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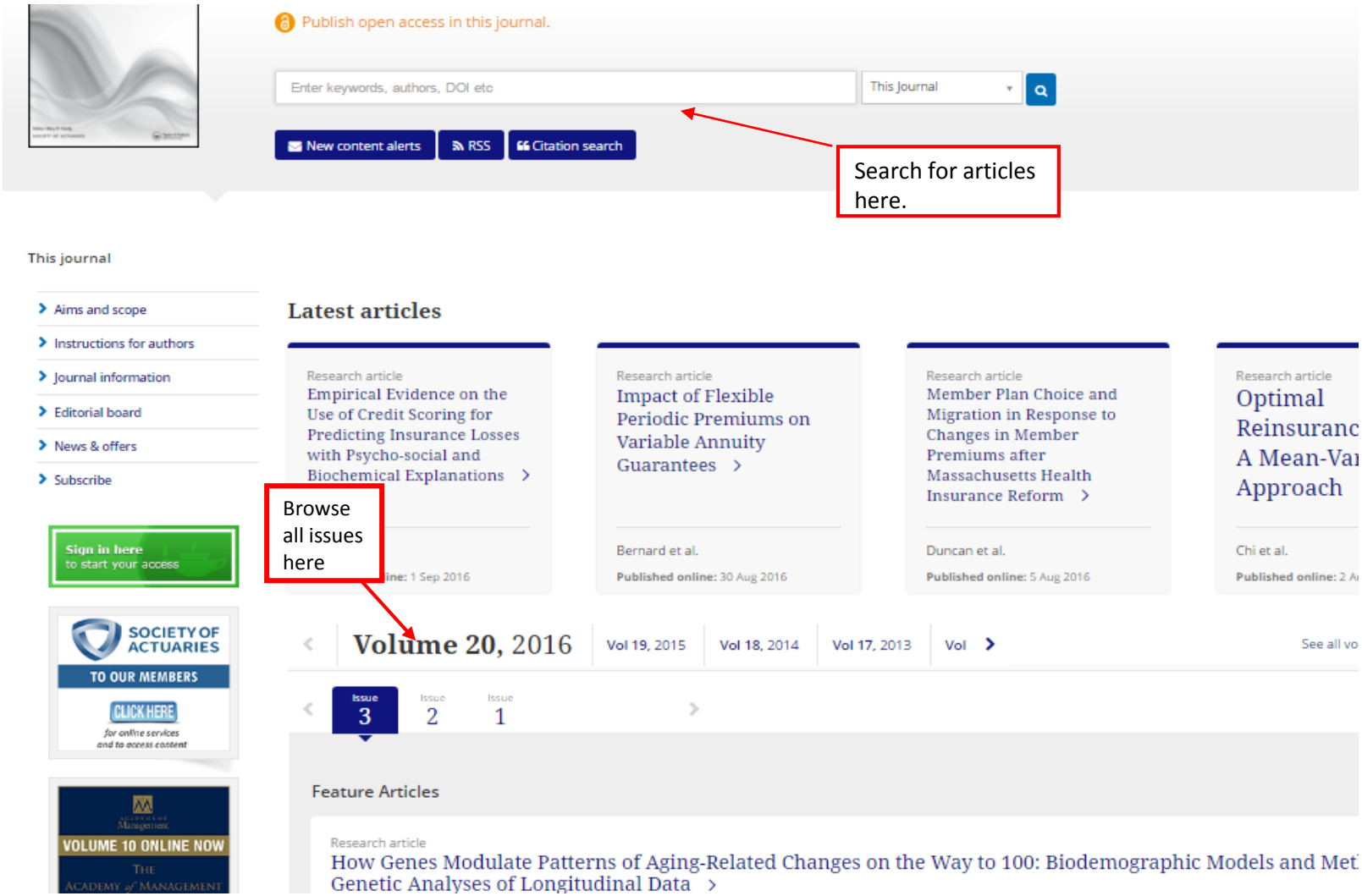

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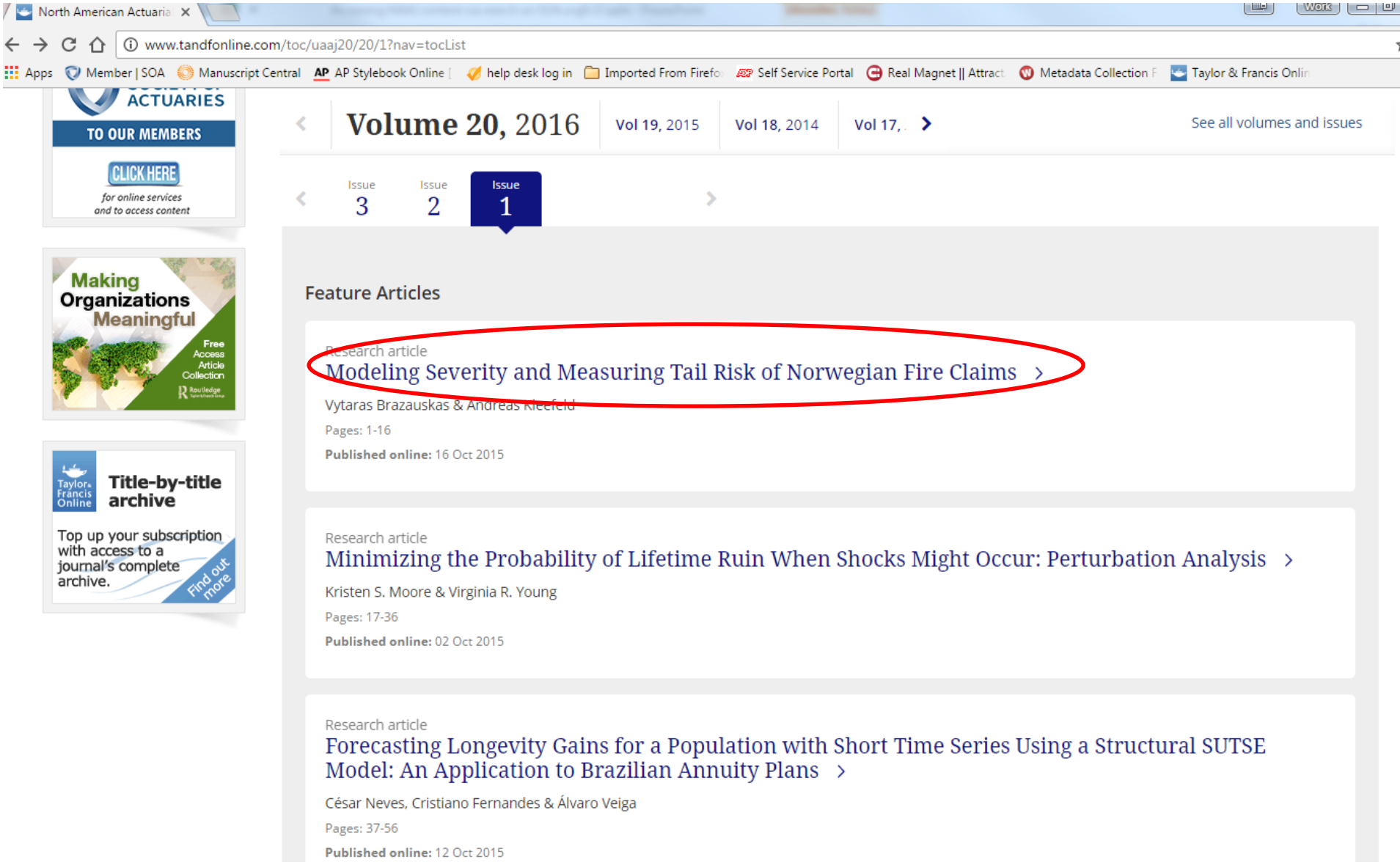

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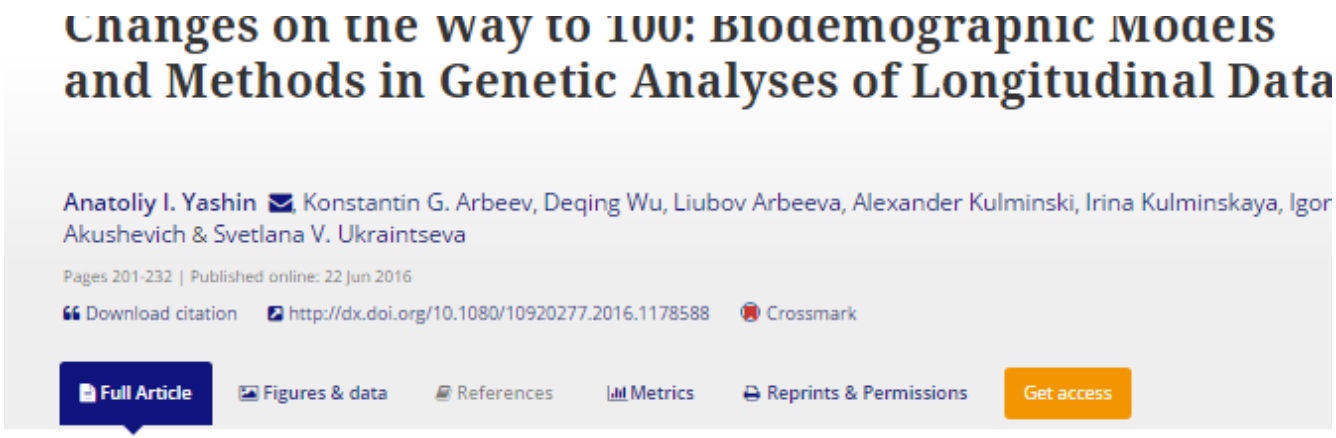

Changes on the Way to 100: Biodemographic Models and Methods in Genetic Analyses of Longitudinal Data

Anatoliy I. Yashin, Konstantin G. Arbeev, Deqing Wu, Liubov Arbeeva, Alexander Kulminski, Irina Kulminskaya, Igor Akushevich & Svetlana V. Ukraintseva

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Abstract

In this article we clarify mechanisms of genetic regulation of human aging and longevity traits. The objective of this article is to address the issues in previous research of not reaching a genome-wide level of statistical significance and lack of replication in the studies of independent populations. We performed GWAS of human life span using different subsets of data from the original Framingham Heart Study cohort corresponding to different quality control procedures, and we used one subset of selected genetic variants for further analyses. We used a simulation study to show that this approach to combining data improves the quality of GWAS with FHS longitudinal data to compare average age trajectories of physiological variables in carriers and noncarriers of selected genetic variants. We used a stochastic process model of human mortality and aging to investigate genetic influence on hidden biomarkers of aging and on dynamic interaction between aging and longevity. We investigated properties of genes related to selected variants and their roles in signaling and metabolic pathways and showed that the use of different quality control procedures results in different sets of genetic variants associated with life span. We selected 24 genetic variants negatively associated with life span and showed that the joint analyses of genetic data at the time of biospecimen collection and follow-up data substantially improved significance of associations of 24 selected SNPs with life span. We also showed

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