

Tobacco exposure associated with oral microbiome anaerobiosis in the New York City Health and Nutrition Examination Study (NYC HANES) II

Francesco Beghini^{1*}

¹Laboratory of Computational Metagenomics - Centre for Integrative Biology - University of Trento - Italy

*francesco.beghini@unitn.it (mailto:francesco.beghini@unitn.it)

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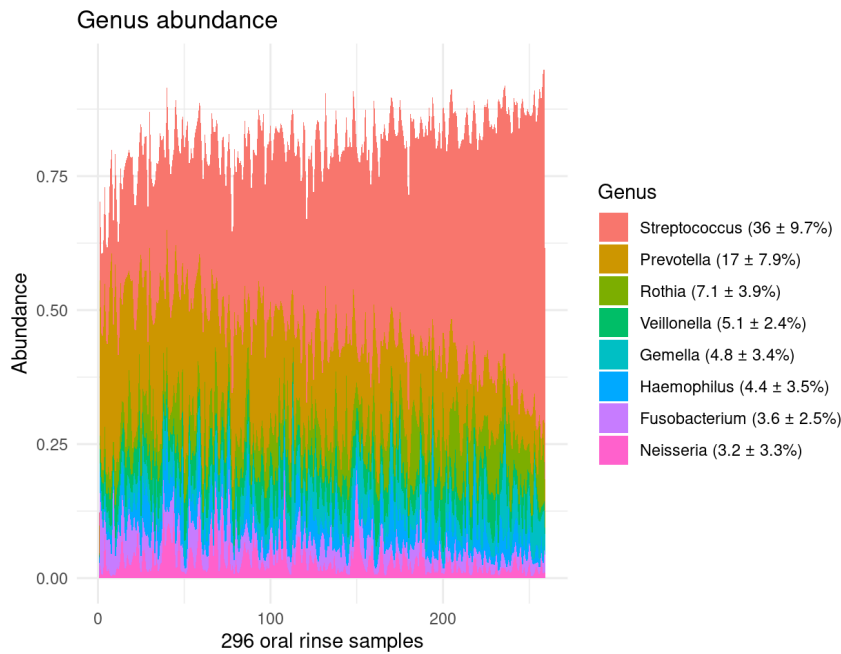
7.7 Cigar/cigarillos smokers vs Never smokers

1 Table 1: Demographics & Descriptive Statistics

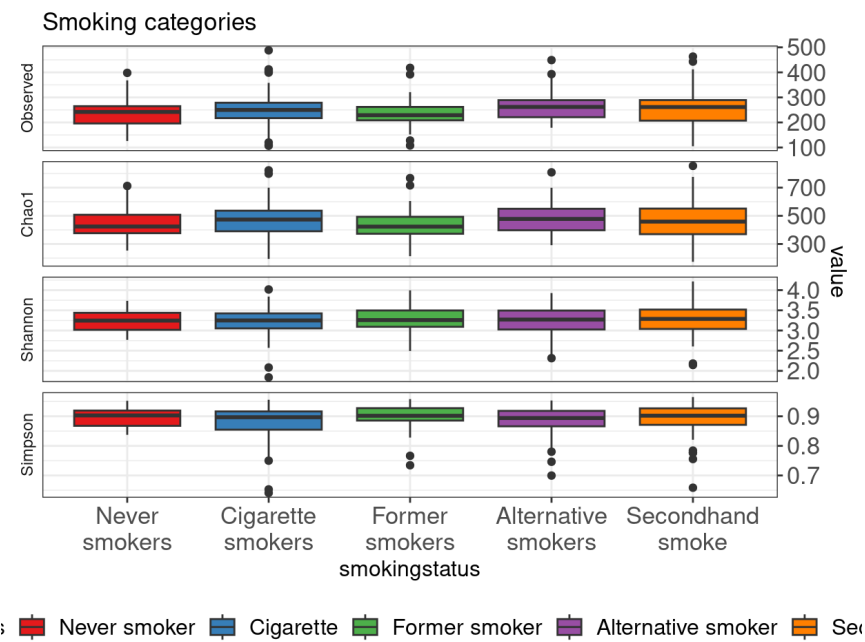
	Never smoker	Cigarette	Former smoker	Alternative smoker	Secondhand
n	43	86	43	49	38
GENDER = Female (%)	28 (65.1)	45 (52.3)	25 (58.1)	22 (44.9)	22 (57.9)
RACE (%)					
Non-Hispanic White	13 (30.2)	24 (27.9)	25 (58.1)	19 (38.8)	10 (26.3)
Non-Hispanic Black	13 (30.2)	33 (38.4)	4 (9.3)	9 (18.4)	11 (28.9)
Hispanic	10 (23.3)	19 (22.1)	10 (23.3)	12 (24.5)	14 (36.8)
Asian	3 (7.0)	9 (10.5)	3 (7.0)	3 (6.1)	2 (5.3)
Other	4 (9.3)	1 (1.2)	1 (2.3)	6 (12.2)	1 (2.6)
EDU4CAT (%)					
College graduate or more	16 (37.2)	18 (20.9)	21 (48.8)	17 (34.7)	9 (23.7)
Less than High school diploma	8 (18.6)	24 (27.9)	4 (9.3)	10 (20.4)	14 (36.8)
High school graduate/GED	7 (16.3)	24 (27.9)	8 (18.6)	11 (22.4)	10 (26.3)
Some College or associate's degree	12 (27.9)	20 (23.3)	10 (23.3)	11 (22.4)	5 (13.2)
SPAGE (mean (SD))	45.42 (16.50)	45.85 (13.07)	55.47 (18.00)	35.59 (16.44)	37.76 (14.70)
AGEGRP5C (%)					
20-29	7 (16.3)	10 (11.6)	3 (7.0)	26 (53.1)	14 (36.8)
30-39	11 (25.6)	17 (19.8)	7 (16.3)	8 (16.3)	11 (28.9)
40-49	10 (23.3)	25 (29.1)	7 (16.3)	4 (8.2)	3 (7.9)
50-59	6 (14.0)	19 (22.1)	8 (18.6)	7 (14.3)	6 (15.8)
60 AND OVER	9 (20.9)	15 (17.4)	18 (41.9)	4 (8.2)	4 (10.5)

	Never smoker	Cigarette	Former smoker	Alternative smoker	Secondhand
DBTS_NEW (%)					
Yes	5 (11.6)	5 (5.8)	7 (16.3)	3 (6.1)	2 (5.3)
No	38 (88.4)	81 (94.2)	36 (83.7)	38 (77.6)	36 (94.7)
NA	0 (0.0)	0 (0.0)	0 (0.0)	8 (16.3)	0 (0.0)
SR_ACTIVE (%)					
Very active	15 (34.9)	27 (31.4)	11 (25.6)	16 (32.7)	17 (44.7)
Somewhat active	20 (46.5)	37 (43.0)	20 (46.5)	25 (51.0)	15 (39.5)
Not very active/not active at all	8 (18.6)	22 (25.6)	12 (27.9)	8 (16.3)	6 (15.8)
INC25KMOD (%)					
Less Than \$20,000	5 (11.6)	31 (36.0)	8 (18.6)	20 (40.8)	14 (36.8)
\$20,000-\$49,999	15 (34.9)	20 (23.3)	9 (20.9)	14 (28.6)	9 (23.7)
\$50,000-\$74,999	6 (14.0)	11 (12.8)	3 (7.0)	6 (12.2)	4 (10.5)
\$75,000-\$99,999	8 (18.6)	4 (4.7)	6 (14.0)	4 (8.2)	2 (5.3)
\$100,000 or More	6 (14.0)	11 (12.8)	13 (30.2)	2 (4.1)	6 (15.8)
NA	3 (7.0)	9 (10.5)	4 (9.3)	3 (6.1)	3 (7.9)
COTININE (median [IQR])	0.04 [0.04, 0.04]	271.49 [189.99, 360.99]	0.04 [0.04, 0.04]	10.54 [0.28, 55.36]	3.01 [1.39, 5.48]
OHQ_3 (%)					
Yes	4 (9.3)	9 (10.5)	5 (11.6)	4 (8.2)	4 (10.5)
No	39 (90.7)	76 (88.4)	38 (88.4)	45 (91.8)	34 (89.5)
NA	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)

2 Microbial composition (8 most abundant genera)



3 Alpha diversity



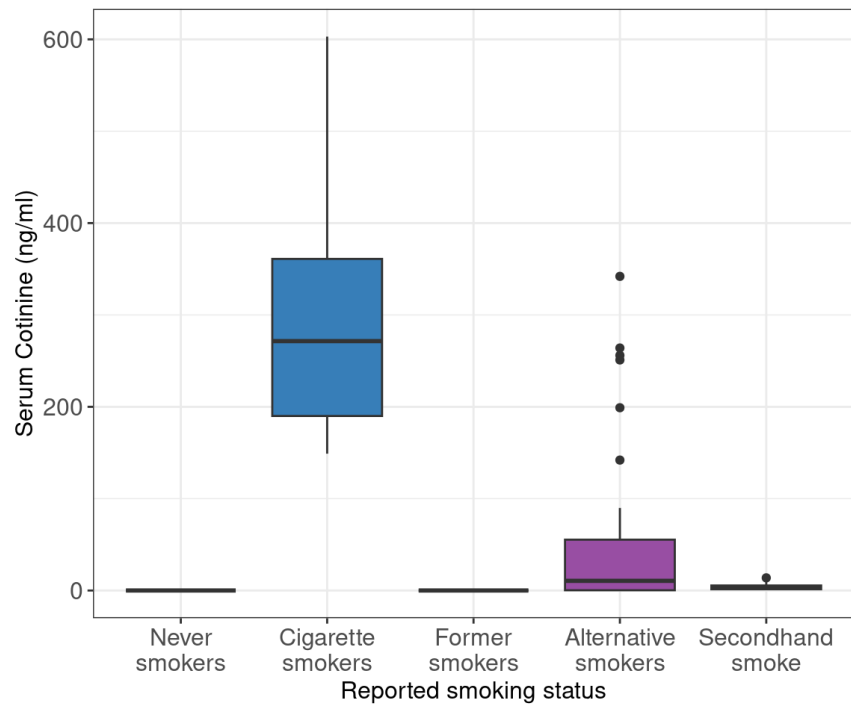
```
##               Df Sum Sq Mean Sq F value Pr(>F)
## smokingstatus  4   0.09  0.02162   0.168  0.954
## Residuals    254  32.62  0.12841

##               Df Sum Sq Mean Sq F value Pr(>F)
## smokingstatus  4 34597   8649     2.12 0.0788 .
## Residuals    254 1036314   4080

## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

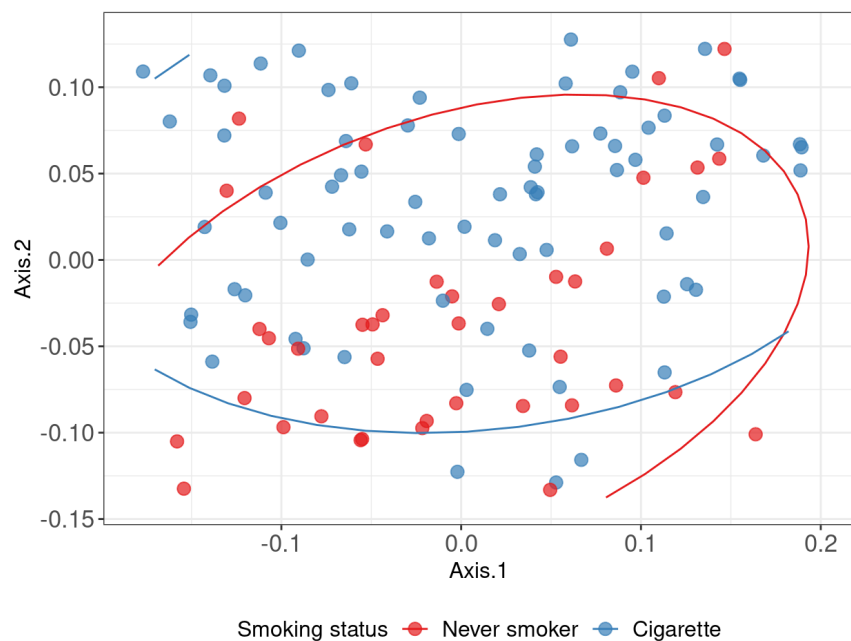
##               Df Sum Sq Mean Sq F value Pr(>F)
## smokingstatus  4  74507   18627     1.33  0.259
## Residuals    254 3556471  14002
```

4 Serum cotinine vs Smoking status

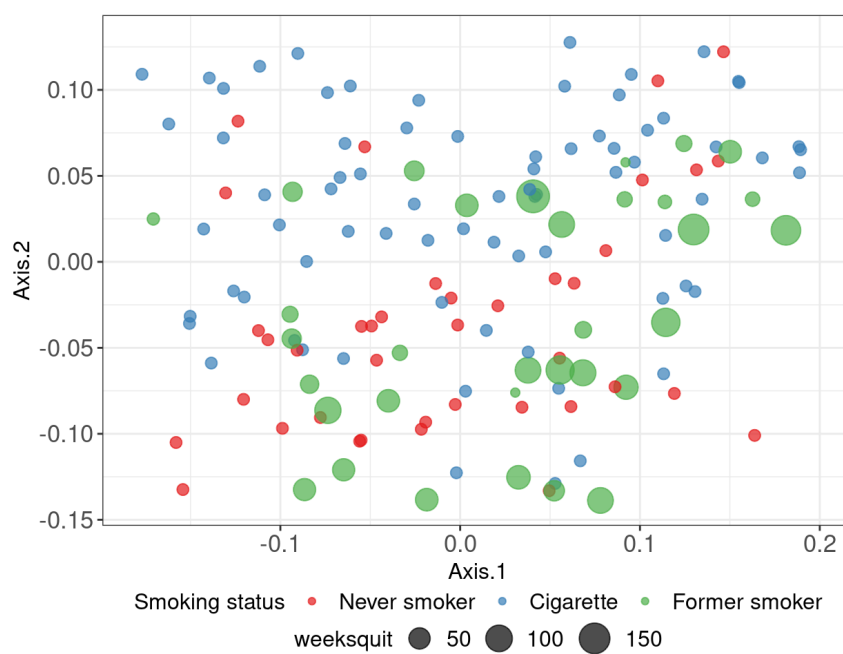


5 Beta Diversity

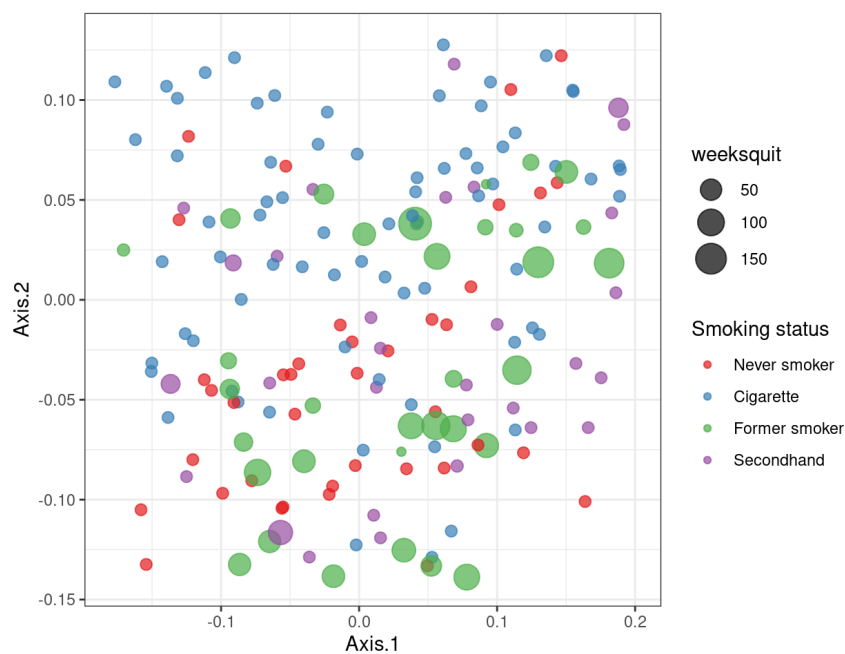
5.1 Cigarette smokers vs Never smokers



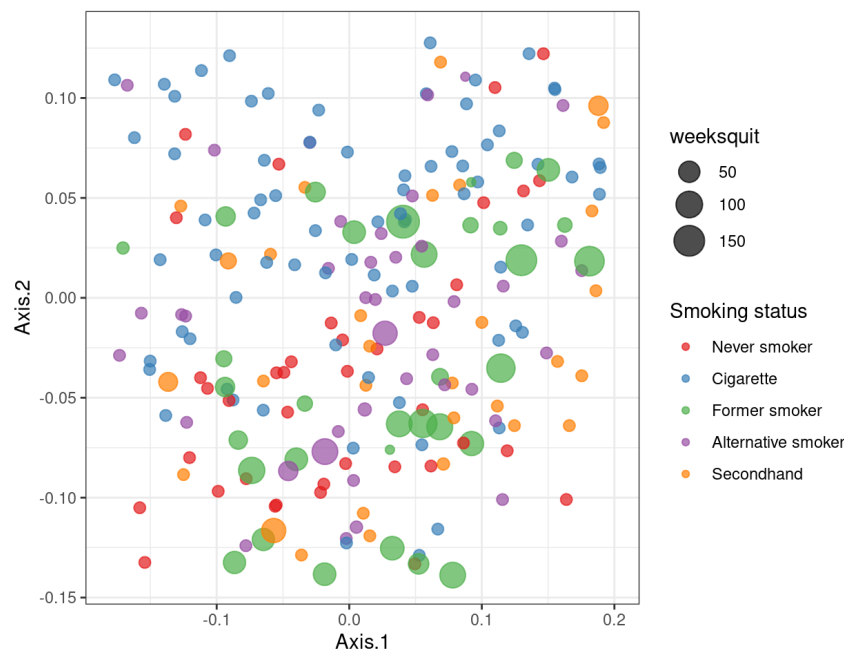
5.2 Cigarette smokers + Never smokers + Former smokers



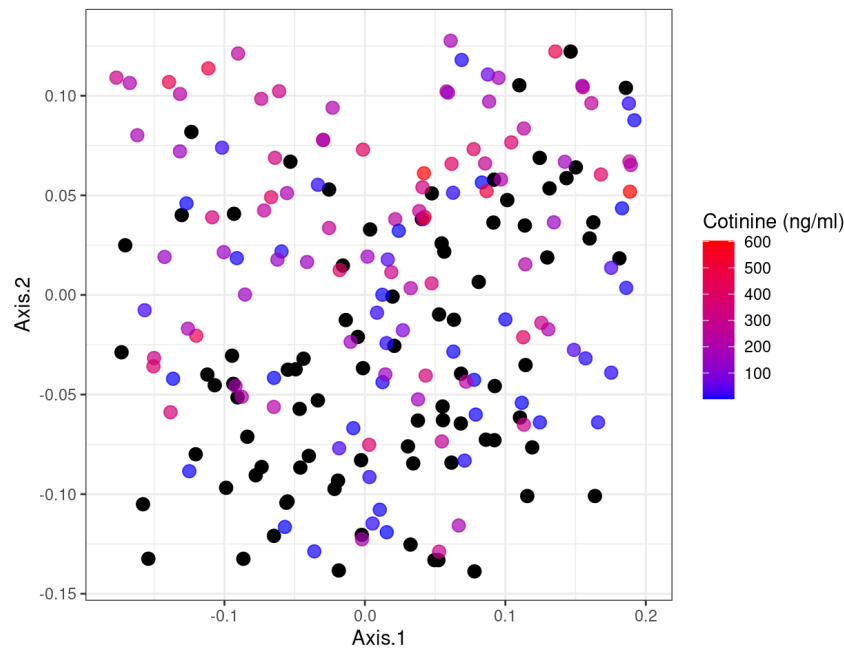
5.3 Cigarette smokers + Never smokers + Former smokers + Secondhand smokers



5.4 All smoking statuses



5.5 Discrete serum blood Cotinine levels



5.5.1 Test group with PERMANOVA (adonis, vegan package)

contrast	r2	pvalue
Never smoker vs Cigarette	0.0509071	0.001
Cigarette vs Former smoker	0.0428646	0.001
Cigarette vs Alternative smoker	0.0308923	0.001
Cigarette vs Secondhand	0.0342012	0.010
Never smoker vs Secondhand	0.0255269	0.079

contrast	r2	pvalue
Never smoker vs Former smoker	0.0174312	0.214
Former smoker vs Alternative smoker	0.0143694	0.267
Alternative smoker vs Secondhand	0.0118004	0.361
Former smoker vs Secondhand	0.0131722	0.375
Never smoker vs Alternative smoker	0.0088171	0.544

```
## Permutation test for adonis under reduced model
## Terms added sequentially (first to last)
## Permutation: free
## Number of permutations: 999
##
## vegan::adonis2(formula = distwu_2cat ~ COTININE, data = metadata_2
##           Df SumOfSqs      R2      F Pr(>F)
## COTININE   1  0.05422 0.04807 6.4136 0.001 ***
## Residual 127  1.07356 0.95193
## Total    128  1.12777 1.00000
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

5.5.1.1 Three categories

```
## Permutation test for adonis under reduced model
## Terms added sequentially (first to last)
## Permutation: free
## Number of permutations: 999
##
## vegan::adonis2(formula = distwu_3cat ~ smokingstatus + RACE + GENE
##           Df SumOfSqs      R2      F Pr(>F)
## smokingstatus  2  0.09210 0.05263 4.8153 0.001 ***
## RACE           4  0.05776 0.03300 1.5098 0.104
## GENDER         1  0.01392 0.00796 1.4560 0.201
## AGEGRP4C       1  0.02326 0.01329 2.4319 0.052 .
## SR_ACTIVE      2  0.01812 0.01036 0.9476 0.458
## EDU3CAT        2  0.02582 0.01476 1.3501 0.193
## DBTS_NEW       1  0.00807 0.00461 0.8439 0.475
## Residual      158  1.51100 0.86340
## Total         171  1.75005 1.00000
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

5.5.1.2 All categories

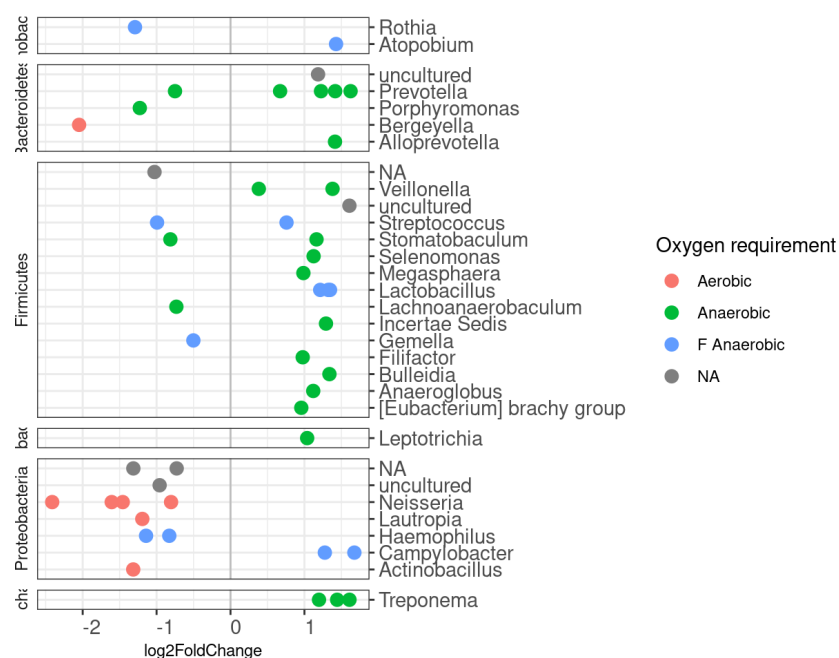

```
## Permutation test for adonis under reduced model
## Terms added sequentially (first to last)
## Permutation: free
## Number of permutations: 999
##
## vegan::adonis2(formula = distwu ~ smokingstatus, data = metadata)
##              Df SumOfSqs      R2      F Pr(>F)
## smokingstatus  4   0.4139 0.04867 3.2487  0.001 ***
## Residual      254   8.0905 0.95133
## Total         258   8.5044 1.00000
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

6 Differential analysis

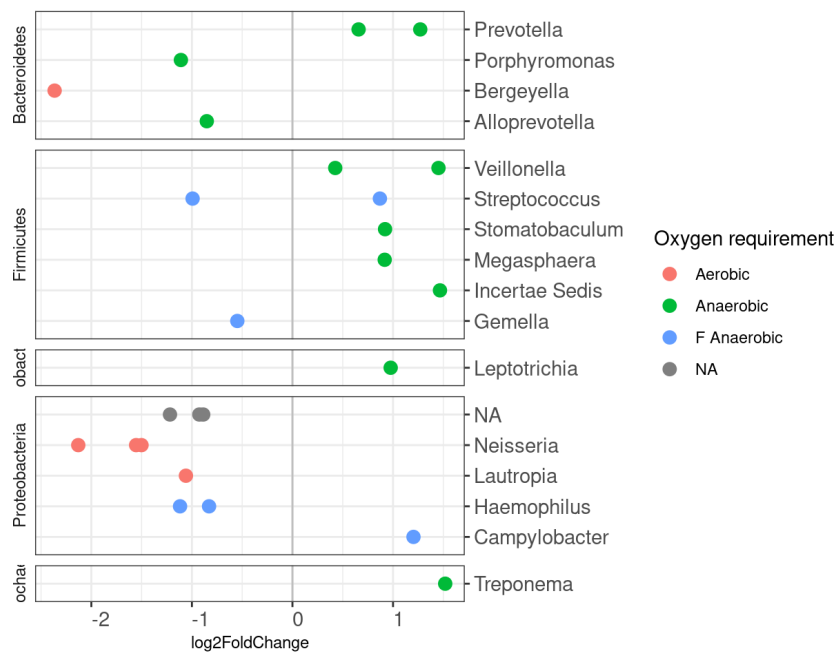
6.1 DESeq2

DESeq2 is presented as sensitivity analysis. Main results are calculated by edgeR.

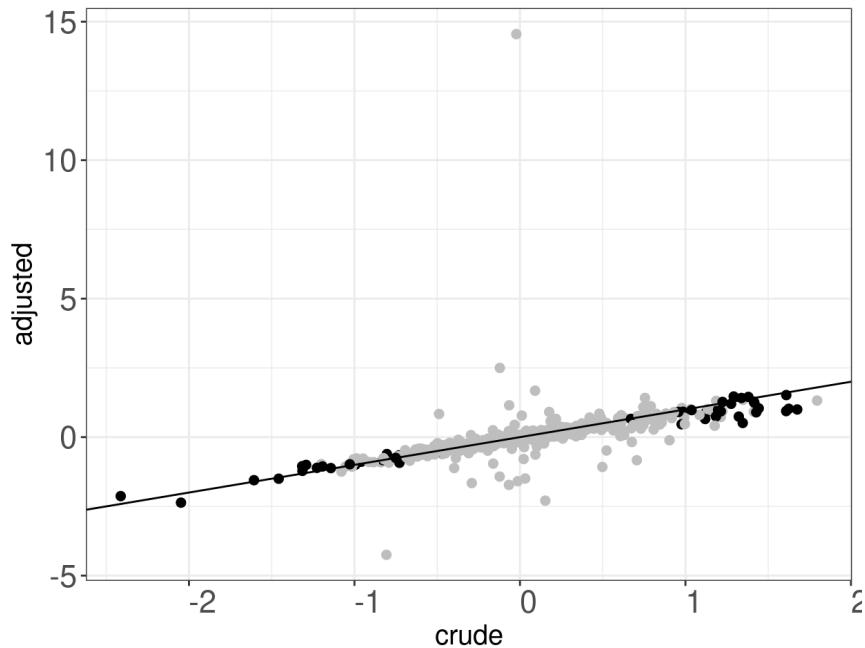
6.1.1 Current smokers vs. never smokers crude



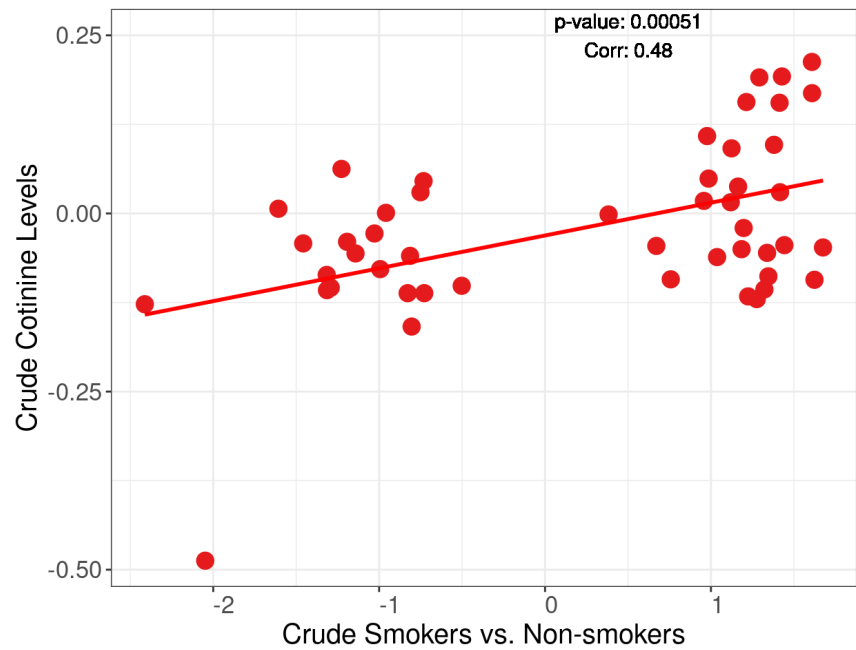
6.1.2 Current smokers vs. never smokers adjusting for confounding



6.1.3 Plot crude vs. adjusted from DESeq2

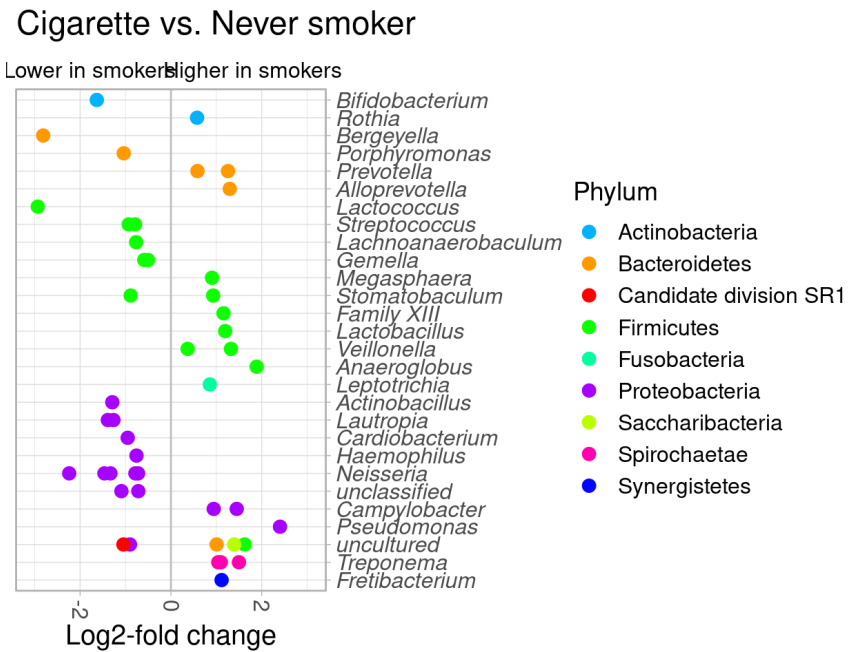


6.1.4 Secondhand vs Cigarette/Never

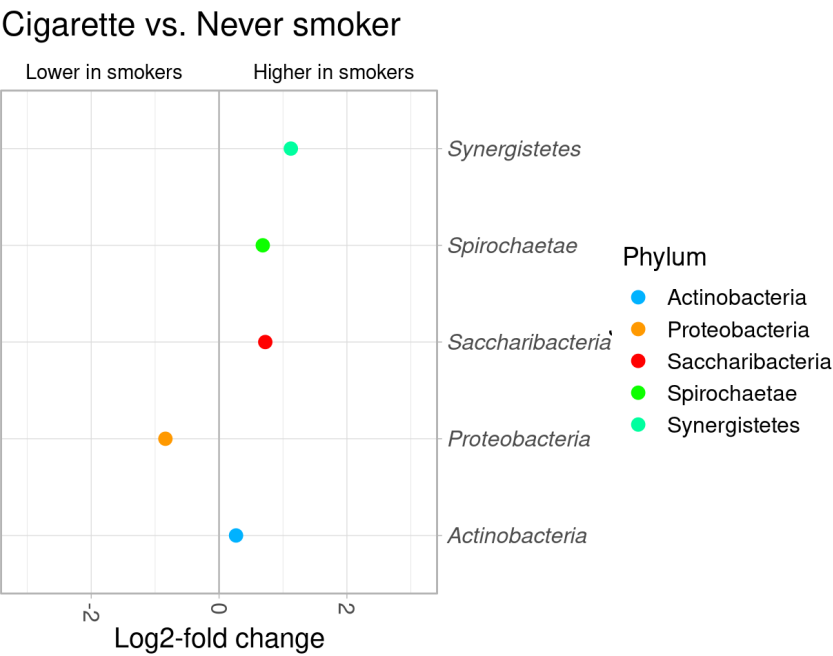


6.2 edgeR

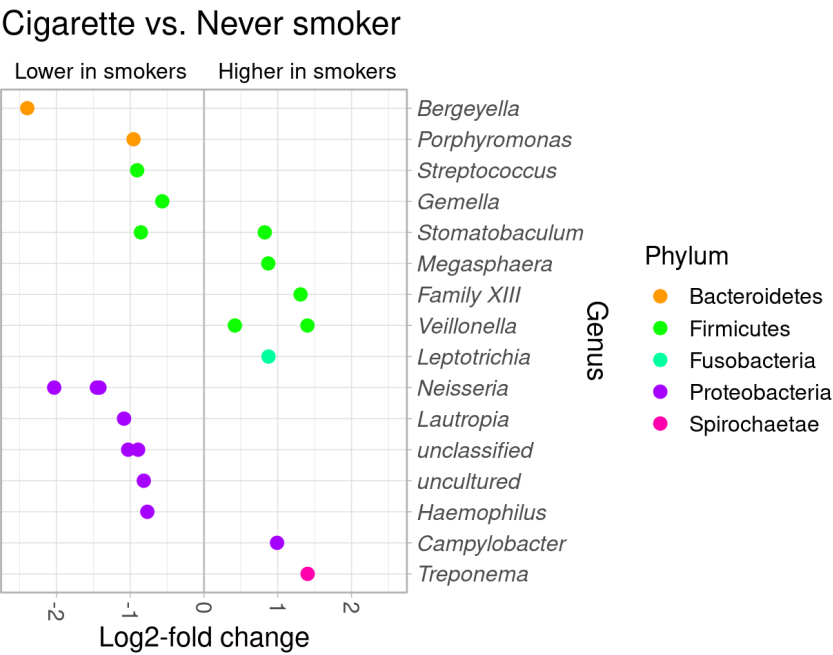
6.2.1 Cigarette smoker vs Never smoker: crude



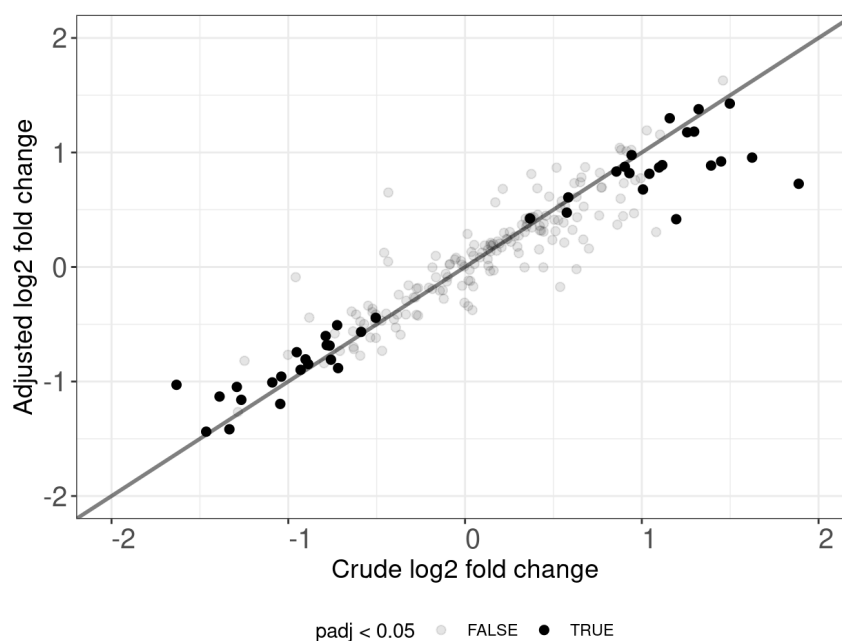
6.3 Cigarette smoker vs Never smoker: crude phylum level



6.3.1 Cigarette smoker vs Never smoker: Adjusted



6.3.2 Plot crude vs adjusted beta coefficients



6.3.3 Secondhand vs Cigarette/Never: only significant OTUs

A function for merging smoking and cotinine edgeR results:

And a plotting function:

Two thresholds for serum cotinine:

```
## [1] 1.0022 1.0394 1.0418 1.0715 1.0915 1.2015 1.2282 1.27
## [10] 1.3822 1.4094 1.5315 1.6918 2.0094 2.5994 2.6759 2.86
## [19] 2.9720 3.0459 3.1082 3.1722 3.4715 3.8394 4.3418 4.52
## [28] 4.7522 5.7220 6.3118 7.1315 7.7382 9.1118 9.6415 10.29
## [37] 10.7915 13.7894
```

```
## Mode FALSE TRUE
## logical 34 4
```

Number of OTUs with FDR < 0.05 and total that passed non-specific screens in both analysis:

```
## Mode FALSE TRUE
## logical 93 28

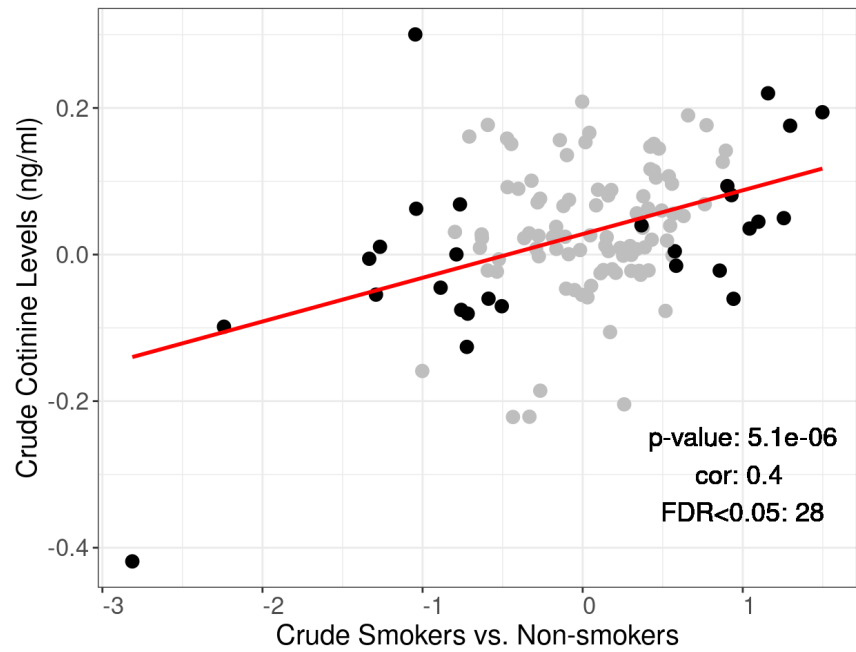
## Mode FALSE TRUE
## logical 87 27
```

Correlation between crude smoking and cotinine coefficients, all OTUs:

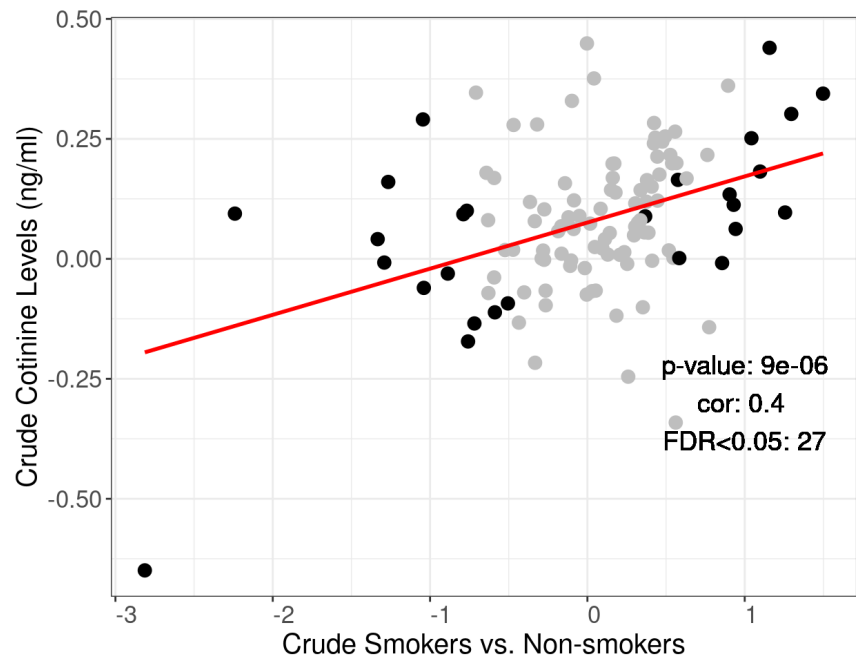
Strict definition of second-hand smoke:

Correlation between crude smoking and cotinine coefficients, FDR < 0.05 in smoking:

All OTUs, black for FDR < 0.05 on smoking coefficients, grey for FDR >= 0.05



Repeat, using the strict definition of second-hand smokers (cotinine < 10)



6.3.4 Adjusted Secondhand vs Adjusted Cigarette/Never: only significant OTUs

Number of differentially abundant OTUs, and total

##	[1]	121
##	Mode	FALSE TRUE
##	logical	63 58
##	Mode	FALSE TRUE
##	logical	38 83

Correlation between adjusted smoking and cotinine coefficients, all OTUs:

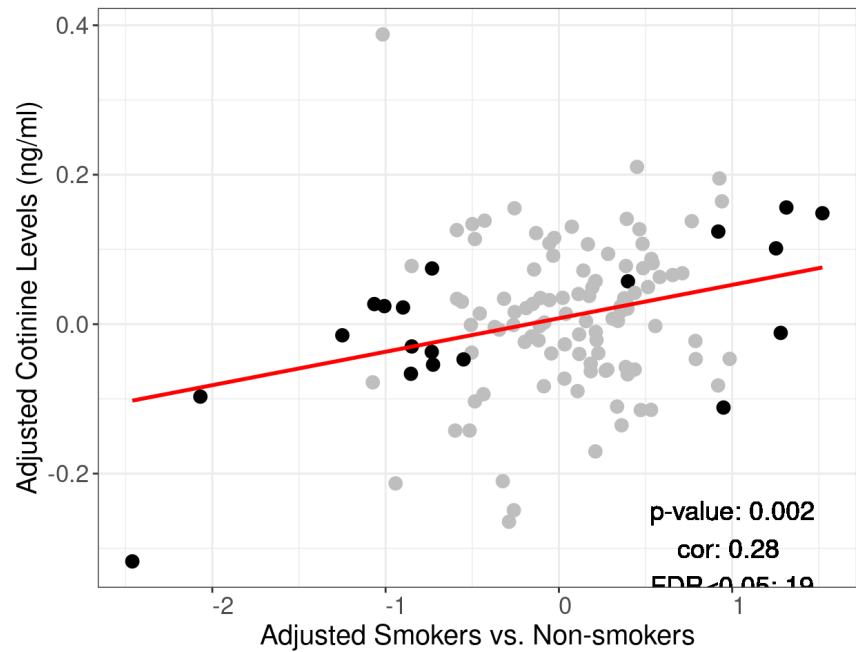
As above, using strict serum cotinine cutoff (<10)

Correlation between adjusted smoking and cotinine coefficients, FDR < 0.05 in smoking:

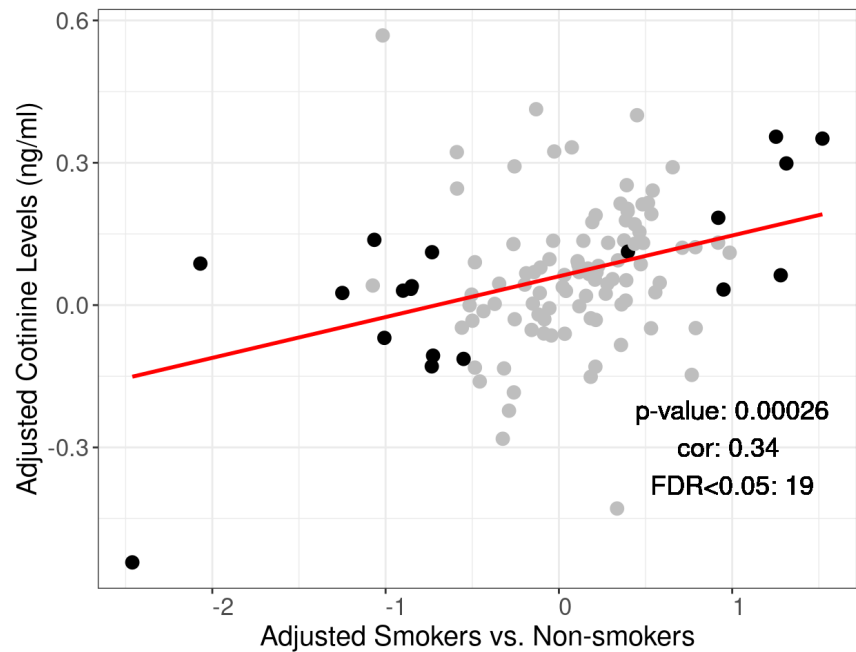
```
##
## Pearson's product-moment correlation
##
## data: logFC_smoking and logFC_cotinine
## t = 3.8131, df = 17, p-value = 0.001391
## alternative hypothesis: true correlation is not equal to 0
## 95 percent confidence interval:
## 0.3249855 0.8660843
## sample estimates:
## cor
## 0.6789709
```

Sensitivity analysis:

```
## , , FDRcutoff = no
##
##      counfounding
## secondhand crude adjusted
## cot14 0.4 0.28
## cot10 0.4 0.34
##
## , , FDRcutoff = yes
##
##      counfounding
## secondhand crude adjusted
## cot14 NA 0.34
## cot10 0 NA
## , , FDRcutoff = no
##
##      counfounding
## secondhand crude adjusted
## cot14 5e-06 2e-03
## cot10 9e-06 3e-04
##
## , , FDRcutoff = yes
##
##      counfounding
## secondhand crude adjusted
## cot14 NA 3e-04
## cot10 0.6 NA
```



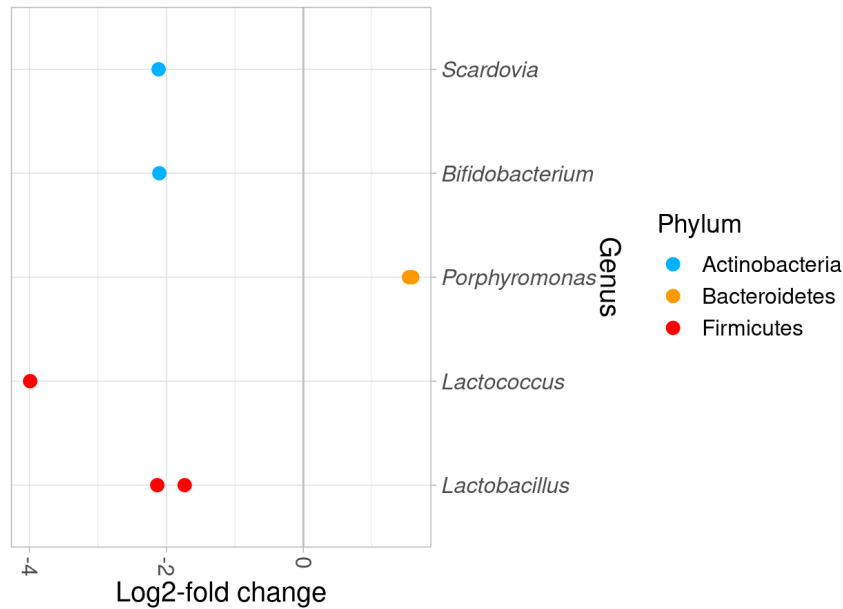
Repeat, using the strict definition of second-hand smokers (cotinine < 10)



6.3.5 Write supplemental file

6.3.6 Alternative smokers vs Never smoker: crude

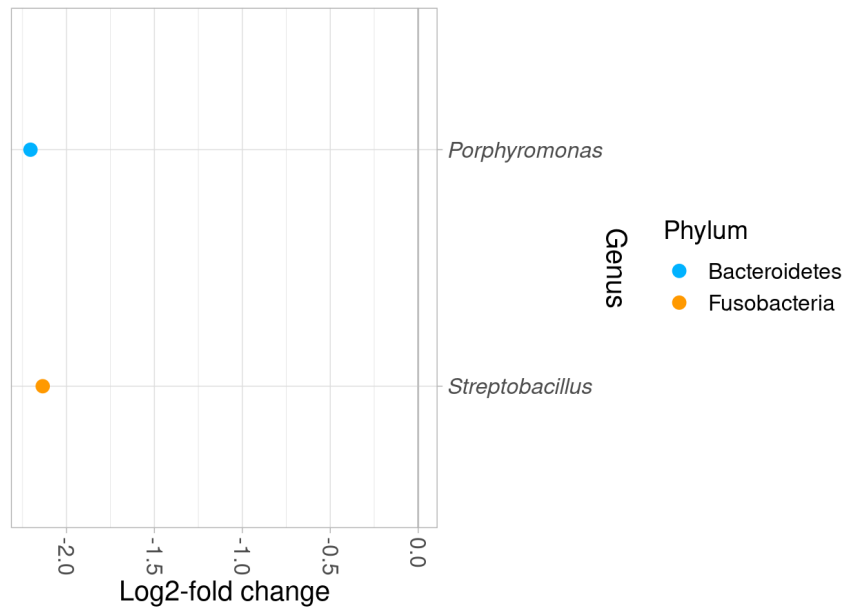
smokingstatus: Alternative smoker vs. Never smoker



6.3.6.1 E-cigarette vs never smokers

6.3.6.2 Hookah pipe vs never smokers

HOOKAH_PIPE: No vs. Yes



6.3.6.3 Cigars and cigarillos vs never smokers

[1] "No results"

7 Analysis on biosis of bacteria

7.1 Odds ratio smokers vs never smokers

```
## $tab
##
##               Enriched in smokers      p0 Depleted in smokers
## OTU is aerobic      23 0.0362776
## OTU is not aerobic  611 0.9637224
##
##               p1 oddsratio      lower      upper
## OTU is aerobic      0.1074219 1.0000000      NA      NA
## OTU is not aerobic  0.8925781 0.3127808 0.1894164 0.5164911 2.682
##
## $measure
## [1] "wald"
##
## $conf.level
## [1] 0.95
##
## $pvalue
## [1] "fisher.exact"
```



```
## $tab
##
##               Enriched in smokers      p0 Depleted in smokers
## OTU is anaerobic    407 0.6419558
## OTU is not anaerobic 227 0.3580442
##
##               p1 oddsratio      lower      upper
## OTU is anaerobic    0.5195312 1.0000000      NA      NA
## OTU is not anaerobic 0.4804688 1.658143 1.307573 2.102704 3.107
##
## $measure
## [1] "wald"
##
## $conf.level
## [1] 0.95
##
## $pvalue
## [1] "fisher.exact"
```

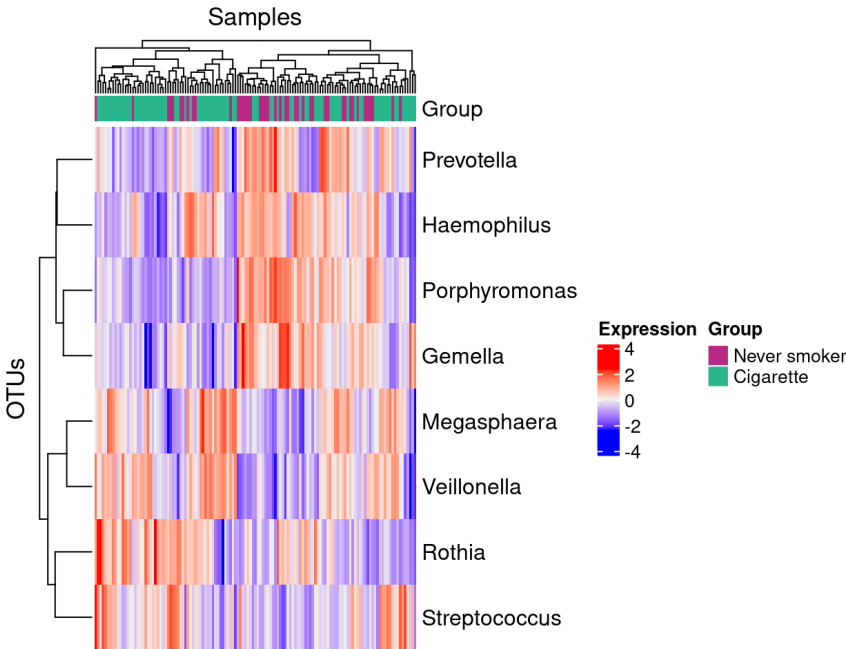


```
## $tab
##
##           Enriched in smokers      p0 Depleted ir
## OTU is F Anaerobic                204 0.3217666
## OTU is not F Anaerobic            430 0.6782334
##
##           p1 oddsratio      lower      upper
## OTU is F Anaerobic    0.3730469 1.0000000      NA      NA
## OTU is not F Anaerobic 0.6269531 0.7973213 0.624298 1.018298 0.6
##
## $measure
## [1] "wald"
##
## $conf.level
## [1] 0.95
##
## $pvalue
## [1] "fisher.exact"
```

7.2 Cigarette smokers vs Never smokers

7.2.1 GSEA

```
## DataFrame with 2 rows and 4 columns
##      GENE.SET      ES      NES      PVAL
## <character> <numeric> <numeric> <numeric>
## 1      fana    -0.322   -0.738    0.769
## 2      anae     0.282    0.545    0.957
```



7.2.2 ORA

```
## 100 permutations completed
## 200 permutations completed
## 300 permutations completed
## 400 permutations completed
## 500 permutations completed
## 600 permutations completed
## 700 permutations completed
## 800 permutations completed
## 900 permutations completed
## 1000 permutations completed

## DataFrame with 2 rows and 4 columns
##      GENE.SET GLOB.STAT NGLOB.STAT      PVAL
## <character> <numeric>  <numeric> <numeric>
## 1      fana          3      0.300    0.186
## 2      anae          5      0.208    0.531
```

7.3 Secondhand smokers

7.3.1 GSEA

```
## DataFrame with 2 rows and 4 columns
##      GENE.SET      ES      NES      PVAL
## <character> <numeric> <numeric> <numeric>
## 1      anae      0.77      1.30      0.164
## 2      fana     -0.50     -1.11      0.360
```

7.3.2 ORA

```
## 100 permutations completed
## 200 permutations completed
## 300 permutations completed
## 400 permutations completed
## 500 permutations completed
## 600 permutations completed
## 700 permutations completed
## 800 permutations completed
## 900 permutations completed
## 1000 permutations completed

## DataFrame with 2 rows and 4 columns
##      GENE.SET GLOB.STAT NGLOB.STAT      PVAL
## <character> <numeric>  <numeric> <numeric>
## 1      anae          0          0      0.001
## 2      fana          0          0      0.001
```


7.5.2 ORA

```
## DataFrame with 2 rows and 4 columns
##      GENE.SET  NR.GENES NR.SIG.GENES      PVAL
## <character> <numeric> <numeric> <numeric>
## 1      anae        23           1    0.697
## 2      fana        10           0    1.000
```

7.6 E-cigarette smokers vs Never smokers

7.6.1 GSEA

```
## DataFrame with 2 rows and 4 columns
##      GENE.SET      ES      NES      PVAL
## <character> <numeric> <numeric> <numeric>
## 1      anae    0.451    1.020    0.466
## 2      fana    0.329    0.832    0.683
```

7.6.2 ORA

```
## DataFrame with 2 rows and 4 columns
##      GENE.SET  NR.GENES NR.SIG.GENES      PVAL
## <character> <numeric> <numeric> <numeric>
## 1      anae        29           0          1
## 2      fana        12           0          1
```

7.7 Cigar/cigarillos smokers vs Never smokers

7.7.1 GSEA

```
## DataFrame with 2 rows and 4 columns
##      GENE.SET      ES      NES      PVAL
## <character> <numeric> <numeric> <numeric>
## 1      anae   -0.487   -0.983    0.508
## 2      fana    0.372    0.813    0.663
```

7.7.2 ORA

```
## DataFrame with 2 rows and 4 columns
##      GENE.SET  NR.GENES NR.SIG.GENES      PVAL
## <character> <numeric> <numeric> <numeric>
## 1      fana        10           1    0.323
## 2      anae        21           0    1.000
```

```
## R version 4.3.0 (2023-04-21)
## Platform: x86_64-pc-linux-gnu (64-bit)
## Running under: Pop!_OS 22.04 LTS
##
## Matrix products: default
## BLAS: /usr/lib/x86_64-linux-gnu/blas/libblas.so.3.10.0
## LAPACK: /usr/lib/x86_64-linux-gnu/lapack/liblapack.so.3.10.0
##
## locale:
## [1] LC_CTYPE=en_US.UTF-8 LC_NUMERIC=C
## [3] LC_TIME=en_US.UTF-8 LC_COLLATE=en_US.UTF-8
## [5] LC_MONETARY=en_US.UTF-8 LC_MESSAGES=en_US.UTF-8
## [7] LC_PAPER=en_US.UTF-8 LC_NAME=C
## [9] LC_ADDRESS=C LC_TELEPHONE=C
## [11] LC_MEASUREMENT=en_US.UTF-8 LC_IDENTIFICATION=C
##
## time zone: America/New_York
## tzcode source: system (glibc)
##
## attached base packages:
## [1] stats graphics grDevices utils datasets methods base
##
## other attached packages:
## [1] edgeR_3.42.2 limma_3.56.0 ggplot2_3.4
## [4] magrittr_2.0.3 dplyr_1.1.2 nychanesmic
## [7] lsr_0.5.2 phyloseq_1.44.0 Biobase_2.6
## [10] BiocGenerics_0.46.0 BiocStyle_2.28.0
##
## loaded via a namespace (and not attached):
## [1] splines_4.3.0 bitops_1.0-7
## [3] tibble_3.2.1 R.oo_1.25.0
## [5] graph_1.78.0 XML_3.99-0.14
## [7] lifecycle_1.0.3 doParallel_1.0.17
## [9] lattice_0.21-8 vroom_1.6.3
## [11] MASS_7.3-59 survey_4.1-1
## [13] sass_0.4.5 rmarkdown_2.21
## [15] jquerylib_0.1.4 yaml_2.3.7
## [17] DBI_1.1.3 RColorBrewer_1.1-3
## [19] ade4_1.7-22 zlibbioc_1.46.0
## [21] Rtsne_0.16 GenomicRanges_1.52.0
## [23] purrr_1.0.1 R.utils_2.12.2
## [25] RCurl_1.98-1.12 circlize_0.4.15
## [27] labelled_2.11.0 GenomeInfoDbData_1.2.10
## [29] IRanges_2.34.0 S4Vectors_0.38.1
## [31] irlba_2.3.5.1 GSVA_1.48.0
## [33] vegan_2.6-4 microbiome_1.22.0
## [35] annotate_1.78.0 DelayedMatrixStats_1.22.0
## [37] permute_0.9-7 codetools_0.2-19
## [39] DelayedArray_0.26.1 tidyselect_1.2.0
## [41] shape_1.4.6 farver_2.1.1
## [43] ScaledMatrix_1.8.0 epitools_0.5-10.1
## [45] matrixStats_0.63.0 stats4_4.3.0
## [47] jsonlite_1.8.4 GetoptLong_1.0.5
## [49] multtest_2.56.0 e1071_1.7-13
## [51] survival_3.5-5 iterators_1.0.14
## [53] foreach_1.5.2 tools_4.3.0
## [55] Rcpp_1.0.10 glue_1.6.2
```

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## [57] xfun_0.39 mgcv_1.8-42
## [59] DESeq2_1.40.1 MatrixGenerics_1.12.0
## [61] GenomeInfoDb_1.36.0 HDF5Array_1.28.1
## [63] withr_2.5.0 BiocManager_1.30.20
## [65] fastmap_1.1.1 mitools_2.4
## [67] rhdf5filters_1.12.1 fansi_1.0.4
## [69] SparseM_1.81 rsvd_1.0.5
## [71] digest_0.6.31 R6_2.5.1
## [73] colorspace_2.1-0 Cairo_1.6-0
## [75] RSQLite_2.3.1 R.methodsS3_1.8.2
## [77] utf8_1.2.3 tidyr_1.3.0
## [79] generics_0.1.3 data.table_1.14.8
## [81] class_7.3-21 httr_1.4.5
## [83] S4Arrays_1.0.1 pkgconfig_2.0.3
## [85] gtable_0.3.3 blob_1.2.4
## [87] ComplexHeatmap_2.16.0 SingleCellExperiment_1.22.0
## [89] XVector_0.40.0 htmltools_0.5.5
## [91] bookdown_0.33 biomformat_1.28.0
## [93] GSEABase_1.62.0 clue_0.3-64
## [95] scales_1.2.1 png_0.1-8
## [97] knitr_1.42 rstudioapi_0.14
## [99] tzdb_0.3.0 reshape2_1.4.4
## [101] rjson_0.2.21 nlme_3.1-162
## [103] proxy_0.4-27 cachem_1.0.8
## [105] zoo_1.8-12 rhdf5_2.44.0
## [107] GlobalOptions_0.1.2 stringr_1.5.0
## [109] safe_3.40.0 parallel_4.3.0
## [111] AnnotationDbi_1.62.1 pillar_1.9.0
## [113] grid_4.3.0 vctrs_0.6.2
## [115] BiocSingular_1.16.0 beachmat_2.16.0
## [117] xtable_1.8-4 cluster_2.1.4
## [119] Rgraphviz_2.44.0 evaluate_0.20
## [121] KEGGgraph_1.60.0 readr_2.1.4
## [123] cli_3.6.1 locfit_1.5-9.7
## [125] compiler_4.3.0 rlang_1.1.1
## [127] crayon_1.5.2 tableone_0.13.2
## [129] labeling_0.4.2 plyr_1.8.8
## [131] forcats_1.0.0 stringi_1.7.12
## [133] BiocParallel_1.34.0 munsell_0.5.0
## [135] Biostrings_2.68.0 Matrix_1.5-4
## [137] sas7bdat_0.7 hms_1.1.3
## [139] sparseMatrixStats_1.12.0 bit64_4.0.5
## [141] Rhdf5lib_1.22.0 KEGGREST_1.40.0
## [143] statmod_1.5.0 SummarizedExperiment_1.30.1
## [145] highr_0.10 haven_2.5.2
## [147] igraph_1.4.2 memoise_2.0.1
## [149] bslib_0.4.2 bit_4.0.5
## [151] EnrichmentBrowser_2.30.0 ape_5.7-1

```