Invited Commentary

Invited Commentary: A Fine Balance—Weighing Risk Factors Against Risk

Michael G. Walsh

Initially submitted July 25, 2008; accepted for publication July 29, 2008.

Fracture risk in the elderly is a composite of frailty, bone quality, and the environment. Factors that precipitate a fall, which is the most important mediator between any risk factor assemblage and fracture, aggregate and interact cumulatively to form a distinct environmental and physical hazard profile. In this issue of the Journal, Wagner et al. (1) describe the association between self-reported balance impairment and incident fracture among balance-discordant twins from the Swedish Twin Registry. The importance of balance to frailty, and thus by extension to fall and fracture risk, cannot be understated. Rubenstein and Josephson showed in a recent review (2) that a balance deficit is responsible for a 3-fold increase in fall risk, placing it among the top 4 risk factors for falls along with gait deficit, history of falls, and lower-extremity weakness. Weakness demonstrated the strongest association with falls (odds ratio = 4.4) across the 16 studies reviewed. This consistent result for balance is further corroborated by the robust finding from the Swedish Twin Registry (1). Moreover, the generalizability of these new data from the Swedish Twin Registry far exceeds that of data from the clinical literature.

Modern epidemiology, resting on the foundation of decades of applied methodological rigor and technological advancement in computing capacity and molecular biology, is comprised of a broad tool kit. Nevertheless, the breadth of our application in some instances has accompanied a parallel diminishing return on its depth. This is highlighted by an important concept in defining disease risk that continues to be grappled with and remains intractable: risk clustering. The concept of risk clustering is a familiar one to those investigating the social determinants of health. At issue is the essential difficulty of identifying and isolating the effects of factors that are often correlated with each other and interact in parallel, or that act as direct mediators in the causal pathways between exposure and disease. Often, both phenomena occur simultaneously. For example, the
difficulty in identifying “race” as an isolated risk factor for early mortality stems from the fact that “race” can be considered a social construct that is inextricably bound to other social constructs such as socioeconomic position, the built environment, and psychosocial stress. The interaction between these factors makes “race” tenuous as a reducible factor that can be clearly delineated in a causal pathway. Additionally, in observational studies we are limited to a finite number of measurable intermediary and confounding factors with which we either try to apportion the degree of risk “attributable” to the factor or adjust for the effects of other factors of interest. Inevitably, there exist important exposures that go unmeasured, which leads to residual unattributable risk and unmeasured confounding.

Musculoskeletal dysfunction in the aging population lends itself naturally to exploration of risk clustering. A brief discussion of frailty is a good place to begin. Frailty represents a syndrome, and therefore it is easily recognizable as a cluster of symptoms. The syndrome is expressed as diminished physiologic reserve, which is characterized by gait and balance abnormality, weight loss, muscle weakness, loss of energy, and diminished physical activity (3–6). Frailty is a serious public health burden; the syndrome is associated with increased risk of falls, low-velocity fracture, significant disability, and mortality (7). Indeed, these sequelae often occur directly in this sequence as a chain reaction. Moreover, the syndrome’s components are generally highly correlated and interactive. For example, physical inactivity leads to increased muscle weakness and diminished gait performance, which in turn makes physical activity, particularly walking, more difficult. This aggregation of risk via cumulative causal pathways hastens the progression of frailty and leads to more substantive disability, which may be directly related to or entirely independent of a traumatic event (e.g., hip fracture).

Falls and their attendant fractures are very much influenced and exacerbated by a person’s degree of frailty. For example, in the review by Rubenstein and Josephson (2), several pooled odds ratios were presented for fall risk. Three important components of frailty—lower-extremity weakness (relative risk (RR) = 4.4, 95% confidence interval (CI): 1.5, 10.3), gait deficit (RR = 2.9, 95% CI: 1.3, 5.6), and balance deficit (RR = 2.9, 95% CI: 1.6, 5.4)—were all associated with significant and substantive increased risks of experiencing a fall (2). In addition, while frailty can act on fracture risk independently of bone quality, the syndrome is nevertheless also associated with bone biology. Muscle weakness is a key component of frailty and is related to decreased physical activity and the subsequent loading of bone. Without the regular loading of bone that comes with muscle exercise, bone architecture changes such that the cancellous structure is compromised by diminished trabeculae (8). Bone chemistry is also affected by way of reduced mineral content (8). Frailty is integral, therefore, to the processes that lead to falls and fractures in the elderly.

Wagner et al. (1) report a robust association between balance impairment and fracture across fracture types and after adjustment for a measure of physical activity and muscle strength (ability to rise from a chair). The results, however, beg 1 question: What does this association tell us about the risk clustering of frailty for fracture? While this result certainly underscores the importance of balance in fracture risk, its isolation does not tell us about the more influential composite of frailty. Indeed, neither the adjusted odds ratio nor the additional quantification of population attributable risk can really be considered a reduction of balance to its isolated effects, simply because of the high degree of correlation and the shared causality with the other components of frailty. This is of particular concern for the development of fall prevention strategies, which must necessarily act on the frailty composite rather than on its isolates. For example, an assistive device may aid in providing balance during ambulation, but without increased physical activity muscle weakness will continue to increase and without gait improvement balance is likely to decline further—both of which will lead to increased frailty and a greater risk of fall and fracture.

This risk clustering conundrum requires a different theoretical framework for quantifying risk, as well as different analytical tools. One such theoretical model allows for both a conceptual and an analytic formulation of the problem: Bayesian networks. The use of directed acyclic graphs (DAG) to hypothesize about and define exposure-outcome causal pathways has become increasingly popular in epidemiology. In a DAG, variables are graphically represented as nodes connected by arcs that describe the relations between them. Key to the concept of the DAG is direction. An arc moving from variable X to variable Y denotes that X is a parent of Y. As a graphical tool, DAGs can help us visualize the ways in which dependencies and independencies manifest themselves among various exposure variables in relation to an outcome. This is particularly useful for scenarios that exhibit a high degree of correlation between different exposures, or in scenarios where a variable(s) is mediating the relation between an exposure and an outcome.

With respect to frailty, we can use a DAG to identify and describe the myriad interrelations between its syndromic components and subsequently graph how these components may direct toward an outcome such as a fall or fracture. The variables represented by the DAG form a Bayesian network if the joint distribution of all variables included in the model is the product of the local distributions of the individual variables and their parents (9). Furthermore, a Bayesian network allows us to quantify our prior knowledge (which may be gained from observational and experimental studies) in the form of a prior distribution, assess that prior distribution given newly generated data, and then finally compute an updated posterior distribution, thus presenting us with a means toward probabilistic testing of causal hypotheses. A Bayesian network also allows us to update the model as new information becomes available, thus adding learning capacity to this approach, which is something standard regression techniques are not able to accommodate.

The findings presented here by Wagner et al. (1) are an invaluable and necessary contribution to the musculoskeletal disease literature highlighting the importance of balance in fracture risk. This commentary does not offer a critique of their work; rather, it offers a challenge to musculoskeletal researchers in particular and epidemiologists in general. Our
challenge is to cautiously embrace complexity where it exists and apply the appropriate methods to incorporate the information that complexity provides rather than operationalize the process of exposure and disease so that the process is more malleable to standard statistical modeling procedures. In the context of frailty and fracture risk, the public health importance will quickly manifest itself as the medical costs of an aging population continue to increase. Interventions will need to focus more on primary prevention and thus will require a systems approach to mitigating risk in general, rather than a streamlined approach to mitigating single risk factors. Moreover, I believe those of us who study musculoskeletal disease, especially trauma, are in a unique position to consider the ways in which risk clustering affects disease, particularly since many of our outcomes follow from multiple and cumulative exposures.

ACKNOWLEDGMENTS

Author affiliation: Departments of Environmental Medicine and Orthopaedic Surgery, Division of Outcomes Studies, Langone Medical Center, New York University, New York, New York.

Conflict of interest: none declared.

REFERENCES