Mortality and morbidity from cardiovascular disease (CVD) is a major global health burden. Geographical disparities in CVD morbidity and mortality are substantial, even within countries. Little is known about the role of independent environmental factors in the development of CVD. One environmental factor that could influence geographical patterns of CVD mortality and risk factors is altitude. Evidence, however, is conflicting. Studies from Peru, Central Asia, and Russia suggested that hypertension is less common at high than at low altitudes, whereas reports from the United States, Italy, and Saudi Arabia showed the opposite.

A similar pattern was reported with respect to blood lipids. An increase in high-density lipoprotein cholesterol with increasing altitude has been reported in India and Spain, whereas no difference and a slight decline in high-density lipoprotein cholesterol were found in Central Asia and Venezuela, respectively. Studies from the United States, Yemen, and Saudi Arabia suggest an increased risk of CVD at higher altitudes, whereas the opposite was shown by a Greek study.

The contradicting results partially reflect the inherent limitations of these studies. The studies were constrained because the populations living at high and low altitudes differed with respect to ethnicity or behavioral risk factors such as smoking and obesity or with respect to access to medical services. Most studies were not carried out in general populations or stem from populations living at very high altitudes and thus under extreme conditions. Finally, effects of changes in altitude of residence during life are rarely considered. Conditions before or shortly after birth could affect CVD mortality and exert a lifelong effect. In England, childhood residence predicted subsequent stroke mortality more strongly than place of residence at death.

With our data, we have the opportunity to study the relationship between altitude and CVD mortality with a longitudinal design and in a large general population. Switzerland offers a unique setting for such analyses because it includes altitudes of residence between 200 and 2000 m with only minimal changes in geographic latitude. The short distances and universal access to health care minimize variations in healthcare use. Another novel feature of this study is the availability of place of birth in addition to place of residence, allowing us to derive a proxy of “lifetime altitude exposure.”

The aim of this study was to examine mortality from coronary heart disease (CHD) and stroke in relation to...
altitude of place of residence in 1990 and at birth with a follow-up of 10 years. In addition, we compared those who changed their range of altitude between birth and 1990 with those who were born at the same range of altitude as their place of residence in 1990. To avoid confounding caused by different climatic conditions (eg, aspect or north versus south of the Alps) or by cultural differences in health behavior and the assignment of causes of death, we restricted our study to residents of German Switzerland (see the Figure).

Methods

Study Population

The Swiss National Cohort is a nationwide longitudinal research platform based on anonymous record linkages of individual data collected by the Swiss Federal Statistical Office. The core cohort consists of the 6.22 million residents who participated in the 1990 census and could be satisfactorily linked to a mortality or 2000 census record. For 476 814 individuals with a 1990 census record (6.9%), no satisfactory link could be found. However, the majority of unlinked records were related to individuals 10 to 29 years of age (6.9%), no satisfactory link could be found. However, the majority of unlinked records were related to individuals 10 to 29 years of age who were not included in our analysis (for more details, see elsewhere). The 1990 and 2000 censuses in Switzerland were carried out with self-administered questionnaires. Nonparticipation is considered to be very low (For the 2000 census, coverage was estimated at 98.6%).

Switzerland comprises 3 major cultural groups: German Swiss (72% of total population), French Swiss (23% of total population), and Italian Swiss (<5% of total population). For homogeneity reasons (see above), residents of French and Italian Switzerland were excluded. Because of the small numbers of CVD deaths at younger ages and the uncertainty of assignment of cause of death at very old ages, we limited the age of inclusion. Individuals were followed up between December 4, 1990, and December 5, 2000 (census dates), and between the 40 and 84 years of age (n=2 009 615). Deaths and person-years were accumulated only in that age span. Thus, the youngest observed subject just had passed his 30th birthday on December 4, 1990, and contributed only 1 day of observation on December 4, 2000. Individuals ≥85 years of age at the 1990 census were excluded, and those reaching their 85th birthday between the census dates were censored. Of these individuals, 345 016 were born abroad and 23 455 did not indicate a place of birth and therefore were excluded from analysis. Thus, the study population amounts to 1 641 144 Swiss and foreign nationals born in Switzerland and contributing 14.52 million person-years.

Variables

Places of residence and birth, educational level, nationality, marital status, and household status were assessed in the 1990 census. Place of birth and place of residence were assessed on the commune level. The 2896 communes (by census 2000) are the smallest administrative units in Switzerland. The altitude of communes in meters above sea level was obtained from the Department of Geography of the University of Zurich. To assess the effect of the difference between the altitude of the place of residence in 1990 and the altitude of the place of birth, we discerned those who “moved up” in altitude (place of residence >200 m above place of birth; n=71 573) and those who “moved down” in altitude (place of residence >200 m below place of birth, n=187 542) from those who did not move (“not moved”: difference in altitude between place of birth and place of residence <200 m). The reference group were those who did not move, ie, those born and in 1990 still living in the same range of altitude. Because all large cities are situated on lower altitudes (commune of Basel, 270 m, 4% of total population in German Switzerland; Zurich, 409 m, 8.3%; Bern, 540 m, 3.2%), a part of the effect of altitude may relate to a urban-rural difference. We thus created an urbanity variable including these 3 cities (living versus not living in one of these cities). Because of their topographical situation, regions in the northwest of German Switzerland have less fog and more sunshine than most other lowland regions of the country. In German Switzerland, only inhabitants of these regions live at altitudes <300 m. We considered this by including a dummy variable in our models. Years of education were estimated from educational level and varied between 8 (less than compulsory schooling) and 19 years (university graduates; for details, see elsewhere). Marital status (married versus not married), household status (private versus collective), and nationality (Swiss versus foreign national) were dichotomized. Causes of death were coded according to the eighth revision of the International Classification of Diseases, Injuries and Causes of Death (ICD-8) until 1994. From 1995 to 2000, the 10th revision (ICD-10) has been used. CHD was defined as ICD-8 codes 410 to 414 or ICD-10 codes I20 to I25; stroke was defined as 430 to 438 (ICD-8) or I60-I69 (ICD-10).

Statistical Analysis

To account for ageing of individuals in the cohort during follow-up, we expanded the person data to person-period data (with the “st” commands of STATA). Thus, we calculated mortality rates (per 100 000 person-years) at different altitudes. We divided the population into 5-year classes with the “stsplit/ageband” command to obtain a more accurate approximation of the effect of ageing of observed individuals on mortality risk. Because individuals could change 5-year age class over the 10 years of observation time, the same individual could contribute person-time to up to 3 age classes. Rates and relative risks were calculated separately for each sex and
adjusted for age by standardization to the World Health Organization Standard Population “Europe (old)” or by including age in a Poisson regression model. We used Poisson regression because mortality data are discrete counts and death is a rare event. Regression models also included years of education, urbanity, altitude of place of residence, and difference in altitude between place of residence and place of birth (3 categories: up-movers, down-movers, nonmovers). Sensitivity analyses also encompassed models with age2, living below 300 m, nationality, household, and marital status. Estimates and 95% confidence intervals (CIs) of the Swiss Heart Survey were weighted to the Swiss population. Analyses were performed with Stata 9.2 (Stata Corp, College Station, Tex).

### Results

#### Participants

Table 1 shows the number and proportion of German Swiss residents by category of place of birth (movers). The proportion of those who did not move tended to decrease with increasing altitude. The numbers of up-movers and down-movers are small in the extreme ranges because the altitude range is limited to 259 to 1960 m and only few people live above 1500 m.

#### Mortality Rates

Numbers of deaths and age-standardized mortality rates (per 100 000 person-years) by sex are shown in Table 2. CHD rates in men and women and stroke rates in men tended to be lower at high than at low altitudes. However, because of the smaller number of residents at high altitudes, the CIs were mostly overlapping as a result of the CIs being larger at higher altitudes. In both sexes, the rates for CHD hardly varied below 900 m. In women, the highest rates for stroke were found between 1200 and 1500 m; in men, the rates were highest at low altitudes (300 to 600 m). Of note are the relatively low rates for stroke at the lowest altitude (<300 m), particularly in women.

#### Relative Risks

Results of the multivariable Poisson regression are given in Table 3. The results shown have consecutively been adjusted for age, sex, education, urbanity, and place of birth category (movers). After adjustment, the mortality risk for CHD decreased by 22% with an increase of 1000 m in the altitude of the place of residence. Compared with those who were born and still lived in 1990 in the same range of altitude, moving had the following effects: Having moved >200 m down in altitude was associated with an additional risk reduction of 4%, and having moved >200 m up was associated with a risk increase of 8%. The mortality risk for stroke decreased after adjustment by 12% with an increase of 1000 m in the altitude of the place of reference. Having moved >200 m down was associated with an additional risk reduction of 7%, and having moved >200 m up had no statistically significant effect. Analyses by sex showed that the effect of altitude tended to be stronger in men (CHD, 0.76 [95% CI, 0.70 to 0.82]; stroke: 0.79 [95% CI, 0.68 to 0.90]) than in women (CHD, 0.81 [95% CI, 0.73 to 0.88]; stroke, 0.97 [95% CI, 0.87 to 1.01]). Additional adjustment for age2, marital status, nationality, and household status had virtually no impact on the results (not shown). When the variable of living below 300 m was added to the model, the protective effect of altitude on CHD and stroke mortality became stronger in both sexes. Living below 300 m was significantly associated with a lower CHD (women) and stroke (men and women) mortality (not shown).

#### Discussion

In the German-speaking part of Switzerland, we found an almost continuous decrease in CHD and stroke mortality with increasing altitude (259 to 1960 m). This effect tended to be stronger in men than in women and for CHD than for stroke. In persons having changed altitude of residence compared with those living in 1990 in the same altitude range in which they were born, a higher place of birth tended to have a protective effect and a lower place of birth tended to have an adverse effect on mortality. To the best of our knowledge, this is the first longitudinal study with individual data of a large homogeneous and representative population showing a protective effect of altitude on CVD mortality. A lower CHD mortality at higher altitudes also has been found in New Mexico (United States), but the effect of altitude might have been confounded by ethnicity. In Colorado (United States),
there was no clear association between altitude and CHD,29 whereas an inverse correlation between altitude and CHD was found on examination of records in the 99 largest cities of the United States with altitudes between 0 and 1650 m.30 Negative correlations with altitude also were found on analysis of mortality from CHD and stroke in 3072 US counties between 0 and 2450 m.3 Consistent with our results, other studies showed that the decrease in mortality with increasing altitude was stronger for CHD than for stroke.3,17,28,30–32 However, all these findings stem from ecological studies with sometimes very skewed distributions and should therefore be interpreted cautiously. In contrast to these investigations from the 1970s, a more recent study from Greece used individual data adjusted for classic CVD risk factors. It found much lower CHD mortality in a village situated at 950 m of altitude compared with 2 villages at sea level.17 However, the sample was comparably small and consisted of volunteers.

There are several potential explanations for the lower mortality from CHD and stroke at higher altitudes. Behavioral CVD risk factors such as obesity, smoking and drinking, poor diet, and physical inactivity could be more common at lower altitudes. On the basis of results from the third Swiss Health Survey (see the online-only Data Supplement), we have no reason to believe that these risk factors differ substantially by altitude. This may also hold true for clinical CVD risk factors (blood pressure, blood lipids, and sugar) as has been shown in Greece.17 Factors not mediated by classic risk factors also could play a role. In England, differences in CVD mortality between cities related not only to variations in behavioral, social, and clinical risk factors but also to differences in climate.2 Swiss regions above 1000 m have less fog than most lower regions and thus are drier and sunnier, particularly during winter.26 Ultraviolet radiation from sunlight may have a substantial impact on CVD. With every 300-m increase in altitude, ultraviolet levels increase by up to 10%,33 and in Switzerland, ultraviolet radiation is substantially stronger at higher than at lower altitudes.25,33 The protective effect of ultraviolet radiation may be mediated by higher concentrations of vitamin D33–36 or by lower blood pressure.17,37 Vitamin D synthesis is increased at high altitudes,38 and even the radiation of relatively small skin areas is sufficient to influence vitamin D synthesis.39 Living at higher altitudes may therefore provide advantages, particularly in winter when vitamin D synthesis is critical at lower altitudes because of the relative lack of sunshine. In Swedish women, venous thromboembolism was increased by 50% during winter and was correlated with low sunshine exposure.40

Generally, in Switzerland, air pollution diminishes with increasing altitude, which is reflected by better lung function.41 Because air pollution is an important risk factor for CVD,42 it could partially explain the difference in CVD mortality between high and low altitudes. However, this effect may be minor because there was no increased mortality in the 3 largest Swiss cities. Diet also could contribute to the beneficial effect of living at higher altitudes because food produced there might be richer in CVD-protective nutrients. For example, cheese and milk from cows in alpine regions (1130 to 1890 m) had a higher content of omega-3 fatty acids and vitamin E than products from lowland cows.43,44 Because dairy products are produced, processed, and consumed locally at all altitude ranges, different intake of included micronutrients between highlanders and lowlanders is likely.

Table 2. Number of Deaths Resulting From CHD and Stroke and Corresponding Age-Standardized Mortality Rates (per 100 000 Person-Years) With 95% CIs, 1990 to 2000, in German Switzerland in Subjects 40 to 84 Years of Age*

<table>
<thead>
<tr>
<th>Residence, † m Above Sea Level</th>
<th>CHD</th>
<th></th>
<th></th>
<th>Stroke</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Person-Years</td>
<td>Deaths</td>
<td>Rate</td>
<td>95% CI</td>
<td>Deaths</td>
<td>Rate</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;300</td>
<td>338 642</td>
<td>1505</td>
<td>289</td>
<td>275–304</td>
<td>407</td>
<td>72</td>
</tr>
<tr>
<td>300–600</td>
<td>5 641 604</td>
<td>19 477</td>
<td>286</td>
<td>282–291</td>
<td>6072</td>
<td>82</td>
</tr>
<tr>
<td>600–900</td>
<td>824 056</td>
<td>3141</td>
<td>290</td>
<td>280–300</td>
<td>927</td>
<td>78</td>
</tr>
<tr>
<td>900–1200</td>
<td>130 181</td>
<td>506</td>
<td>273</td>
<td>249–297</td>
<td>177</td>
<td>81</td>
</tr>
<tr>
<td>1200–1500</td>
<td>64 908</td>
<td>217</td>
<td>246</td>
<td>213–279</td>
<td>67</td>
<td>70</td>
</tr>
<tr>
<td>&gt;1500</td>
<td>31 479</td>
<td>97</td>
<td>242</td>
<td>193–290</td>
<td>31</td>
<td>68</td>
</tr>
<tr>
<td>Total (259–1960)</td>
<td>7 075 870</td>
<td>24 943</td>
<td>286</td>
<td></td>
<td>7681</td>
<td>80</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;300</td>
<td>435 982</td>
<td>892</td>
<td>104</td>
<td>97–111</td>
<td>391</td>
<td>43</td>
</tr>
<tr>
<td>300–600</td>
<td>6 027 854</td>
<td>10 881</td>
<td>105</td>
<td>103–107</td>
<td>6062</td>
<td>56</td>
</tr>
<tr>
<td>600–900</td>
<td>796 301</td>
<td>1688</td>
<td>108</td>
<td>103–114</td>
<td>899</td>
<td>58</td>
</tr>
<tr>
<td>900–1200</td>
<td>106 325</td>
<td>227</td>
<td>98</td>
<td>86–111</td>
<td>138</td>
<td>57</td>
</tr>
<tr>
<td>1200–1500</td>
<td>54 663</td>
<td>96</td>
<td>92</td>
<td>73–110</td>
<td>69</td>
<td>66</td>
</tr>
<tr>
<td>&gt;1500</td>
<td>27 997</td>
<td>41</td>
<td>74</td>
<td>52–97</td>
<td>24</td>
<td>50</td>
</tr>
<tr>
<td>Total (259–1960)</td>
<td>7 449 122</td>
<td>13 825</td>
<td>104</td>
<td></td>
<td>7583</td>
<td>55</td>
</tr>
</tbody>
</table>
As found by others, the protective effect of altitude was more pronounced in men than in women for both CHD and stroke. This finding deserves comment. As shown in the online-only Data Supplement, in Switzerland, men are physically more active than women. Because exercise under moderate hypoxic conditions may provide more health benefit than at sea level, it can be speculated that men benefit more strongly from the effect of altitude. This also could apply to the protective effect of sunlight. It is interesting that the hearts of natives of the Andes mountains were found to be larger than those of height- and weight-matched lowlanders. Such an adaptation also was found in rats, but not in height- and weight-matched lowlanders. This also could apply to the protective effect of living at higher altitudes. Although all down-movers were born at higher altitudes, we do not know at what age they moved. We therefore cannot disentangle the potential contribution of nutritional and environmental effects from other effects of altitude. However, because vitamin D, omega-3 fatty acids, and other nutrients can already have effects during intrauterine growth, they may have an effect even in those who moved shortly after birth. Besides, there may be more direct effects of altitude. Interestingly, the hearts of natives of the Andes mountains were found to be larger than those of height- and weight-matched lowlanders. Such an adaptation also was found in rats, but only when the exposure to altitude occurred during the intrauterine phase. Cardiac adaptation could explain why in most studies the effect of altitude was more pronounced and more sustainable for CHD than for stroke. Genetic factors may explain the low CVD mortality in Andean populations.

In contrast, given that a large proportion of highlanders have been born at lower altitudes (see Table 1), it appears unlikely that genetic adaptation plays a role in the Swiss highland population. As opposed to the general trend, living below 300 m was associated with lower stroke and (to a lesser extent) CHD mortality. In German Switzerland, in regions below 300 m, there is less fog and longer sunshine duration compared with regions between 300 and 1000 m. This
implies that the protective effect of altitude on CVD mortality may be due not only to the effects of altitude per se but also to climatic conditions that prevail at different levels of altitude.

This study has several limitations. We were not able to adjust for classic behavioral and clinical risk factors. Most risk factors, however, are strongly associated with education and other social variables that were included in our models. We thus would not expect results to be affected substantially by inclusion of other risk factors, especially because they probably did not differ by altitude. Our variable for urbanity was somewhat artificial. Even the largest cities in Switzerland are relatively small, and there are no clear boundaries between urban and rural settings. Another limitation is that we had only 1 number on altitude per commune. This could affect the relationship between altitude and mortality in (the few) communes that extend over substantially different altitudes. For methodological reasons (equal handling of surviving and dead), we did not consider change of residence between 1990 and 2000. Finally, the impact of most risk factors on mortality has a latency of ≥20 years. Thus, a comparison of mortality between 1990 and 2000 with risk factors from the Swiss Health Survey 2002 only roughly reflects real associations. However, comparisons with earlier surveys for which altitude is not available suggest that risk factor patterns remained relatively stable in the Swiss population. Although our analysis cannot define causal relationships with risk factors or prove causal pathways for the effect of altitude, it provides a basis for further research. Other strong points of this study are the large sample size, which includes individual data of the entire German Swiss population, and the ethnic homogeneity of highlanders and lowlanders. Unlike other studies, the study population is distributed over all altitudinal belts. In addition, the absence of large differences in geographic latitude in Switzerland and the restriction to German Switzerland avoid confounding/ effect modification as a result of associated differences in sunlight duration or climate or culturally determined behaviors. Another advantage is the availability of place of birth. Analysis of the place of birth supports the findings based on place of residence and therewith argues against the possibility that our numbers are a result of bias caused by regional peculiarities of assignment of cause of death or differences in healthcare use.

Conclusions
The lower CHD and stroke mortality at higher altitudes found in Switzerland is unlikely to be due to differences in classic risk factors but may be a result of differences in climate, diet, or both. Being born at higher altitude appears to exert an additional protective effect. This finding suggests a dose-response relationship between lifetime altitude exposure and mortality.

Appendix
Swiss National Cohort Study Group
The members of the Swiss National Cohort Study Group are Felix Gutzwiller (chairman of the Executive Board), Matthias Bopp (both Zurich), Matthias Egger (chairman of the Scientific Board), Adrian Spoerri, Malcolm Sturdy (data manager), Marcel Zwahlen (all Bern), Charlotte Braun-Fahrlander (Basel), Fred Paccoud (Lausanne), and André Rougemont (Geneva).

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Disclosures
None.

References


**CLINICAL PERSPECTIVE**

Previous studies have suggested that living at higher altitude provides an advantage with respect to cardiovascular disease. However, these studies had serious limitations and yielded conflicting results. We assessed on an individual level the association between altitude and mortality from stroke and coronary heart disease in the general population of German-speaking Switzerland living between 259 and 1960 m above sea level. We found that mortality decreased with increasing altitude and that the effect was stronger for coronary heart disease and in men. In addition, being born at higher altitude provided an independent and sustained beneficial effect on coronary heart disease mortality. Lower mortality at higher altitude did not appear to depend on variations in classic cardiovascular disease risk factors or in sociodemographic characteristics but rather could depend, for example, on age or body mass index. Our findings not only substantiate the concept of a protective effect of altitude on cardiovascular disease mortality but also suggest a dose-dependent and sustained effect.
Lower Mortality From Coronary Heart Disease and Stroke at Higher Altitudes in Switzerland

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for the Swiss National Cohort Study Group

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