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Comparison of Serum Lipoprotein(a) Distribution and its Correlates among Black and White Populations

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Background Epidemiological data on serum lipoprotein(a) (Lp(a)), a presumably strong risk factor for coronary artery disease in White populations, has mostly been derived, in Black populations, from small samples. This study compares the distribution and the determinants of serum Lp(a) in Blacks and in Whites using large representative samples and the same methods in both populations.

Methods The distribution and the correlates of serum Lp(a) were investigated in population-based samples of 701 Blacks in the Seychelles and 634 Whites in Switzerland, aged 25–64 years. Serum Lp(a) was quantified using a commercial immunoradiometric assay.

Results The distribution of serum Lp(a) was similarly skewed in both ethnic groups, but median Lp(a) concentration was about twofold higher in Blacks (210 mg/l) compared to Whites (100 mg/l). The proportions of individuals with elevated serum Lp(a) (>300 mg/l) was about 50% higher in Blacks (37.5%) than in Whites (25.2%). In both ethnic groups, serum Lp(a) was found to correlate with total cholesterol, LDL-cholesterol and apoprotein B but not with HDL-cholesterol, alcohol intake, smoking, and body mass index. The variance in serum Lp(a) concentration explained by any combination of these factors was smaller than 5.3% in the two populations.

Conclusions The measured factors did not explain the higher levels of serum Lp(a) found in Blacks compared to Whites. These findings are consistent with the hypothesis that genetic factors account for much of the variation of serum Lp(a) in both populations.

Lipoprotein(a) (Lp(a)) is a cholesterol-rich lipoprotein found in human serum that resembles low-density lipoprotein (LDL) but contains in addition apolipoprotein(a) (apo(a)) which has close structural homology with plasminogen.[1,2] A single gene appears to determine a size polymorphism of apo(a) which relates to serum Lp(a) concentration and family studies indicate that more than 90% of the inter-individual variation in serum Lp(a) is determined by this gene encoding apo(a).[3,4] Serum Lp(a) concentrations are fairly constant throughout an individual's life but vary between individuals over a wide range (from <0.1 to >4000 mg/l) with a highly skewed distribution, at least in White (Caucasian) populations.[2,5–7] Although its function is not established, Lp(a) has thrombotic and atherogenic properties.[8] Indeed, serum Lp(a) is currently gaining much attention as a quantitative, genetically controlled, independent risk factor for prediction of coronary artery disease in Caucasian populations.[9–13] However, the role of serum Lp(a) as a risk factor for coronary artery disease in Blacks is controversial.[14–16]

Distribution of serum Lp(a) has been repeatedly examined in White populations[2,5–7] although only a few studies included population-based data[17] and not all of them provided the appropriate distribution measures, such as medians and percentiles, needed for comparison between populations. In contrast, few studies have examined serum Lp(a) distribution in Blacks and most of them included small samples and were not designed to be representative of the whole population. When comparing serum Lp(a) distribution

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in Blacks and in Whites, it has been reported that Lp(a) was markedly more Gaussian in Blacks than in Whites,[2,18-21] a finding that is not supported by our data.

This report provides data on serum Lp(a) distribution in the Black population of the Seychelles and in the White population of Switzerland. Large population-based samples and the same study designs and laboratory methods were used for both populations, so that valid comparisons can be drawn between these two ethnically different populations. The relation of serum Lp(a) to other factors was also examined in the two populations.

METHODS

Study Populations

The Seychelles Islands are located in the Indian Ocean, approximately 1800 km east of Kenya and 1800 km north of Mauritius, and are now considered a middle-level income country with an annual gross national product per capita of >US$3500. The population of the Seychelles consists of a mixed rural-urban population. The Seychelles had no indigenous population until 1770 when French settlers arrived, joined later by a large number of people from the eastern coast of Africa and a small number of English, Indians and Chinese.[22]

In the Seychelles, cardiovascular risk factors in the population were determined in 1989 within the framework of the Seychelles Cardiovascular Disease Study.[23] The population screened was the population of Mahé Island, which accounts for approximately 90% of the total population of the Seychelles (66 370). A random sample of the population aged 25–64 years, stratified by sex and age, was drawn; 1081 (86.4%) individuals took part in the survey out of 1251 eligible. This study included only individuals who were of African descent (730) based on external anthropomorphic features as assessed by the same investigator (PB) throughout the whole survey. Serum Lp(a) could not be determined in 29 individuals due to shortage of serum, hence data from 701 individuals were analysed. Detailed sampling procedures, laboratory methods, and socio-demographic data have been reported previously.[24]

In Switzerland, a similar population survey was carried out in 1988–1989 within the framework of the WHO MONICA project. The sampling procedure has been previously reported in detail.[25] Briefly, a two-stage sampling procedure was used to obtain a representative sample of the adult population. A participation rate of 65% was obtained among the 3210 individuals eligible to take part in the survey in the cantons of Vaud and Fribourg. One hundred serum samples were then randomly selected to determine serum Lp(a) in each group stratified for sex- and 10-year age group. This study was further restricted to Swiss nationals and only data from people aged 25–64 years were used in the comparisons with the Seychelles. Hence, data from 634 individuals were analysed.

Laboratory Methods

Frozen fasting (Seychelles) and non-fasting (Switzerland) sera were analysed in Switzerland less than 18 months after blood collection. Serum Lp(a) was measured in one single laboratory using a commercial solid phase two-site immunoradiometric assay (Apo(a) RIA, Pharmacia, Uppsala, Sweden) similar to the one reported by Albers *et al.*[26] The assay was sensitive in the concentration range 0.2 U/l to ⩽8000 U/l which corresponds approximately to mass units 0.1 mg/l to ⩽5600 mg/l. The day to day variation coefficient was less than 6%. No measurable cross-reaction occurred with serum plasminogen or apoprotein B (apoB). Serum total cholesterol was determined enzymatically (Roche, Basel, Switzerland). Serum high density lipoprotein (HDL) cholesterol was similarly quantified after precipitation of the apoB-containing lipoproteins with phosphotungstate and magnesium chloride (Roche). Serum apoproteins A-I (apoA) and apoB were quantified by immunoturbidimetry (Turbitimer™ System, Behring, Marburg, Germany). Serum low density lipoprotein (LDL) cholesterol was calculated (Seychelles) with the Friedewald formula and measured (Switzerland) after precipitation with an amphiphilic polymer (Bio-Mérieux, Lyons, France).

Anthropometric and Lifestyle Variables

Blood pressure, weight and height were measured according to the WHO MONICA study protocol[27] and data on smoking were obtained from a questionnaire. Body mass index was used as an index of obesity (weight (kg)/height $(m)^2$). Alcohol intake was calculated as grams of pure alcohol per day based on a detailed questionnaire on alcohol habits (Seychelles) and dichotomized (consumption of alcohol *versus* no consumption) according to the reported consumption on the previous day (Switzerland).

Statistical Analysis

Normally distributed variables and categorical variables were compared using t- and χ^2 tests, respectively. Because serum Lp(a) was not normally distributed, the Wilcoxon rank-sum test was used to compare medians between sex and race groups. The Mantel-Haenszel test was used to evaluate the association between ethnicity and an elevated level of serum

Lp(a). Multiple logistic regression was used to investigate the association between ethnicity and an elevated serum Lp(a) after adjustment for selected variables. The univariate relation of serum Lp(a) to other variables was examined using the non-parametric Spearman's correlation coefficients within each of the four race and sex groups. Multivariate linear regression was used to explore the independent correlates of serum Lp(a) in Blacks and in Whites separately. Explanatory variables were chosen on the basis of previously demonstrated associations with Lp(a) or because of known relations with blood lipids or lipoproteins. Because of the skewed distribution of serum Lp(a), the natural logarithm was used when fitting models.

RESULTS

Cardiovascular Risk Factors

Race- and sex-specific levels of cardiovascular risk factors are summarized in Table 1. Details of the cardiovascular risk factors distribution have been published elsewhere.[23,28,29] According to the study design, the four sex and race groups were similar in age in both countries. Total cholesterol, LDL-cholesterol, and apoB were higher in Whites compared to Blacks. HDL-cholesterol and apoA were higher in men compared to women in the Seychelles but higher in women compared to men in Switzerland. Body mass index was higher in women compared to men in the Seychelles but higher in men than in women in Switzerland. Different proportions of smokers were found in men (55%) and in women (11%) in the Seychelles while more balanced proportions were found in men (36%) and in women (25%) in Switzerland. High blood pressure was more prevalent in men compared to women in the two countries and more prevalent in the Seychelles compared to Switzerland.

The unusual higher HDL-cholesterol and apoA levels in men compared to women in the Seychelles can mostly be accounted for by the very high consumption of alcohol by men[30] and the much higher prevalence of obesity in women than in men[31] (data not shown). A prevalence of diabetes of 7% in male and in female Seychellois aged 35–64[31] is comparable to the prevalence in Switzerland. Based on clinical experience, hormonal contraception is probably not much less frequently used in the Seychelles than in Switzerland; almost no Seychellois postmenopausal women received replacement hormonal therapy whereas the figure is estimated to be around 10–15% in Switzerland.

Distribution of Serum Lp(a)

Race-, sex-, and age-specific untransformed mean values and selected percentiles of serum Lp(a) are shown in Table 2. Sex- and age-specific median Lp(a) concentrations were approximately twofold higher in Blacks compared to Whites. No clear pattern between serum Lp(a) and age was observed in Black and in White men. In contrast, serum Lp(a) increased

TABLE 1 *Mean values and proportions of some cardiovascular risk factors in Seychellois Blacks and Swiss Whites aged 25–64 years, Seychelles Cardiovascular Disease Study 1989 and MONICA Vaud/Fribourg 1988–1989*

	Seychellois Blacks		Swiss Whites	
	Men	Women	Men	Women
No.	328	371	300	334
Age (years)	45.3±11.2[a]	45.5±11.6	43.8±11.8	44.5±11.8
Total cholesterol (mmol/l)	4.94±1.08	5 35±1.20	6.37±1.14	6.28±1.36
LDL-cholesterol (mmol/l)	2.91±1.12	3.54±1.16	4.12±0.92	3.87±1.09
HDL-cholesterol (mmol/l)	1.52±0.56	1.39±0.37	1.28±0.32	1.54±0.39
Apoprotein A-I (mg/l)	1.50±0.45	1.39±0.32	1.26±0.21	1.42±0.22
Apoprotein B (mg/l)	1.01±0.35	1.13±0.37	1.30±0.33	1.17±0.32
Body mass index (kg/m^2)	23.2±3.90	26.9±6.00	25.5±3.40	24.7±4.50
Cigarette smoking (%)	55.3	11.0	36.3	24.6
Cigarettes per day per smoker	11.1±7.50	6.8±6.4	23.8±11.5	16.3±7.30
Systolic blood pressure (mm Hg)	136±25	132±24	131±15	125±18
Diastolic blood pressure (mm Hg)	89±15	85±15	80±10	75±9
High blood pressure (%)[b]	33.7	27.1	14.3	11.1

[a] Mean ± standard deviation (details of the distribution have been published elsewhere).[23,28,29]

[b] Systolic/diastolic blood pressure ⩾160/95 mm Hg or under antihypertensive treatment.

TABLE 2 *Mean values, standard deviations, and percentiles of serum lipoprotein(a) in Seychellois Blacks and Swiss Whites by race, sex and age, Seychelles Cardiovascular Disease Study 1989 and MONICA Vaud/Fribourg 1988–1989*

	No.	Mean	SD[a]	Percentiles 10	25	50	75	90
Seychellois Blacks								
Men								
25–34	67	272	274	30	74	175	421	631
35–44	80	392	466	39	87	236	571	814
45–54	93	332	467	29	54	182	380	801
55–64	89	391	398	32	93	221	574	950
Total	329	350	414	31	76	214	521	807
Women								
25–34	73	359	433	37	120	213	509	799
35–44	97	261	277	37	77	175	334	599
45–54	93	358	458	51	95	193	450	1012
55–64	109	463	630	44	134	286	537	1170
Total	372	364	479	42	94	208	457	812
Swiss Whites								
Men								
25–34	78	261	487	20	31	71	221	679
35–44	81	262	448	18	31	77	316	835
45–54	65	298	529	19	45	82	259	927
55–64	76	219	328	21	35	98	232	571
Total	300	259	541	19	32	82	251	782
Women								
25–34	82	234	345	24	36	87	279	637
35–44	85	241	308	20	37	105	394	688
45–54	84	259	329	28	53	127	399	626
55–64	83	261	306	21	66	145	348	655
Total	334	249	321	23	46	114	347	637

[a] Standard deviation.

monotonically between 25 and 64 years in White women and a substantial increase occurred in the age group 55–64 in Black women. Median serum Lp(a) was weakly but significantly higher in women than in men in Switzerland (114 *versus* 82 mg/l; $P = 0.024$) while no difference was observed in the Seychelles (208 *versus* 214 mg/l), respectively; $P = 0.641$). Median serum Lp(a) was higher in Blacks than in Whites (210 *versus* 100 mg/l; $P = < 0.001$). Serum Lp(a) values corresponding to the upper percentiles tended to increase with age in Blacks but not in Whites.

The distribution of serum Lp(a) was highly positively skewed in the two populations (skewness in Blacks/Whites: 3.42/3.47) (Figure 1) and could be fairly well normalized through a natural logarithm transformation (resulting skewness in Black/Whites: −0.02/0.04). Serum Lp(a) mean values calculated from the $\log_e$ scale were 184 ± 3.3/198 ± 3.2 mg/l in male/female Seychellois and 94 ± 1.6/119 ± 3.5 mg/l in male/female Swiss.

Figure 2 indicates the proportions of individuals with serum Lp(a) above selected threshold values in the range, 100–1000 mg/l. Blacks had an approximately 50% greater risk than Whites of having serum Lp(a) above the selected thresholds (e.g. risk ratio for Lp(a) >300 mg/l: 1.56; 95% confidence interval [CI] : 1.26–1.75).

We also performed multiple logistic regression to investigate the association between ethnicity and elevated serum Lp(a) levels after adjustment for selected variables (in this analysis serum Lp(a) >300 mg/l was coded as 1 and Lp(a) ⩽300 as 0). The odds ratio (OR) for ethnicity without adjusment (OR = 1.78; 95% CI : 1.40–2.26) did not change after adjustment for sex, age, body mass index, alcohol, and smoking habits (OR = 1.76; 95% CI : 1.39–2.23) but substantially increased after additional adjustment for total cholesterol (OR = 2.26; 95% CI : 1.75–2.93).

Correlates of Serum Lp(a)

Table 3 shows the Spearman's correlation coefficients between serum Lp(a) and selected variables. Total cholesterol and LDL-cholesterol were statistically significant univariate correlates of serum Lp(a) in the four race and sex groups and the magnitude of the correlation coefficients were similar in Blacks compared with Whites. ApoB correlated with serum Lp(a) in all race and sex groups except in Black women.

Multivariate linear regression models were carried out to identify independent predictors of serum Lp(a) in Blacks and in Whites separately. Total cholesterol, apoB and LDL-cholesterol may be considered as surrogates of cholesterol-rich lipoproteins and this is substantiated by Pearson's correlation coefficients between any combination of these three lipids ranging between 0.80 and 0.91 in both races. Therefore, multivariate models included either total cholesterol, apoB or LDL-cholesterol in addition to the other independent variables. Total cholesterol, apoB, or LDL-cholesterol were significantly associated with the logarithm of serum Lp(a) in both Black and White populations after adjustment for the other variables (Table 4). The magnitude of the partial regression coefficients for total cholesterol, LDL-cholesterol, and apoB were similar in Blacks and in Whites, indicating that the effect of these lipids on serum Lp(a) was not modified by race. Sex was a weak but significant multivariate correlate of serum Lp(a) in Whites (regression coefficient = −0.29; standard error =

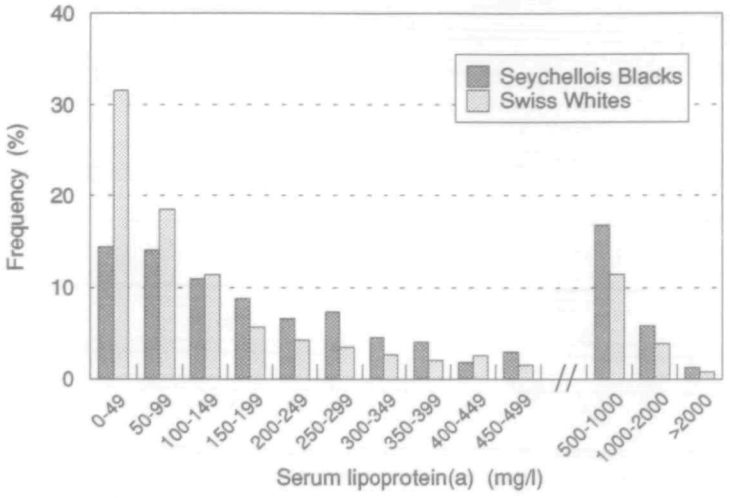

FIGURE 1 *Frequency distribution of serum lipoprotein(a) in Seychellois Blacks and in Swiss Whites, Seychelles Cardiovascular Disease Study 1989 and MONICA Vaud/Fribourg 1988–1989*

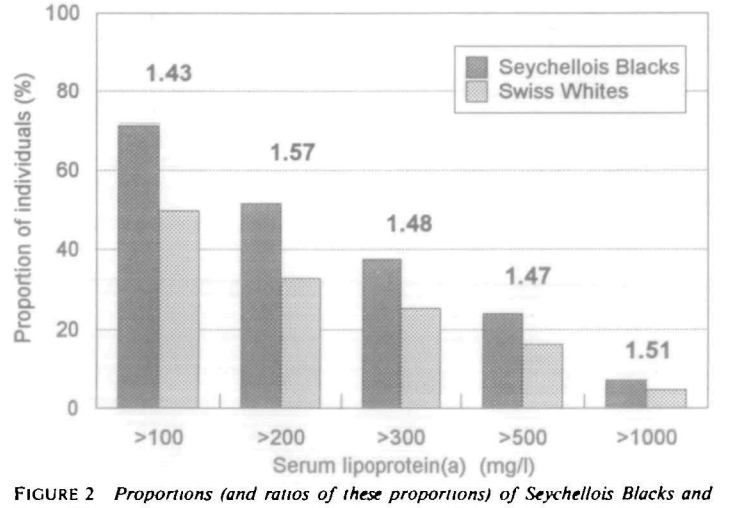

FIGURE 2 *Proportions (and ratios of these proportions) of Seychellois Blacks and Swiss Whites with serum lipoprotein(a) above selected thresholds, Seychelles Cardiovascular Disease Study 1989 and MONICA Vaud/Fribourg 1988–1989*

TABLE 3 *Spearman's correlation coefficients between lipoprotein(a) and selected variables[a] in Seychellois Blacks and Swiss Whites, Seychelles Cardiovascular Disease Study 1989 and MONICA Vaud/Fribourg 1988–1989*

	Total C	LDL-C	Apo B	HDL-C	Apo A-I	BMI	Alcohol	Cigarettes	Age
Seychellois Blacks									
Men	0.15**	0.22***	0.11*	−0.01	−0.06	−0.01	−0.03	−0.01	0.06
Women	0.23***	0.20***	0.06	0.06	0.08	0.01	−0.04	−0.02	0.07
Swiss Whites									
Men	0.17**	0.21***	0.16**	−0.07	−0.02	0.03	0.03	−0.01	0.07
Women	0.20***	0.24***	0.18***	−0.04	−0.03	0.08	0.01	−0.05	0.11*

[a] Total C: total cholesterol; LDL-C: LDL-cholesterol; HDL-C: HDL-cholesterol; BMI: body mass index.
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

TABLE 4 *Regression coefficients of lipids for the prediction of logarithm of serum lipoprotein(a) in models including either total cholesterol, LDL-cholesterol, or apoprotein B in addition to other independent variables,[a] Seychelles Cardiovascular Disease Study 1989 and MONICA Vaud/Fribourg 1988–1989*

	Seychellois Blacks (No. = 701)		Swiss Whites (No. = 634)	
	β[b]	SE[c]	β[b]	SE[c]
Total cholesterol (mmol/l)	0.21	0.04**	0.19	0.04**
LDL-cholesterol (mmol/l)	0.27	0.04**	0.30	0.05**
Apoprotein B (mg/l)	0.34	0.14*	0.60	0.17**

[a] The other independent variables in all models were: age, sex, body mass index, drinking habits, cigarette-smoking, HDL-cholesterol.
[b] Regression coefficient.
[c] Standard error.
* $P < 0.01$; ** $P < 0.001$.

0.12; $P = 0.014$) but not in Blacks. HDL-cholesterol, age, body mass index, smoking, and alcohol did not correlate with serum Lp(a) in the two populations. No linear combination of the independent variables could explain more than 5.3% of the variance of the natural logarithm of serum Lp(a). The variance explained by all variables other than lipids (e.g. age, sex, body mass index, smoking, and alcohol) was smaller than 1% in the two populations.

DISCUSSION

Distribution of serum Lp(a) was highly asymmetrical in both Seychellois Black and Swiss White populations. The similar computed values of skewness in both populations and the fairly constant ratio of the proportions of Black and Whites with serum Lp(a) above a wide range of threshold values indicated that the distribution of serum Lp(a) was similarly skewed in Blacks and in Whites but that serum Lp(a) concentrations were shifted to higher values in Blacks. The distribution of serum Lp(a) in Black Seychellois differed substantially from the nearly Gaussian distribution of serum Lp(a) reported in small groups of Black Sudanese and Congolese[2,19,20] but it was consistent with the distribution of serum Lp(a) found in a large population-based study of Black American children and adolescents.[14] The approximately twofold higher median serum Lp(a) concentrations found in Seychellois Blacks compared to their Swiss White counterparts are however consistent with published data on the ethnic Black/White difference (Table 5). When reading the Table, medians should be preferred to means when comparing serum Lp(a) between different populations because of the highly skewed nature of the distribution of serum Lp(a) and because some laboratory methods are not sensitive to very high values of serum Lp(a) (i.e. falsely low values of some measurements).

Ethnic difference in the distribution of serum Lp(a) raises public health concerns. Indeed, the risk for coronary artery disease in white populations was reported to be increased two to three times for serum Lp(a) >300 mg/l,[11,13] although serum Lp(a) might not be such a strong risk factor for coronary artery disease in Blacks based on the limited data available to date.[14–16] The finding, in our data, that serum Lp(a) values corresponding to the upper percentiles tended to increase with age in Blacks but not in Whites may be related to increased premature deaths in Whites but not in Blacks with high serum Lp(a), which may indirectly support the view that serum Lp(a) is a stronger risk factor in Whites than in Blacks. In our data, approximately 50% more Blacks than Whites had serum Lp(a) above threshold values in the range 100–1000 mg/l (e.g. proportions of Blacks *versus* Whites with serum Lp(a) >300 mg/l: 38% *versus* 24%). Moreover, the odds of having elevated serum Lp(a) in Blacks compared to Whites were further increased when analytical adjustment for equal levels of serum cholesterol was performed. From another standpoint, it has been stated from studies in Caucasian populations that the risk associated with elevated serum Lp(a) was dependent upon jointly elevated serum LDL-cholesterol.[11,32] In this view, serum Lp(a) would be a weaker cardiovascular risk factor in the Seychelles considering that serum LDL-cholesterol was notably lower in the Seychelles than in Switzerland. Since serum Lp(a) may substantially differ in molecular structure across populations,[20] further epidemiological studies will have to consider the possibility that the pathogenic action of Lp(a) might differ depending upon the Lp(a) species and establish the relative proatherogenic and prothrombotic roles of all Lp(a) species and their affiliated apo(a).

The correlates of serum Lp(a) in this study were similar in Blacks and in Whites and were generally consistent with those identified in other reports. Serum Lp(a) did not vary substantially with age in Black and in White men but increased serum Lp(a) levels were found in the older Black and White women. These findings are consistent with other reports in which serum Lp(a) concentration did not vary substantially with age[33] but was increased in postmenopausal women presumably due to the decrease in oestrogen levels.[7,34,35] Total cholesterol, LDL-cholesterol and apoB were significant univariate and multivariate cor-

TABLE 5 *Ethnic (Black/White) difference in serum lipoprotein(a) in selected studies*

Type of population Country	Ref.	Type of assay[a]	Subjects (No.)		Mean Lp(a) (mg/l)		Median Lp(a) (mg/l)	
			Black	White	Black	White	Black	White
General population Seychelles/Switzerland	—	RIA	701	634	357	254	210	100
Children aged 8–17 years USA	14	ELISA	885	1553	297	172	252	94
Adult volunteers/health study Nigeria/Belgium	21	ELISA	60	60	177	160	147	74
Employees USA	18	EID	105	134	313	170	—	—
Healthy people Congo/France	19	EID	81	81	239	107	208	70
Healthy people/population Sudan/Iceland	20	EID	105	184	457	135	—	—

[a] RIA: radioimmunoassay; EID: electroimmunodiffusion; ELISA: enzyme-linked immunosorbent assay.

relates of serum Lp(a) in both Black and White populations. Ethnicity did not modify the relation of these lipids to Lp(a) as suggested by the similar magnitude of the regression coefficients found in Blacks and in Whites. Associations relating serum Lp(a) to LDL-cholesterol or total cholesterol have been noticed in other studies.[7,36,37] The relation of these lipids to serum Lp(a) may however not be causal but rather reflect that measurements of serum total cholesterol, LDL-cholesterol, and apoB also measure cholesterol and apoB contained in the serum lipoprotein Lp(a). In our study, HDL-cholesterol, apoA, body mass index, smoking, alcohol consumption, and sex did not correlate with serum Lp(a) in the two populations, in agreement with studies reporting a lack of association between serum Lp(a) and body mass index,[38] smoking,[7] and alcohol.[37] It is remarkable that any combination of the considered variables explained only very little (<5.3%) of the variance of serum Lp(a) in the two populations. When comparing these two populations, White Swiss and Black Seychellois undoubtedly differ in many respects. However no additional environmental factors have been yet identified to correlate substantially with serum Lp(a) in populations and the ethnic difference in serum Lp(a) found in this study is therefore not likely to be biased by known confounding factors. These findings are consistent with the hypothesis that genetic factors account for most of the variation of serum Lp(a) in both populations.

It has indeed been established that a single gene determines a polymorphism of apo(a) which relates to serum Lp(a) concentration.[2] Heterogeneity among populations in the distribution of alleles of the gene encoding apo(a) may therefore explain some of the observed heterogeneity in serum Lp(a) among various ethnic groups. Interestingly, variability in apo(a) size polymorphisms explained only little of the variation in serum Lp(a) in Blacks compared to other populations (0.19 in Black Sudanese but 0.41 in Tyroleans and 0.77 in Malays).[20] Recent investigations at the apo(a) gene level did, however, demonstrate in Whites that the inter-individual variability in serum Lp(a) could be explained almost entirely by variation at the apo(a) locus while only a fraction was explained by the apo(a) size polymorphism.[4,39] Conducting similar investigations in other ethnic groups may further strengthen the hypothesis that most of the variation of serum Lp(a) is under genetic control in all populations and help elucidate racial differences in serum Lp(a) levels.

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