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Supplementary Materials: Meta-analysis of *NOS3 G894T* Polymorphisms with Air Pollution on the Risk of Ischemic Heart Disease Worldwide

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Table S1. Characteristics of included studies on *NOS3 G894T* genotypes.

Author, Year	Country State or City	Ethnicity	Case, *n*			Controls, *n*			SC[a]	HWE	Quality Score[b]
			GG	GT	TT	GG	GT	TT			
Caucasian											
Granath 2001 [1]	Australia, Perth	Australian	260	248	63	270	287	66	2	Yes	22
Cai 1999 [2]	Australia, Sydney	Australian	286	249	70	66	70	22	2	Yes	13
Dosenko 2006 [3]	Ukraine, Kiev	Ukrainian	76	128	17	24	56	3	1	No	17
Bor-Kucukatay 2010 [4]	Turkey, Denizli	Turkish	48	28	7	50	21	3	2	Yes	17
Alp 2009 [5]	Turkey, Chongqing	Turkish	76	59	11	71	40	11	2	Yes	21
Berdeli 2005 [6]	Turkey, Izmir	Turkish	44	37	34	57	24	2	1	Yes	20
Afrasyap 2004 [7]	Turkey, Mugla	Turkish	114	103	33	74	62	14	1	Yes	21
Aras 2002 [8]	Turkey, Ankara	Turkish	89	87	29	60	48	9	1	Yes	9
Zigra 2013 [9]	Greece, Athens	Greek	43	38	7	50	42	11	1	Yes	19
Dafni 2010 [10]	Greece, Athens	Greek	83	94	27	108	95	15	1	Yes	23
Ragia 2010 [11]	Greece, Alexandroupolis	Greek	74	63	17	72	66	17	2	Yes	22
Andrikopoulos 2008 [12]	Greece, Athens	Greek	722	702	179	352	297	78	2	Yes	19
Vasilakou 2008 [13]	Greece, Athens	Greek	109	85	15	76	74	11	2	Yes	15
Fatini 2004 [14]	Italy, Florence	Italian	185	213	79	236	243	58	1	Yes	15
Colombo 2002 [15]	Italy, Massa	Italian	91	78	32	48	59	7	2	Yes	18
Agema 2004 [16]	Netherlands, Amsterdam,	Dutch	343	333	79	216	270	88	2	Yes	24
Pulkinnen 2000 [17]	Finland, Koupio	Finnish	263	237	59	54	45	11	1	Yes	24
Gluba 2009 [18]	Poland, Lodz	Polish	140	118	19	62	61	11	2	Yes	18
Szperl 2008 [19]	Poland, Warsaw	Polish	69	67	15	39	28	7	1	Yes	22
Gardemann, 2002 [20]	Germany, Giessen	German	924	927	234	256	227	50	1	Yes	19
Poirier 1999 [21]	Ireland-Belfast France-Toulouse Strasbourg, Lille	N. Irish, French	163	156	49	148	219	54	2	Yes	22
Bhandary 2008 [22]	United Kingdom, Plymouth	British	51	91	27	73	51	17	2	Yes	20
Hingorani 1999 [23]	United Kingdom, Cambridge	British	120	71	107	66	58	14	1	Yes	25
Piccoli 2012 [24]	Brazil, Porto Alegre	Brazilian	58	52	18	62	44	7	2	Yes	23
Jaramillo 2010 [25]	Chile, Temuco	Chilean	73	31	8	74	36	2	1	Yes	22
Hispanic											
García-González 2015 [26]	Mexico, Merida	Mexican	62	28	8	68	31	2	2	Yes	22
Vargas-Alarcon 2014 [27]	Mexico, Mexico City	Mexican	280	147	25	173	95	15	1	Yes	18
East Asian											
Hibi 1998 [28]	Japan	Kanagawa	189	32	0	295	62	0	2	Yes	19
Shimasaki 1998 [29]	Japan, Kyoto Kumamoto	Japanese	225	59	1	526	80	1	2	Yes	24
Bae 2010 [30]	South Korea, Jeju	Korean	157	34	1	163	33	0	1	Yes	20
Min 2010 [31]	South Korea, Gwangju	Korean	136	28	4	250	20	0	2	Yes	22
Kim 2007 [32]	South Korea, Seongnam	Korean	119	28	0	181	38	0	1	Yes	24
Park 2004 [33]	South Korea, Seoul	Korean	128	35	1	118	22	2	2	Yes	21
Yoon 2000 [34]	South Korea, Chongno-gu	Korean	94	15	1	110	18	0	1	Yes	24
Wang 2001 [35]	Taiwan, Taipei	Chinese	178	38	2	177	38	3	2	Yes	25
Lin 2008 [36]	China, Taiwan	Chinese	25	89	6	49	23	6	2	Yes	24

Table S1. *Cont.*

Author, Year	Country State or City	Ethnicity	Case, *n* GG	GT	TT	Controls, *n* GG	GT	TT	SC[a]	HWE	Quality Score[b]
Wang* 2011 [37]	China, Louyang	Chinese	151	46	6	163	29	2	2	Yes	23
Cui 2011 [38]	China, Henan	Chinese	125	20	3	99	14	2	1	Yes	21
Huang De 2010 [39]	China, Gansu	Chinese	151	46	6	163	29	2	2	Yes	19
Yusup 2009 [40]	China, Xinjiang	Chinese	35	64	25	24	20	6	1	Yes	20
Jinyu 2009 [41]	China, Changsha	Chinese	77	22	4	89	14	1	2	Yes	22
Ying 2008 [42]	China	Chinese	174	30	3	237	26	1	2	Yes	20
Huang 2008 [43]	China, Gansu	Chinese	152	39	5	162	27	0	2	Yes	21
Qi 2003 [44]	China, ShenYang city	Chinese	86	28	3	85	15	0	2	Yes	20
Wei 2002 [45]	China, Hangzhou	Chinese	84	19	3	98	10	0	1	Yes	23
South Asian											
Arun Kumar 2013 [46]	India, Pondicherry	Indian	213	62	12	238	76	7	1	Yes	16
Narne 2013 [47]	India, Hyderabad	Indian	97	60	3	84	35	2	2	Yes	20
Rai 2012 [48]	India, Pradesh	Indian	159	84	10	119	50	5	1	Yes	21
Saini 2011 [49]	India, New Delhi	Indian	45	15	0	44	6	0	1	Yes	21
Bhanushali 2010 [50]	India, Mumbai	Indian	64	35	1	67	31	2	2	Yes	18
Angeline 2010 [51]	India, Tamil Nadu	Indian	56	30	14	67	31	2	1	Yes	19
Middle East											
Rahimi 2012 [52]	Iran, Kermanshah	Iranian	116	74	17	67	24	1	2	Yes	20
Salimi 2010 [53]	Iran, Zahedan	Iranian	112	103	26	160	84	17	2	Yes	20
Heidari 2016 [54]	Iran, Yazd	Iranian	68	28	12	58	32	0	1	Yes	18
Alkharfy 2010 [55]	Saudi Arabia, Riyadh	Saudi	65	67	10	98	40	7	2	Yes	22
African											
Abdel-Aziz 2013 [56]	Egypt, Zagazig	Egyptian	48	46	22	68	39	12	2	Yes	18
Motawi 2011 [57]	Egypt, Cairo	Egyptian	46	34	20	19	28	3	2	Yes	21
Kallel 2013 [58]	Tunisia, Tunis	Tunisian	163	122	18	128	78	19	2	Yes	20
Abdelhedi 2013 [59]	Tunisia, Tunisia	Tunisian	130	94	25	130	130	35	2	Yes	21
Kerkene 2006 [60]	Tunisia, Monastir	Tunisian	45	44	11	72	43	5	1	Yes	22
Idrissi 2016 [61]	Morocco, Casablanca	Morocco	60	50	8	116	62	6	1	Yes	21

Note. [a]SC: Sources of control: 1 = healthy adults, 2 = adults without cardiovascular disease. HWE = Hardy Weinberg Equilibrium (HWE). [b]Quality Score ranges: 0–30. * = meta-analysis paper + case control study.

Table S2. Pooled meta-analysis: *NOS3* G894T genotypes and risk for ischemic heart disease (IHD) by subgroups.

Genotype. (Number of Studies)	Cases *n* = 13,207 (%)	Controls *n* = 10,021 (%)	Tests of Association Model	RR (95% CI)	*p*
Subgroups					
TT risk > 1–2					
TT (29)	921 (6.97)	398 (3.97)	Random	1.62 (1.38, 1.90)	< 0.0001
GT (29)	3,590 (27.18)	1,973 (19.78)	Random	1.10 (1.03, 1.19)	0.0039
GG (29)	4,674 (35.39)	3,397 (33.89)	Random	0.91 (0.88, 0.94)	< 0.0001
TT + GT (29)	4,511 (34.15)	2,371 (23.66)	Random	1.19 (1.13, 1.27)	< 0.0001
TT risk > 2					
TT (24)	330 (2.49)	108 (1.07)	Fixed	2.44 (1.96, 3.02)	< 0.0001
GT (24)	1201 (9.09)	1031 (10.28)	Random	1.09 (0.96, 1.25)	0.1667
GG (24)	2503 (18.95)	3064 (30.57)	Random	0.92 (0.87, 0.97)	0.0017
TT + GT (24)	1531 (11.59)	1139 (11.36)	Random	1.22 (1.12, 1.33)	< 0.0001
TT risk < 1					
TT (8)	300 (2.27)	253 (2.52)	Fixed	0.85 (0.72, 1.00)	0.053
GT (8)	1275 (9.65)	967 (9.64)	Fixed	0.96 (0.90, 1.02)	0.2863
GG (8)	1436 (10.87)	981 (9.78)	Fixed	1.04 (0.94, 1.15)	0.3904
TT + GT (8)	1575 (11.92)	1220 (12.17)	Random	0.95 (0.88, 1.04)	0.3086
TT + GT risk > 1–2					
TT (48)	1,143 (8.65)	471 (4.70)	Random	1.54 (1.30, 1.83)	< 0.0001
GT (48)	4,356 (32.98)	2,678 (26.72)	Random	1.13 (1.05, 1.22)	0.0007
GG (48)	6,565 (49.70)	6,019 (60.06)	Random	0.90 (0.87, 0.94)	< 0.0001
TT + GT (48)	5,499 (41.63)	3,149 (31.42)	Random	1.21 (1.14, 1.28)	< 0.0001
TT + GT risk < 1					
TT (8)	333 (2.52)	251 (2.50)	Random	1.11 (0.79, 1.55)	0.5281
GT (8)	1,319 (9.98)	1,042 (10.39)	Random	0.95 (0.85, 1.06)	0.3661
GG (8)	1,424 (10.78)	1,009 (10.06)	Random	1.01 (0.88, 1.17)	0.8014
TT + GT (8)	1,652 (12.50)	1,293 (12.90)	Random	0.99 (0.88, 1.11)	0.9328
TT + GT risk mixed					
TT (5)	75 (0.56)	37 (0.03)	Fixed	1.22 (0.84, 1.78)	0.279
GT (5)	391 (2.96)	251 (2.50)	Fixed	0.96 (0.84, 1.09)	0.5728
GG (5)	624 (4.72)	414 (4.13)	Fixed	0.99 (0.92, 1.08)	0.9859
TT + GT (5)	466 (3.52)	288 (2.87)	Fixed	0.99 (0.89, 1.11)	0.9881

Note. CI = confidence interval; RR = risk ratio. Random effects models were used when *Q* or I^2 were significant; otherwise, fixed effects models were used. *TT* risk > 1–2, nine countries: Turkey, Greece, Italy, Finland, Germany, Ireland, Mexico, China, Saudi Arabia; *TT* risk > 2, 10 countries: Ukraine, the United Kingdom, Brazil, Chile, Japan, South Korea, India, Iran, Egypt, Morocco; *TT* risk < 1, four countries: Australia, the Netherlands, Poland, Tunisia; *TT* risk mixed, None. *TT+GT* risk > 1–2, 15 countries: Turkey, Greece, Italy, Finland, Germany, the United Kingdom, Brazil, Korea, China, India, Saudi Arabia, Egypt, Tunisia, Morocco; *TT*+GT risk > 2, None; *TT+GT* risk < 1, five countries: Australia, Ukraine, the Netherlands, Ireland, Iran; *TT+GT* risk mixed, Poland, Chile, Mexico.

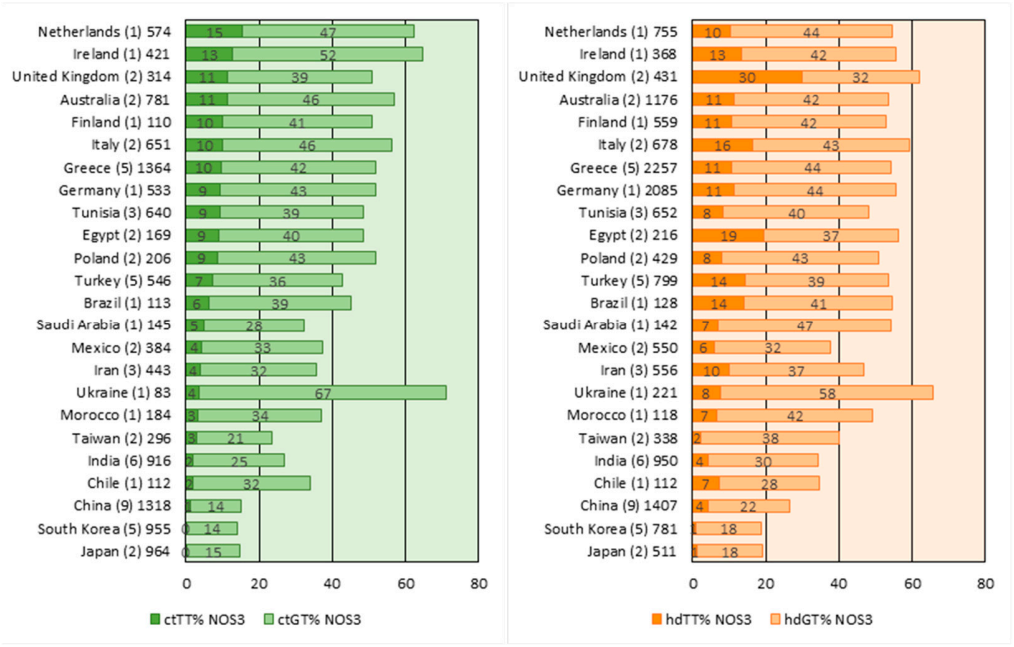

Figure S1. Ranked % *NOS3* homozygous TT and heterozygous GT for groups of control (n = 12,222) and ischemic heart disease (n = 16,219) from 61 study groups per country-race (number of study groups) and sample size.

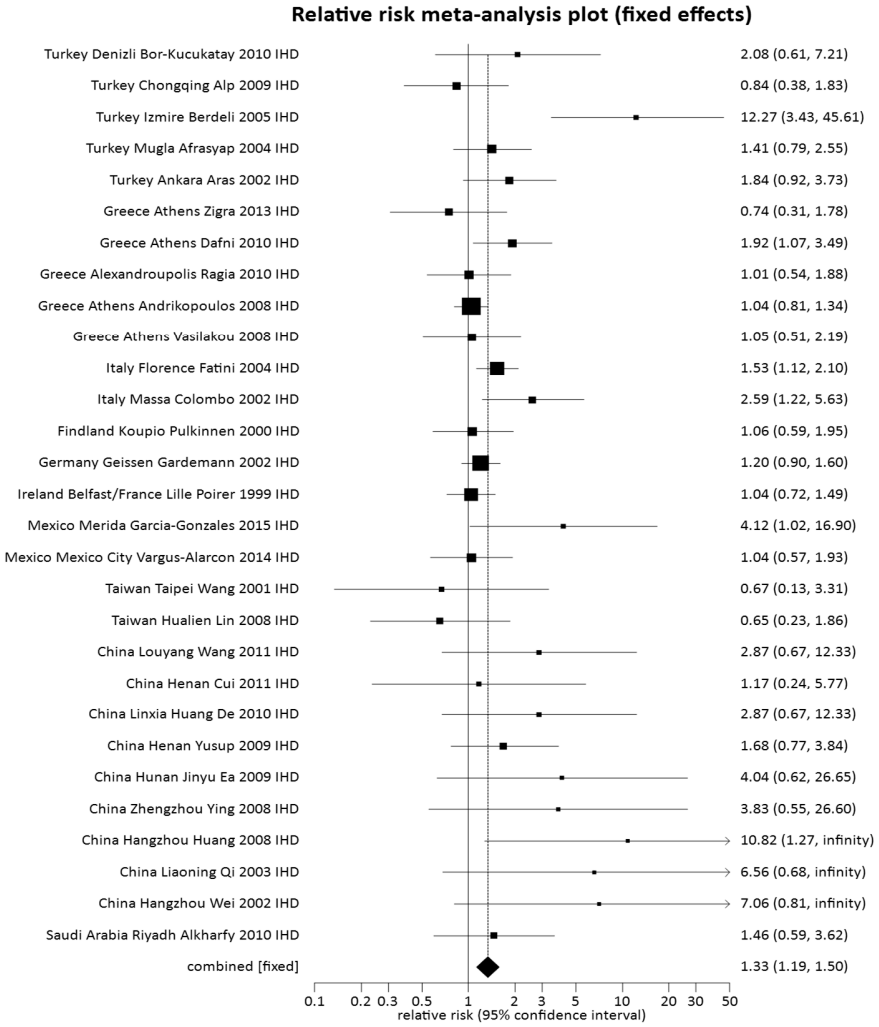

Figure S2. Forest plot for countries with pooled RR > 1–2 for the meta-analysis of the associations between *NOS3* TT genotype and ischemic heart disease (IHD). The midpoint = point effect estimate for each study. The area of the box = weight given to the study. The length of the line = 95% confidence interval for the effect estimate in an individual study. The width of the diamond = 95% confidence interval for the overall effect estimate.

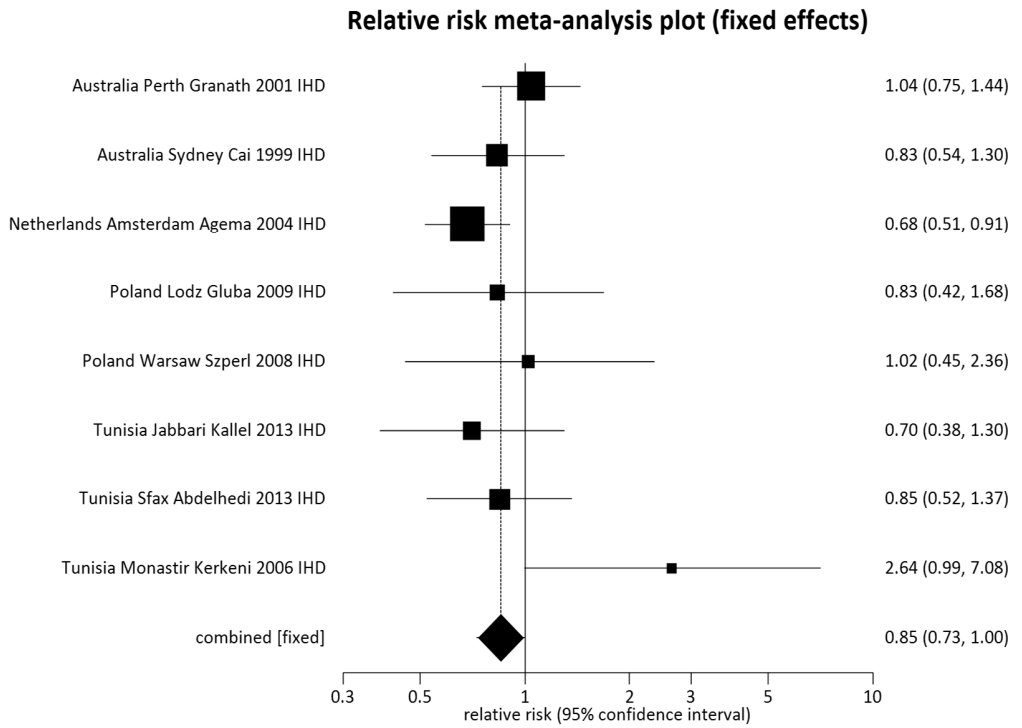

Figure S3. Forest plots for countries with pooled RR < 1 for the meta-analysis of the associations between *NOS3* TT genotypes and ischemic heart disease (IHD). The midpoint = point effect estimate for each study. The area of the box = weight given to the study. The length of the line = 95% confidence interval for the effect estimate in an individual study. The width of the diamond = 95% confidence interval for the overall effect estimate.

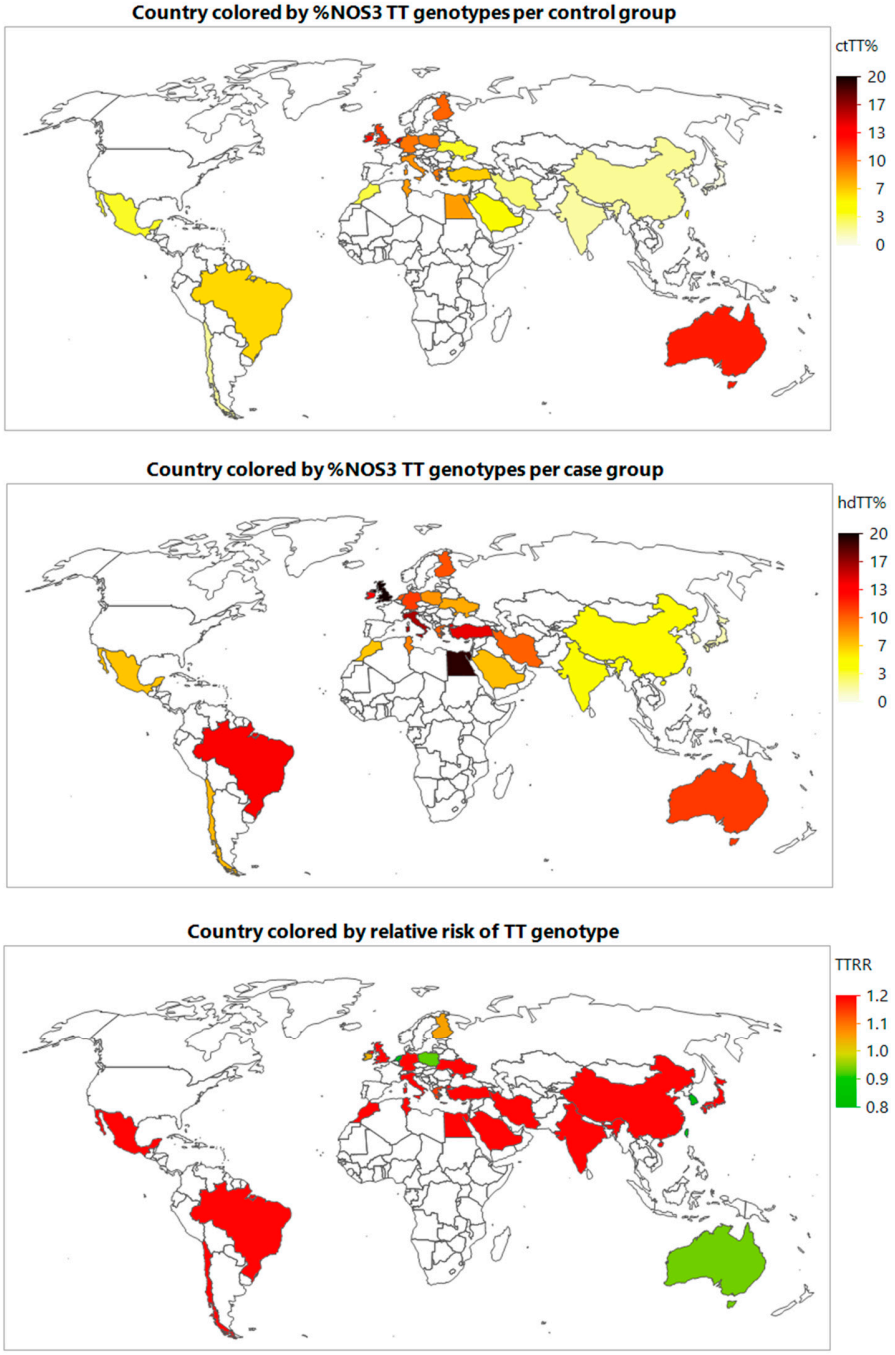

Figure S4. Geographical information map for % *NOS3* TT genotype per control and ischemic heart disease (IHD) groups, and IHD risk.

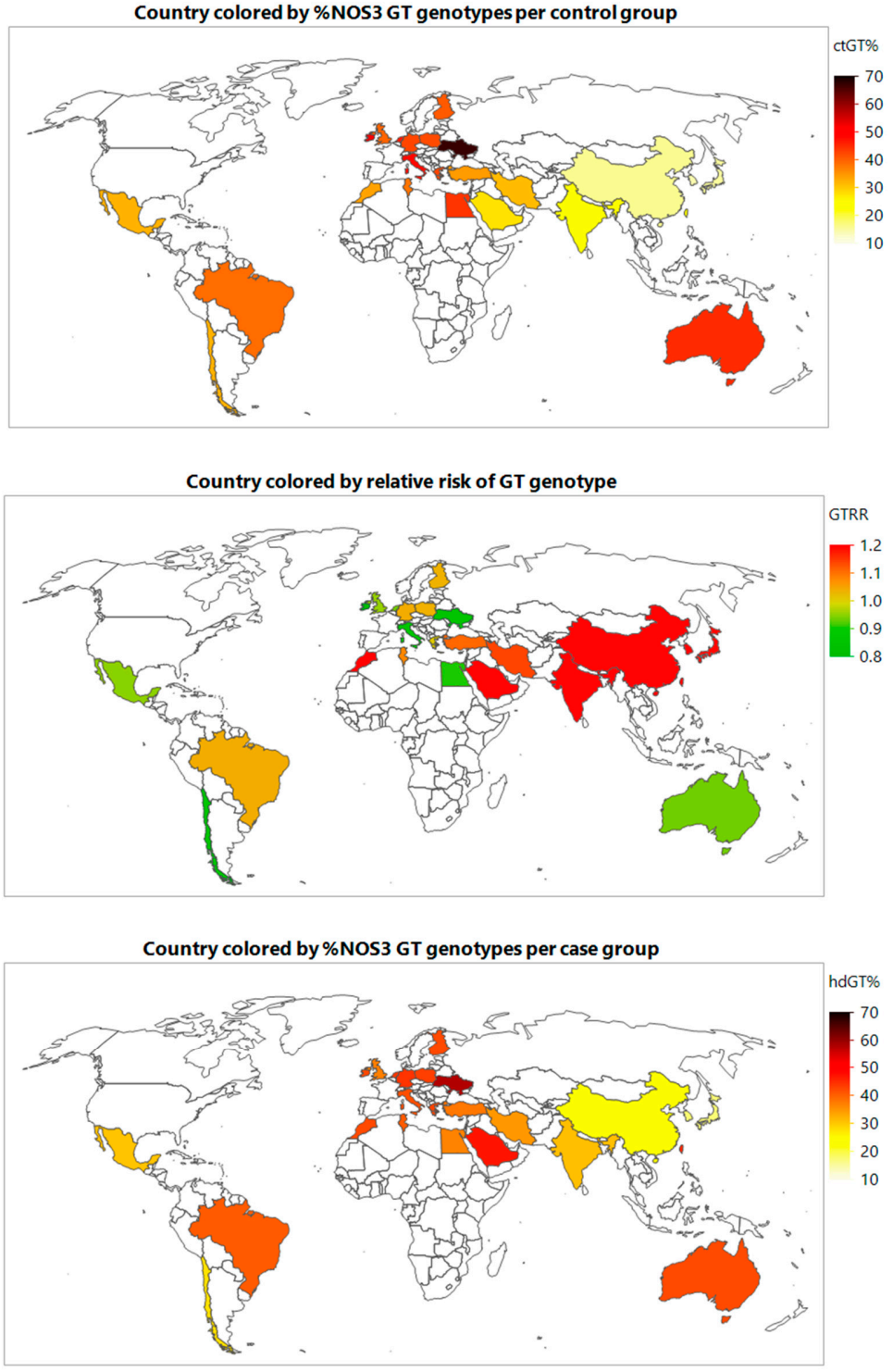

Figure S5. Geographical information map for % *NOS3* GT genotype per control and ischemic heart disease (IHD) groups, and IHD risk.

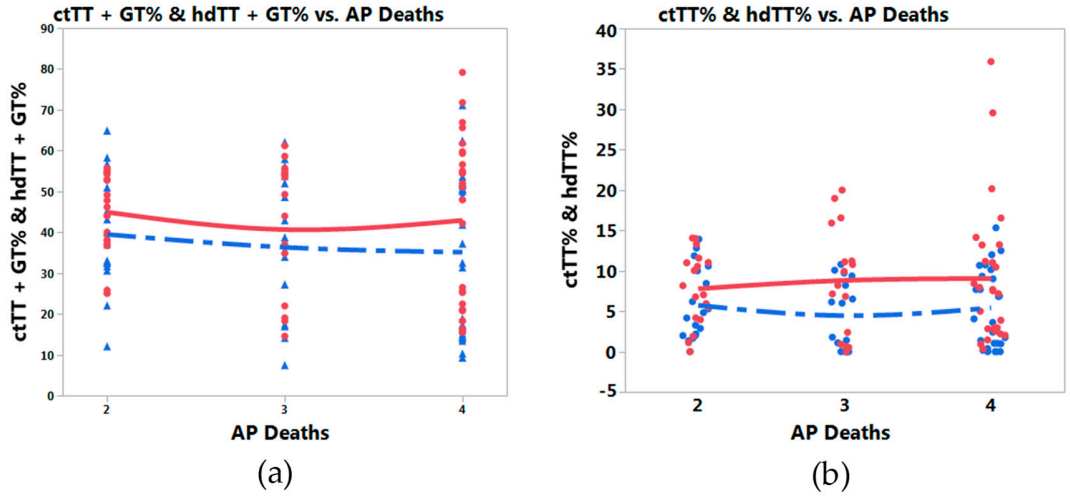

Figure S6. Nonlinear fit of *NOS3* G894T polymorphisms with death from air pollution for all countries: (**a**) TT plus GT polymorphisms, (**b**) TT polymorphism only (AP death: Death rates from air pollution, Levels per million: 2 = 51–100, 3 = 101–250, 4 = 251–400 and greater); case = red (solid line), control = blue (dotted line).

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