Supplementary Material

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| **Supp Table 1. Bifidobacterium Species included in the CCA Model**  Summary of *bifidobacterium* sum composite and species used in rCCA | | | | | | | | |
| ***Bifidobacterium* Sum Composite** | | | | | | ***Bifidobacterium* Species Used in rCCA** | | |
| Bifidobacterium\_adolescentis | | | | | | Bifidobacterium\_longum | | |
| Bifidobacterium\_angulatum | | | | | | Bifidobacterium\_pseudocatenulatum | | |
| Bifidobacterium\_animalis | | | | | | Bifidobacterium\_adolescentis | | |
| Bifidobacterium\_bifidum | | | | | | Bifidobacterium\_bifidum | | |
| Bifidobacterium\_breve | | | | | | Bifidobacterium\_catenulatum | | |
| Bifidobacterium\_catenulatum | | | | | | Bifidobacterium\_breve | | |
| Bifidobacterium\_dentium | | | | | | Bifidobacterium\_angulatum | | |
| Bifidobacterium\_gallinarum | | | | | | Bifidobacterium\_pullorum | | |
| Bifidobacterium\_kashiwanohense | | | | | | Bifidobacterium\_dentium | | |
| Bifidobacterium\_longum | | | | | |  | | |
| Bifidobacterium\_moukalabense | | | | | |  | | |
| Bifidobacterium\_pseudocatenulatum | | | | | |  | | |
| Bifidobacterium\_pseudolongum | | | | | |  | | |
| Bifidobacterium\_pullorum | | | | | |  | | |
| Bifidobacterium\_ruminantium | | | | | |  | | |
| Bifidobacterium\_saeculare | | | | | |  | | |
| Bifidobacterium\_scardovii | | | | | |  | | |
| **Supp Table 2. Location and loading values for DNA methylation PCA first principal component**  CpG, location, and loading value for DNA methylation PCA of each cortisol-related gene | | | |
| *NR3C1* | | | |
| CpG | | Location | r |
| cg07197341 | | OpenSea | 0.97 |
| cg14621978 | | N\_Shore | 0.97 |
| cg08320082 | | N\_Shore | 0.96 |
| cg24052866 | | Island | 0.93 |
| cg13907255 | | OpenSea | 0.92 |
| cg23484741 | | OpenSea | 0.91 |
| cg17342132 | | Island | 0.91 |
| cg12969488 | | OpenSea | 0.89 |
| cg26222722 | | S\_Shore | 0.88 |
| cg16219186 | | S\_Shore | 0.87 |
| cg07715663 | | Island | 0.86 |
| cg25553328 | | N\_Shore | 0.86 |
| cg13079912 | | N\_Shelf | 0.86 |
| cg08845721 | | Island | 0.84 |
| cg23430507 | | OpenSea | 0.84 |
| cg20598211 | | Island | 0.84 |
| cg06770322 | | Island | 0.83 |
| cg08695103 | | Island | -0.83 |
| cg22233604 | | Island | -0.89 |
| cg07637989 | | OpenSea | -0.93 |
| cg03857453 | | Island | -0.95 |
| cg23776787 | | OpenSea | -0.95 |
| cg26720913 | | Island | -0.97 |
| cg03906910 | | OpenSea | -0.98 |
| cg08818984 | | OpenSea | -0.98 |
| *FKBP5* | | | |
| cg23416081 | | N\_Shelf | 0.96 |
| cg03591753 | | S\_Shelf | 0.96 |
| cg20813374 | | S\_Shore | 0.91 |
| cg15929276 | | OpenSea | 0.89 |
| cg14339974 | | OpenSea | 0.87 |
| cg26495008 | | OpenSea | 0.84 |
| cg03245912 | | S\_Shore | 0.83 |
| cg13344434 | | OpenSea | 0.82 |
| cg03546163 | | N\_Shore | 0.80 |
| cg24295963 | | OpenSea | -0.82 |
| cg09318204 | | OpenSea | -0.84 |
| cg06409316 | | OpenSea | -0.85 |
| cg22812853 | | OpenSea | -0.88 |
| cg01731192 | | OpenSea | -0.88 |
| *AVP* | | | |
| cg25551168 | | S\_Shore | 0.97 |
| cg22832788 | | S\_Shore | 0.97 |
| cg08042223 | | Island | 0.96 |
| cg15313891 | | S\_Shore | 0.96 |
| cg16536918 | | S\_Shore | 0.96 |
| cg16339225 | | OpenSea | 0.96 |
| cg23169111 | | S\_Shore | 0.95 |
| cg04632887 | | S\_Shore | 0.94 |
| cg02187522 | | S\_Shore | 0.92 |
| cg05136169 | | S\_Shore | 0.89 |
| cg11125847 | | OpenSea | 0.85 |
| cg01052838 | | S\_Shore | 0.84 |
| cg03279206 | | Island | 0.83 |
| cg24025566 | | S\_Shore | 0.82 |
| *CRH* | | | |
| cg00603617 | | Island | 0.69 |
| cg04227637 | | S\_Shore | 0.56 |
| cg08215831 | | S\_Shore | 0.64 |
| cg16664570 | | S\_Shore | 0.52 |
| cg18640030 | | S\_Shore | 0.61 |
| cg19035496 | | S\_Shore | 0.65 |
| cg19696975 | | S\_Shore | 0.62 |
| cg20329958 | | S\_Shore | 0.50 |
| cg21878188 | | Island | 0.71 |
| cg23027580 | | Island | 0.75 |
| cg23409074 | | S\_Shore | 0.67 |
| cg23990470 | | S\_Shelf | 0.50 |
| *CRHR1* | | | |
| cg15117716 | | OpenSea | 0.97 |
| cg14297797 | | OpenSea | 0.97 |
| cg08119837 | | OpenSea | 0.96 |
| cg20059597 | | OpenSea | 0.94 |
| cg10159607 | | OpenSea | 0.92 |
| cg01448078 | | OpenSea | 0.92 |
| cg07508782 | | OpenSea | 0.90 |
| cg18090064 | | OpenSea | 0.90 |
| cg11760414 | | S\_Shore | 0.90 |
| cg04194664 | | OpenSea | 0.90 |
| cg13947929 | | S\_Shore | 0.89 |
| cg16228356 | | OpenSea | 0.87 |
| cg00025823 | | OpenSea | 0.85 |
| cg01961214 | | OpenSea | 0.84 |
| cg27503360 | | OpenSea | 0.83 |
| cg08929103 | | N\_Shore | 0.82 |
| cg18534039 | | OpenSea | 0.81 |
| *CRHR2* | | | |
| cg27345762 | | OpenSea | 0.97 |
| cg16127724 | | OpenSea | 0.93 |
| cg05366813 | | S\_Shore | 0.90 |
| cg18090898 | | OpenSea | 0.85 |
| cg01049782 | | N\_Shelf | 0.78 |
| cg27605489 | | S\_Shore | 0.73 |
| cg27191795 | | N\_Shelf | 0.71 |
| cg22826063 | | OpenSea | 0.64 |
| cg23185751 | | N\_Shore | 0.53 |
| cg26415343 | | OpenSea | 0.52 |
| cg26262196 | | OpenSea | 0.50 |
| cg02712145 | | Island | -0.52 |
| cg18285819 | | OpenSea | -0.52 |
| cg23068772 | | OpenSea | -0.74 |
| cg22007110 | | OpenSea | -0.90 |
| cg13134297 | | OpenSea | -0.95 |
| **Supp Table 3. HPA gene DNA methylation and *Bifidobacterium* Mediation Model Results**  Results from bifidobacterium mediation model for cortisol-related gene DNA methylation | | | | | | | | | |  |  |  |  |  |
| ***Bifidobacterium*** | | | | | | | | | | | | | | |
|  | **PC1** | | | | | | | | | | **PC2** | | | |
| **Gene** | **Effect** | | | | **Estimate** | | **95% CI Lower** | **95% CI Upper** | | **p-value** | **Estimate** | **95% CI Lower** | **95% CI Upper** | **p-value** |
| *NR3C1* | ACME (Indirect) | | | | -0.26 | | -0.35 | -0.20 | | <2e-16 | 0.08 | 0.02 | 0.15 | 0.01 |
| ADE (Direct) | | | | -0.17 | | -0.26 | -0.09 | | <2e-16 | -0.02 | -0.15 | 0.11 | 0.70 |
| Total Effect | | | | -0.43 | | -0.53 | -0.34 | | <2e-16 | 0.06 | -0.05 | 0.18 | 0.35 |
| Proportion Mediated | | | | 0.60 | | 0.46 | 0.77 | | <2e-16 | 1.40 | -15.52 | 13.94 | 0.36 |
| *FKBP5* | ACME (Indirect) | | | | 0.26 | | 0.18 | 0.35 | | <2e-16 | -0.02 | -0.08 | 0.04 | 0.57 |
| ADE (Direct) | | | | 0.20 | | 0.10 | 0.30 | | <2e-16 | -0.08 | -0.19 | 0.04 | 0.18 |
| Total Effect | | | | 0.45 | | 0.35 | 0.58 | | <2e-16 | -0.10 | -0.19 | 0.01 | 0.09 |
| Proportion Mediated | | | | 0.57 | | 0.42 | 0.74 | | <2e-16 | 0.18 | -0.93 | 2.28 | 0.59 |
| *AVP* | ACME (Indirect) | | | | 0.25 | | 0.19 | 0.35 | | <2e-16 | -0.04 | -0.11 | 0.02 | 0.20 |
| ADE (Direct) | | | | 0.19 | | 0.09 | 0.29 | | <2e-16 | -0.11 | -0.26 | 0.05 | 0.17 |
| Total Effect | | | | 0.44 | | 0.34 | 0.57 | | <2e-16 | -0.15 | -0.28 | 0.01 | 0.07 |
| Proportion Mediated | | | | 0.58 | | 0.43 | 0.77 | | <2e-16 | 0.24 | -0.80 | 1.71 | 0.24 |
| *CRH* | ACME (Indirect) | | | | 0.06 | | -0.01 | 0.14 | | 0.08 | 0.22 | 0.16 | 0.31 | <2e-16 |
| ADE (Direct) | | | | -0.14 | | -0.26 | -0.01 | | 0.03 | 0.23 | 0.10 | 0.35 | <2e-16 |
| Total Effect | | | | -0.08 | | -0.19 | 0.04 | | 0.20 | 0.45 | 0.34 | 0.56 | <2e-16 |
| Proportion Mediated | | | | -0.74 | | -5.99 | 11.78 | | 0.27 | 0.50 | 0.33 | 0.74 | <2e-16 |
| *CRHR1* | ACME (Indirect) | | | | -0.24 | | -0.33 | -0.17 | | <2e-16 | 0.07 | 0.00 | 0.14 | 0.05 |
| ADE (Direct) | | | | -0.18 | | -0.26 | -0.10 | | <2e-16 | 0.06 | -0.07 | 0.21 | 0.41 |
| Total Effect | | | | -0.42 | | -0.52 | -0.33 | | <2e-16 | 0.13 | 0.01 | 0.27 | 0.03 |
| Proportion Mediated | | | | 0.57 | | 0.44 | 0.72 | | <2e-16 | 0.56 | -0.10 | 3.48 | 0.07 |
| *CRHR2* | ACME (Indirect) | | | | -0.25 | | -0.34 | -0.17 | | <2e-16 | 0.00 | -0.07 | 0.06 | 0.94 |
| ADE (Direct) | | | | -0.15 | | -0.25 | -0.07 | | <2e-16 | -0.02 | -0.15 | 0.12 | 0.79 |
| Total Effect | | | | -0.40 | | -0.51 | -0.30 | | <2e-16 | -0.02 | -0.14 | 0.10 | 0.71 |
| Proportion Mediated | | | | 0.62 | | 0.46 | 0.80 | | <2e-16 | 0.07 | -6.57 | 5.07 | 0.99 |

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| **Supp Table 4. rCCA loading values**  *Bifidobacterium species and relevant CpG sites for rCCA loading values* | | |
| **Species** | **1** | **2** |
| *dentium* | -0.5162795 | -0.5865232 |
| *pullorum* | -0.2513151 | -0.4303921 |
| *longum* | -0.0775182 | -0.0224267 |
| *bifidum* | -0.0613539 | 0.08775504 |
| *breve* | -0.0399022 | 0.10309763 |
| *pseudocatenulatum* | -0.0397859 | -0.0036199 |
| *adolescentis* | 0.16844666 | 0.02021967 |
| *catenulatum* | 0.17962143 | -0.0763947 |
| *angulatum* | 0.35697467 | -0.1332335 |
| **CpG sites** |  |  |
| cg21177852OpenSea | -0.3942616 | -0.1945519 |
| cg15374100OpenSea | -0.3333189 | 0.33102419 |
| cg15740681OpenSea | -0.0594358 | 0.82214983 |
| cg23273257OpenSea | -0.1073782 | 0.6398758 |
| cg26081259OpenSea | 0.04534053 | 0.30006248 |
| cg13514002OpenSea | 0.16465816 | -0.1834205 |
| cg24801588OpenSea | -0.6992809 | -0.8662397 |
| cg00407401OpenSea | -0.00882 | -0.2752171 |
| cg19457823OpenSea | 0.14543214 | -0.1518445 |
| cg12741214OpenSea | -0.4038968 | -0.393129 |
| cg04457787OpenSea | 0.30921564 | -0.1180947 |
| cg20728768OpenSea | 0.11791552 | 0.1675821 |
| cg25708981OpenSea | 0.01838977 | 0.050487 |
| cg19645279OpenSea | -0.3241279 | -0.7348054 |
| cg19176661OpenSea | -0.4225496 | -0.7753961 |
| cg07715663OpenSea | -0.2935346 | -0.2817997 |
| cg24052866OpenSea | 0.08535665 | -0.1755195 |
| cg22233604OpenSea | -0.0113963 | -0.2929369 |
| cg03857453OpenSea | 0.21920395 | 0.03339411 |
| cg15115787OpenSea | 0.0400764 | -0.0919471 |
| cg12888360OpenSea | 0.00208003 | -0.0263071 |
| cg08695103OpenSea | 0.1877689 | -0.0587022 |
| cg14621978OpenSea | 0.09658488 | -0.0261181 |
| cg18484679OpenSea | -0.0969505 | 0.14571311 |
| cg16586394OpenSea | 0.18976818 | 0.17532554 |
| cg25535999OpenSea | -0.2740438 | -1.1813729 |
| cg03746860OpenSea | 0.55488971 | -0.3566443 |
| cg20598211OpenSea | -0.2535202 | -0.4100558 |
| cg05483455OpenSea | -0.0222356 | -0.4065891 |
| cg16594263OpenSea | 0.13300942 | -0.8975391 |
| cg16535116OpenSea | 0.07056088 | 0.13301716 |
| cg05900547OpenSea | 0.09782545 | -0.039595 |
| cg19432243OpenSea | 0.29327215 | -0.1243491 |
| cg19820298OpenSea | 0.07911947 | -0.1467218 |
| cg27107893OpenSea | -0.1022033 | -0.0843936 |
| cg06613263N\_Shelf | 0.20552988 | -0.2855971 |
| cg17342132N\_Shore | 0.09618218 | 0.0202124 |
| cg07742588N\_Shore | -0.098931 | 0.40589869 |
| cg00294552N\_Shore | 0.07324702 | -0.0266565 |
| cg16219186N\_Shore | 0.05022031 | 0.41419542 |
| cg08845721N\_Shore | 0.1772182 | -0.1148607 |
| cg12969488N\_Shore | -0.3132103 | -0.1050838 |
| cg07733851N\_Shore | 0.20865758 | 0.60426749 |
| cg18998365N\_Shore | -0.1531644 | 0.17855727 |
| cg27122725N\_Shore | -0.2334812 | 0.0303888 |
| cg06952416N\_Shore | -0.1258449 | -0.2989298 |
| cg06521673Island | 0.6070479 | -0.0386798 |
| cg17617527Island | -0.1746103 | 0.19317724 |
| cg20753294Island | -0.0926425 | -0.2811269 |
| cg18146873Island | 0.34536479 | 0.02842815 |
| cg00629244Island | -0.0485786 | -0.0883446 |
| cg11152298Island | -1.0405413 | -0.1951686 |
| cg18019515Island | -0.2210042 | -0.1226089 |
| cg17860381Island | 0.27710653 | -0.4239218 |
| cg04111177Island | 0.3952946 | -0.2228168 |
| cg15910486Island | -0.0199622 | 0.43654537 |
| cg15645634Island | -0.0288884 | 0.25340756 |
| cg14939152Island | -0.2507246 | 0.06214557 |
| cg18068240Island | 0.05837338 | 0.22414056 |
| cg21209684Island | -0.194978 | 0.0849479 |
| cg01967637Island | 0.14668135 | -0.036122 |
| cg22402730Island | -0.2365491 | -0.3290018 |
| cg19135245Island | -0.0995412 | 0.39526938 |
| cg26464411Island | 0.27988207 | 0.22879005 |
| cg07515400Island | 0.08876877 | -0.0691418 |
| cg06968181Island | -0.01231 | 0.54912352 |
| cg18849621Island | 0.11662806 | -0.259631 |
| cg16335926Island | -0.0279278 | 0.05804791 |
| cg10847032Island | -0.6240987 | 0.21279284 |
| cg21702128Island | 1.15036143 | -0.4434836 |
| cg14558428Island | -0.5263174 | 0.05235186 |
| cg24026230S\_Shore | -0.2421351 | -0.0950428 |
| cg13648501S\_Shore | 0.04839954 | 0.07684558 |
| cg18718518S\_Shore | 0.64672768 | 0.62032161 |
| cg13764763S\_Shore | 0.03577352 | -0.3107141 |
| cg27345592S\_Shore | -0.0903505 | 0.11465174 |
| cg07528216S\_Shelf | -0.4229351 | 0.1614368 |
| cg16224829OpenSea | -0.1804994 | 0.02081734 |
| cg01751279OpenSea | -0.2499042 | -0.0863047 |
| cg23430507OpenSea | 0.18469457 | -0.0378168 |
| cg17349736OpenSea | -0.3826093 | -0.1024642 |
| cg14438279OpenSea | -0.6329859 | 0.242547 |
| cg25579735OpenSea | -0.0966676 | -0.2799676 |
| cg08423118OpenSea | 0.21931333 | 0.01985263 |
| cg23776787OpenSea | -0.0657808 | 0.06669831 |
| cg03906910OpenSea | -0.0307261 | -0.0366242 |
| cg08818984OpenSea | -0.0203066 | 0.06853196 |
| cg26720913OpenSea | -0.1136207 | -0.0179211 |
| cg07589972OpenSea | 0.89737625 | 0.76923044 |
| cg12466613OpenSea | 0.14324952 | 0.09011001 |
| cg21979215OpenSea | -0.0347558 | 0.00299113 |
| cg01294526OpenSea | -0.071142 | -0.0616804 |
| cg11022710OpenSea | -0.2607231 | -0.0541958 |
| cg26222722OpenSea | 0.02440284 | 0.46955723 |
| cg10190339OpenSea | 0.05139366 | -0.6963958 |
| cg19828316OpenSea | 0.01728534 | -0.107954 |
| cg06770322OpenSea | -0.0264473 | -0.3094267 |
| cg07637989OpenSea | -0.1472653 | 0.13536777 |
| cg03778647OpenSea | -0.047395 | -0.1917222 |
| cg08320082OpenSea | 0.07219335 | -0.0204671 |
| cg13907255OpenSea | 0.11386045 | 0.17453522 |
| cg05048928OpenSea | -0.7723566 | -0.4397035 |
| cg01391283OpenSea | 0.38217945 | 0.38912358 |
| cg21030557OpenSea | -0.432312 | 0.36986793 |
| cg25553328OpenSea | 0.27199461 | 0.36484403 |
| cg23328217OpenSea | 0.04675066 | 0.22041069 |
| cg19641581OpenSea | 0.5616814 | -0.4332995 |
| cg07197341OpenSea | 0.14662335 | 0.04484483 |
| cg17779063OpenSea | -0.0433591 | -0.4794733 |
| cg17878320OpenSea | 0.06434329 | 0.21147088 |
| cg21334395OpenSea | 0.08862952 | -0.013846 |
| cg13079912OpenSea | 0.16317126 | -0.0238397 |
| cg23484741OpenSea | 0.10092489 | -0.19762 |