What have the Framingham cohorts taught us about hyperuricemia and gout?

"*With every passing year, the Framingham Heart Study adds to the wealth of information and further offers opportunities to ask new questions, revisit old questions and learn more in the process.*"

KEYWORDS: coronary heart disease ■ diabetes ■ Framingham Heart Study ■ gout ■ heart failure ■ hypertension ■ hyperuricemia

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The cohorts based at Framingham (MA, USA) have, arguably, contributed more to the understanding of human health and disease than any other epidemiologic study. Originally started as a single cohort of 5209 men and women in 1948, The Framingham Heart Study (FHS) was supplemented in 1971 by a second cohort of 5124 men and women, consisting of the offspring of the original cohort and their spouses (the FOS). Most recently (2002), a generation III cohort has been assembled. Participants of these cohorts have been followed-up in regular intervals with rigorous assessment of medical and lifestyle history, physical examination and laboratory measurements [1,2]. These three cohorts initiated over six decades are collectively (and loosely) referred to as the Framingham Study (FS) even though there are significant differences in the type of data collected. We intend to discuss the seminal contributions of the FS in the understanding of causes and consequences of hyperuricemia and gout in this article.

The FS is one of the well-performed epidemiological studies. Hall *et al*. quantified the magnitude of association between serum urate concentration and incident gout after 12 years of follow-up of FS [3]. More importantly, this article made an astute observation that the choice of measurement of serum urate (baseline or highest observed measurement) used for statistical analyses did not influence the strength of association. This assertion has since been validated in other settings. Recently Bhole *et al*. updated the original analyses to reflect 52 years of follow-up and documented that higher levels of serum uric acid increase the risk of gout in a graded manner among women, albeit at a lower pace than men [4]. The respective multivariate risks of gout were 22- and 47-fold in women and men who had uric acid level above 8 mg/dl compared with those below 5 mg/dl. Increasing age, obesity, alcohol consumption, hypertension and diuretic use were associated with the risk of incident gout.

The FS has a checkered history when it comes to the links between hyperuricemia, gout and cardiovascular diseases (CVDs). For centuries, astute clinicians have observed the clustering of CVDs and metabolic diseases among people with gout. Readers may find it interesting that one of the original missions of the FHS was to establish the links between gout and heart diseases, specifically coronary heart disease (CHD) [101]. One of the first studies to emerge from these data on gout and uric acid was conducted by Hall [5]. While discussing various epidemiological approaches to study the correlations among hyperuricemia, hypercholesterolemia, coronary disease and hypertension, he emphasized that "If an association is shown with the passage of time, the observation will have considerable validity. Here again, we must be careful not to assume a cause and effect relationship." As one goes through the series of papers arising from the FS, one can fully appreciate the beauty of this statement.

Hall (in 1965, with a follow-up period of 14 years) found that 75 individuals had incident and prevalent gout [5]. A 10-year incidence of CHD was significantly higher in subjects with gout (18 out of 100) compared with total population (9.2 out of 100). They also showed a trend towards more CHD (along with increased blood pressure and cholesterol levels) in those with higher uric acid levels.

Abbott *et al*. (in 1988, with a follow-up period of 32 years) studied the association between gout without the use of diuretics and risk of CHD [6]. They concluded that men with gout experienced a 60% excess of CHD compared with those without gout, and the association remained

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significant after adjusting for age, systolic blood pressure, total cholesterol, alcohol, BMI and diabetes. For women, no significant associations were observed.

According to Brand *et al*. (in 1985, using data from examinations four to 13, with a follow-up period of 26 years), examination four serum uric acid predicted the subsequent development of CHD, in general, and myocardial infarction, in particular [7]. However, in multivariate analysis, including age, systolic blood pressure, relative weight, cigarette smoking and serum cholesterol, there was no independent relationship between serum uric acid and CHD.

Kannel (in 1987, with a follow-up period of 26 years) stated that the risk of CHD, particularly myocardial infarction, was increased in hyperuricemic persons [8]. The risk ratios were higher in women (twofold) than in men (1.4-fold). Multivariate analysis indicated a moderate independent effect. Women with either symptoms of gout or with symptomatic hyperuricemia were at increased risk of CHD.

Interestingly, Culleton *et al*. (in 1999, with a follow-up period of 22 years; from 1972 to 1994, including original and offspring cohorts) had similar findings [9]. Elevated serum uric acid level was not associated with increased risk for CHD in men after age-adjustment. However, in women, in age-adjusted models, uric acid level was predictive of CHD, death from CVD and death from all causes. There were no associations for both genders after adjustment for CVD risk factors. Culleton *et al*. identified diuretic use as the confounding variable. They maintained that clinically, serum uric acid level should not be used as an indicator of risk for cardiovascular disease; established risk factors should be used to stratify risk [9].

Hyperuricemia is a well-known correlate of diabetes. In fact, the original descriptions of metabolic syndrome included hyperuricemia as a criterion. Earlier analyses of the FHS data were negative for such an association [3]. Bhole *et al*. performed an updated analysis of FHS and FOS [11]. They showed that the risks of Type 2 diabetes per mg/dl increase in serum uric acid levels increased by 20% for the original cohort and 15% for the offspring cohort independent of other known risk factors. This clearly highlights the importance of prospective study with longer follow-up.

That hyperuricemia is a risk factor for poor outcomes among patients with heart failure is well known; what has not been well known is the association between hyperuricemia, gout and the risk of incident heart failure. Krishnan (in 2009, in the FOS, with a median follow-up period of 29 years) analyzed the relationship between baseline serum uric acid and subsequent heart failure [12]. The incidence rate of heart failure was approximately sixfold among those at the highest serum uric acid quartile compared with those at the lowest. The corresponding risk of heart failure remained significant (twofold) after adjusting for relevant risk factors.

Further analyses of the FOS data showed that participants in the highest serum uric acid quartile had significantly higher incidence of all echocardiographic abnormalities during follow-up compared with those in the lowest quartile [13]. In multivariable logistic regression analyses, those in the highest quartile had odds ratios in the range of 4–9 for left ventricular systolic dysfunction and abnormal left ventricular ejection fraction compared with those in the lowest quartile.

Krishnan (in 2012, in the FOS, with a follow-up period of 37 years, from 1971 to 2008), also found that individuals with gout had two- to three-times higher incidence of clinical heart failure and echocardiographic measures of systolic dysfunction compared with those without [14]. Participants with gout also had greater mortality.

Similar to CVD, it is interesting to follow the evaluations of the links between hyperuricemia, gout and hypertension. Hall (in 1965, with a follow-up period of 14 years) showed a trend towards increased blood pressure in individuals with higher uric acid levels [5].

Wilking *et al*. (in 1988, with a follow-up period of 24 years) performed multivariate analyses and concluded that age, sex, all components of blood pressure and increased relative weight in women were associated with isolated systolic hypertension [15]. Serum uric acid did not have any significant association.

Sundström *et al*. (in 2005, with a follow-up period of 4 years from baseline) included FHS and FOS participants free of hypertension, myocardial infarction, heart failure, renal failure or gout in their study [16]. From multivariate analyses, they concluded that serum uric acid level was an independent predictor of hypertension incidence and longitudinal blood pressure progression at short-term follow-up.

Prospective design has strengths and weaknesses that deserve comment. As the prospective data permit interesting *post hoc* analyses, a large number of studies have been conducted using these data. These data being community-based,

the findings have ecological validity and are likely to be generalizable to the US population. The definition of gout in the Framingham cohorts is based on a clinical diagnosis of gout by examining physicians and did not require observation of urate crystals in joint fluid, as was the case in other large epidemiologic studies of gout [17–19]. Serum uric acid assessments were not performed at every examination, an old assessment may be of less utility in determining current risks than a recent one, and this may explain the different results in some of the studies (e.g., for hypertension [15,16]). At the same time, more events occur over the prolonged follow-up in this prospective study that can explain different results in later studies with longer durations of follow-up (e.g., for diabetes(e.g., for diabetes [3,11]). Furthermore, better understanding of confounding variables and in-detail statistical analyses may shed light from different angle on some issues (e.g., for CHD [7,9]).

With every passing year, the FHS adds to the wealth of information and further offers opportunities to ask new questions, revisit old questions and learn more in the process. We believe that the best is yet to come from the Framingham cohorts.

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