**Overall – Specific Aims**

Morgan State University (MSU) is a historically black university with a 150-year track record of educating underrepresented minority (URM) individuals. The MSU administration, led by President David Wilson, in its current strategic plan for 2011-2021, "Growing the Future & Leading the World," has mapped out a strategy (Strategic Goal Number 2 https://www.morgan.edu/about/strategic_plan.html) to become a stronger research institution in line with MSU's new designation as Maryland's **"Preeminent Public Urban Research University."** Some of the steps taken include modernizing its research infrastructure by hiring highly visible and highly qualified Vice Presidents for Research and Economic Development (first Dr. Victor McCrary, member of the National Science Board, and then Dr. Willie May, former director of NIST), creating an Office of Technology Transfer, recruiting deans with strong research backgrounds, hiring faculty members with strong research track records, and establishing Centers of Excellence in targeted research areas.

MSU is an urban institution with a mission to conduct innovative research on urban issues. The overarching goal of the proposed RCMI Center for Urban Health and Health Disparities Research and Innovation (**RCMI@Morgan**) is to embark on innovation and creation of knowledge dealing with urban health issues in Baltimore through both basic biomedical and public health/behavioral science research. Some of the areas of concerns are infectious and cardiovascular Diseases, cancers, food security, health informatics, and addiction (especially opioids). We will build a state-of-the-art infrastructure for each of these research areas to develop and enhance faculty expertise towards achieving national prominence. We anticipate that RCMI@Morgan will achieve increased external research funding, innovations and technology transfer, peer-reviewed publications and presentations, and community engagement and services.

**RCMI@Morgan** has the following four specific aims:

**Specific Aim 1.** Enhance MSU's health disparities research infrastructure and capacity within the areas of basic biomedical and behavioral/public health research in infectious diseases including sexually transmitted diseases, cancers and diabetes, addiction research and abuse prevention, social determinants of health, food security and health informatics.

**Specific Aim 2.** Enhance high-quality research, including translational research, on urban health and health disparities through increased external funding, publications and scientific services to the community.

**Specific Aim 3.** Facilitate collaborations between basic biomedical and social/behavioral faculty researchers and create a collaborative and supportive environment for faculty career development, especially for new and early career faculty.

**Specific Aim 4.** Build sustainable partnerships with two research-intensive institutions, Johns Hopkins University and the University of Maryland, Baltimore, as well as local government and community-based organizations dealing with health disparities.

The RCMI@Morgan will fund some translational research projects and also provide a host of workshops and seminars to educate faculty on the issues of innovation and research commercialization. The establishment of the RCMI@Morgan will strengthen MSU's research infrastructure, technology transfer, and its teaching and service missions.

# Specific Aims

The opioid crisis is a public health emergency, with over 10 million people suffering from opioid misuse in the United States. The acute health hazards of opioid misuse are well characterized, including opioid toxicity and overdose death. Thus far, only these short-term health consequences have been observed, while potential long-term health effects will require decades to become evident. Our project aims to address an overlooked and concerning aspect of widespread opioid use, specifically its potential to impact long-term health as a cause of cancer.

While opium is not commonly used in the US, opium consumption was classified as "carcinogenic to humans" by the International Agency for Research on Cancer (IARC) in September 2020, based on evidence for cancers of the larynx (2.5-fold increase in risk for ever use of opium), lung (2.2-fold), and bladder (2.9-fold). The recognition of opium as a carcinogen raised major concerns about prescription opioids, which are either derived from opium or synthesized in laboratories to mimic its chemical structure. Additional lines of evidence support potential carcinogenicity of prescription opioids, including experimental studies demonstrating tumor initiating and promoting effects, and associations between prescription opioids and lung, liver, pancreas, and urogenital cancers in registry linkage studies. However, it has been impossible to rigorously evaluate whether prescription opioids are associated with cancer incidence or mortality due to paucity of data on opioid use and insufficient statistical power in prospective cohort studies. Additional questions also remain about opium, specifically whether it causes additional types of cancer (such as liver, pancreas, esophagus, stomach, and brain cancers) and whether it acts synergistically with tobacco smoking to cause respiratory cancers.

To overcome these limitations, we initiated the Opioid Cohort Consortium (OPICO) in 2020 with pilot funding for an initial 18 months from the Global Genomic Medicine Collaborative (G2MC). OPICO brings together large-scale prospective cohort studies that have either gathered data on opioid use or have linked participant data to national medication dispensing records. We have used our pilot funding to investigate the availability of opioid data in different cohorts, develop methods for coding opioid exposure, and establish harmonization protocols. We also performed a pilot study in the *45 and Up* cohort to demonstrate the feasibility of defining exposure to prescription opioids using linked medication records, and to generate preliminary data on associations with cancer. Our R01 project will extend the work of OPICO in collaboration with a team of 15 scientists with expertise in pharmacoepidemiology, cancer epidemiology, internal medicine, oncology, genetics, biology, statistics, and pain medicine. We will pursue the following specific aims:

1. **Expand the Opioid Cohort Consortium (OPICO) to include 9 prospective cohorts from the United States, Europe, Australia, and Asia.** We will expand the OPICO to include 9 cohorts, yielding a large-scale data resource with 1.16 million participants, including over 76,000 prescription opioid users and over 28,000 opium users. We will gather opioid use data in each cohort using questionnaire data or via existing linkages to national medication dispensing records.
2. **Determine whether use of prescription opioids is associated with cancer incidence and mortality.** We will assess opioid use in relation to the outcomes of overall and site-specific cancer incidence and mortality. Analyses will compare users of stronger vs. weaker opioids (morphine equivalents), long-term vs. short-term users, and assess dose-response relationships via cumulative opioid use. We will perform stratified and adjusted analyses based on underlying health conditions to control for confounding.
3. **Determine whether use of opium is associated with cancer incidence and investigate its interaction with tobacco smoking in causing cancer.** We will assess whether opium use is associated with risk of incident cancers that were recognized to have 'limited' evidence by the IARC Monograph including brain, pancreas, liver, esophagus, and stomach cancers. Exposure definitions will include ever and cumulative use and will stratify by route of use (smoking or ingestion). We will also assess the joint effects of opium and tobacco in causing lung and laryngeal cancers.

Our work will provide the most robust evidence to date on the long-term health effects of opioid use. For prescription opioids in particular, our study design will allow us to evaluate potential increased risk for cancer, which has been previously unexplored due to methodological limitations. Our results could aid in the development of evidence-based clinical guidelines for using opioids in chronic pain management, as well as comprehensive national prevention policies to reduce the long-term harms of opioid use.

**Specific Aims: SPatial Analysis of Cardiovascular Events (SPACE) in the Golestan Cohort Study**

Cardiovascular disease (CVD) is the leading cause of death in the world, with 80% of global CVD deaths occurring in low- and middle-income countries (LMICs). In Iran, CVD is the leading cause of death and disability. A growing literature demonstrates that environmental risk factors strongly predict CVD events. The strongest evidence is for the following spatial risk factors: air pollution, nearby roadways, population density, proximity to health care facilities, land use mix, and low neighborhood socioeconomic status. New spatial statistical methods can determine the geographic distribution and magnitude of effect of these spatial risk factors on communities, enabling the design of spatially-targeted interventions for communities at risk. To date, however, most studies are conducted in high-income settings and focused on a single spatial risk factor.

The Golestan Cohort Study (GCS) is an ongoing prospective study, initially designed to identify risk factors for esophageal cancer. From 2004 to 2008, the study enrolled 50,045 men and women ages 40-75 across urban and rural Golestan Province in northeastern Iran. Enrollees completed a comprehensive assessment demographics, social and medical history, physical activity and nutritional patterns, and biometrics including BMI, blood pressure, and blood testing. Participants are followed up actively every 12 months, with a follow-up success rate of >99% in the first 7 years. Since inception, the GCS has registered over 2000 validated cardiovascular deaths. Nested within the GCS is the PolyIran Cohort, a cluster randomized controlled trial testing the efficacy of a polypill for prevention of CVD. The PolyIran Cohort includes 8434 subjects monitored closely for specific adverse CVD events.

The objective of this proposal is to identify spatial risk factors associated with CVD and use these variables to generate and validate a spatial model that predicts CVD events in an LMIC setting. Our central hypothesis is that spatial risk factors (e.g. air pollution, proximity to health care facilities, etc.) are associated with CVD beyond traditional risk factors. To test this hypothesis and achieve the overall objective, we propose the following specific aims:

**Aim 1: Identify spatial risk factors independently associated with CVD mortality among individuals in the Golestan Cohort, using a spatial survival model with village/neighborhood-level geocoded data.** We will use existing GCS datasets, maps, and satellite data to generate spatial risk factor (SRF) surfaces for ambient air pollution, population density, land cover, proximity to health centers, proximity to major roadways, and socioeconomic environment. We will use a Cox proportional hazards model to estimate associations between these SRFs and CVD mortality from IHD and stoke within the Golestan Cohort, using traditional CVD risk factors as covariates. We will use a Bayesian spatial random effects survival model (spatial frailty model) to adjust for spatial dependence in the data.

> **Subsidiary Aim 1.1: Identify spatial risk factors independently associated with CVD mortality among individuals in the Golestan Cohort, using a spatial survival model with individual-level geocoded data.** Address Interpolation will be used to geocode the exact home address of each Cohort participant. We will then use the same spatial regression approach described above, but now with true geocodes for home addresses within the cohort, providing greater resolution of SRF surfaces between nearby individuals. We will compare this model to that of Aim 1, to determine whether predictive value improves when participants' home addresses are precisely known rather than approximated.
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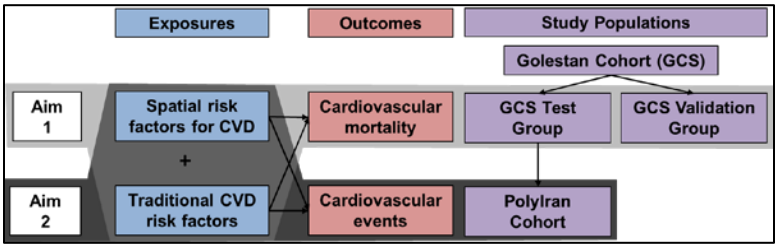
> **Subsidiary Aim 1.2: Validate spatial regression models using spatial risk factors to predict CVD mortality.** We will cross-validate the spatial survival models developed in Aim 1 and Subsidiary Aim 1.1 on a random selection of 5000 GCS enrollees not previously used. Spatial predictors will be validated if they explain variance beyond traditional CVD risk factors.

**Aim 2: Identify spatial risk factors independently associated with the incidence of adverse CVD events among individuals in the PolyIran Cohort, using spatial survival models with geocoded data at both the village/neighborhood and individual levels.** We will create spatial models to estimate the effect of the previously discussed SRFs on major adverse cardiac events recorded in the PolyIran Cohort. Events include fatal and non-fatal stroke and MI, unstable angina, sudden death, heart failure, and coronary revascularization.




We aim to identify relationships between CVD outcomes and spatial risk factors. These relationships can be tested in other LMIC settings in cohorts around the world. This research will motivate interventions to reduce the CVD impact of spatial risk factors, thus reducing the global burden of CVD.

# PROJECT SUMMARY


## Overview:

The Congruent Number Problem asks for a description of all congruent numbers: numbers that are the areas of right triangles with rational-length sides. Though versions of this problem date back over a thousand years, it is presently understood as asking whether there exists a terminating algorithm that can determine if a number is or is not congruent.

The proposed PI for this project is Dr. Thomas A. Hulse, an Assistant Professor of Mathematics at Morgan State University, an HBCU. It has recently been discovered by Dr. Hulse and his collaborators that this problem is closely related to the asymptotic behavior of new families of shifted convolution sums of Fourier coefficients of theta functions. It is proposed that Dr. Hulse study these sums using spectral decomposition, regularization, and averaging tools that have been employed by his group very successfully in the recent past on other relevant projects. He intends to shed new light on this problem using his expertise and these novel techniques in work with his collaborators. Furthermore, Dr. Hulse plans to supervise undergraduate and graduate research assistants in this project, in the process training them in number theory and computational methods.

## Intellectual Merit:

Tunnell's Theorem, proven by Jerrold B. Tunnell in 1983, provides a terminating criterion for the Congruent Number Problem on the condition that a special case of the Birch and Swinnerton-Dyer Conjecture, one of the remaining outstanding Millennium Prize Problems, holds true. As this case has not yet been proven, Tunnell's Theorem can only confirm with certainty that some integers are not congruent.

What is novel about the plan in this proposal is that, unlike Tunnell's Theorem, it does not require an investigation of elliptic curves, their corresponding automorphic forms, nor the Birch-Swinnerton-Dyer Conjecture. It seems to be an independent approach to the problem which might sidestep these issues altogether and, used in concert with Tunnell's Theorem, could provide a special case of the Birch and Swinnerton-Dyer Conjecture and so say when elements of a family of elliptic curves have nonzero rank.

## Broader Impacts:

As the Congruent Number Problem and the Birch and Swinnerton-Dyer Conjectures are both famous problems in mathematics, any progress toward them would help elevate the interest and enthusiasm in mathematics and number theory at Morgan State University, an HBCU in the Baltimore region. Dr. Hulse intends to present details on this and other unsolved problems in number theory as part of a new regular seminar at Morgan State. He will also recruit Morgan students to participate in the research and guide them toward academic and professional success. Promoting study of number theory and its applications, such as to the field of cryptography, will in turn positively impact government and industry by preparing individuals with skills well-suited for careers in national security. The success of these research assistantships will also contribute to elevating the prominence and success of underrepresented groups in STEM. All results will be made public and submitted for publication in peer-reviewed journals and communicated at colloquia, conferences and elsewhere.