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Cross-ancestry GWAS meta-analysis of keloids discovers novel susceptibility loci in diverse populations*

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OBJECTIVES/GOALS: We aimed to conduct an updated genome-wide meta-analysis of keloids in expanded populations, including those most afflicted by keloids. Our overall objective was to improve understanding of keloid development though the identification and further characterization of keloid-associated genes with genetically predicted gene expression (GPGE). METHODS/STUDY POPULATION: We used publicly available summary statistics from several large-scale DNA biobanks, including the UK Biobank, FinnGen, and Biobank Japan. We also leveraged data from the Million Veterans Program and performed genome-wide association studies of keloids in BioVU and eMERGE. For each of these datasets, cases were determined from ICD-9/ICD-10 codes and phecodes. With these data we conducted fixed effects meta-analysis, both across ancestries and stratified by broad ancestry groups. This approach allowed us to consider cumulative evidence for genetic risk factors for keloids and explore potential ancestry-specific components of risk. We used FUMA for functional annotation of results and LDSC to estimate ancestry-specific heritability. We performed GPGE analysis using S-PrediXcan with GTEx v8 tissues. RESULTS/ANTICIPATED RESULTS: We detected 30 (23 novel) genomic risk loci in the cross-ancestry analysis. Major risk loci were broadly consistent between ancestries, with variable effects. Keloid heritability estimates from LDSC were 6%, 21%, and 34% for European, East Asian, and African ancestry, respectively. The top hit (P = 1.7e-77) in the cross-ancestry analysis was at a replicated variant (rs10863683) located downstream of LINC01705. GPGE analysis identified an association between decreased risk of keloids and increased expression of LINC01705 in fibroblasts (P = 3.6e10-20), which are important in wound healing. The top hit in the African-ancestry analysis (P = 5.5e-31) was a novel variant (rs34647667) in a conserved region downstream of ITGA11. ITGA11 encodes a collagen receptor and was previously associated with uterine fibroids. DISCUSSION/SIGNIFICANCE: This work significantly increases the yield of discoveries from keloid genetic association studies, describing both common and ancestry-specific effects. Stark differences in heritability support a potential adaptive origin for keloid disparities. Further work will continue to examine keloids in the broader context of other fibrotic diseases.

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Analyzing Changing Trends in Hepatocellular Carcinoma

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OBJECTIVES/GOALS: To quantify changing trends in hepatocellular carcinoma (HCC) etiologies, mainly hepatitis C related HCC (HCV-HCC), nonalcoholic fatty liver disease related HCC (NAFLD-HCC), and alcoholic liver disease related HCC (ALD-HCC), at a single center as well as compared to large national databases. METHODS/STUDY POPULATION: This is a retrospective longitudinal study using a single-center database of patients presenting with HCC from January 1995 to September 2023. Etiologies were confirmed through patient history, clinical exam, and viral serologies. Trends in rate of etiology were analyzed using linear regression. Further investigation will include survival analysis. To improve generalizability, the single-center data were supplemented with national cross-sectional data from the NHANES database on liver disease prevalence from March 1999 to August 2023. Data were provided through questionnaire, clinical exam, and viral serologies. Trends in rates will be analyzed using linear regression. RESULTS/ANTICIPATED RESULTS: Among the single center cohort, NAFLD-HCC increased at an average rate of 1.3% per year (95% Confidence Interval (CI) = 1.1% to 1.4%) and HCV-HCC decreased at an average rate of -0.56% per year (95% CI = -0.83% to -0.29%). Projecting the linear models for the past ten years forward, HCV-HCC is predicted to take up a lower proportion than NASH-HCC by 2026 and lower proportion than ALD-HCC by 2028. Future results will include analysis of the changing proportions of etiologies for liver transplant and survival analysis for HCC by etiology from the single center cohort. Additionally, national trends in HCC etiologies will be provided from the NHANES database. The trends from liver transplant etiology and NHANES are expected to parallel the preliminary results. DISCUSSION/SIGNIFICANCE: As the prevalence of NAFLD increases in the general population, more cases of NAFLD-HCC will be seen in the future. Understanding the changing trends can guide surveillance recommendations, shape treatment algorithms, and frame research priorities.

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The Effect of Pesticide Exposure on Immunological Responses in Children against SARS-CoV-2

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OBJECTIVES/GOALS: The objective is to assess the effect of pesticide exposure (individually and pesticide mixtures) on the immune response to COVID-19 in children. The goal is to improve scientific knowledge on factors affecting COVID-19 and identify a potentially modifiable factor to reduce disparities in COVID-19 morbidity. METHODS/STUDY POPULATION: Blood samples will be obtained from 50 children with asthma two time points; baseline and 12 months later. SARS-CoV-2 infection or vaccination will be determined with blood exposome RNA analyses.. Immunological response will be measured using neutralizing, phagocytizing, and NK-activating anti-body responses biomarkers. Pesticide exposure will be measured via urinary pesticide metabolites (UPMs). For individual metabolites multivariable analyses for each pesticide will be conducted using generalized estimating equation (GEE) models with compound symmetry correlation to account for the repeated measures design. To assess the pesticide mixture, weighted quantile sum regression (WQS) will be used. RESULTS/ANTICIPATED RESULTS: The main hypothesis is that increased pesticide exposure results in a reduction in the immunological response to SARS-CoV-2 infection and the COVID-19 vaccine. Therefore, we anticipate that increasing concentrations of individual UPMs as well as the increasing index will result in reductions in markers of the immune response to SARS-CoV-2 infection and the COVID-19 vaccine. DISCUSSION/SIGNIFICANCE: Exposure to pesticides is a

modifiable environmental factor. If pesticides are found to alter the immune response to COVID-19 infection and vaccination, these data will provide an evidence base for efforts to reduce pesticide exposure in children.

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Why are Black and Mexican American children more vulnerable than White children to upper respiratory viral infection?

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OBJECTIVES/GOALS: There is an excess risk of upper respiratory infection (URI) among Black and Mexican-American children in the US. Factors that underpin these disparities are largely unknown. We evaluated the extent to which socioeconomic status (SES), serum cotinine, obesity, and household size explained the association between race/ethnicity and URI. METHODS/STUDY POPULATION: We studied children, 6-17 years of age, who identified as Black, Mexican-American, or White in the National Health and Nutritional Examination Survey (2007-2012). URI was defined as a self-reported cough, cold, phlegm, runny nose, or other respiratory illness (excluding hay fever and allergies) in the past 7 days. The proportion of the association between race/ethnicity and URI explained by SES, serum cotinine, obesity, and household size was estimated as the average causal mediation effect (i.e., the indirect effect of race/ethnicity via the mediator) divided by the total effect of race/ethnicity. The average causal mediation effect was derived from survey weighted logistic regression models adjusted for age and sex. RESULTS/ANTICIPATED RESULTS: Black children were nearly 40% and Mexican American children were ~60% more likely to report a URI than those who identified as White (OR, 1.37; 95% CI, 1.06-1.77 and OR, 1.61; 95% CI, 1.21-2.13, respectively). Lower SES explained ~25% of the association between Black and Mexican American identity and URI (percent mediated 24.7; 95% CI, 23.0-26.6 and 26.1; 95% CI, 24.2-28.2, respectively). Obesity explained ~7% of the association between Black and Mexican-American identity and URI (percent mediated, 7.6; 95% CI, 7.3-8.0 and percent mediated, 6.7; 95% CI, 6.4-6.9, respectively). Nicotine exposure explained 8% of the association between Black identity and URI (percent mediated, 7.9; 95% CI, 5.6-10.1). DISCUSSION/SIGNIFICANCE: Lower SES explained a quarter of the association between race/ethnicity and URI. Low SES is a broad concept that may work through different mechanisms to lead to disparities in URI by race/ethnicity. Future research is needed to better understand these mechanisms and to identify modifiable aspects that can serve as targets for intervention.

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School Shootings and Mental Health in the United States

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OBJECTIVES/GOALS: It is estimated that 357,000 children have experienced a school shooting since 1999, yet due to limitations in the firearm violence field broadly, the sequalae are not well understood. The objective of this work is to examine the mental health impacts of school shootings, providing insight into the lasting effects of firearm violence on our communities. METHODS/STUDY POPULATION: We will first conduct a quasi-experimental study using controlled interrupted time series with repeated cross-sectional data to assess school shootings' impact on US mental health. School shooting data is from the K-12 School Shooting Database, and mental health data will be collected via the Behavioral Risk Factor Surveillance System. Second, we will conduct focus groups with community organizations, school administrators, and the public. Interview guides will be developed to explore the mental health impacts of school shootings, to guide the quantitative results interpretation, and assess educational materials' usefulness. Qualitative analysis will occur in NVivo software with codebook refinement through thematic analysis. Results will be triangulated through convergence coding. RESULTS/ANTICIPATED RESULTS: This research is situated within the context of the pervasive mental health challenges in the US, where mental illness poses significant health, social, and economic burdens. Thus, we anticipate finding an association between school shootings and decreased self-reported mental well-being among US adults. Literature suggests that there may be a stronger association among specific subgroups, such as parents with school-aged children or individuals living in close proximity to such incidents. We expect to find heterogeneity in the effect estimate based on school shooting attributes, such as the number of casualties. Through focus groups, we anticipate furthering our comprehension of the broad-ranging effects of school shootings on less quantifiable outcomes and the unique trajectories of recovery. DISCUSSION/ SIGNIFICANCE: This project will contribute needed information on the impact of school shootings and mental health and assist in reducing the frequency and impact of school shootings. Furthermore, we aim to extend our findings beyond the scientific community, translating them into educational resources advocating for policy and public health interventions.

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Identifying Geographic Clusters of H. pylori Associated Metastatic Early-Onset Gastric Cancer: A case-control study in Los Angeles

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OBJECTIVES/GOALS: More young adults (age <50 years) are diagnosed with metastatic gastric cancer (mGC) every year. We will evaluate the association between environmental risk factors (including historical racial residential segregation) clinical, pathologic, molecular features and H.pylori associated early-onset mGC (mE-GC). METHODS/STUDY POPULATION: This retrospective matched case-control study of patients (1:2 by diagnosis year) with mGC (early-onset [E-GC; <50 years]; vs older-onset [O-GC; >50 years]) from 2000-2022 from the Los Angeles Cancer Surveillance Program (LA-CSP) will be enriched by a chart-abstracted cohort from USC Norris Comprehensive Cancer (NCCC). This annotated database captures sociodemographic, medical, and pathologic features of patients treated for mGC at NCCC. It will link to LA-CSP data exploring neighborhood features (obesity rate, poverty,