# Office of Research

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# Publication Highlights

CENTERS FOR HEALTH, WORK & ENVIRONMENT & DEPARTMENT
OF ENVIRONMENTAL AND OCCUPATIONAL HEALTH

#### <u>Identifying and Measuring Administrative Harms Experienced by Hospitalists and Administrative</u> Leaders

Burden, Marisha; Astik, Gopi; Auerbach, Andrew; Bowling, Greg; Kangelaris, Kirsten N.; Keniston, Angela; Kochar, Aveena; Leykum, Luci K.; Linker, Anne S.; Sakumoto, Matthew; Rogers, Kendall; Schwatka, Natalie; Westergaard, Sara JAMA Internal Medicine

#### **ABSTRACT:**

**Importance:** Administrative harm (AH), defined as the adverse consequences of administrative decisions within health care that impact work structure, processes, and programs, is pervasive in medicine, yet poorly understood and described.

**Objective:** To explore common AHs experienced by hospitalist clinicians and administrative leaders, understand the challenges that exist in identifying and measuring AH, and identify potential approaches to mitigate AH. **Design, Setting, and Participants:** A qualitative study using a mixed-methods approach with a 12-question survey and semistructured virtual focus groups was held on June 13 and August 11, 2023. Rapid qualitative methods including templated summaries and matrix analysis were applied. The participants included 2 consortiums comprising hospitalist clinicians, researchers, administrative leaders, and members of a patient and family advisory council.

**Main Outcomes and Measures:** Quantitative data from the survey on specific aspects of experiences related to AH were collected. Focus groups were conducted using a semistructured focus group guide. Themes and subthemes were identified.

Results: Forty-one individuals from 32 different organizations participated in the focus groups, with 32 participants (78%) responding to a brief survey. Survey participants included physicians (91%), administrative professionals (6%), an advanced practice clinician (3%), and those in leadership roles (44%), with participants able to select more than one role. Only 6% of participants were familiar with the term administrative harm to a great extent, 100% felt that collaboration between administrators and clinicians is crucial for reducing AH, and 81% had personally participated in a decision that led to AH to some degree. Three main themes were identified: (1) AH is pervasive and comes from all levels of leadership, and the phenomenon was felt to be widespread and arose from multiple sources within health care systems; (2) organizations lack mechanisms for identification, measurement, and feedback, and these challenges stem from a lack of psychological safety, workplace cultures, and ambiguity in who owns a decision; and (3) organizational pressures were recognized as contributors to AHs. Many ideas were proposed as solutions.

**Conclusions and Relevance:** The findings of this study suggest that AH is widespread with wide-reaching impact, yet organizations do not have mechanisms to identify or address it.

### CENTER FOR GLOBAL HEALTH

# Otitis Media Sequelae and Hearing in Adolescence After Administration of An 11-Valent Conjugate Pneumococcal Vaccine in Infancy: A Prospective Cohort Study with Longterm Follow-Up of The ARIVAC Trial

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Lancet Child and Adolescent Health

#### **Abstract**

**Background:** Pneumococcal conjugate vaccines (PCVs) have been shown in randomized controlled trials and epidemiological studies to prevent acute otitis media caused by vaccine serotype pneumococci, although their role in preventing complications of acute otitis media is less clear. We hypothesized that the 11-valent PCV would reduce the long-term sequelae of acute otitis media, including moderate-to-severe ear disease and hearing loss.

**Methods:** This prospective cohort study, referred to as 11PCV study, included follow-up after 16-20 years of children previously enrolled in 2000-04, at age 6 weeks to 6 months, in the randomized, placebo-controlled, ARIVAC trial of 11-valent PCV for the prevention of radiographical pneumonia. The ARIVAC trial and this 11PCV study were conducted at six study centers in Bohol, Philippines. Ear disease was classified using video-otoscopy review and observations derived from the ear exam. The final classification of the worst ear disease was mild (ie, acute otitis media, otitis media with effusion, healed perforation, or tympanosclerosis), moderate (ie, dry perforation or adhesive otitis media), or severe (chronic suppurative otitis media). Hearing loss was assessed following a standard schema and classified according to the worst ear as mild (>15 to 30 dB puretone average) or moderate-to-profound (>30 dB pure tone average). We calculated the relative and absolute risk reduction in the primary outcome of moderate-to-severe ear disease and the secondary outcomes of mild or moderate-to-profound hearing loss in adolescents who previously received the 11-valent PCV compared with those who received placebo during infancy in ARIVAC.

**Findings:** Of the 15 593 children assessed for eligibility in ARIVAC, 12 194 were randomly assigned and 8926 were alive and could be located for enrolment in this 11PCV study between Sept 19, 2016, and Dec 13, 2019. 8321 (4188 in the vaccine group and 4133 in the placebo group) completed follow-up of the 11PCV study by March 30, 2020, and had sufficient data to classify ear disease and be included in the primary outcome analysis. The primary outcome of the absolute risk reduction in moderate-to-severe ear disease in the vaccine group (310 [7·4%] of 4188) versus those in the placebo group (356 [8·6%] of 4133) was  $1\cdot2\%$  (95% CI  $0\cdot0-2\cdot4$ ; p=0·046) and the relative risk reduction was  $14\cdot1\%$  (0·0 to 26·0). There were no differences in secondary outcomes of mild hearing loss or moderate-to-profound hearing loss between the vaccine and placebo groups.

**Interpretation:** The absolute risk reduction for moderate-to-severe ear disease in adolescence of 1.2% (12 per 1000 children) was almost three times higher than the 0.45% reduction (4.5 per 1000 children) in radiographical pneumonia in the first 2 years of life shown in ARIVAC. Administration of 11-valent PCV in infancy was associated with absolute and relative risk reductions in the sequelae of acute otitis media 16-20 years after the original ARIVAC trial.

## **DEPARTMENT OF BIOSTATISTICS & INFORMATICS**

## Integrative Modeling of Accelerometry-Derived Sleep, Physical Activity, and Circadian Rhythm Domains With Current or Remitted Major Depression

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JAMA Psychiatry

#### Abstract

**Importance:** Accelerometry has been increasingly used as an objective index of sleep, physical activity, and circadian rhythms in people with mood disorders. However, most prior research has focused on sleep or physical activity alone without consideration of the strong within- and cross-domain intercorrelations; and few studies have distinguished between trait and state profiles of accelerometry domains in major depressive disorder (MDD).

**Objectives:** To identify joint and individual components of the domains derived from accelerometry, including sleep, physical activity, and circadian rhythmicity using the Joint and Individual Variation Explained method (JIVE), a novel multimodal integrative dimension-reduction technique; and to examine associations between joint and individual components with current and remitted MDD.

**Design, Setting, and Participants:** This cross-sectional study examined data from the second wave of a population cohort study from Lausanne, Switzerland. Participants included 2317 adults (1164 without MDD, 185 with current MDD, and 968 with remitted MDD) with accelerometry for at least 7 days. Statistical analysis was conducted from January 2021 to June 2023.

**Main Outcomes and Measures:** Features derived from accelerometry for 14 days; current and remitted MDD. Logistic regression adjusted for age, sex, body mass index, and anxiety and substance use disorders.

**Results:** Among 2317 adults included in the study, 1261 (54.42%) were female, and mean (SD) age was 61.79 (9.97) years. JIVE reduced 28 accelerometry features to 3 joint and 6 individual components (1 sleep, 2 physical activity, 3 circadian rhythms). Joint components explained 58.5%, 79.5%, 54.5% of the total variation in sleep, physical activity, and circadian rhythm domains, respectively. Both current and remitted depression were associated with the first 2 joint components that were distinguished by the salience of high-intensity physical activity and amplitude of circadian rhythm and timing of both sleep and physical activity, respectively. MDD had significantly weaker circadian rhythmicity.

**Conclusions and Relevance:** Application of a novel multimodal dimension-reduction technique demonstrates the importance of joint influences of physical activity, circadian rhythms, and timing of both sleep and physical activity with MDD; dampened circadian rhythmicity may constitute a trait marker for MDD. This work illustrates the value of accelerometry as a potential biomarker for subtypes of depression and highlights the importance of consideration of the full 24-hour sleep-wake cycle in future studies.

## DEPARTMENT OF HEALTH SYSTEMS, MANAGEMENT, AND POLICY

<u>Social Vulnerability and Prevalence and Treatment for Mental Health and Substance Use Disorders</u>
Gibbons, Robert D.; Olfson, Mark; Saulsberry, Loren; Edlund, Mark J.; Zangeneh, Sahar; Bareis, Natalie;
Chwastiak, Lydia; Gibbons, Jason B.; Kessler, Ronald C. *JAMA Psychiatry* 

#### Abstract

**Importance:** Community-level social vulnerability (SV) is associated with physical illness and premature mortality. Its association with mental health (MH) and substance use disorders (SUDs) needs further study.

**Objective:** To study associations of SV with clinical diagnoses of MH disorders, SUDs, and related treatments in the US noninstitutionalized population of adults aged 18 years and older.

**Design, Setting, and Participants:** A survey of adults in a national sample of US households between October 2020 and October 2022. Participants drawn from a multistage, clustered, and stratified area probability sample of US households were included, excluding adults older than 65 years because of the difficulty of differentiating mental disorders from symptoms of dementia. The sample also included adults living in prisons, state psychiatric hospitals, and homeless shelters who were excluded from the sample of US households used in these analyses. Each sample household was sent a letter explaining the study and offering the option to complete the household roster online, by phone, or by email. Of the 12,906 adults selected for clinical interviewing in the household sample, 4674 completed clinical interviews.

Main Outcomes and Measures: Main outcomes were Structured Clinical Interview for DSM-5 past-year diagnoses of MH disorders and SUDs and responses to survey questions regarding treatment received. The Social Vulnerability Metric (SVM) and the Area Deprivation Index (ADI) were used to determine SV at the residential zip code level.

**Results:** The analysis involved 4674 participants (2904 [62.13%] female and 1770 [37.87%] male; mean [SD] age, 41.51 [13.41] years). Controlling for measured confounders, the SVM was significantly associated with diagnoses of schizophrenia spectrum disorder (SSD; adjusted odds ratio [aOR], 17.22; 95% CI, 3.05-97.29), opioid use disorder (OUD; aOR, 9.47; 95% CI, 2.30-39.02), stimulant use disorder (aOR, 6.60; 95% CI, 2.01-21.67), bipolar I disorder (aOR, 2.39; 95% CI, 1.19-4.80), posttraumatic stress disorder (aOR, 1.63; 95% CI, 1.06-2.50), and any MH disorder (aOR, 1.44; 95% CI, 1.14-1.83), but not major depressive disorder (MDD), generalized anxiety disorder (GAD), or any SUD. Results were similar for the ADI but generally of lower magnitude (SSD aOR, 11.38; 95% CI, 1.61-80.58; OUD aOR, 2.05; 95% CI, 0.30-14.10; stimulant use disorder aOR, 2.18; 95% CI, 0.52-9.18). Among participants with SSDs, SV was associated with reduced MH treatment (aOR, 0.001; 95% CI, 0.00-0.18) and reduced SUD treatment in participants with OUD or stimulant use disorder (aOR, 0.24; 95% CI, 0.02-2.80).

**Conclusions and Relevance:** In contrast to previous studies using nonclinical symptom-based survey data, we found no association between SV and GAD or MDD. By contrast, there were associations of SV with prevalence of SSD, stimulant use disorder, and OUD with corresponding decreases in treatment. These results suggest that the SVM might assist in developing more comprehensive care models that integrate medical and social care for MH disorders and SUDs.

# LIFECOURSE EPIDEMIOLOGY OF ADIPOSITY & DIABETES CENTER

<u>Maternal Allergy-Preventive Diet Index, Offspring Infant Diet Diversity, and Childhood Allergic Diseases</u>
Venter, Carina; Pickett-Nairne, Kaci; Leung, Donald; Fleischer, David; O'Mahony, Liam; Glueck, Deborah H.;
Dabelea, Dana *Allergy* 

#### Abstract

**Background:** Studies of childhood diet diversity and allergic disease have not examined additional associations with an offspring allergy-linked maternal diet index during pregnancy. We studied both associations in a pre-birth cohort.

**Methods:** Offspring allergic disease diagnoses were obtained from electronic medical records. Maternal and infant diet were self-reported. Adjusted parametric Weibull time-to-event models assessed associations between maternal diet index, infant diet diversity and time to development of allergic rhinitis, atopic dermatitis, asthma, wheeze, IgE-mediated food allergy, and a combined outcome of any allergic disease except for wheeze.

**Results:** Infant diet diversity at 1 year was associated with the risk of the combined outcome between 1 and 4 years of age (p = .002). While both maternal diet index and infant diet diversity at 1 year were associated with the risk of the combined outcome between 1 and 4 years of age (both p < .05), infant diet diversity at 1 year did not modify the association between maternal diet index and the risk of the combined outcome between 1 and 4 years of age (p = .5). The group with the lowest risk of the combined allergy outcome had higher maternal diet index and higher infant diet diversity.

**Conclusions:** The novel finding that both maternal diet index during pregnancy and infant diet diversity at 12 months are associated with the risk of a combined allergic disease outcome points to two targets for preventive interventions: maternal diet index scores during pregnancy and offspring diet diversity during infancy.

## **DEPARTMENT OF EPIDEMIOLOGY**

#### Public Reporting of Heart Transplant Center Performance: Promoting Clarity or Causing Confusion?

Amdani, Shahnawaz; Dewey, Elizabeth N.; Schold, Jesse D.

JACC - Heart Failure

#### **Abstract**

**Background:** Transplant center report cards are publicly available and used by regulators, insurance payers, and importantly patients and families.

**Objectives:** In this study, the authors sought to evaluate the variability in reported public performance ratings of pediatric and adult heart transplant centers.

**Methods:** Program-specific reports from the Scientific Registry of Transplant Recipients from 2017-2021 were used to evaluate stability, volatility, and reliability of 3 publicly reported ratings: waitlist survival (WS), getting to a faster transplant (FT), and post-transplantation graft failure (GF).

**Results:** There were 112 adult and 55 pediatric centers. Over the study period, nearly all centers (98%) had at least 1 change in rating in at least 1 of the tiers. The average time to the first rating change of any magnitude was 12-18 months for all tiers and centers. For adult centers, the most volatile rating was WS (SD: 0.77), followed by GF (SD: 0.76) and then FT (SD: 0.57). For pediatric centers, the most volatile rating was WS (SD: 0.79), followed by both GF (SD: 0.66) and FT (SD: 0.68), which were equally volatile. All tiers except adult FT had an estimated Fleiss's kappa <0.20, indicating poor agreement/consistency across the study period. In addition, the intraclass correlation coefficient for all tiers was <0.50, indicating poor reliability.

**Conclusions:** The current 5-tier reporting of transplant center performance is highly volatile and has poor reliability and consistency. Given the unintended and significant negative consequences these reports can have, critical revision of these ratings is warranted.

# COLORADO STATE UNIVERSITY AND LIFECOURSE EPIDEMIOLOGY OF ADIPOSITY & DIABETES CENTER

<u>Independent and Joint Effects of Neighborhood-Level Environmental and Socioeconomic Exposures on Body Mass Index in Early Childhood: The Environmental Influences on Child Health Outcomes (ECHO) Cohort</u>

Martenies, Sheena E.; Oloo, Alice; Magzamen, Sheryl; Ji, Nan; Khalili, Roxana; Kaur, Simrandeep; Xu, Yan; Yang, Tingyu; Bastain, Theresa M.; Breton, Carrie, V; Farzan, Shohreh F.; Habre, Rima; Dabelea, Dana Environmental Research

#### **Abstract**

Past studies support the hypothesis that the prenatal period influences childhood growth. However, few studies explore the joint effects of exposures that occur simultaneously during pregnancy. To explore the feasibility of using mixtures methods with neighborhood-level environmental exposures, we assessed the effects of multiple prenatal exposures on body mass index (BMI) from birth to age 24 months. We used data from two cohorts: Healthy Start (n = 977) and Maternal and Developmental Risks from Environmental and Social Stressors (MADRES; n = 303). BMI was measured at delivery and 6, 12, and 24 months and standardized as z-scores. We included variables for air pollutants, built and natural environments, food access, and neighborhood socioeconomic status (SES). We used two complementary statistical approaches: single-exposure linear regression and quantile-based g-computation. Models were fit separately for each cohort and time point and were adjusted for relevant covariates. Single-exposure models identified negative associations between NO2 and distance to parks and positive associations between low neighborhood SES and BMI z-scores for Healthy Start participants; for MADRES participants, we observed negative associations between O3 and distance to parks and BMI z-scores. G-computations models produced comparable results for each cohort: higher exposures were generally associated with lower BMI, although results were not significant. Results from the g-computation models, which do not require a priori knowledge of the direction of associations, indicated that the direction of associations between mixture components and BMI varied by cohort and time point. Our study highlights challenges in assessing mixtures effects at the neighborhood level and in harmonizing exposure data across cohorts. For example, geospatial data of neighborhood-level exposures may not fully capture the qualities that might influence health behavior. Studies aiming to harmonize geospatial data from different geographical regions should consider contextual factors when operationalizing exposure variables.

# LIFECOURSE EPIDEMIOLOGY OF ADIPOSITY & DIABETES CENTER, DEPARTMENT OF BIOSTATISTICS & INFORMATICS, AND DEPARTMENT OF EPIDEMIOLOGY

# <u>Maternal Serum Metabolomics in Mid-Pregnancy Identifies Lipid Pathways as a Key Link to Offspring Obesity in Early Childhood</u>

Francis, Ellen C.; Kechris, Katerina; Johnson, Randi K.; Rawal, Shristi; Pathmasiri, Wimal; Rushing, Blake R.; Du, Xiuxia; Jansson, Thomas; Dabelea, Dana; Sumner, Susan J.; Perng, Wei *International Journal of Molecular Sciences* 

#### Abstract

Maternal metabolism during pregnancy shapes offspring health via in utero programming. In the Healthy Start study, we identified five subgroups of pregnant women based on conventional metabolic biomarkers: Reference (n = 360); High HDL-C (n = 289); Dyslipidemic-High TG (n = 149); Dyslipidemic-High FFA (n = 180); Insulin Resistant (IR)-Hyperglycemic (n = 87). These subgroups not only captured metabolic heterogeneity among pregnant participants but were also associated with offspring obesity in early childhood, even among women without obesity or diabetes. Here, we utilize metabolomics data to enrich characterization of the metabolic subgroups and identify key compounds driving between-group differences. We analyzed fasting blood samples from 1065 pregnant women at 18 gestational weeks using untargeted metabolomics. We used weighted gene correlation network analysis (WGCNA) to derive a global network based on the Reference subgroup and characterized distinct metabolite modules representative of the different metabolomic profiles. We used the mummichog algorithm for pathway enrichment and identified key compounds that differed across the subgroups. Eight metabolite modules representing pathways such as the carnitineacylcarnitine translocase system, fatty acid biosynthesis and activation, and glycerophospholipid metabolism were identified. A module that included 189 compounds related to DHA peroxidation, oxidative stress, and sex hormone biosynthesis was elevated in the Insulin Resistant-Hyperglycemic vs. the Reference subgroup. This module was positively correlated with total cholesterol (R:0.10; p-value < 0.0001) and free fatty acids (R:0.07; p-value < 0.05). Oxidative stress and inflammatory pathways may underlie insulin resistance during pregnancy, even below clinical diabetes thresholds. These findings highlight potential therapeutic targets and strategies for pregnancy risk stratification and reveal mechanisms underlying the developmental origins of metabolic disease risk.

## LIFECOURSE EPIDEMIOLOGY OF ADIPOSITY & DIABETES CENTER

## <u>Sociodemographic Correlates of High Cardiovascular Health Across Childhood and Adolescence: A Prospective Study Among 2 Cohorts in the ECHO Consortium</u>

Perng, Wei; Galai, Noya; Zhao, Qi; Litonjua, Augusto; Geiger, Sarah; Sauder, Katherine A.; OShea, T. Michael; Hivert, Marie-France; Oken, Emily; Dabelea, Dana; Aris, Izzuddin M. *Journal of the American Heart Association* 

#### Abstract

**Background:** This study seeks to characterize cardiovascular health (CVH) from early childhood to late adolescence and identify sociodemographic correlates of high CVH that serve as levers for optimizing CVH across early life.

Methods and Results: Among 1530 youth aged 3 to 20 years from 2 cohorts in the ECHO (Environmental Influences on Child Health Outcomes) consortium, we first derived CVH scores on the basis of the Life's Essential 8 construct comprising 4 behavioral (nicotine use/exposure, physical activity, sleep, and diet) and 4 health factors (body mass index, blood pressure, non–high- density lipoprotein cholesterol, and fasting glucose) during early childhood (mean age, 3.5 years), middle childhood (8.0 years), early adolescence (13.3 years), and late adolescence (17.8 years). Next, we used generalized regression to estimate the probability of high (versus not high) CVH with respect to sociodemographic characteristics. Overall CVH score was stable across life stages: 81.2±7.6, 83.3±8.0, and 81.7±8.9 of 100 possible points in early childhood, middle childhood, and early adolescence, respectively. Accordingly, during these life stages, most children (63.3%–71.5%) had high CVH (80 to <100). However, CVH declined by late adolescence, with an average score of 75.5±10.2 and 39.4% high CVH. No children had optimal CVH (score=100) at any time. Correlates of high CVH include non- Hispanic White race and ethnicity, maternal college education, and annual household income >\$70.000. These associations were driven by behavioral factors.

**Conclusions:** Although most youth maintained high CVH across childhood, the decline by late adolescence indicates that cardiovascular disease prevention should occur before the early teen years. Disparities in high CVH over time with respect to sociodemographic characteristics were explained by behavioral factors, pointing toward prevention targets.

## **COLORADO STATE UNIVERSITY**

## <u>Psychometric Properties and Measurement Invariance of the Awareness of Age-Related Change Short Form in Older Adult Samples From Taiwan and Germany</u>

Tseng, Han-Yun; Wu, Chi-Shin; Lee, Chun-Yi; Wu, I-Chien; Chang, Hsing-Yi; Hsu, Chih-Cheng; Hsiung, Chao Agnes; Kaspar, Roman; Wahl, Hans-Werner; Diehl, Manfred *Gerontologist* 

#### **Abstract**

**Background and Objectives:** This study examined the psychometric properties and measurement invariance of the 10-item Awareness of Age-Related Change Short Form (AARC-SF) questionnaire in a Chinese-speaking sample of older adults in Taiwan.

**Research Design and Methods:** Data from 292 participants (Mage = 77.64 years) in the Healthy Aging Longitudinal Study in Taiwan cohort were used for Study 1, whereas data from young-old adult samples in Germany were used for Study 2.

**Results:** Study 1 showed that the AARC-SF had satisfactory reliability and validity for assessing adults' AARC in Taiwan. Analyses confirmed the 2-factor structure of AARC-gains and AARC-losses. Study 2 demonstrated strong measurement invariance across men and women, whereas direct comparisons of the item scores between young-old adults and old-old adults need to be made with caution. Noninvariance of loadings indicated that certain items were more closely linked to AARC-gains and AARC-losses in Taiwan than in Germany. Noninvariance of intercepts suggested potential biases in comparing item scores between Taiwanese and German older adults.

**Discussion and Implications:** The AARC-SF emerged as a reliable and valid instrument for capturing positive and negative subjective aging experiences among Taiwanese older adults. However, it is noteworthy that some items on the AARC-SF may solicit different responses from individuals of different ages and different countries of origin, requiring caution with age group and cross-cultural comparisons.

# DEPARTMENT OF COMMUNITY & BEHAVIORAL HEALTH AND INJURY & VIOLENCE PREVENTION CENTER

## <u>Dose of Product or Product Concentration: A Comparison of Change in Heart Rate by THC Concentration for Participants Using Cannabis Daily and Occasionally</u>

Limbacher, Sarah A.; Godbole, Suneeta; Wrobel, Julia; Wang, George Sam; Brooks-Russell, Ashley Cannabis and Cannabinoid Research

#### **Abstract**

**Introduction:** Studies show that acute cannabis use significantly increases heart rate (HR) and mildly raises blood pressure in the minutes following smoked or inhaled use of cannabis. However, less is known about how the THC concentration of the product or an individual's frequency of use (i.e., tolerance) may affect the magnitude of the change in HR. It is also relatively unexamined how the physical effects of increased HR after acute cannabis use relate to self-reported drug effects or blood THC levels.

**Aims:** To describe the relationship between THC concentration of product used, self-reported subjective intoxication, THC blood levels, and frequency of cannabis use with the change in HR after acute cannabis use.

Materials and Methods: Participants (n = 140) were given 15 min to smoke self-supplied cannabis ad libitum, HR was measured at baseline and an average of 2 min post-cannabis smoking. The ARCI-Marijuana scale and Visual Analog Scales (VAS) were administered, and blood samples were taken at both time points. Participants were asked about their frequency of use. Information about the product used was recorded from the package. Linear regression was used to analyze the relationship between changes in HR (post-pre cannabis use) and post-cannabis use HR, blood THC concentration, THC product concentration, frequency of use, and self-reported drug effect.

**Results:** There was a significantly higher HR among those who smoked cannabis compared to the controls (p < 0.001), which did not significantly differ by frequency of use (p = 0.18). Higher concentration THC (extract) products did not produce a significantly different HR than lower concentration (flower) products (p = 0.096). VAS score was associated with an increase in HR (p < 0.05). Overall, blood THC levels were not significantly related to the change in HR (p = 0.69); however, when probed, there was a slight positive association among the occasional use group only.

**Discussion:** Cardiovascular effects of cannabis consumption may not be as subject to tolerance with daily cannabis use and do not directly increase with THC concentration of the product. This is a departure from other effects (i.e., cognitive, subjective drug effects) where tolerance is well established. These findings also suggest that, at least among those with daily use, higher concentration THC products (>60%) do not necessarily produce cardiovascular physiological effects that are significantly more robust than lower concentration (<20%) products.

## **CENTER FOR INNOVATIVE DESIGN & ANALYSIS**

### <u>Proteomic Networks and Related Genetic Variants Associated with Smoking and Chronic Obstructive</u> <u>Pulmonary Disease</u>

Konigsberg, Iain R.; Vu, Thao; Liu, Weixuan; Litkowski, Elizabeth M.; Pratte, Katherine A.; Vargas, Luciana B.; Gilmore, Niles; Abdel-Hafiz, Mohamed; Manichaikul, Ani; Cho, Michael H.; Hersh, Craig P.; Demeo, Dawn L.; Banaei-Kashani, Farnoush; Bowler, Russell P.; Lange, Leslie A.; Kechris, Katerina J. *BMC Genomics* 

#### **Abstract**

**Background:** Studies have identified individual blood biomarkers associated with chronic obstructive pulmonary disease (COPD) and related phenotypes. However, complex diseases such as COPD typically involve changes in multiple molecules with interconnections that may not be captured when considering single molecular features.

Methods: Leveraging proteomic data from 3,173 COPDGene Non-Hispanic White (NHW) and African American (AA) participants, we applied sparse multiple canonical correlation network analysis (SmCCNet) to 4,776 proteins assayed on the SomaScan v4.0 platform to derive sparse networks of proteins associated with current vs. former smoking status, airflow obstruction, and emphysema quantitated from high-resolution computed tomography scans. We then used NetSHy, a dimension reduction technique leveraging network topology, to produce summary scores of each proteomic network, referred to as NetSHy scores. We next performed a genome-wide association study (GWAS) to identify variants associated with the NetSHy scores, or network quantitative trait loci (nQTLs). Finally, we evaluated the replicability of the networks in an independent cohort, SPIROMICS.

**Results:** We identified networks of 13 to 104 proteins for each phenotype and exposure in NHW and AA, and the derived NetSHy scores significantly associated with the variable of interests. Networks included known (sRAGE, ALPP, MIP1) and novel molecules (CA10, CPB1, HIS3, PXDN) and interactions involved in COPD pathogenesis. We observed 7 nQTL loci associated with NetSHy scores, 4 of which remained after conditional analysis. Networks for smoking status and emphysema, but not airflow obstruction, demonstrated a high degree of replicability across race groups and cohorts.

**Conclusions:** In this work, we apply state-of-the-art molecular network generation and summarization approaches to proteomic data from COPDGene participants to uncover protein networks associated with COPD phenotypes. We further identify genetic associations with networks. This work discovers protein networks containing known and novel proteins and protein interactions associated with clinically relevant COPD phenotypes across race groups and cohorts.