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CHRONIC DISEASE RESEARCH & MICROBOME RESEARCH

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INTRODUCTION

ANALYTICS EXPERIENCE

ABOUT ME

- Seasoned epidemiologist specializing in data science and biostatistics within regulatory-aligned clinical research.
- Led statistical analysis and interpretation of complex data from prospective studies, observational cohorts and clinical trials leveraging advanced analytics skills in SAS, R, and Python.
- Supported evidence generation and communication development through scientific publications and presentations at national and international research conferences.

EDUCATION & SKILLS

EDUCATION

- **PhD** in Epidemiology, University of Minnesota
- **MPH** in Epidemiology, University of Minnesota
- **Graduate Minor** in Biostatistics, University of Minnesota
- **BA** in Medical Laboratory Sciences, Biology and Chemistry, Southwest Minnesota State University
- **Healthcare Informatics**
  - **Biomedical Informatics: Applied Investigation and Analysis in Health Outcomes Research,** University of Texas Medical Branch
  - **Healthcare Data Analytics**, Jesse Andrist, Mayo Clinic Rochester (ELVTR)

SKILLS

- Statistical analysis (SAS, R, Python / Numpy)
- Data interpretation / Data visualization (Excel / Tableau)
- Bioinformatics analysis (Linux high-performance computing)
- Regulatory compliance and submission support
- Good Clinical Practice (GCP) concepts
- Scientific writing and communication
- Teaching and Mentoring in research

PROJECTS – CANCER RESEARCH: INVESTIGATION OF CANCER RISK FACTORS IN A LARGE PROSPECTIVE COHORT OF 14,000 +

Associations of leg length with increased colorectal cancer incidence in the Atherosclerosis Risk in Communities (ARIC) Study

Guillaume Onyeaghala[1], Pamela L. Lutsey[1], Ellen W. Demerath[1], Kristin E. Anderson[1,2], Aaron R. Folsom[1], Corinne E. Joshu[3,4], Elizabeth A. Platz[3-5], Anna E. Prizment[1,2]

[1] Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN. [2] Masonic Cancer Center, University of Minnesota, Minneapolis, MN. [3] Department of Epidemiology, John Hopkins Bloomberg School of Public Health, Baltimore, MD. [4] Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD. [5] Department of Urology and the James Buchanan Brady Urological Institute, Johns Hopkins University School of Medicine, Baltimore, MD

Introduction

- Colorectal cancer is the third most common cancer diagnosed in both men and women in the United States, and the third leading cause of cancer-related deaths in the United States.
- Several epidemiologic studies reported an association between taller people and an increased risk of colorectal cancer[1].
- Possible physiologic explanations include:
  - an increased production of growth hormones during puberty
  - a larger pool of at-risk colonic cells.

Goal of the study

- **Hypothesis**: Long-bone growth, indicated by leg length, would be the component of height that is more strongly associated with colorectal cancer.
- We evaluated the association of leg length, sitting height and total height with colorectal cancer risk in Atherosclerosis Risk in Communities (ARIC) prospective cohort.

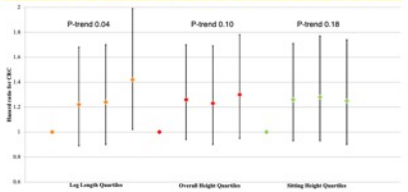
Methods

- The ARIC participants included 14,605 men and women, cancer-free at baseline (1987-1989), and followed until 2006.
  - Leg length was estimated as standing height minus sitting height; these measurements were performed by trained research staff.
  - Colorectal cancers cases were ascertained by linkage to cancer registries and supplemented by hospital records. A total of 344 Incident colorectal cancer cases were identified.
- Cox proportional hazards regression estimated hazard ratios (HR) of colorectal cancer and 95% confidence intervals (CI) across quartiles of height, leg length, and sitting height.
  - The final models were adjusted for age, sex, race, study center, education level, waist-to-hip ratio, female hormone replacement therapy use, and smoking status.

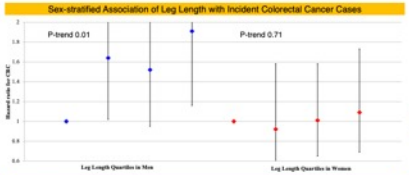
Baseline participant characteristics stratified by sex and leg length quartile in the ARIC Study.

	Sex Specific Leg Quartiles			
Men	Q1	Q2	Q3	Q4
N	1471	1666	2044	1457
Range	38 - 80	81 - 83	84 - 87	88 - 103
Height (cm), median ± sd	169 ± 4.29	174 ± 3.61	178 ± 3.74	183 ± 4.72
Sitting Height (cm), median ± sd	91 ± 3.65	92 ± 3.49	93 ± 3.52	93 ± 3.88
Leg length (cm), median ± sd	79 ± 2.43	82 ± 0.80	85 ± 1.09	90 ± 2.55
Demographics				
Age (yrs), mean ± sd	55.2 ± 5.7	54.4 ± 5.8	54.4 ± 5.7	54.0 ± 5.7
Weight (kg), mean ± sd	175.9 ± 29.1	184.6 ± 30.8	191.6 ± 31.5	198.0 ± 32.1
WHR, mean ± sd	.97 ± .05	.96 ± .05	.96 ± .05	.96 ± .05
Smokers n(%)	414 (22.3)	504 (27.2)	550 (29.7)	385 (20.8)
African American n(%)	167 (10.7)	280 (18.0)	485 (31.2)	622 (40.0)
Education Beyond High School n(%)	626 (39.5)	784 (24.4)	1069 (33.3)	741 (23.1)
Women	Q1	Q2	Q3	Q4
N	1905	2168	1951	1933
Range	37 - 73	74 - 76	77 - 79	80 - 97
Height (cm), median ± sd	156 ± 4.04	161 ± 3.40	164 ± 3.52	169 ± 4.33
Sitting Height (cm), median ± sd	85 ± 3.52	86 ± 3.25	86 ± 3.46	86 ± 3.60
Leg length (cm), median ± sd	72 ± 2.36	75 ± 0.81	78 ± 0.80	82 ± 2.44
Demographics				
Age (yrs), mean ± sd	54.0 ± 5.7	53.7 ± 5.7	53.7 ± 5.7	53.5 ± 5.6
Weight (kg), mean ± sd	150.5 ± 32.9	157.7 ± 35.0	163.9 ± 35.7	176.5 ± 39.9
WHR, mean ± sd	0.89 ± .08	0.89 ± 0.08	0.89 ± 0.08	0.90 ± 0.08
Smokers n(%)	1057 (24.9)	1119 (26.4)	1024 (24.1)	1042 (24.6)
African American n(%)	226 (9.1)	484 (19.6)	668 (27.0)	1095 (44.3)
Education Beyond High School n(%)	711 (22.6)	857 (27.3)	771 (24.6)	800 (25.5)

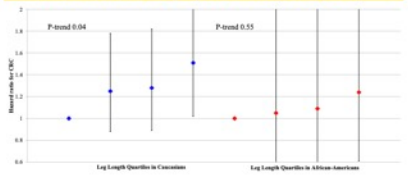
Association of Leg Length, Overall Height and Sitting Height with Incident Colorectal Cancer Cases



Sex-stratified Association of Leg Length with Incident Colorectal Cancer Cases



Race-stratified Association of Leg Length with Incident Colorectal Cancer Cases



Results

- Leg length was correlated with total (Pearson r=0.83), and sitting height (Pearson r=0.52) in the whole cohort.
- Participants in the highest quartile of leg length were at a 42% (95% CI, 1.02-1.99) greater risk of colorectal cancer, relative to the lowest quartile (p-trend=0.04).
- The associations were weaker for
  -- total height: HR=1.30, 95% CI, 0.95-1.78, p-trend=0.10
  -- sitting length: HR=1.25, 95% CI, 0.90-1.74, p-trend=0.18
- For the highest versus the lowest quartile of leg length:
  --Men: HR=1.91, 95% CI, 1.16-3.12
  --Women: HR=1.09, 95% CI, 0.69-1.73; p-interaction=0.16.

  -- Whites: HR=1.51, 95% CI, 1.02-2.26
  -- African-Americans: HR=1.21, 95% CI, 0.61-2.53; p-interaction=0.62.

Conclusions

- Longer leg length was more strongly associated with an increased risk of colorectal cancer than overall height or sitting height.
- This association is most likely driven by biological mechanisms correlated to long bone growth, such as insulin-like growth factor-1, a risk factor for colorectal cancer[2].
- The sex-specific association between longer leg length and CRC risk may be explained by differences in IGF-1 production between males and females during puberty.

Main citations

1. Engeland A, Tretli S, Austad G, Bjorge T. Height and body mass index in relation to colorectal and gallbladder cancer in two million Norwegian men and women. Cancer Causes Control. 2005 Oct;16(8):987-96.
2. Yamaji T, Iwasaki M, Sasazuki S, Tsugane S. Gender difference in the association of insulin and the insulin-like growth factor axis with colorectal neoplasia. Int J Obes (Lond). 2012 Mar;36(3):440-7.

Acknowledgements

The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C). The authors thank the staff and participants of the ARIC study for their important contributions.

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Project Link

ADHERENCE TO AICR/WCRF RECOMMENDATIONS AND RISK OF COLORECTAL CANCER (CRC) IN WHITES AND AFRICAN-AMERICANS IN THE ATHEROSCLEROSIS RISK IN COMMUNITIES (ARIC) STUDY

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INTRODUCTION

- In 2007, the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) prepared a list of 10 Recommendations for Cancer Prevention[1]
- Though incidence of colorectal cancer has been steadily declining since 1985, it remains the 4th most commonly diagnosed cancer in the U.S.[2]
- Lower risk of colorectal cancer has been linked to adherence of the WCRF/AICR cancer prevention recommendations[3], though the impact of race is unknown

OBJECTIVE

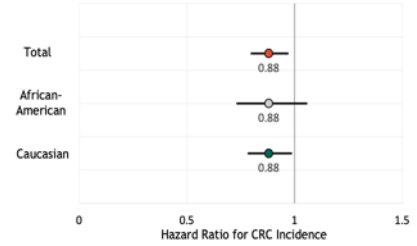
- To evaluate the association between adherence to diet, physical activity, and body weight guidelines and the risk of colorectal cancer development among African-Americans and Caucasians.

METHODS

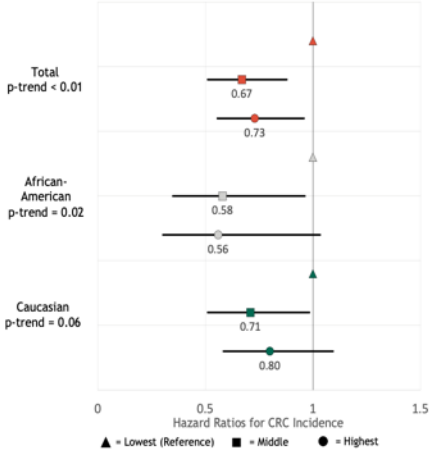
- An adherence score was developed based on the WCRF/AICR cancer prevention guidelines
  - Each recommendation contributed 0, 0.5, or 1 points to the adherence score
  - Adherence scores were categorized as tertiles (Lowest= 0.5 - 4.0, Middle = 4.5 - 5.0, Highest = 5.5 - 8.0)
- 14,031 participants in the ARIC study were cancer-free at their baseline visit (1987-1989), were African-American or Caucasian, and were not missing data used to calculate an 8-component adherence score

WCRF/AICR Recommendation[1]	Included in Score
1. Be as lean as possible without becoming underweight	Yes
2. Be physically active for at least 30 minutes every day. Limit sedentary habits.	Yes
3. Avoid sugary drinks. Limit consumption of energy-dense foods.	Yes
4. Eat more of a variety of vegetables, fruits, whole grains and legumes such as beans.	Yes
5. Limit consumption of red meats (such as beef, pork and lamb) and avoid processed meats.	Yes
6. If consumed at all, limit alcoholic drinks to 2 for men and 1 for women a day.	Yes
7. Limit consumption of salty foods and foods processed with salt (sodium).	Yes
8. Don't use supplements to protect against cancer.	No
9. It is best for mothers to breastfeed exclusively for up to 6 months and then add other liquids and foods.	No
10. After treatment, cancer survivors should follow the recommendations for cancer prevention.	No

ASSOCIATION OF ADHERENCE SCORE WITH INCIDENT COLORECTAL CANCER, CONTINUOUS



ASSOCIATION OF ADHERENCE SCORE WITH INCIDENT COLORECTAL CANCER, TERTILES



RESULTS

- Greater adherence was associated with a 12% lower risk of colorectal cancer (95% CI: 0.80 - 0.97) per 1 score unit. Stratified by race:
  - African-Americans: HR = 0.88, 95% CI 0.73 - 1.06
  - Caucasians: HR 0.88, 95% CI 0.79 - 0.99
- Greater adherence was associated with a 27% lower risk of colorectal cancer (95% CI: 0.55 - 0.95, p_{trend} < 0.01) for the highest versus lowest score tertile. Stratified by race:
  - African-Americans: HR = 0.56, 95% CI 0.30 - 1.03, p_{trend} = 0.02
  - Caucasians: HR = 0.80, 95% CI 0.58 - 1.09, p_{trend} = 0.06

CONCLUSIONS

- Greater adherence to the WCRF/AICR cancer prevention recommendations is associated with a lower risk of CRC development, independent of race
- Categorization by tertiles suggest there may be a threshold number of recommendations followed that is associated with a lower risk of CRC development
- Differences between African-Americans and Caucasians may be due to lower power African-Americans, or potential differences in lifestyle not accounted for in this study

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[1]World Cancer Research Fund / American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington DC: AICR; 2007
[2]National Cancer Institute. Surveillance, Epidemiology, and End Results Program. National Cancer Institute. https://seer.cancer.gov/statfacts/html/colorect.html. Published 2017. Accessed March 7, 2017.
[3]Romaguera D, Vergnaud AC, Peeters P, et al. Is concordance with World Cancer Research Fund/American Institute for Cancer Research guidelines for cancer prevention related to subsequent risk of cancer? Results from the EPIC study. Am J Clin Nutr. 2012;96(1):150-63.

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Project Link

PROJECTS – CANCER RESEARCH: INVESTIGATION OF CANCER RISK FACTORS IN A LARGE PROSPECTIVE COHORT OF 14,000 +

Dietary Magnesium and Colorectal Cancer Risk in the Atherosclerosis Risk in Communities Cohort (ARIC)

Guillaume Onyeaghala[1], Elizabeth Polter[1], Pamela L. Lutsey[1], Aaron R. Folsom[1], Corinne E. Joshu[3,4], Elizabeth A. Platz[3-5], Anna E. Prizment[1,2]

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Introduction

- Colorectal cancer (CRC) is the second leading cause of cancer morbidity and mortality among men and women in the United States.
  - Novel prevention measures are important to decrease the CRC-related incidence and death.
- Previous meta-analyses of prospective cohort studies have found inverse associations between dietary magnesium and the risk of CRC development:
  - Increased magnesium intake has been inversely associated with an 11 to 19% decrease in CRC risk for the highest vs lowest category of magnesium intake.
- Magnesium is involved in multiple biochemical reactions that regulate key cell functions, such as cell proliferation and apoptosis.

Goal of the study

- **Hypothesis**: Participants who meet or exceed the daily dietary recommendations for magnesium intake (300 mg/day) will have a lower CRC risk, compared to those who do not.
- We prospectively evaluated the association of dietary magnesium with colorectal cancer risk in the Atherosclerosis Risk in Communities (ARIC) study, a cohort of middle-aged and older White and African-American men and women.

Methods

- The ARIC study is a prospective cohort study conducted in four centers: Forsyth County, NC; Jackson, Mississippi; Minneapolis, MN; Washington County, MD.
- Participants received five exams in 1987-89, 1990-92, 1993-95, 1996-98, and 2011-2013, which included medical examination and questionnaires.
- Follow-up was conducted via telephone calls annually from 1987-2012 and semi-annually since 2012.
  - Dietary magnesium consumption was determined using a 61-question food frequency questionnaire at Visit 1.
  - Colorectal cancers cases were ascertained by linkage to cancer registries and supplemented by hospital records.
  - A total of 374 incident colorectal cancer cases were identified through 2012 (317 colon, and 57 rectal).
- Cox proportional hazards regression was used to estimate hazard ratios (HR) of CRC and 95% confidence intervals (CI) across categories of dietary magnesium consumption.
- We examined participants who met US recommendations for dietary magnesium intake (>300 mg/day), versus those who did not (reference category).
- The models were adjusted for
  - Model 1: race, center, sex
  - Model 2: Model 1 plus total calorie intake, BMI, physical activity, alcohol intake, dietary calcium intake, dietary fiber intake, C-reactive protein level, aspirin use, cigarette smoking, and hormone replacement therapy for women

Table 1. Baseline participant characteristics stratified by meeting magnesium dietary recommendations in the ARIC Study.

	Meets dietary magnesium recommendation	Does not meet dietary magnesium recommendation	p-value
Dietary magnesium mange (mg/day)	300.01-863.86	31.27-300.00	
No. of participants	3452	10,316	
No. of cases	85	289	
Person-years	44,576	125,422	
Demographics			
Age (yrs), mean ± sd	54.2 ± 5.7	54.0 ± 5.7	0.08
BMI (kg), mean ± sd	27.6 ± 5.2	27.8 ± 5.4	0.09
Total calorie intake (kcal), mean ± sd	2267 ± 590	1416 ± 450	<.0001
Dietary calcium intake (mg), mean ± sd	1021 ± 456	5310 ± 248	<.0001
Dietary fiber intake (g), mean ± sd	25 ± 9	14 ± 6	<.0001
Alcohol intake (g/day), mean ± sd	9 ± 19	5 ± 11	<.0001
Physical activity (per week)	2.6 ± 0.8	2.5 ± 0.8	<.0001
CRP concentration (mg/L)	0.78 ± 1.07	0.87 ± 1.08	<.0001
Smokers n (%)	1279 (36.1)	4627 (44.6)	<.0001
African America n (%)	694 (19.6)	3091 (29.1)	<.0001
Men n(%)	1986 (56.1)	4472 (42.1)	<.0001
Recent aspirin use (%)	1694 (48.2)	4798 (45.6)	0.007

Figure 1. Incidence rates and hazard ratios for colorectal, colon and rectal cancers by daily magnesium intake below and above the US dietary recommendations in the ARIC study

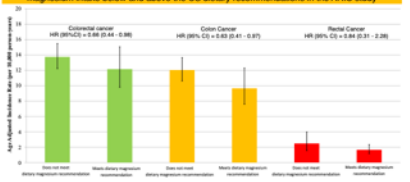


Figure 2. Sex-stratified incidence rates and hazard ratios for colorectal cancer by daily magnesium intake below and above the US dietary recommendations

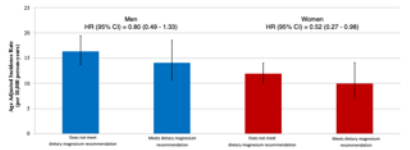
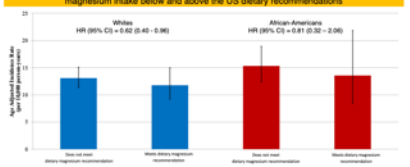


Figure 3. Race-stratified incidence rates and hazard ratios for colorectal cancer by daily magnesium intake below and above the US dietary recommendations



Results

- Participants (54.4% women, 26.7% African-American) were followed for a median of 19.2 years.
- Participants in the highest quartile of dietary magnesium intake had a lower risk of CRC (HR=0.66, 95% CI, 0.44 - 0.98, p-value=0.04) than those in lowest three quartiles combined.
  - There is an indication of an association for both colon and rectal cancer (Figure 1).
- The association for CRC appeared to be inverse for both men and women (Figure 2), and both Whites and African-Americans (Figure 3).
  - p-interaction = 0.74 for gender and 0.62 for race.
- Including lifestyle factors in the model had a significant impact on the association between dietary magnesium and CRC risk (Likelihood Ratio Test p-value < 0.05)
  - Model 1: HR (95% CI) = 0.83 (0.57-1.21).
  - Model 2: HR (95% CI) = 0.66 (0.44 - 0.98).
- We observed no evidence of a linear dose response for the association between dietary magnesium intake (on the logarithmic scale) and CRC risk (p-trend=0.59).

Conclusions

- Our findings support existing evidence of an inverse association between dietary magnesium and colorectal cancer across different populations subgroups, including men and women, Whites and African-Americans.
- A statistically significant inverse association was observed between dietary magnesium intake and colon cancer.
- Limitations
  - Low number of rectal cancer cases and African-Americans.
  - Unable to assess the impact of magnesium from supplement use.

Main citations

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Project Link

Association of absolute lymphocyte count and cancer incidence and mortality: the Atherosclerosis Risk in Communities (ARIC) study

Guillaume Onyeaghala[1], Anna E. Prizment[1,2] Darek Lucas[1], Sarah Davidovics[3,4], Corinne E. Joshu[3,4], Elizabeth A. Platz[3-5], Aaron R. Folsom[1], Kala Visvanathan[3,4]

[1] Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN. [2] Masonic Cancer Center, University of Minnesota, Minneapolis, MN. [3] Department of Epidemiology, John Hopkins Bloomberg School of Public Health, Baltimore, MD. [4] Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD. [5] Department of Urology and the James Buchanan Brady Urological Institute, Johns Hopkins University School of Medicine, Baltimore, MD

Introduction

- Several prospective studies have reported a positive association between total white blood cell (WBC) count, a non-specific marker of systemic inflammation, and cancer incidence and mortality.
- However, subtypes of total WBC count may have distinct roles in inflammation-mediated tumorigenesis
  - This study focused on lymphocytes, a subtype of total white blood cells (WBC), which include B cells and T cells (part of the adaptive immune response), and natural killer (NK) cells (part of the innate immune response).
  - In addition, we also examined the association of granulocytes, another broad subtype of total WBC, which are involved in the acute inflammatory response.
- Elevated lymphocyte and granulocyte levels may be subclinical inflammatory markers of the carcinogenic effects of common exposures, including obesity and cigarette smoke.

Goal of the study

- We hypothesized that higher circulating levels of pre-diagnostic lymphocyte count would be associated with higher cancer incidence and mortality in the Atherosclerosis Risk in Communities (ARIC) study.

Methods

- The ARIC study is a prospective cohort study conducted in four centers: Forsyth County, NC; Jackson, Mississippi; Minneapolis, MN; Washington County, MD.
- Participants received five exams in 1987-89, 1990-92, 1993-95, 1996-98, and 2011-2013, which included medical examination and questionnaires.
  - Cancer incidence and mortality was ascertained by linkage to cancer registries and supplemented by hospital records.
  - In our analytic cohort, 2,914 incident primary cancers and 1,164 cancer deaths occurred during follow up through 2012.
- Total WBC counts and differentials were assessed at baseline. On average, lymphocyte counts constituted 33% (range: 7% - 86%) of WBC count
  - Among Whites: 31% (range: 7% - 82%)
  - Among African-Americans: 40% (range: 7% - 86%)
- The normal range for lymphocyte and granulocyte counts was defined as the mean +/- 2 standard deviations
  - Race-specific lymphocyte and granulocyte counts were categorized as below the normal range, tertiles within the normal range (first tertile was a reference), and above the normal range.

Statistical Analysis

- Cox proportional hazards regression was used to calculate hazard ratios (HR) and 95% confidence intervals (CI) for overall and site-specific cancer incidence and mortality
  - Model 1: Adjusted for age, sex, race, and study center
  - Model 2: Model 1 additionally adjusted for education level, alcohol consumption, smoking history, pack years of smoking, BMI and Physical activity
  - Model 3: Model 2 additionally adjusted for hypertension, diabetes status, history of CVD, aspirin use and hormone therapy + menopausal status for breast cancer

Figure 1. Association between lymphocyte levels, overall cancer incidence and overall cancer mortality

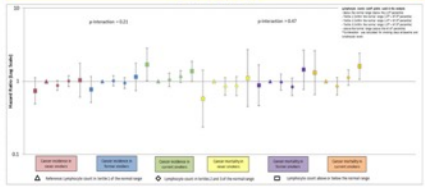


Figure 2. Association between lymphocyte levels, non-lung cancer incidence and non-lung cancer mortality

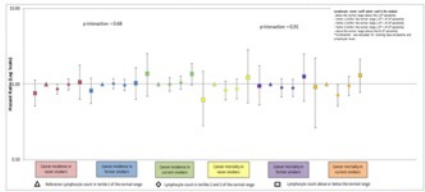
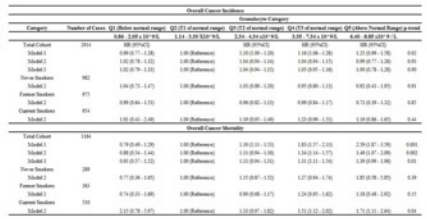


Table 1. Association between granulocyte levels, overall cancer incidence and overall cancer mortality.



Results

- Lymphocyte counts above the normal range were associated with increased overall cancer mortality (HR: 1.44 (95% CI:1.05 - 1.97)), but did not reach statistical significance for overall cancer incidence (HR: 1.26 (95% CI:0.99 - 1.60)).
- When stratified by smoking status, an association was observed among current smokers for both incidence and mortality. Lymphocyte counts above the normal range were associated with increased overall cancer incidence (HR: 1.38 (95% CI:1.00 - 1.89)), and mortality (HR: 1.60 (95% CI:1.06 - 2.42)) (Figure 1).
- The association between increased lymphocyte counts and cancer risk in smokers was not statistically significant when lung cancer cases were excluded (HR: 1.35 (95% CI:0.94 - 1.95) and HR: 1.31 (95% CI:0.75 – 2.30) for non-lung cancer incidence and mortality, respectively) (Figure 2).
- In site specific analyses, lymphocyte counts above the normal range were associated with higher lung cancer mortality (HR: 1.91 (95% CI: 1.14 - 3.19)), but not lung cancer incidence (HR: 1.59 (95% CI: 0.95 - 2.62)). No other site-specific cancer associations were found with increased lymphocyte levels.
- Increased granulocyte counts were associated with increased overall cancer mortality (p-trend = 0.01), but not overall cancer incidence (p-trend=0.90) (Table 1).
- When stratified by smoking status, granulocyte counts above the normal range were associated with increased overall cancer mortality (HR: 1.71 (95% CI:1.11 – 2.64)), but did not reach statistical significance for overall cancer incidence (HR: 1.00 (95% CI:0.78 - 1.28))(Table 1).

Conclusions

- Our findings support existing evidence of a positive association between increased pre-diagnostic lymphocyte counts and increased cancer mortality overall, and increased cancer incidence and mortality in current smokers.
- The association between increased pre-diagnostic lymphocyte counts and cancer risk was attenuated after excluding incident lung cancer cases.

Acknowledgments

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Acknowledgments: The authors thank the staff and participants of the ARIC study for their important contributions. Cancer incidence data have been provided by the Maryland Cancer Registry, Center for Cancer Surveillance and Control, Maryland Department of Health, 201 W. Preston Street, Room 400, Baltimore, MD 21201. We acknowledge the State of Maryland, the Maryland Cigarette Restitution Fund, and the National Program of Cancer Registries (NPCR) of the Centers for Disease Control and Prevention (CDC) for the funds that helped support the availability of the cancer registry data.

Project Link

PROJECTS – CANCER RESEARCH: BIOMARKER DISCOVERY IN A CASE-CONTROL STUDY OF 500+ PARTICIPANTS

Association between MICA polymorphisms, s-MICA levels, and pancreatic cancer risk in a population-based case-control study.

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[3]Department of Laboratory Medicine and Pathology

Introduction

- The etiology of pancreatic cancer remains poorly understood. However, the immune system has been shown to play an important role in the development of pancreatic cancer.
- Abnormal cells express the transmembrane major histocompatibility complex class I chain-related gene A (MICA) protein, which is recognized by receptors present on NK (Natural Killer) and cytotoxic T cells.
- Pancreatic tumor cells release the MICA protein in soluble form (called s-MICA) from the tumor surface and thus avoid immune surveillance.
- In our previous study, a higher serum concentration of the s-MICA protein was associated with increased prevalence odds of pancreatic cancer.
- The MICA gene has a variable number of short tandem repeat (STR) polymorphisms consisting of four, five, six or nine GCT repeats, designated as A4, A5, A6, A7, A8, A9, A10, respectively. Additionally, the A5.1 allele contains an extra guanine (G) insertion resulting in a premature stop codon.

Goal of the study

- **Hypothesis**: Functional variants in the MICA gene are associated with circulating s-MICA levels and pancreatic cancer risk.
- We focused on the A5.1 MICA allele. This allele encodes a MICA protein that is shorter than its normal counterpart and is more easily cleaved from the cell surface.
- We hypothesized that having A5.1 MICA allele is associated with higher circulating s-MICA levels and increased pancreatic cancer risk.

Methods

- Pancreatic cancer cases were recruited in 1994-1998 from all hospitals in the seven-county metropolitan area of the Twin Cities and the Mayo Clinic, MN (N=116).
- Controls were recruited from
  - Drivers' license lists for individuals 20-64 years old
  - the US Health Care Financing Administration records for those aged 65+ years (N=492).
- The analysis was restricted to Caucasians (96% of all participants).
- Gene sequencing of exon 5 of the MICA gene was conducted by next-generation sequencing at the University of Minnesota Genomics Center.
- Allele assignments were based on the number of repeat units in the amplified regions of the MICA gene
- S-MICA levels were measured by enzyme-linked immunoabsorbent assay in the Cytokine reference laboratory.

Statistical analysis

- General linear regression with a log link was used to assess mean s-MICA levels across MICA alleles.
- Unconditional logistic regression was used to calculate the odds ratio (OR) and 95% confidence intervals (CI) for pancreatic cancer in relation to possessing at least once copy of MICA A5.1.
- Three statistical models were created and adjusted for:
  - Model 1: Age, sex (modeled as continuous variables), education (no college vs some college), smoking status (never, former and current)
  - Model 2: Model 1 plus alcohol consumption (no consumption, 1-6 servings per week and 7 or more servings per week), diabetes status (yes vs no)
  - Model 3: Model 2, restricted to non-diabetic participants

Figure 1. Unadjusted s-MICA levels are higher among those with the MICA A5.1 polymorphism

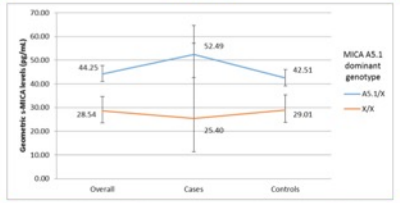


Figure 2. Adjusted s-MICA levels are higher among those with the MICA A5.1 polymorphism

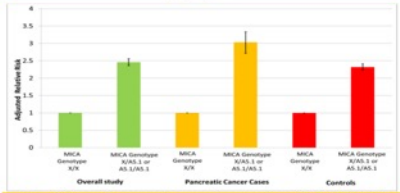
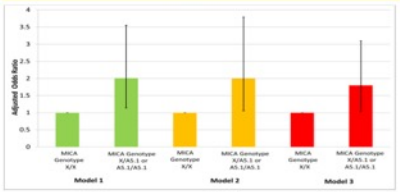


Figure 3. Pancreatic cancer odds are greater among those with the MICA A5.1 polymorphism



Results

- 452 participants (74%) possess at least one copy of the A5.1 allele, with 180 participants being homozygous and 272 participants being heterozygous for MICA A5.1
- After adjustment for confounders, participants with at least one copy of the MICA A5.1 allele had
  - 2.46 (95%CI: 2.36-2.56) times greater mean s-MICA levels than those without the A5.1 allele (Fig. 2).
  - greater pancreatic cancer risk (OR=2.00, 95% CI: 1.06-3.79) compared to those without any A5.1 allele (Fig. 3).
- There were no associations between other functional variants of the MICA STR polymorphism with pancreatic cancer risk or circulating s-MICA levels

Conclusions

- In this population-based case-control study, participants with at least one copy of the MICA A5.1 allele were at in increased risk of pancreatic cancer compared to those without any A5.1 allele.
- Participants with the MICA A5.1 allele had elevated circulating levels of s-MICA in both pancreatic cancer cases and controls.
- Our study supports the role of the MICA A5.1 allele in impaired immune response, which may increase the risk of pancreatic cancer.

Main citations

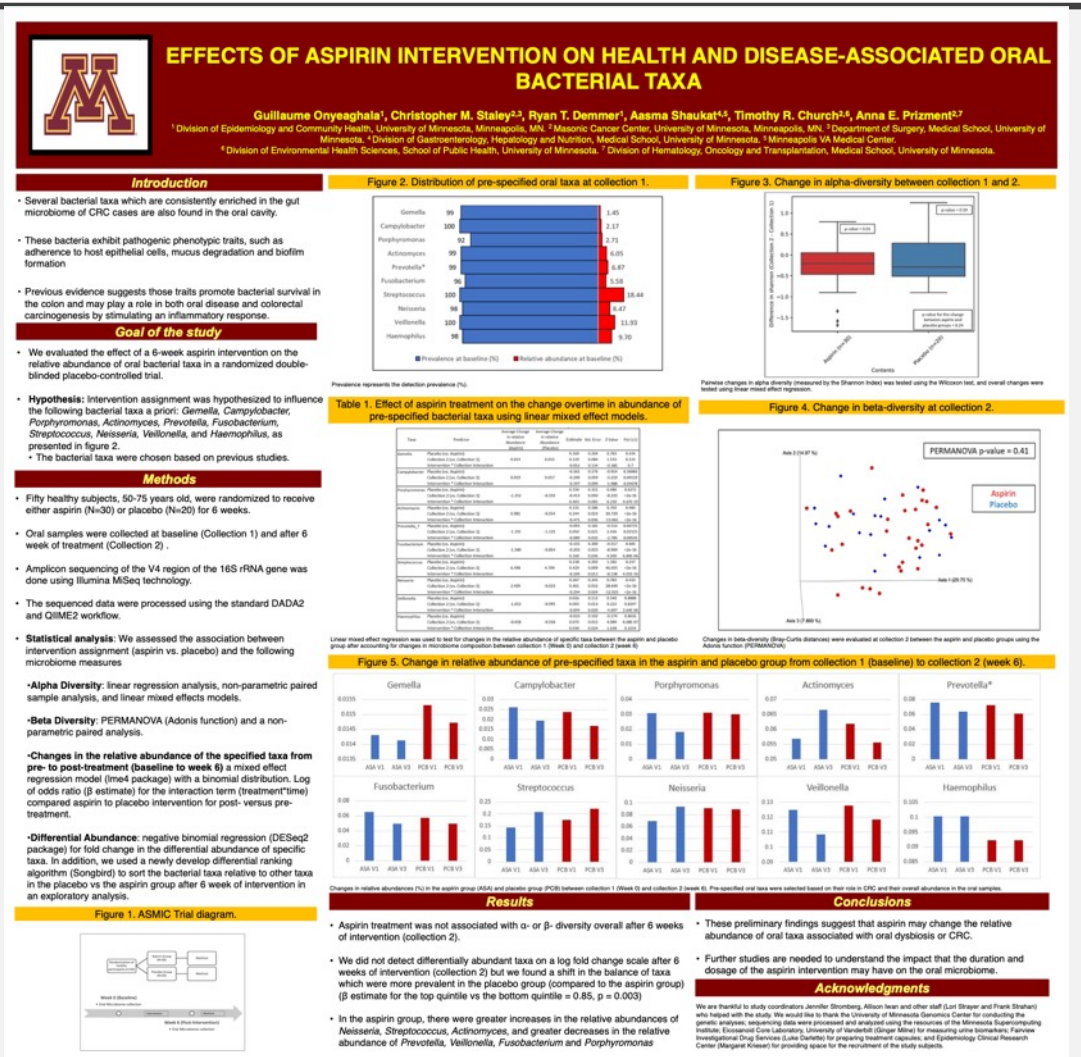
1. Xu X, Rao GS, Groh V, et al. Major histocompatibility complex class I-related chain A/B (MICA/B) expression in tumor tissue and serum of pancreatic cancer: role of uric acid accumulation in gemcitabine-induced MICA/B expression. *BMC Cancer*. 2011;11:194. doi:10.1186/1471-2407-11-194.
2. Dambrauskas Z, Svensson H, Joshi M, Hyltander A, Naredi P, Iresjö BM. Expression of major histocompatibility complex class I-related chain A/B (MICA/B) in pancreatic carcinoma. *Int J Oncol*. 2014;44(1):99-104. doi:10.3892/ijo.2013.2156.
3. Chen D, Gyllensten U. MICA polymorphism: biology and importance in cancer. *Carcinogenesis*. 2014;35(12):2633-2642. doi:10.1093/carcin/bgu215

Acknowledgments

We would like to thank the physicians, research and administrative staff involved in the PANC study, as well as all the study participants. We wish to express our thanks to the University of Minnesota Genomics Center for conducting the genetic analyses and the University of Minnesota Cytokine Reference Laboratory for measuring serum levels of s-MICA for this study.

Project Link

PROJECTS – MICROBIOME RESEARCH: PROPHYLACTIC INVESTIGATION OF ASPIRIN IN A PLACEBO CONTROL CLINICAL TRIAL



EFFECTS OF ASPIRIN INTERVENTION ON HEALTH AND DISEASE-ASSOCIATED ORAL BACTERIAL TAXA

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[6] Division of Environmental Health Sciences, School of Public Health, University of Minnesota. [7] Division of Hematology, Oncology and Transplantation, Medical School, University of Minnesota.

Introduction

- Several bacterial taxa which are consistently enriched in the gut microbiome of CRC cases are also found in the oral cavity.
- These bacteria exhibit pathogenic phenotypic traits, such as adherence to host epithelial cells, mucus degradation and biofilm formation
- Previous evidence suggests those traits promote bacterial survival in the colon and may play a role in both oral disease and colorectal carcinogenesis by stimulating an inflammatory response.

Goal of the study

- We evaluated the effect of a 6-week aspirin intervention on the relative abundance of oral bacterial taxa in a randomized double-blinded placebo-controlled trial.
- **Hypothesis:** Intervention assignment was hypothesized to influence the following bacterial taxa a priori: *Gemella, Campylobacter, Porphyromonas, Actinomyces, Prevotella, Fusobacterium, Streptococcus, Neisseria, Veillonella,* and *Haemophilus*, as presented in figure 2.
  - The bacterial taxa were chosen based on previous studies.

Methods

- Fifty healthy subjects, 50-75 years old, were randomized to receive either aspirin (N=30) or placebo (N=20) for 6 weeks.
- Oral samples were collected at baseline (Collection 1) and after 6 week of treatment (Collection 2) .
- Amplicon sequencing of the V4 region of the 16S rRNA gene was done using Illumina MiSeq technology.
- The sequenced data were processed using the standard DADA2 and QIIME2 workflow.
- **Statistical analysis**: We assessed the association between intervention assignment (aspirin vs. placebo) and the following microbiome measures
  - **Alpha Diversity**: linear regression analysis, non-parametric paired sample analysis, and linear mixed effects models.
  - **Beta Diversity**: PERMANOVA (Adonis function) and a non-parametric paired analysis.
  - **Changes in the relative abundance of the specified taxa from pre- to post-treatment (baseline to week 6)** a mixed effect regression model (lme4 package) with a binomial distribution. Log of odds ratio (β estimate) for the interaction term (treatment*time) compared aspirin to placebo intervention for post- versus pre-treatment.
  - **Differential Abundance**: negative binomial regression (DESeq2 package) for fold change in the differential abundance of specific taxa. In addition, we used a newly develop differential ranking algorithm (Songbird) to sort the bacterial taxa relative to other taxa in the placebo vs the aspirin group after 6 week of intervention in an exploratory analysis.

Figure 1. ASMIC Trial diagram.

Figure 2. Distribution of pre-specified oral taxa at collection 1.

Figure 3. Change in alpha-diversity between collection 1 and 2.

Table 1. Effect of aspirin treatment on the change overtime in abundance of pre-specified bacterial taxa using linear mixed effect models.

Figure 4. Change in beta-diversity at collection 2.

Figure 5. Change in relative abundance of pre-specified taxa in the aspirin and placebo group from collection 1 (baseline) to collection 2 (week 6).

Results

- Aspirin treatment was not associated with α- or β- diversity overall after 6 weeks of intervention (collection 2).
- We did not detect differentially abundant taxa on a log fold change scale after 6 weeks of intervention (collection 2) but we found a shift in the balance of taxa which were more prevalent in the placebo group (compared to the aspirin group) (β estimate for the top quintile vs the bottom quintile = 0.85, p = 0.003)
- In the aspirin group, there were greater increases in the relative abundances of *Neisseria, Streptococcus, Actinomyces,* and greater decreases in the relative abundance of *Prevotella, Veillonella, Fusobacterium* and *Porphyromonas*

Conclusions

- These preliminary findings suggest that aspirin may change the relative abundance of oral taxa associated with oral dysbiosis or CRC.
- Further studies are needed to understand the impact that the duration and dosage of the aspirin intervention may have on the oral microbiome.

Acknowledgments

We are thankful to study coordinators Jennifer Stromberg, Allison Ivan and other staff (Lori Strayer and Frank Strahan) who helped with the study. We would like to thank the University of Minnesota Genomics Center for conducting the genetic analyses, sequencing data were processed and analyzed using the resources of the Minnesota Supercomputing Institute; Eicosanoid Core Laboratory, University of Vanderbilt (Ginger Milne) for measuring urine biomarkers; Fairview Investigational Drug Services (Luke Darlette) for preparing treatment capsules; and Epidemiology Clinical Research Center (Margaret Kriesser) for providing space for the recruitment of the study subjects.

Project Link

PROJECTS – MICROBIOME RESEARCH: MULTIOMICS INVESTIGATION OF STOOL-BASED MICROBIOME BIOMARKERS

Association between fecal microRNAs and beta-glucuronidase activity in kidney transplant recipients..

G. Onyeaghala[1,2], S. Elmer[1], M. H. Khan[6], P. Yang[1], M. Wagner[6], L. Teigen[3], M. Al-Kofahi[5], B. Wu[4], W. Guan[4], C. Staley[6], S. Riad[2], A. Matas[6], R. Remmel[5], W. Oetting[5], C. Dorr[1,2], PA. Jacobson[5], A. Israni[1,2,7]

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INTRODUCTION

- Mycophenolate mofetil (MMF) is used in >90% of kidney transplant recipients.
  - Its inactive metabolite, MPAG, is de-glucuronidated by bacterial beta-glucuronidase in the gut and the active metabolite MPA is reabsorbed back into the blood in a process know as enterohepatic recirculation (EHR).
  - Enterohepatic recirculation increases blood concentrations, enhances immunosuppression and possibly toxicity in kidney transplant recipients.
- Host microRNA (miRNA) can influence the microbiome, leading to changes in beta-glucuronidase levels.

HYPOTHESIS

- We hypothesized that host miRNA levels would be associated with beta-glucuronidase levels in kidney transplant recipients.

METHODS

- Stool samples from 30 participants were collected from the Microbiome and Immunosuppression in Kidney Transplantation (MISSION) prospective study within 60 days post-transplant.
- Fecal miRNA was profiled using the NanoString nCounter human v3 miRNA codeset.
- Beta-glucuronidase activity levels were measured using the Abcam ab234625 beta-Glucuronidase Activity Assay Kit.
- After QC and data normalization, we examined the differential expression of 798 miRNA probes with beta-glucuronidase activity levels.
- In a secondary analysis, we conducted focused analyses of 17 a priori, microbiome associated fecal miRNAs and their association with beta-glucuronidase activity.

RESULTS

Figure 1: Distribution of logfold change in miRNA expression among the top 25 miRNAs (ranked by pvalue)

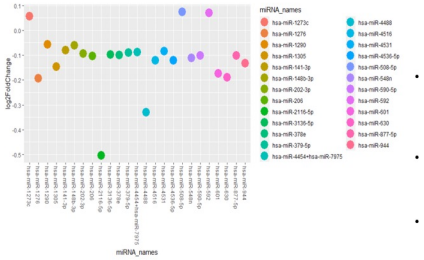
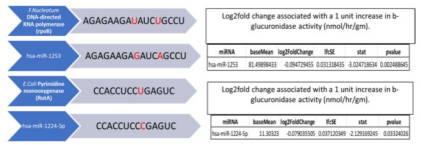


Figure 2: Alignment of microbiota-associated host miRNA-1253 and miRNA-12245p with *F.nucleatum* and *E.coli* targets.



*miRbase alignment data was adapted from Liu et al. (PMID:26764595)

- For data analysis, we performed global differential expression analysis treating beta-glucuronidase as a continuous variable using the DESeq2 package (version 3.15).
  - Detectable mean miRNA expression levels were defined as more than a one count per million.
- At the Bonferroni corrected 0.05 significance level, we found 20 fecal miRNAs associated with beta-glucuronidase activity in this cohort, with miR-2116-5p, miR-4888 and miR-600 being the most abundant **(Figure 1)**.
- In our secondary, focused analyses, we found that miR-1253, miR-1224-5p, miR-194-5p and miR-200a-3p were associated with beta-glucuronidase activity (p-value < 0.05).
- miR-1224-5p was shown to align with *Escherichia. coli* DNA, while miR-1253 was shown to align with *Fusobacterium. nucleatum* DNA **(Figure 2)**.
  - Both organisms are known producers of beta-glucuronidase enzymes.

CONCLUSIONS

- Our preliminary findings show that fecal miRNAs are associated with beta-glucuronidase.
- Further mechanistic studies are needed to validate these findings.
- Given sequence homology, it is feasible that fecal miRNAs may enter bacteria, such as *E. coli* and *F. nucleatum* and potentially regulate bacterial growth or gene transcripts such as beta-glucuronidase.

Acknowledgements: This study was supported in part by NIH/NIAID grant **5R01AI140303** and Hennepin Healthcare Research Institute's Post-doctoral Support Career Development Award

Project Link

Association between MPA Pharmacokinetics and in-vitro Mycophenolic Glucuronide turnover by gut microbiota of Kidney transplant recipients

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[1]Hennepin Healthcare Research Institute [2]Nephrology Division, Hennepin Healthcare, Department of Medicine, University of Minnesota [3]Department of Experimental and Clinical Pharmacology (ECP), University of [illegible] [4]Division of Gastroenterology, Hepatology and Nutrition, University of Minnesota [5]Division of Biostatistics, University of Minnesota [6]Department of Microbiology, University of Minnesota [7]Department of Epidemiology and Biostatistics, University of California-Irvine, [8]Department of Surgery, University of Minnesota [9]School of Public Health, University of Minnesota.

INTRODUCTION

- Mycophenolate mofetil (MMF) is used in >90% of kidney transplant recipients (KTRs).
- Its inactive metabolite, MPAG, is de-glucuronidated by bacterial beta-glucuronidase (BGUS) in the gut and the active metabolite MPA is reabsorbed back into the blood in a process know as enterohepatic recirculation (EHR).
- EHR leads to a secondary MPA peak, increasing MPA blood concentrations, enhancing immunosuppression and possibly toxicity in KTRs.

HYPOTHESIS

- We hypothesized that KTRs with extensive EHR in-vivo would have a gut microbiome with higher MPAG to MPA conversion and performed an anaerobic, in-vitro assay of MPAG conversion to MPA by the stool microbiome.

METHODS

- Participants underwent a pharmacokinetic (PK) study and microbiome stool collection post-kidney-transplant in the Microbiome and Immunosuppression in Kidney Transplantation (MISSION) study.
- Stool samples were exposed to 100ug/mL MPAG diluted in 7mL of Yeast extracts-Casein hydrolysate-fatty acids (YCFA) medium broth under anaerobic conditions in triplicate. The resulting mixture was incubated under anaerobic conditions with aliquots collected at 0, 0.5, 1,1.5 and 2 hours (Fig. 1).
- Aliquots were stored at -80ºC prior to assessing MPA concentrations in triplicate using a mass spectrometry validated assay.
- The V4 region of the 16S rRNA gene was amplified and sequenced on the Illumina MiSeq platform, then analyzed using the QIIME2 pipeline.

RESULTS

Table 1. Demographic characteristics of study participants

Demographics and Pharmacokinetic data (N=9)	
Age at transplant, mean (sd)	55.9 (16.0)
Male , n (%)	6 (67%)
Black or African American, n(%)	3 (33%)
BMI, mean (sd)	27.9 (4.2)
Living Donor, n(%)	5 (55%)
MPA AUC, mean (sd)	0.07 (0.02)
MPA % EHR, mean (sd)	38.0 (0.07)

*The MPA % EHR was defined as MPA AUC5-12 hour / AUC0-12 hour x 100.

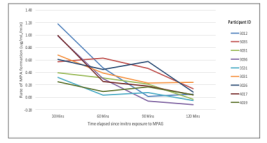

Figure 1: Rate of MPA formation after exposure to MPAG in-vitro. The rate of MPA formation was calculated as (*Ci-Co*)/(*Ti-To*), where *i* represent the timepoint of interest and *o* represents baseline.

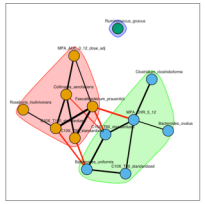

Figure 2: Correlation network map between in-vivo MPA pharmacokinetics (MPA EHR and AUC), in-vitro MPA turnover rates and the relative abundance of pre-specified beta-glucuronidase (BGUS) producing bacteria. The color nodes (orange vs blue vs green) indicate group membership to a specific cluster based on the correlation network. A black line indicates a correlation with another node within the cluster, whereas a red line indicates a correlation with a node outside of the cluster.

Table 2. Correlation analysis between in-vivo PK data and in-vitro MPA assay

	MPA dose adjusted AUC (0-12hours)	MPA %EHR (5-12hours)
Stool MPA concentration at T0	*0.85	0.40
In vitro MPA formation rate at 30 mins	-0.05	-0.36
In vitro MPA formation rate at 60 mins	-0.20	-0.43
In vitro MPA formation rate at 90 mins	-0.20	-0.21
In vitro MPA formation rate at 120 mins	-0.21	-0.19

*The p-value for the Pearson correlation coefficient was < 0.05

- The patient demographics and PK data used in this experiment are shown in Table 1.
- The rate of MPA formation was calculated as (*Ci-Co*)/(*Ti-To*), where *i* represent the timepoint of interest and *o* represents baseline. The rate of MPA formation was highest in the first 30 minutes of the assay and steadily decreased until the 120 mins timepoint (Fig 1).
- We implemented the Louvain Modularity Maximization (LMM) algorithm for community detection, focusing on the correlation between in-vitro MPA levels, MPA AUC, MPA EHR (defined as MPA AUC5-12 hour / AUC0-12 hour x 100) and the relative abundance of BGUS producing bacteria present in more than 10% of the samples (Threshold R=0.3).
- A Pearson correlation analysis between in-vitro MPA levels and PK data showed a positive correlation between MPA AUC and stool MPA concentrations at T (R = 0.85, p-value < 0.05, Table 2).
- Further correlation network analyses suggested that the relative abundance of *B. uniformis*, *B. ovatus* and and *C. clostridioforme* was correlated with invitro MPA formation rate over 30 and 60 minutes, as well as MPA EHR (FIG 2).

CONCLUSIONS

- Our preliminary findings suggest that the relative abundance of specific BGUS producing bacteria are correlated with the rate of MPA formation in an in-vitro setting.
- These data may have implications for the impact of the gut microbiome composition on MPA EHR for KTRs and should be replicated in larger experiments.

Acknowledgements: This study was supported in part by NIH/NIAID grant **5R01AI140303**, the Hennepin Healthcare Research Institute grant, and the Center for Chronic Disease Reduction and Equity Promotion Across Minnesota under Award Number **P50MD017342**

Project Link

PROJECTS – MICROBIOME RESEARCH: GUT MICROBIOME SIGNATURE AND DRUG METABOLISM IN KIDNEY TRANSPLANT RECIPIENTS

Gut microbiome signature associated with mycophenolate mofetil related diarrhea in kidney transplant recipients.

G. Onyeaghala[1,2], D. Vo[2], M. Mohamed[1], A. Saqr[1], B. Sanchez[2], H. Madden[1], J. Munoz[1], L. Teigen[1], C. Dorr[1,2], C. Staley[1], B. Wu[3], W. Guan[1], R El-Rifai[1], A. Matas[1], R. Remmel[1], W. Oetting[1], P. Jacobson[1], A. Israni[1,2]
[1]UMN, Minneapolis, [2]HHRI, Minneapolis, [3]UCI, Irvine

INTRODUCTION

- Mycophenolate mofetil (MMF) is used in >90% of kidney transplant recipients (KTRs) and associated with diarrhea.
- Recipients developing diarrhea are generally managed with lower MMF daily doses or longer dosing intervals, which are associated with reduced adherence to immunosuppression and poorer outcomes.
- MMF is bio-transformed to mycophenolic acid (MPA) the active metabolite and MPA glucuronide (MPAG) an inactive metabolite (MPAG). MPAG is metabolized by gut microbiota esp by beta-glucuronidase (BGUS) producers.

HYPOTHESIS

- We hypothesized that KTRs who experienced severe diarrhea after transplantation would have a distinct microbiome signature, likely associated with the presence of beta-glucuronidase producing bacteria.

METHODS

- The Microbiome and Immunosuppression in Kidney Transplantation (MISSION) study assessed diarrhea posttx twice weekly for 6 months, using a HIPAA compliant text-based survey (Mosio, Inc , Seattle, WA). Diarrhea events were defined using the V 5.0 definition of the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE).
- Diarrhea events of CTCAE grade 2 (increase of 4-6 stools per day compared to the previous week) were the primary outcome.
- A baseline stool sample and 24-hour food recall was collected one-week post-transplant in each participant using the Nutrition Data System for Research (NDSR).
- Shotgun sequencing data from the stool samples were processed using HUMAnN 3.7 and analyzed with MaAsLin2. Zero inflated Poisson regression models were used for a-priori univariate analyses.

RESULTS

Table 1. Characteristics of study participants

	Reported Diarrhea grade 2+ during follow up (n=24)	Did not report severe diarrhea during follow up (n=33)
Demographic Information (n=57)		
Age at transplant, mean (sd)	51.16 (14.05)	54.51 (14.56)
Weight at baseline in kg, mean(sd)	83.34 (16.54)	86.14 (16.67)
White, n(%)	19 (79.2)	20 (60.1)
Male, n(%)	14 (58.3)	24 (72.7)
Clinical Information (n=57)		
Time to first severe diarrhea event in days, median(range)	8 (2 - 152)	NA
Dietary Information (n=41)		
	Reported Diarrhea grade 2+ during follow up (n=19)	Did not report severe diarrhea during follow up (n=22)
Average daily energy intake in kcal, mean(sd)	1925.7 (736.2)	1843.1 (651.2)
Daily total fat consumption in grams, mean(sd)	86.83 (41.2)	70.9 (32.4)
Daily total carbohydrate consumption in grams, mean(sd)	204.2 (80.9)	225.2 (90.3)
Daily total protein consumption in grams, mean(sd)	90.6 (33.2)	82.3 (38.9)
Daily total fiber consumption in grams, mean(sd)	18.6 (8.9)	16.0 (9.5)
HEI score, mean(sd)	53.4 (12.7)	50.6 (15.5)

*41 out of the 57 participants provided a 24-hour dietary recall at baseline.

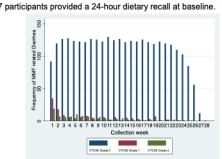

Figure 1: Frequency of diarrhea during the first 6 months of follow up among KTRs taking MMF. During follow up, 138 (4.1%) responses reported CTCAE grade 1 diarrhea and 100 (3%) reported CTCAE grade 2. Twenty-four (42%) participants experienced CTCAE grade 2 diarrhea.

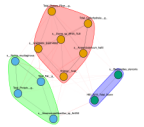

Figure 2: Correlation network between the relative abundance of gut microbiota and dietary indices derived from a 24h food recall at baseline. The color nodes (orange vs blue vs green vs yellow) indicate group membership to a specific cluster Louvain modularity maximization. A black line indicates a correlation with another node within the cluster, whereas a red line indicates a correlation with a node outside of the cluster.

Table 2. Association between bacterial taxa and severe diarrhea (CTCAE grade 2+) during follow-up.

Univariate a-priori analysis of BGUS producing bacteria (n=57)		
Bacterial taxa (species level)	organism prevalence	p-value†
*Bacteroides thetaiotaomicron**	36.80%	0.02
*Clostridium butyricum**	57.80%	0.01
Unadjusted analysis (n=57)		
Bacterial taxa (species level)	organism prevalence	p-value
Anaeromassilibacillus sp An250	15.78%	0.01
Bacteroides stercoris	14.03%	0.02
GGB3537_SGB4727 (Lachnospiraceae)	12.28%	0.03
Dorea sp AF24 7LB	12.28%	0.03
Eubacterium ramulus	10.52%	0.04
GGB9469_SGB14862 (Synergistaceae)	14.03%	0.05
Copracoccus catus	10.52%	0.05
Analysis adjusted for diet at the time of stool collection (n=41)		
Bacterial taxa (species level)	organism prevalence	p-value
Bacteroides_stercoris	19.50%	0.01
Anaerobutyricum_hallii	12.20%	0.02
Anaeromassilibacillus sp An250	17.10%	0.03
Dorea sp AF24 7LB	12.20%	0.03
Rothia_mucilaginosa	12.20%	0.03
GGB9469_SGB14862 (Synergistaceae)	14.60%	0.04

*Beta-glucuronidase producing organisms

†The p-value for the association in the univariate a-priori model was generated using zero inflated Poisson regression. The unadjusted and adjusted microbiome models were analyzed with MaAsLin2, using the first two principal components from the 6 dietary variables shown in table 1 for the adjusted analysis.

- We collected 3298 text-based surveys from 57 participants in the first 6 months post transplant (FIG.1).
- We implemented the Louvain Modularity Maximization (LMM) algorithm for community detection, focusing on the correlation between dietary indices and the relative abundance of gut bacteria present in more than 10% of the samples (Threshold R=0.3, FIG 2).
- Our microbiome association analysis identified several taxa which are possibly associated with the occurrence of severe diarrhea in this cohort of KTRs. However, the findings were not statistically significant after multiple hypothesis testing correction.

CONCLUSIONS

- Our preliminary findings suggest that the relative abundance of some specific taxa is associated with severe diarrhea occurrence in KTRs.
- Interestingly, the *Anaeromassilibacillus* and *Rothia* taxa have previously been associated with diet in other cohorts, but not diarrhea.
- Larger studies are needed to understand the interplay between diarrhea, the gut microbiome and dietary changes posttx.

Acknowledgements: This study was supported by NIH/NIAID grant **5R01AI140303.**

Project Link

Gut microbiome signature associated with mycophenolate mofetil enterohepatic recirculation.

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INTRODUCTION

- Mycophenolate mofetil (MMF) is used in >90% of kidney transplant recipients (KTRs) for immunosuppresion.
- MMF is bio-transformed to mycophenolic acid (MPA), the active metabolite, and MPA glucuronide (MPAG), an inactive metabolite (MPAG). MPAG is metabolized by gut microbiota, particularly by beta-glucuronidase (β-GUS) producers, and MPA is reabsorbed into the blood in a process know as enterohepatic recirculation (EHR).
- EHR leads to a secondary MPA peak, increasing MPA blood concentrations, enhancing immunosuppression and possibly toxicity in KTRs.

HYPOTHESIS

- We hypothesized that KTRs with extensive EHR in-vivo would have a distinct gut microbiome signature associated with EHR.

METHODS

- Participants (n=84, 37 prospective and 47 cross-sectional) underwent a pharmacokinetic (PK) study and microbiome stool collection post-kidney-transplant in the Microbiome and Immunosuppression in Kidney Transplantation (MISSION) study.
- A stool sample and 24-hour food recall was collected at the time of the PK study.
- Shotgun sequencing data from the stool samples were processed using HUMAnN 3.7 and analyzed with MaAsLin2. Zero inflated Poisson regression models were used for a-priori univariate analyses.
- Our main outcome was the MPA % EHR, defined as MPA $AUC_{5\text{-}12}$ / $AUC_{0\text{-}12}$ x 100.
  - In a secondary analysis, we also investigated the following PK parameters: MPA % EHR stratified in tertiles, MPAG AUC, MPA AUC to MPAG AUC between 5 and 12 hrs (window of secondary peak)

RESULTS

Table 1. Participant demographic and baseline characteristics

Variable	Cohort: Prospective (N=37)	Cross-sectional (N= 47)	Full Cohort (N=84)
Age at PK assessment, yr, mean (SD)	53.7 (14.1)	57.3 (12.8)	55.4 (13.4)
Gender, n (%)			
Female	12 (32.4)	11 (23.4)	23 (27.4)
Male	25 (67.6)	36 (76.6)	61 (72.6)
Ancestry, n (%)			
European	26 (70.2)	33 (70.2)	59 (70.2)
Black or African American	8 (21.6)	10 (21.3)	18 (21.4)
Asian or Pacific Islander	2 (5.4)	1 (2.1)	3 (3.6)
Native American	N/A	2 (4.2)	2 (2.4)
Unreported	1 (2.7)	1 (2.1)	2 (2.4)
eGFR, ml/min/1.73m2, mean (SD)*	59.2 (15.3)	69.8 (18.2)	65.13 (17.69)
Total bilirubin, mg/dL, mean (SD)	0.46 (0.57)	0.61 (0.32)	0.54 (0.45)
MMF daily dose, mg, mean (sd)	1234.0 (411.8)	1405.4 (302.5)	1309.5 (375.5)
MPA AUC0-12 hr, mg.h/L, mean (SD)	47.0 (15.2)	42.6 (17.9)	44.6 (16.8)
MPA EHR (AUC5-12 hr/AUC0-12 hr), mean (SD)	0.44 (0.10)	0.38 (0.07)	0.41 (0.09)

*eGFR, estimated glomerular filtration rate. Calculated using race-free eGFR equation.

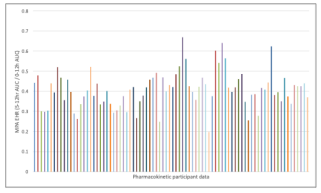


Figure 1: Enterohepatic recirculation variability among KTRs. Enterohepatic recirculation (EHR) was calculated as the ratio of MPA area under the concentration curve (AUC) for hours 5-12 to AUC for hours 0-12.

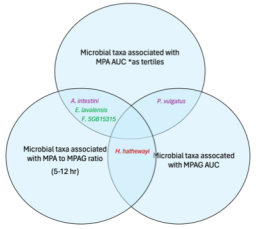
Table 2. Association between bacterial taxa and MPA EHR in the full cohort (n=84) at the time of PK

Bacterial taxa (species level)	Organism prevalence in full cohort	p-value
Faecalibacillus intestinalis	13.10%	0.004
Ruminococcus bromii*	16.70%	0.005
Blautia obeum*	63.10%	0.008
Parabacteroides distasonis*	36.90%	0.015
Gordonibacter pamelaeae	23.80%	0.024
Acidaminococcus intestini	11.90%	0.029

*β-GUS producing organisms

†The p-value for the association was generated with MaAsLin2, adjusting for the cohort variable (prospective vs cross-sectional).

Figure 2. Shared microbiome taxa across multiple PK parameters



The microbial taxa in purple represent associations with the full cohort (n=84), whereas the microbial taxa in green and red represent associations with the prospective (n=37) and cross-sectional (n=47) cohorts, respectively. All associations were generated with MaAsLin2.

- MPA EHR was highly variable within KTRs, among both early (<6 months) KTRs and stable KTRs who have had a transplant for more than 2 years (Figure 1).
- Our microbiome association analysis identified several taxa which are possibly associated with MPA % EHR. However, the findings were not statistically significant after multiple hypothesis testing correction (FDR, Table 2).
- We did not find strong evidence of a consistent group of bacterial taxa associated with multiple PK parameters in our secondary analysis. The the reported taxa were not statistically significant after FDR (Figure 2).

CONCLUSIONS

- Our preliminary findings suggest that the relative abundance of gut taxa is associated with MPA % EHR in KTRs, some of which (*R. bromii, B. obeum and P. distasonis*) have been previously reported as β-GUS producing organisms.
- Larger studies including ascertainment of β-GUS activity are needed to understand the interplay between the gut microbiome and MPA EHR.

Acknowledgements: This study was supported by NIH/NIAID grant **5R01AI140303.**

Project Link

PROJECTS – MICROBIOME RESEARCH: METATRANSCRIPTOMICS AND PHARMACOKINETICS IN KIDNEY TRANSPLANT RECIPIENTS

Gut Microbiome Meta-transcriptomics and Mycophenolate Mofetil Enterohepatic Recirculation Variability in Kidney Transplant Recipients.

G. Onyeaghala[1], D. Vo[1], K. Gupta[1], J. Nguyen[1], M. Mohamed[2], A. Saqr[2], L. Teigen[2], C. Dorr[2], C. Staley[2], W. Guan[2], K. Khanipov[1], G. Golovko[1], R El-Rifai[2], A. Matas[2], R. Remmel[2], W. Oetting[2], P. Jacobson[2], A. Israni[1]

[1]University of Texas Medical Branch, Galveston [2]University of Minnesota, Minneapolis.

INTRODUCTION

- Mycophenolate mofetil (MMF) is used in >90% of kidney transplant recipients (KTRs).
- Its inactive metabolite, MPAG, is de-glucuronidated by bacterial beta-glucuronidase (βGUS) enzymes in the gut and the active metabolite MPA is reabsorbed back into the blood in a process know as enterohepatic recirculation (EHR).
- EHR leads to a second MPA peak, increasing MPA blood concentrations, enhancing immunosuppression and possibly increased toxicity in KTRs.
- The numbers and diversity of βGUS these enzymes is not well defined in KTRs.

HYPOTHESIS

- We investigated the association between a sequencing panel of βGUS enzymes and MPA pharmacokinetic (PK) parameters in KTRs.
- We hypothesized that KTRs with extensive EHR in-vivo would have greater abundance of β GUS in their stool microbiome.

METHODS

- Adult KTRs (37 in a prospective cohort (<6 months post-transplant) and 47 in cross-sectional cohort (2+ years post-transplant)) underwent a 12hr MPA PK study with stool collection.
- Microbiome meta-transcriptomics data were processed and matched against a BLAST database panel of 279 βGUS enzymes from the human microbiome clustered gene indices (HMGC).
- The relative abundance of βGUS transcripts were associated with MPA %EHR ([MPA AUC5-12/AUC0-12] × 100) and the number of EHR peaks observed during the 12hr PK using linear regression models.

RESULTS

Table 1. Demographic characteristics of study participants

Characteristic	Cross-sectional cohort	Prospective cohort	p-value
Number of Participants, count (%)	47 (55.95%)	37 (44.05%)	
Time to PK from transplant (days), mean(sd)	2288 (699)	66.6 (16.1)	<0.05
Race, count (%)			0.69
White	33 (70.2%)	26(70.3%)	
Black or African American	10 (21.3%)	8 (23.5%)	
Asian	1 (2.13%)	2 (5.4%)	
Ethnicity, count (%)			0.61
Hispanic or Latino	2 (4.26%)	4 (10.8%)	
Not Hispanic or Latino	37 (78.7%)	29 (78.4%)	
Donor Status, count (%)			0.31
Living Donor	28 (59.6%)	17 (45.9%)	
Deceased Donor	19 (40.4%)	20 (54.1%)	
Gender, count (%)			0.5
Male	36 (76.6%)	25 (67.6%)	
Female	11 (23.4%)	12 (32.4%)	
Primary cause of Transplant, count (%)			0.68
Diabetes	11 (23.4%)	8 (21.6%)	
Glomerular Disease	13 (27.7%)	7 (18.6%)	
Hypertensive Nephrosclerosis	4 (8.51%)	5 (13.5%)	
Other	7 (14.9%)	10 (27.0%)	
Polycystic Kidney Disease	8 (17%)	5 (13.5%)	
Unknown	4 (8.51%)	2 (5.41%)	
Age at transplant, mean(sd)	56.8 (12.8)	53.5 (14.1)	0.26
eGFR (ml/min/1.73m2), mean(sd)	69.8 (18.2)	59.2 (15.3)	<0.05
Standardized measured creatinine clearance (ml/min/1.73m2), mean(sd)	73.4 (27.7)	65.0 (19.5)	0.12
Total bilirubin (mg/dL), mean(sd)	0.60 (0.33)	0.46 (0.57)	0.18
Albumin (g/dL), mean(sd)	4.2 (0.4)	3.9 (0.4)	<0.05
PPI Use, count(%)	5 (10.6%)	11 (29.7%)	0.06
Antifungal use, count(%)	1 (2.13%)	3 (8.11%)	0.45
Antiviral use, count(%)	3 (6.38%)	36 (97.3)	<0.05
Antibiotic use, count(%)	26 (55.3%)	34 (91.9%)	<0.05
Steroid use, count(%)	7 (14.9%)	22 (59.5%)	<0.05

AUC= area under the curve; EHR = enterohepatic recirculation; PPI = proton pump inhibitor; pk = pharmacokinetic visit

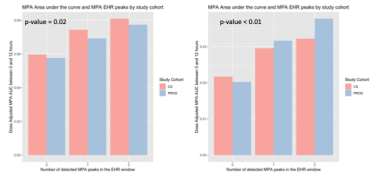


Figure 1: Distribution of MPA AUC $_{0\text{-}12}$ and MPA AUC $_{5\text{-}12}$ across MPA EHR peaks. Pharmacokinetic parameters were determined using noncompartmental analysis. The partial MPA AUC5-12 was selected to represent EHR because the secondary peaks associated with EHR were observed at ≥5 hours post-dose. Secondary peaks were defined as any increase in the plasma concentration after 5 hours post-dose of at least 1 mg/L following a disposition phase (i.e. decreasing concentration).

Table 2. Pearson correlations between βGUS transcripts and MPA PK parameters in the prospective cohort

Measure	Pearson correlation	
	r	p-value
βGUS transcripts - Number of PK Peaks	0.36	0.03
MPA % EHR - Number of PK peaks	0.52	0.001
βGUS transcripts - MPA % EHR	0.24	0.16

*MPA %EHR was calculated as (MPA $AUC_{5\text{-}12}/AUC_{0\text{-}12} \times 100$)

Table 3. Subgroup analysis of the association between the relative abundance of BGUS transcripts and PK parameters restricted to the lowest (0) and highest (2+) number of MPA EHR peaks.

Pharmacokinetic parameters	Overall cohort (n=36)			
	Univariate Model		Multivariate Model	
	Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
AUC 0-12 hrs	53.72 (-54.51, 161.95)	0.34	53.68 (-63.37, 170.72)	0.38
AUC 5-12 hrs	63.54 (9.92, 117.15)	0.38	61.25 (4.72, 117.79)	0.04
EHR	0.88 (0.33, 1.43)	0.04	0.82 (0.24, 1.41)	0.01
	Prospective cohort (n=17)			
	Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
AUC 0-12 hrs	76.40 (-48.98, 201.78)	0.25	59.05 (-86.17, 204.27)	0.44
AUC 5-12 hrs	86.80 (22.81, 150.79)	0.02	77.47 (10.39, 144.54)	0.04
EHR	1.13 (0.31, 1.96)	0.04	1.07 (0.17, 1.97)	0.04
	Cross-sectional cohort (n=19)			
	Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
AUC 0-12 hrs	3.24 (-201.05, 207.52)	0.98	33.49 (-182.98, 249.97)	0.77
AUC 5-12 hrs	10.49 (-83.69, 104.67)	0.83	27.09 (-68.09, 122.26)	0.59
EHR	0.24 (-0.41, 0.89)	0.48	0.35 (-0.33, 1.02)	0.33

*Multivariate model was adjusted for cohort, eGFR (ml/min/1.73m2), albumin, antibiotics use at the time of PK, and steroid use at the time of PK.

- In the prospective cohort, MPA % EHR during the 12-hour PK was associated with the relative abundance of βGUS transcripts (p=0.04) when comparing participants with the lowest (0) and highest (2+) number of MPA EHR peaks.
- In the cross-sectional cohort, no associations were found with PK and relative abundance of βGUS transcripts.

CONCLUSIONS

- These findings suggests that (βGUS) transcripts play a role in MPA variability, captured by the number of peaks during PK. Developing in-vitro panels for these specific βGUS microbial enzymes responsible for EHR will be necessary elucidate their clinical implications.

Acknowledgements: This study was supported in part by NIH/NIAID grant **5R01AI140303,** and the Center for Chronic Disease Reduction and Equity Promotion Across Minnesota under Award Number **P50MD017342**

Project Link

PROJECTS – CHRONIC KIDNEY DISEASE RESEARCH: ADVERSE OUTCOMES POST-TRANSPLANT IN KIDNEY RECIPIENTS

Dietary intake and mycophenolate mofetil-related diarrhea following kidney transplantation

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[4]Division of Biostatistics, University of Minnesota, [5]Department of Experimental and Clinical Pharmacology (ECP), University of Minnesota
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INTRODUCTION

- Mycophenolate mofetil (MMF) is associated with diarrhea.
- Recipients developing diarrhea are generally managed with lower MMF daily doses or dividing the same daily dose into three times a day dosing.
- Shorter dosing intervals are associated with reduced adherence to immunosuppression and poorer outcomes.

HYPOTHESIS

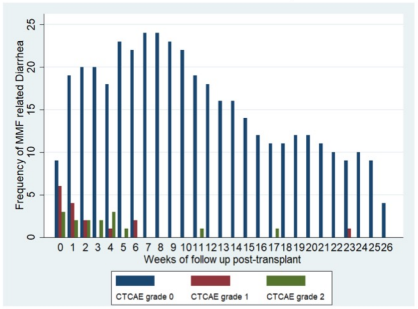
- We hypothesized that dietary fiber or "fermentable oligo-, di-, mono-saccharides and polyols" (FODMAP) intake post-transplantation would be associated with MMF-related diarrhea.

METHODS

- The Microbiome and Immunosuppression in Kidney Transplantation (MISSION) study assessed diarrhea posttx using a HIPPA compliant text-based survey (Mosio, Inc , Seattle, WA).
- Short bi-weekly text message surveys were sent to participants receiving MMF and Tacrolimus 6 months post-transplant to collect diarrhea information. Data from first 12 participants is presented.
- Diarrhea events were defined using the V 5.0 definition of the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE).
- Diarrhea events of CTCAE grade 2 (increase of 4-6 stools per day compared to the previous week) in the first 30 days post transplant was the primary outcome.
- A baseline 48-hour food recall was collected one-week post-transplant in each participant using the Nutrition Data System for Research (NDSR). FODMAP subgroups were our exposure of interest due to their association with diarrhea in previous studies.

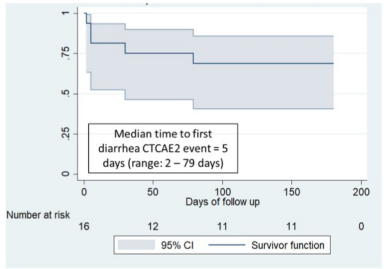
RESULTS

Figure 1: Frequency of MMF-related diarrhea during the first 6 months of follow up



During the first 6 months of follow up, we observed 15 CTCAE grate 1 (3.6% of responses) and 16 CTCAE grade 2 (3.3% of responses) diarrhea events. The majority of diarrhea events (73%) occurred in the first 30 days of follow up.

Figure 2: Kaplan Meier curve for Diarrhea events of CTCAE grade 2+ events during follow up



Data represent the Kaplan Meier estimates for the time to first severe diarrhea event over the first 6 months of follow up. 80% of the reported CTCAE grade 2 diarrhea events occurred in the first 30 days of follow up.

Table 1: Demographic & clinical characteristics of the study participants

Variable	CTCTAE grade 2 diarrhea		
	Did not develop diarrhea in the first month (N=8)	Developed diarrhea in the first month (N=4)	total (N=12)
Male, n(%)	5 (61.5%)	3 (75.0%)	8 (66.67%)
Caucasian, n(%)	6 (75.0%)	3 (75.0%)	9 (75.0%)
Living Donor, n(%)	4 (50.0%)	3 (75.0%)	7 (58.33%)
Former smoker, n(%)	4 (50.0%)	2 (50.0%)	6 (50.0%)
Diabetes pre-transplant, n(%)	2 (25.0%)	2 (50.0%)	4 (33.3%)
bmi, mean (sd)	27.8 (2.6)	29.2 (4.0)	28.3 (3.0)

Table 2: Intake of diet characteristics and FODMAP subgroups between patients with and without diarrhea in the 30 days following 48-hour dietary recall.

	Did not develop diarrhea in the first month (N=8)	Developed diarrhea in the first month (N=4)	P-value (t-test)
	Median (Min, Max)	Median (Min, Max)	
Fiber (g/day)	15.4 (3.8, 55.6)	19.5 (15.3, 22)	0.88*
Soluble Fiber (g/day)	5.2 (0.9, 14.4)	5.8 (2.7, 7.0)	0.7
Insoluble Fiber (g/day)	10.4 (2.9, 37.9)	14 (10.8, 15.5)	0.96*
Mannitol (g/day)	**0.2 (0.02, 0.49)**	**0.46 (0.43, 0.47)**	**0.01***
Sorbitol (g/day)	0.01 (0.00, 0.40)	0.03 (0.00, 0.10)	0.18*
Fructose (g/day)	12.3 (1.7, 24.8)	10.0 (3.9, 15.9)	0.71
Lactose (g/day)	5.9 (0.1, 40.8)	13.6 (9.6, 26.2)	0.78
Percent Calories from Fat (%)	39.9 (23.1, 51.5)	33.2 (29.5, 50.3)	0.5
Percent Calories from Protein (%)	15.8 (9.8, 22.9)	17.0 (12.8, 23.9)	0.55
Poly-Sat fat ratio	1.1 (0.3, 2.6)	0.7 (0.2, 1.2)	0.27

*Sattherthwaite p-value due to unequal variance

CONCLUSIONS

- 73% of the reported diarrhea events (CTCAE grade 1 & grade 2) and 80% of the reported CTCAE grade 2 events occurred within the first 30 days of follow up.
- These preliminary findings suggest an increased dietary intake of polyols may contribute to the development of MMF related diarrhea.
- Similar to other FODMAPs components, mannitol and sorbitol have an osmotic action in the small intestine and are readily fermented by colonic bacteria, leading to altered bowel habits.
- The prospective collection of diarrhea, nutrition and microbiome data will contribute to future interventions to reduce incidence of MMF-related diarrhea in kidney transplantation.

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Project Link

PROJECT – HEALTHCARE DATA ANALYTICS: ELECTRONIC MEDICAL RECORDS MINING FOR IGA-NEPHROPATHY ADVERSE EVENTS

Adverse outcomes associated with IgA Nephropathy (IgAN) recurrence in kidney transplant recipients.

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INTRODUCTION

- Immunoglobulin A nephropathy (IgAN) is the leading cause of glomerulonephritis worldwide and affected individuals have a high lifetime risk of end-stage kidney disease (ESKD).
- Kidney transplantation is the preferred option for IgAN patients who progress to ESKD, However, a previous study reported a 23% IgAN recurrence rate in the transplanted kidney and a 3.7-fold increase in graft rejection in patients with IgAN recurrence.
- Diagnosis of IgAN is challenging as it necessitates a renal biopsy. However, biopsy data is not readily available.

HYPOTHESIS

- Leveraging real-world patient data from electronic medical records (EMRs) across multiple healthcare organizations and the ability to propensity-score match patients on clinical characteristics, we hypothesized that IgAN recurrence would be associated with increased graft failure risk.

METHODS

- TriNetX was used to perform a propensity-score matched study of outcomes in kidney transplant recipients (KTRs) with IgAN as the primary reason for kidney transplantation (12/31/2010 - 12/31/2024).
- Exposures and outcomes of interest were defined using composite ICD and CPT codes.
  - Cohorts were matched based on age, sex, race, ethnicity, BMI, and donor status.
  - Outcomes of interest included IgAN recurrence, kidney transplant rejection, and cytomegalovirus (CMV) infection post-transplant.
  - Cox regression was used to evaluate the outcomes.

RESULTS

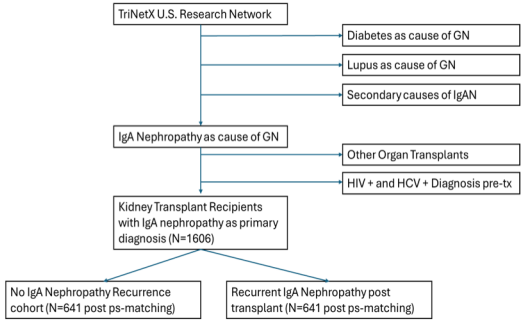

Figure 1: Cohort design for the TrinetX study. Our initial cohort narrowed the database network to adult, viral hepatitis-/HIV-, first-time renal transplant-only recipients with IgA nephropathy as the primary diagnosis for transplant. The sub-cohorts were defined based on the recurrence of IgA nephropathy within the 1st year post-transplant and followed for 5 years for outcomes of interest.

Table 1. Demographic characteristics of study participants pre and post propensity score matching

Patient Characteristics	Before Matching Mean ± SD; n (%)			After Matching Mean ± SD; n (%)		
	IgA Recurrence (n=817)	No IgA Recurrence (n=758)	p-value	IgA Recurrence (n=641)	No IgA Recurrence (n=641)	p-value
Age at Index (yrs)	45.69 ± 13.55	47.90 ± 14.53	<0.05	47.00 ± 13.65	46.70 ± 14.43	0.71
Black or African American	50 (6.12%)	62 (8.18%)	0.11	42 (6.55%)	46 (7.18%)	0.8
Male	491 (60.10%)	457 (60.29%)	0.94	394 (61.47%)	381 (59.44%)	0.46
Living Donor	299 (36.60%)	190 (25.07%)	<0.05	189 (29.48%)	187 (29.17%)	0.9
BMI ≥ 25 kg/m²	512 (62.67%)	464 (61.21%)	0.55	401 (62.56%)	407 (63.49%)	0.73
eGFR ≤ 30 mL/min/1.73 m²	786 (96.21%)	726 (95.78%)	0.66	620 (96.72%)	616 (96.1%)	0.55
CMV infections				199 (30.43%)	150 (22.94%)	
Kidney transplant rejections				279 (42.66%)	253 (38.68%)	

*The p-value was calculated using a t-test for continuous variables and a chi-square test for categorical variables. CMV infections and kidney transplant rejections were determined using composite logical observation identifier names and codes (LOINC) as well as ICD-10 codes.

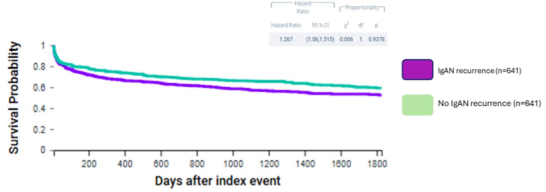

Figure 2: Kaplan-Meier curves for rejection free survival associated with IgAN recurrence over 5 years of follow up among kidney transplant recipients with IgA nephropathy (IgAN). Cohorts were matched based on age, sex, race, ethnicity, BMI, and donor status.

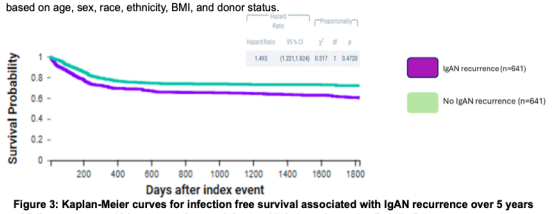

Figure 3: Kaplan-Meier curves for infection free survival associated with IgAN recurrence over 5 years of follow up among kidney transplant recipients with IgA nephropathy (IgAN). Cohorts were matched based on age, sex, race, ethnicity, BMI, and donor status.

- KTRs with IgAN recurrence had 1.27 times greater risk of transplant rejection (95% CI: 1.06-1.51) and 1.49 times greater risk of CMV infection (95% CI: 1.06-1.51) compared to those without recurrence.

CONCLUSIONS

- Our study found that KTRs with IgAN recurrence in the TrinetX database had significantly greater risk of rejection and CMV infection post-transplant.
- Despite limitations in the generalizability of EMR data, this represents an opportunity for further insight into differences in the early post-transplant period to identify modifiable risk factors associated with IgAN recurrence in KTRs

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Project Link