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LITERATURE REVIEW

JIM Reading List

Our Literature Review section continues with another installment of summaries from the medical literature. Our authors have found recent articles that have direct relevance to the practice of insurance medicine. The intent of the reading list is to provide the highlights of articles, not an in-depth analysis. Contributions to the reading list are invited. Please forward your citation and summary to Ted Gossard, MD or Stephanie Hrisko, MD, Associate Editors, Literature Review at GOSSAT2@nationwide.com or stephaniehrisko@thecasongroup.com. We will acknowledge all contributors in each issue's installment.

CARDIOLOGY

1. *Karim S, Chahal CAA, Sherif AA, et al. Re-evaluating the Incidence and Prevalence of Clinical Hypertrophic Cardiomyopathy: An Epidemiological Study of Olmsted County, Minnesota.* Mayo Clin Proc. *2024;99:362-374.*

The prevalence of hypertrophic cardiomyopathy (HCM) in the general population worldwide has been estimated as 0.2% (1 in 500 adults). More recent studies have suggested a higher prevalence with recognition of sub-clinical disease and the gene-positive–phenotype-negative subset. This study is a contemporary re-evaluation of the incidence-rate, prevalence, and natural history of HCM in Olmsted County, Minnesota, from 1984 to 2015 with a comparison to a prior study in the same community evaluating 1975-1984 (the index study). (Codd MB, Sugrue DD, Gersh BJ, et al. Epidemiology of idiopathic dilated and hypertrophic cardiomyopathy. A population-based study in Olmsted County, Minnesota, 1975-1984. *Circulation*. 1989;80:564-572).

Through the Rochester Epidemiology Project medical records linkage system, between January 1, 1984, and December 31, 2015, 270 residents of Olmsted County with HCM were identified. Manual record validation and review of 321 cases excluded 51 determined to more likely represent left ventricular hypertrophy secondary to causes other than HCM. Characteristics included mean age at diagnosis (61.2 years), male (49.3%), median 6.5 years follow-up (2.9-12.4 years), and 101 (37.4%) deaths. Symptoms at diagnosis included dyspnea (49.6%), palpitations (23.7%), lightheadedness (24.1%), chest discomfort (21.5%), and history of syncope (11.5%). Relevant history included atrial fibrillation or flutter (23%), diagnosis of hypertension (59.6%), diabetes (11.1%), coronary artery disease (22.2%), positive family history of HCM or other cardiomyopathies (14.4%), and family history of sudden cardiac death (11.5%).

Echocardiographic characteristics included asymmetric septal hypertrophy (87%), apical hypertrophy morphology (13%), outflow tract obstruction (data for 133 individuals, 61%), mean maximum diastolic septal thickness (16.5±5.0 mm, range 7-38 mm) and either moderate or severe mitral regurgitation (9.6%). During the study period, interventions included

cardiac device implantation [62 (23%); defibrillator in 44, pacemaker 13, and others e.g., loop recorder 5] and septal reduction therapy (surgical septal myectomy 10.7%, alcohol septal ablation 1.5%).

The authors report significantly higher incidence, prevalence, and survival for this epidemiologic cohort compared to the index study. The age- and sex-adjusted HCM incidence rate, 6.6 per 100,000 person-year, increased each decade since the index study. Age-adjusted incidence rates 2010-2015 (7.7/100,000, 95% confidence interval, 5.9 to 9.4) were higher compared to 1984-1989 (4.0/100,000, 95% CI, 2.3 to 5.7), and higher for males compared to females (M 8.8/100,000 vs F 6.2/100,000). The age- and sex-adjusted point prevalence of HCM on January 1, 2016, standardized to the US 1980 White population, was 81.5 per 100,000 (95% CI, 67.7 to 95.3); for males 99.1/100,000 and for females 62.9/100,000 (ratio 1.5). The combined overall standardized mortality rate was higher for HCM compared to the general population; observed to expected hazard ratio (HR) 1.44 (95% CI, 1.21 to 1.71; P<.001). Survival increased each decade over time, yet mortality remains higher than the general population. *Submitted by Marianne E. Cumming, MD.*

2. *Neumann JT, Twerenbold R, Weimann J, et al. Prognostic value of cardiovascular biomarkers in the population.* JAMA. *2024;331:1898-1909*. doi:10.1001/jama.2024.5596

Life insurance medical directors recognized associations between cardiovascular risk factors and all-cause mortality long before the Framingham Heart Study. More than 60 years of clinical cardiovascular risk assessment has contributed to significant decreases in cardiovascular disease mortality and has led to the ongoing enhancement of risk prediction models using major traditional risk factors. This study, based on 28 multinational general population cohorts from 12 countries, investigates whether common cardiac biomarkers [high sensitivity Troponin I (hs-TnI), high sensitivity Troponin T (hs-TnT), N-terminal pro-B-Type natriuretic peptide (NT pro-BNP), and high sensitivity C-reactive protein (hs-CRP)] enhance the intermediate and long-term prediction of atherosclerotic cardiovascular disease events, heart failure, and cardiovascular and all-cause mortality when added to a standard prediction model.

The analysis included data on 164,054 individuals, median age 53.1 years, 52.4% women, 24.8% daily smokers, 41.6% hypertensive, and 6.1% with diabetes, with median 10-year risk using the pooled cohort risk equations (PCE) of 4.9%. Over a median follow-up of 11.8 years, 17,211 incident atherosclerotic cardiovascular disease events, 25,346 deaths from any cause, 6766 cases of heart failure, 4794 incident cases of incident ischemic stroke, and 8024 incident cases of myocardial infarction were reported.

The primary outcome reported was incident atherosclerotic cardiovascular disease events (all fatal and nonfatal, defined by first possible or definite coronary heart disease event, possible or definite ischemic stroke event, coronary revascularization, coronary heart disease death, ischemic stroke death, or unclassifiable death). Secondary outcomes included all-cause mortality, incident heart failure, incident ischemic stroke, and incident myocardial infarction.

All 5 biomarkers, adjusted for sex, cohort, and traditional risk factors (age, smoking status, diabetes, total and HDL cholesterol, systolic blood pressure, and self-reported antihypertensive drugs) were associated with the primary outcome; sub-distribution hazard ratios (HR) per 1-SD change, hs-TnI 1.13 (95% CI, 1.11-1.16); hs-TnT 1.18 (95% CI, 1.12-1.23); NT-proBNP 1.21 (95% CI, 1.18-1.24); BNP 1.14 (95% CI, 1.08-1.22); and hs-CRP 1.14 (95% CI, 1.12-1.16).

All biomarkers were associated with the primary and secondary outcomes. The biomarkers hs-Tn1, NT-proBNP and hs-CRP all were independent predictors and when combined into one model, provided the largest incremental predictive value. The biomarker NT-proBNP, in the multivariable model, showed the highest HRs for all outcomes except for

incident myocardial infarction for which high-sensitivity CRP showed the strongest association. Over the almost 12 years of follow-up, a sustained association of improved risk prediction with the addition of biomarkers to conventional risk factors was observed. The authors highlighted the greater incremental value of biomarkers in older individuals (ages 65 years and older) compared to those under age 65 and opined that as conventional risk factors become less relevant with aging, biomarkers may be promising for prognosis in older populations to identify early, subclinical end-organ damage. *Submitted by Marianne E. Cumming, MD*

3. *Weiss J, Raghu VK, Paruchuri K, et al. Deep Learning to Estimate Cardiovascular Risk From Chest Radiographs: A Risk Prediction Study.* Ann Intern Med. *2024;177:409-441.* https://doi.org/10.7326/M23-18

In this study on artificial intelligence (AI) and the ability to predict the risk of major adverse cardiovascular events (MACE), Harvard investigators assessed the ability of a deep learning computer model using chest x-rays to identify those at risk for future MACE and compared these results with a traditional atherosclerotic cardiovascular disease (ASCVD) risk calculator risk score. Using routine chest films from about 40,000 participants in a longitudinal cancer screening trial, investigators developed a deep-learning model (CXR CVD-Risk) to assess risk for CV death and other future CV events. In a separate group of 11,000 patients, they compared the model's performance to that of the 10-year ASCVD risk score for assessing statin eligibility, defined as an ASCVD score of 7.5% or higher.

The CXR CVD-Risk deep-learning model was developed and externally validated in 8869 outpatients with unknown ASCVD risk (unknown because of missing inputs needed to calculate the ASCVD risk score) and in 2132 outpatients with known risk whose ASCVD risk score could be calculated (mean age 60, both groups). This enabled a risk prediction study measuring and comparing the 10-year MACE predicted by the AI CXR CVD-Risk model vs the traditional ASCVD risk score.

Among those with unknown ASCVD risk and after adjustment for risk factors, those with a risk of 7.5% or higher as predicted by CXR CVD-Risk had a higher 10-year MACE (adjusted HR 1.73). Among those with known ASCVD risk, the CXR CVD-Risk model predicted risk for MACE beyond the ASCVD calculator (aHR 1.88). Additionally, there was concordance on statin eligibility (10-yr risk for MACE >7.5%) between the AI model and the traditional ASCVD risk calculator, with 37% statin eligible under each model.

On the basis of a single CXR, the authors concluded CXR CVD-Risk predicts 10-year MACE beyond the clinical standard. This could provide an opportunity in the clinical management of patients by identifying those who may be at increased risk but whose ASCVD risk score cannot be calculated due to missing data. With regard to the assessment of morbidity and mortality risk, this is another study among many providing evidence for alternative or novel assessments of risk. *Submitted by Ted Gossard, MD*

HEPATOLOGY

4. *Lin H, Lee HW, Yip TC, et al. Vibration-Controlled Transient Elastography Scores to Predict Liver-Related Events in Steatotic Liver Disease.* JAMA. *2024;331:1287-1297.* doi:10.1001/jama.2024.1447

Aims: To compare elastography to noninvasive and invasive tests for prognosis over time in metabolic dysfunction-associated steatotic liver disease (MASLD); both baseline models and serial follow-up over time were analyzed.

Study Design:

- Worldwide
- Age >18
- Natural history cohort
- Diagnosis by various means

- 10,209 patients
- 51 months median follow up
- 15 months median interval to repeat scan
- Elastography-based parameters: Agile 3+, Agile 4, FAST
- Other noninvasive parameters studied: FIB4, NFS, APRI, BARD, AST/ALT

Outcome: Liver-related events (LREs):

- Hepatocellular carcinoma
- Hepatic decompensation (ascites, variceal hemorrhage, encephalopathy, or hepatorenal symptoms)
- Liver transplant
- Liver-related deaths

Results: The Agile scores consistently outperformed the other noninvasive tests in predicting LREs at 3 and 5 years in subgroups stratified by age, sex, presence of diabetes, BMI, and reliability of liver stiffness measurement (LSM). The Agile scores were also stable over time.

Limitations:

- Length of follow up
- Interval of assessment varied
- Tertiary Referral Centers (of note, I practice in Atlanta, not at a tertiary referral center, and our local hepatologist finds a lot of variability in elastography scores)
- The scores used for comparison (said hepatologist above prefers the ELF scores to FIB 4 that was used in this study)

Conclusions: Therefore, the Agile 3+ score may be preferable for prognostic purposes; whereas, the main value of the Agile 4 score is for the diagnosis of MASLD-related cirrhosis. It is also worth noting that the superiority of the Agile scores over LSM alone were marginal. *Submitted by Rachna Relwani, MD*

MORTALITY

5. *Carrero JJ, Fu EL, Sang Y, et al. Discordances Between Creatinine and Cystatin C–Based Estimated GFR and Adverse Clinical Outcomes in Routine Clinical Practice.* Am J Kidney Diseases. *2023;82:534-542*. DOI: 10.1053/j.ajkd.2023.04.002

This interesting article identifies a new mortality-related variable. Specifically, researchers working with data from the Stockholm Creatinine Measurements (SCREAM) project, looked at eGFR based on creatinine and based on cystatin C. In Sweden, cystatin C is much more commonly measured than in other countries due to its inclusion in routine renal function panels, and this study takes advantage of that abundant data. They show that the difference between eGFR as estimated using creatinine and eGFR as estimated using cystatin C is fairly strongly associated with mortality and several other adverse outcomes.

The study population included approximately 158,000 individuals with data in the SCREAM system, with an average age of 62.8 years, 48% female, and with typical rates of comorbidities (59% hypertension, 16% CAD, 18% diabetes). Creatinine-based eGFR tended to be higher than cystatin-based eGFR (mean±sd: 80±26, 73±31, respectively). Individuals were grouped by quartile of the eGFR(cr) minus eGFR(cys). The first quartile had differences of −118 to −19, the second quartile −18 to −7, the 3rd quartile −6 to 4 and the fourth quartile >4. In Cox models controlled for age, sex comorbidities, creatinine-based eGFR and urine albumin:creatinine ratio, the hazard ratio was 2.88 for the first quartile, 1.49 for the second, and 0.74 for the fourth (using the third quartile as the reference group). This is fairly stunning as the hazard ratios are quite high, and there is a protective effect of having a high eGFR difference.

The authors of the study and commentators suggest that the high-risk negative difference may be the result of selective sieving of middle molecular weight molecules such as cystatin C (which is about 5k daltons) compared to small molecules like creatinine (<1k daltons). This phenomenon is called "shrunken pore syndrome," which refers to shrunken or elongated

openings in the glomerular basement membrane. The shrunken pore syndrome is caused by the same pathophysiological processes which eventually result in frank renal failure. These same authors and commentators suggest that cystatin C-based eGFR determinations should play a bigger role in the Kidney Disease Improving Global Outcomes (KDIGO) guidelines for evaluating and managing kidney disease.

For life insurance medicine, these findings offer a strong argument for the more frequent use of cystatin C in the determination of eGFR, especially in individuals within the age group of the study. *Submitted by Steven J. Rigatti, MD, Rigatti Risk Analytics, LLC*

NEUROLOGY

6. *Palmqvist S, Tideman P, Mattsson-Carlgren N, et al. Blood Biomarkers to Detect Alzheimer Disease in Primary Care and Secondary care.* JAMA. *2024;332:1245-1257*. doi:10.1001/jama.2024.13855

This original investigation aimed to examine the ability of blood biomarkers to detect Alzheimer's disease (AD) pathology in patients

AD pathology positivity on CSF or flutemetamol (18F) PET imaging was compared to blood biomarker positivity with the following results:

Cohort	Secondary Care Single Batch (n=300)	Primary Care† Single Batch (n=307)	Secondary Care Continuous Analysis (n=398)	Primary Care† Continuous Analysis (n=208)
Single Cutoff				
APS2 Diagnostic Accuracy	88% (84-91%)	92% (88-95%)	91% (88-94%)	89% (85-93%)
APS2 PPV	88% (83-93%)	91% (87-96%)	91% (87-95%)	88% (81-94%)
APS2 NPV	87% (82-93%)	92% (87-96%)	91% (87-95%)	90% (84-96%)
AUC	0.96 (0.94-0.98)	0.97 (0.95-0.99)	0.97 (0.95-0.98)	0.96 (0.94-0.98)
%p-tau217 Diagnostic Accuracy	91% (87-94%)	88% (85-92%)	90% (87-93%)	90% (86-94%)
%p-tau217 PPV	89% (84-94%)	86% (80-91%)	86% (81-90%)	86% (79-92%)
%p-tau217 NPV	92% (88-97%)	92% (87-96%)	96% (93-99%)	94% (89-99%)
AUC	0.97 (0.95-0.99)	0.96 (0.94-0.98)	0.97 (0.95-0.98)	0.96 (0.93-0.98)
2 Cutoff Approach				
APS2 Diagnostic Accuracy	93% (90-96%)	95% (92-98%)	94% (91-96%)	93% (90-97%)
APS2 PPV	97% (95-100%)	98% (95-100%)	96% (93-99%)	95% (90-100%)
APS2 NPV	89% (84-94%)	93% (88-97%)	91% (87-95%)	92% (87-98%)
%Intermediate*	12% (8-15%)	15% (11-19%)	11% (8-14%)	13% (8-18%)
%p-tau217 Diagnostic Accuracy	93% (90-96%)	91% (87-94%)	93% (90-95%)	91% (87-95%)
%p-tau217 PPV	96% (93-100%)	97% (94-100%)	94% (91-98%)	92% (87-98%)
%p-tau217 NPV	90% (85-94%)	86% (80-91%)	91% (87-95%)	90% (85-96%)
%Intermediate*	6% (3-9%)	8% (5-11%)	6% (3-8%)	4% (2-7%)

Parentheses represent 95% CI.

Single cutoff value approach- utilized a predefined cutoff with 90% specificity for AD pathology.

2 cutoff value approach- utilized 2 cutoffs corresponding to 95% sensitivity and 95% specificity for AD pathology; results between the two were categorized as intermediate.

* Those in intermediate category between the 2 cutoffs were not included in analyses for accuracy, PPV, NPV.

Single batch analysis- all collected samples run at the same time.

Continuous analysis- samples analyzed prospectively in batches twice per month.

† The primary care cohort patients were older, had fewer years of education, had higher prevalence of cardiovascular disease, hyperlipidemia, chronic kidney disease, and diabetes but a lower prevalence of dementia. There was no difference in Alzheimer disease pathology between the cohorts.

PPV = Positive Predictive Value; NPV= Negative Predictive Value.

presenting with cognitive symptoms to primary and secondary care in Sweden. The biomarkers utilized were plasma percentage of p-tau217 alone and the amyloid probability score 2 (APS2- a combination of plasma percentage of p-tau217 and Aβ42:Aβ40 plasma ratio). Participants were classified based on cognitive test results and clinical assessments as having one of the following: subjective cognitive decline, mild cognitive impairment (MCI), or dementia. A total of 1213 patients (mean age 74.2; 48% women) with cognitive symptoms participated.

Of note, the PPVs were suboptimal for accurate identification of AD pathology in patients at the subjective cognitive decline stage regardless of the cutoff value approach used; however, the NPVs were higher in this group (91-94% for APS2 or % p-tau217 alone). Thus, at this stage, blood biomarkers would be more helpful in ruling out AD pathology. Diagnostic accuracy was increased using the 2 cutoff approach driven by increased PPVs.

Clinician and biomarker diagnostic accuracy for AD pathology was compared in the continuous analysis cohorts. Dementia specialists had an accuracy of 71% (95% CI, 67-76%) compared to 92% (95% CI, 89-95%) for APS2 and 91% (95% CI, 88-94%) for percentage of p-tau217 alone. For primary care, the overall diagnostic accuracy was 58% (95% CI, 51-65%) compared to 89% (95% CI, 85-94%) for APS2 and 90% (95% CI, 86-94%) for p-tau217 alone.

The authors emphasize, however, that AD pathology biomarker positivity does not equate to clinical Alzheimer's disease. Biomarker positivity must be interpreted in a clinical context and not serve as a standalone diagnostic test because AD pathology can be asymptomatic for many years. Similarly, cognitive symptoms in some with AD pathology can be primarily a result of other conditions which could lead to misdiagnosis if AD pathology biomarker positivity is incorrectly interpreted. Future studies are needed to validate findings in cohorts from other countries, evaluate fully automated immunoassays that may be more practical for implementation, compare %p-tau217 to p-tau217 alone, and evaluate how the use of blood biomarkers influences clinical care. *Submitted by Stephanie Hrisko, MD*

7. *Lo JW, Crawford JD, Lipnicki DM, et al. Trajectory of Cognitive Decline Before and After Stroke in 14 Population Cohorts.* JAMA Netw Open. *2024;7:e2437133*. doi:10.1001/jamanetworkopen.2024.37133

Aims: To determine if stroke negatively affects brain function both 1) absolutely and 2) rate of decline compared to those with no stroke. Cognitive function was assessed by averaging 4 domains (language, memory, processing speed, and executive function).

Population: 14 international cohort-based studies; Community dwelling adults. The study included 20,860 participants (12,261 [58.8%] female) with a mean (SD) age of 72.9 (8.0) years and mean follow-up of 7.51 (4.2) years.

Results: Acute stroke was associated with a significant decline in global cognition (−0.25 SD; 95% CI, −0.33 to −0.17 SD), the Mini-Mental State Examination, and all cognitive domains. The slope of decline was accelerated in global cognition (−0.038 SD per year; 95% CI, −0.057 to −0.019 SD per year) and all domains except memory. Pre-stroke rate of decline was comparable in both the survivors and those without stroke in all cognitive measures.

Limitations: Varying follow up lengths (3-17 years); potential for missed strokes (all self-reported); ethnically homogeneous group; baseline characteristics between stroke and no stroke groups differed significantly although the magnitude of the differences was small and statistically acceptable.

Conclusions: This extensive study shows the negative effect of stroke on absolute cognition and the increased rate of decline of cognition after stroke compared to those without a stroke. They did look at potential confounders

and found no effect of sex, education, ApoE4, and vascular risk factors. Age did have an effect but that is a known factor. Interestingly, in the control group, vascular risk factors (diabetes, hypertension, high cholesterol, cardiovascular disease, smoking, ApoE4) were associated with a faster cognitive decline. *Submitted by Rachna Relwani, MD*

ONCOLOGY

8. *Newcomb LF, Schenk JM, Zheng Y, et al. Long-Term Outcomes in Patients Using Protocol-Directed Active Surveillance for Prostate Cancer.* JAMA. *2024;331:2084-2093*. doi:10.1001/jama.2024.6695

Active surveillance of low-grade prostate cancer has become a common and accepted standard of practice by many clinicians and preference for their patients, in large part due to concerns regarding the overtreatment of indolent disease and a desire to avoid adverse effects of treatment. A significant concern though is the potential for losing a window of treatability or curability of prostate cancer. In fact, prostate cancer remains the second leading cause of cancer death among men with about 34,700 deaths in the US in 2023. This study, which was conducted throughout 10 US and Canadian academic centers, assesses these risks and concerns at 10 years after diagnosis in those under active surveillance of favorable-risk prostate cancer.

The Canary Prostate Active Surveillance Study (PASS), a prospective observational study initiated in 2008, included 2155 men, median age 63, with favorable-risk cancer and no prior treatment. The median PSA was 5.2, and about 85% were classified as low or very low risk and 15% as favorable intermediate risk cancer. Outcomes measured included incidences of biopsy grade reclassification, treatment, metastasis, prostate cancer mortality, overall mortality and recurrence after treatment (in patients treated after the first biopsy or subsequent surveillance biopsies). Protocol-directed follow-up included PSA testing every 3-6 months, confirmatory biopsies at 6-12 months after diagnosis, and subsequent biopsies every 2 years after diagnosis. Adherence to the protocol was about 90%.

Ten years after diagnosis, the incidence of biopsy grade reclassification was 43% (95%CI, 40-45%), and there was a 49% incidence of treatment (95% CI, 47-52%) with radiotherapy or surgery. About half of the patients maintained their low-grade classification and received no treatment. Progression to metastatic cancer occurred in 21 patients, and there were 3 prostate cancer related deaths. The estimated rates of metastasis or prostate related mortality at 10 years after diagnosis were 1.4% and 0.1%, respectively (overall mortality for the same time period was 5.1%).

The authors concluded that about half of men on active surveillance at 10 years out will remain free of disease progression or the need for treatment (and thus the subsequent potential of toxicities of treatment). As well, less than 2% developed metastatic disease and only 0.1% died of their disease. The authors indicated the results of this study demonstrate that rates of adverse outcomes are not higher and are actually equal for patients eventually treated after several years of surveillance compared to those treated immediately following the first biopsy after diagnosis, and these results thus suggest active surveillance is an effective management strategy for low-risk prostate cancer. *Submitted by Ted Gossard, MD*

PSYCHIATRY

9. *Rosoff DB, Hamandi AM, Bell AS, et al. Major Psychiatric Disorders, Substance Use Behaviors and Longevity.* JAMA Psychiatry. *2024;81:889-901.* doi:10.1001/jamapsychiatry.2024.1429

In this European cohort study, Mendelian randomization (MR) was used to examine associations between the genetic liabilities for

psychiatric disorders, alcohol consumption, smoking, or their comorbidity and longevity outcomes. Genome wide significant single-nucleotide variants (SNVs) for psychiatric disorders, smoking and alcohol consumption were combined to create the following multivariable MR (MVMR) instruments: MVMR evaluating all psychiatric disorders and substance use behaviors simultaneously and separate MVMR instruments assessing the independent associations of psychiatric disorders and alcohol consumption while accounting for smoking behavior.

In a cohort of 709,709 (60.8% female), there were significant genetic correlations between smoking and the following exposures: bipolar disorder, drinks per week, major depression, problematic alcohol use, and schizophrenia. Single variable MR (SVMR) estimates showed negative associations between longevity related to chronic/age-related diseases and genetic liability for major depression, lifetime smoking, and drinks per week. However, MVMR assessing the association of smoking with each of the psychiatric disorders and alcohol use behaviors found that the adverse impact on longevity for major depression, problematic alcohol use, and drinks per week was attenuated while the reduction in longevity remained robustly associated with smoking (β, −0.33; 95% CI −0.38 to −0.28, $p < 0.001$). Thus, the authors concluded that "smoking is an important mediator for reducing healthy aging and increased chronic illness observed in psychiatric populations."

In a cohort of 34,449 (52.3% female), the authors examined the associations of psychiatric disorders and substance use behaviors with increased epigenetic age acceleration (EAA). There were no associations with first generation epigenetic clocks. However, there were SVMR associations between the following: smoking and PhenoAge* (β, 1.76; 95% CI, 0.72-2.79), smoking and GrimAge* (β, 1.75; 95% CI 1.08-2.41), and problematic alcohol use and PhenoAge (β, 0.83; 95% CI, 0.05-1.60) at $p<0.05$. In MVMR analyses, only smoking remained significantly associated with increased EAA for GrimAge (β, 3.40; 95% CI 2.60-4.21) and PhenoAge (β, 1.76; 95% CI 0.72-2.80). The authors highlight the importance of the genetic liability of smoking on healthy aging and longevity; however, they also note that their "findings do not negate the potential impact of the genetic liabilities of psychiatric disorders or alcohol consumption."

Transcriptomic imputation was used to identify tissue-specific transcript-level associations with lifetime smoking and longevity. High confidence genes such as those involved with DNA repair and telomere maintenance may further elucidate how smoking affects aging processes and result in potential targets to mitigate the age-related impacts of smoking. However, the authors suggest the findings be replicated with longitudinal data. Twenty-seven cortical proteins were also identified as potential smoking cessation targets. When incorporating adverse effect profiles, the most promising candidates were LY6H and RIT2.

It is recognized that all aspects of the complex nature of these associations may not be accounted for, and the European cohort may limit generalizability of the study findings. Additional limitations of the study were the possibility that results may be biased or misinterpreted if there was sample overlap between GWASs or if the MR assumptions (relevance, independence, exclusion restriction, homogeneity, consistency, and same population) were not met as presumed. Further, there are no longevity data stratified by sex; thus, there may be an unknown sex effect on smoking longevity associations. Overall, however, the authors concluded that the genetic liability for smoking had an independent adverse effect on longevity and EAA; whereas, the genetic liability for drinking, major depression, bipolar disorder, and schizophrenia did not have such an independent direct adverse effect. *Submitted by Stephanie Hrisko, MD*

* *PhenoAge and GrimAge are second generation epigenetic clocks that measure DNA methylation at specific sites highly correlated with aging.*