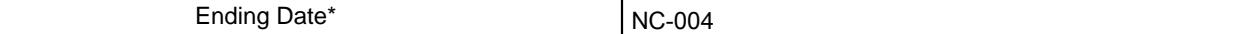


| | | |
|--|--|--|
| PI: Von Holle, Ann | Title: Lifestyle change over time and postmenopausal risk of breast cancer | |
| Received: 06/10/2021 | FOA: PA20-188 | Council: 01/2022 |
| Competition ID: FORMS-F | FOA Title: NIH Pathway to Independence Award (Parent K99/R00 Independent Clinical Trial Not Allowed) | |
| 1 K99 AG076809-01 | Dual: CA,ES | Accession Number: 4590056 |
| IPF: 485439 | Organization: U.S. NATIONAL INST OF ENVIRON HLTH SCIS | |
| Former Number: | Department: Office of the Sci. Director | |
| IRG/SRG: AGCD-1 | AIDS: N | Expedited: N |
| <u>Subtotal Direct Costs</u> <u>(excludes consortium F&A)</u> | Animals: N Humans: N Clinical Trial: N Current HS Code: 10 HESC: N HFT: N | New Investigator: Early Stage Investigator: |
| Year 1: 100,000 | | |
| Year 2: 100,000 | | |
| Year 3: 150,000 | | |
| Year 4: 150,000 | | |
| Year 5: 150,000 | | |
| <hr/> | | |
| <i>Senior/Key Personnel:</i> | <i>Organization:</i> | <i>Role Category:</i> |
| [REDACTED] | National Institute of Environmental Health Sciences, NIH | PD/PI |
| [REDACTED] | National Institute of Environmental Health Sciences | Other Professional-Mentor |
| [REDACTED] | NIEHS | Other Professional-Co-mentor |
| [REDACTED] | Columbia University | Other Professional-Advisor |
| [REDACTED] | NIEHS | Other Professional-Advisor |
| [REDACTED] | University of North Carolina, Chapel Hill | Other Professional-Advisor |

Reference Letters

| | | |
|------------|---|------------|
| [REDACTED] | UNC | 06/10/2021 |
| [REDACTED] | University of California, San Diego | 06/10/2021 |
| [REDACTED] | UNC - Chapel Hill | 06/10/2021 |
| [REDACTED] | National Institute of Environmental Health Sciences | 06/10/2021 |

**APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)**

| | | | |
|--|--|--|------------------------------|
| APPLICATION FOR FEDERAL ASSISTANCE SF 424 (R&R) | | 3. DATE RECEIVED BY STATE | State Application Identifier |
| 1. TYPE OF SUBMISSION* | | 4.a. Federal Identifier | |
| <input type="radio"/> Pre-application <input checked="" type="radio"/> Application <input type="radio"/> Changed/Corrected Application | | b. Agency Routing Number | |
| 2. DATE SUBMITTED | Application Identifier | c. Previous Grants.gov Tracking Number | |
| 5. APPLICANT INFORMATION | | Organizational DUNS*: 0400348600000 | |
| Legal Name*: | National Institute of Environmental Health Sciences, NIH | | |
| Department: | Office of the Sci. Director | | |
| Division: | Div. of Intramural Research | | |
| Street1*: | 111 T.W. Alexander Drive | | |
| Street2: | Box 12233 | | |
| City*: | Research Triangle Park | | |
| County: | Durham | | |
| State*: | NC: North Carolina | | |
| Province: | | | |
| Country*: | USA: UNITED STATES | | |
| ZIP / Postal Code*: | 27709-2233 | | |
| Person to be contacted on matters involving this application | | | |
|  | | | |
| 6. EMPLOYER IDENTIFICATION NUMBER (EIN) or (TIN)* | | 520858115 | |
| 7. TYPE OF APPLICANT* | | X: Other (specify) | |
| Other (Specify): Federal Laboratory (NIH) | | | |
| Small Business Organization Type | | <input type="radio"/> Women Owned <input type="radio"/> Socially and Economically Disadvantaged | |
| 8. TYPE OF APPLICATION* | | If Revision, mark appropriate box(es). | |
| <input checked="" type="radio"/> New <input type="radio"/> Resubmission | | <input type="radio"/> A. Increase Award <input type="radio"/> B. Decrease Award <input type="radio"/> C. Increase Duration | |
| <input type="radio"/> Renewal <input type="radio"/> Continuation <input type="radio"/> Revision | | <input type="radio"/> D. Decrease Duration <input type="radio"/> E. Other (specify): | |
| Is this application being submitted to other agencies?* | | <input type="radio"/> Yes <input checked="" type="radio"/> No What other Agencies? | |
| 9. NAME OF FEDERAL AGENCY* National Institutes of Health | | 10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER TITLE: | |
| 11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT* Lifestyle change over time and postmenopausal risk of breast cancer | | | |
| 12. PROPOSED PROJECT | | 13. CONGRESSIONAL DISTRICTS OF APPLICANT | |
| Start Date*  | | Ending Date*  | |
| | | NC-004 | |

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

Page 2

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

| | | | | | | |
|-----------|------------|------------|------------|------------|------------|------------|
| Prefix: | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| Province: | | | | | | |
| Country*: | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |

15. ESTIMATED PROJECT FUNDING

| | | |
|---------------------------------------|--------------|--|
| a. Total Federal Funds Requested* | \$747,000.00 | 16. IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?* |
| b. Total Non-Federal Funds* | \$0.00 | a. YES <input type="radio"/> THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON: |
| c. Total Federal & Non-Federal Funds* | \$747,000.00 | DATE: |
| d. Estimated Program Income* | \$0.00 | b. NO <input checked="" type="radio"/> PROGRAM IS NOT COVERED BY E.O. 12372; OR <input type="radio"/> PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW |

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

I agree*

* The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION

File Name:

19. AUTHORIZED REPRESENTATIVE

| | | | | | | |
|--|------------|------------|------------|------------|------------|------------|
| Prefix: | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| APPLICATION | File Name: | | | | | |
| 21. COVER LETTER ATTACHMENT File Name:1248-cover_letter.pdf | | | | | | |

424 R&R and PHS-398 Specific

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Project/Performance Site Location(s)

Project/Performance Site Primary Location

I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: National Institute of Environmental Health Sciences, NIH
Duns Number: 0400348600000
Street1*: 111 T.W. Alexander Drive
Street2: Box 12233
City*: Research Triangle Park
County: Durham
State*: NC: North Carolina
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 27709-2233
Project/Performance Site Congressional District*: NC-004

Additional Location(s)

File Name:

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* Yes No

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? Yes NoIf YES, check appropriate exemption number: 1 2 3 4 5 6 7 8If NO, is the IRB review Pending? Yes No

IRB Approval Date:

Human Subject Assurance Number

2. Are Vertebrate Animals Used?* Yes No

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? Yes No

IACUC Approval Date:

Animal Welfare Assurance Number

3. Is proprietary/privileged information included in the application?* Yes No**4.a. Does this project have an actual or potential impact - positive or negative - on the environment?*** Yes No

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed?

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place?* Yes No

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* Yes No

6.a. If yes, identify countries:

6.b. Optional Explanation:

Filename

7. Project Summary/Abstract* 1243-summary.pdf**8. Project Narrative*** 1244-Narrative.pdf**9. Bibliography & References Cited** 1245-references.pdf**10. Facilities & Other Resources** 1246-Facilities and Other Resources Summary.pdf**11. Equipment** 1247-Equipment.pdf

Project Summary/Abstract

Modifiable lifestyle characteristics are among the leading causes of mortality and health outcomes such as breast cancer. Women in the United States have a one in eight chance of being diagnosed with breast cancer in their lifetime, and one out of five postmenopausal breast cancer cases could be eliminated following lifestyle modification. Furthermore, lifestyle characteristics tend to co-occur in individuals. Despite the importance of these characteristics in health prevention research, few studies examine more than one of these measures at a time. Compounding this research gap is the lack of longitudinal evidence for these factors for an aging population, which can inform prevention studies targeting modifiable lifestyle characteristics. In this proposal, I will examine multiple modifiable lifestyle characteristics, including body fatness, alcohol use, exercise, and smoking as they relate to postmenopausal breast cancer outcomes and all-cause mortality. Unlike prior studies, I will examine them simultaneously and longitudinally in a contemporary prospective cohort of 50,884 women sampled throughout the United States with a median age of 56 years at study entry. This rich data resource, along with the novel application of methods to epidemiological research aims, allows me to capture a comprehensive, dynamic, and granular picture of the relationship between lifestyle change with risk of breast cancer and all-cause mortality. First, I will first characterize a group of correlated lifestyle characteristics using factor analysis and assess the composite lifestyle factor change over a decade (Aim 1, K99). To complement this first aim, I will use this opportunity to obtain additional training in areas such as physical activity and obesity epidemiology, aging, and methods development. This training will enhance my knowledge of lifestyle-related exposures and inform the development of all three of my research aims. After characterizing a composite lifestyle factor, I will capture tandem associations between lifestyle factor changes over time with risk of breast cancer and all-cause mortality using newly developed joint analysis models (Aim 2, R00). In the third aim, I will determine to what extent people carrying the highest burden of adverse lifestyle characteristics have greater genetic risk of breast cancer compared to groups with the lowest adverse lifestyle burden (Aim 3, R00). In completing these novel research aims, I will develop a more comprehensive picture of the association between lifestyle change over time with the risk of breast cancer and all-cause mortality. By applying these concepts to a large sample of postmenopausal women, this knowledge has the potential to inform widely applicable areas of public health interventions to improve the health of an aging population.

Project Narrative

Modifiable lifestyle characteristics number among the top ten attributable causes of all-cause mortality and also offer some of the greatest potential to reduce cancer incidence. Current research lacks large-scale evidence for lifestyle change over time and its association with disease specific to women following menopause. Determining how lifestyle characteristics form a correlated measure, change over time, and are related to risk of breast cancer and all-cause mortality could inform intervention policies targeted at postmenopausal women.

REFERENCES

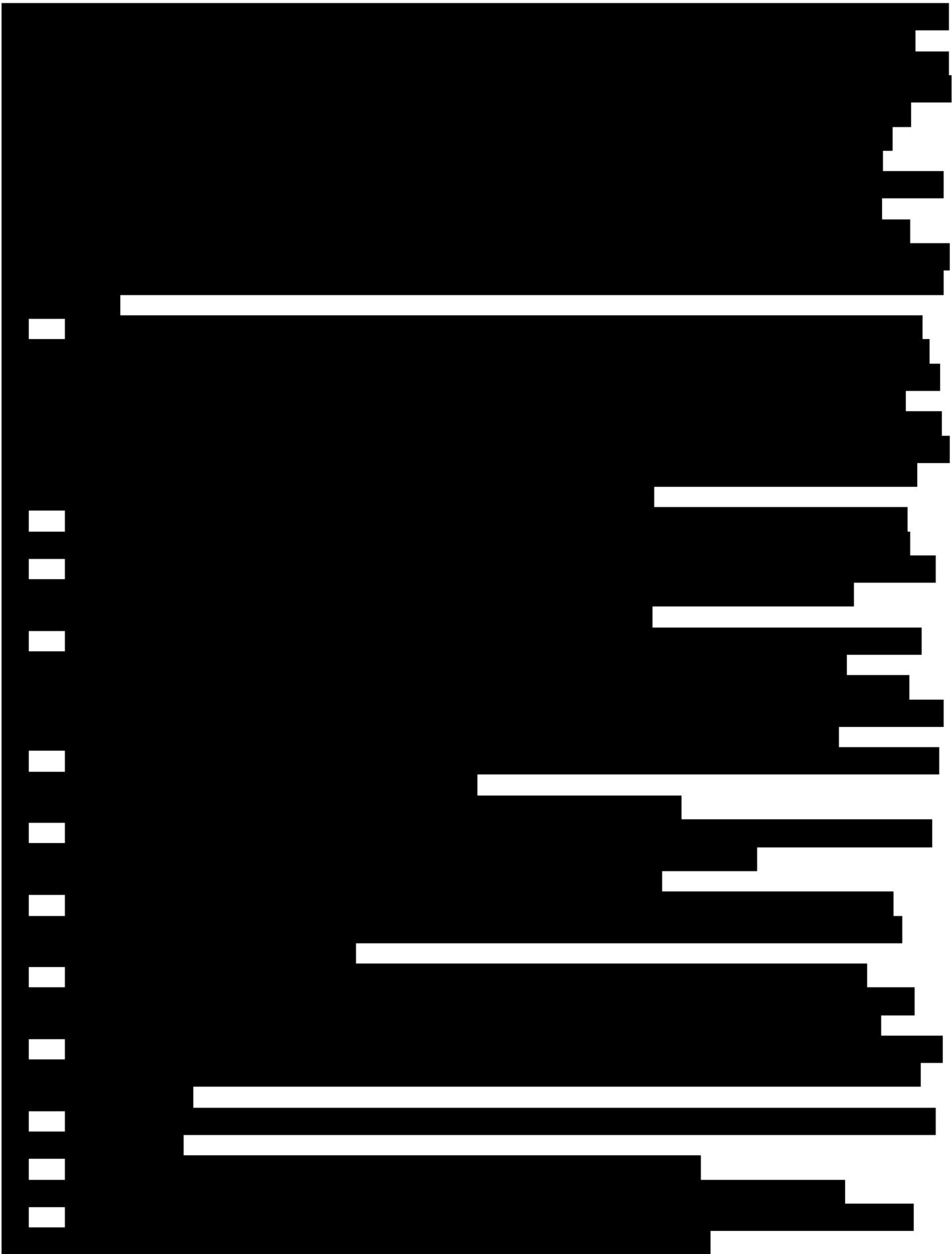
- A bar chart illustrating the distribution of values across 12 categories. The x-axis represents the value range from 0 to 100, and the y-axis represents the categories. The bars are stacked, with the total height of each bar representing the sum of values for that category. Category 1 has the highest total value, followed by Category 2, and so on down to Category 12.

| Category | Value Range (approx.) | Total Value (approx.) |
|----------|-----------------------|-----------------------|
| 1. | 0-10 | 100 |
| 2. | 10-20 | 95 |
| 3. | 20-30 | 90 |
| 4. | 30-40 | 85 |
| 5. | 40-50 | 80 |
| 6. | 50-60 | 75 |
| 7. | 60-70 | 70 |
| 8. | 70-80 | 65 |
| 9. | 80-90 | 60 |
| 10. | 90-100 | 55 |
| 11. | 100-110 | 50 |
| 12. | 110-120 | 45 |



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Facilities and Other Resources Summary

National Institute of Environmental Health Sciences (NIEHS)

During the mentored K99 phase of the award, Dr. Von Holle will have access to a wide array of facilities and resources relevant to her research aims and career development and training goals. Dr. Von Holle is currently an Intramural Research Trainee Award postdoctoral fellow at NIEHS, and this will be the primary point from which she will access the resources listed below.

Biostatistics and Computation Biology Branch (BCBB)

Within the BCBB, Dr. Von Holle has access to researchers working on a wide range of research related to her proposed aims, including time-to-event analyses, genetic epidemiology, and cancer outcomes. This collaborative environment is an excellent place for Dr. Von Holle to launch her K99 mentored phase. The branch also has frequent seminars in which she can participate and informal lunch sessions to discuss analytic issues in an informal environment.

Epidemiology Branch

The Epidemiology Branch offers a complement to the BCBB with eight research groups with different focus areas including genetic, reproductive, and chronic disease epidemiology. Like the BCBB, researchers create a collaborative environment that fosters innovative research. Dr. Von Holle can participate in their numerous seminars within the branch as well as present her work at in-house meeting designed to enhance the quality of research.

Library and Information Services

The NIEHS library, acting in concert with the NIH library, has a full staff dedicated that partners with researchers when accessing information needed to develop their research. Dr. Von Holle will also use their extensive resources for access to journals, books and other documents related to her research aims and career development goals.

Office of Scientific Computing

This group within NIEHS offers support for high performance computing, which Dr. Von Holle will use to accomplish the analyses described in her research plan in addition to support for software use on these platforms.

Office of Fellows' Career Development (OFCD)

The mission of the OFCD is to support fellows during their time at NIEHS so they can advance their professional skills and career development goals. Dr. Von Holle will continue to use the services offered by this office in her K99 mentoring phase so she can advance her management skills as outlined in her training plan. She can also take advantage of their many training workshops that they offer to foster her communication, grant writing, and mentoring skills.

Local Institutes External to NIEHS

The Research Triangle Park area is close to the three largest Tier 1 universities in North Carolina: University of North Carolina, Chapel Hill; Duke University; and North Carolina State University. All of these universities offer many diverse opportunities to attend lectures, workshops, and potential collaborations to enhance Dr. Von Holle's research aims, career goals, and training plans.

Facilities that serve the Sister Study, the data source for the proposed study

Social & Scientific Systems (SSS)

This contract organization is essential for all aspects of the ongoing Sister Study project operations under the leadership of [REDACTED] in the Epidemiology Branch ranging from sample collection to full data management services. As a full service contract organization, SSS is the backbone for the Sister Study data and program management. In their role as the contractor for the Sister Study, they will ensure that Dr. Von Holle receives the de-identified data sets to carry out all three of her K99/R00 aims.

Equipment

Biostatistics and Computational Biology Branch (BCBB), National Institute of Environmental Health Sciences

Dr. Von Holle is a postdoctoral fellow at the BCBB, and she will continue to have access to resources that will assist her in completing her research aims during the mentored K99 phase of her work. As a postdoctoral fellow, she has a personal computer with the necessary software to conduct her analyses, write her manuscripts and communicate with her colleagues. At the NIEHS physical location, Ann has an office with a telephone and high-speed internet access. NIEHS also provides the means for Dr. Von Holle to remotely connect to her work-related resources in a secure manner. Furthermore, within BCBB, Dr. Von Holle has unlimited access to the NIEHS computing clusters and the Mplus Software for high-performance analyses that she will need to complete analyses for her three aims.

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

| PROFILE - Project Director/Principal Investigator | |
|---|------------------------------|
| Prefix: Dr. | First Name*: [REDACTED] |
| [REDACTED] | |
| [REDACTED] | |
| [REDACTED] | |
| [REDACTED] | |
| Phone Number*: | Fax Number: |
| E-Mail*: | [REDACTED] |
| .g., agency login: [REDACTED] | |
| Project Role*: PD/PI | Other Project Role Category: |
| Degree Type: Ph.D. | Degree Year: 2018 |
| Attach Biographical Sketch*: | File Name: [REDACTED] |
| Attach Current & Pending Support: | File Name: [REDACTED] |

PROFILE - Senior/Key Person

Prefix:

This section contains a large amount of redacted information. At the top left, the word "Prefix:" is visible followed by several blacked-out fields. Below this, there are approximately ten horizontal lines, each consisting of a short black bar on the left, a longer black bar in the center, and a short black bar on the right.

This section contains a large amount of redacted information. At the top left, there are several blacked-out fields. Below this, there are approximately ten horizontal lines, each consisting of a short black bar on the left, a longer black bar in the center, and a short black bar on the right.

PROFILE - Senior/Key Person

The figure displays a collection of black rectangular blocks on a white background. A prominent feature on the left is a large, abstract shape resembling the letter 'E', constructed from numerous small black rectangles. To the right of this, there are several horizontal rows of black bars. These bars vary in length and position, creating a sense of organized complexity. The overall composition is minimalist yet intricate, with the black elements forming a clear contrast against the white space.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Von Holle, Ann

eRA COMMONS USER NAME (credential, e.g., agency login): A [REDACTED]

POSITION TITLE: Intramural Research Trainee Award Postdoctoral Fellow

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

| INSTITUTION AND LOCATION | DEGREE (if applicable) | END DATE MM/YYYY | FIELD OF STUDY |
|---|---------------------------|------------------------|-------------------------|
| University of California, San Diego, San Diego, CA | BA | 06/1993 | Applied Mathematics |
| Johns Hopkins School of Public Health, Baltimore, Maryland | MHS | 05/1995 | Population Dynamics |
| University of North Carolina, Chapel Hill, North Carolina | MS | 05/2003 | Biostatistics |
| University of Pennsylvania, Philadelphia, PA | MA | 05/2005 | Demography |
| University of North Carolina, Chapel Hill, Chapel Hill, NC | PHD | 06/2018 | Epidemiology |
| National Institute of Environmental Health Sciences, Research Triangle Park, NC | Postdoctoral Fellow | present | Epidemiological methods |

A. Personal Statement

My long-term career goals are to investigate modifiable risk factors of postmenopausal women as they relate to breast cancer prevention and mortality reduction. My past work as a biostatistician and more recent training in epidemiology motivated my proposed aims and further training to achieve my goals. Prior to my doctoral training in epidemiology, I was able to learn new analytical skills when applying them to population health studies. During this time I furthered my knowledge and applications of structural equation modeling. I took that knowledge and transformed that as a doctoral student preparing my dissertation to focus on longitudinal patterns of infant anthropometric growth and their associations with lipids commonly used as biomarkers for cardiovascular disease. Among our findings, we discovered that lower socioeconomic position is associated with adverse growth characteristics, and faster growth in early infancy is associated with a favorable profile. As a postdoctoral fellow at the National Institute of Environmental Health Sciences in the past three years, I have continued working with biomarkers with an emphasis on time-to-event analyses to investigate breast cancer incidence outcomes and their association with iron biomarkers. In a recent publication, we found little evidence of an association between breast cancer and markers of circulating and stored iron, but a possible protective relationship with very low iron levels. While starting my postdoctoral work, I also completed an analysis that found a relative increase in risk as a woman nears the age of her sibling's breast cancer diagnosis, i.e. correlated timing of onset within families. In conducting studies of breast cancer incidence outcomes with time-to-event methods during my postdoctoral fellowship, accompanied by the focus on the relationship between longitudinal anthropometric measures and chronic disease biomarkers, I will be well positioned to enter a new phase of research and study the role of lifestyle risk factors in the occurrence of breast cancer and all-cause mortality. This proposed K99/R00 research focuses on lifestyle risk factors that are associated with chronic disease, mortality, and postmenopausal breast cancer risk, providing a unique platform upon which I can expand my research expertise while meaningfully contributing to public health. The additional training in advanced joint modeling techniques and in-depth knowledge of the epidemiologic study of lifestyle factors creates a path for me to successfully complete the proposed research and move toward an overarching goal to inform public health prevention measures to reduce breast cancer incidence and mortality.

1. Von Holle A, O'Brien KM, Sandler DP, Weinberg CR. Evidence for familial clustering in breast cancer age of onset. *Int J Epidemiol*. 2021 Mar 3;50(1):97-104. PubMed Central PMCID: PMC7938508.

2. Von Holle A, O'Brien KM, Sandler DP, Janicek R, Weinberg CR. Association Between Serum Iron Biomarkers and Breast Cancer. *Cancer Epidemiol Biomarkers Prev.* 2021 Feb;30(2):422-425. PubMed Central PMCID: PMC7867615.
3. Von Holle A, North KE, Gahagan S, Burrows RA, Blanco E, Lozoff B, Howard AG, Justice A, Graff M, Voruganti VS. Sociodemographic predictors of early postnatal growth: evidence from a Chilean infancy cohort. *BMJ Open.* 2020 Jun 3;10(6):e033695. PubMed Central PMCID: PMC7282289.
4. Von Holle A, North KE, Tao R, Gahagan S. The perils of standardizing infant weight to assess weight change differences across exposure groups. *Ann Epidemiol.* 2018 Aug;28(8):515-520. PubMed PMID: 29936050.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

| | |
|-------------|---|
| 2005 - 2013 | Biostatistician, University of North Carolina, Chapel Hill, Department of Psychiatry, Chapel Hill, NC |
| 1999 - 2000 | Research Analyst, Maryland Health Care Commission, Baltimore, MD |
| 1997 - 1998 | Public Health Specialist, Peace Corps |

Honors

| | |
|-------------|--|
| 2021 - 2021 | Intramural Paper of the Month, Environmental Factor, NIEHS newsletter |
| 2016 - 2018 | Individual Predoctoral Fellowship Award (Award: 16PRE29200008), American Heart Association |
| 2014 - 2016 | Summer travel scholarship award, Summer Institute in Statistical Genetics |
| 2001 - 2005 | T32 predoctoral training fellowship in population studies, NICHD |

C. Contribution to Science

1. Biostatistician at the Center of Excellence for Eating Disorders (CEED)

As a biostatistician at the CEED I had the privilege and opportunity to work on eating disorder research with an eminent group of clinical researchers. Of the 42 papers I worked on at CEED, 20 of them centered on the Norwegian Mother and Child Cohort Study (MoBa), a contemporary birth cohort of more than 100,000 pregnancies. My role as a biostatistician allowed me to successfully collaborate with lead authors in designing and conducting analyses. Of the 20 MoBa publications in which I was a co-author, I had the privilege to be the lead statistician on 15 of them. My role was to ensure that analyses accurately reflected the hypotheses posited by the researchers. In turn, this body of work can support researchers seeking well quantified research on children and mothers with eating disorders in areas such as basic epidemiologic information, postpartum weight change and child growth trajectories.

- a. Perrin EM, Von Holle A, Zerwas S, Skinner AC, Reba-Harrelson L, Hamer RM, Stoltenberg C, Torgersen L, Reichborn-Kjennerud T, Bulik CM. Weight-for-length trajectories in the first year of life in children of mothers with eating disorders in a large Norwegian Cohort. *Int J Eat Disord.* 2015 May;48(4):406-14. PubMed Central PMCID: PMC4482472.
- b. Zerwas SC, Von Holle A, Perrin EM, Cockrell Skinner A, Reba-Harrelson L, Hamer RM, Stoltenberg C, Torgersen L, Reichborn-Kjennerud T, Bulik CM. Gestational and postpartum weight change patterns in mothers with eating disorders. *Eur Eat Disord Rev.* 2014 Nov;22(6):397-404. PubMed Central PMCID: PMC4205262.
- c. Von Holle A, Pinheiro AP, Thornton LM, Klump KL, Berrettini WH, Brandt H, Crawford S, Crow S, Fichter MM, Halmi KA, Johnson C, Kaplan AS, Keel P, La Via M, Mitchell J, Strober M, Woodside DB, Kaye WH, Bulik CM. Temporal patterns of recovery across eating disorder subtypes. *Aust N Z J Psychiatry.* 2008 Feb;42(2):108-17. PubMed PMID: 18197505.
- d. Bulik CM, Von Holle A, Hamer R, Knoph Berg C, Torgersen L, Magnus P, Stoltenberg C, Siega-Riz AM, Sullivan P, Reichborn-Kjennerud T. Patterns of remission, continuation and incidence of broadly

defined eating disorders during early pregnancy in the Norwegian Mother and Child Cohort Study (MoBa). *Psychol Med.* 2007 Aug;37(8):1109-18. PubMed Central PMCID: PMC2657803.

2. Doctoral work at the Department of Epidemiology at the University of North Carolina, Chapel Hill

In my dissertation research, I wanted to better understand associations between early infant growth and lipid levels in adolescence. The “Developmental Origins of Health and Disease” theoretical framework informed my three aims, which, similar to my postdoctoral work, centered on a set of biomarker outcomes -- in this case the lipid biomarkers related to cardiovascular disease risk. To fund my dissertation work, I was fortunate to get an individual two-year American Heart Association predoctoral fellowship (2016-2018). When determining the extent to which associations exist between infant growth and lipid outcomes, I used nonlinear mixed effects models and latent class growth mixture modeling to characterize growth as an exposure. Through the three years I spent developing the ideas and plans, analyzing the data, and interpreting the results, I had some unexpected findings that included the association between relatively faster growth and a favorable lipid profile in the first five months of life. I also found in my first aim that the socioeconomic position of an infant’s family can play a role in growth even at the earliest times of life, with lower socioeconomic position linked with slower and less favorable growth. These findings are not in line with most evidence to date and could point towards windows of time that have distinct growth profiles and unique associations that may not be consistent over age.

- a. Von Holle A, North KE, Gahagan S, Burrows RA, Blanco E, Lozoff B, Howard AG, Justice A, Graff M, Voruganti VS. Sociodemographic predictors of early postnatal growth: evidence from a Chilean infancy cohort. *BMJ Open.* 2020 Jun 3;10(6):e033695. PubMed Central PMCID: PMC7282289.
- b. Von Holle A, North KE, Tao R, Gahagan S. The perils of standardizing infant weight to assess weight change differences across exposure groups. *Ann Epidemiol.* 2018 Aug;28(8):515-520. PubMed PMID: 29936050.

3. Postdoctoral training at the National Institute of Environmental Health Sciences

I have transitioned to a research focus in my postdoctoral work on a breast cancer cohort, a rewarding research domain that has allowed me to develop productive research spanning both cardiovascular disease and cancer outcomes. These outcomes are two of the most frequently occurring diseases for women in the United States and share common modifiable risk factors. My methodological focus on longitudinal changes shifted from mixed effects and latent class models to survival models with time-dependent covariates. The first manuscript from my postdoctoral work addresses familial correlation of breast cancer ages of onset. Our goal was to determine if a woman currently without a breast cancer diagnosis who had a sister diagnosed with cancer has higher relative breast cancer risk when closer to the age at diagnosis of the previously affected sister. We found evidence supporting such an increase, and this original work offers the potential for use in diagnostic screening of women a first-degree family history. Another line of research includes the study of circulating and stored iron levels as a biomarker. When assessing association between iron and breast cancer incidence, we found little evidence that higher iron levels increase breast cancer risk but did find evidence that very low levels of iron could be protective. If replicated, these findings can support new perspectives on this active area of research on associations between iron and cancer.

- a. Von Holle A, O'Brien KM, Sandler DP, Weinberg CR. Evidence for familial clustering in breast cancer age of onset. *Int J Epidemiol.* 2021 Mar 3;50(1):97-104. PubMed Central PMCID: PMC7938508.
- b. Von Holle A, O'Brien KM, Sandler DP, Janicek R, Weinberg CR. Association Between Serum Iron Biomarkers and Breast Cancer. *Cancer Epidemiol Biomarkers Prev.* 2021 Feb;30(2):422-425. PubMed Central PMCID: PMC7867615.

BIOGRAPHICAL SKETCH

NAME: [REDACTED]



1.



[REDACTED]
Source: [REDACTED]

BIOGRAPHICAL SKETCH

NAME: _____

[View Details](#) | [Edit](#) | [Delete](#)

ANSWER The answer is 1000. The first two digits of the product are 10.

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 | | |

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[REDACTED] [REDACTED] [REDACTED] [REDACTED]

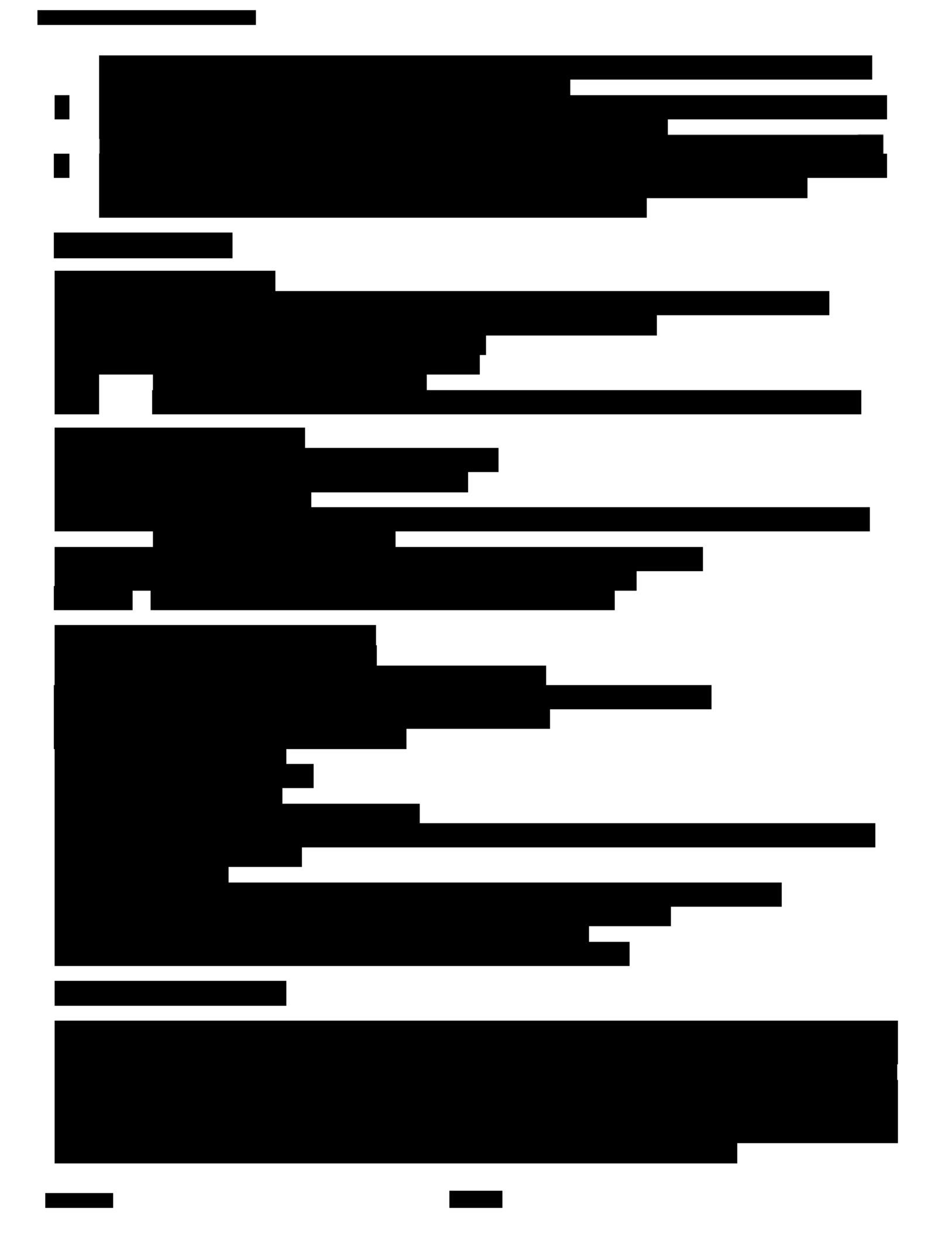
[REDACTED] [REDACTED] [REDACTED] [REDACTED]

ANSWER The answer is (A). The first two digits of the number 1234567890 are 12.

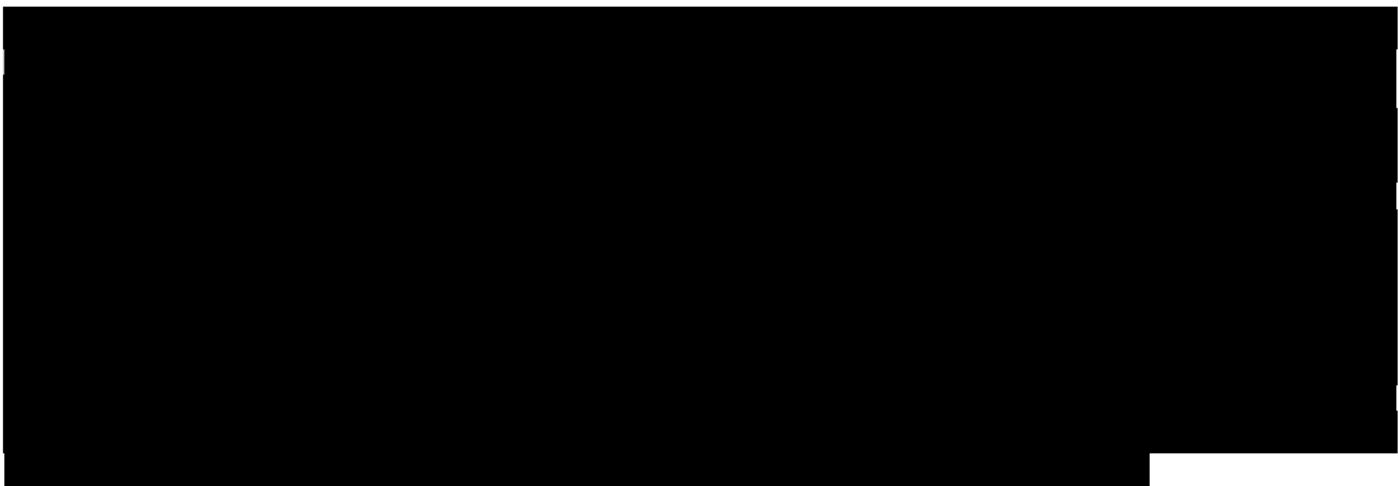
A large black rectangular box used for redacting sensitive information.

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1.



A bar chart illustrating the distribution of a variable across 15 categories. The x-axis represents the categories, and the y-axis represents frequency or density. The bars are black with white outlines.

| Category | Approximate Peak Value |
|----------|------------------------|
| 1 | 15 |
| 2 | 10 |
| 3 | 10 |
| 4 | 10 |
| 5 | 10 |
| 6 | 10 |
| 7 | 10 |
| 8 | 10 |
| 9 | 10 |
| 10 | 10 |
| 11 | 10 |
| 12 | 10 |
| 13 | 10 |
| 14 | 10 |
| 15 | 5 |



BIOGRAPHICAL SKETCH

The image consists of two main black shapes against a white background. On the left, there is a large, irregular, jagged black shape that occupies most of the vertical space. On the right, there is a smaller, more organized black shape composed of several horizontal bars of varying lengths. The overall contrast is very high, making the black shapes stand out sharply against the white background.



a.



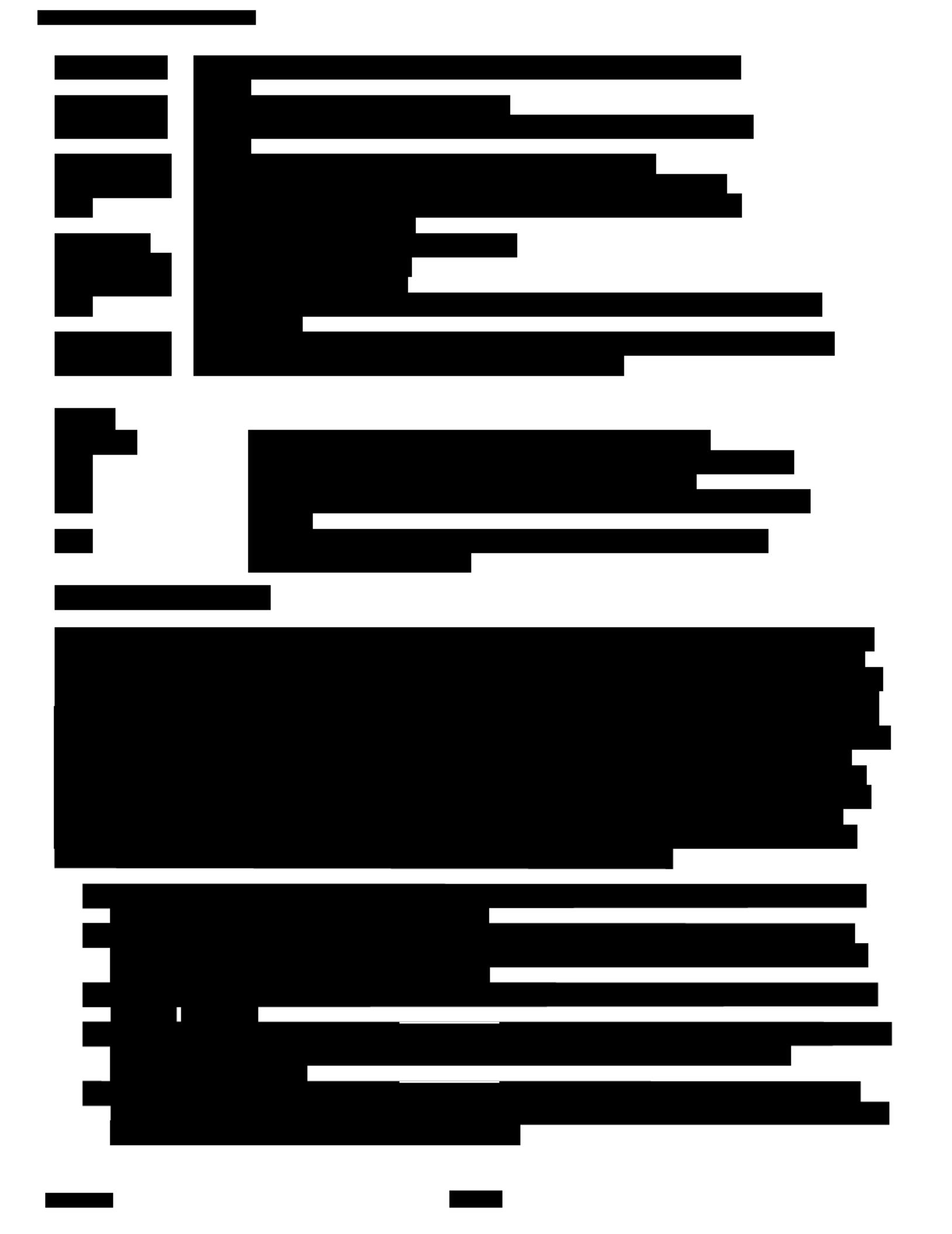




BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**



2.

[REDACTED]



BIOGRAPHICAL SKETCH

ANSWER The answer is 1000. The first two digits of the number 1000 are 10.

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Figure 1. A schematic diagram of the experimental setup for the measurement of the absorption coefficient of the sample.

[REDACTED]

ANSWER **QUESTION**

Figure 1. The effect of the number of training samples on the performance of the proposed model.

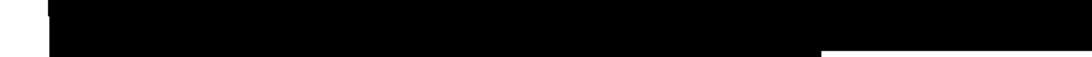
ANSWER The answer is (A). The first two digits of the number 12345678901234567890 are 12.

A large black rectangular box is positioned at the bottom of the page, spanning most of the width. It is used to redact sensitive information.

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10. The following is a list of statements concerning the use of the Internet by teenagers. Please indicate whether you agree or disagree with each statement.

the first time in the history of the world, the people of the United States have
gathered together on the occasion of their independence, and have, in the name
of the nation, solemnly dedicated themselves to the proposition that all men
are created equal; that they are endowed by their Creator with certain
unalienable rights; that among these are life, liberty, and the pursuit of
happiness; that to secure these rights, governments are instituted among
men, deriving their just powers from the consent of the governed; that
whenever any form of government becomes destructive of these ends,
it is the right of the people to alter or to abolish it, and to institute
new government, laying its foundation on such principles, and
organizing its powers in such form, as to them shall seem most likely
to effect their safety and happiness. This has been the declaration
of the United States of America.

A 



C.

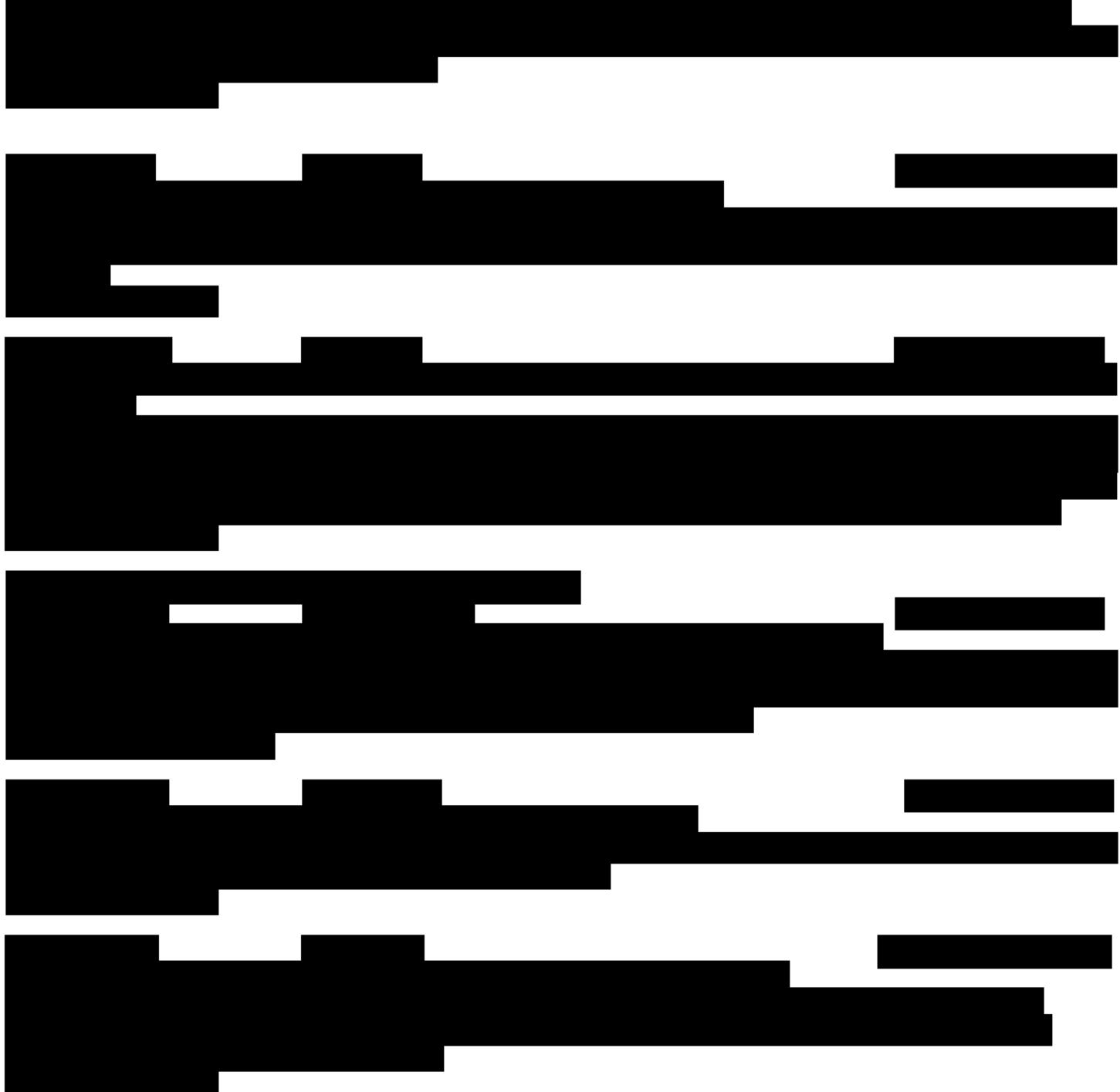




R21DA053708

Lancaster (PI)

3/1/2021 - 2/28/2025



Current Research Support



Current Research Support

This figure is a black and white graphic representation. It begins with a series of approximately ten horizontal bars of varying lengths at the top. Below this is a large rectangular area divided into a 4x4 grid of smaller rectangles. Each of these smaller rectangles contains a black bar of a specific length, creating a pattern where the total width of the bars in each row and column varies. The bottom of the figure is dominated by a single, very thick horizontal bar.

Current Research Support



RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

ORGANIZATIONAL DUNS*: 0400348600000

Budget Type*: ● Project ○ Subaward/Consortium**Enter name of Organization:** National Institute of Environmental Health Sciences, NIH

Start Date*: 04-01-2022

End Date*: 03-31-2023

Budget Period: 1

| A. Senior/Key Person | | | | | | | | | | | | |
|--|-------------|---------|------------|--------|---------------|-------------|----------|----------|--------|--------------------------------|----------------|-----------------------|
| Prefix | First Name* | Middle | Last Name* | Suffix | Project Role* | Base | Calendar | Academic | Summer | Requested | Fringe | Funds Requested (\$)* |
| | | | | | | Salary (\$) | Months | Months | Months | Salary (\$)* | Benefits (\$)* | |
| 1 . Dr. | Ann | Frances | Von Holle | | PD/PI | 100,000.00 | 12.00 | | | 100,000.00 | 0.00 | 100,000.00 |
| Total Funds Requested for all Senior Key Persons in the attached file | | | | | | | | | | | | |
| Additional Senior Key Persons: File Name: | | | | | | | | | | Total Senior/Key Person | | 100,000.00 |

| B. Other Personnel | | | | | | | | | | | |
|--|---------------|----------|--------|----------|--------|--------|--------|------------------------|------------------|------------------------------|--|
| Number of Personnel* | Project Role* | Calendar | Months | Academic | Months | Summer | Months | Requested Salary (\$)* | Fringe Benefits* | Funds Requested (\$)* | |
| | | | | | | | | | | | |
| Total Number Other Personnel | | | | | | | | | | Total Other Personnel | |
| Total Salary, Wages and Fringe Benefits (A+B) | | | | | | | | | | 100,000.00 | |

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

ORGANIZATIONAL DUNS*: 0400348600000

Budget Type*: Project Subaward/Consortium

Organization: National Institute of Environmental Health Sciences, NIH

Start Date*: 04-01-2022

End Date*: 03-31-2023

Budget Period: 1

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item

Funds Requested (\$)*

Total funds requested for all equipment listed in the attached file

Total Equipment

Additional Equipment: File Name:

D. Travel

Funds Requested (\$)*

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

Total Travel Cost

E. Participant/Trainee Support Costs

Funds Requested (\$)*

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees

Total Participant Trainee Support Costs

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1**ORGANIZATIONAL DUNS*:** 0400348600000**Budget Type*:** Project Subaward/Consortium**Organization:** National Institute of Environmental Health Sciences, NIH**Start Date*:** 04-01-2022**End Date*:** 03-31-2023**Budget Period:** 1

| F. Other Direct Costs | Funds Requested (\$)* |
|---------------------------------|------------------------------|
| Total Other Direct Costs | |

| G. Direct Costs | Funds Requested (\$)* |
|--------------------------------------|------------------------------|
| Total Direct Costs (A thru F) | 100,000.00 |

| H. Indirect Costs | Indirect Cost Type | Indirect Cost Rate (%) | Indirect Cost Base (\$) | Funds Requested (\$)* |
|---|---------------------------|-------------------------------|--------------------------------|------------------------------|
| Total Indirect Costs | | | | |
| Cognizant Federal Agency | | | | |
| (Agency Name, POC Name, and POC Phone Number) | | | | |

| I. Total Direct and Indirect Costs | Funds Requested (\$)* |
|--|------------------------------|
| Total Direct and Indirect Institutional Costs (G + H) | 100,000.00 |

| J. Fee | Funds Requested (\$)* |
|---------------|------------------------------|
| | |

| K. Total Costs and Fee | Funds Requested (\$)* |
|-------------------------------|------------------------------|
| | 100,000.00 |

| | |
|---------------------------------|---|
| L. Budget Justification* | File Name: 1242-Budget Justification.pdf (Only attach one file.) |
|---------------------------------|---|

RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

ORGANIZATIONAL DUNS*: 0400348600000

Budget Type*: ● Project ○ Subaward/Consortium**Enter name of Organization:** National Institute of Environmental Health Sciences, NIH

Start Date*: 04-01-2023

End Date*: 03-31-2024

Budget Period: 2

| A. Senior/Key Person | | | | | | | | | | | | |
|--|-------------|---------|------------|--------|---------------|-------------|----------|----------|--------|--------------------------------|----------------|-----------------------|
| Prefix | First Name* | Middle | Last Name* | Suffix | Project Role* | Base | Calendar | Academic | Summer | Requested | Fringe | Funds Requested (\$)* |
| | | | | | | Salary (\$) | Months | Months | Months | Salary (\$)* | Benefits (\$)* | |
| 1 . Dr. | Ann | Frances | Von Holle | | PD/PI | 100,000.00 | 12.00 | | | 100,000.00 | 0.00 | 100,000.00 |
| Total Funds Requested for all Senior Key Persons in the attached file | | | | | | | | | | | | |
| Additional Senior Key Persons: File Name: | | | | | | | | | | Total Senior/Key Person | | 100,000.00 |

| B. Other Personnel | | | | | | | | | | | |
|--|---------------|----------|--------|----------|--------|--------|--------|------------------------|------------------|------------------------------|--|
| Number of Personnel* | Project Role* | Calendar | Months | Academic | Months | Summer | Months | Requested Salary (\$)* | Fringe Benefits* | Funds Requested (\$)* | |
| | | | | | | | | | | | |
| Total Number Other Personnel | | | | | | | | | | Total Other Personnel | |
| Total Salary, Wages and Fringe Benefits (A+B) | | | | | | | | | | 100,000.00 | |

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2

ORGANIZATIONAL DUNS*: 0400348600000

Budget Type*: Project Subaward/Consortium

Organization: National Institute of Environmental Health Sciences, NIH

Start Date*: 04-01-2023

End Date*: 03-31-2024

Budget Period: 2

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item

Funds Requested (\$)*

Total funds requested for all equipment listed in the attached file

Total Equipment

Additional Equipment: File Name:

D. Travel

Funds Requested (\$)*

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

Total Travel Cost

E. Participant/Trainee Support Costs

Funds Requested (\$)*

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees

Total Participant Trainee Support Costs

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2**ORGANIZATIONAL DUNS*:** 0400348600000**Budget Type*:** Project Subaward/Consortium**Organization:** National Institute of Environmental Health Sciences, NIH**Start Date*:** 04-01-2023**End Date*:** 03-31-2024**Budget Period:** 2

| F. Other Direct Costs | Funds Requested (\$)* |
|---------------------------------|------------------------------|
| Total Other Direct Costs | |

| G. Direct Costs | Funds Requested (\$)* |
|--------------------------------------|------------------------------|
| Total Direct Costs (A thru F) | 100,000.00 |

| H. Indirect Costs | Indirect Cost Type | Indirect Cost Rate (%) | Indirect Cost Base (\$) | Funds Requested (\$)* |
|---|---------------------------|-------------------------------|--------------------------------|------------------------------|
| Total Indirect Costs | | | | |
| Cognizant Federal Agency | | | | |
| (Agency Name, POC Name, and POC Phone Number) | | | | |

| I. Total Direct and Indirect Costs | Funds Requested (\$)* |
|--|------------------------------|
| Total Direct and Indirect Institutional Costs (G + H) | 100,000.00 |

| J. Fee | Funds Requested (\$)* |
|---------------|------------------------------|
| | |

| K. Total Costs and Fee | Funds Requested (\$)* |
|-------------------------------|------------------------------|
| | 100,000.00 |

| | |
|---------------------------------|---|
| L. Budget Justification* | File Name: 1242-Budget Justification.pdf (Only attach one file.) |
|---------------------------------|---|

RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

ORGANIZATIONAL DUNS*: 0400348600000

Budget Type*: ● Project ○ Subaward/Consortium**Enter name of Organization:** National Institute of Environmental Health Sciences, NIH

Start Date*: 04-01-2024

End Date*: 03-31-2025

Budget Period: 3

| A. Senior/Key Person | | | | | | | | | | | | |
|--|-------------|---------|------------|--------|---------------|-------------|----------|----------|--------|--------------------------------|----------------|-----------------------|
| Prefix | First Name* | Middle | Last Name* | Suffix | Project Role* | Base | Calendar | Academic | Summer | Requested | Fringe | Funds Requested (\$)* |
| | | | | | | Salary (\$) | Months | Months | Months | Salary (\$)* | Benefits (\$)* | |
| 1 . Dr. | Ann | Frances | Von Holle | | PD/PI | 100,000.00 | 12.00 | | | 100,000.00 | 0.00 | 100,000.00 |
| Total Funds Requested for all Senior Key Persons in the attached file | | | | | | | | | | | | |
| Additional Senior Key Persons: File Name: | | | | | | | | | | Total Senior/Key Person | | 100,000.00 |

| B. Other Personnel | | | | | | | | | | | | |
|--|---------------|------------------------------|--|--|--|----------|--------|--------|--------|--|------------------|-----------------------|
| Number of Personnel* | Project Role* | Calendar Months | | | | Academic | Months | Summer | Months | Requested Salary (\$)* | Fringe Benefits* | Funds Requested (\$)* |
| | | Total Number Other Personnel | | | | | | | | | | |
| | | | | | | | | | | Total Salary, Wages and Fringe Benefits (A+B) | | 100,000.00 |
| RESEARCH & RELATED Budget {A-B} (Funds Requested) | | | | | | | | | | | | |

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3

ORGANIZATIONAL DUNS*: 0400348600000

Budget Type*: Project Subaward/Consortium

Organization: National Institute of Environmental Health Sciences, NIH

Start Date*: 04-01-2024

End Date*: 03-31-2025

Budget Period: 3

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item

Funds Requested (\$)*

Total funds requested for all equipment listed in the attached file

Total Equipment

Additional Equipment: File Name:

D. Travel

Funds Requested (\$)*

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

Total Travel Cost

E. Participant/Trainee Support Costs

Funds Requested (\$)*

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees

Total Participant Trainee Support Costs

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3**ORGANIZATIONAL DUNS*:** 0400348600000**Budget Type*:** ● Project ○ Subaward/Consortium**Organization:** National Institute of Environmental Health Sciences, NIH**Start Date*:** 04-01-2024**End Date*:** 03-31-2025**Budget Period:** 3

| F. Other Direct Costs | Funds Requested (\$)* |
|---|---------------------------------|
| 1. Materials and Supplies | 50,000.00 |
| 2. Publication Costs | |
| 3. Consultant Services | |
| 4. ADP/Computer Services | |
| 5. Subawards/Consortium/Contractual Costs | |
| 6. Equipment or Facility Rental/User Fees | |
| 7. Alterations and Renovations | |
| | Total Other Direct Costs |
| | 50,000.00 |

| G. Direct Costs | Funds Requested (\$)* |
|------------------------|--------------------------------------|
| | Total Direct Costs (A thru F) |
| | 150,000.00 |

| H. Indirect Costs | Indirect Cost Type | Indirect Cost Rate (%) | Indirect Cost Base (\$) | Funds Requested (\$)* |
|--|---------------------------|-------------------------------|--------------------------------|------------------------------|
| 1 . Institutional Allocation | | 39.75 | 249,000.00 | 99,000.00 |
| | | | | Total Indirect Costs |
| | | | | 99,000.00 |
| Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) | | | | |

| I. Total Direct and Indirect Costs | Funds Requested (\$)* |
|---|--|
| | Total Direct and Indirect Institutional Costs (G + H) |
| | 249,000.00 |

| J. Fee | Funds Requested (\$)* |
|---------------|------------------------------|
| | |

| K. Total Costs and Fee | Funds Requested (\$)* |
|-------------------------------|------------------------------|
| | 249,000.00 |

| L. Budget Justification* | File Name: 1242-Budget Justification.pdf (Only attach one file.) |
|---------------------------------|---|
| | |

RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 4

ORGANIZATIONAL DUNS*: 0400348600000

Budget Type*: ● Project ○ Subaward/Consortium**Enter name of Organization:** National Institute of Environmental Health Sciences, NIH

Start Date*: 04-01-2025

End Date*: 03-31-2026

Budget Period: 4

| A. Senior/Key Person | | | | | | | | | | | | |
|--|-------------|---------|------------|--------|---------------|-------------|----------|----------|--------|--------------------------------|----------------|-----------------------|
| Prefix | First Name* | Middle | Last Name* | Suffix | Project Role* | Base | Calendar | Academic | Summer | Requested | Fringe | Funds Requested (\$)* |
| | | | | | | Salary (\$) | Months | Months | Months | Salary (\$)* | Benefits (\$)* | |
| 1 . Dr. | Ann | Frances | Von Holle | | PD/PI | 100,000.00 | 12.00 | | | 100,000.00 | 0.00 | 100,000.00 |
| Total Funds Requested for all Senior Key Persons in the attached file | | | | | | | | | | | | |
| Additional Senior Key Persons: File Name: | | | | | | | | | | Total Senior/Key Person | | 100,000.00 |

| B. Other Personnel | | | | | | | | | | | |
|--|---------------|----------|--------|----------|--------|--------|--------|------------------------|------------------|------------------------------|--|
| Number of Personnel* | Project Role* | Calendar | Months | Academic | Months | Summer | Months | Requested Salary (\$)* | Fringe Benefits* | Funds Requested (\$)* | |
| | | | | | | | | | | | |
| Total Number Other Personnel | | | | | | | | | | Total Other Personnel | |
| Total Salary, Wages and Fringe Benefits (A+B) | | | | | | | | | | 100,000.00 | |

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 4

ORGANIZATIONAL DUNS*: 0400348600000

Budget Type*: Project Subaward/Consortium

Organization: National Institute of Environmental Health Sciences, NIH

Start Date*: 04-01-2025

End Date*: 03-31-2026

Budget Period: 4

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item

Funds Requested (\$)*

Total funds requested for all equipment listed in the attached file

Total Equipment

Additional Equipment: File Name:

D. Travel

Funds Requested (\$)*

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

Total Travel Cost

E. Participant/Trainee Support Costs

Funds Requested (\$)*

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees

Total Participant Trainee Support Costs

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 4**ORGANIZATIONAL DUNS*:** 0400348600000**Budget Type*:** ● Project ○ Subaward/Consortium**Organization:** National Institute of Environmental Health Sciences, NIH**Start Date*:** 04-01-2025**End Date*:** 03-31-2026**Budget Period:** 4

| F. Other Direct Costs | Funds Requested (\$)* |
|---|---------------------------------|
| 1. Materials and Supplies | 50,000.00 |
| 2. Publication Costs | |
| 3. Consultant Services | |
| 4. ADP/Computer Services | |
| 5. Subawards/Consortium/Contractual Costs | |
| 6. Equipment or Facility Rental/User Fees | |
| 7. Alterations and Renovations | |
| | Total Other Direct Costs |
| | 50,000.00 |

| G. Direct Costs | Funds Requested (\$)* |
|------------------------|--------------------------------------|
| | Total Direct Costs (A thru F) |
| | 150,000.00 |

| H. Indirect Costs | Indirect Cost Type | Indirect Cost Rate (%) | Indirect Cost Base (\$) | Funds Requested (\$)* |
|--|---------------------------|-------------------------------|--------------------------------|------------------------------|
| 1 . Institutional Allocation | | 39.75 | 249,000.00 | 99,000.00 |
| | | | | Total Indirect Costs |
| | | | | 99,000.00 |
| Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) | | | | |

| I. Total Direct and Indirect Costs | Funds Requested (\$)* |
|---|--|
| | Total Direct and Indirect Institutional Costs (G + H) |
| | 249,000.00 |

| J. Fee | Funds Requested (\$)* |
|---------------|------------------------------|
| | |

| K. Total Costs and Fee | Funds Requested (\$)* |
|-------------------------------|------------------------------|
| | 249,000.00 |

| L. Budget Justification* | File Name: 1242-Budget Justification.pdf (Only attach one file.) |
|---------------------------------|---|
| | |

RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 5

ORGANIZATIONAL DUNS*: 0400348600000

Budget Type*: ● Project ○ Subaward/Consortium**Enter name of Organization:** National Institute of Environmental Health Sciences, NIH

Start Date*: 04-01-2026

End Date*: 03-31-2027

Budget Period: 5

| A. Senior/Key Person | | | | | | | | | | | | |
|--|-------------|---------|------------|--------|---------------|-------------|----------|----------|--------|--------------------------------|----------------|-----------------------|
| Prefix | First Name* | Middle | Last Name* | Suffix | Project Role* | Base | Calendar | Academic | Summer | Requested | Fringe | Funds Requested (\$)* |
| | | | | | | Salary (\$) | Months | Months | Months | Salary (\$)* | Benefits (\$)* | |
| 1 . Dr. | Ann | Frances | Von Holle | | PD/PI | 100,000.00 | 12.00 | | | 100,000.00 | 0.00 | 100,000.00 |
| Total Funds Requested for all Senior Key Persons in the attached file | | | | | | | | | | | | |
| Additional Senior Key Persons: File Name: | | | | | | | | | | Total Senior/Key Person | | 100,000.00 |

| B. Other Personnel | | | | | | | | | | | |
|--|---------------|----------|--------|----------|--------|--------|--------|------------------------|------------------|------------------------------|--|
| Number of Personnel* | Project Role* | Calendar | Months | Academic | Months | Summer | Months | Requested Salary (\$)* | Fringe Benefits* | Funds Requested (\$)* | |
| | | | | | | | | | | | |
| Total Number Other Personnel | | | | | | | | | | Total Other Personnel | |
| Total Salary, Wages and Fringe Benefits (A+B) | | | | | | | | | | 100,000.00 | |

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 5

ORGANIZATIONAL DUNS*: 0400348600000

Budget Type*: Project Subaward/Consortium

Organization: National Institute of Environmental Health Sciences, NIH

Start Date*: 04-01-2026

End Date*: 03-31-2027

Budget Period: 5

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item

Funds Requested (\$)*

Total funds requested for all equipment listed in the attached file

Total Equipment

Additional Equipment: File Name:

D. Travel

Funds Requested (\$)*

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

Total Travel Cost

E. Participant/Trainee Support Costs

Funds Requested (\$)*

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees

Total Participant Trainee Support Costs

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 5**ORGANIZATIONAL DUNS*:** 0400348600000**Budget Type*:** ● Project ○ Subaward/Consortium**Organization:** National Institute of Environmental Health Sciences, NIH**Start Date*:** 04-01-2026**End Date*:** 03-31-2027**Budget Period:** 5

| F. Other Direct Costs | Funds Requested (\$)* |
|---|---------------------------------|
| 1. Materials and Supplies | 50,000.00 |
| 2. Publication Costs | |
| 3. Consultant Services | |
| 4. ADP/Computer Services | |
| 5. Subawards/Consortium/Contractual Costs | |
| 6. Equipment or Facility Rental/User Fees | |
| 7. Alterations and Renovations | |
| | Total Other Direct Costs |
| | 50,000.00 |

| G. Direct Costs | Funds Requested (\$)* |
|------------------------|--------------------------------------|
| | Total Direct Costs (A thru F) |
| | 150,000.00 |

| H. Indirect Costs | Indirect Cost Type | Indirect Cost Rate (%) | Indirect Cost Base (\$) | Funds Requested (\$)* |
|--|---------------------------|-------------------------------|--------------------------------|------------------------------|
| 1 . Institutional Allocation | | 39.75 | 249,000.00 | 99,000.00 |
| | | | | Total Indirect Costs |
| | | | | 99,000.00 |
| Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) | | | | |

| I. Total Direct and Indirect Costs | Funds Requested (\$)* |
|---|--|
| | Total Direct and Indirect Institutional Costs (G + H) |
| | 249,000.00 |

| J. Fee | Funds Requested (\$)* |
|---------------|------------------------------|
| | |

| K. Total Costs and Fee | Funds Requested (\$)* |
|-------------------------------|------------------------------|
| | 249,000.00 |

| L. Budget Justification* | File Name: 1242-Budget Justification.pdf (Only attach one file.) |
|---------------------------------|---|
| | |

RESEARCH & RELATED Budget {F-K} (Funds Requested)

5-YEAR BUDGET JUSTIFICATION

Budget Justification Years 1 and 2 –the K99 training years

All research expenses of my postdoctoral training period are borne by the Division of Intramural Research, NIEHS. No funds are requested during the K99 training period at NIEHS. In the event that I seek additional training at a different institution in completing my preparation for the academic position, I shall request and adjustment of the K99 budget to permit my training to continue in a non-NIH laboratory.

Budget Justification for Years 3, 4, and 5 –the R00 academic institutional years

In the event that an award is made and I am successful in obtaining an academic position, a detailed budget will be submitted during the activation phase of that R00 award. The maximal award for R00 years is \$249,000 per year including direct and indirect costs. That figure is used in this application for planning and budget projection purposes.

A salary amount of \$100,000 in each year is indicated, representing 100% of my time devoted to this grant, and a typical starting salary at an academic institution.

Materials and supplies are lumped together in the amount of \$50,000 for each year as an estimation of the amount anticipated for research costs. The distribution of this amount across other categories will take place during the budget request submitted during the activation of the R00 portion.

An institutional allocation in the amount of \$99,000 per year (39.75% indirect cost rate) is included for each R00 year as a typical amount for this category. This amount will be adjusted according to the institution's negotiated rate at the time of submission of the R00 portion.

RESEARCH & RELATED BUDGET - Cumulative Budget

| | Totals (\$) |
|---|-------------|
| Section A, Senior/Key Person | 500,000.00 |
| Section B, Other Personnel | |
| Total Number Other Personnel | |
| Total Salary, Wages and Fringe Benefits (A+B) | 500,000.00 |
| Section C, Equipment | |
| Section D, Travel | |
| 1. Domestic | |
| 2. Foreign | |
| Section E, Participant/Trainee Support Costs | |
| 1. Tuition/Fees/Health Insurance | |
| 2. Stipends | |
| 3. Travel | |
| 4. Subsistence | |
| 5. Other | |
| 6. Number of Participants/Trainees | |
| Section F, Other Direct Costs | 150,000.00 |
| 1. Materials and Supplies | 150,000.00 |
| 2. Publication Costs | |
| 3. Consultant Services | |
| 4. ADP/Computer Services | |
| 5. Subawards/Consortium/Contractual Costs | |
| 6. Equipment or Facility Rental/User Fees | |
| 7. Alterations and Renovations | |
| 8. Other 1 | |
| 9. Other 2 | |
| 10. Other 3 | |
| Section G, Direct Costs (A thru F) | 650,000.00 |
| Section H, Indirect Costs | 297,000.00 |
| Section I, Total Direct and Indirect Costs (G + H) | 947,000.00 |
| Section J, Fee | |
| Section K, Total Costs and Fee (I + J) | 947,000.00 |

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

Expiration Date: 02/28/2023

1. Vertebrate Animals Section

Are vertebrate animals euthanized? Yes No

If "Yes" to euthanasia

Is the method consistent with American Veterinary Medical Association (AVMA) guidelines?

Yes No

If "No" to AVMA guidelines, describe method and provide scientific justification

.....

2. *Program Income Section

*Is program income anticipated during the periods for which the grant support is requested?

Yes No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period *Anticipated Amount (\$) *Source(s)

PHS 398 Cover Page Supplement

3. Human Embryonic Stem Cells Section

*Does the proposed project involve human embryonic stem cells? Yes No

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, check the box indicating that one from the registry will be used:

Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Cell Line(s) (Example: 0004):

4. Human Fetal Tissue Section

*Does the proposed project involve human fetal tissue obtained from elective abortions? Yes No

If "yes" then provide the HFT Compliance Assurance

If "yes" then provide the HFT Sample IRB Consent Form

5. Inventions and Patents Section (Renewal applications)

*Inventions and Patents: Yes No

If the answer is "Yes" then please answer the following:

*Previously Reported: Yes No

6. Change of Investigator/Change of Institution Section

Change of Project Director/Principal Investigator

Name of former Project Director/Principal Investigator

Prefix:

*First Name:

Middle Name:

*Last Name:

Suffix:

Change of Grantee Institution

*Name of former institution:

PHS 398 Career Development Award Supplemental Form

OMB Number: 0925-0001

Expiration Date: 02/28/2023

| | |
|---|---|
| Introduction 1. Introduction to Application (for Resubmission and Revision applications) | |
| Candidate Section 2. Candidate Information and Goals for Career Development | 1234-career-development-training.pdf |
| Research Plan Section 3. Specific Aims 4. Research Strategy* 5. Progress Report Publication List (for Renewal applications) 6. Training in the Responsible Conduct of Research | 1235-specific aims.pdf 1236-research-strategy.pdf 1237-RCR.pdf |
| Other Candidate Information Section 7. Candidate's Plan to Provide Mentoring | |
| Mentor, Co-Mentor, Consultant, Collaborators Section 8. Plans and Statements of Mentor and Co-Mentor(s) 9. Letters of Support from Collaborators, Contributors, and Consultants | 1238-mentor-letters-20210609.pdf 1239-LOS-avh.pdf |
| Environment and Institutional Commitment to Candidate Section 10. Description of Institutional Environment 11. Institutional Commitment to Candidate's Research Career Development 12. Description of Candidate's Contribution to Program Goals | 1240-Institutional Environment.pdf 1241-K99-institutional-commitment-letter-avh-20210604.pdf |
| Other Research Plan Section 13. Vertebrate Animals 14. Select Agent Research 15. Consortium/Contractual Arrangements 16. Resource Sharing 17. Authentication of Key Biological and/or Chemical Resources | |
| Appendix 18. Appendix | |

PHS 398 Career Development Award Supplemental Form

Citizenship*:

19. U.S. Citizen or Non-Citizen National?* Yes No

If no, select most appropriate Non-U.S. Citizen option

- With a Permanent U.S. Resident Visa
- With a Temporary U.S. Visa
- Not Residing in the U.S.

If you are a non-U.S. citizen with a temporary visa applying for an award that requires permanent residency status, and expect to be granted a permanent resident visa by the start date of the award, check here:

CANDIDATE INFORMATION AND GOALS FOR CAREER DEVELOPMENT

I am a postdoctoral fellow at the National Institute of Environmental Health Sciences within the Biostatistics and Computational Biology branch. **Broadly speaking, my career goal is to transition into an independent research career focusing on the role of co-occurring modifiable factors to prevent disease unique to women transitioning into midlife past their reproductive years.** The sections that follow demonstrate how my background, including work experience and training, have supported my career goals, led me to the research proposed here, and informed my next steps outlined in the training objectives.

A. Candidate background

A1. Prior graduate and applied research

My masters-level academic degrees in population health, demography, and biostatistics converged into my position as a biostatistician at the University of North Carolina, Department of Psychiatry for more than eight years. In this role, I collaborated with a diverse group of researchers ranging from undergraduate students to faculty in psychiatry and psychology who were writing manuscripts based on both clinical and observational data. This opportunity allowed me to advance my statistical analysis skills in structural equation modeling, learn all aspects of manuscript writing, and observe principal investigators engage in successful grant writing. In applying advanced analytic methods to data from population health studies, these rich experiences motivated my long term goal to establish myself as an independent investigator focusing on public health outcomes.

A2. Dissertation research (University of North Carolina)

In a decision to further my career goals to become an independent researcher in public health, I enrolled in the doctoral program in Epidemiology at the University of North Carolina, Chapel Hill. My coursework in epidemiology enabled me to study methods focusing on the occurrence of disease as a means to better understand and identify causes of disease. During my training in cardiovascular and genetic epidemiology, I developed a dissertation under the mentorship of Dr. Kari E. North that characterized early infant child growth in a cohort of Chilean infants and its impact on lipid levels in adolescence. My aims, similar to my postdoctoral work described below, centered on a set of biomarker measures – in this case lipid biomarkers related to cardiovascular disease risk. To fund my dissertation work, I obtained an external two-year American Heart Association predoctoral fellowship award (16PRE29200008). When determining the extent to which associations exist between infant growth and lipid outcomes, I furthered my knowledge of longitudinal methods that I had first learned as a statistician working in the UNC Department of Psychiatry, including nonlinear mixed effects models and latent class growth mixture modeling, to characterize growth as an exposure. I used an initial paper I independently developed examining the best measures to characterize infant growth¹ to inform my approach in assessing a longitudinal measure of anthropometric measures as an exposure. Within my three aims I was able to: 1) characterize determinants of infant growth applying advanced longitudinal analytic methods;² 2) assess the association between infant growth including latent growth patterns and lipid levels (under review at AJE); and 3) determine if infant growth functions as an effect modifier of candidate genetic variants associated with lipid levels.

A3. Postdoctoral studies (National Institute of Environmental Health Studies)

Extending my interest in longitudinal exposures and health outcomes in epidemiological research, I have strengthened my experience in time-to-event models with a focus on breast cancer incidence in a large contemporary U.S.-wide study. At the start of my postdoctoral studies, I studied familial correlation of age of onset in sisters³ with implications for underlying early life exposures and genetic factors. More recent work continues my focus on biomarkers within the Sister Study, examining serum iron biomarkers and their: a) association with breast cancer incidence;⁴ b) association with common lifestyle predictors; and c) and correspondence with toenail measures. My work with the Sister Study data sources has strengthened my understanding of the unique and promising aspects of this rich and well-characterized longitudinal data source, preparing me to conduct the proposed research. Research spanning both my dissertation work and postdoctoral fellowship enabled me to conceptualize research problems for both longitudinal exposures within a life course perspective and time-to-event data as it will be applied to a sample of postmenopausal women.

My goals are to apply the knowledge I have gained in methodological and epidemiological research areas to the study of lifestyle exposures and their relationship with cancer and all-cause mortality as women move into their post-reproductive years. To do so I will require further training in aging research, lifestyle exposures, as well as joint analysis models that are part of nascent research that combines both longitudinal exposures and time to event models.

B. Career goals and objectives

Building research that focuses on modifiable factors and changing risk of disease over age and time focused on women's post-reproductive years within epidemiology is a long-term goal of mine with the ultimate purpose to prevent breast cancer cases and premature mortality.

Following my work experience and training in statistical and epidemiological methods focusing on biomarkers and risk of disease, I am planning a new direction in research that is aligned with my long-term career goals. Certain lifestyle characteristics figure strongly during the postmenopausal years in women's risk of breast cancer and number as some of the top ten risk factors for mortality and chronic disease, emphasizing the ability to cross over into study of other outcomes such as mortality. My training objectives and mentoring plan are designed to enhance my knowledge of these lifestyle factors and support the successful completion of my three aims to understand how modifiable factors of lifestyle co-occur, change over time, and relate to disease risk. Once I establish that knowledge, I plan to launch my R00 independent research phase in which I will first investigate associations between the well-defined lifestyle factor changes and breast cancer incidence and all-cause mortality. After that step, I will investigate the role that lifestyle may influence the genetic association with breast cancer risk and all-cause mortality. By focusing on lifestyle factors specific to the postmenopausal age range, the proposed research work would focus on these factors as they operate through a life course perspective and could inform areas of lifestyle change that could improve the health of adults as they age – both goals in the NIA strategic plan.⁵ I plan to capitalize on the knowledge I have gained of factors associated with breast cancer risk and their dependency on certain age and time periods. At the same time, I will rely on my training plan during the K99 phase to extend my research in a direction spanning advanced structural equation modeling, joint analysis, and lifestyle exposures that will set me on a path independent from that of my mentor.

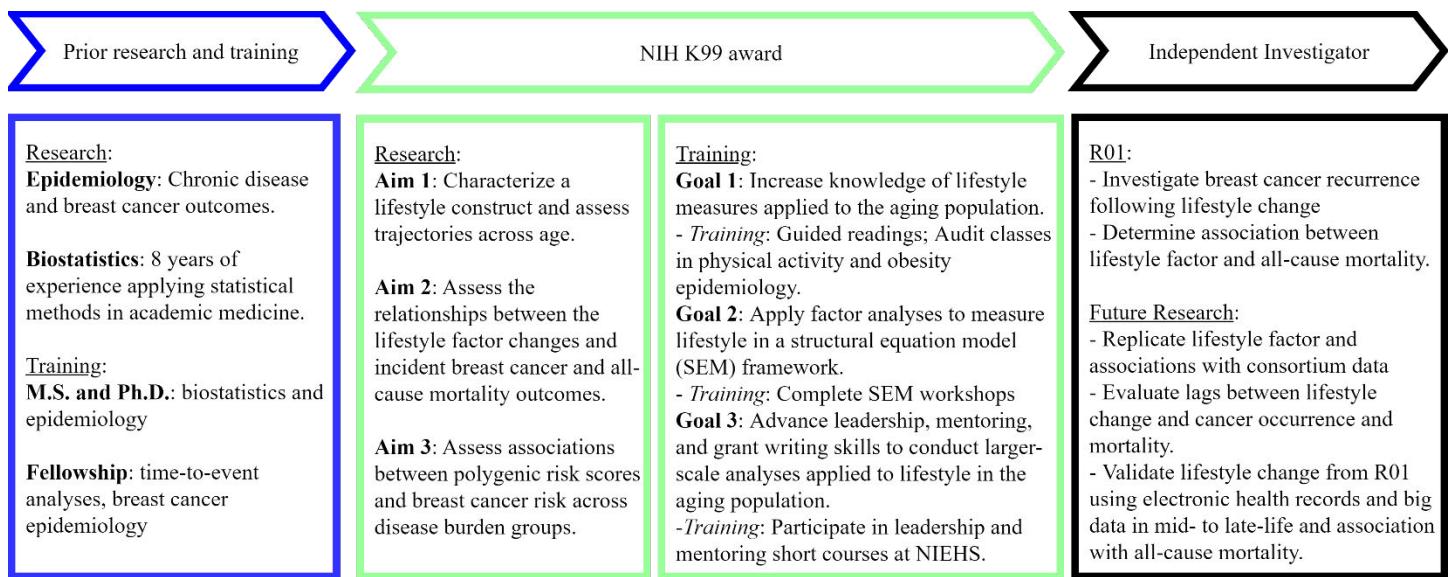


Figure 1. Career Timeline

C. Career development and training

To best attain my outlined career goals and address the three proposed research aims (Figure 1), I will take advantage of the training opportunities described below to establish myself as an independent investigator studying modifiable lifestyle change following midlife to prevent disease.

C1. Mentoring team and collaborators

I have assembled a mentoring team that will provide excellent support and guidance as I embark on a new research path involving common modifiable factors and outcomes such as breast cancer in a group of postmenopausal women (Table 1). My primary mentor, **Dr. Clarice R. Weinberg**, a pioneer in the field of epidemiologic methods and a principal investigator for the Sister Study, will continue guiding me as I follow my K99 training period during the first two years. As a postdoctoral fellow in her lab, I meet with her on a weekly basis to plan, develop and write manuscripts related to work based on Sister Study samples. My mentor and co-mentor, **Dr. Clarice Weinberg** and **Dr. Dale Sandler**, are experts in breast cancer epidemiology as well as possessing an extensive and accomplished history of mentorship. Being the principal investigators for the Sister Study, they will guide me regarding lifestyle change within this ongoing contemporary cohort. As I launch into the independent investigator path, I will also draw on the expertise of my mentoring committee, each member fitting within distinct areas of research in which I will need guidance. I will rely on **Dr. Shanshan Zhao's** expertise in time-to-event modeling as I conduct joint model analyses to understand the relationship between longitudinal factors and risk in a sample of postmenopausal women. As an expert in structural equation models, **Dr. Nisha Gottfredson's** mentorship will be essential to conduct best practices when capturing the lifestyle information through factor analysis. **Dr. Mary Beth Terry** will play a crucial role as I conduct epidemiologic research related to lifestyle and genetic factors following menopause and their relationship with breast cancer incidence. As I learn from and collaborate with these mentors, I will be able to work independently, but I will also embrace the value in their guided perspectives that can set my career trajectory on an effective and productive course. This mentoring plan will include continuing my weekly meetings with my mentor and having as-needed individual correspondence in the form of email and meetings with my mentorship team (Table 2) as I develop, analyze the data, and write the manuscripts for these proposed projects. Guidance from my mentorship team will be paramount as I search for faculty positions and start my own research group.

Table 1: Mentorship Team

| Name | Associated Specific Aims / Training Goals | Position | Proposed Role | Expertise |
|-------------------------------|---|---|---|---|
| Clarice R. Weinberg, Ph.D. | Research: 1, 2, 3; Training: 1, 3, 4 | Principal Investigator, Biostatistics and Computational Biology Branch, NIEHS | Primary mentor | Breast cancer, methods and genetic epidemiology |
| Dale P. Sandler, Ph.D. | Research: 1, 2, 3; Training: 1, 3, 4 | Principal Investigator, Epidemiology Branch, NIEHS | Secondary co-mentor | Lifecourse and breast cancer epidemiology |
| Shanshan Zhao, Ph.D. | Research: 1, 2, 3; Training: 2 | Principal Investigator, Biostatistics and Computational Biology Branch, NIEHS | Advisor, statistical methodology | Biostatistics, time to event analyses |
| Mary Beth Terry, Ph.D. | Research: 1, 2, 3; Training: 1, 3 | Professor, Epidemiology, Columbia Mailman School of Public Health | Advisor, lifestyle and genetic epidemiology | Genetic and cancer epidemiology |
| Nisha Gottfredson, Ph.D. | Research: 1, 2, 3; Training: 2 | Assistant Professor, Department of Health Behavior, UNC | Advisor, statistical methodology | Factor analysis, longitudinal methods |

C2. Training objectives

My training objectives in the first two years of the proposed award will draw on the rich interdisciplinary resources available in the Research Triangle Park area and online offerings from across the United States. These activities will include attending seminars, auditing classes, and individual guided readings through mentoring activities (Table 2).

Table 2: Training Timeline

| Milestones/Benchmarks | K99 | | R00 | | |
|--|---------|---------|---------|---------|---------|
| | Year 1 | Year2 | Year1 | Year2 | Year3 |
| Mentoring Meetings | | | | | |
| Weekly meetings with primary mentor | x (5%) | x (5%) | | | |
| Bi-annual meeting with mentorship committee | | x (1%) | x (1%) | x (1%) | x (1%) |
| Individual meetings and/or communication on an as-needed basis regarding unanticipated analytic and/or subject matter problems | x (2%) | x (5%) | x (2%) | x (1%) | x (1%) |
| Research | | | | | |
| Statistical analyses of lifestyle factor and its longitudinal change (Aim 1) | x (55%) | x (25%) | | | |
| Draft and submit manuscript (Aim 1) | x (20%) | x (20%) | | | |
| Statistical analyses of lifestyle factor and breast cancer risk | | x (10%) | x (40%) | x (25%) | |
| Draft and submit manuscript (Aim 2) | | | x (30%) | x (20%) | |
| Statistical analyses of polygenic risk scores and lifestyle risk burden (Aim 3) | | | x (30%) | x (40%) | x (50%) |
| Draft and submit manuscript (Aim 3) | | | | | |

| Milestones/Benchmarks | K99 | | R00 | | |
|---|---------|---------|---------|---------|--------|
| | Year 1 | Year2 | Year1 | Year2 | Year3 |
| Coursework | | | | | |
| Audit "Physical activity epidemiology and public health (EPID 810)" | x (10%) | | | | |
| Audit "Obesity Epidemiology (EPID 814)" | | x (10%) | | | |
| Seminars, workshops, journal clubs | | | | | |
| UNC Bowles Center for Alcohol Studies Spring Seminar Series | x (1%) | x (1%) | | | |
| NIEHS reproductive journal club | x (1%) | x (1%) | | | |
| UNC Odum Institute short course: Introduction to structural equation models | x (2%) | | | | |
| American Society on Aging summer short course: Managing Health & Chronic Conditions in Older Adults | x (2%) | | | | |
| National meetings | | | | | |
| Attend 1-2 meetings per year including SER, ASPO, AACR, and ASHG | x (2%) | x (2%) | x (2%) | x (2%) | x (3%) |
| Faculty job search and grant writing | | | | | |
| Conduct academic faculty job search | | x (15%) | | | |
| R01 idea development | | x (5%) | x (25%) | x (20%) | |
| R01 submission | | | x (1%) | x (5%) | |

Training objective 1: Increase knowledge of lifestyle measures relevant to the aging population.

I will audit physical activity (year 1) and obesity epidemiology (year 2) classes. I will attend the spring seminar series at UNC Bowles Center for Alcohol Studies (<https://www.med.unc.edu/alcohol/spring-2019-seminar-series/>) (years 1 and 2). To gain knowledge of modifiable lifestyle factors in the aging population, I will attend a summer short course, "Managing Health & Chronic Conditions in Older Adults," offered by American Society on Aging and the USC School of Gerontology (Summer, year 1).

Training objective 2: Apply novel methodological analyses, including factor analyses to measure lifestyle in a structural equation model (SEM) framework and joint analyses.

Training will include completion of a SEM summer short course offered by Inter-university Consortium for Political and Social Research (ICPSR) in collaboration with the Odum Institute (year 1). During the first and second years I will consult with Dr. Gottfredson regarding the lifestyle factor analyses during the analyses for Aim 1, and I will follow any guidelines for directed readings related to my work. In the second year I will consult with Dr. Zhao with respect to the joint longitudinal and time-to-event models so I can apply the best modeling approaches and follow her suggested directed readings that overlap and support my proposed aims.

Training objective 3: Present research at nationally representative conferences.

This objective will serve multiple goals of: 1) networking as I conduct my search for a faculty position, 2) interacting with experts and leaders who can offer new perspectives and opinions that I can use to improve the proposed work and inform my R01 application, and 3) bringing awareness of the completed scientific work in this proposal.

Training objective 4: Advance leadership, mentoring, and grant writing skills to conduct larger-scale analyses applied to lifestyle in the aging population.

I will participate in leadership and mentoring short courses at NIEHS, which include the "Management Bootcamp" offered by the NIH Office of Intramural Training and Education (OITE) to learn management concepts independent of the research environment but necessary to develop constructive leadership skills and expand my work by leading a research lab. I will also take advantage of the grant-writing workshops and seminars offered by the OITE. Furthermore, my mentoring team, all of whom have successfully written large-scale grants, will provide individual advice when I start the R01 application process (years 4-5).

C3. Plans for transition to independence

I can take these learning steps towards these goals to develop an independent research career trajectory as an epidemiologist leveraging advanced methods to focus on modifiable exposures in postmenopausal women as they relate to cancer and mortality outcomes. Pursuing this work will build on work accomplished by my primary mentor but also diverge in a new direction of lifestyle factors, separate from environmental factors, as an exposure in the domain of breast cancer incidence and all-cause mortality.

SPECIFIC AIMS

Body size, alcohol use, physical activity, diet, and tobacco use count among the leading risk factors of mortality in the United States, yet less than ten percent of NIH-funded prevention research projects examine more than one of these indicators. These lifestyle risk factors are also associated with breast cancer, the second most common cancer for women in the United States, who experience a 1 in 8 risk of being diagnosed across their lifetime. What remains unclear is how correlated individual lifestyle indicators comprise a co-existing entity, i.e. a healthy lifestyle factor, and if change in this healthy lifestyle construct is associated with breast cancer incidence. These health-promoting lifestyle constructs can also interact with genetic risk factors. Furthermore, it is unknown if people with extreme lifestyle measures carry a disproportionate breast cancer burden — also characterized as “risk inequality.” Defining risk inequality measures that involve modifiable behaviors remains an important and underdeveloped area of research in public health. With better knowledge of this association, we could do better at identifying subgroups providing optimal targets for breast cancer prevention.

Our overarching goal is to better understand the role of healthy lifestyle trajectories as they relate to breast cancer incidence, all-cause mortality, and their interplay with genetic factors. To address this goal, we plan a three-pronged analytic approach using data from a large contemporary large U.S. cohort of women. First, we will use factor analysis to estimate a healthy lifestyle construct and determine if this construct varies across age and racial/ethnic groups. Second, we will assess patterns of change over time in this construct that could influence breast cancer risk and all-cause mortality, through joint modeling of longitudinal effects using time-to-event models. Lastly, we will use risk inequality methods to characterize the concentration of disease burden across the range of lifestyle indicators and use this inequality assessment to determine if it modifies genetic risk of breast cancer through gene-environment models. Postmenopausal women who have an unfavorable lifestyle profile and carry a disproportionate disease burden may demonstrate stronger genetic associations with breast cancer risk than those in lower disease-burden groups. It is vitally important to not only characterize a constellation of lifestyle indicators that influence cancer and all-cause mortality outcomes, but to also understand how lifestyle factor changes over time influence these outcomes. This advance in our understanding would help clarify carcinogenic pathways and also highlight critical areas of intervention in midlife, providing important insights into avenues of prevention.

Aim 1 (K99): Using factor analysis, characterize a lifestyle construct from correlated lifestyle characteristics in a contemporary cohort of women and determine trajectories of this factor over a ten-year follow-up period during mid- to late-life.

Hypothesis 1: Correlated lifestyle indicators will fit within one factor, and this factor will have similarly correlated characteristics as age increases.

Aim 2 (R00): Assess the relationships between the lifestyle factor changes over time and incident breast cancer and all-cause mortality outcomes.

Hypothesis 2: Groups with improving lifestyle trajectories are at lower risk for breast cancer and all-cause mortality.

Aim 3 (R00): Assess associations between genetic risk scores and breast cancer risk for lifestyle groups with highest disease burden compared to groups with lowest burden.

Hypothesis 3: Groups carrying a disproportionately higher lifestyle-based disease burden will display stronger genetic associations with cancer incidence compared to those with a lower burden.

Evidence from this research can provide knowledge in an understudied area of breast cancer and mortality prevention to help understand how groups of related modifiable lifestyle indicators: 1) form a construct, 2) change over time and influence breast cancer incidence, and 3) modify genetic risk. This knowledge can help target the most impactful domains within lifestyle characteristics to reduce the growing burden of disease for women aging past menopause.

RESEARCH STRATEGY

1.1 Background and Significance

Common modifiable health risk factors in the United States include body fatness, exercise, and alcohol use, which also are leading causes of mortality and are shared with other health outcomes such as breast cancer. Despite the importance of these factors, less than 35 percent of NIH-funded prevention research studies measured these modifiable lifestyle factors and less than four percent of all research projects consider more than one leading risk factor contributing to all-cause mortality.⁶ Many of the leading risk factors mentioned above co-occur in individuals, and their study as an aggregate measure would create a more efficient use of measures of health and well-being as well as capturing a meaningful measure of correlated risk factors. This approach will also follow building research that points towards patterns of multiple lifestyle factors as creating a favorable environment for cancer rather than single causes.⁷ Developing this unique approach to understand leading modifiable lifestyle factors also aligns with the NIA strategic plan⁵ to improve the understanding of both: 1) individual effects on aging through a life course perspective and 2) factors that can improve the health of adults as they age with an eye towards informing intervention policies.

Certain lifestyle risk factors for postmenopausal women have a strong body of evidence supporting associations with breast cancer incidence, including body fatness,^{8–11} physical activity,^{12–15} alcohol use,^{16–19} and smoking status.^{20–24} At a minimum, risk-attributable fraction estimates indicate that one out of five postmenopausal breast cancer cases could be eliminated following modification of lifestyle, with body fatness, alcohol consumption, physical activity, and smoking contributing to this estimate.^{25–27} Importantly, these lifestyle risk factors that are associated with breast cancer are also among the top ten attributable causes of all-cause mortality.²⁸

The lifestyle risk factors mentioned above, such as alcohol use, also happen to have the strongest relationship with risk during the postmenopausal period. By focusing on the postmenopausal time, we can target risk factors that are sensitive for an aging population. Body fatness is another risk factor with a distinct positive association with breast cancer after menopause.²⁹ Taking advantage of the propensity for change in risk by lifestyle around that time can provide meaningful and actionable knowledge for interventions. Also, leveraging characteristics of a lifestyle factor, with a reduced dimension from several lifestyle indicators into one measure that incorporates the correlations between lifestyle indicators, could be a powerful tool to assess lifestyle change over time and to determine what patterns currently exist in a large U.S.-wide population of women entering the menopausal phase of their lives.

Studies of lifestyle change exist for women diagnosed with breast cancer, but no study to date has addressed this question prospectively in women without a diagnosis of breast cancer. This research gap creates a unique opportunity to better characterize the common risk predictors and examine change across the life course, considered two of the six critical areas of research by the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR).⁷ Longitudinal changes in a combined lifestyle factor index and its joint association with breast cancer incidence and all-cause mortality can capture the association between lifestyle change and its association with risk of disease and death.³⁰

Considerable research supports both the role of modifiable lifestyle factors, as noted above, and the genetic underpinnings of breast cancer risk. Combining these two exposures through gene by environment (hereafter “GXE”) analyses, forms our third research aim. Recent research considering GXE does not provide evidence of multiplicative interactions between genetic and certain lifestyle factors,^{31–33} but may point towards additive interactions related to breast cancer.³⁴ Our approach in Aim 3 to quantify breast cancer risk concentrations^{35–37} allows us to specify additive interactions and determine if groups bearing larger burdens of risk have stronger associations between genetic variants and breast cancer risk compared to the lowest risk groups. Considering this is an active area of research, it is important to fill these research gaps to determine if well-defined lifestyle factors modify the genetic associations with disease, which would be a novel contribution to this field of research. If so, lifestyle interventions could be personalized based on genetic susceptibility to breast cancer.

1.2 Innovation

1.2.1 Characterize lifestyle change over time

Lifestyle is commonly assessed on a cross-sectional basis, one variable at a time, to study associations with breast cancer risk. We will use data from a large prospective contemporary breast cancer cohort with four follow-up times, which allows us to assess longitudinal change. The factor analysis approach is novel for lifestyle research, and we can leverage correlated lifestyle indicators and summarize them in one measure.

1.2.2 Assess change in lifestyle in tandem with risk of breast cancer

Following implementation of the first aim, we will simultaneously evaluate the association between longitudinal change in the lifestyle factor, considered the exposure, and breast cancer risk with time-to-event data. Joint modeling of longitudinal change of an exposure and time to event data is a recently developed statistical application that has not been used in the context of associations between lifestyle and breast cancer risk and its use can provide a more granular picture of lifestyle change and cancer risk.

1.2.3 Use novel definition of risk associated with lifestyle groups to evaluate modification by established genetic underpinnings of breast cancer risk

Gene-environment analyses commonly assess the change in genetic risk across continuous or categorical measures of an exposure — lifestyle being one example. As an alternative, we plan to define the exposure in terms of its risk concentration using a common measure from economics that is just finding its way into the field of public health: the Lorenz curve. Assessing the exposure in this manner, common in fields such as economics, is less common in public health and has not been used to assess modifications of polygenic associations with breast cancer risk. Our aim is to use this novel application to determine if certain lifestyle groups with the highest burden of risk have stronger polygenic associations with breast cancer risk compared to groups with the lowest burden of risk. We can also use this knowledge to understand how shifting the burden of risk can affect public health interventions.

1.3 Approach

1.3.1 Overall research design

1.3.1.1 Participants and Setting

Sister Study cohort: The proposed study is part of a contemporary prospective cohort of 50,884 women ages 35-74 years of age from 2003 to 2009 who have not been diagnosed with breast cancer upon entry but have a previously diagnosed sister. I plan to use my K99/R00 award to assess a factor-analysis-based healthy lifestyle index based on each of four Sister Study follow-up questionnaires. We will choose healthy lifestyle indicators according to the World Cancer Research Fund and the American Institute for Cancer Research and the availability of repeated measures over the four follow-up surveys. The lifestyle factor will include indicators of body fatness, physical activity, alcohol use, and smoking. In addition to determining the relationship between the lifestyle factor index and breast cancer risk, this work will enable the R01 component to determine if certain lifestyle groups with the largest burden of lifestyle-based risk display stronger genetic associations with disease than groups carrying the lowest burden.

1.3.1.2 Data collection

The most recent Sister Study follow-up survey was between 2017-2019, the fourth follow-up, after three bi-annual follow-up surveys approximately 2-3 years apart following the enrollment period between 2003-2009. Participation in these surveys ranged from 95% in the first follow-up survey to 85% in the most recent fourth follow-up (Figure 1). Aims 1-3 will use the lifestyle measures from all four follow-up surveys in the subset of postmenopausal women. Data collection and management is centrally managed by contract through Social & Scientific Systems with a de-identified data release system that has been in place since 2003. We expect this reliable and structured data management system — including thorough data cleaning and handling — to continue throughout our study period, and we consider this efficiency a strength of our proposed research.

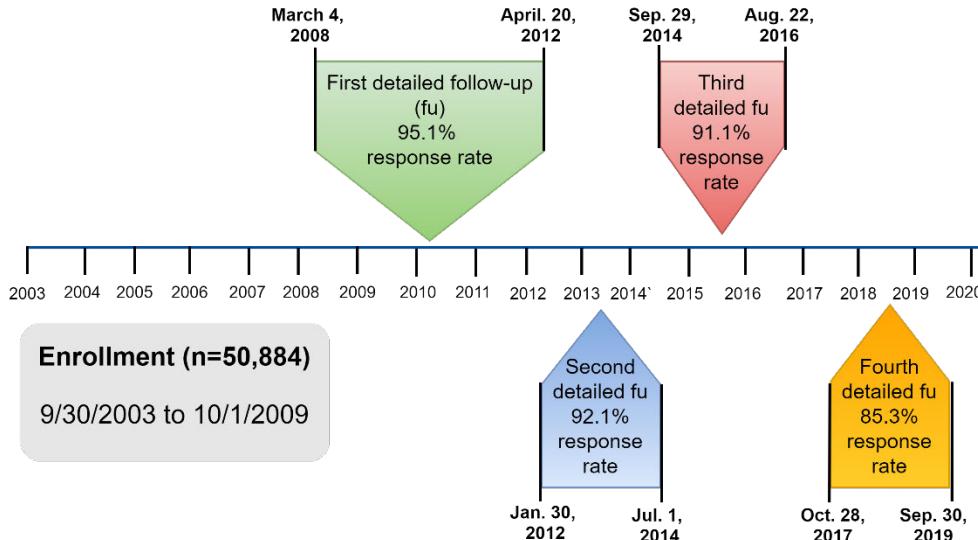


Figure 1. Follow-up information for the Sister Study

determine trajectories of these groups over a ten-year follow-up period during mid-life to late-life. To attain this aim, we will test the *working hypothesis* that correlated lifestyle factors associated with breast cancer risk will be defined as a single index, which will be consistently defined as an individual ages. Our *approach* to test this hypothesis will employ confirmatory factor analysis (CFA)^{38,39} to estimate a single factor as well as multi-level modeling to assess the factor change over age-time in a contemporary cohort exceeding 50,000 women. The *rationale* for this aim is to establish a well-characterized lifestyle factor reflecting the correlations of lifestyle indicators and its change over a ten-year age span. Upon completion of Aim 1, we *expect* to improve our understanding of distinct patterns of lifestyle change. Our findings from Aim 1 will assist the assessment of associations between lifestyle change and breast cancer risk in Aim 2.

1.3.2.2 Methods

Statistical analysis

We will use confirmatory factor analysis to identify a lifestyle construct from three variables representing evidence-based lifestyle components associated with breast cancer incidence, also called indicators: BMI, alcohol use, physical activity, and cigarette smoking. We will evaluate this factor across commonly studied subgroups, including racial/ethnic groups and molecular subtypes, to evaluate similarity across groups. If the factor loadings are similar across the subgroups and time, we will then pool the groups; otherwise, subsequent analyses will be stratified by the subgroups. Following assessment of factors at each of the four follow-up surveys, we will estimate longitudinal trajectories of these factors in postmenopausal women using a 'Curve-of-Factors Model' (CFM)⁴⁰ (Figure 2).

1.3.2.3 Expected Results/Outcomes

The main outcome is a lifestyle factor with three indicators, including body fatness, physical activity, and alcohol use. Estimates include cross-sectional measures of the lifestyle factor and trajectories over the four follow-up times. We expect the lifestyle indicators to have strong loadings to support the factor, and we expect the factor to remain equivalent over time to allow the assessment of longitudinal trajectories. We also expect there to be multiple trajectories of lifestyle change in this cohort of postmenopausal women.

1.3.2.4 Potential problems and alternative strategies

The lifestyle factor is a composite of various indicators, and it may not have a similar structure over time and/or across subgroups mentioned in Section 1.3.2.2, also known as measurement equivalence or invariance. If this measurement invariance assumption is violated then we cannot compare the lifestyle factor across time or across subgroups. Instead, some solutions include looking at each of the lifestyle indicators individually to assess their change over time and/or stratifying the lifestyle construct by subgroups.

1.3.2 Specific Aim 1: Characterize a lifestyle construct from indicators in a contemporary cohort of women and assess trajectories across age.

1.3.2.1 Introduction

Lifestyle is a frequent focus of health research, however research on lifestyle as a composite and inter-related measure as well as its change over time is needed. Our *objective* for this aim is to characterize several lifestyle indicators as a single index and

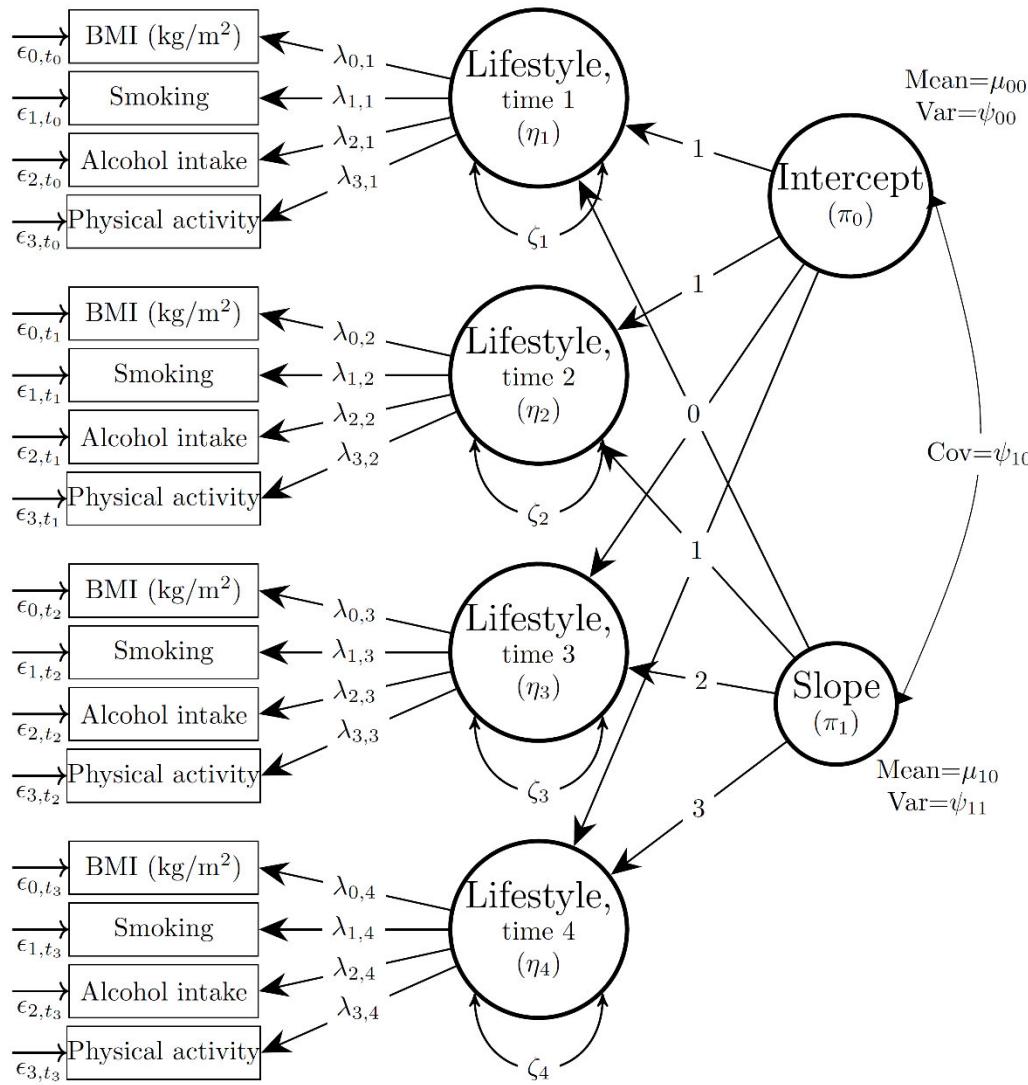


Figure 2. Curve-of-Factors Model for three key lifestyle indicators in postmenopausal women across four follow-up times.

factor followed by joint modeling of longitudinal and time to event methods to capture associations between lifestyle change and breast cancer risk and all-cause mortality. The *rationale* for this aim is to expand upon the existing, mostly cross-sectional, knowledge of lifestyle and breast cancer to add evidence regarding the role of healthy lifestyle change in reducing breast cancer incidence, necessary to understand how to best target prevention efforts. Upon completion of Aim 2, we *expect* to identify levels of lifestyle change associated with breast cancer incidence and all-cause mortality, which can inform prevention efforts.

1.3.3.2 Methods

Statistical analysis

Following characterization of a lifestyle factor and its change over both age and time in Aim 1, we will assess longitudinal trajectories of the factor, a “Curve-of-Factors” model, and time-to-event analyses via joint latent class models. These models allow us to assess the association between lifestyle change and risk of breast cancer all-cause mortality simultaneously over the four follow-up time points. The joint latent variable growth-survival analysis entails simultaneously specifying an intercept and slope from the lifestyle factor longitudinal model (Figure 2) and a time-to-event model for incident outcomes (Figure 3). Estimates from these joint regression models will yield estimates of the association between a lifestyle factor as a time-dependent

1.3.3 Specific Aim 2: Assess the relationships between the lifestyle factor changes and incident breast cancer and all-cause mortality outcomes.

1.3.3.1 Introduction
Lifestyle changes in midlife may set the stage for higher risk of breast cancer incidence and mortality yet no lifestyle measure exists as one comprehensive exposure. Our *objective* is to assess the change of a lifestyle factor over time and assess the association between these changes and breast cancer risk and all-cause mortality. To achieve this objective, we will test the *working hypothesis* that groups with improving lifestyle trajectories are at lower risk for breast cancer incidence and all-cause mortality. Our *approach* to test this hypothesis will be to identify correlated lifestyle characteristics associated with a “healthy lifestyle”

covariate and breast cancer incidence. Advantages of these models include the ability to accommodate simultaneous changes in exposure and risk over age-time, to better capture the role of lifestyle change in risk.

1.3.3.3 Expected Results/Outcomes

The expected outcomes are estimates of associations between longitudinal lifestyle factor patterns of change and breast cancer incidence and all cause mortality.

1.3.3.4 Potential problems and alternative strategies

As mentioned in section 1.3.2.4, we may not have factors that remain consistent over time. If that scenario

occurs, then we will treat each of the lifestyle variables related to postmenopausal breast cancer separately. Although this alternate analysis will no longer address co-occurring lifestyle variables, which we consider a strength of this proposed study, the analyses will still yield valuable information regarding simultaneous change over time with breast cancer risk for each of the lifestyle variables. This information does not exist in the literature and will still address the research gap. Also, different lifestyle factor specification over time will also constitute valuable information that motivate future research to determine predictors of these changes. For example, the association between exercise and body fatness may attenuate over time, leading to questions regarding what environmental conditions may influence this change. The potential challenges that may occur with the proposed research strategy have solutions,

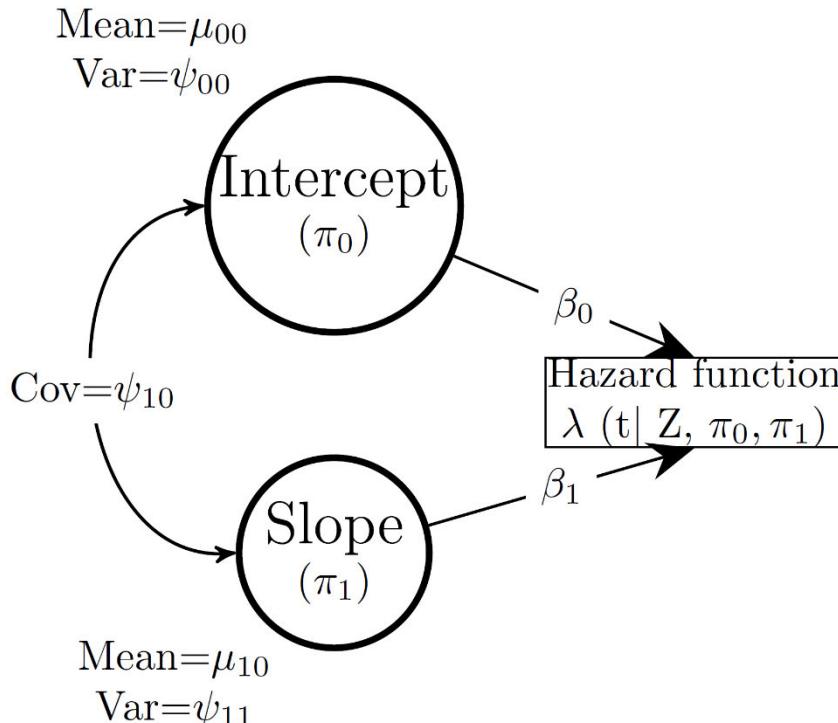


Figure 3. Model for joint analysis of factors and time to event models.

and the conditions that motivate this change are also of interest for this field of research.

1.3.4 Specific Aim 3: Assess associations between polygenic risk scores and breast cancer risk for lifestyle groups with highest disease burden compared to groups with lowest burden.

1.3.4.1 Introduction

Lifestyle and underlying genetic factors play an important role in cancer incidence yet the role of lifestyle as a modifier of the gene-breast cancer risk association remains under active investigation. The *objective* of this aim is to assess whether the joint effect of genetics and postmenopausal lifestyle characteristics is additive for breast cancer risk. To achieve our objective, we will test our *hypothesis* that women with adverse lifestyle characteristics and who are expected to have a disproportionately higher disease burden will also demonstrate stronger genetic associations with cancer incidence on an absolute scale compared to women with a favorable lifestyle and lower disease burden. Our *approach* to test this hypothesis will be in two steps: 1) to find high/low risk burden groups through risk inequality estimates determined by Lorenz curves of breast cancer risk concentration conditional on lifestyle factors, and 2) to determine additive effect modification of the genetic association with breast cancer risk by the high/low risk burden groups in time-to-event regression models. The *rationale* for this aim is to better understand how risk inequality can affect the impact of genetic variants on breast cancer risk and to use this information to identify subpopulations that would benefit most from prevention efforts. Once we accomplish our aim, we *expect* to identify groups with multiple, co-occurring

adverse lifestyle characteristics that have both higher breast cancer risk and display stronger genetic associations with breast cancer risk, supporting a role of risk inequality in gene-environment associations.

1.3.4.2 Methods

Statistical analysis

To assess effect modification of the genetic association with breast cancer incidence by lifestyle factors, we will create a risk inequality covariate and a polygenic risk score (PRS) to use in time-to-event regression models. To characterize risk inequality in breast cancer burden, we will use Lorenz curves, a method first used in the field of economics but of increasing use in epidemiology and public health,^{35,36,41,42} to estimate the concentration of absolute breast cancer risk conditional on lifestyle factors. Parametric time-to-event models enable the estimation of absolute breast cancer risk at attained ages for each individual according to their lifestyle factor values. At pre-specified attained ages (50-54, 55-59, 60-64, 65-70, etc...), we can estimate absolute breast cancer risk predicted from the lifestyle factor values then plot the cumulative number of risks versus individual cumulative absolute risk values ordered from lowest to highest risk to create a Lorenz curve (Figure 4). Should the curve follow a 1:1 diagonal line, the estimated risk would be evenly distributed across individuals. Conversely, a Lorenz curve deviating from a diagonal line indicates a disproportionate distribution of risk. In the example shown in Figure 4, 14% of people in this sample carry 25% of the absolute risk. Using that Lorenz curve, we will identify people who belong to upper and lower proportions of the sample with the highest and lowest concentration of risk to serve as the index and referent groups of a risk inequality variable, respectively. For example, we can then identify, characterize, and compare those individuals carrying the highest and lowest deciles of risk burden. This risk inequality approach also allows us to identify groups of lifestyle factors with a disproportionate amount of breast cancer incidence. In the second step, the breast cancer polygenic risk score and risk inequality variable will then be covariates in subsequent time-to-event

models to determine the presence of effect modification of the genetic associations due to uneven distribution of breast cancer risk.

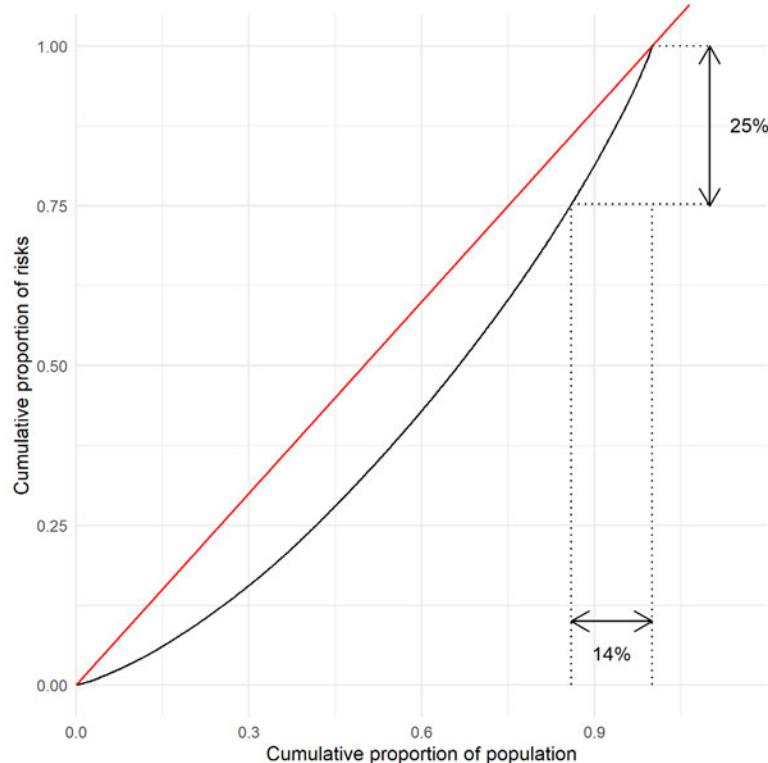


Figure 4. Sample Lorenz curve for lifestyle factors and risk.

1.3.4.3 Expected Results/Outcomes

The expected outcome will be estimates of differences in associations between polygenic risk scores and breast cancer incidence by groups of lifestyle characteristics carrying largest and smallest burdens of risk according to risk inequality measures.

1.3.4.4 Potential Problems and alternative strategies

In this aim we are relying on the distribution of breast cancer risk to be unequal to an extent that powers our comparisons of the genetic associations with breast cancer risk. This approach may not work if the concentrations of risk are evenly distributed, a situation we do not anticipate occurring given evidence for modifiable factors for breast cancer risk in this absolute risk reduction framework.³⁶ However, if this scenario occurs then we will consider separating out the risk factors and assessing them independently, under the assumption that both the risk factor and polygenic risk score are related to the incidence outcome.

If more than five percent of observations for combinations of the modifiable risk factors are missing, then we plan to incorporate multiple imputation methods^{43,44} to account for the missing data and allow us to proceed with planned analyses.

1.3.5 Preliminary data

In our exploratory analyses with self-reported data from 32,534 Sister Study participants who were postmenopausal at study entry, we found evidence to support a lifestyle factor at study entry. The factor loadings from the lifestyle factor (Figure 5), with three key lifestyle indicators, represent the association between a one unit increase in the standardized factor and that particular indicator. Fit indices are favorable with a Comparative Fit Index of 0.94 and root mean square error of 0.078. We will assume similar favorable model fit for the three subsequent time periods.

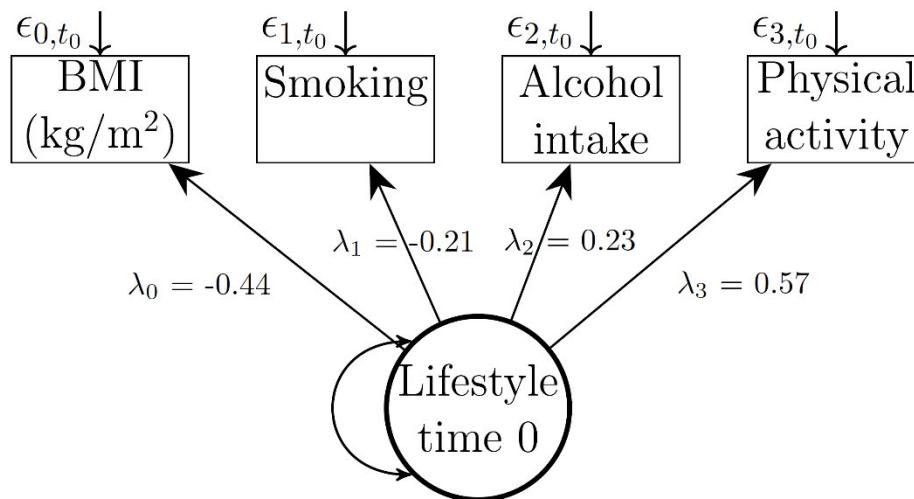


Figure 5. Factor analysis demonstration for three key lifestyle indicators in postmenopausal women at study entry.

indicators^{46,47} and alcohol use.⁴⁸ Inverse associations exist between physical activity⁴⁹ and a healthy diet^{50,51} with little evidence of an association with tobacco use.⁵² In Aim 2 we plan to use a lifestyle factor characterized by elements with the strongest body of evidence during *postmenopause* according to the World Cancer Research Fund,⁵³ including body fatness, physical activity, smoking, and alcohol use indicators, to determine how changes in this factor over time impact risk of breast cancer.

1.3.6 Sample size and statistical power

This study includes the subset of women in the Sister Study who are postmenopausal at study entry ($n>30,000$). Aim 1 centers on a structural equation model describing lifestyle factors in this group of women and their change over four time points. Using Monte Carlo simulations ($n=1,000$) with Mplus software⁵⁴ to estimate the power, we found that sample sizes of 500, 1,000, and 5,000 yielded statistical power of >0.95 , to detect a slope of 0.25 ($se=0.50$) for four evenly spaced lifestyle factors with three continuous normally distributed indicators and an alpha level of 0.05. For Aim 2, we used the same specifications from aim 1 in simulations to estimate the power to detect an association between the slope of lifestyle factor change over time and breast cancer incidence assuming a baseline hazard of 300 cases per 100,000 person-years and a hazard ratio of 1.2 ($se=0.04$). We found a power of 0.30, 0.56, and 0.99 at sample sizes of 500, 1,000, and 5,000, respectively. For Aim 3, we have a different analytical approach that compares absolute hazard differences for a one standard deviation change in the polygenic risk score for the lifestyle groups with the upper and lower decile of risk burden as demonstrated in Figure 4. According to this analytic design, our power when comparing the highest to the lowest decile of the risk burden was 0.53, 0.99 and 1 for 10%, 25%, and 50% increases, respectively, at an alpha level of 0.05 and sample size of 2,000 cases. Under these assumptions, we believe the sample size for these three aims are sufficiently powered to detect the proposed coefficient values with at least a power of 0.8 and alpha level of 0.05. These assumptions would also hold for mortality outcomes, which are more numerous than incident breast cancer cases in this sample of women with

1.3.5.1 Preliminary studies

Certain lifestyle characteristics are associated with postmenopausal breast cancer incidence in a large body of literature, including body fatness,⁸ alcohol use,¹⁶ physical activity,¹² and diet.⁴⁵ These important indicators have also been separately studied in relation to breast cancer risk in our proposed sample from the Sister Study. Measures of associations between lifestyle factors at study entry and breast cancer risk in the Sister Study include positive associations between body fatness

a median age exceeding 50 years at study enrollment. Importantly, the large sample size available through the Sister Study that allows us the ability to detect an effect remains even if we have to subset our sample by racial/ethnic groups or by molecular subtype groups, with participant counts as low as 500 for the first aim and 5,000 in the second aim.

1.3.7 Timeline and future directions

The timeline for the sequence of work necessary to complete the three aims is shown in Table 1. The estimates of association between lifestyle trajectories with breast cancer incidence and all-cause mortality from Aims 1 and 2 will be the first type of analysis of this kind, and form a basis for replication – consortial data being an ideal data source. Considering these trajectories continue beyond the first ten years of observation we observed in these aims, future analyses can also include longer follow-up times upon completion of the three aims to accommodate time lags between lifestyle and breast cancer incidence. Considering breast cancer recurrence and associations with lifestyle change is another important area of research that would be a natural extension of the proposed research. The broad applicability of these common risk factors, outcomes, and methods offers great potential for other types of future research and avenues for independent investigations. Two other promising downstream projects include: 1) change in lifestyle and associations with breast cancer incidence and all-cause mortality following major life events in mid- to late-life including menopause, retirement and bereavement, and 2) measures of epigenetic activity following lifestyle changes and its impact on breast cancer incidence and all-cause mortality stemming from work in Aim 3.

| | 2022 (Year 1) | 2023 (Year 2) | 2024 (Year 3) | 2025 (Year 4) | 2026 (Year 5) |
|------------------------------------|------------------|------------------|------------------|------------------|------------------|
| Aim 1 | | | | | |
| Data handling | | | | | |
| Analyses | | | | | |
| Manuscript preparation | | | | | |
| Manuscript submission and revision | | | | | |
| Aim 2 | | | | | |
| Data handling | | | | | |
| Analyses | | | | | |
| Manuscript preparation | | | | | |
| Manuscript submission and revision | | | | | |
| Aim 3 | | | | | |
| Data handling | | | | | |
| Analyses | | | | | |
| Manuscript preparation | | | | | |
| Manuscript submission and revision | | | | | |
| R01 grant writing/submission | | | | | |
| Initial submission | | | | | |

Table 1. Timeline

Responsible Conduct of Research (RCR) training at NIEHS

All NIEHS trainees and scientists participate in annual mandatory training in the Responsible Conduct of Research, under the direction of the NIH Committee on Scientific Conduct and Ethics. This training includes an array of required training that start as they begin their fellowship and follow with annual required participation in more training. Upon arrival to the NIEHS, trainees must take an online training course offered by NIH that covers the official NIH policy and procedures titled, "Guidelines for the Conduct of Research in the Intramural Research Program at NIH." While at NIEHS, trainees must continue their training in the "Responsible Conduct of Research", and their progress is tracked within NIEHS to ensure completion of the required elements of training. Continued training also includes a one-hour annual in-person training on ethics of research that is case-based and interactive. Topics for the ethics training are relevant to a broad audience of research-based scientists, and the course is administered by a doctoral-level bioethicist at NIEHS, who reports to the Deputy Ethics Counselor of the Institute. By following these required training components, trainees acquire a total of eight training hours in the Responsible Conduct of Research. The eight hours are divided into three components including: case studies in research ethics, an online training module on RCR, and attendance at a 6-hour in-person discussion of ethical research practices. In addition to research ethics topics as listed above, trainees are also required to complete an annual online training in computer security that covers data integrity, security procedures and how to handle 'Personal Identifiable Information'.

Prior instruction and participation in responsible conduct of research training

As an Intramural Research Trainee Award Postdoctoral Fellow at NIEHS, Ann has and is participating in the required responsible conduct of research training listed above. The specific courses she has taken since starting her fellowship in 2018 are listed in the table below.

| Date of Training | Course Name | Credit hours |
|--------------------|--|--------------|
| 9/4 and 10/10/2018 | Annual Review of Ethical Cases | 2 |
| 3/4/2019 | Responsible Conduct of Research (RCR): Online Training Module | 1 |
| 3/5/2019 | Discussion of Ethical Research Practices | 3 |
| 5/3/2019 | Research Mentor Training: Establishing Expectations and Effective Communications | 2 |
| 5/17/2019 | Research Mentor Training: Assessing Understanding/Ethics/Diversity | 2 |
| 5/31/2019 | Research Mentor Training: Identifying Mentor Challenges | 2 |
| 7/31/2019 | Introduction to "My Laboratory" | 1 |
| 7/31/2019 | Reproducibility Training | 1 |
| 2/10- 2/11/2020 | "Your Rights and Responsibilities as an NIH Trainee" Training | |
| 9/9/2020 | Annual Review of Ethics Cases | 1 |
| 9/18/2020 | Annual Review of Ethical Cases | 1 |
| 4/30/2021 | Research Mentor Training: Establishing Expectations and Effective Communications | 0.75 |
| 5/14/2021 | Research Mentor Training: Assessing Understanding & Fostering Ethics | 0.75 |
| 5/28/2021 | Research Mentor Training: Understanding Diversity & Identifying Mentoring Challenges | 0.75 |

Plans to receive responsible conduct of research training during the mentored K99 phase

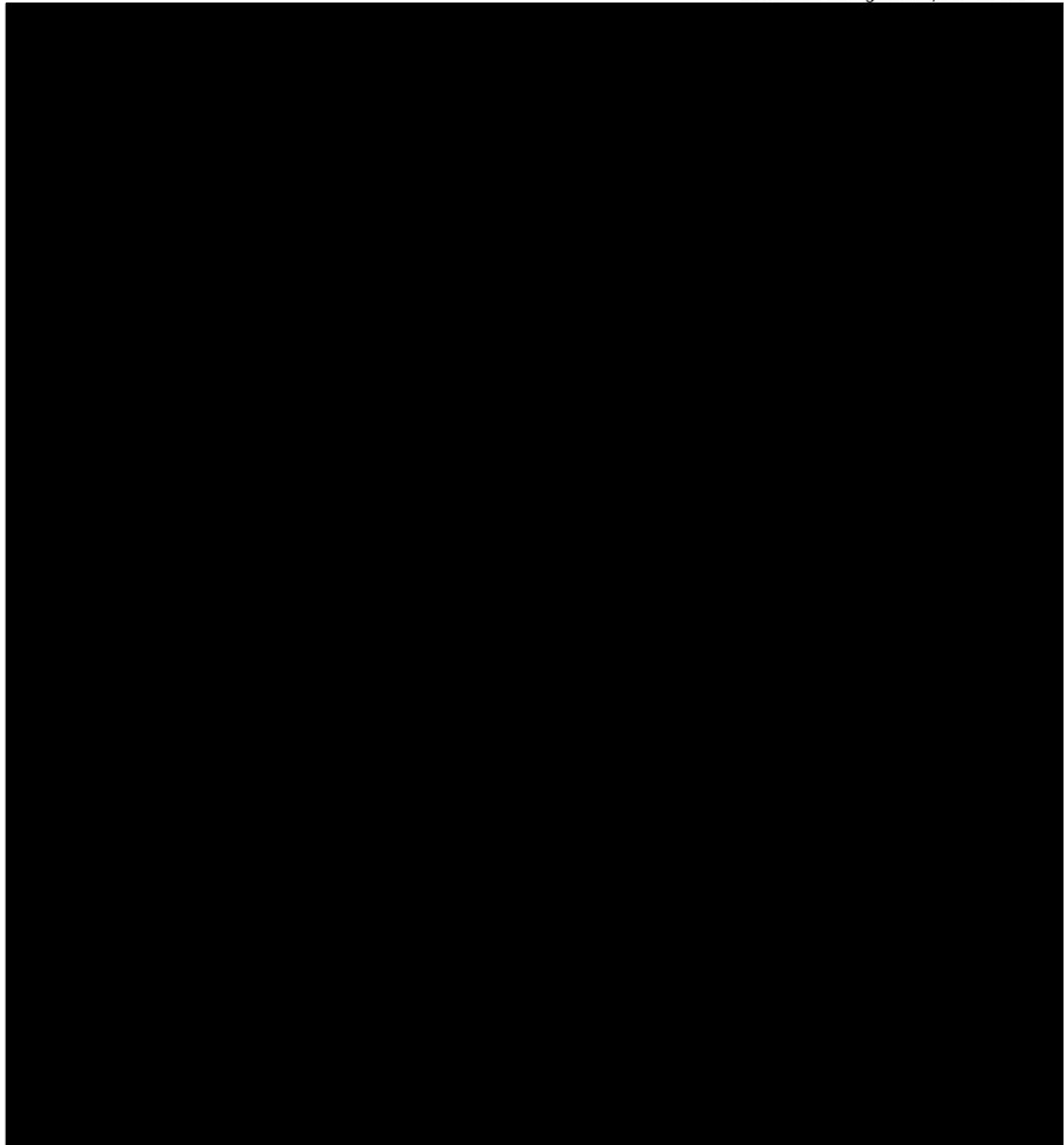
Dr. Von Holle will have the following plan to receive instruction so she can meet the required frequency of RCR training. First, she will continue to follow all annual required RCR training at NIEHS that is mentioned above. Second, she will continue to enlist the support of her mentor during her weekly meetings. Discussions at these meetings can include topics such as conflict of interest, manuscript authorship, and research ethics in general. Last, she will plan to attend at least two one-time topical seminars per year offered by the NIEHS Ethics Office.

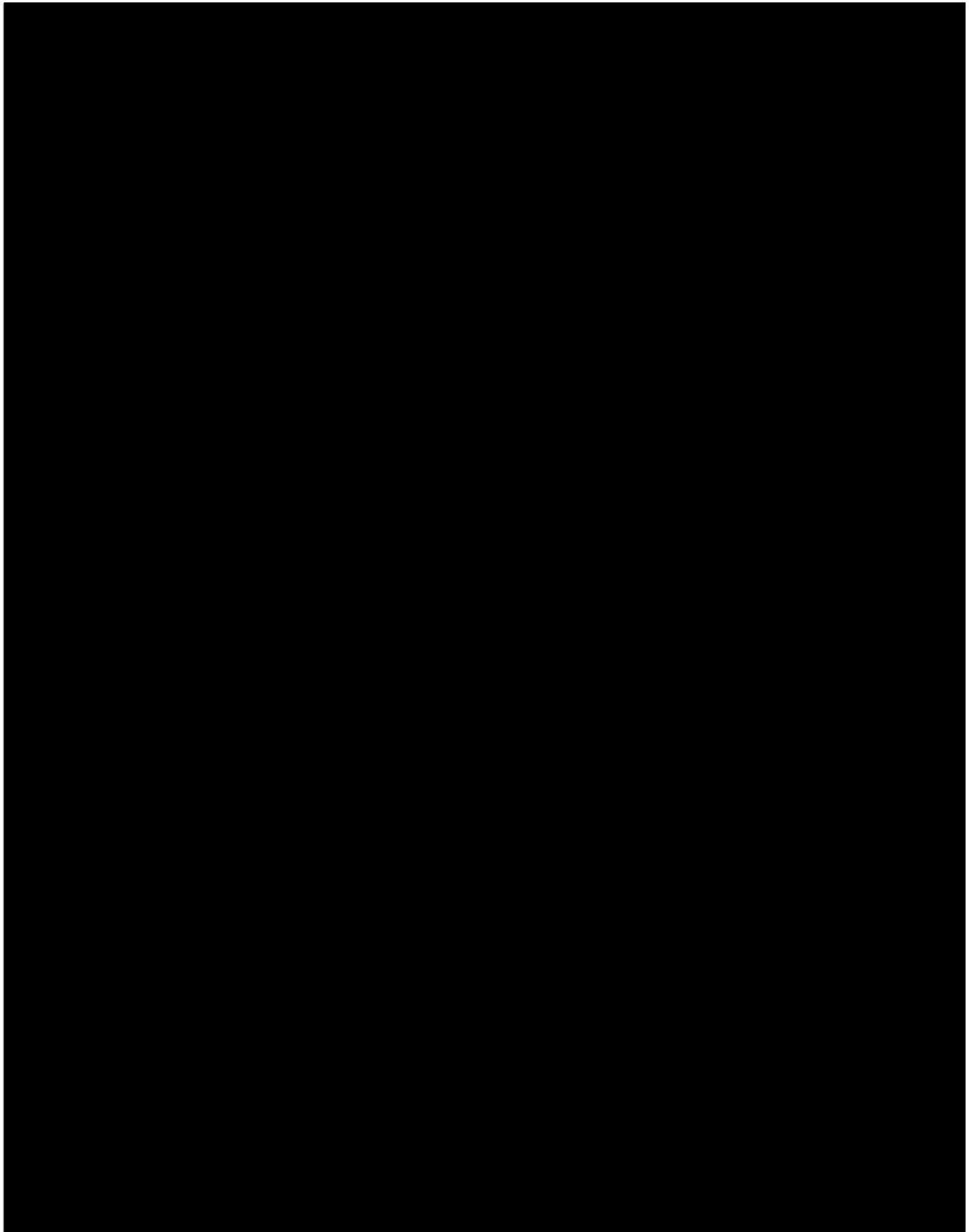


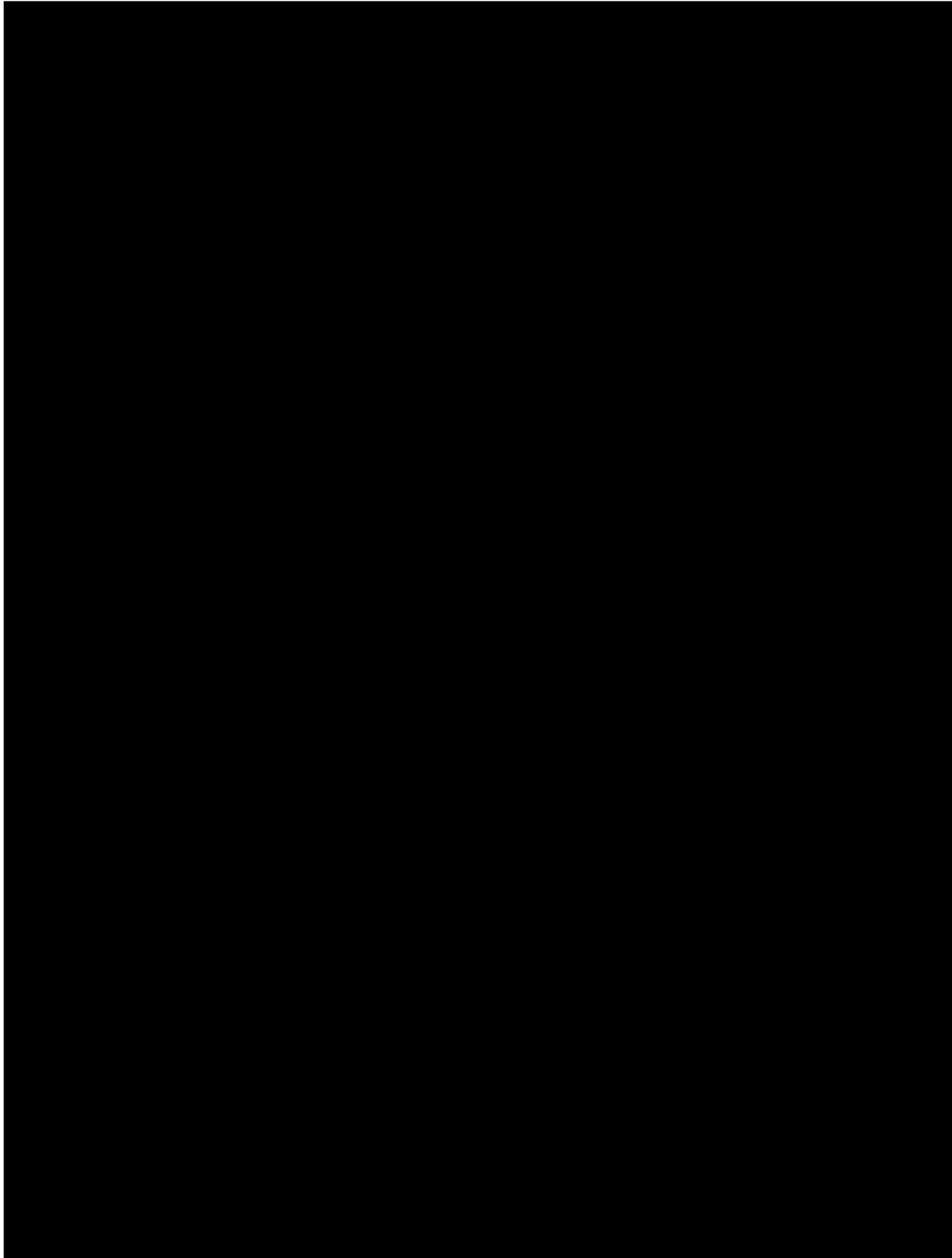
DEPARTMENT OF HEALTH & HUMAN SERVICES

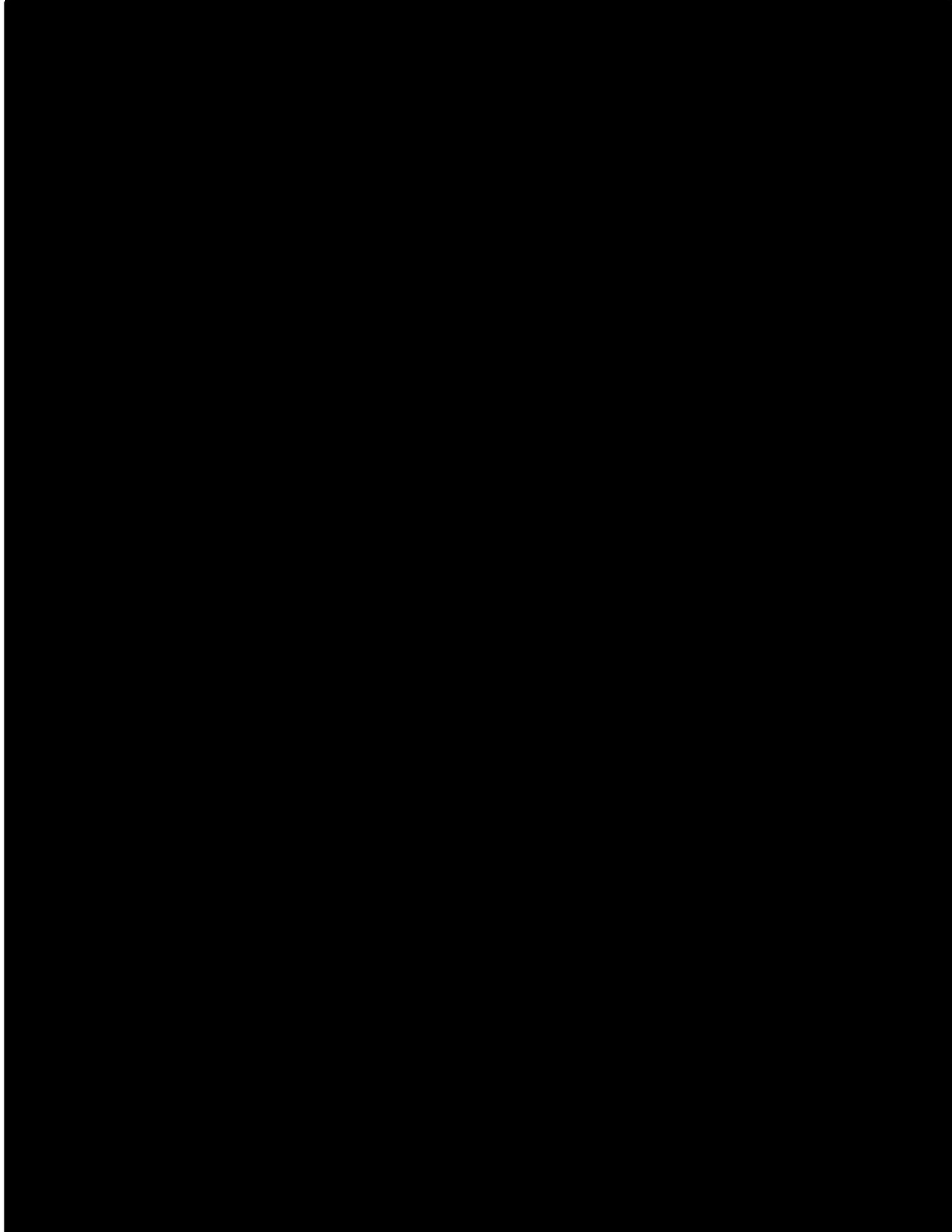
Public Health Service

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

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May 19, 2021



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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Description of Institutional Environment

The NIEHS Intramural Research Division offers both a dynamic and well-established training environment for Dr. Von Holle. With over 200 fellows and postdoctoral scientists each year engaging in research at NIEHS, there are many opportunities to learn from research across diverse disciplines and gain new perspectives as she completes and innovates upon her research. Also, at the institutional-level, the computing resources and software available through the Office of Scientific Computing at NIEHS will help her do large-scale and computationally demanding analyses as her research plan demands. For example, this office provides Ann access to the scientific software like Mplus that she needs to do the structural equation modeling techniques she will start using with her first aim. Furthermore, this software can be run on the high performance computing servers at NIEHS that will enable her to perform analyses as fast as possible. Trainees receive support in these areas to help them accomplish their research with the necessary computing power.

Within the Epidemiology and Biostatistics and Computational Biology branches at NIEHS, Ann will have access to a capable and extensive body of research expertise. Dr. Clarice R. Weinberg, her primary mentor, and a principal investigator at NIEHS, will continue her investment in Dr. Von Holle's progress. Her mentoring will entail continuing her weekly meetings with Ann to review her progress, working on manuscript development, and planning future steps in her job search and grant writing -- to name some of the most important elements of her career development and mentoring plan. With Dr. Weinberg, Dr. Dale P. Sandler will co-mentor Ann. Dr. Sandler is the chief of the Epidemiology Branch at NIEHS and the principal investigator of the Sister Study that started and continues at NIEHS. In this capacity, Dr. Sandler will ensure Ann has access to the Sister Study data that she needs throughout her time of the K99/R00 investigations. As co-mentor, she will also provide resources to Ann that are relevant to the epidemiological components of her research studying lifestyle exposures in the Sister Study population, as well as assist her in her job search towards the end of her mentored K99 phase. Another member of her mentorship team, Dr. Shanshan Zhao, an exceedingly talented biostatistician engaged in time-to-event research at NIEHS, will also be invaluable as Ann investigates breast cancer and mortality events occurring within the Sister Study.

In addition to the mentoring resources at NIEHS, Dr. Von Holle can avail herself of the institution-wide research integrity resources that are required for trainees and will be of particular use during her K99 mentoring phase. First, we have an Ethics Office, which provides required yearly ethics case discussions centered on contemporary topics selected by the NIH Committee on Scientific Conduct and Ethics. This office is also responsible for other required training including: computer security awareness, prevention of sexual harassment training, and disability awareness training. Second, the Office of Intramural Training and Education (OITE), under the direction of the Office of the Scientific Director, offers different training programs that can promote Ann's training and career development goals. She can enroll in speaking, writing, grant writing, and management courses. OITE also draws on the experiences of many successful independent investigators to share their scientific expertise in one-time sessions focused on domains such as grant writing, manuscript publication skills, and organization strategies. For example, a principal investigator who recently won the mentor-of-the-year award at NIEHS led a two-hour session on tips for manuscript development and publication for trainees. These resources are unique to our institute, and they offer Ann opportunities to enhance her career development goals.

In sum, the research environment at NIEHS is an outstanding place for Ann to pursue her proposed research aims, training and career development during the mentored K99 phase of her research. She will benefit from the well-established offices at NIEHS dedicated to supporting advanced scientific research. The independent investigators with advanced research programs from NIEHS that are a part of Ann's mentorship team will without a doubt offer her strong support in all her K99 mentoring phase research, training and career development. Finally, we have training in place for all levels of scientific research, and it can be a place for her to launch her independent career as an investigator, as many have done before her.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

June 3, 2021

RE: Institutional Commitment to PI - K99 mentoring
phase: Application of Ann Von Holle, Ph.D.

National Institutes of Health
National Institute of
Environmental Health Sciences
P. O. Box 12233
Research Triangle Park, NC 27709
Website: <http://www.niehs.nih.gov>

Dear Review Committee:

PHS Human Subjects and Clinical Trials Information

OMB Number: 0925-0001

Expiration Date: 02/28/2023

Use of Human Specimens and/or Data

Does any of the proposed research in the application involve human specimens and/or data *

Yes No

Provide an explanation for any use of human specimens and/or data not considered to be human subjects research.

1258-Human Subjects.pdf

Are Human Subjects Involved

Yes No

Is the Project Exempt from Federal regulations?

Yes No

Exemption Number

1 2 3 4 5 6 7 8

Other Requested Information

Explanation for any use of human specimens and/or data not considered to be human subjects research

My K99/R00 proposal does not involve human subjects. I will use data that involves human data from the Sister Study, led by Dr. Dale Sandler at the National Institute of Environmental Health Sciences (NIEHS). The data I propose to use, through the fourth follow-up survey ending in 2019, has already been collected. These data were not collected specifically for my proposed research. I cannot link any the information I will receive to do my analyses with any identifiable private information of living individuals due to the data release process described below.

The Sister Study data management is run by Social & Scientific Systems, a contract organization described in the 'Facilities and Other Resources Summary' section of this proposal. Their headquarters is in Silver Spring, MD, and they have a local company office close to NIEHS at 4505 Emperor Blvd Suite 400 Durham, NC, 27703. When this contract organization provides data to Sister Study data users such as myself, all data is de-identified with pseudo IDs. Also, certain types of variables may not be released to recipients given the potential to identify individuals. Any links to the de-identified data are held under secure conditions by the Sister Study Contractor. All studies are approved by the Sister Study steering committee and processed through the 'Sister Study Tracking and Review System' (STaRs; www.sisterstudystars.org). The K99 part of this proposal has been approved by the Sister Study Steering Committee as part of an 'Early Study Concept' submission, and principal investigators of the Sister Study are part of my mentorship team.