  |  | GO:0016529 | CC | Sarcoplasmic reticulum | 0.003 |  |  |
|  |  | GO:0032272 | BP | Negative regulation of protein polymerization | 0.004 |  |  |
|  |  | GO:1900747 | BP | Negative regulation of vascular endothelial growth factor signaling pathway | 0.004 |  |  |
|  |  | GO:0043242 | BP | Negative regulation of protein-containing complex disassembly | 0.004 |  |  |
|  |  | GO:0016528 | CC | Sarcoplasm | 0.004 |  |  |
| **Transcription-translation** | 163 | GO:0000466 | BP | Maturation of 5.8s rRNA from tricistronic rRNA transcript (ssu-rRNA, 5.8s rRNA, lsu-rRNA) | 0.001 | -0.18 (0.005) | -0.18 (0.005) |
|  |  | GO:1903313 | BP | Positive regulation of mRNA metabolic process | 0.001 |  |  |

|  |  |  |  |  |  |  |  |
|---|---|---|---|---|---|---|---|
|  |  | GO:0030684 | CC | Preribosome | 0.001 |  |  |
|  |  | GO:0030686 | CC | 90s preribosome | 0.001 |  |  |
|  |  | GO:0005684 | CC | U2-type spliceosomal complex | 0.001 |  |  |
|  |  | GO:0070273 | MF | Phosphatidylinositol-4-phosphate binding | 0.001 |  |  |
|  |  | GO:0042054 | MF | Histone methyltransferase activity | 0.001 |  |  |
|  |  | GO:0000460 | BP | Maturation of 5.8s rRNA | 0.002 |  |  |
|  |  | GO:0010314 | MF | Phosphatidylinositol-5-phosphate binding | 0.004 |  |  |
|  |  | GO:0018027 | BP | Peptidyl-lysine dimethylation | 0.005 |  |  |
|  |  | GO:0048026 | BP | Positive regulation of mRNA splicing, via spliceosome | 0.005 |  |  |
|  |  | GO:0008276 | MF | Protein methyltransferase activity | 0.005 |  |  |
|  |  | GO:0043325 | MF | Phosphatidylinositol-3,4-bisphosphate binding | 0.008 |  |  |
|  |  | GO:0048188 | CC | Set1c/compass complex | 0.01 |  |  |
|  |  | GO:0071006 | CC | U2-type catalytic step 1 spliceosome | 0.01 |  |  |
|  |  | GO:0010494 | CC | Cytoplasmic stress granule | 0.01 |  |  |
|  |  | GO:0030291 | MF | Protein serine/threonine kinase inhibitor activity | 0.01 |  |  |
|  |  | GO:0030515 | MF | snoRNA binding | 0.01 |  |  |
|  |  | GO:0034511 | MF | U3 snoRNA binding | 0.01 |  |  |
|  |  | GO:0042162 | MF | Telomeric DNA binding | 0.01 |  |  |
| **Granulocyte** | 128 | GO:0070820 | CC | Tertiary granule | <0.001 | 0.13 (0.04) | 0.13 (0.04) |
|  |  | GO:0042581 | CC | Specific granule | <0.001 |  |  |
|  |  | GO:0070821 | CC | Tertiary granule membrane | <0.001 |  |  |
|  |  | GO:0035579 | CC | Specific granule membrane | <0.001 |  |  |
|  |  | GO:1904724 | CC | Tertiary granule lumen | <0.001 |  |  |
|  |  | GO:0043312 | BP | Neutrophil degranulation | <0.001 |  |  |
|  |  | GO:0002283 | BP | Neutrophil activation involved in immune response | <0.001 |  |  |

| | | | |
|---|---|---|---|
| GO:0002446 | BP | Neutrophil mediated immunity | <0.001 |
| GO:0042119 | BP | Neutrophil activation | <0.001 |
| GO:0032496 | BP | Response to lipopolysaccharide | <0.001 |
| GO:0071222 | BP | Cellular response to lipopolysaccharide | <0.001 |
| GO:0071219 | BP | Cellular response to molecule of bacterial origin | <0.001 |
| GO:0071216 | BP | Cellular response to biotic stimulus | <0.001 |
| GO:0002573 | BP | Myeloid leukocyte differentiation | <0.001 |
| GO:0002761 | BP | Regulation of myeloid leukocyte differentiation | <0.001 |
| GO:1904705 | BP | Regulation of vascular associated smooth muscle cell proliferation | <0.001 |
| GO:1990874 | BP | Vascular associated smooth muscle cell proliferation | <0.001 |
| GO:0071621 | BP | Granulocyte chemotaxis | <0.001 |
| GO:0048661 | BP | Positive regulation of smooth muscle cell proliferation | <0.001 |
| GO:1903977 | BP | Positive regulation of glial cell migration | <0.001 |

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Abbreviations: ATP, adenosine triphosphate; BP, biological process; CC, cellular component; FDR, false discovery rate; HR, host response; IFN, interferon; IL, interleukin; MF, molecular function; PPV, positive pressure ventilation

[*] The top 20 pathways with the highest FDR or pathways with P-values of $<0.05$ are shown.

[†] FDR is calculated based on the p-value of the pathway enrichment analysis in each module.

[‡] Spearman's coefficients between the eigenvalue (the first principal component) of corresponding module and PPV or intensive care use were estimated.

**Supplemental Table 4. Assigned microbial species of each module of weighted gene co-expression network analysis in nasopharyngeal airway microbial composition**

| **Microbial composition module** | **Number of assigned species** | **Microbial species*** | **Correlation coefficient[†] (P- value)** | |
|---|---|---|---|---|
| | | | **PPV** | **Intensive care treatment** |
| ***S. pneumonia/S. aureus*** | 4 | *Streptococcus pneumoniae, Staphylococcus aureus, Escherichia coli, Lactobacillus vaginalis* | 0.16<br>(0.01) | 0.12<br>(0.05) |
| **MC-1** | 151 | *Abiotrophia defectiva, Achromobacter xylosoxidans, Acidovorax ebreus, Acidovorax temperans, Acinetobacter baumannii, Acinetobacter johnsonii, Acinetobacter junii, Acinetobacter lwoffii, Acinetobacter radioresistens, Actinomyces dentalis, Actinomyces graevenitzii, Actinomyces johnsonii, Actinomyces massiliensis, Actinomyces naeslundii, Actinomyces viscosus, Aerococcus viridan, Afipia broomeae, Agrobacterium tumefaciens, Alloiococcus otitis, Anaerococcus prevotii, Anaerococcus tetradius, Anoxybacillus flavithermus, Arsenicicoccus bolidensis, Arthrospira platensis, Atopobium parvulum, Atopobium vaginae, Bacillus anthracis, Bacillus clausii, Bacillus subtilis, Bifidobacterium animalis, Bifidobacterium longum Bordetella pertussis, Bradyrhizobium elkanii, Brevundimonas diminuta, Brochothrix thermosphacta, Burkholderia cepacia, Capnocytophaga leadbetteri, Cardiobacterium hominis, Comamonas testosteroni, Corynebacterium accolens, Corynebacterium afermentans, Corynebacterium amycolatum, Corynebacterium appendicis, Corynebacterium aurimucosum, Corynebacterium coyleae, Corynebacterium durum, Corynebacterium jeikeium, Corynebacterium kroppenstedtii, Corynebacterium matruchotii, Corynebacterium otitidis, Corynebacterium pilbarense, Corynebacterium simulans, Corynebacterium singulare, Corynebacterium striatum, Corynebacterium tuberculostearicum, Corynebacterium urealyticum, Cronobacter sakazakii, Cupriavidus gilardii, Cutibacterium acnes, Cutibacterium avidum, Cutibacterium granulosum, Delftia acidovorans, Dialister micraerophilus, Dietzia cinnamea, Dolosigranulum pigrum, Enhydrobacter aerosaccus, Enterobacter cancerogenus, Enterobacter hormaechei, Enterococcus durans, Enterococcus faecalis, Enterococcus italicus, Finegoldia magna, Gardnerella vaginalis, Granulicatella adiacens, Haematobacter missouriensis, Jonquetella anthropi, Klebsiella pneumoniae, Kluyvera ascorbata, Kocuria palustris, Kocuria rhizophila, Kytococcus sedentarius,* | 0.11<br>(0.10) | 0.022<br>(0.70) |

|  |  |  |  |  |
|---|---|---|---|---|
|  |  | *Lactobacillus acidophilus, Lactobacillus brevis, Lactobacillus casei, Lactobacillus crispatus, Lactobacillus fermentum, Lactobacillus gasseri, Lactobacillus iners, Lactobacillus plantarum, Lactobacillus rhamnosus, Lactobacillus salivarius, Lactococcus lactis, Lautropia mirabilis, Lawsonella clevelandensis, Listeria monocytogenes, Lysinibacillus fusiformis, Megasphaera micronuciformis, Mesorhizobium loti, Microbacterium flavescens, Microbacterium ginsengisoli, Micrococcus luteus, Mitsuokella multacida, Mobiluncus mulieris, Moraxella osloensis, Mycobacterium tuberculosis, Mycolicibacterium neoaurum, Neisseria sicca, Neisseria subflava, Ochrobactrum anthropi, Paenibacillus glucanolyticus, Paenibacillus phoenicis, Paracoccus yeei, Peptidiphaga gingivicola, Peptoniphilus harei, Peptostreptococcus anaerobius, Prevotella buccalis, Proteus mirabilis, Pseudomonas aeruginosa, Pseudomonas fluorescens, Pseudomonas oleovoran, Pseudomonas stutzeri, Pseudopropionibacterium propionicum, Pseudoramibacter alactolyticus, Ralstonia pickettii, Roseomonas gilardii, Roseomonas mucosa, Rothia aeria, Rothia dentocariosa, Rothia mucilaginosa, Sanguibacter keddieii, Schaalia odontolytica, Serratia marcescens, Staphylococcus capitisStaphylococcus caprae, Staphylococcus cohnii, Staphylococcus epidermidis, Staphylococcus hominis, Staphylococcus pettenkoferi, Staphylococcus warneri, Stenotrophomonas maltophilia, Stenotrophomonas nitritireducens, Streptococcus australis, Streptococcus gordonii, Streptococcus salivarius, Streptococcus sanguinis, Streptococcus thermophilus, Treponema vincentii, Variovorax paradoxus, Veillonella parvula, Yersinia pestis* |  |  |
| ***Moraxella*** | 3 | *Moraxella catarrhalis, Moraxella lincolnii, Moraxella nonliquefaciens* | -0.09<br>(0.10) | -0.07<br>(0.30) |
| ***Streptococcus*** | 13 | *Streptococcus agalactiae, Streptococcus anginosus, Streptococcus constellatus, Streptococcus downei, Streptococcus intermedius, Streptococcus mutans, Streptococcus oralis, Streptococcus peroris, Streptococcus pyogenes, Streptococcus sinensis, Streptococcus sobrinus, Streptococcus vestibularis, Enterococcus saccharolyticus* | 0.08<br>(0.20) | 0.05<br>(0.40) |
| ***Haemophilus*** | 5 | *Haemophilus aegyptius, Haemophilus ducreyi, Haemophilus influenzae, Haemophilus paraphrohaemolyticus, Haemophilus pittmaniae* | 0.05<br>(0.40) | 0.0005<br>(0.99) |

| | | | | |
|---|---|---|---|---|
| **MC-2** | 105 | *Aggregatibacter aphrophilus, Alloprevotella rava, Alloprevotella tannerae, Alloscardovia omnicolens, Anaerococcus lactolyticus, Bacteroides pyogenes, Bulleidia extructa, Campylobacter concisus, Campylobacter rectus, Campylobacter showae, Capnocytophaga gingivalis, Capnocytophaga granulosa, Capnocytophaga haemolytica, Capnocytophaga ochracea, Capnocytophaga sputigena, Catonella morbi, Eggerthia catenaformis, Eikenella corrodens, Fusobacterium gonidiaformans, Fusobacterium hwasookii, Fusobacterium nucleatum, Fusobacterium periodonticum, Gemella haemolysans, Gemella morbillorum, Gemella sanguinis, Granulicatella elegans, Haemophilus haemolyticus, Haemophilus parahaemolyticus, Haemophilus parainfluenzae, Haemophilus sputorum, Johnsonella ignava, Kingella denitrificans, Kingella kingae, Kingella oralis, Lachnoanaerobaculum orale, Lachnoanaerobaculum saburreum, Lachnoanaerobaculum umeaense, Leptotrichia buccalis, Leptotrichia goodfellowii, Leptotrichia hofstadii, Leptotrichia shahii, Leptotrichia wadei, Mogibacterium pumilum, Neisseria bacilliformis, Neisseria cinerea, Neisseria elongata, Neisseria flavescens, Neisseria gonorrhoeae, Neisseria lactamica, Neisseria macacae, Neisseria meningitidis, Neisseria mucosa, Neisseria oralis, Neisseria polysaccharea, Neisseria weaveri, Oribacterium asaccharolyticum, Oribacterium parvum, Parvimonas micra, Peptoniphilus lacrimalis, Peptostreptococcus stomatis, Porphyromonas asaccharolytica, Porphyromonas catoniae, Porphyromonas endodontalis, Porphyromonas gingivalis, Porphyromonas pasteri, Porphyromonas uenonis, Prevotella baroniae, Prevotella bivia, Prevotella buccae, Prevotella denticola, Prevotella enoeca, Prevotella fusca, Prevotella histicola, Prevotella intermedia, Prevotella loescheii, Prevotella maculosa, Prevotella marshii, Prevotella melaninogenica, Prevotella micans, Prevotella multiformis, Prevotella nanceiensis, Prevotella nigrescens, Prevotella oralis, Prevotella oris, Prevotella oulorum, Prevotella pallens, Prevotella pleuritidis, Prevotella saccharolytica, Prevotella salivae, Prevotella scopos, Prevotella shahii, Prevotella veroralis, Schaalia meyeri, Selenomonas infelix, Selenomonas sputigena, Shuttleworthia satelles, Simonsiella muelleri, Solobacterium moorei, Stomatobaculum longum, Streptococcus mitis, Tannerella forsythia, Veillonella atypica, Veillonella denticariosi, Veillonella dispar, Veillonella rogosae* | -0.05<br>(0.50) | -0.04<br>(0.60) |
| **MC-3** | 3 | *Caldilinea aerophila, Desulfomicrobium orale, Micavibrio aeruginosavorus* | 0.02<br>(0.70) | -0.03<br>(0.70) |

Abbreviations: MC, microbial composition; PPV, positive pressure ventilation

[*] All assigned microbial species are shown.

[†] Spearman's correlation coefficients between the eigenvalue (the first principal component) of corresponding module and PPV or intensive care use were estimated.

**Supplemental Table 5. Pathway enrichment analysis of each module of weighted gene co-expression network analysis in nasopharyngeal airway microbial function**

| Microbial function module | Number of assigned genes | GO ID | Category | Pathway* | FDR† | Correlation coefficient ‡ (P- value) | |
|---|---|---|---|---|---|---|---|
| | | | | | | **PPV** | **Intensive treatment care** |
| **Plasma membrane** | 367 | GO:0031226 | CC | Intrinsic component of plasma membrane | 0.002 | -0.36 (<0.001) | -0.24 (<0.001) |
| | | GO:0005887 | CC | Integral component of plasma membrane | 0.002 | | |
| **mRNA metabolism** | 229 | GO:0006402 | BP | mRNA catabolic process | <0.001 | -0.23 (<0.001) | -0.11 (0.07) |
| | | GO:0016071 | BP | mRNA metabolic process | <0.001 | | |
| | | GO:0006401 | BP | RNA catabolic process | 0.001 | | |
| | | GO:0010605 | BP | Negative regulation of macromolecule metabolic process | 0.002 | | |
| | | GO:0009892 | BP | Negative regulation of metabolic process | 0.002 | | |
| | | GO:0016070 | BP | RNA metabolic process | 0.002 | | |
| | | GO:0010467 | BP | Gene expression | 0.002 | | |
| **BCAA metabolism** | 10 | GO:0009081 | BP | Branched-chain amino acid metabolic process | 0.03 | -0.19 (0.004) | -0.07 (0.249) |
| | | GO:0009082 | BP | Branched-chain amino acid biosynthetic process | 0.03 | | |
| | | GO:0006549 | BP | Isoleucine metabolic process | 0.03 | | |
| | | GO:0009097 | BP | Isoleucine biosynthetic process | 0.03 | | |
| | | GO:0045271 | CC | Respiratory chain complex I | 0.03 | | |
| | | GO:0045272 | CC | Plasma membrane respiratory chain complex I | 0.03 | | |
| | | GO:0030964 | CC | NADH dehydrogenase complex | 0.03 | | |
| | | GO:0050136 | MF | NADH dehydrogenase (quinone) activity | 0.03 | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | GO:0008137 | MF | NADH dehydrogenase (ubiquinone) activity | 0.03 | | |
| | | GO:0003954 | MF | NADH dehydrogenase activity | 0.03 | | |
| | | GO:0048038 | MF | Quinone binding | 0.03 | | |
| | | GO:0016655 | MF | Oxidoreductase activity, acting on NAD(P)H, quinone or similar compound as acceptor | 0.03 | | |
| **Oxidative stress response** | 5 | GO:0034599 | BP | Cellular response to oxidative stress | 0.03 | -0.16 (0.01) | -0.06 (0.28) |
| | | GO:0098869 | BP | Cellular oxidant detoxification | 0.03 | | |
| | | GO:1901701 | BP | Cellular response to oxygen-containing compound | 0.03 | | |
| | | GO:0097237 | BP | Cellular response to toxic substance | 0.03 | | |
| | | GO:1990748 | BP | Cellular detoxification | 0.03 | | |
| | | GO:0045454 | BP | Cell redox homeostasis | 0.03 | | |
| | | GO:1901698 | BP | Response to nitrogen compound | 0.03 | | |
| | | GO:0043086 | BP | Negative regulation of catalytic activity | 0.03 | | |
| | | GO:0050790 | BP | Regulation of catalytic activity | 0.03 | | |
| | | GO:0000028 | BP | Ribosomal small subunit assembly | 0.03 | | |
| | | GO:0044092 | BP | Negative regulation of molecular function | 0.03 | | |
| | | GO:0072657 | BP | Protein localization to membrane | 0.03 | | |
| | | GO:0006935 | BP | Chemotaxis | 0.03 | | |
| | | GO:0042330 | BP | Taxis | 0.03 | | |
| | | GO:0019220 | BP | Regulation of phosphate metabolic process | 0.03 | | |
| | | GO:0051174 | BP | Regulation of phosphorus metabolic process | 0.03 | | |
| | | GO:0010243 | BP | Response to organonitrogen compound | 0.03 | | |
| | | GO:0032879 | BP | Regulation of localization | 0.03 | | |
| | | GO:0016209 | MF | Antioxidant activity | 0.03 | | |
| | | GO:0004857 | MF | Enzyme inhibitor activity | 0.03 | | |
| | | GO:0004601 | MF | Peroxidase activity | 0.03 | | |

|  |  |  |  |  |  |  |  |
|---|---|---|---|---|---|---|---|
|  |  | GO:0016684 | MF | Oxidoreductase activity, acting on peroxide as acceptor | 0.03 |  |  |
|  |  | GO:0038023 | MF | Signaling receptor activity | 0.03 |  |  |
| **NADH** | 7 | GO:0016655 | MF | Oxidoreductase activity, acting on NAD(P)H, quinone or similar compound as acceptor | 0.02 | -0.13 (0.04) | -0.09 (0.15) |
|  |  | GO:0008137 | MF | NADH dehydrogenase (ubiquinone) activity | 0.02 |  |  |
|  |  | GO:0050136 | MF | NADH dehydrogenase (quinone) activity | 0.02 |  |  |
|  |  | GO:0003954 | MF | NADH dehydrogenase activity | 0.02 |  |  |
|  |  | GO:0008649 | MF | rRNA methyltransferase activity | 0.02 |  |  |
|  |  | GO:0140102 | MF | Catalytic activity, acting on a rRNA | 0.02 |  |  |
|  |  | GO:0048038 | MF | Quinone binding | 0.02 |  |  |
|  |  | GO:0008171 | MF | O-methyltransferase activity | 0.02 |  |  |
|  |  | GO:0045271 | CC | Respiratory chain complex I | 0.02 |  |  |
|  |  | GO:0045272 | CC | Plasma membrane respiratory chain complex I | 0.02 |  |  |
|  |  | GO:0030964 | CC | NADH dehydrogenase complex | 0.02 |  |  |
|  |  | GO:0031167 | BP | rRNA methylation | 0.02 |  |  |
| **Protein secretion** | 7 | GO:0009306 | BP | Protein secretion | 0.02 | 0.001 (0.99) | 0.13 (0.049) |
|  |  | GO:0002790 | BP | Peptide secretion | 0.02 |  |  |
|  |  | GO:0032940 | BP | Secretion by cell | 0.02 |  |  |
|  |  | GO:0046903 | BP | Secretion | 0.02 |  |  |
|  |  | GO:0035592 | BP | Establishment of protein localization to extracellular region | 0.02 |  |  |
|  |  | GO:0071692 | BP | Protein localization to extracellular region | 0.02 |  |  |
|  |  | GO:0071806 | BP | Protein transmembrane transport | 0.02 |  |  |
| **MF-1** | 17 | No assigned |  |  |  | -0.16 (0.01) | -0.05 (0.40) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **MF-2** | 12 | GO:0015179 | MF | L-amino acid transmembrane transporter activity | 0.03 | -0.14<br>(0.03) | -0.09<br>(0.18) |

Abbreviations: BP, biological process; CC, cellular component; FDR, false discovery rate; HR, host response; IFN, interferon; IL, interleukin; NADH, nicotinamide adenine dinucleotide; MF (in GO), molecular function; MF (in modules), microbial function; PPV, positive pressure ventilation

[*] The top 20 pathways with the highest FDR or pathways with P-values of <0.05 are shown.

[†] FDR is calculated based on the p-value of the pathway enrichment analysis in each module.

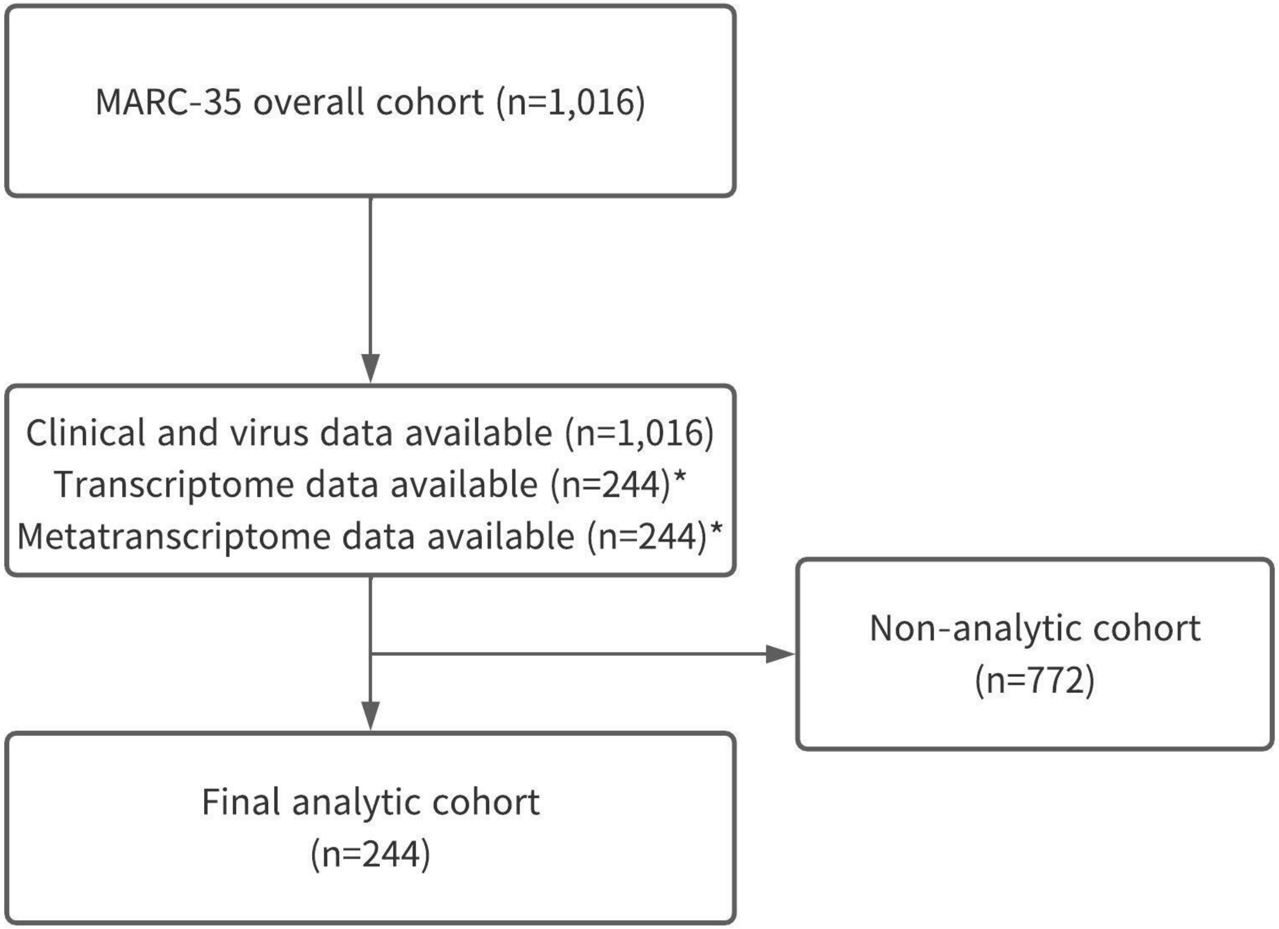
[‡] Spearman's coefficients between the eigenvalue (the first principal component) of corresponding module and PPV or intensive care use were estimated.

**Supplemental Table 6.** Primers for respiratory pathogen testing

| **Pathogen** | **Target gene** | **Primer name** | **Primer/Probe Sequence** |
|---|---|---|---|
| RSV A | Nucleoprotein | RSVA Fwd. | AGA TCA ACT TCT GTC ATC CAG CAA |
| | | RSVA Rev. | TTC TGC ACA TCA TAA TTA GGA GTA TCA AT |
| | | RSVA Probe | CAC CAT CCA ACG GAG CAC AGG AGA T |
| RSV B | Nucleoprotein | RSVB Fwd. | AAG ATG CAA ATC ATA AAT TCA CAG GA |
| | | RSVB Rev. | TGA TAT CCA GCA TCT TTA AGT ATC TTT ATA GTG |
| | | RSVB Probe | AGG TAT GTT ATA TGC TAT GTC CAG GTT AGG AAG GGA A |
| RSV A* | Nucleoprotein | LTRSVA Fwd. | GATACACTCAACAAAGATCAACTTCTGTCA |
| | | LTRSVA Rev. | AGGAGTGTCAATGCTGTCTCCTGTG |
| | | LT RSVA Probe | TCCAGCAAATACACCATCCAACGGAG |
| RSV B* | Nucleoprotein | LTRSVB Fwd. | CTGTGTATAGCTGCCCTTGTAATAACC |
| | | LTRSVB Rev. | GACATTGTTTGCCCTCCTAATTACTGC |
| | | LTRSVB Probe | AGCAGCAGGAGATAGATCAGGTCTTACA |
| Influenza A | Matrix | FluA Fwd. | GAC CRA TCC TGT CAC CTC TGA |
| | | FluA Rev. | AGG GCA TTY TGG ACA AAK CGT CTA |
| | | FluA Probe | TGC AGT CCT CGC TCA CGT GGC ACG |
| Influenza B | Nucleoprotein | FluB Fwd. | AAG ACC TRA GAG TTT TGT CTG CAY T |
| | | FluB Rev. | ATC AGA GCT GCY CCC ATT |
| | | FluB Probe | TGC AAG GGT TTC CAY GTT CCA GCA |
| Parainfluenza-1 | Polymerase | PIV-1 Fwd. | ACA GAT GAA ATT TTC AAG TGC TAC TTT AGT |
| | | PIV-1 Rev. | GCC TCT TTT AAT GCC ATA TTA TCA TTA GA |
| | | PIV-1 Probe | ATG GTA ATA AAT CGA CTC GCT |
| Parainfluenza-2 | Polymerase | PIV-2 Fwd. | TGC ATG TTT TAT AAC TAC TGA TCT TGC TAA |
| | | PIV-2 Rev. | GTT CGA GCA AAA TGG ATT ATG GT |
| | | PIV-2 Probe | ACT GTC TTC AAT GGA GAT AT |
| Parainfluenza-3 | Nucleoprotein | PIV-3 Fwd. | TGT TGA GCC TAT TTG ATA CAT TTA ATG C |
| | | PIV-3 Rev. | ATG ATA GCT CCA CCA GCT GAT TTT |
| | | PIV-3 Probe | CGT AGG CAA GAA AAC ATA A |
| Rhinovirus | 5’UTR | HRV Fwd | CY+ AGC C+T GCG TGG C (+ is LNA base) |
| | | HRV Rev. | GAA ACA CGG ACA CCC AAA GTA |
| | | HRV Probe | TCC TCC GGC CCC TGA ATG YGG C |
| Human Metapneumovirus | Nucleoprotein | HMPV Fwd. | CAT ATA AGC ATG CTA TAT TAA AAG AGT CTC |
| | | HMPV Rev. | CCT ATT TCT GCA TAT TTG TAA TCA G |
| | | HMPV Probe | TGY AAT GAT GAG GGT GTC ACT GCG GTT G |
| Enterovirus | 5’UTR | Ent Fwd. | GAT TGT CAC CAT AAG CAG C |
| | | Ent Rev | CCC CTG AAT GCG GCT AAT C |
| | | Ent Probe | CGG AAC CGA CTA CTT TGG GTG TCC GT |
| Human Corona virus 229E | Nucleoprotein | 229E Fwd. | TCT GCC AAG AGT CTT GCT CG |
| | | 229E Rev. | AGC ATA GCA GCT GTT GAC GG |
| | | 229E Probe | TGG CCA CAA CAC CTG CAC TTC C |
| Human Corona virus OC43 | Nucleoprotein | OC43 Fwd. | CAT CAG GAG GGA ATG TTG TAC C |
| | | OC43 Rev. | TAC TGG TCT TTA GCA TGC GGT C |
| | | OC43 Probe | CAG CAG TTG ACG CTG GTT GCC ATC |

|  |  |  |  |
|---|---|---|---|
| Human Corona virus HKU1 | Replicase 1B | HKU1 Fwd. | CCT TGC GAA TGA ATG TGC T |
|  |  | HKU1 Rev. | TTG CAT CAC CAC TGC TAG TAC CAC |
|  |  | HKU1 Probe | TGT GTG GCG GTT GCT ATT ATG TTA AGC CTG |
| Human Corona virus NL63 | Nucleoprotein | NL63 Fwd. | GAC CAA AGC ACT GAA TAA CAT TTT CC |
|  |  | NL63 Rev. | ACC TAA TAA GCC TCT TTC TCA ACC C |
|  |  | NL63 Probe | AAC ACG CTT CCA ACG AGG TTT CTT CAA CTG AG |
| Adenovirus | Hexon | Adeno Fwd. | CAG GAC GCC TCG GRG TAY CTS AG |
|  |  | Adeno Rev. | GGA GCC ACV GTG GGR TT |
|  |  | Adeno Probe | CCG GGT CTG GTG CAG TTT GCC C |
| Bocavirus | Non-structural protein 1 | Boca Fwd. | TGC AGA CAA CGC YTA GTT GTT T |
|  |  | Boca Rev. | CTG TCC CGC CCA AGA TAC A |
|  |  | Boca Probe | CCA GGA TTG GGT GGA ACC TGC AAA |
| *Mycoplasma pneumoniae* | CARDS toxin | Myco Fwd. | TTT GGT AGC TGG TTA CGG GAA T |
|  |  | Myco Rev. | GGT CGG CAC GAA TTT CAT ATA AG |
|  |  | Myco Probe | TGT ACC AGA GCA CCC CAG AAG GGC T |
| *Bordetella pertussis* (Screening assay) | IS481 | ISBordo Fwd. | GCG TGC AGA TTC GTC GTA C |
|  |  | ISBordo Rev. | TGA TGG TGC CTA TTT TAC GG |
|  |  | ISBordo Probe | ACC CTC GAT TCT TCC GT |
| *Bordetella pertussis* (Confirmatory assay) | Toxin | Bordo Fwd. | GCG TGC AGA TTC GTC GTA C |
|  |  | Bordo Rev. | AGG GCA TTY TGG ACA AAK CGT CTA |
|  |  | Bordo Probe | TGC AGT CCT CGC TCA CTG GGC ACG |

**Supplemental Figure 1. Study flow diagram**

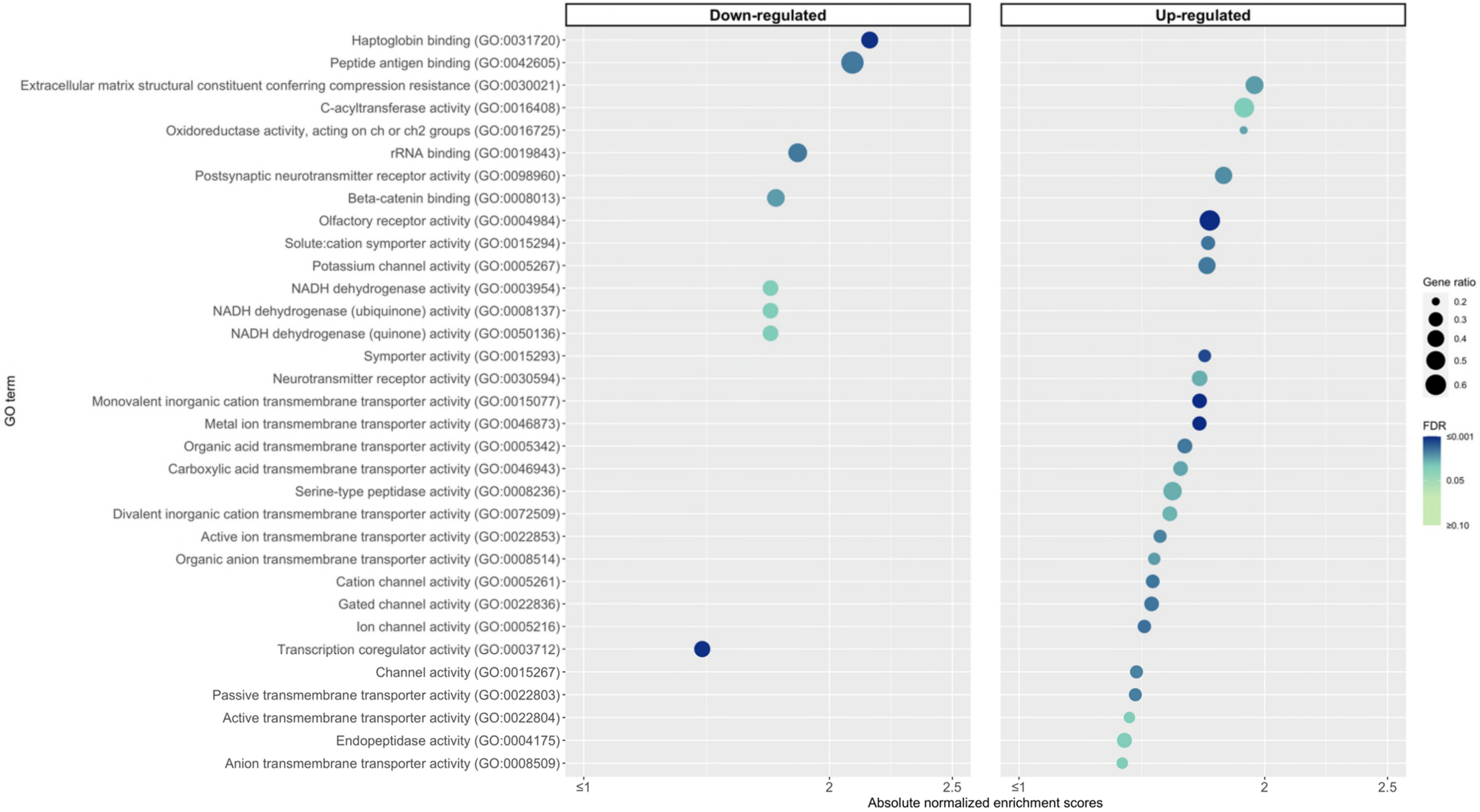


The differences in the analytic and non-analytic cohorts are summarized in **Supplemental Table 1**.

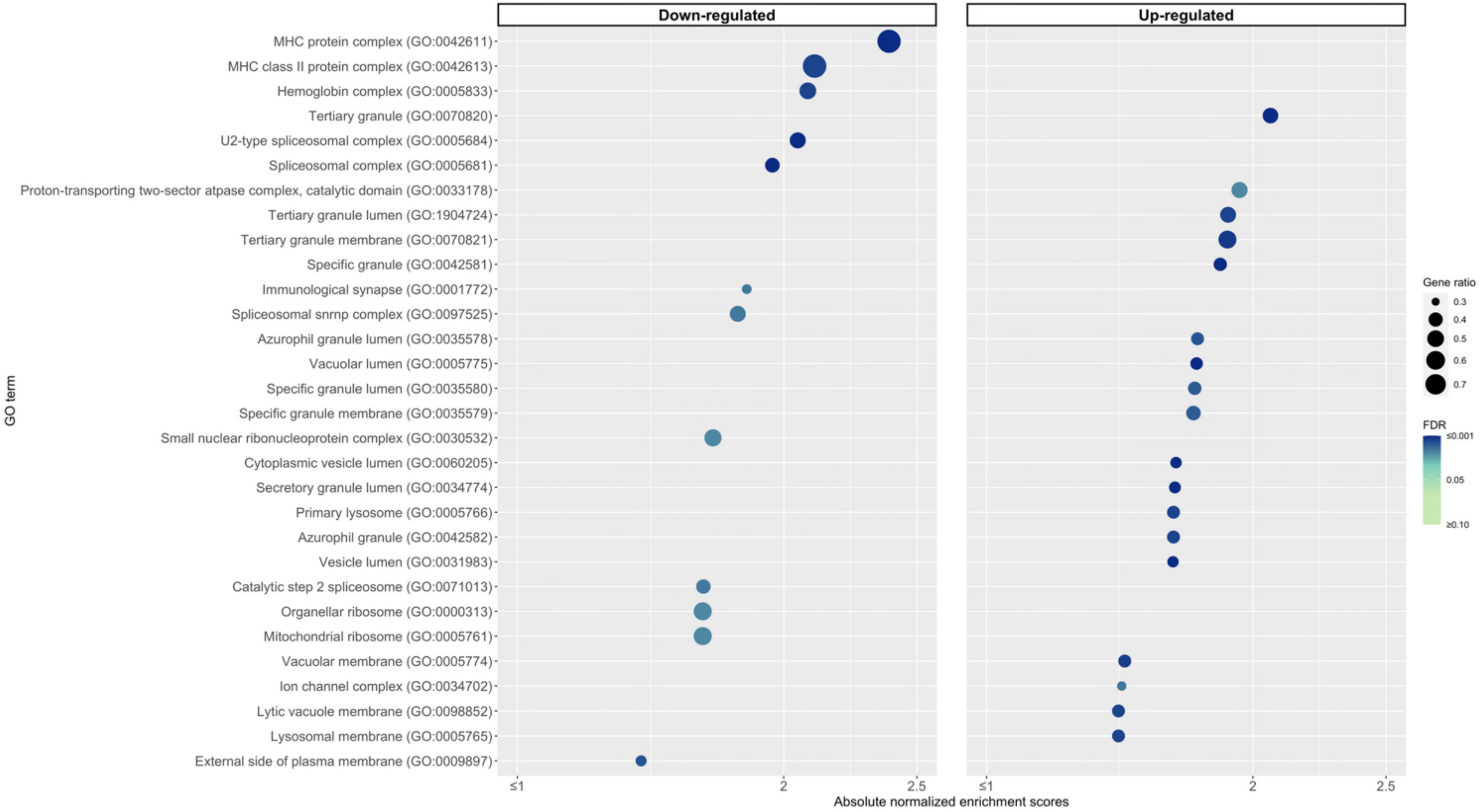
* The transcriptome and metatranscriptome data were obtained in 244 infants who were *randomly* selected from the overall cohort

**Supplemental Figure 2. Gene set enrichment analysis of host transcriptome data with regard to the use of positive pressure ventilation in infants hospitalized for bronchiolitis**

**A)**



**B)**

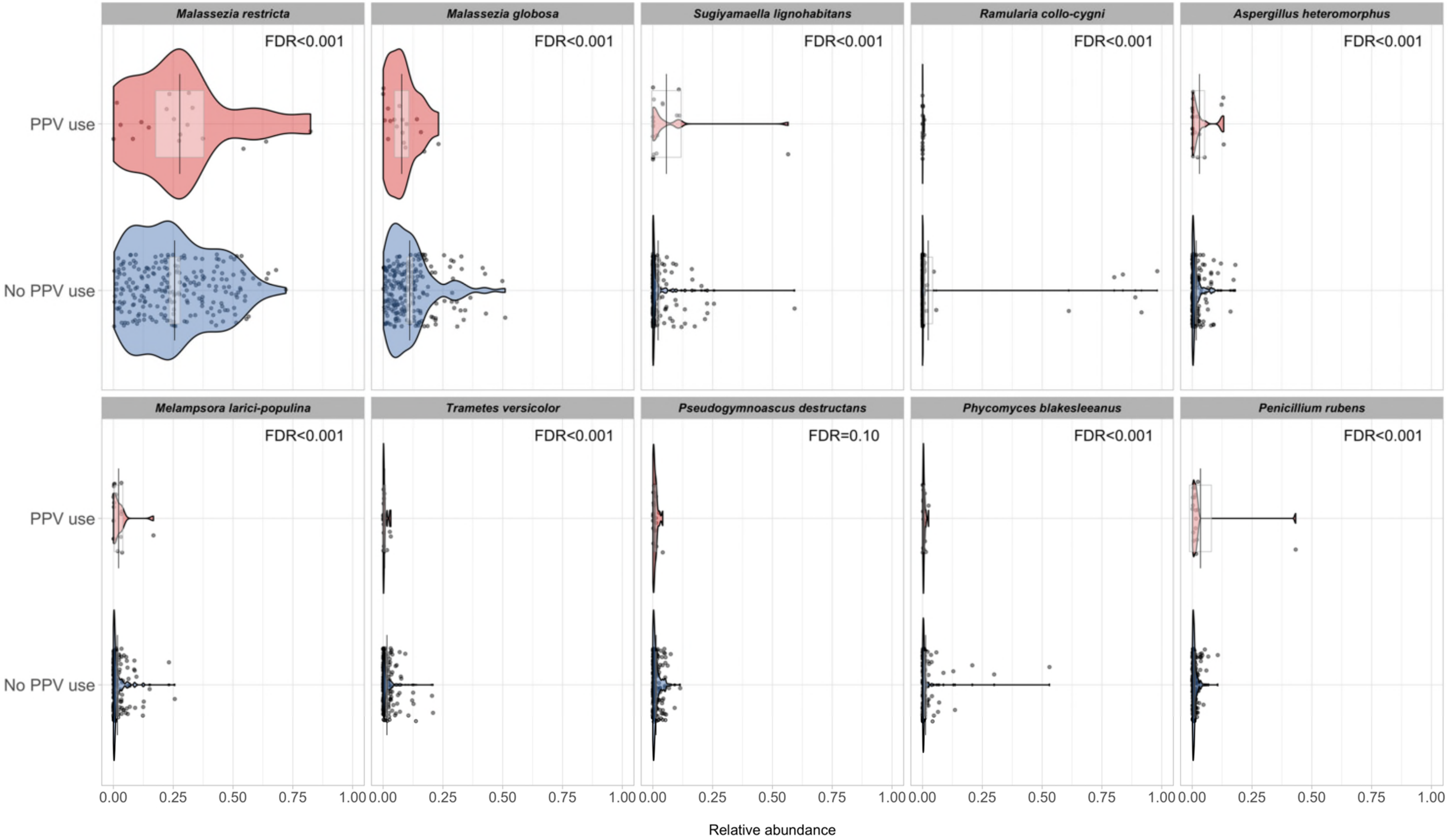

Down-regulated
Up-regulated
MHC protein complex (GO:0042611)
MHC class II protein complex (GO:0042613)
Hemoglobin complex (GO:0005833)
Tertiary granule (GO:0070820)
U2-type spliceosomal complex (GO:0005684)
Spliceosomal complex (GO:0005681)
Proton-transporting two-sector atpase complex, catalytic domain (GO:0033178)
Tertiary granule lumen (GO:1904724)
Tertiary granule membrane (GO:0070821)
Specific granule (GO:0042581)
Immunological synapse (GO:0001772)
Spliceosomal snrnp complex (GO:0097525)
Azurophil granule lumen (GO:0035578)
Vacuolar lumen (GO:0005775)
Specific granule lumen (GO:0035580)
Specific granule membrane (GO:0035579)
Small nuclear ribonucleoprotein complex (GO:0030532)
Cytoplasmic vesicle lumen (GO:0060205)
Secretory granule lumen (GO:0034774)
Primary lysosome (GO:0005766)
Azurophil granule (GO:0042582)
Vesicle lumen (GO:0031983)
Catalytic step 2 spliceosome (GO:0071013)
Organellar ribosome (GO:0000313)
Mitochondrial ribosome (GO:0005761)
Vacuolar membrane (GO:0005774)
Ion channel complex (GO:0034702)
Lytic vacuole membrane (GO:0098852)
Lysosomal membrane (GO:0005765)
External side of plasma membrane (GO:0009897)
GO term
≤1
2
2.5
≤1
2
2.5
Absolute normalized enrichment scores
Gene ratio
0.3
0.4
0.5
0.6
0.7
FDR
≤0.001
0.05
≥0.10

**A)** GO molecular function. **B)** GO cellular component.

We showed 30 host pathways with the most significant FDR in the gene set enrichment analysis (GSEA) with down-regulated pathways on the left side and up-regulated pathways on the right side. We also showed the absolute normalized enrichment score, FDR, and the gene ratio for the corresponding pathways.

Abbreviations: FDR, false discovery rate; GO, gene ontology; GSEA, gene set enrichment analysis; MHC, major histocompatibility complex; NADH, nicotinamide adenine dinucleotide; PPV, positive pressure ventilation

**Supplemental Figure 3. Relationship of abundant fungal species with the risk of higher severity in infants hospitalized for bronchiolitis**

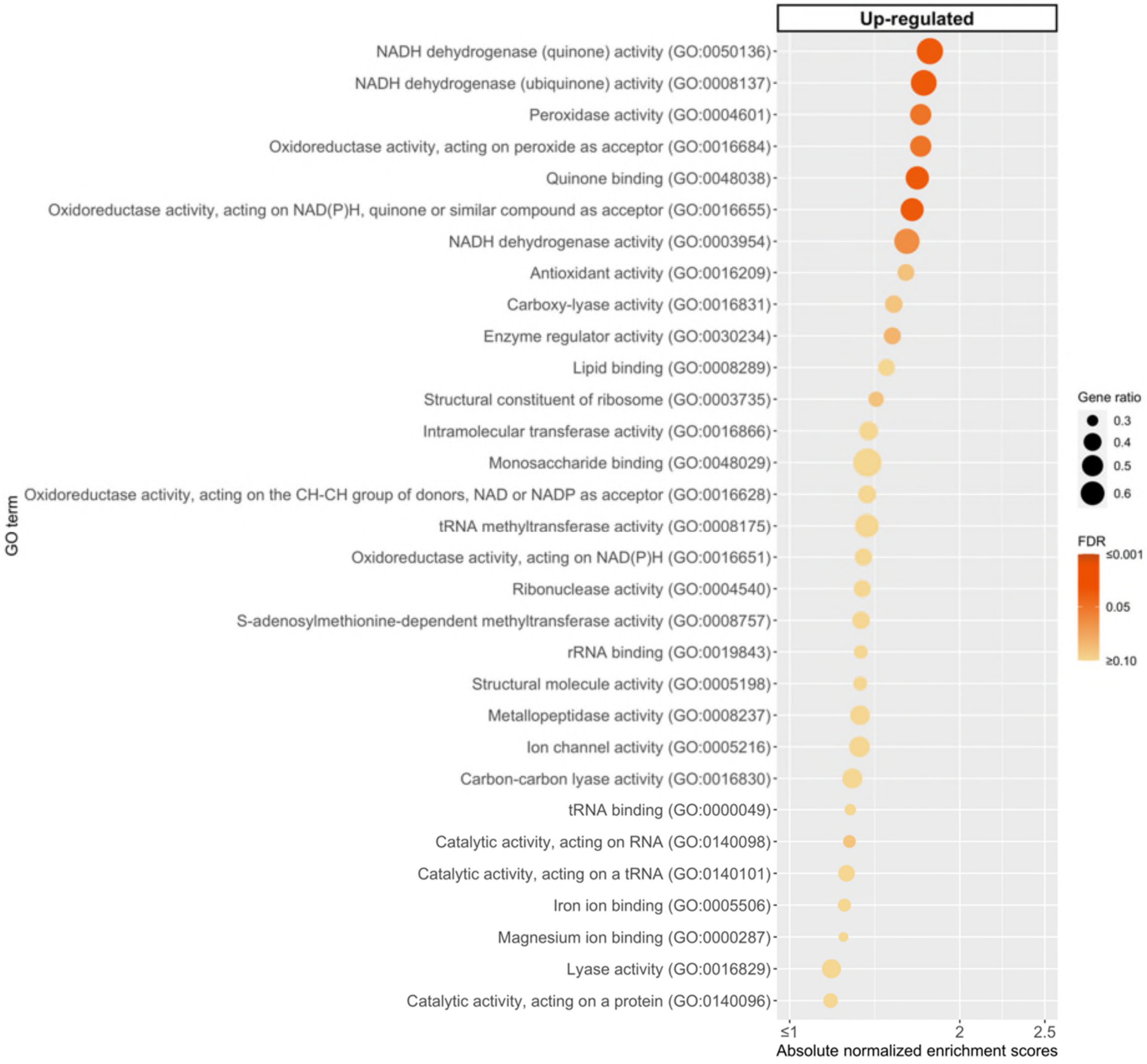


The pirate plots show the comparison of the distribution of annotated ten most abundant fungal species in the nasopharyngeal airway of infants hospitalized for bronchiolitis, according to the PPV use. Each point represents each infant. The grey bar and rectangle represent the mean and 95% confidence interval. In the violin plots, the width represents the probability that infants take on a specific relative abundance. The between-group differences in the abundance were tested by fitting Poisson regression models. n = 244 biologically independent samples.

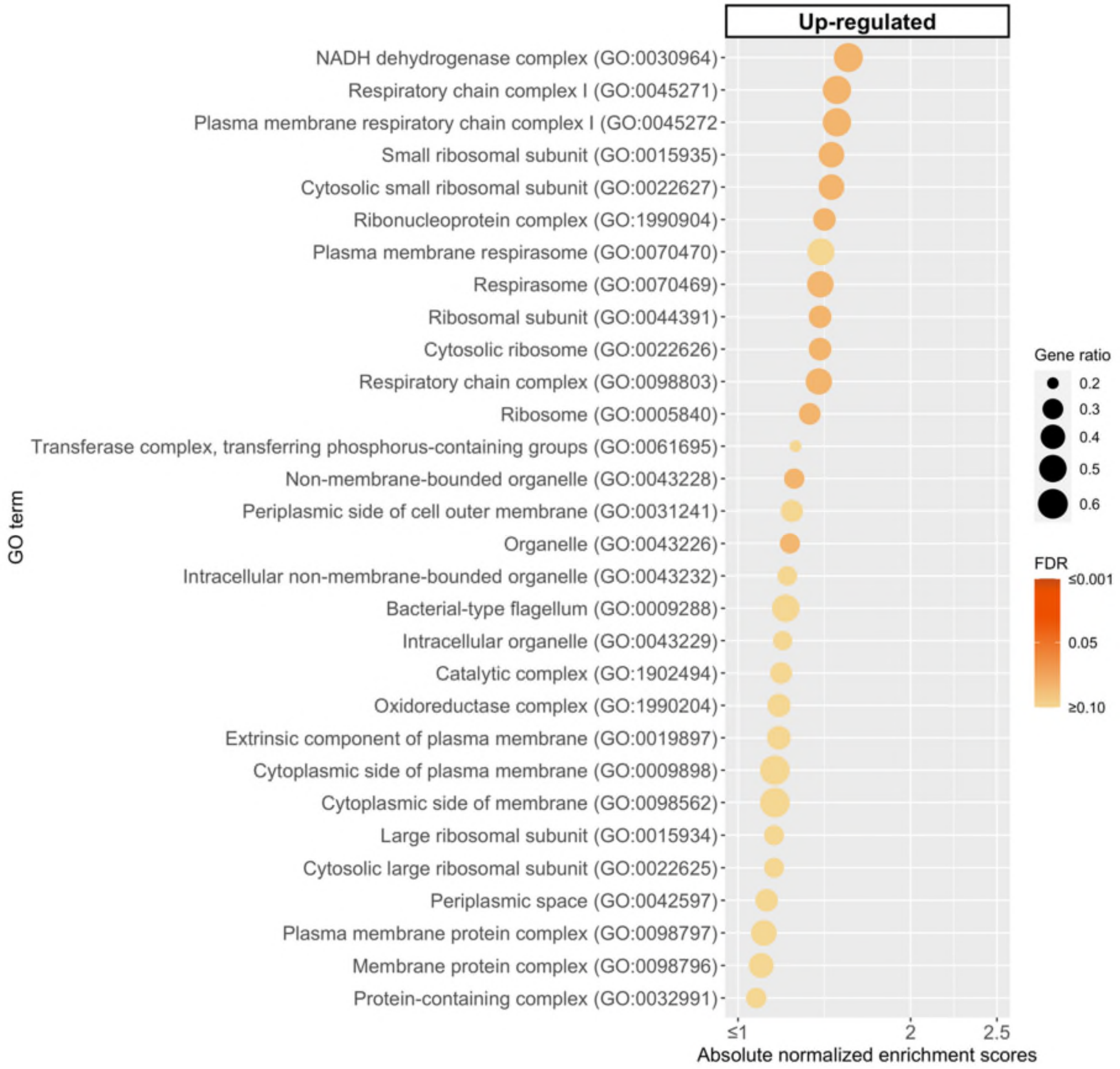
Abbreviations: FDR, false discovery rate; PPV, positive pressure ventilation

**Supplemental Figure 4. Gene set enrichment analysis of microbial function data with regard to the use of positive pressure ventilation in infants hospitalized for bronchiolitis**

**A)**



**B)**

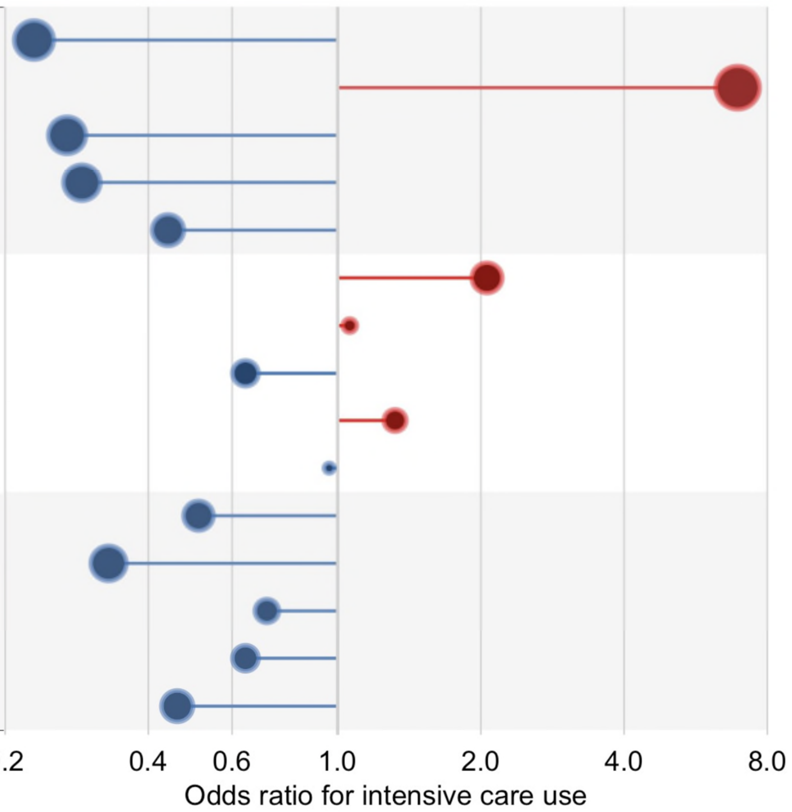


**A)** GO molecular function. **B)** GO cellular component. Gene set enrichment analysis (GSEA) of the metatranscriptome data. We showed 30 microbial functional pathways (GO biological process) with the most significant FDR in the gene set enrichment analysis (GSEA). Down-regulated pathways were not detected. We also showed the normalized enrichment score, FDR, and the gene ratio for the corresponding pathways.

Abbreviations: FDR, false discovery rate; GO, gene ontology; GSEA, gene set enrichment analysis NADH, nicotinamide adenine dinucleotide

**Supplemental Figure 5. Sensitivity analysis: Integrated relationship of the dual-transcriptome modules with the risk of intensive care use in infants hospitalized for bronchiolitis**

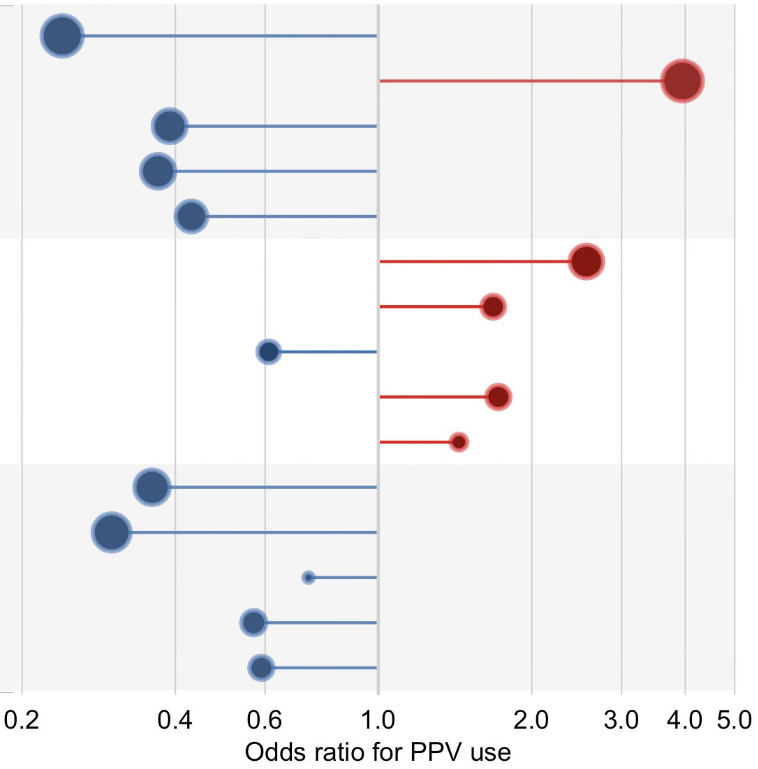
| Module | Odds ratio (95% CI) |
|---|---|
| **T cell regulation module** | 0.23 (0.08-0.62) |
| **Neutrophil/IL-1 module** | 6.93 (2.48-21.6) |
| **GPCR module** | 0.27 (0.09-0.69) |
| **Type I IFN module** | 0.29 (0.09-0.72) |
| HR-1 module | 0.44 (0.16-1.03) |
| *S. pneumoniae*/*S. aureus* module | 2.06 (0.79-5.24) |
| MC-1 module | 1.06 (0.41-2.73) |
| *Moraxella* module | 0.64 (0.21-2.01) |
| *Streptcoccus* module | 1.32 (0.47-3.84) |
| *Haemophilus* module | 0.96 (0.32-2.87) |
| **Plasma membrane module** | 0.33 (0.16-0.76) |
| mRNA metabolism module | 0.51 (0.24-1.22) |
| BCAA metabolism module | 0.71 (0.04-1.78) |
| Oxidative stress response module | 0.64 (0.11-2.08) |
| **NADH module** | 0.46 (0.02-0.71) |



The adjusted odds ratio for the outcome was estimated per one unit increased in the eigen-value (the first principal component) of the corresponding module by fitting a multivariable logistic regression model with ridge regularization. 95% CIs were estimated by a bootstrap method with 2,000 replicates. In the model, we adjusted for age, sex, race/ethnicity, and respiratory virus. Statistically significant modules are in **bold**.
Abbreviations: BCAA, branched-chain amino acid; FDR, false discovery rate; GPCR, G-protein-coupled receptor; HR, host response; IFN, interferon; IL, interleukin; NADH, nicotinamide adenine dinucleotide hydrogen; MC, microbial composition

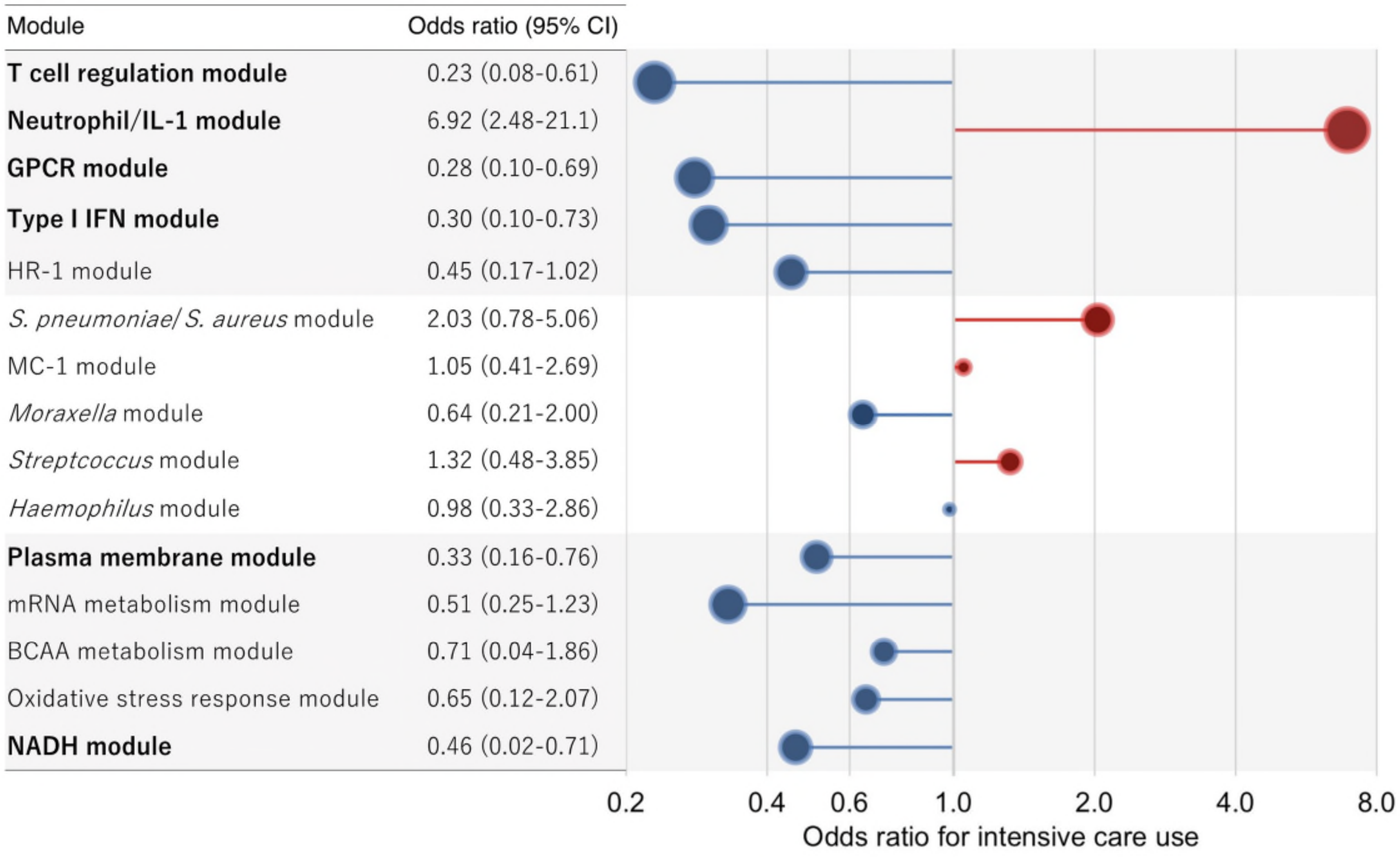
**Supplemental Figure 6. Sensitivity analysis adjusting for age, sex, race/ethnicity, and virus: Integrated relationship of the dual-transcriptome modules with the risk of positive pressure ventilation use in infants hospitalized for bronchiolitis**

| Modules | Odds ratio (95% CI) |
|---|---|
| **T cell regulation module** | 0.24 (0.11-0.53) |
| **Neutrophil/IL-1 module** | 3.95 (1.71-10.1) |
| **GPCR module** | 0.39 (0.16-0.78) |
| **Type I IFN module** | 0.37 (0.14-0.75) |
| **HR-1 module** | 0.43 (0.17-0.98) |
| S. pneumoniae/S. aureus **module** | 2.56 (1.19-5.81) |
| MC-1 module | 1.68 (0.75-3.80) |
| Moraxella module | 0.61 (0.24-1.46) |
| Streptcoccus module | 1.72 (0.67-4.27) |
| Haemophilus module | 1.44 (0.60-3.68) |
| **Plasma membrane module** | 0.30 (0.16-0.50) |
| **mRNA metabolism module** | 0.36 (0.20-0.64) |
| **BCAA metabolism module** | 0.73 (0.05-0.88) |
| **Oxidative stress response module** | 0.57 (0.07-0.78) |
| **NADH module** | 0.59 (0.06-0.80) |



The adjusted odds ratio for the outcome was estimated per one unit increased in the eigen-value (the first principal component) of the corresponding module by fitting a multivariable logistic regression model with ridge regularization. In the model, we adjusted for age, sex, and respiratory virus. 95% CIs were estimated by a bootstrap method with 2,000 replicates. Statistically significant modules are in **bold**.
Abbreviations: BCAA, branched-chain amino acid; FDR, false discovery rate; GPCR, G-protein-coupled receptor; HR, host response; IFN, interferon; IL, interleukin; NADH, nicotinamide adenine dinucleotide hydrogen; MC, microbial composition

**Supplemental Figure 7. Sensitivity analysis adjusting for age, sex, race/ethnicity, and virus: Integrated relationship of the dual-transcriptome modules with the risk of intensive care use in infants hospitalized for bronchiolitis**

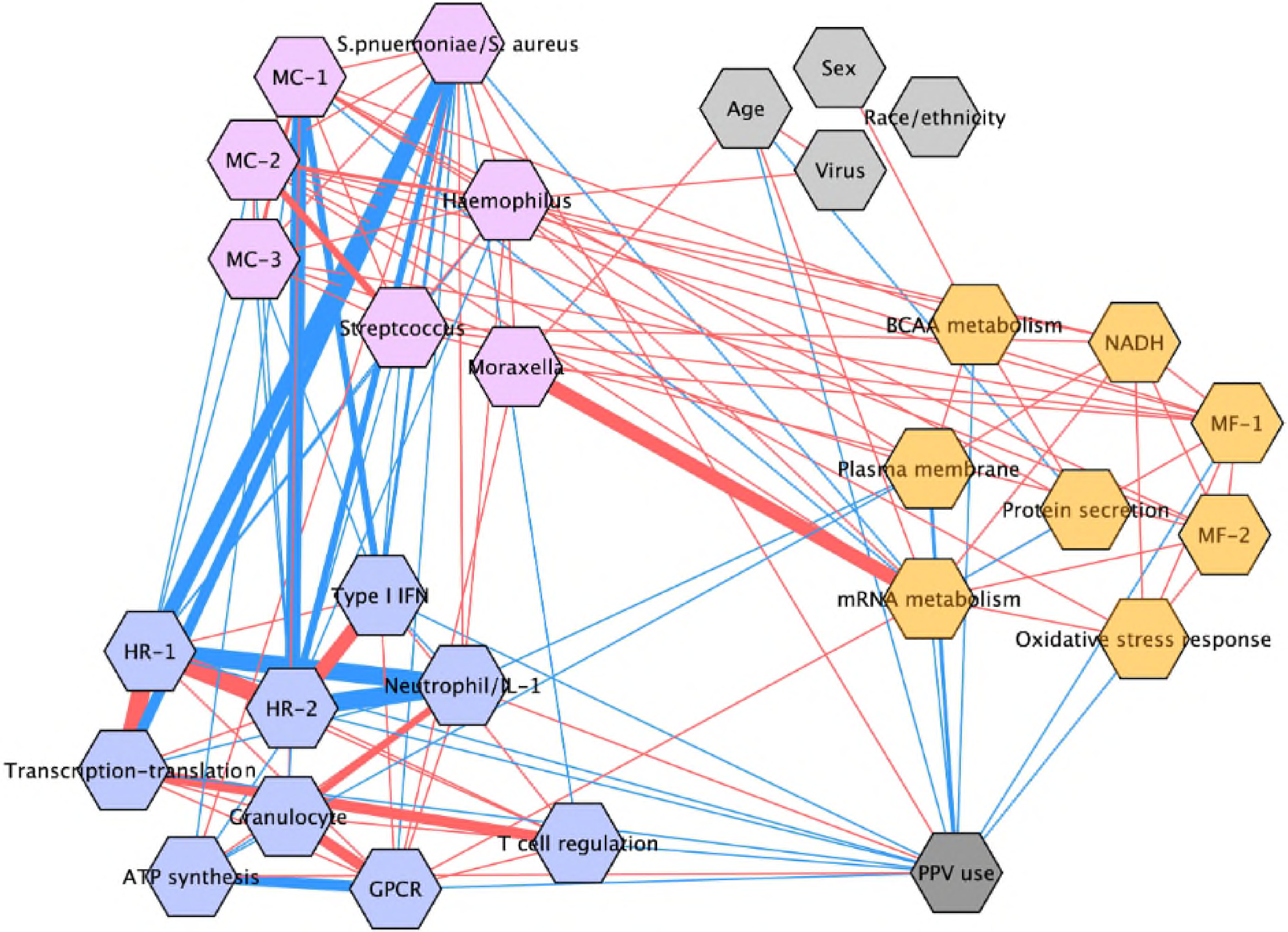


| Module | Odds ratio (95% CI) |
|---|---|
| **T cell regulation module** | 0.23 (0.08-0.61) |
| **Neutrophil/IL-1 module** | 6.92 (2.48-21.1) |
| **GPCR module** | 0.28 (0.10-0.69) |
| **Type I IFN module** | 0.30 (0.10-0.73) |
| HR-1 module | 0.45 (0.17-1.02) |
| *S. pneumoniae*/ *S. aureus* module | 2.03 (0.78-5.06) |
| MC-1 module | 1.05 (0.41-2.69) |
| *Moraxella* module | 0.64 (0.21-2.00) |
| *Streptcoccus* module | 1.32 (0.48-3.85) |
| *Haemophilus* module | 0.98 (0.33-2.86) |
| **Plasma membrane module** | 0.33 (0.16-0.76) |
| mRNA metabolism module | 0.51 (0.25-1.23) |
| BCAA metabolism module | 0.71 (0.04-1.86) |
| Oxidative stress response module | 0.65 (0.12-2.07) |
| **NADH module** | 0.46 (0.02-0.71) |

The adjusted odds ratio for the outcome was estimated per one unit increased in the eigen-value (the first principal component) of the corresponding module by fitting a multivariable logistic regression model with ridge regularization. In the model, we adjusted for age, sex, race/ethnicity, and respiratory virus. 95% CIs were estimated by a bootstrap method with 2,000 replicates. Statistically significant modules are in **bold**.

Abbreviations: BCAA, branched-chain amino acid; FDR, false discovery rate; GPCR, G-protein-coupled receptor; HR, host response; IFN, interferon; IL, interleukin; NADH, nicotinamide adenine dinucleotide hydrogen; MC, microbial composition

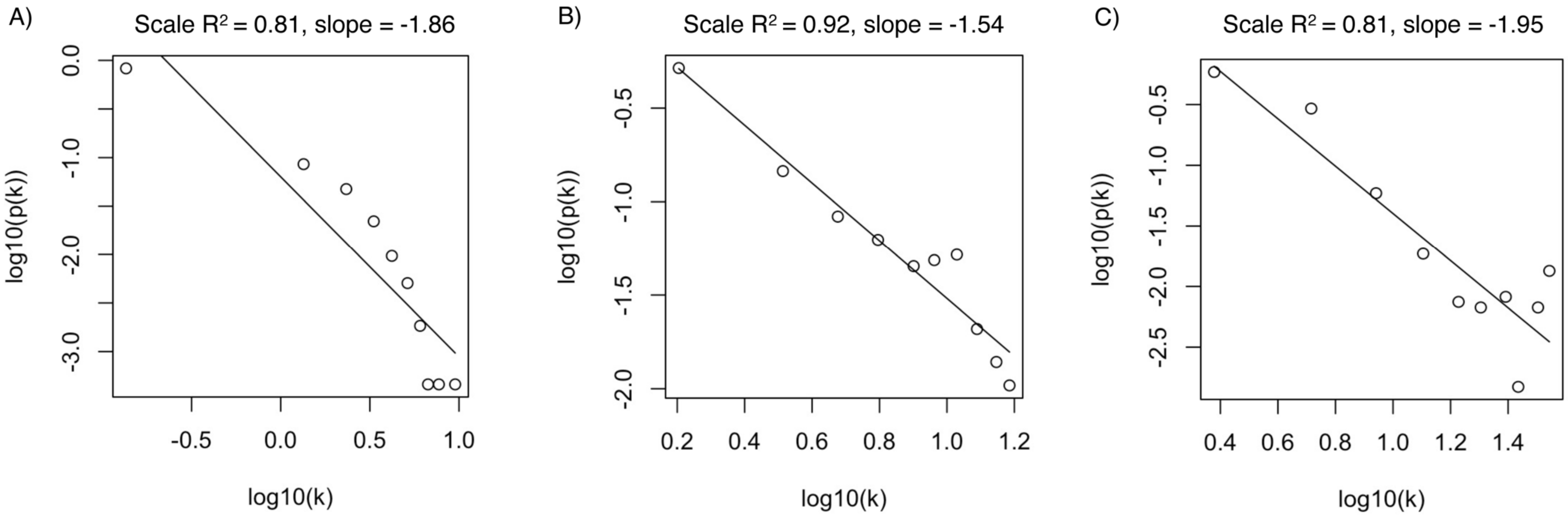
**Supplemental Figure 8. Correlation network of major clinical variables and dual-transcriptome modules**



Nodes are represented by different colors corresponding to clinical variables and module categories. Edges show correlations between two variables and/or nodes. Edges with a Pearson correlation of greater than 0.15 are shown. Positive correlations are displayed as red; negative correlations are displayed as blue. Edge thickness is proportional to the strength of the correlation.

Abbreviations: ATP, adenosine triphosphate; BCAA, branched-chain amino acid; FDR, false discovery rate; GPCR, G-protein-coupled receptor; HR, host response; IFN, interferon; IL, interleukin; NADH, nicotinamide adenine dinucleotide hydrogen; MC, microbial composition; MF, microbial function

**Supplemental Figure 9. Log-log plot of whole-network connectivity distribution of host response, microbial composition, and microbial function**



The x-axis indicates the logarithm of whole network connectivity; the y-axis indicates the logarithm of the corresponding frequency. On these plots, the distribution approximately follows a straight line, which implies an approximately scale-free topology in each dataset.

**A)** Host response data
**B)** Microbial composition data
**C)** Microbial function data