

# BMJ Open Does living at moderate altitudes in Austria affect mortality rates of various causes? An ecological study

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## ABSTRACT

**Objectives** The effects of altitude residence on ageing, longevity and mortality are poorly understood. While adaptations to chronic exposure to altitude may exert beneficial effects on cardiovascular risk factors and some types of cancer, an elevated risk to die from chronic respiratory diseases has been reported. Moreover, high-altitude residence may be correlated with increased depression and suicide rates. The present study tested the hypothesis that living at moderate altitudes (up to 2000 m) is associated with reduced mortality from all causes.

**Setting and participants** We used a dataset comprising all deaths (n=467 834) across 10 years of a country (Austria) characterised by varying levels of altitudes up to 2000 m.

**Main outcome measures** Total number of deaths, age-standardised mortality rates (ASMRs) per 100 000 population, cause-specific ASMRs.

**Results** ASMRs for residents living in higher (>1000 m) versus lower (<251 m) altitude regions (with agriculture employment below 3%) were 485.8 versus 597.0 (rate ratio and 95% CI 0.81 (0.72 to 0.92); p<0.001) for men and 284.6 versus 365.5 (0.78; 0.66 to 0.91); p=0.002) for women. Higher levels of agriculture employment did not influence mortality rates. Diseases of the circulatory system and cancers were main contributors to lower mortality rates at higher altitude. Residence at higher altitude did not negatively affect mortality rates from any other diseases. We highlight gender effects and—beside environmental factors—also discuss socioeconomic factors that may be responsible for conflicting results with data from other populations.

**Conclusions** Living at moderate altitude (1000–2000 m) elicits beneficial effects on all-cause mortality for both sexes, primarily due to lower ASMRs from circulatory diseases and cancer. The presented analysis on cause-specific ASMRs over a 10-year period among the entire population of an alpine country will contribute to a better understanding on the effects of altitude-related mortality.

## INTRODUCTION

Lower mortality from coronary artery disease (CAD) and stroke (–22% and –12% per 1000 m above sea level (asl)) was reported from individuals living at moderate altitudes (up to about 2000 m)<sup>1</sup> and the risk of dying from neurodegenerative disease, that is, Alzheimer's disease, was about 50% lower at

## Strengths and limitations of this study

- Altitude-dependent mortality rates of various causes and for both sexes have been calculated over a 10-year period (2003–2012) from data of the Austrian Mortality Registries.
- According to our previous study, the data were allocated to five altitude of residence categories (<250 m, 251–500 m, 501–750 m, 751–1000 m and >1000 m up to about 2000 m, the highest community in Austria).
- In order to avoid confounding from migration to large cities, only deaths of people living in communities with a population below 20 000 were included in our analyses.
- Altitude-dependent suicide rates were separately calculated for three altitude categories (<500 m, 501–1000 m, >1000 m) including all deaths from the overall population.
- The most important limitations of the present study arise from the lack of information on sociocultural, socioeconomic and lifestyle factors of people living at different altitudes.

moderate altitude when compared with low-altitude dwellers.<sup>2</sup> We recently confirmed the altitude-related mortality risk reduction concerning CAD and stroke in Austria and demonstrated similar beneficial altitude effects on cancer mortality.<sup>3</sup> Age-standardised mortality rates (ASMRs) from male colorectal cancer and female breast cancer decreased almost linearly from low to moderate altitude by 45% and 38%, respectively.

The beneficial effects of specific environmental conditions, including moderate hypoxia stimuli, at altitudes up to about 2000 m on cardiovascular risk factors likely contributed to the lowering of cancer mortality. Whereas increasing agriculture employment was independently related to the diminished ASMR from ischaemic heart disease (by about 15% for men and women), only the increasing altitude was associated with the reduction in cancer mortality.<sup>3</sup>



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Health effects of altitude may be modulated by changes in and complex interactions between the specific terrain, socioeconomic and environmental (climatic) conditions. The increasing levels of hypoxia, cold and solar radiation with gain in altitude are closely interrelated and difficult to distinguish based on the results of epidemiological studies.

Barometric pressure and the related inspiratory ( $\text{piO}_2$ ) and alveolar ( $\text{pAO}_2$ ) oxygen partial pressures decrease from 760 mm Hg ( $\text{piO}_2$  and  $\text{pAO}_2$ : 159 mm Hg and 99 mm Hg) at sea level to about 569 mm Hg (119 mm Hg and 59 mm Hg) at the altitude of 2000 m<sup>4</sup> (figure 1). Although, based on the oxygen–haemoglobin dissociation curve, there is only a slight decline in the oxygen saturation of the arterial blood at those moderate altitudes, this decline may be more pronounced during conditions like intensive physical activity or sleep.<sup>5,6</sup> Thus, hypoxia-related activation of the hypoxia-inducible factor (HIF) pathway, promoting the expression of dozens of genes to support the maintenance of tissue oxygen supply,<sup>7</sup> may even occur at moderate altitude. Such adaptations to hypoxia are thought to mediate the larger part of beneficial altitude effects.

Ambient temperature decreases by about 6.5°C per 1000 m gain in altitude. Generally, people are well protected from unfavourable health effects of cold, for example, by heated homes and appropriate clothing, but some exposure during work, exercise and so on remains and may induce beneficial adaptations. Such adaptations to repeated cold exposures include, for example, blunted sympathetic stress responses (habituation) associated with improved stress tolerance and increased basal metabolic rates putatively counteracting obesity.<sup>8,9</sup> On the other hand, cold and dry air is known to negatively affect patients with respiratory diseases and to provoke exercise-induced asthma in certain athletes.<sup>10</sup>

Global irradiation increases (on days with clear sky) by about 8% per 1000 m gain in altitude.<sup>11</sup> Potential adverse effects on health through solar ultraviolet (UV) radiation, for example on the skin and the eyes, are long known.<sup>12</sup> More recent studies, however, indicate that solar UV radiation at altitude may also favourably impact on the human organism, for example, by attenuation of gastrointestinal cancer development<sup>13</sup> and improved cardiovascular health, likely mediated by UV action on vitamin D synthesis.<sup>14</sup> Moreover, vitamin D independent pathways could play an important role like the UV mediated mobilisation of nitric oxide stores from the skin into the systemic circulation.<sup>14</sup>

The influence of specific moderate altitude conditions has also been discussed for mental health factors. Contrary to the beneficial effects of altitude residence on all-cause mortality, the influence of altitude on depression and suicide rates remains unclear. Increased symptoms of depression and suicide rates have been reported in moderate altitudes (the threshold value for increased suicide rates lies approximately between 600 and 900 m)<sup>15–17</sup> and were attributed mainly to the hypobaric

hypoxia-induced alteration in serotonin metabolism and brain bioenergetics<sup>18</sup> and independently to other factors such as the socioeconomic status.<sup>18,19</sup> Other studies<sup>20</sup> did not observe any relationship between altitude of residence and suicides or question a prominent influence of underlying physiological and cellular mechanisms in this association<sup>21</sup> as compared with demographic (rural residence, population density), social (poverty, unemployment rate, education level) or personal (age, race, gender) characteristics.<sup>22</sup> Overall, while there is accumulating evidence linking altitude residence and suicides, most have been reported in the USA<sup>15–18</sup> and mostly in men. Similarly, it was suggested that even moderate altitude is associated with increased mortality in patients with chronic respiratory disease.<sup>23</sup> These authors suggested the lower oxygen partial pressure and increased solar radiation at altitudes to be potentially detrimental for respiratory diseases. Therefore, we hypothesised that living at moderate altitudes in Austria would also increase the risk to die from respiratory diseases and potentially outweigh the altitude related protective effects on all-cause mortality. Although several studies have previously reported effects of high-altitude residence on mortality from selected disease classes, the individual contributions of the major causes of mortality to potential benefits of altitude are poorly understood. Therefore, in this study we aimed to analyse altitude-dependent mortality rates from all causes, and contributing major disease classes including diseases of the circulatory, respiratory and digestive system as well as cancers and suicides.

## METHODS

Altitude-dependent mortality data from the Austrian Mortality Registries, Statistik Austria<sup>24</sup> were evaluated like in our previous study.<sup>3</sup> The observation period included mortality data from 2003 through 2012. In order to avoid confounding from (rather short-term) migration (due to job opportunities, school/university attendance, etc, which are more available in communities with a population above 20 000) we decided to include only deaths in people living in communities with a population below 20 000 (except for suicides, which have been analysed separately). Five altitude categories, that is, <251 m, 251–500 m, 501–750 m, 751–1000, >1000 m (up

| Altitude (m)          | 200 | 1000 | 2000 |
|-----------------------|-----|------|------|
| PB (mmHg)             | 738 | 659  | 569  |
| $\text{piO}_2$ (mmHg) | 154 | 138  | 119  |
| $\text{pAO}_2$ (mmHg) | 94  | 78   | 59   |
| Temperature (°C)      | 15  | 9.8  | 3.3  |
| SR (% increase)       | -   | 6.4  | 14.4 |

**Figure 1** Altitude-dependent environmental conditions. The influence of altitude on selected environmental conditions for three exemplary altitudes are shown. While increasing altitudes are associated with reduced barometric pressure (PB), inspiratory ( $\text{piO}_2$ ) and alveolar ( $\text{pAO}_2$ ) oxygen partial pressures and temperature, solar radiation (SR) is elevated in higher altitudes.

to the highest community of about 2000 m) have been considered. The main reason for the use of this specific categorisation is our intent to ensure comparability to our previous study, for which the same categorisation was applied.<sup>3</sup> Moreover, the use of these five categories permits the evaluation of a potential linear relationship between mortality rates and altitude. The influence of agriculture environments was evaluated by consideration of varying percentages of agriculture employment (<3%, 3%–7% and >7%). Beside all-cause mortality, mortality from all cancers (ICD-10: C00–C97), from diseases of the circulatory system (ICD-10: I00–I99), diseases of the respiratory system (ICD-10: J00–J99), diseases of the digestive system (K00–K93) and from external causes, including for example injuries, poisoning and suicides (V01–Y89), were analysed for Austrian men and women that died between 2003 and 2012 in Austria. Separate altitude-dependent (<500 m, 500–1000 m and >1000 m) analyses were performed for suicides (ICD-10: X60–X84), also including communities with a population >20 000. ASMRs per 100 000 population and 95% CIs, based on the assumption that the data follow a Poisson distribution, are reported (provided by Statistik Austria).<sup>24</sup>

Suicide rates were compared by  $\chi^2$  tests. For the calculation of differences between mortality rates (p values) and rate ratios (95% CI) the calculator from SciStat.com was used (last accessed on 3 August 2020) which is based on the guidelines of Sahai and Khurshid.<sup>25</sup>

### Patients and public involvement

Since this study was based on publically available and anonymised data from the Austrian Mortality Registries (Statistik Austria), it was not possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

### RESULTS

ASMRs per 100 000 population and 95% CIs were calculated from reported cases of death according to the cause of death, as depicted in table 1.

A marked reduction of mortality from all causes was observed with increasing altitude of residence (figure 2A,B) for both men and women. Major causes of mortality contributing to this effect were cancers (figure 2C,D) and diseases of the circulatory system

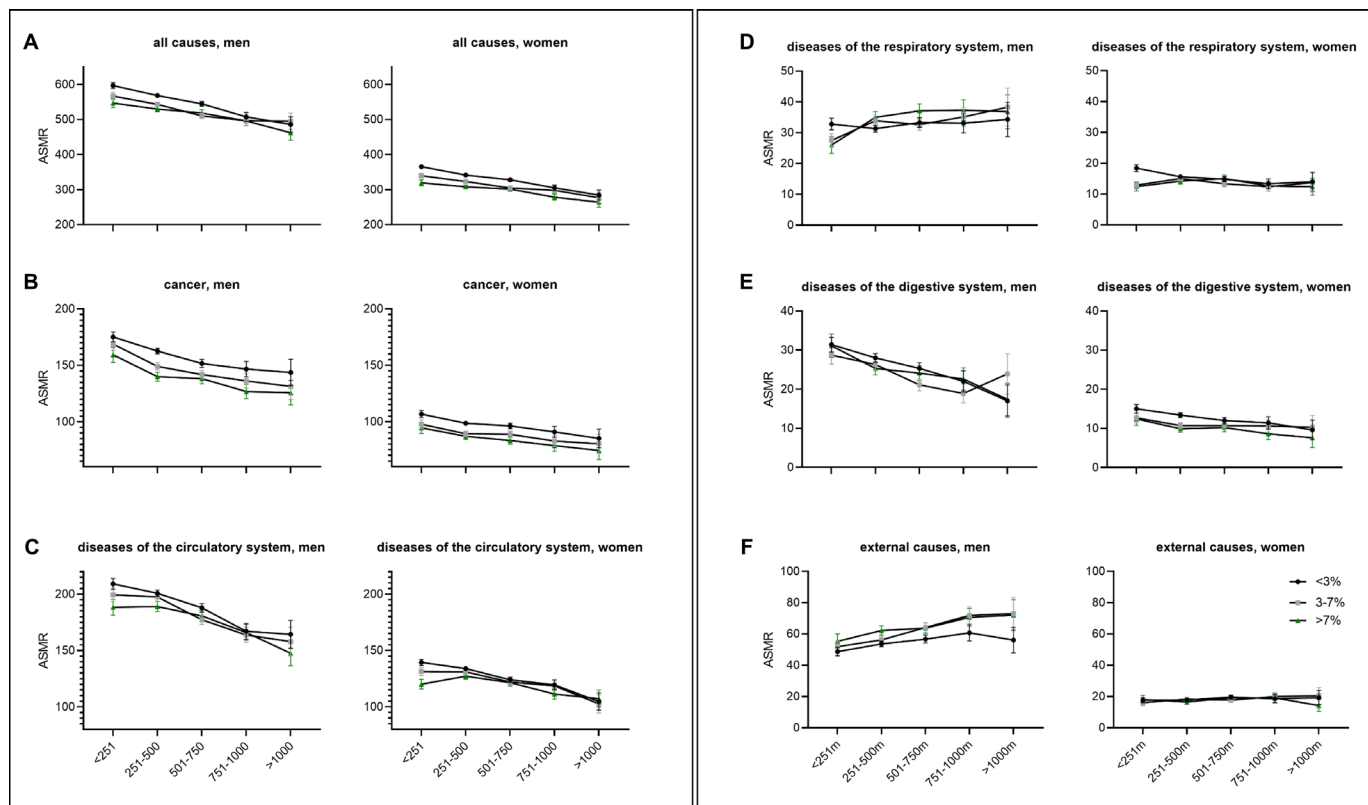
(figure 2E,F). While diseases of the respiratory system (figure 2G,H) were not beneficially affected by increasing altitudes, diseases of the digestive system (figure 2I,J) appeared to be, in particular for men (figure 2I). External causes of mortality (including injuries and poisoning, figure 2K,L) were not reduced in higher altitude populations. Total mortality from residual diseases amounted around 15%, includes a wide array of heterogeneous other disease classes (ICD-10 A00–B99, D01–H95, L00–R99) and were not further analysed. Different rates of agricultural employment are considered in the figures but turned out to not significantly affect mortality for all analysed causes in both men (table 2A) and women (table 2B). Differences between mortality rates of communities with <3% and >7% of agricultural employment were analysed in table 2.

Calculation of differences between mortality rates at low (<250 m) versus moderate (>1000 m) altitudes confirmed the beneficial effects of increasing altitude of residence on mortality of all causes for men (table 3A) and women (table 3B). These effects were mainly carried by benefits for diseases of the circulatory system, while mortality from all cancers was just significant or trending towards reduced mortality in higher altitudes.

In contrast, diseases of the respiratory system were slightly (not statistically significant) elevated with increasing altitude of residence for men (figure 2A and table 3A) and were unaffected by altitude of residence for women (figure 2B and table 3B). Although diseases of the digestive system account for only around 4% of mortality cases in the observed populations, mortality from such diseases was significantly reduced at higher altitudes for men (figure 2I and table 3A) but not for women (figure 2J and table 3B). Externally caused mortality overall was not significantly modulated by altitude (table 3A and B). Based on the debated role of altitude of residence on suicide rates, numbers of suicides were extracted from external causes and are depicted normalised to the Austrian population in figure 3. Men living at altitude <500 m had a lower suicide rate than their counterparts living at 501–1000 m ( $p < 0.05$ ), independently of their age. This was also observed in women aged 35–64 ( $p < 0.05$ ). Interestingly, such a difference was observed neither in men nor in women between higher altitudes (501–1000 vs >1000 m) ( $p$  values >0.05).

**Table 1** Causes of death for men and women (numbers of deaths during the observation period are indicated)

| Cause of death                     | ICD-10  | Men     | Women   | Total   |
|------------------------------------|---------|---------|---------|---------|
| All causes                         |         | 224 866 | 242 968 | 467 834 |
| All cancers                        | C00–C97 | 64 370  | 54 191  | 118 561 |
| Diseases of the circulatory system | I00–I99 | 83 619  | 117 483 | 201 102 |
| Diseases of the respiratory system | J00–J99 | 14 634  | 12 498  | 27 132  |
| Diseases of the digestive system   | K00–K93 | 10 422  | 8 169   | 18 591  |
| External causes of mortality       | V01–Y89 | 19 070  | 9 147   | 28 217  |



**Figure 2** Effects of altitude residence on mortality from various causes. Age-standardised mortality rates (ASMRs, 95% CI) adjusted for altitude of residence (x-axis, in metres) for mortality from all causes (A), all cancers (B), diseases of the circulatory system (C), diseases of the respiratory system (D), diseases of the digestive system (E) and of external causes (F) for men and women. Different levels of agriculture employment are indicated in (F) (<3%, 3%–7% and >7%).

Overall, mortality rates were significantly higher in men compared with women in regions with high and low agriculture employment (rate ratios; 95% CI 1.72; 1.49 to 1.99 and 1.66; 1.45 to 1.90) and at high and low altitude (1.75; 1.50 to 2.04 and 1.67; 1.46 to 1.91). These relationships between sexes are similar for all types of mortality (figure 2).

In summary, mortality from all causes was smaller in moderate altitudes as compared with low altitudes. This was mainly due to the pronounced beneficial effect of higher altitudes of residence on diseases of the circulatory system and on cancers. Also, diseases of the digestive system were reduced in higher altitudes, whereas diseases of the respiratory system and externally caused mortality are not statistically affected but may even increase slightly in occurrence with higher altitudes for men.

## DISCUSSION

Although mortality rates were clearly lower for women than for men, mortality from all causes declined with increasing altitude similarly in both sexes of the studied population. Mortality rates were significantly lower (about 15%–20%, table 3A) in those living at moderate altitudes, that is >1000m up to about 2000m, when compared with those living below 250m. Mortality from all circulatory diseases, all cancers, and all diseases of the

digestive system (more pronounced in men) were major contributors to the altitude-related mortality reduction. In contrast, living at higher altitudes was not associated with lower mortality from respiratory diseases or external causes, like accidents or poisoning. The level of agriculture employment did not significantly impact on mortality rates.

Although modulatory effects of high and moderate altitude on longevity have been discussed, for example, for populations in Bolivia<sup>26</sup> and Tibet,<sup>27</sup> the USA<sup>28</sup> and various regions of the Alps,<sup>1,3</sup> how high-altitude residence affects longevity and mortality remains poorly understood. Findings do not provide a clear picture but it can be ventured to say that moderate altitudes (up to 2000–2500 m) are more protective than high or even very high altitudes.<sup>29</sup>

The lower mortality from circulatory diseases and certain cancers with increasing elevation (within the moderate altitude range) have previously been reported from Switzerland, Austria and the USA.<sup>1,3,28</sup> Beside the slightly lower oxygenation at moderate altitudes, climate changes with increasing height like reduced ambient temperature, elevated UV-radiation and/or reduced air-pollution but also different physical activity and dietary behaviour may all act as potentially protective factors.<sup>1,28</sup> In line with effects on mortality, also lower incidences of



**Table 2A** Comparison of age-standardised mortality rates (ASMRs, per 100 000 population) between regions with low (<3%) and high (>7%) agriculture employment for men

| Mortality cause      | ASMRs                  |       | Rate ratio (95% CI) | P value |
|----------------------|------------------------|-------|---------------------|---------|
|                      | Agriculture employment |       |                     |         |
|                      | <3%                    | >7%   |                     |         |
| All-causes           | 561.8                  | 521.6 | 0.93 (0.82 to 1.05) | 0.22    |
| All cancers          | 160.8                  | 140.0 | 0.87 (0.69 to 1.10) | 0.23    |
| D.circulatory system | 196.1                  | 181.7 | 0.93 (0.75 to 1.14) | 0.47    |
| D.respiratory system | 32.2                   | 34.7  | 1.09 (0.66 to 1.82) | 0.71    |
| D.digestive system   | 27.3                   | 25.1  | 0.93 (0.52 to 1.66) | 0.78    |
| External             | 54.1                   | 63.1  | 1.17 (0.80 to 1.71) | 0.41    |

**Table 2B** Comparison of age-standardised mortality rates (ASMRs, per 100 000 population) between regions with low (<3%) and high (>7%) agriculture employment for women

| Mortality cause      | ASMRs                  |       | Rate ratio (95% CI) | P value |
|----------------------|------------------------|-------|---------------------|---------|
|                      | Agriculture employment |       |                     |         |
|                      | <3%                    | >7%   |                     |         |
| All-causes           | 339.0                  | 302.4 | 0.89 (0.76 to 1.04) | 0.14    |
| All cancers          | 98.7                   | 85.5  | 0.87 (0.64 to 1.17) | 0.34    |
| D.circulatory system | 130.9                  | 121.7 | 0.93 (0.72 to 1.20) | 0.57    |
| D.respiratory system | 15.7                   | 13.9  | 0.88 (0.40 to 1.91) | 0.72    |
| D.digestive system   | 13.1                   | 10.1  | 0.77 (0.30 to 1.90) | 0.53    |
| External             | 18.3                   | 17.7  | 0.97 (0.78 to 1.20) | 0.75    |

cardiovascular diseases have been demonstrated in residents of higher altitudes.<sup>30 31</sup>

Residence at higher elevations has furthermore been reported to be associated with positive effects on some types of cancer,<sup>32</sup> while other types may even be negatively affected by high-altitude conditions.<sup>29</sup> We previously demonstrated beneficial effects of living at moderate elevations on male colorectal and female breast cancer mortality.<sup>3</sup> Thiersch and Swenson recently presented in their review a lower cancer mortality over a broad spectrum of cancer types at higher altitudes.<sup>33</sup> These authors suggested that the majority of the physiological adaptive processes occurring at altitude (reactive oxygen species and their detoxification, and the HIFs) might help to explain mechanisms responsible for the mortality reduction. Another study however, found a positive association between mortality rates and the risk of death from most types of cancer and high altitude in the Ecuadorian population living at an altitude greater than 2000 m asl.<sup>34</sup> There are several potential explanations for the contrasting findings including varying responses between different ethnicities, differences in physical activity and dietary behaviour, and/or increasing negative effects at altitudes over 2500 m. Less data are available on changes of mortality in higher regions on non-cancer diseases of the digestive system but metabolic alterations observed at greater heights, potentially also influenced by physical

activity and dietary patterns, as discussed by Thiersch and Swenson,<sup>33</sup> may play important pathophysiological roles. Unfortunately, we do not have data on these variables for different altitude regions but the lacking significance of agriculture employment (as a surrogate for physical activity and dietary habits) on mortality may indicate a greater importance of climatic factors.

In contrast to the mortality causes presented earlier, moderate altitudes did not beneficially impact on mortality from external causes (including accidents, poisoning and suicides) and respiratory diseases.

Whereas it seems logically that the mountainous terrain and the harsher environmental conditions (cold, wind, snow, ice, etc) at higher altitudes may be rather related with accidents than low-altitude conditions, the impact of high altitude on mortality from respiratory diseases is less clear. Increased mortality, for example, due to chronic obstructive pulmonary disease in higher altitudes has been previously reported.<sup>35</sup> Recently, Hwang and colleagues found greater mortality rates from respiratory diseases, primarily chronic lower respiratory disease, even at a moderate altitude, also without difference between sexes.<sup>23</sup> Our data do not show significantly increased mortality rates from respiratory diseases with gain in altitude but also no beneficial effect of altitude. This may be at least partly explained by the somewhat lower altitudes in our study compared with that of Hwang and

**Table 3A** Comparison of age-standardised mortality rates (ASMRs, per 100 000 population) between regions at lower (<251 m) and higher (>1000 m) altitudes for regions with different agriculture employment (<3%, 3%–7%, >7%) for men

| Mortality cause      | ASMRs                                |         | Rate ratio (95% CI) | P value |
|----------------------|--------------------------------------|---------|---------------------|---------|
|                      | Altitude                             |         |                     |         |
|                      | <251 m                               | >1000 m |                     |         |
|                      | <b>Agriculture employment &lt;3%</b> |         |                     |         |
| All-causes           | 597.0                                | 485.8   | 0.81 (0.72 to 0.92) | <0.001  |
| All cancers          | 175.2                                | 143.7   | 0.82 (0.66 to 1.03) | 0.08    |
| D.circulatory system | 209.2                                | 164.4   | 0.78 (0.64 to 0.97) | 0.02    |
| D.respiratory system | 32.8                                 | 34.3    | 1.03 (0.62 to 1.72) | 0.90    |
| D.digestive system   | 31.4                                 | 17.0    | 0.55 (0.28 to 0.99) | 0.04    |
| External             | 48.7                                 | 56.1    | 1.14 (0.76 to 1.71) | 0.49    |
|                      | <b>Agriculture employment 3%–7%</b>  |         |                     |         |
| All-causes           | 566.9                                | 494.8   | 0.87 (0.77 to 0.99) | 0.03    |
| All cancers          | 168.9                                | 131.3   | 0.78 (0.61 to 0.98) | 0.03    |
| D.circulatory system | 199.5                                | 158.0   | 0.79 (0.64 to 0.98) | 0.03    |
| D.respiratory system | 27.5                                 | 38.3    | 1.36 (0.81 to 2.30) | 0.22    |
| D.digestive system   | 28.7                                 | 23.9    | 0.83 (0.46 to 1.47) | 0.49    |
| External             | 51.9                                 | 73      | 1.40 (0.97 to 2.04) | 0.06    |
|                      | <b>Agriculture employment &gt;7%</b> |         |                     |         |
| All-causes           | 547.0                                | 462.4   | 0.84 (0.74 to 0.96) | 0.008   |
| All cancers          | 159.3                                | 125.7   | 0.79 (0.62 to 1.01) | 0.05    |
| D.circulatory system | 188.4                                | 147.6   | 0.79 (0.63 to 0.98) | 0.03    |
| D.respiratory system | 26.0                                 | 36.8    | 1.42 (0.84 to 2.44) | 0.17    |
| D.digestive system   | 31.1                                 | 17.4    | 0.55 (0.28 to 1.02) | 0.04    |
| External             | 55.3                                 | 72.0    | 1.31 (0.91 to 1.89) | 0.13    |

**Table 3B** Comparison of age-standardised mortality rates (ASMRs, per 100 000 population) between regions at lower (<251 m) and higher (>1000 m) altitudes for regions with different agriculture employment (<3%, 3%–7%, >7%) for women

| Mortality cause      | ASMRs                                |         | Rate ratio (95% CI) | P value |
|----------------------|--------------------------------------|---------|---------------------|---------|
|                      | Altitude                             |         |                     |         |
|                      | <251 m                               | >1000 m |                     |         |
|                      | <b>Agriculture employment &lt;3%</b> |         |                     |         |
| All-causes           | 365.5                                | 284.6   | 0.78 (0.66 to 0.91) | 0.002   |
| All cancers          | 106.7                                | 85.1    | 0.79 (0.59 to 1.07) | 0.11    |
| D.circulatory system | 139.4                                | 104.7   | 0.76 (0.58 to 0.98) | 0.03    |
| D.respiratory system | 18.4                                 | 14.0    | 0.78 (0.36 to 1.66) | 0.48    |
| D.digestive system   | 15.0                                 | 9.6     | 0.67 (0.27 to 1.59) | 0.32    |
| External             | 17.7                                 | 19.3    | 1.06 (0.52 to 2.13) | 0.87    |
|                      | <b>Agriculture employment 3%–7%</b>  |         |                     |         |
| All-causes           | 339.6                                | 277.2   | 0.81 (0.69 to 0.96) | 0.01    |
| All cancers          | 97.8                                 | 80.4    | 0.82 (0.60 to 1.11) | 0.18    |
| D.circulatory system | 131.3                                | 102.6   | 0.81 (0.62 to 1.06) | 0.11    |
| D.respiratory system | 12.9                                 | 13.7    | 1.08 (0.47 to 2.49) | 0.85    |
| D.digestive system   | 12.7                                 | 10.3    | 0.83 (0.32 to 2.10) | 0.67    |
| External             | 16.1                                 | 20.5    | 1.31 (0.65 to 2.69) | 0.41    |
|                      | <b>Agriculture employment &gt;7%</b> |         |                     |         |
| All-causes           | 319.5                                | 264.3   | 0.83 (0.70 to 0.97) | 0.02    |

Continued

Table 3B Continued

|                      | ASMRs    |         | Rate ratio (95% CI) | P value |
|----------------------|----------|---------|---------------------|---------|
|                      | Altitude |         |                     |         |
|                      | <251 m   | >1000 m |                     |         |
| All cancers          | 94.5     | 74.4    | 0.78 (0.57 to 1.07) | 0.11    |
| D.circulatory system | 120.1    | 107.3   | 0.89 (0.68 to 1.17) | 0.39    |
| D.respiratory system | 12.4     | 12.4    | 1.00 (-)            | 1.0     |
| D.digestive system   | 12.4     | 7.6     | 0.67 (0.24 to 1.77) | 0.37    |
| External             | 18.1     | 14.3    | 0.78 (0.36 to 1.66) | 0.48    |

colleagues.<sup>23</sup> Mechanisms contributing to the lacking beneficial or even aggravating effects of moderate altitude may include the lower ambient oxygen partial pressure, leading to a reduced alveolar–arterial gradient, the increased solar radiation, and/or the low ambient temperature and humidity in higher regions.<sup>23</sup> Moreover, altitude-induced compensatory hyperventilation resulting in increased fatigue of inspiratory muscles may not be tolerated by pulmonary patients. Whereas most of these factors have been proposed to provoke physiological adaptations associated with beneficial effects on circulatory diseases and cancer,<sup>1 3 29 33</sup> such adaptations may not occur in the respiratory system or those conditions may even be detrimental. Of course, it cannot be excluded that differences in medical care between the various regions contribute to the observed differences in mortality from respiratory diseases.

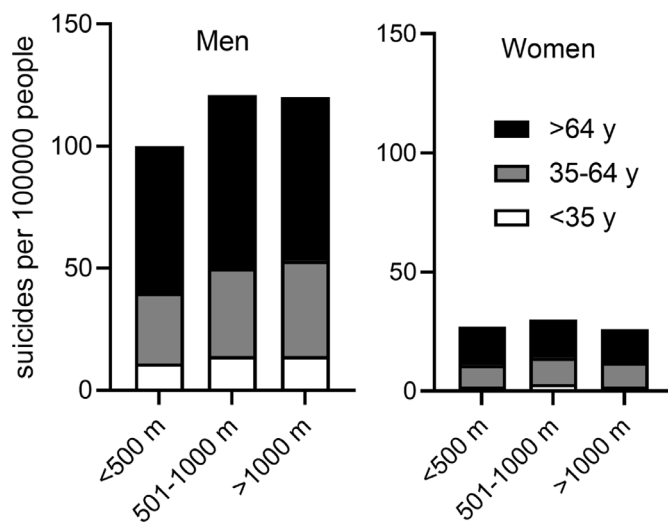
In the present study higher suicide rates in men of all ages and in women aged 35–64 between altitudes <500 m and 501–1000 m were observed. Since there was no difference in both men and women between altitudes 501–1000 and >1000 m where the hypoxic stimulus is more severe, one may speculate that the debated ‘biological’ influence of altitude is likely negligible and consequently that most

of the differences are mainly due to demographic or social factors, as previously suggested.<sup>22</sup>

Given the predominantly beneficial effects on mortality of moderate altitude residents as described in this and previous studies, it is of obvious interest to explore the potentials of the environmental climatic conditions at moderate altitude, in particular that of slight hypoxia stimuli, on human ageing, longevity and mortality in future studies. Clearly, transient exposure especially to higher altitudes and hypoxia is associated with several risks, in particular for patients and older people that have to be considered.<sup>36</sup> These are specifically hypoxaemia, increased sympathetic vasoconstrictor activation, increased oxidative stress, pulmonary hypertension, obstructive sleep apnoeas, arrhythmias, alterations of postural control and others. Such risks may be associated with oxidative and DNA damage and classical high-altitude illnesses, such as acute mountain sickness, as well as high altitude pulmonary and cerebral oedema.<sup>37</sup> These dangers are, however, of much lower relevance in moderate altitudes as the ones studied here (around 1000–2000 m). Furthermore, the beneficial effects of altitude residence on mortality reported in the present study together with several reports of intervention studies related to ageing hold promise for considerable benefits of hypoxia/high altitude exposure.<sup>36</sup> For example, hypoxia interventions have been reported to be useful for high altitude acclimatisation,<sup>38</sup> to increase weight loss in overweight-to-obese persons,<sup>39</sup> to increase aerobic capacity and exercise tolerance<sup>40</sup> and to improve a range of diseases,<sup>41–44</sup> often through cardioprotective effects.<sup>45–46</sup>

The most important limitations arise from the lack of information on sociocultural, socioeconomic and lifestyle factors of people living at different altitudes. In addition, influential effects and interactions of various climate conditions cannot be disentangled in the present study design. However, results, based on a large number of deaths from various causes show distinct differences of mortality between altitude categories, indicating that the collectivity of altitude-specific conditions reduces overall mortality.

In summary, we report that the pronounced impact of moderate altitude residence on mortality from all causes is mediated in particular by reduction of circulatory and digestive diseases, as well of cancers but not by



**Figure 3** Effects of altitude residence on suicide rates. The number of suicides per 100 000 people of the age, gender and altitude of residence adjusted Austrian population is shown.



respiratory diseases and suicides. This indicates that living at moderate altitudes may be even more beneficial than living at high altitudes, where deaths from respiratory diseases and suicide-rates seem to be increased. How and to which extent these beneficial conditions can be safely exploited for interventional strategies (moderate altitude sojourns or exposure to artificial hypoxia) to improve healthy ageing and reduce mortality and morbidity will be an important topic to be addressed in future studies.

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