

Supplementary Appendix

Supplementary Table A: Overrepresented and underrepresented diseases among published RCTs.

Disease	Burden of Disease in 2010 GBD (10 ⁶ DALYs)	Number of Trials	Number of participants	Trials per 10 ⁶ DALY	Participants per 10 ³ DALYs
Top 5 over represented diseases					
Female infertility	0.13	18	5420	143.7	43.3
Adverse medical treatment	4.1	59	15385	14.5	3.8
Male infertility	0.17	2	350	11.6	2.0
Peripheral vascular disease	0.99	11	1281	11.1	1.3
ADHD	0.49	4	286	8.1	0.6
Top 5 under represented diseases with at least one trial performed					
Neonatal sepsis	44.2	1	303	0.023	0.007
RSV	20.5	1	185	0.049	0.009
Rotavirus	18.6	1	80	0.054	0.004
Self-harm	36.7	2	44	0.055	0.001
Neonatal encephalopathy	50.1	3	83	0.060	0.002

Supplementary Table B. Proportional trial evidence for 239 diseases included in the analysis.

Disease	Burden of Disease in 2010 GBD (10 ⁶ DALYs)	Trials per 10 ⁶ DALY	Participants per 10 ³ DALYs
2-Wheel road injury	12.26613	0.1630506	30.73504
4-Wheel road injury	28.233306	0.1416766	1.310509
Abortion	2.137875	0.9355084	80.45372
Acne vulgaris	4.001774	1.749224	59.72351
Acute hepatitis A	4.350753	0	0
Acute hepatitis B	4.674198	0	0
Acute hepatitis C	0.518024	0	0
Acute hepatitis E	3.714528	0	0
ADHD	0.491466	8.138915	581.9324
Adverse medical treatment	4.081823	14.45433	3769.149
Alcohol use disorders	17.644107	0.4534092	23.18054
Alopecia areata	1.352474	0.7393857	73.93858
Alzheimer's disease	11.349286	0.4405563	49.07798
Amoebiasis	2.23698	0	0
Amphetamine use	2.616857	1.146413	42.03516
Animal contact (non-venomous)	0.929252	0	0
Animal contact (venomous)	2.729424	0	0
Anxiety disorders	26.825552	0.5218905	54.42572
Aortic aneurysm	3.162603	0.6323905	27.50899
Appendicitis	1.483465	2.022292	440.8597
Ascariasis	1.31476	0	0
Asperger's	3.659126	0	0
Assault by firearm	11.145549	0	0
Assault by other means	7.526365	0	0
Assault by sharp object	7.095015	0	0
Asthma	22.459097	0.7569316	122.801
Atrial fibrillation	3.598465	1.667378	345.9809
Autism	4.006692	0.7487473	69.88309
Bacterial skin diseases	2.869052	0	0
Benign prostatic hyperplasia	6.834035	0.4389793	31.60651
Bicycle road injury	4.645239	0	0
Bipolar disorder	12.867117	0.3885874	54.40224
Bladder cancer	3.014549	0	0
Brain cancer	6.059657	0.4950775	34.82045
Breast cancer	12.017906	2.246648	936.9352
Campylobacter	7.540956	0	0
Cannabis use	2.057161	0.4861068	77.77709
Cardiomyopathy	11.150769	0.986479	173.4409
Cataract	4.732057	1.479272	282.3297
Cellulitis	1.291503	0	0
Cervical cancer	6.439566	0.7764499	223.9281
Chagas	0.546257	0	0
Chlamydia	0.714185	1.400197	985.739
Cholera	4.462747	0	0
Cirrhosis alcohol	8.574931	0.116619	2.682237
Cirrhosis hepatitis B	8.989534	0.5562024	81.20554
Cirrhosis hepatitis C	7.452314	0.805119	47.50203
Cirrhosis other	6.010697	0	0
Cleft lip & palate	0.570507	0	0
Cocaine use	1.110067	1.801693	91.88634
Colorectal cancer	14.422303	0.8320447	402.2936
Conduct disorder	5.75329	0	0
Congenital heart anomalies	15.457213	0	0
COPD	76.731358	0.1563898	9.487646
Cryptosporidiosis	8.372348	0	0
Cysticercosis	0.50342	0	0
Decubitus ulcer	1.205652	0	0
Dengue	0.824787	2.424869	104.2693
Dental caries	4.983849	0.2006481	4.012963
Diabetes	46.823256	1.324128	141.1692

Diabetic CKD	4.674963	1.497338	1936.486
Diphtheria	0.235826	0	0
Down's syndrome	1.774969	0	0
Drowning	19.741515	0	0
Dysthymia	11.084412	0	0
Eating disorders	2.160635	1.851308	127.2774
Echinococcosis	0.143935	0	0
Eczema	8.89681	0.674399	81.04028
Edentulism	4.62125	0.2163917	1.29835
Encephalitis	7.140901	0	0
Endocarditis	1.581748	0	0
Endometriosis	0.544826	1.835448	587.3435
Enteropathogenic E coli	7.542324	0	0
Enterotoxigenic E coli	6.893812	0	0
Epilepsy	17.428592	0.1721309	2.180325
Esophageal cancer	8.942658	0.3354707	37.23725
Falls	35.385079	0.1978235	39.4234
Female infertility	0.125272	143.6873	43265.85
Fibroids	3.061566	0	0
Fire	19.009628	0	0
Food-borne trematodiasis	1.875398	0.5332202	40.52473
Forces of nature	13.386933	0.2240991	24.12801
Fungal skin diseases	2.302796	0.4342547	30.39783
G6PD deficiency	0.302587	0	0
Gall bladder diseases	2.245056	4.454232	432.5059
Gallbladder cancer	3.034467	0.3295472	27.02287
Gastritis & duodenitis	1.196618	0.8356886	331.7684
Genital prolapse	1.816629	0.5504701	33.02821
Glaucoma	0.943064	4.241494	379.6137
Glomerulonephritis	3.684246	0	0
Gonorrhoea	0.282219	0	0
Gout	0.113977	0	0
HiB meningitis	6.610643	0	0
HiB pneumonia	21.315298	0	0
HIV (other)	66.599553	0.2402419	104.34
HIV-TB	14.947814	0.0668994	47.63238
Hodgkin's lymphoma	0.647046	0	0
Hookworm	3.230828	0.3095182	623.9886
Hypertensive CKD	4.599471	0.4348326	36.30853
Hypertensive heart disease	15.324193	0	0
Inflammatory bowel disease	2.874986	1.739139	159.3051
Influenza	19.244148	0.6235662	567.5491
Inguinal & femoral hernia	0.792083	1.262494	393.8981
Intellectual disability	1.042686	1.918123	326.0809
Interstitial lung diseases	2.233179	0.4477921	5.821298
Intestinal obstructions	3.728798	0	0
Iodine deficiency	4.026746	0.2483395	50.90959
Iron-deficiency anemia	45.338235	0.1985079	40.45151
Ischemic heart disease	129.8199	0.4698817	83.53881
Kidney cancers	3.676301	0.2720126	41.34591
Larynx cancer	2.366619	0	0
Leishmaniasis	3.316872	0	0
Leprosy	0.006062	0	0
Leukemia	9.555732	0.7325446	82.77754
Liver cancer alcohol	3.781619	0	0
Liver cancer hepatitis B	8.937873	0.4475338	50.6832
Liver cancer hepatitis C	4.141073	0.7244499	47.33073
Liver cancer other	2.250275	0	0
Low back pain	83.063498	0.1685458	13.07434
Lung cancer	32.404655	0.1851586	18.70102
Lymphatic filariasis	2.774687	0	0
Macular degeneration	1.329288	4.513695	2002.576
Major depressive disorder	63.179254	0.4906674	61.23846
Malaria	82.685191	0.1209406	104.0089
Male infertility	0.172724	11.57917	2026.354

Maternal hemorrhage	3.289193	0.3040259	24.32207
Maternal hypertension	2.797477	0	0
Maternal sepsis	1.308766	0	0
Measles	10.419744	0	0
Mechanical forces (firearm)	4.624455	0.2162417	9.947118
Melanoma	1.169439	3.420444	843.1393
Meningococcal	5.16341	0	0
Migraine	22.362326	0.1341542	16.32209
Mouth cancer	3.227847	0.309804	17.03922
Multiple sclerosis	1.075184	3.720294	245.5394
Myeloma	1.474772	1.356142	184.4353
Nasopharynx cancer	2.007443	1.992585	269.4971
Neck pain	33.640233	0.1189052	15.39823
Neonatal encephalopathy	50.149575	0.059821	1.655049
Neonatal sepsis	44.236491	0.0226058	6.849549
Neural tube defects	6.372372	0	0
Non-Hodgkin lymphoma	5.859806	0.8532706	265.7085
Non-melanoma skin cancer	0.79838	0	0
Obstructed labor	1.792401	1.673733	470.8768
Onchocerciasis	0.494038	0	0
Opioid use	9.151516	0.3278145	44.47351
Osteoarthritis	17.135221	1.984217	163.6979
Other cancers	16.615309	0.1203709	112.9681
Other cardio & circulatory	17.021033	0.9400135	331.5898
Other chromosomal anomalies	1.760893	0	0
Other CKD	11.876894	1.768139	661.9576
Other congenital anomalies	12.951329	0	0
Other diarrheal diseases	21.915816	0.0912583	14.41881
Other digestive diseases	10.197014	1.569087	155.2415
Other drug use	5.058556	0.3953697	27.4782
Other endocrine	11.357643	1.937022	294.1631
Other gynecological disorders	0.704975	5.67396	726.2669
Other hearing loss	15.760566	0.126899	11.16711
Other hemog	3.979473	0.5025791	96.99776
Other infectious diseases	17.715475	0.1128956	9.483234
Other lower respiratory	27.288583	0.1465814	86.9228
Other maternal disorders	4.778155	1.465001	218.4944
Other mechanical forces	7.097469	0.5635812	27.0519
Other meningitis	9.563333	0	0
Other mental & behavioral	1.482111	18.21726	3703.501
Other musculoskeletal	30.856331	1.425963	183.9817
Other neonatal disorders	30.591125	0.0326892	6.733979
Other neurological disorders	17.869337	1.231159	131.6221
Other NTD	4.724286	0	0
Other nutritional deficiencies	0.294673	30.54233	3939.96
Other pharynx cancer	2.741908	0	0
Other respiratory diseases	13.940006	0.9325678	108.8952
Other road injury	5.974351	0	0
Other sense organ disorders	0.135503	125.4585	17158.29
Other skin diseases	4.972765	2.815335	133.3262
Other STDs	0.235993	0	0
Other transport injuries	6.095578	0	0
Other unintentional injuries	18.368597	0.4355259	15.29785
Other urinary diseases	2.295725	8.276253	1082.011
Other vision loss	6.239985	0.1602568	6.410272
Otitis media	4.680034	0	0
Ovarian cancer	4.118191	0.9713002	92.51635
Pancreatic cancer	6.160582	0.3246447	31.81518
Pancreatitis	2.354034	1.274408	77.31409
Parkinson's disease	1.91806	4.170881	201.245
Pedestrian road injury	25.636008	0	0
Peptic ulcer	6.718099	0.4465549	125.9285
Periodontal disease	5.410094	2.772595	136.4117
Peripheral vascular disease	0.994927	11.05609	1287.532
Pneumococcal meningitis	8.023761	0	0

Pneumococcal pneumonia	26.906232	0.0743322	18.02556
Pneumoconiosis	2.581591	0	0
Poisonings	8.933867	0.1119336	4.02961
Polycystic ovary	2.755776	0	0
Premenstrual syndrome	1.248597	0	0
Preterm birth complications	76.981719	0.2208316	46.14082
Prostate cancer	3.786622	2.640876	785.1325
Protein-energy malnutrition	34.874497	0.0860227	11.44102
Pruritus	2.086447	0	0
Psoriasis	1.058735	1.889047	248.4097
Pyelonephritis & UTI	3.107507	1.930808	2590.501
Rabies	1.46226	0	0
Refraction disorders	5.593023	0.8939709	65.08109
Rheumatic heart disease	10.149866	0.0985235	8.473019
Rheumatoid arthritis	4.814764	1.869251	503.2438
Rotavirus	18.649674	0.0536202	4.289619
RSV pneumonia	20.472377	0.0488463	9.036567
Salmonella	4.846654	0	0
Scabies	1.579681	0	0
Schistosomiasis	3.308963	0	0
Schizophrenia	14.999473	1.266711	82.00288
Self-harm	36.654294	0.0545639	1.200405
Shigellosis	7.051798	0	0
Sickle cell	5.641008	0.1772733	15.60005
SIDS	1.892841	0	0
Stomach cancer	16.412709	0.1827852	12.24661
Stroke	102.2323	0.1956329	11.91404
Syphilis	9.578123	0	0
Tension-type headache	1.778681	0	0
Testicular cancer	0.313269	0	0
Tetanus	4.663339	0	0
Thalassemia	5.716739	0	0
Thyroid cancer	0.8363	2.391486	96.85519
Trachoma	0.334401	0	0
Trichomoniasis	0.16711	0	0
Trichuriasis	0.638186	0	0
Trypanosomiasis	0.560281	0	0
Tuberculosis	49.396246	0.0607334	5.526736
Typhoid fevers	12.238564	0	0
Upper respiratory infections	1.866265	4.286637	1231.872
Urolithiasis	1.113321	3.592854	342.2194
Urticaria	2.599596	0.3846751	33.85141
Uterine cancer	1.271911	0	0
Varicella	0.581053	0	0
Vascular intestinal disorders	1.100471	0.9087018	78.14835
Viral skin diseases	2.730778	0	0
Vitamin A deficiency	0.806402	1.240076	33.48206
War & legal intervention	0.959771	0	0
Whooping cough	7.018086	0	0

Supplementary Table C. Linear regression analysis of the log-transformed number of trials and log-transformed number of participants randomized using log-transformed total DALYs and the log transformed ratio of DALYs in low-income regions to high-income regions as predictors. Univariable analysis with log(total DALYs) indicates a poor association between number of trials (Model 1. $R^2 = 0.14$) and number of participants (Model 3. $R^2 = 0.11$)

	(1) Log(Trials+1)	(2) Log(Trials+1)	(3) Log(Participants+1)	(4) Log(Participants+1)
Coefficients (SE, p-value)¹				
Log(DALYs)	0.276 (SE 0.044, p<0.001)	0.265 (SE 0.041, p<0.001)	0.749 (SE 0.136, p<0.001)	0.713 (0.127, p<0.001)
Log(Ratio of DALYs in Low-income Regions to High-income Regions)		-0.121 (SE 0.020, p<0.001)		-0.382 (0.062, p<0.001)
Observations	239	239	239	239
R-squared	0.14	0.26	0.11	0.24

¹Results are regression coefficients with standard errors and p-values in brackets.

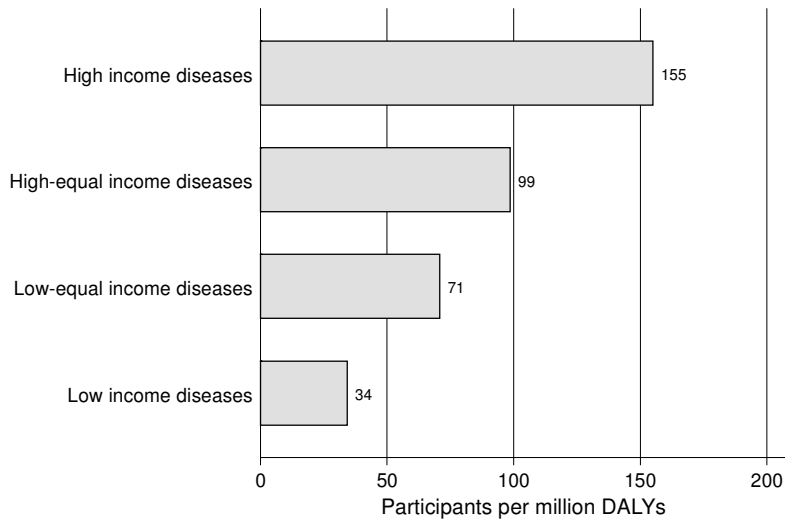
Supplementary Table D. Sensitivity regression analysis of the log-transformed number of trials and log-transformed number of participants randomized using log-transformed total DALYs and ratio of DALYs in low income regions to high income regions as predictors. No offset of 1 was added and diseases with no trials were excluded.

	(1)	(2)	(3)	(4)
Coefficients (SE, p-value)¹				
	Log(Trials)	Log(Trials)	Log(Participants)	Log(Participants)
Log(DALYs)	0.233 (SE 0.062, p<0.001)	0.269 (SE 0.061, p<0.001)	0.240 (SE 0.092, p=0.010)	0.254 (0.094, p=0.007)
Log(Ratio of DALYs in Low-income Regions to High-income Regions)		-0.119 (SE 0.041, p<0.001)		-0.048 (0.063, p=0.448)
Observations	144	144	144	144
R-squared	0.09	0.13	0.05	0.05

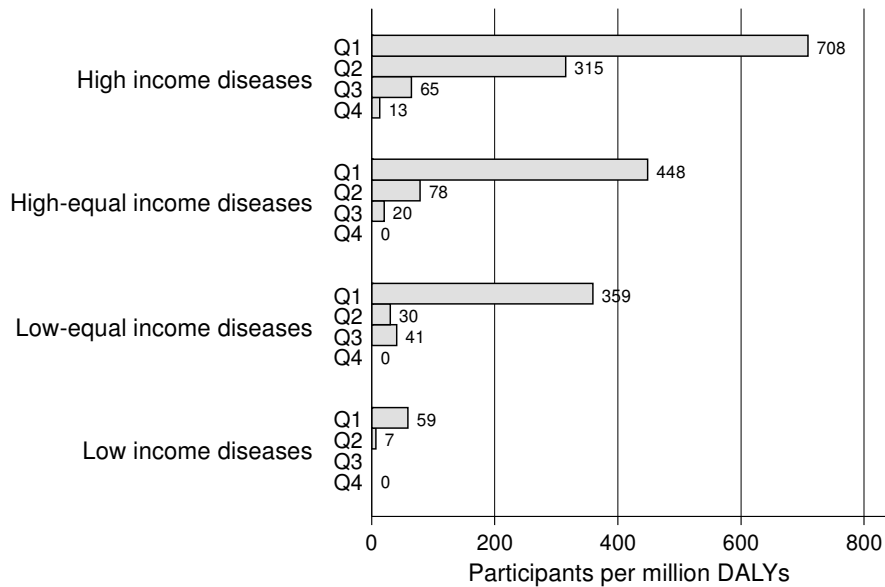
¹Results are regression coefficients with standard errors and p-values in brackets.

Supplementary Figure A. Participants per million DALYs for 239 diseases, classified into high-income, high-equal, low-equal and low-income diseases. (A) Participants per million DALYs for diseases predominant in high-income regions (top) to diseases predominant in low-income regions (bottom). (B) Variation of trials per million DALYs within disease-income categories. Note that scale on (B) is five times greater than that on (A).

A.

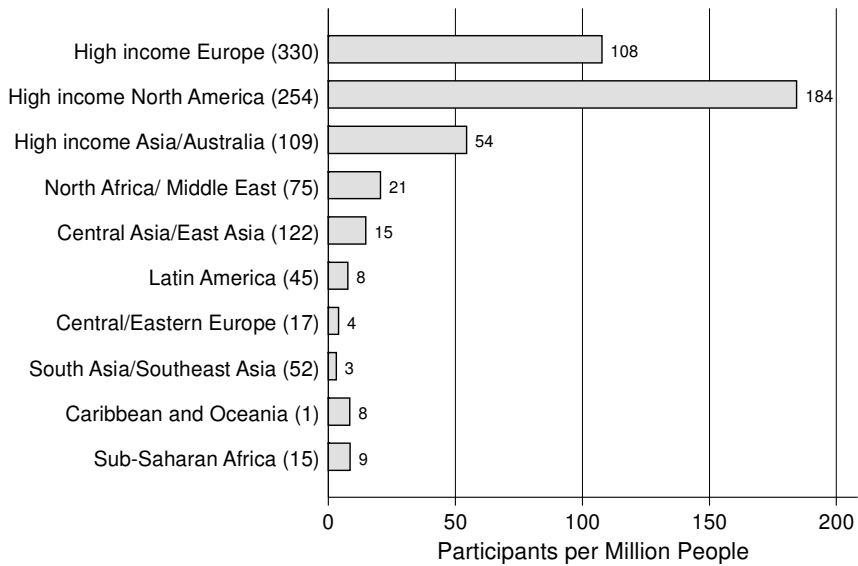


B.

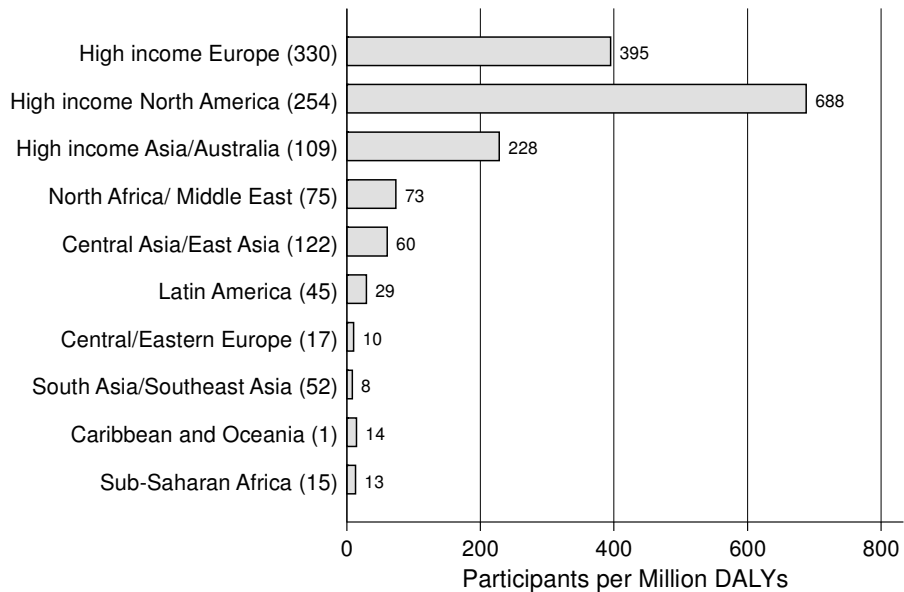


Supplementary Figure B. A. Number of randomized participants per one million population for ten regions. B. Number of randomized participants per one million DALYs for ten regions. C. Spearman's correlation coefficient between burden of disease (total DALYs in each region) and number of trials conducted for ten regions.

A.



B.



C.

