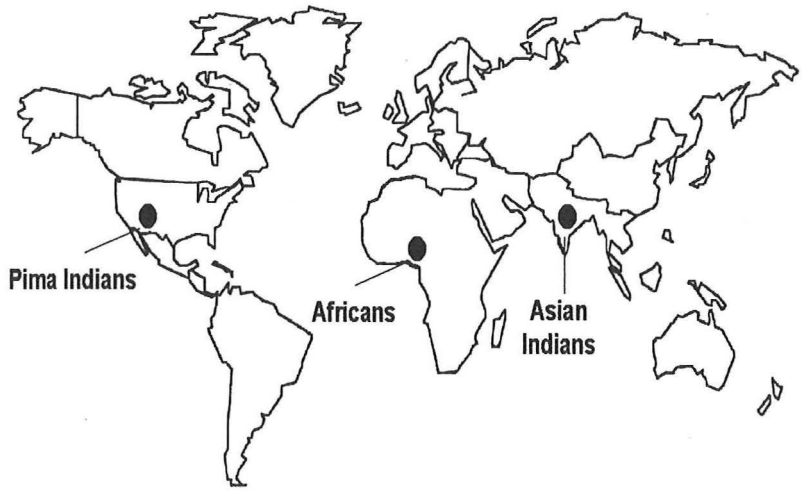
Ethnic Differences in Coronary Artery Disease: Presentation, Progression and Prognosis



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This is to acknowledge that Helen H. Hobbs has disclosed no financial interests or other relationships with commercial concerns related directly or indirectly to this program.

INTRODUCTION

The primacy of hypercholesterolemia as a cardiac risk factor. Coronary artery disease (CAD) is the major cause of death in Western societies, but not in most other populations of the world. A key contributing factor to the high rates of CAD in industrialized countries is the elevated plasma levels of cholesterol in these populations; the entire distribution of the plasma cholesterol levels is shifted to the right in Western societies (Fig. 1). Since CAD mortality is directly related to plasma cholesterol levels (Fig. 2) (Stamler *et al.*, 1986; Chen *et al.*, 1991), Western societies are burdened by a significantly higher rate of CAD. Although hypercholesterolemia plays a critical *permissive* role in CAD, other cardiac risk factors contribute to the relatively high frequency of CAD associated with industrialization, including smoking, diabetes and hypertension (Kannel, 1988). These risk factors, together with dyslipidemias, age and gender, account for ~75-85% of total coronary risk (Wilson *et al.*, 1998). The remaining 15-25% of cardiac risk is yet to be defined (Wilson *et al.*, 1998).

Fig.1

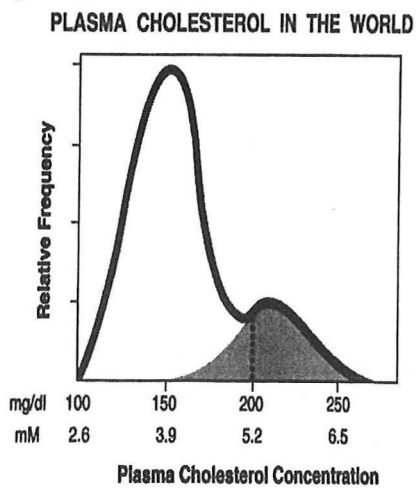
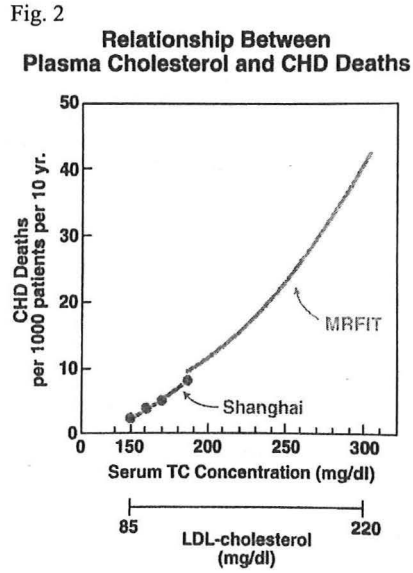


Fig. 2

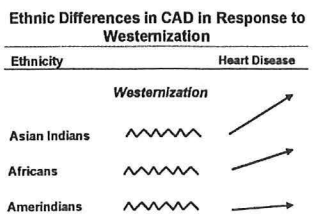


The genetic factors that predispose to CAD are largely undefined. Genetic factors account for ~50% of cardiac risk. Many of the known cardiac risk factors (hypertension, diabetes and hypercholesterolemia) have major genetic components, but other, yet-to-be-identified genetic factors also contribute significantly to the development of CAD (Snowden *et al.*, 1982). Efforts to identify the gene sequences responsible for conferring CAD risk have largely been unrevealing. Over 1000 papers have been published to assess the relationship between common sequence variants and CAD, but none have convincingly been shown to add any significant predictive value to the classic cardiac risk profiling.

Ethnic differences in CAD susceptibility provide the opportunity to identify new cardiac risk factors. An alternative strategy to identify new CAD risk factors is to compare the prevalence and incidence of CAD in different ethnic groups. The underlying assumption in these studies is that any observed differences in CAD between ethnic groups are attributable to genetic differences between the groups. Although this assumption is complicated by the existence of substantial inter-ethnic, non-genetic differences, it is worth reviewing the epidemiological data that supports there being fundamental

differences associated with ethnicity that contribute to CAD susceptibility. I will focus on three ethnic groups that differ in CAD risk in response to Westernization: the Asian Indians, Africans, and Amerindians (Pima Indians) (Fig. 3).

Fig. 3



HIGH RATE OF CAD IN WESTERNIZED ASIAN INDIANS

Asian Indian immigrants in Singapore, Africa and the Caribbean have high rates of CAD. The first reports that Asian Indians may have an increased incidence of CAD came from Singapore, Africa, Fiji and the West Indies (for review, see McKeigue *et al.*, 1989). Indian immigrants in these diverse locales were noted to have significantly higher rates of CAD than the indigenous populations, or immigrants from other countries. As an example, a large autopsy study performed in Singapore found a ~5-fold increased incidence of CAD in Indian men compared to Chinese men (Danaraj *et al.*, 1959). Another study found that an estimated 43% of the deaths in Asian Indian residents of Kampala, Uganda were caused by CAD; in contrast, death due to CAD was very rare in native Africans (Shaper *et al.*, 1959). Comparison of the dietary composition and plasma cholesterol levels in these two ethnic groups provided a clue as to the reason for this ethnic difference in CAD death rates. The fat content of the African diet was much lower than that of the Asian Indians (~15% vs. ~40%) (Fig. 4). The major source of dietary fat in the Africans was peanuts. Although most of the Asian Indians were vegetarians, they consumed dairy products and their major dietary sources of fat were ghee (clarified butter) and cottonseed oil. Ghee is obtained by heating butter, and is not only rich in saturated fat, but also in oxidized lipids that may have adverse vascular effects. Not surprisingly, the plasma cholesterol levels were significantly higher in the Asians than in the Africans (Fig. 5).

Fig. 4

Dietary Fat Content and Source in Africans and Asian Indians of Kampala, Uganda (1959)

	Africans	Asian Indians
Dietary fat (%) content (%)	10-15%	30-45%
Major source(s) of dietary fat	peanuts	cottonseed oil ghee (clarified butter)

Shaper *et al.*, Lancet: 534, 1959

Fig. 5

Plasma Cholesterol Levels in African and Asian Indian Men in Kampala, Uganda (1959)

	Serum Cholesterol (mg%)	
Age	African (n=317)	Asian Indian (n=354)
12	166	206
20	164	218
40	145	248

Shaper *et al.*, Lancet: 534, 1959

Asian Indians in England and South Africa have higher rates of CAD despite having similar plasma cholesterol levels. Subsequent studies from Europe and South Africa demonstrated that the CAD death rates in Asian Indians were higher than the indigenous populations, despite similar plasma levels of cholesterol. Shown in Fig. 6 are the CAD mortality rates from England (1970-1983). The mortality rates were classified based on the country of origin of the subjects and standardized by comparison with age- and sex-matched English men and women (Balarajan *et al.*, 1991). Subjects born in India, Pakistan, Bangladesh and Sri Lanka were collectively referred to as "Indians" in this study. The standardized CAD mortality rates in the Indian men and women were 36% and 46% higher than English subjects, respectively. The inter-ethnic differences in standardized mortality rates were even greater in the younger age group. Indian men, age 20-49, had a 65% increase in rate of ischemic heart disease when compared to

Englishmen of similar age (data not shown). The change in mortality rate between 1970-72 and 1979-83 was also measured in this study. The CAD mortality rate fell in Western Europeans, as it did in Americans (data not shown), during this time period. In contrast, the CAD mortality rates *increased* in Asian Indians over this same time period. Individuals from the Caribbean, who were mostly of African descent, had a strikingly low CAD mortality rate, which dropped over the decade; but West Indians had a much higher mortality rate from strokes (Balarajan *et al.*, 1991).

Other smaller, observational studies from England also reported a higher incidence of CAD in Asian Indians and a lower incidence of CAD in Africans and Caribbean immigrants (Cruickshank *et al.*, 1980; Pedoe *et al.*, 1975).

The incidence of CAD in Asian Indians living in South Africa is also higher than in the local Caucasian population. White South Africans have the highest rate of ischemic heart disease in the world (Wyndham *et al.*, 1978), which is a distinction that unfortunately is equaled or surpassed by the South African Indians (Fig. 7 and 8) (Seedat *et al.*, 1982; Derry *et al.*, 1987).

Fig. 6 **Mortality from Ischemic Heart Disease (ages 20-69) in Britain by County of Birth (1970-72 ; 1979-83)**

	Standardized Mortality Rate(%)		% Change (1970-72 to1979-83)	
Country of Origin	Men	Women	M	W
Indian subcontinent	136	146	+6	+13
Western Europe	77	81	-8	-7
Caribbean*	45	76	-8	-15

* Had highest mortality from strokes Balarajan *et al.* BMJ 302: 560, 1991

Fig. 7

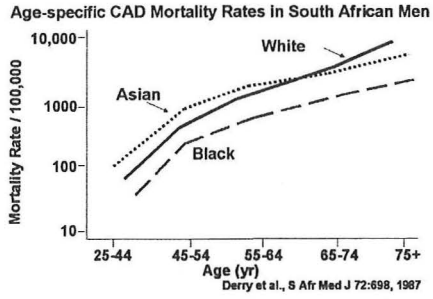
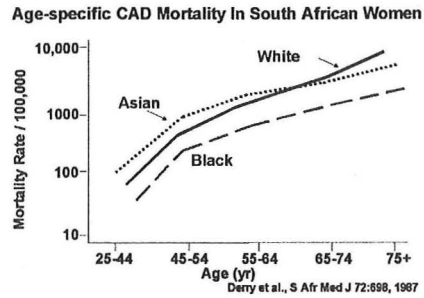


Fig. 8



A more recent study compared the relative age-standardized rates of CAD in the Chinese, Malay and Indians in Singapore and found the rates in Indians to be almost four times that of the Chinese and twice that of the Malay (Hughes *et al.*, 1990).

The rate of CAD in urban Indians is similar to rates in Western countries. Do Asian Indians living in India also have a higher rate of CAD, as would be expected if the major cause of the increase were due to ethnic-specific genetic differences? Unfortunately, no large, population-based studies have been performed in India to provide an accurate assessment of CAD incidence or mortality rates. One survey in a northern Indian city estimated CAD prevalence by screening for EKG changes; they found that the prevalence of CAD was similar to that estimated for Tecumseh, MI (Sarvothan *et al.*, 1968). In underdeveloped populations, CAD usually first appears in the upper socioeconomic groups and then filters down to the lower socioeconomic groups (Marmot *et al.*, 1978). This is true in urban India where there is a direct relationship between CAD rate and socioeconomic status. Surprisingly, socioeconomic status appears to have no effect on CAD risk in Asian Indians residing outside of India (McKeigue *et al.*, 1989); this suggests that any differences in lifestyle associated with socioeconomic status contribute only modestly to cardiac risk compared to the shared ethnic susceptibility to CAD.

The prevalence of diabetes, hypertriglyceridemia and reduced plasma levels of HDL-cholesterol are high in Asian Indians. So why do Westernized Asian Indians have such elevated rates of CAD? The plasma levels of cholesterol and blood pressure levels do not differ significantly between Asian Indians and Caucasians (Fig. 9). In general, Asian Indian men have a similar or lower frequency of smoking than the local populations, with the one exception being the Bangladeshi, who are very heavy smokers (Silman *et al.*, 1985). Overseas Asian Indians tend to have a higher plasma level of triglycerides and lower plasma levels of HDL-cholesterol. Asian Indians in England consume a diet rich in polyunsaturated fatty acids (P/S ratio of .85 compared to .28 for the British), which may contribute to the lower plasma levels of HDL-cholesterol seen in some studies (McKeigue *et al.*, 1985).

Asian Indians also have higher plasma levels of Lp(a) than Caucasians (but lower than Africans)(Low *et al.*, 1996). In one small study, the mean plasma Lp(a) levels was higher in Indians with angiographically-documented CAD than in those with no CAD (27 vs. 15 mg/dl) (Gupta *et al.*, 1996). Additional prospective studies will be required to assess the magnitude of the risk associated with a high Lp(a) in Indians.

Fig. 9

Comparison of Cardiac Risk Factors in Asian Indians (I) and British (B)

Cholesterol:	**I ≈ B**
Hypertension:	**I ≥ B**
Smoking:	**I ≈ B**
↑TG and ↓HDL-C	**I > B**
Lp(a)	**I > B**
Diabetes:	**I >> B**

Fig. 10

Prevalence of Glucose Intolerance in South Asians: 75 g Glucose Load, 2-h Plasma Glucose > 11.0 mmol/l

Year	Place	Sex	Age	Diabetes(%)
1983	Fiji	M	35-	25%
		F	35-	22%
1985	South Africa	M & F	30-	22%
1988	India	M & F	45-64	29%
1988	London	M	35-69	22%
		F	35-69	23%
1987	U.S.A Whites	M & F	45-64	10%
	Blacks	M & F	45-64	18%

McKeigue, J Clin Epidemiol 42: 597-609

The most striking difference between Indians and most other ethnic groups is the higher incidence of diabetes. An excess of glucose intolerance and insulin resistance has been noted in Asian Indians in many different countries of the world (Fig. 10) (for review, see McKeigue *et al.*, 1989). On average, 25% of the Asian Indian population has glucose intolerance (as defined by a 2 h glucose of >11 mmol/l after a 75 gm glucose load) and/or overt diabetes. No gender-specific difference in the frequency of diabetes has been observed in Asian Indians, which is unlike most other ethnic groups, where diabetic females predominate. Grundy and his colleagues have shown that non-diabetic Asian Indian men have significantly lower glucose disposal rates and more truncal subcutaneous fat than do Caucasians (Chandalia *et al.*, 1999). An understanding of the molecular basis for these metabolic differences may provide insights into why this ethnic group is more susceptible to CAD, and allow for the development of a more targeted prevention strategy in Asian Indians.

Differences in risk factor profiles do not explain the higher rates of CAD in Asian Indians. The higher frequency of insulin resistance in Asian Indians may contribute to, but does not fully account for, the higher incidence of CAD in this population. The other factors that contribute to the increased susceptibility to CAD in Asian Indians are not known, but have the following characteristics:

(1) They are equally important in Indian men and women, since the magnitude of the increase in CAD risk is similar in both sexes.

(2) They are shared by a wide range of individuals from various geographical locales, including India, Pakistan and Bangladesh.
(3) Their effect is dependent on the exposure to other risk factors associated with urbanization or migration, since rural Indians have very low rates of CAD.

THE INCREASING RATE OF CAD IN AFRICAN-AMERICANS

The first epidemiological study to examine CAD in Blacks: The Evans County Study (1960). The Framingham study was the first large, population-based study to examine the epidemiology of heart disease. This study provided fundamental insights into factors contributing to cardiac risk and is one of the great success stories of the National Institutes of Health. A major limitation of the study, which was recognized in the early 1960's, was the low number of African-Americans and other minorities included in the study. Framingham is over 95% Caucasian, so the relevance of its findings to other ethnic groups is questionable.

A general mindset evolved in the 1960's that individuals of Africans descent were "immune" to CAD. This conclusion was based on the experience of physicians in Africa and other regions of the world where ischemic coronary disease was noted to be distinctly uncommon in African immigrants (see above). As is the case in India, very few studies have been performed to assess the true incidence of CAD in Africa. The three most common causes of heart disease in Ibadan, Nigeria are hypertensive cardiomyopathy, rheumatic heart disease, and dilated cardiomyopathy of unknown etiology (Fig. 11) (Akinkugbe *et al.*, 1990). The prevalence of hypertension in Nigeria ranges from 5% to 20% in urban adults and is rare in rural regions. Ischemic heart disease comprises only 5% of heart disease in Africa, even in urban areas.

Africans have low plasma levels of cholesterol, but the levels are rising in association with increasing income and Westernization. High-income Africans and Europeans have similar mean plasma levels of cholesterol (Fig. 12). It can be anticipated that the incidence of CAD events will progressively rise in Africa with any increase in prosperity, unless preventive measures are instituted.

Fig. 11

Heart Disease in Africa

- Hypertensive heart diseases (28%)
- Rheumatic heart disease (22%)
- Dilated Cardiomyopathy (23%)
- Ischemic heart disease (5%)

Akinkugbe *et al.*, Cardiovasc Clin 21:377-91

Fig. 12

Relationship Between Mean Total Plasma Cholesterol and Income in Nigerians

Year	Income		
	Low	High	European
1958	138	202	204
1968	146	208	219
1980	143	193	
1988		187	209

Akinkugbe *et al.*, Cardiovasc Clin 21:377-91

The concept that individuals of African descent have very low rates of ischemic heart disease was supported by the clinical impressions of a handful of physicians working in Southern locales of the United States, where the incidence of CAD among Whites is high. Based on these anecdotal reports, the NIH sponsored its first population-based study of CAD in the racially mixed population of Evans County, Georgia (McDonough *et al.*, 1965). Evans County is located 60 miles from Savannah. The ethnic composition of this rural county was 66% Black and 33% White at the time the sample was collected (1960-1962). Blood was collected from every person between the ages of 40 and 74; each person also received a careful physical exam and EKG. A random sample of 50% percent of the county residents

between ages 15 and 39 years were also included in the study. A total of 3,102 of the 3,377 eligible subjects in the county were sampled. The first major finding of this study is shown in Fig. 13 (Cassel *et al.*, 1971; Hames *et al.*, 1996). The prevalence of CAD was strikingly lower in Black men than in White men. Black men had a greater than 3-fold lower CAD prevalence than White men (2% vs. 7%). The difference between Black and White women was much more modest (3.4% vs. 3.7%).

Fig. 13

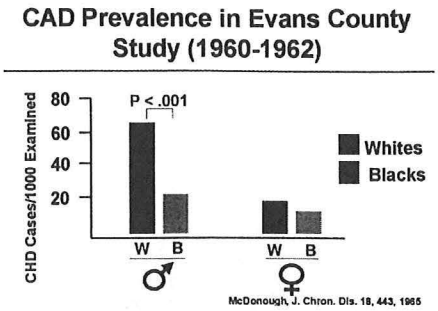
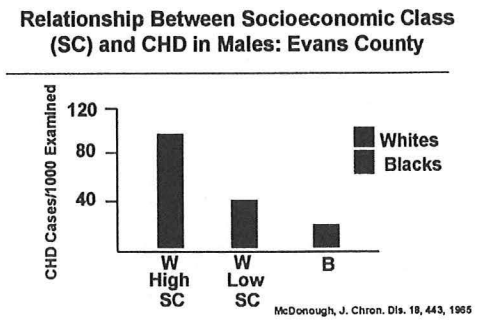


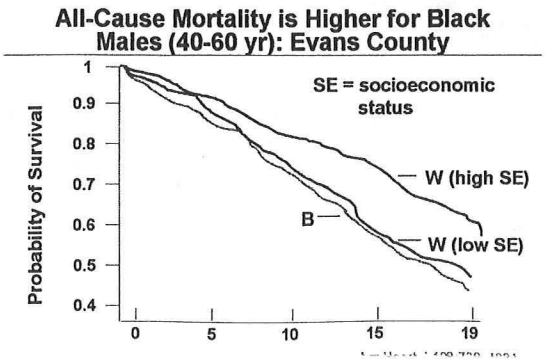
Fig. 14



Socioeconomic differences between Blacks and Whites contribute to lower CAD rates in Black men in Evans County. To determine if the observed difference in CAD prevalence was due to a difference in socioeconomic status between Blacks and Whites living in rural Georgia, a comparison of the CAD prevalence between White men with a high socioeconomic status, White men with low socioeconomic status, and Black men was performed (Fig. 14). The prevalence of CAD in the Whites with a low socioeconomic status was more similar to that seen in the Blacks, who were almost exclusively of low socioeconomic status. These data strongly suggest that a substantial portion of the ethnic difference in CAD prevalence in men was due to factors associated with socioeconomic status, rather than being due to ethnic-specific differences in disease susceptibility. No significant difference in CAD prevalence was seen between White women of high and low socioeconomic status, so a similar analysis could not be performed in women.

All-cause mortality rate in Black men is higher than White men in Evans County. The population of Evans County was followed closely over the ensuing 19 years (Tyroler *et al.*, 1984; Hames *et al.*, 1993). A comparison of the overall mortality rate in the Black and White men in Evans County is shown in Fig. 15. The mortality rate was significantly higher in Black men than in White men of high socioeconomic status. Black and White men of low socioeconomic status had similar mortality rates. Thus, the life expectancy for Black men was significantly lower than for White men in Evans County, and this difference was not simply due to differences in ethnicity. This data provided the first clue that socioeconomic status contributed significantly to ethnic differences in CAD in the United States and revealed a higher total mortality rate in Blacks than Whites. The difference in total mortality rates between these two ethnic groups has continued to widen.

Fig. 15



CAD is examined in a population of urban Blacks: the Charleston Heart study (1960). A second population-based study was initiated in 1960 in an urban area. The Charleston Heart Study included a random sample of the Charleston population over the age of 35 years (Peery *et al.*, 1971). In 1964, after it became obvious in the Evans County study that socioeconomic status contributed importantly to cardiac risk, the sample was supplemented with Charleston Blacks of high socioeconomic status. Shown in Fig. 16 is a comparison of the relative prevalence of CAD in men and women in the two Southern studies. In Charleston, like Evans County, the prevalence of CAD was lower in Black than White men, although the difference was not as large. A major difference between these two studies was that the prevalence of CAD was similar in Black and White women in the Charleston Heart Study.

Fig. 16

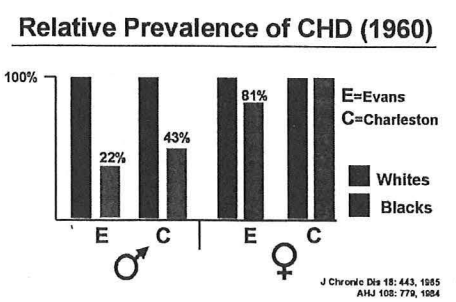
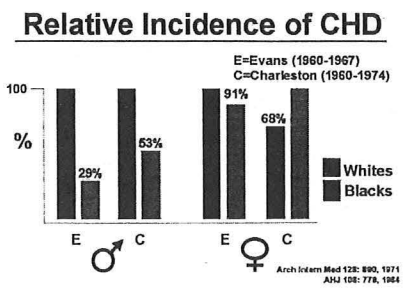


Fig. 17



The incidence of CAD and the CAD mortality rates are higher in Black women in Charleston. The relative incidences of CAD and the relative mortality rates for CAD in both the Evans and the Charleston studies are shown in Figures 17 and 18, respectively (Cassel *et al.*, 1971). In the Charleston Heart study, both the incidence of CAD and the mortality rate from CAD were higher in Black women than White women, which has been a fairly consistent finding, up until today. Too few CAD deaths occurred in the women of Evans County to analyze the mortality rates in this group.

Fig. 18

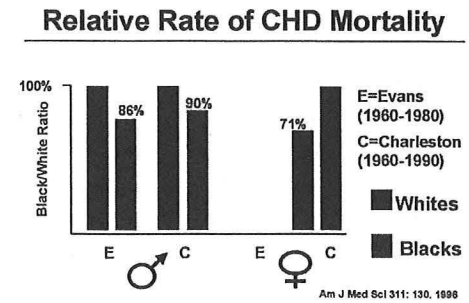
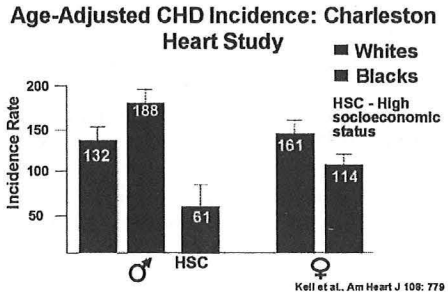


Fig. 19



Improved socioeconomic status is associated with improved CAD status in Black men in Charleston. Due to the supplementation of the Black cohort with Black men from the high socioeconomic group in the Charleston Heart study, the effect of socioeconomic status on CAD incidence could be examined in Blacks (Fig. 19) (Keil *et al.*, 1984). The high-socioeconomic Black men had a significantly lower age-adjusted

CHD incidence than either the White men or other Black men in the study, which resembles the present-day inverse relationship between socioeconomic status and CAD events. The change in relationship between socioeconomic status and CAD incidence from a direct relationship (as seen in the Whites in the Evans County study) to an indirect relationship (as seen in the Blacks in the Charleston follow-up study), reflects the general pattern seen in populations in association with urbanization (Marmot et al.,1978). CAD first appears in high socioeconomic groups and then the incidence falls with that group, with improved health habits and access to care.

Black men in Evans County and Charleston have a lower prevalence and incidence of CAD and a lower CAD mortality rate, which is not explained by differences in cardiac risk factor prevalence.

So, why did the southern Black men in these two studies have a lower prevalence and incidence of CHD, as well as a lower CAD mortality rate? Some of the characteristics of the Black and White cohorts from the Charleston Heart Study are summarized in Fig. 20; the risk factor profiles in the participants of the Evans County Study were similar (data not shown). The plasma cholesterol levels were lower and HDL-cholesterol (C) levels were higher (data not shown, see below) in the Blacks (Keil *et al.*, 1991). The weights of the two groups were not significantly different (data not shown). The mean blood pressure levels of the Blacks were significantly higher than the Whites, with the most pronounced difference being between the two groups of women. Systolic hypertension (BP>150) was associated with a 2-3 fold higher CHD mortality in this study (Keil *et al.*, 1993). Not surprisingly, the higher blood pressures were associated with more left ventricular hypertrophy. Fewer Black women smoked, but Black women had a 2-3 fold higher frequency of diabetes. Thus, for most cardiac risk factors, Blacks had a similar or worse risk profile, especially Black women.

Did Blacks (especially Black men) have lower than expected rates of CAD, given their worse cardiac risk profile, because of an ethnic-specific response to the risk factors? The magnitude of CAD disease burden associated with the cardiac risk factors did not differ between Whites and Blacks (Keil *et al.*, 1993). Thus, neither a difference in frequency of the major risk factors, nor an ethnic-specific difference in the effect of the cardiac risk factors explained the lower than expected risk of CAD in the Blacks in these studies.

Fig. 20

Cardiac Risk Factor Profiles: Charleston

	Men		Women	
Variable	Black (n=333)	White (n=652)	Black (n=453)	White (n=739)
Cholesterol	221	237	234	232
SBP	153	141	162	139
DBP	90	84	92	82
Smoking (%)	56	61	26	40
Diabetes	2.4	3.4	5.7	2.2
EKG-LVH	1.7	0.8	10.5	6.0
Laboring	50.8	1.7	46.7	0.6

Keil *et al.*, 1991

The life-styles and the socioeconomic status of the Blacks and Whites in these studies were very different. In the Charleston study, a much higher proportion of the Blacks performed manual labor (Fig. 20), and their educational level was lower. The significantly greater daily physical exertion of the Blacks may have protected them from the effects of the other cardiac risk factors.

The lower access to medical care of Blacks (especially Black men) in these two southeastern locales during the time period in which these studies were performed may contribute to the observed lower rate of CHD in the Black men. But further evidence that Blacks had lower than expected rates of CHD than expected based on cardiac risk profiling was provided by a large general survey of the US population.

Black men have lower rates of CAD mortality than expected by cardiac risk profiling: NHANES I (1971-1990). The next large population-based study that compared the incidence of CAD in Blacks and

Whites was the NHANES 1 Epidemiological Study (Miller *et al.*, 1978). This study sampled individuals between the ages of 25 and 74 who had no history of heart disease at baseline (1971-1975). The cohort was followed for 19 years with only 5.5% being lost to follow-up. Shown in Figures 21 and 22 are the proportion of the men who survived free of CAD over the time-course of the study (Gillum *et al.*, 1997). Black men fared better than White men in all three age categories, although the differences between the ethnic groups were greater in the 55-64 and the 65-74 year age groups. Young Black women fared more poorly than age-matched White women, but the older Black women had less CAD than the age-matched Whites. When these data were adjusted for the presence of cardiac risk factors, the Black and White women had similar rates of CAD but the Black men had significantly lower than expected rates of CAD, which was a sex-specific pattern also seen in Multiple Risk Factor Intervention Trial (data not shown). These finding are consistent with Black men enjoying relative protection from CAD over the time period studied.

Fig. 21

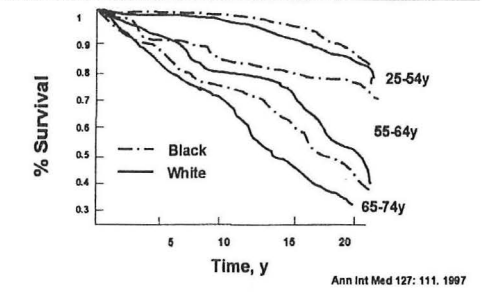
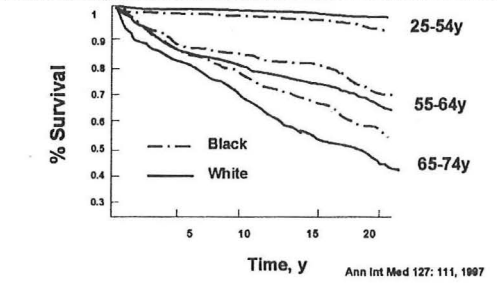


Fig. 22



Blacks have higher total mortality and total cardiovascular mortality rates but similar CAD rates to Whites. A subset of the NHANES cohort (years 35-64) was followed for 13 years. The total mortality was 2- to 3-fold higher in the Blacks than in the Whites (data not shown) (Otten *et al.*, 1990). Approximately 54% of the deaths in both the Blacks and the Whites were due to cardiovascular disease, which included ischemic heart disease, hypertensive disease, cerebrovascular disease and other heart disease (cardiomyositis, valvular disease, etc.) (Fig. 23). The relative rates of total cardiovascular deaths were 34% higher in Blacks than Whites, largely due to a higher rate of death due to hypertensive and cerebrovascular disease. The mortality rate ratio for ischemic disease between the two groups was not significantly different (1.04); ischemic heart disease was the cause of death in 25.9% of the Black and 33.1% of the Whites. Thus, although the total cardiovascular disease mortality rate is higher in Blacks, the rate of ischemic disease was not.

Fig. 23

Age-Adjusted Mortality Rates for Whites and Blacks (35-77 yr)- 1971-1984

Category of Death (*International Classification Codes*)	Whites		Blacks		Blacks/ Whites Mortality Rate Ratio
	Deaths (n)	Mortality Rate (%)	Deaths (n)	Mortality Rate (%)	
Cardiovascular (*390-448*)	809	53.8	196	54.4	1.34
Ischemic (*410-414*)	499	33.1	93	25.9	1.04
Hypertensive (*402, 404*)	20	1.3	16	4.4	4.39
Cerebrovascular (*430-438*)	137	9.2	50	13.8	1.98
Other heart (*415-429*)	105	7.0	29	8.1	1.54

Otten *et al.*, JAMA 263: 845-850

This study demonstrates a general problem in this literature. Total cardiovascular mortality rates are not the same as CAD mortality rates; this is particularly true in Blacks, due to the higher prevalence of hypertension-associated cardiovascular deaths. Total cardiovascular mortality rates are uniformly higher in Blacks than Whites, whereas data supporting a higher rate of ischemic cardiac death in Blacks is more problematic and less convincing, as discussed below.

Other common problems encountered when CAD incidence and mortality rates in Blacks are compared to Whites are the following, which will be discussed below:

- Crude death rates for CAD are meaningless, since the Black population is younger than the White population
- Age adjustment cannot substitute for age-specific rates
- Greater inaccuracy of diagnosis on death certificate
- Undercounting of Blacks, especially Black men

More Blacks die at a younger age of CAD (and non-cardiac) deaths. An apparent paradox exists: Blacks have a greater risk factor exposure and yet do not have a proportionally higher rate of CAD than Whites. A contributing factor to this paradox may be that the death rate from CAD (as well as non-cardiac causes) is higher in the younger age groups in Blacks, so there are proportionally fewer Blacks in the older age groups, when coronary disease is more common. An analysis of the age-specific mortality rates from ischemic heart disease in individuals over the age of 35 was performed using mortality data collected by the Center for Disease Control and population data from the Census Bureau (MMWR). As expected, the *absolute* rate of CAD deaths in men was significantly higher than that seen in women except in the very elderly (over age 85) (data not shown). Two major differences were seen between the Blacks and Whites (Figs. 24 and 25). Blacks outnumbered Whites in CAD mortality in all age groups, except the elderly. The most dramatic differences in CAD mortality were in the younger age groups, where Black women died of CAD at 2-3 times the rate of White women. Interestingly, the age-adjusted rates of CAD deaths were similar in the two ethnic groups in this study. The higher rates of CAD deaths in the younger Blacks were balanced by lower rates in the elderly Blacks. Moreover, the non-cardiac mortality rate in Blacks was higher than Whites in the younger age groups.

Fig. 24

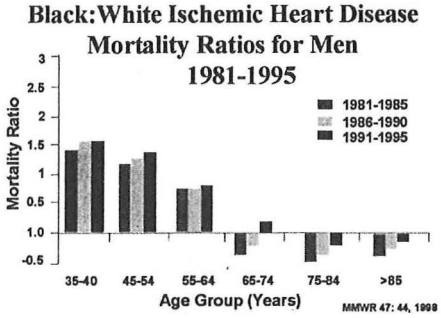
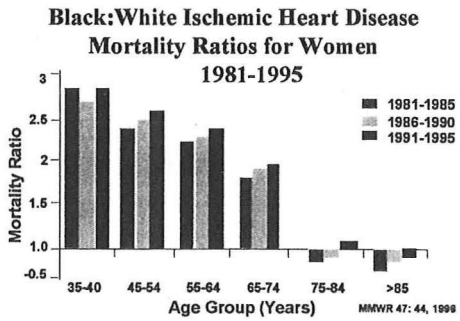


Fig. 25



In support of Blacks having more CAD events at an early age were the findings of the National Hospital Discharge Survey, which looked at the rates of admissions for acute myocardial infarctions. Under age 50, the rate is higher in Blacks than Whites but this pattern reverses in the older age group (over 50 years) (Roig *et al.*, 1987) [Fig. 26]. The mean age for MIs in this study was five years younger in Blacks than Whites.

Fig. 26

National Hospital Discharge Survey: Admission Rate for MI

- **< age 50: Blacks > Whites**
- **> age 50: Whites > Blacks**
- **Mean age of Blacks with MI is 5 yr younger than Whites**

Am J Public Health 79: 437, 1989

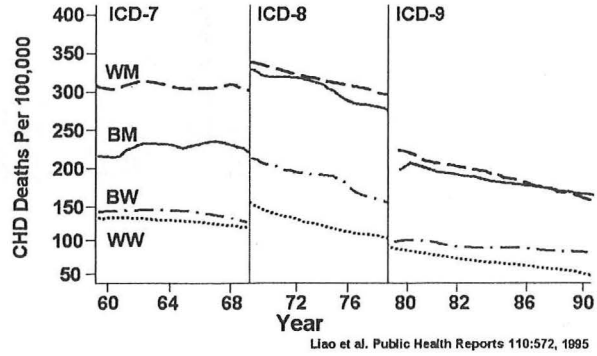
A major problem with CAD mortality data, especially in Blacks, is inaccurate diagnoses. The accuracy of any analysis of CAD mortality data depends on the reliability of the diagnostic classification, which has been shown to be problematic (Sorlie *et al.*, 1987). A higher proportion of young Blacks die outside hospitals (see below), and CAD may be the presumptive diagnosis, but not the correct diagnosis. In Baltimore in the early 1970's, the vital statistics were rigorously compared with clinical and autopsy data; deaths were misclassified as being due to CAD in 33% of the Black men, compared to 18% of the White men. In the Community Cardiovascular Surveillance Program, which examined the data supporting all CAD events and deaths at 12 US sites, only 50% of CHD deaths and events in Blacks could be verified upon review of clinical and autopsy data (Lee *et al.*, 1990).

The rate of deaths due to coronary heart disease is falling more rapidly in Whites than Blacks. The rate of death from coronary heart disease has fallen consistently and persistently in the White population of America since the 1960's. Has a similar trend been seen in Blacks? The age-adjusted coronary heart disease mortality rates in White and Black men and women are shown in Fig. 27 (Liao *et al.*, 1995). The data are broken into three sections due to the use of different International Classification of Disease (ICD) codes to diagnose coronary heart disease during these periods (ICD 410-415). Between 1960 and 1968, Black men had a much lower rate of coronary heart disease deaths than Whites; Black women had a slightly higher coronary heart disease mortality rate during this time span. Between 1969 and 1979, death due to hypertensive cardiac disease was included in the analysis, which accounts for the dramatic increase in the rate of coronary heart disease deaths in the Blacks within this time period. Between 1980 and 1990 the rates of coronary heart disease deaths fell in all four groups, but the rate of reduction leveled out in both Black men and Black women. As a result, the age-adjusted rate of coronary heart disease in Black men has outpaced that of White men since ~1986, and the difference in rates between Black and White women continues to diverge.

This analysis may actually underestimate the rate of coronary heart disease mortality, since the data has been age-adjusted and a greater proportion of cardiac events occur in the elderly. Another potential problem with this analysis is that the major subgroup being assessed is the elderly (over 60 years old) who were born in the 1920's, and do not reflect the current environment (Kuller, 1995).

Fig. 27

Age-Adjusted Coronary Heart Disease Mortality, United States, 1960-91



Liao et al. Public Health Reports 110:572, 1995

The ethnic paradox: Blacks have a higher prevalence of cardiac risk factors (hypertension, diabetes, and obesity) than Whites but not a proportionally higher rate of CAD. What is the reason for these observed ethnic differences in cardiac events? A comparison of the prevalence of risk factors in Blacks and Whites from NHANES II and III (ages 20-74), is shown in Fig. 28 (Kuller *et al.*, 1995). The prevalence of hypertension, diabetes and obesity are significantly higher in the Black population. These risk factors are physiologically interdependent and cluster together more commonly in Blacks than Whites (Hutchinson *et al.*, 1997).

Kaufman *et al.* (1995) examined the frequency of hypertension in seven different cohorts of Africans or individuals of African descent (Fig. 29). As expected, the prevalence of hypertension in women increased with movement out of Africa. To determine the effect of obesity on blood pressure, he determined the prevalence of hypertension expected after normalization of the BMI; the consistency of reduction in blood pressure across such diverse populations is striking. He estimated that the increase in body weight associated with emigration explains about 40% of the associated increase in blood pressure.

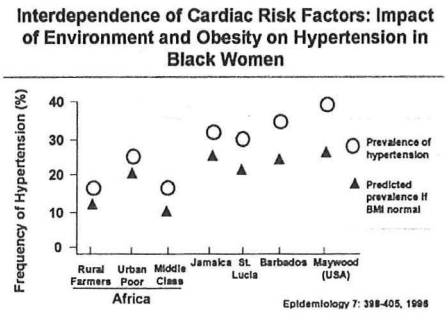
Fig. 28

Comparison of Prevalence of Age-Adjusted Risk Factor Profiles (NHANES II & III) (Ages 20-74)

	Men %		Women %	
	Whites	Blacks	Whites	Blacks
Hypertension	43.1	48.5	31	45
Obesity	24.9	27.5	25	46.1
Diabetes	2.9	4.4	3.1	5.5

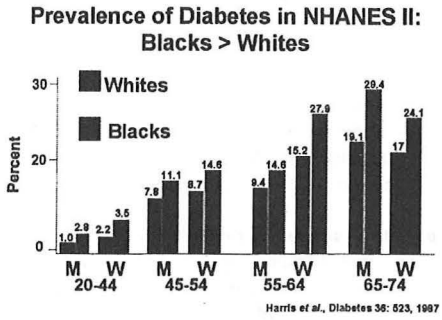
Kuller, Public Health Reports 110: 672, 1995

Fig. 29



Another striking difference in the risk factor profile of Blacks and Whites that is also a consequence of the higher rate of obesity, is the much higher rate of insulin resistance and diabetes in Blacks (Fig. 30).

Figure 30A



Comparison of Risk Factor Profiles in Blacks and Whites

Cholesterol:	**B ≈ W**
Smoking:	**B ≈ W**
Hypertension:	**B >> W**
Diabetes:	**B > W**
Obesity:	**B > W**

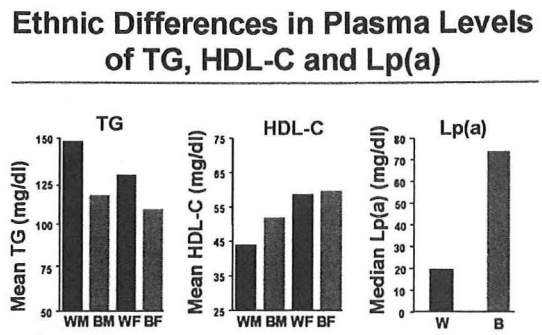
*** Higher percentage of Blacks smoke, but smoke fewer cigarettes**

Public Health Report 110: 672, 1995

Blacks have lower plasma triglyceride levels and higher plasma levels of HDL-cholesterol (men only). The plasma levels of cholesterol or the LDL-cholesterol do not differ between Blacks and Whites (data not shown). However, there are other differences in lipid and lipoprotein levels between Blacks and Whites. Despite having a higher incidence of obesity and diabetes, Blacks have significantly lower plasma levels of triglycerides (Fig. 31). The metabolic and molecular basis for this apparent contradiction is a major focus of study in the Reynolds grant. Having a high triglyceride level may be a more powerful cardiac risk factor in Blacks than Whites (Freedman *et al.*, 1988).

In general, there is an inverse relationship between the plasma levels of triglycerides and HDL-cholesterol. Thus, it is not be surprising that the plasma levels of HDL-cholesterol are significantly higher in Black men than White men since Black men have significantly lower plasma triglyceride levels. Jonathan Cohen has shown that sequence polymorphisms in hepatic lipase contribute to the higher plasma HDL-cholesterol levels in Black men (Cohen *et al.*, 1999). Why Black women do not also have higher HDL-cholesterol levels than White women is not known.

Fig. 31



Blacks have 3-4 fold higher median plasma Lp(a) levels, but not an associated increase in CAD. The most dramatic difference in lipoprotein levels between the two ethnic groups is in the plasma levels of lipoprotein(a) [Lp(a)]. High plasma levels of Lp(a) are an independent risk factor for the development of CAD in Caucasians. Blacks have 3-4 fold higher mean plasma levels of Lp(a) (Guyton *et al.*, 1985), and yet do not have a correspondingly higher rate of CAD. Only a few small studies have been performed to examine the question of whether plasma levels of Lp(a) are an independent risk for CAD in Blacks (Moliterno *et al.*, 1995). None of these studies have convincingly demonstrated that high plasma levels of Lp(a) is a cardiac risk factor in Blacks.

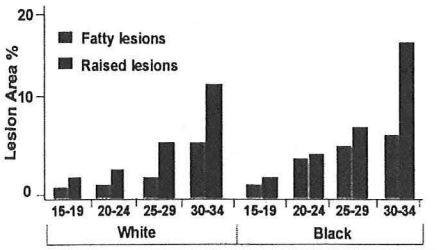
Apo(a) is highly polymorphic is size and it may be that the size of the apo(a) isoforms are more important than the level of Lp(a) (Sandholzer *et al.*, 1997). In general small apo(a) isoforms are associated with higher plasma levels of Lp(a), so it has not been possible to convincingly demonstrate that apo(a) isoform size is a cardiac risk factor that is independent of plasma Lp(a) level. In Blacks the relationship between apo(a) isoform size and plasma level of Lp(a) is different. Both small- and medium-sized apo(a) isoforms are associated with high plasma levels of Lp(a) (Marcovina *et al.*, 1996). In the Reynolds project we will examine if apo(a) isoforms of smaller size are associated with coronary atherosclerosis in Blacks.

Pathological differences in coronary atherosclerosis in Blacks and Whites; young Blacks have more fatty lesions but not significantly more raised plaques in their coronary arteries than Whites. Do the pathological lesions in the coronary arteries differ in character or quantity between Blacks and Whites? This question has been addressed by the Pathological Determinants of Atherosclerosis in Youth (P-DAY) Study, where the right coronary arteries were collected from accident victims, ages 15-34. As had previously been observed in young men who died in Korea, fatty lesions were readily apparent in the

youngest age group. Half of the samples from the 15- to 19-year-olds had intimal fatty lesions in the RCA. By age 34, 80% of the sample had lesions. Shown in Fig. 32 and 33 are comparisons of the fatty and raised lesion areas in the right coronary arteries of Black and White men and women, respectively. Note that at every age Blacks have significantly more fatty lesions than Whites (Strong *et al.*, 1999). Blacks tend to have more raised lesions, although the difference in this parameter between the ethnic groups is not statistically significant.

Fig. 32

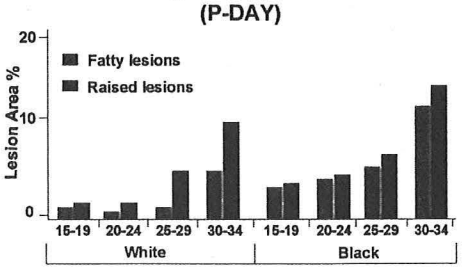
Comparison of Right Coronary Artery Lesion Area in Young Black and White Men (P-DAY)



JAMA 281: 727, 1999

Fig. 33

Comparison of Right Coronary Artery Lesion Area in Young Black and White Women (P-DAY)



JAMA 281: 727, 1999

The most sensitive current methodology to detect coronary atherosclerosis noninvasively is using Electron Beam Computer Tomography (EBCT), which detects calcium within lesions. This will be the method that will be used in the Reynolds project to assess for the presence of coronary atherosclerosis. A comparison between the prevalence of raised plaques and calcification in the P-DAY study is shown in Fig. 34 and 35. For the same prevalence of fibrous plaques, Whites tend to have more calcified plaques than Blacks, especially the women.

Fig. 34

Comparison of Prevalence of Complicated and Calcified Lesions in RCA of Black and White Men (P-DAY)

Age	n (W/B)	Prevalence of Lesions (%)			
		Fibrous Plaque		Calcified	
		White	Black	White	Black
15-24	453/571	25	28	0	0
25-29	287/326	39	42	2.4	0.3
30-34	244/222	51	49	2.9	2.7

Strong, JAMA 281: 727,1999

Fig. 35

Comparison of Prevalence of Complicated and Calcified Lesions in RCA of Blacks and White Women (P-DAY)

Age	n (W/B)	Prevalence of Lesions			
		Fibrous Plaque		Calcified Lesions	
		White	Black	White	Black
15-24	168/41	10	15	0	0
25-29	103/96	21	25	1.0	0
30-34	90/87	32	38	5.6	1.1

Strong, JAMA 281: 727, 1999

The observation that Blacks may have less coronary calcification is supported by two other studies. The first small study compared the prevalence of coronary calcium using digital subtraction fluoroscopy and found that African-Americans had a significantly lower prevalence of calcium when compared to Asian Indians and Caucasians (Tang *et al.*, 1995). An autopsy study also noted a decrease in calcification in Blacks relative to Whites, after controlling for the amount of fibrous plaques (Eggen *et al.*, 1965). The results of these studies suggest there may be ethnic differences in lesion development and maturation.

These differences may result in ethnic-specific differences in clinical outcome, especially if lesion calcification is related to plaque stability.

Blacks also have a significant increase in the thickness of the common carotid wall, but not the wall of the internal carotid (Manolio *et al.*, 1994; Howard *et al.*, 1993). It has been proposed that these localized differences in wall thickness may reflect differential regional responses of the media and intima. The common carotid is subjected to a higher blood flow and more elevated blood pressures, which are more common in Blacks, whereas the internal carotid may be more sensitive to factors that affect the intima, which may be less important in Blacks.

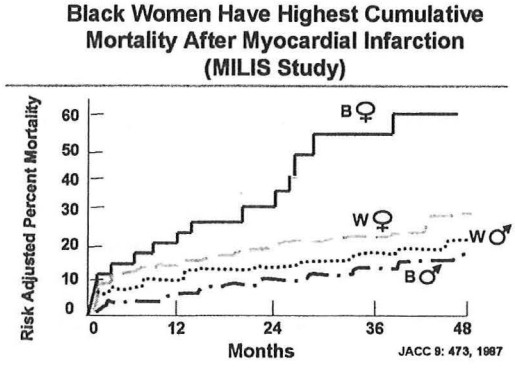
Multiple factors contribute to the increasing CAD mortality in Blacks. What are the factors that contribute to the increasing rates of CAD mortality in Blacks? First, as previously reviewed, the cardiac risk profile of the Black population continues to worsen. As the BMIs of Blacks increase, so do the rates of hypertension, diabetes and hyperlipidemia. The higher rate of CAD mortality in Blacks cannot be attributed to ethnic differences in the RESPONSE to risk factors, as reviewed previously.

Possible factors that may contribute to the increase in CAD mortality in Blacks are the following:

(1) A higher rate of out-of-hospital deaths
(2) Fewer invasive procedures
(3) A poorer prognosis after having an MI due to more severe disease or co-morbidity
(4) Poor diagnostic criteria for ischemic disease in Blacks
(5) Lower socioeconomic class

More Blacks die suddenly and outside of hospitals. A greater proportion of Blacks who die from CAD do so before ever reaching the hospital (Gillum, 1989). The proportions of CHD deaths that are classified as sudden deaths are higher in young (<55 years) Blacks than Whites (Lee *et al.*, 1990). In general, the time that elapses between the onset of chest pain and arrival at the hospital is longer in Blacks than Whites (Cooper *et al.*, 1986). Problems with transportation can also occur. Blacks call 911 and use ambulances less frequently than Whites (Cooper *et al.*, 1986). There is no evidence that the chest pain that occurs in association with MIs differs in quality or severity in Blacks when compared to Whites. An exception may be Black women. In the Community Cardiovascular Surveillance Study, 60% of the Black women classified as having died of CAD had no prior history of chest pain (compared to 11% of White women) (Lee *et al.*, 1990). There may be less knowledge regarding the signs and symptoms of CAD in Black communities.

Fig. 36



Black women have a particularly poor prognosis after having an MI. In most studies, Blacks and Whites admitted to a hospital for management of an acute MI have similar survival rates (Roig *et al.*, 1987). Blacks have a worse prognosis after being discharged from the hospital for an MI, and this is especially true for Black women. Patients in the Mortality after Myocardial Infarction Study (MILIS) were followed for up to 48 months after myocardial infarction and the risk-adjusted mortality was determined for Black and White men and women (Fig. 36) (Tofler *et al.*, 1987). Black women had the lowest survival rate, despite the fact that they had the highest ejection fraction at cardiac catheterization. Black men

actually did slightly better than White men in this study. Although LVH has not consistently been shown to be an independent poor prognosticator in patients who suffer MIs, it may be so, especially in Black women.

The poorer prognosis in Blacks after a MI may reflect the fact that Blacks tend to be sicker when they have a MI. In the Community Cardiovascular Surveillance Study, the CHD mortality rates were higher but the rates of nonfatal MIs were significantly lower in Blacks (Lee *et al.*, 1990): thus, the proportion of total MIs that are fatal is twice as high in Blacks than in Whites. In the Beta Blocker Heart Attack Trial, Blacks had a significantly higher frequency of non-mural MIs, which may put them at greater risk of having a subsequent deadly, ischemic event (Haywood, 1984). Ethnic differences in the usage of drugs that decrease MI recurrence, such as lipid-lowering agents and aspirin, may explain some of the observed differences in post-MI outcome; no studies have been performed to systematically compare post-MI prescribing and compliance patterns between ethnic groups.

Fewer cardiac procedures are performed in Blacks. Another very consistent ethnic difference is the markedly decreased frequency of cardiac procedures performed in Blacks after MIs (for review see Ford *et al.*, 1995) (Fig. 37). On average, Blacks are 30-40% less likely to undergo coronary angiography than Whites, given the same clinical presentation. CABG and angioplasties are ~2-3 fold less likely to be performed in Blacks who have had MIs than in Whites (Oberman *et al.*, 1984; Ayanian *et al.* 1993; Ford *et al.*, 1995). The differences in procedures performed on Blacks cannot be attributed to differences in disease severity, the number of co-morbid conditions or the ability to pay (Wenneker *et al.* 1989). Even in an ethnically homogenous population in Canada, where there is universal health care coverage, there is a strong inverse relationship between income and mortality (Alter *et al.*, 1999). Behavioral and cultural differences, rather than ethnicity are likely to be responsible for the low rate of invasive cardiac procedures in Blacks. No studies have systematically examined whether there are ethnic differences in the rate of acceptance for the performance of procedures, including angioplasty and surgery, which may differ between the groups. In some studies Blacks have been found to be less likely to agree to have a CABG than Whites (Maynard *et al.*, 1986).

Fig. 37

Ethnic Differences in Cardiac Procedures Whites:Blacks

	White:Black
Angioplasty	~ 1.4
PTCA	~ 2.0
CABG	2 - 3

Ford, *Health Serv Res.* 30: 237-62

Blacks have a higher frequency of angina than Whites. The data from the Charleston Heart Study is shown in Figure 38. Note the very high frequency of angina in Black women.

In the Hypertension Detection and Follow-up Program, Black women had the highest percentage of subjects with angina (Fig. 39), but the presence of angina had no predictive value of CAD mortality (Langford *et al.*, 1984). In White and Black men and in White women, those that died in the follow-up period were 2-3 fold more likely to have had angina. In Black women no difference was seen in the frequency of cardiac deaths between the women who did or did not have angina (Haywood et al., 1984). In the Community Cardiovascular Surveillance Program Study, the highest rate of misclassification of nonfatal CAD on the hospital discharge summary occurred in Black women (Lee *et al.*, 1990).

Fig. 38

Incidence of Angina: Charleston Heart Study (1960-1974)

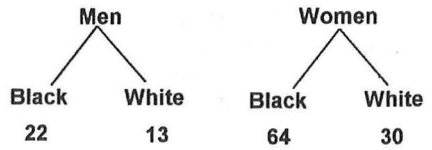


Fig. 39

Frequency of Angina More Common in Black Women: Hypertension Detection and Follow-Up Program

	n	Angina (%)	Deaths % Angina, yes	Deaths % Angina, no
White Men	1896	5.1	13.5	5.3
Black Men	1065	7.7	22.1	9.8
White Women	1180	8.6	9.8	4.6
Black Women	1344	9.9	5.3	5.0

Haywood, *Am Heart J* 108: 797, 1984

Another problem with the diagnosis of CAD in Blacks stems from ethnic differences in the frequency of EKG abnormalities. Since left ventricular hypertrophy is so common in Blacks, there is a 2-4 fold higher frequency of increased R-wave voltage and left axis deviation. Blacks have a 3-5 fold higher frequency of major T-wave changes. Black women have a 2-fold increase in ST elevations. It was also noted in the Charleston study that these EKG changes were less predictive of events (Bartel *et al.*, 1971; Keil *et al.*, 1991). The baseline EKG abnormalities may contribute to the reduced sensitivity and specificity of exercise tests in Black women (Simmons *et al.*,1988).

The problem of chest pain in Blacks, especially Black women. Black women are renowned for having angina of sufficient severity to warrant cardiac catheterization, and then being found to have clean coronaries at catheterization (personal communication, Richard Lange). In the Coronary Artery Surgery Study, a higher percentage of both Black men and women who presented with chest pain had clean coronaries at cardiac catheterization (47% vs. 20% in the men and 67% vs. 54% in the women) (Maynard *et al.*, 1986). The Blacks in this study had more cardiac risk factors than the Whites, but were also younger (mean age 46 vs. 52 years), which is typical of most series. In general, Blacks presenting to hospitals with angina are younger, have more associated cardiac risk, but have a higher frequency of clean coronaries on catheterization than do Whites.

The highest rate of sudden death in the Community Cardiovascular Surveillance Program Study due to CHD was in the Black women (Lee *et al.*, 1990) and yet Black women were three times less likely to have had evidence of CAD prior to the event than other subjects. This begs the question as to whether the high rate of CHD deaths in Black women are due to ischemic CAD, or some other cause. It has been hypothesized that the high rate of non-ischemic angina in Black women may be a consequence of hypertensive cardiomyopathy or due to reflux esophagitis secondary to obesity. Alternatively, the chest pain may be ischemic in etiology but due to small vessel disease or subendocardial ischemia resulting from LVH (Simmons *et al.*, 1988). Careful post-mortem studies are needed to determine the true cause of out-of-hospital deaths, particularly in Black women.

The paradox of Blacks having more clean coronaries but also more severe CAD at catheterization. The poor post-MI prognosis and high rate of sudden out-of-hospital cardiac deaths in Blacks may be because Blacks with CAD have more severe disease or more co-morbidity. Angiography findings for the Cook County Hospital Disease Registry confirmed a high frequency of clean coronaries at cardiac catheterization in Blacks, but those Blacks that had disease had more severe disease (Simmons *et al.*, 1988).

Environmental and behavioral factors are the major contributors to the increasing CAD mortality in Blacks. Environmental and behavioral factors, rather than genetic factors, are the major cause of the increase in CAD mortality in Blacks in this country. The worsening CAD health status of Blacks since the Evans County Study and the Charleston Heart Study reflect the changes in diet, physical activity, weight and behavior that have occurred in the Black population in the last third of this century. The resultant increases in the incidence of obesity and diabetes and the persistently high levels of inadequately controlled hypertension have all contributed to the worsening CAD status of Blacks in America. If anything, genetic factors have lessened the cardiac ischemic impact of the ever-worsening risk profile of Blacks.

Poorly defined factors associated with socioeconomic status and ethnic-specific cultural and environmental differences contribute substantially to overall risk in African-Americans. It been estimated that the increased prevalence of cardiac risk factors accounts for about 31% of the excess mortality in Blacks and that family income accounts for ~38% of the difference in total mortality between the races (Otten *et al.*, 1990). The difficulty (and perhaps impossibility) of controlling for differences in socioeconomic status between Blacks and Whites so as to identify the genetic factors cannot be underestimated and has been thoughtfully explored (Kaufman *et al.*, 1997). A dramatic illustration of this point is the recent determination of the likelihood that a 15-year-old would reach the age of 65 in

populations of Blacks and Whites from four different regions of the United States. There was as much variability within the ethnic groups, as between the ethnic groups. For example, only 37% of Blacks in Harlem will reach the age of 65 whereas 75% of Blacks living across the river will reach that age. Whites in Queens have only a slightly higher survival rate (80%) than Blacks in the same locale (Geronimus *et al.* 1996).

The epidemiological evolution of cardiovascular disease in Blacks. Richard Gillum (CDC) has attempted to provide a six-step model for the evolution of the increase in cardiovascular disease in Blacks associated with Westernization (Gillum *et al.* 1996) (Fig.40). The progressive increase in affluence and the associated increase in saturated fat and salt intake that accompanies urbanization and Westernization have a step-wise and progressive effect on hypertensive and ischemic heart disease.

Fig. 40

Stages in the Evolution of Cardiovascular Disease Among Individuals of African Descent

Stage	Affluence	Sat. fat	Salt	Smoking	Cardiovascular Disease	
					Hypertensive	Ischemic
1	0	+	+	0	0	0
2	+	++	++	+	++	0
3	++	++	+++	++	++++	+
4	++	+++	++++	+++	++++	++
5	+++	++++	++++	++++	++++	++++
6	++++	+++	+++	+++	++	+++

Gillum, NEJM 335: 1597-99

Representative examples of populations that fall within each stage:
Stage 1 : Precolonial Africans and modern rural and traditional Africans
Stage 2 : Modern urban Africans
Stage 3: Black populations in the West Indies
Stage 4: Modern rural populations of the Southern USA
Stage 5: Poor inner city dwellers in USA
Stage 6: Affluent inner-city or suburban dwellers in USA

Data supporting this model comes from a recent study that compared the rates of coronary heart disease (CHD) mortality between 1990 and 1992 in three groups of Black men (left) and women (right) in New York City: those who had been born in the South, the Caribbean and the Northeast (Fig. 42 and 43) (Fang *et al.*, 1996). The Southern Blacks had the highest CHD mortality rate and the Caribbean-born Blacks, the lowest mortality rate. The Southern Blacks are moving from stage 4 to stage 5. Some Northeastern Blacks are moving from stage 5 to stage 6, so they have an overall lower rate of CAD. The Caribbean Blacks were exposed to a lower levels of risk (stage 3) before moving to the city and since immigration selects for the better-educated, they enter at Stage 6 as well as Stage 5 when they immigrate to the US, and thus have a lower rate of CAD.

Fig. 41

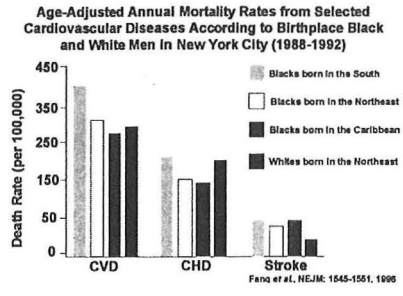


Fig. 42

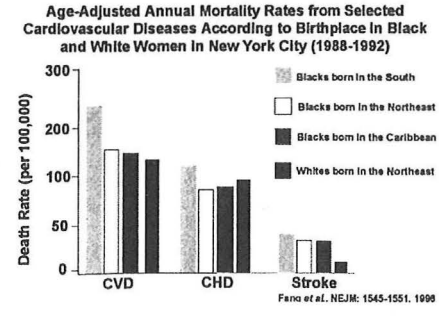


Fig. 42

Blacks appear to be less susceptible to CAD, but have similar CAD rates due to a worsening risk factor profile and socioeconomic factors. In summary, Blacks appear to have a similar or decreased genetic susceptibility to CAD, as evidenced by an increased cardiac risk burden, but similar incidence of CAD. Black men have lower, and Black women have higher than expected rates of CAD based on their risk profiles. The lower plasma levels of triglycerides and higher plasma levels of HDL-C in Black men may contribute to this relative protection. Black women have more obesity and hypertension, which may be a particularly virulent combination of risks. As clinicians, we appear to be particularly deficient in diagnosing coronary artery disease in Black women, which has negatively impacted their outcome.

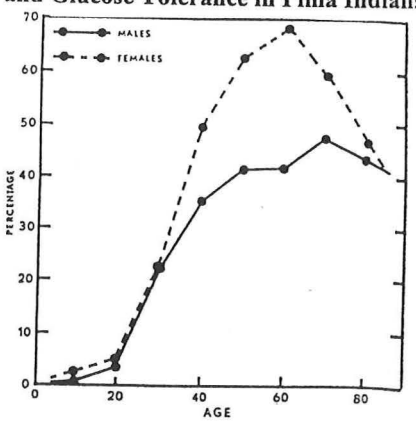
The apparent paradox of Blacks having 3-4 fold higher mean plasma levels of Lp(a) and yet no higher incidence of CAD suggests an important genetic difference between ethnic groups that might provide interesting new insights regarding this perplexing risk factor. Plaque morphology differences between Blacks and Whites may provide clues as to potential ethnic differences in the response to risk factors at the vessel wall. A major goal of the Reynolds Study will be to examine these issues.

ARE PIMA INDIANS PROTECTED FROM HEART DISEASE?

The Pima Indians are one of the best-studied Indian tribes in the United States. They number ~6000 and have lived in the desert in central Arizona for 2000 years. Since 1859 they have lived on a reservation and since 1965 the National Institute of Health has maintained a Field Study Center in Arizona to study the Pimas.

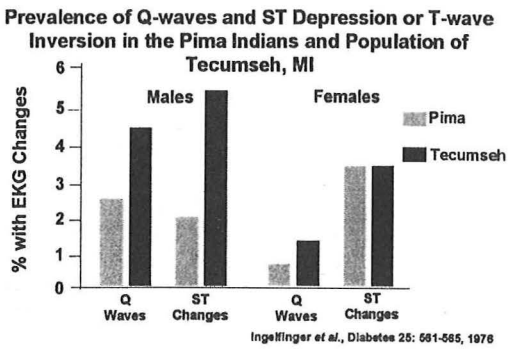
The Pima Indians have the highest frequency of diabetes in the world. Elliot Joslin, the founder of the Joslin Clinic, visited the Pima Indians in 1937 and estimated that the prevalence of diabetes was similar to the general US population. Within 20 years, there was an estimated 10-fold increase in the frequency of diabetes on the same reservation. And since 1954, the frequency has continued to rise so that by 1971 the Pimas had the highest frequency of diabetes in the world. Shown in Fig. 43 is the age-specific prevalence of overt diabetes and glucose intolerance (glucose >160 mg/dl after 75 gm glucose load) in 1971 (Bennett *et al.*, 1971). Not only has the prevalence continued to increase astronomically (65% between 1970 and 1980) but also the disease is starting to occur at an earlier age (Bennett, 1999).

Fig. 43



Bennett et al., Lancet *i*:126, 1971

Fig. 44



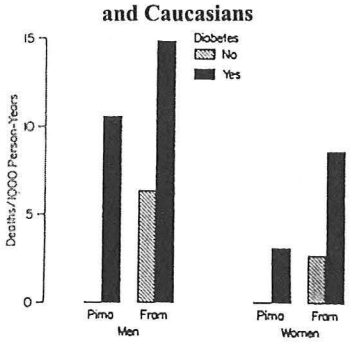
CAD rates in Pimas are low despite the high frequency of diabetes. In 1967 Sievers and his colleagues reported a four-fold lower incidence of CAD in American Indians, including the Pimas, than found in the Framingham study (Sievers *et al.*, 1967). The frequency of diabetes in those that had a MI was 75% compared to 40-45% in the general population of American Indians. Diabetes in the Pimas is associated with all the expected vascular complications and Pimas who are diabetic have an 80% higher mortality rate (Sievers *et al.*, 1992).

In 1976, the prevalence of CAD was estimated in 701 half- or full-blooded Pima Indians older than 40 years of age, as assessed by EKG changes and postmortem exams (Ingelfinger *et al.*, 1976). A total of 45% of the sample had glucose intolerance, defined as a serum glucose over 200 mg/dl 2 h after a 75 gm carbohydrate load. Around 20% of the sample had diabetes for at least 20 years, and diabetic retinopathy and nephropathy were present in 33% and 20% of the diabetics, respectively. Despite the high frequency of diabetes in the Pimas, the prevalence of EKG changes suggestive of ischemic heart disease (Q waves, ST-T wave changes, left and complete bundle branch blacks) were significantly less common than that seen in age- and sex- matched Caucasians (mostly non-diabetics) from Tecumseh, MI (Fig. 44).

Between 1975 and 1984, the incidence of CAD in the Pima Indians (ages 50-79 years) was estimated to be half that seen in age-, sex- and diabetes-matched subjects from the Framingham study (Nelson *et al.*, 1990). No CAD deaths were seen in nondiabetic subjects (compared to 28 in diabetics) (Fig. 45).

Fig. 45

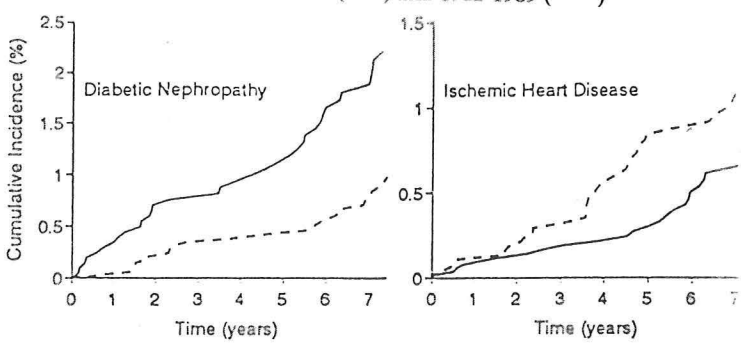
Incidence of CAD in Pimas and Caucasians



Nelson et al., Circulation 81:993, 1990

Fig. 46

Changing Cumulative Death Rates in Pimas (>35) Between 1975-1982 (——) and 1982-1989 (------)



Sievers et al., Diabetes Care 19:110,1996

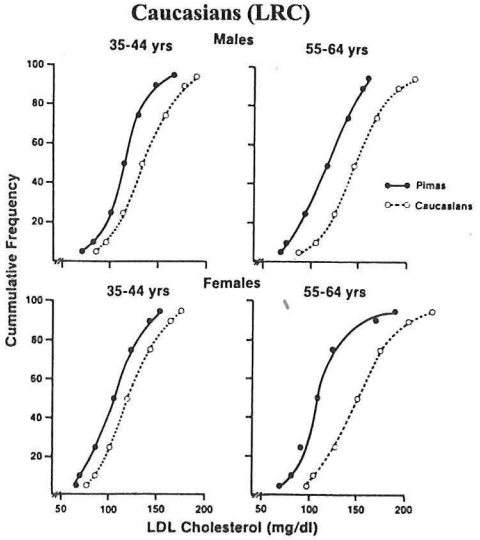
Increasing CAD rate in the Pimas diabetics. The major cause of death in diabetic Pima Indians between 1974 and 1984 was diabetic nephropathy, and not ischemic heart disease (Sievers *et al.*, 1986). By the late 1980's the death rate from diabetic nephropathy declined, and ischemic heart disease became the most common cause of death in Pimas (Sievers *et al.*, 1996) (Fig. 46). The increased life expectancy associated with diabetic nephropathy has been associated with more "opportunity" for the development of CAD. No change in total mortality rates occurred in the Pima Indians between 1975 and 1989. The decrease in the death rate from diabetic nephropathy was balanced by an increase in death from CAD (Sievers *et al.*, 1996). Although the death rate from CAD is increasing in the Pimas, it remains very low.

Low frequency of smoking and low plasma cholesterol levels contribute to reduced CAD rates in Pimas. A number of factors likely contribute to the surprisingly low prevalence of CAD in the Pima Indians. First, until recently, smoking was very uncommon among the Pimas. Second, Pimas have lower plasma levels of cholesterol and LDL-C levels, despite the high frequency of obesity. A comparison of the frequency distribution of plasma LDL-C levels in Pimas (506 males , 885 females; >15 years; either 100%

or 50% Pima ancestry) and age and sex-matched Caucasians from the Lipids Research Clinics (LRC) Study is shown in Fig. 47. The levels of plasma LDL-C are significantly lower in the Pimas (Howard *et al.*, 1983). An interesting difference between the Pimas and the Caucasians is that the plasma levels of LDL do not increase with age in the Pimas, as they do in US Caucasians. As shown by Grundy (1972), Pimas secrete a higher percentage of cholesterol into their bile, which may contribute to the lower plasma levels of LDL-C (at the price of a marked increase in frequency of biliary stone disease).

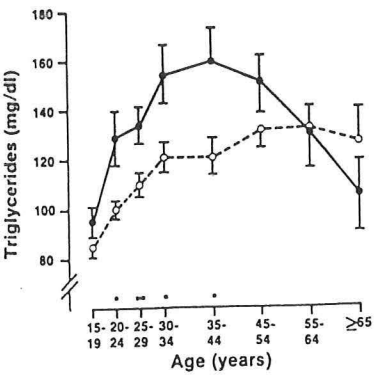
No sex difference is apparent in the plasma levels of HDL-C in Pimas. Female Pimas have plasma HDL-C levels that are significantly lower than their Caucasians counterparts (Fig. 48) (Howard *et al.*, 1983). The mean difference in plasma HDL-C between the two groups is 11 mg/dl. Although female Pimas have higher plasma triglyceride levels than Caucasian females, they are significantly lower than male Pimas (Fig. 49). Thus, the relatively greater reduction in plasma HDL-C levels in females Pimas versus male Pimas is not attributable to higher plasma triglyceride levels.

Fig. 47 **Cumulative Frequecy Distribution of Plasma LDL-C in Pimas and Caucasians (LRC)**



Howard et al., Circulation 68:718,1883

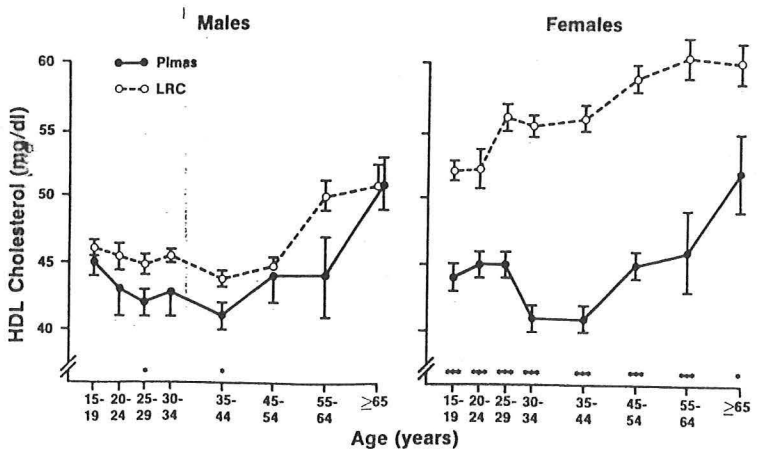
Fig. 49 **Plasma Triglceride Levels in Male (●) and Female (O) Pimas**



Howard et al., Circulation 68:718,1883

Plasma HDL-C Levels in Pimas and Caucasians (LRC)

Fig. 48



Howard et al. Circulation 68:718 1883

What is the relationship between obesity and these lipid abnormalities in the Pimas? The difference in plasma lipid levels cannot be attributed to differences in dietary lipid composition (Reid *et al.*, 1971). There is no relationship between BMI and plasma LDL-C in the Pimas, as there is in Caucasians. The plasma triglyceride levels are positively correlated with obesity in Pima men, but not Pima women; however, the correlation is not as great as has been seen in other ethnic groups. Metabolic studies of VLDL metabolism in Pimas reveal little to no increase in VLDL-triglyceride overproduction with obesity (Howard *et. al.*, 1980). Although BMI and plasma HDL-C are inversely related in both male and female Pimas, obesity does not account for most of the reduction in plasma HDL-C levels found in Pima women. Thus, the lower plasma levels of HDL-C in Pimas may be independent of VLDL metabolism.

The Pimas have a decreased in susceptibility to CAD. Despite having a very high incidence of obesity and diabetes, the Pimas have a much lower CAD mortality rate than Caucasians. The end-organ damage from diabetes, especially renal disease, appears not to differ from other ethnic groups, and diabetic Pimas are at increased risk or heart disease; thus, it does not appear that the disease process differs significantly in the Pimas.

Although hypertension is less frequent in Pimas, the disease is associated with significant morbidity, particularly in the diabetics, and contributes to the high rate of renal nephropathy (Sievers *et al.*, 1999). Pimas smoke significantly less and have significantly lower plasma levels of LDL-C, which contributes to their lower incidence of disease. It is remarkable that Pima women have much lower plasma HDL-C levels than Caucasian women and yet have a strikingly lower rate of CAD, supporting that low HDL-C alone is not a risk factor. Pimas differ in their VLDL metabolism (Egusa *et al.,* 1982) with a higher percentage of their hepatically-derived triglyceride-rich particles being rapidly cleared from the circulation, resulting in fewer circulating VLDL remnants and LDL, which likely contributes to their relative protection from CAD.

IDENTIFYING GENES THAT CONTRIBUTE TO ETHNIC-SPECIFIC DIFFERNCES IN CAD

Ethnic differences in cardiac risk factor profiles do not always predict differences in CAD risk. Shown in Fig. 50 is a comparison of the *relative* frequency of cardiac risk factors in the three ethnic groups. The relative cardiac protection that Pima Indians enjoy, despite having the highest frequencies of diabetes, obesity and the lowest plasma levels of HDL-C of the four ethnic groups, demonstrate how much we do not know about the pathogenesis of coronary artery disease. Like Pimas, Westernized Asian Indians have a high rate of diabetes, and yet these two ethnic groups differ dramatically in their susceptibility to ischemic heart disease. Asian Indians have the greatest apparent susceptibility to and highest rate of CAD. Further characterization and comparison of the glucose and lipid metabolic profiles between Asian Indians and Pima Indians will be particularly revealing.

African-Americans have less CAD than expected, given their high cardiac risk profile burden. They may be somewhat protected from epicardial coronary artery disease, but they are not protected from cardiovascular disease. Blacks die young of heart disease, and we do not really know why. The combination of hypertensive cardiomyopathy and ischemic heart disease, which is common in this population, appears to be particularly deadly, although this has not been adequately explored and quantitated.

Socioeconomic factors play an important role in all four ethnic groups. Without ingestion of a Western diet, CAD would be an uncommon occurrence irrespective of ethnicity. However, the relative role of socioeconomic status differs between populations. Socioeconomic factors play the greatest relative role in CAD mortality in Blacks and the least role in Asian Indians. Only modest improvements in socioeconomic status are associated with significant increases in cardiac risk in Asian Indians.

Fig. 50

Relative Magnitude of Major Cardiac Risk Factors With Westernization

	↑↑ BP	Diabetes	↑↑ Chol	Smoking	CAD
Asian Indians	++	+++	++	++	+++
Africans	++++	++	++	+++	++
Pimas	+	++++	+	+	+
Caucasian Americans	++	+	++	+++	++

Do genetic differences between ethnic groups contribute to differences in CAD? Although this question will be a challenge to answer, it is very likely that ethnic-specific sequence variants contribute to the observed ethnic differences in susceptibilities to CAD. More detailed studies to characterize ethnic-specific differences in energy utilization, glucose and lipid metabolism, the inflammatory response and lesion morphology will provide clues as to the pathways involved in the observed ethnic differences in CAD susceptibility. Identification of the critical pathways will provide candidate genes, whose sequences can be screened for common ethnic-specific variants.

Evidence suggests that the genetic underpinning to many of the well-established cardiac risk factors, including diabetes, hypertension and dyslipidemias, differ between ethnic groups. When the technology becomes available to identify sequence variants in the human genome on a very large scale, sequence differences between ethnic groups will be identified that account for the ethnic-specific differences in risk associated with the well-established cardiac risk factors. Comparisons between the genome sequences of different ethnic groups may also reveal new, yet-to-be-identified risk factors, such as those involved in the inflammatory and the vessel wall response associated with the development of atherosclerosis. Identification of these ethnic-specific sequence differences may provide clues to enable the development of new, more specific diagnostic tools and therapeutic agents that can modify cardiac risk in ways we can now only imagine.

Final comments. All four ethnic groups would have very low rates of heart disease if there had been no industrial revolution. During most of our evolution, we have been hunters and gatherers (Fig. 51). Our genes have been selected for a diet rich in fruits and vegetables and lean meats, and for high levels of physical activity throughout life. As the French fry-chewing, TV-watching, middle-aged sloth succinctly puts it: "I've have grown too big for my genes." (Fig. 52).

Fig. 51

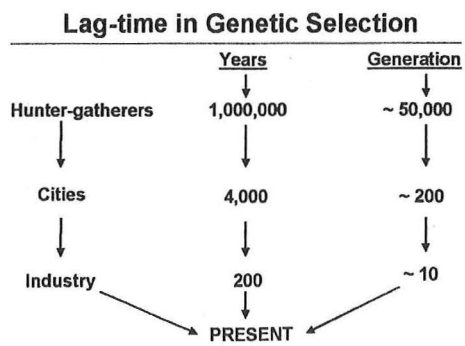


Fig. 52

"I've grown too big for my genes!"

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