Engaging the Osteological Paradox:

A Study of Frailty and Survivorship in the 1918 Influenza Pandemic

by

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ABSTRACT

Published in 1992, “The osteological paradox: problems of inferring prehistoric health from skeletal samples” highlighted the limitations of interpreting population health from archaeological skeletal samples. The authors drew the attention of the bioarchaeological community to several unfounded assumptions in the field of paleopathology. They cautioned that bioarchaeologists needed to expand their methodological and theoretical toolkits and examine how variation in frailty influences mortality outcomes. This dissertation undertakes this task by 1) establishing a new approach for handling missing paleopathology data that facilitates the use of new analytical methods for exploring frailty and resiliency in skeletal data, and 2) investigating the role of prior frailty in shaping selective mortality in an underexplored epidemic context. The first section takes the initial step of assessing current techniques for handling missing data in bioarchaeology and testing protocols for imputation of missing paleopathology variables. A review of major bioarchaeological journals searching for terms describing the treatment of missing data are compiled. The articles are sorted by subject topic and into categories based on the statistical and theoretical rigor of how missing data are handled. A case study test of eight methods for handling missing data is conducted to determine which methods best produce unbiased parameter estimates. The second section explores how pre-existing frailty influenced mortality during the 1918 influenza pandemic. Skeletal lesion data are collected from a sample of 424 individuals from the Hamann-Todd Documented Collection. Using Kaplan-Meier and Cox proportional hazards, this chapter tests whether individuals who were healthy

(i.e. non-frail) were equally likely to die during the flu as frail individuals. Results indicate that imputation is underused in bioarchaeology, therefore procedures for imputing ordinal and continuous paleopathology data are established. The findings of the second section reveal that while a greater proportion of non-frail individuals died during the 1918 pandemic compared to pre-flu times, frail individuals were more likely to die at all times. The outcomes of this dissertation help expand the types of statistical analyses that can be performed using paleopathology data. They contribute to the field's knowledge of selective mortality and differential frailty during a major historical pandemic.

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CHAPTER 1

INTRODUCTION

Paleopathology, or the study of past health, explores the origins of health disparity, and the role of disease in the evolution of human biology and society (Buikstra and Roberts 2012; Grauer 2012; Mcilvaine and Reitsema 2013; Temple and Goodman 2014). Studying health in ancient contexts elucidates the effects of major cultural and environmental transitions on the human condition, and how social structures and human ingenuity have influenced our biology over time.

Bioarchaeologists commonly examine past health through the lens of stress. Stress is defined broadly as disruption to biological homeostasis caused by disease, nutritional, environmental, and/or cultural perturbation (Brown 1981; Huss-Ashmore et al. 1982; Bush and Zvelebil 1991; Goodman et al. 1984). Bodily tissues attempt to compensate for this disruption through a process known as allostasis (McEwen 1998; McEwen 2005; Klaus 2014) resulting in what are known as indicators of skeletal stress. Bioarchaeologists have compiled a vast suite of physical changes to the human skeleton to investigate the effects of stress in the past. Many are general reflections of long-term poor health such as reduced stature, structural asymmetry, cortical structure, low sexual dimorphism, altered subadult growth curves, malocclusion, musculoskeletal markers and osteoporosis (Buikstra and Cook, 1980; Huss-Ashmore et al., 1982; Goodman et al., 1984). Others such as Harris lines, periosteal reactions, porotic hyperostosis, cribra orbitalia, dental defects, and skeletal indicators of infectious disease are considered indicative of acute stress events (Brown, 1981; Goodman et al., 1988).

Bioarchaeologists differentiate between nonspecific indicators of skeletal stress, and skeletal changes that are pathognomonic of certain disease processes (e.g. tuberculosis, syphilis, diffuse idiopathic skeletal hyperostosis). The pattern and appearance of the latter can be used to diagnose specific illnesses. Nonspecific indicators, however, cannot be used to identify a specific disease or stressor. Bone tissue can respond to injury or disease in a limited number of ways: by depositing bone, or by removing bone. While a nonspecific indicator of skeletal stress may have a certain cause (e.g. starvation), the lesion will not be distinguishable from a lesion caused by another stressor and are thus nonspecific.

Inadequate health due to stress caused by cultural, nutritional, and environmental factors can permanently shape the human body, causing skeletal lesions, stunted growth, and structural abnormalities (Buikstra and Cook 1980; Goodman et al. 1984; Huss-Ashmore et al. 1982). Bioarchaeologists use nonspecific indicators of skeletal stress to examine health while drawing connections to broader cultural and sociological change (Larsen 1997).

In 1992, Wood et al. published "The osteological paradox: problems of inferring prehistoric health from skeletal samples" – an article that raised fundamental concerns about the ability to make straightforward interpretations about past health from skeletal assemblages. The authors coalesced their arguments around three main topics: demographic nonstationarity, selective mortality and hidden heterogeneity.

Demographic nonstationarity refers to the non-static nature of real populations. A stationary population is one in which fertility and mortality rates do not change over time

and are both equal to zero, there is no population movement or migration, and the size of the population remains constant, and the number of individuals who die at each age remains constant (Coale 1956; Hoppa and Vaupel 2002; Lotka 1977; Milner et al. 2008; Sattenspiel and Harpending 1983). Virtually no real-life populations are perfectly stationary, however one of the foundations of paleodemographic analyses is that the living population from which the cemetery sample is derived was stationary. Milner et al. (2008) surmised that this assumption occurred in the early days of paleodemography when life tables – which are founded on demographic stationarity – were adopted as a standard technique. The belief at the time that human population growth had been almost zero for most of prehistoric history supported the approach (Alesan et al. 1999). The assumption posed significant problems for demographic interpretations estimated from skeletal samples. Age-at-death distributions more strongly reflect fertility rates rather than mortality rates (Coale 1956; Johansson and Horowitz 1986; Milner et al. 2008; Sattenspiel and Harpending 1983). As a result, fluctuating mortality profiles may be a greater reflection of changing fertility rates rather than mortality in the past.

Selective mortality refers to the idea that "all individuals do not have an equal chance of entering the skeletal sample at each age" (Milner et al., 2008; p. 586). The individuals who comprise a skeletal sample are the non-survivors of a population. The most frail of each age cohort are selectively eliminated from the living population (Vaupel et al. 1979). Assuming lesions are reflective of frailty, selective mortality results in the least healthy individuals of a skeletal series being more likely to exhibit skeletal lesions. The prevalence of lesions in the skeletal sample will therefore overestimate the

prevalence of illness in the living population from which the assemblage is drawn, causing it to appear as though the living population was less healthy than it was.

Hidden Heterogeneity in risks refers to the fact that while alive, the individuals who will eventually compose a skeletal sample, differed in their "underlying frailty and susceptibility to disease and death" (Wood et al., 1992, p. 345; Vaupel et al. 1979). The causes for this underlying variation in frailty are innumerable and may include genetics (Johnson et al. 1998; Lawrence et al. 2021; Sathyan and Verghese 2020; Taylor 2010; Wailoo 2014), environmental conditions (Dent et al. 2020; Loucks et al. 2011; Martins et al. 2020), mal- or undernutrition (Hayward et al. 2013; Larsen et al. 2001; Mummert et al. 2011), early life stresses (Armelagos et al. 2009; Barker et al. 1993; Barker 1998; Maniam et al. 2014), among others. Furthermore, it can be difficult, if not impossible, to identify sources of differential frailty in the past using skeletal remains (Milner et al. 2008). Wood et al (1992) indicated that hidden variation in frailty hinders the ability of bioarchaeologists to make sweeping statements about health in the past as aggregate data on lesion frequencies cannot capture this variation. By failing to account for individual and subgroup heterogeneity, our perception of the prevalence of disease in the living population will be skewed.

One of the other important concepts highlighted by Wood et al. (1992) was that skeletal lesions may reflect survival rather than increased frailty and mortality, as was the standard interpretation by most paleopathologists. Skeletal lesions take weeks, months or even years to manifest, therefore a population with a high frequency of stress lesions could reflect a healthier, more robust group than one with no lesions at all, with

individuals of this latter group having perished before lesions could develop.

Wood et al. (1992) were not the first to recognize these issues. Cook and Buikstra (1979) acknowledged that the juvenile skeletal record may be inherently biased if the more sick individuals are entering the record at younger ages than others. Ortner (1991) questioned the assumption that the presence of skeletal pathology is indicative of poor health. Why did Wood et al. (1992) become so influential? The journal in which the article was published appealed to broader audience and was more aggressive than previous publications that addressed this issue. Furthermore, the format in which Wood et al. (1992) appeared required comments to be published with the article, so generating academic dialogue was a fundamental aspect of the paper (Buikstra, personal communication). DeWitte and Stojanowski (2015) hypothesize that the timing of the article may play a role. It was published around the time of the Columbian quincentennial, a period during which the impact of colonialism on the health of indigenous peoples was a popular research topic (Baker and Kealhofer 1996; Larsen 1994; Larsen 2001; Larsen et al. 2001). The field was ready for a critical discussion of the methods and theory in bioarchaeology. Furthermore, while previous researchers had discussed problems inherent in skeletal samples, these concerns were not the main argument of their articles as they were for Wood et al. (1992).

Reactions to the Osteological Paradox

While most bioarchaeologists recognized the importance of the limitations articulated by Wood et al., not all agreed, contending that the problems were insignificant or easily overcome. Goodman and Martin (2002) maintained that heterogeneity in frailty

is not invisible in the skeletal record but is evident in “differing mortality profiles” (p. 13) and is clearly elucidated when scholars use multiple indicators of stress in their analyses (see also Goodman, 1993). Cohen et al. (1994) asserted that “heterogeneity, differential frailty, and selective mortality, although real, do not play quantitatively as important a selective role in the creation of cemetery samples” (p. 631) as maintained by Wood et al.

Despite the widespread acknowledgement of the osteological paradox having vital consequences for paleopathology and paleodemography, few publications in the ensuing decades sought to accept the challenge (Boldsen 1997; Garland 2020; Kyle et al. 2018; Lukacs 1994; McCool et al. 2021; Novak et al. 2017; O'Donnell 2019; Wright and Chew 1998; Wright and Yoder 2003). DeWitte and Stojanowski (2015) showed that the concerns raised by the osteological paradox were being handled in one of four ways: 1) as an brief mention as an “important theoretical contribution,” 2) as a “potential study limitation” but with no real engagement with the material, 3) as an ad hoc explanation when results about the distribution of disease do not align with previous hypotheses, and 4) articles engaging with the osteological paradox by exploring frailty and mortality in bioarchaeological contexts. Most articles fell into the first, second and third categories, with only a handful in the fourth.

The past five years, however, have seen a notable increase in the number of publications dedicated to serious engagements with the osteological paradox. Considerable effort has been focused on identifying sources of heterogeneous frailty in the past (Cheverko 2018; DeWitte 2009; DeWitte 2012; DeWitte et al. 2016; Jatautis et al. 2018; Marklein 2020; Marklein et al. 2016; Newman and Gowland 2017; Temple

2019; Yaussy and DeWitte 2019; Yaussy et al. 2016). Using a set of dental casts with known genealogical information, Lawrence et al. (2021) showed that linear enamel hypoplasia may have a "heritable component" that was accounted for by genetic relatedness as well as shared household environment of family members. The authors suggested that one of the hidden forces influencing heterogeneity in the risk of developing LEH may be due to genetic susceptibility. Yaussy (2019) used an intersectional approach to examine how gender and class identities shaped health and mortality in 18th and 19th century England. She found variable interactions between the multiple identities and the manifestation of stress indicators, ultimately concluding that having at least one marginalized identity (low socioeconomic status or female) was associated with earlier mortality.

No longer content with assuming that skeletal lesions are direct indicators of frailty, many scholars have adopted frameworks to interpret lesions to variably reflect frailty and/or resilience (Berger and Wang 2017; Hoover and Hudson 2016; Marklein and Crews 2017; Marklein et al. 2016; Godde et al. 2020; Godde and Hens 2021), as well as how frailty and the risk of mortality may vary over the life course (Agarwal 2016; Dewitte 2014b; McCool et al. 2021). McFadden and Oxenham (2020) tested how the risk of mortality due to cribra orbitalia may vary between juveniles and adults. They re-analyzed pathology data collected for the Global History of Health Project using Kaplan-Meier and Cox regression analyses. A large portion of the samples that had a statistically significant relationship between cribra orbitalia and survival when juveniles were included had no relationship once juveniles were eliminated from the sample. These

results suggest that cribra orbitalia may be associated with increased mortality in juveniles, but increased survival in adults.

New analytical methods that rely on fewer assumptions about the relationship between skeletal lesions and frailty – such as survival and hazards analysis, odds ratios, and multi-state models – are being used to explore the associations between skeletal lesions, mortality, and other biological and cultural factors (Cheverko and Hubbe 2017; DeWitte and Wood 2008; Kelmelis et al. 2017; Kyle et al. 2018; Redfern et al. 2019; Redfern et al. 2015; Sołtysiak 2015; Usher 2000; Walter and DeWitte 2017). Using a combination of survivorship, hazards models, and stable isotope analysis, McCool et al. (2021) investigated temporal variation in lesion severity and frequency in a Peruvian sample. Their results revealed that the force of selective mortality associated with cranial lesions changed across the phases of the Late Intermediate Period.

Research Orientation

A key assertion of the osteological paradox is that scholars must be more critical of how skeletal lesions are analyzed and how they are interpreted. This dissertation seeks to advance knowledge about analysis and interpretation through two distinctive objectives.

The first goal is to advance our methods for analyzing paleopathology data. Paleopathology data frequently include a mix of data types, including continuous, ordinal, binary, metric, and non-metric data, age-ranges, and descriptions. Compared to other social science fields, the sample sizes are generally small. As a result, missing data can have an enormous impact on the range of applicable statistical analyses, the power to

detect meaningful differences, and the potential biases introduced into the sample composition (Allison 2001; Baraldi and Enders 2010; De Leeuw et al. 2003; Enders 2010; Finch 2010; Graham 2009; Howell 2007; Kang 2013; McKnight et al. 2007; Myers 2011; Osborne 2013; Peng et al. 2006; van Buuren 2018). The first section of this dissertation aims to advance our knowledge of methods for handling missing data in bioarchaeology and paleopathology. This will encourage bioarchaeologists and paleopathologists to explore new analytical methods for investigating the osteological paradox along with other important topics.

The second goal of this dissertation is to further interrogate the relationship between skeletal frailty and mortality using a unique pandemic context. This section builds on the results of the first section by incorporating new missing data methods into paleopathology analyses. One of the barriers to exploring aspects of the osteological paradox in the past, particularly heterogeneity in risks, has been a lack of temporal or demographic control over the samples. The individuals in an assemblage often died over a long period of time, and therefore they did not necessarily experience the same socio-cultural environment or climate (DeWitte and Stojanowski 2015; Kyle et al. 2018; Lawrence et al. 2021; Stojanowski 2013). This chronological bias prevents meaningful inter- and intra-sample comparisons. To properly understand skeletal stress lesions and their utility as indicators of frailty or resilience, as well as examine individual variation in health, the ideal study sample is a group of individuals who died within a short time frame and experienced a single substantial stress event (Wood et al. 1992; Temple 2019).

Epidemics are therefore an ideal context in which to examine variation in frailty and resilience.

Many of the initial advances in paleoepidemiology and paleodemography have been made within "catastrophic" burial contexts – contexts where usually large numbers of individuals were interred within a short time as a result of famine, violence, or an outbreak of epidemic disease (Gowland and Chamberlain 2005; Keckler 1997; Margerison and Knusel 2002). For example, DeWitte and colleagues explored the impact of pre-existing frailty during the Black Death (DeWitte 2009; DeWitte 2014a; DeWitte and Wood 2008; Zarulli et al. 2018). DeWitte and Wood (2008) demonstrated that the Black Death did not kill indiscriminately, but that prior frailty increased the risk of mortality and sex may have been an additional risk factor (DeWitte 2009). This section of the dissertation expands on this work by exploring selective mortality during the 1918 influenza pandemic and the role of prior frailty in contributing to increased risk of death.

The 1918 influenza pandemic is an excellent case study for investigating skeletal lesions and differential frailty in the past. There is a remarkable amount of scholarship on the pandemic, which was used to formulate hypotheses and interpret the results within appropriate historical and biological contexts. Numerous books and articles have described the historical trajectory of the pandemic (Aligne 2016; Barry 2004; Barry 2005; Chowell et al. 2010; Erkoreka 2010; Jester et al. 2019; Oxford et al. 2002; Patterson and Pyle 1991; Shanks and Brundage 2012; Taubenberger and Morens 2006), explored risk factors for increased morbidity and mortality (Afkhami 2003; Ammon 2001; Bengtsson et al. 2018; Dahal et al. 2018; Herring and Sattenspiel 2007; Johnson 2001; Mamelund

2003; Mamelund 2004; Mamelund 2011; Mamelund and Dimka 2019; McCracken and Curson 2003; McSweeny et al. 2007; Murray et al. 2006; Noymer and Garenne 2000; Oei and Nishiura 2012; Økland and Mamelund 2019; Paskoff and Sattenspiel 2019; Paynter et al. 2011; Pinnelli and Mancini 1998; Rice 1988; Tripp and Sawchuk 2017; Tuckel et al. 2006; Wilson and Baker 2008; Zürcher et al. 2016), and detailed the structure and behavior of the 1918 virus itself (Basler et al. 2001; de Wit et al. 2018; Kobasa et al. 2007; Kobasa et al. 2004; Oxford and Gill 2018; Reid et al. 1999; Reid et al. 2004; Reid et al. 2000; Stevens et al. 2004; Taubenberger et al. 1997; Tumpey et al. 2005).

Skeletal data for this dissertation were obtained from the Hamann-Todd Documented Osteological Collections – a documented skeletal collection containing individuals who died in Cleveland, Ohio, prior to and during the 1918 pandemic. Each individual has associated records on age-at-death and cause of death, eliminating uncertainty that may arise from traditional osteological age-at-death methods (Buckberry 2015; Hoppa and Vaupel 2002; Milner et al. 2008) and uncertainty about death due to other causes. The assemblage also provides an appropriate comparative sample to assess changes in selective mortality during the 1918 flu.

Structure of the Dissertation

In addition to the introduction and the concluding chapters, this dissertation is organized into two sections, the first containing two chapters and the second containing one chapter. The second chapter explores the handling of missing data within the field of bioarchaeology. Missing data are a frequent and unavoidable challenge in bioarchaeo-logical research, yet how missing data introduce bias or invalidate statistical analyses are

infrequently made explicit. There is no consensus on best practices for the treatment or reporting of missing data. As an initial step in taking stock and exploring approaches to missing data in bioarchaeology, this study reviews bioarchaeological publications to ascertain what methods are currently used to handle them. Over 1000 bioarchaeology articles (2011-2020) from four major anthropology journals were surveyed, searching for the terms “missing,” “absent,” “unobserv,” “replace,” and “imputat” when used to refer to missing data. The articles so identified were then categorized by one of eight bioarchaeological subtopics and scored according to a set of six broad approaches for handling missing data. The results reveal broad themes in how missing data are treated in bioarchaeology, laying the groundwork for new missing data methods in the field.

Chapter 3 builds on the results of chapter 2 by exploring the use of imputation to handle missing paleopathology data. An overview of missing data management in the social sciences and in bioarchaeology is provided, followed by a test of imputation and deletion methods for handling missing data. In the test, missing data were simulated on complete datasets of ordinal (n=287) and continuous (n=369) bioarchaeological data. Missing values were imputed using six imputation methods (predictive mean matching, mean, random, random forest, expectation maximization, stochastic regression) and the success of each at obtaining the parameters of the original dataset compared with listwise and pairwise deletion.

Chapter 4 applies all the techniques and contextual information learned in the previous chapters to test the impact of prior frailty on mortality and survival in the 1918 influenza pandemic. A large amount of contemporary anecdotal evidence reports that

"healthy young adults" were among the greatest risk group during the pandemic (Glezen 1996; Hoffman 2011; Luk et al. 2001; Short et al. 2018; Taubenberger and Morens 2006). Despite little scientific evidence, these accounts have been incorporated into modern-day academic scholarship, perpetuating the idea that the 1918 virus killed healthy individuals. Much research on the 1918 flu utilizes data from demographic records – most of which do not contain individual-level information on chronic health conditions, nutritional or environmental stresses, or other illnesses that render a person "unhealthy." By using a novel bioarchaeological approach, we can combine individual-level information on health and stress gleaned from the skeletal remains of individuals who died in 1918 to ask the question: were healthy individuals dying during the 1918 pandemic? Or did a currently unidentified underlying frailty contribute to increased mortality?

Skeletal lesion data on porotic hyperostosis, cribra orbitalia, linear enamel hypoplasia, periodontal disease, and tibial periosteal lesions were obtained from a sample of 424 individuals from the Hamann-Todd documented osteological collection. The sample was separated into a control group (those who died prior to the 1918 pandemic) and a flu group (those who died during the pandemic). Skeletal data were analyzed alongside age-at-death information using Kaplan-Meier survival and Cox proportional hazards analysis. The results inform our understanding of frailty and selective mortality in the 1918 flu and in broader bioarchaeological contexts.

The final chapter summarizes the results of the dissertation. It reviews the goals and findings of each chapter, assessing how they engage with the osteological paradox

and contribute to bioarchaeological knowledge and our understanding of the 1918 influenza pandemic. Future research that builds on the results found in the previous chapters is proposed, including investigating sources of heterogeneity in frailty during the 1918 flu, and additional testing of imputation in bioarchaeology. The dissertation concludes with an overview of the intellectual merits of this project and how the results expand our knowledge of the 1918 flu, advance methods and theory in bioarchaeology, and elucidate the interactions between people and pathogens in an epidemic context.

CHAPTER 2

MISSING DATA IN BIOARCHAEOLOGY I: A REVIEW OF THE LITERATURE

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Missing data commonly occur in nearly all types of quantitative research, including medicine, ecology, psychology, education, communication, and biology (Altman and Bland 2007; Dong and Peng 2013; Enders 2010; McKnight et al. 2007; Van Buuren 2018b). However, most introductory statistics texts do not discuss missing data, what causes them, how to treat them, or how they influence the validity of statistical analyses (Allison 2001; Altman and Bland 2007). The lack of attention paid to missing data means that most researchers simply delete cases, individuals, or variables that are missing values with little understanding of potential bias introduced (Acock 2005; Enders 2010; Harel et al. 2008; King et al. 1998). Many scholars may be unaware that alternative options for handling missing data exist (McKnight et al. 2007).

Missing data are a particularly inevitable challenge in bioarchaeological research. Preservation and recovery factors beginning at the death of the individual and lasting through curation affect skeletal element preservation and attendant data quality and quantity. Specialized mortuary treatment, secondary burial practices, taphonomy, burial environment, excavation, cleaning, transport, and curation all shape skeletal assemblages (Gordon and Buikstra 1981; Nawrocki 1995; Stodder 2008; Walker et al. 1988). Archaeological and historical assemblages are incomplete, fragmentary, and regularly have taphonomic changes obscuring bone surfaces. Skeletons from identified collections

are generally more complete, but still suffer from missing elements taken for destructive sampling and the loss of small bones such as those of the hands and feet, sesamoids, and coccygeal elements. In addition to these postmortem biases in skeletal completeness, antemortem events such as tooth loss and wear can exclude elements and individuals from downstream analyses.

Despite these pervasive problems, there are no standardized methods for handling or reporting missing data. Often, missing data are not considered from the outset of a project, accounted for in project design, or explicitly documented in publications. This can lead to inconsistent and non-replicable results, systemically biased datasets and conclusions, and inhibit the use of results as comparative data or in meta-analyses (De Leeuw et al. 2003; Finch 2010; McKnight et al. 2007; Quintero and LeBoulluec 2018; Von Elm et al. 2007). Lack of engagement with missing data is also a barrier to implementing more advanced statistics and hypothesis testing. Most statistical tests require that no cells have missing data (Graham 2012) and deletion approaches generally reduce the sample size significantly, resulting in a loss of statistical power and an inability to explore interactions among many variables.

Scholars in other areas of the social sciences such as psychology and epidemiology have noted a similar lack of protocols for handling and reporting missing data and have thus developed guidelines for moving forward (Burton and Altman 2004; Jeličić et al. 2009; Von Elm et al. 2007; Wilkinson 1999). As an initial step toward increasing the theoretical and statistical rigor of missing data treatments in bioarchaeology, this paper surveys the state of missing data in the field – examining what

methods are used to handle missingness, and how missingness is reported in publications. To accomplish these objectives, this paper begins with a brief overview of missing data theory followed by a bioarchaeology literature review in which we assess how researchers approach missing data and how missing data are reported. Guided by the literature review results, we address why accounting for missing data is a critical aspect of scientific rigor and provide recommendations for bioarchaeologists to improve their handling and reporting of missing data.

Rubin (1976) defined three categories of missing data based on different causes of missingness. The first of these, missing completely at random (MCAR), occurs when a value is missing due to a cause that is unrelated to that variable or any other variables in the dataset (Enders 2010; McKnight et al. 2007; Quintero and LeBoulluec 2018). MCAR data are likely rare among bioarchaeological datasets but could occur when skeletons are only partially recovered due to an incomplete excavation grid or when taphonomic processes vary stochastically across mortuary deposits, resulting in some poorly preserved skeletal elements or cortical surfaces. The second category is missing at random (MAR). A value is MAR when the cause of the missingness is related to some variable in the dataset but not the variable of interest (Enders 2010; Myers 2011; Schafer and Graham 2002). Dental morphology data are generally MAR. While dental wear in older individuals results in trait missingness, an individual's age does not impact their dental morphology. The third category is missing not at random (MNAR or NMAR). MNAR occurs when the cause of a missing value is dependent on that variable or when the cause of missingness is unknown (Little and Rubin 2002; Van Buuren 2018b). A

common example of MNAR data is dental enamel defects (DEDs). DEDs are pervasive in the bioarchaeological record and are a frequently recorded pathology. DEDs are often unobservable in older individuals, as the labial or buccal tooth surfaces can be obscured by dental wear. In much bioarchaeological research, however, there is an assumed relationship between DEDs and survivorship (age-at-death) (see Bhaskaran and Smeeth, 2014 for examples of MAR, MCAR, and MNAR variables). Data that are MCAR or MAR are less problematic than MNAR and are often referred to as "ignorable" (Allison 2001; Enders 2010; Graham 2012; Osborne 2013). Deleting data that are MCAR or MAR, however, will result in a decline in statistical power due to a decreased sample size, but because MCAR and MAR data are missing in ways that are "random," their absence should not introduce bias into the dataset (Graham 2009; Howell 2007; Myers 2011). MNAR, however, are problematic and are also referred to as "nonignorable" (Allison 2001; Graham 2009; Graham 2012). The probability of missingness is dependent on the missing data; it is almost impossible to know the true extent of that relationship, therefore it is not possible to control for or compensate for the missingness (Graham 2012; Howell 2007; McKnight et al. 2007). Data missing not at random can result in a substantially biased dataset, as it means that information vital to answering the research question is absent (De Leeuw et al. 2003; Finch 2010; Graham 2009; Osborne 2013).

There are many methodological and theoretical approaches for eliminating or handling missing data. Deletion methods are by far the most common, especially in the social sciences (Altman and Bland 2007; Harel et al. 2008; King et al. 1998). Case-wise or list-wise deletion involves removing entire cases or individuals from a dataset for all

analyses if any values are missing. Pairwise deletion involves removing individuals with missing data on a test-by-test basis, creating slightly different samples for each analysis in order to maximize the available data (Allison 2001; Howell 2007; Little and Rubin 2002; Quintero and LeBoulluec 2018). Imputation involves inserting plausible values in place of missing variables (Allison 2001; McKnight et al. 2007; Schafer and Graham 2002). A wide variety of imputation methods exist, the simplest being mean imputation, in which the variable mean is substituted for a missing value. Other, more complex methods include maximum likelihood, stochastic regression, and multiple imputation. Numerous books and articles exist describing specific imputation techniques, their statistical assumptions, advantages, and disadvantages (De Waal et al. 2011; Finch 2010; Graham 2012; McKnight et al. 2007; Musil et al. 2002; Quintero and LeBoulluec 2018; Schafer and Graham 2002; Van Buuren 2018a).

Materials and Methods

The objective of this literature review is to determine if there are commonly used methods for handling missing data in bioarchaeology, whether these methods vary by bioarchaeological subtopic, and if there is any variation in methods and treatment over time.

Articles reporting human skeletal elements, mummified remains, or materials derived from human remains (i.e. dental casts) were compiled from the last 10 years of four major anthropology journals: American Journal of Physical Anthropology (2011-2020), Bioarchaeology International (2017-2020), International Journal of Paleopathology (2011-2020), and International Journal of Osteoarchaeology (2011-

2020). Bioarchaeology International began in 2017, therefore only the most recent four years are included through volume 4 number 1, which was the most recent issue available at the time of the current study. Research articles and reports were included; commentaries, literature reviews, book reviews or annual meeting programs were excluded. Case studies, osteobiographies, and differential diagnoses were omitted, as this investigation focuses on population-level studies. Articles with very small samples sizes tended to present individual osteobiographies, while those with larger samples more often analyzed the individuals using a population approach. Therefore, publications reporting a sample size of fewer than 10 individuals were eliminated. In choosing to focus upon bioarchaeology, we excluded paleoanthropology and forensic anthropology by including articles studying materials dating to the Holocene (~10kya) through approximately 50 years ago. The aim was to stay strictly within the purview of bioarchaeology, therefore papers comparing anatomically modern humans to primates or other hominins were also excluded. This resulted in approximately 1000 articles (see Figure 1 for literature review flowchart).

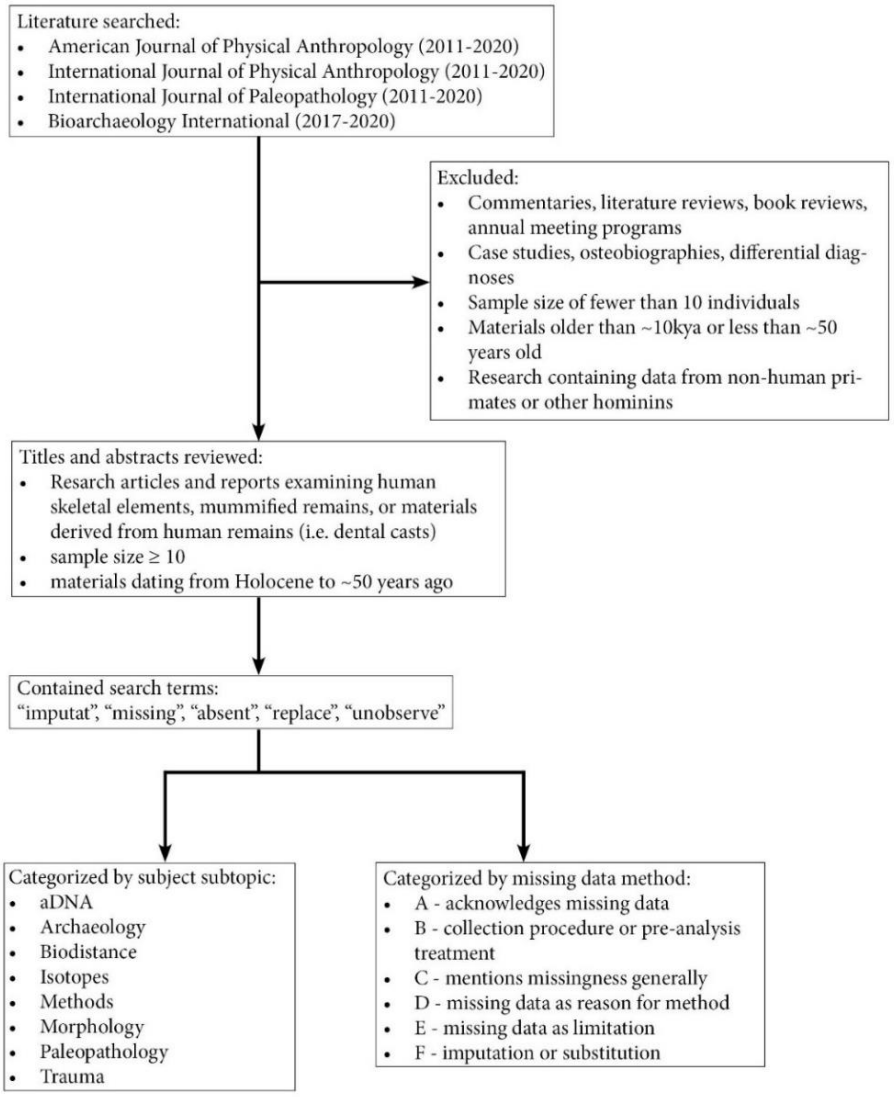
Each article was searched for the following terms: “missing,” “absent,” “imputat,” “replace,” and “unobserv.” Articles that employed any of these words in the context of missing data were compiled for further analysis by the first author. Note that these five terms did not necessarily capture every instance of missing data.

An original goal of this review was to catalog the frequency of specific procedures used during data collection (e.g. antimere substitution) and pre-analysis data treatments (e.g. case deletion, imputation). However, there was a lack of consistency in

the language authors used to describe their methods, how they conceptualized their missing data, where in the article missing data were addressed, and whether this

Figure 1.

Literature Review Flow Chart.



information was included in the publication. Literature reviews of missing data in other disciplines have experienced similar difficulties (Klebanoff and Cole 2008; Lang and Little 2018; Peugh and Enders 2004; Powney et al. 2014). As a result, the research aim shifted to explore broader patterns in how bioarchaeological researchers engage with missing data, ranging from data collection procedures, theoretical considerations, and discussions of the impact of missing data. How missing data were discussed was therefore categorized according to the following six general missing data methods (Table 1).

A: The authors acknowledged there were values missing from their data. They stated, for example, that "unfused epiphyses are commonly missing," or present summary data and indicate where certain data were unobservable or absent.

B: The researchers implemented procedures during data collection or pre-analysis data treatment to control for or minimize missing data. Examples included antimere substitution, excluding individuals who did not meet a minimum threshold of completeness, omitting individuals/elements with damage or pathology, or creating an index in which variable categories are collapsed to optimize available data.

C: The article discussed missing data generally as a concern – usually in the introduction or in the conclusion – but not directly related to the study sample. For example, "Traditionally, anthropologists have relied on morphological or metric criteria for sex determination, but none of these approaches are 100% accurate, especially when skeletons are incomplete and more sexually dimorphic bones, like the innominate, are *absent* or are very fragmented" (Garcia 2012, p. 361).

D: The article mentioned the presence of missing data as a reason for choosing a specific statistical method or as an important aspect of the method chosen. For example, numerous studies justified their use of mean measure of divergence as it can handle large amounts of missing data (e.g. Ragsdale and Edgar 2015).

Table 1.

Six Missing Data Methods

Category	Explanation
A	• Acknowledges missing data in the sample • e.g. "unfused epiphyses were commonly missing"
B	• Uses a collection procedure or pre-analysis data treatment to control for or minimize missing data • e.g. substituting right for left • e.g. excluding individuals who may be missing certain skeletal elements
C	• Mentions missingness in intro/conclusion generally as a concern or limitation • e.g. "Traditionally, anthropologists have relied on morphological or metric criteria for sex determination, but none of these approaches are 100% accurate, especially when skeletons are incomplete and more sexually dimorphic bones, like the innominate, are *absent* or are very fragmented" (Garcia p. 361 2012; IJOA)
D	• Mentions missing data as a reason for choosing a specific statistical method or as an important aspect of the method chosen
E	• Mentions missing data as a potential limitation for their results • e.g. renders the sample not entirely representative or limits statistical power
F	• Performs imputation or substitution for missing data • e.g. linear regression, mean replacement

E: The article cited missing data as a potential limitation for the results and conclusions. For example, the authors discussed how missing data may have reduced the statistical power to detect meaningful differences or how patterns of missingness biased the skeletal sample causing it to be unrepresentative of the original population.

F: The study used imputation to replace missing data with statistically generated values. A single article could be assigned to more than one missing data method category. For instance, it was common for articles that performed some type of statistical imputation (F) to first use a method such as antimere substitution (B) to minimize missing data and also state that their statistical method allowed missing data (D).

Each article was further categorized into one of eight subject subtopics according to the paper's main research question (Table 2). Topics within bioarchaeology have preferred analytical methods, unique types of data, and draw from different non-anthropological fields to inform their methods and theory. Examining how these topics variously handle missing data provides insight into broader patterns within the field. **Pathology** articles included those studying health and disease, paleoepidemiology, musculoskeletal markers, dental wear, and cranial and dental modification. Articles categorized under **morphology** included studies of tooth shape, stature, limb and cranial shape (when not used for biodistance studies). **Methods** articles had the goal of creating or testing a method such as age estimation or statistics; they have employed morphology or musculoskeletal markers but the focus of the paper was on the method. For example Stojanowski and Hubbard (2017) evaluated "what variables and methods best identify known relatives within [a] sample (p. 814)" in biological distance analyses. Since the

Table 2.

Eight Bioarchaeological Subtopics

Category	Explanation
Pathology	Health and disease, paleoepidemiology, musculoskeletal markers, cranial and dental modification, dental wear
Morphology	Stature (when not in framework of poor health), limb and cranial shape (when not used for biological distance), tooth shape
Methods	Creating or testing a method (e.g. aging, sexing, statistics) May use morphology or musculoskeletal markers but the focus of the paper is on the method
Biodistance	Using metric or nonmetric data to examine biological affinity
aDNA	Ancient DNA to examine migration, biological affinity
Isotopes	Using isotopes from skeletal elements to examine diet, migration, lifeways
Trauma	Skeletal trauma, warfare
Archaeology	Using bioarchaeological methods to explore an overall cultural context, or lifeway. Doing basic osteological methods to establish a context

goal of this paper was to inform and refine biodistance methodology, this paper was placed in "methods" rather than "biodistance." **Biodistance** articles used metric or nonmetric traits to examine biological affinity and migration. Similarly, papers on **ancient DNA** explored biological affinity or migration but using ancient DNA. **Isotopes** articles use isotopes from skeletal elements or preserved tissues to examine diet, migration, and past lifeways. **Trauma** studies explored skeletal trauma and past violence.

Finally, **archaeology** articles used bioarchaeological methods to explore an overall cultural context. Several articles in this category involved establishing the age and sex profiles of a new skeletal assemblage, emphasizing the importance of a new archaeological context.

Results

Of the approximately 1000 bioarchaeology articles compiled, 277 mention missing data using one of the five search terms. A total of 142 were from the American Journal of Physical Anthropology, 93 from the International Journal of Osteoarchaeology, 32 from International Journal of Paleopathology, and 10 from Bioarchaeology International. The number of articles per year remained relatively consistent, ranging between 23-33 articles per year and averaging 27.7 per year. Nine articles could not be meaningfully categorized into a single subject and were thus placed into two categories and double counted. For example, Redfern et al. (2017) examined the association between multiple skeletal trauma and health status; it was therefore placed in both the trauma and pathology categories. The other 723 articles excluded from further analysis had study designs that discussed missingness in terms other than the five selected, did not have missing data, or did not disclose the presence of missing data. It would not be appropriate to generate summary statistics using the full 1000, therefore the following results will focus on 277 scorable articles.

Overall, the most common missing data method found was B. A total of 137 articles (49.5%) employed a technique during data collection or data cleaning to limit missing data (Table 3). Note that due to double counting eight articles and because a single article

may have been tallied in multiple missingness categories the column sums in table 3 will not add up to 277. The most frequently used technique was antimere substitution (i.e. substituting the right element if the left was damaged or absent) or excluding individuals that failed to meet a minimum number of necessary observable elements. The second most common missing data method was A (n=116, 41.9%), which indicated the presence of missing data in the study. Only 22 articles employed missing data method D. Notably, few articles used missing data methods C (n=14) and E (n=25). A total of 44 articles used missing data method F (imputation). Table 3 also summarizes the number of articles per bioarchaeological subject topic. The majority are in pathology (n=126), followed by morphology (n=68) and methods (n=58) while the fewest are from isotopes (n=15) and ancient DNA (n=9).

Table 3.

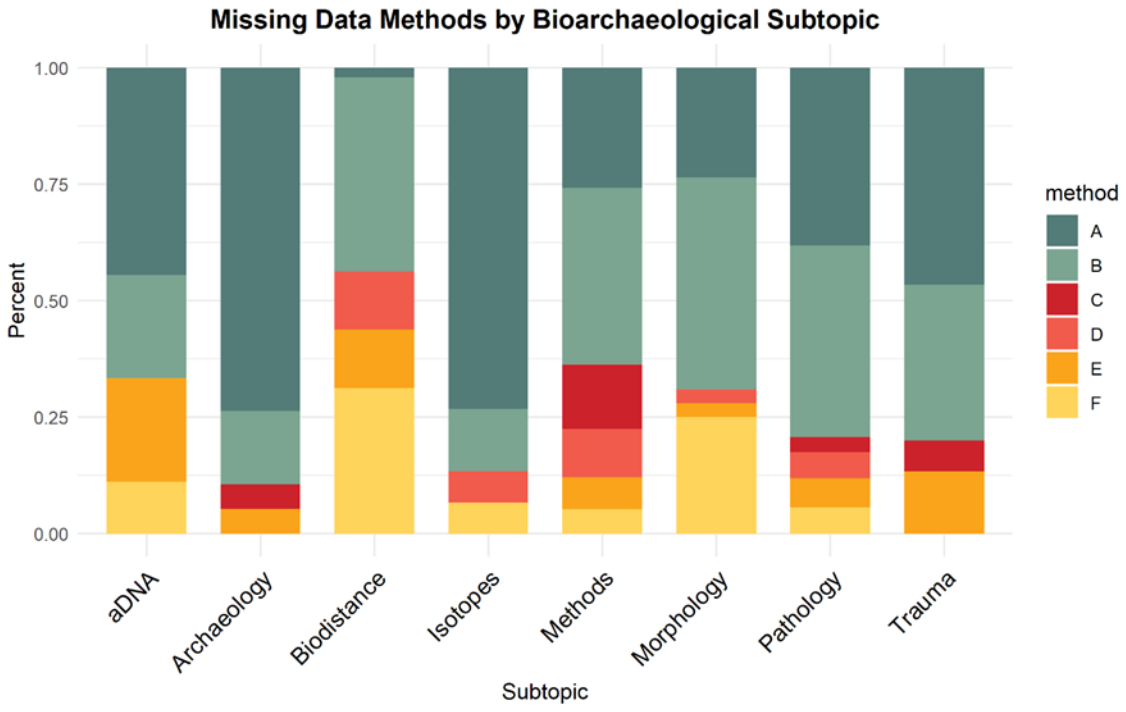
Summary Literature Review Results

	A	**B**	**C**	**D**	**E**	**F**	**total**
aDNA	4	2	0	0	2	1	9
Archaeology	14	3	1	0	1	0	19
Biodistance	1	20	0	6	6	15	48
Isotopes	11	2	0	1	0	1	15
Methods	15	22	8	6	4	3	58
morphology	16	31	0	2	2	17	68
Pathology	48	52	4	7	8	7	126
Trauma	7	5	1	0	2	0	15
total	116	137	14	22	25	44	

Figure 2 shows the percentage of each missing data method by subject topic. Given that the International Journal of Paleopathology and Bioarchaeology International focus heavily on skeletal pathology it is unsurprising there are so many articles in this area. The vast majority (80%) of pathology articles utilized missing data methods A or B – the least rigorous. Despite the large number of articles missing data in relation to their collection procedures or indicating that there are missing data in their samples, only 5.6% mentioned missing data as a potential problem or limitation for their results. Morphology contains the second greatest number of articles using a missing data method (n=68). Not quite half employed missing data method B. Morphology also has the second largest

Figure 2.

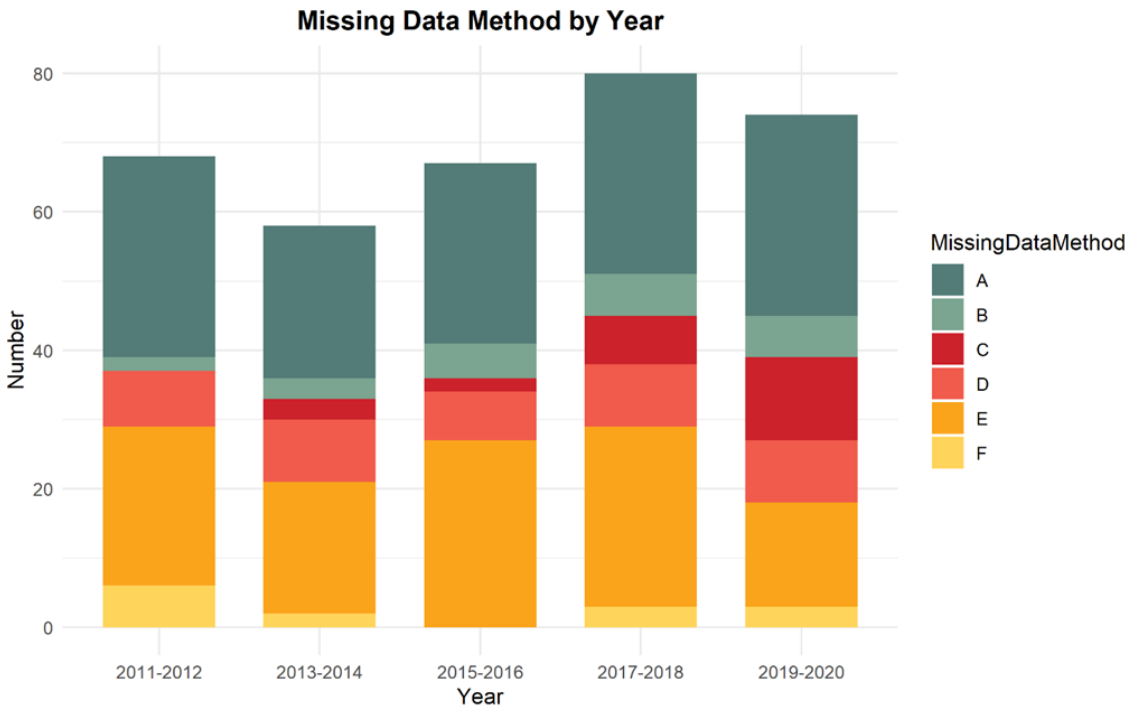
Barplot Showing Percentage of Missing Data Method by Subtopic



percentage (25%) of articles doing imputation. On the other hand, comparatively few articles of this topic discussed missing data as a potential concern or a limitation for their results (E). A total of 58 articles were categorized into the methods subfield. Most employed missing data methods A and B. Methods papers also had the greatest percentage (11%) of articles that considered the ability to handle missing data as an important aspect of their statistical methods selection (D) and papers falling in missing data method A (14%) – discussing missingness generally as a concern or limitation. A total of 48 biodistance articles used a missing data method, about half of which used collection procedure to minimize missing data (B). Compared to the other subjects, a greater proportion of the biodistance articles fell into missingness category D (missing data as a reason for choosing a specific statistical method) or F (imputation). Trauma was among the smallest subject group (n=15) and displayed the lowest diversity in the techniques for handling missing data, with over 40% used method A. Only 15 articles that employed a missing data method could be categorized as "isotopes," 11 of which acknowledged missing data (A). A single isotopes article used imputation (Allen et al. 2020); however, this article falls into two subject categories, the other being biodistance. Finally, only 9 articles categorized into the aDNA topic, most of which detail the presence of missing data (A) or mention missing data as a limitation for their results (E). Figure 3 shows how patterns in missing data methods have varied over time. The number of articles in each missingness category remains relatively constant over the past 10 years – indicating very little temporal change. There is a slight increase in the number of articles that discussed how missing data in the samples was a limitation for their results

Figure 3.

Trends in the Usage Of Missing Data Methods Over Time



and interpretations (E). Finally, only four articles (Falys and Prangle 2015; Luna 2019; Niinimäki 2012; Niinimäki and Baiges Sotos 2013) stated that there were no missing data in their sample or that missing data treatments were unnecessary. It is possible that many of the 723 articles also had no missing data but did not mention it in the text.

Discussion

This literature review explores how bioarchaeologists handle missing data by reviewing published articles from the last ten years from four major journals. In general,

we find that the most prevalent missing data methods were those deemed the least statistically or theoretically rigorous (A and B). The most frequent method employed a collection procedure to limit missingness such as antimere substitution or excluding individuals who fail to meet a minimum threshold of completeness (B). The ubiquity this method reveals that these are the base procedures for handling missing data in bioarchaeology. Indeed, substituting the right element when the left is unavailable is established in Standards for Data Collection from Human Skeletal Remains (Buikstra and Ubelaker 1994) for cranial, postcranial, and dental measurements. Furthermore, these results suggest that missing data is anticipated and planned for in bioarchaeological studies despite a lack of discussion of missing data in the field. Few authors explicitly considered missing data as an important aspect of a statistical analyses (D), indicating that analytical approaches are infrequently dictated by missing data. Examination of the impact of missing data was rare as were wider discussions of the statistical and interpretive limitations imposed by missing data – particularly given the number of articles explicitly pointing out missing values in their skeletal data.

Each bioarchaeological topic has its own preferred techniques for conceptualizing and handling missing data. For example, pathology and trauma articles engage with missing data in the least rigorous ways. Both areas tend to focus on highly contextualized patterns of pathology and trauma and their data are more likely to be counts of particular lesions or injuries. General descriptive statistics and univariate analyses may be seen as appropriate in these cases and more sophisticated techniques to handle missing data viewed as unnecessary.

Biodistance and morphology – areas which tend to be the most statistically advanced in bioarchaeology – used the most rigorous approaches for missing data. These articles more often explicitly used statistical methods that allow missing data and were more cognizant of analytical methods that can be biased by missingness. This may be because multivariate statistics, such as would be used in biodistance or morphological analyses, do not permit missing data – causing scholars in these areas to deal with their missing data on a statistically more sophisticated level.

Despite its frequent use in other fields, imputation of missing data is uncommon in bioarchaeology. It was expected that the number of articles using imputation would increase over time as the computational power of standard laptops has grown and statistical software packages for imputation have become widely available. However, the number of articles imputing missing data remained constant over the past 10 years.

Two articles had the explicit goal of examining or developing missing data methods in bioarchaeology and were thus excluded from analysis. Auerbach (2011) developed mathematical formulae for estimating vertebral heights, femoral and tibial lengths, and talocalcaneal height when skeletal elements were absent, as previous methods did not facilitate handling missing data. Auerbach's article represents one of the few instances of a protocol devised specifically to minimize obstacles due to missing skeletal data that does not involve deletion. Additional work in this vein would permit researchers not only to maximize the use of all available information, but also allow greater exploitation of the information contained in highly fragmentary and/or commingled assemblages. For example, formulae could be developed that estimate

bucco-lingual or mesio-distal dental measurements for missing or damaged teeth given measurements of the available teeth. Such techniques could be broadened beyond continuous data with the development of models that predict the probable sex estimation score of missing elements (e.g. glabella) given the recorded scores of available elements within a population context. Auerbach (2011) also draws the reader's attention to the importance of handling missing data properly rather than ignoring them, explaining how patterns of missingness in skeletal samples are usually assumed to be missing at random, when in fact biases in preservation may cause data to be missing not at random, generating a sample that is unrepresentative of the original population.

Stojanowski and Johnson (2015) examined how dental wear influences the scoring of dental non-metric traits – in particular how higher levels of wear may result in trait downgrading. They found notable inconsistencies in when observers scored a dental non-metric trait versus when they coded it as missing or unobservable due to dental attrition, a bias that had the potential to support inaccurate interpretations about global dental patterns and population movement. Their conclusions show how profoundly missing data can affect inferences about the past when not handled adequately.

The paucity of articles with the stated goal of exploring missing data suggests that bioarchaeology is not critically engaging with missing data methods or theory – a concern given the ubiquity of missing data in the field. The lack of engagement with missing data indicates that researchers are not considering how missing data may bias statistical analyses and ensuing results and conclusions. This study shows that the most common method for dealing with missing data is category B (antimere substitution or

deletion). Though pairwise and case-wise deletion are among the most simple methods for dealing with missing data, their use relies on the most conservative assumptions: less than 5% total missingness and that missingness is completely random (Graham 2009; Little and Rubin 2002). When the patterns of missing data do not meet these criteria and pairwise or case-wise deletion are employed, the results can be skewed, presenting an incomplete and biased outcome (McKnight et al. 2007). Bioarchaeological data are likely to be MNAR and therefore fail the requirements for pairwise and case-wise deletion, though this has not been explored in detail. More porous pathological skeletal elements are less likely to preserve over time or survive excavation; they may be separated from the rest of the individual and placed in an entirely different collection specializing in pathology. Smaller, lighter, and more fragile bones such as those belonging to children or females may be less likely to be recovered during excavation (Bello et al. 2006; Gordon and Buikstra 1981; Holt and Benfer 2000; Mays 1992; Stojanowski et al. 2002; Walker et al. 1988). Such biases are an inherent and yet unknowable part of bioarchaeological data.

Based on the findings from this literature review, it is not standard practice in bioarchaeology to critically examine patterns of missingness in the data during the study design phase or in publication. The management of missing data in bioarchaeology has important implications for the scientific rigor of the research and the future of the field. Missing data can substantially decrease sample sizes, limiting the power of the study to detect meaningful differences between groups (Graham 2009; Kang 2013; McKnight et al. 2007; Peng et al. 2006). Most bioarchaeological studies do not perform power analyses so it is unclear whether those with small sample sizes are capable of producing

meaningful results. Failure to disclose missing data can also create uncertainty in a research article; the number of individuals listed in one section may not match the number presented in another, if pairwise deletion were performed but not described in the methods.

Furthermore, missing data have a significant impact on what statistical analyses are possible (Peng et al. 2006). Multivariate methods incorporate multiple variables in a single test, allowing the researcher not only to control for but also investigate the interactions between many variables simultaneously. These methods facilitate a more realistic understanding of how study outcomes are influenced by the interaction of biological, social, and material variables. Most multivariate statistics methods, however, such as principle components analysis, discriminant analysis, or generalized linear models, do not permit missing data – potentially causing researchers to gravitate to more simple analytical methods and neglect more complex statistics that could reveal more nuanced patterns in bioarchaeological data.

More advanced statistical methods can be excellent tools for bioarchaeologists to address some of the concerns raised by Wood et al. (1992) in the osteological paradox. The use of simple statistics such as lesion counts and frequencies to infer past population health will overestimate the prevalence of skeletal lesions in a population, providing a biased and false understanding of past health. Elementary statistical tests also rely on straightforward – and potentially erroneous – assumptions about the relationship between lesions and individual health and mortality. Advanced analytical methods allow researchers to investigate ancient health without requiring such assumptions. Survival

and hazards models, for instance, have been used successfully to investigate sources of increased morbidity and mortality in the past, without presupposing that skeletal lesions are indicative of poor health (DeWitte 2014; DeWitte 2015; DeWitte et al. 2013; Godde et al. 2020; Redfern and DeWitte 2011).

Despite an abundance of approaches for handling missing data, they are rarely discussed in most fields and often go unreported (Harel et al. 2008; Lang and Little 2018; Powney et al. 2014; Sylvestre 2011; Wood et al. 2004). In many ways, there is an unrecognized taboo against discussing missing data – the assumption being that a study with missing data was badly designed and poorly executed (Van Buuren 2018b). To avoid such censure, authors often gloss-over areas of their sample with missing data, sometimes eliminating entire variables and sub-groups behind-the-scenes. Missing data have been described by researchers as a "dirty little secret" (Peugh and Enders 2004; p. 540), and may be widely regarded as "a nuisance that is best hidden" (Burton and Altman 2004 p. 6). In reality, "contrary to the old adage that the best solution to missing data is not to have them, there are times when building missing data into the overall measurement design is the best use of limited resources" (Graham 2009, p. 551). Focusing only on complete datasets privileges certain contexts such as those with better preservation (Auerbach 2011; Holt and Benfer 2000). Incorporating, exploring, and working with missing data provides a more holistic and less biased understanding of all the data and maximizes a researcher's time, energy, and finances.

Missing data are critical component of the data planning, collection, and analysis processes and should be reported and discussed. Upon publication, however, missing data

are often concealed or undisclosed. Small details such as pre-analysis data treatments and excluded samples are often removed due to word limits. Including this information facilitates study repeatability and transparency, particularly for students and early career researchers who may be unfamiliar with the standard protocols. Including information on the cause and patterns of missing data in the sample informs the reader of important biases in recovery, preservation, and curation, an understanding of which is essential for a baseline assumption in much bioarchaeological research: the study sample is representative of the population. Clarity in the study design and execution helps the authors, readers, and reviewers evaluate the research and assess the interpretations. Furthermore, a clear understanding of the research design and sample composition is essential if the study is to be included in meta-analyses (Von Elm et al. 2007).

Numerous authors from other fields have recognized systemic inconsistencies in missing data reporting and created guidelines to improve the rigor of research design and publishing in their respective areas (Akl et al. 2015; Burton and Altman 2004; Jeličić et al. 2009; Wilkinson 1999). Following their example, we propose several recommendations to increase bioarchaeological engagement with missing data and transparency in study design. (1) Bioarchaeologists should publish detailed descriptions of data collection procedures, detailing how individuals were selected for inclusion. (2) Researchers should document specific causes of missing data (e.g. is the tooth missing, broken, worn, unerupted, etc.) rather than only recording "NA." (3) Publications should include any pre-analysis data treatments or data cleaning, as well as justifications for these decisions. (4) Authors should disclose when missing data are present – or if there

are no missing data – and provide exact numbers of individuals and variables excluded for each analysis. (5) Discussion sections should describe how missing data impacts sample representativeness and research findings. (6) When appropriate, implementation of Little's MCAR test (Little 1988) can reveal patterns in missing data and indicate when missing data may be problematic. Numerous statistical tutorials and packages for this test exist for R, SPSS, and Stata. According to the results of this research, imputation of missing data is underused in bioarchaeology but has great potential for future use. We recommend exploring imputation of various kinds of bioarchaeological data and ascertaining which methods are appropriate. Greater collaboration with statisticians will be beneficial in this regard.

This study has several limitations. Four of the most well-known journals in bioarchaeology were chosen for analysis, yet it is possible that papers engaging in more critical discussions of missing data theory and procedures to handle missing data may be published in more methods-oriented journals. As mentioned above, articles included in our analysis were identified using one of the five keywords. Those that discussed missing data without using one of the keywords were not included; our results may therefore underestimate certain types of missing data methods. We provide an overview of missing data in bioarchaeology only and do not provide comparative data from other areas. Further research of missing data in other fields in anthropology such as archaeology or evolutionary anthropology would provide a greater understanding of how anthropologists as a whole handle missing data and provide guidance for future bioarchaeologists.

Conclusion

Overall, the results of this study suggest bioarchaeology lacks a strong foundation in missing data methods and theory. Theoretically and statistically rigorous approaches for handling missing data are infrequently used while the least sophisticated methods for treating missing data are by far the most prevalent. We find that certain bioarchaeological subfields employ favored techniques for missing data, and that patterns in missing data methods have remained relatively constant over the past ten years. Researchers need to improve their awareness of missing data in their samples and appropriate methods for managing missing data. Small steps such as clearly reporting pre-analysis data treatments and patterns of missingness in publications, discussing the biases and limitations missing data presents, and exploring alternative methods such as imputation can address fundamental concerns in the field and improve the statistical rigor of our analyses.

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CHAPTER 3

MISSING DATA IN BIOARCHAEOLOGY II: A TEST OF MULTIPLE IMPUTATION

Missing data are ubiquitous in the social sciences. Bioarchaeological data may be lost due to myriad factors including differential preservation, selective excavation, post-mortem damage, pathology, transcription errors or computer crashes. When not handled properly, missing values can introduce substantial bias into a dataset, leading to erroneous study results and flawed interpretations. Furthermore, most statistical tests require datasets with no missing data. Despite the importance of missing data, their treatment is often unreported in the social sciences, including bioarchaeology. If they are addressed, the least statistically and theoretically rigorous methods are generally used (see previous chapter). The goal of this paper is to explore techniques for handling missing data, focusing on the use of imputation to manage missing bioarchaeology and paleopathology data. Our target audience includes anthropologists who have basic statistical and programming knowledge, but they need not be statistical experts; methods are explained conceptually rather than mathematically. This paper has two sections. Part 1 details background information on data types, categories of missing data, deletion and imputation methods, and the use of imputation in the social sciences. Part 2 focuses on bioarchaeology and paleopathology, discussing special challenges with handling these data and concludes with a case study test of eight methods for handling missing ordinal and continuous paleopathology data.

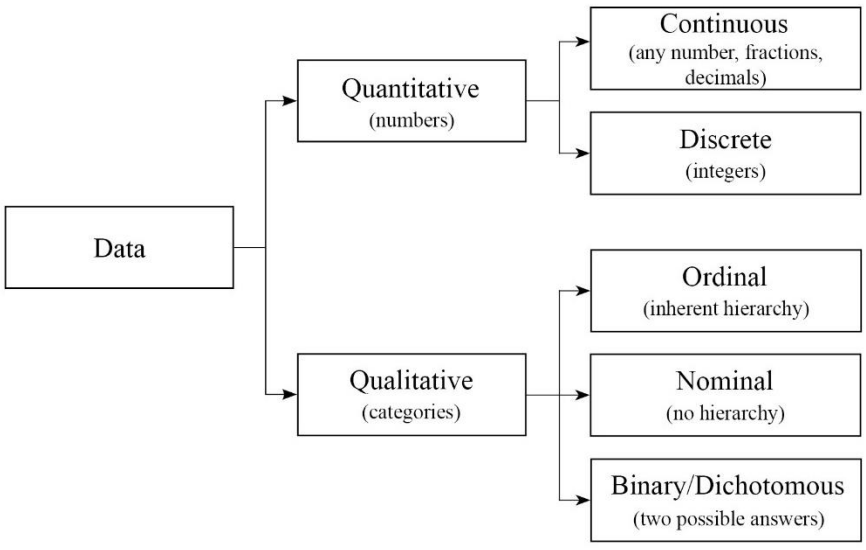
Part I: Background

Data Types

Researchers must be aware of the data classes involved in their analyses to ensure consistent data recording and the application of appropriate statistical analysis. Data types determine appropriate techniques for managing missing data. Data can be partitioned into two broad categories: quantitative and qualitative (figure 4). Quantitative data are numerical and can only be expressed using numbers (Quintero and LeBoulluec 2018; Ranganathan and Gogtay 2019). Qualitative data are categorical, generally describing

Figure 4.

Flow Chart Showing Classes of Data.



some aspect or characteristic of the data, and cannot be expressed by numbers in a way that is mathematically meaningful (Ranganathan and Gogtay 2019; Verma 2016). There are two subtypes of quantitative data: continuous and discrete. Continuous data may be any number – including decimals and fractions – and can be continuously subdivided into smaller units (Quintero and LeBoulluec 2018). Femoral length is an example of continuous data; a meter can be divided into centimeters, millimeters, and so on and can be expressed as a fraction or with decimals. Note that simply because a caliper only displays 1 decimal place does not mean the data are not continuous; it means the measurement tool is not capable of capturing the full data. Discrete data can only be expressed in whole integers that are mathematically meaningful (King and Eckersley 2019; Ranganathan and Gogtay 2019) and cannot be subdivided into smaller parts. For example, the number of patients will be in whole integers only (i.e., 2.5 patients is not a valid response). There are three subtypes of qualitative data: ordinal, nominal, and binary. Ordinal data are categorical data with an inherent hierarchy; the data can be ranked but neither the value of that rank, nor the differences between the ranks can be measured or mathematically expressed (King and Eckersley 2019; Shreffler and Huecker 2020; Verma 2016). For example, the estimated age of a person could be "young adult," "middle adult," or "old adult." There is a meaningful order to these categories, but the differences between them cannot be conveyed with numbers. Nominal data are categorical data that have no inherent order such as sex, country, or species (King and Eckersley 2019; Quintero and LeBoulluec 2018; Shreffler and Huecker 2020). Binary data are categorical

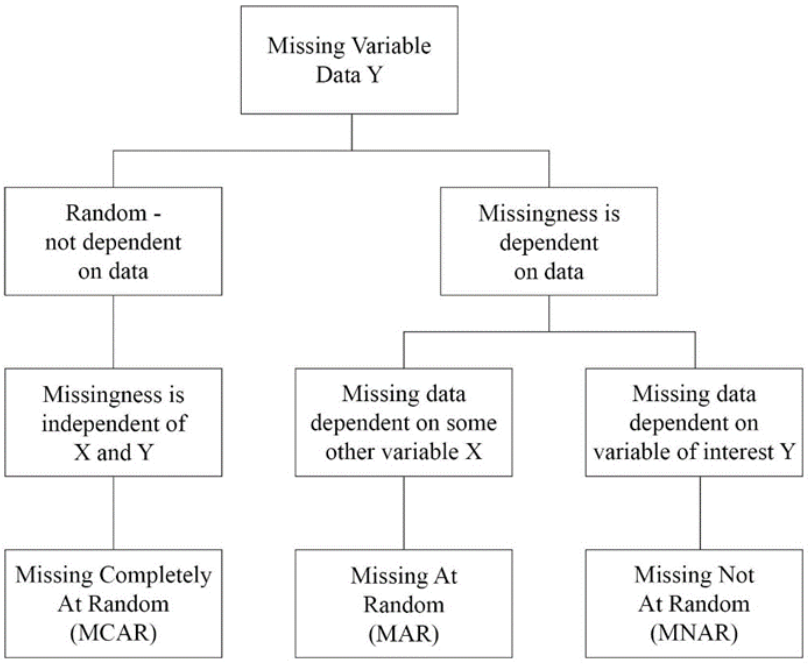
data that have only two possible answers (e.g., Yes/No, Present/Absent) and can be ordinal or nominal.

Classes of Missing Data

The best way to manage missing data will be determined by how and why the data are missing. Rubin (1976) described three main categories of missing data: missing completely at random, missing at random, and missing not at random (Figure 5). Data are described as missing completely at random (MCAR) when the reason the data are missing is unrelated to the pattern of missingness or any other variables of interest in the data set (Graham et al. 1997; Pepinsky 2018; Quintero and LeBoulluec 2018). If we have

Figure 5.

Rubin's Three Categories of Missing Data



collected two variables (X and Y), data are MCAR "if the probability of missing data on Y is unrelated to the value of Y itself or to the values of any other variables in the data set" (Allison, 2001; p. 3). For example, in a dataset containing information on age (X) and femoral length (Y), data on femoral length would be MCAR if their missingness depends on something other than age or femoral length.

The second category is missing at random (MAR). Data are missing at random if the pattern of missingness depends on some variable in the dataset that is not the variable of interest (Graham et al. 2007; Pepinsky 2018; Quintero and LeBoulluec 2018). Data are MAR if the probability of missing data on Y depends on the variable X but not on Y (Allison 2001). Using the above example, femoral length (Y) data would be missing at random if the missingness depended on age (X) but not on femoral length (Y).

The third category of missing data is missing not at random (MNAR), also called not missing at random (NMAR). Data are described as MNAR if the probability of missingness depends on the missing data; i.e. if the probability of missing data on Y depends on Y (Pepinsky 2018; Quintero and LeBoulluec 2018). For example, data missing under the variable femoral length (Y) would be MNAR if the data are missing because of femoral length (Y). In practice, this may be because the researcher opted to exclude individuals with unusually short or long femurs, or because only "normal" femurs were accessioned to the museum collection. MNAR is most concerning to researchers as it will likely introduce bias into the dataset. MNAR has also been referred to as *inaccessible* missingness as both the cause and the probability of missingness is unknown (Graham 2012; van Buuren 2018). In bioarchaeology (and paleopathology in

particular), missing data likely fall into a combination of all three categories and it may be impossible to discern which variables belong in which category (Morris et al. 2014; Myers 2011).

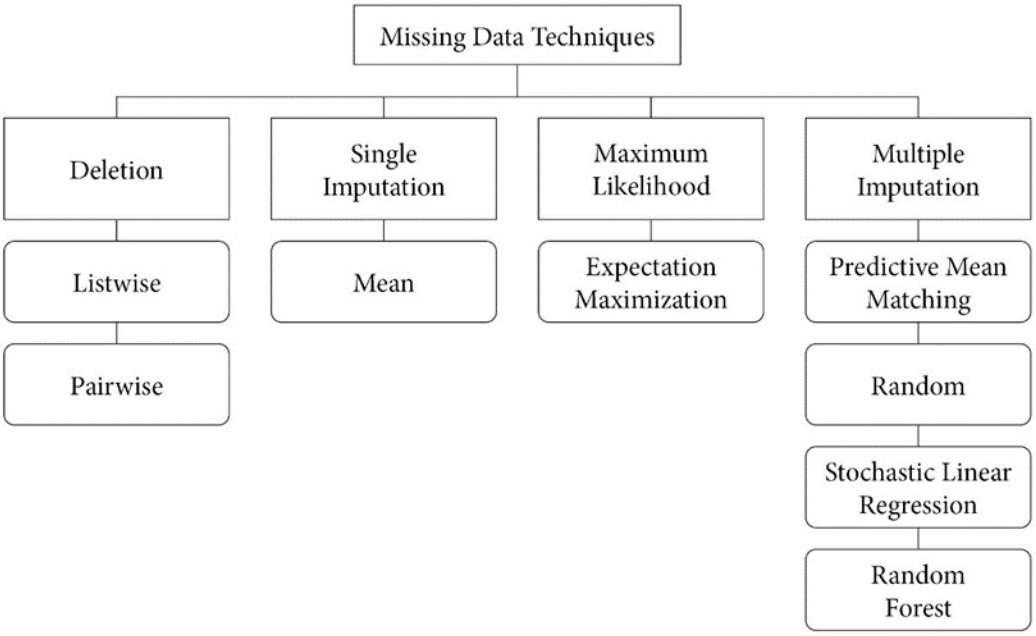
Deletion and Imputation Methods

Most statistical analyses do not permit missing data. Therefore, there is an abundance of techniques for handling missing data, including removing individuals or variables with missing values, or inserting plausible values in place of missing values. Selected, common methods are described below (see figure 6).

Listwise deletion (aka case-wise deletion) involves the removal of an individual and all its data – an entire row in a spreadsheet – if any data for that individual are missing (Allison 2001; Graham 2012; van Buuren 2018). This is the default method employed by statistical software programs SAS, SPSS, and Stata (van Buuren 2018). Listwise deletion has the advantage of being easy to understand, simple to execute, and does not require advanced statistical knowledge or software (Allison 2001; Meeyai 2016). It creates a complete dataset that allows one to proceed with statistical analysis (Baraldi and Enders 2010). If, however, the amount of missing data is even moderate, listwise deletion can result in an enormous decrease in sample size and subsequent loss of statistical power (Baraldi and Enders 2010; Graham 2012). The amount of missing data may be so great that an entire variable will be deleted. If the data are not MCAR, listwise deletion can introduce substantial bias into final p-values and confidence intervals (Allison 2001; Baraldi and Enders 2010). Many statisticians consider listwise deletion to

Figure 6.

Missing Data Methods Discussed in Chapter



be the worst of all possible techniques for handling missing data (Allison 2001; King et al. 1998; van Buuren 2018; Wilkinson 1999).

Pairwise Deletion (aka available case analysis) involves dropping cases or individuals based on variables present for each analysis (Allison 2001; Graham 2012; van Buuren 2018). For example, an individual missing a periodontal disease score will be deleted from any analyses requiring periodontal disease as a variable but included in other tests. This approach is easy to perform and has the benefit of making use of all available data, greatly maximizing the sample size. On the other hand, each analysis uses a slightly different sample, generating results that may not be comparable or can even

disagree (Myers 2011; Newman 2014; van Ginkel et al. 2020). Published tables may list different sample sizes, which can be confusing and misleading if not appropriately explained. Repeatedly running similar analyses on overlapping samples raises concerns of alpha inflation. If the data are not MCAR, pairwise deletion can create bias in the parameter estimates (Allison 2001; Baraldi and Enders 2010). Furthermore, as each analysis is based on a slightly different sample, there is no straightforward procedure for calculating the standard error for the entire sample (Graham 2012).

Imputation, defined as inserting a plausible value in place of a missing value, is an alternative to deletion methods for handling missing data (Allison 2001; Schafer 1999; Schafer and Graham 2002). Imputation is a broad term that encompasses numerous frameworks and mathematical models for producing and selecting the imputed values.

Maximum Likelihood is an imputation approach that estimates the most likely parameters (mean and standard deviation) based on the observed data. The algorithm selects values that "maximize the probability of observing what has, in fact, been observed" (Allison, 2001; p. 13).

Expectation maximization (EM) is a form of maximum likelihood imputation. This method uses a two-step iterative process. In the E-step, a missing value is imputed based on what would be expected given other values in the dataset (Dempster et al. 1977; Graham 2012; Newman 2003). In the M-step, the algorithm checks whether the new value has the highest probability of being a good fit with the rest of data. If not, the process begins again, imputing a more likely value until all missing data have been replaced with the most likely values (Musil et al. 2002). Expectation maximization

procedures generally perform better than mean imputation or deletion methods (Nelwamondo et al. 2007). One potential drawback to expectation maximization is that it produces standard errors that may be narrower than those of the true data (Musil et al. 2002).

Single imputation replaces a missing value with a single substitute value, whereas *multiple imputation* replaces a single missing value with multiple possible values drawn from a distribution. Instead of selecting a single value to impute and hoping that it is the best, multiple values reflecting the uncertainty and variation in imputing unknown values (Allison 2000; Finch 2010; Little and Rubin 2002; van Buuren 2018).

The process of multiple imputation involves three main steps (Graham 2012). First, the data are imputed, creating many imputed datasets where the number of imputed datasets is expressed by the variable *m*. The exact mathematical approach for generating values to be substituted for the missing values can be performed in a variety of ways (e.g., regression, random forest). The *m* imputed datasets will differ slightly as the imputed values will all be different, "reflecting our uncertainty about what to impute" (van Buuren, 2018; p. 20). Second, each of the *m* datasets are analyzed separately using the desired statistical analysis. If the original research design required a logistic regression, the regression would be performed on each of the *m* datasets, producing *m* coefficients, standard errors, and p-values. Third, the *m* coefficients, standard errors, and p-values are combined into a single coefficient, a single standard error, and a single p-value using Rubin's Rules (Rubin 1987). Rubin's rules are a set of equations for properly pooling parameter estimates. While the researcher may be tempted to switch steps two

and three, thus pooling the imputed datasets and analyzing the single pooled dataset, this violates Rubin's Rules. Pooling the estimates too early eliminates the variation multiple imputation introduces into the datasets.

Mean Replacement is a form of single imputation that computes the mean of each variable and substitutes the mean for each missing data point (Little and Rubin 2002). It has the benefit of being easy to understand and implement but will decrease the variance of the sample, causing large amounts of missing data to have an increasingly negative impact (Osborne 2013). Mean imputation is also known to artificially increase the strength of the relationships between variables (Graham 2012; Musil et al. 2002).

Regression imputation uses the data to build a model that will predict the best values to substitute for missing data. As with standard regression procedure, a model is fitted with the variable containing the missing data set as the dependent variable. The model coefficients predict appropriate values to impute. Regression imputation is relatively easy to understand and utilizes more of the information in the dataset (Graham 2012; Musil et al. 2002). On the other hand, as the imputed values will generally lie on the regression line, the data variance will be lowered and the correlations between variables artificially inflated (Graham 2012; van Buuren 2018; Zhang 2016).

Stochastic regression imputation corrects for the over correlation between variables by adding random "noise" to the model (Newman 2003; van Buuren 2018). One way to add this noise is by randomly selecting residuals and adding that value to the prediction (Enders 2010; Little and Rubin 2002; van Buuren 2018). Stochastic regression has the advantage of being able to produce unbiased parameters when the data are MCAR

or MAR but will produce narrow standard errors (Allison 2001; Enders 2010).

Random Forest imputation uses a decision tree approach to predict the best values to impute. A bootstrapped random subset of samples is created to build multiple regression trees for each variable (Shah et al. 2014). The behavior of the data as it is run through the trees predicts the best values for the missing data. Random forest imputation is a commonly used method in epidemiology (Henriksson et al. 2016; Shah et al. 2014; Weng et al. 2019), and is capable of handling mixed data types and variable interactions (Stekhoven and Bühlmann 2012; Tang and Ishwaran 2017; Waljee et al. 2013). Random forest imputation can also be perceived as a black box technique, with little understanding of how the decision trees are being grown (Breiman 2001).

Hot deck imputation is a broad "record matching technique" in which missing values from an individual (the recipient) are replaced by observed values from a similar case (the donor) (Kaiser, 1983, p. 1). There are a variety of methods that can be used for determining what "similar" means and selecting an appropriate donor (Little and Rubin 2002). Depending on the approach used, hot deck imputation can be relatively easy to understand and execute and some forms (e.g. random, sequential, last observation carried forward) work well with categorical data (De Waal et al. 2011; Hardt et al. 2013). Since substitute values are drawn from variables already in the dataset, this approach will impute realistic values that reflect the actual data (Andridge and Little 2010; Siddique and Belin 2008). Hot deck methods are used frequently by the US Census Bureau and other governmental agencies (Andridge and Little 2010). There is, however, less evaluative information on hot deck methods (Little and Rubin 2002).

Random hot deck imputation forms a donor pool of complete cases that have other variables with values similar to those of the case with missing data. A donor is selected at random from the pool and the donor's variable is used to fill in the missing value for the recipient (Bechtel et al. 2011; De Waal et al. 2011).

Predictive mean matching is another form of hot deck imputation. In this method, a missing value is imputed by selecting an observed outcome from a case with a similar predicted mean (Bailey et al. 2020; Little 1988; Vink et al. 2014). Because predictive mean matching selects values from other donor cases within the dataset, imputed values will always fit with the observed range of values (Kleinke 2018; Vink et al. 2014). A potential disadvantage to predictive mean matching is that it may not be acceptable for use with small sample sizes as the pool of available observed outcomes with a similar case mean will be small (Kleinke 2018).

Of the imputation methods surveyed here, the authors believe that there are many advantages to multiple imputation. Under the right set of circumstances, it can produce unbiased estimates even if the data are not MCAR (Allison 2001). Once the *m* imputed datasets are created, they can be used repeatedly for any number of different analyses (Schafer and Graham 2002). Most statistical software programs, including SPSS, SAS, Stata, and R are able to perform multiple imputation. On the other hand, multiple imputation can be unwieldy, intimidating, and easy to do incorrectly. However, it is generally believed to be one of the best methods for handling missing data (Allison 2001; Graham 2012; van Buuren 2018).

How many imputations (*m*) are necessary to best estimate the parameters of interest? Technically, since the more imputations one does the more precise the estimates, it is generally better to do more. However, the higher the *m* the longer the computer will take to run the analysis and the more computational storage required. Due to these drawbacks, initial recommendations suggested that as few as 3-5 imputations were more than adequate (Schafer and Olsen 1998). As computing power and statistical software has advanced, performing large numbers of imputations is no longer a challenge. Von Hippel (2009) recommends "the number of imputations should be similar to the percentage of cases that are incomplete" (p. 278); i.e. If 30% of the data are missing, one should perform *m*=30 imputations. Graham et al. (2007) finds that low numbers of imputations can have a significant decrease in statistical power and introduce bias. They recommend that for low levels of missingness (<15%), one should perform 10-20 imputations and for higher levels of missingness (20-40%) one should perform at least 40 imputations to preserve a high level of statistical power.

Imputation in other fields

While missing data are a problem in nearly all fields of research, some disciplines have adopted advanced methods for handling missing data more quickly than others. A coarse examination of the literature suggests that the social and behavioral sciences have been slow to accept more computationally and statistically intensive methods such as multiple imputation or regression, whereas the natural and ecological sciences use such methods more commonly.

Many scholars in psychology, political science, sociology, and economics use imputation methods. The data missing in these studies frequently stem from surveys in which responses are missing because the respondent did not understand the question, declined to answer, or was unable to complete the survey (Krause et al. 2018). Turney (2015) examined how paternal incarceration may be a cause of food insecurity for children, using multiple imputation to impute missing survey answers on how often a child has been hungry or how often they skipped meals. Evans and Smokowski (2015) test how social capital – as measured by proxies such as social support and mental health – predicted the likelihood of intervening in school bullying. They imputed missing survey data on demographic factors such as ethnicity and religion, and responses on parental support, school satisfaction, and optimism about the future. Within the social sciences, imputation of missing variables appears to be more common in social network analyses than other fields (Huisman 2009; Krause et al. 2018), possibly because the analysis of social networks is sensitive to missing data (Huisman 2009).

Researchers in the natural and ecological sciences have adopted imputation techniques as standard for dealing with missing data. Mean imputation, multiple imputation, and random forest imputation have been used to impute a diverse suite of plant and animal traits such as leaf area, seed mass, plant height, animal body mass, litter size, diet diversity, sociality, and generation length (Bird et al. 2020; Cooke et al. 2019; Cooke et al. 2020; Grilo et al. 2020; Ordonez and Svenning 2017; Pacifici et al. 2013; Taugourdeau et al. 2014). Divíšek et al. (2018) for example, searched for patterns of traits that could be indicators of invasive plant species and imputed missing data on leaf area,

plant height, and seed weight. While investigating how certain traits relate to ecological strategies, Cooke et al. (2020) used multiple imputation to impute body mass, habitat breadth, generation length, diet, and litter/clutch size.

Imputation of missing demographic or health data is commonplace within epidemiological and clinical medical studies (Barnard and Meng 1999; Bodnar et al. 2006; Costello et al. 2014; Ferrie et al. 2005; Petersen et al. 2014; Zeka et al. 2006). Lassale et al. (2018) imputed missing body measurements, testing the association between obesity and coronary heart disease. Dam et al. (2016) used multiple imputation to impute missing values for age, education, smoking, and health status to examine whether increased alcohol use in postmenopausal women increased their risk of breast cancer while decreasing their risk of coronary heart disease.

Part II: Missing Data in Bioarchaeology and Paleopathology

Raw bioarchaeological data come in a wide variety of types including lesion counts, age ranges, continuous measurements, sex estimations, descriptions, and nonmetric trait scores. Paleopathology data have their own suite of unique characteristics that make them more challenging to analyze than data from other fields. The data are often a mix of continuous, categorical, and binary variables. Many statistical tests do not work well with categorical data or do not accept mixed data types. Unlike continuous data, categorical and binary data have a low range of possible values. For example, according to Standards for Data Collection from Human Skeletal Remains (Buikstra and Ubelaker 1994), porotic hyperostosis should be recorded as 0, 1, 2, 3, or 4 – with 0 as no expression, and 4 as the highest expression. Some of the more statistically complicated

methods for imputing missing data do not work well with such a narrow range of values. On the other hand, because of this low range, less computationally intensive methods may be successful. A randomly imputed number selected from 0-4 will be more likely to be correct than one selected from 0-100.

Another challenge with bioarchaeological data is that we regularly collect data that are MNAR, yet we fail to account for those biases in our analyses or interpretations. For example, most scoring procedures for periodontal disease code missing teeth as NA or not scorable (e.g. Kerr, 1988) . However, in cases of extreme periodontal disease, tooth loss will occur (Lindhe et al. 1983; Morelli et al. 2018; Ong 1998; Ramseier et al. 2017). Antemortem tooth loss may therefore be the highest expression of periodontal disease. Scoring teeth missing antemortem as NA introduces MNAR values, creating a biased dataset.

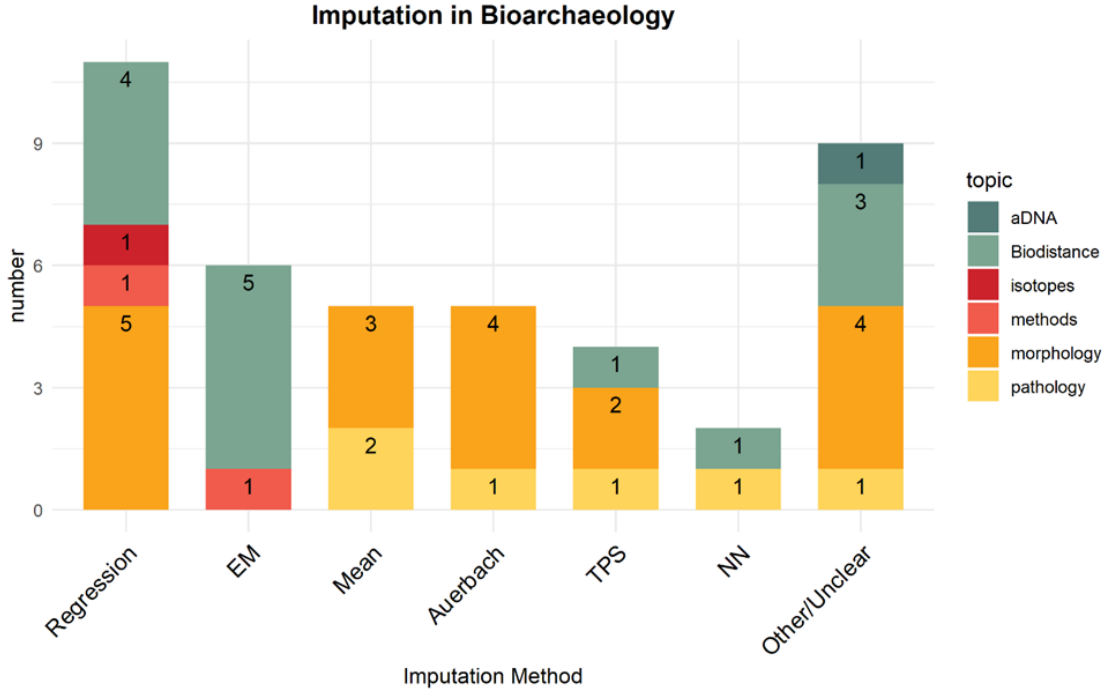
The Use of Imputation in Bioarchaeology

The previous chapter on missing data in bioarchaeology assessed how bioarchaeologists handle and report missing data. We surveyed bioarchaeology articles from 4 major anthropology journals published between 2010-2020, searching for the following terms: “absent,” “imputat,” “missing,” “unobserv,” and “replace” used in the context of missing data. The articles were categorized according to the level of statistical and theoretical rigor used to handle missing data. According to our results, only 41 articles out of 277 identified using some form of imputation to handle their missing data – most of which were biodistance or morphology studies.

Within these articles, a variety of imputation methods were employed (Figure 7). Regression imputation was the most common (n=11) including linear, multiple and PCA regression to estimate missing values. Six articles used expectation maximization – all of which were biodistance papers. Mean imputation (n=5) was also frequently used to handle missing data. Five articles used specific regression-based equations published by Auerbach (2011) and Auerbach et al. (2005) to estimate measurements of missing

Figure 7.

Barplot Showing Imputation Approaches Used by Each Bioarchaeology Subtopic.



Note. *Mean = mean; Regression = regression; EM = expectation maximization; NN = nearest neighbor; TPS = thin plate spline; Auerbach = Auerbach; Other/Unclear = other/unclear*

skeletal elements. Several geometric morphometric articles (n=4) employed thin plate spline to reconstruct missing areas. Two articles used nearest neighbor techniques for imputation of missing data. Finally, nine articles used other, less common approaches or were not specific about their statistical method. Willman et al. (2012), for example, "visually reconstruct[ed] a worn cusp tip" (p. 41). Ibáñez-Gimeno et al. (2013) imputed the median in place of missing values. Reyes-Centeno et al. (2017) imputed missing landmarks by "reflected relabeling of the bilateral homologue" (p. 272). Two others used multiple imputation, specifically the *mice* R package, but did not identify a specific statistical technique. Overall, these results show that there is a wide variety of imputation methods used in bioarchaeology, even within subject topics.

Case study: a test of imputation methods in paleopathology

Given the complexities of bioarchaeological data, the second aim of this paper is to discover which imputation technique (if any) is appropriate for imputing missing ordinal and continuous paleopathology data. To accomplish this goal, we simulated missing data on two complete bioarchaeological datasets (i.e. no missing data) and tested multiple methods for imputing ordinal paleopathology data and continuous skeletal measurements alongside pairwise and listwise deletion to discover which approach best obtained the parameters of the original dataset.

Ordinal missing data were simulated on a complete dataset of 287 individuals from the Hamann-Todd Documented Skeletal Collection. The individuals included a mix of males, females, Black individuals and white individuals ranging in age from 18 to 80 years. Demographic data were not included in the imputation analyses. Recorded

paleopathology data included porotic hyperostosis, cribra orbitalia, periodontal disease, linear enamel hypoplasia, and periosteal lesions of the tibia. The range of ordinal values for each were porotic hyperostosis: 0-2; cribra orbitalia: 0-3; periodontal disease: 0-4; linear enamel hypoplasia: 0-3; periostosis: 0-3.

Continuous missing data were simulated on a complete dataset of 369 individuals from the same collection. Variables included left and right femoral lengths – measured in centimeters – and the antero-posterior (AP) and transverse (TR) vertebral neural canal diameters of T1, T5, T10, L1 and L3 – measured in millimeters.

Five different datasets with 5%, 10%, 20%, 30%, and 40% of the data missing were created using the R package *imputeR* (v2.2; Feng et al., 2020) resulting in 50 simulated missing datasets for ordinal and continuous data combined. To accurately reflect patterns of missingness found in a genuine bioarchaeology dataset, five additional datasets with percentages of missingness that were equal to the percent missing for each variable from the entire pooled sample. Missing data were simulated as MCAR, MAR and MNAR using the R package *missMethods* (v0.2.0; Rockel, 2020). For the ordinal data, percentages of missingness were set at porotic hyperostosis = 12.5%, cribra orbitalia = 20%, periodontal disease = 25%, linear enamel hypoplasia = 30%, and periostosis = 10%. For continuous data, the following percentages of missingness were selected: femoral length right = 10%, femoral length left = 10%, T1AP = 15%, T1TR = 10%, T5AP = 12.5%, T5TR = 10%, T10AP = 15%, T10TR = 15%, L1AP = 20%, L1TR = 15%, L3AP = 20%, L3TR = 15%.

Imputation Methods

Six imputation methods were selected: predictive mean matching, random replacement, mean replacement, expectation maximization, random forest, and stochastic linear regression (continuous data only). These methods were chosen as they are among the more commonly used in the social sciences. Excellent statistical packages have been created for each, making these methods easy to implement and more accessible to non-experts. The methods represent a wide range of statistical approaches and range from mathematically simple (e.g., mean imputation), to complex (e.g. expectation maximization or stochastic linear regression). This list also includes the most common imputation methods used by bioarchaeologists.

Several methods make use of the *mice* package (v3.11.0; van Buuren and Groothuis-Oudshoorn, 2011): random replacement, mean replacement, predictive mean matching, and stochastic linear regression. For each, m=10 imputations were performed with 50 iterations. In a few instances, a single R package did not work well for both ordinal and continuous data and two different packages had to be used. Random forest imputation of ordinal data was executed with the *missForest* package (v1.4; Stekhoven, 2013), while for continuous data *mice* was used. Similarly, imputation via expectation maximization for ordinal data was performed using *TestDataImputation* (v1.1; Dai et al., 2019) while for continuous data *missMethods* (v0.2.0; Rockel, 2020) was used. All analyses were performed in RStudio version 1.1.456 (Rstudio Team, 2016).

Assessing success

The success of each imputation method was assessed by comparing the mean and variance of the imputed datasets with those of the original using percent error; a lower percentage indicates a better fit. Success was also assessed using Kendall's rank correlation coefficient and Cohen's kappa where 1 indicates perfect agreement and 0 no agreement; a value approaching 1 indicates a better fit. For pairwise and listwise deletion only the mean and variance could be assessed since these methods create no corresponding dataset. Cohen's kappa and Kendall's tau have been used in other similar imputation test cases; however, they may not be the most effective for assessing imputation success. The goal of imputation is to not to recover the exact values missing from the dataset, but to "preserve important characteristics of the data set as a whole" (Graham, 2009, p. 559). Cohen's kappa and Kendall's tau assess pairwise agreement between the original and imputed values, which is not the point of imputation, and may be less important than other broad parameters.

Case Study Results

Ordinal Data The results are presented in Tables 4-9; Tables 4, 5, and 6 present outcomes for 5%, 10%, 20%, 30%, and 40% missing data while Tables 7, 8 and 9 present findings for the MCAR, MAR, and MNAR datasets. Tables 4, 5, 7, and 8 show the percent error for the mean and variance and the Kendall's tau and Cohen's kappa coefficients. Tables 6 and 9 present the performance rankings of each imputation method on the dataset. Imputation methods will increase the sample variance, therefore the percent error for the variance is generally the highest.

Table 4.

Evaluation Criteria for Percentages of Missing Ordinal Data

	5%		10%		20%		30%		40%	
	M	V	M	V	M	V	M	V	M	V
PMM	1.44	3.95	1.87	7.48	4.67	14.93	3.98	29.17	7.73	37.06
Ran	1.51	2.18	2.33	3.46	4.75	6.43	3.88	4.60	6.95	5.18
M	1.44	3.95	1.87	7.48	4.67	14.93	3.98	29.17	7.73	37.06
EM	2.87	2.87	2.87	2.87	5.84	5.84	4.35	4.35	NA	NA
RF	1.96	3.24	2.26	6.09	5.43	10.23	5.72	23.51	14.36	26.44
Pair	0.94	2.12	1.27	1.39	4.24	4.78	2.74	6.23	2.18	6.61
List	2.41	4.03	5.78	3.59	9.29	10.32	15.94	20.21	17.99	23.87

Mean and variance shown as percent error

Cell values are the average of scores for the 5 pathology scores.

Evaluation Criteria
M = mean
V = variance

Imputation Methods
PMM = predictive mean matching
Ran = random
M = mean
EM = Expectation Maximization
RF = Random Forest
Pair = Pairwise deletion
List = Listwise Deletion

Table 5.

Evaluation Criteria for Percentages of Ordinal Missing Data

	5%		10%		20%		30%		40%	
	T	K	T	K	T	K	T	K	T	K
PMM	0.95	0.93	0.90	0.85	0.81	0.71	0.71	0.58	0.639	0.47
Ran	0.95	0.92	0.91	0.85	0.82	0.71	0.71	0.57	0.61	0.47
M	0.92	0.95	0.84	0.91	0.73	0.85	0.57	0.74	0.47	0.68
EM	0.95	0.95	0.90	0.90	0.82	0.81	0.70	0.72	0.60	0.61
RF	0.95	0.92	0.90	0.84	0.81	0.70	0.70	0.57	0.60	0.47

Kendall's Tau and Cohen's Kappa are the test statistics

Cell values are the average of scores for the 5 pathology scores.

Evaluation Criteria
T = Kendall's Tau
K = Cohen's Kappa

Imputation Methods
PMM = predictive mean matching
Ran = random
M = mean
EM = Expectation Maximization
RF = Random Forest
Pair = Pairwise deletion
List = Listwise Deletion

Table 6.

Imputation Rankings for Arbitrary Percentages of Ordinal Missing Data.

	5%				10%				20%				30%				40%				**Final**
	M	V	T	K	M	V	T	K	M	V	T	K	M	V	T	K	M	V	T	K	
PMM	2	5	1	3	2	6	4	4	2	6	3	3	3	6	2	3	3	5	1	3	**4**
Ran	3	2	4	4	4	3	1	3	3	3	1	4	2	2	1	4	2	1	2	4	**2**
M	2	5	5	2	2	6	5	1	2	6	5	1	3	6	5	1	3	5	5	1	**5**
EM	1	3	3	1	5	2	3	2	5	2	2	2	4	1	4	2	NA	NA	4	2	**2**
RF	4	4	2	5	3	5	2	5	4	4	4	5	5	5	3	5	4	4	3	5	**6**
Pair	1	1	NA	NA	1	1	NA	NA	1	1	NA	NA	1	3	NA	NA	1	2	NA	NA	**1**
List	5	7	NA	NA	6	4	NA	NA	6	5	NA	NA	6	4	NA	NA	5	3	NA	NA	**7**

Cell values are the average of the 5 pathology rankings.

Evaluation Criteria
M = mean
V = variance
T = Kendall's Tau
K = Cohen's Kappa

Imputation Methods
PMM = predictive mean matching
Ran = random
M = mean
EM = Expectation Maximization
RF = Random Forest
Pair = Pairwise deletion
List = Listwise Deletion

For the arbitrary 5%, 10%, 20%, 30%, and 40% missing datasets, pairwise deletion performed best while listwise deletion was by far the worst. When the amount of missing data is low there is no notable difference in performance for any imputation method; the sample means remain close to the original and the tau and kappa coefficients are high. At 20% missing data the percent error for the mean remains below 5% and the tau and kappa remain in an acceptable range. At 30% and above, however, all the imputation methods become problematic. Random imputation performed surprisingly well, being the best method for data MNAR. This is likely due to the narrow range of possible values to impute with these ordinal data. As we will see with the results of the continuous data, this method is not as effective when used on data with greater variance.

As seen in Tables 7 and 8, all imputation methods perform reasonably well when the data are MCAR and MAR. The percent error for the mean remains below 5% for all except listwise deletion. For MNAR data the mean percent error is much higher. Nearly all imputation methods for data MCAR, MAR, and MNAR have Kendall's tau and Cohen's kappa coefficients in an acceptable range, indicating good agreement between the imputed data and the original dataset. Tables 6 and 9 show the final rankings for the five imputation methods. Overall, pairwise deletion was best able to recover the mean and variance of the original dataset, however Kendall's tau and Cohen's kappa could not be assessed. Expectation maximization was the best imputation method among the datasets with realistic patterns of missing data. Overall, no single imputation method was best able to recover the parameters of the original dataset in all categories of missing data.

Table 7.

Evaluation Criteria for Ordinal MCAR, MAR, and MNAR Datasets

	MCAR		MAR		MNAR	
	M	V	M	V	M	V
PMM	2.78	16.41	3.04	17.03	11.74	24.52
Ran	2.26	16.55	2.50	17.52	2.50	17.52
M	1.92	18.72	2.35	19.32	12.08	26.53
EM	2.76	14.77	2.30	15.64	9.70	23.11
RF	2.21	15.15	4.52	15.47	11.02	22.51
Pair	1.92	3.01	2.35	3.97	12.08	8.70
List	4.19	5.38	6.70	11.03	12.99	9.14

Mean and variance presented as percent error

Cell values are the average of the 5 pathology scores.

Evaluation Criteria
M = mean
V = variance

Imputation Methods
PMM = predictive mean matching
Ran = random
M = mean
EM = Expectation Maximization
RF = Random Forest
Pair = Pairwise deletion
List = Listwise Deletion

Table 8.

Evaluation Criteria for Ordinal MCAR, MAR, and MNAR Datasets

	MCAR		MAR		MNAR	
	T	K	T	K	T	K
PMM	0.71	0.81	0.79	0.71	0.77	0.71
Ran	0.71	0.80	0.79	0.71	0.79	0.72
M	0.71	0.82	0.81	0.71	0.79	0.70
EM	0.72	0.81	0.79	0.72	0.78	0.71
RF	0.71	0.80	0.78	0.71	0.77	0.70
Pair	NA	NA	NA	NA	NA	NA
List	NA	NA	NA	NA	NA	NA

Mean and variance presented as percent error

Cell values are the average of the 5 pathology scores.

Evaluation Criteria
T = Kendall's Tau
K = Cohen's Kappa

Imputation Methods
PMM = predictive mean matching
Ran = random
M = mean
EM = Expectation Maximization
RF = Random Forest
Pair = Pairwise deletion
List = Listwise Deletion

Table 9.

Imputation Rankings for Ordinal MCAR, MAR, and MNAR Datasets

	MCAR				MAR				MNAR				**Final**
	M	V	T	K	M	V	T	K	M	V	T	K	
PMM	6	5	2	2	3	5	4	3	4	6	5	3	**5**
Ran	4	6	3	4	5	6	2	2	1	3	1	1	**3**
M	1	7	4	1	1	7	1	4	5	7	2	4	**3**
EM	5	3	1	3	4	4	3	1	2	5	3	2	**2**
RF	3	4	4	5	6	3	5	4	3	4	4	4	**6**
Pair	1	1	NA	NA	1	1	NA	NA	5	1	NA	NA	**1**
List	7	2	NA	NA	7	2	NA	NA	7	2	NA	NA	**7**

Cell values are the average of the 5 pathology rankings.

Evaluation Criteria
M = mean
V = variance
T = Kendall's Tau
K = Cohen's Kappa

Imputation Methods
PMM = predictive mean matching
Ran = random
M = mean
EM = Expectation Maximization
RF = Random Forest
Pair = Pairwise deletion
List = Listwise Deletion

Continuous Data The results for continuous data are presented in Tables 10-15; Tables 10, 11, and 12 present outcomes for the 5%, 10%, 20%, 30%, and 40% missing data while Tables 13, 14, and 15 show findings for the MCAR, MAR, and MNAR datasets. The percent error for both the means and the variances are lower for continuous data, indicating that obtaining the parameters of the original dataset was far more successful with continuous compared to ordinal data. The highest percent error for the mean across all imputed continuous datasets was only 1.56% (MNAR random imputation), well below the majority of the percent errors for ordinal data. For the 5%, 10%, 20%, 30% and 40% missing datasets, predictive mean matching performed best across nearly all percentages of missingness, with stochastic regression a close second. For the 5%, 10%, 20%, 30% and 40% datasets, the more advanced imputation methods (predictive mean matching, expectation maximization, random forest, and stochastic regression) had high levels of success obtaining the original mean up through 40% missing data. Pairwise deletion performed comparably to random number and mean imputation, likely because pairwise deletion maintains the sample variance better than imputation methods – increasing its appearance of success in the rankings. Listwise deletion performed poorly compared to all the other methods. Estimates of success were not obtainable for listwise deletion of 40% missingness because the sample size had decreased so significantly.

According to the results for the MCAR, MAR, and MNAR datasets, all imputation and deletion methods were relatively successful at recovering the means of the MCAR and MAR datasets, particularly compared to the results of the ordinal data.

Table 10.

Evaluation Criteria for Arbitrary Percentages of Missing Continuous Data

	5%		10%		20%		30%		40%	
	M	V	M	V	M	V	M	V	M	V
PMM	0.05	1.6	0.05	2.87	6.48	6.48	0.18	11.18	0.22	15.78
Ran	0.09	5.57	0.13	8.46	18.62	18.62	0.24	28.62	0.37	36.88
M	0.09	6.19	0.12	9.58	20.79	20.79	0.22	31.61	0.36	41.02
EM	0.05	1.50	0.06	2.34	5.35	5.35	0.21	8.45	0.20	11.60
RF	0.06	3.01	0.06	4.24	10.40	10.40	0.19	18.13	0.27	25.39
Reg	0.05	1.62	0.06	2.39	6.24	6.24	0.17	10.25	0.28	14.09
Pair	0.09	1.33	0.12	1.43	2.54	2.54	0.22	3.27	0.36	4.51
List	0.95	4.39	0.78	11.28	30.85	30.85	1.72	43.26	NA	NA

Mean and variance shown as percent error

Cell values are the average of scores for the 5 pathology scores.

Evaluation Criteria
M = mean
V = variance

Imputation Methods
PMM = predictive mean matching
Ran = random
M = mean
EM = Expectation Maximization
RF = Random Forest
Reg = Stochastic Regression
Pair = Pairwise deletion
List = Listwise Deletion

Table 11.

Evaluation Criteria for Arbitrary Percentages of Missing Continuous Data

	5%		10%		20%		30%		40%	
	T	K	T	K	T	K	T	K	T	K
PMM	0.97	0.94	0.95	0.90	0.90	0.80	0.84	0.70	0.76	0.59
Ran	0.94	0.94	0.89	0.90	0.790	0.80	0.68	0.70	0.58	0.59
M	0.94	0.94	0.90	0.90	0.81	0.80	0.73	0.70	0.65	0.59
EM	0.96	0.94	0.94	0.90	0.88	0.80	0.83	0.70	0.75	0.59
RF	0.97	0.94	0.94	0.90	0.88	0.80	0.82	0.70	0.75	0.59
Reg	0.97	0.94	0.95	0.90	0.89	0.80	0.83	0.70	0.77	0.59
Pair	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
List	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Kendall's Tau and Cohen's Kappa are the test statistics

Cell values are the average of scores for the 5 pathology scores.

Evaluation Criteria
T = Kendall's Tau
K = Cohen's Kappa

Imputation Methods
PMM = predictive mean matching
Ran = random
M = mean
EM = Expectation Maximization
RF = Random Forest
Reg = Stochastic Regression
Pair = Pairwise deletion
List = Listwise Deletion

Table 12.

Imputation Rankings for Arbitrary Percentages of Continuous Missing Data.

	5%				10%				20%				30%				40%				**Final**
	M	V	T	K	M	V	T	K	M	V	T	K	M	V	T	K	M	V	T	K	
PMM	2	3	1	2	1	4	1	3	1	4	1	3	2	4	2	1	2	4	2	1	**1**
Ran	5	7	6	3	6	6	6	3	6	6	6	3	6	5	6	1	5	6	6	3	**7**
M	6	8	5	2	5	7	5	2	5	7	5	2	5	6	5	2	6	7	5	4	**6**
EM	1	2	4	2	4	2	4	2	4	2	4	2	4	2	3	2	1	2	3	4	**3**
RF	4	5	3	1	3	5	3	1	2	5	3	1	3	5	4	1	3	5	4	2	**4**
Reg	3	4	2	2	2	3	2	2	3	3	2	2	1	3	1	2	4	3	1	4	**2**
Pair	6	1	NA	NA	5	1	NA	NA	5	1	NA	NA	5	1	NA	NA	6	1	NA	NA	**5**
List	8	6	NA	NA	7	8	NA	NA	7	8	NA	NA	7	8	NA	NA	NA	NA	NA	NA	**8**

Cell values are the average of the 5 pathology rankings.

Evaluation Criteria
M = mean
V = variance
T = Kendall's Tau
K = Cohen's Kappa

Imputation Methods
PMM = predictive mean matching
Ran = random
M = mean
EM = Expectation Maximization
RF = Random Forest
Reg = Stochastic Regression
Pair = Pairwise deletion
List = Listwise Deletion

Table 13.

Evaluation Criteria for Continuous MCAR, MAR, and MNAR Datasets

	MCAR		MAR		MNAR	
	M	V	M	V	M	V
PMM	0.07	4.05	0.13	6.13	0.28	6.61
Ran	0.15	11.70	0.30	14.02	0.78	14.11
M	0.15	13.12	0.30	15.32	0.77	15.51
EM	0.08	3.77	0.14	4.67	0.28	5.48
RF	0.10	6.58	0.16	8.51	0.42	8.92
Reg	0.07	3.64	0.13	5.66	0.28	6.20
Pair	0.15	2.16	0.30	2.47	0.77	2.69
List	0.68	7.07	1.22	12.35	3.70	13.50

Mean and variance presented as percent error

Cell values are the average of the 5 pathology scores.

Evaluation Criteria
M = mean
V = variance

Imputation Methods
PMM = predictive mean matching
Ran = random
M = mean
EM = Expectation Maximization
RF = Random Forest
Reg = Stochastic Regression
Pair = Pairwise deletion
List = Listwise Deletion

Table 14.

Evaluation Criteria for Continuous MCAR, MAR, and MNAR Datasets

	MCAR		MAR		MNAR	
	T	K	T	K	T	K
PMM	0.93	0.86	0.92	0.86	0.92	0.86
Ran	0.86	0.86	0.85	0.86	0.85	0.86
M	0.87	0.86	0.87	0.86	0.87	0.86
EM	0.92	0.86	0.91	0.86	0.91	0.86
RF	0.92	0.86	0.92	0.86	0.91	0.86
Reg	0.93	0.86	0.92	0.86	0.92	0.86
Pair	NA	NA	NA	NA	NA	NA
List	NA	NA	NA	NA	NA	NA

Kendalls's Tau and Cohen's Kappa are the test statistics

Cell values are the average of the 5 pathology scores.

Evaluation Criteria
T = Kendall's Tau
K – Cohen's Kappa

Imputation Methods
PMM = predictive mean matching
Ran = random
M = mean
EM = Expectation Maximization
RF = Random Forest
Reg = Stochastic Regression
Pair = Pairwise deletion
List = Listwise Deletion

Table 15.

Evaluation Criteria for Continuous MCAR, MAR, and MNAR Datasets

	MCAR				MAR				MNAR				**Final**
	M	V	T	K	M	V	T	K	M	V	T	K	
PMM	1	4	3	2	1	4	1	1	3	4	4	1	**2**
Ran	5	7	4	6	5	7	4	6	6	7	4	6	**7**
M	6	8	2	5	6	8	2	5	5	8	1	5	**6**
EM	3	3	2	4	3	2	2	4	1	2	1	4	**3**
RF	4	5	1	3	4	5	3	3	4	5	4	3	**5**
Reg	2	2	2	1	2	3	2	2	2	3	1	2	**1**
Pair	6	1	NA	NA	6	1	NA	NA	6	1	NA	NA	**4**
List	8	6	NA	NA	8	6	NA	NA	8	6	NA	NA	**8**

Cell values are the average of the 5 pathology rankings.

Evaluation Criteria
M = mean
V = variance
T = Kendall's Tau
K = Cohen's Kappa

Imputation Methods
PMM = predictive mean matching
Ran = random
M = mean
EM = Expectation Maximization
RF = Random Forest
Reg = Stochastic Regression
Pair = Pairwise deletion
List = Listwise Deletion

Mean and random imputation performed poorly compared to imputation and in some cases did worse than pairwise deletion or listwise deletion. Expectation maximization and stochastic regression worked well for data that are MNAR. A pattern is evident in the Cohen's kappa and Kendall's tau coefficients in which variables tend to have similar, if not identical, results across all imputation methods. The percent error for T5AP, L1AP and L3AP, which had the highest percentages of missingness, are highest regardless of the imputation or deletion method employed. This indicates that the percentage of missingness may play a greater role in the ability to recover original dataset parameters than the imputation method used. For MCAR, MAR, and MNAR data, stochastic regression and predictive mean matching performed best, expectation maximization and random forest imputation ranked toward the middle, and other methods ranked at the bottom.

Case Study Discussion

For ordinal data, no imputation or deletion method performed significantly better than any others across all datasets. This uniformity likely reflects problems inherent in paleopathology data: the low range of possible values, high inter-variable correlation, and variable percentages of missingness. Imputation of ordinal MNAR data was unsuccessful for every missing data method, although random imputation performed well across the MCAR, MAR, and MNAR datasets. We suspect this was the result of random chance in which the algorithm was able to impute the exact original value. For continuous data, both predictive mean matching and stochastic regression performed well across all types of data, including those missing not at random (MNAR).

Despite expert caution against pairwise deletion (Allison 2001; Graham 2012; Kang 2013; van Buuren 2018), this method performed well for ordinal data. Because pairwise deletion performs better in obtaining the original variance than imputation, its standing in the rankings is elevated. For continuous data, pairwise deletion did not perform as well as stochastic regression, predictive mean matching, or expectation maximization for any dataset. Deletion methods cause a high rate of data loss that can be especially problematic if the data are MNAR. Paleopathologists generally have such small sample sizes any method that reduces the data further is suboptimal and may result in a biased dataset and decreased analytical power.

Given its ability to work with multiple data types, we expected random forest imputation to work better for ordinal data, yet it performed poorly in nearly all instances. Finding an R package that could smoothly perform random forest imputation for this type of ordinal data was also difficult. It is probably the narrow range of possible values resulted in a reduced ability to form discrete decision trees. Random forest might not be advisable for similar ordinal paleopathology data.

Critics of imputation claim these approaches "make up data," invoking various justifications for continuing to use deletion methods (Osborne 2013; Schafer 1999; van Ginkel et al. 2020). Studies have shown, however, that imputed data are often better able to recover the original parameter estimates and be more easily replicable by other researchers than deletion methods (King et al. 1998; Osborne 2013). Using an epidemiological dataset which examined the association between blood transfusions and BMI after hip surgery, Pedersen et al. (2017) compared the results of multiple imputation

with listwise deletion alongside the full dataset. Multiple imputation generated results that more closely matched those of the full dataset and correctly identified additional variables of importance. The results using listwise deletion had larger standard errors and failed to identify gender as a confounding variable. Fichman and Cummings (2003) reanalyzed data from a study by Kraut et al. (1998) who examined the impact of internet usage on depression while largely using deletion to handle missing data. Fichman and Cummings (2003) used multiple imputation to eliminate missing data in Kraut et al.'s (1998) sample – increasing the sample size from 169 to 363 – and reanalyzed the data. The original results of Kraut et al.'s (1998) study showed that increased internet usage was associated with increased depression. Using the entire sample, however, Fichman and Cummings (2003) found no significant relationship between the amount of time spent on the internet and higher depression scores. The findings of this study support the conclusions of this prior research. Listwise deletion was the worst at recovering the parameters of the original skeletal sample. If the data are MNAR, listwise deletion is the least appropriate method to employ for ordinal or continuous paleopathology data.

Numerous scholars have drawn attention to the dearth of advanced statistical analyses in bioarchaeology (Agarwal 2016; Konigsberg and Frankenberg 2013). Recent years have seen a surge in more advanced methods such as hazards models, survival analysis, and linear regression. However, much research – particularly paleopathology and trauma analysis – still depends on relatively simple statistical analyses such as chi-squared or ANOVAs. Reliance on more simple statistics represents a major stumbling block to the advancement of paleopathology. Analyses such as the ANOVA, t-test, or

chi-squared have strict statistical assumptions about the data such as normal distribution or equal variances; inappropriate use of such tests can result in flawed results. As paleopathology data rarely adhere to these assumptions, data often must be aggregated or binned in ways that obscure vitally important patterns. More sophisticated analyses allow data to be explored on a spectrum rather than by arbitrary bins.

Another serious drawback of the simpler methods is their failure to account for the concerns raised by Wood et al. (1992) in the Osteological Paradox. Because of selective mortality, straightforward percentages or counts of pathology lesions from a skeletal sample will overestimate our understanding of disease prevalence in the living population. The authors explain how aggregating data for more simple analyses prevents us from accounting for variation in individual frailty, obscuring not only important variation in disease experience but also the potential presence of subpopulations.

How much missing data is too much? There is little clear guidance on the maximum amount of missing data allowed before missing data methods or statistical analyses become too biased (Dong and Peng 2013; Hardt et al. 2013; Meeyai 2016; Saunders et al. 2006). The definition of a "small" amount of missingness varies from <5% to <20% missingness (Little and Rubin 2002; Tabachnick et al. 2007). Some statisticians caution that bias may occur in samples with more than 10% of the data missing and that samples with over 40% missing should be used for "hypothesis generating" only (Madley-Dowd et al., 2019, p. 64). Others recommend a maximum of 30% missingness when imputing missing data and no more than 20% with samples sizes of 50 or lower (Hardt et al. 2013). On the other hand, under tightly controlled

circumstances, authors have managed to successfully impute and analyze datasets with much higher percentages of missing data. Madley-Dowd et al. (2019) imputed up to 80% missing MCAR and MAR data employing multiple imputation with auxiliary variables. Meeyai (2016) was able to recover unbiased parameters for MCAR data with 60% of the values missing for samples greater than n=1000. Graham et al. (2007) obtained unbiased regression coefficients with a 90% fraction of missing information but found that statistical power dropped considerably after 50% missingness even with *m*=20 imputations.

The percent of missing information may not be the most important consideration when faced with missing data. Sample size is an important factor; 20% missingness may have a greater impact with a sample size of 50 than with a sample size of 500 (Meeyai 2016; Saunders et al. 2006). The class of missingness – MCAR, MAR, or MNAR – will also affect how much missing data is acceptable. Even a small amount of MNAR values may result in a biased dataset no matter what imputation method is used (Dong and Peng 2013; Tabachnick et al. 2007). Whether the missing values are among the independent and/or dependent variables will also impact the success of missing data methods and ultimate statistical analyses (Saunders et al. 2006).

This study has several limitations. First, according to Rubin's Rules (Rubin 1987), statistical analyses are to be performed on each of the *m* datasets, and the final parameters of interest (e.g. p-values, confidence intervals, etc.) pooled at the very end using the equations designed by Rubin. The approach used in this paper, however, pools the multiply imputed datasets and assesses success at the end. Testing the success of

imputation on every type of statistical analysis bioarchaeologists use is beyond the scope of a single paper and the approach employed here is intended as a first step. Additional study is needed to test the success of imputation using different statistical analyses. Second, the success of imputation and deletion methods will depend not only on the percent of missing data, but also on the sample size. The samples used here (ordinal n=287; continuous n=369) are rather large compared to most paleopathology datasets. Additional research is needed to compare the results found here with those from smaller samples. Third, this study tests the success of missing data methods on ordinal and continuous data separately, however many bioarchaeologists collect mixed data types. Further research should identify which methods are successful at imputing mixed data including continuous, ordinal, and binary values.

Conclusion

The primary aim of this paper is to provide background on missing data methods and theory, highlighting how imputation can be used to manage missing bioarchaeology and paleopathology data. There are a great number of approaches for handling missing data, including deleting absent data or imputing missing values. While each technique has advantages and disadvantages, imputation methods are generally recommended over deletion. Other fields in the natural and social sciences commonly make use of imputation. Bioarchaeological research, however, seldom uses imputation to handle missing data. This paper tests the ability of eight methods to yield unbiased parameter estimates when handling missing ordinal and continuous bioarchaeological data. Results demonstrated that no single method performed best in all circumstances, suggesting there

is no “one-size-fits-all” solution to the missing data problem. Listwise deletion performed the worst for both ordinal and continuous data, introducing the most error into the dataset, while pairwise deletion performed well for ordinal variables but ranked toward the bottom for continuous data. Ultimately, the best method for handling missing continuous data was stochastic regression or predictive mean matching. Stochastic regression is particularly useful when the data may be missing not at random (MNAR). We intend for these findings to encourage the use of more advanced methods to handle missing data in bioarchaeology. With greater control over the data, bioarchaeologists can explore sources of bias and implement statistically rigorous analyses.

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CHAPTER 4

FRAILTY AND SURVIVORSHIP IN THE 1918 INFLUENZA PANDEMIC

Though largely forgotten by the public (Crosby 2003; Hume 2000; Stanwell-Smith 2019), the 1918 influenza is one of the most well-studied historical pandemics. An intriguing aspect of the 1918 flu was the unusual age-at-death distribution. Seasonal outbreaks and epidemics of influenza are generally fatal to young children and the elderly, yet the 1918 virus was unusually deadly to adults between the ages of 20-40 years old – commonly assumed to be the most resilient segment of a population (Barry 2004; Barry 2005; Crosby 2003; Gagnon et al. 2013; Luk et al. 2001; Shanks and Brundage 2012; Simonsen et al. 1998; Taubenberger and Morens 2006). Another remarkable feature of the pandemic was that the illness struck adults who otherwise had appeared perfectly healthy. It has become widely accepted that the 1918 virus killed "healthy young adults," however this has not been explicitly tested. Were these adults truly healthy? Or was there some underlying frailty yet to be identified? Much of the research on the 1918 flu relies on data obtained from historical records such as medical records, vital statistics, census data, and life insurance records. These data often do not include individual-level information on co-morbidities, health conditions, or general environmental, nutritional, and chronic stressors and may therefore be inadequate for testing whether the people who died were healthy.

In this paper, we use a bioarchaeological approach to explicitly interrogate the hypothesis that healthy individuals were as likely to die as non-healthy individuals during the pandemic. Poor health due to environmental, social, nutritional, or disease stresses

can leave permanent impressions on the skeleton such as reduced stature, structural asymmetry, abnormal subadult growth, poor teeth, or skeletal lesions (e.g. Buikstra and Cook 1980; Goodman et al. 1984; Larsen 1997). These stresses and their associated skeletal markers have been correlated with increased morbidity and mortality. Here, we assess patterns of these nonspecific indicators of skeletal stress to examine changes in individual- and population-level health during the 1918 pandemic.

Background

The 1918 influenza pandemic was one of the deadliest global outbreaks of disease since the Black Death. An estimated one-third of the world's population became infected with the virus (Crosby 2003; Taubenberger and Morens 2006) and approximately 50 million people died (Jordan 1927; Olson et al. 2005; Patterson and Pyle 1991; Johnson and Mueller 2002; Taubenberger and Morens 2006). Most of the deaths were caused by secondary bacterial pneumonia infection rather than the influenza virus itself (Shanks and Brundage 2012). Despite the enormous amount of scholarship dedicated to the 1918 pandemic, many questions about the event remain unresolved.

The high death rate among young adults remains one of the most studied and yet most mysterious features of the pandemic (Barry 2004; Barry 2005; Crosby 2003; Luk et al. 2001; Simonsen et al. 1998; Taubenberger and Morens 2006). Normal mortality curves form a U-shaped distribution, with most deaths occurring among the very young and the very old. The mortality curve for the 1918 flu pandemic, however, produced a W-shaped age-at-death distribution with deaths occurring among young children and the elderly, but with a spike in the death rate among young adults (Ahmed et al. 2007;

Noymer and Garenne 2000; Shanks and Brundage 2012; Taubenberger and Morens 2006). In a survey of data collected from the United States and Canada, Gagnon et al. (2013) found that the greatest mortality was in adults who were 28 years old. Between 1918-1919, the mortality rate of individuals between 15-34 due to pneumonia and influenza was more than twenty times higher than previous years (Taubenberger and Morens 2006). Though several theories have been advanced, scholars remain unsure why young adults died at a rate that was so much greater than expected.

One prominent explanation for the unusually high young adult mortality is the "cytokine storm" hypothesis. Cytokines are a class of proteins that are released as part of the immune system response (Chousterman et al. 2017; Tisoncik et al. 2012). Researchers speculate that the 1918 virus provoked an excessive release of cytokines – the cytokine storm – that lead to lung inflammation, respiratory distress, and systemic organ failure (de Wit et al. 2018; Ferrara et al. 1993; Kash et al. 2006; Kobasa et al. 2004; Osterholm 2005; Tisoncik et al. 2012). Those with strong immune systems – generally young adults – would have been at greatest risk for cytokine storms (Ma et al. 2011).

Co-infection with tuberculosis and influenza is another possible explanation for the high mortality rate among young adults. Numerous studies have found a relationship between tuberculosis infection and increased morbidity and mortality in 1918 (Espersen 1954; Noymer and Garenne 2000; Oei and Nishiura 2012; Zürcher et al. 2016; Mamelund and Dimka 2019). Tuberculosis is more prevalent in young adults compared to children or older adults (Dye 2006; Rothman 1994; Schaaf et al. 2010; Shryock and Association 1904). Tuberculosis commonly causes necrosis in lung tissues, creating cavities that

become opportune sites for secondary bacterial infection (Gadkowski and Stout 2008; Noymer and Garenne 2000).

An additional reason for high young adult mortality in 1918 is prior exposure to another influenza virus that impaired the immune system's ability to respond to the 1918 virus (Gagnon et al. 2015; Hallman and Gagnon 2014; Shanks and Brundage 2012). The "original antigenic sin" hypothesis proposes that the immune system adapts to the first viral strain encountered. It becomes effective at combating that particular strain, but less able to withstand other strains (Davenport et al. 1953; Francis Jr 1955; Kim et al. 2009). Individuals born around 1889-1890 may have imprinted on the "Russian Flu" virus, and their immune systems were then unable to effectively fight the 1918 virus (Gagnon et al. 2013; Hallman and Gagnon 2014).

The age-at-death distribution of the 1918 pandemic was notable not only due to the over-representation of young adults, but the underrepresentation of older adults (Mamelund 2011), which Worobey et al. (2014) contend could not have been caused by exposure to a single previous pandemic. Numerous influenza viruses had circulated prior to 1918 including an H1N1 between 1830-1847, H1N8 in 1847-1889, H3N8 in 1889-1890, and H1N8 in 1900-1918. Worobey et al. (2014) hypothesize that exposure to hemagglutinin 1 (H1) and neuraminidase 1 (N1) subtypes provided immunity in the 1918 pandemic. The immune systems of those born between 1889-1890 who were exposed only to the H3 and N8 subtypes, were unable to fight the H1 or N1 subtypes. Individuals born in the 1830s were exposed to the N1 and N1 subtypes and had greater survival in 1918 despite being in their 80's in 1918. Meanwhile those born between 1847-1889 were

exposed only to the H1 subtype, conferring some immunity in 1918 and contributing to the low than anticipated morality rate among older adults.

Contemporary reports of the 1918 pandemic noted that the victims of the virus were not only young adults, but "healthy young adults" (Glezen 1996; Hoffman 2011; Luk et al. 2001; Short et al. 2018; Taubenberger and Morens 2006). The illness "seemed to be as fatal to strong adults as to young children and to the old and debilitated" (Phipson, 1923, p. 516). Daland (1919), a medical doctor at the US Naval Hospital in Philadelphia, reported that "most of the patients were between the ages of twenty to twenty-six years and were in unusually good physical condition" (p. 63). France (1919), a medical doctor from Virginia, noted that while many of patients he saw who died from pneumonia had previously been treated for other ailments such as tuberculosis, pellagra or heart problems, "a large percentage were young men apparently healthy and vigorous" (p. 39). 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" (1996 p. 66). Despite numerous accounts echoing these sentiments, there are few concrete, scientific data to support these claims.

Bioarchaeology and Frailty

Bioarchaeology is the study of human skeletal remains within past contexts (Buikstra 1977; Larsen 1997). While previous studies on selective mortality during the 1918 flu have relied on primary archival documents or on viral DNA extracted from only a few individuals, bioarchaeological data allow us to target the individual disease experience from a biological perspective. Life events such as trauma, environmental stress, and disease shape

overall growth and morphology, leaving permanent markers on the skeleton and dentition. These data can be aggregated to provide a population-level understanding of selective mortality during the 1918 flu.

Stress is defined broadly as disruption to biological homeostasis caused by disease, nutritional, environmental, and/or cultural perturbation (Brown 1981; Buikstra and Cook 1980; Bush and Zvelebil 1991; Edinborough and Rando 2020; Goodman et al. 1988; Huss-Ashmore et al. 1982; Klaus 2014; Selye 1976). Bodily tissues attempt to compensate for this disruption through a process known as allostasis (McEwen 1998; McEwen 2005), resulting in what are known as nonspecific indicators of skeletal stress (Klaus 2014). Many of these indicators, such as reduced stature or structural asymmetry, reflect very long-term adverse health conditions (Buikstra and Cook 1980; Goodman et al. 1984; Huss-Ashmore et al. 1982) while others such as periosteal reactions, porotic hyperostosis, cribra orbitalia, and dental defects can be indicative of acute stress events (Brown 1981; Goodman et al. 1988).

Accumulation of nonspecific indicators of skeletal stress have been correlated with increased frailty (DeWitte and Wood 2008; Wood et al. 1992). Frailty – defined as the increased susceptibility to death (Vaupel et al. 1979; Wood et al. 1992) – has become a useful framework for examining social, environmental, and biological processes that cause certain people to be at higher risk for increased mortality (Marklein et al. 2016; Redfern and DeWitte 2011; Usher 2000). DeWitte and colleagues, for example, have explored the impact of pre-existing frailty during the Black Death (DeWitte 2009; DeWitte 2014; DeWitte and Wood 2008; Zarulli et al. 2018). DeWitte and Wood (2008)

demonstrated that the Black Death did not kill indiscriminately, but that prior frailty increased the risk of mortality. More refined research has shown, however, the presence or absence of nonspecific indicators of skeletal stress is inadequate for determining whether a person was frail (DeWitte 2014; Grauer 1993; Mays et al. 2002; Novak and Šlaus 2010; Wood et al. 1992). Skeletal tissues take weeks or months to react to a stressor. As lesions take time to develop, the most frail person will die before lesions manifest. The presence of lesions may reflect a person who was resilient – at least resilient enough to withstand the initial onslaught of stress or disease. DeWitte (2014) made advances in this area by parsing skeletal lesions more finely – demonstrating that active skeletal stress lesions were associated with significantly increased mortality while healed lesions were associated with greater survival. This study builds upon previous research on stress and pandemics to explore assumptions about the 1918 influenza pandemic. It uses a bioarchaeological approach to examine the question: were healthy individuals dying during the 1918 pandemic? Based on prior assumptions, we hypothesize that non-frail (i.e. healthy) individuals were equally likely to die as frail individuals in 1918.

Materials and Methods

Data were collected from the Hamann-Todd Documented Osteological Collection housed at the Cleveland Museum of Natural History. The Hamann-Todd is comprised of over 3,000 individuals who were born between 1825-1910 (De La Cova 2010) and died between 1910-1938 in Cleveland, Ohio and surrounding areas (Mensforth and Latimer 1989). The majority of the individuals were of low socioeconomic status and died in

almshouses or public hospitals (De La Cova 2010; Hunt and Albanese 2005). Their unclaimed bodies were dissected in anatomy classes and then the bones were cleaned, labeled, and added to the collection. Nearly every individual is accompanied by archival documentation on their name, age-at-death, date of death, sex, race, and cause of death (Jones-Kern and Latimer 1996). The exact dates of death are recorded by month, however dates of birth are less certain. Many of the individuals' ages end in a 0 or 5 – a phenomenon known as age heaping (Stockwell and Wicks 1974; Szołtysek et al. 2018) – suggesting that the precise age for many was estimated rather than truly known. The sample used here included 424 individuals: 371 males and 53 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. All individuals in the flu group did not necessarily have a cause of death that was listed as influenza or pneumonia. However, it is likely that influenza played a contributing factor in at least some of these other deaths.

Data Collection Methods

Data were collected on five nonspecific indicators of skeletal stress that manifest at various ages from the skeleton and dentition. Porotic hyperostosis and cribra orbitalia refer to abnormal porosity to the external surface of the cranium or on the inner surface of the eye orbits and may be caused by systemic illnesses such as iron deficiency anemia, high parasite load or scurvy (McFadden and Oxenham 2020; Stuart-Macadam 1991; Walker et al. 2009; Wapler et al. 2004). The presence or absence of porotic hyperostosis and cribra orbitalia was recorded using macroscopic observation following Buikstra and

Ubelaker (1994). Periostosis refers to inflammation of the periosteum caused by physical trauma, local or systemic infection (Roberts and Manchester 2007; Roberts 2019; Weston 2012). In the skeleton, it manifests as new bone formation. Periostosis of the tibia was recorded through macroscopic observation collected on the anterior shaft of the tibia (Buikstra and Ubelaker 1994; DeWitte 2014; Weston 2012). Whether the lesion was active, healed, or mixed (in the process of healing, or reactivating) was also recorded (Lallo 1973; Weston 2008). Periodontal disease is caused by a bacterial infection in the oral cavity that destroys the gums, periodontal ligament, cementum and alveolar bone (DeWitte and Bekvalac 2010; Pihlstrom et al. 2005). The severity of periodontal disease was scored following standards set by Kerr (1988) and the maximum score in each quadrant of the oral cavity recorded. Linear enamel hypoplasia (LEH) are linear defects in tooth enamel produced by disruption in the process of enamel formation caused by systemic stress, malnutrition or disease in childhood (Goodman and Rose 1990; Keita and Boyce 2001). The presence of LEH was recorded on the anterior teeth following Starling and Stock (2007). Missing skeletal lesion data were imputed using the "pmm" function of the mice R package (van Buuren and Groothuis-Oudshoorn 2011).

Analytical Methods

The individuals of the Hamann-Todd were separated into two groups based on whether they 1) never experienced the pandemic (control group), or 2) died during the pandemic (flu group). The pandemic struck Cleveland between September 1918-March 1919. The flu group (n=83) includes individuals who died during this seven-month period. The control group (n= 341) includes those who died prior to the pandemic (1910-

August 1918). Frailty status was determined using skeletal lesion data in two ways. First, skeletal lesion data were combined to create a frailty index (FI). An individual with at least two frailty indicators was given FI=1 and those with zero or one frailty lesion FI=0. This decision was based on testing the survivorship of the pooled samples and selecting the number of lesions that had the greatest discriminatory power. Second, the effect of activity status (active, mixed, or healed) of periosteal lesions of the tibia was assessed.

An active lesion is characterized by woven or unremodeled new bone formation resulting from osteoblastic activity and indicates local or systemic injury or disease processes that were ongoing at the time of death (DeWitte 2014). 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. Active lesions have been correlated with lower survivorship – i.e. greater frailty – than mixed or healed lesions (DeWitte 2014).

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. In this case, the effect of time period (control=0, flu=1) on survival was assessed and statistical significance evaluated using the log rank test (α=0.05). If non-frail (healthy) people were equally likely to die as frail people during the 1918 pandemic, we expect to find no difference in survivorship or median survival time between frail and non-frail individuals during the flu. A hazard ratio expresses the differences in the risk of death between two or more groups. The change in the risk of

death in flu vs. control group was assessed using Cox proportional hazards analysis (Miller Jr 1981) modeling period of death (control or flu) as the covariate. The Cox model is semiparametric and does not specify the baseline hazard, meaning 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. If non-frail people were as likely to die as frail people during the 1918 pandemic, we expect to find no difference in the hazard ratio/risk of mortality between the non-frail and the frail individuals during the flu. All analyses were performed in RStudio Version 1.1.456 (Rstudio Team, 2016).

Results

Figures 8 and 9 show the results of the Kaplan-Meier survival curves for the control and flu groups using the frailty index. The control group shows a difference in survivorship between frail and non-frail individuals. Frail individuals had lower survivorship than those who were non-frail though the difference is not statistically significant (p=0.16). The median survival time for frail individuals was 44 years and for the non-frail was slightly longer at 45 years (Table 16). The results of the Cox proportional hazards analysis for the control group show a similar picture. The results are interpreted using the hazard ratios. Values that are greater than 1 indicate a risk of death that is greater than the reference group (here the reference is FI=0). Values equal to 1 indicate no difference in the risk of death between groups. Values less than 1 indicate a

risk of death that is less than that of the reference group. In the control group (Table 17), frail individuals were 1.1974 times more likely to die than those who were non-frail.

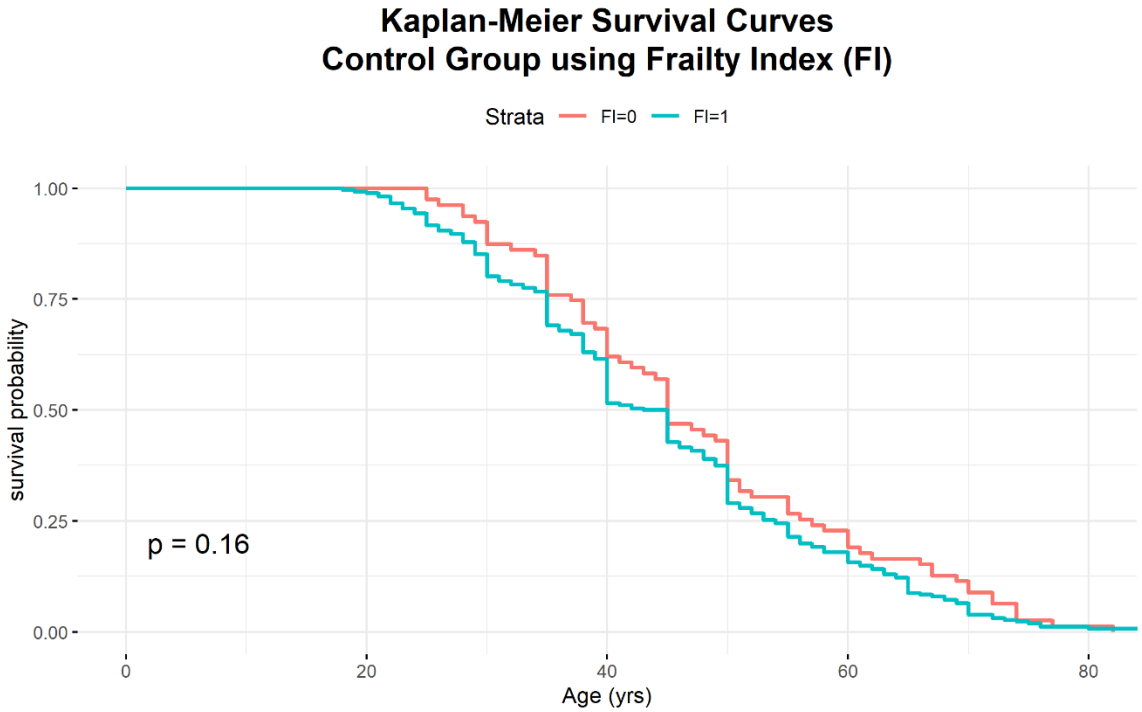
During the flu, we see that the difference in survivorship between the frail and the non-frail remains is similar to the frail vs non-frail difference in the control group (Figure 9). The median survival times for the frail and the non-frail in both the control and flu groups decrease by six years. Focusing on the flu sample, according to the results of the Cox proportional hazards analysis, the frail were 1.1275 times more likely to die than the non-frail, reflecting an increased risk of death for those with skeletal lesions, albeit a small and non-statistically significant one.

Figures 10 and 11 present the Kaplan-Meier curves using periosteal lesion activity as a reflection of frailty. In the control group, we can see that 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 indicated no significant difference between survival of individuals with active vs healed ($p = 0.52$) and active vs mixed ($p=0.29$) periosteal lesions. There is a 6 and 7 year difference in the median survival time between individuals with active lesions and those with healed or mixed lesions (table 18).

According to the results of the Cox proportional hazards analysis, having active or healed lesions was associated with an increase in the risk of death in the control group (table 19). Note that the reference group is mixed lesions because that group had the greatest survival according to the Kaplan-Meier analysis and the sample sizes change

Figure 8.

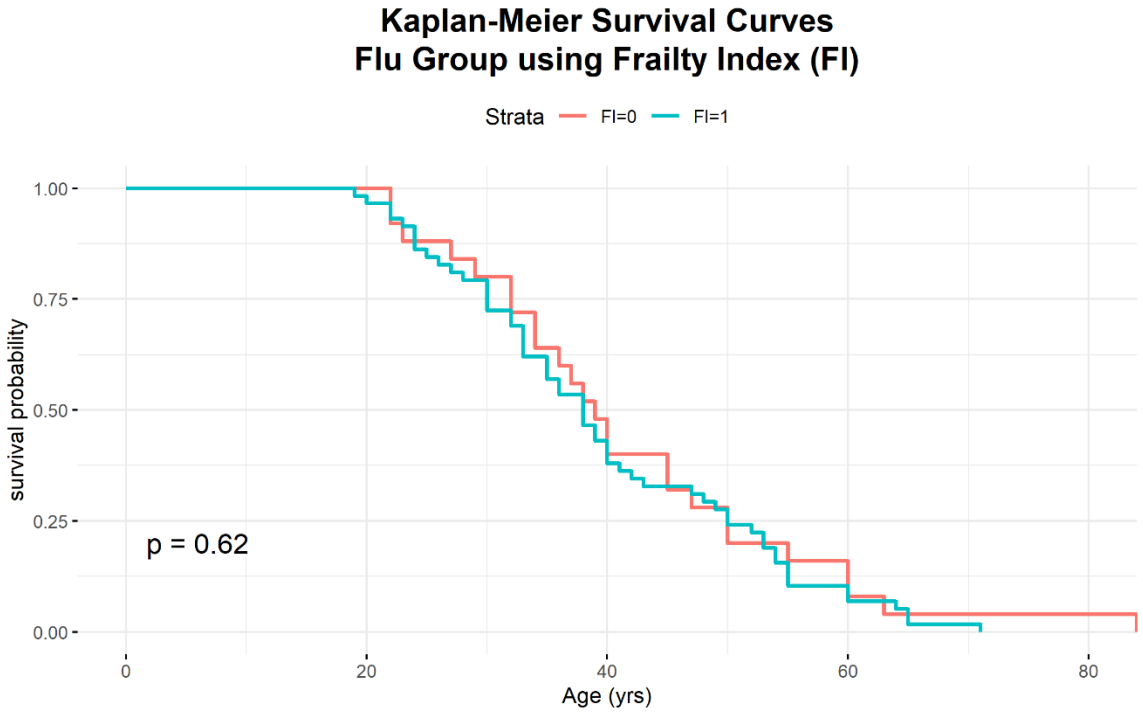
Kaplan-Meier Survival Curves of Control Group Using Frailty Index



Note. Survivorship curves show the non-frail (red line) compared to the frail (green line) in the control group using the frailty index. P-value (0.16) is the result of the log-rank test.

Figure 9.

Kaplan-Meier Survival Curves of Flu Group Using Frailty Index



Note. Survivorship curves show the non-frail (red line) compared to the frail (green line) in those who died during the 1918 influenza pandemic using the frailty index. P-value (0.62) is the result of the log-rank test.

Table 16.

Results of Survival Analysis Using Frailty Index.

	Lesion Status	N	Median survival time (years)	Lower 0.95	Upper 0.95
Control	FI=0 – non-frail	79	45	42	50
	FI=1 – frail	262	44	40	45
Flu	FI=0 – non-frail	25	39	34	50
	FI=1 – frail	58	38	35	42

Table 17.

Cox Proportional Hazards Results for Frailty Index.

	Hazard Ratio	p-value	Lower 0.95	Upper 0.95
Control - Frail	1.20	0.16	0.93	1.54
Flu - Frail	1.11	0.62	0.70	1.18

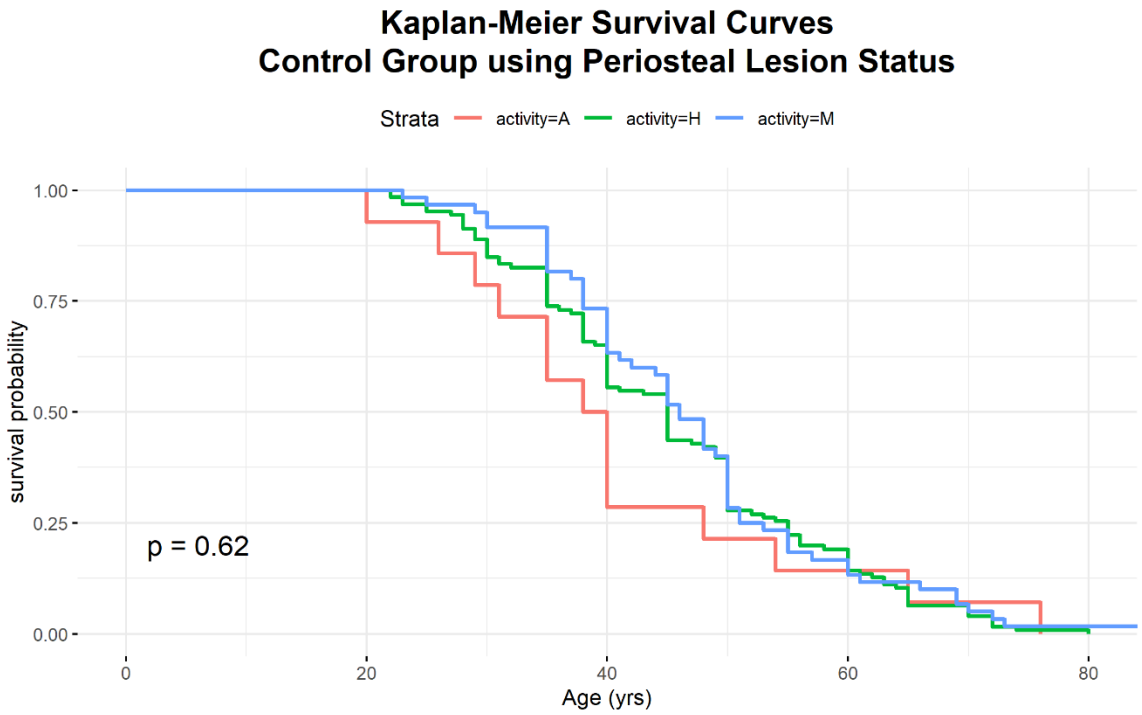
Note. Hazard ratios are in relation to non-frail individuals.

individuals with no periosteal lesions are not included. In the control group having active or healed lesions was associated with a greater risk of death compared to mixed lesions. Those with active lesions were 1.3 times more likely to die and those with healed about 1.1 times more likely to die.

Within the flu group (figure 11), individuals with active lesions showed the lowest survival values, but the survivorship of those with healed lesions decreased by a much greater magnitude. The median survival time for those with active lesions decreases only from 39 to 36 years while the median survival time for those with healed lesions decreases from 45 years to 38.5 years. During the flu, those with mixed lesions had greater survivorship than those with active lesions though the difference was not significant ($p=0.091$). According to the results of the Cox proportional hazards analysis (table 19), having active or healed lesions is still associated with an increase in the risk of mortality compared to mixed lesions. In the flu group active lesions were associated with a 2.9 times greater likelihood of death and healed lesions a 1.59 times greater likelihood. According to these results there is a greater risk of death associated with active lesions in the flu compared to the control.

Figure. 10

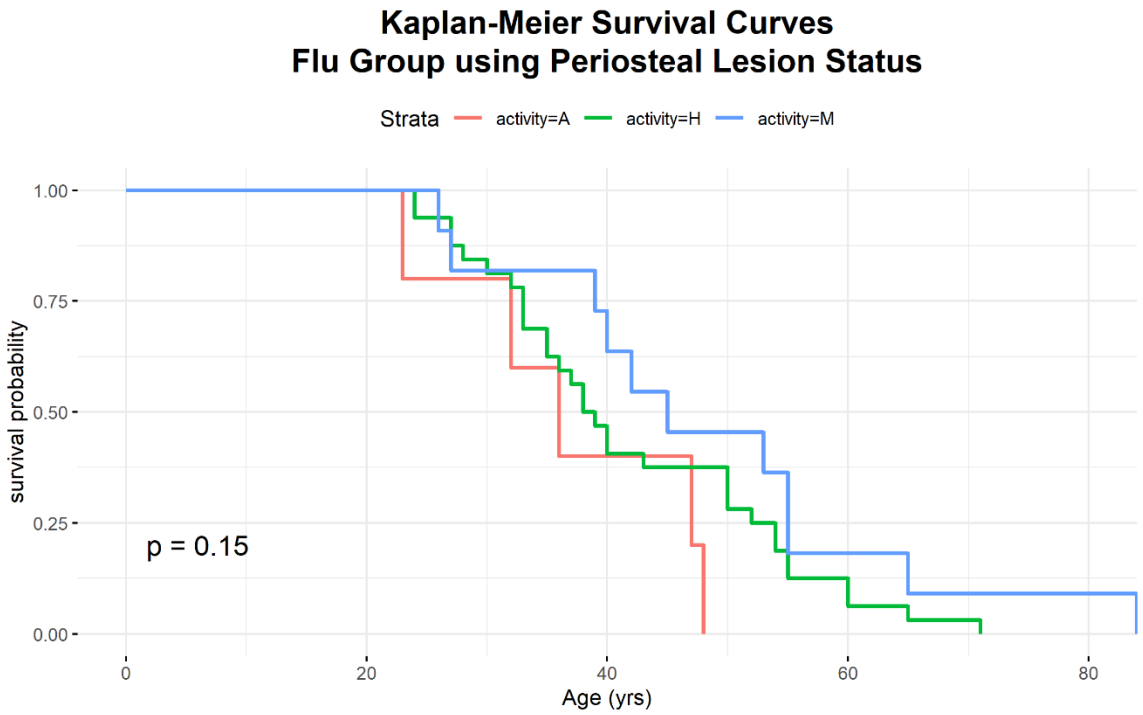
Kaplan-Meier Survival Curves of Control Group Using Periosteal Lesions



Note. Survivorship curves show survivorship of those with active (red), mixed (blue) and healed (green) periosteal lesions of the tibia in the control group. P-value (0.62) is the result of the log-rank test.

Figure 11.

Kaplan-Meier Survival Curves of Flu Group Using Periosteal Lesions



Note. Survivorship curves show survivorship of those with active (red), mixed (blue) and healed (green) periosteal lesions of the tibia in those who died in the 1918 flu pandemic. P-value (0.15) is the result of the log-rank test.

Table 18.

Kaplan-Meier Survival Results for Periosteal Lesion Activity Status

	Lesion Status	N	Median survival time (yrs)	Lower 0.95	Upper 0.95
Control	Active	14	39	35	65
	Mixed	60	46	42	40
	Healed	126	45	40	40
Flu	Active	5	36	32	NA
	Mixed	11	45	40	NA
	Healed	32	38.5	35	50

Table 19.

Cox Proportional Hazards Results for Periosteal Lesion Activity Status.

	Lesion status	Hazard Ratio	Lower 0.95	Upper 0.95
Control	Active	1.31	0.73	2.35
	Healed	1.10	0.81	1.50
Flu	Active	2.90	0.94	8.70
	Healed	1.59	0.78	3.25

Note. Hazard ratios are in relation to mixed tibial lesions.

Discussion

The results reveal a complicated picture of frailty and survival during the 1918 pandemic. In both pandemic and non-pandemic periods, frail individuals were more likely to die. During the flu, however, non-frail individuals died at a slightly greater rate than they did prior to the pandemic. Given that the global crude mortality rate of the 1918 flu was around 2.5% (Johnson and Mueller 2002; Patterson and Pyle 1991; Taubenberger 2005; Taubenberger and Morens 2006), or even as low as ~1% in the United States (Viboud et al. 2013), this small difference is expected. Based on the results reported here, the force of selective mortality decreased during the 1918 influenza pandemic, albeit very slightly. This means that healthy, non-frail individuals were more likely to die during the pandemic compared to non-pandemic times. However, non-frail individuals were not equally likely to die as frail individuals; those with frailty indicators were still more likely to die during the pandemic.

Considering the unusual mortality of young adults, a greater decrease in selective mortality was expected for those between 20-40 years old. In Figure 9, a greater separation between the survival curves for the frail and non-frail between the ages of 20-40 is visible. Though the difference is slight, this suggests that frailty had a greater impact on mortality for young adults compared to older adults.

Given that we do find modest support for increased frailty for young adults, do these offer support for any of the hypotheses discussed previously for the cause of high young adult mortality in 1918? We discuss implications for the cytokine storm hypothesis, and the tuberculosis co-morbidity model.

A central assumption of the cytokine storm hypothesis is that the young adults who died were the most healthy individuals. The results found here partially support this hypothesis: due to the decrease in selective mortality more non-frail people were dying who would have been at risk for the cytokine storm. However, frail individuals were still more likely to die, suggesting that the cytokine storm could not have been the sole explanation for the unusual mortality in the 1918 pandemic.

Based on these findings, we suggest that a broader interaction between periodontal disease and influenza may have increased the risk of cytokine storms. As mentioned above, a cytokine storm occurs when the immune system releases excessive cytokines – a class of pro-inflammatory proteins. Periodontal disease is caused by dysregulation of inflammatory processes, which includes cytokine activity (Andrukhov et al. 2011; Hegde and Awan 2019; Okada and Murakami 1998; Ramadan et al. 2020; Seymour and Gemmell 2001). Periodontal disease has also been linked with other chronic inflammatory conditions such as rheumatoid arthritis (Berthelot and Le Goff 2010; Bingham III and Moni 2013; Detert et al. 2010; Potempa et al. 2017) and inflammatory bowel disease (Piras et al. 2017; Poyato-Borrego et al. 2020; She et al. 2020; Vavricka et al. 2013), as well as pneumonia and chronic obstructive pulmonary disorder (Azarpazhooh and Leake 2006; Raghavendran et al. 2007; Scannapieco et al. 2003). Periodontal disease has been associated with low levels of systemic inflammation (Acharya et al. 2017; Hajishengallis and Chavakis 2021; Loos 2005; Marouf et al. 2021; Molayem and Pontes 2020).

There is little scholarship exploring how coinfection with periodontal disease and the influenza virus influences morbidity and mortality. However, recent research suggests that Covid-19-periodontitis coinfection may place patients at greater risk for cytokine storms and poor health outcomes (Botros et al. 2020; Fabri 2020; Gupta and Sahni 2020; Hajizadeh et al. 2021; Kara et al. 2020; Marouf et al. 2021; Molayem and Pontes 2020; Sahni and Gupta 2020; Siddharthan et al. 2020; Sukumar and Tadepalli 2021). As of yet, this hypothesis has not been able to be extensively tested. Marouf et al. (2021) found that Covid-19 patients with pre-existing periodontal disease had greater likelihood of requiring ventilators, admission to the ICU, and death. Larvin et al. (2020) found that while individuals with self-reported periodontal disease had no greater risk of Covid-19 infection, those with painful/bleeding gums were almost two times as likely to die of Covid-19 compared to the control group. While there are important differences between SARS-CoV-2 and the 1918 H1N1 influenza, it is likely that a co-occurrence of periodontal disease and influenza increased the risk of an out-of-control inflammatory response and elevated the risk of death. Furthermore, a person with periodontal disease would have been perceived as "healthy" by those around them even though they had an underlying source of frailty.

The results of this study may also shed light on the tuberculosis hypothesis. Previous studies have found a relationship between tuberculosis and influenza mortality in 1918 (Espersen 1954; Herring and Sattenspiel 2007; Mamelund and Dimka 2019; Noymer and Garenne 2000; Oei and Nishiura 2012; Tripp et al. 2018; Zürcher et al. 2016). Noymer (2009), however, argues that tuberculosis may not have been a direct risk

factor for increased influenza mortality, but that the association may be due to coincidental overlapping groups of at-risk individuals. The results found here support the hypothesis that tuberculosis was a direct risk factor for influenza mortality – namely that frail individuals were more likely to die. However, if tuberculosis were a significant risk factor for mortality in 1918, how do we explain the report of "healthy" individuals?

While the effects of latent tuberculosis infection are understudied, latent TB has been associated with increased chronic inflammation (Cowan et al. 2012; Huaman et al. 2016; Jensen et al. 2013; LaVergne et al. 2020; Naik et al. 2020) as well as greater risk of other adverse health outcomes (Huaman et al. 2018; Naik et al. 2020). Studies have reported a correlation between prior tuberculosis infection and worse outcomes from influenza (Abadom et al. 2016; Archer et al. 2009; Puvanalingam et al. 2011; Walaza et al. 2020). Crespo et al. (2017) found that cells previously exposed to *M. tuberculosis* showed an inflammatory response when subsequently exposed to *P. gingivalis*, one of the types of bacterial responsible for periodontal disease (PD). The authors conclude that "chronic infections like TB … may cause a systemic inflammatory shift that can affect other inflammatory processes such as the one present in PD" (p. 143). Crespo et al. (2017) further proposes a framework for examining latent tuberculosis in the bioarchaeological record. Individuals with latent TB would express a hyperinflammatory phenotype, which would result in osteological evidence of periodontal disease, but no skeletal evidence of tuberculosis. These expectations align well with the results found here. Individuals with latent tuberculosis, have no discernible symptoms (Barry et al. 2009; CDC.gov 2020; Pai and Rodrigues 2015), and in a time before testing was widely

available could have easily been viewed as "healthy." It seems possible, then, that latent tuberculosis could be responsible for the high mortality rate among young adults in 1918, the perception of these individuals as "healthy," as well as the increased risk of death due to frailty markers found here.

Implications for Bioarchaeology

The results of this study have implications for our understanding of stress, skeletal lesions, and frailty in the bioarchaeological record. Collecting descriptive statistics on lesion activity status has been common for decades (Andrushko 2007; Bartelink 2006; Berger and Wang 2017; Buikstra and Ubelaker 1994; Rose 1989; Shuler 2011; Šlaus 2000). While the understanding of healed skeletal lesions as a reflection of recovery and resilience is not new (e.g. Mensforth et al. 1978), Wood et al. (1992) were among the first to amplify this idea within bioarchaeology and emphasize the role lesion status may play in revealing variation in frailty. Summarizing data from an Oneota sample, Wood et al. (1992) showed that active cranial lesions are more common in individuals who died in childhood while healed/healing lesions are more common among those who survived to adulthood. Bauder (2009) and Marx (2011) used the proportion of active to healed/healing lesions as a "survivorship index," assuming that healed lesions are indicative of greater survival. DeWitte (2014), however, was the first to explicitly test the impact of lesion status on survivorship. Using Kaplan-Meier survival analyses, she demonstrated that individuals with active tibial periosteal lesions had the lowest survivorship, and individuals with mixed and healed lesions had middling and greatest survivorship, respectively. Budd and Wissler (2016) replicated DeWitte's (2014) study

using a Nubian sample and found similar results. This study, however, finds that individuals with mixed periosteal lesions had greater survival than those with healed lesions, as do the aggregate results of Schwalenberg (2020). Using a sample of individuals from Colonial Period Peru, Phillips (2019) found that the presence of periosteal lesions of the tibia was associated with increased survival rather than mortality. These varying results suggest that lesion activity status is more complicated than previously thought and may be context and sample-dependent. More studies that explore the connection between lesion status and mortality are needed to understand this variation and develop a more holistic picture of the relationship between skeletal lesions and frailty.

The results found here also expand our knowledge of the impact of lesion status across the life course. DeWitte's (2014) study included individuals of all ages, but all with active lesions and approximately half of those with mixed lesions are below the age of 20. The sample used by Phillips (2019) is mostly adult individuals over the age of 15. Given that anyone who has made it to adulthood is a survivor, it is possible that the impact of lesion activity (or even lesions in general) may vary over the life span and decrease in adulthood. Figure 1 from DeWitte (2014) showed that the strength of selective mortality associated with lesions tapers off after age 40. Similarly, our Figure 3 shows that after age 50, lesion activity status plays almost no role in shaping variation in mortality. The results found by McFadden and Oxenham (2020) support the hypothesis that the risk of mortality associated with nonspecific indicators of skeletal stress can vary over time. They reanalyzed data on cribra orbitalia from the Global History of Health

Project, separating juveniles from the samples. They found that approximately half of the samples demonstrating a significant relationship between cribra orbitalia and survival in combined samples, showed no relationship after juveniles were removed.

This study contributes to our understanding of selective mortality in diverse burial contexts. DeWitte and Wood (2008) used bioarchaeological data to test the assumption that the Black Death was not selective regarding frailty. Like the results found here, frail individuals were more likely to die than the non-frail during this epidemic event. We hypothesize that all deaths due to natural causes, i.e. excluding accident/homicide/suicide, are subject to selective mortality. While epidemic events show a decrease in the strength of selective mortality, resulting in more non-frail individuals dying, the most frail will always be at the greatest risk (Kyle et al. 2018). This has implications for our understanding of burial contexts and selective mortality. Singleton or mass burials – if they result from natural causes such famine or disease – will never be entirely catastrophic and will contain the frailest individuals of a population. The only wholly catastrophic assemblage – meaning that all members of the population, regardless of frailty status, are equally likely to be included – may be one caused by a mass casualty event such as war, accident, or massacre. To fully investigate selective mortality in bioarchaeological assemblages, researchers need to recognize the limitations of their samples and may need to be creative when searching for unique burial contexts.

This paper has several limitations. Firstly, the small sample size, particularly of the flu group, means that some of the statistical analyses were underpowered. While trends in the data can be seen, statistical significance could not be properly assessed.

Secondly, while the ages at death listed for the individuals of the Hamann-Todd are generally accurate, the evidence of "age-heaping" suggests that some non-random variation may have been introduced into the analyses.

Conclusion

This paper used a bioarchaeological approach to test the assumption that healthy individuals were as likely to die as frail individuals during the 1918 influenza pandemic. Using Kaplan-Meier survival and Cox proportional hazards analysis, we show that while more non-frail individuals died during the pandemic compared to the pre-flu period, frail individuals were more likely to die overall. These results enhance our understanding of the unusual age-at-death distribution during the 1918 flu. Demonstrating that frail individuals were more likely to die in 1918 allows new critical investigation into previous explanations. We also propose a novel hypothesis that systemic inflammation due to periodontal disease may have increased the risk of cytokine storms during the influenza pandemic and contributed to greater mortality among young adults. This research demonstrates how bioarchaeology can inform our perspectives on historical pandemics and contribute valuable new insight to public health research. Additional study in this area can increase our knowledge of differential frailty in past and present contexts, enhancing our ability to mitigate the effects of pandemics.

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CHAPTER 5

CONCLUSION

This dissertation engages the osteological paradox by improving the methodological handling of bioarchaeological data and contributing to our understanding of skeletal lesions as indicators of frailty and resilience. It builds on previous scholarship to show that ideas expressed by Wood et al. (1992) should be viewed as a framework for elevating our understanding of the interactions between skeletal lesions, frailty and survival as well as how they are shaped by biological, demographic, and cultural factors, rather than as a challenge that needs to be "solved." Chapter 2 presents background information on the handling of missing data in bioarchaeology while Chapter 3 demonstrates how imputation of missing paleopathology data can enhance bioarchaeologists' ability to analyze skeletal lesions. Chapter 4 incorporates methods proposed in Chapters 2 and 3 to analyze skeletal data from the Hamann-Todd Collection to answer the question: were healthy individuals as likely to die as frail individuals during the 1918 influenza pandemic? Together, these chapters contribute to a more nuanced understanding of the relationship between frailty, selective mortality, and skeletal lesions.

Summary of Results

This dissertation had two primary goals: 1) to establish a new approach for the handling of missing paleopathology data that will facilitate the use of new analytical methods for exploring frailty and resiliency in skeletal data, and 2) to investigate the role of prior frailty in shaping selective mortality in the 1918 influenza pandemic using a

novel bioarchaeological approach. How these goals were achieved in the preceding chapters is discussed below.

Chapter 2 broadly explored how missing data are handled in bioarchaeology by conducting a review of the literature. All bioarchaeology articles published between 2011-2020 from four anthropology journals (*American Journal of Physical Anthropology, International Journal of Paleopathology, International Journal of Osteoarchaeology, Bioarchaeology International*) were reviewed. Each article was searched for the following terms when used in the context of missing data: "absent," "imputat," "replace," "missing," and "unobserv." We identified 276 articles that met the search term criteria that were further categorized by subject topic and by the level of theoretical and statistical rigor in which missing data were managed.

The results revealed considerable variety in how bioarchaeologists handle missing data, yet overall they rely on the least rigorous approaches. Methods such as antimere substitution and deletion are used widely across subject topics. Archaeology, pathology, and trauma articles used more basic missing data methods, while those such as biodistance and morphology more often employed advanced statistics. Despite the ubiquity of missing data, theoretical considerations of how they introduce bias are uncommon and standards for reporting are inconsistent. In Chapter 2 I propose a series of recommendations to improve techniques for handling and reporting missing data. These consist of (1) detailed descriptions of procedures for data collection, (2) explanations of any pre-analysis data treatments, (3) disclosing the presence of missing data in the sample, or when there are no missing data, (4) considerations of how missing data may

impact sample representativeness, and (5) testing for problematic patterns of missing data. Greater attention to these issues will increase the statistical rigor of the field, address fundamental areas of concern, and lead to new areas of anthropological inquiry.

Chapter 3 built upon Chapter 2 in developing and testing a new methodology for handling missing bioarchaeology data. Imputation is widely considered the best method for managing missing values, yet the results of Chapter 2 suggest it is underused in bioarchaeology. To determine the best technique for bioarchaeological data, a test of six imputation methods (predictive mean matching, mean, random, random forest, expectation maximization, stochastic regression) was conducted on a sample of ordinal and continuous variables. The success of each method at obtaining unbiased estimates of the sample mean, variance, Kendall's tau, and Cohen's Kappa were compared with listwise and pairwise deletion.

In all instances, listwise deletion was least successful at obtaining the original parameters. Pairwise deletion performed well for ordinal data but ranked toward the bottom for continuous data. Imputation of continuous data was successful for 40% missingness, with stochastic regression and predictive mean matching ranked highest. Imputation of ordinal pathology data was more difficult, but several imputation methods were able to recover original parameter estimates with up to 30% missingness. These findings support the use of imputation methods over deletion for handling missing bioarchaeological and paleopathology data, especially when the data are continuous. Whereas deletion methods reduce sample size, imputation maintains sample size, improving statistical power and preventing bias from being introduced into the dataset.

Chapter 4 expanded our knowledge of the relationship between frailty and mortality by testing the widely held assumption that adults who died during the 1918 influenza pandemic were "healthy." Skeletal pathology and age-at-death data were collected from 424 individuals from the Hamann-Todd Documented Collection. Presence/absence data and activity status were collected on five nonspecific indicators of skeletal stress known to be correlated with increased frailty in this sample (porotic hyperostosis, cribra orbitalia, linear enamel hypoplasia, periodontal disease, and periosteal lesions of the tibia). Missing data were imputed following the recommendations established in Chapter 3. Individuals were deemed frail if they had at least two skeletal stress indicators or active periosteal lesions. The sample was separated into a flu group (n=83) and a control group (n=341).

Using Kaplan-Meier survival and Cox proportional hazards analyses, I tested if individuals who were non-frail were equally as likely to die as those who were frail during the 1918 flu. The results demonstrated that while more non-frail individuals did die during the pandemic compared to non-pandemic times, frail individuals were more likely to die during both time periods. These findings suggest that at least some of the individuals perceived as "healthy" in 1918 had some underlying frailty that was captured in the bioarchaeological data. Furthermore, the conclusions of this chapter increase our understanding of selective mortality during epidemic events.

Future directions and Intellectual Merit

The results of this dissertation lay the groundwork for future research on missing data methods in paleopathology as well as investigating selective mortality and frailty

within the context of the 1918 influenza pandemic. As mentioned in Chapter 3, the sample sizes for testing the imputation of missing continuous and ordinal values were quite large compared to most paleopathology studies. The techniques that worked best with a larger sample may be less appropriate with a smaller one. Additional imputation case tests are required to clarify which missing data method works best given different sample sizes.

Chapter 4 hypothesized that systemic inflammation caused by periodontal disease may have increased the risk of cytokine storms during the 1918 flu. This interaction may have contributed directly to the unusually high mortality among young adults as well as the perception that people who were dying were "healthy." Increasing the sample size by incorporating more individuals and collecting more detailed information on the severity and activity of periodontal disease would help further tease out this potential relationship.

This research established that differential frailty played a role in contributing to selective mortality in the 1918 influenza pandemic. The next step is to identify additional specific risk factors that may shape variation in frailty and resilience. Previous scholarship has suggested that a variety of factors influenced the risk of morbidity and mortality during the 1918 flu. These include socioeconomic status (Bengtsson et al. 2018; Grantz et al. 2016; Mamelund 2006; Mamelund 2018; McCracken and Curson 2003; Murray et al. 2006; Tuckel et al. 2006), race and racism (Britten 1932; Dahal et al. 2018; Gamble 2010; Herring and Sattenspiel 2007; Mamelund 2001; Mamelund 2011; Økland and Mamelund 2019; Pool 1973; Schmitt and Nordyke 1999; Shanks et al. 2012; Tomkins 1992; Wilson and Baker 2008), and sex/gender roles (Ammon 2001;

Brennaman 2019; Paskoff and Sattenspiel 2019; Rice 2018; Tuckel et al. 2006; Wilson et al. 2014; Winslow and Rogers 1920). The findings of these studies, however, have generated mixed results about how and why these factors contributed to increased morbidity and mortality. For example, some authors have reported that African Americans experienced lower rates of morbidity and mortality during the fall wave of the pandemic compared to white Americans (Britten 1932; Frankel and Dublin 1919; Frost 1920; Garrett 2008; Opie et al. 1919). Økland and Mamelund (2019), on the other hand, found that white Americans experienced greater morbidity in fall of 1918, but African Americans had greater case fatality. Combined with data obtained from documentation and historical records, bioarchaeological analyses can help untangle these uncertainties by examining how intersecting identities affected frailty and survival in 1918.

Another research agenda that will stem from this dissertation is investigating how selective mortality during the 1918 influenza shaped the lives of the survivors. As mentioned previously, prior research on the Black Death demonstrated that pre-existing frailty influenced the risk of death from the Black Death (DeWitte 2009; DeWitte 2014a; DeWitte and Hughes-Morey 2012). Due to the removal of large numbers of frail individuals from the population, post-epidemic populations experienced increased survivorship for almost two centuries compared to those who lived before the epidemic (DeWitte 2014b). Interestingly, males experienced greater increase in post-epidemic survivorship greater than did females (DeWitte 2018). Very few studies have considered the long-term impacts of the 1918 flu on population health and demography. This

research program will have strong implications for our ability to elucidate the long-term transformative power of disease to shape human biology and society.

The results of this dissertation first and foremost expand our knowledge of the 1918 influenza pandemic. Scholars are still unsure why age-at-death distribution was so unusual, why certain populations suffered catastrophic mortality rates, and why there was substantial variation in mortality. This dissertation demonstrated that underlying frailty influenced mortality in 1918. These results will contribute to the dialogue on why young adults were disproportionately at risk. They can be used to bolster certain theories such as the cytokine storm and tuberculosis hypotheses.

This study is the first to utilize bioarchaeological data to examine the 1918 influenza and demonstrates the potential for additional study in this area as well as for other historical pandemics. Seasonal and epidemic influenza represents an enormous drain on social and economic resources caused by lost work-days, hospitalizations, medical visits and deaths (Molinari et al. 2007; Reed et al. 2015). Many of the viral strains of influenza that continue to plague the world population are descendants of the 1918 H1N1 virus (Taubenberger and Morens 2006). By continuing to risk factors for increased influenza mortality and characterizing how the disease may spread differently in various populations, these avenues of research can aid with predicting how a future influenza outbreak could affect modern populations.

Bioanthropological study of epidemics is a relatively new area of inquiry yet it has permitted valuable new insight into heterogeneous frailty and selective mortality. The new discipline has stimulating the growth of a variety of subfields including

paleodemography, paleoepidemiology, and paleopathology. However, because of the relative novelty of this research, our understanding of changing patterns of mortality and survivorship in epidemic contexts is largely founded on work conducted on the Black Death in Europe. This dissertation provides an invaluable comparative datapoint for assessing how frailty and selective mortality may vary during an entirely different epidemic event.

This dissertation enriches the knowledge base and theory of anthropology and related fields, as it combines methods and theory from multiple disciplines including bioarchaeology, epidemiology, demography, and statistics to examine the origins and evolution of human health and selective mortality. By identifying the foundations of differential survival, this project will augment our understanding of how the forces of natural selection shape biological vulnerability within our species.

By drawing attention to the widespread use of deletion methods for handling missing data in bioarchaeology, this dissertation also provides a framework for the use of imputation to manage missing values in paleopathology datasets. Statistically and theoretically rigorous approaches to missing data will improve the size and composition of bioarchaeological datasets and permit the use of more advanced statistical analyses – opening new realms of inquiry for bioarchaeologists and paleodemographers.

Pandemics on the scale of the 1918 influenza and the current Covid-19 have a remarkable ability to shape human society, genetics, and immunity. At the same time, human behavior can force change in pathogen behavior and biology. Elucidating this complex human-pathogen relationship helps us understand variation in pathogen

virulence and infectious disease etiology. This dissertation adds temporal depth to our understandings of the long-term interactions between humans and their disease environment, improving our scientific knowledge of human-pathogen coevolution.

As we saw in 2020, the threat of devastating global pandemics is high. In this increasingly interconnected world, it is likely that Covid-19 will not be the last one many of us face in our lifetimes. As such, we must already begin thinking about risk factors for infection, cultural and biological sources of resilience, how to distribute health warnings, combating fake information, and ensuring equitable access to medical care. This dissertation shows how anthropologists and social scientists can contribute vital information and unique perspectives to this area of discourse (DeWitte 2016; van Doren 2021). We are trained to understand how human biology is shaped by social, cultural, and historical contexts in ways that medical professionals often are not. We know that structural inequalities shape morbidity and mortality and that historical context is key to understanding them. This dissertation adds temporal depth to our understandings of the long-term interactions between humans and their disease environment and the development of health disparity. Despite being able to contribute nuanced perspectives on how social factors shape one's health, recent history has shown that epidemiologists and medical doctors are unlikely invite social scientists and anthropologists to be part of their conversation. This dissertation integrates commonly used types of demographic information, that may seem more familiar and reliable, with novel skeletal data. We hope that research such as this will help break down the barrier separating the social scientists from the hard scientists leading to greater collaboration between disciplines. Multiple

perspectives will expand our knowledge of pandemic risk factors and combating future outbreaks.

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APPENDIX A

AUTHOR CONTRIBUTIONS

Chapter 2 of this dissertation was coauthored. Kelly Blevins has granted her permission for a modified version of this publication to be included in this dissertation.