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Frailty and survival in the 1918 influenza pandemic

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One of the most well-known yet least understood aspects of the 1918 influenza pandemic is the disproportionately high mortality among young adults. Contemporary accounts further describe the victims as healthy young adults, which is contrary to the understanding of selective mortality, which posits that individuals with the highest frailty within a group are at the greatest risk of death. We use a bioarchaeological approach, combining individual-level information on health and stress gleaned from the skeletal remains of individuals who died in 1918 to determine whether healthy individuals were dying during the 1918 pandemic or whether underlying frailty contributed to an increased risk of mortality. Skeletal data on tibial periosteal new bone formation were obtained from 369 individuals from the Hamann–Todd documented osteological collection in Cleveland, Ohio. Skeletal data were analyzed alongside known age at death using Kaplan–Meier survival and Cox proportional hazards analysis. The results suggest that frail or unhealthy individuals were more likely to die during the pandemic than those who were not frail. During the flu, the estimated hazards for individuals with periosteal lesions that were active at the time of death were over two times higher compared to the control group. The results contradict prior assumptions about selective mortality during the 1918 influenza pandemic. Even among young adults, not everyone was equally likely to die—those with evidence of systemic stress suffered greater mortality. These findings provide time depth to our understanding of how variation in life experiences can impact morbidity and mortality even during a pandemic caused by a novel pathogen.

1918 influenza pandemic | paleoepidemiology | frailty | bioarchaeology

Significance

The COVID-19 pandemic showed how social, environmental, and biological circumstances can shape the likelihood of disease and death, even with respect to a disease for which no one has preexisting adaptive immunity. The 1918 influenza pandemic killed an estimated 50 million people worldwide. So many people fell ill that doctors at the time believed that healthy people were equally likely to die as those who were already sick or frail. We analyze bioarchaeological data on age at death and skeletal lesions from 369 individuals who died prior to and during the 1918 influenza pandemic in the United States. The results further show that even in the past, people with evidence of prior environmental, social, and nutritional stress were most likely to die.

Selective mortality is the process by which individuals with the highest frailty within each age cohort have the greatest risk of death and are selectively eliminated from the living population (1). In contexts of normal disease and aging processes, the force of selective mortality is high—i.e., the least healthy individuals at any particular age are most likely to die. Compared to these normal, "attritional," death processes, catastrophic death events such as epidemics and natural disasters are often assumed to be less selective—meaning that a wider range of people will die rather than only the most frail, sick, or vulnerable. While research has demonstrated that the strength of selective mortality decreases during these events (2), selective mortality may never be completely eliminated, and certain people will still be more likely to die compared to others. Even during natural disasters in which all affected individuals should be equally susceptible, social, biological, and economic factors influence survival. For example, during the 2011 Great Japan Earthquake, older individuals with physical limitations and who thus would have had greater difficulty evacuating were more likely to be among the dead or missing (3). Similarly, areas of the United States with a high percentage of mobile homes—and therefore inhabited by people of lower socioeconomic status and with lower governmental investment in public safety—experience more tornado fatalities (4).

The effects of selective mortality are also felt during outbreaks of infectious disease. Preexisting medical conditions are additional common risk factors for poor health outcomes from infectious disease. For example, individuals with asthma, congestive heart failure, and chronic obstructive pulmonary disorder have higher rates of hospitalization from influenza (5). Racism and institutional discrimination can amplify these effects. Early in the COVID-19 pandemic, hospitalization rates were much higher among minoritized individuals such as American Indians and African Americans compared to white Americans (6, 7). Similar patterns in selective mortality were also present in past pandemics. In London in 1349 AD during the medieval plague pandemic (now commonly called the Black Death), which had an estimated mortality rate of up to 30 to 50%, certain groups were still more likely to die than others (8). Individuals who had previously suffered environmental, nutritional, and disease stressors experienced a greater risk of death from the plague compared to their healthier peers (2, 9, 10). As seen from these examples, selective mortality is frequently strongest against those who are physiologically, immunologically, economically, and socially disadvantaged.

During the 1918 influenza pandemic, overall, an estimated one-third of the world's population became infected with the virus and approximately 25 to 50 million people

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(~1.3 to 3% of the global population) died from the flu (11–13). Comparatively, as of July 2023, it is estimated that approximately 6.95 million people (~0.09% of the current global population) have died worldwide from COVID-19, most deaths occurring in individuals over age 65, and at least 43% of the world's population has had Covid* (14). During the 1918 pandemic, young adults—typically the most biologically resilient segment of a population—experienced unusually high mortality. From 1918 to 1919, the pneumonia and influenza mortality rate of individuals between the ages of 15 and 34 y was more than twenty times higher compared to the mortality rate from pneumonia and influenza in the same age group in previous years (11). Further, it was perceived, both in the medical community and broader public, that the 1918 virus killed not only young adults but healthy young adults—suggesting that this pandemic was not selective with regard to health or frailty (11, 15–18). A medical doctor at the US Naval Hospital in Philadelphia reported that "most of the patients were between the ages of 20 to 26 y and were in unusually good physical condition" (19). The illness "seemed to be as fatal to strong adults as to young children and to the old and debilitated" (20). Similarly, a physician from Virginia noted that "a large percentage [of flu victims] were young men apparently healthy and vigorous" (21). According to present-day influenza researcher W. Paul Glezen, "[it] was not just the weak and infirm who were taken away but the flower and strength of the land" (18). *Look Homeward, Angel* is a semi-autobiographical account of early life in 1900's North Carolina by Thomas Wolfe. In the novel, the protagonist's brother dies from the 1918 flu, and his mother remarks: "They have all been down sick with the flu … It seems to get the big strong ones first" (22). This perception was likely repeated in scientific literature until it became an accepted belief about the pandemic that endures in current-day studies; it did not matter if you were healthy or sick, all young adults were equally likely to die from the flu. In the early 1900s, polio was similarly perceived as an unpredictable disease that could strike anywhere. In fact, polio often struck clean, well-kept homes of the middle and upper classes and spared dense urban areas and orphanages (23, 24).

Anecdotal accounts about the high death rate among healthy young adults can be found throughout the literature on the 1918 flu; however, there are, as far as our searches have revealed, no concrete scientific data to support these claims. Previous work by Dimka and Mamelund demonstrated that individuals with physical and intellectual disabilities and those with active tuberculosis were at a significantly increased risk of death from the 1918 flu, suggesting that prior frailty played a role in influenza mortality (25, 26). These findings, however, do not explain the perception that "healthy" adults were dying. Were these adults truly healthy? Or was there some underlying frailty yet to be identified among those who died? Here, we further explore the behavior of selective mortality by testing the assumption that healthy individuals were as likely to die as nonhealthy individuals during the 1918 influenza pandemic.

Much of the research on the 1918 flu relies on data obtained from historical records such as vital statistics, census data, and life insurance records. These data often do not include individual-level information on comorbidities, health conditions, or general environmental, nutritional, and chronic stressors from throughout a person's lifespan and may therefore be inadequate for testing whether the people who died were healthy. Bioarchaeological data, however, have the power to capture the individual disease experience from a biological and life course perspective. Bioarchaeology is the study of human skeletal remains from past contexts (27). Poor health due to environmental, social, nutritional, or disease stresses can leave permanent modifications on the skeleton such as reduced stature, structural asymmetry, abnormal subadult growth, developmental tooth defects, or skeletal lesions (27–29). These data can be aggregated to provide a population-level understanding of how these stresses impacted selective mortality during the 1918 flu.

Stress is defined broadly as disruption to biological homeostasis caused by disease, nutritional, environmental, and/or cultural perturbation (28, 30–33). Bodily tissues attempt to compensate for this disruption through a process known as allostasis (34) resulting in what are known as nonspecific indicators of skeletal stress (32). Many of these indicators, such as reduced stature or structural asymmetry, reflect long-term adverse health conditions (28, 29, 31), while others such as periosteal reactions, porotic hyperostosis, cribra orbitalia, and dental defects can be indicative of acute stress events (30).

Accumulation of nonspecific indicators of skeletal stress has been correlated with increased frailty (2, 35). Frailty—defined here as the increased susceptibility to death (1, 35)—is a framework for examining past social, environmental, and biological processes that cause certain people to be at higher risk for increased morbidity and mortality (36). Here, we use a bioarchaeological approach to examine the question: Did healthy individuals die during the 1918 pandemic? If the perception of the pandemic holds true, we expect to find that nonfrail (i.e., healthy) individuals (those lacking skeletal stress indicators that have been found to be negatively associated with survivorship) were equally likely to die as frail individuals in 1918.

To address this research question, data on age at death, date of death, and indicators of skeletal stress were collected from 369 individuals from the Hamann–Todd Documented skeletal collection housed at the Cleveland Museum of Natural History. The Hamann–Todd is composed of over 3,000 individuals who were born between 1825 and 1910 (37) and died between 1910 and 1938 in Cleveland, Ohio (38). The sample was separated into two groups based on whether they died before the pandemic (control group, n = 288) or died during the pandemic (flu group, n = 81). The pandemic struck Cleveland roughly between September 1918 through March 1919. The flu group includes individuals who died during that 7-mo period.

Frailty was determined using the presence/absence and activity status (active, mixed, or healed) of periosteal lesions of the tibia (*SI Appendix*), a commonly used indicator of stress in biological anthropology. Periosteal new bone formation occurs in response to inflammation of the periosteum caused by physical trauma, local, or systemic infection (39, 40). In the skeleton, it manifests as new bone formation. An active lesion is characterized by woven or unremodeled new bone resulting from osteoblastic activity and indicates local or systemic injury or disease processes that were ongoing at the time of death. Active lesions have been correlated with lower survivorship—i.e., greater frailty—compared to mixed or healed lesions (41). A mixed lesion contains both active and healing tissues at the time of death; it may be in the process of healing or was healing and is in the process of becoming active again. A healed lesion is characterized by smooth, remodeled bone, indicating a lesion that was not active at the time of death (42). A figure showing tibial periosteal lesions in various stages of healing is available under *SI Appendix*.

The data were analyzed using Kaplan–Meier survival and Cox proportional hazards analysis. While still a relatively new approach in biological anthropology, these analyses have been used to

*According to the WHO Dashboard, as of July 2023 there have been over 767 million confirmed cases of COVID-19 globally—only 9.5% of the total population. However, this includes only reported cases and certainly underestimates the true number of people who have had COVID-19.

investigate the relationship between skeletal lesions and mortality (9, 43, 44). Here, Cox proportional hazards analysis was used to assess how lesion status affected the risk of death during the flu pandemic. The model was run with the timescale as age at death in years, the event was dying during the flu (1) or control group (0), and the baseline hazard was birth, or $h(t_0)$. Frailty was the covariate, specifically lesion status (active, healed, mixed), with mixed lesions as the reference group. Statistical significance was assessed at $\alpha = 0.1$.

Using tibial periosteal lesions, particularly active lesions as the indicator of frailty, we investigate whether the prevailing perception of the 1918 flu as killing healthy adults reflected reality. If nonfrail (healthy) people were equally likely to die as frail people during the 1918 pandemic, we expect no difference in survivorship, median survival time, or in the hazard ratio (HR)/risk of mortality between frail and nonfrail individuals during the flu.

Results

Figs. 1 and 2 present the Kaplan–Meier curves using periosteal lesion activity as a reflection of frailty. Note that because individuals with 0 lesions were excluded from analyses, the sample size used for analyses decreased from 369 to 248 (control = 200, flu = 48). In the control group (Fig. 1), those with active lesions (i.e., the most frail) had the lowest survivorship, and those with mixed lesions had the greatest survivorship. Separate log-rank tests indicate no significant difference in survival between individuals with active vs. healed ($P = 0.52$) and active vs. mixed ($P = 0.29$) periosteal lesions. There is a 6-y difference in the median survival time between individuals with active lesions and those with healed lesions and a 7-y difference in the median survival time between those with active and mixed lesions (Table 1).

The Kaplan–Meier results for the flu group (Fig. 2) show that the lowest survival values were found for individuals with active lesions. The median survival time for those with active lesions is 36 y (compared to 39 y in the control group), while the median survival time for those with healed lesions is 38.5 y (compared to 45 y in the control group). A post hoc log-rank test demonstrated that during the flu, individuals with mixed lesions had significantly greater survivorship than those with active lesions ($\alpha = 0.1$, $P = 0.091$).

For the Cox proportional hazards analysis (Table 2), HRs that are greater than 1 indicate a risk of death that is greater than that of the reference group (mixed lesions). The results show that having active lesions was associated with a statistically significantly increased risk of death during the 1918 flu. For those with active lesions, the risk of death during the 1918 flu is 2.7 times greater compared to those with mixed lesions ($\alpha = 0.1$, $P = 0.0647$). The full R output for the Cox model is available under *SI Appendix*.

Discussion

The results of this study reveal a complicated picture of frailty and survival during the 1918 pandemic in Cleveland, Ohio. The Kaplan–Meier survival analysis indicates that individuals with active lesions had the lowest survival in both the control and flu groups, indicating that in both time periods, frail individuals had a greater risk of mortality compared to those with healed or mixed lesions, which is consistent with our understanding of the relationship between frailty and selective mortality. Based on the results of the hazards analysis, during the 1918 flu, the hazard of death is 2.7 times or 170% greater for those with active lesions compared to those with mixed lesions.

Based on the anecdotal evidence that the 1918 flu killed healthy adults, we hypothesized that frail and healthy individuals would be equally likely to die. The results of this study suggest that healthy individuals were not equally likely to die; frail individuals in this sample had a statistically significantly higher likelihood of dying during the 1918 flu compared to their healthy counterparts. These results contradict past and current perceptions of the pandemic that healthy people were as likely to die as anyone else from the flu. Furthermore, the results are comparable to those found in similar studies of past pandemics. DeWitte and Wood (2) found that individuals with periosteal lesions of the tibia were about 50% more likely to die during the Black Death than those without. Similarly, Godde et al. (9) demonstrated that individuals with frailty markers had a 3.7-fold increase in the risk of death during the Black Death than similarly aged and sexed counterparts without frailty markers.

If healthy people were not more likely, or even equally likely to die as frail individuals during the 1918 flu, how do we explain the

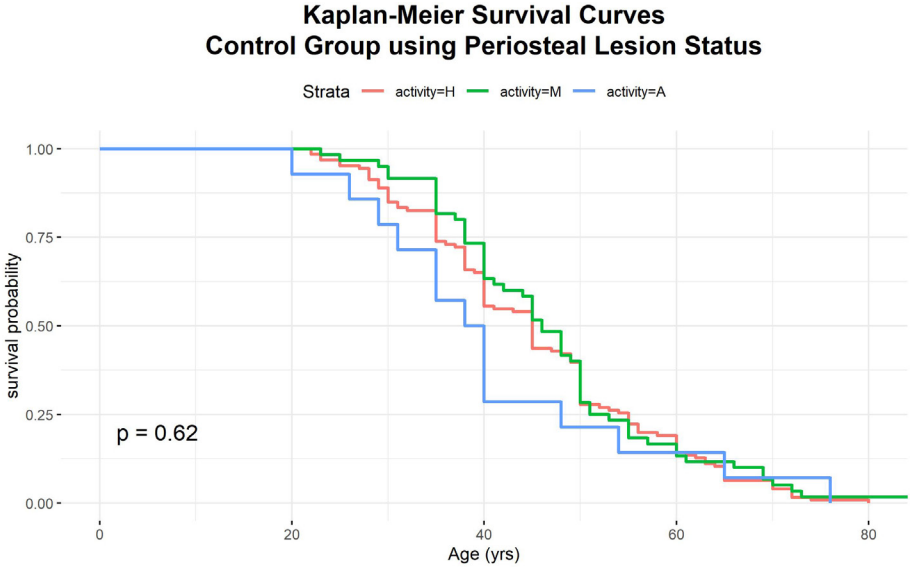

Fig. 1. Survivorship curves show survivorship of those with healed (H, in red), mixed (M, in green), and active (A, in blue) periosteal lesions of the tibia in the control group. *P*-value (0.62) is the result of the log-rank test showing no statistically significant differences in survival among those with healed, mixed, or active lesions in the control group.

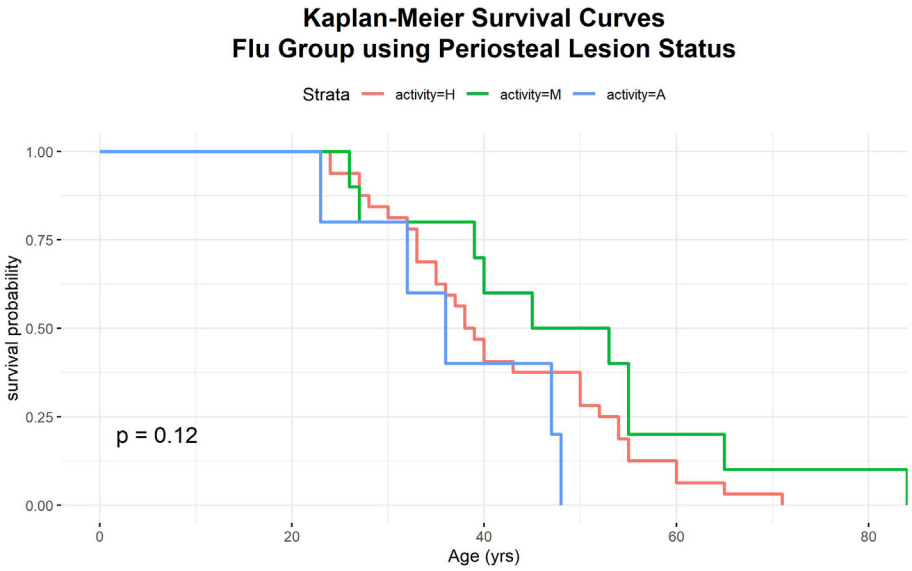

Fig. 2. Survivorship curves show survivorship of those with healed (H, in red), mixed (M, in green), and active (A, in blue) periosteal lesions of the tibia in those who died in the 1918 flu pandemic. *P*-value (0.12) is the result of the log-rank test showing no statistically significant differences in survival among those with healed, mixed, or active lesions in the flu group.

popularly held perception that they were? The results of the survival analysis indicate that the median survival time for all three types of lesions decreased during the pandemic compared to the control period—albeit only a year for mixed lesions. This suggests that the strength of selective mortality decreased during the 1918 flu as the likelihood of death for everyone—frail and nonfrail—increased. A healthy person (i.e., one with healed periosteal lesions of the tibia) was more likely to die during the flu than prior to the pandemic. Previous work suggests a similar decrease in the strength of selective mortality during the Black Death in London, as healthy individuals who would not have died under ordinary circumstances experienced an increase in risk of death compared to nonplague years (2).

Our results do not support the hypothesis of this paper: Healthy individuals were not equally likely to die as frail individuals during the 1918 flu, and further, the risk of death for everyone increased during the pandemic indicating that more healthy people died during the pandemic than would have in normal, nonpandemic times. It is possible the perception that healthy adults were equally likely to die of the flu reflects the fact that young adults were certainly at greater risk in the 1918 flu. Young adults are generally assumed to be healthy and at lower risk of death from disease compared to elderly adults or infants. Unusually high numbers of deaths among young adults would have been memorable and disruptive to both labor force and family life, producing long-lasting demographic and social changes. Without having an understanding of the heterogeneity in frailty that likely existed within the cohort of young people exposed to the 1918 flu, it is reasonable that observations, by people experiencing the pandemic first-hand, of high levels of mortality for this age group would have inspired beliefs that the pandemic disproportionately killed healthy young people.

Overall, the results demonstrate that for this sample, frail individuals were not equally likely to die as nonfrail individuals during the pandemic, which refutes the assumption that healthy young adults were as likely to die as anyone else in 1918. These findings suggest that there was some underlying source of frailty among the victims of the 1918 flu. Whatever the cause of this underlying frailty, it is important to note that the methods used here cannot explain specific frailty mechanisms, nor can they elucidate a specific person's frailty status. The tibial periosteal lesions themselves are not the proximate cause for increased frailty or mortality during the 1918 flu. Periosteal lesions are a proxy for underlying mechanisms that produce frailty (e.g., inflammation) and that, in turn, are shaped by broader processes including biological, social, and cultural factors; however, given their multiple causative factors, they almost certainly do not reflect any specific individual intrinsic biological frailty. Rather, they can be informative about general patterns of frailty at the aggregate level.

The problem of interpreting skeletal lesions in the archaeological record is widely known (35). Skeletal lesions take weeks, months, or even years to manifest; therefore, a sample with a high frequency of stress lesions could reflect a healthier, more resilient and robust group than one with no lesions at all, with individuals of the latter

Table 1. Kaplan–Meier survival results for periosteal lesion activity status and frequency of each lesion as a percentage of the control or flu group. Survival was not calculated for individuals with 0 lesions.

	Lesion status	N	Frequency	Median survival time (yrs)	Lower 0.95	Upper 0.95
Control	Active	14	0.049	39	35	65
	Mixed	60	0.208	46	42	40
	Healed	126	0.438	45	40	40
	No lesions	88	0.306	NA	NA	NA
Flu	Active	5	0.062	36	32	NA
	Mixed	11	0.316	45	40	NA
	Healed	32	0.395	38.5	35	50
	No lesions	33	0.407	NA	NA	NA

Table 2. Cox proportional hazards results for periosteal lesion activity status. HRs are in relation to mixed tibial lesions.

Lesion status	HR	Lower 0.95	Upper 0.95	*P*-value
Active	2.76	0.94	8.08	0.065*
Healed	1.58	0.78	3.22	0.21

*Statistical significance at $\alpha = 0.1$.

group having perished before lesions could develop. Conversely, it is also possible that the most robust individuals in a group may be able to combat an infection completely, resulting in no lesions. Individuals without lesions, then, may represent either the most frail or the least frail in a sample, and there is currently no way to distinguish between the two. Because of this, the data were explored in greater detail using lesion status rather than presence/absence. Active lesions have been found to be a greater indicator of increased risk of death compared to those with healed, mixed, or no lesions. Furthermore, healed lesions indicate that the individual had recovered from the illness or stress event. Based only on skeletal evidence, it is not possible to know whether a person with healed lesions was more biologically resilient after the event or whether they experienced permanent immunological scarring that would have left them increased at risk of future disease and death. We therefore separated frailty status into 3 groups based on the activity of the periosteal lesions (active, healed, and mixed) so as not to interpret the meaning of the skeletal lesions a priori and eliminated all individuals who had 0 tibial lesions. As the focus of this paper was on clarifying the impact of frailty in the 1918 flu, we elected to exclude individuals without lesions to reduce uncertainty about frailty status.

It is important to emphasize that these results represent the experience of the 1918 flu in Cleveland, Ohio. Not only did the governmental response to the pandemic vary by city in the United States, each city also varied in their demographic, economic, and geographic composition. Additional study is needed to determine whether the results found here apply to other contexts. Note also that the Hamann–Todd Documented skeletal collection is composed of individuals who were unclaimed at the time of death. These individuals are more likely to represent lower socioeconomic status groups and immigrants and therefore may not fully reflect the variation in morbidity and mortality experienced by the total living population in Cleveland in 1918.

Another limitation is the relatively small sizes of the subsamples used in this study. Despite being able to achieve statistical significance at the 0.1 level, the CIs for all tests are large. Very small sample sizes in bioarchaeological and paleopathological research are common, as skeletal material is rare. Power analyses and achieving statistical significance are frequently not possible. Analysis of these particular data suggests that prior frailty influenced mortality during the 1918 influenza pandemic, although the results might be strengthened if examined with larger sample sizes.

Finally, the results contribute to our understanding of the role of frailty and selective mortality in past pandemics. COVID-19 has clearly demonstrated that even in a massive pandemic not everyone is equally likely to die. Immunological, social, and structural issues mean that some people are more vulnerable in these events. Our findings further demonstrate how anthropology can inform our perspectives on historical pandemics and contribute valuable insight into public health research.

Materials and Methods

Skeletal Sample. Data were collected from the Hamann–Todd Human Osteological Collection housed at the Cleveland Museum of Natural History in Cleveland, Ohio. The majority of the individuals were of low socioeconomic status and died in almshouses or public hospitals (37, 45). The sample used here included 369 adult individuals: 310 males and 59 females. Only individuals who died of natural causes (e.g., pneumonia, tuberculosis, myocarditis, influenza, cancer, etc.) were included; deaths of unknown causes, or as a result of accident, homicide, or suicide, were excluded from analyses. In order to maximize the sample size, both 1918 flu and the control groups include individuals who died from influenza and pneumonia as well as other diseases such as tuberculosis and myocarditis. Medical history for the individuals in the Hamann–Todd is not known. It is therefore not possible to know whether an individual suffered another disease during life unless it was listed as the cause of death or left diagnostic evidence on their skeleton. All data were collected by the first author. To reduce data collection bias, data for 10% of the sample were recollected and checked for observer error.

Skeletal Stress Indicators. Periostosis refers to the deposition of new bone caused by a reaction of the periosteum (39, 42). Because bone tissue can only react to disease or injury in two ways (bone resorption or bone proliferation), periosteal reactions have many possible causes including physical trauma, tuberculosis, leprosy, drug use, arthritis, cancer, and systemic infection (46–49). Periosteal new bone formation is also part of the normal growth process and is therefore commonly found on infant and juvenile remains. Due to the broad array of possible causes of periostosis, periosteal new bone formation is often interpreted broadly in biological anthropology as a nonspecific indicator of stress indicative of systemic stress or infection. Periosteal lesions of the tibia were examined by the first author through macroscopic observation of the anterior shaft of the tibia (40, 41, 49) and recorded as active, mixed, or healed. Since we use periostosis as an indicator of generalized systemic stress or infection, individuals with evidence of previous trauma, local osteomyelitis, or cancerous growths to the tibias were excluded.

Analytical Methods. The sample was separated into two groups based on whether the individuals: 1) never experienced the pandemic (control group) or 2) died during the pandemic (flu group). The pandemic struck Cleveland, Ohio, between September 1918 and March 1919. The flu group (n = 81) includes individuals who died during this 7-mo period. The control group (n = 288) includes those who died prior to the pandemic (1910–August 1918). Frailty was determined using activity status (active, mixed, or healed) of periosteal lesions of the tibia.

The data were analyzed using Kaplan–Meier survival and Cox proportional hazards analysis. Survival analysis models the effect of certain variables on the time elapsed until an event occurs. For the Kaplan–Meier, the effect of frailty status on survival was assessed separately for the control and flu groups, and statistical significance was evaluated using the log-rank test ($\alpha = 0.1$).

The difference in the risk of death between the flu and control group was assessed using Cox proportional hazards analysis. The HR expresses the differences in the risk of death between two or more groups. The Cox model is semiparametric, meaning that it does not assume that the survival times will follow a specific type of distribution. This makes it optimal for paleopathology analyses when the underlying hazard models are unknown and sample sizes are often insufficient for estimating model parameters. The proportional hazards assumption for the Cox model was assessed using the Schoenfeld test. All p-values for the Schoenfeld test were nonsignificant, indicating that the hazards are proportional. All analyses were performed using the survival package in R (50). The complete R output for the Cox proportional hazards results is available as *SI Appendix*.

Missing skeletal lesion data were imputed using the "pmm" function of the mice R package following previous recommendations (51, 52). Transforming HRs to a percent was calculated by (1-HR) × 100%. All analyses were performed in RStudio Version 1.1.456.

Data, Materials, and Software Availability. All R code for data analysis and missing data imputation are available on the first author's GitHub (53) (https://github.com/acwissler/lifendeath). Paleopathology data are the property of the Cleveland Museum of Natural History and can be obtained by contacting the Biological Anthropology Collections Manager and with permission from the first author.

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