Meta-Analyses of Epigenetics Risk Factors for Cardiovascular Health: APOA5 Human Gene Variations Across Different Race-Ethnicity Groups

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Faculty Disclosure

Faculty Name	Yen-Chun Lin, PhD, RN
Conflicts of interest:	None
Employer:	National Taiwan University
Sponsorship / Commercial support	None

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Conflicts of interest:	None
Employer:	Azusa Pacific University
Sponsorship / Commercial support	None

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Conflicts of interest:	None
Employer:	Azusa Pacific University
Sponsorship / Commercial support	None

Introduction

- Cardiovascular Disease (CVD) - leading cause of death worldwide.

- Increased plasma total cholesterol (TC), triglyceride (TG) and decreased high density lipoprotein cholesterol (HDL-C) → CVD.

- Apolipoprotein A5 (APOA5, rs662799) gene polymorphism influence on TG, TC and HDL-C.

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Purpose

- Meta-analysis to identify the association of APOA5 1131T>C gene variations with CVD in various populations and the related lifestyle risk factors for CVD prevention.

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APOA5

- Located on chromosome 11q23
- -1131T>C - a single nucleotide polymorphism (SNP) in the promoter region of the APOA5 gene
- The **C** allele has been associated with higher triglyceride levels
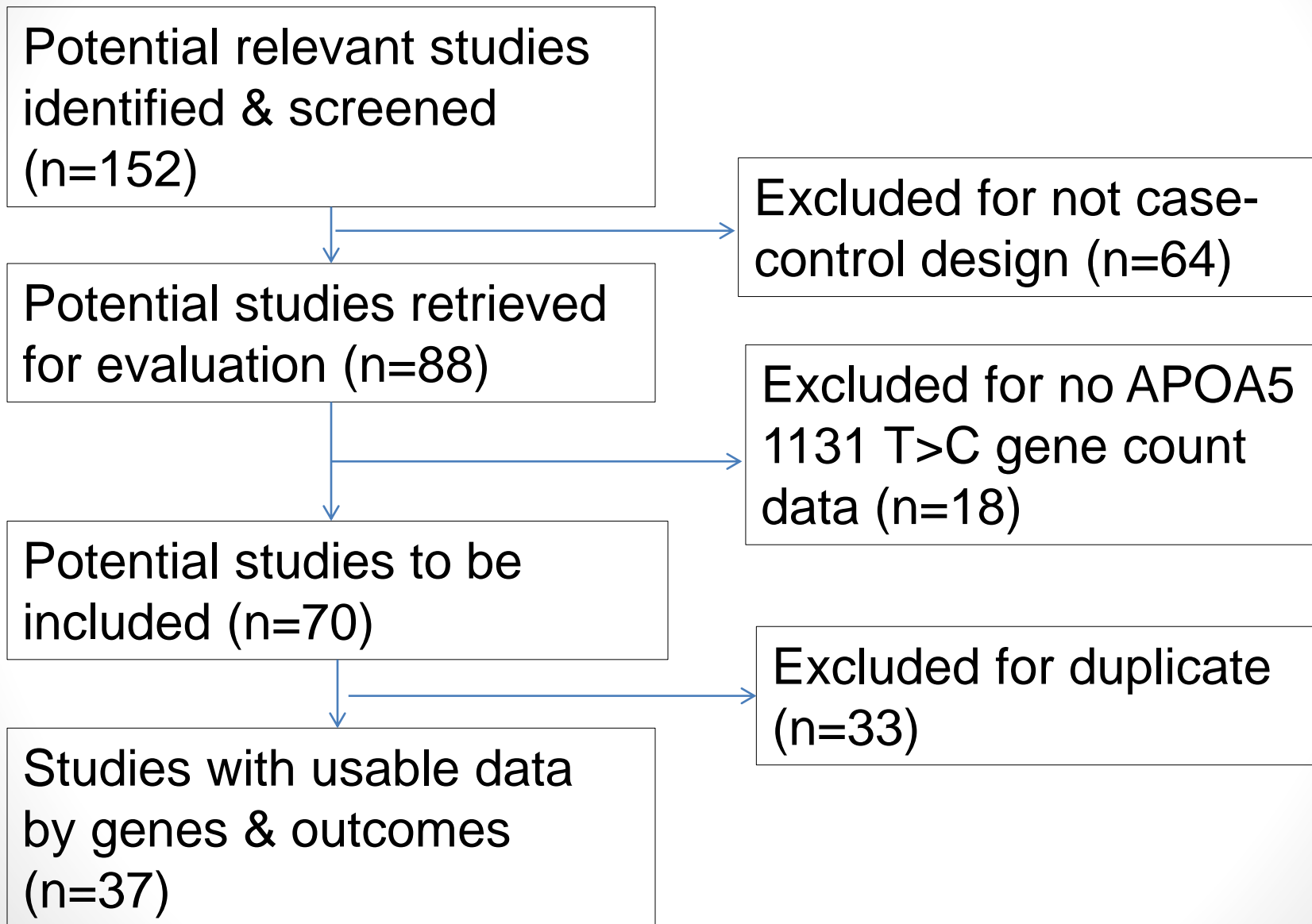
APOA5, CVD, and Lifestyle

- Variations of the APOA5 associated with TG and TCHO and subsequently increasing the risk of CAD.

- Confounding lifestyle risk factors
  - Smoking
  - Alcohol intake
  - Physical inactivity

Publication Search and Key Words

- PubMed, on-line databases were searched

- Key word: Apolipoprotein A5, C1131T, dyslipidemia, CAD, case control, meta-analysis, smoking, alcohol intake, physical activity.

Progression of Selecting Studies

Potential relevant studies identified & screened (n=152)

Excluded for not case-control design (n=64)

Potential studies retrieved for evaluation (n=88)

Excluded for no APOA5 1131 T>C gene count data (n=18)

Potential studies to be included (n=70)

Excluded for duplicate (n=33)

Studies with usable data by genes & outcomes (n=37)

Pooled relative risk of APOA5 1131T>C

Gene type (n studies)	Case N (%)	Control N (%)	RR (95% CI)	p-value
TT (37)	6548 (59.4)	13818 (69.3)	0.82 (0.78-0.87)	p<0.0001
TC (34)	3473 (31.5)	5179 (26.0)	1.21 (1.14-1.29)	p<0.0001
CC (34)	1009 (9.1)	939 (4.7)	2.04 (1.70-2.45)	p<0.0001

Pooled relative risk of APOA5 1131T>C - Asian

Gene type (n studies)	Case N (%)	Control N (%)	RR (95% CI)	p-value
TT (20)	2332 (38.8)	5104 (50.6)	0.73 (0.67-0.81)	p<0.0001
TC (20)	2770 (46.0)	4148 (41.1)	1.13 (1.07-1.18)	p<0.0001
CC (20)	916 (15.2)	836 (8.3)	1.92 (1.58-2.33)	p<0.0001

Pooled relative risk of APOA5 1131T>C - European

Gene type (n studies)	Case N (%)	Control N (%)	RR (95% CI)	p-value
TT (17)	4126 (83.8)	8714 (88.5)	0.91 (0.88-0.94)	p<0.0001
TC (14)	703 (14.3)	1031 (10.5)	1.56 (1.27-1.91)	p<0.0001
CC (14)	93 (1.9)	103 (1.0)	2.82 (1.80-4.43)	p<0.0001

APOA5 TC – European (1 outlier)

Relative risk meta-analysis plot (random effects)

Czech	2.00 (1.37, 2.79)
Czech	0.76 (0.57, 1.01)
Hungary	1.72 (1.14, 2.60)
Hungary	1.90 (1.07, 3.42)
Hungary	1.39 (0.86, 2.27)
Italy	1.16 (0.83, 1.64)
France	1.81 (1.04, 3.23)
Spain	2.34 (1.51, 3.60)
Brazil	1.56 (1.11, 2.22)
Brazil	1.56 (0.81, 3.02)
Brazil	1.16 (0.69, 1.95)
Brazil	1.22 (0.80, 1.86)
Canada	1.74 (1.24, 2.45)
Canada	2.82 (1.84, 4.28)
combined [random]	1.56 (1.27, 1.91)

relative risk (95% confidence interval)

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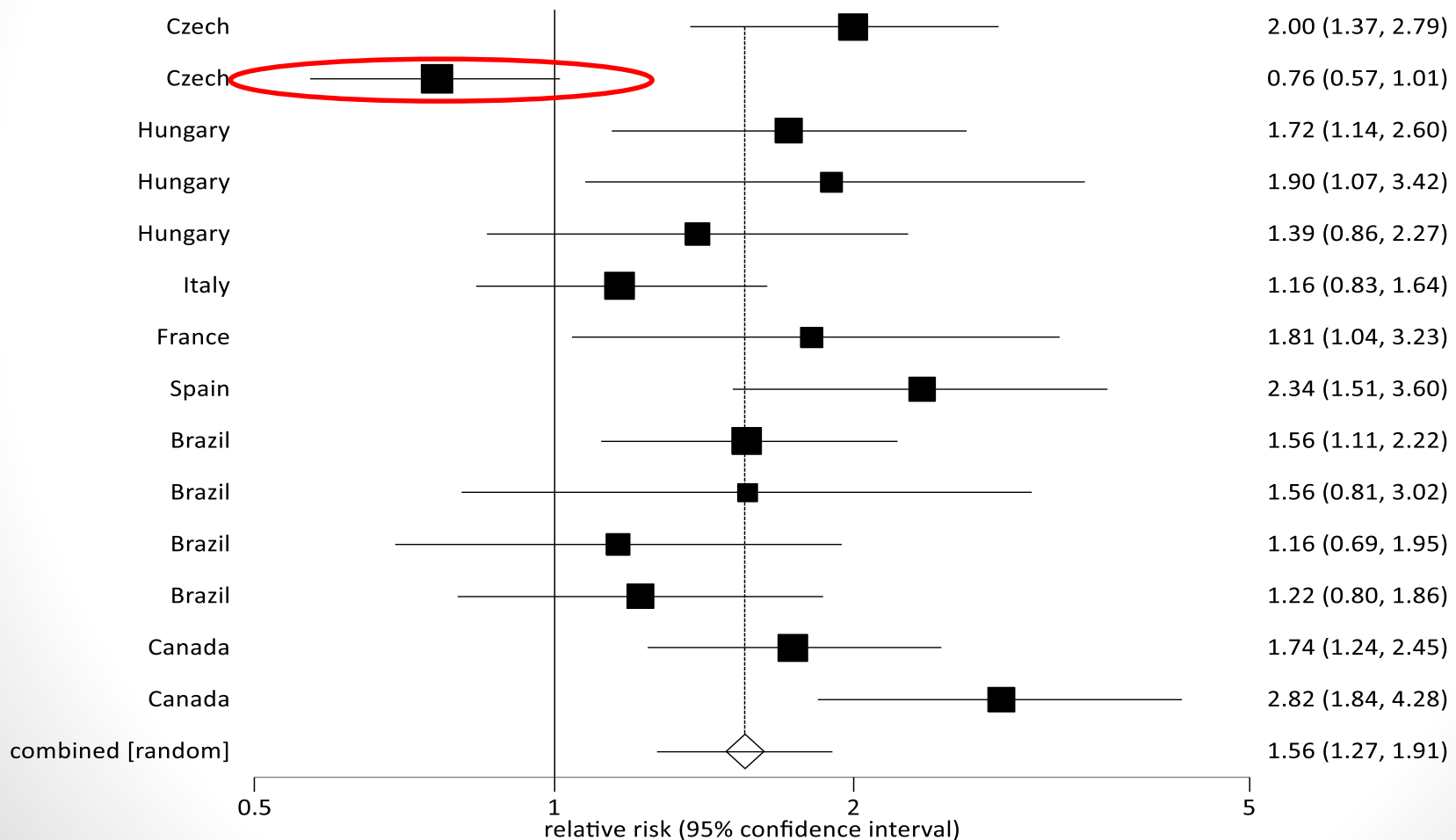
APOA5 TC – European, Bias Plot

Bias assessment plot
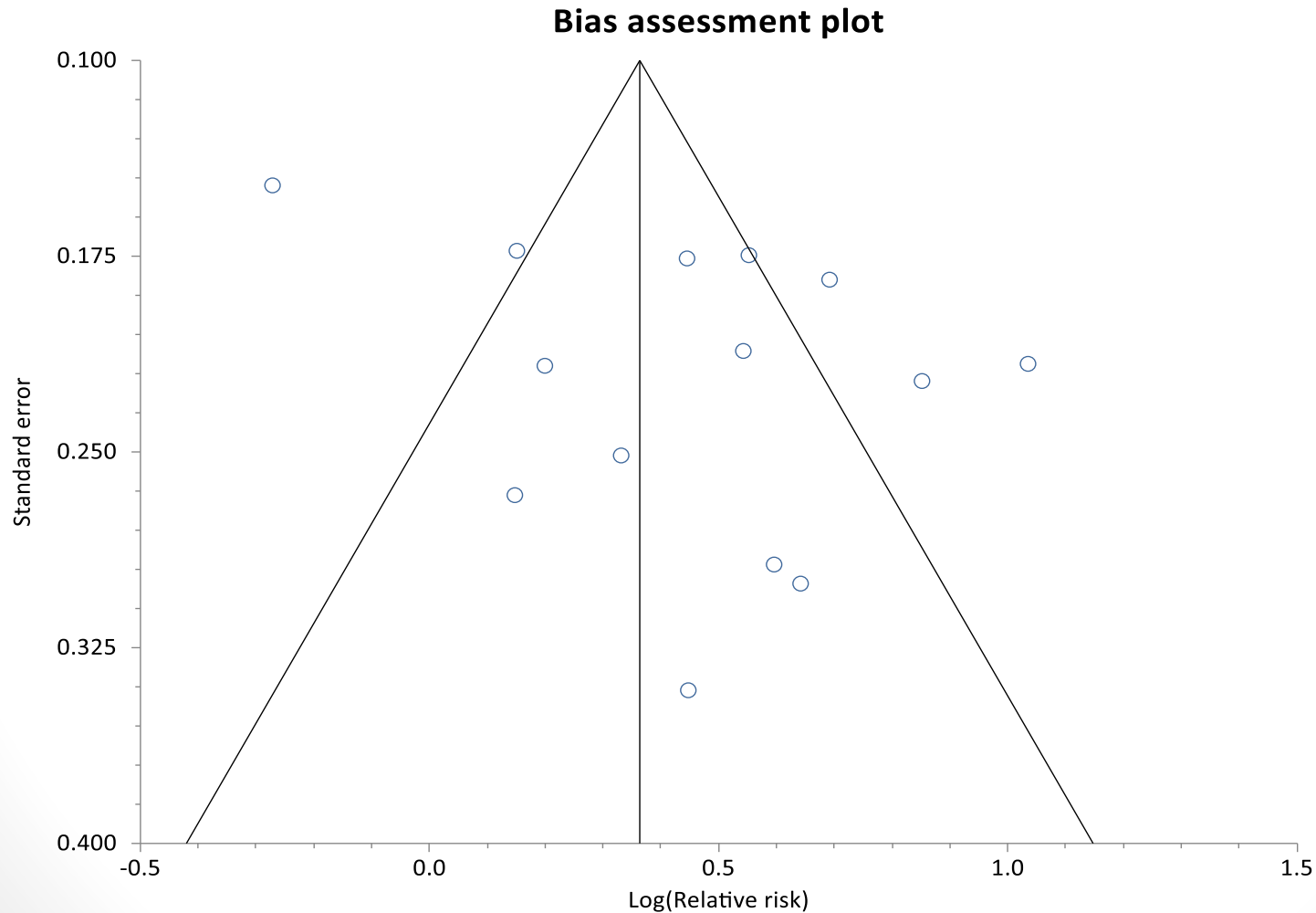
Cochrane Q and I^2 before and after the exclusion of 1 outlier - European

Gene type TC (N studies)	I^2 95% CI	Cochran Q	p-value
Before (14)	69.4 (40.3 – 81)	42.48	p<0.0001
After (13)	35.1 (0 – 65.3)	18.5	P=0.1013

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Pooled relative risk of APOA5 TC - European (1 Outlier deleted)

Gene type (n studies)	Case N (%)	Control N (%)	RR (95% CI)	p-value
TT (17)	4126 (84.6)	8714 (91.8)	0.91 (0.88-0.94)	p<0.0001
TC (13)	657 (13.5)	676 (7.1)	1.66 (1.43-1.93)	p<0.0001
CC (14)	93 (1.9)	103 (1.1)	2.82 (1.80-4.43)	p<0.0001

APOA5 TC - European after the exclusion of the outlier
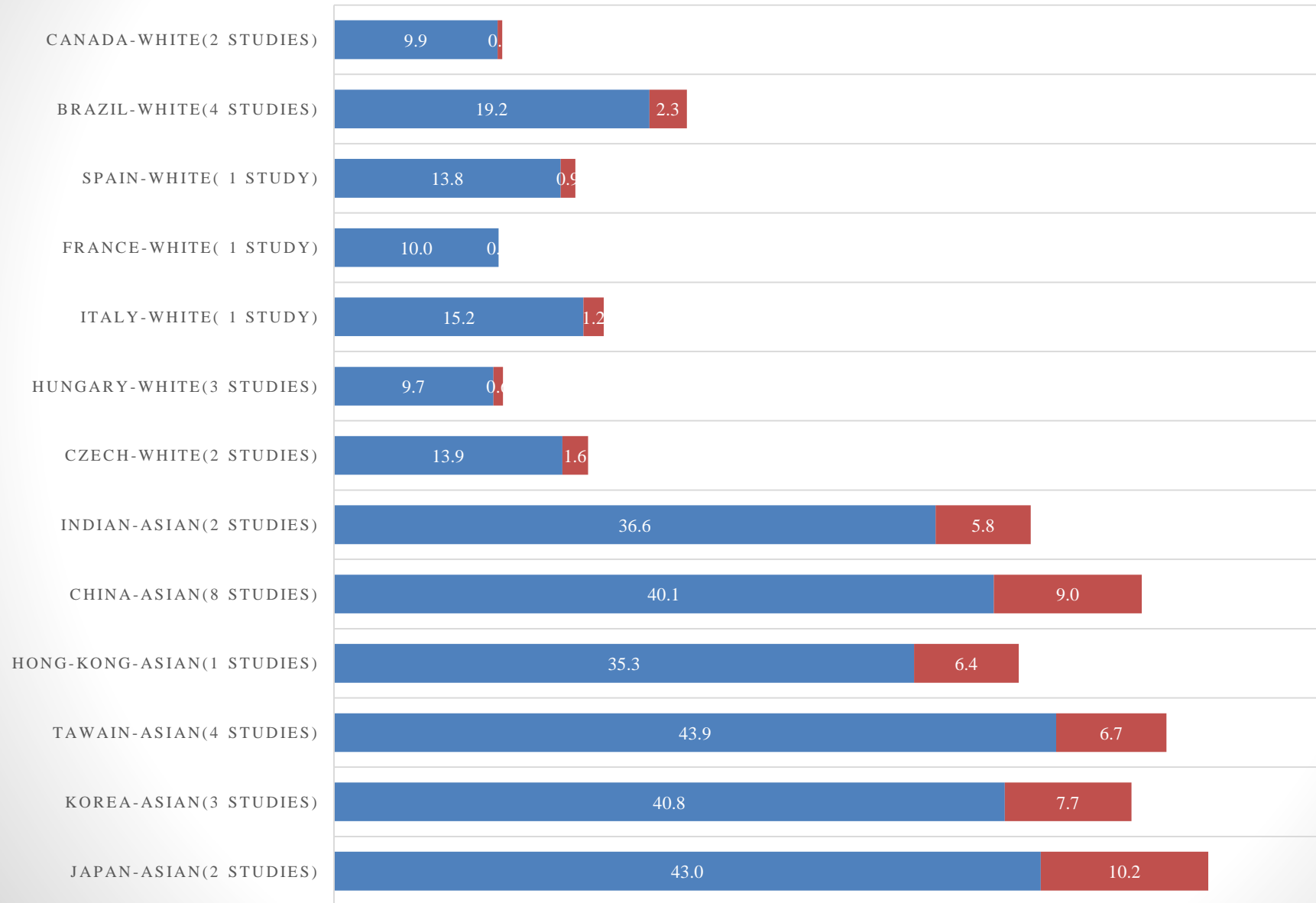

Relative risk meta-analysis plot (random effects)

Study	Relative risk (95% CI)
Czech	2.00 (1.37, 2.79)
Hungary	1.72 (1.14, 2.60)
Hungary	1.90 (1.07, 3.42)
Hungary	1.39 (0.86, 2.27)
Italy	1.16 (0.83, 1.64)
France	1.81 (1.04, 3.23)
Spain	2.34 (1.51, 3.60)
Brazil	1.56 (1.11, 2.22)
Brazil	1.56 (0.81, 3.02)
Brazil	1.16 (0.69, 1.95)
Brazil	1.22 (0.80, 1.86)
Canada	1.74 (1.24, 2.45)
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combined [random]	1.66 (1.43, 1.93)

relative risk (95% confidence interval)

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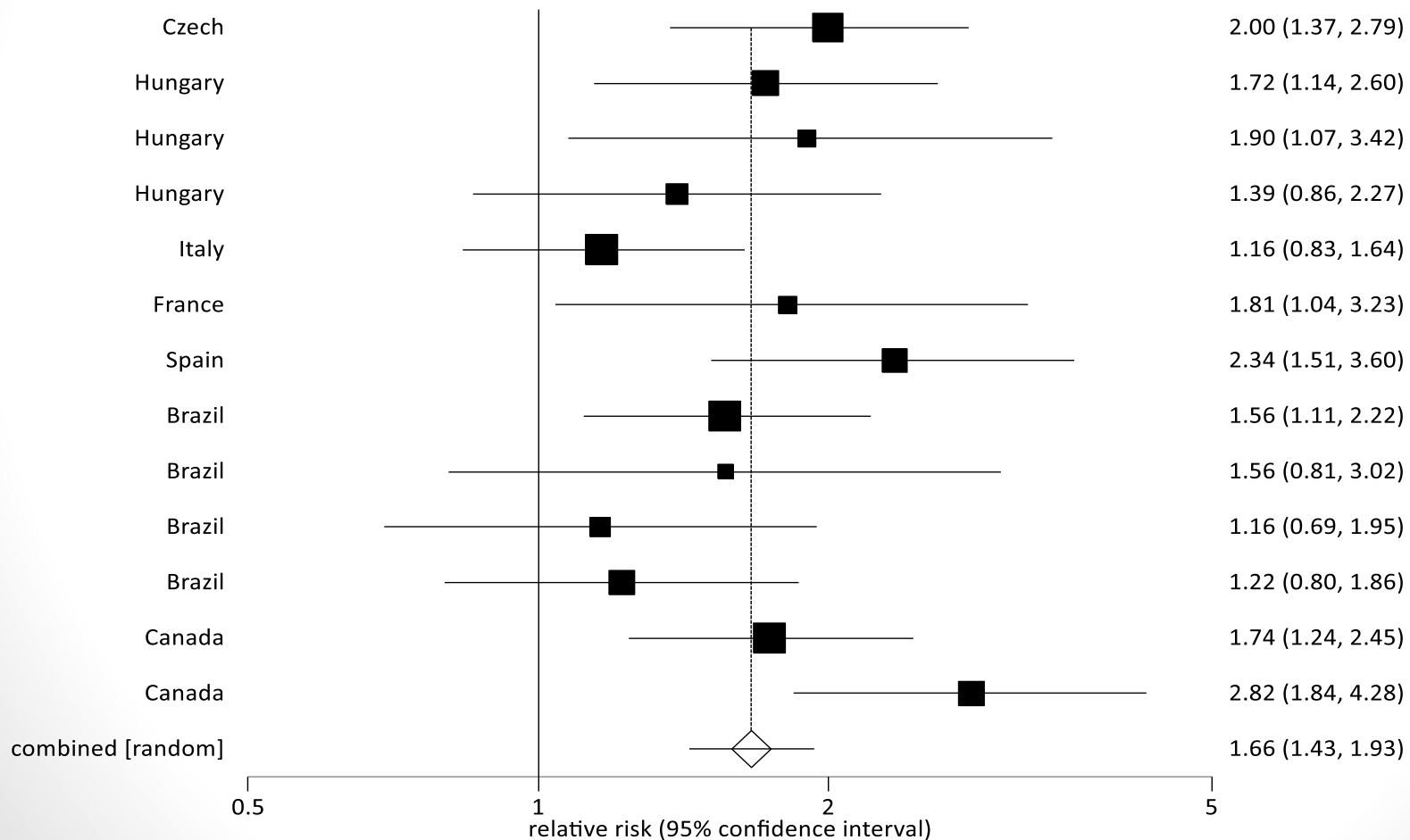
Lifestyles and CVD

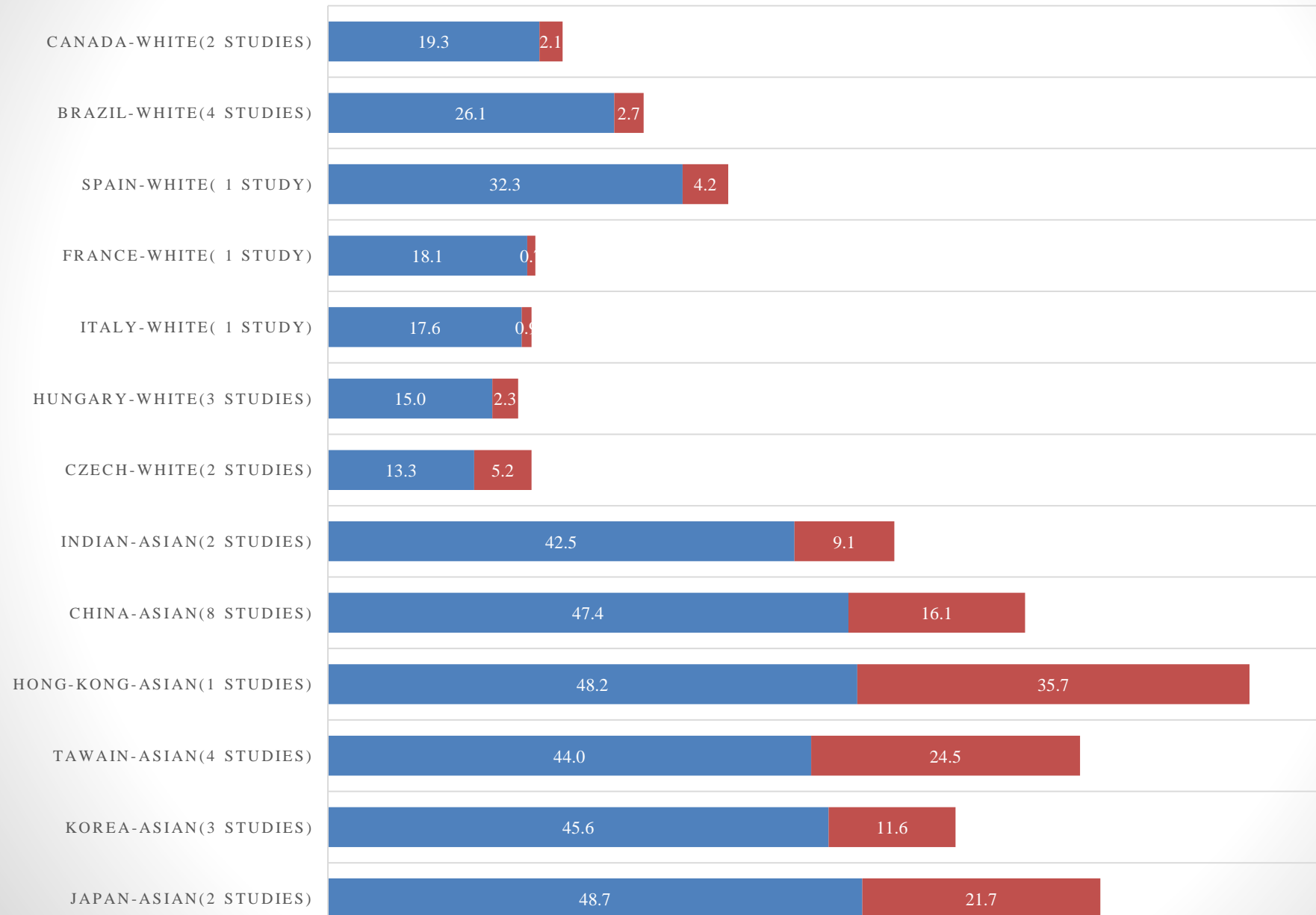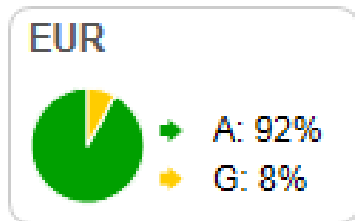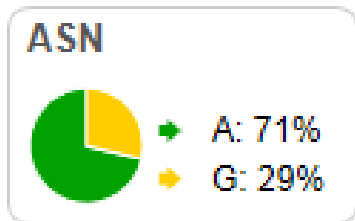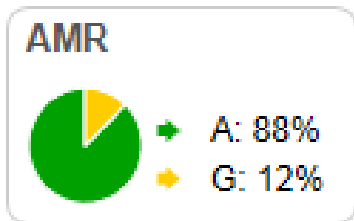| Lifestyle (n studies)	Cases N (%)	Control N (%)	RR (95% CI)	P-value
Smoking (23)	2573 (37.6)	3135 (21.4)	1.57 (1.32 - 1.87)	p<0.0001
Alcohol (10)	1667 (48.4)	3971 (46.1)	1.03 (0.84 - 1.27)	p=0.7515
Physical Inactivity (4)	232 (49.8)	486 (48.4)	1.15 (0.87-1.53)	P =0.3403

Gene mutation (TC+CC) in control group

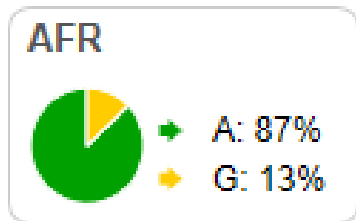Legend: ■ TC control % ■ CC control %

Country/Ethnicity (Studies)	TC control %	CC control %
CANADA-WHITE(2 STUDIES)	9.9	0.
BRAZIL-WHITE(4 STUDIES)	19.2	2.3
SPAIN-WHITE(1 STUDY)	13.8	0.9
FRANCE-WHITE(1 STUDY)	10.0	0.
ITALY-WHITE(1 STUDY)	15.2	1.2
HUNGARY-WHITE(3 STUDIES)	9.7	0.
CZECH-WHITE(2 STUDIES)	13.9	1.6
INDIAN-ASIAN(2 STUDIES)	36.6	5.8
CHINA-ASIAN(8 STUDIES)	40.1	9.0
HONG-KONG-ASIAN(1 STUDIES)	35.3	6.4
TAWAIN-ASIAN(4 STUDIES)	43.9	6.7
KOREA-ASIAN(3 STUDIES)	40.8	7.7
JAPAN-ASIAN(2 STUDIES)	43.0	10.2

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Gene mutation (TC+CC) in case group

Legend: ■ TC case % ■ CC case %

Country-Ethnicity (Studies)	TC case %	CC case %
CANADA-WHITE(2 STUDIES)	19.3	2.1
BRAZIL-WHITE(4 STUDIES)	26.1	2.7
SPAIN-WHITE(1 STUDY)	32.3	4.2
FRANCE-WHITE(1 STUDY)	18.1	0.?
ITALY-WHITE(1 STUDY)	17.6	0.9
HUNGARY-WHITE(3 STUDIES)	15.0	2.3
CZECH-WHITE(2 STUDIES)	13.3	5.2
INDIAN-ASIAN(2 STUDIES)	42.5	9.1
CHINA-ASIAN(8 STUDIES)	47.4	16.1
HONG-KONG-ASIAN(1 STUDIES)	48.2	35.7
TAWAIN-ASIAN(4 STUDIES)	44.0	24.5
KOREA-ASIAN(3 STUDIES)	45.6	11.6
JAPAN-ASIAN(2 STUDIES)	48.7	21.7

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ALL
- A: 85%
- G: 15%

AFR
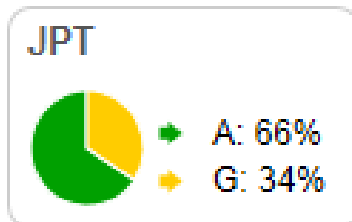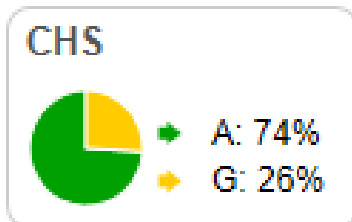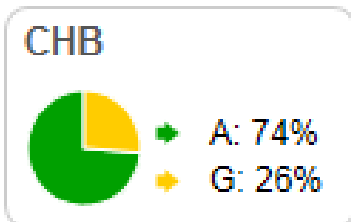- A: 87%
- G: 13%

AMR
- A: 88%
- G: 12%

ASN
- A: 71%
- G: 29%

EUR
- A: 92%
- G: 8%

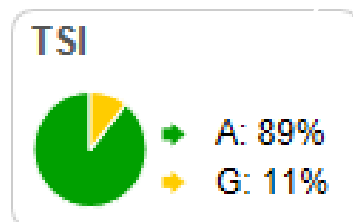Sub-populations ⊞   Sub-populations ⊟   Sub-populations ⊟   Sub-populations ⊟

AMR sub-populations

CLM
- A: 88%
- G: 12%

MXL
- A: 84%
- G: 16%

PUR
- A: 91%
- G: 9%

ASN sub-populations

CHB
- A: 74%
- G: 26%

CHS
- A: 74%
- G: 26%

JPT
- A: 66%
- G: 34%

EUR sub-populations

CEU
- A: 92%
- G: 8%

FIN
- A: 94%
- G: 6%

GBR
- A: 93%
- G: 7%

IBS
- A: 93%
- G: 7%

TSI
- A: 89%
- G: 11%
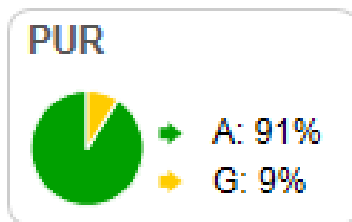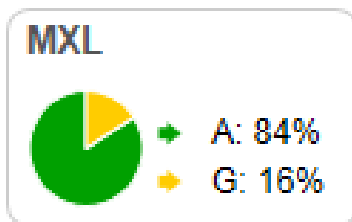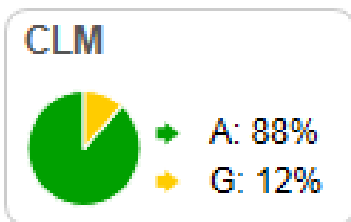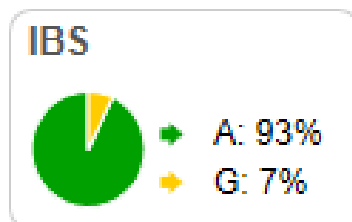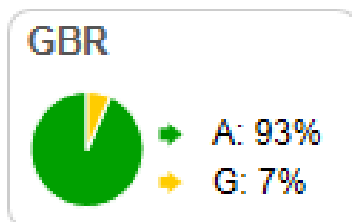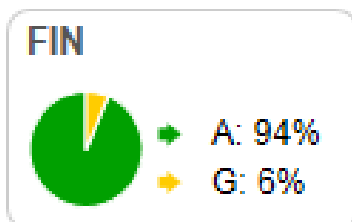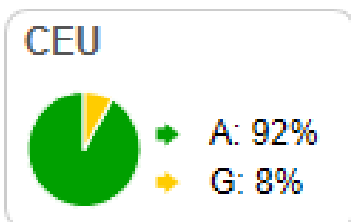
APOA5 1131T>C: C allele frequencies (gene mutation) is higher in Asia than other countries.

City, populations, mutation rates

year	author	Country-City	N population	% control/case
2007	Matsunaga	Japan-Nagoya	2,270,389 (2013)	53.1/70.3
2012	Hishida	Japan-Fukuoka	1,504,643 (2013)	
2009	Jang	Korea-Seoul	10,140,000 (2013)	48.5/57.2
2010	Park	Korea-Seoul	10,140,000 (2013)	
2013	Kim	Korea-Kyunggi-do	12,093,000 (2011)	
2008	Huang	Taiwan-Majia	6,598 (2014)	50.6/68.5
2006 2008 2008	Hsu Hsu Chien	Taiwan-Taipei	2,688,140 (2014)	
2008	Liu	Hong Kong	7,184,000 (2013)	41.6/83.9
2005	Liu	China-Sichuan	80,800,000 (2012)	49.0/63.5
2004 2007	Bi Yu	China-Beijing	21,150,000 (2013)	
2011	Li	China-Guangxi	46,800,000 (2012)	
2013	Long	China-Hengyang	7,141,462 (2010)	
2010	Ashokkumar	Indian-Chennai	8,917,749 (2011)	42.4/51.6
2011	Bhaskar	Indian-Hyderabad	6,809,970 (2011)	

City, populations, mutation rates

year	author	Country-City	N population	% control/case
2004 2007 2010	Szalai Maasz Jaromi	Hungary-Budapest	1,741,041 (2013)	10.3/17.3
2003 2004	Horineq Hubacek	Czech- Prague	1,243,201 (2014)	15.4/18.5
2014	Novotny	Czech-Olomouc	101,003 (2011)	
2007	Martinelli	Italy-Verona	253,409 (2012)	16.4/18.5
2008	Charriere	France-Bron Cedex	39,488 (2006)	10.0/18.9
2008	Sousa	Spain-Barcelona	1,620,943 (2011)	14.7/36.5
2013	Ferreira	Brazil-Minas Gerais	19,855,332 (2012)	
2011 2012	Brito Soter	Brazil-Belo Horizonte	2,479,175 (2013)	21.4/28.7
2010	Prochaska	Brazil-Parana	10,444,526 (2010)	
2008	Wang	Canada-Ontario	12,851,821 (2011)	10.2/21.4

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Deaths from air pollution in 2004

Urban air pollution deaths/1 million population

- >400
- 250-400
- 150-250
- 50-150
- 0-50
- no deaths
- no data
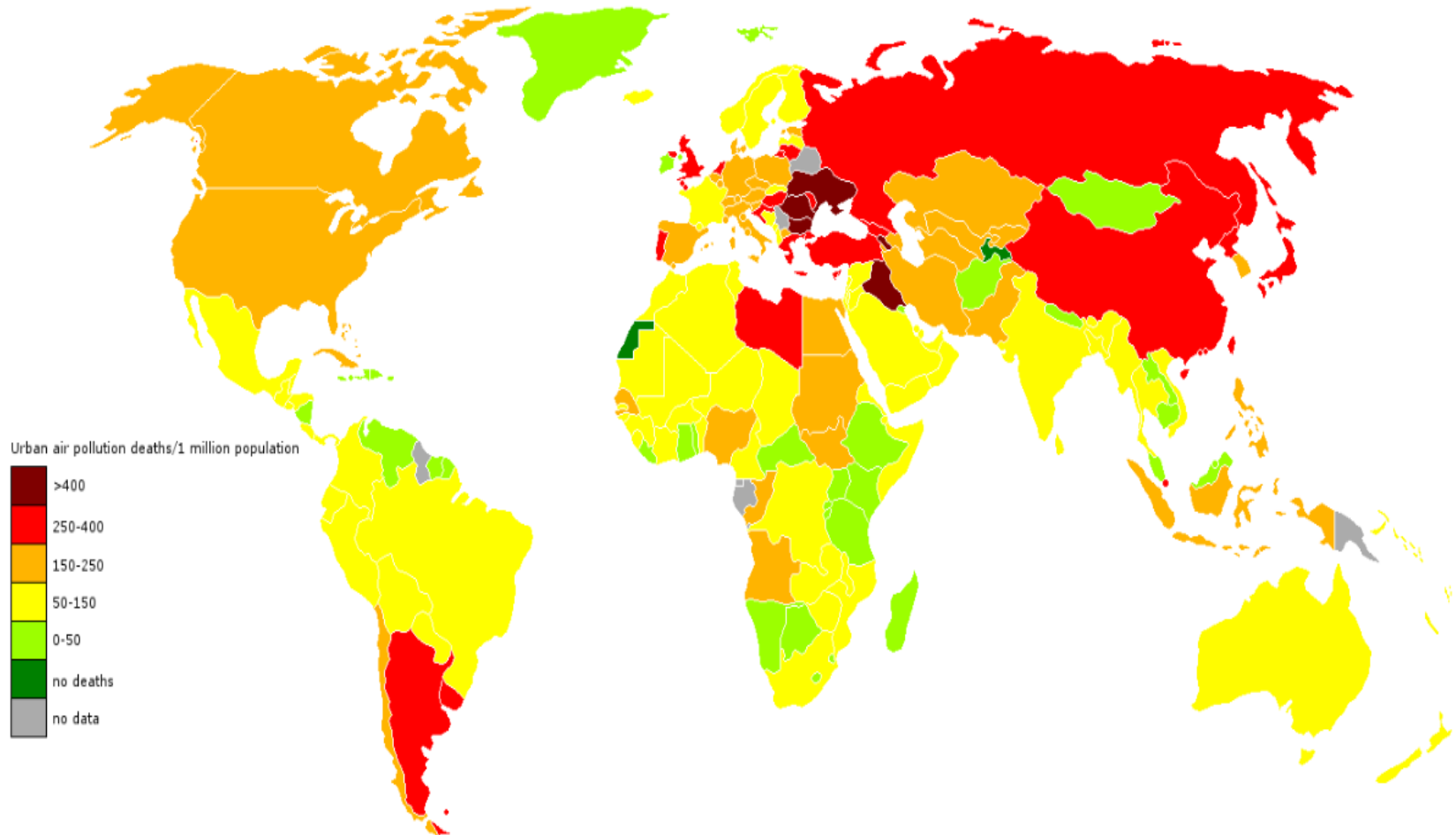
Conclusion and Discussion

- APOA5 1131 TC & CC gene mutation associated with increased CVD risks

  - Subgroup analyses: Asians, Caucasians significant.

  - mutations Asians>Caucasian.

- Gene-environment interaction

  - confounding variables, lifestyles

  - environment, pollutions

Thank you!!