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IRB_00144804 **Created:** 6/25/2021 2:55 PM

PI: Amanda Bakian PhD/Epidemiologist **Submitted:** 3/3/2022

Title: The influence of multiple environmental exposures on suicide risk

IRB_00144804
1. Contacts and Title

1. Study Introduction

1. **Responsible Investigator:**
Amanda Bakian

Email	Training	CoI Date
amanda.bakian@hsc.utah.edu	4/25/2024 MG	2/6/2025

a. **Position of the Investigator:**

- (●) **Faculty or** Non-Academic Equivalent
- ( ) Student
- ( ) Staff
- ( ) Resident/Fellow
- ( ) Other

2. **Contact Persons for the Responsible Investigator:**

Name	Email	Training
Emily Sullivan	Emily.Sullivan@hsc.utah.edu	2/26/2024 MG
Jennifer West	jennifer.a.west@utah.edu	4/7/2025 SMCG

3. **Guests of the Responsible Investigator:**

Last Name	First Name	E-Mail
Gibson	Marie	marie.gibson@hci.utah.edu

4. **What type of application is being submitted?**
New Study Application (or Amendment/Continuing Review)

5. **Title Of Study:**
The influence of multiple environmental exposures on suicide risk

6. **Study Purposes and Objectives:**

Suicide is the 10th leading cause of death in the United States with the national economic costs of suicide deaths approximated to be $53 billion annually. While suicide's etiology is complex, heritability for suicide death is estimated to be close to 50% and it is widely hypothesized that interactions between an underlying genetic predisposition and proximal environmental factors are in suicide's causal pathway. Current research points to weather and ambient air pollution exposures among the major proximal environmental risk factors for suicide. We recently reported a 20%

increased risk of suicide following short-term exposure to nitrogen dioxide and a 5% increased risk following short-term exposure to fine particulate matter among suicide decedents in Salt Lake County, Utah. Among Utah suicide decedents, we have measured higher frequencies of deleterious gene variants in the inflammation pathway (i.e. *NRXN1*, *SP110*) compared with controls in a family-based gene by environment interaction analysis. Complementary studies investigating the relationship between weather factors and suicide conducted outside of Utah have found peak increases of 3.8%, 3.1%, and 15% in suicide risk associated with exposure to each 1°C increase in temperature, 1 MW/m^2 increase in solar radiation, and with drought, respectively. While research has focused largely on their independent effects, exposure to weather and ambient air pollution occurs simultaneously and their effects on suicide risk may be additive or synergistic. Moreover, research points to heterogeneity in a person's susceptibility to suicide following exposure to weather and air pollution based on as yet unknown underlying individual, familial, and genetic characteristics. **We propose to investigate the gaps in current knowledge by disentangling the individual, additive, and synergistic associations among weather and ambient air pollution exposures on suicide risk. Furthermore, we will identify the individual, familial, and genetic characteristics that moderate the relationship among weather and air pollution exposures and suicide. Our study has three specific aims:**

Aim 1. Determine the individual, additive and synergistic effects of weather and ambient air pollution on suicide risk: We will use a nested case-control design (N > 10,000 suicide cases) analyzed in a multi-exposure Bayesian framework to determine the individual, additive, and synergistic effects of short-term ambient air pollutant (fine particulate matter, nitrogen dioxide, and ozone) and weather (e.g. temperature, precipitation, and sunlight) exposures associated with suicide death in Utah from 2000 to 2021. We will test the hypothesis that the synergistic effects of specific ambient air pollutant and weather exposures on suicide are greater than ambient air pollutant and weather exposures' individual and additive effects.

Aim 2. Identify the individual and familial characteristics moderating suicide risk: We will use a nested case-control design (N > 10,000 suicide cases) analyzed in a multi-exposure Bayesian framework to identify the individual and familial characteristics (e.g. sex, co-occurring medical conditions, psychopathology, early adverse life conditions, membership in a high-suicide risk extended family) that moderate the individual, additive, and synergistic associations among short-term ambient air pollutant and weather exposures and suicide death in Utah from 2000 to 2021.

Aim 3. Test for gene by weather and air pollution interactions: We will leverage currently existing molecular data (i.e. whole genome sequence and PsychArray) from 5,580 population-ascertained Utah suicide cases from 2000 to 2021 to conduct case-only and case-crossover analyses to identify genetic variants interacting with short-term ambient air pollutant and weather exposures to increase suicide risk. Prioritized gene variants for gene-environment interaction analyses will be identified from locally conducted genome wide association, shared genomic sequence, and rare genetic variant studies.

7. **Is this a multi-site study, where more than one site needs IRB approval?**
   ○ Yes ● **No**

8. **Background and Introduction:**

Suicide deaths are a major public health problem: Suicide is the 10th leading cause of death in the United States; over 44,000 individuals die by suicide in the US every year.[40] The economic toll of suicide is considerable with the national costs of suicide death estimated at $53 billion annually.[41] Although potentially preventable, U.S. suicide rates climbed 30% between 1999 and 2016.[42] Utah has the fifth highest age-adjusted suicide rate in the nation,[40] and **suicide is the leading cause of death among Utah youth ages 10 through 21**.[43] The proposed project will use a population-wide sample of Utah suicide deaths from 2000-2021, a majority of which have DNA samples and unprecedented individual and familial data. Utah encompasses a high suicide-risk population (i.e. majority White, non-Hispanic (80.6%) with the lowest median age in the US)[44] ensuring generalizability of study findings. While other suicidal behaviors such as suicide ideation and attempts are of considerable public health concern, their population-wide ascertainment, including severity and timing, is challenging. Further, demographic and behavioral predictors successfully differentiate suicide deaths from suicide ideators and attempters[45,46] suggesting that while they share overlapping features, they are distinct populations. ***The current study will focus on suicide deaths, an extreme, well-defined outcome for which the identification of proximal modifiable risk factors is of critical importance.***

Weather and air pollution exposures as proximal risk factors for suicide: The etiology of suicide is complex. It is believed to result from the interaction between distal factors that manifest as underlying vulnerabilities and short-term factors that immediately precede a suicide.[47] Historically, research on proximal risk factors for suicide has focused on stressful life events[48], psychopathology,[49-52] and co-occurring medical conditions.[53-56]

Reducing suicide death's growing incidence necessitates expanding and improving our understanding of suicide's proximal risk factors. Despite early recognition that suicide frequency correlates with weather,[57,58] research on the association of short-term weather exposures with suicide is relatively sparse with studies using vastly different designs making cross-study comparisons difficult. Peak suicide rates have been shown to be positively correlated with increasing durations of sunshine or solar radiation,[59-62] increasing ambient temperature,[63-66] and

decreasing precipitation.[67,68] The effects of temperature and sunshine duration on suicide appear to be heterogeneous and vary by sex, method of death, and age.[61,65]

Recently, the suicide causal paradigm has expanded to include chemical environmental exposures, such as ambient air pollutants, as proximal risk factors. We reported a heightened risk of suicide following short-term exposure to fine particulate matter ($PM_{2.5}$) and nitrogen dioxide (NO_2) in Salt Lake County, Utah from 2000-2010.[18] Our study expanded upon research conducted in the Republic of Korea[20] and Taiwan[69] that identified an increased risk of suicide associated with transient PM exposure. Since our publication, additional research has confirmed and extended our findings by linking increasing concentrations of $PM_{2.5}$, coarse particulate matter (PM_{10}), NO_2, sulfur dioxide (SO_2) and ground level ozone (O_3) with suicide deaths in culturally, geographically, and meteorologically diverse locations including Japan,[21] China,[12] Belgium,[22] Northeast Asian cities,[23] and South Korea.[70] Subgroup analyses highlight heterogeneity in suicide risk associated with transient air pollution as a function of underlying characteristics including sex,[12,18,20,21] age[18,20] and season.[12,18,20-22,69]

Weather and air pollution mixtures: Weather variables and ambient air pollutants are highly correlated in space and time.[71] For example, air pollutants attenuate the amount of solar radiation reaching the ground[72,73] while precipitation improves air quality via particle scavenging.[74] To date, studies have largely focused on single pollutant or weather exposure effects on suicide. While ambient air pollution studies have been careful to control for the confounding effects of weather variables,[18-23,68] studies of weather and suicide have not controlled for the effects of air pollutants.[59-68] ***Thus, complex combinations of air pollutant and weather variables, which more realistically reflect daily exposure, have not been examined in regards to suicide***. Studies of single exposures may underestimate the true burden of weather and air pollutants on suicide[75] limiting the potential effectiveness of interventions based on their findings.

Potential mechanisms: Strong evidence from epidemiologic and animal-based research implicates the serotonergic system[76-78] and the inflammatory and oxidative stress pathways[79-83] in suicide; these mechanisms may also underlie ambient air pollution's link with suicide. Exposure to air pollutants may decrease respiratory function leading to reduced oxygen saturation, oxidative stress, and hypoxemia.[84,85] Brains of hypoxic individuals show increases in tyrosine hydroxylase and its product, dopamine, as well as decreases in tryptophan hydroxylase and its product serotonin.[85] Decreased levels of serotonin are implicated in the neurobiology of suicide[86] and increased suicide rates have been observed among populations that experience hypoxia including individuals living at higher elevations,[87,88] smokers[89,90] and asthmatics.[56] Ambient air pollutants produce peripheral and central nervous system (CNS) inflammation.[91] Inflammation may be linked to suicide through the release of pro-inflammatory cytokines such as tumor necrosis factor (TNF) and interleukin-6 (IL-6) that alter CNS function by disrupting the production and transport of neurotransmitters.[92] Significantly increased levels of mRNA and protein expression of IL-6 and TNF have been measured in the prefrontal cortex of suicide cases versus controls.[81]

Similarly, the serotonergic system may play a role in the relationship between weather and suicide. Serotonin metabolite 5-hydroxyindoleacetic (5-HIAA) concentrations in human cerebrospinal fluid and serotonin turnover by the brain are correlated strongly with season and daily sunshine duration.[93,94] Suicide is associated with reduced cerebrospinal levels of 5-HIAA[95-97]and serotonin transporter binding in the CNS.[98,99] Negative associations have been detected between L-tryptophan, a serotonin precursor, and seasonal variation in the number of violent suicides and increasing ambient temperature.[100] ***The proposed study will provide critical insights into potential biological mechanisms underpinning suicide and will lead to research with animal models that will validate our epidemiologic and mechanistic discoveries.***

Genetic factors and gene by environment interactions for suicide: Suicide aggregates in families and the heritability of suicide is nearly 50%.[101,102]Recent case-control genetic studies using candidate gene, family-based and genome-wide association designs have resulted in promising findings of genetic risk factors for suicide.[14,103-108] GxE interactions for suicide to date have largely focused on the interaction between early life adversity and serotonergic system genes such as *5-HTTLPR*.[47,109] While evidence points to the involvement of serotonergic and inflammatory/oxidative stress pathways, alternative mechanisms may be activated following short-term air pollution/weather exposure such as the hypothalamus-pituitary-adrenal axis.[110,111] While we expect some results may implicate these pathways, the proposed investigation accommodates multiple plausible biological pathways through a genome-wide approach. ***Our study will allow discovery of new risk variants and comprehensive gene by environment (GxE) analyses given the availability of rich exposure, individual-level, familial, and molecular data for over 5,500 suicide cases.***

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2. Study Location and Sponsors

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1. **Add all locations applying for approval of research via the University of Utah IRB or Human Research Protection Program (HRPP).**

   Click the appropriate button(s) below to add locations:

	Site Name	Investigators Name	Covered Entity	Sub Sites
View	University of Utah	Amanda Bakian	Yes	

2. **Will a Central IRB (CIRB) or Single IRB (SIRB) model be used for review of this study for the sites listed in this application?**

   ○ Yes ● **No**

3. **Indicate the source(s) of funding obtained or applied for to support this study.**

	Sponsor	Sponsor Type	Sponsor Contact Information	Prime Sponsor	Prime Sponsor Type	OrgID
View	NIH NATIONAL INSTITUTE ENVIRONL HLTH SCI	Federal Government				11202

4. **Does this study have functions assigned to a Contract Research Organization (CRO)?**

   ○ Yes ● **No**

5. **Does this study involve use of the Utah Resource for Genetic and Epidemiologic Research (RGE)?**
   Examples: Utah Population Database (UPDB), Utah Cancer Registry (UCR), All Payers Claims Database (APCD), etc.

   ● **Yes** ○ No

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Addition of a Site

1. **Site Name:**
   University of Utah

2. **Site Principal Investigator**
   ☑ **Mark if Same as Responsible Investigator (syncs with investigator on the first page)**
   Amanda Bakian

Email	Training	CoI Date
amanda.bakian@hsc.utah.edu	4/25/2024 MG	2/6/2025

   a. **Position of the Site Principal Investigator**
   Faculty or Non-Academic Equivalent

   b. **Will the Site PI consent participants?** ○ Yes ● **No**

3. **Site Contact Persons, if different from the Site PI:**
   ☑ **Mark if Same as Contacts for Responsible Investigator (syncs with contacts on the first page)**

Name	Email	Training
Emily Sullivan	Emily.Sullivan@hsc.utah.edu	2/26/2024 MG
Jennifer West	jennifer.a.west@utah.edu	4/7/2025 SMCG

4. **Site Staff and Sub-Investigators**

Name	Email	Training	Obtaining Consent	CoI Date
Linda Amoafo	Linda.Amoafo@utah.edu	10/7/2022 M	☐	3/26/2025
Danli Chen	u6010503@utah.edu	10/20/2022 MCG	☐	2/6/2025
Hilary Coon	hilary.coon@utah.edu	12/3/2024 SMG	☐	6/17/2025
TERESA DEATLEY	u6053792@utah.edu	10/8/2024 M	☐	5/23/2025
Anna Docherty	docherty.anna@gmail.com	7/27/2022 M	☐	2/12/2025
Md Imdadul Haque	u1545780@utah.edu	10/9/2024 M	☐	1/7/2025
Brandy Hill	brandy.hill@hci@utah.edu	10/10/2024 SM	☐	2/24/2025

Name	Email	Training	Obtaining Consent	CoI Date
Mert Karatas	u6051109@utah.edu	7/5/2023 MG	☐	6/12/2025
Brooks Keeshin	brooks.keeshin@hsc.utah.edu	3/20/2023 MCG	☐	1/6/2025
Brenna Kelly	brenna.kelly@hsc.utah.edu	4/4/2024 MC	☐	9/28/2024
Dirga Lamichhane	u6051215@utah.edu	4/21/2023 MG	☐	4/3/2024
Kailey Mahoney	u1485696@utah.edu	1/10/2025 SMG	☐	1/6/2025
Daniel Mendoza	daniel.mendoza@utah.edu	1/9/2024 M	☐	6/13/2025
Nicolas Nunez	nicolas.a.nunez@hsc.utah.edu	9/24/2023 MCG	☐	2/9/2025
Emily Sullivan	Emily.Sullivan@hsc.utah.edu	2/26/2024 MG	☐	6/4/2025
Marissa Taddie	marissa.taddie@utah.edu	3/28/2023 MG	☐	5/26/2025
Douglas Tharp	doug.tharp@hsc.utah.edu	3/5/2025 SMG	☐	9/25/2024
James VanDerslice	jim.vanderslice@utah.edu	9/24/2022 MG	☐	3/17/2025
Deanna Wall	u6057578@utah.edu	1/29/2025 SMG	☐	5/15/2025
Yue Zhang	zhang.yue@hsc.utah.edu	5/13/2025 MCG	☐	6/7/2025

5. **Site Guests:**

Name	Email	Training
Melissa Chaveste	mchaveste@sonomatech.com	
Tyler Fenske	tfenske@sonomatech.com	
Fred Lurmann	fred@sonomatech.com	
Nathan Pavlovic	npavlovic@sonomatech.com	

6. **Select HIPAA coverage for this study:**
   Study procedures will be conducted within a HIPAA Covered Entity at this site (HIPAA Privacy Rule applies)

7. **Select the study procedures that will be conducted at this site:**
   - Data collection
   - Data analysis

8. **Select the University of Utah department responsible for this research:**
   PSYCHIATRY

9. **Add any additional sites that are part of this performance group**
   There are no items to display

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IRB_00144804
IRB Smart Form

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Sponsor Information

a. Are you receiving award or contract management for the sponsored funds through the University of Utah Office of Sponsored Projects?

● **Yes** ○ No

If yes, select the associated OSP Proposal ID/DSS through eAward to link it to the ERICA system.

You must have a fully approved Proposal ID/DSS number through eProposal which will show up in eAward after OSP has integrated the ID. To access the eAward application, use the instructions on the OSP website.

Link to a Proposal ID/DSS through eAward

Proposal ID/DSS: 10057452
PI: BAKIAN,AMANDA VIRGINIE
Sponsor: NIH NATIONAL INSTITUTE ENVIRONL HLTH SCI
Prime Sponsor:
Department:
Short Title: BAKIAN NIEHS 2020
Sponsor Award Number: 5R01ES032028-04
Type: Federal Government
Award Start Date: 5/1/2021
Award End Date: 2/28/2026
Prime Sponsor Type:

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IRB_00144804
3. Participants

3. Participants

1. Ages of Participants:

7 to 17 years old	(Parental permission and assent form needed)
18 and older	(Consent form needed)

2. Specific age range of participants (e.g., 7-12 years old, 60+, etc.):
>7 years

3. Indicate any vulnerable participant groups (other than children) included:

None

If "Other", please specify:

If "None" and no children are involved, answer the following question.
Has the participant selection process overprotected potential subjects who are considered vulnerable so that they are denied opportunities to participate in research?

○ Yes ● **No**

4. Number of participants to be included and/or enrolled in this entire study, across all study locations: ~11,000 suicides; ~110,000 controls

5. Characteristics of Participants/Inclusion Criteria:

A nested case-control design will be used in Aims 1 and 2 and will include all suicides in Utah from 2000 to 2021 (N~10,749 by 2021). Each suicide case will be matched by sex and birth year to ten non-suicide controls (N~107,490) in UPDB using at-risk sampling where selected controls must be alive at the time of the suicide case's death (the event day). No other criteria will be used to match cases. The study is requesting access to ~11,000 suicides and ~110,000 controls. A 1:5 matching has already been conducted for the majority of Utah suicide deaths through Hilary Coon's (study co-investigator) IRB 00044244. Under this IRB, additional matching will be done so that there are a total of 10 non-suicide controls matched to each suicide death.

6. Participant Exclusion Criteria:

None

7. Is a substantial percentage of the participant population anticipated to be non-English speaking?

○ Yes ● **No**

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IRB_00144804
- Vulnerable Populations

Vulnerable Populations

Justification Requirements for the Inclusion of Vulnerable Populations

1. * **How does the nature of the research require or justify using the proposed subject population:**
The study will investigate the relationship between multiple environmental exposures and suicide risk. Individuals die by suicide across the lifespan, and excluding children or other vulnerable populations from the study would introduce bias. Therefore, we will include all suicide deaths in our study.

2. * **Would it be possible to conduct the study with other, less vulnerable subjects?**
○ Yes ● **No**

If yes, justify the inclusion of vulnerable subjects:

3. * **Is this population being included primarily for the convenience of the researcher?**
○ Yes ● **No**

If yes, explain:

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IRB_00144804
4. Study Information

4. Study Information

1. **Design of Study (select all that apply):**

   - [x] **Non-Experimental and/or Descriptive Research Design:**

     Secondary/Archival Data Analysis or Retrospective Chart Review

   - [ ] **Experimental and/or Interventional Research Design:**

     There are no items to display

   - [ ] **Development of a research resource (repositories, databases, etc.)**

     There are no items to display

   - [ ] **Other**

2. **Does your study involve the use of any placebo?**
   ○ Yes ● **No**

3. **Length of entire study, from initiation through closeout:**
   Eight years

4. **How will participants be recruited or identified for inclusion in the study?**

   a. **Select all methods that will be used:**

   Written or electronic record review

   Other

   Utah suicide deaths will be identified from co-Investigator Hilary Coon's IRB 00044244 and from Utah Death Certificates. Controls already pulled by Pedigree and Population Resource (PPR) staff at UPDB for IRB_00044244 may also be used in this study. Additional matched controls will be identified by PPR staff as necessary via the Utah Population Database.

   b. **Describe the recruitment/participant identification process in detail (e.g. who will review charts or records, who can refer participants to the study, where will flyers be posted, how often will recruitment letters be sent, when will follow-up phone calls be made, etc.):**

   Utah suicide deaths will be identified from co-Investigator Hilary Coon's IRB 00044244 and from Utah Death Certificates. Controls already pulled by Pedigree and Population Resource (PPR) staff at UPDB for IRB_00044244 may also be used in this study. Additional matched controls will be identified by PPR staff as necessary via the Utah Population Database. All suicides in Utah from January 1, 2000-December 31, 2021 will be included in the study. They will each be matched 1:10 by birth year and sex to a set of controls using at-risk sampling. The matching will be done by PPR staff using the UPDB.

5. **How will consent be obtained?**

   Waiver or Alteration of Informed Consent

6. **Describe all the procedures chronologically, from screening/enrollment through study closeout, which will be completed in the research project.**

1. Suicide deaths from 2000-2021 will be identified through co-Investigator Hilary Coon's IRB 00044244 and from Utah Death Certificates.

2. We will add to the existing matching of suicide deaths to controls that has been done under IRB 00044244 so that all suicide deaths identified from step 1 will be matched 1:10 to a comparison group based on sex and birth year using at-risk sampling.

3. Geocoded residential address at time of case's death for the suicide cases and their matched controls will be acquired from death certificates (for decedents) and other sources in the UPDB (for matched controls). Geocoded residential address at time of case's death for suicide cases will also be acquired from the Utah State Office of the Medical Examiner and acquired via Hilary Coon's IRB 00044244. To protect the identify of the suicide deaths and matched controls, the geocoded residential addresses from suicide deaths and their matched controls will not be shared with the entire study team. At the University of Utah, only Jim VanDerslice, Marissa Taddie and Doug Tharp will have access to the geocodes so that they can link the geocoded locations with ambient air pollution and weather exposures as well as to contextual measures (e.g. census block measures of median household income). We will need date of death for estimating environmental exposures. Only team members involved with data analysis will have access to date of death. At the U of U, geocoded residential address information and date of death will only be stored on the Center for High Performance Computing's protected environment, and Jim VanDerslice's GIS lab server (for data linkage).

4. Ambient air pollution exposures (to PM2.5, NO2, O3) will be assessed on the day of suicide and up to two weeks preceding the suicide for cases and controls.

5. Weather and other ambient exposures (to temperature, precipitation, solar radiation, air pressure, length of day, pollen) will be assessed on the day of suicide and up to two weeks preceding the suicide for cases and controls.

6. Other individual-level data will be acquired from UPDB and the Office of the Medical Examiner. Much of this data is already available through Hilary Coon's IRB 00044244. More specifically, through IRB 00044244, we will request demographic data such as sex and age at time for death, birth certificate variables such as birth weight, gestational age and birth complications, measures of familial risk such as the familial risk of suicide or major depressive disorder, and ICD9/10 claims data from the University of Utah, Intermountain Healthcare, All Payers Claim Database, the Health facilities, Emergency department, and ambulatory care databases. The individual-level data from UPDB accessed via IRB 00044244 will be used to conduct Aim 2 (investigate factors that moderate the relationship between short-term weather and ambient air pollution and risk of suicide). We will not request duplicate data from what is already available under IRB 00044244. Additional data will be requested as needed such as the The Utah DEmographic Childhood ADverse Exposures (DECADE) scale, which is a reliable and standardized interval-level measure of early life stress developed within UPDB.

7. Contextual measures and social determinants of health (e.g. census block-level measures of median household income) will be acquired for suicide deaths and matched controls.

8. To help with conducting exposure assignments, limited PII will be shared with co-investigators from Sonoma Techonologies, a sub-contractor to the University of Utah for this NIH-funded project, so they can use their modeling techniques to generate measures of exposure to vehicular emissions, pollen, ambient air quality, meteorological conditions, and land use measures to be used as part of the analysis of environmental contributors to suicide. They will use their access to traffic, ambient air pollution, meteorological, and pollen models to assign measures of exposure to vehicular emissions, ambient air pollutants (e.g. nitrogen dioxide, fine particulate matter, ozone), pollen, meteorological factors (e.g. solar radiation, precipitation, temperature, wet bulb temperature, relative humidity), pollen concentrations, and land use for each case and control in our study. To do so they will need residential locations corresponding to residential histories during the relevant exposure periods for suicide decedents and their matched controls from 2000-present. These exposure periods are: 1) daily exposure measures on each day within one month following and two months prior to the date of death (short-term exposure and used in case-control and case-crossover study designs), and 2). Average exposure starting from 2000 to date of death (long-term exposure).

We will share: 1) a proxy id (generated by the study team and different from the existing UPDB proxy ID), 2) residential location(s) (residential histories) and, when relevant, location(s) and name of the subject's school (coordinates and full address) for each case and control, and 3) known date ranges for each location in the residential histories for each case and control over the two exposure periods. School is based on which school capture area the residence is located. To further protect the identities of study subjects, we will include 'dummy' study subjects at a 5 dummy subjects:1 study subject (both cases and controls) ratio in addition. These observations will be indistinguishable from the actual subjects in terms of the data provided. These addresses will be generated from a random selection of residential addresses publicly available from the Utah Geospatial Resource Center (gis.utah.gov). In this way it will be very difficult to identify which individuals are actual study subjects. This method has been used by other studies such as the NIH-funded multi-center national Environmental influences on Child Health Outcomes (ECHO) Program (https://www.nih.gov/research-training/environmental-influences-child-health-outcomes-echo-program). Sonoma Technologies has also utilized this method in studies.

Sonoma Technology will assign ambient air pollutant concentrations; metrics of traffic exposure, meteorological parameters, pollen, and proximity to various types land cover whereby:

- The air pollutant information will be assigned using 1x1 km spatial resolution daily models of $PM_{2.5}$, NO_2, and O_3 concentrations developed by Dr. Joel Schwartz's team at Harvard.
- Exposure to traffic will be characterized using proximity to major roadways, traffic load or density metrics, and line-source dispersion model concentrations estimates of contributions from local on-road vehicle emissions. These assignments rely on accurate geographic representation of the roadway system. The density and dispersion model estimates depend on traffic volumes. The dispersion model estimates also depend on local meteorological conditions (wind speed and direction and atmospheric conditions) and vehicle fleet emission rates. The traffic assignments pose the highest accuracy requirements on subject locations because the influence of roadways is known to fall off rapidly with distance from roadways.
- Information on pollen and spore counts will be assigned based on point information provided by pollensense.com. These assignments have strong seasonality and depend on local vegetation types which varies spatially.
- Temperature, humidity, solar radiation, precipitation, and wet bulb globe temperature will be assigned using national meteorological models with daily or hourly resolution, and high spatial resolution (varying from 1x1 km to 9x9 km).
- Proximity to vegetation and greenspace will be assigned based on satellite-derived information on greenness as measured by the normalized difference vegetation index (NDVI) which is available monthly at 0.25 x 0.25 km resolution and annually at 30 m resolution. Additional land cover variables (N=37) may be assigned from the National Land Cover Database which has 30 m resolution.

9. Once exposure assignments are made by Sonoma Tech, they will be returned along with proxy IDs and dates corresponding to the exposure assignments to the research team at the University of Utah.

10. Once the data has been cleaned and prepared, the statistical analysis will be conducted.

7. **Are all procedures for research purposes only (non-standard or non-standard of care procedures)?**
   ● **Yes** ○ No

   If no, list the procedures that are performed for research purposes only (non-standard or non-standard of care procedures):

8. **Is there a safety monitoring plan for this study?**
   ○ Yes ● **No**

9. **Provide a summary of the statistical methods, data analysis, or data interpretation planned for this study. Factors for determining the proposed sample size (e.g., power) should be stated.**

   Aim 1.

   Bayesian kernel machine regression (BKMR) is a method that handles complex, correlated exposures by regressing a health outcome (i.e. suicide) on a flexible function of a multiple environmental exposure mixture, which is specified using a kernel function.[170,171] We propose to use BKMR because it 1) does not require assumptions of linearity and additivity in modeling the relationship between exposure and outcome, 2) aids in pinpointing the exposures within the complex mixture driving relationships, 3) estimates the functional forms of the exposure-response curve, 4) supports inference of independent, additive and synergistic effects, and 5) handles spatial dependencies and multicollinearity among the data. In addition, the use of a Bayesian modeling approach supports the incorporation of previous knowledge on the relationship between suicide and environmental exposures into the analysis in the form of prior probability specification. BMKR will be used to model our binary suicide case/control outcome and a number of different models will be fit with varying complexity. First, BMKR requires the selection of multiple model components including a variable-selection procedure (to identify the important exposures), a kernel function (to specify the form of the exposure-response function, e.g. Gaussian or polynomial kernel functions), and model parameter prior probabilities. We will vary these model components to investigate differences in model fit and performance as judged by the Bayesian information criterion. A distributed lag structure will be incorporated in the form of B-splines into the models to identify the peak exposure period within the two-weeks preceding the suicide. The model will include a vector of covariates to control for confounding. Inference will be based on the posterior probabilities for each exposure (either a weather or air pollutant variable) when the pointwise 95% confidence band does not contain zero. Cross-sectional plots and heat maps of the exposure-response relationship (effect) at different levels of the exposures will be constructed. As the models will follow a hierarchical formulation, a Gibbs sampler will be

implemented for generating Markov chains. Additional multi-exposure analytical approaches may be considered to compare with BKMR including dimension reduction methods (e.g. weighted quantile sum regression), variable selection methods (penalized methods), and methods for grouping observations (e.g. random forests).[172]

Aim 2.

Risk factor identification: We have a unique opportunity to identify specific individual and familial characteristics from a diverse pool of potential characteristics (all variables listed in table 3 will be considered) that increase a person's susceptibility to suicide following exposure to a weather/air pollution mixture. We will first use variance inflation factors (VIF)[173] to detect if multicollinearity is present among the list of individual-level and familial variables (predictors). If none of the potential predictors has VIF > 4, we will treat all predictors as independent predictors and perform multivariable logistic regression analysis with the Least Absolute Shrinkage and Selection Operator (LASSO)[174] to identify the subset of potential predictors that are truly informative for predicting suicide. The final model for suicide will be determined based on the optimal penalty term using 10-fold cross validation criteria. By imposing some penalty in the regression model fitting, LASSO approach can shrink the coefficients of unimportant predictors to zero while retaining the important ones (where coefficients are nonzero). Thus, the final models will include all important predictors with parsimonious representation, enhanced interpretability, and improved prediction precision. When multicollinearity is a concern among the potential predictors (VIF>4), we will perform multivariable logistic regression analysis with the Elastic Net[175] instead of LASSO. Similar to LASSO, Elastic Net will also select optimal penalty term using 10-fold cross validation criteria and unbiased regression coefficients will be estimated from unpenalized multivariate logistic regression using the selected factors.

Phenotype by Environment (PxE) models: A series of BMKR models will be formulated to test for PxE interactions using individual and familial characteristics found to be associated with suicide by the LASSO and Elastic Net analyses. Known individual and familial risk factors for suicide (i.e. prior attempt, sex, age, race/ethnicity, psychopathology, season) will also be examined. The interaction effect will be captured through the addition to the BMKR models of the individual-level or familial variable as a covariate and a second kernel function that specifies the PxE interaction (a PxE kernel). Separate models will be formulated for each PxE interaction test.

PxE BMKR models are a novel contribution to the field of multi-environmental exposure modeling. Therefore, we also propose fitting non-Bayesian kernel machine (KM) models[176-178] to compare with the BMKR models. The KM models will model our suicide outcome and include three vector-valued functions specified using kernel functions that capture the phenotype, environment, and phenotype-environment effects. Covariates for model adjustment will be included as a separate vector. KM models allow for the testing of overall model effects, PxE interactions, and conditional P and E effects simultaneously.

Power analysis for Aims 1 and 2: The nested case-control analysis will include at least 10,000 suicide cases and 50,000 controls. A power analysis was conducted using the power procedure in SAS 9.4[179] assuming a logistic response with a response probability of suicide of 0.50, a normally distributed air pollutant predictor variable, normally distributed meteorological variables, an alpha of 0.05, total sample sizes of 60,000 and an effect size of 5%. The resulting power was greater than 0.80 indicating satisfactory power for detecting differences in the association between ambient air pollution exposure and suicide assuming effect sizes similar to ones measured in Bakian et al.[18] Although the models fit in the power analysis are only proxies for the more complicated models proposed in this application, it justifies our proposed sample sizes. Given the relatively large sample size available for conducting the nested case-control analysis, we do not anticipate power to be a limitation.

Aim 3.

Based on previous work, we anticipate that future GWAS and RV studies will yield ≥60 total common genes and rare variants for suicide. Gene filtering will be done based on functional annotation, prior evidence of GxE interaction, biological pathway analysis, and gene burden tests to reduce the number of prioritized genes for GxE analysis to 5-10 depending on molecular data availability by end of the study (see Power analysis below). First, gene annotation will be conducted using Biofilter 2.0, a comprehensive software tool that accesses data from multiple, publically available human genetic data resources.[185] Environmental exposure annotation will then be done using the Comparative Toxicogenomics Database. Next, a pathway analysis will be conducted to aggregate genes into functionally meaningful biological pathways. Should evidence suggest a particular pathway of interest, then the GxE analysis may be focused entirely on a particular gene set, which may provide increased explanatory power for suicide death. FUMA GENE2FUNC software[120] will be used to determine pathway enrichments in the Gene Ontology (GO)[186] compared to all genes in the genome. FUMA provides p-values for enrichment based tests adjusted for multiple testing using the Benjamini-Hochberg false discovery rate method.[187]

While tests of individual variants may achieve significance, we hypothesize that our target rare genes will contain multiple important variants in cases. Burden tests are specifically designed to test this hypothesis, and collapse the presence of multiple rare variants into a single score. We will apply flexible analysis tools that account for distant familial relationships, and allow stratifying by sex and/or using sex as a moderator, weighting variants using

annotation, or allowing variants to be in alternate directions across the gene. Methods allowing some, or all, of this flexibility include Skat,[188] PLINK/SEQ, [189] SCORE-Seq, [190] and VAT.[191]

GxE interaction analyses: We will apply two modeling approaches to test for GxE interactions among suicide cases. First, generalized linear mixed models in a case-only design will be used.[192] Case-only GxE tests have been shown to be better powered than standard case-control tests.[193] Cases will be categorized by the environmental exposures (absent vs present) assessed in Aim 1. Genetic exposures will be coded similarly as dichotomous or polytomous variables based on presence/absence of particular variants. GxE can be quantified using the interaction odds ratio, which is compared with the hypothetical effect size when the effect of both factors is multiplied. Separate binary or polytomous logistic regression models will be fit for each combination of environmental and genetic exposure with correction for multiple comparison using the Benjamini-Hochberg[187] (or similar) procedure. Models will include critical covariates such as sex and ancestry principle components to adjust for confounding and a "family" random effect to control for within family effects.

Alternatively, case-crossover models will be formulated to test for dose-response GxE relationships. In contrast to the case-only design, environmental exposures can be treated as continuous or categorized into quantiles. Genetic exposures will be coded as binary or polytomous variables. In a case-crossover design, each case serves as its own control.[194,195] Strengths of using a time-stratified case-crossover design include minimization of time-trend bias and built-in control of seasonality, day of the week effects, and cross-subject variability (e.g. individual-level behaviors such as smoking).[38] While the case-only design may identify a suicide subset for whom sensitivity to exposure is the result of particular genotypes, the case-crossover design will provide information about dose-response relationships.

Power analysis: The powerGWASinteraction[196] package in R was used to determine study power to detect significant GxE interactions. A sample size of at least 2,691 cases (current study sample is >5,500) is required for the study to be powered at 80% to detect a significant GxE interaction based on a Bonferroni adjusted alpha of 0.01 (test of five GxE interactions), a gene prevalence of 0.2, an exposure prevalence of 0

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PI: Amanda Bakian PhD/Epidemiologist

Submitted: 3/3/2022

Title: The influence of multiple environmental exposures on suicide risk

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- Request for Waiver of Consent

Request for Waiver or Alteration of Consent

* Requested Waivers

	Date Created	Type of Request	Purpose of Waiver Request
View	6/25/2021	Waiver of Informed Consent	The study uses secondary data collection and analysis.

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IRB_00144804
IRB Smart Form

PI: Amanda Bakian PhD/Epidemiologist **Submitted:** 3/3/2022

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Request for Waiver or Alteration of Consent

1. **Purpose of the Waiver Request:**
   The study uses secondary data collection and analysis.

2. **Type of Request:**
   Waiver of Informed Consent

3. **List the identifying information you plan to collect or keep a link to (e.g. names, dates, or identification numbers such as social security numbers or medical record numbers, etc.).**
   Date of death
   Geocoded residential location at time of death for suicide death
   Geocoded residential location at time of matched suicide for controls

4. **Explain why the research could not be practicably conducted without using identifiable information. Examples of such explanation could include the following:**
   The study requires accurate information about the environmental exposure experienced by the suicide death and matched controls on the day of suicide and the days leading up to the suicide. Identifiable information is necessary to know what day the decedent died and the location of the suicide death and matched control so that exposures can be accurately estimated.

5. **Explain why the research could not practicably be conducted without the waiver or alteration. For example, complete the following sentence "If I had to obtain consent, the research could not be conducted because...":**
   It is not possible to obtain consent from non-living subjects. Controls are from the general population and will be matched to suicide decedents. It will not be possible or practical to acquire consent from 110,000 matched controls in the eight year timeline of this study.

6. **Explain why the research and privacy risk of the research are no more than *minimal:***
   Because the main risk is breach of confidentiality to family members of the suicide decedents or to the matched controls and procedures are in place to make such breaches very unlikely.

7. **Describe the measures you will take to ensure the waiver or alteration will not adversely affect the rights and welfare of the *subjects:***
   The identifying information to be collected from the suicide decedents and matched controls will be used to assess exposure to ambient air pollution and weather variables. Such information will not adversely affect the rights and welfare of the study subjects.

8. **Explain how you will, if applicable and appropriate, provide the subjects with additional pertinent information *after* they have participated in the study, or indicate *"Not applicable":***

No applicable. Study participants will not be informed of their participation in the study as providing participants pertinent information after participation is not appropriate; the results would have no effect on the individuals.

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5. Data Monitoring

5. Data Monitoring Plan

1. **Privacy Protections:** Privacy refers to persons and to their interest in controlling access of others to themselves. Privacy can be defined in terms of having control over the extent, timing and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others. **What precautions will be used to ensure subject privacy is protected?**

Select all that apply:

The collection of information about participants is limited to the amount necessary to achieve the aims of the research, so that no unneeded information is being collected

Other or additional details (specify):

Identifying details from suicide deaths and matched controls will be limited to geocoded residential address at time of death and date of death. Access to geocoded residential address at time of death will be limited to Jim VanDerslice, Marissa Taddie and Doug Tharp at the University of Utah so that they can link the locations to air pollution and weather exposures and contextual factors to examined in this study. To protect the identity of the suicides, no additional identifying information that could be used in conjunction with geocoded residential address will be maintained with the geocodes such as age at death or sex of the decedent. Geocodes and date of death will be stored on CHPC and Jim VanDerslice's GIS servers, and any data analysis will be done only on computers with password access, behind the university firewall, and with full encryption. Similarly, geocodes will be stored on encrypted servers behind firewalls at Sonoma Technologies and data will only be accessible from computers with password accessibility. No genetic data will be acquired from relatives of suicide decedents.

Geocoded residential addresses for cases and controls along with a random selection of addresses from non-study participants will be shared with co-Investigators from Sonoma Technologies so that they can assign additional exposure measures to the suicide deaths and matched controls. When PII is sent to Sonoma Technology, it agrees to comply with the requirements of 45 C.F.R. Parts 160 and 164, which is the Privacy Rule of the Health Insurance Portability and Accountability Act of 1996 ("HIPAA Privacy Rule"). The confidential data are encrypted, isolated, and will accessible only by the four individuals being added to the study as part of this amendment. These individuals have completed CITI training and have signed UPDB confidentiality agreements. They have been provided PHI for numerous other studies. Some of these a listed in the supplemental documentation ("Sonoma Tech collaborations").

2. **Confidentiality Precautions:** Confidentiality is an extension of the concept of privacy; it refers to the subject's understanding of, and agreement to, the ways identifiable information will be stored and shared. Identifiable information can be printed information, electronic information or visual information such as photographs. **What precautions will be used to maintain the confidentiality of identifiable information?**

Select all that apply:

Storing research data on password protected computers or in locked cabinets or offices

Participant identifiers will be stored separately from the coded, participant data

Other or additional details (specify):

Only aggregate data will shared outside the study team. Genetic data will only be derived from suicide decedents and not from living subjects.

3. **Will photos, audio recordings, or video recordings, or medical images of participants be made during the study?**

○ Yes ● **No**

If yes, describe the recording/images and what will become of them after creation (e.g., shown at scientific meetings, stored in the medical/research record, transcribed, erased, etc.):

4. **How will study data and documentation be monitored throughout the study?**

Select all that apply:

Other or additional details (specify):

Other additional details (specify):
Data will be updated regularly based on new exposure assessment measures. At this time, we will examine the data to ensure that data has not been corrupted.

5. **Who will be the primary monitor of the study data and documentation?**

Select all that apply:

Principal Investigator

Other or additional details (specify):

6. **How often is study data and documentation monitoring planned (e.g., monthly, twice a year, annually, after N participants are enrolled, etc.)?**
At least twice a year and after data is updated

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6. Risks and Benefits

6. Risks and Benefits

1. Describe the reasonable foreseeable risks or discomforts to the participants:

The genetic data derived for this study will be conducted under Hilary Coon's IRB 00044244. We will use results from the analyses conducted as part of her research (e.g. prioritized genes, variants) in Aim 3 of our study. The primary risk is breach of confidentiality and privacy. However, we feel that efforts are in place to avoid such events. Specifically, genetic data will only be accessed from suicide decedents. The data is maintained on CHPC servers, which are maintained behind University of Utah firewalls. The data is only accessible to team members with approved access and credentials. The only original genetic data to be produced through this project will come from Sanger sequencing of SNP genotyping.

2. Describe the potential benefits to society AND to participants (do not include compensation):

Potential benefits are primarily to society as the research will yield new insight into how ambient air pollutants and weather variables influence the risk of suicide. Once such information is known, then it can be translated into public health actions to reduce risk, especially among the most vulnerable.

3. Are there any costs to the participants from participation in research?

○ Yes ● **No**

If yes, specify:

4. Is there any compensation to the participants?

○ Yes ● **No**

a. **If yes, answer the following:**
Specify overall amount:

b. **Specify when participants will be paid (e.g. at each visit, at end of study, etc.):**

c. **If applicable, please specify payment by visit or other time interval (e.g. $10 per visit, etc.):**

d. **If applicable, explain plan for prorating payments if participant does not complete the study:**

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7. HIPAA & the Covered Entity

7. HIPAA and the Covered Entity

1. **Does this study involve Protected Health Information (PHI) or de-identified health information?**
   ● **Yes** ○ No

   a. **Select the method(s) of authorization that will be used:**
   Waiver or Alteration of Authorization

   b. **Will PHI be disclosed outside the Covered Entity?**
   ● **Yes** ○ No

   To whom?
   Sonoma Technology

   And for what purposes?
   Sonoma Technologies may use their access to traffic, ambient air pollution, meteorological, pollen models, and contextual data to assign measures of exposure to vehicular emissions, ambient air pollutants (e.g. nitrogen dioxide, fine particulate matter, ozone), pollen, meteorological factors (e.g. solar radiation, precipitation, temperature, wet bulb temperature, relative humidity), pollen concentrations, and land use for each case and control in our study. They will use their modeling techniques to generate measures of exposure to vehicular emissions, pollen, ambient air quality, meteorological conditions, and land use measures to be used as part of the analysis of environmental contributors to suicide death. Following assignment of exposures, the data will be returned to Dr. Bakian for statistical analysis at the University of Utah. PHI (as geocoded residential histories) will be disclosed to fulfill study aims as funded by the National Institute of Environmental Health Sciences.

Does this study involve any of the following:

2. **The investigational use of a drug?**
   ○ Yes ● **No**
   Mark yes, for an expanded access application.

3. **The investigational use of a medical device or humanitarian use device?**
   ○ Yes ● **No**
   Mark yes, for an expanded access application.

4. **The investigational use of a dietary supplement, food, or cosmetic?**
   ○ Yes ● **No**

5. **Is this an investigator-initiated drug or device trial lead by the Principal Investigator'**
   ○ Yes ● **No**
   All investigator-initiated drug or device trials are required to have a full research protocol attached to the Documents and Attachments page.

6. **Will this study involve the use of an imaging modality from the department of Radiology?**
   ○ Yes ● **No**

7. **Exposure to radioisotopes or ionizing radiation?**
   ○ Yes ● **No**

8. **Genetic testing and/or analysis of genetic data?**
   ● **Yes** ○ No

9. **Creating or sending data and/or samples to a repository to be saved for future research uses?**
   ○ Yes ● **No**

10. **Are you:**
    - **Collecting samples of blood, organs or tissues from participants for research purposes;**
    - **Introducing Recombinant or Synthetic Nucleic Acids (e.g. viral vectors, oligonucleotides) or cells containing recombinant nucleic acids (e.g. CAR-T) into participants; OR**
    - **Introducing other biological materials (e.g. bacteria, viruses) into participants.**

    ○ Yes ● **No**

11. **Does this study involve any of the following?**
    - **Cancer Patients**
    - **Cancer Hypothesis**
    - **Cancer risk reduction**
    - **Cancer prevention**

    ○ Yes ● **No**

12. **Any component of the Clinical and Translational Science Institute (CTSI)?**
    ● **Yes** ○ No

    The Clinical Research Unit (CRU)?
    ○ Yes ● **No**

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- Request for Waiver of Authorization

Request for Waiver or Alteration of Authorization

Request for Waiver of Authorization for Recruitment Only

This option must only be used if you are reviewing PHI in order to identify eligible participants BEFORE approaching them to obtain consent and authorization. All other waiver requests must be entered below.

Other Requests for Waivers of Authorization:

- *Click "Add" below to add a new waiver request to this application.*
- *Click the waiver name link to edit a waiver that has already been created.*
- *To delete a waiver request, contact the IRB.*

	Date Created	Type of Request	Purpose of Waiver Request
View	8/16/2021	Waiver of Authorization	The study entails record review.

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IRB Smart Form

PI: Amanda Bakian PhD/Epidemiologist **Submitted:** 3/3/2022

Title: The influence of multiple environmental exposures on suicide risk

Request for Waiver or Alteration of Authorization

1. **Purpose of the Waiver Request:**
   The study entails record review.
2. **Type of Request:**
   Waiver of Authorization
3. **List the identifying information you plan to collect or keep a link to (e.g. names, dates, or identification numbers such as social security numbers or medical record numbers, etc).**
   Date of Death
   Geocoded residential address at time of death for suicide decedents
   Geocoded residential address around the time of death of the suicide decedent for the matched controls
4. **Explain why the *PHI* to be used or disclosed is the minimum necessary to accomplish the research objectives:**
   The research aims to further our understanding of the relationship between exposures to ambient air pollutants and weather variables and risk of suicide death. Date of death and geocoded residential address is necessary for making accurate estimates of exposure to ambient air pollution and weather.
5. **Explain why the research could not practicably be conducted without the waiver of authorization.** *For example, complete the following sentence: "If I had to obtain authorization, the research could not be conducted because..."*
   If I had to obtain authorization, the research could not be conducted because authorization can not be obtained from suicide decedents and it is not possible to receive authorization from >100,000 matched controls in the time available to conduct this study.
6. **Describe your plan to protect the identifiers from improper use and disclosure, and indicate where the *PHI* will be stored and who will have access:**
   PHI will be stored on the Center for High Performance Computing servers and Huntsman Cancer Institute servers. Both servers are behind University of Utah firewalls. Only study team members will have access to the PHI; access will not be possible without approved credentials. At Sonoma Technologies, the confidential data are encrypted, isolated, and will accessible only by the four co-investigators who are part of this study from Sonoma Technologies.
7. **The identifiers must be destroyed at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law. Describe how and when you will destroy the identifiers, or justify their retention:**
   Identifiers will only retained through the duration of the study, which is expected to last for 8 years. At the conclusion of the study, identifiers will be deleted from the datasets used in the study.
8. **Describe the measures you will take to ensure the PHI will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study,**

or for other research approved by the IRB:

The PHI will be stored on University of Utah servers (HCI and CHPC) behind University of Utah firewalls and access will only be granted to study personnel who are granted approval to access the data stored on the server. Similarly, at Sonoma Technologies, the PHI will be stored behind their firewall on an encrypted server, which is only accessible to study personnel. Ensuring the safety of the PHI and non-permittance to reuse or disclose to any other persons or entities will be discussed with study personnel on an annual basis.

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- - Information for Accounting of Disclosures

Information for Accounting of Disclosures

1. **Earliest planned date of disclosure:** 8/15/2024
2. **Latest planned date of disclosure:** 12/31/2027
3. **Name and address of the entity or person outside of the Covered Entity who will receive the Protected Health Information:**
   Fred Lurmann, Manager of Exposure Assessment Studies
   Sonoma Technology
   1450 N. McDowell Blvd
   Petaluma, CA 94954
4. **A brief description of the PHI disclosed:**
   The dataset will contain geocoded addresses, which are considered identifiable under the common rule. However, the sample size is large enough so that the geocoded addresses could describe several individuals (linked to residential location not individual).
5. **A brief statement of the purpose of the disclosure that reasonably informs the individual whose information is disclosed of the basis for the disclosure:**
   Sonoma Technologies may use their access to traffic, ambient air pollution, meteorological, pollen models, and contextual data to assign measures of exposure to vehicular emissions, ambient air pollutants (e.g. nitrogen dioxide, fine particulate matter, ozone), pollen, meteorological factors (e.g. solar radiation, precipitation, temperature, wet bulb temperature, relative humidity), pollen concentrations, and land use for each case and control in our study. They will use their modeling techniques to generate measures of exposure to vehicular emissions, pollen, ambient air quality, meteorological conditions, and land use measures to be used as part of the analysis of environmental contributors to suicide death. Following assignment of exposures, the data will be returned to Dr. Bakian for statistical analysis at the University of Utah. Disclosure is necessary to fulfill obligations of R01 funding from the NIH. Sonoma Technology is a subaward on the R01.

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- Genetic Research

PI: Amanda Bakian PhD/Epidemiologist

Submitted: 3/3/2022

Title: The influence of multiple environmental exposures on suicide risk

Genetic Research

1. **Describe the risks to participants in regard to genetic testing, including applicable risks to privacy and confidentiality, as well as psychological and social risks.**

   The genetic data derived for this study will be conducted under Hilary Coon's IRB 00044244. We will use results from the analyses conducted as part of her research (e.g. prioritized genes, variants) in Aim 3 of our study. The primary risk is breach of confidentiality and privacy. However, we feel that efforts are in place to avoid such events. Specifically, genetic data will only be accessed from suicide decedents. The data is maintained on CHPC servers, which are maintained behind University of Utah firewalls. The data is only accessible to team members with approved access and credentials. The only original genetic data to be produced through this project will come from Sanger sequencing of SNP genotyping.

2. **Describe the privacy protections in place for participants in regard to genetic testing. This includes how family member privacy will be protected.**
   Identifying details from suicide deaths and matched controls will be limited to geocoded residential address at time of death and date of death. Access to geocoded residential address at time of death will be limited to Jim VanDerslice, Marissa Taddie and Doug Tharp at the University of Utah so that they can link the locations to air pollution and weather exposures and contextual factors to examined in this study. To protect the identity of the suicides, no additional identifying information that could be used in conjunction with geocoded residential address will be maintained with the geocodes such as age at death or sex of the decedent. Geocodes and date of death will be stored on CHPC and Jim VanDerslice's GIS servers, and any data analysis will be done only on computers with password access, behind the university firewall, and with full encryption. Similarly, geocodes will be stored on encrypted servers behind firewalls at Sonoma Technologies and data will only be accessible from computers with password accessibility. No genetic data will be acquired from relatives of suicide decedents.

   Geocoded residential addresses for cases and controls along with a random selection of addresses from non-study participants will be shared with co-Investigators from Sonoma Technologies so that they can assign additional exposure measures to the suicide deaths and matched controls. When PII is sent to Sonoma Technology, it agrees to comply with the requirements of 45 C.F.R. Parts 160 and 164, which is the Privacy Rule of the Health Insurance Portability and Accountability Act of 1996 ("HIPAA Privacy Rule"). The confidential data are encrypted, isolated, and will accessible only by the four individuals being added to the study as part of this amendment. These individuals have completed CITI training and have signed UPDB confidentiality agreements. They have been provided PHI for numerous other studies. Some of these a listed in the supplemental documentation ("Sonoma Tech collaborations").

3. **Are you performing whole genome or whole exome sequencing?**
   ○ Yes ● **No**

4. **Describe the confidentiality protections in place for participants' genetic information. Discuss if and how data will be shared and protected outside the local study team.**
   Only aggregate data will shared outside the study team. Genetic data will only be derived from suicide decedents and not from living subjects.

5. **Will incidental findings relevant to individuals or families be communicated to the participants?**
   ○ Yes ● **No**
   If yes, answer the questions below:

   a. **Describe the process for determining which incidental findings will be returned to the participants. Describe the information and expert consultation that will be used to make this determination.**

   b. **Indicate the process that will be used to return information about incidental finding to participants:**
   There are no items to display
   If Other, describe and justify the process that will be used:

6. **Will genetic information or samples be submitted to a national or international database because of this research?**

● **Yes**
○ No

Indicate all databases with which the genetic information will be shared.

Database Short Name	Name
dbGaP	NCBI - Database of Genotype and Phenotype

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8. Resources and Responsibilities

8. Resources and Responsibilities

1. * **State and justify the qualifications of the study staff:**

Amanda V. Bakian, PhD is an Associate Professor in the Department of Psychiatry and Huntsman Mental Health Institute at the University of Utah and will oversee all aspects of the project. She has expertise in study design, statistics, epidemiology, and ecology and has been applying these expertise to investigate environmental contributors to suicide for more than six years.

Hilary Coon, PhD is a Professor in the Department of Psychiatry at the University of Utah and Director of the Utah Suicide Genetics Research Study. Her expertise are in genetic epidemiology, and she has spent much of her career looking for genetic risk factors associated with suicide and autism spectrum disorder using family and population-based approaches. Dr. Coon will work with Drs. Docherty and Bakian to prioritize genes for gene-environment interaction follow up. Further, she will assist with designing and supervising the analysis of gene-environment interactions for suicide in Aim 3. Dr. Coon will also help with manuscript preparation and dissemination of results.

Anna Docherty, PhD is is an Assistant Professor in the Department of Psychiatry at the University of Utah whose work focuses on psychiatric genomics and methods development. Dr. Docherty is affiliated with the Virginia Institute for Psychiatric and Behavioral Genetics (VIPBG) and she contributes to the analysis of Psychiatric Genomics Consortium (PGC) data within the Schizophrenia Working Group. She has ten years of experience in psychiatric genomics and bioinformatics, receiving NIMH and NARSAD grants and early career awards for this work, and more than 10 years of experience in neuropsychiatry and psychiatric nosology. Dr. Docherty will provide gene findings from her ongoing genome-wide association studies of suicide death, assist with the gene by environment analyses and provide input on study design, consult on issues relating to clinical/psychiatric phenotyping and nosology, and assist with the preparation and writing of manuscripts.

Yue Zhang, PhD is an Associate Professor in the Division of Epidemiology, Department of Internal Medicine at the University of Utah and a member of the University of Utah's Study Design and Biostatistics Center. Dr. Zhang is a biostatistician with research and method development interests in Bayesian and causal inference, clustered and longitudinal data analysis, and air pollution epidemiology. Dr. Zhang will assist with study design, Bayesian model formulation and other statistical issues, and the analysis of gene by environment interactions.

James VanDerslice, PhD is a Professor in the Division of Public Health, Department of Family and Preventive Medicine at the University of Utah. Dr. VanDerslice is an environmental scientist with a background in environmental engineering whose research focuses on evaluating human exposures to chemical and microbiological hazards in the environment. Dr. VanDerslice will work with Dr. Mendoza to develop Wasatch Front specific ambient air pollution exposure models whose performance will be compared with the National hybrid model's, provide input into study design, oversee the calculation of the LEADS data, and contribute to the drafting of presentations and manuscripts.

Daniel Mendoza, PhD is an Assistant Professor in the Department of Atmospheric Sciences. Dr. Mendoza's expertise are air pollution exposure assessment and geographic information science (GIS) and he has played a central role in the development of the Hestia high resolution approach to model criteria pollutants in urban areas. Dr. Mendoza help manage the ambient air pollution and weather exposure assessment data. Dr. Mendoza will also be responsible for GIS activities and will assist with study design and the preparation of presentations and manuscripts.

DougTharp is a doctoral student in the Department of Geography and a Research Associate in the Department of Psychiatry. He will assist with the acquisition of contextual risk factors, assist with data management and analysis.

Danli Chen, MS has a Bachelor of Science degree in Computer Science and a Master of Science degree in Statistics. Ms. Chen has experience in the management of large datasets and is currently working with the Utah Suicide Genetics Research Study. She will maintain all phenotypic data from the OME, UPDB, and Utah NVDRS and will assist in the calculation of the LEADS data. She will provide QC and descriptive analyses of the demographic, clinical and familial data. Under the direction of Drs. Bakian, Zhang

and Docherty she assist with the data analysis for all three Aims. She will also assist with manuscript preparation and disseminating results.

Emily Sullivan, MS, MPH, is a Program Manager for the Utah Suicide Genetics Research Study in the Department of Psychiatry and Huntsman Mental Health Institute. Her expertise is in public health, implementation science and project performance. Ms. Sullivan will assist with team communication, data acquisition, and project direction.

Marissa Taddie, MS is a geographical information scientist in the Department of Family and Preventive Medicine. She will assist with the acquisition of spatially explicit data in a GIS framework and will work with Drs. VanDerslice and Mendoza.

Linda Amoafo, MS is a doctoral student in the Department of Population of Health Sciences pursuing a PhD in biostatistics. She will work with Dr. Zhang in the formulation of multiple exposure models.

Michael Torre, PhD is a biostatistician with the CTSI's Study Design and Biostatistics Center. He has expertise in spatial analysis and machine learning. He will assist with data cleaning, management, and the formulation of exposure assessment models.

David Crockett (Director of the Intermountain Healthcare Biorepository), is the Intermountain Healthcare PI as listed on Dr. Hilary Coon's University of Utah IRB 00044244 as well as Dr. Coon's Intermountain Healthcare IRB 1024977. He is leading a team of IH colleagues on IRB 00044244, which supports data acquisition for that IRB.

Mr. Ken Pena is the honest broker to access Intermountain Healthcare data under IRB and Intermountain Healthcare IRB 1024977. The honest broker pulls records with ICD9/ICD10 codes for transfer to the UPDB with the IH Linkage ID used by the UPDB.

Joel Schwartz, PhD is a Professor of Environmental Epidemiology at the Department of Environmental Health and the Department of Epidemiology, and Co-Director of the Harvard Center for Risk Analysis at the Harvard T.H. Chan School of Public Health. Dr. Schwartz will supervise a postdoc who will update his exposure models for daily PM2.5, O3, and NO2 on a 1km resolution for the U.S., which will be used for the participants in this study. Dr. Schwartz will also provide study design input and advice on using the exposure data. He will receive aggregated data only for this study.

Fred Lurmann, MS is an engineer and Manager of Exposure Assessment Studies at Sonoma Technology, Inc. He has been involved with collection, management, and analysis of data for the assessment of exposure to air pollution for 40 years. He will oversee all work performed at STI for this study, including the air pollution and meteorological assignments and manuscript preparation. He will receive aggregated data only for this study.

Nathan Pavlovic, MS, is the Lead Geospatial Data Scientist at Sonoma Technology, Inc. He specializes in geographic information systems (GIS), data analysis, and fire science and conducts analyses related to air pollution impact assessments and wildland fires. He will be conducting analysis of data related to air pollution and meteorological exposure. He will receive aggregated data only for this study.

Dirga Lamichhane, PhD, is a Postdoctoral Fellow in Dr. Bakian's lab. He has expertise in air pollution epidemiology, and will lead, design and analyze some of substudies described in this IRB application. He will work with data provided from the OME and UPDB and will have access to data with identifiers.

Melissa Chaveste, BS, is an Atmospheric Scientist at Sonoma Technologies. Ms. Chaveste will apply her expertise in near-road air pollution exposure assessment to assign near road air pollution and related exposures to suicide deaths and their matched controls based on their residential locations.

Tyler Fenske, MS, is an Air Quality Scientist at Sonoma Technologies. Mr. Fenske will apply his expertise in Python programming and atmospheric sciences to assist with the assignment of air pollution, pollen, and context exposures to suicide deaths and their matched controls based on their residential locations.

Tess DeAtley, PhD, is a social and behavioral scientist and member of the Utah Suicide Mortality Risk Study. She has expertise in study design and analysis, and will be investigating the influence of nicotine exposure on suicide.

Md. Imdadul Haque, is a graduate research assistant in the Department of Family and Preventive Medicine. He will assist with some analysis, which will provide him with training opportunities in psychiatric epidemiology.

Brandy Hill, PhD is a Postdoctoral Fellow at the Huntsman Cancer Institute and the Huntsman Mental Health Institute with expertise in air pollution epidemiology. She will be investigating the association between hair cortisol levels in suicide decedents and residential location.

Mert Karatas, MD, is a research associate who is interested in gaining expertise in epidemiology. He will support analyses related to prescription patterns in suicide deaths versus controls.

Nicolas Nunez, MD, is research-track psychiatry resident in HMHI with clinical and research expertise in suicide. He is interested in investigator environmental risk trajectories for suicide death.

Deanna Wall, MHA, is a clinical research coordinator at HMHI. She has expertise in project management and administration. She will assist with team management, publication preparation, and administration.

Kailey Mahoney, is a graduate research assistant in the Department of Family and Preventive Medicine. She has expertise in public health and geography. She will assist with the development of heat exposure metrics.

2. * **Describe the training that study staff and investigators will receive in order to be informed about the protocol and understand their research-related duties and functions:**

   All study investigators have received the grant proposal that was funded for this project. The team will be organized into smaller groups based on their role on the project including an analysis group, an air quality/weather exposure group, and a genetics group. While the larger study team will meet every other week, the smaller teams will meet every month to discuss the study protocol and research-related duties and functions. We will also use Microsoft Teams to help improve communication.

3. * **Describe the facilities where the research activities will be performed (e.g. hospitals, clinics, laboratories, classrooms/schools, offices, tissue banks, etc.).**

   As the study involves secondary data analysis, all work/analyses will be conducted on computers either in offices at the University of Utah or home offices for University of Utah investigators or in offices at Sonoma Technology. Office spaces are located primarily in research park. At the University of Utah, data will be stored on CHPC, HCI, and RedCap servers and will accessed remotely. At Sonoma Technology, offices are located at 1450 N. McDowell Blvd, Suite 200, Petaluma, California and data will be stored on servers at Sonoma Technology's Petaluma Data Center. A data transfer agreement is in progress and no data will be shared until it is fully executed.

   External Collaborators:

   David Crockett (Director of the Intermountain Healthcare Biorepository), is the Intermountain Healthcare PI as listed on Dr. Hilary Coon's University of Utah IRB 00044244 as well as Dr. Coon's Intermountain Healthcare IRB 1024977. He is leading a team of IH colleagues on IRB 00044244, which supports data acquisition for that IRB.

   Joel Schwartz, PhD is a Professor of Environmental Epidemiology at the Department of Environmental Health and the Department of Epidemiology, and Co-Director of the Harvard Center for Risk Analysis at the Harvard T.H. Chan School of Public Health. Dr. Schwartz will supervise a postdoc who will update his exposure models for daily PM2.5, O3, and NO2 on a 1km resolution for the U.S., which will be used for the participants in this study. Dr. Schwartz will also provide study design input and advice on using the exposure data. He will receive aggregated data only for this study.

   Fred Lurmann, MS is an engineer and Manager of Exposure Assessment Studies at Sonoma Technology, Inc. He has been involved with collection, management, and analysis of data for the assessment of exposure to air pollution for 40 years. He will oversee all work performed at STI for this study by Nathan Pavlovic, Melissa Chaveste, and Tyler Fenske, including the air pollution and meteorological assignments and manuscript preparation. Sonoma Technology will be provided residential addresses/histories, which will be stored behind their firewalls on encrypted servers. Sonoma technology team members will access the data from password protected computers in their company offices.

4. * **Describe the medical or psychological resources available at this site (and other participating sites, if applicable) that participants might require as a consequence of the research. If not applicable, please state.**

   Not applicable as research involves secondary data analysis.

IRB_00144804

Created: 6/25/2021 2:55 PM

IRB_00144804
Documents and Attachments

PI: Amanda Bakian PhD/Epidemiologist

Submitted: 3/3/2022

Title: The influence of multiple environmental exposures on suicide risk

Documents and Attachments

If any of your documents (such as investigational brochures, sponsor protocols, advertisements, etc.) are not available in an electronic format, please scan and save them as PDF files or contact our office for assistance.

Naming Documents: Please use the title field to clearly indicate the content of each form. The name you enter will be listed on your approval letter. Use names that will differentiate from earlier versions.

Examples:
Consent Document Control Group 04/14/05
Consent Document Treatment Group 4/14/05
Sponsor Protocol 04/14/05 Version 2
Assent Document(Highlighted Changes)

Apple/Macintosh Users:MS Word documents must have a .doc file extension. See ERICA home page for instructions.

Print View: IRB Draft Protocol Summary

eProtocol Summary:

Name	Version	Date Created	Date Modified	Date Approved
There are no items to display				

Consent Documents, Consent Cover Letters, Consent Information Sheets, Consent Scripts, etc.:

Name	Version	Date Created	Date Modified	Date Approved
There are no items to display				

Parental Permission Documents:

Name	Version	Date Created	Date Modified	Date Approved
There are no items to display				

Assent Documents:

Name	Version	Date Created	Date Modified	Date Approved
There are no items to display				

VA Consent Documents:

Name	Version	Date Created	Date Modified	Date Approved
There are no items to display				

Surveys, Questionnaires, Interview Scripts, etc.:

Name	Version	Date Created	Date Modified	Date Approved
There are no items to display				

Full Protocol (company protocol, sponsor protocol, investigator-initiated protocol, etc.):

Name	Version	Date Created	Date Modified	Date Approved
There are no items to display				

Investigational Brochure (IB) for Investigational Drug or Drug/Device Package Insert:

Name	Version	Date Created	Date Modified	Date Approved

There are no items to display

Grant Application:

The Federal Government is a direct or indirect sponsor of your research. You are required to provide a copy of the grant proposal, grant award, or sub-award.

By submitting to the IRB, you are confirming the grant and the study protocol are consistent (Design, Study Population, Study Objectives and Goals, Test Interventions and Procedures, etc.)

Name	Version	Date Created	Date Modified	Date Approved

There are no items to display

Literature Cited/References:

Name	Version	Date Created	Date Modified	Date Approved

There are no items to display

Principal Investigator's Scholarly Record (CV/Resume):

Name	Version	Date Created	Date Modified	Date Approved
Bakian_CV_March2022(0.05)	0.05	10/29/2014 4:58 PM	7/1/2022 10:57 AM	
Bilder CV(0.01)	0.01	7/8/2022 2:26 PM	7/8/2022 2:26 PM	

Faculty Sponsor's Scholarly Record (CV/Resume):

Name	Version	Date Created	Date Modified	Date Approved

There are no items to display

Other Stamped Documents:

Name	Version	Date Created	Date Modified	Date Approved

There are no items to display

Recruitment Materials, Advertisements, etc.:

Name	Version	Date Created	Date Modified	Date Approved

There are no items to display

Other Documents:

Name	Version	Date Created	Date Modified	Date Approved

There are no items to display

IRB_00144804

Created: 6/25/2021 2:55 PM

IRB_00144804
Ancillary Applications

PI: Amanda Bakian PhD/Epidemiologist

Submitted: 3/3/2022

Title: The influence of multiple environmental exposures on suicide risk

Ancillary Application

This page should be used for submitting human research applications to the following ancillary committees:

Resource for Genetic and Epidemiologic Research (RGE) for access to the Utah Population Database (UPDB) and Utah Cancer Registry (UCR)
Phone: 801-581-6351
Website: https://rge.utah.edu/

Radiological Drug Research Committee Human Use Subcommittee (RDRC-HUS)
Phone: 801-581-6141
HUS Website: https://rso.utah.edu/committees/hus-rsc.php
RDRC Website: https://rso.utah.edu/committees/rdrc.php

Institutional Biosafety Committee (IBC)
Phone: 801-581-6590
Website: https://ibc.utah.edu

	ID	Name	Status
●	RGE_00005295	The influence of multiple environmental exposures on suicide risk	RGE Approved

IRB_00144804 **Created:** 6/25/2021 2:55 PM **IRB_00144804** Finish

PI: Amanda Bakian PhD/Epidemiologist **Submitted:** 3/3/2022

Title: The influence of multiple environmental exposures on suicide risk

Finish Instructions

Finish Instructions

1. **To view errors, select the "Validate" option at the top-left of the page. If you have errors on your application, you won't be able to submit it to the IRB.**
2. **Selecting the Finish button will NOT submit the application to the IRB.**
   You MUST select the "Submit" option on the workspace once you've selected the "Finish" button.
3. **If your study has a faculty sponsor: Once the PI submits the application, it will be sent to the faculty sponsor for final approval. The IRB cannot review the study until the faculty sponsor submits the application to the IRB.**