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Review Article

Lipoprotein(a): An underrecognized genetic risk factor for malignant coronary artery disease in young Indians

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ABSTRACT

Malignant coronary artery disease (CAD) refers to a severe and extensive atherosclerotic process involving multiple coronary arteries in young individuals (aged <45 years in men and <50 years in women) with a low or no burden of established risk factors. Indians, in general, develop acute myocardial infarction (AMI) about 10 years earlier; AMI rates are threefold to fivefold higher in young Indians than in other populations. Although established CAD risk factors have a predictive value, they do not fully account for the excessive burden of CAD in young Indians. Lipoprotein(a) (Lp(a)) is increasingly recognized as the strongest known genetic risk factor for premature CAD, with high levels observed in Indians with malignant CAD. High Lp(a) levels confer a twofold to threefold risk of CAD—a risk similar to that of established risk factors, including diabetes. South Asians have the second highest Lp(a) levels and the highest risk of AMI from the elevated levels, more than double the risk observed in people of European descent. Approximately 25% of Indians and other South Asians have elevated Lp(a) levels (≥50 mg/dl), rendering Lp(a) a risk factor of great importance, similar to or surpassing diabetes. Lp(a) measurement is ready for clinical use and should be an essential part of all CAD research in Indians.

1. Introduction

Lipoproteins (in decreasing order of buoyancy chylomicrons, very low density, intermediate density, low density and high density) are complex aggregates of lipids and proteins that render the hydrophobic lipids (such as cholesterol and fatty acids) compatible with the aqueous environment of body fluids and enable their transport throughout the body. This trafficking function is important as cholesterol is essential for normal functioning of cells as it is a cell membrane constituent as well as a precursor of steroid hormones. Surface proteins called apoproteins (apolipoproteins) add to the structure, stability and solubility of lipoproteins.

Lipoprotein(a) (Lp(a)) is distinct from the other lipoproteins both structurally and metabolically. Lp(a) consists of a low-density lipoprotein (LDL)–like particle containing a specific highly polymorphic glycoprotein named apolipoprotein(a) (apo(a)) that is covalently bound via a disulfide bond to the apoB100 of the particle.

The apo(a) component of Lp(a) is proatherogenic and prothrombotic. Apo(a) binds to plasminogen-binding sites, blocking plasminogen from interacting with thromboplastin-activating factor (t-PA), thus preventing cleavage of plasminogen to plasmin and clot dissolution. Lp(a) also interferes with the plasmin-binding sites on the clots. Lp(a) has multiple other effects as well: It stimulates the production of plasminogen activator inhibitor-1 (PAI-1), leading to a reduced ability of t-PA to activate clot dissolution. Increased PAI-1 also leads to enhanced proinflammatory events by activating monocyte adhesion to the vessel wall. Lp(a) also modulates platelet

Abbreviations: ACS, acute coronary syndrome; AMI, acute myocardial infarction; ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CVD, cardiovascular disease; GBD, global burden of disease; Lp(a), lipoprotein(a); LOLIPOPS, Lessons from the London Life Sciences Population Study; MACE, major acute cardiovascular events; MASALA, The Mediators of Atherosclerosis in South Asians Living in America; MR, Mendelian randomization; MRR, mortality rate ratio; MVD, multivessel disease; NHLBI, National Heart, Lung, and Blood Institute; OR, odds ratio; TVD, triple-vessel disease; SMR, Standardized mortality ratio.

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activation by interfering with the interaction of platelets with exposed collagen fibers in the injured vessel wall. Lp(a) is shown to stimulate smooth muscle cell (SMC) growth through inactivation of transforming growth factor-β (TGF-β). Activated TGF-β inhibits the proliferation and migration of the SMC setting and accelerates the process of blood vessel stenosis.[1–3]

More information on Lp(a) including genetic and clinical implications was presented in our recent extensive review.[1] In whites (people of European descent), there was a consistent relationship of Lp(a) levels with coronary artery disease (CAD) and acute myocardial infarction (AMI) risk starting at ~20–30 mg/dl; the risk increases as the Lp(a) level increases.[3] Among people of various ethnic origins, both Lp(a) level and CAD risk imparted by Lp(a) vary markedly from that of the white population.[4]

In this review, as the title indicates, our focus is on malignant CAD in young Indians.[5–7] To provide context, we briefly discuss the magnitude of CAD burden in Indians globally and present evidence for the pathogenic role of Lp(a) in this population with the highest risk of CAD.[8–11] We propose that Lp(a) merits recognition as an atherosclerotic cardiovascular disease (ASCVD) risk factor of major importance similar to diabetes in Indians.

South Asians comprise the largest ethnic group, numbering 1.9 billion people in the world including 3.9 million in the United States (US).[10] The term South Asians refers to people with ancestral origin from the Indian subcontinent—primarily India, Pakistan, Bangladesh, and Sri Lanka. Most studies conducted outside the subcontinent have aggregated South Asians as a group; obviously, the studies within India were conducted exclusively on Indians. While this review focuses on Indians, most statements and conclusions are equally applicable to all South Asians and the terms are used interchangeably.

2. CAD burden on Indians

2.1. Epidemiology of CAD in the Indian diaspora

The CAD rates among immigrants, in general, are intermediate between those of their country of origin and the host country; the rates ultimately blend with the prevalent rates of the adopted country after two or three successive generations, depending on the degree and speed of acculturation in conjunction with the prevailing rates for the respective countries.[12] Indians (and other South Asians) are a singular exception to this rule, in that they have higher rates of CAD than the dominant population of the adopted country—a fact that raises the possibility of a genetic risk factor with a high prevalence.[12]

The epidemiology of CAD in Indians (particularly, the young), the pioneering researchers, and the countries where the studies were conducted are chronologically depicted in Table 1.[3–5,9,13–28] The earliest reports of high rates of CAD in Indians were based on >10,000 autopsies in the 1950s that showed a 7- to 20-fold higher rate of coronary atherosclerosis compared to the Chinese in Singapore.[13,29] The incidence,[16,22,30–32] prevalence,[23,33] and mortality,[14,19,34,35] from premature CAD, in Indians and other South Asians have been among the highest reported for any ethnic group in countries as diverse as the US,[36] United Kingdom (UK),[19,32,37] France,[37] Denmark,[37] Canada,[38,39] Qatar,[40] Malaysia,[41] Singapore,[14,42] Mauritius,[43] Italy,[44] South Africa,[45] Fiji, and Trinidad.[17] In the US, the age-adjusted CAD mortality in Indians when compared to whites is lower but the proportionate mortality rates are higher (43% higher in Indian men and 12% higher in Indian women).[46] The prevalence of CAD is 89%–300% higher among Indian men than among whites in the US.[23] The approximately twofold higher mortality rate ratios (MRRs) for South Asian men and women for CAD and stroke compared to native white populations in European countries are shown in Table 2.[37] The CAD mortality rates have been declining in the Indian diaspora, but the rate of decline is slower than the rates for those born in the UK, so that the MRR for CAD for the Indian diaspora has shown an increase over the years.[22,47,48] Many studies confirm a higher morbidity and mortality in South Asians than in whites following AMI, percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG) surgery.[49–51] Of note, the all-cause mortality among Indians is similar to whites, and this is attributed to high CAD mortality that is balanced by low rates of cancer deaths.[52–54]

2.2. Epidemiology and burden of CAD and CVD in India

India is experiencing an escalating epidemic of CAD and CVD.[55] The contribution of CVD to total deaths and disease burden in India has almost doubled since 1990. In 2016, an estimated 2.8 million Indians died from CVD.[56] Overall, CVD contributed to 28% of the total deaths in India in 2016, compared to 15% in 1990.[56] The CVD spectrum among Indians is similar to Caucasians (CAD deaths >2 times stroke deaths) and unlike that of other Asians (stroke deaths >2 times CAD deaths).[12,56,57] The burden of CVD varies markedly within India, with Kerala, Punjab, and Tamil Nadu having the highest prevalence of CAD, high cholesterol, and high blood pressure.[55] CVD has now become the leading cause of mortality in all parts of India, including the poorer states and rural areas.[55] The prevalence of CAD has increased sevenfold in urban India and fourfold in rural areas between 1970 and 2013, with a current prevalence of 14% in the urban and 7% in the rural populations.[34] The number of patients with CAD also increased to 24 million in 2016. CAD was the leading cause of deaths (18% of all deaths), while stroke was the fifth leading cause (7% of total deaths) in India in 2016.[55] The latest data from the Million Death Study indicate that age-standardized CAD mortality rates in rural areas have surpassed those in urban areas in men (255 *vs* 234 per 100,000) and women (135 *vs* 127).[56]

The age-standardized CVD mortality in India, compared to the U.S, is significantly higher for men (325/100,000 *vs* 190/100,000) and women (225/100,000 *vs* 140/100,000).[34] This is also true in the UK.[19] India currently has the highest burden of acute coronary syndrome (ACS) and ST elevation MI (STEMI) in the world.[56] STEMI is the common form of presentation accounting for two-thirds of all AMI in India *vs* one-third in the US.[34,35,57] Pakistan and Bangladesh have also reported very high rates of CAD.[58–60] Recent estimates from the global burden of disease (GBD) study shows that between 1990 and 2010, CAD mortality in South Asia increased by 88% compared to a 35% decline globally.[61] The number of CAD deaths in South Asia is predicted to increase by another 50% by 2030, unless aggressive preventive efforts are undertaken.[62]

2.3. Premature CVD deaths in Indians

In terms of societal and economic loss, the goal of preventive medicine is the prevention of death before its “natural time” so that the individual can contribute maximally to society. The GBD task force has defined premature CVD mortality as CVD deaths occurring in people aged <70 years.[63] Globally, there were 5.9 million premature CVD deaths in 2013, which is projected to increase to 7.8 million by 2025, reflecting a 32% increase.[63] In the Million Death Study, 62% of all CVD deaths in India were premature deaths,[56] whereas a GBD study determined this proportion to be 54%.[55]

Table 1
Coronary artery disease in Indians: a global chronology of research contributions.

Year	Author	Contributing countries
		Singapore
1959	Danaraj, T.J.[13]	The very first large autopsy study shows 7× higher CAD rates in Indians than Chinese.
1990	Hughes, K.[14]	Indians have threefold higher incidence and mortality from CAD *vs* the Chinese.
1996	Low, P.S.[15]	Ethnic differences in plasma Lp(a) levels in the umbilical cord are concordant with adult CAD mortality differences between Indians and Chinese.
2000	Heng, D.M.[16]	Threefold higher CAD incidence in Indians compared to the Chinese persists over decades.
		Trinidad
1989	Miller, G.J[17]	Indians have double the incidence and mortality from CAD compared with whites (after adjusting for established risk factors, insulin resistance, and glucose intolerance).
		United Kingdom
1989	Hughes, L.O[18]	Higher incidence and early onset of CAD with South Asians aged <40 years having 5 times greater AMI than age-matched whites.
1991	Balarajan, R[19]	Increasing SMR for CAD with decreasing age in South Asians; compared to whites, the SMR for CAD was double at age <40 years and triple at age <30 years.
1992	Mckeigue, P[20]	Insulin resistance hypothesis is proposed as the unifying explanation for the high rates of both diabetes and CAD in South Asians.
2006	Forouhi, N[21]	Large prospective studies, especially the LOLIPOPS, show that South Asians have double the risk of CAD
2014	Tan, S.T[22]	after adjusting for established risk factors, insulin resistance, diabetes, and even socioeconomic status.
		United States
1995	Enas, E.A[5]	Indians develop malignant CAD at a young age, despite a lower prevalence of established risk factors (the Indian Paradox), except for diabetes.
1996	Enas, E.A[23]	3–4× higher prevalence of CAD among Indian physicians compared to whites.
1997	Enas, E.A[24]	Elevated Lp(a) provides a genetic predisposition premature CAD in Indians.
2000	Enas, E.A[9]	The high rates of CAD first observed in the Indian diaspora extend to those living in the Indian subcontinent—the latter having worse disease and outcome.
2007	Enas, E.A[25]	A highly atherogenic South Asian dyslipidemia plays a more important role for than diabetes for CAD in Indians.
2018	Tsimikas, S[3]	25% of South Asians have elevated Lp(a) levels in the atherothrombotic range.
		Canada and India
2000	Anand, S[26]	South Asians have more of the emerging CAD risk factors (fibrinogen, homocysteine, Lp(a), and plasminogen activator inhibitor-1) possibly contributing to their heightened risk of CAD
2004	Yusuf, S[27]	The PAR from abnormal lipids to AMI is 5 times greater than diabetes (49% versus 10%) across the globe.
2007	Joshi, P[28]	The PAR from abnormal lipids to AMI is 4 times greater than diabetes (49% versus 12%) for South Asians.
2018	Pare, G[4]	The INTERHEART Lp(a) study (n = 12,943 involving 7 largest ethnic groups) shows that South Asians have the highest risk of AMI from elevated Lp(a) and the second highest level of Lp(a).

AMI = acute myocardial infarction; CAD = coronary artery disease; Lp(a) = lipoprotein(a); LOLIPOPS = London Life Sciences Population study; PAR = population-attributable risk; SMR = standardized mortality rate.
Ref 3–5,9,13–28.

Table 2
Mortality rate ratio for CVD, CAD, and stroke in South Asians compared to whites (designated as 1) in selected European countries.

	CVD			CAD			Stroke		
	M + F	M	F	M + F	M	F	M + F	M	F
England	1.44	1.4	1.5	1.63	1.5	1.9	1.53	1.6	1.6
France	1.37	1.2	1.5	1.62	1.5	1.8	2.03	2.0	2.1
Denmark	1.91	2.2	1.1	2.02	2.4	0.9	1.90	2.4	1.1

CAD = coronary artery disease; CVD cardiovascular disease; F = female; M = male.
Ref 37.

South Asia's share of global premature CVD deaths is projected to increase from 29% in 2013 to 33% by 2025.[63]

3. Malignant CAD in young Indians

Indians are particularly susceptible to premature CAD leading to AMI at an earlier age.[5,9,64] In a study of 877 patients with angiographically documented CAD in India, more than one-half of patients were <55 years and one-third were <45 years, with a mean age of 48 years.[65] Despite the young age, multivessel disease (MVD) which includes double-vessel disease (DVD), three-vessel disease (TVD), and left main disease was found in 79% of patients. Additionally, coronary atherosclerosis was generally diffuse with multiple sites of obstruction in most vessels.[65] In another large Indian study, the median age of CABG surgery was 60 years; 6% of CABG was performed in those aged <45 years.[66]

3.1. Extreme prematurity

'Malignant CAD' is a term coined by Enas and Mehta[5] in 1995, wherein they highlighted the unique features of CAD in young Indians. CAD in Indians can be classified into 3 types as shown in Table 3.[5–7] The excess burden of CAD in Indians is largely due to type 1 and to a lesser extent type III but does not relate to type II CAD. The 3 hallmarks of malignant CAD in Indians are (1) extreme prematurity, (2) extreme severity, and (3) high mortality at a young age. A notable element, that can be considered the fourth feature of malignant CAD, is that established risk factors are at low levels or absent.

CAD in young people (aged <45 years in men and <50 years in women) is strikingly more common in Indians—10% to 15% of all CAD—compared to 2%–5% reported in Western populations.[18,67] The incidence of ACS among young Indians is 5 times higher than that in whites in the UK,[18] 4 times higher than that in Italians,[44] and 13 times higher than that in the Chinese in Singapore.[68] Indians accounted for 56% of CAD in the young in Malaysia[41] and 71% in Qatar.[40] Among all patients with ACS, those aged <45 years account for 2–3% among whites,[69–71] but is as high as 10–15% in India.[27,72]

Table 3
Classification of coronary artery disease in Indians based on characteristics.

Type I or malignant CAD
- Extremely premature with clinical manifestations, <45 years of age in men, <50 years in women.
- Often presents as acute myocardial infarction rather than as stable angina.
- Low prevalence of established risk factors: diabetes, hypertension, high cholesterol; but tobacco use often high in men.
- High prevalence of family history of premature CAD or sudden death.
- High prevalence of elevated lipoprotein(a), homocysteine, PAI-I, and other emerging risk factors.
- Diffuse and extensive atherosclerosis, often involving the entire length of the artery that may masquerade as "small coronary arteries."
- Common occurrence of left main and/or three-vessel disease.
- Seen more frequently in South Asians (10–15%) and less frequently in other populations (2–5%).

Type II or standard CAD
- Standard type of CAD prevalent throughout the world.
- First manifestation of CAD typically noted after the age of 65 years and often presenting as angina rather than ACS.
- High prevalence of established risk factors.
- Low prevalence of elevated lipoprotein(a) and other emerging risk factors.
- Wide range in severity of atherosclerosis from mild to severe disease.

Type III or mixed
- Clinical manifestations typically between the age of 45 and 65 years.
- Triggered by moderate levels of established and emerging risk factors.
- Moderate severity of atherosclerosis, intermediate between type I and Type II.

ACS = acute coronary syndrome; CAD = coronary artery disease; PAI-1 = plasminogen activator inhibitor-1.
Ref 5–7.

In a large study involving over 5000 confirmed first-ever MI cases and over 5000 controls in Bangladesh, AMI occurred in 46% of those aged <50 years[73]; the mean age of patients with AMI was 53 years. In a large single-center study of patients with ACS ($n = 8268$) in India, 820 (10%) were aged <40 years (with a mean age of 35 years).[74] Strikingly, 611 (75%) of those aged <40 years had STEMI.

3.2. Extreme severity

In Western countries, angiographic studies of young patients with AMI reveal less extensive and less severe coronary atherosclerosis, often limited to single-vessel disease, or no disease at all, resulting in relatively good short-term and long-term prognosis.[69–71] In sharp contrast, coronary atherosclerosis in young Indians is clinically aggressive, severe, extensive, diffuse, and malignant, often resembling the disease pattern of older individuals.[40,42,65,72,75,76] In a comparative study of survivors of AMI aged <45 years in the UK, Indians had a greater burden of TVD (54% vs. 21%) and a greater atheroma score (3.66 vs. 1.99).[18] A similar comparative study in the US showed that Bangladeshis have more extensive and severe CAD and TVD (53% vs. 26% $p = .002$), despite the fact that they were younger (56.1 vs. 62.4 years, $p = .001$), had lower body mass indexes (BMI 25.2 vs. 27.2 kg/m^2 $p = .017$), and lower rates of smoking (40% vs. 58%, $p = .041$), respectively, compared with whites.[77,78] The prevalence of established risk factors including diabetes was similar and would not explain the premature onset and severity of CAD in South Asians both in the US and UK.

In an analysis of 820 patients with ACS (aged <40 years in India), 611 (75%) had STEMI and 144 (19%) had left main or MVD indicating greater severity.[74] In an angiographic study of 200 consecutive patients with ACS aged ≤35 years (30% Indians) in Kuwait, 65% had significant CAD and 22% had total occlusion of a significant size vessel.[79] Another angiographic study of 60 patients aged <35 years in Kuwait reported that South Asians had fewer established risk factors yet more severe coronary atherosclerosis than those from

Table 4
Angiographic studies showing high prevalence of TVD and MVD in young Indians and non-Indians with CAD and/or ACS.

Year	Author	Age	Number	TVD %	MVD %	DM %	Country
Indians							
1986	Kaul, U[81]	<40 years	104	40%	66%	5%	North India
1989	Krishnaswami, S[65]	<48 years	877	55%	79%	18%	South India
1989	Pahlajani, DB[82]	<45 years	92	37%	71%	13%	North India
1990	Sharma, SN[83]	<40 years	125	45%	NR	NR	North India
1990	Sharma, SN[83]	>40 years	125	53%	NR	NR	North India
1992	Pinto, R.J[84]	Premenopausal women	47	35%	53%	24%	North India
2000	Gambhir, J.K[85]	<40 years	50	4%	19%	10%	North India
2002	Ranjith, N[86]	<45 years	245	52%	72%	NR	South Africa
2005	Tewari,S[72]	<40 years	219	15%	47%	14%	North India
2005	Ranjith, N[45]	<45 years	458	48%	72%	21%	South Africa
2014	Deora,S[74]	<40 years	820	6%	19%	14%	South India
2014	Bhardwaj, R[87]	<40 years	124	8%	15%	8%	North India
2018	Pillay, AK[88]	<35 years	100	N/A	42%	N/R	South Africa
Non-Indians							
2011	Christus, T[79]	<35 years	200	15%	19%	NR	Kuwait
1988	Wolfe MW[89]	<35 years	35	14%	N/A	3%	United States
1987	Klein, LW[75]	<40 years	73	19	50%	N/R	United States
1995	Zimmerman, FH[90]	<35 years	294 (M)	15%	39%	3%	United States
1995	Zimmerman, FH[90]	<45 years	210 (F)	13%	29%	9%	United States
1999	Glover, MU[91]	<35 years	100	42%	68%	N/R	United States

ACS = acute coronary syndrome; AMI = acute myocardial infarction; CAD = coronary artery disease; DM = diabetes; MVD = multivessel disease and comprises two-vessel, three-vessel, and left main disease; NR = not reported; TVD = three-vessel disease.

the Arab world.[80] About half of the patients needed coronary revascularization procedures; 32% received PCI; and 14% received CABG surgery.[80] The extent and severity of CAD was greater in Indian than in Arab patients in this and other studies.[79,80]

A list of studies demonstrating a high prevalence of TVD and MVD among young Indians in India and other countries is presented in Table 4.[45,65,72,74,75,79,81–91] Another large ACS study ($n = 2290$) in South Africa found TVD in 48% of patients aged <45 years and 14% required CABG.[45,86] Sharma et al,[83] studied 250 Indian patients with CAD comparing those aged ≤40 years to those aged >40 years and found no significant difference in the prevalence of TVD (45% *vs* 53%; P = NS), diffuse disease (28% vs. 31% P = NS), and coronary collaterals (33% *vs* 45% P = NS).[83] These features are typically found in patients with diabetes but are also common in young Indians without diabetes.[5] This phenomenon may be termed diabetic-like coronary arteries in the absence of diabetes.

Overall, TVD is found in nearly half of all young Indians and one-third of premenopausal women undergoing coronary angiography for clinical indications[45,72] (Table 4). Epidemiologic data suggest a complex relationship between risk factors, CAD severity, and CAD events. Diabetes, hypertension, and age predict severity, whereas low-density lipoprotein cholesterol (LDL-C) and smoking do not, suggesting that different mechanisms drive atheroma accumulation and stenosis development.[65,85]

Contrary to the commonly held notion, Indians, in general, do not have small coronary arteries; only Indians with a smaller body habitus have smaller coronary arteries.[92] Coronary artery size when indexed to the body surface area is not statistically different in Indian men and women and compared to Caucasians.[93] However, many South Asians have extensive and diffuse atherosclerosis and greater plaque burden throughout the arteries, which may masquerade and get misinterpreted as small coronary arteries on angiography.[6]

3.3. High CAD mortality rates

The average age at the time of the first heart attack in the US was 66 years in men and 72 years in women.[57] In 2015, MI caused 114,000 deaths in the US. Of all deaths from CVD in the US, only 19% occurred in those aged <65 years and 36% in those aged <75 years[57]; more than half the CVD deaths in women and one-third of deaths in men occurred in Americans aged >85 years.[57] Of all the deaths from CVD, the percentage of deaths in those aged <45 years is 1% for whites, 4% for blacks,[94] and 8% for Indian Americans in the US.[36] Balarajan et al[19] used standardized mortality ratios (SMRs) to compare CAD death rates between whites and Indians stratified by age groups in the UK. The study showed a paradoxical increase in relative risk of CAD deaths with decreasing age. Using the SMR 100 as standard for whites, Indians had an SMR of 136, at ages 20–69 (36% higher CAD mortality). Notably, the SMR for CAD among Indians increased to 165 at ages 20–49, to 210 at ages 30–39, and to 313 at ages 20–29.[19] Sobering data from UK indicates that Indian physicians die 10 years earlier than white physicians.[95] In a study of 4 Indians who suffered an AMI between the ages of 18 and 22, matching whites could not be found in the UK.[96]

3.4. Diabetes and established risk factors insufficient to explain malignant CAD

Although the modifiable established risk factors (dyslipidemia, hypertension, smoking, and diabetes) are undoubtedly major contributors to CAD, they do not fully explain malignant CAD in young Indians and point to the presence of other driver(s).[21,22,64,97] Approximately 25–30% of Indian patients with CAD have total cholesterol <150 mg/dl and/or LDL <100 mg/dl.[65,98] Cholesterol and LDL-C levels in Indians with and without CAD are 20–30 mg/dl lower than those in their Western counterparts.[65,98] The prevalence of diabetes in Indians of all ages is 3–4 times higher than that in whites in the UK and the US.[99,100] Although diabetes is a major contributor to CAD in the middle-aged individuals, its prevalence is low, in the range of 5–15% in young Indians[27] (Table 4). In the INTERHEART study, the prevalence of diabetes in South Asians aged <40 years was <1%.[28]

Strikingly, Indians develop more metabolic abnormalities and metabolic syndrome at a lower BMI.[101,102] But high prevalence of insulin resistance, metabolic syndrome, and diabetes has failed to explain the heightened incidence of CAD in Indians and other South Asians in prospective studies in Trinidad and the UK.[17,21,22] Compared to whites, all minorities in the US (Native Americans, Hispanics, Chinese, Japanese Filipinos, and blacks) have higher rates of diabetes but lower rates of CAD, except for Indians.[12,103]

3.5. A paradigm shift in focus from high rates to high risk of CAD

South Asians, compared to whites, have 40% to 180% higher rates of CAD incidence and mortality than predicted by established risk factors and risk prediction equations.[21,22,97,104] Two prospective studies from UK—a country with free and universal access to health care—are particularly illustrative. The Southall and Brent Revisited study compared CAD mortality in 1420 South Asian men and 1787 European men.[21] During a follow-up of 16 years, South Asians had double the CAD mortality, which persisted after adjustment for risk factors, including obesity, diabetes, insulin resistance, blood lipids, hypertension, and smoking.[21,104] Although the baseline diabetes prevalence was 3 times more common in South Asians and African Caribbeans compared to whites, the incidence of CAD was 70% higher among South Asians but 35% lower among African Caribbeans, during an extended follow-up of 21 years.[104] Metabolic risk factors including insulin resistance, dyslipidemia, and abdominal obesity and the 9 modifiable INTERHEART risk factors did not fully explain the ethnic differences in CAD incidence in these populations.[104] In fact, only one-third of the excess risk of CAD in South Asians could be explained by the measured metabolic risk factors indicating the need to look for genetic risk factors.[104]

3.6. Lessons from the London Life Sciences Population Study (LOLIPOPS)

The LOLIPOPS investigated the reasons for the higher susceptibility of Indians to CVD compared to Europeans by prospectively following up a large cohort with oversampling of South Asian men and women (South Asians 16,774; whites 7032).[22] Compared to Europeans, the odds ratio (OR) for the incidence of CAD in South Asians after adjustment for age and gender was 2.55 (2.26–2.87, $p < 0.001$), which increased to 2.67 (2.33–3.06 $p < 0.001$) after adjustments for cholesterol and smoking. The OR decreased to 2.28 (1.97–2.63 $p < 0.001$), when adjustments were made for obesity, abdominal obesity, hypertension, and diabetes. Further adjustments for homeostatic model assessment insulin resistance, triglycerides, and high density lipoprotein (HDL) decreased the OR to 1.81 (1.54–2.11, p 0.001) Fig. 1.[22] This largest prospective study of South Asians has confirmed a nearly twofold higher incidence of CAD compared to Europeans at all age groups.[22] Thus, prospective data refute the widely held view that the excess CAD risk in South Asians compared to Europeans is largely attributable to established risk factors, especially abdominal adiposity, insulin resistance, diabetes, and related metabolic disturbances.[22]

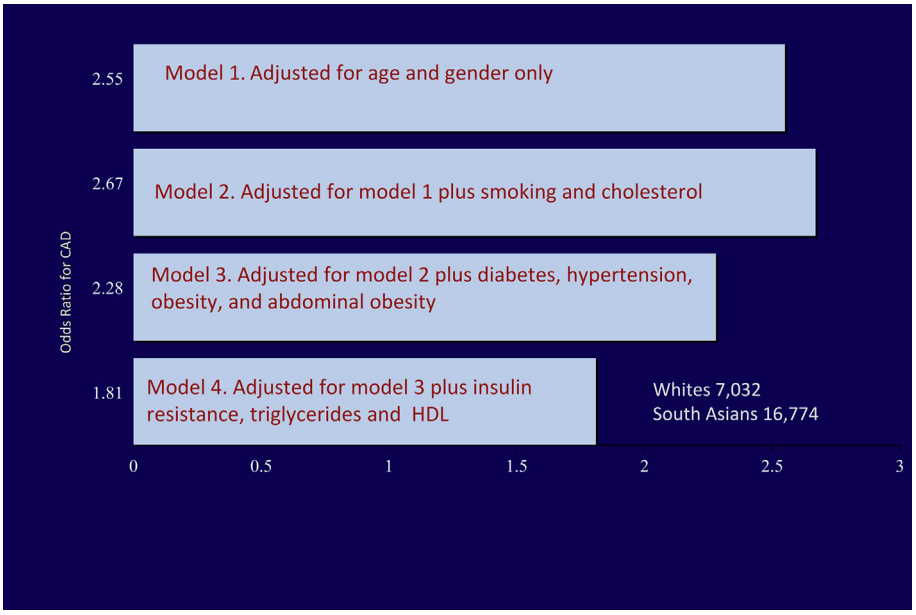

Fig. 1. Age-adjusted odds ratio for 10-yr CAD incidence of in South Asians compared with whites after adjustments for risk factors in the UK.[22] CAD = coronary artery disease.

4. Role of elevated Lp(a) in malignant CAD in Indians

We described the characteristics and impact of malignant CAD on Indians (3.1–3.3) and elucidated that the established risk factors do not constitute a satisfactory explanation (3.4–3.6). Our hypothesis is that a genetic risk factor with a high prevalence such as Lp(a) is playing a causal role in malignant, premature CAD in Indians. High Lp(a) has a prevalence of 25%, which is 2–3 times higher than prevalence of diabetes (8.5% national prevalence).

Lp(a) and South Asian ethnicity are both recognized as ASCVD risk enhancers in the recently published 2018 cholesterol clinical practice guidelines.[105] The importance of Lp(a) as an important, independent, highly prevalent genetic cause of premature CAD in diverse populations has been reviewed recently.[1–3] The 3 hallmarks described for malignant CAD in Indians—the extreme prematurity, extreme severity, and high mortality at younger ages—are also the hallmarks of CAD in patients with markedly elevated Lp(a) levels.[6] Measurement of Lp(a) is universally recommended in young patients with CAD/AMI who defy an explanation for risks from established risk factors.[3,106] Young Indians with malignant CAD is one such population in which there is a strong association of elevated Lp(a) with CAD.[85,107] The intersection between these two risk enhancers on malignant CAD in young Indians is further explored in the following section.

4.1. Elevated Lp(a) levels in South Asians

Enas et al[108,109] were the first to report high Lp(a) levels among Indians residing in the US. Lp(a) levels ≥30 mg/dl were found in 25% and >20 mg/dl in 44% of Indians.[109,110] Subsequent studies from around the world have confirmed the higher levels of Lp(a) in South Asians, compared to whites and Chinese in countries as diverse as US,[111] UK,[112] Canada,[109] Singapore,[15,113] Australia,[114] and India.[115] Migrant and resident South Asians have similar levels.[111,112] The median Lp(a) level was 13 mg/dl in a study of 751 healthy subjects in India.[115]

4.2. Lp(a)—a causal genetic factor for CAD in Indians

An extensive body of data support elevated Lp(a) concentration and/or variants of Lp(a) gene as underappreciated causal factor(s) for premature CAD.[1,3,116,117] Lp(a) genotypes (assessed as kringle IV_2 copy number variation in the LPA gene) and genetic risk score comprising multiple single-nucleotide polymorphisms are strongly associated with both plasma Lp(a) levels and CAD risk, thereby fulfilling the criterion for causality in Mendelian randomization approach.[117] Elevated Lp(a) concentration provides a genetic predisposition to CAD and AMI in Indians, and nutritional and environmental factors further increase the risk.[24,111,112]

Many case–control studies have shown an association of high Lp(a) levels with CAD, AMI, and stroke, especially in young Indians (Table 5).[4,85,107,111,115,118–132] However, it must be also noted that most studies of premature CVD in India did not measure Lp(a) but virtually all that did measure found significantly elevated Lp(a) levels (Table 5). In a study of 70 patients with ACS (aged <55 years) having minimal or no established risk factors, Mukherjee et al[133] found high Lp(a) in 41%. Likewise, Bansal et al[134] in a small case–control study of 30 Indians aged <30 years and documented premature CAD and 30 age- and gender-matched healthy individuals found that Lp (a), apoA1, and apoB were better discriminators of premature CAD as compared to conventional lipid parameters. In the Pakistan Risk of Myocardial Infarction Study—a cohort of 9015 patients with AMI and 8629 matched controls—Lp(a) concentration was an independent and causal risk factor for CAD.[135]

4.3. Lp(a), vulnerable plaque, and ACS

Elevated Lp(a) is strongly associated with the development of high-risk vulnerable plaques with complex morphology (thin cap fibroatheroma heavily infiltrated by macrophages and rare SMCs overlying a large necrotic core) that are prone to rupture.[136–138] Large amounts of Lp(a) are concentrated in the culprit lesions in patients with ACS than in patients with stable angina.[139] Elevated Lp(a) levels are associated with biomarkers of plaque destabilization and rupture.[139–141] As a plaque ruptures, the procoagulant and antifibrinolytic milieu associated with elevated Lp(a) allows the

Table 5
Lipoprotein(a) levels in Indians with CAD or stroke compared to age-matched controls.

Year	Author	Number		Mean Lp(a) level (mg/dl)		*p* value
		#Cases	#Control	Cases	Control	
A. 45 years or less						
1996	Christopher, R[118]	50 stroke	50	23.1 ± 24.3	11.7 ± 11	<0.001
2000	Gambhir, JK[85]	50 CAD	50	35.0 ± 32.4	20.3 ± 17.0	<0.002
				26.7 median	13.8 median	
2001	Isser, HS[107]	50 AMI	50	22.28 ± 5.4	9.28 ± 22.59	<0.002
2003	Angeline, T[119]	65 AMI	50	58.6 ± 3.20	19.70 ± 0.18	<0.05
2013	Wadhwa, A[120]	40 AMI	40	38.74 ± 26.15	20.54 ± 16.27	<0.05
B. More than 45 years						
1998	Mohan, V[121]	100 CAD	100	24.6 ± 3.0	15.1 ± 3.3	<0.05
2000	Gupta, R[122]	48 AMI	23	11.95 ± 2.8	6.68 ± 3.4	<0.05
2000	Vasisht, S[123]	88 CAD	83	40.90 ± 34.05	24.27 ± 24.92	<0.05
				29.4 median	16.2 median	
2000	Chopra, V[124]	74 CAD	53	105 ± 565	23 ± 76	<0.01
2001	Hoogeveen, RC[111]	57 CAD	46	12.65 ± 9.40	9.15 ± 7.33	<0.05
2003	Geethanjali, FS[125]	254 CAD	480	27.4 median	17.6 median	<0.001
2003	Govindaraju,V[126]	300 CAD	200	32.18 ± 1.37	29.94 ± 2.59	NS
2004	Rajasekhar, D[127]	151CAD	49	24.79 ± 18.99	16.04 ± 17.53	<0.01
2004	Tewari, S[128]	110 CIMT	75	32.1 ± 22.1	26.4 ± 24.2	0.05
2005	Ashavaid, TF[115]	None	751	NA	12.9 median	
2007	Sharobeem, KM[129]	55 stroke	85	19.9[a] (14.0–28.5)	15.1[a] (11.4–20.1)	0.037
2008	Gambhir, JK[130]	220 CAD	160	30.00	12.7 median	<0.05.
2013	Ashfaq, F[131]	270 CAD	90	48.7 ± 23.8	18.9 ± 11.1	$p < 0.0001$
2014	Yusuf, J[132]	450 CAD	150	30.30 median	20.0 median	<0.001
2017	Pare, G[4]	948 AMI	881	18.9 median	13.8 median	<0.001

AMI = acute myocardial infarction; CAD = coronary artery disease; NA = not available; Lp(a) = lipoprotein(a).
[a] Geometric mean.

superimposed thrombus to form and enlarge rapidly and occlude coronary arteries abruptly resulting in severe ACS and large STEMI.[138,142,143]

4.4. Lp(a)-years and premature CAD

The Lp(a) level is genetically determined, present, and expressed at birth, doubles to the adult level within 6–9 months and thereafter remains constant for the remainder of life.[144] This lifelong exposure to elevated Lp(a) results in accelerated atherosclerosis, leading to AMI approximately 10–20 years earlier than that occurring from established risk factors.[5,85,107,118,119] In the Prospective Cardiovascular Munster study[145]—by far the largest study of AMI survivors aged <45 years ($n = 504$)—an Lp(a) level ≥20 mg/dl (measured in fresh plasma) was a better predictor of CAD than the established risk factors.

The cumulative adverse effects of smoking have been quantified by estimating the pack-years of exposure, which incorporates both the quantity and duration of smoking. For example, a 40-year-old person who has smoked 2 packs of cigarettes for 20 years has 40 pack-years of cumulative exposure, which puts him at a higher risk of AMI than a light smoker or nonsmoker. A similar concept of cumulative exposure to LDL-C and Lp(a)is evolving.[146] For example, a 40-year-old person with an LDL-C of 200 mg/dl would have a cumulative exposure of 8000-mg LDL-years (200 × 40); this individual would be more likely to have an AMI than a person with an LDL of 100 mg/dl, whose cumulative exposure is only 4000 LDL-years (100 × 40). Likewise, elevated Lp(a) is strongly associated with premature AMI in a level-dependent manner.[143,147–149] This can also be demonstrated with a simple predictive calculation of Lp(a)-years (Lp(a) level × age). Thus, a 40-year-old person with Lp(a) 100 mg/dl has 4000 Lp(a)-years (100 × 40), while another 40-year-old person with Lp(a) of 10 mg/dl would have 400 Lp(a)-years (10 × 40). The former is at a high risk for advanced CAD and AMI, while the latter is not, assuming other risk factors are comparable in both. Preliminary data suggest that 4000 Lp(a)-years and 8000 LDL-years have comparable risk of AMI.[150]

4.5. Lp(a) and premature CAD in Indian women

Premature and severe CAD is recorded also in Indian women despite their very low rates of tobacco use.[151] The significantly higher CAD and stroke MRR in South Asian women in the UK and France is shown in Table 2. Premature onset of CAD in Indian women is highlighted by a large contemporary study (2010–2011) of 6867 patients diagnosed with CAD; 1167 (17%) were women with a mean age of 56 years, *vs* 57 years in men.[152] This absence of age difference between Indian men and women is in sharp contrast to Western countries, where women manifest CAD 10–20 years later than in men. Strikingly, 425 (36%) of these women with CAD were premenopausal, and they had very low prevalence of established risk factors: smoking and family history <1%, obesity and diabetes 4%, and hypertension 6%.[152] Thus, premature and severe CAD among Indian women, including premenopausal women, is unexplained by established risk factors including diabetes and smoking.

Lp(a) is a strong predictor of premature CAD with a greater risk in premenopausal women than in postmenopausal women.[153,154] In a study of 292 consecutive Swedish women aged <65 years with ACS and matched controls, Lp(a) was the strongest risk factor. In the overall study participants, the multivariable adjusted OR for ACS in the highest versus lowest quartile of Lp(a) was 2.9 (95% confidence interval [CI], 1.6 to 5.0; $p < .001$ for trend). Strikingly, the OR for ACS from Lp(a) was double for premenopausal (OR 5.1 95% CI, 1.4 to 18.4) than postmenopausal women (OR 2.4 (95% CI, 1.3–4.5).[153] Elevated Lp(a) in offspring is associated with a history of increased maternal CVD mortality.[155] Other complications associated with elevated Lp(a) in women include AMI during pregnancy,[156] placental insufficiency, fetal growth retardation, recurrent miscarriages, still birth, and so on.[157–159]

4.6. Lp(a) and severity of CAD in Indians

The failure of the known risk factors (diabetes, smoking, family history of CAD, hypertension, waist circumference, and dyslipidemia) to explain the CAD severity in Indians was noted as early as 1994 in a large angiographic study ($n = 1666$).[160] In contrast, the Lp(a) level and/or LPA genetic score are associated with increased extent and severity of CAD and ACS in diverse populations.[131,132,137–139,161–169] Lp(a) levels are also correlated with coronary artery calcium score—a robust biomarker of extent of coronary plaque burden and future risk of AMI even in people aged <45 years.[167,170–172]

4.7. Lp(a) is a biological marker of family history of premature CAD

Parents of children with Lp(a) >25 mg/dl have 2.5-fold increased incidence of MI.[173] Genetic studies have confirmed Lp(a) as the best biological markers and the strongest genetic component of CAD that is not mediated by apoB or LDL-C.[174] High prevalence of elevated Lp(a) levels in healthy young subjects with a history of premature CAD in siblings, parents, or grandparents has led to the designation of high Lp(a) as a substitute for a family history of premature CAD.[173–175] Many studies confirm high Lp(a) levels in Indians and South Asians with family history of CAD.[107,130,176]

Compared with Chinese in Singapore, Indians have had a threefold to fourfold higher CAD rates, first observed in 1959. Ethnic differences in plasma Lp(a) levels are present and expressed at birth.[175,177] Indian newborns have significantly higher levels (in cord blood) than Chinese newborns. The Lp(a) level in cord blood is reflective of the adult Lp(a) level.[15] Strikingly, the ranking of Lp(a) levels at birth was concordant with the relative CAD mortality rates for the respective adult populations of Singapore observed over the past 60 years.[15] These data lent credence to our hypothesis that elevated Lp(a) is the biological marker of the heightened risk of CAD observed in the Indians worldwide.

5. Lp(a): CAD risk and recommended threshold for Indians

5.1. Increased CAD risk from Lp(a) in Indians

Jha et al[178] hypothesized and Banerjee et al[179] demonstrated a higher risk of CAD from high Lp(a) in Indians in a small study. The INTERHEART Lp(a) study—by far the largest case–control study on Lp(a) and AMI—measured Lp(a) levels in a total of 12,943 subjects comprising 7 largest ethnic groups across the world.[4] South Asians were well represented ($n = 1829$), with 948 cases and 881 age- and gender-matched controls. This study convincingly demonstrated that Lp(a) is an independent risk factor for AMI in diverse populations.[4] South Asians had increased Lp(a) levels than whites (14 mg/dl *vs*. 10 mg/dl).[4] The ethnic differences in Lp(a) levels in cases and controls a as well as the differences in the OR for AMI are given Table 6.[4] Notably, the OR for AMI with elevated Lp(a) was the highest in South Asians and more than double that of whites (OR 2.14 *vs* 1.36 $p < 0.001$).[4] This phenomenon is analogous to the threefold higher risk of stroke from hypertension in African Americans than in whites.[180]

Concomitant presence of South Asian dyslipidemia characterized by the LDL particles that are highly enriched with apoB and Lp(a)may provide a plausible explanation for the heightened risk of CAD from Lp(a) is South Asians.[25,110,181] The apoB/apoA1 ratio has been shown to be a better predictor of AMI than other lipid indices.[181,182] South Asians have higher apoB/apoA1 ratio (1.53 *vs* 1.47) than whites, despite having a lower total cholesterol level (184 mg/dl vs. 204 mg/dl).[28,181] From a clinical perspective, the point to note here is that LDL-C and total cholesterol level may markedly underestimate CAD risk in South Asians. Besides, the HDL particles are depleted of apoA1 and offer little protection.[25,181,183] Mendelian randomization (MR) analyses have recently challenged the protective effects of HDL. In one such analysis involving 33,000 AMI cases and 130,000 controls, high or very high high-density lipoprotein cholesterol (HDL-C) from birth provided no protection against AMI.[184] The 2018 cholesterol clinical practice guidelines[105] have introduced many high-risk conditions and risk enhancers for future risk of ASCVD; many of which including high triglycerides and metabolic syndrome are more common in South Asians than in other populations (Table 7).[105,185]

5.2. Rationale for a lower Lp(a) threshold for CAD Indians

In 2010, the European Atherosclerosis Society recommended an Lp(a) high-risk threshold of >50 mg/dl (125 nmol/L), which represented the 80th percentile for the European population.[106] In 2018, the National Heart, Lung, and Blood Institute (NHLBI) endorsed an Lp(a) high-risk range of >30–50 mg/dl (75–125 nmol/L) to accommodate the implications of more recent studies.[3] In the Framingham Heart Study, the 75th percentile of Lp(a) distribution was 30 mg/dl and 90th percentile was 38 mg/dl.[186] Most epidemiologic and case–control studies that measured Lp(a) in fresh plasma[145,150,187,188] as well as an updated review of epidemiological and MR studies from Copenhagen population have shown a risk range of 20–30 mg/dl.[189] This new analysis included 58,340 subjects, measured Lp(a) in fresh samples using isoform-insensitive assays, corrected for regression dilution bias, recorded 1897 validated AMI, and also focused on those with extremely high Lp(a) levels.[189]

The overwhelming majority of studies from India have found elevated CAD risk at Lp(a) levels ≥20 mg/dl.[85,111,131,190] A study of healthy subjects in India ($n = 751$) found a median Lp(a) of 13 mg/

Table 6
Ethnic differences in the risk of acute myocardial infarction from Lp(a) >50 mg/dl (adjusted for age, sex, apoA, and apoB).[4]

Ethnicity	Number of participants		% of participants with Lp(a) >50 mg/dl %		OR (95% CI) for AMI for Lp(a) >50 mg/dl	
	Cases	Controls	Cases	Controls	Cases	*p*-value
Europeans	951	897	17.7	13.5	1.36 (1.05–1.76)	0.021
South Asians	948	870	18.2	8.51	2.14 (1.59–2.89)	<0.001
Chinese	2034	2385	5.9	3.4	1.62 (1.20–2.15)	0.002
Southeast Asians	600	607	12.5	6.6	1.83 (1.17–2.88)	0.009
Latin Americans	731	732	20.9	13.6	1.67 (1.25–2.22)	<0.001
Arabs	528	822	14.8	12.0	1.13 (0.80-1.59)	0.485
Africans	294	474	25.9	26.6	0.92 (0.65–1.31)	0.659
Total	6086	6789	13.0	11.0	1.48 (1.32–1.67)	0 < 0.001
Heterogeneity						0.007

apoA = apolipoprotein A; apoB = apolipoprotein B; Lp(a) = lipoprotein(a); NA = not applicable; OR = odds ratio; AMI = acute myocardial infarction; CI = confidence interval.

Table 7
High-risk conditions and risk-enhancing factors for future ASCVD events that favor high-intensity statin therapy.[105,186]

Very high-risk conditions	Risk-enhancing factors
Recent ACS (within the past 12 months)	South Asian ancestry[a]
History of multiple MI or stroke	Elevated lipoprotein(a) ≥50 mg/dl or ≥125 nmol/L[a]
History of single MI or stroke with multiple high-risk conditions	Elevated apolipoprotein *B* ≥130 mg/dl[a]
Symptomatic peripheral arterial disease	LDL-C ≥160 mg/dl or non–HDL-C > 190 mg/dl
High-risk conditions	Hypertriglyceridemia (≥175 mg/dl)[a]
Age ≥65 y	C-reactive protein ≥2 mg/dl[a]
Heterozygous FH	Metabolic syndrome[a]
CABG surgery or PCI	Family history of premature ASCVD
Diabetes[a]	(male age <55 y; female age <65 y)
Hypertension	Chronic inflammatory conditions
Chronic kidney disease (eGFR 15–59 ml/min)[a]	(psoriasis, rheumatoid arthritis, or HIV/AIDS)
Current smoking	Premature menopause before age 40 y
Persistently elevated LDL-C ≥100 mg/dl despite maximally tolerated statin therapy and ezetimibe[a]	History of preeclampsia
History of CHF	

ACS = acute coronary syndrome; AIDS = acquired autoimmune disease ASCVD = atherosclerotic cardiovascular disease; CABG = coronary artery bypass graft; CHF = congestive heart failure; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; FH = familial hypercholesterolemia; HIV = human immunodeficiency virus; LDL-C = low-density lipoprotein cholesterol; PCI = percutaneous coronary intervention; MI = myocardial infarction; HDL = high-density lipoprotein.
[a] Conditions that are more common in South Asians.

dl; the 75th percentile of Lp(a) was 25 mg/dl, 90th percentile was 47 mg/dl, and 95th percentile was 57 mg/dl.[115] Other studies have shown similar median Lp(a) levels among Indians and South Asians without CAD (Table 5). A study of young Indians (<45 years) with AMI found Lp(a) ≥20 mg/dl in 70% of Indians with CAD but only 10% had Lp(a) >30 mg/dl.[107] In the INTERHEART Lp(a) study, OR for AMI from Lp(a) >50 mg/dl was significantly higher in South Asians (OR 2.14) than in whites (OR 1.36).[4]

The studies, as described previously, specifically the finding of 25 mg/dl as the 75th percentile in healthy subjects and the significantly higher OR for AMI from elevated Lp(a), lead us to propose ≥30 mg dl (>75 nmol) as the threshold to use for risk assessment in Indians. The difficulty in setting a precise number as the threshold for the Lp(a) level is demonstrated by the NHLBI endorsing an Lp(a) high-risk range of >30–50 mg/dl (75–125 nmol/L). The NHLBI has also stressed the need for determining ethnic specific Lp(a) thresholds.[3]

5.3. The population-attributable risk from Lp(a) for CAD in Indians

The NHLBI working group has estimated that 1.43 billion of the world population as having Lp(a) ≥50 mg/dl, of whom 469 million are South Asians.[3] For comparison, India has 69 million people with diabetes and 36 million with prediabetes according to the data from the International Diabetes Federation Atlas; the prevalence of diabetes is 8.5% and prediabetes is 5%,[191] compared with 25% for elevated Lp(a).[3] The prevalence of elevated Lp(a) among Indians in the US was 25% using a threshold of ≥30 mg/dl.[127] The NHLBI also estimates 25% of South Asians having elevated Lp(a), even though the latter used a higher threshold of ≥50 mg/dl. Accordingly, the burden of elevated Lp(a) in Indians is higher than that for diabetes.

The impact of elevated Lp(a) on AMI can be best captured by population-attributable risk (PAR) which captures both the prevalence of Lp(a) and the OR conferred by elevated Lp(a). PAR may vary by gender, ethnicity, disease, and age. For example, the OR from smoking for AMI is 2.43 among South Asians but the PAR is 6 times higher in men (42%) than in women (7%) due to lower rates of smoking in women.[27,28] Likewise, the PAR from hypertension is 3 times higher for stroke[192] than for AMI, whereas the PAR from lipids is 2 times higher for AMI than for stroke.[27] In the predominantly white population in Framingham Offspring Study, the PAR for premature CAD from elevated Lp(a) >30 mg/dl (PAR 9%) was comparable to total cholesterol >240 mg/dl (PAR 10%), and nearly double that of diabetes (PAR 5%).[150]

Table 8
Prevalence, odds ratio, and population-attributable risk (PAR) for AMI in South Asians in the INTERHEART Study.[4,28]

Risk factors	Prevalence %	Odds ratio (OR)	PAR%
High apoB/apoA1 ratio	44	2.57	47%
Current smoking	41	2.57	38%
Hypertension	13	2.92	19%
Diabetes mellitus	10	2.52	12%
Lipoprotein(a) >50 mg/dl[a]	9	2.14	10%

apoA1 = apolipoprotein A1; apoB = apolipoprotein B; AMI = acute myocardial infarction.
[a] The National Heart, Lung, and Blood Institute estimate a higher prevalence of 25% among South Asians.

Table 8[4,28] shows the prevalence, OR, and PAR for AMI for the five major risk factors among South Asians. The PAR for AMI for Lp(a) >50 mg/dl was 10%, which was similar to that of diabetes (12%). Of note, prevalence of elevated Lp(a) in the INTERHEART study was less than half that estimated by the NHLBI (9% versus 25%).[3,4] The PAR for AMI may surpass that of diabetes if future studies using fresh plasma confirm the 25% prevalence estimated by the NHLBI consensus.[3] Of note, small Lp(a) isoforms that predominate in patients with CAD have been shown to deteriorate more rapidly than larger isoform found in healthy controls.[193] Because such selective deterioration may decrease the prevalence of high Lp(a) levels, every effort should be made to measure Lp(a) levels in fresh plasma, especially when prevalence data are collected. Besides, the PAR in Indians aged <45 years may be significantly higher than that in older people. For example, a study of Japanese Americans has demonstrated increasing PAR with decreasing age. The overall PAR for AMI from high Lp(a) was 14% but was double at 28% in those aged <60 years.[187] As noted earlier, the OR for CAD from elevated Lp(a) was more than double in premenopausal women (OR 5.1) compared to postmenopausal women (OR 2.4).[153]

6. Stroke, diabetes, and dietary trans fats

6.1. Lp(a) and stroke

South Asians have higher rates of stroke than whites (Table 2).[37] A case–control study of 50 patients aged <40 years with ischemic stroke and 50 age- and gender-matched control subjects found elevated Lp(a) to be the only risk factor that was significantly higher in patients (23.1 ± 24.3 *vs* 11.7 ± 11 $p < 0.001$) *vs* controls.[118] Other studies have shown both Lp(a) and the apoB/apoA1 ratio to be

predictors of ischemic stroke.[129] A high level of Lp(a) is also associated with increased severity and poorer long-term prognosis for stroke in Indians.[194] Collectively, these studies show that Lp(a) is an important but underrecognized cause of early and advanced atherosclerosis and ischemic stroke in Indians.[118,195]

6.2. Counterintuitive effects of Lp(a) on diabetes and insulin resistance

Preliminary reports have suggested an inverse association between the LDL-C level and diabetes.[196] A similar inverse relationship of Lp(a) with diabetes, insulin resistance, and metabolic syndrome has been reported in many prospective studies.[172,197,198] An analysis of 134,707 subjects from several studies followed up for 5–20 years has shown a 25% lower incidence of diabetes in participants with a high *vs* low Lp(a) level.[198] Further, the genetic protection against diabetes is reduced with very low Lp(a) <5 mg/dl and/or very large Lp(a) isoforms (estimated to be found in 10% of the world's population).[198,199]

The presence of either diabetes or high Lp(a) is associated with a twofold to threefold risk of CAD compared to people without these conditions.[3,200,201] While some studies have shown an association of elevated Lp(a) levels with higher risk and severity of CAD in patients with diabetes,[202] other studies have shown a paradoxically lower risk of CAD in patients who have both elevated Lp(a) and diabetes.[198,203,204] A 12-year follow-up of 2308 men and women with diabetes (from 2 large prospective studies), plasma Lp(a) levels, and Lp(a) genetic score were not associated with CVD incidence or mortality.[204] How increased Lp(a) protects against diabetes, while accelerating atherothrombosis, has become a focus of intense research. This heterogeneity in the association of Lp(a) and CVD risk between diabetic patients and general population needs confirmation in Indian patients. These important unanswered questions beg for answers, through well-designed studies, as South Asians have a high prevalence of all 3—elevated Lp(a) (25%), diabetes (9%), and CAD (7–14%) and a high absolute burden of CAD (2.8 million annual CVD deaths).

6.3. Lp(a) and high trans fat intake

Lp(a) levels are genetically determined with only a negligible contribution from diet with the exception of consumption of trans fats, which can significantly increase Lp(a), along with increase in LDL-C and triglycerides and decrease in HDL-C.[205,206] Heating/frying and reuse of edible fats/oils induce chemical changes such as formation of trans fatty acids.[207] Fried food is generally used as a substitute for high trans fat intake as the process of deep-frying itself generates trans fat as mentioned in research studies .[208] Fried food is generally considered a treat and is consumed at breakfast, lunch, and dinner and as snacks at home and at restaurants by Indians around the world.[208] Fried food, fast food (mostly fried), and vanaspati (also called vegetable ghee) are 3 major sources of trans fats in India. Vanaspati is a form of partially hydrogenated vegetable oil. It is used as a substitute for more expensive ghee or butter for cooking and deep-frying. Approximately 10 different brands of vanaspati are available in India with some brands having trans fat content as high as 40% of the calories.[209]

Unlike other populations, the correlation between Lp(a) isoforms and Lp(a) levels is weaker in Indians,[125] suggesting a nongenetic contributor such as dietary trans fat. The potential role of high consumption of trans fats through fried food and vanaspati as significant contributors to elevated Lp(a) levels (with large and small isoforms) needs to be further investigated. Other potential contributors to high Lp(a) may be the culturally driven marital practices (such as endogamy)[210] in most of South Asia and parental consanguinity in some communities and regions.[211]

It is worth noting that Indians are traditionally vegetarians, financially constrained, and as a result consume large amounts of carbohydrate in the form of starchy vegetables and rice. These lifestyle trends may well be additionally contributory to high triglycerides, which in turn could contribute to CAD; besides the biological risk pathway for Lp(a), there could be an additional factor contributory to premature atherosclerosis.[208] A recent study highlights the importance of the dietary inflammatory index and cardio metabolic risk in US adults through an analysis of dietary intake, biochemical data, and anthropometrics over 7 years (2005–2012) and concludes that diet plays an important role in the occurrence of CVD.[212]

7. Testing for and management of elevated Lp(a)

7.1. Testing for elevated Lp(a)

We have recently reviewed in detail the issues related to measuring Lp(a) levels.[1] Lp(a) should be measured by an assay insensitive to isoform size and reported in nmol/l to reflect the Lp(a) particle concentration.[1] Because storage conditions and duration can mask high Lp(a), care should be taken to measure Lp(a) in fresh plasma.[1] Because the Lp(a) level is stable over a lifespan, the test need not be repeated. An important exception is in those who had Lp(a) measured as cholesterol by vertical auto profile.[213] These individuals should have the Lp(a) measured by an assay insensitive to Lp(a) isoform.

7.2. Management of elevated Lp(a)

The major elements in management of Lp(a) were reviewed recently.[1] Aspirin therapy has been shown to lower the Lp(a) level and the risk from elevated Lp(a),[214,215] but the Food and Drug Administration (FDA) has not approved the use of aspirin for this indication. In the absence of any FDA-approved Lp(a)-lowering medications, the mainstay of management of elevated Lp(a) at present is to lower LDL-C to the lowest safe levels possible.[105] Both LDL-C and Lp(a) are independent predictors of CAD, with a fivefold risk when both levels are elevated underscoring the need for aggressive LDL-C–lowering therapy.[216]

The 2018 cholesterol clinical practice guidelines recognize not only high-risk conditions but also risk-enhancing factors to identify those at high risk for CVD events (Table 7).[12,105,185] Most of the established risk factors are now incorporated under high-risk conditions, except family history of premature CVD (now listed as a risk enhancer).[105] Notably, South Asian ethnicity along with abnormalities more common in South Asians—elevated Lp(a) ≥50 mg/dl, LDL-C >160 mg/dl, triglycerides >175 mg/dl, and metabolic syndrome—is now recognized as a risk-enhancing factor.[12,105] Most South Asians with elevated Lp(a) may require high-intensity statin therapy, especially if they have one or more risk-enhancing factors or high-risk conditions present. A 50% reduction in LDL achieved with high-intensity statin therapy yields greater benefits than 30% reduction achieved with moderate-intensity statin therapy. Given that the benefits of the LDL-C–lowering therapy are directly proportional to the baseline ASCVD risk, and degree of LDL-C reduction, it behooves us to initiate and maintain high-intensity statin therapy, when maximal ASCVD risk reduction is desired. Such therapy should be continued at least until the age of 75 years in the absence of comorbidities that significantly reduce life span as the benefits of such therapy continue to accumulate.[105]

Table 9
Management of elevated Lp(a) in Indians,[6,105] non–HDL-C goal <100 mg/dl and LDL-C goal of <70 mg/dl.

	Lp(a) levels and risk factors	Management
A	Lp(a) >30–49 mg/dl No high-risk conditions[a] No risk-enhancing factors[b] (Also see Table 7)	Lifestyle modification to prevent the development of high-risk conditions and risk-enhancing factors Plus moderate-intensity statin therapy[c] (High-intensity statin therapy if LDL –C and non-HDL-C goals if the LDL goals are not met)
B	Lp(a) >30–49 mg/dl plus high-risk conditions or risk-enhancing factors	Intensive lifestyle modification plus high-intensity statin therapy[d]
C	Lp(a) ≥50 mg/dl No high-risk conditions No risk-enhancing factors	Intensive lifestyle modification plus high-intensity statin therapy plus ezetimibe if needed
D	Lp(a) ≥50 mg/dl plus high-risk conditions or risk-enhancing factors	Intensive lifestyle modification plus high-intensity statin therapy plus ezetimibe and/or PCSK9 inhibitors if needed

ACS = acute coronary syndrome; CABG coronary artery bypass surgery; CHF = congestive heart failure; CVD = cardiovascular disease; LDL-C low-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; Lp(a) = lipoprotein(a); Non–HDL-C = non–high-density lipoprotein cholesterol; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention; apoB = apolipoprotein B.

[a] Includes ACS, history of myocardial infarction, stroke, PAD, CABG, PCI; HeFH; tobacco use; hypertension; diabetes; chronic kidney disease, age ≥65 years; persistently elevated LDL-C >100 mg/dl despite maximally tolerated statin therapy and ezetimibe, LDL-C >160 mg/dl without statin therapy, or history of CHF.

[b] Includes South Asian ethnicity, Lp(a) ≥50 mg/dl, family history of premature CVD, metabolic syndrome, premature menopause <40 years, chronic inflammatory conditions, apoB ≥ 130 mg/dl.

[c] Includes rosuvastatin 5–10 mg or atorvastatin 10–20 mg and lower LDL-C by 30–50%.

[d] Includes rosuvastatin 20–40 mg or atorvastatin 40–80 mg and lower LDL-C by >50%.

In addition to maximally tolerated statin therapy, some at high risk of ASCVD (e.g. CVD, diabetes, or high Lp(a)) may also require ezetimibe and PCSK9 inhibitors. Strategies for management of elevated Lp(a) is given in Table 9.[105] Recent prospective data and meta-analysis indicate that those with ultralow LDL (<40 mg/dl) have the lowest CVD risk, which is achievable with PCSK9 inhibitors.[217–220] Of note, statin therapy reduces ASCVD risk without reducing elevated Lp(a), which remains a major determinant of residual risk, even when LDL-C is reduced to <55 mg/dl.[221–223] Clearly, this observation underscores the need to develop effective Lp(a)-lowering therapy.

8. Synthesis and clinical implications

As we, in our multiple roles as learners, researchers, and clinicians, ponder the serious problem of increased CAD in Indians and, in particular, the subset of malignant CAD in young Indians, it becomes clear that there is no single, simple explanation or solution to this enigma. Here, we presented our thesis that high Lp(a) is an important inherited CAD risk factor with a prevalence surpassing that of diabetes. Concomitant presence of South Asian dyslipidemia and a host of other risk enhancers may further increase the risk (Table 7).Not only does elevated Lp(a) in young Indians correlate better than established risk factors with malignant CAD but it also correlates well with all 3 of the hallmarks of malignant CAD (extreme prematurity, extreme severity, and high mortality).[6] No other risk factor carries this degree of correlation. The cumulative evidence presented in this article positions Lp(a) as a key player in the pathogenesis of malignant CAD in Indians worldwide and also as a biologic marker of malignant CAD in the young. For these important reasons and because the Lp(a) level can improve the risk prediction for MI, a onetime measurement of Lp(a) is recommended in young Indians with a personal or a family history of premature CAD. It may also be reasonable to measure Lp(a) in all Indians aged <65 years, at any time after two years of age. The cost of the Lp(a) test is generally similar to that of a generic lipid profile. We urge all researchers to direct attention to Lp(a) levels and its deleterious effects when combined with South Asian dyslipidemia in Indians.

Although CAD is incurable, the disease is largely preventable, treatable, and even partly reversible, as experienced in resource-rich countries. Since its peak in 1968, the age-standardized mortality rate per 100, 000 has decreased by 68% for CAD and 77% for stroke in the US.[224] The identification, treatment, and control of 3 major risk factors—tobacco use, hypertension, and high cholesterol (but not diabetes)—account for this spectacular decline.[225] In the future, along with the control of established risk factors, the detection and treatment of elevated Lp(a) should further reduce the CVD burden in India.

9. Summary

Both elevated LP (a) and South Asian ethnicity are recognized as ASCVD risk enhancers in the 2018 cholesterol clinical practice guidelines. The Lp(a) level in umbilical cord blood reflects the adult level that is reached by two years of age and is maintained throughout one's lifespan.[15] As a result, in people with elevated Lp(a), accelerated atherothrombosis begins soon after birth and progresses relentlessly leading to malignant CAD, ACS, and stroke at a very young age. In general, Indians and other South Asians develop AMI approximately 10 years earlier with a threefold to fivefold higher incidence in those aged <45 years. The LOLIPOPS, by far the largest prospective study of South Asians to date, has demonstrated a twofold incidence of CAD compared to whites, adjusted for established risk factors and emerging risk factors (Fig. 1). Based on the data presented in this article, we strongly propose Lp(a) as the missing biological factor in the causation of malignant CAD in young Indians, a fact that had eluded researchers for more than half a century.

For any given level of cholesterol and LDL-C, Indians have a greater risk of CAD, at least in part due to the substantial enrichment of LDL with Lp(a), which is included in the calculated LDL reported by the laboratory. Because of the heightened risk conferred by Lp(a) in South Asians, an Lp(a) threshold of ≥30 mg/dl (75 nmol/l) should be considered high and ≥50 mg/dl (≥125 nmol/l) should be considered very high. An estimated 25% of South Asians have Lp(a) >50 mg/dl, compared with <10% having diabetes. While awaiting the availability of Lp(a)-lowering therapies, high-intensity statin therapy to ultralow LDL-C should remain the mainstay of management of elevated Lp(a) levels. We urge researchers on CAD in Indians to include Lp(a) level measurements. Such data then should be incorporated in future revisions of ASCVD risk scores as these scores presently underestimate the risk in Indians and other South Asians.

Conflict of interest

All authors have none to declare.

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Appendix A. Supplementary data

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