CHAPTER EIGHT

Sex and Frailty

Patterns from Catastrophic and Attritional Assemblages in Medieval Europe

Sharon N. DeWitte

IN LIVING HUMAN POPULATIONS, THERE ARE IMPORTANT SEX DIFFERentials in risks of mortality, and in the majority of living populations that have been studied, females tend to face lower age-specific mortality rates at most or all ages and to live longer than males (Lopez and Ruzicka 1984; Coale 1991; Teriokhin et al. 2004; Case and Paxson 2005). For example, in the overwhelming majority of 225 populations for which data are available, female life expectancy at birth was longer than that for males, and in many cases the differences were quite dramatic (https://www.cia.gov/library/publications the-world-factbook/index.html). There are few exceptions to this general pattern; male life expectancy exceeds female life expectancy in less than 3% of the countries observed. The worldwide patterns of age-specific mortality rates in living populations are similar to those observed for life expectancy. As shown in table 8.1, age-specific mortality rates were higher for males than for females in every age interval from birth to 100 years in the majority of regions around the world in 2009 (World Health Organization 2012).

Sex differentials in mortality that favor females exist, in part, because males are more susceptible to a wide variety of diseases caused by viruses, bacteria, parasites, and fungi (e.g., Brabin and Brabin 1992; Klein 2000; Noymer and Garenne 2000; Wells 2000; Owens 2002; Pennell et al. 2012). The prevalence or incidence of many diseases, such as tuberculosis, meningitis, respiratory infections, and hepatitis, also is higher in males than

Table 8.1 Regions Worldwide ($n = 193$) Where Male Age-Specific Mortality Was Higher than Female Age-Specific Mortality in 2009

AGE (YEARS)	NUMBER	%
< 1	180	93.26
1–4	128	66.32
5–9	146	75.65
10–14	153	79.27
15–19	167	86.53
20–24	173	89.64
25–29	163	84.46
30–34	165	85.49
35–39	177	91.71
40–44	188	97.41
45–49	190	98.45
50–54	189	97.93
55–59	189	97.93
60–64	187	96.89
65–69	186	96.37
70–74	189	97.93
75–79	182	94.30
80–84	184	95.34
85–89	179	92.75
90–94	169	87.56
95–99	165	85.49

Source: World Health Organization 2012

females (Rustgi 2007; Falagas et al. 2007; Oren et al. 2011; Case et al. 2012; Mobarak 2012). For many diseases, even when the prevalence or incidence is quite similar for males and females, or in some cases even higher in females, males tend to suffer more severe symptoms and face higher risks of death (Acuna-Soto et al. 2000; Leone et al. 2004; Jansen et al. 2007; Diaz 2011).

Males are also at higher risk of morbidity and death from many degenerative diseases, such as cardiovascular diseases, diabetes, malignant neoplasms, and cirrhosis of the liver (e.g., Lopez 1984; Pilote et al. 2007; Kalra et al. 2008; Silbiger and Neugarten 2008). Many external causes of death, such as accident, suicide, homicide, and interpersonal violence, disproportionately affect males (World Health Organization 2008). Similarly, male fetuses and

neonates are more likely than females to die from such external causes as birth trauma, intrauterine hypoxia, and birth asphyxia (Waldron 1998).

Males do not suffer disproportionately from all diseases. Malaria and toxoplasmosis, for example, more severely affect females even though the incidences of the diseases are frequently similar in both sexes (Vlassoff and Bonilla 1994; Roberts et al. 2001). Mortality from measles and influenza is significantly higher for females compared to males from birth to age 45 (Garenne 1994; Klein et al. 2011). Some degenerative diseases also disproportionately affect females. For example, there is a higher prevalence of chronic obstructive pulmonary disease, arthritis, reproductive cancers, and autoimmune disorders among females (Case and Paxson 2005; Fairweather et al. 2008; Cote and Chapman 2009; Amur et al. 2011; Pennell et al. 2012; Sawalha et al. 2012), and females are more likely to suffer more severe symptoms and higher mortality from stroke and diabetes (Moriyama 1984; Reeves et al. 2008).

Obviously, maternal mortality (death while pregnant or during a short period after giving birth) exclusively affects females (Kamel 1984), and pregnancy itself can increase susceptibility to certain diseases (Roberts et al. 2001; Rothberg et al. 2008). In populations where differentials favoring males exist, they are often attributed to the complications associated with pregnancy and childbirth, which are viewed as ultimately acting to balance the natural female advantages (see Lopez and Ruzicka 1984; Gage 1994).

Explanations for Sex Differentials

Despite the existence of some causes of death that disproportionately affect females, and a few exceptions to the general worldwide pattern of longer life expectancies and lower mortality rates for females, they appear to be generally less frail than males. In fact, in many cases where males seem to fair better overall, male fetal and neonatal mortality rates are nonetheless higher, and physiological stress appears to negatively affect male prenatal growth more strongly (Chen et al. 1981; Bhatia 1984; Stinson 1985). Both phenomena are often interpreted as reflecting the "innate frailty" (Bhatia 1984:167) or "higher biological risk" (Chen et al. 1981:57) of males. Essentially, higher risks of morbidity and mortality for males are viewed by many researchers as the natural biological condition. Exceptions where sex differentials favor males—at least at ages for which maternal mortality does not offer a satisfactory explanation—are often explained in terms of cultural factors (e.g., preferential provisioning of food or medical care to males in cultures with patrilineal

inheritance) or behavioral differences that create heterogeneity in exposure to risk factors (Chen et al. 1981; Stinson 1985; United Nations 2011).

In addition to the nearly universal patterns of sex differentials in longevity and in susceptibility to and risks of death from disease in humans, there are many species of mammals, fish, birds, reptiles, and insects in which females live longer and males suffer disproportionately from a variety of diseases (Clutton-Brock et al. 1982; Klein 2000; Moore and Wilson 2002; Owens 2002; May 2007; Zuk and Stoehr 2010). Such pan-species patterns further indicate that sex differences in mortality are due at least in part to fundamental biological differences between the sexes (Retherford 1975). There are several possible mechanisms underlying the observed sex differentials in morbidity and mortality, including the effects of sex hormones, genetic differences, and behavioral differences.

Sex hormones greatly influence susceptibility to and severity of disease (Klein and Roberts 2010). In general, estrogens enhance immune competence, whereas androgens reduce it, and females thus tend to mount stronger immune responses (Ahmed et al. 2010; Klein and Huber 2010). The immune-enhancing effects of estrogens include the upregulation of pro-inflammatory cytokines and associated molecules, increasing the phagocytic activity of macrophages, increasing the activity of interferon-producing killer dendritic cells, enhancing antibody production by B cells, and enhancing CD4+ T cell differentiation (Ahmed et al. 2010; Klein and Roberts 2010). Androgens tend to reduce immune competence by, among other things, suppressing pro-inflammatory responses, limiting the size of the thymus, limiting macrophage activity, reducing the function of CD4+ T cells, and inhibiting mast cell/basophil activity (Ahmed et al. 2010; Alexander et al. 2010). Numerous studies have demonstrated the beneficial effects of estrogen (or the costs of a lack of sufficient estrogen) with respect to infectious and degenerative diseases (e.g., Leone et al. 2004; Choi and McLaughlin 2007).

Sex differentials in morbidity and mortality associated with infectious and parasitic diseases can result from differences in behavior. For example, the higher prevalence and severity of certain parasitic infections (e.g., schistosomiasis) in females in many populations result from females' heightened risk of exposure to pathogens in water (which contains the disease agents themselves or their vectors) while engaging in gendered activities like food preparation and fetching water for the household (Vlassoff and Bonilla 1994). In the case of bubonic plague, the prevalence is higher for men in the United States (Butler 1989; Poland 1989) because hunting and ranching activities, which increase

one's risk of encountering infected animal vectors, are more commonly engaged in by men (Cleri et al. 1997; Perry and Fetherston 1997). On the other hand, in Tanzania, women are more commonly infected by bubonic plague, likely because of differences in sleeping locations (men sleep in beds, women sleep on the floor) or differences in outdoor activities that increase the risk of exposure for women (Davis et al. 2006; Kamugisha et al. 2007).

Sex differentials in extrinsic causes of mortality are partly the result of males engaging more frequently in risk-taking behaviors that might result in injury or death. Such behavioral variances are the result of differences in both socialization and sex hormones (Waldron 1998).

Differences between the sexes are also thought to result from variation in access to and utilization of health care. Excess female mortality during childhood is found in several areas of the world where parents are less likely to obtain medical care, including vaccinations, for daughters compared to sons (United Nations 2011). In other populations, men suffer higher morbidity and mortality from many diseases (even when controlling for sex-specific conditions) because they are less likely to seek medical care and are less likely to comply with medical treatment (Oksuzyan et al. 2008). The sex differentials associated with some degenerative diseases are also the result, in part, of behavioral differences, such as higher rates of cigarette smoking and alcohol consumption among men; both behaviors are linked to excess mortality from such causes as coronary heart disease, certain cancers, and cirrhosis of the liver (Hetzel 1984; Lopez 1984).

Some behavioral differences between the sexes that are associated with variation in morbidity and mortality are ultimately associated with hormonal differences. For example, sex hormones might influence sex differentials in age-specific mortality rates or life expectancies via higher rates of injury in males, since exposure to higher testosterone levels is associated with higher activity levels, risk taking, and physical aggression (Waldron 1998). Aggressive behavior itself might result in increased androgen concentrations in the body and thus increased susceptibility to infection via the immunosuppressive effects of such hormones (Klein 2000).

Genetic differences, beyond those that underlie differences in sex hormone production, also determine some sex differentials in mortality. For example, diseases that are caused by recessive X-linked genes, such as X-linked immunodeficiency syndromes, disproportionately affect males (Waldron 1984, 1998). There is evidence of a genetic component to sex differences in hypertension, since the second X chromosome in females appears to play a

role in maintaining normal blood pressure independent of the effect of sex hormones (Sandberg and Ji 2012). Similarly, lupus is more common in females, at least partly because of X-linked gene dosing effects, since males with Klinefelter syndrome (XXY) develop lupus at approximately the same rate as females do (Sawalha et al. 2012). Researchers have found several examples in mouse models of sexually dimorphic loci that affect viral infection severity and disease susceptibility genes, whose effects are moderated by sex hormones (Klein and Huber 2010).

Sex Differentials in the Past

The pervasiveness of female advantages in living populations has prompted many researchers to examine sex patterns of morbidity and mortality in the past. Such studies have primarily been done using historical records, but unfortunately good documentary data on sex and age patterns of disease and mortality are generally limited to the last 200 years and are not available for all populations. According to Bullough and Campbell (1980), in the ancient and medieval periods it was generally believed that men lived longer than women, and beginning in the fourteenth century, some documents indicate that women lived longer than men. Unfortunately, there are few empirical data to confirm such patterns. There is some historical evidence that mortality rates were lower for females in seventeenth-century London (Graunt 1975), but data on ages at death for both sexes in past populations are generally not available prior to the eighteenth century (Wrigley and Schofield 1981; Gage 2005). According to Coale (1991) and Retherford (1975), mortality rates have been lower for females in European populations in general since at least the mid-nineteenth century.

Empirical data from archaeological sites may allow for a more thorough examination of the antiquity of sex differentials in morbidity and mortality. Skeletal samples, though not completely free of biases themselves, can in many cases provide data that are missing from existing historical documents. For example, skeletal samples may provide data for people who were marginalized and therefore not represented in historical data, or may provide the only data available for past populations with no surviving written demographic records.

There is a long history of bioarchaeological examination of sex differences in mortality, and these studies have revealed a variety of often conflicting patterns and temporal trends. Bennett (1973), for example, estimates

higher life expectancies for females in a prehistoric southwestern United States sample, and Nagaoka and colleagues (2006) similarly find higher life expectancies for females in a medieval sample from Japan. However, Šlaus (2000) reports lower mean age at death among females in a medieval Croatian sample, and Storey and colleagues (2002) find significantly fewer females than males above the age of 40 at the Mayan site of Xcaret. Högberg and colleagues (1987), using life table analyses of medieval Swedish skeletal remains, estimate higher mortality rates for females between the ages of 14 and 59, but lower mortality rates for females compared to males at advanced adult ages, a pattern they ascribe to high maternal mortality at younger ages.

Bioarchaeological studies of sex differences in skeletal stress markers have also revealed variable patterns. Many studies have found higher frequencies of skeletal lesions among males in the past. For example, studies of prehistoric Native American samples by Ortner (1998), Larsen (1998), and Cassidy (1984) find higher frequencies of periosteal lesions (indicative of inflammation of the periosteal membrane covering bone in response to nonspecific infection or trauma) in males than in females. According to Guatelli-Steinberg and Lukacs (1999), when significant differences in enamel hypoplasia (enamel defects indicative of disease or malnutrition during childhood) exist in skeletal samples, there is generally a higher frequency in males.

In contrast, many other studies have found higher frequencies of lesions in females. For example, both Cucina and colleagues (2006) and Mittler and Van Gerven (1994) report higher frequencies of cribra orbitalia (porous lesions in the eye sockets often attributed to childhood anemia) in adult females at a second- to third-century Roman site and in a medieval Nubian sample, respectively. Similarly, King and colleagues (2005) find a higher frequency of linear enamel hypoplasia among females in samples from eighteenth- and nineteenth-century London, and Lukacs (2008 and this volume) has reported a general trend of higher dental caries frequencies in females, particularly in agricultural contexts.

Limitations of Bioarchaeological Studies of Sex Differentials

The varying patterns of sex differentials found in previous bioarchaeological studies might reflect real, underlying population or temporal differences in health and mortality. However, some of the observed variation might be the result, at least in part, of the limitations of the skeletal data and the methods used in those studies.

Although numerous studies have demonstrated that various skeletal stress markers are reliable indicators of frailty (e.g., Larsen 1997; Usher 2000; Roberts and Manchester 2005; DeWitte and Wood 2008; DeWitte and Bekvalac 2010; DeWitte and Hughes-Morey 2012), it is potentially problematic to compare raw frequencies of stress markers in order to evaluate differences in health. Doing so assumes that stress markers indicate identical levels of frailty for all individuals, and that might not always be the case. Despite frequent assumptions to the contrary, the stress markers that are typically used in bioarchaeological studies might not always indicate poor health (Ortner 1991; Wood et al. 1992; Milner et al. 2008). In order for individuals to develop a stress marker that can later be identified in their skeletal remains, they must be minimally healthy enough to survive a physiological stressor long enough for the stress marker to form to a detectable level. Some individuals in a skeletal sample might lack stress markers despite exposure to stress because they were very frail and died before skeletal stress markers had an opportunity to form. Other individuals in a sample might lack stress markers because they had low frailty and were either fortunate enough to avoid exposure to a particular stressor or had immune systems sufficiently robust to fight off disease before lesion formation could occur. The presence of skeletal stress markers might actually indicate relatively good health or low frailty in some cases, but this will not be apparent in a simple dichotomous comparison of lesion frequencies.

Attempts to infer health status from skeletal stress marker frequencies are also complicated by the fact that many stress markers are nonspecific, that is, a single stress marker can be caused by a variety of stressors, such as infectious disease, malnutrition, or traumatic injury. Thus, a single stress marker might be associated with a variety of physiological stressors that might have had varying effects on risks of mortality.

As with skeletal stress markers, there are problems with inferring health and mortality patterns using age-at-death data. Many bioarchaeological studies use traditional methods of age estimation, which have a tendency to underestimate older adult ages (Van Gerven and Armelagos 1983; Buikstra and Konigsberg 1985; Müller et al. 2002; Milner and Boldsen 2012). This occurs because traditional age estimates are biased toward known-age reference samples, which tend to be composed predominantly of young individuals (Bocquet-Appel and Masset 1982; Müller et al. 2002). Another limitation is the use of broad terminal age intervals (e.g., 50+), because of the difficulty of estimating age in older adults (Buikstra and Konigsberg 1985; Boldsen

et al. 2002). Combined, these limitations mean that analyses of sex differentials based on traditional age estimates will not be able to discern reliably (if at all) the patterns that might have existed at later ages, that is, precisely those ages at which sex differentials in many living populations become most dramatic (Retherford 1975; Moriyama 1984).

Several researchers have relied on life tables for assessing sex differences in mortality (e.g., Högberg et al. 1987). Life tables are representations of a population's age-specific mortality rates, survival rates, and other related measures. The construction of life tables using paleodemographic data is based on the assumption that the age-at-death distribution of a skeletal sample is equivalent to the cohort's age-at-death column in a life table (Milner et al. 2008). However, this is true only when the population that gave rise to a cemetery was stationary (i.e., closed to migration, with an intrinsic rate of increase equal to zero, and age-specific mortality and fertility rates that did not change over time), a condition that is not always met (Milner et al. 2008). Furthermore, life table analysis requires the estimation of the central mortality rate for each age interval. The reliable estimation of these parameters requires huge sample sizes and information about the original population at risk, neither of which are usually available to bioarchaeologists (Wood et al. 2002).

Hazards Analysis in Bioarchaeology

Many researchers argue that some form of hazards analysis is the most powerful way to derive information from the small samples typical of paleodemography (Gage 1988; Konigsberg and Frankenberg 1992, 2002; Buikstra 1997; Hoppa and Vaupel 2002; Wood et al. 2002), and some bioarchaeological work on sex differentials has utilized this approach. An analysis of sex differences in preindustrial and industrial revolution samples from London (DeWitte 2014) using hazards models found similar risks of mortality between the sexes in the earlier sample, but a higher risk for males in the industrial sample. Similar excess mortality among males during industrialization has also been observed in some historic data, and some researchers have attributed the differentials to social factors, including accidents at work (Vallin 1991).

Wilson (2010, 2014) uses a hazards analysis approach to assess temporal trends in mortality across Late Woodland and Mississippian samples and reports evidence of mortality crossovers. Female mortality rates were much higher than those of males (sometimes as much as twice as high) at young

adult ages, but were lower at middle and older adult ages, indicating the effects of high maternal mortality for females during their reproductive years. Kreger (2010) estimates adult mortality using a hazards model for postclassic Cholula, Mexico, and finds similar mortality rates between the sexes at younger adult ages, but excess male mortality at older ages.

The results of this research using hazards analysis approaches are promising, but the paucity of such studies indicates that further work needs to be done to deepen our understanding of the antiquity of sex differentials under a variety of conditions.

Sex Differentials in Frailty: The Case of the Black Death

My research addresses whether females experienced survival advantages compared to males in medieval Europe. I previously assessed sex differentials in frailty using skeletal material from the East Smithfield cemetery in northeastern London, an exclusively Black Death cemetery dated to the first outbreak of the medieval plague in London in 1349–1350 (DeWitte 2010b). In that study, I used hazards analysis to test whether exposure to physiological stress before the Black Death arrived in London (i.e., health history) subsequently affected the risk of death during the epidemic in the same way for adult males and females, or whether one sex was better buffered (i.e., less frail) than the other during the epidemic.

The previous study (DeWitte 2010b) reveals that there was excess mortality associated with skeletal stress markers for both sexes, but there was a higher excess mortality for males. These results suggest that both adult males and females who were already in poor health before the Black Death were more likely than their healthier peers to die during the epidemic, but the effects of previous physiological stress on risk of death were stronger for males. These results further suggest that females were less frail than males in this population; females with histories of physiological stress were better able to resist dying during the epidemic than were males with similar histories of stress.

The advantage of using the East Smithfield cemetery to examine sex differentials in medieval mortality is that the vast majority, if not all, of the individuals interred there died from the same cause of death in a very short period of time (several months). I was able to examine mortality patterns without the potential confounders of different causes of death or different temporal trends in mortality and fertility patterns (i.e., demographic nonstationarity), either of which might have obscured differences between the sexes. However, my focus

on the East Smithfield cemetery raised the question of whether the results are unique to the Black Death or are more widely reflective of general medieval mortality patterns. This chapter builds on my previous work by examining sex differences in the effects of physiological stress on risk of death in a normal, non-epidemic (i.e., attritional) cemetery sample from medieval Denmark for comparison with the results from East Smithfield.

Materials and Methods

EAST SMITHFIELD BLACK DEATH SKELETAL SAMPLE

As mentioned above, my analysis of the sex differential in frailty during the Black Death was conducted using a sample from the East Smithfield cemetery in London (DeWitte 2010b). This burial ground is one of only a few excavated cemeteries with both documentary and archaeological evidence clearly linking it to the fourteenth-century Black Death (Grainger et al. 2008). East Smithfield was used for the burial of victims of the Black Death in London during 1348–1350. According to records from the Church of the Holy Trinity, which note the exact location and dimensions of the burial ground, the East Smithfield cemetery was founded in late 1348 in anticipation of the overwhelming mortality associated with the Black Death (Hawkins 1990). During excavation, more than 600 individuals were disinterred from East Smithfield and are now in the care of the Museum of London's Centre for Human Bioarchaeology. Stratigraphic evidence indicates that the burials were completed in a single phase, and there is no evidence of interments after 1350 (Grainger et al. 2008). Most, if not all, of the individuals buried in the East Smithfield cemetery died as a result of the Black Death.

I selected a sample of 299 adults (173 males, 126 females) from the East Smithfield cemetery. This sample comprises all of the excavated adults from the burial ground who were preserved well enough to provide sufficient data on age, sex, and the presence of certain skeletal stress markers. Because of the difficulties associated with determining sex in juveniles, this study only examined patterns of mortality among adults.

ATTRITIONAL MEDIEVAL MORTALITY SKELETAL SAMPLE

The results previously obtained from East Smithfield (DeWitte 2010b) were compared to those from normal, non-epidemic mortality samples from

two medieval Danish urban parish cemeteries: St. Albani Church in Odense and St. Mikkel Church in Viborg, both of which date to the 1100s to mid-1500s and are part of the Anthropological Database at Odense University (ADBOU) collection. Given evidence that the Black Death targeted the sick and the elderly (DeWitte and Wood 2008; DeWitte 2010a) and caused dramatic demographic changes (Bowsky 1971; Hatcher 1977; Gottfried 1983; Herlihy 1997; Cohn 2002), and that catastrophic mortality can affect demographic patterns in the surviving population for decades (Paine 2000), for this study, I wanted to avoid using a post–Black Death sample as a comparison sample for East Smithfield. One major advantage of the Danish cemeteries is that they allow for the selection of a pre–Black Death sample based on the arm positions of the interred individuals (Kieffer-Olsen 1993; Jantzen et al. 1994). For comparison with East Smithfield, I selected a sample from the Danish cemeteries of adults interred with arm positions used exclusively or predominantly before the Black Death arrived in Denmark in 1350.

There are several other advantages to using the Danish cemeteries as a comparison for East Smithfield. The combined Danish sample is sufficiently large to allow for the estimation of the parameters of the model used in this study. Also, there were many economic, demographic, and social similarities between the English and Danish medieval populations up to the time of the Black Death (Benedictow 1993; Sawyer and Sawyer 1993; Poulsen 1997; Widgren 1997; Roesdahl 1999). The Danish cemeteries are also from urban areas, similar in kind, if not in scale, to London at the time. Last, there were probably genetic similarities between the two populations, which persist today, as a result of the preconquest Norse settlement of England (e.g., Capelli et al. 2003). These similarities between the English and Danish populations mean that differences between the two samples can be at least partly attributed to differences between Black Death and normal mortality. However, potential population variations must also be considered as an explanation for differences between the samples.

I selected a combined sample of 196 individuals (109 males, 87 females) from the St. Mikkel and St. Albani church cemeteries. This sample includes all of the adults (dated to 1100–1350) from these cemeteries who died before the Black Death arrived in Denmark in 1350 and were preserved well enough to yield data on age, sex, and the skeletal stress markers described below.

AGE ESTIMATION

Ages were estimated using transition analysis (Boldsen et al. 2002), an approach that avoids the problem of age mimicry associated with traditional methods (Bocquet-Appel and Masset 1982; Boldsen et al. 2002). The general approach of transition analysis begins with estimating, from a known-age reference sample, the conditional probability that a skeleton exhibits a certain age indicator stage, given the individual's known age. This conditional probability is then combined with a prior distribution of ages at death (either a uniform prior or an informed prior distribution based on documentary information) using Bayes' theorem to determine the posterior probability that a skeleton in the unknown-age target sample died at a certain age, given that it displays particular age indicator stages.

For this study, transition analysis was applied to skeletal age indicators present on the pubic symphysis and iliac auricular surface and to cranial suture closure as described by Boldsen and colleagues (2002). The ADBOU age estimation software was used to determine individual ages at death. The ADBOU program uses a conditional probability estimated from the Smithsonian Institution's Terry Collection of age indicators given age. The program also uses a prior age-at-death distribution based on data from seventeenth-century Danish rural parish records. Using Bayes' theorem, the ADBOU program combines the informative prior and the conditional probability to calculate the highest posterior point estimate of age for each individual in the sample. One major advantage of transition analysis, compared to traditional methods, is that it provides point estimates of age for all adult ages, even for older individuals, thus removing the potential limitation of a broad terminal age interval.

SEX ESTIMATION

I determined sex based on sexually dimorphic features of the skull and pelvis using the standards described in Buikstra and Ubelaker (1994). The following features of the skull were scored: the glabella/supraorbital ridge, the supraorbital margin, the mastoid process, the external occipital protuberance/nuchal crest, and the mental eminence. The following features of the pelvis were also scored: the ventral arc of the pubis, the subpubic concavity, the ischiopubic ramus ridge, and the greater sciatic notch.

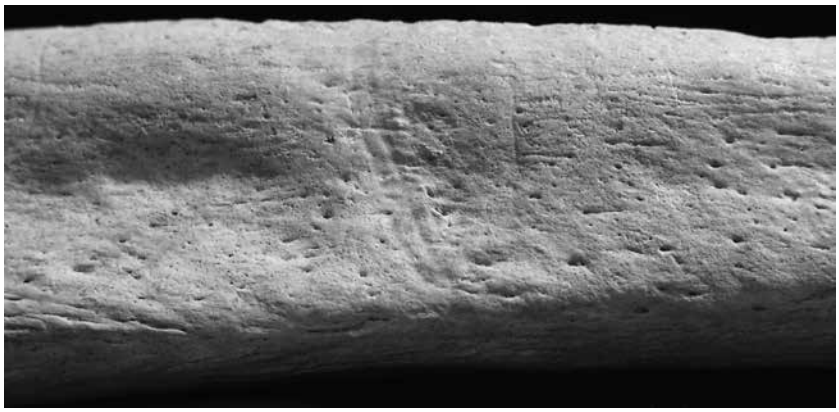

Figure 8.1 Periosteal new bone formation on an adult tibia (from DeWitte and Bekvalac 2011). The rough, irregular surface of the tibia is a result of the abnormal excess growth of bone.

SKELETAL STRESS MARKERS

This study analyzes the risk of death associated with the following nonspecific skeletal markers of physiological stress: tibial periosteal lesions (periosteal new bone formation), porotic hyperostosis, cribra orbitalia, and linear enamel hypoplasia. Periosteal new bone formation (fig. 8.1) can occur at any age and is the abnormal proliferation of bone that occurs as part of an inflammatory response to trauma or infection (factors that damage the periosteum or lift it from the surface of the underlying bone) (Larsen 1997; Ortner 2003; Weston 2008). I focus on periosteal new bone formation on the tibia because studies have repeatedly demonstrated that such lesions commonly affect the tibia and because the tibia is a robust bone that is often well preserved in skeletal samples (Eisenberg 1991; Milner 1991; Larsen 1997; Roberts and Manchester 2005).

Porotic hyperostosis and cribra orbitalia (fig. 8.2) are lesions on the cranial vault bones and orbital roofs, respectively, which are characterized by a porous appearance of the outer table of the affected bone that is often associated with expansion of the underlying diploic bone (Mensforth et al. 1978; Ortner 2003). Both of these skeletal lesions are usually attributed to anemia or other etiologies that occur during childhood and that result in an expansion of the bone marrow and thus an expansion of the surrounding diploic bone. Both stress markers, if formed during childhood, can be retained into adulthood and thus provide a long-term record of childhood health history (Walker et al. 2009).

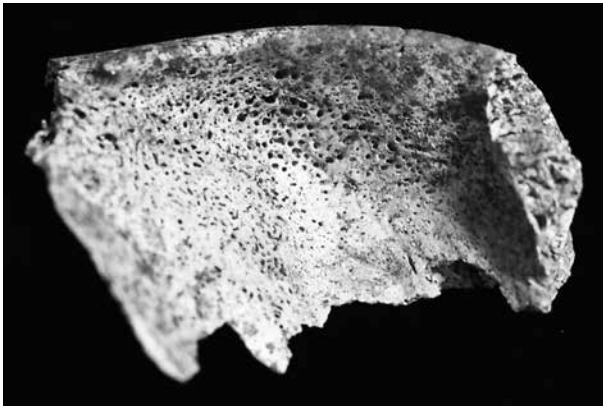

Figure 8.2 The porous appearance of the bone on the roof of this child's orbit is characteristic of cribra orbitalia. Photo courtesy Sharon DeWitte.

For the current study, the cranial vault was scored for porotic hyperostosis, and the roofs of both orbits were scored for cribra orbitalia.

Linear enamel hypoplasia is a tooth defect caused by the disruption of enamel formation during childhood; such disruption can occur in response to infection or malnutrition (Huss-Ashmore et al. 1982; Dahlberg 1991; Roberts and Manchester 2005). Though enamel hypoplasia occurs only while the teeth are developing during childhood, because enamel, once formed, is not subject to remodeling, enamel defects can be retained well into adulthood (until the surface of the tooth is worn away) (Roberts and Manchester 2005). Linear enamel hypoplasias appear as horizontal lines of varying width on the surface of the affected tooth. For the current study, linear enamel hypoplasias were identified macroscopically on the buccal surface of the mandibular canines. Only permanent teeth with very little or no wear were scored. Linear enamel hypoplasia was scored as "present" if one or more depressions on the surface of the tooth were palpable and visible to the naked eye.

MODEL

The risk of death associated with skeletal stress markers among adults in the Danish cemeteries was assessed using a multistate model of health and

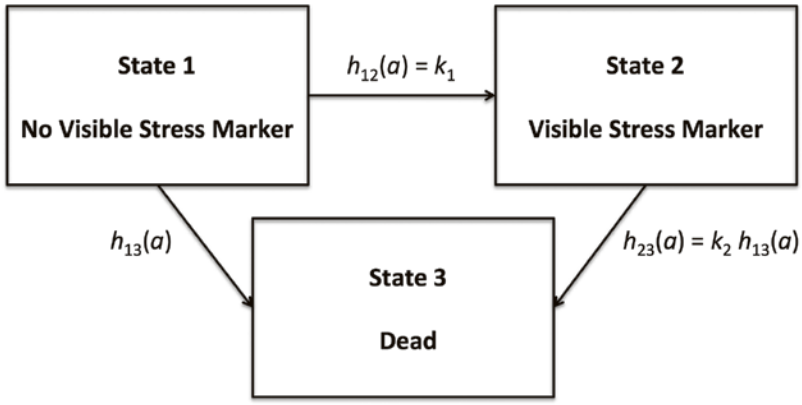

Figure 8.3 Multistate model of health and mortality (modified from Usher 2000).

mortality (Usher 2000). The model (fig. 8.3) has three, non-overlapping states: state 1 includes individuals without skeletal stress markers, state 2 includes those with stress markers, and state 3 is death. Everyone in the skeletal sample used for this study was observed in state 3, so states 1 and 2 represent the two possible living states the individuals could have been in immediately before they died. The transitions from either of the two living states to death are determined by age-specific hazard rates. The model allows for variation in the hazard rates between each of the two living states and death; thus, the model can be used to estimate differences in risk of death between those with and without stress markers.

For this study, the baseline risk of death from state 1, $h_{13}(a)$, was estimated as a Gompertz-Makeham model: $h(a) = \alpha_1 + \alpha_2 e^{\beta a}$ In this model, α_1 is the constant age-independent risk of mortality, and $\alpha_2 e^{\beta a}$ is the exponentially increasing senescent risk of mortality (Gage 1988). Because it is often not possible to determine the age at which an individual experienced physiological stress sufficient to cause a stress marker, the hazard of moving from state 1 to state 2, $h_{12}(a)$, was estimated as an exponentially random variable k_1. The hazard of dying from state 2, $h_{23}(a)$, was modeled as proportional to the baseline age-specific risk of dying from state 1. Under the proportional hazards specification, k_2 is a proportional term on the Gompertz-Makeham function and is thus independent of age. The k_2 parameter value indicates the proportional difference in risk of death between individuals with and

without stress markers. Estimated k_2 values greater than, less than, or equal to one indicate that individuals with stress markers were at higher, lower, or equal risk of dying, respectively, compared to peers without stress markers.

To evaluate sex differences in the excess mortality associated with skeletal stress markers and thus whether previous exposure to stressors had the same effect on risk of death for males and females, sex was modeled as a covariate (females = 0, males = 1) affecting the k_2 parameter in the Usher model. A significant positive or negative estimate for the parameter representing the effect of the sex covariate would suggest that the excess mortality associated with stress markers was higher or lower, respectively, for males. The model was fit separately to data on the presence of each of the stress markers described above. Maximum likelihood analysis was used to estimate the parameters for this study using Holman's (2005) MLE program. Likelihood ratio tests (LRTs) were used to evaluate the fit of the full model, which included all of the parameters of the Usher model plus the parameter representing the effect of the sex covariate, compared to the reduced model, which did not include sex as a covariate. The LRT therefore tests the null hypothesis that the risk of death associated with stress markers was the same for males and females. The LRT was computed as follows:

$$\text{LRT} = -2[\ln(L_{\text{reduced}}) - \ln(L_{\text{full}})]$$

LRT approximates a χ^2 distribution with $df = 1$. It should be noted that the errors associated with age estimates were not taken into account when using the Usher model. Therefore, the estimated values of the k_2 parameter and the parameter representing the effect of the sex covariate should be viewed as general, qualitative measures of the excess mortality associated with stress markers and the sex differences thereof.

Results

The maximum likelihood estimates of k_2 and the estimated values of the parameter representing the effect of the sex covariate, along with their standard errors and the results from the likelihood ratio tests, are shown in table 8.2. The results indicate that stress markers are associated with increased risk of mortality for both sexes combined. Further, for all stress markers, the estimated values of the parameter representing the effect of

Table 8.2 Maximum Likelihood Estimates of $k2$ and the Effect of the Sex Covariate (0 = female, 1 = male) with Associated Standard Errors, and the Results of the Likelihood Ratio Test of the Null Hypothesis

	EAST SMITHFIELD			DENMARK		
Stress Marker	$k2$ (SE)	Sex (SE)	LRT	$k2$ (SE)	Sex (SE)	LRT
Periosteal lesions	1.74 (0.30)	0.47 (0.28)	50.8*	7.77 (3.33)	0 (0.29)	0
Porotic hyperostosis	1.72 (0.27)	1.71 (0.33)	15.6*	2.80 (1.1)	0.93 (0.33)	7.25*
Cribra orbitalia	1.90 (0.60)	0.84 (0.36)	5.45*	3.64 (2.17)	0.99 (0.14)	2.03
Linear enamel hypoplasia	2.90 (1.39)	1.3 (0.54)	12.3*	9.9 (1.23)	0.44 (0.80)	0.24

Notes: Effect of sex covariate = 0; * = $p < 0.01$.

sex covariate are positive, suggesting that the excess mortality associated with those stress markers was higher for males. In the Danish sample, the results of the LRT for porotic hyperostosis indicate that including the sex covariate improved the fit of the model ($p = 0.007$); however, for the other stress markers, the results of the LRTs are not significant, and thus the observed sex differences for those must be considered inconclusive. In general, the results from the Danish sample are similar to the patterns observed in East Smithfield, although in the latter cemetery all skeletal stress markers were associated with significantly higher excess mortality in males.

Discussion

The estimated values of the excess mortality associated with skeletal stress markers provide evidence that under conditions of normal medieval mortality in Denmark, regardless of sex, people with skeletal indicators of exposure to physiological stress faced elevated risks of mortality compared to their peers without such stress markers. These results are consistent with previous analyses of these stress markers (Usher 2000; DeWitte and Wood 2008; DeWitte 2010b). Further, the estimated values of the effect of sex on the excess mortality associated with skeletal stress markers indicate that in the medieval population of Denmark, under normal mortality conditions, adult females were better able than males to resist death despite exposures to stressors sufficient to cause porotic hyperostosis. This suggests that frailty was lower for females compared to males in this population, at least under some circumstances.

The differences between the East Smithfield and Danish samples (i.e., significantly higher excess mortality among males compared to females for all stress markers in the former but for only one stress marker, porotic hyperostosis, in the latter) might reflect population variation in sex differences in frailty. There might have been a stronger distinction in frailty between males and females in medieval England compared to medieval Denmark. Perhaps in Denmark, males and females exposed to the physiological stressors associated with cribra orbitalia, periosteal lesions, and enamel hypoplasia really did face roughly equal risks of dying. A lack of sex differentials in the Danish sample might reflect differences between the Danish and English populations in diet, disease environment, behavior, or genetics, all of which might have affected disease experience and risk of mortality.

The differences between the two samples might also be an artifact of sex differentials and selective mortality operating differently at different ages. That is, there might have been strong sex differentials in frailty between the sexes in both populations, but in Denmark the effects of such differentials and their interaction with selective mortality operated primarily during childhood and adolescence, whereas such interactions might have occurred predominantly at older ages or equally throughout the life course in England. If selective mortality were a stronger force during subadult ages in the Danish population compared to the English population, sex differentials would not be apparent in the Danish sample used in this study, since it includes only adults who survived the effects of selective mortality at younger ages. If selective mortality were stronger at younger ages, particularly for males, in Denmark compared to England, it would have weeded out a larger proportion of frailer individuals at earlier ages in the Danish population compared to England. Such selective mortality at young ages would have produced less variation in frailty between the sexes at older ages and thus fewer distinct differences between adult males and females in the risk of mortality associated with stress markers in the Danish sample. Such a possibility of stronger selective mortality during childhood in Denmark, resulting in relatively reduced heterogeneity in frailty among adults, was suggested as a possible explanation for the lack of a significant association between adult stature and risk of mortality in the same Danish sample used in the study described here (DeWitte and Hughes-Morey 2012). However, there is currently no independent evidence of stronger selective mortality during childhood in Denmark.

Alternatively, the lack of a significant effect of sex on the excess mortality associated with cribra orbitalia, tibial periosteal lesions, and enamel hypoplasia in the Danish sample might be an artifact of maternal mortality operating in the normal mortality sample but not in the catastrophic Black Death sample. In the Danish sample, it is possible that maternal mortality during reproductive ages increased mortality rates for females compared to males at those ages, as has been observed in living populations and inferred from other bioarchaeological studies. Perhaps in the Danish population, maternal mortality overcame the inherent biological advantages of females during the reproductive ages, and perhaps pregnant females were more vulnerable to dying from a variety of causes—as occurs in modern populations with malaria, measles, and other diseases. Such an elevation of female mortality during reproductive ages could have obscured differences between the sexes in the excess mortality associated with stress markers that might have existed at pre- or postreproductive ages.

Given that this analysis examines the effects of each stress marker on adult mortality across all adult ages simultaneously, without allowing for variation with age, changes in excess mortality during reproductive ages will not be apparent here. Maternal mortality would not have similarly obscured an effect of sex on excess mortality associated with stress markers in the East Smithfield sample because the cemetery housed people who primarily (if not exclusively) died from the Black Death and not from other causes, including maternal mortality. Further examination of the possible effect of maternal mortality on the sex patterns of excess mortality associated with stress markers would require the use of a model that allows for variation in the effect of the sex covariate with age. Such an analysis has the potential to reveal whether the excess mortality for females increased during reproductive ages, which would suggest an effect of maternal mortality. However, modeling variation in age would require the estimation of additional parameters and thus larger sample sizes than those available for this study.

Last, the differences between the two samples might be the result of variation in sample size, that is, the combined Danish sample may be too small to allow for the estimation of statistically significant parameter values.

In my previous study of East Smithfield, I raised the possibility that the significant estimated effect of sex on the excess mortality associated with stress markers might reflect sex differences in selective mortality during the Black Death, rather than a higher average frailty of males. That is, the

results might have indicated that the Black Death was selective with respect to frailty among both males and females, but that it discriminated less strongly between females with and without preexisting health conditions than it did for males. It is possible that the Black Death was not as strongly selective with respect to frailty among females compared to males. If this were the case, then the lower risk of mortality associated with stress markers among females compared to males in East Smithfield was the result of the Black Death killing a greater proportion of otherwise healthy females than healthy males, rather than reflecting lower average frailty among females compared to males. However, the results of the current study using a normal mortality sample, combined with the results from a previous study (DeWitte 2009) that failed to reveal a significant difference in risk of death during the Black Death between males and females, suggest that the more parsimonious interpretation of the findings is that females were less frail than males, at least under certain conditions of medieval mortality.

The results of this study might reflect gendered patterns of access to food in medieval Europe, given that nutritional status can strongly influence immune competence (Floud et al. 1990; Scrimshaw 2003; Hughes and Kelly 2006; Fernandes 2008; Jones et al. 2010). Poor nutritional status negatively affects all aspects of the immune response, including the production of pro-inflammatory cytokines, the production of antibodies, and the activity of natural killer cells (Jackson and Calder 2004). In living populations, nutritional status is a significant factor in determining the frequency and severity with which people suffer from a variety of infectious diseases (Gage et al. 2012). The association between nutritional status and immune competence is so powerful that deaths during famines are often the result not of starvation itself, but of attendant infectious disease (Ó Gráda 1999).

The apparent superior ability of females in these medieval populations to resist death despite exposure to physiological stressors might indicate that medieval women had better nutritional status and thus superior immune competence compared to men. Alternatively, given that there are currently no data to suggest that women actually had preferential access to food or better nutritional status in this population, women might have had roughly the same nutritional status as men, and therefore were not nutritionally compromised compared to men. By not being relatively nutritionally compromised, women would have been able to achieve their innate biological advantages compared to men. Another alternative explanation for these results is that men did indeed have preferential access to food, but diet in general was so

poor during this period that such access had no discernible beneficial effects on male immune competence.

There is little direct evidence regarding dietary differences between men and women in medieval Europe. Because of patterns of inheritance and ownership of property, sons were often preferred over daughters in many areas of medieval Europe, so one might expect that there was preferential treatment of sons, including provisioning with more or better food. Further, there is some evidence that women received substantially lower wages than men in medieval Europe and had limited control over property (Green 1994; Bardsley 1999), which might have negatively impacted access to food resources for some women during adulthood. However, according to Bullough and Campbell (1980), improvements in diet, particularly increases in dietary protein and iron, following the adoption of the three-field system of agriculture in the ninth century might have disproportionately benefited females by reducing the risk of iron-deficiency anemia, to which females are inherently more susceptible, given the iron-depleting processes of pregnancy, childbirth, menstruation, and lactation.

Empirical research on what people were actually eating in medieval Europe would help to resolve the question of whether women were well nourished compared to men and thus capable of achieving their biological potentials with respect to morbidity and mortality. Stable isotope analyses are a promising avenue of research that can reveal dietary patterns at the levels of both the individual and the population. To date, however, existing stable isotope studies, though informative about small-scale patterns in diet, have not revealed consistent dietary patterns by sex in medieval populations (Mays 1997; Richards et al. 2006; Muldner and Richards 2007; Szostek et al. 2009; Yoder 2010).

Conclusion

The results of this study are consistent with those from a previous analysis of sex differences in frailty during the Black Death, though in this study the results were not statistically significant for all of the skeletal stress markers examined. At the very least, the combined results suggest that differentials favoring females might have been operating in medieval European populations. The lack of significant differences between males and females for all observed skeletal stress markers in the normal mortality sample from Denmark and the consistent differences between the sexes in the Black Death

sample highlight the potential utility of samples in which most, if not all, individuals died from a single cause.

Acknowledgments

I would like to thank Sabrina Agarwal and Julie Wesp for organizing the Society for American Archaeology session that motivated this study. I am very grateful to Jelena Bekvalac and Rebecca Redfern at the Museum of London's Centre for Human Bioarchaeology and to Jesper Boldsen at the University of Southern Denmark for providing access to the East Smithfield and Danish skeletons and for generously providing the physical facilities for this work. I would also like to thank Erica Huff for organizing and synthesizing the data on age-specific mortality rates available from the World Health Organization. The skeletal data for this study were collected using funding from the National Science Foundation (BCS-0406252), the Wenner-Gren Foundation (7142), and the American Scandinavian Foundation.

References Cited

Acuna-Soto R, Maguire JH, Wirth DF. 2000. Gender distribution in asymptomatic and invasive amebiasis. American Journal of Gastroenterology 95:1277–1283.

Ahmed SA, Karpuzoglu E, Khan D. 2010. Effects of sex steroids on innate and adaptive immunity. In: Klein SL, Roberts C, editors. Sex hormones and immunity to infection. Heidelberg: Springer. p 19–51.

Alexander J, Irving K, Snider H, Satoskar A. 2010. Sex hormones and regulation of host responses against parasites. In: Klein SL, Roberts C, editors. Sex hormones and immunity to infection. Heidelberg: Springer. p 147–186.

Amur S, Parekh A, Mummaneni P. 2011. Sex differences and genomics in autoimmune diseases. Journal of Autoimmunology 38:J254–J265.

Bardsley S. 1999. Women's work reconsidered: Gender and wage differentiation in late medieval England. Past and Present 165:3–29.

Benedictow OJ. 1993. Plague in the late medieval Nordic countries: Epidemiological studies. Oslo: Middelalderforlaget.

Bennett KA. 1973. On the estimation of some demographic characteristics on a prehistoric population from the American Southwest. American Journal of Physical Anthropology 39:223–231.

Bhatia S. 1984. Traditional practices affecting female health and survival: Evidence from countries of South Asia. In: Lopez AD, Ruzicka LT, editors. Sex differentials in mortality: Trends, determinants, and consequences. Canberra: Department of Demography, Australian National University. p 165–191.

Bocquet-Appel JP, Masset C. 1982. Farewell to paleodemography. Journal of Human Evolution 11:321–333.

Boldsen JL, Milner GR, Konigsberg LW, Wood JW. 2002. Transition analysis: A new method for estimating age from skeletons. In: Hoppa RD, Vaupel JW, editors. Paleodemography: Age distributions from skeletal samples. Cambridge: Cambridge University Press. p 73–106.

Bowsky WM. 1971. The Black Death: A turning point in history? New York: Holt, Rinehart and Winston.

Brabin L, Brabin BJ. 1992. Parasitic infections in women and their consequences. Advances in Parasitology 31:1–60.

Buikstra JE. 1997. Paleodemography: Context and promise. In: Paine RR, editor. Integrating archaeological demography: Multidisciplinary approaches to prehistoric population. Carbondale: Center for Archaeological Investigations, Southern Illinois University. p 367–380.

Buikstra JE, Konigsberg LW. 1985. Paleodemography: Critiques and controversies. American Anthropologist 87:316–333.

Buikstra JE, Ubelaker DH, editors. 1994. Standards for data collection from human skeletal remains: Proceedings of a seminar at the Field Museum of Natural History. Fayetteville: Arkansas Archaeological Survey Press.

Bullough V, Campbell C. 1980. Female longevity and diet in the Middle Ages. Speculum 55:317–325.

Butler T. 1989. The Black Death past and present. 1: Plague in the 1980s. Transactions of the Royal Society of Tropical Medicine and Hygiene 83:458–460.

Capelli C, Redhead N, Abernethy JK, Gratrix F, Wilson JF, Moen T, Hervig T, Richards M, Stumpf MP, Underhill PA, et al. 2003. A Y chromosome census of the British Isles. Current Biology 13:979–984.

Case A, Paxson C. 2005. Sex differences in morbidity and mortality. Demography 42:189–214.

Case LK, Toussaint L, Moussawi M, Roberts B, Saligrama N, Brossay L, Huber SA, Teuscher C. 2012. Chromosome Y regulates survival following murine coxsackievirus B3 infection. G3 (Bethesda, MD) 2:115–121.

Cassidy CM. 1984. Skeletal evidence for prehistoric subsistence adaptation in the central Ohio River valley. In: Cohen MN, Armelagos GJ, editors. Paleopathology at the origins of agriculture. New York: Academic. p 307–345.

Chen LC, Huq E, D'Souza S. 1981. Sex bias in the family allocation of food and health care in rural Bangladesh. Population and Development Review 7:55–70.

Choi BG, McLaughlin MA. 2007. Why men's hearts break: Cardiovascular effects of sex steroids. Endocrinology and Metabolism Clinics of North America 36:365–377.

Cleri DJ, Vernaleo JR, Lombardi LJ, Rabbat MS, Mathew A, Marton R, Reyelt MC. 1997. Plague pneumonia disease caused by *Yersinia pestis*. Seminars in Respiratory Infections 12:12–23.

Clutton-Brock TH, Guinness FE, Albon SD. 1982. Red deer: Behavior and ecology of two sexes. Chicago, IL: University of Chicago Press.

Coale AJ. 1991. Excess female mortality and the balance of the sexes in the population: An estimate of the number of "missing females." Population and Development Review 17:517–523.

Cohn SK. 2002. The Black Death transformed: Disease and culture in early Renaissance Europe. London: Arnold.

Cote CG, Chapman KR. 2009. Diagnosis and treatment considerations for women with COPD. International Journal of Clinical Practice 63:486–493.

Cucina A, Vargiu R, Mancinelli D, Ricci R, Santandrea E, Catalano P, Coppa A. 2006. The necropolis of Vallerano (Rome, 2nd–3rd century AD): An anthropological perspective on the ancient Romans in the suburbium. International Journal of Osteoarchaeology 16:104–117.

Dahlberg AA. 1991. Interpretations of general problems in amelogenesis. In: Ortner DJ, Aufderheide AC, editors. Human paleopathology: Current syntheses and future options. Washington, DC: Smithsonian Institution Press. p 269–272.

Davis S, Makundi RH, Machang'u RS, Leirs H. 2006. Demographic and spatio-temporal variation in human plague at a persistent focus in Tanzania. Acta Tropica 100:133–141.

DeWitte SN. 2009. The effect of sex on risk of mortality during the Black Death in London, A.D. 1349–1350. American Journal of Physical Anthropology 139:222–234.

———. 2010a. Age patterns of mortality during the Black Death in London, A.D. 1349–1350. Journal of Archaeological Science 37:3394–3400.

———. 2010b. Sex differentials in frailty in medieval England. American Journal of Physical Anthropology 143:285–297.

———. 2014. Modeling the second epidemiological transition in London: Patterns of mortality and frailty during industrialization. In: Zuckerman M, editor. Moving the middle to the foreground: Revisiting the second epidemiological transition. New York: Wiley-Liss. p 35–54.

DeWitte SN, Bekvalac J. 2010. Oral health and frailty in the medieval English cemetery of St. Mary Graces. American Journal of Physical Anthropology 142:341–354.

———. 2011. The association between periodontal disease and periosteal lesions in the St. Mary Graces cemetery, London, England, A.D. 1350–1538. American Journal of Physical Anthropology 146:609–618.

DeWitte SN, Hughes-Morey G. 2012. Stature and frailty during the Black Death: The effect of stature on risks of epidemic mortality in London, A.D. 1348–1350. Journal of Archaeological Science 39:1412–1419.

DeWitte SN, Wood JW. 2008. Selectivity of the Black Death with respect to preexisting health. Proceedings of the National Academy of Sciences USA 105:1436–1441.

Diaz JH. 2011. The public health threat from *Balamuthia mandrillaris* in the southern United States. Journal of the Louisiana State Medical Society 163:197–204.

Eisenberg LE. 1991. Mississippian cultural terminations in middle Tennessee: What the bioarcheological evidence can tell us. In: Powell ML, Bridges PS, Mires AM, editors. What mean these bones. Tuscaloosa: University of Alabama Press. p 70–88.

Fairweather D, Frisancho-Kiss S, Rose NR. 2008. Sex differences in autoimmune disease from a pathological perspective. American Journal of Pathology 173:600–609.

Falagas ME, Vardakas KZ, Mourtzoukou EG. 2007. Sex differences in the incidence and severity of respiratory tract infections. Respiratory Medicine 101:1845–1863.

Fernandes G. 2008. Progress in nutritional immunology. Immunologic Research 40:244–261.

Floud R, Wachter KW, Gregory A. 1990. Height, health and history: Nutritional status in the United Kingdom, 1750–1980. Cambridge: Cambridge University Press.

Gage TB. 1988. Mathematical hazard models of mortality: An alternative to model life tables. American Journal of Physical Anthropology 76:429–441.

———. 1994. Population variation in cause of death: Level, gender, and period effects. Demography 31:271–296.

———. 2005. Are modern environments really bad for us? Revisiting the demographic and epidemiologic transitions. American Journal of Physical Anthropology 41(Suppl):96–117.

Gage TB, DeWitte S, Wood JW. 2012. Demography. 1: Mortality and migration. In: Stinson S, Bogin B, O'Rourke D, editors. Human biology: An evolutionary and biocultural perspective. Hoboken, NJ: Wiley-Blackwell. p 695–756.

Garenne M. 1994. Sex differences in measles mortality: A world review. International Journal of Epidemiology 23:632–642.

Gottfried RS. 1983. The Black Death: Natural and human disaster in medieval Europe. New York: Free Press.

Grainger I, Hawkins D, Cowal L, Mikulski R. 2008. The Black Death cemetery, East Smithfield, London. Monograph 43. London: Museum of London Archaeology Service.

Graunt J. 1975. Natural and political observations mentioned in a following index and made upon the bills of mortality. New York: Arno.

Green M. 1994. Documenting medieval women's medical practice. In: García Ballester L, editor. Practical medicine from Salerno to the Black Death. Cambridge: Cambridge University Press. p 322–352.

Guatelli-Steinberg D, Lukacs JR. 1999. Interpreting sex differences in enamel hypoplasia in human and non-human primates: Developmental, environmental, and cultural considerations. American Journal of Physical Anthropology 110:73–126.

Hatcher J. 1977. Plague, population, and the English economy, 1348–1530. London: Macmillan.

Hawkins D. 1990. Black Death and the new London cemeteries of 1348. Antiquity 64:637–642.

Herlihy D. 1997. The Black Death and the transformation of the West. Cambridge, MA: Harvard University Press.

Hetzel BS. 1984. Life style factors in sex differentials in mortality in developed countries. In: Lopez AD, Ruzicka LT, editors. Sex differentials in mortality: Trends, determinants, and consequences. Canberra: Department of Demography, Australian National University. p 247–277.

Högberg U, Iregren E, Siven C-H, Diener L. 1987. Maternal deaths in medieval Sweden: An osteological and life table analysis. Journal of Biosocial Science 19:495–503.

Holman DJ. 2005. MLE: A programming language for building likelihood models. Version 2.1. Seattle, WA.

Hoppa RD, Vaupel JW, editors. 2002. Paleodemography: Age distributions from skeletal samples. Cambridge: Cambridge University Press.

Hughes S, Kelly P. 2006. Interactions of malnutrition and immune impairment, with specific reference to immunity against parasites. Parasite Immunology 28:577–588.

Huss-Ashmore R, Goodman AH, Armelagos GJ. 1982. Nutritional inference from paleopathology. Advances in Archaeological Method and Theory 5:395–473.

Jackson A, Calder P. 2004. Severe undernutrition and immunity. In: Gershwin M, Neste P, Keen C, editors. Handbook of nutrition and immunity. Totowa, NJ: Humana. p 71–92.

Jansen A, Stark K, Schneider T, Schoneberg I. 2007. Sex differences in clinical leptospirosis in Germany: 1997–2005. Clinical Infectious Diseases 44:e69–e72.

Jantzen C, Kieffer-Olsen J, Madsen PK. 1994. De sma brodres hus i Ribe. In: Gelius W, Guldberg M, Stoumann I, editors. Mark og Montre Årbog for kunst- og kulturhistorie 30. Ribe: Ribe Amts Museumsråd. p 26–36.

Jones KDJ, Berkley JA, Warner JO. 2010. Perinatal nutrition and immunity to infection. Pediatric Allergy and Immunology 21:564–576.

Kalra M, Mayes J, Assefa S, Kaul AK, Kaul R. 2008. Role of sex steroid receptors in pathobiology of hepatocellular carcinoma. World Journal of Gastroenterology 14:5945–5961.

Kamel NM. 1984. Determinants and patterns of female mortality associated with women's reproductive role. In: Lopez AD, Ruzicka LT, editors. Sex differentials in mortality: Trends, determinants, and consequences. Canberra: Department of Demography, Australian National University. p 179–191.

Kamugisha ML, Gesase S, Minja D, Mgema S, Mlwilo TD, Mayala BK, Msingwa S, Massaga JJ, Lemnge MM. 2007. Pattern and spatial distribution of plague in Lushoto, north-eastern Tanzania. Tanzania Health Research Bulletin 9:12–18.

Kieffer-Olsen J. 1993. Grav og gravskike i det middelalderlige Danmark. Aarhus, Denmark: Aarhus University.

King T, Humphrey LT, Hillson S. 2005. Linear enamel hypoplasias as indicators of systemic physiological stress: Evidence from two known age-at-death and sex populations from postmedieval London. American Journal of Physical Anthropology 128:547–559.

Klein SL. 2000. The effects of hormones on sex differences in infection: From genes to behavior. Neuroscience and Biobehavioral Reviews 24:627–638.

Klein SL, Hodgson A, Robinson DP. 2011. Mechanisms of sex disparities in influenza pathogenesis. Journal of Leukocyte Biology 92:67–73.

Klein SL, Huber S. 2010. Sex differences in susceptibility to viral infection. In: Klein SL, Roberts C, editors. Sex hormones and immunity to infection. Heidelberg: Springer. p 93–122.

Klein SL, Roberts C, editors. 2010. Sex hormones and immunity to infection. Heidelberg: Springer.

Konigsberg LW, Frankenberg SR. 1992. Estimation of age structure in anthropological demography. American Journal of Physical Anthropology 89:235–256.

———. 2002. Deconstructing death in paleodemography. American Journal of Physical Anthropology 117:297–309.

Kreger MB. 2010. Urban population dynamics in a preindustrial New World city: Morbidity, mortality, and immigration in postclassic Cholula. University Park: Pennsylvania State University Press.

Larsen CS. 1997. Bioarchaeology: Interpreting behavior from the human skeleton. New York: Cambridge University Press.

———. 1998. Gender, health, and activity in foragers and farmers in the American Southeast: Implications for social organization in the Georgia Bight. In: Grauer AL, Stuart-Macadam P, editors. Sex and gender in paleopathological perspective. Cambridge: Cambridge University Press. p 165–187.

Leone M, Honstettre A, Lepidi H, Capo C, Bayard F, Raoult D, Mege JL. 2004. Effect of sex on *Coxiella burnetii* infection: Protective role of 17-beta-estradiol. Journal of Infectious Diseases 189:339–345.

Lopez AD. 1984. The sex mortality differential in developed countries. In: Lopez AD, Ruzicka LT, editors. Sex differentials in mortality: Trends, determinants, and consequences. Canberra: Department of Demography, Australian National University. p 53–120.

Lopez AD, Ruzicka LT, editors. 1984. Sex differentials in mortality: Trends, determinants, and consequences. Canberra: Department of Demography, Australian National University.

Lukacs JR. 2008. Fertility and agriculture accentuate sex differences in dental caries rates. Current Anthropology 49:901–914.

May RC. 2007. Gender, immunity and the regulation of longevity. Bioessays 29:795–802.

Mays SA. 1997. Carbon stable isotope ratios in mediaeval and later human skeletons from northern England. Journal of Archaeological Science 24:561–567.

Mensforth RP, Lovejoy CO, Lallo JW, Armelagos GJ. 1978. The role of constitutional factors, diet, and infectious disease in the etiology of porotic hyperostosis and periosteal reactions in prehistoric infants and children. Medical Anthropology 2:1–58.

Milner GR. 1991. Health and cultural change in the late prehistoric American bottom, Illinois. In: Powell ML, Bridges PS, Mires AM, editors. What mean these bones? Tuscaloosa: University of Alabama Press. p 52–69.

Milner GR, Boldsen JL. 2012. Transition analysis: A validation study with known-age modern American skeletons. American Journal of Physical Anthropology 148:98–110.

Milner GR, Wood JW, Boldsen JL. 2008. Paleodemography. In: Katzenberg M, Saunders S, editors. Biological anthropology of the human skeleton, 2nd ed. New York: Wiley. p 561–600.

Mittler DM, Van Gerven DP. 1994. Developmental, diachronic, and demographic analysis of cribra orbitalia in the medieval Christian populations of Kulubnarti. American Journal of Physical Anthropology 93:287–297.

Mobarak EI. 2012. Trend, features and outcome of meningitis in the communicable diseases hospital, Alexandria, Egypt, 1997–2006. Journal of the Egyptian Public Health Association 87:16–23.

Moore SL, Wilson K. 2002. Parasites as a viability cost of sexual selection in natural populations of mammals. Science 297:2015–2018.

Moriyama IM. 1984. The determinants of sex differentials in mortality. In: Lopez AD, Ruzicka LT, editors. Sex differentials in mortality: Trends, determinants, and consequences. Canberra: Department of Demography, Australian National University. p 279–295.

Muldner G, Richards MP. 2007. Diet and diversity at later medieval Fishergate: The isotopic evidence. American Journal of Physical Anthropology 134:162–174.

Müller HG, Love B, Hoppa RD. 2002. Semiparametric method for estimating paleodemographic profiles from age indicator data. American Journal of Physical Anthropology 117:1–14.

Nagaoka T, Hirata K, Yokota E, Matsu'ura S. 2006. Paleodemography of a medieval population in Japan: Analysis of human skeletal remains from the Yuigahama-minami site. American Journal of Physical Anthropology 131:1–14.

Noymer A, Garenne M. 2000. The 1918 influenza epidemic's effects on sex differentials in mortality in the United States. Population and Development Review 26:565–581.

Ó Gráda C. 1999. Black '47 and beyond: The great Irish famine in history, economy, and memory. Princeton, NJ: Princeton University Press.

Oksuzyan A, Juel K, Vaupel JW, Christensen K. 2008. Men: Good health and high mortality: Sex differences in health and aging. Aging Clinical and Experimental Research 20:91–102.

Oren E, Winston CA, Pratt R, Robison VA, Narita M. 2011. Epidemiology of urban tuberculosis in the United States, 2000–2007. American Journal of Public Health 101:1256–1263.

Ortner DJ. 1991. Theoretical and methodological issues in paleopathology. In: Ortner DJ, Aufderheide AC, editors. Human paleopathology: Current syntheses and future options. Washington, DC: Smithsonian Institution Press. p 5–11.

———. 1998. Male-female immune reactivity and its implications for interpreting evidence in human skeletal paleopathology. In: Grauer AL, Stuart-Macadam P, editors. Sex and gender in paleopathological perspective. Cambridge: Cambridge University Press. p 79–92.

———, editor. 2003. Identification of pathological conditions in human skeletal remains. Amsterdam: Academic.

Owens IP. 2002. Ecology and evolution: Sex differences in mortality rate. Science 297:2008–2009.

Paine RR. 2000. If a population crashes in prehistory, and there is no paleodemographer there to hear it, does it make a sound? American Journal of Physical Anthropology 112:181–190.

Pennell LM, Galligan CL, Fish EN. 2012. Sex affects immunity. Journal of Autoimmunology 38:J282–J291.

Perry RD, Fetherston JD. 1997. *Yersinia pestis*: Etiologic agent of plague. Clinical Microbiology Reviews 10:35–66.

Pilote L, Dasgupta K, Guru V, Humphries KH, McGrath J, Norris C, Rabi D, Tremblay J, Alamian A, Barnett T, et al. 2007. A comprehensive view of sex-specific issues related to cardiovascular disease. Canadian Medical Association Journal 176:S1–S44.

Poland JD. 1989. Plague. In: Hoeprich PD, Jordan MC, editors. Infectious diseases: A modern treatise of infectious processes, 4th ed. Philadelphia, PA: Lippincott. p 1296–1306.

Poulsen B. 1997. Agricultural technology in medieval Denmark. In: Astill GG, Langdon J, editors. Medieval farming and technology: The impact of agricultural change in northwest Europe. Leiden: Brill. p 115–146.

Reeves MJ, Bushnell CD, Howard G, Gargano JW, Duncan PW, Lynch G, Khatiwoda A, Lisabeth L. 2008. Sex differences in stroke: Epidemiology, clinical presentation, medical care, and outcomes. Lancet Neurology 7:915–926.

Retherford RD. 1975. The changing sex differential in mortality. Westport, CT: Greenwood.

Richards MP, Fuller BT, Molleson TI. 2006. Stable isotope palaeodietary study of humans and fauna from the multi-period (Iron Age, Viking and late medieval) site of Newark Bay, Orkney. Journal of Archaeological Science 33:122–131.

Roberts CA, Manchester K. 2005. The archaeology of disease. Ithaca, NY: Cornell University Press.

Roberts CW, Walker W, Alexander J. 2001. Sex-associated hormones and immunity to protozoan parasites. Clinical Microbiology Reviews 14:476–488.

Roesdahl E, editor. 1999. Dagligliv i Danmarks middelalder: En arkæologisk kulturhistorie. Copenhagen: Nordisk.

Rothberg MB, Haessler SD, Brown RB. 2008. Complications of viral influenza. American Journal of Medicine 121:258–264.

Rustgi VK. 2007. The epidemiology of hepatitis C infection in the United States. Journal of Gastroenterology 42:513–521.

Sandberg K, Ji H. 2012. Sex differences in primary hypertension. Biology of Sex Differences 3:7.

Sawalha AH, Wang L, Nadig A, Somers EC, McCune WJ, Hughes T, Merrill JT, Scofield RH, Strickland FM, Richardson B. 2012. Sex-specific differences in the relationship between genetic susceptibility, T cell DNA demethylation and lupus flare severity. Journal of Autoimmunology 38:J216–222.

Sawyer B, Sawyer PH. 1993. Medieval Scandinavia: From conversion to Reformation, circa 800–1500. Minneapolis: University of Minnesota Press.

Scrimshaw NS. 2003. Historical concepts of interactions, synergism and antagonism between nutrition and infection. Journal of Nutrition 133:316S–321S.

Silbiger S, Neugarten J. 2008. Gender and human chronic renal disease. Gender Medicine 5(Suppl A):S3–S10.

Šlaus M. 2000. Biocultural analysis of sex differences in mortality profiles and stress levels in the late medieval population from Nova Rača, Croatia. American Journal of Physical Anthropology 111:193–209.

Stinson S. 1985. Sex differences in environmental sensitivity during growth and development. American Journal of Physical Anthropology 28:123–147.

Storey R, Morfin LM, Smith V. 2002. Social disruption and the Maya civilization of Mesoamerica: A study of health and economy of the last thousand years. In: Steckel RH, Rose JC, editors. The backbone of history: Health and nutrition in the western hemisphere. New York: Cambridge University Press. p 283–306.

Szostek K, Glab H, Pudlo A. 2009. The use of strontium and barium analyses for the reconstruction of the diet of the early medieval coastal population of Gdansk (Poland): A preliminary study. Homo 60:359–372.

Teriokhin AT, Budilova EV, Thomas F, Guegan J-F. 2004. Worldwide variation in life-span sexual dimorphism and sex-specific environmental mortality rates. Human Biology 76:623–641.

United Nations. 2011. Sex differentials in childhood mortality. United Nations publication ST/ESA/SER.A/314. http://www.un.org/esa/population/publications/SexDifChildMort/SexDifferentialsChildhoodMortality.pdf.

Usher BM. 2000. A multistate model of health and mortality for paleodemography: Tirup cemetery. PhD diss., Pennsylvania State University.

Vallin J. 1991. Mortality in Europe from 1720 to 1914: Long-term trends and changes in patterns by age and sex. In: Schofield R, Reher DS, Bideau A, editors. The decline of mortality in Europe. Oxford: Clarendon. p 38–67.

Van Gerven DP, Armelagos GJ. 1983. Farewell to paleodemography? Rumors of its death have been greatly exaggerated. Journal of Human Evolution 12:353–360.

Vlassoff C, Bonilla E. 1994. Gender-related differences in the impact of tropical diseases on women: What do we know? Journal of Biosocial Science 26:37–53.

Waldron I. 1984. The role of genetic and biological factors in sex differences in mortality. In: Lopez AD, Ruzicka LT, editors. Sex differentials in mortality: Trends, determinants, and consequences. Canberra: Department of Demography, Australian National University. p 141–164.

———. 1998. Sex differences in infant and early child mortality: Major causes of death and possible biological causes. In: United Nations Department of Economic and Social Affairs, editor. Too young to die: Genes or gender? New York: United Nations. p 64–83.

Walker PL, Bathurst RR, Richman R, Gjerdrum T, Andrushko VA. 2009. The causes of porotic hyperostosis and cribra orbitalia: A reappraisal of the iron-deficiency-anemia hypothesis. American Journal of Physical Anthropology 139:109–125.

Wells JC. 2000. Natural selection and sex differences in morbidity and mortality in early life. Journal of Theoretical Biology 202:65–76.

Weston DA. 2008. Investigating the specificity of periosteal reactions in pathology museum specimens. American Journal of Physical Anthropology 137:48–59.

Widgren M. 1997. Fields and field systems in Scandinavia during the Middle Ages. In: Astill GG, Langdon J, editors. Medieval farming and technology: The impact of agricultural change in northwest Europe. Leiden: Brill. p 173–192.

Wilson JJ. 2010. Modeling life through death in late prehistoric west-central Illinois: An assessment of paleodemographic and paleoepidemiological variability. PhD diss., Binghamton University, SUNY.

———. 2014. Paradox and promise: Research on the role of recent advances in paleodemography and paleoepidemiology to the study of "health" in precolumbian societies. American Journal of Physical Anthropology 155:268–280.

Wood JW, Holman DJ, O'Connor KA, Ferrell RJ. 2002. Mortality models for paleodemography. In: Hoppa RD, Vaupel JW, editors. Paleodemography: Age distributions from skeletal samples. Cambridge: Cambridge University Press. p 129–168.

Wood JW, Milner GR, Harpending HC, Weiss KM. 1992. The osteological paradox: Problems of inferring prehistoric health from skeletal samples. Current Anthropology 33:343–370.

World Health Organization. 2008. The global burden of disease: 2004 update. Geneva: WHO Press.

———. 2012. Life tables for WHO member states. http://www.who.int/healthinfo/statistics/mortality_life_tables/en/.

Wrigley EA, Schofield RS. 1981. The population history of England, 1541–1871: A reconstruction. London: Arnold.

Yoder C. 2010. Diet in medieval Denmark: A regional and temporal comparison. Journal of Archaeological Science 37:2224–2236.

Zuk M, Stoehr AM. 2010. Sex differences in susceptibility to infection: An evolutionary perspective. In: Klein SL, Roberts C, editors. Sex hormones and immunity to infection. Heidelberg: Springer. p 1–17.