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Review article

# Coronary heart disease in Indian Asians

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## ABSTRACT

The Indian Asian population accounts for a fifth of all global deaths from coronary heart disease (CHD). CHD deaths on the Indian subcontinent have doubled since 1990, and are predicted to rise a further 50% by 2030. Reasons underlying the increased CHD mortality among Indian Asians remain unknown. Although conventional cardiovascular risk factors contribute to CHD in Indian Asians as in other populations, these do not account for their increased risk. Type-2 diabetes, insulin resistance and related metabolic disturbances are more prevalent amongst Indian Asians than Europeans, and have been proposed as major determinants of higher CHD risk among Indian Asians. However, this view is not supported by prospective data. Genome-wide association studies have not identified differences in allele frequencies or effect sizes in known loci to explain the increased CHD risk in Indian Asians. Limited knowledge of mechanisms underlying higher CHD risk amongst Indian Asians presents a major obstacle to reducing the burden of CHD in this population. Systems biology approaches such as genomics, epigenomics, metabolomics and transcriptomics, provide a non-biased approach for discovery of novel biomarkers and disease pathways underlying CHD. Incorporation of these 'omic' approaches in prospective Indian Asian cohorts such as the London Life Sciences Population Study (LOLIPOP) provide an exciting opportunity for the identification of new risk factors underlying CHD in this high risk population.

*Keywords:* Coronary heart disease, Indian Asian, LOLIPOP, genome, epigenome, metabolome, GWAS

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## INTRODUCTION

Coronary heart disease is the leading cause of death worldwide, responsible for over 7 million deaths annually. Indian Asians (people originating from India, Pakistan, Bangladesh and Sri Lanka) comprise one quarter of the globe's population and are at high risk of developing CHD. Recent estimates from the Global Burden of Disease (GBD) 2010 Study[1] indicate that CHD deaths are highest in South Asia, increasing by 87.8% between 1990 and 2010, second only to East Asia (Table 1). This is predicted to increase a further 50% by 2030.[2] CHD prevalence is presently twice as high in urban compared to rural India (10–12% vs. 4–5%).[3,4] With CHD rates increasing more quickly in urban vs. rural areas (Figure 1), and compounded by the current rapid rate of urbanization in India,[5] this may result in an underestimation of CHD mortality projections. India experiences amongst the highest number of potentially productive life years lost due to cardiovascular disease; 9.2 million years in 2000, expected to double to 17.9 million years by 2030.[6] The World Health Organisation estimated that India lost 8.7 billion US dollars in national income due to combined mortality from CHD, stroke and diabetes in 2005.[7]

### Epidemiology of CHD in Indian Asians

High CHD mortality rates have also been reported in migrant Indian Asian populations in England and Wales,[8,9] the United States,[10,11] Canada,[12,13] Singapore,[14,15] Mauritius,[16,17] South Africa,[18] and Trinidad[19] (Table 2). In the UK, Indian Asians have ~2-fold higher CHD mortality compared to Europeans. Overall CHD mortality rates have fallen in most minority ethnic groups residing in England and Wales since 1980,[8] including those born on the Indian subcontinent. Importantly, increasing mortality rate ratio figures for Indian Asians compared to Europeans suggest that the overall observed decline in CHD mortality is slower amongst UK Indian Asian populations (Table 3).

Conventional CHD risk factors are known to have a pivotal role in CHD in all populations, including Indian Asians (Table 4). INTERHEART, a case-control study of 15,152 first myocardial infarction cases and 14,820 controls recruited from 52 countries[20] (including 2,171 Indian Asian cases and 2,573 controls), compared hazard ratios and population-attributable risk fractions (PAR) for major CHD risk factors (smoking, hypertension, diabetes, central obesity, dyslipidaemia, physical activity level, psychosocial factors, alcohol, fruit and vegetable consumption). In the INTERHEART study, these nine modifiable risk factors collectively account for ~88% of CHD in Indian Asians, similar to other populations (Table 5). INTERHEART was not designed to address reasons underlying differences in CHD risk between population groups.

**Table 1. Number of CHD deaths in different regions (% change in number of deaths from previous available total). Data derived from GBD 2010.[1] GBD definition of countries in South Asia comprises Afghanistan, Bangladesh, Bhutan, India, Nepal and Pakistan. East Asia comprises China, North Korea, and Taiwan.**

| Region | 1990 | 2010 | % change |
|---|---|---|---|
| Asia | | | |
| East Asia | 472,158 | 992,163 | +110.1% |
| South Asia | 704,833 | 1,323,551 | +87.8% |
| South East Asia | 215,719 | 383,323 | +77.7% |
| Asia Pacific, High-income | 113,347 | 166,853 | +47.2% |
| Central Asia | 138,157 | 184,167 | +33.3% |
| Australasia | 42,128 | 37,738 | −10.4% |
| Europe | | | |
| Eastern Europe | 834,783 | 1,115,213 | +33.6% |
| Central Europe | 331,497 | 344,139 | +3.8% |
| Western Europe | 929,366 | 745,590 | −19.8% |
| Africa | | | |
| North Africa & Middle East | 263,978 | 418,019 | +58.4% |
| Sub-Saharan Africa | 144,713 | 217,397 | +50.2% |
| America | | | |
| South America | 275,187 | 422,584 | +53.6% |
| North America, High-income | 703,057 | 619,377 | −11.9% |
| Others | | | |
| Oceania | 2,552 | 4,581 | +79.5% |
| Caribbean | 40,315 | 54,576 | +35.4% |
| Global | 5,211,790 | 7,029,270 | +34.9% |

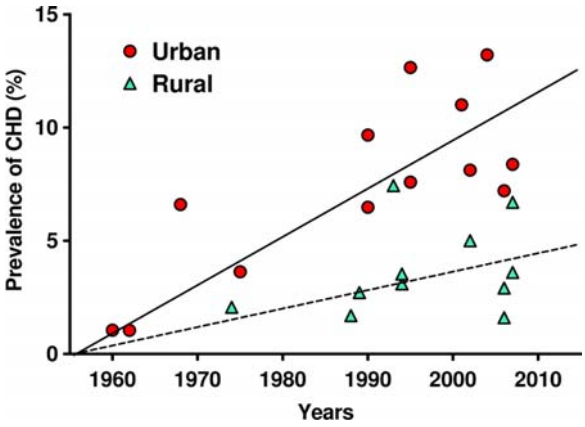


**Figure 1. Secular trends in the prevalence of coronary heart disease in rural and urban India (adapted from Gupta et al.[3]).**

Previous studies showed that the differences in prevalence of smoking, hypertension, and dyslipidaemia were not consistently pointing to higher risk amongst UK Indian Asian sub-groups compared to Europeans. These studies argued that conventional risk factors did not explain the ~40% excess CHD mortality among Indian Asians.[21,22] In contrast, type-2 diabetes (T2D), insulin resistance and related metabolic disturbances (i.e. high triglycerides, low high-density lipoprotein cholesterol, central obesity) were found to be more prevalent amongst Indian Asians than Europeans[23]; in multivariate regression models, insulin resistance accounted for ~70% of the excess risk of major Q waves (representing CHD mortality risk) in Indian Asians compared to Europeans.[23] Most previous studies amongst Indian Asians have been either cross-sectional or case-control in design and hence the contribution of risk factors to incident CHD has not been possible to assess in this population. Thus reasons underlying the excess risk of CHD amongst Indian Asians compared to Europeans, and other population groups, remain poorly understood.

The Southall and Brent Revisited (SABRE) Study was a prospective comparison of CHD mortality among UK Indian Asian and European men[24] ($n$ = 1,420 and 1,787 respectively). SABRE confirmed a ~2-fold excess CHD risk amongst Indian Asian men, which persisted after adjustment for CHD risk factors including obesity, diabetes, insulin resistance, blood lipids, blood pressure and smoking (Table 6). These prospective data do not support the widely held view that the excess CHD risk amongst Indian Asians compared to Europeans is largely attributable to central adiposity, insulin resistance or diabetes. However, SABRE did not investigate the role of diet, physical activity, or genetic risk factors and did not study women.

The LOLIPOP study was established to investigate the reasons underlying higher susceptibility among Indian Asians to diabetes and cardiovascular disease, compared to Europeans. LOLIPOP is a prospective cohort of ~24,000 Indian Asian and European men and women. Participants were recruited from the lists of local General Practitioners, thus providing a representative sample of the population living in West London. Participants have had detailed clinical cardiovascular (including 12-lead electrocardiogram) and biochemical characterisation, with assessment of diet and physical

**Table 2. Age-standardised CHD mortality (per 100,000) for populations in different countries over the listed period.**

| Country | Malaysia | | South Africa | | Canada | | Singapore | | England & Wales | |
|---|---|---|---|---|---|---|---|---|---|---|
| Period | 1968–1993 | | 1989 | | 1989–1993 | | 1991–1999 | | 1999–2003 | |
| Population | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female |
| Indian Asian | 367 | 74 | 226 | 113 | 247 | 120 | 165 | 73 | 242 | 84 |
| European | – | – | 139 | 55 | 260 | 90 | – | – | 133 | 39 |
| Chinese | 106 | 31 | – | – | 90 | 37 | 63 | 25 | – | – |
| Black | – | – | 11 | 8 | – | – | – | – | – | – |
| Malay | 142 | 33 | – | – | – | – | 128 | 71 | – | – |

**Table 3. Mortality rate ratios (95% confidence intervals) for UK Indian Asians (mortality rates for persons born in England and Wales taken as reference).[7]**

| Mortality Rate Ratios | 1979–1983 | 1989–1993 | 1999–2003 |
|---|---|---|---|
| India (male) | 1.40 (1.35–1.45) | 1.41 (1.36–1.45) | 1.44 (1.38–1.50) |
| Pakistan (male) | 1.14 (1.04–1.24) | 1.52 (1.43–1.60) | 1.93 (1.82–2.03) |
| Bangladesh (male) | 1.36 (1.14–1.58) | 1.69 (1.51–1.85) | 2.11 (1.90–2.31) |
| India (female) | 1.58 (1.47–1.68) | 1.71 (1.61–1.81) | 1.84 (1.72–1.95) |
| Pakistan (female) | 1.14 (0.85–1.42) | 1.33 (1.14–1.53) | 2.45 (2.21–2.68) |

activity. Blood samples have been stored for future analysis. Subsets of participants have genome-wide scans ($n \sim 20{,}000$), whole genome ($n \sim 400$) or whole exome sequencing ($n \sim 2{,}000$), metabolome-wide ($n \sim 15{,}000$) and epigenome-wide scans ($n \sim 3{,}300$).[25–27] A representative LOLIPOP sample of Indian Asians ($n \sim 1{,}000$) and Europeans ($n \sim 1{,}000$) have also had echocardiography,[28] 24hr blood pressure, 24hr holter monitor, cardiac computed tomography (calcium scores), carotid intima media thickness[29] (with plaque characterisation), to examine the role of subclinical risk factors to high rates of CHD in Indian Asians.

Characteristics of LOLIPOP participants are shown in Table 7. Indian Asians have a ~2-fold higher prevalence of CHD compared to Europeans which is evident at all age-groups (Figure 2). In multivariate regression analysis, the odds ratio (OR) for CHD was 2.11 (95% C.I. 1.86–2.40, $p < 0.001$) amongst Indian Asians compared to Europeans after adjustment for age, sex and conventional CHD risk factors (Table 8). After additional correction for insulin resistance, triglycerides and HDL cholesterol, a nearly 2-fold excess risk of CHD remained amongst Indian Asians compared to Europeans (OR 1.81, 95% C.I. 1.54–2.11, $p < 0.001$). LOLIPOP results therefore show that the higher risk of CHD amongst UK Indian Asians is not explained by conventional risk factors, insulin resistance and related metabolic disturbances.

LOLIPOP participants are completing ~10 year follow-up for cardiovascular events as well as other major health outcomes. Ascertainment of events is being carried out through a multi-faceted approach including events occurring in primary care, hospital events, face-to-face follow-up, and national mortality records. This effort is expected to yield in excess of 2,000 cardiovascular events, making it possible to conduct the first well-powered investigation into the role of established, emerging and novel risk factors to incident cardiovascular events amongst Indian Asians, and help identify the reasons underlying their excess of CHD risk compared to Europeans.

## Genomic, epigenomic and metabolomic approaches to identify novel CHD risk factors among Indian Asians

Studies in Indian Asian families show that cardiovascular risk factors are heritable.[30] Genome-wide association studies (GWAS) amongst Indian Asians and Europeans together identify a total of 51 single nucleotide polymorphisms (SNPs, from 45 loci) associated with CHD.[31–34] These individual variants each have a modest effect size, with odds ratios of 1.05–1.30 per risk allele copy, and in aggregate account for only a small proportion of the total predicted genetic variance. We have found no

**Table 4. Odds ratios for acute myocardial infarction in the INTERHEART study.[20]**

| Risk factor | South Asian* | Western European | Central & Eastern European | Overall |
|---|---|---|---|---|
| Smoking[#] | 2.43 | 1.96 | 1.92 | 2.27 |
| Hypertension[@] | 2.89 | 2.22 | 2.11 | 2.48 |
| Diabetes[@] | 2.48 | 4.29 | 2.61 | 3.08 |
| Central obesity[^] | 2.43 | 4.50 | 1.74 | 2.24 |
| Psychosocial factors[$] | 2.15 | 1.14 | 3.92 | 2.51 |
| ApoB/A1 ratio[&] | 3.81 | 3.76 | 2.20 | 3.87 |

* South Asian defined as persons from Bangladesh, India, Nepal, Pakistan or Sri Lanka.
[#] Includes current (individuals who smoked any tobacco in the previous 12 months) and former smokers.
^ Upper tertile vs. lowest tertile (waist-hip ratio of 0•90 and 0•95 in men and 0•83 and 0•90 in women used to divide participants into tertiles).
[$] A model-dependent index combining positive exposure to depression, perceived stress at home or work (general stress), low locus of control, and major life events, all referenced against non-exposure for all five factors
[&] ApoB/A1 ratio (top vs. lowest quintile).

**Table 5. Population attributable risk (%) for acute MI associated with nine modifiable risk factors amongst South Asians in INTERHEART.[20]**

| South Asians (Cases = 2,171, Controls = 2,573) | Population attributable risk | | |
|---|---|---|---|
| | All | Males | Females |
| Smoking (current or previous) | 37.4 | 42.0 | 7.1 |
| Fruits and Vegetables | 18.3 | 16.0 | 30.6 |
| Exercise[£] | 27.1 | 25.5 | 45.0 |
| Alcohol[#] | −5.5 | −5.7 | 26.0 |
| Hypertension* | 19.3 | 17.8 | 28.9 |
| Type-2 diabetes* | 11.8 | 10.5 | 20.5 |
| Central obesity | 37.7 | 36.0 | 48.7 |
| Psychosocial factors | 15.9 | 13.9 | 29.2 |
| ApoB/A1 ratio | 58.7 | 60.2 | 52.1 |
| All nine risk factors | 89.4 | 88.4 | 99.3 |

[£] Deemed physically active if participants were regularly involved in moderate (walking, cycling, or gardening) or strenuous exercise (jogging, football, and vigorous swimming) for ≥4 hours per week.
[#] Regular consumption defined as alcohol intake three or more times a week.
* Self-reported.

significant differences in either allele frequencies or odds ratios for these known CHD SNPs (discovered in Europeans) between Indian Asians and Europeans (Figure 3). Our results therefore imply that reported genetic variants thus far do not account for the increased risk of CHD amongst Indian Asians compared to Europeans. However, these findings do not exclude a role for genetic factors since the GWAS approach is not well designed to identify either low frequency or rare variants, which could make an important contribution to the "missing heritability".[35] Furthermore, the available GWAS arrays are based on HapMap data[36] from predominantly European populations and thus do not capture Indian Asian-specific genetic variation contributing to CHD. Previous studies provide evidence for population-specific genetic variation increasing susceptibility to cardiovascular disease in Indian Asians. A 25-base pair deletion in the gene encoding cardiac myosin binding protein C (MYBPC3), found in ~4% of the population of Indian Asian ancestry, but absent amongst Europeans, is associated with an ~7-fold increased risk of heart failure in Indian populations.[37]

The lack of a systematic catalogue of Indian Asian-specific genetic variation is a major limitation to the identification of the genetic factors contributing to CHD in this population, and underlies the strategy of whole genome (WGS) and whole exome sequencing (WES) amongst Indian Asians participating in the LOLIPOP study. The 1000 Genomes project is actively extending the catalogue of known human variants down to a frequency of ~1% through WGS of target populations. LOLIPOP has carried out WGS ($n \sim 400$) and WES ($n \sim 2{,}000$) in order to catalogue Indian Asian-specific genetic variation. Results of this effort will help in the design of future studies assessing the contribution of Indian Asian-specific variants (including low frequency and rare variants) to the excess risk of CHD amongst Indian Asians compared to Europeans.

**Table 6. CHD mortality amongst 1,420 Indian Asian and 1,787 European men participating in the SABRE study. Study period from 1988–2006.[24]**

| Risk factors[#] | Hazard ratio (95% CI) | *P* |
|---|---|---|
| Age | 1.82 (1.34–2.47) | <0.001 |
| Age + smoking + total cholesterol | 2.29 (1.63–3.23) | <0.001 |
| Age, smoking, total cholesterol + HDL cholesterol + systolic blood pressure + diabetes | 1.76 (1.23–2.51) | 0.002 |
| Age, smoking, total cholesterol + HDL cholesterol + systolic blood pressure + HOMA-IR | 1.90 (1.33–2.74) | <0.001 |
| Age, smoking, total cholesterol + component features of metabolic syndrome[#] | 1.88 (1.32–2.67) | <0.001 |
| Age, smoking, total cholesterol + composite definition of IDF metabolic syndrome* | 2.20 (1.54–3.14) | <0.001 |

[#] Metabolic syndrome components entered as continuous variables (waist circumference, HDL cholesterol, triglycerides, fasting glucose, systolic blood pressure).
* IDF metabolic syndrome definition: waist circumference ≥94 cm European men or ≥90 cm Indian Asian men, plus any 2 of the following 4 factors: (1) fasting glucose ≥5.6 mmol/l or previously diagnosed diabetes; (2) triglycerides ≥1.7 mmol/l or specific treatment for this lipid abnormality; (3) HDL-cholesterol < 1.03 mmol/l in men or specific treatment for this lipid abnormality; or (4) high blood pressure (≥130/≥85 mmHg, or antihypertensive medication use). All models adjusted for socio-economic status.

**Table 7. Clinical characteristics of LOLIPOP participants. Results presented as mean (standard deviation) or percentage.**

| | Indian Asians | Europeans | *P* |
|---|---|---|---|
| *n* | **16,774** | **7,032** | |
| Age (years) | 50.5 (11.2) | 52.3 (11.6) | <0.001 |
| Male (%) | 61.2 | 59.6 | 0.017 |
| Coronary heart disease (%) | 10.5 | 5.6 | <0.001 |
| Type-2 diabetes[#] (%) | 18.5 | 7.4 | <0.001 |
| History of hypertension (%) | 29.4 | 20.3 | <0.001 |
| Ever Smoked (%) | 18.7 | 57.2 | <0.001 |
| Fasting glucose (mmol/L) | 5.6 (1.6) | 5.2 (1.1) | <0.001 |
| Fasting insulin (mU/L) | 10.5 (9.8) | 7.6 (8.0) | <0.001 |
| HOMA-IR[$] | 2.6 (3.0) | 1.8 (2.2) | <0.001 |
| Body mass index (kg/m$^2$) | 27.0 (4.7) | 27.0 (5.3) | 0.190 |
| Waist-hip ratio | 0.94 (0.08) | 0.91 (0.08) | <0.001 |
| Total cholesterol (mmol/L) | 5.22 (1.08) | 5.43 (1.09) | <0.001 |
| HDL cholesterol (mmol/L) | 1.25 (0.33) | 1.39 (0.40) | <0.001 |
| LDL cholesterol (mmol/L) | 3.19 (0.90) | 3.34 (0.93) | <0.001 |
| Triglycerides (mmol/L) | 1.44 (1.00) | 1.25 (0.92) | <0.001 |

[#] Includes participants with undiagnosed type-2 diabetes
[$] Homeostatic model assessment – insulin resistance

Epigenetic factors which are known to alter gene function, but are not the result of changes in the DNA sequence,[38] are increasingly considered to have a role in susceptibility to cardiovascular disease. Epigenetic regulation of gene function is determined by reversible molecular processes such as histone binding of DNA and methylation at cytosine residues, both of which influence transcription factor binding and accessibility of DNA to the polymerase enzymes. The role of epigenetics is well established in cellular differentiation. More recent evidence suggests that epigenetic patterns of gene regulation may also occur in response to environmental insults, and underlie susceptibility to future disease. In the context of cardiovascular disease, several studies suggest that in utero or early life exposure to a poor nutritional environment may predispose to the development of cardiovascular disease in adult life. More than 96% of low birth-weight occurs in the developing world, with highest incidence in Indian Asians (7.1% of live births).[39] Birth cohort studies show that maternal undernutrition, low birth-weight, and rapid postnatal child growth are all associated with increased risk of CHD in the off-spring.[40,41] These risks appear to be trans-generational raising the possibility that epigenetic mechanisms may underlie part of the increased risk of cardiovascular disease amongst Indian Asians.[42]

Technological advances have enabled nuclear magnetic resonance (NMR) spectrometry to detect a wide variety of metabolites from dietary, gut microbial, and host metabolism sources in one analytical

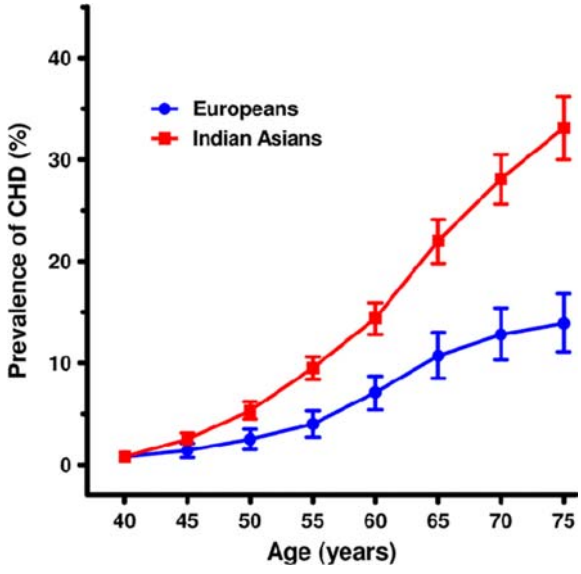


**Figure 2. Prevalence of coronary heart disease (95% confidence interval) amongst the 16,774 UK Indian Asian and 7,032 European participants in the LOLIPOP study.**

**Table 8. Multivariate regression analysis showing the odds ratio for coronary heart disease amongst Indian Asians compared to Europeans in the LOLIPOP study.**

| Model | Risk factors | Odds ratio Indian Asians vs. Europeans | P |
|---|---|---|---|
| A | Age + sex | 2.55 (2.26–2.87) | <0.001 |
| B | Model A + ever smoked + total cholesterol | 2.67 (2.33–3.06) | <0.001 |
| C | Model B + history of hypertension + type-2 diabetes | 2.23 (1.94–2.57) | <0.001 |
| D | Model C + body mass index + waist-hip ratio | 2.28 (1.97–2.63) | <0.001 |
| E | Model D + triglycerides + HDL cholesterol + HOMA-IR[#] | 1.81 (1.54–2.11) | <0.001 |

[#] Homeostatic model assessment – insulin resistance

sweep. Bioinformatic approaches now allow combined analysis of metabolic phenotypes with genomic, epigenomic, and transcriptomic markers providing greater insight into potential mechanisms underlying cardiovascular disorders.[43] The incorporation of these 'omic' markers (genomics, metabolomics and epigenomics) into the prospective LOLIPOP study design provides an exciting opportunity for discovery of novel risk factors and disease mechanisms underlying the excess risk of CHD amongst the Indian Asian population.

## Strategies to reduce CHD amongst Indian Asians

Reasons underlying the 2-fold increased CHD risk amongst Indian Asians compared to Europeans remain poorly understood. The high CHD rates amongst Indian Asians nevertheless necessitate urgent attention. Priorities should include optimal management of Indian Asians with established CHD, treatment of those with cardiovascular risk factors, and of first degree relatives of Indian Asians with premature CHD. Measures to improve education and management of cardiovascular risk factors in the population are also required. Healthcare organisations and professionals need awareness of the higher risk of CHD and adverse outcomes faced by Indian Asians. Comprehensive screening for cardiovascular risk factors such as diabetes, hypertension and dyslipidaemia needs to be targeted in this population. Of the available risk stratification tools, the Framingham Risk Score (FRS)[44] has been shown to underestimate CHD risk amongst Indian Asians thus limiting its usage. Modifications to improve FRS discrimination amongst Indian Asians have been suggested, such as multiplying the FRS by a factor of 1.4 (for males),[45] or adding 10 years to the patients age.[46] QRISK2[47] is a contemporary cardiovascular risk prediction tool developed and independently validated in UK populations.[48,49] The QRISK2 algorithm takes ethnicity and deprivation into account, and is continuously updated, but the study population is mainly Caucasian (~1% Indian Asian). QRISK2 has not been externally validated in Indian Asians.

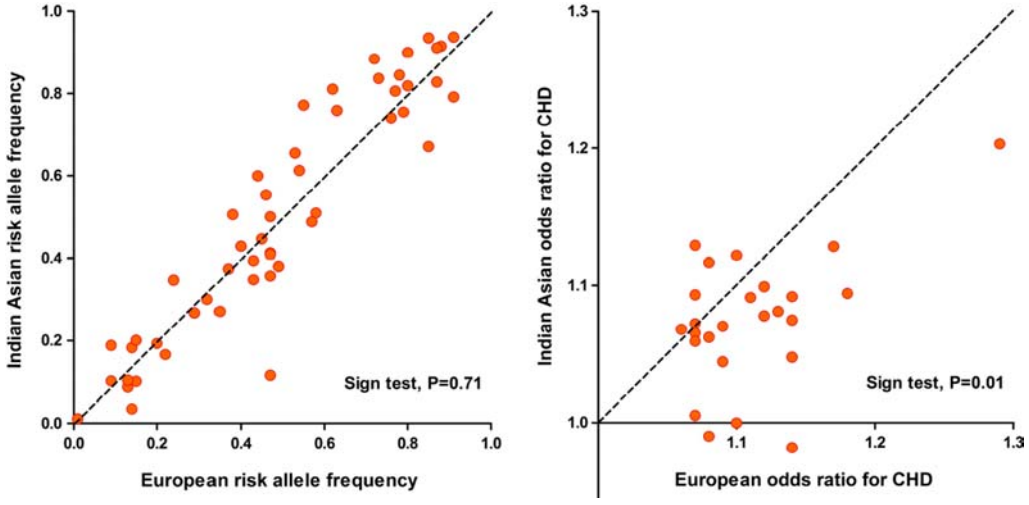


**Figure 3. Risk allele frequencies or effect sizes (odds ratio) of known CHD SNPs (n = 51*) in Indian Asians (LOLIPOP data) against Europeans (in published data).[32–34] *Effect sizes of known CHD SNPs in European populations available for only 26 variants; published odds ratios for other variants include Indian Asian data.**

Despite CHD being a major threat and huge public health challenge, it has attracted limited response from governments of the Indian Subcontinent. Only 1.1% of the Gross Domestic Product was spent on healthcare[50] in India (2008-9), lower than most other emerging economies. Major inequities based on gender, caste, geography, and social status persist.[50,51] Government funding and policymakers need to establish preventative strategies to reduce the burden of CHD and its risk factors. Additionally, major investment is required into research aimed at understanding increased susceptibility to CHD amongst Indian Asians.

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