DISCOVERING RISK FACTORS FOR CORONARY DISEASE IN ASIAN INDIANS: A SYSTEMATIC REVIEW

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LEARNING OBJECTIVES:

- Identify available evidence for identification of risk factors of heart disease in the Asian Indian population.
- Recognize implications for practice for clinicians caring for AI population.
BACKGROUND

Asian Indians

- The fastest growing minorities in the United States (U.S. Census, 2010)
- Largest subgroup of Asians known as South Asians
- Trace origin of birth by ancestors born or who are natives of India
  - Widely interchangeable terms: Indian, South Asians, Indo-American, Indian-American
BACKGROUND

- WHO predicts Mortality will exceed 2.4 million in Ais in 2020
- Heart Disease rate 2-4 times higher than other ethnic groups
- One in four cardiac patients in the world will be an AI
- Heart Disease rate is four-fold than Americans (Enas, 2005)

BACKGROUND

- Heart Disease occurs prematurely in AI (Enas, 2008)
- Heart disease occurs 5-10 years earlier (Enas & Senthilkumar, 2002)
- Heart Disease - leading cause of death in AI’s (AHA, 2006)
- First attack usually occurring before their 40\textsuperscript{th} birthday (Enas & Senthilkumar, 2002)
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 I, Armstrong MA, Sidney, 1994

- The risk is even higher among children and grandchildren of AI immigrants due to adoption of Western lifestyle.
  (Enas, 2005)

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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

- AHA Identified the following:
  - Major cause of death among Asian/Pacific Islander (API)
  - In 2008, CAD deaths for API: Males 33.2%, females 34.4%. Estimated prevalence for Asian Indians 3.9%
  - 2010 Census: 14.5 million Asians in the US, with AI second largest group population 2.6 million
  - National data on the incidence of CAD among AI is unavailable

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?
**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

- Quantitative studies on the risk factors of AI to CAD
- No randomized controlled trials (RCTs)
- Observational design (cohort, case-control), and descriptive surveys.
**Exclusion Criteria**

Non-research based text:
- Reports
- Expert opinion papers
- Narratives
- Commentaries

Studies with a primary focus on:
- Participants from other countries in South Asia (Pakistan, Bangladesh and Sri Lanka) other than India

Studies on:
- AI children, cerebrovascular disease, TIA, PVD, CHF, and cardiac arrhythmias
SEARCH STRATEGY

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

Pub Med and CINAHL (limited search) to identify key terms in the title, abstract, and keywords of any relevant articles.

Medline, Health Stream, Science Direct, Dissertation Abstracts International, DARE, Psycho Info, Biomed Central, and ISI Current Contents and Web of Science (Extensive search)

Reference list and bibliographies of retrieved articles/additional relevant studies
INITIAL KEYWORDS AND PHRASES

- Coronary artery disease
- Coronary heart disease
- Screening
- Prevalence
- Indian Americans
- Asian Americans
- Risk factors
- Heart disease
- South Asians
- Asian Indians
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

Relevance assessed based on title, abstract, & MeSH terms

Full report from studies meeting the inclusion criteria

Two reviewers plus an associate reviewer assessed the studies
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

45 included studies

14 case-control studies
13 cohort studies
18 descriptive studies

Country study was conducted:

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

Meta-analysis was performed using the JBI-MAStARI software.

A fixed and random effect model chosen due to the variability in the interventions.

Chi square statistic, with $p < 0.01$ showing statistically significant heterogeneity.
# Modifiable Risk Factors: Hypertension

## Results

**HTN not prevalent among AI with CAD**

<table>
<thead>
<tr>
<th>Study</th>
<th>DerSimonian &amp; Laird Relative Risk (Risk Ratio)</th>
<th>Weight (CI 95% Random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maitra, A. et al (2009)</td>
<td></td>
<td>18.05% 5.68 (3.43,9.40)</td>
</tr>
<tr>
<td>Vinukonda, G., Mohammad, N.S., Jain, J.N, Ch...</td>
<td></td>
<td>17.45% 2.77 (1.56,4.92)</td>
</tr>
<tr>
<td>Gambhir, J., Kaur, H., Prabh, K., Morrisett, J. a...</td>
<td></td>
<td>14.32% 4.95 (1.98,12.37)</td>
</tr>
<tr>
<td>Goel, P.K. et al (2003)</td>
<td></td>
<td>20.14% 1.12 (0.97,1.29)</td>
</tr>
<tr>
<td>Mukherjee, M., Brouilette, S., Stevens, S. &amp;am...</td>
<td></td>
<td>19.61% 1.98 (1.51,2.60)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td>100.00% 3.10 (1.64,5.87)</td>
</tr>
</tbody>
</table>

Overall Z=3.48, P=0.0006

Heterogeneity Chi squared=73.82, P=0.0

Results (p<0.0006, chi-square 73.82)
**Modifiable Risk Factors: Hypertension**

<table>
<thead>
<tr>
<th>Study</th>
<th>DerSimonian &amp; Laird Relative Risk (Risk Ratio)</th>
<th>Weight (CI 95% Random)</th>
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</thead>
<tbody>
<tr>
<td>Liem, S.S. et al. (2009)</td>
<td></td>
<td>14.7% 1.21 (1.05,1.38)</td>
</tr>
<tr>
<td>Ye, J., Rust, G., Baltrus, P. and Daniels, E. (200__)</td>
<td></td>
<td>13.97% 0.83 (0.34,0.55)</td>
</tr>
<tr>
<td>Beithola, R., et al. (2010)</td>
<td></td>
<td>13.87% 1.63 (1.26,2.12)</td>
</tr>
<tr>
<td>Williams, E.D., Stamataki, E., Chandola, T., &amp;...</td>
<td></td>
<td>14.41% 1.06 (0.87,1.27)</td>
</tr>
<tr>
<td>Chambers et al. (2001)</td>
<td></td>
<td>14.33% 1.72 (1.40,2.10)</td>
</tr>
<tr>
<td>Vallapuri, S., Gupta, D., Tahwar, K., Billie, M., ...</td>
<td></td>
<td>14.43% 1.11 (0.92,1.34)</td>
</tr>
<tr>
<td>Chambers, J.C. et al. (2000)</td>
<td></td>
<td>14.13% 2.30 (1.87,2.83)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>100.00% 1.22 (0.86,1.22)</td>
</tr>
</tbody>
</table>

Favours Treatment: 0.0
Favours Control: 1.0

Overall Z=1.13, P=0.2628
Heterogeneity Chi squared=129.30, P=0.0

7 pooled studies

p=0.1236, chi-square 147.26

Non-AI found to be more hypertensive than AI
Modifiable risk factors: Total Cholesterol

<table>
<thead>
<tr>
<th>Study</th>
<th>DerSimonian &amp; Laird WMD</th>
<th>Weight (CI 95% Random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramachandran, A, et al. (2001)</td>
<td>1.03% 0.30 (0.09,0.51)</td>
<td></td>
</tr>
<tr>
<td>Mohan, V, Deepa, R, Rani, S, and Premalath...</td>
<td>31.42% 0.82 (0.53,1.11)</td>
<td></td>
</tr>
<tr>
<td>Gambhir, J, Kaur, H, Prabhi, K, Morrisett, J, a...</td>
<td>11.0% 1.40 (4.64,23.56)</td>
<td></td>
</tr>
<tr>
<td>Mukherjee, M, Brouillette, S, Stevens, S, &amp;an...</td>
<td>31.86% 0.10 (-0.10,0.30)</td>
<td></td>
</tr>
<tr>
<td>Hoogeveen, R, et al (2001)</td>
<td>0.48% 31.60 (17.26,45.94)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>100.00% 1.50 (0.50,2.50)</td>
<td></td>
</tr>
<tr>
<td>Favours Treatment 6-1.0</td>
<td>0.0</td>
<td>61.0Favours Control</td>
</tr>
<tr>
<td>Overall Z=2.95, P=0.0032</td>
<td></td>
<td>Heterogeneity Chi squared=125.44, P=0.0</td>
</tr>
</tbody>
</table>

6 pooled studies (chi-square 123.44, p<0.0001)

No significance between the two groups
**Modifiable Risk Factors: LDL Cholesterol**

**CAD vs. non-CAD group**

6 pooled studies

Chi-square 105.5, p< 0.0001

Meta-analysis showed significant heterogeneity
**Modifiable risk factors: Diabetes**

- AI more likely to be diabetic (OR=2.27, 95% CI=1.633.20) (Ye, Rust, Baltrus & Daniels 2009).
- Prevalence of diabetes was higher (Tewari et al, 2005).
- AI More hyperglycemic than Europeans leading to an impaired CV autonomic function and an increased CAD risk (Bathula et al. 2010).


MODIFIABLE RISK FACTORS:

DIABETES

Pooling of seven studies comparing AI (n=4638) and non-AI (n=89398) showed that diabetes was prevalent more in the non-AI group (χ²=101.95, p=0.0004).

DIABETES

Overall: 24.3%, p<0.001

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MODIFIABLE RISK FACTORS: BMI

- 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/m\(^2\) (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/m\(^2\) to define overweight in AI (Mohan et al, 2001)

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 (41-55yrs) 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)

**Modifiable Risk Factors: Alcohol**

<table>
<thead>
<tr>
<th>Impact of alcohol on CAD: Compared between Alcohol users and life time abstainers</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP, FBS, HDL-C higher, and tobacco use higher in alcohol users</td>
</tr>
</tbody>
</table>

(Roy et al; 2010)

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MODIFIABLE RISK FACTORS: PHYSICAL INACTIVITY

AI were physically inactive than Whites (OR=1.50, 95% CI=1.22-1.84, p=0.04)
(Ye et al., 2009)

AI were more physically inactive than Whites (47% vs. 28.1% p<0.001), which contributed to their excess CAD mortality
(Williams, Stamatakis, Chandola & Harner, 2010).

Level of physical activity measured was low in the CAD group (p=0.0006).
(Rastogi et al. 2004)

MODIFIABLE RISK FACTORS:
Diet

- 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)

MODIFIABLE RISK FACTORS: URBANIZATION AND MIGRATION

BMI, blood pressure, serum cholesterol, and triglycerides were higher in migrant Asian Indians (95%CI were $\geq 6.6 - 13.1$ higher).

(Patel et al 2010).

**Non-modifiable Risk Factors: Genetics**

- 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).

<table>
<thead>
<tr>
<th>APOA1</th>
<th>75G&gt;A and +83C&gt;T SNPs</th>
<th>APOC3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sac1 SNP and the APOA5</td>
<td>S19W SNP in the Apol11q gene cluster</td>
<td></td>
</tr>
</tbody>
</table>

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**References**


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) (Mukerjee, Brouilette, 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)

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).

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)
Non-modifiable Risk factors: Age

- 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

**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 \((\text{Chambers et al; 2000})\)
- Elevated level was found to increase the risk of CAD \((95\% \text{CI}: 1.93-10.82)\).
- 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 \((\text{OR: 1.96, 95\% CI: 1.06-3.61})\) and GCPIIC1561T \((\text{OR: 2.09, 95\% CI: 1.09-3.97})\), were found to be associated with risk for CAD \((\text{Vinukonda et al. 2007})\)
Emerging Risk Factors: Adiponectin

- 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).
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) (Geetanjali et al, 2003)
EMERGING RISK FACTORS: C-REACTIVE PROTEIN

- CRP to be strongly associated with CAD (OR: 1.649, p=0.040) and diabetes (OR: 2.264, p=0.008) (Mohan, Deepa, Velmurugan, & Premalatha, 2005)
- AI also had significantly higher concentration of hs-CRP which might have contributed to their increased for CAD (Chandalia et al, 2003).
- CRP concentrations were higher in healthy AI which was associated to greater central obesity (BMI <25 kg/m², p = 0.001), and insulin resistance in AI (p = 0.001).


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)
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 FACTORS

- Alcohol not cardio-protective
- Physical inactivity
- Lower concentration of omega-3 Fatty acids
- Lower levels of Vitamin B12
- Migration & Urbanization
SUMMARY: NON-MODIFIABLE RISK FACTORS

- 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.
- 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 has 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 AND IMPLICATIONS FOR PRACTICE

- CAD occurs at a younger age in AI than other ethnic groups.
- Findings for this study can be utilized in identification of early screening guidelines for AI population.
- Culturally appropriate strategies to reduce CAD risk should be put in place.
- Increase awareness of AI risk through education to decrease the growing epidemic.
IMPLICATIONS FOR RESEARCH

- Establishment of screening guidelines for CAD risk factors in AI population need to be further explored.
- Randomized controlled trials on the effective screening and prevention strategies should be instituted.
- Further research on effective programs aimed at educating the public related to this epidemic should be considered.


