RESEARCH REPORT

Residence in mountainous compared with lowland areas in relation to total and coronary mortality. A study in rural Greece

Nikos Baibas, Antonia Trichopoulou, Eftihios Voridis, Dimitrios Trichopoulos

See end of article for authors' affiliations
....

Correspondence to:
Dr N Baibas, Department of Hygiene and Epidemiology, University of Athens Medical School, 75 Mikras Asias Street, 115 27 Athens, Greece; nbaibas@nut.uoa.gr

Accepted for publication 29 September 2004
....

Study objective: To investigate the association of residence in mountainous or lowland areas with total and coronary mortality, in a cohort with 15 years of follow up.

Design and setting: Prospective study, based on the adult population of two lowland and one mountainous village in rural Greece. Baseline measurements on sociodemographic, lifestyle, somatometric, clinical, and biochemical variables were recorded in 1981 during a health survey and total and coronary deaths were ascertained on the basis of death certificates up to 1996.

Participants: 1198 men and women, who had participated in the 1981 survey. Analyses are based on 504 men and 646 women with complete data.

Main results: There were 150 deaths among men and 140 among women (coronary deaths: 34 and 33 respectively). In multivariate analysis with Cox regression, after adjustment for age, education, body weight, smoking, alcohol consumption, systolic blood pressure, serum total cholesterol, blood glucose, serum triglycerides, and serum uric acid, total and coronary mortality were lower for residents of the mountainous village in comparison with residents of the lowland villages (hazard ratios (95% confidence intervals) for men and women, respectively: total mortality, 0.57 (0.38 to 0.84) and 0.69 (0.47 to 1.02); coronary mortality, 0.39 (0.16 to 0.98) and 0.46 (0.20 to 1.05)).

Conclusions: Residence in mountainous areas seems to have a ''protective effect'' from total and coronary mortality. Increased physical activity from walking on rugged terrains under conditions of moderate hypoxia among the mountain residents could explain these findings.

P opulations residing in mountainous areas have been reported to have lower mortality rates, especially for coronary heart disease, as compared with lowland populations.[1][2] A suggested underlying mechanism was the cardiovascular protection of high altitude dwellers deriving from strenuous daily physical activities.[1–4]

More favourable levels of cardiovascular risk factor levels in high altitude dwellers have also been reported, especially with respect to hypertension,[5–7] blood lipids,[8][9] and diabetes mellitus.[10] Hypoxia, dietary habits, and physical activity levels, have been considered to account for the favourable risk profiles observed in these high altitude populations.

In Greece mortality rates for all causes and for coronary heart disease are among the lowest when compared with other developed countries.[11] Urban-rural differences in mortality patterns have also been recorded,[12] with areas of rural and generally mountainous Greece exhibiting consistently lower rates for total and coronary mortality, in comparison with urban areas.

In 1981 one of the authors coordinated an extensive general health survey in three villages located about 200 km from Athens. One of these villages (Arahova, A) is in a mountainous area of the Sterea Hellas region, at 950 metres altitude, whereas the two others (Zevgolatio, B1 and Aidonia, B2) are in plains in the Peloponnesus region. In the context of a doctoral thesis, a series of visits were undertaken in 1996 to ascertain survival status of those who had participated in the survey. These data allowed us to evaluate the hypothesis that residents of mountainous areas may have lower rates of coronary and total mortality in comparison with residents of lowland villages, with more detailed control of potential confounders that has been accomplished in earlier investigations.

METHODS

The study population consisted of 1198 inhabitants (587 in village A, 478 in B1, and 133 in B2), representing 32% of the total adult population of the three villages. The visits to the villages were arranged in collaboration with the local general practitioners and the town leaders who viewed the occasion as a welcome opportunity. In 1981 no informed consent was considered mandatory but all participants were volunteers who enthusiastically took up the opportunity to be examined by specialists, at a time when health services in rural Greece were rudimentary. In all three villages, the principal occupations were farming and animal breeding whereas women were mainly responsible for household activities. Data collected included information on age, gender, years of schooling, smoking habits, alcohol consumption, body weight, and systolic and diastolic blood pressure. Blood samples were also taken for measurements of packed cell volume, total serum cholesterol (Lieberman method),[13] blood glucose (glucose-oxidase method),[14] serum triglycerides (enzymatic method),[15] and serum uric acid (colorimetric method).[16]

By June 1996, 308 study participants had died and for all the deceased the date of death was recorded and death certificates were retrieved from the local municipal registries. The retrieval of vital status and cause of deaths was approved by the University of Athens, Medical School Ethical Committee. Only nine persons were lost to follow up and these were not included among the 1198 study participants. From the information in the death certificates, cause of death was ascertained by a board certified internist. For this analysis, the deceased were classified as having died from coronary heart disease (ICD-9 codes 410–414 and all cases of sudden cardiac death: code 427.5) or non-coronary death.

Table 1 Distribution of 504 men and 646 women, by altitude of residence and by demographic, lifestyle, clinical, and selected biochemical variables (three villages in Greece, in 1981)

	Men (%)		Women (%)	
	Mountainous	Lowland	Mountainous	Lowland
Variables	village (A)	villages (B1+B2)	village (A)	villages (B1+B2)
Age (y)				
25–34	2 (0.9)	14 (4.9)	22 (6.4)	22 (7.3)
35–44	27 (12.2)	33 (11.7)	41 (11.9)	51 (16.9)
45–54	52 (23.5)	64 (22.6)	88 (25.5)	69 (22.9)
55–64	50 (22.6)	59 (20.8)	73 (21.2)	75 (24.9)
65–74	53 (24.0)	82 (29.0)	78 (22.6)	58 (19.3)
75+	37 (16.7)	31 (11.0)	43 (12.5)	26 (8.6)
p value*	0.16		0.032	
Education				
lower†	144 (65.2)	195 (68.9)	55 (15.9)	67 (22.3)
higher	77 (34.8)	88 (31.1)	290 (84.1)	234 (77.7)
p value*	0.374		0.044	
Body weight in kg (quartiles)				
1st (upper cut off)	69	66	58	60
2nd (median)	76	73	65	66
3rd (upper cut off)	84	83	73	73
p value*	0.059		0.276	
Tobacco smoking				
never smoker	127 (57.5)	148 (52.3)	343 (99.4)	296 (98.3)
ever smoker	94 (42.5)	135 (47.7)	2 (0.6)	5 (1.7)
p value*	0.286		–	
Alcohol consumption				
none	29 (13.1)	86 (30.4)	289 (83.8)	226 (75.1)
moderate (≤2 glasses/day)	104 (47.1)	147 (51.9)	55 (15.9)	75 (24.9)
higher (>2 glasses/day)	88 (39.8)	50 (17.7)	1 (0.3)	0 (0)
p value*	<0.001		0.008	
Systolic blood pressure, in mm Hg (quartiles)				
1st (upper cut off)	125	120	120	120
2nd (median)	140	135	140	130
3rd (upper cut off)	160	150	160	150
p value*	<0.001		0.002	
Blood glucose, in mg/100 ml (quartiles)				
1st (upper cut off)	77	75	78	75
2nd (median)	85	88	85	85
3rd (upper cut off)	94	102	92	100
p value*	0.451		0.011	
Total serum cholesterol, in mmol/l (quartiles)				
1st (upper cut off)	5.38	4.91	5.40	5.09
2nd (median)	6.10	5.56	6.05	5.82
3rd (upper cut off)	6.95	6.21	6.75	6.46
p value*	<0.001		<0.001	
Serum uric acid, in mg/100 ml (quartiles)				
1st (upper cut off)	5.3	4.5	4.0	4.0
2nd (median)	6.1	5.3	4.7	4.8
3rd (upper cut off)	7.2	6.4	5.7	5.8
p value*	<0.001		0.638	
Serum triglycerides, in mg/100 ml (quartiles)				
1st (upper cut off)	87	70	74	62
2nd (median)	121	100	98	80
3rd (upper cut off)	176	145	134	110
p value*	<0.001		<0.001	
Packed cell volume% (quartiles)				
1st (upper cut off)	47	43	43	40
2nd (median)	50	46	45	42
3rd (upper cut off)	52	48	47	45
p value*	<0.001		<0.001	

*Two tailed p values from t test between means or from χ^2. †Lower educational level representing up to six years of schooling for men and illiteracy for women.

From the 1198 study participants, complete data on all the variables of interest were available for 1150 subjects and all analyses were carried out on that sample. The distributions of all baseline variables between residents of the mountainous village and residents of the sea level villages were compared with t test for continuous and χ^2 for categorical variables.

After initial cross classification and comparisons of total and coronary deaths between mountainous and lowland villages with χ^2, among men and women, the data were modelled through Cox regression. Separate models were fitted for men and women as well as for total and coronary mortality. When coronary mortality was the outcome of interest, people who had died from other causes were censored at the time of their death. Predictor variables were age (continuous, in 10 year increment), village (mountainous compared with lowland that is A compared with B1+B2), education (for men, those with six or more years compared with others; for women, any schooling compared with none), body weight (continuous, in 1 kg increment), tobacco smoking (ever compared with never), alcohol drinking

Table 2 Number of deaths overall and from coronary heart disease, by gender and mountainous or lowland place of residence (three villages in Greece, 1981 to 1996)

Village	Men			Women		
	Participants	All deaths	Coronary deaths	Participants	All deaths	Coronary deaths
Mountainous (A)	221	60 (27%)	11 (5%)	345	73 (21%)	16 (5%)
Lowland (B1+B2)	283	90 (32%)	23 (8%)	301	67 (22%)	17 (6%)
p value*		0.257	0.162		0.735	0.561

*Two tailed p values from χ^2.

(none, up to two glasses per day, more than two glasses per day, categorically), systolic blood pressure (continuous, in 10 mm Hg increment), blood glucose (continuous, in 10 mg/100 ml increment), total serum cholesterol (continuous, in 10 mg/100 ml increment), serum uric acid (continuous, in 1 mg/100 ml increment), and serum triglycerides (continuous, in 10 mg/100 ml increment). All analyses were performed with SPSS.

RESULTS

Table 1 gives the demographic, lifestyle, clinical, and biochemical characteristics of the 1150 study participants by gender and by altitude of residence. In comparison with men in the lowland villages, men in the mountainous village were heavier drinkers and had higher values of systolic blood pressure, total serum cholesterol, serum uric acid, serum triglycerides, and packed cell volume (in all instances p<0.05). In comparison with women in the lowland villages, women in the mountainous village were somewhat older and more educated, consumed less alcohol, and had lower blood glucose levels, but similarly to men they had higher systolic blood pressure, total serum cholesterol, serum triglycerides, and packed cell volume (in all instances p<0.05). Overall, residents of the mountainous village had a somewhat worse coronary risk profile in comparison with residents of lowland villages.

The median follow up was 168.59 months or 14.0 years (minimum: 0.7 months, corresponding to an early death of a study participant, maximum: 190.5 months), with 290 (25%) of the participants having died by June 1996. There were 150 deaths among men (30%) and 140 deaths among women (22%), with coronary heart disease accounting for 23% (34 deaths) and 24% (33 deaths) of all deaths among men and women respectively. In crude analysis, total and coronary cumulative mortality, without accounting for time of death,

were somewhat lower among the mountainous village residents than among the lowland residents, especially among men, but none of these differences were statistically significant (table 2).

In Cox analyses with adjustment for age but without controlling for any of the potential confounders, hazard ratios were generally lower among both men and women in the mountainous rather than in the lowland villages, with respect to both total and coronary mortality, notwithstanding the better coronary profile of the lowland villages. The hazard ratios and 95% confidence intervals comparing mountainous with lowland villagers were for total mortality: 0.67 (0.48 to 0.93) and 0.64 (0.46 to 0.90) for men and women respectively. The corresponding values for coronary mortality were 0.48 (0.23 to 0.99) and 0.51 (0.25 to 1.01).

Table 3 gives the results from the multivariate analysis of death from all causes. Statistically significant positive associations with total mortality were observed for age, smoking, systolic blood pressure, blood glucose, and total serum cholesterol among men and for age, educational level, and blood glucose among women. Living in the mountainous village (A) as compared with residence in the lowland ones (B1 and B2) exhibited an apparent "protective" effect that was more evident among men than among women. Among men total mortality was somewhat lower among moderate alcohol consumers than among non-drinkers although the results were statistically not significant. Serum uric acid, body weight, and serum triglycerides were unrelated to total mortality in both sexes.

Table 4 presents the mutually adjusted hazard ratios for death from coronary heart disease. Age, tobacco smoking, blood glucose and, in a borderline way, systolic blood pressure, and uric acid were positively associated with coronary mortality among men, while among women positive associations were evident with respect to age, education,

Table 3 Cox regression derived hazard ratios for deaths from all causes (and 95% confidence intervals), by the indicated predictor variables (three villages in Greece, 1981 to 1996)

Variables	Increment/category	Men (total deaths: 150)		Women (total deaths: 140)	
		Hazard ratio	95% CI	Hazard ratio	95% CI
Age	10 years	3.13	2.54, 3.86	3.79	2.98, 4.82
Village	B1+B2 (sea level)	1.00 (reference)		1.00 (reference)	
	A (950 m)	0.57	0.38, 0.84	0.69	0.47, 1.02
Educational level	Lower*	1.00 (reference)		1.00 (reference)	
	Higher	1.27	0.90, 1.79	1.49	1.01, 2.20
Body weight	1 kg	0.99	0.98, 1.00	1.00	0.98, 1.01
Tobacco smoking	never smoker	1.00 (reference)		not included (only seven smokers)	
	ever smoker	1.71	1.20, 2.42		
Alcohol consumption	none	1.00 (reference)		1.00 (reference)	
	moderate ($\leqslant$2 glasses/day)	0.76	0.51, 1.12	1.17	0.78, 1.75
	High (>2 glasses/day)	0.94	0.58, 1.50	not included (only one heavy drinker)	
Systolic blood pressure	10 mm Hg	1.12	1.04, 1.21	1.02	0.95, 1.10
Blood glucose	10 mg/100 ml	1.06	1.02, 1.10	1.11	1.06, 1.16
Total serum cholesterol	10 mg/100 ml	1.04	1.00, 1.09	0.97	0.93, 1.01
Serum uric acid	1 mg/100 ml	1.03	0.92, 1.15	1.05	0.93, 1.18
Serum triglycerides	10 mg/100 ml	0.99	0.97, 1.02	1.01	0.98, 1.04

*Lower educational level representing up to six years of schooling for men and illiteracy for women.

Table 4 Cox regression derived hazard ratios for deaths from coronary heart disease (and 95% confidence intervals), by the indicated predictor variables (three villages in Greece, 1981 to 1996)

Variables	Increment/category	Men (coronary deaths: 34)		Women (coronary deaths: 33)	
		Hazard ratio	95% CI	Hazard ratio	95% CI
Age	10 years	3.29	2.10, 5.14	5.88	3.33, 10.38
Village	B1+B2 (sea level)	1.00 (reference)		1.00 (reference)	
	A (950 m)	0.39	0.16, 0.98	0.46	0.20, 1.05
Educational level	Lower*	1.00 (reference)		1.00 (reference)	
	Higher	1.03	0.49, 2.17	2.48	1.07, 5.74
Body weight	1 kg	1.01	0.98, 1.04	0.99	0.96, 1.02
Tobacco smoking	never smoker	1.00 (reference)		not included (only seven smokers)	
	ever smoker	2.48	1.20, 5.10		
Alcohol consumption	none	1.00 (reference)		1.00 (reference)	
	moderate (⩽2 glasses/day)	0.66	0.29, 1.48	0.68	0.26, 1.76
	High (>2 glasses/day)	0.99	0.37, 2.67	not included (only one heavy drinker)	
Systolic blood pressure	10 mm Hg	1.18	0.99, 1.40	0.97	0.83, 1.12
Blood glucose	10 mg/100 ml	1.09	1.01, 1.18	1.18	1.10, 1.26
Total serum cholesterol	10 mg/100 ml	1.05	0.97, 1.15	1.01	0.92, 1.10
Serum uric acid	1 mg/100 ml	1.23	0.99, 1.52	1.28	1.01, 1.63
Serum triglycerides	10 mg/100 ml	0.96	0.90, 1.02	0.98	0.92, 1.05

*Lower educational level representing up to six years of schooling for men and illiteracy for women.

blood glucose, and uric acid. Residents of the mountainous village in comparison with residents of the lowland villages had lower mortality from coronary heart disease by 61% (p = 0.044) and by 54% (p = 0.064) among men and women respectively.

DISCUSSION

There are few studies concerning a possible association between altitude of residence and mortality overall or from coronary heart disease and those that have been undertaken have not fully adjusted for cardiovascular risk factors and were conducted in heterogeneous populations consisting of different ethnic subgroups.[1–4] We investigated the association of residence in mountainous or lowland areas with total and coronary mortality, among subjects from three Greek villages, taking into account classic cardiovascular risk factors as potential confounders. The study was based on a moderately large sample of rural Greek men and women with common ethnic, demographic, and occupational characteristics. The prospective design, the very low proportion of participants who were lost to follow up, and the reliance on deaths rather than incident events, provide safeguards against major selection and information bias. Our study has also certain limitations. Participants were self selected volunteers although this is unavoidable in an epidemiological study and generally does not represent an important drawback in cohort designs. We had no good information of prevalent morbidity at baseline even though the whole campaign, on which this study has relied, was focusing on apparently healthy people. We had no information on diet and the study was not large enough to permit investigation of possible interactions of altitude with gender or other factors with respect to total and coronary mortality. The findings with respect to education were unexpected in that persons, and especially women, with higher education had higher mortality, but education in villages of rural Greece has different connotations than those generally attributed to higher education in contemporary societies. For example, women of lower education may be physically more active and adhere more closely to the traditional and presumably healthy dietary pattern.

The important finding of this study is that residents of the mountainous village as compared with residents of the lowland villages had lower mortality from all causes and even lower mortality from coronary heart disease. The contrast was more evident among men than among women. The expected directions in the associations of most classic risk

What this paper adds

- Residents of mountainous areas have been reported to have lower total and coronary mortality in comparison with residents of lowland areas, but the earlier studies had inadequate control of potential confounders and have not explored whether the apparent favourable effects of living in mountainous areas are mediated through the modulation of traditional cardiovascular risk factors.

- This study shows that residents of mountainous areas have lower total and coronary mortality in comparison with residents of lowland areas, after adjustment for cardiovascular risk factors as potential confounders. The apparent protective effect of high altitude is not mediated by traditional risk factors like hypertension or blood lipid concentrations, as values of these factors were generally higher in high rather than low altitude residents. The evidence points to higher physical activity of residents of mountainous areas as an important beneficial factor.

factors with total and coronary mortality provide indirect support to the validity of the altitude findings.

Residence at high altitudes produces physiological changes for adaptation to long term hypoxemic conditions.[17] Adaptive phenomena involve respiratory,[18] cardiovascular,[18] and haematological parameters,[19] which have been shown to vary between people residing in variable altitudes. Many of these studies relied on people living in extreme altitudes and facing also malnutrition problems and endemic diseases.[20 21] In our study the mountainous village was located at a moderate altitude of 950 m above sea level but packed cell volume values were higher for the mountain dwellers compared with the lowland inhabitants, showing a degree of adaptation to altitude. Thus, our results may be more generalisable to the prevailing conditions in most countries.

Factors associated with total and coronary mortality that could not be accounted for in this study, were high density lipoprotein cholesterol (HDL) serum concentrations,[22] dietary habits,[11] and body fat distribution.[23] Although HDL concentrations have been reported to be affected by altitude,[8 9] and altitude can also affect the flora and the fauna of any

particular habitat, we consider HDL and diet as mostly intermediate variables the effects of which may not have had to be adjusted for even if relevant data were available. In reality however, the enrolment data were collected at a time when the importance of HDL and body fat distribution had not been reported and diet ascertainment techniques at the individual level for epidemiological purposes were still rudimentary.

There exists extensive literature on the cardioprotective effect of daily physical activity,[24] which has been found to reduce total and coronary mortality in epidemiological studies.[25][26] Experimental studies have shown that the physiological strain and the energy cost of walking are greater on uphill slopes than on level grounds.[27] In addition, acclimatisation to the hypoxic conditions of moderate and high altitudes has been found to improve endurance in athletes,[28] and hypoxic exercise may convey greater health benefit than physical activity at sea level.[29] Therefore it can be argued, that the common daily activities of the study participants (farming and animal breeding), may represent higher levels of daily physical workload for the residents of the mountainous village than for the lowland residents. This hypothesis could explain the lower total and coronary mortality rates found among the mountain dwellers, as well as the gender differences in the magnitude of the observed effect, as the engagement of women in household activities may imply less aerobic physical activity compared with men.

In conclusion, in a prospective rural population study we have found lower total and coronary mortality for mountain dwellers as compared with lowland inhabitants, after detailed adjustment for classic risk factors. Increased physical activity under conditions of moderate hypoxia among the mountain residents could explain these findings.

ACKNOWLEDGEMENTS

. . . .

Authors' affiliations
N Baibas, A Trichopoulou, Department of Hygiene and Epidemiology, University of Athens, Medical School, Athens, Greece
E Voridis, Euroclinic, Department of Cardiology, Athens, Greece
D Trichopoulos, Department of Epidemiology, Harvard School of Public Health, Boston, USA

REFERENCES
1 **Mortimer E Jr**, Monson R, MacMahon B. Reduction in mortality from coronary heart disease in men residing at high altitude. *N Engl J Med* 1977;**296**:581–5.
2 **Ashouri K**, Ahmed ME, Kardash MO, *et al.* Acute myocardial infarction at high altitude: the experience in Asir region, Southern Saudi Arabia. *Ethn Dis* 1994;**4**:82–6.
3 **Buechley R**, Key C, Morris D, *et al.* Altitude and ischemic heart disease in tri-cultural New Mexico: an example of confounding. *Am J Epidemiol* 1979;**109**:663–6.
4 **Mortimer E Jr**, Monson R, MacMahon B. Comment on ''Altitude and ischemic heart disease in tri-cultural New Mexico: an example of confounding. '' *Am J Epidemiol*, 1979;**109**:719–20.
5 **Liu L**. Epidemiology of hypertension and cardiovascular disease—China experience. *Clin Exp Hypertens A* 1990;**12**:831–44.
6 **He J**, Tell GS, Tang YC, *et al.* Effect of migration on blood pressure: the Yi people study. *Epidemiology* 1991;**2**:88–97.
7 **Smith C**. Blood pressure of Sherpa men in modernizing Nepal. *Am J Human Biol* 1999;**11**:469–79.
8 **Dominguez CS**, Cabrera DA, Bosa OF, *et al.* High density lipoprotein cholesterol increases with living altitude. *Int J Epidemiol* 2000;**29**:65–70.
9 **Aitbaev KA**. The levels of high density lipoprotein cholesterol and other lipids in the native population of the mountain region of Kirghizia. (In Russian). *Vorp Med Khim* 1985;**31**:58–61.
10 **Santos JL**, Perez-Bravo F, Carrasco E, *et al.* Low prevalence of type 2 diabetes despite high average body mass index in the Ayamara natives from Chile. *Nutrition* 2001;**17**:305–9.
11 **Trichopoulou A**, Costacou T, Bamia C, *et al.* Adherence to a Mediterranean diet and survival in a Greek population. *N Engl J Med* 2003;**348**:2599–608.
12 **Kalapothaki V**, Kalandidi A, Katsouyanni K, *et al.* The health of the Greek population. (In Greek). *Materia Medica Greca* 1992;**20**:91–164.
13 **Vincent D**, Lagreu R. Simplified and rapid method for the determination of serum cholesterol by the Lieberman reaction. *Laboratorio* 1950;**10**:517–20.
14 **Rosevear JW**, Pfaff KJ, Service FJ, *et al.* Glucose oxidase method for continuous automated blood glucose determination. *Clin Chem* 1969;**15**:680–98.
15 **Bucolo G**, David H. Quantitative determination of serum triglycerides by the use of enzymes. *Clin Chem* 1973;**19**:476–82.
16 **Paolaggi F**, Ryckewaert A, Kahn MF, *et al.* Comparative value of Folin's colorimetric method and Praetorius' enzyme method for the determination of uricemia and uraturia. (In French). *Pathol Biol* 1964;**12**:589–93.
17 **Ramirez G**, Bittle PA, Rosen R, *et al.* High altitude living: genetic and environmental adaptation. *Aviat Space Environ Med* 1999;**70**:73–81.
18 **Domej W**, Schwaberger G. Respiratory adaptation to altitude and risk factors due to respiratory illnesses. (In German). *Wien Med Wochenschr* 2000;**150**:163–8.
19 **Beall CM**, Brittenham GM, Strohl KP, *et al.* Hemoglobin concentration of high-altitude Tibetans and Bolivian Ayamara. *Am J Phys Anthropol* 1998;**106**:385–400.
20 **Moore LG**, Armaza F, Villena M, *et al.* Comparative aspects of high-altitude adaptation in human populations. *Adv Exp Med Biol* 2000;**475**:45–62.
21 **Harris NS**, Crawford PB, Yangzom Y, *et al.* Nutritional and health status of Tibetan children living at high altitudes. *N Engl J Med* 2001;**344**:341–7.
22 **Stampfer MJ**, Sacks FM, Salvini S, *et al.* A prospective study of cholesterol, apolipoproteins and the risk of myocardial infarction. *N Engl J Med* 1991;**325**:373–81.
23 **National Institutes of Health**. Clinical guidelines on the identification, evaluation, and treatment, of overweight and obesity in adults. The evidence report. *Obes Res* 1998;**6**(suppl 2):P51–209.
24 **Pate RR**, Pratt M, Blair SN, *et al.* Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA* 1995;**273**:402–7.
25 **Dorn JP**, Cerny FJ, Epstein LH, *et al.* Work and leisure time physical activity and mortality in men and women from a general population sample. *Ann Epidemiol* 1999;**9**:366–73.
26 **Leon AS**, Myers MJ, Connett J. Leisure time physical activity and the 16-year risks of mortality from coronary heart disease and all causes in the multiple risk factor intervention trial (MRFIT). *Int J Sports Med* 1997;**18**(suppl 3):208–15.
27 **Minetti AE**, Moia C, Roi GS, *et al.* Energy cost of walking and running at extreme uphill and downhill slopes. *J Appl Physiol* 2002;**93**:1039–46.
28 **Katayama K**, Matsuo H, Ishida K, *et al.* Intermittent hypoxia improves endurance performance and submaximal exercise efficiency. *High Alt Med Biol* 2003;**4**:291–304.
29 **Stray-Gundersen J**, Chapman RF, Levine BD. ''Living high-training low'' altitude training improves sea level performance in male and female elite runners. *J Appl Physiol* 2001;**91**:1113–20.