

Asian Indians and Premature Heart Disease: A Systematic Review

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Disclosure

No known conflicts of interest



Objectives:

- Discuss the best available evidence for identification of risk factors of heart disease in the Asian Indian population through SR.
- Discuss the findings of the SR on Asian Indians and premature heart disease.
- Discuss implications to practice and research.



Background

Asian Indians

- The second largest subgroup of Asians in the United States (U.S. Census, 2015)
- Trace origin of birth by ancestors born or who are natives of India
- Interchangeable terms: Indian, South Asians, Indo-American, Indian-American



Background

- WHO predicts Mortality will exceed 2.4 million in AIs
- One in four cardiac patients in the world will be an AI
- Heart Disease rate 2-4 times higher than other ethnic groups
- Heart Disease rate is four-fold than Americans
(Enas, 2005)



Background

- Heart Disease occurs prematurely in Asian Indians
- Heart disease occurs 5-10 years earlier (Enas, 2008; Enas & Senthilkumar, 2002)
- Leading cause of death in AI's (AHA, 2006)
- First attack usually occurring before their 40th birthday (Enas & Senthilkumar, 2002)

American Heart Association. (2007). Heart disease and stroke statistics—2007 Update

Enas, E. (2008, June 27). A. Heart Disease Growing Threat for Indians, study warns.

India Abroad, p. S10.

Enas, E.A., & Senthilkumar, A. (2002). Coronary artery disease in Asian Indians: An update and Review [online]. *Internet Journal of Cardiology*, 1 (2).



Background

- Asian Indians lack the traditional risk factors.

(Enas &

Senthilkumar, 2002 & Gupta, Brister & Verma, 2006)

- CADI Study by AAPI on Hospitalized Patients in California.

- ▶ CAD Rate 4 times higher in AI than rest of the population.

Klatsky AL, Tekawa



Sidney, 994

- The risk is even higher among children and grandchildren of AI immigrants due to adoption of Western lifestyle.

(Enas, 2005)

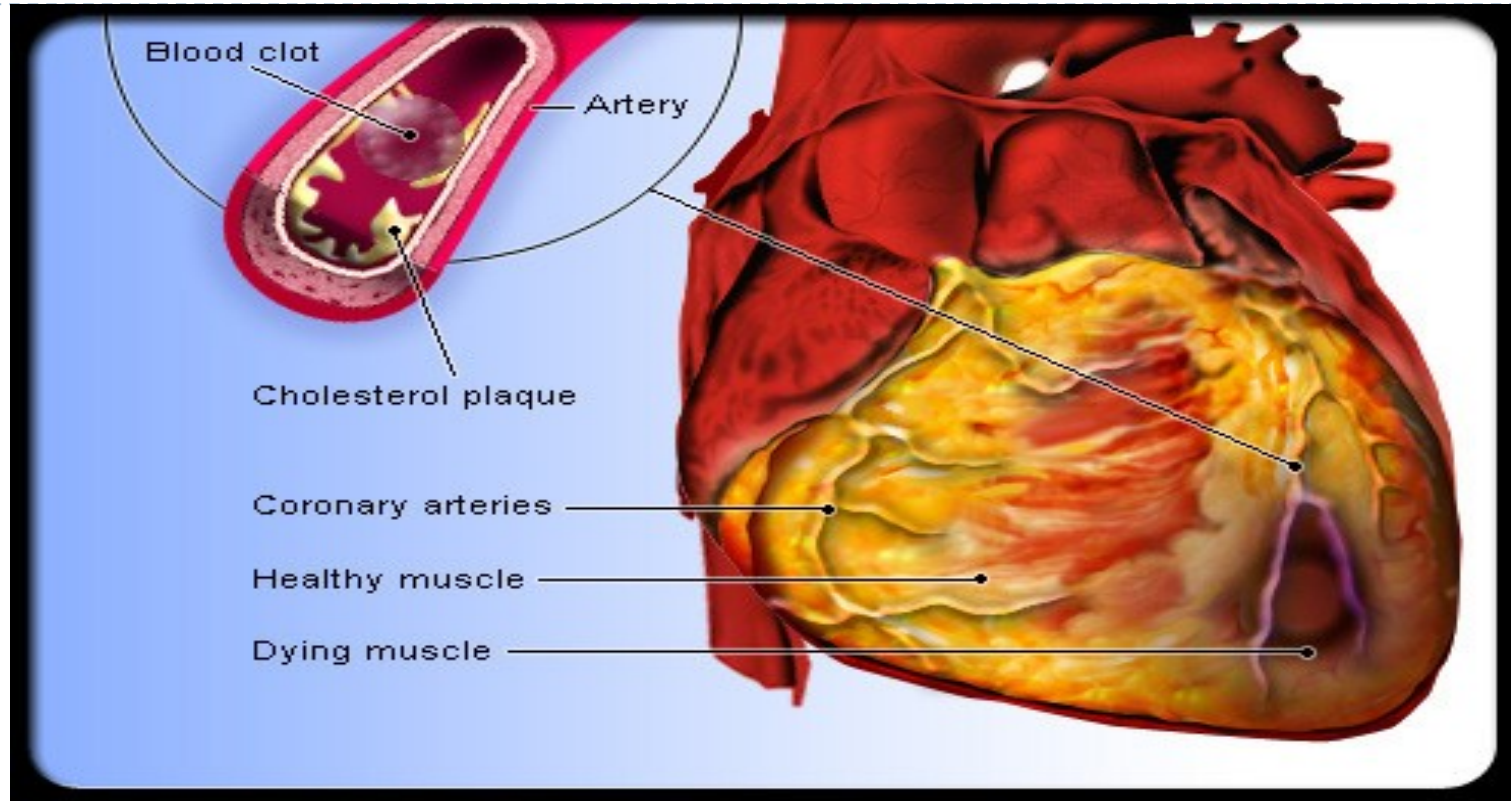
Enas, E.A., & Senthilkumar, A. (2002). Coronary artery disease in Asian Indians: An update and Review [online]. *Internet Journal of Cardiology*, 1 (2).

Enas E.A. (2005). How to beat the heart disease epidemic among South Asians: prevention and management guide for Asian Indians and their doctors. Downers Grove: *Advanced Heart Lipid Clinic*.

Gupta, M., Brister, S., & Verma, S. (2006). Is South Asian ethnicity an independent cardiovascular risk factor? *Canadian Journal of Cardiology*, 22(3), 193-197.

Klatsky, A.L., Tekawa, I., Armstrong, M.A., & Sidney, S. (1994). The risk of hospitalization for ischemic heart disease among Asian Americans in Northern California. *American Journal of Public Health*, 84, 1672-1675.

Coronary Artery Disease



CAD or atherosclerosis is the result of high levels of cholesterol and is an ongoing inflammatory process resulting in plaque formation along the arteries (Ross, 1999)

Background



American Heart Association. (2010). Call to action: Cardiovascular disease among Asian Americans. *Circulation*, 122, 1242-1252.



Research Questions:

- What are the modifiable risk factors for CAD that is exhibited by Asian Indians?
- What are the non-modifiable risk factors for CAD that is exhibited by Asian Indians?
- What are the emerging risk factors of CAD seen among Asian Indians?



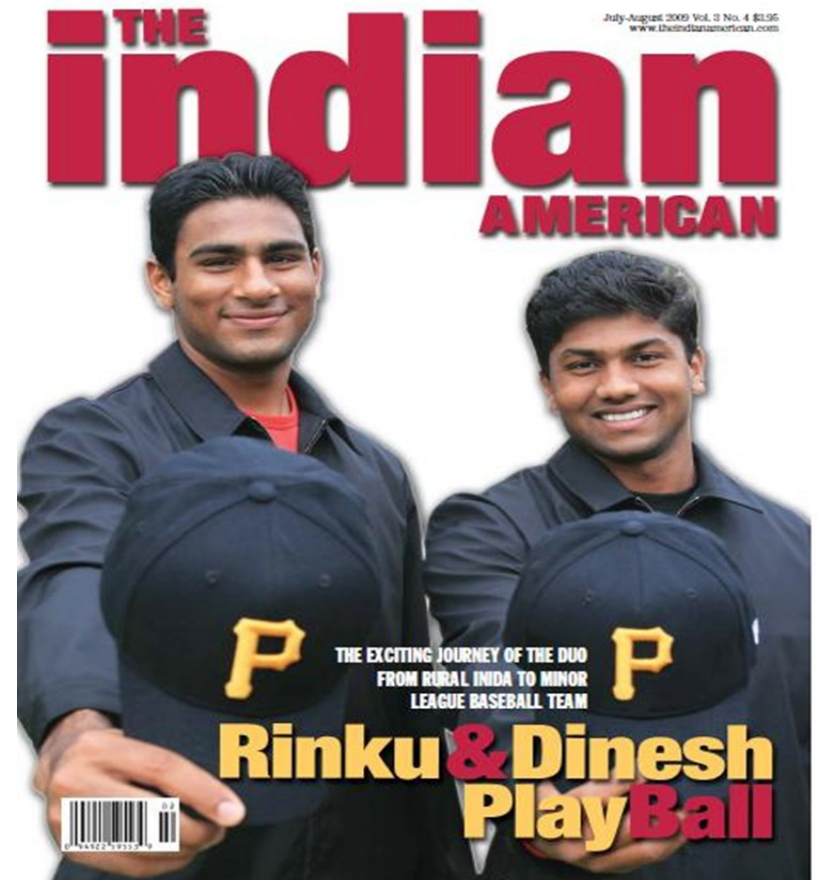
Inclusion Criteria



Inclusion Criteria

Type of Participants

- ▶ Asian Indians who had CAD or who were at risk of developing CAD
- ▶ “Asian Indians” are people who trace their origin to the country of India
- ▶ Both AI male and female adults, 18 years plus, in various countries with diverse socio-economic and religious background



Inclusion Criteria

Types of Outcomes

Modifiable risk factors:

- ▶ Alcohol intake
- ▶ Smoking
- ▶ Dietary practices
- ▶ Lack of exercise
- ▶ Migration
- ▶ Hyperlipidemia
- ▶ Metabolic syndrome
- ▶ HTN and DM.

Non-modifiable risk factors:

- ▶ Family History
- ▶ Genetics
- ▶ Age

The emerging risk factors:

- ▶ Fibrinogen
 - ▶ Homocysteine
 - ▶ Elevated Lp (a)
 - ▶ C-reactive protein
-



- Inclusion Criteria -

Types of Studies



Exclusion Criteria

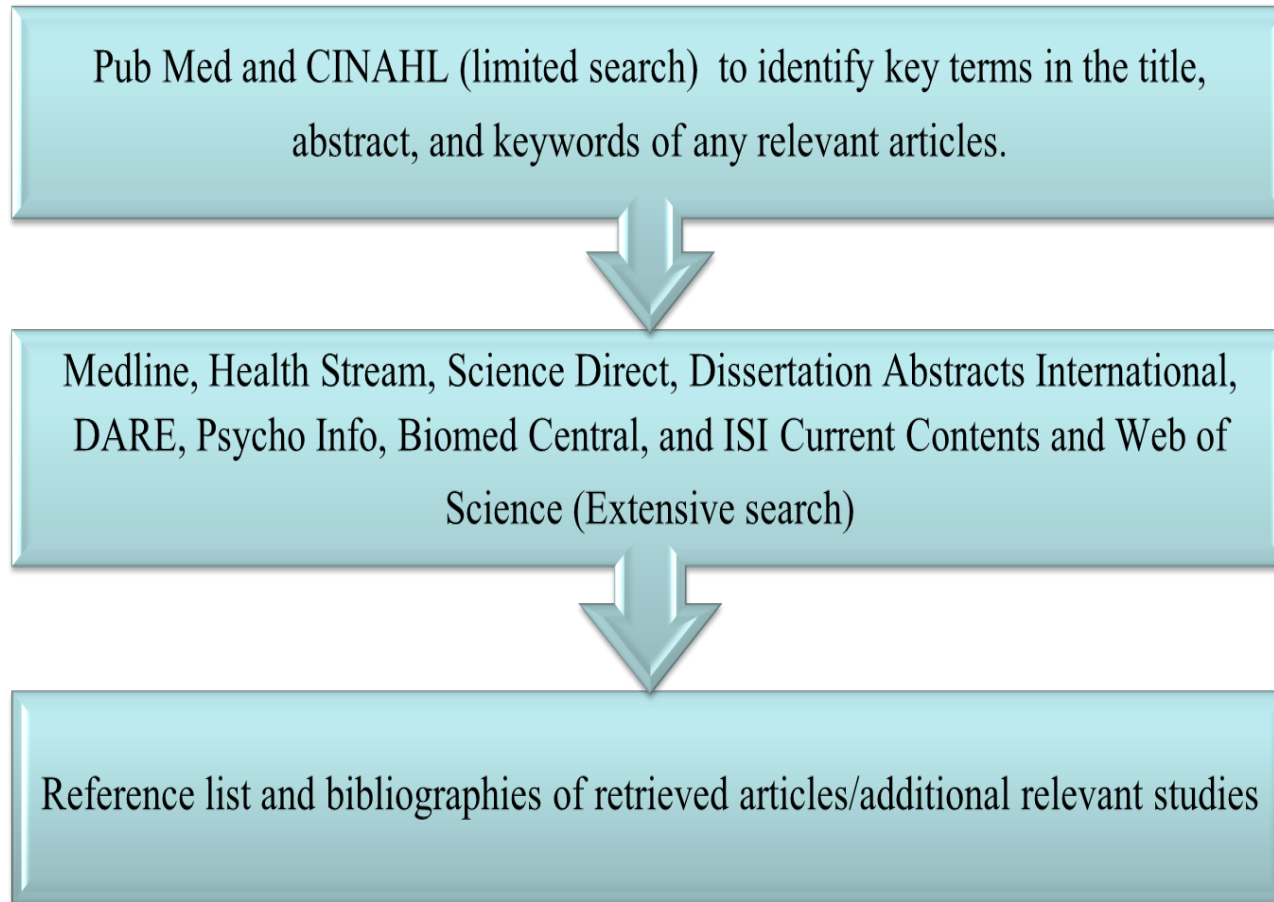


Search Strategy

- Current activity in JBI and Cochrane
- Published and unpublished quantitative research papers in English language (2000-2011)



3 Step Search Strategy



Initial Keywords and Phrases



Grey literature and unpublished studies

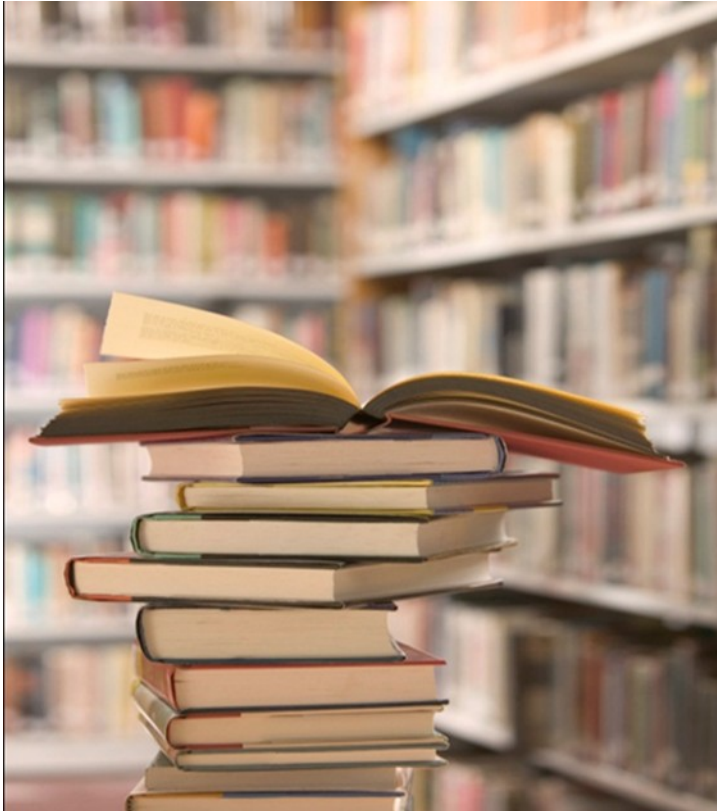
- ▶ New York Academy of Medicine
- ▶ National Library of Medicine, NIH
- ▶ Asian Indian websites such as American Associations of Physicians of Indian Origin (AAPI)
- ▶ AHA along with American College of Cardiology guidelines was reviewed and matched for the best available evidence.
- ▶ CDC, WHO, AHA, MedNar, Google MD, and Virginia Henderson Library of Sigma Theta Tau International websites were also searched.
- ▶ Contacted authors, experts & organizations involved with AI



Search Strategy



Assessment of Methodological Quality



- Methodological validity assessed by 2 independent reviewers using standardized critical appraisal instruments from the JBI Meta Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI).
- Disagreements resolved through discussion/with a third reviewer



Data Collection (Quantitative Data)

- Standardized data extraction tool from JBI-MAStARI
- Authors of studies were contacted for missing information
- Disagreements discussed and resolved by a third reviewer.
- Included specific details about the interventions, populations, study methods and outcomes from review question and specific objectives.



Data Collection (Quantitative papers)

Results

- Where possible, were pooled in the meta-analysis using JBI-MAStARI.
- Results were subjected to double data entry.
- Heterogeneity:
 - ▶ Chi-square
 - ▶ Subgroup analyses

Effect sizes

- OR (for categorical data)
- weighted mean differences (for continuous data)
- 95% CI



Methodological quality

n = 39,945

Country study was conducted:

- 21- India
 - 9 - USA
 - 8 - UK
 - 2 - Australia
 - 2 - Singapore
 - 2 - South Africa
 - 1 - Netherlands
 - 1 - Israel
-



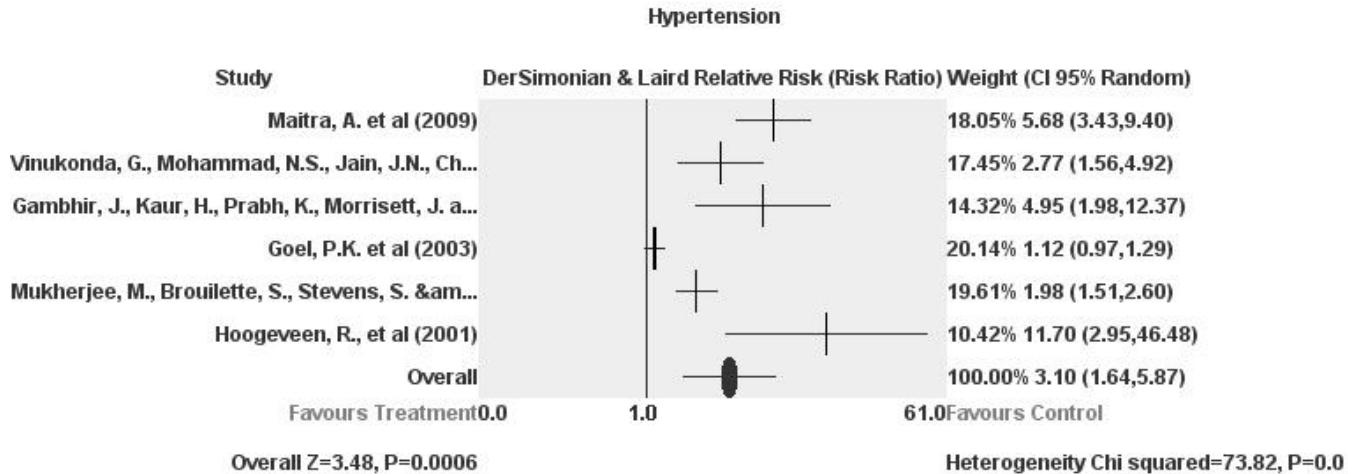
Results



Quantitative Evidence on Modifiable risk factors

C
A
D

n=
3179

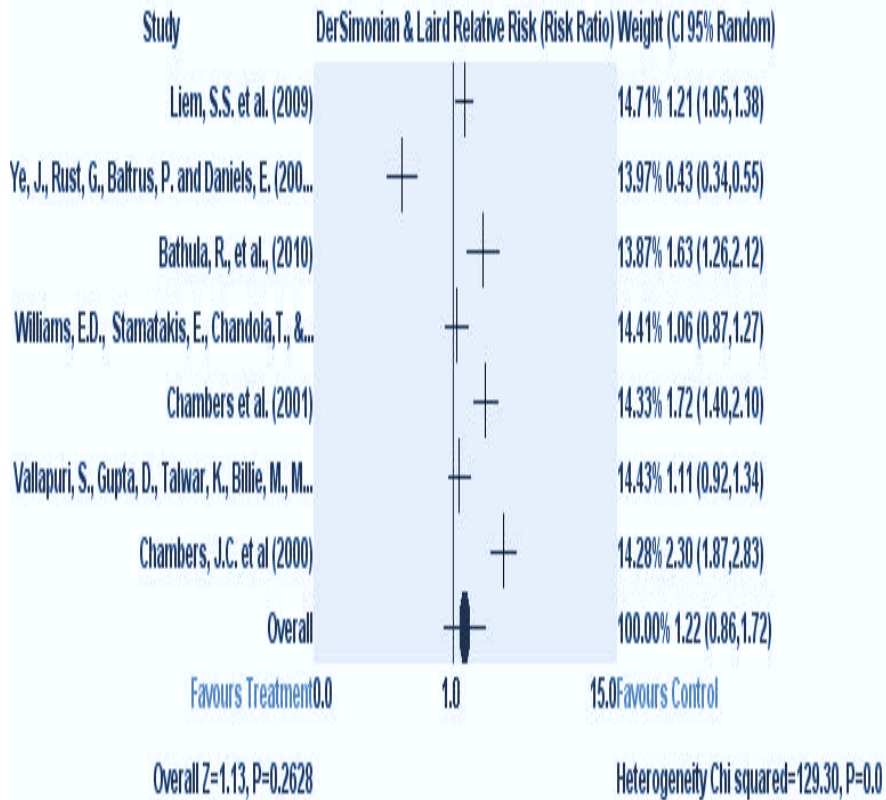


no
n
C
A
D

n=969

Quantitative Evidence on Modifiable risk factors

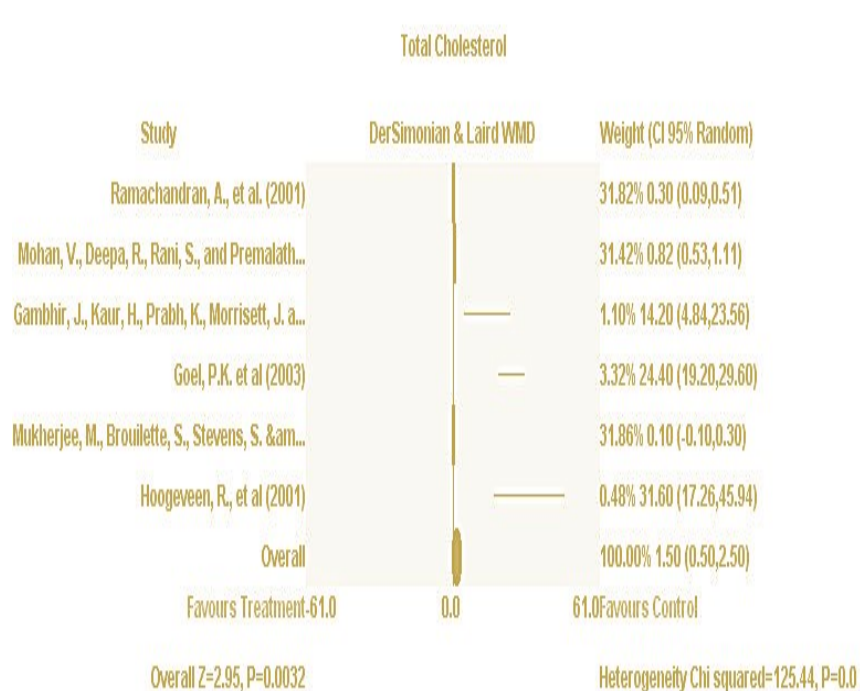
Hypertension



Quantitative Evidence on Modifiable risk factors

Total Cholesterol

CAD group and the control group



No significance between the two groups

Quantitative Evidence on Modifiable risk factors

CAD vs. non-CAD group

LDL Cholesterol



Meta-analysis showed significant heterogeneity

Quantitative Evidence on Modifiable risk factors

▶ Results not pooled in Meta Analysis

- **Univariate analysis:**
 - ▶ Cholesterol, Triglycerides ($p=0.003$), abnormalities in the fractions of cholesterol and oxidized LDL antibodies were significantly associated with CAD (Ramachandran et al. 2001).
- **Multivariate analysis:**
 - ▶ VLDL to HDL ($p=0.037$) strongly associated with CAD. (Ramachandran et al. 2001)
- **Subgroup analysis:**
 - ▶ younger patients (≤ 40 yrs) had higher lipid values vs. older age group (41-55 years) (Tewari et al., 2005; Goel et al., 2003).

Ramachandran, A., Sathyamurthy, I., Snehalatha, C., Satyavani, K., Selvaraj, S., Misra, J., et al. (2001). Risk variables for coronary artery disease in Asian Indians. *American Journal of Cardiology*, 87, 267-271.

Tewari, S., Kumar, S., Kapoor, A., Singh, U., Agarwal, A., Bharati, B.B., et al. (2005). Premature Coronary Artery disease in North India: An Angiographic study of 1971 patients. *Indian Heart Journal*, 57, 311-318.

Goel, P.K., Bharti, B.B., Pandey, C.M., Singh, U., Tewari, S., Kapoor, A., et al. (2003). A tertiary care hospital- based study of conventional risk factors including lipid profile in proven coronary artery disease. *Indian Heart Journal*, 55, 234-240.

Quantitative Evidence on Modifiable risk factors

Dyslipidemia

- Prevalence of CAD seen with increase of :
 - ▶ TC (trend chi- square 26.2 $p < 0.001$)
 - ▶ LDL-C (trend chi-square 24.5, $p < 0.001$)
 - ▶ Triglycerides (trend chi-square: 9.96, $p = 0.002$)
 - ▶ TC/HDL ratio (trend chi-square: 6.14, $p = 0.0132$) (Mohan et al., 2001)
- Impaired reverse cholesterol transport , due to the smaller particle size resulting in higher rates of CAD in AI (Bhalodkar, 2005)
- Fasting triglycerides, a discriminator of CHD risk in AI population (Patel et al, 2010)

Bhalodkar, N.C, Blum, S., Rana, T., Bhalodkar, A., Kitchappa, R., & Enas, E.A. (2005). Effect of leisure time exercise on High-Density Lipoprotein Cholesterol, its subclasses and size in Asian Indians. *American Journal of Cardiology*, 96, 98-100.

Patel, R.T., Lev, E.I., Vaduganathan, M., Guthikonda, S., Bergeron, A., Maresh, K., et al. (2007). Platelet reactivity among Asian Indians and Caucasians. *Platelets*, 18(4), 261-265.



Quantitative Evidence on Modifiable risk factors

Diabetes

- AI more likely to be diabetic (OR=2.27, 95% CI=1.63-3.20)
(Ye, Rust, Baltrus & Daniels 2009).
- Prevalence of diabetes was higher
(Tewari et al, 2005).
- More hyperglycemic than Europeans leading to an impaired CV autonomic function and an increased CAD risk (Bathula et al. 2010).

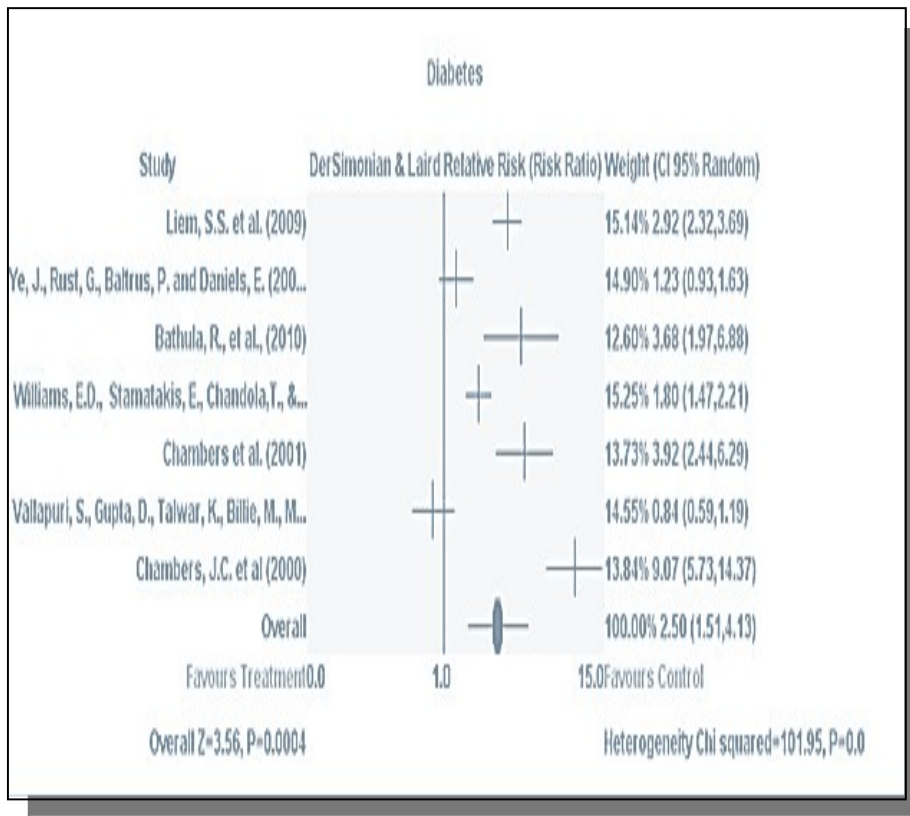
Bathula, R., Hughes, A.D., Paneral, R., Potter, J., McG Thom, S.A., Francis, A.C. et al. (2010). Indian Asians have poorer cardiovascular autonomic function than Europeans: this is due to greater hyperglycemia and may contribute to their greater risk of heart disease. *Diabetologia*, 53, 2120-2128.

Tewari, S., Kumar, S., Kapoor, A., Singh, U., Agarwal, A., Bharati, B.B., et al. (2005). Premature Coronary Artery disease in North India: An Angiographic study of 1971 patients. *Indian Heart Journal*, 57, 311-318.

Ye, J., Rust, G., Baltrus, P., & Daniels, E. (2009). Cardiovascular Risk factors among Asian Americans: Results from a national health survey. *Annals of Epidemiology*, 19 (10), 718-723.

Quantitative Evidence on Modifiable risk factors

Pooled Studies



DIABETES

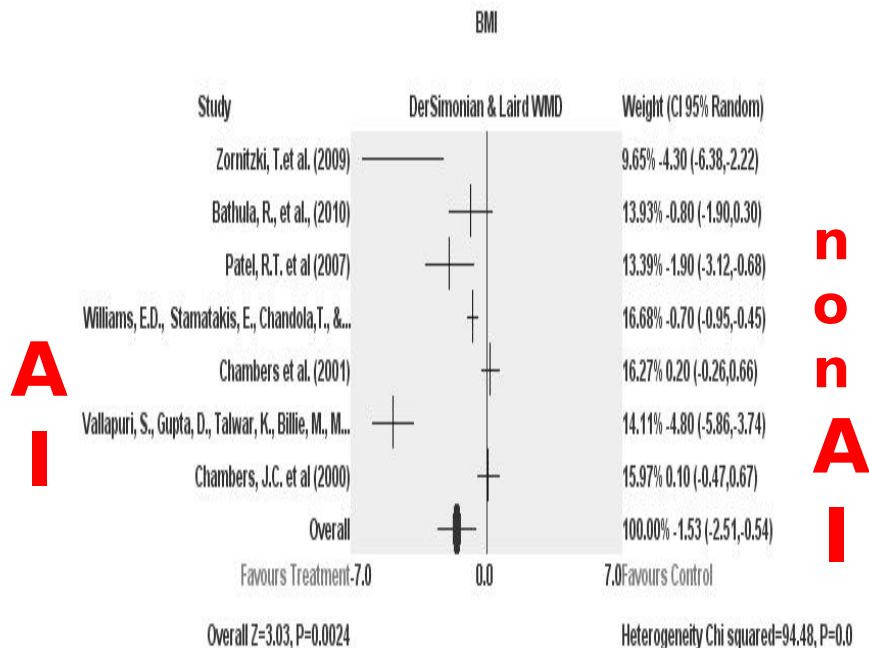
- Pooling of seven studies comparing AI (n=4638) and non-AI (n=89398) with diabetes showed that diabetes was prevalent more in the non-AI group ($\chi^2=101.95$ p=0.0004).

Quantitative Evidence on Modifiable risk factors

Diabetes

- HbA1C showed a strong association with CAD (OR:2.6, 95% CI:1.23-5.63; $p=0.01$)
 - ▶ Associated with other CAD risk factors: BMI ($p<0.001$), SBP ($p=0.028$), DBP ($p=0.017$) WC ($p<0.001$).
 - ▶ Associated with serum cholesterol ($p<0.001$), triglycerides ($p<0.001$), and LDL-C ($p<0.001$). (Dilley et al, 2007)

Quantitative Evidence on Modifiable risk factors

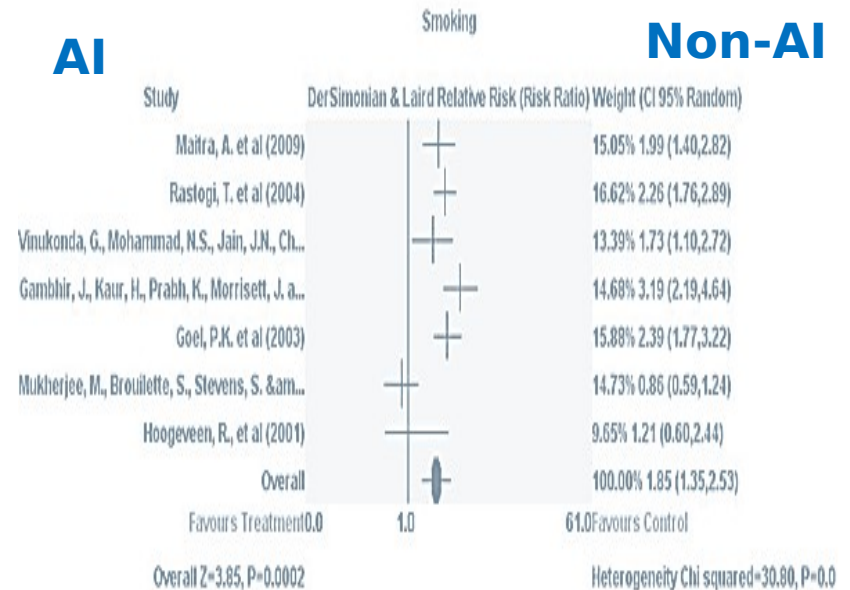
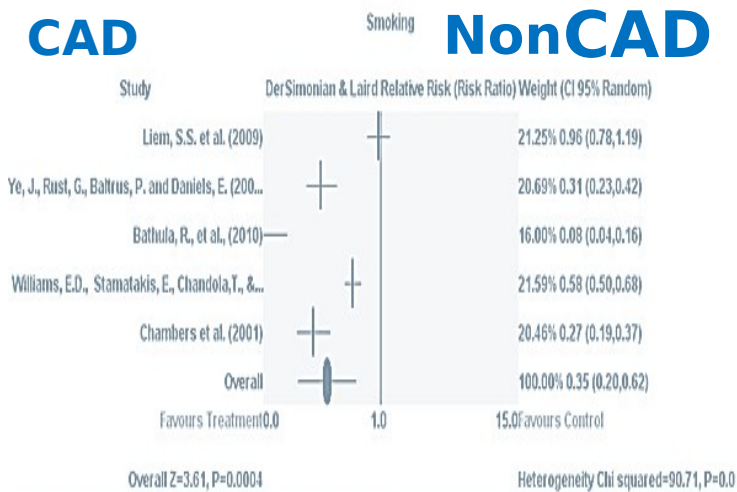


- 7 studies pooled; CAD group with higher BMI, results statistically significant (p<0.0001, Chi square 100.7).
- CURES by WHO : large cross-sectional study (n = 2350), Asia Pacific BMI, & WC cut points among AI in relation to cardio- metabolic risk factors
- BMI cut point to identify cardio metabolic risk factors: 23 kg/m² (males & females)
 - Men: WC 87 cm (34.3 inches)
 - Women: 82 cm (32.3 inches)
- Study confirmed the WHO Asia Pacific guidelines of BMI of 23 kg/m² to define overweight in AI

(Mohan et al, 2001)

Quantitative Evidence on Modifiable risk factors

Smoking



- CAD vs non-CAD group 5 studies pooled; CAD group with higher rates of smoking (p<0.0001, Chi-square 128.45)
- Un-pooled Sub group analysis: Smoking significantly prevalent in the younger age group (less than or equal to 40 years)

47.48% than the older group (41-

Tewari, S., Kumar, S., Kapoor, A., Singh, U., Agarwal, A., Bharati, B.B., et al. (2005). Premature Coronary Artery disease in North India: An Angiographic study of 197 patients. *Indian Heart Journal*, 57, 21-26

55yrs) 40.04% (p=0.04 (Tewari, 2005)

- AI and non-AI: 7 studies pooled; Smoking less prevalent among AI group (p<0.0001 Chi-square 30.80)

Quantitative Evidence on Modifiable risk factors

(Roy et al; 2010)

Quantitative Evidence on Modifiable risk factors

Physical Inactivity



Rastogi, T., Reddy, S.K., Vaz, M., Spiegelman, D., Prabhakaran, D., Willet, W.C. et al. (2004). Diet and risk of ischemic heart disease in India. *American Journal of Clinical Nutrition*, 79, 582-592.

Williams, E.D., Stamatakis, E., Chandola, T., & Hamer, M. (2011). Physical activity behavior and coronary heart disease mortality among South Asian people in the UK: an observational longitudinal study. *Heart*, 97(8), 655-659.

Ye, J., Rust, G., Baltrus, P., & Daniels, E. (2009). Cardiovascular Risk factors among Asian Americans: Results from a national health survey. *Annals of Epidemiology*, 19 (10), 718-723.

Quantitative Evidence on Modifiable risk factors

- Inverse association with green-leafy vegetables
- Use of mustard oil lowers the risk of CAD
- Fruit & vegetable consumption was protective (Radhika et al, 2008)
- Decreased Vit. B12 concentration, due to vegetarian diet, leading to elevated homocysteine (Kumar et al, 2009)
- Lower plasma concentration of omega-3 fatty acids and selenium
- Higher concentrations of arachidonic acid and saturated fatty acids due to lower intake of marine foods resulting to susceptibility CHD acids (Manav, Su, Hughes, Lee, & Ong, 2004)

Kumar, J., Garg, G., Sundaramoorthy, E., Prasad, V.P., Karthikeyan, G., Ramakrishnan, L. et al. (2009). Vitamin B12 deficiency is associated with coronary artery disease in an Indian population. *Clinical Chem Lab Medicine*, 47(3), 334-338.

Manav, Su, J., Hughes, K., Lee, H.P., & Ong, C.N. (2004). Omega-3 fatty acids and selenium as coronary heart disease modifying factors in Asian Indian and Chinese males. *Nutrition*, 20, 967-973.

Radhika, G., Sudha, V., Sathya, R.M., Ganesan, A., & Mohan, V. (2008). Association of fruits and vegetable intake with cardiovascular risk factors in urban south Indians. *British Journal of Nutrition*, 99, 398-405.

Quantitative Evidence on Modifiable risk factors



Quantitative Evidence Non-modifiable Risk factors

Genetics

75G>A and
+83C>T
SNPs APOC3

Sac1 SNP and
the APOA5

S19W SNP in the
Apo11q gene
cluster

- 4 genetic variants with premature CAD as well as with lipids and lipoproteins in a group of affected siblings belonging to AI families with significant history of CAD (Shanker et al. 2008).
 - ▶ There was a relationship between circulating lipids and traditional coronary risk factors in this group.
- Lower levels of Coenzyme Q10 (CoQ10) identified in AI increased their susceptibility to CAD. (Hughes, Lee, Feng, Lee & Ong, 2002).

Quantitative Evidence Non-modifiable Risk factors

Anatomy

Smaller Arteries

- A statistically significant difference in the mean diameter of the left main ($p=0.005$), left anterior descending ($p=0.014$), left circumflex ($p=0.001$), and right coronary arteries ($p=0.021$).

(Makaryus et al., 2005)

Telomere Biology and LV mass

- Telomere biology is altered in subjects with CAD. AI with CAD has shorter telomeres than those without CAD ($p=0.002$) (Mukherjee, Brouillette, Stevens, Shetty & Samani, 2011).
- Higher left ventricular mass was associated with an increased risk of CAD in AI ($p=0.05$) (Kumaran et al. 2002)

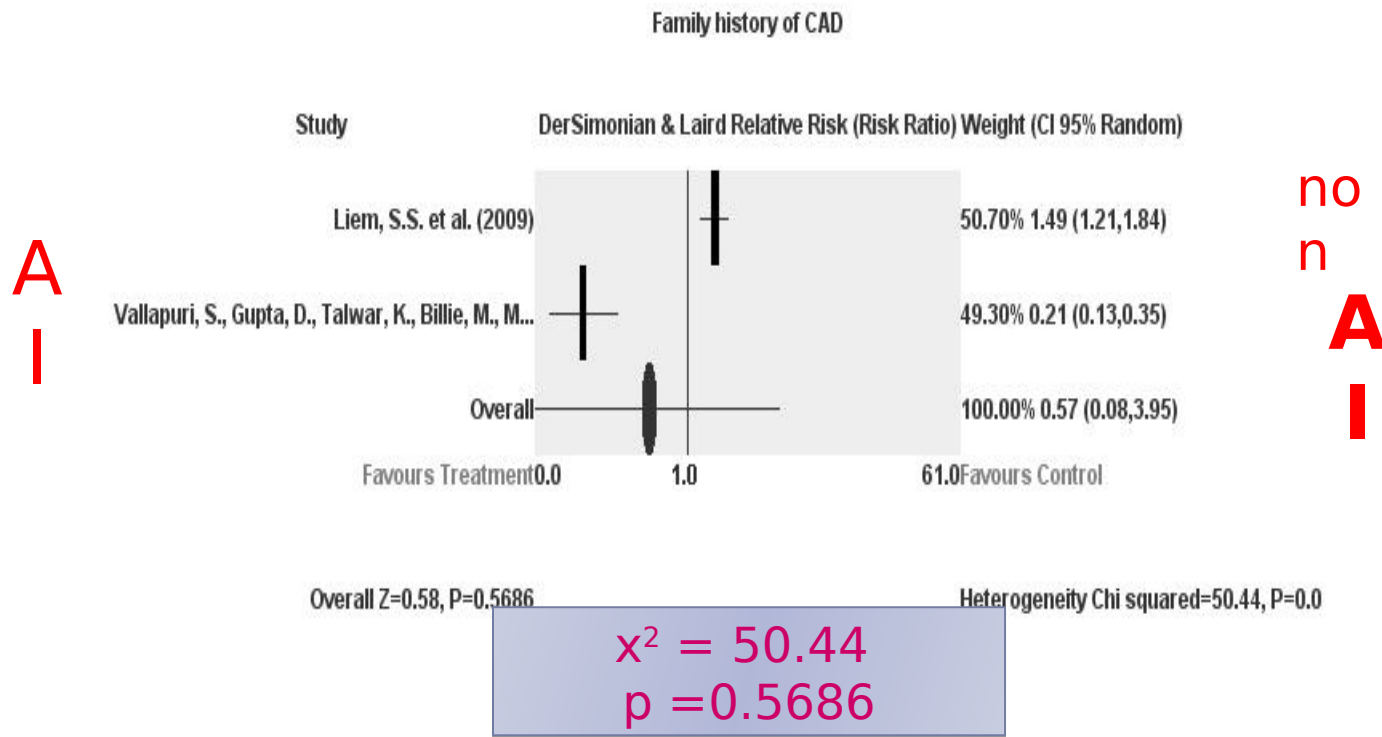
Kumaran, K., Fall, C.D., Martyn, C.M., Vijayakumar, M., Stein, C.E., & Shier, R. (2002). Left ventricular mass and arterial compliance: relation to coronary heart disease. *International Journal of Cardiology*, 83, 1-9.

Makaryus, A.N., Dhama, B., Raince, J., Raince, A., Garyali, S., Labana, S.S., Kaplan, B.M., Park, C., & Jauhar, R. (2005). Coronary artery diameter as a risk factor for Acute Coronary Syndromes in Asian-Indians. *American Journal of Cardiology*, 96, 778-780.

Mukherjee, M., Brouillette, S., Stevens, S., Shetty, K.R., & Samani, N.J. (2009). Association of shorter telomeres with coronary artery disease in Indian subjects. *Heart*, 95, 669-673.

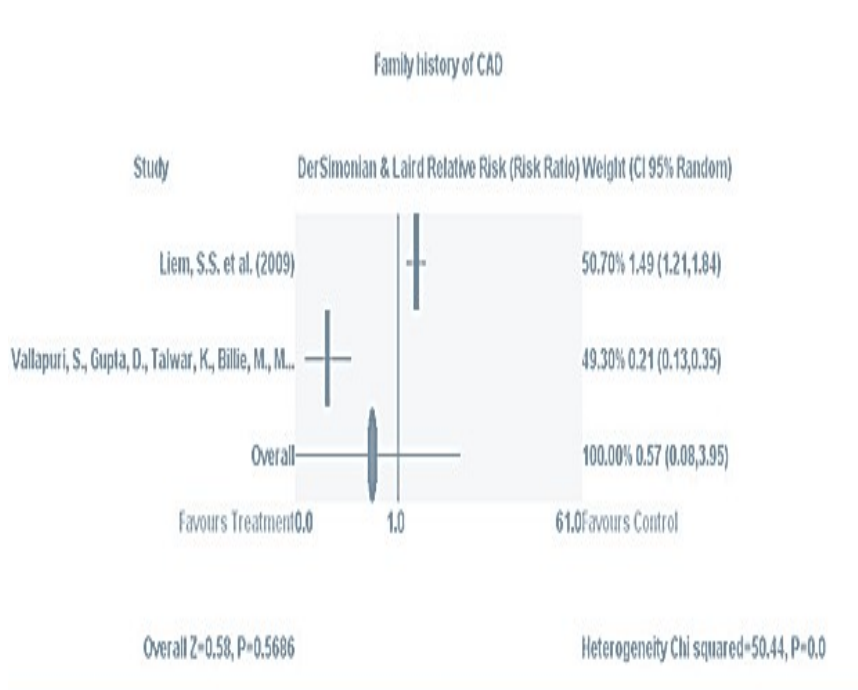
Quantitative Evidence on Non-Modifiable risk factors

FAMILY HISTORY



Quantitative Evidence on Non- Modifiable risk factors

Family History of CAD



- Pooling of two studies in this category did not show any statistically significant difference between the CAD group and the control group; $p= 0.7872$, Chi - square= 50.44.
- In the risk factor analysis of a cohort of 1971 patients, 205 patients (10.4%) had family history of premature CAD (Tewari et al, 2005).

Quantitative Evidence on Emerging risk factors

Fibrinogen

- Described as an independent pro-arteriosclerotic agent.
 - Found in a diabetic subjects with CAD
 - A significant trend with fibrinogen (chi-square 6.3, $p=0.012$),
 - ▶ no significant association with CAD (chi-square 6.6, $p=0.09$).
- (Ramachandran et al., 2001)

Quantitative Evidence Non-modifiable Risk factors

- Multiple logistic regression analysis identified age (OR 1.05 $p < 0.001$) as the risk factor for CAD.
- Younger AI patients had a more atherogenic lipid profile than older sub-groups for CAD.

Mohan et al. 2001

Quantitative Evidence on Emerging risk factors

Plasma Homocysteine

- Level is found to be higher in AI with CAD was than with controls (p=0.001)
- Identified as a novel and independent risk factor for CAD in AI (Chambers et al; 2000)
- Elevated level was found to increase the risk of CAD (95%CI: 1.93-10.82).
- Elevated homocysteine may contribute as much as two-fold CAD deaths in AI. This difference was explained by a lower Vitamin B12 and folate levels. Dietary vitamin supplementation may reduce the risk
- The two genetic determinants: MTHFRC677T (OR: 1.96, 95%CI: 1.06-3.61) and GCPIIC1561T (OR: 2.09, 95% CI: 1.09-3.97), were found to be associated with risk for CAD
(Vinukonda et al. 2007)



Quantitative Evidence on Emerging risk factors

Adipopectin

- Total adiponectin and HMW adiponectin were positively associated with coronary artery angiographic findings using Gensini index score in AI (Zornitzki et al, 2009)
- AI had greater extent of CAD than Caucasian by the Gensini score ($p < 0.0001$) (Vallapuri et al., 2002).



Quantitative Evidence on Emerging risk factors

Lipoprotein (a)

- Lp(a) levels were 2.5 times higher in CAD patients compared to controls (Gambhir et al, 2008).
 - Lp (a) level is a significant predictor of CAD in young AI.
 - Elevated Lp (a) levels confers genetic predisposition to CAD in young AI.
- Lp (a) was significantly increased (50% higher) in CAD AI patients than the controls ($p < 0.001$) (Geethanjali et al, 2003)

Gambhir, J.K., Kaur, H., Prabhu, K.M., Morrisett, J.D., & Gambhir, D.S. (2008). Association between lipoprotein(a) levels, apo (a) isoforms and family history of premature CAD in young Asian Indians. *Clinical Biochemistry*, 41, 453-458.

Geethanjali, F.S., Luthra, K., Lingehel, A., Kanagasaba, P., Jacob, J., Srivastava, L.M. et al. (2003). Analysis of the apo (a) size polymorphism in Asian Indian populations: association with Lp(a) concentration and coronary heart disease. *Atherosclerosis*, 169, 121-130.

Quantitative Evidence on Emerging risk factors

C- Reactive Protein

Chandalia, M., Cabo-Chan, A.V., Devaraj, S., Ishwarlal, J., Grundy, S.M., & Abate, N. (2003). Elevated Plasma High-Sensitivity C-Reactive Protein concentrations in Asian Indians living in United States. *Journal of Clinical Endocrinology & Metabolism*, 88 (8), 3773-3776.

▶ Mohan, V., Deepa, R., Velmurugan, K. & Premalatha, G. (2005). Association of C-reactive protein with body fat, diabetes and coronary artery disease in Asian Indians: The Chennai Urban Rural Epidemiology Study. *Diabetic*

Quantitative Evidence on Emerging risk factors

Platelets

- Platelet activation is an important factor in the pathogenesis of CAD.
- AA-stimulated P-selectin expression ($p < 0.02$) and TRAP stimulated platelet formation was significantly higher in AI than Caucasians ($p < 0.02$).
 - ▶ This disparity in platelet reactivity among AI predisposes to as higher CAD rates. (Patel et al., 2007)

Quantitative Evidence on Emerging risk factors

Aspirin resistance

- Aspirin resistance in AI cohort patients with documented heart disease was 38.1%.
- Patients with elevated absolute urinary dehydrthromboxane levels (>320pg/ml) on chronic aspirin therapy constituted a high risk subset for recurrent vascular events.

Thomson, John, George, Joseph & Jose, 2009

Summary

- Hypertension: not a risk factor of CAD in AI
- TC & LDL: prevalent in AI, but results not statistically significant. Triglycerides was prevalent ; results statistically significant.
- TC, LDL, & triglycerides were not related to CAD in AI.
- Diabetes, not a risk factor for CAD in AI.
- AI had higher BMI compared to non-AI.
- BMI: Not associated with CAD.
- Although smoking was less prevalent in AI compared to non-AI; smoking increased the risk of CAD in AI.



Summary: Modifiable risk factor

- Alcohol not cardio-protective
- Physical inactivity
- Lower concentration of omega-3 Fatty acids
- Lower levels of Vitamin B12
- Migration & Urbanization



Summary: Non-modifiable

- Genes: premature heart disease.
- Narrow coronary arteries
- Shorter telomeres
- Higher left ventricle mass
- Family history: Strong predictor
- Age: young



Summary: Emerging Risk Factors

- Fibrinogen a pro- arteriosclerotic agent
- Plasma homocysteine an independent risk factor
- Lipoprotein (a): Higher, strongly associated with CAD
- Higher C-reactive protein concentration: higher CAD risk
- Aspirin resistance: increased CAD



Discussion

- SR undertaken to identify the risk factors of CAD in AI.
- Meta-analysis was conducted to add greater objectivity to the findings thereby increasing the ability to extract definitive conclusions from the studies detailed in this review.
- Findings to be interpreted cautiously as a random effect model was used; there is a potential for the results of small studies to over or underestimate the risk of CAD in AI.

Limitations

- Studies in English language only.
- Studies in other languages might have impacted the results.
- Excluding the studies on AI children might have resulted in missing additional evidence in exploring genetics as a risk factor for CAD in AI.

Conclusion

- Risk of CAD is often underestimated because historically AI has not been perceived as having the traditional risk factors for CAD.
- In fact AI are exposed to those very same risk factors.
- Traditional factors may not be the most important etiologies for CAD in AI and that genetics along with the emerging risk factors might be a contributing factor

Implications for Practice

- CAD occurs at a younger age in AI than other ethnic groups. Early screening, identification and intervention remain crucial.
- Broader use of lower target goals such as cut –off points for BMI and WC for AI as recommended by WHO is needed to identify CAD risk.
- Lower threshold for intervention, lower target goals for treatment.
- Need for more stringent guidelines since they are predisposed to CAD.
- Culturally appropriate strategies to reduce CAD risk should be put in place.
- Urgent action at individual, societal and governmental level needed to decrease the growing epidemic among AI.



Implications for Research

- Effectiveness of screening for CAD risk factors in AI population to be explored.
- Randomized controlled trials on the effective screening and prevention strategies are priority for this group.
- Primary research on the opportunities to improve risk factor reduction and to influence behavior modification is also recommended.

