Mortality on Mount Everest, 1921-2006: descriptive study

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ABSTRACT
Objective To examine patterns of mortality among climbers on Mount Everest over an 86 year period.
Design Descriptive study.
Setting Climbing expeditions to Mount Everest, 1921-2006.
Participants 14 138 mountaineers; 8030 climbers and 6108 sherpas.
Main outcome measure Circumstances of deaths.
Results The mortality rate among mountaineers above base camp was 1.3%. Deaths could be classified as involving trauma (objective hazards or falls, n=113), as non-traumatic (high altitude illness, hypothermia, or sudden death, n=52), or as a disappearance (body never found, n=27). During the spring climbing seasons from 1982 to 2006, 82.3% of deaths of climbers occurred during an attempt at reaching the summit. The death rate during all descents via standard routes was higher for climbers than for sherpas (2.7% (43/1585) v 0.4% (5/1231), P<0.001; all mountaineers 1.9%). Of 94 mountaineers who died after climbing above 8000 m, 53 (56%) died during descent from the summit, 16 (17%) after turning back, 9 (10%) during the ascent, 4 (5%) before leaving the final camp, and for 12 (13%) the stage of the summit bid was unknown. The median time to reach the summit via standard routes was higher for survivors than for non-survivors (0900-0959 v 1300-1359, P<0.001). Profound fatigue (n=34), cognitive changes (n=21), and ataxia (n=12) were the commonest symptoms reported in non-survivors, whereas respiratory distress (n=5), headache (n=0), and nausea or vomiting (n=3) were rarely described.
Conclusions Debilitating symptoms consistent with high altitude cerebral oedema commonly present during descent from the summit of Mount Everest. Profound fatigue and late times in reaching the summit are early features associated with subsequent death.

INTRODUCTION
At 8850 m above sea level, the summit of Mount Everest is the highest point on earth. Since the 1920s, thousands of mountaineers have tried to scale Everest, and many have died during the attempt. Despite this, Everest and other major peaks in the Himalayan mountain range continue to attract increasing numbers of climbers, with a significant associated mortality during expeditions. We examined the circumstances of deaths on Mount Everest to establish patterns of mortality among mountaineers on a large Himalayan peak.

METHODS
We carried out a retrospective study of all deaths during climbing expeditions on Everest during 1921-2006. The population studied included all members (listed on expedition permits) and employees of these expeditions. We identified deaths through published accounts of expeditions and by searching the Himalayan Database, a computerised registry of climbing expeditions to registered peaks in the Nepalese Himalayas. We located accounts of deaths from these sources, by searching the internet or by direct contact with mountaineers. We classified the source of the reports as direct contact (interview or correspondence with the authors), miscellaneous, or based on accounts in journals, books, the Himalayan Database, and the internet. We classified the reports by authorship: eyewitness, expedition members or employees who were not eyewitnesses, or secondary (authors not part of the expedition).

For statistical purposes we counted repeat visits and successes on reaching the summit as independent events. We defined the altitude of death as that at which a fatality occurred or was estimated to have occurred, from where a fall occurred, or from where a non-survivor was initially evacuated. A fatal incident was defined as an event involving one or more people on the same expedition, or climbing together, during a single trip between camps. In incidents where mountaineers died at different altitudes, we estimated the altitude of death as that at which a fatality occurred or was estimated to have occurred. We defined a single trip between camps as the final encampment on any route before technical (roped) climbing began.

Four doctors who were experienced in managing high altitude illness independently examined the accounts of deaths. Three of these reviewers had
reached the summit of Everest themselves; one had turned back at 8300 m. Two had climbed from Tibet, and the other two had climbed from Nepal. We pooled the analyses. Disagreements on classification of deaths were resolved by consensus. Deaths involving trauma were classified by the type of trauma. We categorised high altitude cerebral or pulmonary oedema as high altitude illness, using accepted diagnostic criteria or by virtue of a reliable report. We also classified deaths as high altitude illness if a specific diagnosis of cerebral or pulmonary oedema could not be established, symptoms of acute mountain sickness were present, and no other primary cause of the symptoms was evident. Death due to exposure was classified as hypothermia. Sudden death was defined as abrupt death without previous progressive symptoms. We listed death as unclassified when a single primary cause could not be established. Deaths were classified as disappearances if the death or the immediate cause of death was not witnessed and the body was not found.

We examined the accounts of deaths in mountaineers who reached 8000 m to determine the stage of the climb, the climbing speed of the mountaineer compared with team mates, and the mention of visual disturbances and diagnostic symptoms of high altitude illness. From the Himalayan Database we obtained the times mountaineers reached the summit.

Statistical analysis

We used the Fleiss’ kappa method to analyse the inter-rater agreement for classification of death. For univariable analyses of binary and categorical outcomes we used a χ² test or Fisher’s exact test. We used the two sided t tests or a Wilcoxon rank sum test to compare continuous outcomes, including summit time and the number of deaths due to objective hazards per incident, whenever appropriate. We used SAS software version 9 as the main tool for statistical analysis.

**RESULTS**

Table 1 outlines the characteristics of the study population. Overall, 341 accounts were analysed, including 136 notes from the Himalayan Database, 106 journal reports, 31 books, 32 direct accounts by 22 climbers, 14 web based accounts, and 7 miscellaneous sources. In total, 154 fatal incidents resulting in 212 deaths were identified. Of these deaths, 72 were reported by at least an eyewitness author, 55 by at least an expedition member author, and the remaining 85 were solely by secondary authorship. Survivors witnessed 127 deaths or the immediate circumstances of death (objective hazard, sudden death, in extremis, immediate evidence of a fall), 58 immediate circumstances had not been witnessed but the body was found, and 27 people had disappeared without their final moments being reported.

For the classification of all 212 deaths, there was unanimous independent agreement for 165 (78%) of the classifications. The Fleiss κ value for inter-rater agreement was 0.63, P<0.001 (substantial agreement). Of deaths classified at all altitudes, fatal cerebral oedema occurred at a higher altitude than fatal pulmonary oedema (7 v 5; 8276 [SD 791] m v 6229 [SD 104] m, P<0.001). Table 2 provides the classification of deaths above base camp; see www.himalayandatabase.com for further data.

Above base camp, 103 incidents involving climbers occurred at a higher mean altitude than 44 involving sherpas (7854 [SD 918] m v 6927 [SD 116] m, P<0.001). Thirty seven incidents involved objective hazards, with

**Weather analysis**

To assess the role of adverse weather in fatal incidents, we examined the accounts of deaths during May from 1975 to 2006, as this period included most deaths. Each reviewer independently scored the probability that adverse weather contributed to a fatal outcome as very probable (score 1), probable (2), possible (3), or unlikely or unknown (4). By adding these weather scores together, we identified days when deterioration in weather probably did (score ≤3) or did not (>3) play a part in deaths above 7000 m. We also identified days on the summit without deaths from the Himalayan Database. The representative meteorological conditions of days with these three outcomes were then computed using a compositing technique for the barometric pressure at 9000 m above sea level, based on fields from the reanalysis project of the National Center for Environmental Prediction, a dataset that includes all available meteorological observations and that is applicable to analysis of weather conditions on Everest.
more sherpas killed per incident than climbers (1.18 v 0.54, P=0.02). The mean altitude of events involving objective hazards was 6381 (SD 661) m.

The death rate during all descents from the summit via the standard routes was higher for climbers than for sherpas (2.7% (43/1585) v 0.4% (5/1231), P<0.001; all mountaineers 1.9%). Figure 1 presents the mortality and distribution of deaths on the standard routes during the spring climbing seasons of 1982 to 2006. Of 77 deaths, 55 occurred during bids for the summit (51 climbers, four sherpas, 71%) and 22 during preparation of the route (11 climbers, 11 sherpas, 29%). Six incidents involving objective hazards resulted in eight deaths on the standard south route; no deaths occurred on the north route in this category.

Table 3 presents data on the mountaineers who died after reaching 8000 m. Fifty three (56%) died during the descent, 16 (17%) after turning back below the summit, and nine (10%) during the ascent. The stage of the summit bid was unknown for 12 mountaineers (13%), and four (5%) died before leaving the final camp. Of a subset of 23 mountaineers who climbed without supplemental oxygen, 11 (48%) died during the descent, 4 (17%) after turning back, and 4 (17%) during the ascent, and in 4 (17%) the stage was unknown. Median time to reach the summit via standard routes was earlier for survivors than for non-survivors (0900-0950 (interquartile range 0800-0859 to 1100-1159) v 1300-1359 (1100-1159 to 1600-1659), P<0.001). Thirty seven mountaineers died or were in extremis in the presence of witnesses, 34 fell behind team members before becoming debilitated or dying, the circumstances of 11 were unknown as they died with all team members and therefore without report, 11 climbed alone, and one could not be classified as the account was insufficient.

Of these 94 mountaineers who died, 33 had symptoms attributable to high altitude illness and six had symptoms of either high altitude illness or hypothermia, or both. The symptoms and numbers of mountaineers, respectively, were profound fatigue or exhaustion (n=34), confusion or coma (21), ataxia (12), respiratory disturbances (5), nausea or vomiting (3), and headache (0). Of 32 falls, 12 were not closely witnessed, eight involved climbers described as confused or exhausted, seven occurred in treacherous conditions, and in five cases the accounts were unclear.

Table 1 | Population characteristics of mountaineers on Everest, 1921-2006. Values are numbers (percentages) unless stated otherwise

<table>
<thead>
<tr>
<th>Variables</th>
<th>Climbers (n=8030)</th>
<th>Sherpas (n=6108)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>7404 (92.2)</td>
<td>6106 (99.9)</td>
<td>13510</td>
</tr>
<tr>
<td>Female</td>
<td>626 (7.8)</td>
<td>2 (0.1)</td>
<td>628</td>
</tr>
<tr>
<td>Mean (SD) age (years) (range)</td>
<td>36.5 (8.9) (12-74)</td>
<td>^</td>
<td>^</td>
</tr>
<tr>
<td>Overall total</td>
<td>8030</td>
<td>6108</td>
<td>14138</td>
</tr>
</tbody>
</table>

Summit ascents:

<table>
<thead>
<tr>
<th>Year</th>
<th>Climbers</th>
<th>Sherpas</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1953-81 (all)</td>
<td>94 (5.3)</td>
<td>23 (1.8)</td>
<td>117 (3.8)</td>
</tr>
<tr>
<td>1982-2006:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-spring</td>
<td>663 (37.5)</td>
<td>661 (51.2)</td>
<td>1324 (43.3)</td>
</tr>
<tr>
<td>N-spring</td>
<td>732 (41.4)</td>
<td>484 (37.5)</td>
<td>1216 (39.8)</td>
</tr>
<tr>
<td>Other†</td>
<td>279 (15.8)</td>
<td>122 (9.4)</td>
<td>401 (13.1)</td>
</tr>
<tr>
<td>Total</td>
<td>1768</td>
<td>1290</td>
<td>3058</td>
</tr>
</tbody>
</table>

S-spring=standard Nepalese route via South Col or Southeast Ridge, or minor variants, during April to June; N-spring=standard Tibetan route via North Col or Northeast Ridge, or minor variants, during April to June.

Population includes estimates of expedition size and roles of mountaineers (climbers or sherpas) for Chinese expeditions, 1960-79, on north side of Everest. Percentages may not add up to 100% owing to rounding.

*Data were unreliable.
†All other routes such as West Ridge or North Face approaches, or attempts on all routes during seasons other than spring.
Table 2 | Classification of deaths of mountaineers climbing above base camp*, 1921-2006.
Values are numbers of people killed unless stated otherwise

<table>
<thead>
<tr>
<th>Classification</th>
<th>Climbers</th>
<th>Sherpas</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma:</td>
<td>54</td>
<td>59</td>
<td>113</td>
</tr>
<tr>
<td>Objective hazards</td>
<td>20</td>
<td>47</td>
<td>67</td>
</tr>
<tr>
<td>Falls</td>
<td>34</td>
<td>12</td>
<td>46</td>
</tr>
<tr>
<td>Non-trauma:</td>
<td>46</td>
<td>6</td>
<td>52</td>
</tr>
<tr>
<td>High altitude illness</td>
<td>12</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>11</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Sudden death</td>
<td>7</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Unclassified</td>
<td>16</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>Disappeared</td>
<td>25</td>
<td>2</td>
<td>27</td>
</tr>
<tr>
<td>Total</td>
<td>125</td>
<td>67</td>
<td>192</td>
</tr>
<tr>
<td>Total death rate (%)</td>
<td>1.6</td>
<td>1.1</td>
<td>1.3</td>
</tr>
</tbody>
</table>

*Last encampment on any route before technical (roped) climbing began (base camp in Nepal, advanced base camp in Tibet).

Of the 27 climbers who disappeared, 12 had evidence of neurological dysfunction or profound fatigue, 1 had pulmonary oedema, 9 may have fallen without evidence of previous dysfunction, and 5 disappeared without report of their condition. Of 11 deaths classified as high altitude illness, 6 were due to cerebral oedema, 2 involved cerebral oedema but possible subsequent respiratory difficulties, 1 involved both neurological and pulmonary symptoms, and 2 involved debilitating fatigue, the subsequent course of which was unclear. Of the 14 unclassified deaths, the relative contribution of hypothermia and high altitude illness was unclear in six climbers who collapsed or were found comatose, the non-traumatic deaths of six climbers found dead without adequate details were described as unknown, and in two cases accounts conflicted. Two climbers died suddenly (one had pre-existing asthma, the other a brain tumour), one death involved a myocardial infarction, and two climbers collapsed suddenly from unknown causes. One climber had noticeable cognitive impairment and fatigue before developing severe hypothermia in a storm. Of seven cases of visual disturbances, four were painless, two were painful, and one was related to a brain tumour.

During May 1975 to 2006, deaths occurred on 31% of days when mountaineers reached the summit (44/141; fig 2). Deterioration in weather played a part in 25% of deaths (14/56) on 6% of these days (8/141). The largest class of deaths involved objective hazards such as avalanches, icefall collapses, crevasses, and falling rock. Sherpas were killed at a greater rate per incident than climbers (1.18 vs 0.54, P<0.02), with 70% of deaths in sherpas classified in this category. These

Figure 2 presents a chart of mean barometric pressure at 9000 m for days when mountaineers reached the summit, and for weather related deaths and non-weather related deaths above 7000 m.

DISCUSSION
This study examined the patterns of deaths over an 86 year period on Mount Everest (1921-2006). The mortality above base camp was 1.3% (table 2). Most sherpas were killed in incidents on the lower slopes, whereas most climbers died above 8000 m. Climbers typically died during descent from the summit, often developing cognitive impairment and ataxia, symptoms of high altitude cerebral oedema. Profound fatigue, late summit times, and the tendency to fall behind companions were common early features of non-survivors.

Strength and limitations
The strength of this study lies in the meticulous records kept over four decades by Katmandu based journalist Elizabeth Hawley, whose work is the foundation of the Himalayan Database. An assessment of deaths was, however, limited by the variability of accounts and circumstances. While there was substantial agreement between the independent reviewers on classification of the deaths (Fleiss’ κ=0.63, P<0.001), categorisation was achieved using a descriptive classification system. This approach may underestimate underlying problems, such as neurological dysfunction leading to falls, disappearances, or vulnerability to hypothermia at extreme altitude. The widespread use of supplemental oxygen may affect physiological responses to altitude, and a precise association between altitude and symptoms cannot be made. Although a retrospective study can only show an association and not prove causality, this simple descriptive technique nevertheless allows for broad patterns of mortality to be detected.

Comparison with other mountains
The death rate among climbers on Denali (6194 m), Alaska, during 1903-2006 was 0.03%, whereas the overall death rate on Mount Rainier (4392 m), Washington, during 1987-1996 was 0.02%. The mortality among expedition members during 1950-2006 on Himalayan peaks such as Annapurna (8091 m) and Cho Oyo (8201 m) were 0.46% and 0.65%, respectively. As with Everest, these four peaks are scaled by large numbers of relatively inexperienced climbers using standard routes. The death rate on Everest is therefore greater than that of lower mountains attempted by similar populations of climbers.

Distribution of deaths
The largest class of deaths involved objective hazards such as avalanches, icefall collapses, crevasses, and falling rock. Sherpas were killed at a greater rate per incident than climbers (1.18 vs 0.54, P<0.02), with 70% of deaths in sherpas classified in this category. These

Table 3 | Classification of deaths above 8000 m on Everest. Values are numbers (percentages)

<table>
<thead>
<tr>
<th>Category</th>
<th>Climbers</th>
<th>Sherpas</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fall</td>
<td>23 (28)</td>
<td>9 (75)</td>
<td>32 (34)</td>
</tr>
<tr>
<td>Disappeared</td>
<td>25 (31)</td>
<td>2 (17)</td>
<td>27 (29)</td>
</tr>
<tr>
<td>High altitude illness</td>
<td>11 (13)</td>
<td>0</td>
<td>11 (13)</td>
</tr>
<tr>
<td>Unclassified</td>
<td>13 (16)</td>
<td>1 (8)</td>
<td>14 (15)</td>
</tr>
<tr>
<td>Sudden death</td>
<td>5 (6)</td>
<td>0</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Objective hazard</td>
<td>3 (4)</td>
<td>0</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>2 (2)</td>
<td>0</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Total</td>
<td>82 (87)</td>
<td>12 (13)</td>
<td>94</td>
</tr>
</tbody>
</table>

Percentages may not add up to 100% owing to rounding.
Profound fatigue and late summit times are early features of non-survivors. Cognitive impairment and ataxia, symptoms of cerebral oedema, are often present.

Most climbers on Mount Everest die above 8000 m, usually during descent from the summit. Gross cognitive impairment and ataxia, findings consistent with high altitude cerebral oedema, are likely to occur. These symptoms are more likely to survive because they turn back earlier. However, anecdotal accounts of the rapid onset of cerebral oedema at very high altitudes without preceding headache or vomiting have been reported. The mechanisms of the headache of cerebral oedema are unclear but may relate to the acute distension of the afferent innervated blood vessels and meninges at the base of the brain during raised intracranial pressure. An acute decrease in intravascular volume is a normal physiological response to high altitude, and dehydration, due to the increased physiological demands and the practicalities of melting sufficient snow, is a common problem above 8000 m. Acute decreases in fluid volumes may slow the increase in intracranial pressure and related headache after fluid extravasation. Ataxia and confusion may occur with a lesser degree of oedema, due to the hypoxaemia at extreme altitude. We speculate that at extreme altitude, headache, nausea, and vomiting are unreliable heralds of fatal cerebral oedema, whereas debilitating ataxia and impaired consciousness present earlier than these symptoms. Profound fatigue, reflected in significantly lower summit times, was an early symptom of subsequent non-survivors.

Deaths above 8000 m

In contrast to the deaths from objective hazards at lower altitudes, climbers died during the descent from the summit at a greater rate than did sherpas (2.5% vs 0.2%, \( P < 0.001 \)). On the Tibet and Nepal routes, 3.4% and 1.7% of climbers, respectively, did not return from the summit. Gross cognitive impairment and ataxia were common among non-survivors. These progressive symptoms and delayed presentation are consistent with high altitude cerebral oedema, a vasogenic oedema predominantly caused by failure of vascular endothelial fluid regulation after inadequate acclimatisation to hypoxia. Acute hypoxaemia during descent due to the exhaustion of supplemental oxygen supplies used by most climbers is another potential explanation for this distribution of symptoms. A similar pattern of death during descent is, however, seen in climbers with and without supplemental oxygen above 8000 m. Arterial oxygenation decreases during strenuous exercise at high altitude, so maximal hypoxaemia would occur during vigorous exertion just below the summit. However, we identified only two cases of sudden death that occurred during active ascent, both in climbers using supplemental oxygen. Failures of supplemental oxygen circuits during ascent are not unusual, yet we did not detect any deaths directly attributable to this. Among non-survivors, neurological dysfunction and possibly the susceptibility to acute hypoxia after exhaustion of supplemental oxygen therefore typically progress with time at extreme altitude. This is characteristic of the cerebrovascular leak and disruption of fluid homoeostasis of high altitude cerebral oedema, rather than of acute hypoxaemia alone. In addition, hypoxic neurological dysfunction at extreme altitude may involve other pathophysiological mechanisms not prominent at lower elevations.

Respiratory distress, nausea, vomiting, and headache, common indicators of altitude illness at 2500-5000 m, were rarely noted in non-survivors above 8000 m. This may be because people with these symptoms are more likely to survive because they turn back earlier. However, anecdotal accounts of the rapid onset of cerebral oedema at very high altitudes without preceding headache or vomiting have been reported. The mechanisms of the headache of cerebral oedema are unclear but may relate to the acute distension of the afferent innervated blood vessels and meninges at the base of the brain during raised intracranial pressure. An acute decrease in intravascular volume is a normal physiological response to high altitude, and dehydration, due to the increased physiological demands and the practicalities of melting sufficient snow, is a common problem above 8000 m. Acute decreases in fluid volumes may slow the increase in intracranial pressure and related headache after fluid extravasation. Ataxia and confusion may occur with a lesser degree of oedema, due to the hypoxaemia at extreme altitude. We speculate that at extreme altitude, headache, nausea, and vomiting are unreliable heralds of fatal cerebral oedema, whereas debilitating ataxia and impaired consciousness present earlier than these symptoms. Profound fatigue, reflected in significantly lower summit times, was an early symptom of subsequent non-survivors.

Atmospheric factors other than hypoxia also compound physiological stress at extreme altitudes. Although hypothermia and strong wind exacerbate the problems of a hypoxic environment, only 5.7% of summit days during the peak summit month of May had deaths associated with weather that was worse than baseline (8/141, \( P < 0.05 \)). Painful retinal burns due to the intense ultraviolet radiation were identified only in two non-survivors. Mountaineering factors such as inexperience, inadequate teamwork, and the absence of protective ropes on the summit routes may play significant roles. However, similar problems might be expected on peaks such as Rainier and Denali, where the death rate is considerably lower. The difficulty of rescue at extreme altitude undoubtedly increases mortality compared with lower altitudes, but this does not cause the primary problems leading to the need for rescue. Although these factors variously contribute to...
deaths, they cannot in isolation adequately explain the cluster of deaths at extreme altitude.

Acclimatisation to extreme altitude

Since neurological symptoms are present in many non-survivors, critical questions include whether adequate acclimatisation is possible at this altitude and, if so, how can it best be achieved.\(^2\)\(^,\)\(^3\)\(^0\) Climbers died at over six times the rate of sherpas during the descent from the summit. Recent trends on the standard routes are for climbers to spend more time at lower altitudes before making a rapid ascent, whereas sherpas spend more time above base camp preparing the route.\(^2\)\(^1\) The differing mortality during descent may be related to better acclimatisation by sherpas due to prolonged time at higher altitudes. However, selection for employment during an expedition may involve a bias for the ability to perform at altitude. Most sherpas are of Sherpa extraction, an ethnic group from the Nepali highland whose name has become synonymous with the exceptionally hardy porters of high altitude. This group and others born and resident at high altitudes may have superior congenital and acquired adaptations to hypoxia compared with their lowland employers.\(^1\)\(^4\)\(^5\)\(^6\)\(^7\) As employees, sherpas may be less likely to climb alone and hence are more likely to be rescued. While one subpopulation of mountaineers can acclimatise sufficiently to climb Everest using supplemental oxygen with relatively low mortality, the interaction and relative importance of the differences between populations and acclimatisation profiles requires further study.

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**Contributors:** PGF, JSW, AIS, CHI, JLS, and RCR constructed the classification system. PGF collected the accounts and interviewed climbers. PGF, JSW, AIS, and CHI analysed the reports. GWKM and JLS analysed the weather patterns. HZ provided data from the Himalayan Database. HZ did the statistical analysis. PGF wrote the manuscript; and Armin Gruen and Martin Sauerbier (Institute of Geodesy and Photogrammetry, Switzerland) for data and assistance in constructing the route profile.

**Ethical approval:** This study was approved by the institutional review board of Massachusetts General Hospital.

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