INTRODUCTION: One goal of reducing fracture risk is to maintain bone stiffness and strength with aging despite a net loss in bone mass. It is well recognized that age-related bone loss is often accompanied by continued periosteal apposition [1]. Because variation in the amount of periosteal expansion may be a major contributor to fracture risk [2], having a better understanding of the factors contributing to the inter-individual variation in this biological process will benefit efforts to reduce fracture incidence. Many factors contributing to the variation in periosteal expansion have been identified, but a critical, largely neglected factor is external bone size. Prior theoretical work [3] did not incorporate the inter-individual variation in acquired trait sets exhibited by human long bones [4], and thus it was unclear how the amount of periosteal apposition should vary among individuals to maintain strength with aging. We hypothesized that because human long bones show a pattern of acquired trait sets (Fig 1), the amount of periosteal expansion required to maintain strength during aging will depend on external bone size. To test our hypothesis, we developed a new, more general, mathematical model that predicts the periosteal expansion rate required to maintain strength during aging based on the inter-individual variation in adult bone morphology and tissue-quality and the endocortical bone loss and tissue-modulus degradation that occur with aging. We also determined how the periosteal expansion rate must change over time to maintain stiffness.

METHODS: Whole bone bending stiffness is proportional to the product, EI (tissue-modulus x moment of inertia). Unlike the prior published model [3], we include both tissue-quality and morphological traits, because a) the pattern of trait sets acquired by individuals include interactions among these traits and b) the degradation of tissue-modulus with aging must be compensated by increases in periosteal expansion beyond that expected for endocortical bone loss. We modeled diaphyses as right cylinders with a circular cross-section (R = outer width/2, r = inner width/2) and assumed that apposition and resorption occur uniformly around the cortex. Periosteal apposition rate (dR/dt) can be written as a function of endocortical resorption rate (dr/dt), the rate of degradation in tissue-modulus (dE/dt), adult bone morphology (r/R) and tissue-modulus (E). The periosteal apposition rate required to maintain whole bone stiffness, EI, over time (dEI/dt = 0) can be written as:

\[ dR/dt = (1/\pi)(1/E)(1/R^3) dE/dt + (r/R)^3 dr/dt \]

To determine how periosteal expansion rate depends on external bone size, we used this equation to predict how dR/dt should change to maintain a constant stiffness over time (dEI/dt = 0) across a population with diaphyseal cross-sectional morphologies that varied in width (R = 8.5 - 13 mm) similar to human tibiae [4]. We imposed the constraint that each bone started with the same mass (i.e., same CtAr) and adjusted dr/dt so all structures lost 40% of the original CtAr by age 90. To assess how periosteal apposition must change over time to maintain stiffness and whether this relationship varies with adult bone width, the periosteal apposition rate was plotted as a function of age for 5 bones spanning the range of external sizes examined above.

RESULTS: The differential equation indicated that periosteal expansion rate (dR/dt) is linearly related to the rate of endocortical resorption or marrow expansion (dr/dt), the rate of change in whole bone stiffness (dE/dt = 0), and the rate of change in tissue-modulus (dE/dt). Importantly, dR/dt was inversely related to adult tissue-modulus and highly nonlinearly related to adult bone morphology (1/R^3 and r/R^3).

The net bone loss by 90 years of age, which considers both loss and gain, was ~2x greater for slender bones compared to robust bones despite EI being held fixed over time (dEI/dt = 0). The difference in net bone loss can be explained by the dependence of periosteal apposition on adult bone size: the periosteal apposition rate required to compensate for endocortical bone loss was ~3-times greater for robust bones compared to slender bones (Fig 2). Degrading tissue-modulus by 2%/decade substantially increased dR/dt for all bone sizes (25-50%) compared to the case when dE/dt = 0. Importantly, dR/dt increased over time to maintain whole bone stiffness and the age-change in dR/dt varied with adult bone size (Fig 3). As resorption progresses during aging, the endocortical surface moves further from the neutral axis and thus requires a progressively greater amount of periosteal apposition to maintain stiffness. Although slender bones required significantly less periosteal expansion to compensate for endocortical bone loss compared to robust bones, the amount of apposition required to maintain strength over time increased to a much greater extent for slender bones compared to robust bones.

DISCUSSION: Our model predicts that the amount of periosteal expansion required to maintain strength during aging is highly dependent on external bone size and increases substantially over time. Periosteal apposition rate shows a strong size effect because individuals acquire specific trait sets to buffer variants affecting robustness. This results in predictable associations among components in the model, specifically the term r/R, which varies negatively with bone size (Fig 1) and is a dominant term affecting periosteal expansion. This size dependence has not been incorporated into clinical studies. These results indicate that the degree to which periosteal cells must be stimulated to add new bone periosteally depends greatly on bone size and increases progressively with advancing age. This is a critically important outcome, particularly considering that stimulatory factors for bone apposition (e.g., loading, hormones, etc) decrease with aging, and thus the individual variation in adult morphology alone may create a progressively worse situation that is more pronounced in individuals with slender bones. Because the periosteum is a critical target for prophylactic treatment [5], knowing that periosteal expansion depends on adult bone morphology and time is essential for developing advanced diagnostics, treatment targets, and treatment feedback that will improve identification of at-risk individuals and will provide critical insight into the cellular activity that is required to maintain bone strength with aging on an individualized basis. Future work will use the model to study the emergent behavior of a population with varying degrees of loss and apposition and compare to existing clinical studies.