

Review Article

Effects of Living at Higher Altitudes on Mortality: A Narrative Review

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ABSTRACT: Beside genetic and life-style characteristics environmental factors may profoundly influence mortality and life expectancy. The high altitude climate comprises a set of conditions bearing the potential of modifying morbidity and mortality of approximately 400 million people who are permanently residing at elevations above 1500 meters. However, epidemiological data on the effects of high altitude living on mortality from major diseases are inconsistent probably due to differences in ethnicity, behavioral factors and the complex interactions with environmental conditions. The available data indicate that residency at higher altitudes are associated with lower mortality from cardiovascular diseases, stroke and certain types of cancer. In contrast mortality from COPD and probably also from lower respiratory tract infections is rather elevated. It may be argued that moderate altitudes are more protective than high or even very high altitudes. Whereas living at higher elevations may frequently protect from development of diseases, it could adversely affect mortality when diseases progress. Corroborating and expanding these findings would be helpful for optimization of medical care and disease management in the aging residents of higher altitudes.

Key words: High altitude, hypoxia, UV radiation, physical activity, disease, mortality

Beside genetic and life-style characteristics environmental factors may profoundly influence life expectancy [1]. A variety of gene-environment interactions have been demonstrated to have impact on the development of major diseases at advanced ages like cardiovascular and neurodegenerative diseases, diabetes mellitus, and cancer [2, 3]. The high altitude climate comprises a set of conditions bearing the potential of modifying morbidity and mortality of approximately 400 million people who are permanently residing at elevations above 1500 meters [4]. Low barometric pressure and related low partial pressure of oxygen (hypoxia) and increased ultra violet radiation are components of the high altitude climate which are probably interacting in a complex way with genes and other environmental factors [5, 6]. In addition, the outcomes will be influenced by the level of altitude (moderate altitude: 1500 – 2500 m; high altitude: 2500 – 3500 m; very high altitude: > 3500 m),

working and housing conditions, behavioral patterns like physical activity, nutrition, smoking and alcohol consumption, and the availability of medical care. It is obvious that some of the altitude-associated conditions may have different impacts on risk factors for developing various diseases and associated mortality or life expectancy. High altitude may have protective effects on cardiovascular diseases and harmful effects on chronic pulmonary disease (COPD) [7] and beneficial effects on mortality from some types of cancer [8]. Mechanisms responsible for these effects are largely unexplored and remain extremely speculative [6, 7, 8]. There are only very few papers evaluating the impact of high altitude living on mortality from major diseases. This, however, would be important to improve preventive medicine in high altitude regions and would probably enhance the general understanding of gene-environmental interactions influencing the development and progression of major

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diseases at advanced ages. Thus, the main goal of the present paper is to present an overview, extracted from the available literature, on the mortality from major diseases when living at higher altitudes.

Altitude effects on mortality from cardiovascular diseases and stroke

Epidemiological data

Observations from populations of the Andes indicate that both coronary heart disease (CHD) and myocardial infarction are uncommon among residents at high altitude. In a consecutive series of necropsies performed at about 14000 feet (~ 4260 m) there was no case of myocardial infarction or of even moderate coronary artery disease [9]. Large epidemiological studies in the 1970ties confirmed lower mortality from CHD in people residing at higher elevations. Mortimer and colleagues found decreasing mortality rates at altitudes from 914 to over 2135 m in New Mexico [10]. Mortality declined predominantly in males and was 72% at the highest locations compared to the county group below 1220 m. Voors et al. confirmed the negative relationship between altitude and mortality in the highest 99 out of 100 largest cities of the United States up to an altitude of 1650 m [11]. These findings have also been confirmed by more recent studies. In Switzerland the age-standardized mortality rates (per 100,000 person-years) from CHD decreased in men from 289 (95% CI: 275-304) below 300 m of altitude to 242 (193-290) at altitudes above 1500 m and in women from 104 (97-111) < 300 m to 74 (52-97) > 1500 to 1960 m [6]. Mortality rates remained essentially unchanged up to 900 m and then started to decline. The decrease of mortality from stroke was less convincing when compared to that of CHD. After adjustment for age, sex, education, and urbanity the mortality risk for CHD decreased by 22% and that for stroke by 12% per 1000 m increase of altitude [6]. Similar observations have been reported from mortality and population data of the United States (2001 through 2005) for altitudes up to >2500 m [7]. However, reduced mortality from CHD in this study was more consistent for women than for men. Again, mortality reduction from stroke was less pronounced and was not statistically significant below 1500 m [7]. Even larger benefits from living in mountainous areas have been reported from Greece [12]. When compared to two lowland villages (Zevgolatio and Aidoniain in the plains of the Peloponnesus region) the hazard ratio for coronary mortality was 0.39 (0.16 to 0.98) for men and 0.46 (0.20 to 1.05) for women living in a mountainous village in rural Greece (Arahova in the Sterea Hellas region, 950 m). Lower mortality from cardiovascular events were also reported for dialysis patients [13] as well as improved

survival after heart transplantation [14] in patients living at higher elevation compared to lower ones. There are only very few studies indicating rather detrimental effects of altitude residence on the risk of heart disease which might at least partly be explained by the more extreme conditions of the higher elevations (1500 – 3500 m) where people lived [15]. This is supported by the study of Virues-Ortega et al. demonstrating increasing overall mortality from altitudes between 1500 to 2900m and \geq 3000 [4]. Of course, differences in ethnicity, behavioral aspects, or medical care between low and high elevations might also contribute to the explanation of the conflicting results. Chronic mountain sickness represents another serious problem arising at higher altitudes (> 3000m) contributing to increased mortality [16].

How may altitude affect mortality from CHD and stroke?

Physical activity and fitness level

Authors of the early studies, in the 1970ties, suggested increased daily physical activity and the related higher fitness level to be potentially responsible for the observed beneficial effects of living at higher elevations [10] but recent studies do not believe this would be an essential explanation for the differences of life expectancy between populations of low and higher altitudes [6]. However, no study actually ruled out differences in regular physical activity and fitness between these populations. Nowadays it is well established that regular physical activity reduces all traditional risk factors for cardiovascular disease and stroke, i.e. systemic arterial hypertension, elevated low-density and reduced high-density lipoproteins, increased triglyceride levels, insulin resistance and glucose intolerance [17]. At least in the Alps, e.g. in Austria, France, Italy, and Switzerland, higher elevations are typically situated in mountainous areas. They are mostly characterized by a hilly and rugged terrain challenging exercise performance of residents during work and leisure activities [18]. In fact, there are many studies consistently showing a linear dose-response relation between the fitness level and mortality. Kokkinos and colleagues for example demonstrated an approximately 20% lower mortality risk for subjects with an exercise capacity of 5-7 metabolic equivalents (METs; 1 MET = 3.5 mlO₂·min⁻¹·kg⁻¹) compared to those achieving below 5 METs [19]. Exercising in the mountains may favour the development of a relatively high fitness level because 5-7 METs are required even for slow uphill walking [18, 20]. If physical activity and fitness are increased at higher altitudes this might well explain part of the lower mortality observed. In contrast, when diseases progress, cardiorespiratory

systems may be rapidly overstressed even during light physical activities, thereby increasing the mortality risk.

Hypoxia

The moderate hypoxia stimulus at altitudes up to 2500 m has been suggested as a potential contributor to the beneficial effects on cardiovascular health [7, 21]. From a biological perspective it has been hypothesized that hypoxia inducible factor (HIF) pathways might mediate the reduction of cardiovascular mortality at altitude [13]. HIF-1 is a key regulator of processes such as erythropoiesis, angiogenesis, apoptosis and metabolism [13, 22], which might all have impact on the cardiovascular and cerebrovascular systems. Adaptation effects might partly explain the lower systemic systolic and diastolic blood pressures and lower atherogenic lipoprotein cholesterol (C-LDL) in residents of higher compared to lower regions [23, 24]. High altitude hypoxia could also protect against cardiovascular disease by lowering hepcidin and reticuloendothelial iron storage [25]. Hepcidin has been suggested as a risk factor for atherosclerosis and may be down regulated by HIF which induces erythropoietin and ferroportin [25].

In addition, exercising at altitude may represent a superimposed intermittent hypoxia-like stimulus causing beneficial pre-conditioning effects [26]. It is thought that adaptation to such intermittent hypoxia stimuli which are largely related to nitric oxide production may provide protection against subsequent more severe and prolonged hypoxia as well as protection against other stresses [26, 27]. Effects of this type of intermittent hypoxia include cardioprotection, vasoprotection, neuroprotection, and antistress defense [27]. For example, downhill skiing in alpine regions represents a model of intermittent hypoxia. It has recently been demonstrated that prevalences of hypercholesterolemia, systemic hypertension, diabetes, frequency of mental stress and the occurrence of memory deficits declined in regular downhill skiers with increasing yearly skiing frequency perhaps partially as a consequence of intermittent hypoxia [28]. Adaptation effects to moderate altitudes seem to occur rapidly as it has been shown that the risk of sudden cardiac death decreases steeply after sleeping only one night at higher elevations (> 700 m) [29]. Taken together, it may be the moderate stress imposed by moderate altitude that favours protective adaptations.

UV-radiation

Levels of ultraviolet radiation increase by about 10% with every 300 m increase in altitude and may profoundly influence cardiovascular mortality [30]. Protective effects of ultraviolet radiation are mediated by the higher

concentrations of Vitamin D, probably by reducing the risk of thrombus formation [31]. Increased cardiovascular and cerebrovascular risk may result from Vitamin D deficiency due to the related increase in parathyroid hormone, which increases insulin resistance and is associated with diabetes, hypertension, and inflammation [32].

Air pollution

Decreasing air pollution with increasing altitude may represent another potentially contributing factor to the CHD mortality reduction [6]. The relationship between the exposure to air pollution (short- and long-term) and cardiovascular events has been demonstrated by epidemiological studies. Responsible mechanisms may include enhanced coagulation (thrombosis), acute vasoconstriction, a propensity for arrhythmias, and systemic inflammatory responses promoting progression of atherosclerosis [33].

Concluding remarks

Both, behavior patterns and the various environmental conditions of the altitude climate may contribute to the lowering of cardiovascular and cerebrovascular overall mortality which seems to be more distinctive when living at moderate altitudes. However, when diseases progress, living at high altitude may become detrimental.

Altitude effects on mortality from COPD

Epidemiological data

Male sex, older age, smoking, air pollution and probably also living at higher altitudes are well-known independent risk factors for chronic obstructive pulmonary disease (COPD) [34]. Whether living at higher altitudes is associated with higher or lower prevalences of COPD remains equivocal. Whereas Menezes et al. [35] and Laniado-Laborin et al. [36] found an inverse relationship between altitude and the COPD prevalence, the opposite has been reported by Caballero et al. [34]. Although the regression analysis in the study by Caballero et al. demonstrated a positive association between COPD prevalence and altitude, this association disappears when the city at the highest altitude (Bogota, 2640m) was compared with the city at the lowest altitude (Barranquilla, 18m) [34, 36]. However, there is a broad consensus that mortality from COPD increases with altitude [7, 37]. Cote et al. reported a significant association between COPD and both altitude and smoking [37]. They found that COPD mortality rose by 1/100,000 for each 95m increase of altitude or every 5.4 increase in

mean packs consumed per capita per year. Similar effects have been reported by Ezzati et al. [7]. COPD mortality was 3-4/10,000 greater at altitudes above 1000 m compared to regions within 100m of sea level. In addition, Colorado death records from 1959 to 1976 indicate higher emphysema mortality at these higher elevations when compared with the overall population [38]. There is only one study reporting that mortality was not elevated in COPD patients living at higher altitudes (Mexico City) [39]. The authors hypothesized that this discrepancy might be due to differences in occupational exposures and to the fact that they examined data from a later period when supplemental oxygen use was more prevalent [39]. Taken together existing evidence suggests that long-term residence at high altitude is a potential problem for COPD patients and it seems reasonable that patients suffering from COPD would benefit when migrating to lower altitudes.

How may altitude affect mortality from COPD?

Explaining the lower COPD prevalence at higher altitudes, Laniado-Laborin and colleagues suggested that altitude could induce a greater growth of the airways compared with lung size, resulting in an increase of the FEV1/FVC ratio [36]. However, in patients suffering from COPD it has been assumed that even modestly lower ambient oxygen levels from impaired breathing and gas exchange might favour hypoxia and potentiate pulmonary hypertension and the associated development of cor pulmonale [7, 40]. Survival in COPD is adversely affected by pulmonary hypertension depending on the severity of resting mean pulmonary artery pressure [40]. A dose-response relationship between daily hours of oxygen use and survival has been demonstrated. Besides, the presence of chronic mountain sickness may contribute to COPD mortality [41]. Chronic mountain sickness is associated with decreased alveolar ventilation due to a blunted hypoxic ventilatory response leading to low arterial oxygen levels, increased pulmonary hypertension and excessive erythrocytosis [16, 41].

Concluding remarks

Based on the available epidemiological data it seems to be conceivable that the COPD prevalence is lower but mortality is higher at altitude. In other words, the risk to suffer from COPD might be reduced when living at higher elevations but when suffering from COPD the mortality risk rises. Thus, COPD patients, especially when disease progresses would benefit from moving down to more oxygen rich sea level regions.

Altitude effects on mortality from cancer

Epidemiological data

An early study performed in La Paz (Bolivia, ~ 4000m) indicated a higher prevalence for cancer of the cervix, the gallbladder and the thyroid gland in females when compared to other Andean populations [42]. Males have been found to suffer from unusually high rates of testicular cancer [42]. In contrast Amsel et al. reported, based on a 20-year observation period (1950-1969), reduced cancer mortality in high altitude counties [43]. Weinberg et al. (1987) showed that mortality was negatively related to altitude for cancers of the trachea, bronchus, and lung, stomach, small or large intestine, female breast, multiple myeloma, and leukemia considering the time period 1960–1969 [44]. Data from a mountainous region in Spain found a tendency of increased prevalence of melanoma at higher altitudes [45]. Youk et al. demonstrated reduced cancer mortality of people living at altitudes higher than 2134m compared to those living below 305m [8]. Their data are based on mortality and population data of the United States and covered the period from 1950 to 2004. Age-adjusted mortality rates of all cancers, of respiratory system cancers, of non-Hodgkin's lymphoma, and of breast cancer in women were lower at higher elevations [8]. In a recent paper, Torres et al. demonstrated for the Americans a concentration of mortality from gastric cancer in the mountainous areas along the Pacific Rim, following the geography of the Andes sierra, from Venezuela to Chile, and the Sierra Madre and Cordillera de Centroamérica, from southern Mexico to Costa Rica [46]. However, Torres et al. suggested altitude only to be a surrogate for host genetic, bacterial, dietary, and environmental factors that may cluster in the mountainous regions [46].

How may altitude affect mortality from cancer?

In their early study, Amsel et al. speculated that levels of cellular pH at higher altitudes, controlling protein synthesis and mitosis in tumour cells could make cancer cells less likely to grow [43]. Weinberg and colleagues suggested that oxygen produces toxic effects at physiologic levels, and that the effects observed at altitude could reflect an interaction between oxygen levels and background radiation [44]. More likely however, increased Vitamin D levels mediated by the elevated UV radiation at altitude might contribute to the protection against development of cancer. The biologically active form of Vitamin D is recognized to inhibit cell proliferation and to favour differentiation into normally functioning cells [47]. Moreover, Vitamin D has been shown to stabilize chromosomal structure and to protect

against endogenously and exogenously induced chromosomal aberrations [47].

When cancer has developed living at altitude might be less beneficial because HIF-1, stabilized under hypoxic conditions, is known to immortalize tumors by inducing key genes in cancer biology, including angiogenesis, glycolysis, invasion, and metastasis [48].

UV radiation which increases with altitude is the main modifiable risk factor for the development of cutaneous melanoma [45]. Nevertheless, the association between altitude and melanoma prevalence is rather weak which might be partly explained by the protective effects mentioned above. If present, differences in regular physical activity between residents of low and higher elevations may also influence cancer mortality. Strong preventive effects against cancer have been attributed to regular and vigorous physical exercise [49]. Regular exercise has been suggested to reduce cancer incidence up to 40% and these beneficial effects seem to be most pronounced for colorectal and breast cancer [49].

Concluding remarks

Living at higher altitudes may be protective against at least some types of cancer. Again, mortality may be profoundly modified by the complex interactions between behavioral and environmental conditions.

Miscellaneous

Suicide rates seem to be higher at higher altitudes [50]. Betz et al. demonstrated that victims at high and low altitudes differ significantly by multiple demographic, psychiatric, and suicide characteristics. The authors suggest these factors, rather than hypoxia or altitude, to be responsible for the increased suicide rates at high altitude [50]. Based on death certificates from Mexico (1993-1997) the mortality rate for tuberculosis decreased with altitude of residence but was increased for pneumonia and influenza [51]. Whereas beneficial effects on tuberculosis mortality have been attributed to altitude and dryness, altitude related hypoxemia might have negative impact on the outcome of pneumonia and influenza [52]. Finally, children living at high elevations are at special health risk related to hypoxemia during infancy and during acute lower respiratory infections [53].

Conclusions

Interactions between genetic, behavioral and environmental conditions at altitude are complex and may differently impact on mortality from various diseases. Living at higher altitudes seems to be associated with lower mortality from cardiovascular diseases, stroke and

certain types of cancer. In contrast mortality from COPD and probably also from lower respiratory tract infections seems to be increased. It may be argued that moderate altitudes are more protective than high or even very high altitudes. Whereas residency at altitude may frequently protect from development of diseases, it could adversely affect mortality when diseases progress. Corroborating and expanding these findings would be helpful for optimization of medical care and disease management in the aging residents of higher altitudes.

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