

High density lipoprotein cholesterol increases with living altitude

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Background	The relationship between high density lipoprotein cholesterol (HDL) serum level and the altitude at which people live is controversial.
Methods	A cross-sectional study was carried out in the adult population (30–64 years) of the Island of El Hierro (Canary Islands, Spain). In all, 594 individuals representative of the El Hierro population for gender, age, district and the altitude at which they lived were included. The factors measured included HDL, living altitude, body mass index (BMI), smoking habits, alcohol consumption, diabetes, menopause in women, and physical activity and dietary habits.
Results	The HDL showed a correlation with living altitude ($r = 0.14$, $P < 0.01$) and with BMI ($r = -0.19$, $P < 0.01$). Smokers had lower HDL levels than ex-smokers and non-smokers ($P < 0.05$). Men who were moderate drinkers had higher HDL levels than heavy or mild drinkers and non-drinkers ($P < 0.01$). Physical activity was only related to HDL in men with levels >1.52 mmol/l, who walked on the average more than the rest ($P < 0.05$). Variables not showing the expected relationship with HDL were diabetes and the menopause in women (probably due to a low statistical power of their subsamples). Regression analysis, with HDL as dependent variable showed that the association between HDL and altitude persists when taking altitude as a categorical or a continuous variable.
Conclusions	High density lipoprotein cholesterol levels are linearly and significantly increased when living at a higher altitude. This fact should be taken into account when comparing cardiovascular risk in populations living at different altitudes.
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Within Spain which has one of the lowest rates of ischaemic heart disease when compared to other developed countries,¹ the Canary Islands is the Spanish region with the highest mortality due to this cause.^{2,3}

Several studies^{4–6} have demonstrated a negative correlation between high density lipoprotein cholesterol serum levels (HDL) and the incidence of coronary heart disease. Body mass index (BMI), smoking, physical activity, and alcohol consumption are factors which have been most frequently related to variations in serum HDL, also women exhibit higher mean levels of HDL than men.⁴

A lower mortality from coronary heart disease has been observed in populations living in areas of high altitude.^{7,8} Moreover, higher levels of serum HDL have been detected in those who live at high altitudes,^{9,10} and increases in HDL have been observed in a population migrating from lower altitudes to high mountain regions.¹¹ However, the effect of living at higher altitudes in itself is difficult to quantify, as there are other variables that must be taken into account such as genetic factors, diet and physical activity. The purpose of this research was to evaluate the distribution of HDL in the adult population of El Hierro island according to the altitude at which they normally live, and study its relationship with other factors that could affect this distribution.

Subjects and Methods

Geographical and subject characteristics

The island of El Hierro, in the southwest of the Canarian archipelago, has a population of 7161, according to the 1991 census. It is divided into two municipal districts (Valverde and Frontera); its inhabitants are mostly native and most live at

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around median altitude. Its hilly topography (a maximum altitude of 1501 m and an area of 287 km²) makes it the island with the second highest mean gradient in the world, and thus it has provided us with an ideal location for our research since it simplifies the procedure of selecting groups of population living at different altitudes.

Study design and sample selection

This cross-sectional study of the adult population (age range 30–64 years) was carried out from October 1993 to October 1994. A stratified random sample was obtained on the basis of municipality, age, and gender. For a confidence interval of 95%, an estimated prevalence of coronary heart disease of 3%, and a mean error of $\pm 1.4\%$, the estimated sample size was 570 subjects. However, the final sample was 594 due to the success of the enrolment campaign.

Subjects, procedures, and methods

The subjects, with the provision of an extra 25% of possible participants in case of absentees, were invited to enrol in the study through an explanatory letter sent by mail. In the letter subjects were asked to attend the primary health centre nearest to their homes after an overnight fast. Each individual was assigned the altitude at which he/she normally lived (census data). Subsequently, subjects were categorized into three altitude groups: a shore group (those living <351 m above sea level), an intermediate group (351–799 m), and a mountain group (800–1050 m). The following equipment was used in the present study: three Seca[®] scales incorporating measuring rods, graded at 100 g and 1 mm intervals respectively, an Hitachi 705 Autoanalyser (Boehringer Mannheim), test material of the same make for determining serum levels of total cholesterol, triglycerides, HDL and glucose. The HDL levels were determined by the phosphotungstic acid and magnesium chloride precipitation method, while glucose, total cholesterol (TC) and triglycerides (TG) were determined by colorimetric enzymatic tests. Low density lipoprotein (LDL) cholesterol was defined as $TG < 4.52$ mmol/l, as $LDL = TC - HDL - TG/2.2$.¹⁵ Quality control was carried out every 20 tests by calibration with Precinorm U[®] and Precipath U[®].

Data collection

Initially a 5-ml fasting blood sample was obtained by venipuncture from all participants who attended at the health centre as requested. This sample was sent to the laboratory at Valverde Hospital for later testing. Individuals were also weighed, measured, and asked to answer a questionnaire regarding smoking habits, physical activity, alcohol consumption, diet, and medical history (including personal details, place of birth and menstrual history). Blood pressure was measured with the subjects in a seated position, employing a mercury sphygmomanometer. Cardiac health was assessed by electrocardiogram.

Data classification

The BMI was calculated as weight in kg divided by height in m². Alcohol consumption, in g/day, was calculated by multiplying ml of consumed alcohol by proof of beverages by density of alcohol (0.8) and dividing the result by 100. Subjects were considered as: non-drinkers, mild (1–20 g alcohol/day), moderate (21–59 g/day), and heavy drinkers (>59 g/day). The USA

National Diabetes Data Group criteria¹³ were used for detection of diabetes; subjects were considered diabetics if: (a) they declared themselves as such during the enrolment questionnaire and were treated with insulin or antidiabetic drugs, (b) they had a fasting serum glucose of ≥ 11.1 mmol/l (≥ 200 mg/dl), (c) a fasting serum glucose level of ≥ 7.8 mmol/l (≥ 140 mg/dl) on at least two occasions, or (d) they were found to have serum glucose levels of ≥ 11.1 mmol/l 2 h after an oral loading dose of 75 g glucose. The criteria of Ford *et al.*¹⁴ were used to establish physical activity, by adding up activity at work and at home, time spent walking other than work and leisure, and that spent in leisure activities. The global physical activity was calculated by multiplying METS of each activity by the number of hours per week and by the individual's weight in kg, and it was expressed in kcal/week. Subjects were also classified as consumers (or not) of a list of main foodstuffs twice a week.

Statistical analysis

Data analysis was carried out with the SPSS program. Initially, we carried out a univariate descriptive analysis of the variables. For the bivariate analysis, the possible relationship between categorical variables was analysed by the Pearson χ^2 test. The association between categorical and continuous variables was analysed by t-Student test whenever the categorical variable was binary and by means of variance analysis, if not. The relationship between continuous variables was assessed by means of the Pearson correlation coefficient. For multivariate analysis, the linear regression model used HDL as the dependent variable, altitude as the independent variable, and as possible confounders, place of birth, age, gender, BMI, smoking, alcohol consumption, diabetes, menstrual status, and physical activity apart from the variables that resulted from interaction of these. All results with a value of $P < 0.05$ were deemed significant. Quantitative values are expressed as mean \pm SD.

Results

Although 606 people responded to the enrolment invitation, 12 were excluded because of errors or omissions in data collection. Those participating were representative for gender, age, altitude and municipal district (Table 1). Of the sample, 76% were native islanders, 14% had been born in other Canary islands, 4% were from the Spanish mainland, and 6% were born in a foreign country. In all, 59% of those not native to the island had been living there for more than 10 years. The distribution of the non-biochemical variables according to altitude are shown in Table 2. Even though the association of prevalence of diabetes and altitude did not reach statistical significance, a correlation was detected between altitude and glucaemia ($r = 0.1$, $P < 0.01$), before and after adjusting for the remaining variables.

The average value for HDL was 1.38 ± 0.38 mmol/l (men 1.30 ± 0.37 mmol/l, women 1.47 ± 0.38 mmol/l) ($P < 0.01$). The HDL serum levels were significantly lower in the shore group than in the other two groups ($P < 0.01$) (Figure 1). When HDL levels and altitude were considered as continuous quantitative variables, a positive correlation was observed ($r = 0.14$, $P < 0.01$).

The native islanders had lower levels of HDL (1.37 ± 0.38 mmol/l versus 1.45 ± 0.40 mmol/l, $P < 0.05$). The BMI correlated negatively with HDL levels ($r = -0.19$, $P < 0.01$). Smokers had lower levels of HDL (1.33 ± 0.36 mmol/l) than

Table 1 Characteristics of the adult population of El Hierro and the sample

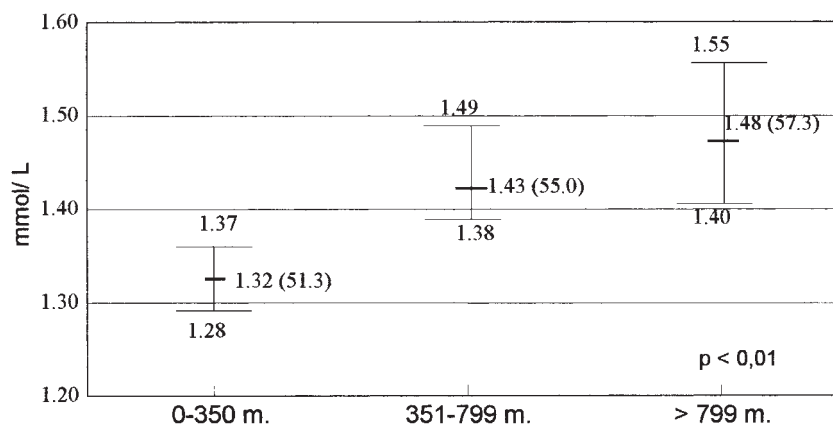
	El Hierro n (%)	Sample n (%)
Male	1453 (51.4)	306 (50.4)
Female	1370 (48.5)	300 (49.5)
Age		
30–39	918 (32.5)	191 (31.5)
40–49	734 (26.0)	157 (25.9)
50–59	759 (26.8)	169 (27.8)
60–64	412 (14.6)	89 (14.7)
District		
Valverde	1383 (48.9)	302 (49.8)
Frontera	1440 (51.1)	304 (50.2)
Altitude (m)		
<351	1347 (47.7)	275 (45.4)
351–799	937 (33.2)	221 (36.5)
≥800	539 (19.1)	110 (18.2)
Whole population	2823 (100)	606 (100)

Table 2 Values of the studied variables according to altitude

Altitude	<351 m (n = 270)	351–799 m (n = 218)	≥800 m (n = 106)	P (χ^2 or ANOVA)
Natives (%)	71	77	87	<0.01
Age (x ± SD)	46.30 ± 10.10	47 ± 10.30	48.30 ± 10.70	0.95
Gender (% male)	53	49	45	0.28
Body mass index (x ± SD)	27.80 ± 4.50	27.40 ± 3.80	28.10 ± 4.30	0.24
Smokers (%)	31	25	15	<0.01
Drinkers (%)	42	39	35	0.50
Diabetics (%)	5	6	11	0.08
Menopausal women (%)	41	46	47	0.68
Physical activity^a (x ± SD)	4971 ± 3372	6081 ± 3843	6020 ± 3822	<0.01
Foodstuff^b				
Meat	67	63	77	0.05
Fish	38	35	44	0.28
Salads or pulses	75	87	81	<0.01
Whole milk	44	48	40	0.50
Eggs	69	72	59	0.07

^a Total physical activity in kcal/week.

^b Percentage of people that consume such foodstuff ≥2/week.

**Figure 1** Mean values of high density lipoprotein cholesterol in mmol/l (mg/dl) and 95% confidence intervals for the three altitude groups

ex-smokers (1.35 ± 0.40 mmol/l) and non-smokers (1.42 ± 0.38 mmol/l) ($P < 0.05$). Men who drank moderately had higher levels of HDL (1.49 ± 0.40 mmol/l) than those who were heavy drinkers (1.38 ± 0.44 mmol/l), non-drinkers (1.25 ± 0.32 mmol/l) or mild drinkers (1.23 ± 0.37 mmol/l) ($P < 0.01$). The differences in the HDL levels of diabetics ($n = 39$) and non-diabetics were not significant (1.41 ± 0.36 mmol/l versus 1.39 ± 0.39 mmol/l respectively, $P = 0.77$). Furthermore, no differences in HDL ($P = 0.32$) were observed among the 128 women who were menopausal (1.45 ± 0.38 mmol/l) and the 160 women who were non-menopausal (1.50 ± 0.37 mmol/l).

The only relationship found between HDL levels and physical activity was observed in the case of walking: men with HDL levels >59 mg/dl (69 subjects) walked on average more than the rest (2625 ± 3769 versus 1839 ± 2586 kcal/week; $P < 0.05$). Men whose total physical activity amounted to >2000 kcal/week showed lower heart frequencies than those who were less physically active ($P < 0.05$), while women showed lower heart frequencies if they carried out activity equivalent to ≥ 4900 kcal/week ($P < 0.05$).

No differences were observed in HDL between those who consumed the foodstuffs studied twice or more per week and those that did not.

For the purpose of discerning if the association between altitude and HDL levels could be caused by one of the known variables acting as a confounding factor, a multiple linear regression analysis was carried out in which all the mentioned factors were included. Two models were set out; in the first one altitude was considered a categorical variable (Table 3A), and in the second one altitude was taken as a continuous variable (Table 3B). The residuals showed a normal distribution in both cases with mean values of 0 ± 0.36 . Initially both regression models were tried including total physical activity but later physical expenditure during walking was substituted, however the final result did not vary in either case. Because of the bivariate association between altitude and glucaemia, this too was included in the models as an independent variable.

Other factors like TG ($r = -0.01$, $P = 0.86$), systolic blood pressure ($r < 0.05$, $P = 0.27$) and diastolic blood pressure ($r = 0.01$, $P = 0.28$), were not associated with altitude. Low density lipoprotein was initially correlated with altitude in the bivariate analysis ($r = 0.09$, $P < 0.05$) but this association disappeared after adjusting for the remaining variables included in the model.

Discussion

There are few references concerning a positive correlation between altitude and HDL serum levels in population groups and those that we have found^{9–11} had difficulty in finding a geographical area with a suitable accessible population. Evaluating the effect of altitude on HDL is also difficult as it is affected by many other factors. The island of El Hierro combines most of the ideal conditions for such studying such phenomenon, because of its particular topographical and demographic characteristics.

We have noted an association between living at higher altitudes and higher levels of HDL, which remains throughout the multivariate analysis, both when altitude is considered as a categorized variable and when it is considered a continuous quantitative variable. This association has also been described by Sharma⁹ and Aytbaev,^{10,11} but they did not take into account possible confounders. Perhaps genetic or other socio-ecological factors which were not considered in our study could explain the fact that those native to the island exhibited lower levels of HDL than those born elsewhere. All other variables which were associated with HDL levels had been previously described, i.e. female gender, BMI,¹⁵ smoking¹⁶ and alcohol consumption.^{17,18}

Table 3A Variables included in the multiple linear regression model (altitude as categorical variable). Dependent variable high density lipoprotein cholesterol (mmol/l). $R^2 = 0.15$

Variable	B	SE B	T	Sign T
Low level altitude ^a	-0.100679	0.034431	-2.924	0.0036
El Hierro native ^b	-0.091361	0.036367	-2.512	0.0123
Gender ^c	-0.214592	0.032913	-6.520	<0.0001
Alcohol (g/day)	0.002634	6.8096E-04	3.869	0.0001
Body mass index (kg/m ²)	-0.019414	0.003708	-5.235	<0.0001
Smoker ^d	-0.089398	0.037016	-2.415	0.0160
Glucaemia (mmol/l)	9.48842E-04	0.011570	0.082	0.9347
Physical activity ^e (kcal/week)	2.31505E-06	4.2759E-06	0.541	0.5884
High-level altitude ^f	0.051220	0.043380	1.181	0.2382
(Constant)	2.121877	0.114615	18.513	<0.0001

Table 3B Variables included in the multiple linear regression model (altitude: continuous (m)). Dependent variable high density lipoprotein cholesterol (mmol/l). $R^2 = 0.15$

Variable	B	SE B	T	Sign T
Altitude	2.12249E-04	6.2272E-05	3.408	0.0007
El Hierro native ^b	-0.091371	0.036492	-2.504	0.0126
Gender ^c	-0.215813	0.032981	-6.544	<0.0001
Alcohol (g/day)	0.002619	6.8252E-04	3.837	0.0001
Body mass index (kg/m ²)	-0.020089	0.003695	-5.437	<0.0001
Smoker ^d	-0.085594	0.037193	-2.301	0.0217
Glucaemia (mmol/l)	0.004940	0.011442	0.432	0.6661
Physical activity ^e (kcal/week)	2.57281E-06	4.2756E-06	0.602	0.5476
(Constant)	1.985253	0.115024	17.260	<0.0001

^a Corresponds to living at medium and mountain altitudes compared to shore levels (0 = others; 1 = living at <351 m).

^b 0 = born elsewhere; 1 = native of El Hierro.

^c 0 = female; 1 = male.

^d 0 = non-smoker or ex-smoker; 1 = active smoker.

^e Global physical activity.

^f Corresponds to living at mountain altitude compared to medium and shore levels (0 = others; 1 = living at >800 m).

Diabetic patients usually have decreased levels of HDL when compared to non-diabetics.¹⁹ This fact was not detected in this study probably due to the lowered statistical power of the subsample of diabetics. But it may be that the greater proportion of diabetics in the mountain group (Table 2), in conjunction with the increasing of HDL with altitude, attenuated the expected decrease of HDL in diabetics. The same problem of lack of power could explain the fact that though it has been reported that levels of HDL tend to be lower in menopausal women,²⁰ this could not be proven in menopausal women of El Hierro. Although eating habits were not associated with HDL values, it could be because we did not study nutrients. However, no food-stuff has been previously clearly associated with HDL changes.

The association observed between HDL levels and physical activity in men only during walking could be explained by the fact that in this case there was an energy expenditure of >2000 kcal/week, which is considered the accepted cardioprotective threshold.²¹ The global physical activity was absent from the final regression models, and this could possibly be due to at least two reasons. First, it could be that the questionnaire carried out during the study was not sufficiently precise when measuring physical activity. However, we found that physical activity and cardiac frequency were consistently related, indicating that the questionnaire was not imprecise in its evaluations. Second, this could be explained by the type of activity; it seems that HDL levels are increased only with aerobic activity, and this has been proven in the case of sportsmen that practice anaerobic exercises and who do not show higher HDL serum levels than control groups.²² Thus, in El Hierro, physical activity carried out by women is mainly of doing house chores, an activity which is not necessarily aerobic. This could explain to some degree why cardiac frequency values in women decrease only after they have spent a higher amount of energy than men.

Another possible limitation of this study is that temperature was not taken into account. It is obvious that at higher altitudes the ambient temperature is lower. Although it is known that colder temperatures produce an increased breakdown of triglycerides in muscle and adipose tissues, it has not yet been proven that the same happens with plasma triglycerides in humans.²³ In addition, we have not found any community study which establishes that there is an increase in serum levels of HDL at lower temperatures, although Elwood²⁴ has described the opposite effect.

The presence of higher levels of HDL at higher altitudes could be originated by changes produced in hepatic tissue. It seems that there is a re-adaptation of the body to periodic altitude hypoxaemic conditions, which in some unknown way would alter lipidic oxidation at hepatic level.²⁵ Ferezou *et al.*,²⁶ proved that levels of HDL increased and levels of triglyceride-rich lipoproteins decreased in six subjects who were transported from low altitudes to high altitudes at 4350 m to an observatory in the Alps, thus suggesting that hypoxia induced lipolysis of plasma triglycerides and, in addition, an increase of serum HDL. In their study the effects of physical activity, cold exposure and dietary conditions were controlled, but the sample size was too small and altitude was extreme, rendering it of limited interest for large populations. The altitudes at which El Hierro inhabitants live do not exceed 1050 m above sea level, and as is shown in Table 3B, there is a linear relationship between altitude and HDL, metre by metre, which suggests that the

effects of a mild sustained hypoxia could induce an increase of HDL levels.

Because of its cross-sectional design, our study does not allow us to establish a causal relationship. But it is the first one, to our knowledge, in which the relationship between high density lipoproteins and altitude has been analysed by means of a multivariant model, considering the possible influence of other variables which could act as confounders. We think that living altitude should be taken into account when comparing cardiovascular risk in populations living at different altitudes.

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