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RESEARCH ARTICLE

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The biological index of frailty: A new index for the assessment of frailty in human skeletal remains

Nicoletta Zedda | Barbara Bramanti | Emanuela Gualdi-Russo | Elena Ceraico | Natascia Rinaldo

Department of Neurosciences and Rehabilitation, Faculty of Medicine, University of Ferrara, Ferrara, Italy

Correspondence
Nicoletta Zedda, Barbara Bramanti, and Emanuela Gualdi-Russo, Department of Neurosciences and Rehabilitation, Faculty of Medicine, University of Ferrara, Ferrara, Italy.
Email: zddnlt@unife.it, barbara.bramanti@unife.it, and emanuela.gualdi@unife.it

Abstract

Objective: Frailty is the physiological stress that individuals suffer during their life. In past populations, frailty is conventionally assessed through the occurrence of different biomarkers of biological stress. Some efforts have been made to propose indexes that combine all biomarkers. However, these indices have some critical limitations: they cannot be used on incomplete skeletons, do not consider the severity and/or healing of lesions, and assign equal importance to different biomarkers. To address these limitations, we propose a new index to assess frailty in skeletal individuals.

Material and Methods: By statistically analyzing a large amount of osteological data available from the Museum of London, and using a Logit model, we were able to define a different weight for each reported biomarker of frailty, based on their importance in increasing the risk of premature death for the individuals.

Results: The biological index of frailty (BIF) is the weighted mean of all biomarkers scored on the individuals, according to a different degree of importance assigned to each one. It also considers the severity and healing of the biomarkers when this is relevant to diagnose frailty. We applied BIF on a sample of Monastics and Non-Monastics from medieval England and compared it with the skeletal index of frailty (SFI).

Discussion: BIF is the first frailty index that gives a different weight to each skeletal biomarker of stress, considers both severity and healing of the lesions, and can be applied on partial skeletal remains. The comparison with SFI showed that BIF is applicable to a larger number of skeletal individuals, revealing new differences between the Monastic and the Non-Monastic groups.

KEYWORDS
bioarchaeology, biomarker of stress, frailty, pathology, skeletal health

1 | INTRODUCTION

Assessing the health conditions of past populations is one of the principal goals of bioarchaeology. Health as a holistic concept is difficult to define and measure in a living population, and the difficulty increases as we approach past populations (Reitsema & McIlvaine, 2014).

In recent years, the concepts of biological stress and frailty have been hotly debated in bioarchaeology and have become focal points in the research of both paleopathologists and paleo-epidemiologists (DeWitte, 2010a; Kyle et al., 2018; Marklein et al., 2016; Milner & Boldsen, 2017).

Frailty can be defined as the state of physiological stress that an individual suffered during his/her life and that caused his/her susceptibility to diseases and death (DeWitte, 2010a; Fried et al., 2001; Mitnitski et al., 2001; Wallace et al., 2019). In current medical studies, frailty is considered one of the primary causes of premature death, especially in older people (Dent et al., 2016), since it increases the individual vulnerability to stressors (i.e., diseases and infections) (Morley et al., 2013). Frailty in living populations is assessed through a plethora of physical, physiological and psychological biomarkers that measure the level of biological stress (Fried et al., 1998, 2001).

The evaluation of frailty in past individuals is challenging; both paleopathologists and paleo-epidemiologists can only rely upon skeletal biomarkers of stress, physiological modifications left on the skeleton (Van Schaik et al., 2014). Nevertheless, skeletal biomarkers of stress can be considered a good proxy for assessing health conditions in individuals of the past (Reitsema & McIlvaine, 2014). Thus, and although new methodologies, like paleoproteomics (Scott et al., 2016), epigenetic and ancient DNA investigations (Gokhman et al., 2017), or isotopic analyses (D'Ortenzio et al., 2015) are widening our knowledge about health in past populations, the reconstruction of frailty through the analysis of skeletal biomarkers remains essential to complete the global picture.

Different studies have compared the health status of two or more populations (DeWitte & Bekvalac, 2010; Kyle et al., 2018; Lowman et al., 2019; Novak et al., 2018) using single biomarkers of stress. While it is worth considering each biomarker separately, as it can give information on dissimilarities in diet, and in expositions to infections and genetic diseases, it is also essential to consider the overall health of individuals. This goal can be achieved by combining more biomarkers together in a single index that can estimate frailty both on single individuals and on a population. Two indexes have been proposed previously, the health index of Steckel and Rose (Steckel & Rose, 2002) that utilizes seven skeletal biomarkers of health, and the skeletal frailty index (SFI) of Marklein et al. (Marklein et al., 2016; Marklein & Crews, 2017) that combines 13 biomarkers of stress.

Both indexes are very useful in assessing frailty, nonetheless they have some limitations: the health index does not consider healing status and severity of the lesions, thus overestimates mild or healed lesions. Besides not considering the severity or healing status of the lesions as well (except for nonspecific periostitis), the SFI requires all biomarkers to be observable in the individuals under test. Doing so, the sample size might be drastically reduced, especially when the human remains are very fragmented. Lastly, both indexes consider each biomarker to contribute equally to frailty.

We propose and describe a new index, the biological index of frailty (BIF) that overcomes the main limitations of the previously proposed ones: BIF can be used on partial skeletons, where possible, considers both healing conditions and severity of the lesion, and attributes a different weight to each biomarker, based on its importance in enhancing the susceptibility to death. We applied BIF on the osteological data of Monastic and Non-Monastic individuals from Medieval England (the WORD database), the same data also used by Marklein et al. (Marklein et al., 2016; Marklein & Crews, 2017), to allow a direct comparison between BIF and SFI. Moreover, we propose a new classification system for frailty, which provides a direct indication of the condition of a single individual or a group, based on the distribution of the index in the population under consideration.

1.1 | Health status reconstruction based on biomarkers of frailty

For the assessment of frailty, we considered all skeletal and tooth biomarkers that indicate nonspecific stress associated with a higher risk of death, while they are not the direct cause of the individual death. Therefore, some biomarkers previously included in the analysis of frailty like neoplasm (Marklein et al., 2016; Marklein & Crews, 2017) or specific infections, were not taken into consideration in our index. The biomarkers considered for the new index, and their correlation to frailty, are detailed below.

1.1.1 | Short stature

Short stature is defined as a value that falls into the first quartile of the stature distribution for a specific sex, and population group (Marklein et al., 2016). It is well known that adult stature is influenced by both genetic and environmental factors (NCD Risk Factor Collaboration, 2016; Rani et al., 2020; Steckel, 1995). Among these, environmental stressors (Bozzoli et al., 2009), chronic stress (Roberts & Manchester, 2005), poor nutritional intake (Walker et al., 2007), and diseases (Rani et al., 2020) are among the main factors that could affect stature during development (Rani et al., 2020). Malnutrition in particular is a major factor affecting growth and development (Pérez-Ríos et al., 2019; Rani et al., 2020). Several studies have demonstrated the association of growth impairment with poor health outcomes later in life (McGovern, 2014), with cardiovascular diseases (Paajanen et al., 2010), and with an increase in morbidity and risk of dying young (Deaton, 2007; McEniry, 2013). The association between short stature and poor health outcomes was observed both in living and skeletal populations (DeWitte & Hughes-Morey, 2012; Gunnell et al., 2001; Kemkes-Grottenthaler, 2005). For these reasons, stature can be used as a proxy of general health status, which in particular reflects early-life growing conditions (Akachi & Canning, 2010; McGovern, 2014; NCD Risk Factor Collaboration, 2020).

1.1.2 | Low body mass

While in current developing and developed countries overweight and obesity are one of the main health threats (World Health Organization, 2000), in the populations of least developed countries, as well as in those of the past, underweight and undernutrition can be considered major factors in increasing the risk of death. Low body mass reflects deficiencies during growth and is associated with higher mortality, especially in older individuals (Fried et al., 1998). There are several methodologies to assess body mass from different skeletal districts (Elliott et al., 2016; Grine et al., 1995; Lacoste Jeanson et al., 2017; McHenry, 1992; Ruff, 1994; Ruff et al., 1991, 2005, 2012). Nonetheless, the femoral head diameter is mostly proved to correlate with the body mass and, more specifically, with the lean mass of the individual (Pomeroy et al., 2018; Ruff et al., 1997) and is, therefore, a good proxy for body mass.

1.1.3 | Linear enamel hypoplasia

Linear enamel hypoplasia (LEH) manifests as horizontal grooves on the tooth enamel surface due to an interruption of the amelogenesis during metabolic stress. The disruption is usually due to environmental factors, with malnutrition being the most common cause (Goodman et al., 1980). Several studies attributed the presence of hypoplasia to deficiencies of different nutrients like calcium (Nikiforuk & Fraser, 1981), or Vitamin D and A (Coumoulus & Mellanby, 1947; Rugg-Gunn et al., 1998) during growth, and in general to malnutrition (Gualdi-Russo et al., 2017; Masterson et al., 2017). Serious diseases can also stop the activity of the ameloblasts: severe diarrhoeal events, chickenpox, and other infectious diseases affecting children can be linked to the development of hypoplastic lines on the surface of the primary teeth's crown (Duray, 1996; Hillson, 1996; Sarnat & Schour, 1941). Different studies have noticed a lower life expectancy for individuals with LEH, an observation that supports the hypothesis that physiological stress early in life adversely affects the adult life and subsequently, enhances the risk of premature death (Barker & Osmond, 1986; Boldsen, 2007; Miszkiewicz, 2015; Steckel & Rose, 2002).

1.1.4 | Periodontal disease

Inflammation of the gum, if untreated, develops in periodontitis, a chronic infectious disease caused by bacteria, which results in alveolar bone loss and eventually tooth loss (Hillson, 1996; Ortner, 2003; Regezi et al., 2000). Oral health is strongly correlated with systemic health. In modern living populations, periodontal disease is often associated with cardiovascular diseases, but also respiratory disease, cancers, and, in general, is considered a strong indicator of the risk of mortality (Ajwani et al., 2003; DeWitte & Bekvalac, 2010; Garcia et al., 2001). In fact, when the pathogens causing periodontal disease enter the bloodstream through the ulcerated gingival tissue, they generate inflammatory responses producing cytokines (DeWitte & Bekvalac, 2010; Loos, 2005; Spahr et al., 2006) that could lead to or accelerate atherosclerosis (Demmer & Desvarieux, 2006; Dorn et al., 2000), but also facilitates the onset or progression of respiratory disease (Pan et al., 2009) and increase the risks of certain cancers (Meyer et al., 2008). A significant correlation between periodontitis and an increased risk of mortality was observed also in past populations (DeWitte, 2010b; DeWitte & Bekvalac, 2010; Marklein et al., 2016).

1.1.5 | Nonspecific periostitis

Periostitis is an inflammation of the periosteum –the membrane that covers most bones– that can also result in periosteal new bone formation. The periosteum houses the osteoblasts and is therefore involved in both bone growth and bone repair and is the first tissue that responds to an insult affecting the bone, like trauma, infections, and tumors (Dwek, 2010). The response of the periosteum can be aggressive, and cause the rapid deposition of woven new bone, which develops in plaque-like deposits and irregular elevations on the bone surfaces (active periostitis). In case of less intense insults, or of remodeling and replacement of the woven bone, the process can be slower (inactive periosteal reaction), and results in an organized layering of the new bone, with a plaque-like surface texture similar to that of healthy tissue (Ortner, 2003; Rana et al., 2009; Steckel & Rose, 2002). Periostitis can be found in association with specific infections like tuberculosis or leprosy, with metabolic diseases, like scurvy, or with trauma, but it can also be due to nonspecific infections (Ortner, 2003).

Nonspecific periostitis is often used in bioarchaeology to evaluate the health status of past populations (DeWitte, 2014a; Goodman & Martin, 2002; Marklein et al., 2016; Steckel & Rose, 2002). Differentiating between active and healing/healed (inactive) new bone formation is an important issue. It has been proven that the risk of death is different for the two forms, with a higher risk for individuals with active lesions (DeWitte, 2014a).

1.1.6 | Rickets/osteomalacia

Vitamin D is a steroid hormone involved in calcium homeostasis; it is essential for the mineralization process during bone growth, as well as in adult life for bone remodeling (Ives, 2018; Meyer, 2016; Ortner, 2003). Vitamin D deficiency, which is mainly caused by the lack of sunlight and malnutrition, disrupts, and delays the formation of cartilages and their replacement with bone tissue in infants and children (rickets), as well as the formation of new bone and its remodeling in adults (osteomalacia) (Ives, 2018). Both pathologies are defects of the bone mineralization process and cause softening and deformation of some bones, especially those of the legs and the pelvis, which are more affected by gravitational forces (Brickley et al., 2005; Mays & Brickley, 2018; Waldron, 2008). Other signs of vitamin D deficiency

are swelling of the costochondral junctions, thinning of some areas of the skull, and in case of osteomalacia, pseudofractures, or incomplete fractures with a poorly mineralized bone callus, usually on ribs or scapula (Mays & Brickley, 2018; Waldron, 2008).

Vitamin D is crucial for human life, it supports the immune system and is a key factor for bones' health; its deficiency increases susceptibility to other diseases and the risk of death (Mays et al., 2006; Mays & Brickley, 2018; Ngari et al., 2018).

1.1.7 | Cribra orbitalia and porotic hyperostosis

Cribra orbitalia (CO) and porotic hyperostosis (PH) are lesions generally considered as caused by genetic or acquired anemia (Angel, 1966; Goodman & Martin, 2002). They appear as cribrotic lesions on the orbital roofs (CO) and cranial vault (PH) and are caused by the expansion of the trabecular bone and the subsequent reabsorbing of the cortical external bone lamina (Martin & Goodman, 2002; Rivera & Mirazón, 2017). Different studies on their etiology have identified distinct causes for PH and CO (Brickley, 2018; Rinaldo et al., 2019; Rivera & Mirazón, 2017). For this reason, we consider them separately in our index. Regardless of their etiology, CO and PH seem to be correlated indicators in individuals affected by endured pathological conditions due to poor nutrition or infectious diseases, an observation that led to the assumption that combined CO and PH lesions are indicative of increased frailty (Hens et al., 2019) with consequent higher mortality risk (O'Donnell, 2019; O'Donnell et al., 2020; Piperata et al., 2014; Rothschild, 2012). Like periostitis, CO, and PH can be observed in different forms, from active to healing/healed (inactive), possibly associated with different degrees of frailty (Rinaldo et al., 2019).

1.1.8 | Osteoarthritis and other joint diseases

Osteoarthritis (OA) and, in general, all degenerative joint diseases (DJD) are among the most common conditions that can be found in human skeletal remains, as they are associated with repetitive movements, aging, and musculoskeletal stress (Buikstra & DeWitte, 2019) even if their pathogenesis remains mainly unclear (Fusco et al., 2017). OA affects the joints that are mostly subjected to stress, such as knees, hips, the small joints of the hands, and those of the feet (Klaus et al., 2009; Larsen, 1995). The earliest clinical manifestations of OA are diminished joint space and joint pain, conditions that cannot be recorded on skeletal material. Paleopathologists must base their diagnosis on other more severe manifestations such as eburnation, sclerosis, the porosity of the subchondral bone, and osteophytes (Waldron, 2008). Although OA is probably the most common DJD, we should also mention rotator cuff disease (RCD), rheumatoid arthritis, and all other types of arthropathies, including gout (Burt et al., 2013; Rothschild, 2019; Waldron, 2008).

As rheumatic joint disease and DJD are among the most painful and disabling pathologies, and OA is considered one of the leading causes of disability and inability to perform daily activities (Fusco et al., 2017), and is associated with other pathologies and a higher risk of mortality (Cleveland & Callahan, 2017; Hochberg, 2008), we propose to consider them as biomarkers of frailty.

1.1.9 | Vertebral degenerative diseases

The spine, and in detail the synovial joints of the facets, are often affected by OA, in particular in the cervical and lumbar regions of the spine (Prescher, 1998). OA of the vertebral facets implies the functional failure of the whole synovial facet joints and is usually associated with degenerative disc disease (Gellhorn et al., 2013). Intervertebral disc disease (IVD) is a degeneration of the vertebral disc with the nucleus bulging outwards associated with the collapsing of the annulus (Shankar et al., 2009). It is very commonly observed in skeletal assemblages, especially in the cervical and lower lumbar regions. IVD causes pitting and marginal osteophytosis, and it is associated with aging (Waldron, 2008). Other diseases that can affect the spine are ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome, and diffuse idiopathic skeletal hyperostosis (DISH) (Burt et al., 2013).

As OA of the facets joint, IVD and other diseases of the spine are often associated with back neck pain (Borenstein et al., 2004; Gellhorn et al., 2013), lower back pain (Kos et al., 2019), and difficulties in performing daily activities, resulting in a higher risk of death (Kauppila, 2009; Neva et al., 2001), they should be considered as biomarkers of frailty.

1.1.10 | Trauma

Skeletal trauma and fractures are longly been recorded and regarded in paleopathological and anthropological studies as one of the most reliable indicators of living conditions and quality of life (Domett & Tayles, 2006). Physical trauma can lead to impaired mobility, loss of functional independence, and diminished health-related quality of life (Costa et al., 2008), thus might increase the individual physiological frailty (Phillips et al., 2013). For the development of BIF, we decided to include all the evidence of antemortem trauma that can be found on the skeletons, including fragility fractures caused by osteoporosis (OP). We decided to exclude perimortem trauma as it may be related to the cause of death of the individual and have had no time to result in frailty.

1.1.11 | Osteoporosis

OP is a complex metabolic disorder characterized by a decrease in bone mass and bone quality with a consequent increase in fracture risk (Rachner et al., 2011). OP is defined by the World Health Organization as an amount of bone mass 2.5 SD or more below the average of normal bone density in a young adult (Kanis et al., 1994). OP can be categorized as primary or secondary. Primary OP, or age-related OP, is the most common form of the disease and occurs in postmenopausal women or the elderly of both sexes (Agarwal & Stout, 2003;

Dobbs et al., 1999). Secondary OP, on the other hand, is the result of a variety of conditions and identifiable pathologies, such as cystic fibrosis, rheumatoid arthritis, immobility, diabetes mellitus, and nutrition deficiencies (Agarwal & Stout, 2003; Miazgowski et al., 2012). Given its association with poor health status and lifestyle and consequently with an increase of the individual general frailty, we decided to include both primary and secondary OP as a proxy for poor general health.

2 | MATERIALS AND METHODS

2.1 | Sample

For the creation of the BIF, we used the osteological data from the open-access Wellcome Osteological Research Database, WORD, of the Museum of London (https://www.museumoflondon.org.uk/collections/other-collection-databases-and-libraries/centre-human-bioarchaeology/osteological-database).

The assessment of sex and age at death of the individuals and the description of the biomarkers of stress is reported according to the human osteology method statement (Power, 2012). Sex diagnosis was carried out only on adults through a macroscopic assessment of the skull and pelvis (Power, 2012).

For our study, we excluded individuals aged 11 years or less, according to the Buikstra and Ubelaker classification (Buikstra & Ubelaker, 1994), because children's skeletons are fragile and often under-represented or are partial in skeletal assemblies (Mays et al., 2017). Unlike Marklein et al. (2016), we included in our analysis adolescents because they were already part of the social community in medieval England (Lewis, 2016), thus subjected to stress as adults. Moreover, unlike those who died in their childhood, individuals who survived childhood and died as adolescents might have lived enough to make the signs of physiological stress, if present during their earlier life, be manifest in their skeleton (Yaussy & DeWitte, 2018).

For the development of the index BIF, we used data coming from 863 skeletons from the Monastic cemeteries of St. Merton Priory ($N = 662$) and Bermondsey Abbey ($N = 201$), and 427 complete skeletons from the Non-Monastic cemeteries of Guildhall Yard ($N = 51$), Spital Square ($N = 43$), St. Benet Sherehog ($N = 25$), and St. Mary Graces ($N = 308$). We further applied BIF conventionally on all individuals of the same collections with at least three detectable biomarkers of stress, to test its consistency in case of incomplete skeletons.

We compared the results obtained with the application of our frailty index (BIF) with those achieved previously by another group implementing the SFI (Marklein et al., 2016; Marklein & Crews, 2017) on the same Monastic and Non-Monastic populations included in the WORD database.

2.2 | Scoring methods

We developed evaluation forms for the scoring of the single biomarkers (Figure S1), based on the methods reported in the scientific literature, and another form for the calculation of the frailty index BIF (Figure 1). For BIF, each biomarker was scored as 1 if present and 0 if absent, following the indications reported below and summarized in Table 1. It is worth noting that for the Monastic and Non-Monastic samples only some biomarkers, which were reported in the database, could be analyzed.

- Short stature: we consider short statures, and score them as "1," all estimated statures falling into the first quartile of the male or female stature distribution, as calculated for the population considered. This biomarker is evaluable on the skeleton if at least one complete long bone is present and measurable. For the calculation of the stature distribution, we recommend using equations specific for sex and population (Gualdi-Russo et al., 2018). If possible, left bones should be used to calculate the final stature of an individual.
  For our sample of Monastic and Non-Monastic populations, we used the equations proposed by Pearson (Pearson, 1899). Individuals with a stature below 164.5 cm for men and below 152.8 cm for women, were considered conventionally short-statured in our sample.
- Low body mass: Equations based on the measure of the femoral head diameter are not always accurate, and more population-specific equations are needed. Therefore, we suggest using directly the measure of the femoral head diameter as a proxy of undernutrition in our index, without the indirect calculation of the body mass. Similarly to stature, body mass can be estimated only in adults with diagnosed sex, and male and female measurements should be considered separately. Individuals, who are deemed frail, are those with a femoral head maximum diameter within the first quartile of the male or female measurements of the population.

In our sample, the individuals with a femoral head diameter smaller than 47 mm for males and 42 mm for females were scored as "1." At least one complete femoral head should be present for the analysis of this biomarker.

- LEH: LEH can manifest in single or multiple lines. Considering that one line corresponds to a single event of stress and multiple lines to chronic stress (Goodman et al., 1980; Miszkiewicz, 2015), LEH is considered present if at least one tooth presents multiple visible grooves of enamel hypoplasia (Score "1"). If all evaluable teeth are without defects, or only a single line of hypoplasia is present on one tooth, we consider LEH absent. To detect the absence, at least one canine or one maxillary incisive should be present and observable, since anterior teeth are considered the most sensitive to physiological stress (Armelagos et al., 2009; Goodman et al., 1980; Goodman & Rose, 1990).
- Periodontal disease: Among the different methods existing for the evaluation of periodontal disease, the authors of the WORD database used a method that evaluates the retraction of the alveolar bone, measuring the distance between the cementum–enamel conjunction and the alveolar crest (Brothwell, 1981). The length of the root exposed should not, anyway, be the only parameter for the diagnosis of periodontitis because it can be due to a

Skeletal biomarker		Weight		Score (1 or 0)	W * S
Short Stature		1			
Low Body Mass		3			
Linear Enamel Hypoplasia		3			
Rickets/Osteomalacia		1			
Periodontal Disease		1			
Cribra Orbitalia+	severity 1	1 active	0.5 healing/healed		
	severity 2,3,4	3 active	1.5 healing/healed		
Porotic Hyperostosis+	severity 1	1 active	0.5 healing/healed		
	severity 2,3,4	3 active	1.5 healing/healed		
Periostitis+		2 active	1 healing/healed		
Joint diseases		1			
Vertebral disease		1			
Trauma		2			
Osteoporosis		1			
Total		Max 22			

$$Biological\ Index\ of\ Frailty = \frac{\Sigma\ (W * S)}{\Sigma\ W} * 100 =$$

(based on at least 3 biomarkers) 0-21 low frailty; 21-53 medium frailty; 53-100 high frailty

+If the biomarker is not present (score "0") the weight considered is 3 for CO and PH and 2 for periostitis

FIGURE 1 Evaluation form of the biological index of frailty (BIF)

compensatory eruption with aging (Ogden, 2008). New methods consider the buccal morphology of the alveolar margins combined with the measurement of the retraction of the alveolar bone to create a scoring system that can correctly distinguish between the natural process of reabsorption of the bone due to aging and the presence of an inflammation of the periodontium (Hillson, 1996; Ogden, 2008). Ogden (2008) defines four levels for the scoring of periodontitis: 1 indicates the absence of the disease; 2–4 indicate the presence of periodontitis, respectively mild, moderate and severe. While not used in the WORD database, we recommend Ogden's scoring for periodontitis for future analyses. If at least one tooth manifests degree from 2 to 4 of Ogden's scoring, or, as it is in our sample, one of the periodontitis degrees of Brothwell's scoring (Brothwell, 1981, p. 155), periodontitis is considered present. Otherwise, it is absent. As posterior teeth are the most affected by periodontal disease (Ogden, 2008), there should be, conventionally, at least one observable posterior tooth and half jawbone to consider the biomarker evaluable.

- Nonspecific periostitis/osteomyelitis: When signs of infection of the periosteum are observed, periostitis can be scored as present. Since the risk of death is different for active and healed lesions (Dewitte, 2012), the degree of healing should be recorded: active lesions (no healing) are constituted by the disorganized formation of new woven bone; remodeled lesions (healed) show lamellar bone resulting from the remodeling and substitution of woven bone; mixed lesions (healing), with mixed woven and lamellar new bone, indicate that the infection is still active but the healing process is started. As the shafts of long bones, especially of tibiae, are the most affected by nonspecific periostitis (DeWitte, 2014b), at least one tibial diaphysis should be observable to determine the

TABLE 1 Scoring criteria for the biomarkers of stress for BIF

Biomarker	Presence of the stress biomarker score "1"	Absence of the stress biomarker score "0"
Short stature	The stature falls into the first quartile of the distribution of male or female adult's statures of the considered population.	The stature is not in the first quartile of the males and female adult's distribution. At least one long bone should be present and measurable to estimate stature.
Low body mass	The maximum femoral head diameter falls into the first quartile of male or female adult's distribution of the considered population.	The femoral head diameter falls above the first quartile of male or female adult's distribution. At least one femoral head should be observable and measurable.
Linear enamel hypoplasia	Presence of at least one tooth with a visible groove of hypoplasia.	No tooth presents hypoplasia. At least one canine or one maxillary incisive should be observable (Goodman & Rose, 1990).
Periodontal disease	The morphology of the alveolar bone corresponds to periodontitis from Grade 2 to Grade 4 (Ogden, 2008).	The alveolar bone is normal (Grade 1 of the Ogden (2008) scoring system). At least one posterior tooth and half jawbone should be observable.
Periostitis	At least one bone shows evidence of new bone formation. Operators should differentiate between active, remodeled and mixed lesions (DeWitte, 2014b).	No bone presents signs of periostitis. At least one tibial shaft should be observable (DeWitte, 2014b).
Rickets/osteomalacia	Presence of lower limb deformity and other signs of Vitamin D deficiency (Waldron, 2008).	No signs of vitamin D deficiency. At least one lower limb's long bone should be observable.
Cribra orbitalia	Presence of porous lesions on the orbital roofs. Degrees of severity and healing should be recorded (Rinaldo et al., 2019).	No porous lesion is visible on the orbital roofs. At least one orbital roof should be observable.
Porotic hyperostosis	Presence of porous lesions on the cranial vault. Degrees of severity and healing should be scored (Rinaldo et al., 2019).	No porous lesion is visible on the cranial vault. At least half of the skull should be observable.
Osteoarthritis and other joint disease	Presence of OA or other DJD on at least one joint (Waldron, 2008).	No evidence of OA or other DJD. At least 10 joints (2/3 of the main joints) should be observable.
Vertebral diseases	Presence of IVD, OA or other pathologies of the non-synovial joints of the spine on at least one vertebra.	No disease on vertebras. At least 16 vertebras (2/3 of the spinal column) should be present and observable.
Trauma	At least one ante-mortem trauma is present (Scianò et al., 2020).	No trauma is visible. At least 2/3 of the skeleton should be observable.
Osteoporosis	BMD is under the diagnostic threshold for osteoporosis, evaluated with clinical techniques.	Normal BMD.

Abbreviations: BIF, biological index of frailty; BMD, bone mineral density; IVD, intervertebral disc disease.

absence of periostitis in the individual. Trauma can also cause a periosteal reaction, but the response is usually localized, unilateral, and of small entity. Therefore, the periosteal reaction caused by trauma should not be considered as nonspecific periostitis but should be scored as trauma.

- Rickets/osteomalacia: If any sign of Vitamin D deficiency is recognized on the skeleton, (bowing of the leg bones due to defects in mineralization, but also enlarged, fraying or porous epiphysis, and others signs (Mays & Brickley, 2018; Waldron, 2008)), then we assign Score 1 to the individuals diagnosed with rickets or osteomalacia. Since the manifestation is generally both evident and bilateral, we consider it absent if at least one femur or tibia is observable and without deformations.
- Cribra orbitalia and porotic hyperostosis: At least one orbital roof and half of the cranial vault should be observable to determine the presence or absence of the lesions indicated as CO and PH. Both healing and severity degrees should be reported (Rinaldo et al., 2019), as different degrees of severity and healing will have different weights in the index (Figure 1). Degree 1 of severity of both PH and CO is very often observed in skeletal remains and can be easily confused with normal microporosity of the cranial vault (Roberts & Manchester, 2005), or be due to a mild scalp infection, all conditions that not seriously affect the health status of an individual. Different is the case of CO and PH with degrees 2–4, therefore we propose to evaluate degree 1 of severity separately from more severe manifestations for both pathologies (see Table 2).

Unfortunately, in the WORLD sample, only a few cases of PH are recorded, therefore it was not possible to evaluate this marker in this study.

- Osteoarthritis and degenerative joint disease: The biomarker is considered present if at least one joint shows evidence of OA or other DJD. The diagnostic criteria proposed by Waldron (Waldron, 2008) should be considered for the record of OA. OA is present if there is evidence of eburnation or at least two of the following bone alterations: marginal osteophytes, new bone on the joint surface, pitting on the joint surface, alteration in join contour (Buikstra, 2019; Waldron, 2008). Other conditions of DJD that should be recorded are RCD, rheumatoid arthritis, and other arthropathies, and gout (following the diagnostic criteria of Waldron, 2008). The biomarker is considered absent if there is no evidence of the pathologies and if more than 50% of the area of at least 2/3 of the main appendicular joints on both sides is observable (accounting for 10 of 16 joints). The main appendicular joints to evaluate are the acromioclavicular joints, elbow joints, wrist joints, hip joints, knee joints, ankle joints, hand joints, and foot joints, which are considered the most common sites for the record of OA and DJD (Buikstra, 2019; Klaus et al., 2009; Larsen, 1995; Waldron, 2008; Woo & Pak, 2013). For simplicity, we considered the OA of the synovial joints of the spine and all the other degenerative diseases of the spine in a separate section.
- Vertebral degenerative diseases: To score this biomarker of frailty, all degenerative diseases of the spine should be considered, since they cause similar effects on the individual health, although they have different aetiologies. This marker includes the OA of the synovial joints (facets) of the spine, IVD, and other pathologies that could affect the non-synovial joints of the spine. For the diagnosis of OA of the synovial joints of the spine and IVD, we decided to follow the criteria proposed by Waldron (Waldron, 2008). IVD is considered present if at least one vertebra presents both pitting on the inferior or superior surface of the vertebral bodies and marginal osteophyte (Waldron, 2008). For a diagnosis of other diseases affecting non-synovial joints of the spine, we chose to follow the description reported by Burt and colleagues (Burt et al., 2013). This biomarker is present if one of the diseases affects at least one vertebra. It is considered absent if none of the vertebrae is affected, with at least 16 vertebras (2/3 of total vertebras) observable. We do not consider Schmorl'd nodes, as their association with frailty is not definite (Kyere et al., 2012; Mattei & Rehman, 2014; Sonne-Holm et al., 2013).
- Trauma: Every evidence of antemortem trauma should be recorded. We exclude perimortem trauma since it could not contribute to increasing the frailty of the individual. For this reason, only fractures and trauma healed or with evidence of a healing process (Scianò et al., 2020) should be considered present and scored with 1. Individuals with 2/3 of the skeleton preserved that showed no evidence of trauma should be scored with 0. If less than 67% of the skeleton is preserved this biomarker should not be evaluated.
- OP: Fragility fractures are already considered in the trauma section, even if they might be a consequence of OP and low bone mineral density (BMD), like Colles' fractures, hip fractures and vertebral fractures (Curate, 2014; Curate et al., 2016). Thus, OP should be here assessed only through clinical techniques, like Dexa, histomorphometry, metacarpal radiogrammetry, and CT scans (Agarwal & Stout, 2003; Curate, 2014), or other newly developed techniques for the diagnosis of bone loss in paleopathology, such as QUS (Rinaldo et al., 2018). For the calculation of the index, a score of 1 is given if OP is diagnosed through one of the methods cited (i.e., if the values of BMD, usually T-scores and Z-scores, fall below the threshold set for each diagnostic method); 0 indicates no bone loss or OP. In our sample, OP was not diagnosed with clinical techniques, therefore we could not evaluate this biomarker.

TABLE 2 Logit estimates of the correlation between stress biomarkers with relative odds of premature death, 95% confidence intervals are reported

Biomarkers	Odds ratio	Lower CL 95.0%	Upper CL 95.0%	Weight assigned
Short stature	0.7034	0.1892	2.6148	1
Low body mass	2.4831	0.6654	9.2667	3
Linear enamel hypoplasia	3.3431	0.4943	22.6110	3
Active periostitis	1.4290	0.3165	6.4526	2
Healing periostitis	0.1766	0.0144	2.1617	1
Healed periostitis	0.5735	0.1186	2.7734	1
Periodontal disease	0.0817[a]	0.0102	0.6563	1
CO severity 1	0.0000	0.0000	0.0000	1
CO severity 2-4	3.6470	0.3218	41.3306	3
Rickets/osteomalacia	0.0000	0.0000	0.0000	1
Joint disease	0.1513[a]	0.0215	1.0656	1
Vertebral disease	0.2804	0.0895	0.8781	1
Trauma	1.4555	0.3299	6.4214	2

[a]Statistically significant value.

2.3 | Statistical analysis

In order to assign a weight to each biological marker of frailty, we performed a logistic regression model (Logit model) to estimate the odds ratio (ORs and 95% CI) of dying prematurely (dependent variable) for each biomarker added as an independent categorical variable. Premature death was determined by calculating the mean life expectancy at birth of the analyzed necropolis using a life table (Chamberlain, 2006; Mallegni & Lippi, 2009). We supposed that individuals who died prematurely (before the mean life expectancy of that population) should show biomarkers that contributed more to the individual frailty. Each biomarker was added as a categorical dichotomous variable (presence/absence) with the exception of CO for which we considered separately Grade 1 of severity (absence/Grade 1 of severity/Grade 2–3-4 of severity) (Rinaldo et al., 2019); and periostitis/osteomyelitis for which we considered the degree of healing (absence/active/healed/healing). We decided to exclude PH from the statistical analysis because there were few recorded cases, and OP since in the WORD database OP is assessed through the presence of fragility fractures, which we considered among traumas.

Accordingly to the results of the logit model, we attributed a weight of 1 to the biomarkers with an odds ratio <1; a weight of 2 to those markers with a ratio between 1 and 1.9, and, finally, a weight of 3 to those biomarkers with a ratio equal to or greater than 2, since they probably are the best indicators for frailty, independently from the age of the individuals.

Descriptive statistical analysis was performed (mean and SD for continuous variable and percentage for categorical variables) for each considered variable. For the proposed classification scheme, the interquartile range was calculated as the difference between the third and first quartiles. To detect differences in frailty between subsamples, we performed a *t*-test between the Monastic and Non-Monastic groups and between sexes, analysis of variance between the different age classes (Buikstra & Ubelaker, 1994), and analysis of covariance (ANCOVA) adjusted for age between Monastics and Non-Monastics. All statistical tests were carried out on STATISTICA for Windows (version 11.0, StatSoft, Tulsa, OK). The SFI data used for the comparisons were taken from Marklein et al. (2016) and Marklein and Crews (2017).

3 | RESULTS

3.1 | Biological index of frailty

The mean life expectancy of the individuals in the six necropolis resulted in 34 years of age (Table S1). The results of the logistic regression model are presented in Table 2. No single biomarker significantly resulted as a determinant of premature individual death, whereas some of them showed odds <1, thus contribute less to premature (<34 years of age) death, since they are associated with aging. Regardless, for all biomarkers under consideration, several studies have demonstrated their overall association with frailty, while not being the direct cause of death; thus, we propose to have all of them accounted in BIF, but with varying degrees of importance (weights). Based on the results obtained, we assigned a weight to each trait toward frailty and risk of death with values from 1 to 3. A weight of 3 indicates the greatest importance and a weight of 1 the least.

Concerning the weight to be assigned to some biomarkers, as we could not evaluate it directly, we decided to assign to PH the same weight values of CO, because both lesions may be consequences of a nutritional deficiency. Similarly, we assigned OP the same weight (1) as other biomarkers connected with aging (nonspecific periostitis, vertebral and joint disease).

Regarding the process of healing of the lesions, the database provided information only for periostitis, for which, as shown in Table 2, the odd ratio was higher for the active lesions than for the healing/healed ones, as expected. We, therefore, decided to apply the same results to CO and PH assigning to healing/healed lesions conventionally half the value of the active ones. Figure 1 shows the form for the calculation of the BIF. A score of "1" means that the individual presented the biomarker, a score of "0" that the biomarker is not present. The box must be kept empty if the biomarker is not observable. After filling the form for each biomarker score, individual scores are multiplied by one, two, or three, based on the biomarker importance (weight) for the estimation of frailty (Figure 1). Once this phase is completed, we finally come to the application of the new frailty index, whose formula is as follows:

$$\text{Biological Index of Frailty (BIF)} = \frac{\Sigma\,(\text{Weight}*\text{Score})}{\Sigma\,\text{Weight}}*100.$$

The result is adjusted for the sum of the weights of all assessable biomarkers. By doing so, even incomplete skeletons can be evaluated without underestimating frailty due to nonassessable biomarkers. At least three observable biomarkers are conventionally deemed necessary for the calculation of the index.

According to the BIF distribution, we established the three following categories: low frailty for values 0–21 (first quartile), medium frailty for values 21–53 (second quartile-third quartile), high frailty for values 53–100 (last quartile).

3.2 | Comparison between BIF and SFI in a sample of Monastic and Non-Monastic individuals

We have calculated BIF from the data of the Monastic and Non-Monastic skeletal samples. The index was obtained for all individuals over 12 years of age at death, with at least three observable biomarkers of stress. Doing so, we obtained BIF-values for a total of 1009 individuals, 692 Monastics and 317 Non-Monastics. Subsequently, we compared our index with SFI, the index of Marklein et al. (2016).

The Monastic population had a significantly higher frailty index BIF than the Non-Monastic one, with values falling into the intermediate category of frailty in both cases (Table 3). A statistical difference between these subsamples was reported also by Marklein et al. (2016) using the SFI, but their size was definitely smaller

($n = 134$). Moreover, we found a statistical difference between the two sexes within each subsample, with males having higher frailty (greater BIF) than females, while no differences were evidenced by Marklein et al. with the SFI (Marklein et al., 2016), probably because of the small size of the female subsample (Table 3). We also observed a statistically significant difference among the different classes of age; the difference is in accordance with the findings of Marklein et al. (2016) even if the age categories used were different (Table 3).

Since the difference between the age classes is highly significant, we repeated the comparison between Monastics and Non-Monastics by ANCOVA adjusted for age (Table 4), and we confirmed that the difference is significant ($p < 0.0001$). ANCOVA, performed to assess sex differences when adjusted for age, is not statistically significant ($p = 0.1039$). If we consider Monastic and Non-Monastic men and women separately, anyway, we see that there is a different trend: there is no statistical difference in frailty between males from the two groups (Monastics and Non-Monastics), while there is a statistical difference between females, with the Monastic ones showing the highest degree of frailty. Similar statistically relevant differences were found using the SFI (Marklein et al., 2016; Marklein & Crews, 2017).

4 | DISCUSSION

Assessing the general health status of a population has become increasingly important in bioarchaeology, and the need for an index that encompasses all biomarkers of health and frailty has been underlined several times in the literature (Mcilvaine, 2015).

There are different frailty indices proposed for living populations (Abete et al., 2017; Burn et al., 2018; Sacco et al., 2018; Wallace et al., 2019), however, to our knowledge, only two indices have been proposed for skeletal remains so far (Marklein et al., 2016; Marklein & Crews, 2017; Steckel & Rose, 2002). Typically, biomarkers of stress are analyzed separately (Dewitte, 2012; Mays et al., 2006; Novak et al., 2018; Salvadei et al., 2001), while the above indexes have the merit of considering all stress biomarkers together. Nonetheless, the two existing indexes (health index and SFI) have some important limitations, that we have tried to overcome with the BIF.

BIF differs substantially from the other indexes of frailty: firstly, it gives for the first time a different weight to each skeletal biomarker of stress, based on their importance in increasing the risk of premature death for the individuals. Secondly, and again for the first time, both severity and healing status of evaluable biomarkers are considered in the index. There are different degrees of severity in periostitis as well as in CO and PH manifestations (Rinaldo et al., 2019), and the results of the Logistic model showed that lower grades of periostitis and CO severity were less correlated with the probability of dying young than higher severity degrees. Unfortunately, we could not test if the same relationship exists for PH, as only few cases of PH was reported in the whole sample, probably because of the use of different scoring parameters. We assumed that the relationship is the same as for CO, but further analyses are needed. Moreover, on the database of the Museum of London, healing was considered only for nonspecific periostitis, and we noticed that active lesions had a higher odd ratio than healed ones, as already demonstrated by DeWitte (DeWitte, 2014b).

Even if it was not possible to test whether the same relationship exists for the porous lesions of the cranial vault (PH) and orbital roofs (CO), the positive association between active CO and PH lesions and a higher risk of dying has been previously highlighted in the literature (O'Donnell, 2019). Furthermore, following the Osteological paradox theory (Wood et al., 1992), individuals with healed lesions are believed to have better health status than those without lesions of the same age cohort. Nevertheless, physiological stress occurring during childhood, that leaves signs of healed lesions in the adult skeleton,

TABLE 3 Comparisons between Monastic and Non-Monastic subsamples and between sexes by BIF and SFI (Marklein et al., 2016)

	BIF (this study)				SFI (Marklein et al., 2016)		
Subsample	***N.***	**Mean (SD)**	***p*-value**	**Subsample**	***N.***	**Mean (SD)**	***p*-value**
Lifestyle			**0.0000**[a]	Lifestyle			**0.015**[b]
Monastic	692	40.28 (22.57)		Monastic	74	3.42 (1.41)	
Non-Monastic	317	31.58 (22.99)		Non-Monastic	60	2.80 (1.47)	
Sex			**0.0083**[a]	Sex			0.33[b]
Male	741	39.56 (22.60)		Male	111	3.20 (1.46)	
Female	132	33.94 (21.98)		Female	23	2.87 (1.52)	
Age			**0.0004**[b]	Age			**0.041**[b]
12–17	43	26.24 (25.40)		18–25	22	3.00 (1.31)	
18–35	264	34.90 (21.87)		26–35	29	2.62 (1.55)	
36–45	387	39.38 (21.89)		36–45	55	3.18 (1.40)	
>46	166	38.84 (21.20)		>46	28	3.71 (1.47)	

Note: Statistically significant *p*-values are indicated in bold.
Abbreviations: BIF, biological index of frailty; SFI, skeletal index of frailty.
[a]*t*-test.
[b]Analysis of variance.

TABLE 4 ANCOVA between Monastic and Non-Monastic individuals using BIF and SFI (Marklein et al., 2016; Marklein & Crews, 2017)

Monastic versus Non-Monastic	Monastic	Non-Monastic	
	Mean (SD)	Mean (SD)	*p*-value
BIF			
Tot ($n = 1009$)	40.28 (22.57)	31.58 (22.99)	**0.0000**
Males ($n = 741$)	40.71 (22.44)	35.58 (22.78)	0.1014
Females ($n = 132$)	43.23 (20.86)	28.80 (20.99)	**0.0009**
SFI			
Tot ($n = 134$)	3.42 (1.41)	2.80 (1.47)	**0.058**[a]
Males ($n = 111$)	3.12 (0.16)	2.77 (0.23)	0.474
Females ($n = 23$)	3.83 (0.48)	2.41 (0.29)	**0.030**

Note: Statistically significant *p*-values are indicated in bold.
Abbreviations: ANCOVA, analysis of covariance; BIF, biological index of frailty; SFI, skeletal index of frailty.
[a]This *p*-value was considered significant in the original paper (Marklein et al., 2016).

could create a weaker immune system and a frailer body according to the "Developmental Origins of Health and Disease" paradigm (Armelagos et al., 2009; Barker & Osmond, 1986; Gillman, 2005; Gluckman et al., 2015; O'Donnell, 2019; Temple, 2019). Consistently with the latter theory, we assigned a weight, albeit low (0.5–1.5 according to the severity degree), to healed lesions in our index.

Thirdly, thanks to the implementation of a weighted mean, the BIF can also be applied to incomplete skeletal remains, assuming that at least three skeletal biomarkers are detectable. This feature makes possible the investigation of frailty even in ancient and poor preserved skeletal series. Indeed, the more biomarkers can be observed, the more precise the analysis is, but the weighted mean of at least three biomarkers should ensure a reliable estimation, as we have seen comparing BIF with SFI.

The results of our work demonstrated how the new index of frailty can be successfully used on archaeological skeletal remains. In particular, the application of the new index on Monastic and Non-Monastic medieval populations from the Museum of London revealed the suitability and applicability of BIF. General differences previously observed by Marklein et al (Marklein et al., 2016) were detected with our index as well, and the frailty of the Monastic group was demonstrated to be higher than that of the Non-Monastic one. However, unlike the SFI, the BIF could be applied to a large number of individuals, and by doing so, BIF permitted to highlight more differences than SFI in the two populations, that is, to observe differences of frailty between the females of the two groups.

The innovations implemented in BIF ensure the applicability of this index to a larger segment of the population, expanding the survey to include those skeletons that would be discarded due to their fragmentary condition. Marklein et al. (2016) also stressed the importance of having a larger number of individuals, by proposing in a subsequent study an SFI with a reduced number of biomarkers (Marklein & Crews, 2017). With the BIF, we could maintain a high number of biomarkers while examining a larger sample size. Based on the same population, we examined 1009 individuals with 12 biomarkers, whereas Marklein et al. (Marklein et al., 2016) could apply the SFI to 134 individuals with 13 biomarkers, or 517 individuals with fewer biomarkers with the modified SFI composed by six biomarkers (Marklein & Crews, 2017).

It was previously observed by DeWitte et al. (Dewitte et al., 2013) that Monastic individuals from medieval times lived longer than Non-Monastic people, an observation that has been confirmed by our mortality table (Table S2). The Monastic population was composed of clerical men and women, yet also noble individuals were sometimes buried with the clericals (Dewitte et al., 2013). Moreover, during the Middle Ages, those who joined the clergy were mostly people from noble families, usually second children who could not inherit the assets of their family. Therefore, the longer lifespan of the Monastic population was probably due to better living conditions and diet, but they were subjected to higher morbidity, as the higher degree of frailty scored both by SFI (Marklein et al., 2016) and BIF demonstrated. A similar trend is observed in sex comparisons: females show higher frailty values than males. This phenomenon is known even in modern human societies where women show poorer health and greater longevity than men, the so-called "male–female health-survival paradox" (Gordon et al., 2018).

Skeletal frailty is a reflection of physiological stress that cumulates over the years and reflects an individual relative risk of dying when compared with others of the same age group: for this reason, age at death should always be considered as a determinant variable when making comparisons between groups. Using age as the covariate in the ANCOVA, we noticed how only for women the difference in frailty between the two groups still exists (Table 4). Non-Monastic women died younger than Monastic ones and generally before having the time for the signs of stress to become manifest on the skeleton.

Our work has several strengths that we have already discussed. In addition, we provide a new evaluation form for the scoring of different biomarkers (Figure S1), defining them thoroughly in the methods section. However, some limitations of our study should also be mentioned. First, there is no unanimous consensus in the literature regarding which indicators should be considered most important for the assessment of frailty. To overcome this issue, we relied on the statistical analysis of known indicators collected from a large sample size, but further studies are needed to confirm our choices. Also, concerning biomarkers, it is necessary to emphasize that the database used did not allow us to assess the importance of PH and OP, and the healing status of the porotic lesions. It will, therefore, be necessary to integrate our findings in the future, using other

databases that also consider those variables, so that the weight attributed to these biomarkers can be confirmed or not. Finally, the BIF in this form is only useful from the age of 12 years, while for children below this age the index should be adapted and tested.

We hope the new index will be used in further bioarcheological studies, to improve the index itself and our interpretation of health in the past.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Nicoletta Zedda: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); project administration (equal); resources (equal); validation (equal); writing–original draft (equal). **Barbara Bramanti:** Project administration (equal); resources (equal); supervision (equal); writing–view and editing (equal). **Emanuela Gualdi-Russo:** Conceptualization (equal); formal analysis (equal); methodology (equal); writing–review and editing (equal). **Elena Ceraico:** Data curation (equal); investigation (equal); methodology (equal); validation (equal). **Natascia Rinaldo:** Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); project administration (equal); supervision (equal); visualization (equal); writing–original draft (equal).

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated during the current study.

ORCID

Nicoletta Zedda https://orcid.org/0000-0003-2899-2884
Barbara Bramanti https://orcid.org/0000-0002-5433-663X
Emanuela Gualdi-Russo https://orcid.org/0000-0002-7274-547X
Natascia Rinaldo https://orcid.org/0000-0002-6972-3085

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