Online Supplementary Information (OSI) for: Ma, Li, & Gotelli “Diversity-Disease Relationships and Shared Species Analyses for the Human Microbiome-Associated Diseases” *The ISME Journal*

(I) Supplement to “Materials and Methods” (Shared Species Analysis: SSA)—Shared Species Analysis Algorithms (A1 and A2)

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Table S3A. The results from the analysis (using ***Algorithm A1***) of shared species between the healthy and diseased samples. Shared OTUs were detected in both healthy and diseased individuals. The expected number of shared OTUs was taken as the average of 1000 simulations from a randomization test in which the pooled set of reads were randomly re-assigned to healthy or diseased status. Among 41 comparisons of the 27 case studies, only 1 case showed no significant changes in the shared species between the healthy and diseased microbiome groups.

Table S3B. The results from the analysis (with ***A2 algorithm***) of shared species between the healthy and diseased samples. Shared OTUs were detected in both healthy and diseased individuals. The expected number of shared OTUs was taken as the average of 1000 simulations from a randomization test in which the pooled set of *microbiome samples* was randomly re-assigned to healthy or diseased status (*i.e.,* randomly divided into the healthy or diseased group). Among 41 comparisons of the 27 case studies, 21 cases showed no significant differences in the shared species between the healthy and diseased microbiome groups (p>0.05), and 20 cases showed decreased numbers of shared species (p<0.05).

Table S4. A summary on the diversity-disease relationships (DDRs) in the 31 case studies cited in the Appendix S1 of Johnson et al (2015) in “Frontiers in research on biodiversity and disease” *Ecology Letters*.

Fig S1. A diagram showing the shared species analysis using ***Algorithm A1***:

Fig S2. A diagram showing the shared species analysis using ***Algorithm A2***:

Supplement to "Materials and Methods"—
Shared Species Analysis Algorithms (A1 and A2)

Data Preparation

Assume there are two treatments: the healthy and diseased, and the healthy treatment contains *a* microbiome samples (Table 1) and the diseased treatment contains *b* samples (Table 2). Further assume that the total reads (the total abundances) in the healthy treatment is *A*, and that in the diseased is *B*, as computed in Tables 1 & 2.

Table 1. The OTU table of the healthy treatment (group)

Sample ID	**OTU 1**	**OTU 2**	**OTU 3**	**… …**	**OTU *N***
Sample *1*	x_{11}	x_{12}	x_{13}	… …	x_{1N}
Sample *2*	x_{21}	x_{22}	x_{23}	… …	x_{2N}
Sample *3*	x_{31}	x_{32}	x_{33}	… …	x_{3N}
… …	… …	… …	… …	… …	… …
Sample *a*	x_{a1}	x_{a2}	x_{a3}	… …	x_{aN}
Column Sum*	x_{+1}	x_{+2}	x_{+3}	… …	x_{+N}

The column sum of OTU *j* is $x_{+j} = \sum_{i=1}^{a} x_{ij}$, and the total reads of in the *a* samples of the healthy treatment is $A = \sum_{i=1}^{a}\sum_{j=1}^{N} x_{ij}$.

Table 2. The OTU table of the diseased treatment (group)

Sample ID	**OTU 1**	**OTU 2**	**OTU 3**	**… …**	**OTU *N***
Sample *1*	y_{11}	y_{12}	y_{13}	… …	y_{1N}
Sample *2*	y_{21}	y_{22}	y_{23}	… …	y_{2N}
Sample *3*	y_{31}	y_{32}	y_{33}	… …	y_{3N}
… …	… …	… …	… …	… …	… …
Sample *b*	y_{b1}	y_{b2}	y_{b3}	… …	y_{bN}
Column Sum*	y_{+1}	y_{+2}	y_{+3}	… …	y_{+N}

The column sum of OTU *j* is $y_{+j} = \sum_{i=1}^{b} y_{ij}$, and the total reads of in the *a* samples of the healthy treatment is $B = \sum_{i=1}^{b}\sum_{j=1}^{N} y_{ij}$

Algorithm A1: The Shared Species Analysis through "Random Reassignments" of both OTUs and Samples

Step (1) Compute the column sums for the healthy and diseased treatments, respectively, *i.e.,* the total number of population abundances for each species (OTU) in either healthy or diseased treatment.

Step (2) Pool together the *A* reads (individuals from the healthy treatment) and *B* reads (individuals from the diseased treatment), and obtained *A*+*B* reads (individuals) without caring the *identities* (which OTUs, but each OTU still keep track of its name or label) or *sources* (from the healthy or diseased samples). The structure of OTU table is gone at this step, regardless their row or column numbers in the original OTU table.

Step (3) Randomly select A reads for the healthy treatment, and recount the number of reads (individuals) for each kind of OTU (each species). The leftover reads are assigned to the diseased treatment, and similarly, recount the number of reads (individuals) for each kind of OTU (species) in the diseased treatment.
Step (4) Repeat Step (3) for 1000 times, and compute the number of shared OTUs between the healthy and diseased for each repetition.
Step (5) Compute pseudo-p value as follows:
Let D be the times when the number of *shared species* from 1000 times of random sampling (*i.e.*, random re-assignments) exceeded the number of *shared species observed*. A pseudo p-value can be computed as:

$$p = D/1000$$

If p-value<0.05, then we conclude that the difference in shared species cannot be attributed to random effect alone, and disease is very likely to have a significant effect on the number of shared species.

Fig S1 below shows the process of random reassignment with an example of only 3 OTUs, 12 & 16 reads (bacterial individuals) from the healthy and diseased treatments, respectively.

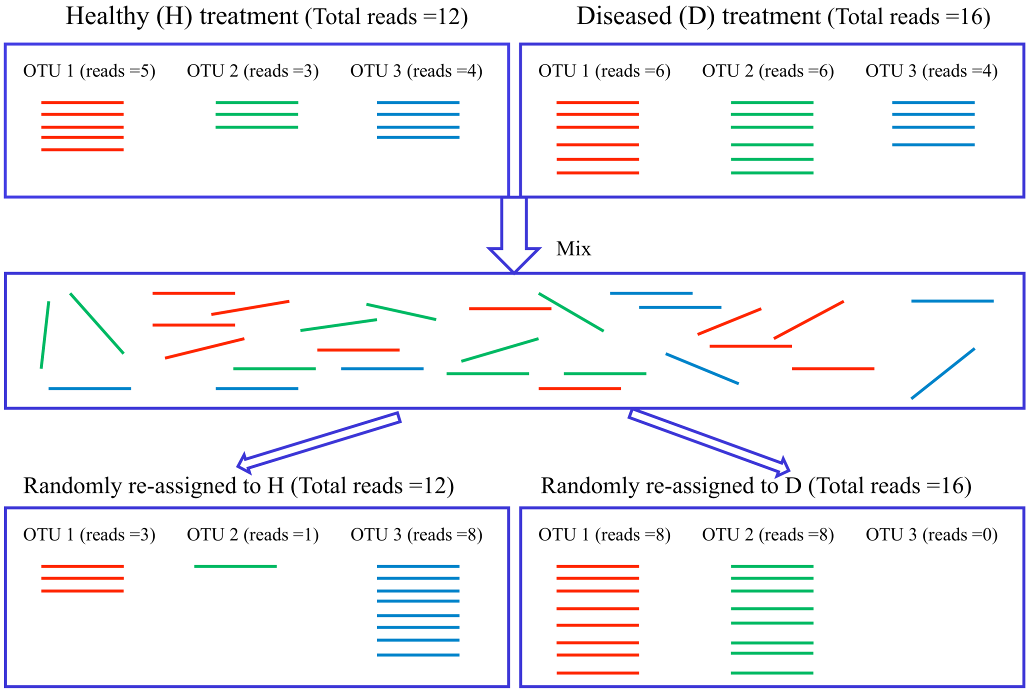

Fig S1. A diagram showing the shared species analysis using ***Algorithm A1***: 16S-rRNA reads (bacterial individuals) are represented with lines of various colors (different colors for different kinds of species or OTUs); the intermediate box contains mixed reads, without orders but each read keeping track of its identity (OTU number or species name); 3 species or OTUs were assumed, and 12 & 16 reads were assumed in the healthy and diseased treatments, respectively.

Algorithm A2: The Shared Species Analysis through "Random Reassignments" of Samples only.

Step (1) Pool together all microbiome samples from the healthy and diseased treatments. That is, mix $a+b$ samples in Tables 1 & 2.
Step (2) Randomly select a samples from the mixed samples as the healthy treatment, and treat the leftover b samples as the diseased treatment. See Fig S1 below for the process.

Step (3) Repeat step (2) 1000 times and compute the shared species number between the healthy and diseased samples for each time of the random sampling.

Step (4) Compute pseudo-p value

Let D be the times when the number of *shared species* from 1000 times of random sampling (*i.e*., random re-assignments) exceeded the number of *shared species observed*. A pseudo p-value can be computed as

$$p=D/1000$$

If p-value<0.05, then we conclude that the difference in shared species cannot be attributed to random effect alone, and hence the decrease of shared species is most likely caused by disease. Instead, if p-value>0.05, the decreased number of shared species is most likely due to random effect, rather than due to disease.

Fig S2 below shows the process of random reassignment of the samples with an example of only 3 OTUs, 12 & 16 reads (bacterial individuals) from the healthy and diseased treatments, respectively.

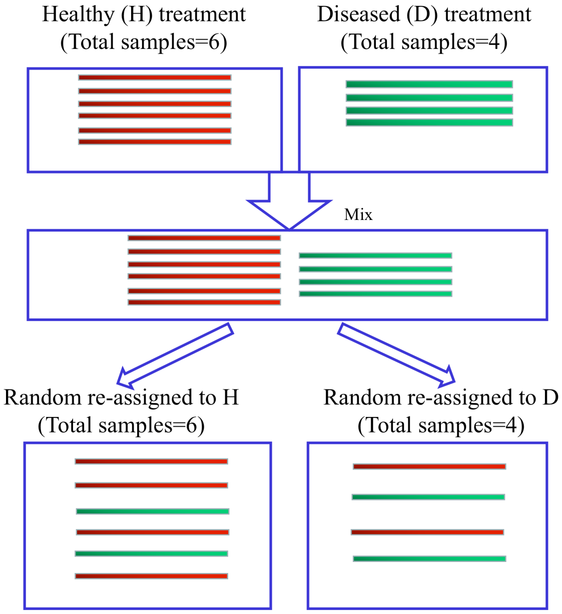

Fig S2. A diagram showing the shared species analysis using ***Algorithm A2***: the top left and right boxes contain 6 healthy and 4 microbiome samples, respectively. The middle box contains mixed samples of 10 samples, pooled from the healthy (6 samples) and diseased (4 samples) groups. In the bottom, the pooled samples were reassigned randomly to the healthy and diseased groups again, but the samples were randomly mixed here.

Table S1. Twenty-seven 16S-rRNA metagenomic datasets utilized to analyze diversity-disease relationships (DDRs)

Index	**Sites**	**Disease**	**Groups**	**References***
1	Gut	IBD (Inflammatory Bowel Disease)	Crohn's disease (CD) (18), Ulcerative colitis (UC) (38), Healthy (18)	Papa et al (2012)
2			CD (251) , UC (324), Healthy (62)	Halfvarson et al (2017)
3		Obesity	Lean (61), Obese (196) and Overweight (24)	Turnbaugh et al (2009)
4		CRC	Cancer (46) vs. Healthy (56)	Wang et al (2012)
5		HIV	Non-treatment (7) vs. ART treatment (11)	Neff et al (2018)
6			WithART(14), WithoutART(12), Healthy (22)	Lozupone et al (2013)
7			HIV Negative (20) *vs.* Positive (40)	McHardy et al (2013)
8		Type 1 diabetes and Obesity	Normal T1D (33) vs Normal Healthy (33)	Kim, Jane
			Obesity T1D (24) vs. Obesity Healthy (26)	
9		Gout	Disease (41) vs. Healthy (42)	Guo et al (2015)
10		MHE	MHE (25), Cirrhotic (25), Healthy (25)	Zhang et al (2013)
11		Parkinson's Disease	Disease (205) vs. Healthy (133)	Hill-Burns et al 2017)
12		Schizophrenia	Disease (25). vs. Healthy (25)	Dilip V. Jeste (UC San Diego)
13		Autism, Neurotypical	Autism (88), Neurotypical (41), Healthy (14)	Kang et al (2017)
14		Atherosclerosis	Disease (15) vs. Healthy (15)	Koren et al (2010)
15	Oral	Atherosclerosis	Disease (14) vs. Healthy (15)	Koren et al (2010)
16		Periodontitis	PB (22), PnB (22), Healthy (17)	Abusleme et al (2013)
17			Disease (29), Control (29), Healthy (29)	Griffen et al (2012)
18		Smoking	Smoking (6) vs. Non-smoking (9)	Lazarevic et al (2010)
19			Smoking (74) vs. Non-smoking (72)	Charlson et al (2010)
20	Nostril	Smoking	Smoking (74) vs. Non-smoking (71)	Charlson et al (2010)
21	Skin	Psoriasis	Disease (77), Control (83), Healthy (76)	Alekseyenko et al (2013)
22	Lung	Cystic Fibrosis (CF)	End of Treatment (23) vs. Exacerbation (23)	Fodor et al (2012)
23			Disease (16) vs. Healthy (10)	Blainey et al 2012)
24		HIV	Disease (82) vs. Healthy (77)	Lozupone et al (2013)
25	Vaginal	Bacterial Vaginosis (BV)	ABV, SBV, Healthy	
26	Semen	Infertile	Abnormal (33), Subnormal (28), Normal (35). Genus level and species level	Weng et al 2014
27	Milk	Mastitis	Mastitis (4) *vs.* Healthy (16)	Urbaniak (2015)

Table S2. The *mean* and *standard error* of the Hill numbers (diversity) for each treatment in each of the 27 case studies, as well as the results (*d*-statistic and *p*-value) for the effect-size test of the microbiome-associated disease on diversity (the highlighted cells contains significant effect sizes with *p*-value=0.05)

Sites	**Diseases**	**Treatments**		**Statistics**	**Diversity in Hill Numbers**					**Asymptomatic Estimation**		
					q=0	*q=1*	*q=2*	*q=3*	*q=4*	*q=0*	*q=1*	*q=2*
Gut	IBD (Inflammatory Bowel Disease)	1	Healthy	Mean	170.500	34.466	16.565	12.298	10.508	254.768	35.988	16.651
				Std. Err.	15.034	3.675	1.926	1.412	1.180	24.684	3.861	1.939
			CD	Mean	157.944	32.605	15.574	11.453	9.757	238.684	33.956	15.652
				Std. Err.	13.713	3.133	1.497	1.088	0.918	20.012	3.310	1.509
			UC	Mean	102.868	19.974	10.354	7.983	6.953	161.313	20.735	10.409
				Std. Err.	9.508	2.523	1.399	1.051	0.887	14.895	2.666	1.413
			Healthy vs. CD	Cohen's *d*	0.180	0.070	0.060	0.090	0.100	0.150	0.070	0.060
				p-value of *d*	0.590	0.840	0.850	0.800	0.770	0.660	0.830	0.850
			Healthy vs. UC	Cohen's *d*	1.120	0.960	0.810	0.770	0.760	1.010	0.970	0.810
				p-value of *d*	<0.001	<0.001	0.010	0.010	0.010	<0.001	<0.001	0.010

		2	Healthy	Mean	1287.081	47.145	16.518	11.224	9.269	1821.898	48.844	16.853
				Std. Err.	77.562	4.318	1.750	1.166	0.935	101.651	4.373	1.795
			CD	Mean	784.084	25.538	11.464	8.607	7.425	1168.244	28.512	12.782
				Std. Err.	28.642	1.234	0.534	0.394	0.333	38.672	1.425	0.762
			UC	Mean	1192.549	41.229	16.658	11.957	10.078	1699.290	44.007	17.347
				Std. Err.	28.819	1.405	0.603	0.431	0.357	38.497	1.475	0.658
			Healthy vs. CD	Cohen’s *d*	0.810	0.720	0.360	0.260	0.230	0.790	0.660	0.290
				p-value of *d*	<0.001	<0.001	0.010	0.070	0.110	<0.001	<0.001	0.040
			Healthy vs. UC	Cohen’s *d*	0.140	0.130	-0.090	-0.150	-0.170	0.140	0.090	-0.110
				p-value of *d*	0.310	0.360	0.540	0.280	0.210	0.330	0.520	0.440
	Obesity	3	Lean	Mean	263.180	64.712	26.818	17.896	14.494	398.035	70.961	27.278
				Std. Err.	12.031	2.617	1.484	1.033	0.835	16.033	2.923	1.534
			Overweight	Mean	275.042	65.688	27.625	18.876	15.420	396.811	70.955	28.024
				Std. Err.	20.234	5.749	3.515	2.576	2.099	26.433	6.300	3.625
			Obesity	Mean	233.163	61.409	25.711	17.446	14.273	348.373	67.514	26.202
				Std. Err.	4.887	1.711	1.007	0.739	0.613	7.324	1.910	1.042
			Lean vs. Overweight	Cohen’s *d*	-0.130	0.010	0.010	-0.020	-0.030	0.010	0.050	0.020
				p-value of *d*	0.600	0.960	0.960	0.940	0.900	0.970	0.850	0.940
			Lean vs. Obesity	Cohen’s *d*	0.350	0.200	0.140	0.110	0.090	0.430	0.190	0.140
				p-value of *d*	0.020	0.180	0.350	0.460	0.530	<0.001	0.210	0.350
	Cancer	4	Healthy	Mean	167.536	39.797	15.944	11.420	9.729	301.083	46.863	16.229
				Std. Err.	5.886	2.226	0.988	0.713	0.606	11.174	2.764	1.023
			Cancer	Mean	136.739	29.688	12.259	8.938	7.681	220.802	33.621	12.456
				Std. Err.	7.064	1.794	0.852	0.615	0.519	12.416	2.083	0.880
			Healthy vs. Cancer	Cohen’s *d*	0.650	0.670	0.550	0.520	0.500	0.920	0.720	0.550
				p-value of *d*	<0.001	<0.001	0.010	0.010	0.020	<0.001	<0.001	0.010
	HIV	5	Negative	Mean	781.405	58.486	22.079	15.208	12.564	1066.929	61.936	22.436
				Std. Err.	49.588	3.938	1.788	1.264	1.031	70.258	4.470	1.918
			Treatment	Mean	803.700	58.707	22.488	15.597	12.972	1127.109	64.302	22.969
				Std. Err.	72.075	3.692	1.550	1.110	0.927	92.443	4.349	1.638
			Non-treat	Mean	621.500	50.195	19.304	13.166	10.906	898.516	57.410	19.754
				Std. Err.	86.129	4.663	1.780	1.196	1.000	107.597	5.857	1.855
			Negative vs. Treatment	Cohen’s *d*	0.020	-0.060	-0.100	-0.110	-0.120	-0.070	-0.140	-0.110
				p-value of *d*	0.950	0.800	0.680	0.650	0.610	0.760	0.560	0.640
			Negative vs. Non-treat	Cohen’s *d*	0.450	0.350	0.260	0.280	0.280	0.360	0.150	0.230
				p-value of *d*	0.120	0.220	0.360	0.320	0.320	0.210	0.590	0.410
		6	Negative	Mean	537.318	55.688	21.581	14.699	12.030	823.936	57.413	21.617
				Std. Err.	39.985	6.609	2.983	1.960	1.542	56.040	6.749	2.992
			Treatment	Mean	497.643	40.657	15.383	10.828	9.129	756.213	41.461	15.396
				Std. Err.	30.094	5.525	2.222	1.525	1.267	38.885	5.666	2.225
			Non-treat	Mean	593.750	65.218	24.101	16.171	13.193	865.520	66.877	24.138
				Std. Err.	43.668	6.304	2.745	1.876	1.504	58.398	6.477	2.750
			Negative vs. Treatment	Cohen’s *d*	0.100	0.520	0.490	0.460	0.430	0.130	0.560	0.490
				p-value of *d*	0.780	0.150	0.170	0.190	0.220	0.700	0.120	0.170
			Negative vs. Non-treat	Cohen’s *d*	-0.390	-0.480	-0.350	-0.300	-0.290	-0.260	-0.460	-0.340
				p-value of *d*	0.290	0.190	0.350	0.410	0.420	0.480	0.210	0.350
		7	Negative	Mean	505.950	28.323	12.156	9.141	7.934	740.090	28.458	12.158
				Std. Err.	20.044	2.491	1.207	0.890	0.756	27.086	2.507	1.208
			Positive	Mean	470.150	25.209	9.987	7.258	6.238	680.065	25.328	9.988
				Std. Err.	20.701	2.251	0.919	0.648	0.545	30.363	2.265	0.919
			Negative vs. Positive	Cohen’s *d*	0.390	0.340	0.450	0.530	0.560	0.460	0.340	0.450
				p-value of *d*	0.170	0.220	0.110	0.060	0.050	0.100	0.220	0.110
	T1D (Lean)	8	Normal-Healthy	Mean	727.727	42.460	16.695	11.635	9.663	952.367	42.934	16.763
				Std. Err.	41.991	3.979	1.698	1.148	0.927	53.431	3.952	1.686
			Normal-T1D	Mean	677.813	34.823	13.128	9.230	7.766	883.228	35.047	13.141
				Std. Err.	42.337	3.644	1.393	0.924	0.740	52.103	3.666	1.391
			Healthy vs. T1D	Cohen’s *d*	0.140	0.340	0.380	0.380	0.370	0.160	0.360	0.390
				p-value of *d*	0.570	0.180	0.140	0.140	0.140	0.530	0.150	0.130
	T1D (Obesity)		Obesity-Healthy	Mean	864.231	41.114	14.488	9.846	8.151	1114.182	41.467	14.826
				Std. Err.	46.008	3.806	1.542	1.000	0.770	56.133	3.768	1.506
			Obesity-T1D	Mean	723.417	42.751	14.462	9.671	8.015	926.518	43.185	14.503
				Std. Err.	67.435	3.746	1.372	0.929	0.766	84.563	3.745	1.362

			Healthy vs. T1D	Cohen’s *d*	0.440	-0.070	<0.001	0.040	0.040	0.460	-0.070	0.050
				p-value of *d*	0.130	0.800	0.990	0.900	0.890	0.120	0.810	0.870
	Gout	9	Healthy	Mean	234.333	26.818	11.044	8.155	7.027	386.201	27.948	11.070
				Std. Err.	12.645	2.547	1.099	0.801	0.674	24.881	2.724	1.104
			Gout	Mean	169.756	18.354	8.109	6.152	5.376	267.979	18.979	8.127
				Std. Err.	13.676	2.293	1.029	0.748	0.628	25.657	2.437	1.034
			Healthy vs. Gout	Cohen’s *d*	0.830	0.600	0.490	0.460	0.450	0.830	0.600	0.490
				p-value of *d*	<0.001	0.010	0.030	0.040	0.050	<0.001	0.010	0.030
	MHE	10	Healthy	Mean	129.640	42.776	20.762	14.828	12.378	231.301	54.554	22.702
				Std. Err.	15.118	5.811	3.449	2.572	2.148	25.222	7.662	4.008
			Control	Mean	132.640	30.219	15.086	11.086	9.445	220.050	36.409	15.955
				Std. Err.	17.914	5.569	2.942	2.082	1.735	26.756	6.848	3.160
			MHE	Mean	118.750	33.493	15.665	11.044	9.232	229.645	43.693	16.914
				Std. Err.	10.567	4.290	2.378	1.666	1.367	16.152	6.139	2.705
			Healthy vs. MHE	Cohen’s *d*	0.030	0.280	0.290	0.300	0.300	-0.140	0.220	0.270
				p-value of *d*	0.910	0.340	0.310	0.300	0.300	0.630	0.440	0.360
			Control vs. MHE	Cohen’s *d*	0.100	-0.200	-0.100	-0.050	-0.020	-0.210	-0.270	-0.110
				p-value of *d*	0.730	0.500	0.740	0.870	0.940	0.470	0.350	0.700
	Parkinson’s Disease	11	Healthy	Mean	164.902	25.405	11.968	8.943	7.718	173.584	25.683	11.988
				Std. Err.	5.493	1.300	0.678	0.502	0.422	5.910	1.322	0.680
			PD	Mean	176.585	26.604	12.211	9.031	7.752	186.844	26.909	12.250
				Std. Err.	4.599	0.982	0.464	0.332	0.276	4.996	0.997	0.464
			Healthy vs. PD	Cohen’s *d*	-0.160	-0.100	-0.060	-0.050	-0.040	-0.170	-0.100	-0.070
				p-value of *d*	0.150	0.390	0.570	0.640	0.690	0.130	0.390	0.540
	Schizophrenia	12	Healthy	Mean	596.880	40.556	15.654	11.016	9.230	894.326	41.228	15.666
				Std. Err.	38.207	4.958	2.411	1.653	1.320	52.770	5.063	2.415
			Disease	Mean	541.120	38.376	15.385	11.038	9.375	814.625	39.092	15.398
				Std. Err.	38.692	3.756	1.456	1.001	0.829	54.200	3.851	1.458
			Healthy vs. Disease	Cohen’s *d*	0.310	0.100	-0.030	-0.070	-0.100	0.310	0.100	-0.030
				p-value of *d*	0.290	0.730	0.910	0.790	0.730	0.270	0.740	0.910
	Autism	13	Healthy	Mean	136.214	26.156	14.318	11.083	9.574	143.062	26.341	14.343
				Std. Err.	14.561	4.641	2.882	2.253	1.924	15.549	4.688	2.891
			Autism	Mean	149.636	23.278	11.165	8.300	7.120	157.472	23.451	11.178
				Std. Err.	5.743	1.474	0.799	0.593	0.500	6.074	1.487	0.800
			Neurotypical	Mean	137.195	20.067	9.973	7.564	6.562	143.577	20.193	9.985
				Std. Err.	8.734	2.131	1.129	0.828	0.696	9.386	2.151	1.132
			Healthy vs. Autism	Cohen’s *d*	-0.220	0.130	0.260	0.300	0.310	-0.220	0.130	0.260
				p-value of *d*	0.450	0.660	0.360	0.300	0.280	0.440	0.660	0.360
			Healthy vs. Neurotypical	Cohen’s *d*	-0.040	0.330	0.410	0.430	0.430	-0.020	0.330	0.410
				p-value of *d*	0.910	0.290	0.190	0.180	0.170	0.940	0.290	0.190
	Atheroscierosis	14	Healthy	Mean	444.867	136.258	54.655	35.802	28.722	708.177	156.960	55.957
				Std. Err.	16.999	9.687	5.784	4.109	3.357	33.355	11.699	6.024
			Disease	Mean	470.667	133.827	55.620	37.023	29.622	748.447	152.671	56.824
				Std. Err.	27.925	16.161	7.921	5.368	4.295	41.267	19.003	8.188
			Healthy vs. Disease	Cohen’s *d*	-0.220	0.160	0.050	0.010	0.010	-0.230	0.180	0.060
				p-value of *d*	0.550	0.670	0.880	0.980	0.980	0.530	0.620	0.870
Oral	Atheroscierosis	15	Healthy	Mean	157.733	26.011	11.594	8.563	7.358	224.580	27.120	11.671
				Std. Err.	11.002	5.180	2.698	1.967	1.638	14.737	5.500	2.736
			Disease	Mean	215.286	37.642	13.867	9.331	7.730	283.238	38.931	13.914
				Std. Err.	17.402	5.203	2.201	1.455	1.165	23.660	5.415	2.213
			Healthy vs. Disease	Cohen’s *d*	-0.970	-0.600	-0.320	-0.210	-0.160	-0.720	-0.590	-0.320
				p-value of *d*	0.020	0.130	0.390	0.590	0.680	0.070	0.130	0.400
	Periodontitis	16	Healthy	Mean	70.000	12.022	6.251	4.941	4.407	104.304	12.745	6.320
				Std. Err.	6.215	2.522	1.333	1.018	0.883	8.190	2.807	1.367
			PB	Mean	108.682	27.190	13.207	9.701	8.279	152.325	28.901	13.381
				Std. Err.	6.128	3.258	1.784	1.303	1.085	8.572	3.567	1.831
			PnB	Mean	102.773	27.319	14.842	11.454	9.953	145.003	29.057	15.080
				Std. Err.	6.452	3.099	1.855	1.459	1.268	7.623	3.389	1.908
			Healthy vs. PB	Cohen’s *d*	-1.440	-1.240	-1.050	-0.980	-0.950	-1.300	-1.210	-1.050
				p-value of *d*	<0.001	<0.001	<0.001	0.010	0.010	<0.001	<0.001	<0.001
			Healthy vs. PnB	Cohen’s *d*	-1.160	-1.180	-1.160	-1.140	-1.130	-1.160	-1.160	-1.160
				p-value of *d*	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

		17	Healthy	Mean	141.138	65.735	38.716	29.025	24.608	143.151	67.048	39.194
				Std. Err.	5.889	4.394	3.397	2.765	2.397	6.076	4.530	3.485
			Control	Mean	169.552	80.297	44.597	31.590	25.941	172.792	81.861	45.096
				Std. Err.	6.442	4.121	3.052	2.522	2.202	6.764	4.242	3.117
			Disease	Mean	182.966	93.665	53.861	38.480	31.535	186.536	95.821	54.663
				Std. Err.	5.114	3.660	3.398	2.933	2.557	5.108	3.817	3.514
			Healthy vs. Disease	Cohen's *d*	-1.400	-1.310	-0.880	-0.660	-0.560	-1.430	-1.310	-0.880
				p-value of *d*	<0.001	<0.001	<0.001	0.020	0.040	<0.001	<0.001	<0.001
			Control vs. Disease	Cohen's *d*	-0.450	-0.650	-0.540	-0.470	-0.440	-0.450	-0.650	-0.540
				p-value of *d*	0.100	0.020	0.050	0.080	0.100	0.090	0.020	0.050
	Smoking	18	Non-Smoker	Mean	297.333	59.616	21.197	14.462	12.059	941.822	74.033	21.517
				Std. Err.	33.182	5.049	2.524	2.095	1.895	144.906	6.450	2.608
			Smoker	Mean	331.333	55.189	18.756	12.240	9.967	1173.781	67.595	18.914
				Std. Err.	94.503	12.538	3.751	2.203	1.731	435.874	15.113	3.770
			Non-Smoker vs. Smoker	Cohen's *d*	-0.090	0.280	0.330	0.390	0.420	-0.160	0.310	0.350
				p-value of *d*	0.870	0.600	0.540	0.480	0.440	0.760	0.570	0.530
		19	Non-Smoker	Mean	107.056	11.231	4.582	3.580	3.213	211.813	12.238	4.602
				Std. Err.	5.597	0.920	0.290	0.206	0.177	12.297	1.084	0.294
			Smoker	Mean	126.392	17.742	7.431	5.605	4.905	266.912	19.809	7.498
				Std. Err.	7.618	1.539	0.730	0.530	0.446	16.274	1.740	0.751
			Non-Smoker vs. Smoker	Cohen's *d*	-0.300	-0.650	-0.630	-0.620	-0.610	-0.400	-0.660	-0.600
				p-value of *d*	0.080	<0.001	<0.001	<0.001	<0.001	0.020	<0.001	<0.001
		20	Non-Smoker	Mean	126.181	34.011	16.869	12.544	10.753	197.698	36.732	17.172
				Std. Err.	4.463	1.371	0.875	0.709	0.625	7.920	1.510	0.910
			Smoker	Mean	116.425	32.783	17.362	13.165	11.325	188.087	36.057	18.067
				Std. Err.	5.306	1.819	0.928	0.711	0.616	9.238	2.126	1.030
			Non-Smoker vs. Smoker	Cohen's *d*	0.260	0.150	-0.040	-0.090	-0.100	0.160	0.120	-0.080
				p-value of *d*	0.120	0.360	0.810	0.570	0.530	0.340	0.490	0.650
Skin	Psoriasis	21	Control	Mean	137.494	43.405	18.610	12.909	10.744	140.617	46.295	19.083
				Std. Err.	6.249	2.019	0.986	0.703	0.579	6.460	2.196	1.039
			Normal	Mean	132.605	49.481	23.484	16.360	13.540	135.638	53.347	24.508
				Std. Err.	6.232	2.821	1.642	1.200	1.002	6.446	3.114	1.793
			Lesion	Mean	128.234	45.083	20.387	13.999	11.528	131.221	48.462	21.167
				Std. Err.	5.991	2.760	1.630	1.178	0.970	6.194	3.026	1.746
			Control vs. Lesion	Cohen's *d*	0.170	-0.020	-0.050	-0.030	-0.020	0.170	-0.030	-0.070
				p-value of *d*	0.290	0.900	0.730	0.830	0.900	0.300	0.840	0.670
			Normal vs. Lesion	Cohen's *d*	0.080	0.180	0.240	0.260	0.270	0.080	0.180	0.240
				p-value of *d*	0.620	0.260	0.140	0.110	0.100	0.620	0.260	0.140
Lung	Cystic Fibrosis (CF)	22	Treated	Mean	29.720	3.735	2.296	1.984	1.854	37.689	3.758	2.297
				Std. Err.	3.231	0.561	0.316	0.246	0.213	3.851	0.566	0.317
			Exacerbation	Mean	40.440	4.652	2.630	2.214	2.051	52.211	4.688	2.632
				Std. Err.	3.909	0.929	0.498	0.380	0.331	4.936	0.938	0.500
			Treated vs. Exacerbation	Cohen's *d*	-0.600	-0.210	-0.130	-0.120	-0.110	-0.650	-0.210	-0.130
				p-value of *d*	0.040	0.470	0.650	0.690	0.690	0.030	0.460	0.650
		23	Healthy	Mean	60.667	25.856	15.640	12.295	10.781	61.794	27.019	16.284
				Std. Err.	7.587	2.331	1.544	1.266	1.109	7.641	2.392	1.724
			Disease	Mean	42.750	15.526	10.649	8.872	7.958	43.725	15.681	10.707
				Std. Err.	3.790	1.755	1.300	1.103	0.996	3.843	1.778	1.309
			Healthy vs. Disease	Cohen's *d*	0.870	1.530	1.090	0.920	0.870	0.880	1.630	1.130
				p-value of *d*	0.060	<0.001	0.020	0.050	0.060	0.060	<0.001	0.020
	HIV	24	Negative	Mean	251.194	34.640	17.540	13.170	11.243	401.789	36.891	19.145
				Std. Err.	20.905	3.757	1.884	1.363	1.124	31.370	4.076	2.485
			Positive	Mean	262.756	34.337	15.975	11.471	9.644	404.129	35.522	16.077
				Std. Err.	24.697	4.493	1.948	1.297	1.038	37.058	4.718	1.959
			Negative vs. Positive	Cohen's *d*	-0.060	0.060	0.140	0.190	0.220	0.010	0.090	0.190
				p-value of *d*	0.760	0.770	0.470	0.320	0.270	0.960	0.660	0.330
Vaginal	BV	25	Healthy	Mean	7.544	1.709	1.415	1.344	1.313	9.704	1.715	1.415
				Std. Err.	0.613	0.082	0.051	0.043	0.040	0.926	0.083	0.051
			BV	Mean	21.701	6.736	4.637	3.966	3.646	27.650	6.800	4.651
				Std. Err.	0.680	0.292	0.214	0.183	0.166	1.110	0.295	0.215
			Healthy vs. BV	Cohen's *d*	-2.230	-2.520	-2.240	-2.120	-2.070	-1.900	-2.520	-2.230
				p-value of *d*	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Semen	Infertile (Genus level)	26	Normal	Mean	129.286	20.648	9.233	6.834	5.901	153.896	21.042	9.262
				Std. Err.	5.522	1.431	0.771	0.570	0.484	6.182	1.475	0.777
			Subnormal	Mean	136.821	22.644	9.733	6.970	5.933	157.600	23.071	9.766
				Std. Err.	6.138	1.752	0.895	0.608	0.495	6.027	1.815	0.903
			Abnormal	Mean	138.182	23.609	11.138	8.192	7.014	171.071	24.077	11.177
				Std. Err.	7.070	1.830	0.977	0.711	0.598	7.891	1.881	0.985
			Normal vs. Subnormal	Cohen's *d*	-0.240	-0.230	-0.100	-0.050	-0.020	-0.130	-0.220	-0.100
				p-value of *d*	0.350	0.370	0.690	0.860	0.940	0.620	0.380	0.690
			Normal vs. Abnormal	Cohen's *d*	-0.220	-0.280	-0.340	-0.330	-0.330	-0.400	-0.280	-0.330
				p-value of *d*	0.370	0.260	0.170	0.180	0.190	0.110	0.260	0.180
	Infertile Species level)		Normal	Mean	525.771	87.557	27.113	16.723	13.185	764.343	96.505	27.444
				Std. Err.	37.004	10.194	3.674	2.136	1.593	52.841	11.706	3.756
			Subnormal	Mean	580.500	97.792	32.950	21.037	16.749	828.139	107.539	33.519
				Std. Err.	48.263	14.207	5.808	3.510	2.657	65.145	16.160	5.962
			Abnormal	Mean	604.515	103.857	35.913	22.741	17.925	865.191	114.174	36.547
				Std. Err.	55.264	14.777	5.899	3.667	2.780	73.190	16.648	6.068
			Normal vs. Subnormal	Cohen's *d*	-0.230	-0.150	-0.180	-0.220	-0.240	-0.200	-0.140	-0.180
				p-value of *d*	0.380	0.550	0.490	0.400	0.350	0.440	0.570	0.490
			Normal vs. Abnormal	Cohen's *d*	-0.240	-0.190	-0.280	-0.320	-0.330	-0.240	-0.180	-0.280
				p-value of *d*	0.320	0.430	0.260	0.200	0.180	0.320	0.460	0.250
Milk	Mastitis	27	Healthy	Mean	85.688	10.923	5.450	4.305	3.852	94.066	10.941	5.451
				Std. Err.	1.477	1.143	0.608	0.475	0.419	2.641	1.146	0.609
			Mastitis	Mean	83.750	9.693	4.482	3.599	3.280	89.751	9.715	4.484
				Std. Err.	4.230	2.134	1.054	0.796	0.706	4.489	2.144	1.055
			Healthy vs. Mastitis	Cohen's *d*	0.250	0.240	0.390	0.370	0.340	0.460	0.240	0.390
				p-value of *d*	0.660	0.670	0.490	0.510	0.550	0.430	0.670	0.490

Table S3A. The results from the analysis (with ***A1 algorithm***) of shared species between the healthy and diseased samples. Shared OTUs were detected in both healthy and diseased individuals. The expected number of shared OTUs was taken as the average of 1000 simulations from a randomization test in which the pooled set of reads were randomly re-assigned to healthy or diseased status. Among 41 comparisons of the 27 case studies, only 1 case showed no significant changes in the shared species between the healthy and diseased microbiome groups.

Microbiome	**Disease**	**Index**	**Healthy**	**Diseased**	**Observed Shared OTUs**	**Expected Shared OTUs**	***p-value***
Gut	IBD (Inflammatory Bowel Disease)	1	Healthy	CD	597	792.734	< 0.01
			Healthy	UC	627	919.766	< 0.01
		2	Healthy	CD	5368	6417.533	< 0.01
			Healthy	UC	5869	6446.158	< 0.01
	Obesity	3	Lean	Overweight	1172	1387.208	< 0.01
			Lean	Obesity	1498	1714.379	< 0.01
	Cancer	4	Healthy	Cancer	2190	3970.857	< 0.01
	HIV	5	Negative	Treatment	3253	3771.407	< 0.01
			Negative	Non-treatment	2681	3319.944	< 0.01
		6	Negative	Treatment	1678	2293.157	< 0.01
			Negative	Non-treatment	1593	2338.103	< 0.01
		7	Negative	Positive	1857	2320.653	< 0.01
	T1D (Lean)	8	Healthy	T1D	2423	2840.267	< 0.01
	T1D (Obesity)		Healthy	T1D	2340	2764.854	< 0.01
	Gout	9	Healthy	Gout	1139	1723.811	< 0.01
	MHE	10	Healthy	MHE	676	929.581	< 0.01
			Control	MHE	730	946.121	< 0.01
	Parkinson’s Disease	11	Healthy	PD	2029	6818.997	< 0.01
	Schizophrenia	12	Healthy	Schizophrenia	2308	2898.745	< 0.01
	Autism	13	Healthy	Autism	489	1612.343	< 0.01
			Healthy	Neurotypical	446	1111.665	< 0.01
	Atherosclerosis	14	Healthy	Atherosclerosis	1796	2279.417	< 0.01
Oral	Atherosclerosis	15	Healthy	Atherosclerosis	524	672.700	< 0.01
	Periodontitis	16	Healthy	PB	273	494.961	< 0.01
			Healthy	PnB	268	483.720	< 0.01
		17	Healthy	Disease	1223	6002.413	< 0.01
			Control	Disease	0	7018.481	< 0.01
	Smoking	18	Non-smoking	Smoking	252	600.084	< 0.01
		19	Non-smoking	Smoking	946	1169.389	< 0.01
		20	Non-smoking	Smoking	682	841.023	< 0.01
Skin	Psoriasis	21	Control	Lesion	2072	3089.354	< 0.01
			Normal	Lesion	2274	3090.757	< 0.01
Lung	Cystic Fibrosis (CF)	22	End of Treatment	Exacerbation	132	156.941	< 0.01
		23	Healthy	CF	137	214.216	< 0.01
	HIV	24	Negative	Positive	1876	2330.410	< 0.01
Vaginal	BV	25	Healthy	BV	110	107.984	0.97
Semen	Infertile (Genus level)	26	Normal	Subnormal	379	455.336	< 0.01
			Normal	Abnormal	398	457.451	< 0.01
	Infertile Species level)		Normal	Subnormal	3029	3724.597	< 0.01
			Normal	Abnormal	3165	3910.306	< 0.01
Milk	Mastitis	27	Healthy	Mastitis	107	111.859	< 0.01

Table S3B. The results from the analysis (with ***A2 algorithm***) of shared species between the healthy and diseased samples. Shared OTUs were detected in both healthy and diseased individuals. The expected number of shared OTUs was taken as the average of 1000 simulations from a randomization test in which the pooled set of *microbiome samples* was randomly re-assigned to healthy or diseased status (*i.e.,* randomly divided into the healthy or diseased group). Among 41 comparisons of the 27 case studies, 21 cases showed no significant differences in the shared species between the healthy and diseased microbiome groups (*p*>0.05), and 20 cases showed decreased numbers of shared species (p<0.05).

Microbiome	**Disease**	**Case #**	**Healthy**	**Diseased**	**Observed Shared OTUs**	**Reads randomization**		**Samples randomization**	
						Expected Shared OTUs	***p-value***	**Expected Shared OTUs**	***p-value***
Gut	IBD (Inflammatory Bowel Disease)	1	Healthy	CD	597	792.734	< 0.01	614.419	0.085
			Healthy	UC	627	919.766	< 0.01	676.986	0.063
		2	Healthy	CD	5368	6417.533	< 0.01	5597.138	0.073
			Healthy	UC	5869	6446.158	< 0.01	6138.878	0.011
	Obesity	3	Lean	Overweight	1172	1387.208	< 0.01	1216.361	0.1
			Lean	Obesity	1498	1714.379	< 0.01	1518.899	0.244
	Cancer	4	Healthy	Cancer	2190	3970.857	< 0.01	2338.181	<0.001
	HIV	5	Negative	Treatment	3253	3771.407	< 0.01	3350.387	0.033
			Negative	Non-treatment	2681	3319.944	< 0.01	2892.884	0.016
		6	Negative	Treatment	1678	2293.157	< 0.01	1875	<0.001
			Negative	Non-treatment	1593	2338.103	< 0.01	1881.04	<0.001
		7	Negative	Positive	1857	2320.653	< 0.01	1847.563	0.547
	T1D (Lean)	8	Healthy	T1D	2423	2840.267	< 0.01	2422.456	0.499
	T1D (Obesity)		Healthy	T1D	2340	2764.854	< 0.01	2353.185	0.267
	Gout	9	Healthy	Gout	1139	1723.811	< 0.01	1250.023	0.002
	MHE	10	Healthy	MHE	676	929.581	< 0.01	735.756	0.002
			Control	MHE	730	946.121	< 0.01	752.483	0.122
	Parkinson's Disease	11	Healthy	PD	2029	6818.997	< 0.01	2062.102	0.109
	Schizophrenia	12	Healthy	Schizophrenia	2308	2898.745	< 0.01	2381.662	0.012
	Autism	13	Healthy	Autism	489	1612.343	< 0.01	544.127	0.134
			Healthy	Neurotypical	446	1111.665	< 0.01	554.003	0.022
	Atherosclerosis	14	Healthy	Atherosclerosis	1796	2279.417	< 0.01	1799.076	0.408
Oral	Atherosclerosis	15	Healthy	Atherosclerosis	524	672.700	< 0.01	552.981	0.006
	Periodontitis	16	Healthy	PB	273	494.961	< 0.01	382.138	<0.001
			Healthy	PnB	268	483.720	< 0.01	373.133	<0.001
		17	Healthy	Disease	1223	6002.413	< 0.01	1412.453	0.088
			Control	Disease	0	7018.481	< 0.01	1438.043	<0.001
	Smoking	18	Non-smoking	Smoking	252	600.084	< 0.01	396.148	<0.001
		19	Non-smoking	Smoking	946	1169.389	< 0.01	1060.256	<0.001
		20	Non-smoking	Smoking	682	841.023	< 0.01	733.883	0.001
Skin	Psoriasis	21	Control	Lesion	2072	3089.354	< 0.01	2167.521	0.001
			Normal	Lesion	2274	3090.757	< 0.01	2182.458	0.992
Lung	Cystic Fibrosis (CF)	22	End of Treatment	Exacerbation	132	156.941	< 0.01	138.15	0.046
		23	Healthy	CF	137	214.216	< 0.01	158.231	0.042
	HIV	24	Negative	Positive	1876	2330.410	< 0.01	1891.658	0.243
Vaginal	BV	25	Healthy	BV	110	107.984	0.97	104.087	0.985
Semen	Infertile (Genus level)	26	Normal	Subnormal	379	455.336	< 0.01	378.834	0.525
			Normal	Abnormal	398	457.451	< 0.01	394.929	0.706
	Infertile Species level)		Normal	Subnormal	3029	3724.597	< 0.01	2941.005	0.915
			Normal	Abnormal	3165	3910.306	< 0.01	3165.035	0.466
Milk	Mastitis	27	Healthy	Mastitis	107	111.859	< 0.01	106.558	0.61
Percentage of cases with lowered shared species = 20/41=49%									

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Table S4. A summary on the diversity-disease relationships (DDRs) in the 31 case studies cited in the Appendix S1 of Johnson et al (2015) in “Frontiers in research on biodiversity and disease” *Ecology Letters*. From 82 cases in Johnson et al.’s (2015), we filtered out the *non-human* or *non-microbiome* diseases, and only keep 31 cases of human microbiome associated diseases.

Case #	Disease	DDR Pattern	References**
[1]	Cystic Fibrosis (CF)	Species Richness **[≈]**	Fodor. et al (2012) *PLoS ONE*
[2]	Cystic Fibrosis (CF)	Shannon Index **[–]**	Blainey. et al (2012) *Sci. Transl. Med*
[3]	Chronic Rhinosinusitis	Shannon Index **[–]**	Abreu. et al (2012) *Sci. Transl. Med*
[4]	Cystic Fibrosis (CF)	Shannon Index **[–]**	Filkins. et al (2012) *J. Bacteriol*
[5]	Acute Otitis Media Pathogens	Shannon Index **[–]**	Pettigrew et al (2012) *Appl. Environ. Microbiol.*
[6]	Cystic Fibrosis (CF)	Shannon Index **[–]**	Zhao et al (2012) *PNAS*
[7]	Cystic Fibrosis (CF)	Shannon Index Species Richness **[–]**	Delhaes et al (2012) *PLoS ONE*
[8]	Chronic obstructive pulmonary disease	Shannon Index Species Richness **[–]**	Zakharkina et al (2013) *PLoS ONE*
[9]	Obstructive pulmonary disease	Shannon Index Simpson Index **[–]**	Pragman et al (2012) *PLoS ONE*
[10]	Wheezing	Shannon Index **[≈]**	Cardenas et al (2012) *PLoS ONE*
[11]	Cystic Fibrosis (CF)	Species Richness **[–]**	Stressmann et al (2012) *Thorax*
[12]	Pulmonary tuberculosis	Shannon Index **[+]**	Cui et al (2012) *BMC Microbiol.*
[13]	Periodontitis	Shannon Index Simpson Index [–]	Junemann et al (2012) *PLoS ONE*
[14]	Periodontitis	Shannon Index **[+]**	Liu et al (2012) *PLoS ONE*
[15]	Dental caries, Periodontitis	Shannon Index **[–]**	Ahmed et al (2012) *Afr. J. Microbiol. Res.*
[16]	Candida (fungal) Infection	Shannon Index Simpson Index [–]	Kraneveldet al (2012) *PLoS ONE*
[17]	Endodontic infection	Shannon Index Simpson Index [–]	Hsiao et al (2012) *BMC Genomics*
[18]	Dental caries	Shannon Index **[–]**	Gross et al. (2012) *PLoS ONE*
[19]	Periodontal disease, NORA (new-onset rheumatoid arthritis)	Shannon Index **[≈]**	Scher et al (2012) *Arthritis Rheum*
[20]	Atopic dermatitis (AD)	Shannon Index **[–]**	Kong et al (2012) *Genome Res.*
[21]	Allergy	Species Richness **[–]**	Hanski et al (2012) PNAS
[22]	Eczema (Dermatitis)	Shannon Index **[–]**	Ismail et al (2012) *Pediat. Allerg. Immu.*
[23]	Atopic eczema	Shannon Index **[–]**	Abrahamsson et al (2012) *J. Allergy Clin. Immun*
[24]	IC (Interstitial Cystitis) or PBS (Painful Bladder Syndrome)	Shannon, Richness, Simpson [–]	Siddiqui et al (2012) *BMC Microbiol*
[25]	Human Papilloma Virus (HPV)	Species Richness [+]	Lee et al (2013) *PLoS ONE*
[26]	Vulvovaginal candidiasis (VVC)	Shannon Index, Species Richness [+]	Liu et al (2013) *PLoS ONE*
[27]	Colorectal Cancer (CRC)	Shannon Index [–]	Ahn et al (2013) *JNCI*
[28]	Inflammatory bowel disease (IBD)	Shannon Index [–]	Andoh et al (2012) *J. Gastroenterol*
[29]	Colorectal Adenoma	Shannon Index, Species Richness [≈]	Sanapareddy et al. (2012) *ISMEJ*
[30]	Recurrent Clostridium Difficile Infection (RCDI)	Shannon Index [–]	Song et al (2013) *PLoS One*
[31]	Clostridium difficile infection (CDI) & CD–negative nosocomial diarrhea	Shannon Index, Species Richness [–]	Antharam et al. (2013) *J. Clin. Microbiol*
Diversity decreased in diseased samples		74% (23 out of 31)	
Diversity increased in diseased samples		13% (4 out of 31)	
No changes in diseased samples		13% (4 out of 31)	

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