

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/>		
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Shanshan Zhao	NIEHS	Other Professional-Advisor
Nisha Gottfredson	University of North Carolina, Chapel Hill	Other Professional-Advisor

Reference Letters

Kari North	UNC	06/10/2021
Sheila Gahagan	University of California, San Diego	06/10/2021
Annie Green Howard	UNC - Chapel Hill	06/10/2021
Alison Motsinger-Reif	National Institute of Environmental Health Sciences	06/10/2021

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			
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Position/Title:	Director, Office of Fellows' Career Dev.		
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Phone Number*:	984-287-3651	Fax Number:	Email: tammy.collins@nih.gov
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"/> Renewal	<input type="radio"/> Continuation	<input type="radio"/> C. Increase Duration	<input type="radio"/> D. Decrease Duration
	<input type="radio"/> Revision	<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 Start Date* 04/01/2022		13. CONGRESSIONAL DISTRICTS OF APPLICANT Ending Date* 03/31/2027	
		NC-004	

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE**14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION**

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 Phone Number*: 984-287-4468 Fax Number: Email*: ann.vonholle@nih.gov

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	\$747,000.00
b. Total Non-Federal Funds*	\$0.00
c. Total Federal & Non-Federal Funds*	\$747,000.00
d. Estimated Program Income*	\$0.00

16. IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

- a. YES THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:
 DATE:
- b. NO PROGRAM IS NOT COVERED BY E.O. 12372; OR
 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: Dr. First Name*: Tammy Middle Name: R.L. Last Name*: Collins Suffix:
 Position/Title*: Director, Office of Fellows' Career Dev.
 Organization 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: MD A2-01, Room A226
 City*: Research Triangle Park
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 State*: NC: North Carolina
 Province:
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 ZIP / Postal Code*: 27709-2233
 Phone Number*: 984-287-3651 Fax Number: Email*: tammy.collins@nih.gov

Signature of Authorized Representative*

Tammy R Collins

Date Signed*

06/10/2021

20. PRE-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 Yes No 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.

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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 Dr. Dale Sandler 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*: Ann	Middle Name Frances	Last Name*: Von Holle
Position/Title*:	IRTA Fellow		
Organization 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		
Phone Number*:	984-287-4468	Fax Number:	
E-Mail*:	ann.vonholle@nih.gov		
Credential, e.g., agency login: ANNTHONYHOLLE			
Project Role*:	PD/PI		
Degree Type:	Ph.D.		
Attach Biographical Sketch*:	File Name:	1249-Ann-K99-biosketch.pdf	
Attach Current & Pending Support:	File Name:	1250-Current Research Support - Von Holle.pdf	

PROFILE - Senior/Key Person				
Prefix: Dr.	First Name*: Clarice	Middle Name R.	Last Name*: Weinberg	Suffix:
Position/Title*:	Principal Investigator			
Organization Name*:	National Institute of Environmental Health Sciences			
Department:	BCBB			
Division:	Div. of Intramural Research			
Street1*:	PO Box 12233			
Street2:				
City*:	Research Triangle Park			
County:	NC			
State*:	NC: North Carolina			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	27709-2233			
Phone Number*:	984-287-3697		Fax Number:	
E-Mail*:	weinberg@niehs.nih.gov			
Credential, e.g., agency login: ClariceWeinberg				
Project Role*:	Other Professional	Other Project Role Category: Mentor		
Degree Type:	Ph.D.	Degree Year: 1980		
Attach Biographical Sketch*:	File Name:	1251-biosketchWeinbergrev2-update.pdf		
Attach Current & Pending Support:	File Name:	1252-Current Research Support - Weinberg 2021 (1).pdf		

PROFILE - Senior/Key Person				
Prefix: Dr.	First Name*: Dale	Middle Name Health	Last Name*: Sandler	Suffix:
Position/Title*:	Senior Investigator and Chief, EB			
Organization Name*:	NIEHS			
Department:	Epidemiology Branch			
Division:	Div. of Intramural Research			
Street1*:	PO Box 12233 Mail Drop A3-03			
Street2:	111 TW Alexander Drive			
City*:	Research Triangle Park			
County:				
State*:	NC: North Carolina			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	27709-2233			
Phone Number*:	984-287-3711		Fax Number:	
E-Mail*:	sandler@niehs.nih.gov			
Credential, e.g., agency login: DPSAND				
Project Role*:	Other Professional	Other Project Role Category: Co-mentor		
Degree Type:	Ph.D.	Degree Year: 1979		
Attach Biographical Sketch*:	File Name:	1253-Biosketch_Sandler_VonHolleK99.pdf		
Attach Current & Pending Support:	File Name:	1254-Current Research Support - Sandler 2021 (1).pdf		

PROFILE - Senior/Key Person				
Prefix: Dr.	First Name*: Mary Beth	Middle Name	Last Name*: Terry	Suffix:
Position/Title*:	Professor			
Organization Name*:	Columbia University			
Department:	Epidemiology			
Division:				
Street1*:	722 West 168th Street			
Street2:	Room 1611			
City*:	New York			
County:				
State*:	NY: New York			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	10032-0000			
Phone Number*:	212-305-4915		Fax Number:	
E-Mail*:	mt146@columbia.edu			
Credential, e.g., agency login: MBTNYC				
Project Role*:	Other Professional		Other Project Role Category: Advisor	
Degree Type:	Ph.D.			
Degree Year:	1999			
Attach Biographical Sketch*:	File Name:	1255-Terry_biosketch.1-kathleen-rev.pdf		
Attach Current & Pending Support:	File Name:			

PROFILE - Senior/Key Person				
Prefix: Dr.	First Name*: Shanshan	Middle Name Health	Last Name*: Zhao	Suffix:
Position/Title*:	Principal Investigator			
Organization Name*:	NIEHS			
Department:	BCBB			
Division:	Div. Intramural Research			
Street1*:	PO Box 12233 Mail Drop A3-03			
Street2:	111 TW Alexander Drive			
City*:	Research Triangle Park			
County:	NC			
State*:	NC: North Carolina			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	27709-2233			
Phone Number*:	984-287-3702		Fax Number:	
E-Mail*:	shanshan.zhao@nih.gov			
Credential, e.g., agency login: szhao1				
Project Role*:	Other Professional		Other Project Role Category: Advisor	
Degree Type:	Ph.D.			
Degree Year:	2012			
Attach Biographical Sketch*:	File Name:	1256-Zhao_Biosketch_20210528.pdf		
Attach Current & Pending Support:	File Name:			

PROFILE - Senior/Key Person				
Prefix: Dr.	First Name*: Nisha	Middle Name	Last Name*: Gottfredson	Suffix:
Position/Title*:	Assistant Professor			
Organization Name*:	University of North Carolina, Chapel Hill			
Department:	Health Behavior			
Division:				
Street1*:	319C Rosenau Hall			
Street2:	CB #7440			
City*:	Chapel Hill			
County:				
State*:	NC: North Carolina			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	27599-0000			
Phone Number*:	919-445-9385		Fax Number:	
E-Mail*:	gottfredson@unc.edu			
Credential, e.g., agency login: NISHA_GOTTFREDSON				
Project Role*:	Other Professional		Other Project Role Category: Advisor	
Degree Type:	Ph.D.		Degree Year: 2011	
Attach Biographical Sketch*:	File Name:	1257-Gottfredson Biosketch Von Holle 5.19 2021.pdf		
Attach Current & Pending Support:	File Name:			

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): ANNTHONOLLE

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: Clarice R. Weinberg, Ph.D.

eRA COMMONS USER NAME (credential, e.g., agency login): ClariceWeinberg

POSITION TITLE: Senior Investigator, Biostatistics and Computational Biology Branch

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
Simmons College, Boston, MA	B.S.	05/1972	Mathematics
Brandeis University Waltham, MA	M.A.	05/1974	Mathematics
University of Washington, Seattle, WA	Ph.D.	12/1980	Biomathematics

A. Personal Statement

I am a biostatistician with substantial experience in epidemiology, currently a tenured Senior Investigator at the National Institute of Environmental Health Sciences, National Institutes of Health (NIH/NIEHS), in the Biostatistics and Computational Biology Branch. My research has focused on devising improved methods for design and analysis of epidemiologic studies, and applying those methods to epidemiologic research. Much of my work has concerned methods and applications specific to reproductive, radiation, genetic, environmental and, most recently, cancer epidemiology. Examples include devising study designs based on pooling of bio-specimens prior to assay, new methods of analysis for biomarkers when a high fraction of determinations fall below the assay limit of detection, and statistical genetics methods for family-based inference. Our impact is extended by providing free software to the public, and advising users in applying the methods. I have mentored 23 UNC doctoral students (serving as primary for 5), 2 currently, and 8 postdoctoral fellows at NIEHS. I serve as co-PI for the NIEHS prospective Sister Study (<http://sisterstudy.niehs.nih.gov/English/index1.htm>), for which we have assembled a cohort of 50,884 women who had never had breast cancer themselves at enrollment but were each the sister of a woman with breast cancer. As a biostatistician, I must secure outside funding for scientific projects that I lead and I was funded by Susan G. Komen for the Cure to launch my own companion case-control study, based on families with daughters discordant for young-onset breast cancer (and their parents). This "Two Sister Study" (<http://sisterstudy.niehs.nih.gov/English/2sis.htm>) yielded extensive genetic and environmental data. With my extensive research history directly related to the Sister Study and mentoring experience, I will support Ann as her primary mentor. This mentoring support will begin with her K99 mentored phase, with plans to continue our weekly meetings to discuss her research, responsible conduct of research, and future plans. Towards the end of her mentored phase I will also provide career-related advice during her job search and grant writing efforts.

B. Positions, Scientific Appointments and Honors**Positions and Scientific Appointments**

- 1980 - 1983 Acting Assistant Professor, Department of Biostatistics, Univ. of Washington, Seattle, WA
- 1980 - 1983 Acting Director, Biostatistics Core, Diabetes/Endocrinology Research Center, University of Washington, Seattle, WA
- 1989 - date Adjunct Professor, Department of Biostatistics, University of North Carolina, Chapel Hill, NC
- 1997 - date Adjunct Professor, Department of Epidemiology, University of North Carolina, Chapel Hill, NC
- 1983 - date Mathematical Statistician, Biostatistics and Computational Biology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, NC
- 1997 - date Chief, Biostatistics and Computational Biology Branch, NIEHS, Research Triangle Park, NC
- 1993 - 1999 Member, the Committee to Study the Mortality of Military Personnel Present at Atmospheric Tests of Nuclear Weapons, under the Institute of Medicine, National Academy of Sciences.
- Member, Subcommittee on Methods

	Member, Working Group on Dosimetry
1999 - 2002	Statistical editor, <i>American Journal of Epidemiology</i>
2000 - 2004	Member, Review Committee, Health Effects Institute, Cambridge, MA.
2001 - 2004	Member, committee to Review the Dose Reconstruction Program of the Defense Threat Reduction Agency, Board on Radiation Effects Research, the National Academies.
2001 - 2006	Member, Science Council for Radiation Effects Research Foundation, Hiroshima, Japan, for the Board on Radiation Effects Research, National Academies.
2007 – date	Member, American Epidemiological Society.
2007 - 2013	Statistical editor, <i>American Journal of Epidemiology</i>
2013 - date	Associate editor, <i>American Journal of Epidemiology</i>

Honors

1995	elected Fellow, American Statistical Association
1996	NIH Merit Award
1998	Bernard G. Greenberg Distinguished Lecturer, Dept. of Biostatistics, University of North Carolina.
2005	recipient, Nathan Mantel Award for lifetime statistical contributions to epidemiology
2005	recipient, Janet Norwood Award for contributions by a woman in statistics
2007	elected member, American Epidemiological Society
2009	Norman E. Breslow Distinguished Lecture, University of Washington, Seattle
2010	NIH Award of Merit (group) for the Sister Study
2010	Lowell Reed Lecture, American Public Health Association
2017	Director's Award for Outstanding Intramural Research, NIEHS
2019	Wacholder Distinguished Lecture at the National Cancer Institute
2020	Named a University of Washington School of Public Health "Changemaker," Among 50 out of 11,000 alumni https://sph.washington.edu/50-changemakers-public-health

C. Contributions to Science

Statistical methods for studying human fertility. Motivated by the North Carolina Early Pregnancy Study, I developed improved statistical approaches for studying human fertility, permitting assessment of sperm survival *in vivo*, the viable lifetime of the ovum *in vivo* and effects of environmental exposures on human reproduction.

1. Weinberg, C.R. and Gladen, B. The beta-geometric distribution applied to comparative fecundability studies. *Biometrics* **42**:547-560, 1986.
2. Weinberg, C.R., Gladen, B., and Wilcox, A.J. Models relating the timing of intercourse to the probability of conception and the sex of the baby. *Biometrics*, **50**(2): 358-367, 1994.
3. Weinberg, C.R., Baird, D.D., and Wilcox, A.J. Sources of bias in studies of time to pregnancy. *Statistics in Medicine*, **13**: 671-681, 1994.
4. Wilcox, A.J., Weinberg, C.R., and Baird, D.D. Timing of sexual intercourse in relation to ovulation - Effects on the probability of conception, survival of the pregnancy, and sex of the baby. *New England Journal of Medicine*, **333**(23): 1517-1521, 1995.

Confounding and causal inference in observational studies. My paper in 1993 challenged existing notions of confounding adjustment in epidemiology and raised key questions that helped usher in the age of directed acyclic graph theory, which has transformed how epidemiologists think about control of confounding bias in causal inference.

1. Weinberg, C.R. Toward a clearer definition of confounding. *American Journal of Epidemiology*, **137**(1): 1-8, 1993.

Family-based methods for identifying gene variants that contribute to young-onset disease. In 1998, I proposed an approach for genetic analysis of case-parent triad data that was robust to genetic population structure and offered major advantages over existing transmission-distortion approaches: the method enables inclusion of data from families with incomplete genotype information, permits assessment of maternal effects that act through the prenatal environment and can affect the health of offspring through their life course, and enables identification of parent-of-origin effects based on variants of imprinted genes.

1. Weinberg, C.R., Wilcox, A.J. and Lie, R.T. A log-linear approach to case-parent triad data: Assessing effects of disease genes that act directly or through maternal effects, and may be subject to parental imprinting. *American Journal of Human Genetics* **62**(4): 969-978, 1998.
2. Wilcox, A.J., Weinberg, C.R. and Lie, R.T. Distinguishing the effects of maternal and offspring genes through studies of 'case-parent triads.' *American Journal of Epidemiology* **148**(9): 893-901, 1998.
3. Weinberg, C.R. Allowing for missing parents in genetic studies of case-parent triads. *American Journal of Human Genetics* **64**(4): 1186-1193, 1999.
4. Weinberg, C.R. Methods for detection of parent-of-origin effects in genetic studies of case-parents triads. *American Journal of Human Genetics* **65**: 229-235, 1999.
5. Weinberg, C.R., Shi, M., and Umbach, D.M. Family-based case-control approaches to study the role of genetics, Chapter 26 in Handbook of Statistical Methods for Case-control Studies, edited by Borgan, Breslow, Chatterjee, Gail, Scott and Wild, CRC Press, Chapman and Hall, 2018.

Improving efficiency in environmental epidemiology through specimen pooling. Our paper on pooling published in 1999 was the first to propose and develop efficient methods based on specimen pooling for case-control studies, and spawned a new area of research in biostatistics/epidemiology.

1. Weinberg, C.R. and Umbach, D.M. Using pooled exposure assessment to improve efficiency in case-control studies. *Biometrics* **55**(3): 718-726, 1999.
2. Saha-Chaudhuri, P., Umbach, D.M. and Weinberg, C.R. Pooled exposure assessment for matched case-control studies. *Epidemiology* **22**(5): 704-12, 2011.
3. Saha Chaudhuri, P. and Weinberg, C.R. Specimen pooling for efficient use of bio-specimens in studies of time to a common event. *American Journal of Epidemiology* **178**(1): 126-135, 2013 (PMID 23821316).
4. Weinberg, C.R. and Umbach, D.M. Correction to "Using pooled exposure assessment to improve efficiency in case-control studies." (vol 55, p 718, 1999) *Biometrics* **70**(4):1061-1061, 2014.

Finding causal variants on the X chromosome. We developed a powerful and robust approach for identifying causative genetic variants on the X chromosome and extended it to allow effects of haplotypes.

1. Wise, A.S., Shi, M. and Weinberg, C.R. Learning about the X from our parents. *Frontiers in Genetics*, Feb 10; **6**:15, 2015.
2. Wise, A.S.* , Shi, M.* and Weinberg, C.R. Family-based multi-SNP X-chromosome analysis using parent information. *Frontiers in Genetics*, #178821, Feb 22;7:20, 2016. (*Joint first authors.)

A complete list of published work can be found at the following URL:

<https://www.ncbi.nlm.nih.gov/sites/myncbi/clarice.weinberg.1/bibliography/40974810/public/?sortby=pubDate&sdirection=descending>

D. Research Support

Source: Susan G. Komen for the Cure
Title: *the Two Sister Study*, a family-based study of genetic and environmental causes of young-onset breast cancer
Role: PI
Dates: 2007-2013

Source: National Institutes of Health, Office of Dietary Supplements
Title: The Joint Effects of Vitamin D, Genetics and Epigenetics in the Prevention of Breast Cancer
Role: Co-investigator (Principal Mentor, for Principal Investigator, Katie O'Brien, postdoctoral fellow)
Dates: 2014-2015

Source: Director's Award, NIEHS
Title: The Role of Iron in Breast Cancer Etiology and Survival
Role: PI
Dates: 2018-2019

Source: Office of Dietary Supplements, NIH
Title: Vitamin D and Breast Cancer in African-Americans: A Prospective Cohort Study
Role: Co-investigator
Dates: 2019-2020

BIOGRAPHICAL SKETCH

NAME: Dale P. Sandler, Ph.D.

eRA COMMONS USER NAME: DPSAND

POSITION TITLE: Senior Investigator and Chief, Epidemiology Branch

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
Boston University, Boston, MA	BA	05/1972	Mathematics
Yale University School of Medicine, New Haven, CT	MPH	05/1975	Epidemiology
Johns Hopkins University, Baltimore, MD	PhD	11/1979	Epidemiology

A. Personal Statement

My research focuses on environmental risk factors for chronic diseases. This work includes the impact of early life exposures, reproductive factors, lifestyle, occupational, and environmental exposures, and is carried out largely in the context of prospective cohort studies. I am principal investigator of ***The Sister Study***, a prospective cohort study of more than 50,000 sisters of women who have had breast cancer, designed to identify environmental and genetic factors that contribute to breast cancer and other health conditions in women (www.sisterstudy.niehs.nih.gov). Study participants provided extensive questionnaire data and biologic samples at enrollment, are followed annually for cancer incidence, and provide comprehensive follow-up information every 3 years. Women who developed breast cancer as of 2015 and a random sample of the cohort also provided a second set of blood, urine, and house dust samples about 5 years after enrollment. Using Sister Study data, I have published studies of lifestyle and environmental risk factors for breast cancer, obesity, and metabolic dysfunction, and have carried out agnostic and focused studies of genetic and epigenetic factors. Recent work includes studies of breast cancer and other outcomes in relation to exposure to air pollution and toxic metals at enrollment addresses and studies of dietary patterns. The cohort provides opportunities to study non-breast cancer outcomes, including recently, obesity and weight gain in relation to exposure to artificial light at night while sleeping (Park et al., 2019). The comprehensive data allow us to address complex questions such as the competing actions of diabetes and metformin treatment in relation to breast cancer risk (Park et al., 2021), and studies of associations with biomarkers such as vitamin D levels (O'Brien et al., 2017). My work is highly collaborative; I contribute data to many research consortia for breast, ovarian, and other cancers. Several extramural investigators have received grants for studies that leverage the Sister Study cohort. To address questions that cannot be studied well in a single cohort, I helped to establish a consortium of more than 20 prospective studies designed to collectively study premenopausal breast cancer. Through this pooling effort, we recently showed that breast cancer risk is increased shortly after a pregnancy and that this risk can last more than 20 years (Nichols et al., 2019). I am also Principal Investigator or co-Principal Investigator of two other large cohorts, the ***GuLF STUDY***, a study of health effects associated with oil spill cleanup (www.gulfstudy.nih.gov), and the ***Agricultural Health Study***, a study of health effects associated with pesticides and other agricultural exposures (www.aghealth.nih.gov). As PI of the Sister Study, I will provide Dr. Von Holle with access to needed data and share information needed to fully understand and take advantage of the comprehensive data we have collected. As co-mentor for her proposed K99/R00 research and training, I will advise on study design and data interpretation as well as professional development and career advancement, taking advantage of my experience as Epidemiology Branch Chief at NIEHS and years of experience mentoring other trainees and tenure track investigators.

1. O'Brien KM, Sandler DP, Taylor JA, Weinberg CR. Serum vitamin D and breast cancer within five years. Environ Health Perspect 2017; 125:077004. DOI: 10.1289/EHP943. E-pub 6 Jul 2017. PMID: 28728134.
2. *Nichols HB, *Schoemaker MJ, Cai J, Xu J, Wright LB, Brook MN, Jones ME, [multiple contributing authors in alphabetical order], ^Swerdlow AJ, ^Sandler DP (*Co-first authors; ^Co-senior authors).

- Breast cancer risk after recent childbirth: a pooled analysis in 15 prospective studies. *Annals Internal Med* 2019; 170:22-30. E-Pub 11 Dec 2018. PMID: 30534999.
3. Park YM, White AJ, Jackson CL, Weinberg CR, Sandler DP. Association of exposure to artificial light at night while sleeping with risk of obesity in women. *JAMA Intern Med* 2019; 10.1001/jamainternmed.2019.0571. E-pub 10 June 2019. PMID: 31180469. 3591PMCID: PMC6563591.
 4. Park YM, Bookwalter DB, O'Brien KM, Jackson CL, Weinberg CR, **Sandler DP**. A Prospective Study of Type 2 diabetes, metformin use, and risk of breast cancer. In press, *Annals Oncol* 2021: Doi: 10.1016/j.annonc.2020.12.008. E-E-pub 29 Jan 2021. PMID:33416778.

Positions and Honors

Positions and Employment

- 1979-1989 Staff Fellow, National Institute of Environmental Health Sciences (NIEHS), NIH, RTP, NC
1990-2001 Chief, Environmental and Molecular Epidemiology Section, NIEHS
1995-2000 Deputy Chief, Epidemiology Branch, NIEHS
2001-2003 Acting Chief, Epidemiology Branch, NIEHS
2004- Chief, Epidemiology Branch, NIEHS
1996- Adjunct Professor, Department of Epidemiology, University of North Carolina, Chapel Hill, NC

Other Professional Experience

- 1991-1998 President, American College of Epidemiology
1999-2000 Editor, American Journal of Epidemiology
2001-2007 Editor, Epidemiology
2009-2013 Member, Scientific, Translational and Clinical Scientific Review Committee, Cancer Prevention and Research Institute of Texas
2011-2017 Member, Steering Committee, Deepwater Horizon Research Consortium
2014-2017 Member, NIH DIR Epidemiology/Biometry Tenure Review Panel
2017-date Chair, NIH DIR Epidemiology/Biometry Tenure Review Panel

Honors and other scientific recognition

- Fellow, American College of Epidemiology
Elected to Membership, American Epidemiological Society, 1999
American College of Epidemiology Leadership and Distinguished Service Award, 2003
American College of Epidemiology Leadership Recognition, 2007
NIH Director's Award (The Sister Study), 2009
NIEHS Director's Award, 2009
NIEHS Scientist of the Year, 2010
NIEHS Directors Award, 2010
NIH Director's Award (The GuLF STUDY), 2011
Alpha Chapter, Delta Omega Honorary Society in Public Health, Johns Hopkins School of Public Health, 2012
NIEHS Mentor of the Year, 2013
NIH Merit Award, 2014
Nathan Davis Award for Outstanding Government Service, American Medical Association, 2015
Distinguished Scholar, Division of Cancer Epidemiology and Genetics, NCI, 2018
NIH Graduate Partnerships Program Outstanding Mentor Award, 2019
NIH Director's Award, 2019 (The Agricultural Health Study Research Team)

B. Contributions to Science

I have made multiple significant contributions to understanding environmental and lifestyle contributors to chronic diseases in adults. My work is unusual in its breadth and scope and is characterized by the use of novel methods and the incorporation of a range of biomarkers and approaches. The contribution for which I will be most credited is the creation of large-scale state-of-the-art cohorts that serve as platforms for studying a wide-range of hypotheses. My work has been cited over 18,000 times with an h-index of 71 according to the Web of Science. Google Scholar notes more than 33,000 citations, an h-index of 97 and an i10-index of 398. See bibliography at: <http://www.ncbi.nlm.nih.gov/sites/myncbi/dale.sandler.1/bibliography/48049936/public/>.

1. ***The Sister Study: Environmental and Genetic Contributors to Risk for Breast Cancer and Other Diseases in Sisters of Women with Breast Cancer.*** There was concern among breast cancer advocates that increasing breast cancer incidence between 1970 and the early 1990s was due to parallel increases in exposure to endocrine disrupting chemicals linked to mammary gland tumors and breast cancer in experimental studies. To address this, I developed a prospective study that overcomes the potential bias in case-control studies resulting from measuring exposures after breast cancer diagnosis. While prospective studies can be inefficient, the incidence of breast cancer among first-degree relatives is at least two-fold and, as we later demonstrated, the prevalence of any relevant gene variants and shared exposures is also increased among sisters of women with breast cancer. Thus, the Sister Study is more efficient than other cohorts and has greater statistical power for detecting gene-environment interactions. More than 200 papers have come from the cohort to date. Papers have focused on early life exposures, lifestyle factors, dietary patterns, environmental exposures such as air pollution, genetic factors, and hormonal and other exposure biomarkers related to breast cancer. With nearly 4000 incident breast cancer cases to date, we can now study genetic and epigenetic factors in breast cancer risk, risk prediction, and outcomes.
 - a. Sandler DP, Hodgson ME, Deming-Halverson SL, Juras PS, D'Aloisio AD, Suarez L, Kleeberger C, Shore DL, Bilhorn A, DeRoo LA, Taylor JA, Weinberg CR for the Sister Study team. *The Sister Study: Baseline methods and participant characteristics.* Environ Health Perspect 2017; 125:127003. E-pub 20 Dec 2017. PMID: 29373861. PMCID: PMC5963586.
 - b. Xu Z, Sandler DP, Taylor JA. Blood DNA methylation and breast cancer: A prospective case-cohort analysis in the Sister Study. *J Natl Cancer Inst* 2020; 112:87-94. doi.org/10.1093/jnci/djz065. E-pub 15 Apr 2019. PMID: 30989176. PMCID: 7489106.
 - c. Eberle C, Sandler DP, Taylor KW, White AJ. Hair dye and chemical straightener use and breast cancer risk in a large population of black and white women. *Int J Cancer* 2020; 147:383-391. DOI 10.1002/ijc.32738. E-pub 4 Dec 2019. PMID: 31797377. PMCID: PMC7246134.
 - d. Von Holle A, O'Brien KM, Sandler DP, Weinberg CR. Evidence for familial clustering in breast cancer age at onset. *Int J Epidemiol* 2021; 50:97-104. DOI:10.1093/ije/dyaa201, E-pub 28 Nov 2020. PMID: 33247915. PMCID: PMC7938508.
2. ***The Agricultural Health Study.*** This cohort study, a collaboration with the National Cancer Institute, was initially planned to assess cancer risk associated with use of pesticides. I helped to expand the study to spouses of applicators and added research on non-cancer endpoints plausibly linked to pesticides. The cohort, followed since enrollment in 1993-1997, is the largest cohort of licensed pesticide applicators in the US. It is unique in its characterization of exposures and outcomes in family members and the extensive exposure information collected. Since farmers and their families live where they work, wives and children incur bystander exposures that are relevant to the wider US population. We were among the first to report that pesticides, notably organochlorine insecticides, were associated with increased risk for developing diabetes and replicated this finding in a study of wives of pesticide applicators. We also showed that pesticide use is associated with risk for thyroid disease in applicators and spouses, Parkinson's disease, respiratory outcomes including wheeze and asthma, rheumatoid arthritis, and adverse reproductive outcomes such as gestational diabetes.
 - a. Hoppin JA, Umbach DM, London SJ, Henneberger PK, Kullman GJ, Alavanja MCR, Sandler DP. Pesticides and atopic and non-atopic asthma among farm women in the Agricultural Health Study cohort. *Am J Resp Crit Care Med* 2008; 177:11-18. PMC2176117.
 - b. Meyer A, Sandler DP, Beane-Freeman LE, Hofmann JN, Parks CG. Pesticide exposure and risk of rheumatoid arthritis among licensed male pesticide applicators in the Agricultural Health Study. In press, *Environ Health Perspect* 2017; 125 (7):077010. DOI:10.1289/EHP1013. E-pub 17 July 2017. PMID: 28718769. PMCID: PMC5744649.
 - c. Shrestha S, Parks CG, Goldner WS, Kamel F, Umbach DM, Ward MH, Lerro C, Koutros S, Hofmann JN, Beane Freeman LE, Sandler DP. Pesticide use and incident hypothyroidism in pesticide applicators in the Agricultural Health Study. *Environ Health Perspect* 2018; 126(9): 97008.doi.org/10.1289/EHP3194. E-pub 26 Sep 2018. PMID: 30256155. PMCID: PMC6375417.
 - d. Shrestha S, Parks CG, Umbach DM, Richards-Barber M, Hofmann JN, Chen H, Blair A, Beane Freeman LE, Tanner CM, Kamel F, Sandler DP. Pesticide use and incident Parkinson's disease in a cohort of farmers and their spouses. *Environmental Research* 2020. DOI: 10.1016/j.environres.2020; 191:110186. E-pub 10 Sep 2020. PMID: 32919961.

3. **The Gulf Long-term Follow-up Study (GuLF STUDY).** The GuLF STUDY was carried out to address a potential environmental health disaster following the *Deepwater Horizon* drilling rig explosion and subsequent oil spill in the Gulf of Mexico in April 2010. We enrolled (2011 and 2013) more than 30,000 oil spill clean-up workers and others who completed safety training but did not work on the clean-up and have been following them for self-reported health changes, cancer incidence, and mortality. Cohort members residing in one of five Gulf states completed home exams with collection of biological samples and measurement of blood pressure and lung function. A subgroup residing within 60 miles of a study clinic in Mobile, Alabama or New Orleans, Louisiana underwent a comprehensive clinical exam including additional lung function testing, standardized assessment of neurobehavioral function and comprehensive evaluation of mental health status and substance abuse. The study is distinguished by the level of effort devoted to exposure assessment in contrast to other oil spill studies that focus on work status or distance of the spill.
- a. Kwok RK, Engel LS, Miller AK, Blair A, Curry MD, Jackson WB, Stewart PA, Stenzel MR, Birnbaum LS, **Sandler DP** for the GuLF STUDY Research Team. The GuLF STUDY: A prospective study of persons involved in the *Deepwater Horizon* oil spill response and clean-up. *Environ Health Perspect* 2017; 125:570-578. PMID: 28362265. PMCID: PMC5382003.
 - b. Kwok RK, McGrath JA, Lowe SR, Engel LS, Jackson WB, Curry MD, Payne J, Galea S, **Sandler DP**. Mental health indicators associated with the 2010 *Deepwater Horizon* oil-spill: A cross-sectional analysis of the GuLF STUDY. *Lancet Public Health* 2017; 2:e560-e567. PMID: 29253441.
 - c. Gam KB, Kwok RK, Engel LS, Curry MD, Stewart PA, Stenzel MR, McGrath JA, Jackson WB, Jensen RL, Lichtveld MY, Miller AK, Keil A, **Sandler DP**. Lung function in oil spill response workers 1-3 years after the Deepwater Horizon disaster. *Epidemiology* 2018; 29:315-322. E-pub 29 Jan 2018. PMID:2938142.
 - d. Lawrence KG, Keil AP, Garantziotis S, Stewart PA, Stenzel MR, McGrath JA, Jackson WB, Curry MD, Kwok RK, Engel LS, **Sandler DP**. Lung function in oil spill responders 4-6 years after the Deepwater Horizon disaster. *J Tox & Environ Health, Part A: Current Issues* 2020; 83:233-248. DOI: 10.1080/15287394.2020.1745111. E-pub 5 Apr 2020. PMID: 32249687. PMCID: pending

C. Research Support

Current NIH Intramural Research Support

ENVIRONMENTAL AND GENETIC RISK FACTORS FOR BREAST CANCER: THE SISTER STUDY
NIEHS ZO1-ES044005 (Sandler) 2003-date

HEALTH EFFECTS OF EXPOSURES IN AGRICULTURE
NIEHS ZO1- ES049030 (Sandler) 2001-date

GULF LONGITUDINAL FOLLOW-UP (GULF) STUDY
NIEHS ZO1-ES102945 (Sandler) 2010-date

THE TWO SISTER STUDY
NIEHS ES102245 (Weinberg; Sandler Co-Investigator)) 2010-2016

Outside Funding (since 2010)

As an NIH Intramural investigator, salary and most research costs are funded by the Intramural Research Program budget of the National Institute of Environmental Health Sciences. However, additional funding has been awarded by NIH-wide and other governmental sources and competitive grants:

Department of Defense Breast Cancer Research Program (S. Kim, NIEHS Fellow) 2009-2012
URINARY LEVELS OF PROSTAGLANDIN E2 METABOLITE AND RISK OF INCIDENT BREAST CANCER
Role: Mentor

Centers for Disease Control (D.P. Sandler)	2011-2013
QUALITY OF LIFE IN BREAST CANCER SURVIVORS AND THE IMPACT OF A BREAST CANCER	
DIAGNOSIS ON FAMILIES	
Role: Principal Investigator	
Avon Foundation (H. Nichols)	2012-2014
REPRODUCTIVE HORMONES, CENTRAL ADIPOSITY, AND OXIDATIVE STRESS IN PREMENOPAUSAL	
WOMEN	
Role: Co-Investigator	
NCI U01. (P. Tranifar)	2017-2020
INTEGRATING MAMMOGRAMS IN ANALYSIS OF GENES AND ENVIRONMENT IN SISTERS (IMAGES)	
Role: Co-Investigator.	
Department of Defenses (W81xWH-17-1-0536). (H. Chen)	2017-2021.
AIR POLLUTANTS AS TRIGGERS OF PARKINSON'S DISEASE VIA THE OLFACTORY SYSTEM.	
Role: Co-Investigator	
NIH R01 (ES-27696-01A1) (J. Kaufman)	2017-2020
AIR POLLUTANTS AND CARDIOVASCULAR RISK: INVESTIGATING THRESHOLDS WITH POOLED	
COHORTS AND ELECTRONIC HEALTH RECORDS.	
Role: Co-Investigator	
NIH Office of Dietary Supplements (M. Park, NIEHS Postdoctoral fellow)	2017-2018
β-CAROTINE SUPPLEMENTS, DIETARY AND CIRCULATING CAROTENOIDS, OXIDATIVE STRESS, AND	
INFLAMMATION IN RELATION TO BREAST CANCER RISK	
Role: Mentor	
NIH Office of Research on Women's Health (Alexandra White)	2019-2020
TOXIC METALS AND BREAST CANCER RISK.	
Role: Co-investigator	
NIH Office of Dietary Supplements (Katie O'Brien)	2017-2018
VITAMIN D AND BREAST CANCER IN AFRICAN AMERICAN WOMEN: A PROSPECTIVE COHORT STUDY.	
Role: Mentor	

BIOGRAPHICAL SKETCH

NAME: Mary Beth Terry, Ph.D.

ERA COMMONS USER NAME (credential, e.g., agency login): MBTNYC

POSITION TITLE: Professor of Epidemiology

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)	Completion Date MM/YYYY	FIELD OF STUDY
George Washington University, Washington, D.C.	BA	05/1988	International Affairs
University of Washington, Seattle, Washington	MA	05/1990	Economics
Columbia University New York, New York	Ph.D.	05/1999	Epidemiology

A. Personal Statement

My research focuses on etiology and prevention of cancer with a primary focus on breast cancer. I have led molecular epidemiologic studies focusing on the role of genetics, epigenetics, and other biomarkers in modifying and sometimes mediating the effects of environmental exposures for over 20 years. Currently, I lead large family-based cohorts which integrate pedigree, clinical, genetic and epidemiologic data. I have served as the PI for the New York site of the Breast Cancer Family Registry (BCFR) for over 15 years and I currently serve as Contact PI for the entire international BCFR. I also serve as the contact PI of DNA Repair Phenotype: the missing link in Breast Cancer Risk Assessment. In addition to my research, I have served as Associate Director for Education for the Herbert Irving Comprehensive Center (HICCC). I am also a Co-Director of the HICCC CURE program and Co-Leader of our Population Sciences Program and I am an MPI on our NCI T32 Training Grant in Population Sciences. I also serve as MPI of the HICCC T32 in cancer epidemiology and I am a committed mentor and dedicated to training the next generation. In 2013 I received the Dean's inaugural award for mentoring. With this background, I am well positioned to advise Dr. Von Holle as she moves into her mentored K99 phase and through the R00 phase, especially with respect to her third aim to examine gene-environment interactions.

B. Positions and Honors**Positions and Employment**

1990-1993	Econometrician, Systems Research and Applications (SRA) Corporation; Arlington, VA; Resource Management Program, Systems Analysis Group.
1993-1994	Research Assistant, New York University Medical Center; New York, NY; Department of Environmental Medicine.
1994-1999	Research Analyst, Columbia University School of Public Health; Division of Epidemiology; New York, NY.
1996	National Science Foundation Graduate Fellow to National Cancer Center, Tokyo, Japan.
1996-1999	Adjunct Professor of Epidemiology and Health Economics, New York University, Wagner School of Public Service, New York, NY.
1999-2005	Assistant Professor of Epidemiology, Joseph L. Mailman School of Public Health, Columbia University
2005-2009	Associate Professor of Epidemiology, Joseph L. Mailman School of Public Health, Columbia University
2009-2013	Associate Professor (with tenure) of Epidemiology, Joseph L. Mailman School of Public Health, Columbia University
2013-present	Professor (with tenure) of Epidemiology, Joseph L. Mailman School of Public Health, Columbia University

Other Experience, Honors, and Professional Memberships

1996-present	American Society for Preventive Oncology (ASPO)
2007-present	ASPO Executive Board Member, Elected October, 2007
2007-present	ASPO Screening Interest Group Chair
2002-present	Society for Epidemiologic Research

2001-present	American Association for Cancer Research
2001-present	Elected Member, Alumni Executive Board, Mailman School of Public Health, Columbia University, New York, NY
2009-present	Member Advisory Board, The Arkansas Women's Health Cohort (Spit for the Cure), University of Arkansas Medical Center
2009-present	Invited Member, Advisory Board for the Patient-Oriented Research Master's Program (MS/POR) of the Mailman School of Public Health
2009-present	Invited Member, Scientific Advisory Council, City University of New York, School of Public Health
2010-present	Accepted Member, Glenda Garvey Teaching Academy Columbia University
2013	Dean's Excellence in Mentoring Award
2018	Susan Bulkeley Leadership Award, International Breast Cancer Nutrition Network
2019-present	Associate Director for Population Science and Community Outreach, Herbert Irving Comprehensive Cancer Center

Other Professional Activities: Peer Review Panels

International Panels:

2007	Member, Scientific Review Panel, National Cancer Institute of Canada (February)
2008	Member, Scientific Review Panel, National Cancer Institute of Canada (February)
2009	Member, Medical Research Council (UK) Ad-hoc Review Committee
2010	Member, Scientific Review Panel, National Cancer Institute of Canada (February)
2011	Chair, Scientific Review Panel, National Cancer Institute of Canada (February)

NIH panels:

2001	Member, Scientific Review Group (EDC2), NCI/NIH (February)
2003	Member, Scientific Review Group (EDC2), NCI/NIH (June)
2004	Member, Scientific Review Group (ZRG 1HOP N02), NCI/NIH (July)
2006	Member, Scientific Review Group (ZRG 1HOP N03), NCI/NIH (November)
2007	Member, Scientific Review Group (ZRG 1HOP N03 M), NCI/NIH (November)
2009-2012	Standing Member, Scientific Review Group (NCI-F), Nominated 2008, Term from January 2009- January 2012, Committee to Review Training Grant Applications and Career Development Awards.
2009	Member, Scientific Review Group (NIH/EPIC Member CF SEP) NCI/NIH (June)
2014	Member, PDQ, NCI Guidelines Committee for Breast and Ovarian Cancer
2014	Member, NCI K22 Scientific Review Committee (NCI ZCA1 RTRB)
2018	Member, Board of Scientific Counselors, DCEG, NCI

Other Governmental Panels:

2006	Member, Molecular Biology and Genetics Panel 2, Department of Defense, Breast Cancer Research Program (August)
2009	Member, Review Committee for the NCI Nutritional Epidemiology Branch (May)
2010	Member, Contract Review for Women's Health Initiative Extension, NHLBI
2013	Member, Site-Visit Team, Minnesota Cancer Comprehensive Center
2014	Member, Site-Visit Team, NCI Hormonal Cancers Branch
2015	Ad hoc Member, NCI P01 Review Panel
2017	Member, Site-Visit Team, NCI Epidemiology and Biostatistics, OD

C. Contribution to Science

1. Molecular and Tumor Heterogeneity of Breast Cancer Risk: When I started leading my own research projects in 1999, the importance of tumor heterogeneity for treatment was becoming increasingly clear. It was less clear whether etiologic factors differed by breast cancer molecular subtype and histology. Clear differences in risk factors by tumor subtype provide essential evidence that risk factor associations, particularly for factors that cannot be randomized (e.g., oral contraceptive use, parity, breast feeding, and smoking), with breast cancer risk are causal as it is unlikely that measurement issues with the reporting of exposure information differ by tumor subtype. For example, we were the first to provide evidence that oral contraceptive use is implicated in Cyclin D breast tumors, a cell cycle protein that is regulated by the hormonal environment. We provided the first evidence that the association between aspirin and NSAID use and breast cancer risk was associated with hormone receptive positive tumors, a finding that was subsequently supported by more mechanistic work. We also showed that the increased risk of estrogen receptor negative breast cancer from multiparity can be mitigated by breastfeeding.

- a. Reproductive risk factors and oestrogen/progesterone receptor-negative breast cancer in the Breast Cancer Family Registry. Work ME, John EM, Andrulis IL, Knight JA, Liao Y, Mulligan AM, Southey MC, Giles GG, Dite GS, Apicella C, Hibshoosh H, Hopper JL, **Terry MB**. *Br J Cancer*. 2014 Mar 4;110(5):1367-77. Epub 2014 Feb 18. PMID: 24548865. PMC3950851.
- b. Risk factors for uncommon histologic subtypes of breast cancer using centralized pathology review in the Breast Cancer Family Registry. Work ME, Andrulis IL, John EM, Hopper JL, Liao Y, Zhang FF, Knight JA, West DW, Milne L, Giles GG, Longacre TA, O'Malley F, Mulligan AM, Southey MC, Hibshoosh H, **Terry MB**. *Breast Cancer Res Treat*. 2012 Apr 25. PMID: 22527103.
- c. Association of frequency and duration of aspirin use and hormone receptor status with breast cancer risk. **Terry MB**, Gammon MD, Zhang FF, Tawfik H, Teitelbaum SL, Britton JA, Subbaramaiah K, Dannenberg AJ, Neugut AI. *JAMA*. 2004 May 26;291(20):2433-40. PMID: 15161893.
- d. Oral contraceptive use and cyclin D1 overexpression in breast cancer among young women. **Terry MB**, Gammon MD, Schoenberg JB, Brinton LA, Arber N, Hibshoosh H. *Cancer Epidemiol Biomarkers Prev*. 2002 Oct;11(10 Pt 1):1100-3. PMID: 12376514.

2. Role of the Environment and Markers of the Environment across the Lifecourse. Most research on environmental factors and breast cancer risk has focused on average risk women, and most studies of high risk women has focused on genes. In a series of studies, we have shown that biomarkers that are altered throughout the lifecourse by exogenous and endogenous factors play a role in modifying cancer risk even within high risk families. We have shown that women who were affected with breast cancer had lower global DNA methylation, poorer DNA repair, and higher levels of oxidative stress than their unaffected sisters, suggesting that the environment has an impact even within high risk women. Further, we have shown that exposure to known carcinogens, like prenatal smoke, can affect DNA methylation markers later in life.

- a. Prenatal Smoke Exposure and Genomic DNA Methylation in a Multi-ethnic Urban Birth Cohort. Flom JD, Ferris JS, Liao Y, Tehranifar P, Belessiotis Richards C, Cho YH, Gonzalez K, Santella RM, **Terry MB**. *Cancer Epidemiol Biomarkers Prev*. 2011 Oct 12. PMID: 21994404. PMC3559183.
- b. DNA double-strand break repair genotype and phenotype and breast cancer risk within sisters from the New York site of the Breast Cancer Family Registry (BCFR). Wu HC, Delgado-Cruzata L, Machella N, Wang Q, Santella RM, **Terry MB**. *Cancer Causes Control*. 2013 Dec; 24(12):2157-68. PMID: 24062231. PMC3947831.
- c. Dependence of cancer risk from environmental exposures on underlying genetic susceptibility: an illustration with polycyclic aromatic hydrocarbons and breast cancer. Shen J, Liao Y, Hopper JL, Goldberg M, Santella RM, **Terry MB**. *Br J Cancer*. 2017 Apr 25;116(9):1229-1233. PMID: 28350789. PMC5418454.
- d. Associations of prenatal exposure to polycyclic aromatic hydrocarbons with pubertal timing and body composition in adolescent girls: implication for breast cancer risk. Kehm RD, Oskar S, Tehranifar P, Zeinomar N, Rundle AG, Herbstman JB, Perera F, Miller RL, **Terry MB**. *Environmental Research*. 2020; doi:10.1016/j.envres.2020.110369.

3. Studies of Mammographic Density. Studies of lifecourse risk factors for diseases of long induction require intermediate markers. I have conducted birth cohort, community, and longitudinal studies of breast density. This collection of work has shown that prenatal exposures can influence breast density, that breast density tracks with exposures across first and second generation immigrants, and that changes in breast density predict cancer risk. Specifically, women whose breast density does not decrease over time are more likely to go on to be diagnosed with invasive breast cancer than women whose breast density declines with time. This suggests, ultimately, that within-individual changes may be more predictive of risk than single time point comparisons across women.

- a. Changes in mammographic density over time in breast cancer cases and women at high risk for breast cancer. Work ME, Reimers LL, Quante AS, Crew KD, Whiffen A, **Terry MB**. *Int J Cancer*. 2014 Oct 1;135(7):1740-4. PMID: 24599445. PMC4107003.
- b. Nonsteroidal anti-inflammatory drugs and change in mammographic density: a cohort study using pharmacy records on over 29,000 postmenopausal women. **Terry MB**, Buist DS, Trentham-Dietz A, James-Todd TM, Liao Y. *Cancer Epidemiol Biomarkers Prev*. 2008 May;17(5):1088-95. PMID: 18483330. PMC4072457.
- c. Risk factors for a causal intermediate and an endpoint: reconciling differences. **Terry MB**, Neugut AI, Schwartz S, Susser E. *Am J Epidemiol*. 2000 Feb 15;151(4):339-45. PMID: 10695592

- d. Do Birth Weight and Weight Gain During Infancy and Early Childhood Explain Variation in Mammographic Density in Women in Midlife? Results From Cohort and Sibling Analyses. **Terry MB**, Cohn BA, Goldberg M, Flom JD, Wei Y, Houghton LC, Tehranifar P, McDonald JA, Protacio A, Cirillo P, Michels KB. *Am J Epidemiol.* 2019 Feb 1;188(2):294-304. PMID: 30383202. PMC6357809.

4. The Role of Early Life Factors and Cancer and Chronic Disease Risk. I have been following four U.S. birth cohorts of women born in the late 1950s and early 1960s for their health in midlife. These studies support that prenatal smoke exposure and early life growth affect age at menarche, menopause, and breast density.

- a. Prenatal smoke exposure and mammographic density in mid-life. **Terry MB**, Schaefer CA, Flom JD, Wei Y, Tehranifar P, Liao Y, Buka S, Michels KB. *Journal of Developmental Origins of Health and Disease.* 2011; 2(6), 340–352. PMID: 23378890 PMC3559186
- b. Maternal anthropometry and mammographic density in adult daughters. Michels KB, Cohn BA, Goldberg M, Flom JD, Dougan M, **Terry MB**. *Pediatrics.* 2016 Nov; 138(Suppl 1):S34-S41. PMID: 27940975. PMC5080867.
- c. Birth weight, postnatal growth, and age at menarche. **Terry MB**, Ferris JS, Tehranifar P, Wei Y, Flom JD. *Am J Epidemiol.* 2009 Jul 1;170(1):72-9 . Epub 2009 May 13. PMID: 19439580. PMC2733039.
- d. Maternal, birth, and early-life influences on adult body size in women. **Terry MB**, Wei Y, Esserman D. *Am J Epidemiol.* 2007 Jul 1;166(1):5-13. Epub 2007 Apr 29. PMID: 17470452.

5. Risk Assessment in High Risk Women. For the past 20 years, I have been following family cohorts to ascertain gene and environmental interactions for breast cancer risk. This work has led to a focus on evaluating risk assessment methods and family history measurement in high risk women.

- a. Cohort profile: The Breast Cancer Prospective Family Study Cohort (ProF-SC). **Terry MB**, Phillips KA, Daly MB, John EM, Andrulis IL, Buys SS, Goldgar DE, Knight JA, Whittemore AS, Chung WK, Apicella C, Hopper JL. *Int J Epidemiol.* 2016 Jun; 45(3):683-92. PMID: 26174520. PMC5005937.
- b. Risk-Reducing Oophorectomy and Breast Cancer Risk Across the Spectrum of Familial Risk. **Terry MB**, Daly MB, Phillips KA, Ma X, Zeinomar N, Leoce N, Dite GS, MacInnis RJ, Chung WK, Knight JA, Southey MC, Milne RL, Goldgar D, Giles GG, Weideman PC, Glendon G, Buchsbaum R, Andrulis IL, John EM, Buys SS, Hopper JL. *J Natl Cancer Inst.* 2019 Mar 1; 111(3):331-334. PMID: 30496449. PMC6410936.
- c. 10-year performance of four models of breast cancer risk: a validation study. **Terry MB**, Liao Y, Whittemore AS, Leoce N, Buchsbaum R, Zeinomar N, Dite GS, Chung WK, Knight JA, Southey MC, Milne RL, Goldgar D, Giles GG, McLachlan SA, Friedlander ML, Weideman PC, Glendon G, Nesci S, Andrulis IL, John EM, Phillips KA, Daly MB, Buys SS, Hopper JL, MacInnis RJ. *Lancet Oncol.* 2019 Feb 21. pii: S1470-2045(18)30902-1. PMID: 30799262.
- d. The Influence of Number and Timing of Pregnancies on Breast Cancer Risk for Women With BRCA1 or BRCA2 Mutations. **Terry MB**, Liao Y, Kast K, et al. *JNCI Cancer Spectr.* 2018 Dec; 2(4):pky078. PMID: 30873510. PMC6405439.

Complete List of Published Work in MyBibliography:

<http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/45801043/?sort=date&direction=ascending>.

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

5U01ES026122-04 (Terry, Miller) 09/30/15-06/30/21

NIEHS, Pregnancy and Prenatal PAHs and other Environmental Exposures and Breast Cancer
This study looks at levels of environmental exposure to polycyclic aromatic hydrocarbons (PAH) in Dominican and African-American mothers and daughters who are currently participating in the Columbia Center for Children's Environmental Health birth cohort study.

2U01CA164920-06 (Terry (contact PI), Andrulis, Hopper, Daly, Hopper, Buys, John) 05/01/18-04/30/23

National Cancer Institute

Breast Cancer Family Cohort

The major goals of this project are to create a resource for genetic studies of breast and ovarian cancer by recruiting high-risk families through clinical and community settings to facilitate gene-environment research.

1U01ES029660-01 (Terry (contact PI), Wu, Brenner) 09/15/18-06/30/23

National Institute of Environmental Health Sciences

DNA Repair Phenotype: the Missing Link in Breast Cancer Risk Assessment

This research examines whether double strand breast DNA repair capacity, measured in blood, increases breast cancer risk, is modified by genetic and/or epigenetic factors and whether it improves risk assessment.

No award number (Santella) (Role: co-PI) 10/01/06-09/30/21

The Breast Cancer Research Foundation, Environmental Exposures, Epigenetics and Breast Cancer Risk

This study investigates the role of DNA repair (Santella) and DNA methylation (Terry) on breast cancer risk using a discordant sibling design.

5P30CA013696-45 (Rutgi) (Role: Associate Director) 07/01/03-06/30/21

NCI/NICH

This grant supports the leadership of Columbia University's laboratory, clinical and population-based cancer research programs and shared resources serving Columbia University's Cancer Center members.

5R01CA204119-03 (Genkinger) (Role: co-Investigator) 03/08/16-02/28/21

NIH/NCI, Early Detection of Ovarian Cancer Through Epigenetic Factors in the WHI

No routine screening method for ovarian cancer exists; yet early detection vastly improves survival. This project focuses on identification of markers for early detection in a large prospective study. By identifying biomarkers, this research will inform screening tools and risk assessment models for this highly lethal disease.

5R01HG008980-04 (Wei) (Role: co-Investigator) 05/17/16-02/28/21

NIH/NHGRI, Develop Quantile Analysis tools for sequencing and EQTL Studies

The project will develop quantile analysis tools to the Expression Quantitative Trait Loci (eQTLs) in single/multiple tissues, and to identify the associations between infrequent/rare variants with human complex traits using next generation sequencing data.

5R01MD011506-05 (Tehranifar) (Role: co-Investigator) 09/01/16-05/31/21

National Institute on Minority Health and Health Disparities/NIH/DHHS

Impact of breast density information disclosure in racially diverse populations

This study investigates a broad range of physiological outcomes and breast cancer screening behaviors in relation to disclosure of breast density information in a racially/ethnically diverse population.

5U01CA203993-02 (Tehranifar) (Role: co-Investigator) 09/01/16-05/31/21

NIH/NCI

Integrating Mammograms in Analyses of Genes and Environment in Sisters (IMAGES)

This study investigates longitudinal changes in mammographic density in relation to breast cancer risk and improves risk prediction models and clinical risk stratification in a large prospective cohort of women.

5T32CA094061-17 (Neugut (contact PI), Terry MPI) 09/07/17-08/31/22

NIH/NCI Training program in cancer-related population sciences

Relevant Completed Research Support

5R01CA159868-05 (Terry, Hopper) 07/01/11-04/30/18

NCI/NIH, Genes, Environment, and Breast Cancer Risk: The 15 year follow-up of the Prof-SC

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: Zhao, Shanshan

eRA COMMONS USER NAME (credential, e.g., agency login): szhao1

POSITION TITLE: Principal Investigator

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)	Completion Date MM/YYYY	FIELD OF STUDY
Peking University, Beijing, China	B.S.	07/2005	Applied Mathematics
University of Iowa, Iowa City, IA	M.S.	07/2007	Biostatistics
University of Washington, Seattle, WA	Ph.D.	10/2012	Biostatistics
Fred Hutchinson Cancer Research Center	Postdoctoral Fellow	12/2014	Biostatistics

A. Personal Statement

My research interest and expertise are in developing statistical methods for disease risk assessment and prediction. I am solid trained in general biostatistics methods and have made important contribution to statistical methodology development in areas of survival data analysis, mediation analysis and biomarker studies. I have also collaborated extensively with cancer and environmental epidemiologists to assess population level disease risk and predict individual level risk. In the area of multivariate time-to-event data, I have developed both nonparametric (1) and semiparametric (2) approaches with my collaborator, and we recently published a book (3) on this topic. I have experience applying these methods to analyze multivariate health outcomes in large prospective cohorts (4). With my expertise in this specific area, I will contribute to Aim 2, in both methods/software development and real data analysis.

1. Prentice R.L., **Zhao S.** (2018). Nonparametric Estimation of the Multivariate Survivor Function: the Multivariate Kaplan-Meier Estimator. *Lifetime Data Analysis*, 24 (1): 3-27. PMID: 27677472; PMCID: PMC5373162; DOI: 10.1007/s10985-016-93830y.
2. Prentice R., **Zhao S.** (2020). Regression Models and Multivariate Life Tables. *Journal of American Statistical Association*. PMID: 31128619; PMCID: PMC Journal – In Process; DOI: 10.1080/01621459.2020.1713792.
3. Prentice R.L., **Zhao S.** (2019). The Statistical Analysis of Multivariate Failure Time Data: A Marginal Modeling Approach. *Chapman & Hall/CRC Press*.
4. Prentice R., Aragaki A.K, Chlebowski R.T., **Zhao S.**, Anderson G.L., Rossouw J.E., Wallace R., Banack H., Shadyab A.H., Qi L., Snively B.M., Gass M., Manson J.E. (2020). Dual Outcome Intention-to-Treat Analyses in the Women's Health Initiative Randomized Controlled Hormone Therapy Trials. *American Journal of Epidemiology*. PMID: 32314781; PMCID: PMC7443766; DOI: 10.1093/aje/kwaa033.

B. Positions and Honors**Positions and Employment**

2012 – 2014	Postdoctoral Research Fellow, Fred Hutchinson Cancer Research Center
2015 – Present	Principal Investigator, Biostatistics and Computational Biology Branch, National Institute of Environmental Health Sciences/NIH
2017 – Present	Adjunct Assistant Professor, University of North Carolina at Chapel Hill

Other Experience and Professional Memberships

2011 - 2012	Member, Western North American Region (WNAR), International Biometrics Society
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2007 - Present	Member, Alpha Phi Chapter of the Delta Omega Public Health Honorary Society
2008 - Present	Member, American Statistical Association
2012 - Present	Member, Eastern North American Region (ENAR), International Biometric Society
2015 – Present	Member, International Chinese Statistical Association (ICSA)
2016 – Present	Organizer, Biostatistics and Bioinformatics Short Courses, NIEHS/NIH
2017	Member, Search Committee for Chief of Biostatistics and Computational Biology Branch, NIEHS / NIH
2017 – 2021	NIH Fellow Award of Research Excellence
2017 – Present	Academic Editor, PLOS One
2018 – Present	Associate Editor, Biometrics
2019	Member, Search Committee for NIH Earl Stadtman Investigator in Biostatistics and Bioinformatics
2019 – Present	Chair, Lifetime Data Science 2023 Conference Local Organization Committee Chair, Webinar Committee, ASA Lifetime Data Science Section
2020 – Present	

Honors

2007-2009	Pfizer Award for Graduate Student, University of Washington
2014	ASA Biometrics Section David P. Byar Young Investigator Travel Award
2019	NIEHS Scientific Director's Award for Research Excellence
2019	NIEHS Group Special Act Award for Biostatistics and Bioinformatics Short Courses
2020	NIEHS Merit Award for Leadership in Executing the Biostatistics and Bioinformatics Short Courses

C. Contribution to Science

1. Statistical Methods for Disease Risk Assessment and Prediction: I develop statistical methods for disease risk assessment and prediction, to provide tools for researchers to investigate the relationship between risk factors and health outcomes and make accurate disease risk prediction. The two main statistical areas I have been focusing on are time-to event outcomes and mediation analysis. Working with my collaborator Dr. Ross Prentice, I created the opportunity to understand an individual's susceptibility to multiple diseases throughout the life span by developing a nonparametric approach (**1a**) and a semiparametric regression approach (**1b**) for joint modeling of times to multiple interrelated diseases. We recently published a book on this topic which provided a thorough and rigorous discussion of existing methods in this area, as well as described our newly proposed methods (**1c**). In the area of mediation analysis, I developed a calibration approach to recover the true mediation effect in the setting where the outcome is a right censored event time and the mediator is measured with error (**1d**). I have also proposed a group-sequential design and the corresponding analysis strategy in a post-licensure medical product safety surveillance study setting (**1e**).

- 1a.** Prentice R.L., **Zhao S.** (2019). The Statistical Analysis of Multivariate Failure Time Data: A Marginal Modeling Approach. *Chapman & Hall/CRC Press*.
- 1b.** Prentice R.L., **Zhao S.** (2018). Nonparametric Estimation of the Multivariate Survivor Function: the Multivariate Kaplan-Meier Estimator. *Lifetime Data Analysis*, 24 (1): 3-27. PMID: 27677472; PMCID: PMC5373162; DOI: 10.1007/s10985-016-93830y.
- 1c.** Prentice R., **Zhao S.**. Individual and Composite Outcomes in Multivariate Failure Time Data Analysis. *JRSS-B*. Accepted.
- 1d.** **Zhao S.**, Prentice R.L. (2014). Covariate Measurement Error Correction Methods in Mediation Analysis with Failure Time Data. *Biometrics*, 70: 835-844. PMID:25139469; PMCID: PMC4276494; DOI:10.1111/biom.12205.
- 1e.** **Zhao S.**, Cook A.J., Jackson L.A., Nelson J.C. (2012). Statistical Performance of Group Sequential Methods for Post-Licensure Medical Product Safety Surveillance: A Simulation Study. *Statistics and Its Interface*. 5: 381-390. DOI:10.4310/SII.2012.v5.n4.a1.

2. Statistical Methods in Cancer Research: I developed a series of statistical tools to characterize the spatial and temporal distribution of breast cancer risk (**2a**), motivated by the NIEHS Sister Study. We further related the observed spatial distribution to social and environmental risk factors that vary across spatial areas as well as to influential events, such as natural disasters and public health policy changes (**2b**). By applying these methods to data from the NIEHS Sister Study data and to publicly available datasets, such as the Surveillance, Epidemiology, and End Results (SEER) data, we investigated breast cancer incidence and mortality rates in different regions across years. The methods we proposed are not limited to breast cancer research. I have also developed an efficient design for biomarker studies to save precious biospecimens and minimize cost (**2c**), and developed a pipeline to identify novel prognostic biomarkers based on multiple studies with application to prostate cancer (**2d**).

- 2a.** Carroll R., Lawson A.B., **Zhao S.** (2018). Temporally dependent accelerated failure time model for capturing the impact of events that alter survival in disease mapping. *Biostatistics*. PMID: 29939209; PMCID: PMC Journal - In Process; DOI:10.1093/biostatistics/kxy023.
- 2b.** Carroll R., **Zhao S.** (2018). Gaining Relevance from the Random: Interpreting Observed Spatial Heterogeneity. *Spatial and Spatial Temporal Epidemiology*, 25:11-17. PMID: 29751888; PMCID: PMC Journal - In Process; DOI: 10.1016/j.sste.2018.01.002.
- 2c.** **Zhao S.**, Zheng Y., Prentice R.L., Feng, Z. (2015). Two-Stage Biomarker Panel Study and Estimation Allowing Early Termination for Futility. *Biostatistics*: 16: 799-812. PMID: 25964662; PMCID: PMC4570581; DOI: 10.1093/biostatistics/kxv017.
- 2d.** **Zhao S.**, Geybels M.S., Leonardson A., Rubicz R., Kolb S., Yan Q., Klotzle B., Bibikova M., Hurtado-Coll A., Troyer D., Lance R., Lin D.W., Wright J.L., Ostrander E.A., Fan J.B., Feng Z., Stanford J.L. (2017). Epigenome-Wide Tumor DNA Methylation Profiling Identifies Novel Prognostic Biomarkers of Metastatic-Lethal Progression in Men Diagnosed with Clinically Localized Prostate Cancer. *Clinical Cancer Research*, 23 (1): 311-319. PMID: 27358489; PMCID: PMC5199634; DOI:10.1158/1078-0432.CCR-16-0549.

3. Collaborative Studies in Epidemiology: I collaborate extensively with epidemiologist to address critical scientific questions with powerful statistical tools. I have contributed to breast cancer research in understanding the mediation effect of sex hormone in the relationship between hormone therapy and breast cancer risk (**3a**). We also identified a panel of DNA methylation biomarkers in predicting prostate cancer metastasis and death among patients with localized prostate cancer (**3b**). I collaborated on a project to identify DNA methylation biomarkers that can be used as a surrogate for maternal smoking, which is usually reported with bias (**3c**). Recently, I have collaborated on environmental studies to understand the effects of chemical mixtures on health outcomes (**3d**).

- 3a.** **Zhao S.**, Chlebowski R.T., Anderson G., Kuller L.H., Manson J.E., Gass M., Patterson R., Rohan T.E., Lane D.S., Beresford S.A.A, Lavasani, S., Rossouw, J.E., Prentice R.L. (2014). Sex Hormone Associations with Breast Cancer Risk and the Mediation of Randomized Trial Postmenopausal Hormone Therapy Effects. *Breast Cancer Research*. 16: R30. PMID: 24670297; PMCID: PMC4053241; DOI: 10.1186/bcr3632.
- 3b.** **Zhao S.**, Geybels M.S., Leonardson A., Rubicz R., Kolb S., Yan Q., Klotzle B., Bibikova M., Hurtado-Coll A., Troyer D., Lance R., Lin D.W., Wright J.L., Ostrander E.A., Fan J.B., Feng Z., Stanford J.L. (2017). Epigenome-Wide Tumor DNA Methylation Profiling Identifies Novel Prognostic Biomarkers of Metastatic-Lethal Progression in Men Diagnosed with Clinically Localized Prostate Cancer. *Clinical Cancer Research*, 23 (1): 311-319. PMID: 27358489; PMCID: PMC5199634; DOI:10.1158/1078-0432.CCR-16-0549.
- 3c.** Reese S.E., **Zhao S.**, Wu M.C., Joubert B.R., Parr C.L., H_aerg S.E., Ueland P.M., Nilsen R.M., Midttun O., Vollset S.E., Peddada, S.D., NystadW., London S.J. (2017). DNA Methylation Score as a Biomarker in Newborns for Sustained Maternal Smoking during Pregnancy. *Environmental Health Perspectives*, 125 (4): 760-766. PMID:27323799; PMCID: PMC5391987; DOI: 10.1289/EHP333.
- 3d.** Kim S.S., Meeker J.D., Carroll R., **Zhao S.**, Mourgas M.J., Richards M.J., Aung M., Cantonwine D.E., McElrath T.F., Ferguson K.K. (2018). Urinary trace metals individually and in mixtures in association with preterm birth. *Environmental International*, 121: 582-590. PMID: 30300816; PMCID: PMC6233299; DOI: 10.1016/j.envint.2018.09.052.

Complete List of Published Work in My Bibliography:
<https://www.ncbi.nlm.nih.gov/myncbi/shanshan.zhao.1/bibliography/public/>

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

ZIA ES103307, NIH/NIEHS Intramural Research Grant Zhao, S. (PI) 2017 – present
Statistical Methods in Disease Risk Assessment and Prediction
Statistical methods assist a successful epidemiology study from several aspects, such as efficient design, valid data analysis and accurate interpretation. The goal of this project is to develop statistical methods in two main areas: general statistical methods for disease risk assessment and prediction, and statistical methods for breast cancer risk research motivated by the NIEHS Sister Study. These developed statistical methods will help epidemiology studies to have more efficient design and more accurate results.

ZIA ES103308, NIH/NIEHS Intramural Research Grant Zhao, S. (PI) 2017 – present
Application of Statistical Methods in Epidemiology
The goal of this project is to help scientists in epidemiology and basic sciences to use correct statistical methods for analyzing their data. Statistical methods are chosen to account for different study designs and sampling schemes, as well as different data type. In addition, we help scientists to correctly interpret their results.

BIOGRAPHICAL SKETCH

NAME: Gottfredson, Nisha Claire

eRA COMMONS USER NAME (credential, e.g., agency login): NISHA_GOTTFREDSON

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Pitzer College, Claremont, California	B.A.	05/2006	Psychology & Mathematics
University of North Carolina, Chapel Hill	M.A.	08/2008	Quantitative Psychology
University of North Carolina, Chapel Hill	Ph.D.	05/2011	Quantitative Psychology

A. Personal Statement

I will serve as an advisor on Dr. Von Holle's K99 training committee. Dr. Von Holle is a highly skilled statistician, and my role is to support her goal of learning about and applying latent variable models (including factor analysis, structural equation models, and latent growth models). My background in applied latent variable modeling, specifically for research questions about development over time, makes me well-qualified for this role. I am an expert in developing and applying latent variable approaches to improve measurement of developmental processes (see references below). In addition, I have taught courses and given trainings on longitudinal modeling and psychometric models and I am confident that I will be able to provide Dr. Von Holle with the training materials that she needs to succeed in her training plan. I have collaborated with Dr. Von Holle in the past and I very much look forward to the opportunity to work with her again.

Relevant Publications:

- a. Zerwas, S., **Von Holle, A.**, Watson, H., **Gottfredson, N.C.**, & Bulik, C. M. (2014). Childhood anxiety trajectories and adolescent disordered eating: Findings from the NICHD study of early child care and youth development, *International Journal of Eating Disorders*, 47, 784-792. PMCID: PMC4425370
- b. **Gottfredson NC**, Cole VT, Giordano M, Bauer DJ, Hussong AM & Ennett ST. (2019). Simplifying the implementation of modern scale scoring methods with an automated R package: automated Moderated nonlinear factor analysis (aMNLFA). *Addict Behav*, 94, 65-73. PMCID: PMC6483881.
- c. **Gottfredson, NC**, Stucky, BD, & Panter, AT. (in press). Item-level factor analysis. In *APA Handbook of Research Methods in Psychology, 2nd Edition*. Eds. Cooper, Long, Rindskopf, & Sher. Washington, DC: APA Books.
- d. Yilmaz, Z., **Gottfredson, N.C.***, Zerwas, S., Bulik, C., & Micali, N. (2019). Developmental premorbid body mass index trajectories of adolescents with eating disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*, 58, 191-199. PMCID: PMC6766404.

*First two authors contributed equally

B. Positions and Honors**Positions and Employment**

- 2000-2004 Research Assistant, Department of Criminology, University of Maryland, College Park
 2004-2006 Research Assistant, Department of Psychology, Pomona and Pitzer College, Claremont, CA
 2007-2009 Research Associate, Pacific Institute for Research and Evaluation, Chapel Hill, NC
 2008 Research Assistant, Health Behavior, University of North Carolina, Chapel Hill
 2006-2011 Research Assistant, Quantitative Psychology, University of North Carolina, Chapel Hill
 2011-2013 Postdoctoral Researcher, Center for Developmental Epidemiology and Transdisciplinary Prevention Research Center, Duke University, Durham, NC
 2012-2017 Consultant, Catalyst Behavioral Sciences, Miami, FL

2013	Statistician/Investigator, Frank Porter Graham Child Development Institute, Chapel Hill, NC
2014-2015	Senior Investigator, Center for Developmental Science, Chapel Hill, NC
2013-	Adjunct Professor, Department of Psychology, University of North Carolina, Chapel Hill
2015-	Assistant Professor, Department of Health Behavior, UNC Gillings School of Global Public Health, Chapel Hill, NC
2015-	Faculty Affiliate, Center for Developmental Science, Chapel Hill, NC

Professional Memberships and Service

2009-2011	Quantitative Psychology Representative, Science Student Council, American Psychological Association
2005-	Member, Division 5 (Quantitative & Qualitative Methods), American Psychological Association
2008-	Ad hoc journal reviewer
2015-	Member, Society for Prevention Research
2016-	Member, Society for Behavioral Medicine
2016-	Member, Division 50 (Psychology of Addiction), American Psychological Association
2019-	National Academy of Sciences Health Parenting in Primary Care Collaborative
2019	Abstract reviewer, <i>Society for Behavioral Medicine</i> and <i>Society for Prevention Research</i>
2020-	Consulting advisor, <i>Campus and Community Coalition: Chapel Hill Downtown Partnership</i>
2021-	NIH Grant Reviewer
2021-	Consulting editor, <i>Psychology of Addictive Behaviors</i>

Honors and Awards

2005	Sigma Xi Undergraduate Research Honors Society, Claremont Colleges
2005	Psi Chi Psychology Honors Society, Claremont Colleges
2006	Graduated with honors, Pitzer College
2009	Lyle V. Jones Award for Outstanding Scholarship and Citizenship as a Doctoral Student
2009	Society for Multivariate and Experimental Psychology Tanaka Award for Most Outstanding Paper published in the journal of <i>Multivariate Behavioral Research</i> in 2008
2019	Delta Omega National Public Health Honorary Society

C. Contributions to Science

As a quantitative psychologist with a background in developmental science and prevention science, my research contributions consist of a mixture of advances in the development and application of statistical methodology and improved understanding of the developmental etiology of behavioral disorders, including identification of prevention targets. I have authored over 80 peer-reviewed publications. In the manuscripts highlighted below, * indicates student authorship.

1. Advancing model fidelity and measurement quality within longitudinal models. Human behavior and theoretical models used to explain human behavior are complex and, often, difficult to measure. Quantitative models, particularly those involving latent variables, can be useful for providing insights into noisy and non-deterministic behavior. However, the models are only useful if they are constructed thoughtfully and only if they are robust to minor misspecification. I have contributed to the field of quantitative psychology by adapting latent variable models so that they are better suited to reality. For example, my dissertation and several subsequent publications focused on the problem of nonignorable missingness in longitudinal models. Whereas most analytic techniques assume ignorable missingness, this is often an unrealistic assumption. In this vein, I developed a shared parameter mixture model for handling nonignorable missingness. Other contributions have involved adapting confirmatory factor analysis models to accommodate differential item functioning and impact due to covariates and adapting the residual covariance structure of multilevel models to accommodate 'rolling' group membership over time.

- a. **Gottfredson, N. C.**, Sterba, S. K., & Jackson, K. (2017). Explicating the conditions under which multilevel multiple imputation mitigates bias resulting from random coefficient-dependent missing longitudinal data. *Prevention Science*, 18, 12-19. PMCID: PMC5235951
- b. Curran, P. J., Cole, V., Bauer, D. J., Hussong, A. M., & **Gottfredson, N. C.** (2016). Improving factor score estimation through the use of observed background characteristics. *Structural Equation Modeling: An Interdisciplinary Journal*, 1-18. PMCID: PMC5526637

- c. **Gottfredson, N.C.**, Bauer, D.J., & Baldwin, S. (2014). Modeling change in the presence of non-randomly missing data: Evaluating a Shared Parameter Mixture Model. *Structural Equation Modeling*, 21, 196-209. PMCID: PMC4084916
- d. Bauer, D.J., **Gottfredson, N.C.**, Dean, D., & Zucker, R. A. (2012). Analyzing repeated measures data on individuals nested within groups: Accounting for dynamic group effects. *Psychological Methods*, 17, 1-14.

2. Reducing barriers to implementation of statistical methodology. Advances to quantitative models are only useful if they are implemented in applied research. Often, statistical advances go unnoticed and unapplied by researchers who would benefit from them. Some of my most useful contributions to science have been those that identify and remove barriers to implementing complex methods. For example, I developed a software package in R for researchers wishing to implement the moderated nonlinear factor analysis model to accommodate differential item functioning in complex data, I published a YouTube video demonstrating implementation of Directed Acyclic Graphs, and I developed a simple method for researchers to correct for bias resulting from small level 1 sample sizes in multilevel models.

- a. **Gottfredson NC**, Cole VT, Giordano M, Bauer DJ, Hussong AM & Ennett ST. (2019). Simplifying the implementation of modern scale scoring methods with an automated R package: automated Moderated nonlinear factor analysis (aMNLFA). *Addict Behav*, 94, 65-73. PMCID: PMC6483881.
- b. Wouk, K.G.*, Bauer, A. & **Gottfredson, N.C.** (2019). How to implement Directed Acyclic Graphs to reduce bias in addiction research. *Addictive Behaviors*, 94, 109-116. PMID: 30292573 / PMCID: Pending [**Senior Author**]
- c. **Gottfredson NC**. (2019). A straightforward approach for coping with unreliability of person means when parsing within-person and between-person effects in longitudinal studies. *Addict Behav*, 94, 156-161. PMCID: PMC6435441.
- d. Hoyle, R. & **Gottfredson, N. C.** (2015). Sample size considerations in prevention research applications of multilevel modeling and structural equation modeling. *Prevention Science*, 16, 987-996. PMCID: PMC4207737

3. Use of longitudinal, population-based samples to characterize the developmental etiology of psychological and behavioral phenotypes, and how these phenotypes relate to one another over time.

The developmental concept of “multifinality” posits that early experiences and environmental contexts may give rise to a variety of potential outcomes. The concept of “heterotypic discontinuity” suggests that the same underlying trait may be expressed differently at different stages of development. I have used large-scale panel data to provide insight into the developmental course of anxiety and depression, substance use and substance use disorder and eating disorders using the concepts of multifinality and heterotypic discontinuity. A shared internalizing process partially explains some of the comorbidities that have been observed in these mental and behavioral traits.

- e. Yilmaz, Z., **Gottfredson, N.C.**, Zerwas, S., Bulik, C., & Micali, N. (2019). Developmental premorbid body mass index trajectories of adolescents with eating disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*, 58, 191-199. PMCID: PMC6766404. [**First two authors contributed equally**]
- f. **Gottfredson, N.C.**, Rhodes, B.E.* , & Ennett, S.T. (2019). Demographic moderation of the prediction of adolescent alcohol involvement trajectories. *Prevention Science*, 20, 811-823. PMCID: PMC6395564.
- g. Zerwas, S., Von Holle, A., Watson, H., **Gottfredson, N.C.**, & Bulik, C. M. (2014). Childhood anxiety trajectories and adolescent disordered eating: Findings from the NICHD study of early child care and youth development, *International Journal of Eating Disorders*, 47, 784-792. PMCID: PMC4425370
- h. **Gottfredson, N. C.**, Foshee, V. A., Ennett, S. T., Habertick, B., & Smolen, A. (2014). Genetic heterogeneity in adolescents' depressive symptoms in response to victimization. *Journal of Clinical Child and Adolescent Psychology*. PMCID: PMC4229484

4. Identifying targets for relapse prevention. As PI of a NIDA-funded K01 award, I used a measurement burst design to investigate real-time precursors to drug cravings and lapses among individuals in recovery for addiction. I hypothesized that individuals who cope with cravings by using alternative substances, including tobacco and comfort food, would be less likely to experience a successful recovery. This was true for tobacco

use but was not entirely true for food. Rather, after disaggregating within-person and between-person effects, it is evident that some individuals are predisposed toward both polysubstance use and “food addiction,” and that there is no temporal association between cravings and consumption of unhealthy foods. Another study led by my student found that poor sleep quality increases drug cravings in real time, and that this effect may be mediated by diminished willpower.

- a. Rhodes, B.E.* & **Gottfredson, N.C.** (2020, E-pub ahead of print). Effects of tobacco on affect and craving during opioid addiction and recovery: An ecological momentary assessment study. *Addictive Behaviors*. PMID: 32151892 / PMCID: Pending. **[Senior author]**
- b. **Gottfredson, N.C.** & Sokol, R.L.* (2019). Explaining excessive weight gain during early recovery from addiction. *Substance Use & Misuse*, 54, 769-778. PMCID: PMC6474807.
- c. Freeman, L.K.* & **Gottfredson, N.C.** (2018). Using ecological momentary assessment to assess the temporal relationship between sleep quality and cravings in individuals recovering from substance use disorders. *Addictive Behaviors*, 83, 95-101. PMCID: PMC7080296. **[Senior Author]**

Complete List of Published Work in MyBibliography:

<https://www.ncbi.nlm.nih.gov/pubmed/?term=Gottfredson+NC%5BAuthor%5D+or+Gottfredson+N%5BAuthor%5D>

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

R21CA260092 **Gottfredson (PI)** **5/1/2021-4/30/2023**
Building a reinforcement learning tool for individually tailoring just-in-time adaptive interventions: Extending the reach of mHealth technology for improved weight loss outcomes
The objective of this project is to develop a user-friendly, web-based application (Adapt) that reads in and analyzes user data in real-time.
Role: Principle Investigator

R01: HD093901 **Stuebe (PI)** **9/7/2018-7/31/2023**
Mood, Mother, and Child: The Psychobiology of Dyadic Resilience
This study identifies the psychobiological underpinnings of resilience among mother-child dyads exposed to maternal depression, a common and morbid condition that impacts the health of more than 400,000 mother-infant dyads every year.
Role: Co-Investigator

R01DA051578 **Clark (PI)** **9/30/2020 - 7/31/2025**
Substance Use among Biracial Adolescents and Emerging Adults: The Double Jeopardy Hypothesis
We propose to study the 4 subgroups of biracial youth that our prior research has shown to have the highest risk of substance use. Discoveries made during the course of the proposed research will help accelerate the refinement of existing prevention and intervention programs for biracial adolescents and emerging adults, and will speed translation of its findings into public health practice.
Role: Co-Investigator

R01: CA246600 **Noar (PI)** **9/17/2019-8/31/2022**
Advancing Perceived Message Effectiveness: A New Measure for Youth Prevention Media Campaigns
The primary goal of the proposed project is to develop and validate an effects PME scale for adolescent tobacco prevention ads using rigorous scale development methods. Another goal is to compare the performance of this new scale to the FDA's message PME scale in a longitudinal validation experiment.
Role: Co-Investigator

R01: DA049155 **Noar (PI)** **6/1/2020-5/31/2025**
Impact of e-cigarette prevention messages on adolescents.
The primary goal of the proposed project is to advance the science of how to communicate about e-cigarettes in ways that prevent adolescent use.
Role: Co-Investigator

R21DA053708 Lancaster (PI) 3/1/2021 - 2/28/2025
Measuring resilience to intersectional stigma for people who inject drugs in need of HIV prevention
The goal of this study is to explore mechanisms of resilience to intersectional stigma of drug use and HIV prevention among people who inject drugs.
Role: Co-Investigator

R01CA246606 Brewer (PI) 9/0/2020 - 8/31/2023
Understanding uncontrolled vaping among vulnerable populations
The overall goal of the proposed research is to understand uncontrolled vaping and restraint strategies, which likely vary substantially across vulnerable populations, different device types, and dual use with combustible cigarettes.
Role: Co-Investigator

R01: MD012832 Kneipp (PI) 6/10/2019-1/31/2024
NC Works4Health: Reducing Chronic Disease Risk in Socioeconomically Disadvantaged, Unemployed Populations
Particularly for socioeconomically disadvantaged adults, unemployment can trigger a cascade of stress-related coping and behavioral processes that increase risk factors for chronic disease. Interventions to mitigate chronic disease risks while in employment programs at the individual level, and to provide supervisory supports at the employer level could have a positive, cumulative impact on reducing health inequities within communities.
Role: Co-Investigator

Completed Research Support (past 3 years; selected)
K01: DA035153 Gottfredson (PI) 5/01/2014-4/30/2020
The Impact of Affect Regulatory Mechanisms and Binge Eating on Drug Recovery
The goal of the research supported by this early researcher career development award is to understand circumstances leading to compensatory binge eating in individuals recovering from substance dependence and to evaluate whether and how this behavior relates to relapse and recovery.
Role: Principal Investigator

R01: DA037215 Hussong (PI) 9/15/2014-8/31/2019
Peer Mechanisms in the Internalizing Pathway to Substance Use
This prospective study evaluates the role of peer social networks on the development of an internalizing pathway to substance use and disorder in a large adolescent sample.
Role: Co-Investigator

R01MH110186 Pettifor (PI) 04/22/2016-01/31/2021
Multilevel mechanisms of HIV acquisition in young South African women
The overall objective of this application is to determine the effect and mechanisms of effect of key social determinants measured at multiple levels (e.g., individual, household, and community) that influence HIV acquisition in young women in South Africa.
Role: Co-Investigator

Current Research Support

Last Name, First Name, MI: Von Holle, Ann, F

eRA Commons Username: ANNVONHOLLE

Position Title: Intramural Research Trainee Award Postdoctoral Fellow

Laboratory or Branch name: Biostatistics and Computational Biology Branch

Group name: Biostatistics Methods in Epidemiology

I am an Intramural Research Trainee Award postdoctoral fellow in Dr. Weinberg's research group. Her funding is listed below.

Dr. Clarice R. Weinberg's Current Projects:

Project Number	Description or Title	Current Fiscal Year Dates*	Amount
1 ZIA ES040006-24	STATISTICAL METHODS IN EPIDEMIOLOGY--GENERAL	10/01/2019 – 09/30/2020	\$132,652
1 ZIA ES040007-24	STATISTICAL METHODS FOR GENETIC EPIDEMIOLOGY	10/01/2019 – 09/30/2020	\$127,666
1 ZIA ES102245-14	THE TWO SISTER STUDY	10/01/2019 – 09/30/2020	\$216,433
1 ZIA ES103086-09	APPLICATIONS OF METHODS IN COLLABORATIVE SCIENCE	10/01/2019 – 09/30/2020	\$1,995
	<i>Contracts used</i>	<i>Same</i>	\$965,000
	<i>Core Lab Support</i>	<i>Same</i>	\$0

* Fiscal Years always begin Oct 1 and end Sept 30. So, for the CURRENT year, it is 10/01/2019 – 9/30/2020

Pending: **None**

Current Research Support

Mentor Last Name, First Name, MI: Weinberg, Clarice R.

Mentor eRA Commons Username: ClariceWeinberg

Position Title: Senior Investigator

Laboratory or Branch name: Biostatistics and Computational Biology Branch

Group name: Biostatistics Methods in Epidemiology

Current Projects:

Project Number	Description or Title	Current Fiscal Year Dates*	Amount
1 ZIA ES040006-24	STATISTICAL METHODS IN EPIDEMIOLOGY--GENERAL	10/01/2019 – 09/30/2020	\$132,652
1 ZIA ES040007-24	STATISTICAL METHODS FOR GENETIC EPIDEMIOLOGY	10/01/2019 – 09/30/2020	\$127,666
1 ZIA ES102245-14	THE TWO SISTER STUDY	10/01/2019 – 09/30/2020	\$216,433
1 ZIA ES103086-09	APPLICATIONS OF METHODS IN COLLABORATIVE SCIENCE	10/01/2019 – 09/30/2020	\$1,995
	<i>Contracts used</i>	<i>Same</i>	\$965,000
	<i>Core Lab Support</i>	<i>Same</i>	\$0

* Fiscal Years always begin Oct 1 and end Sept 30. So, for the CURRENT year, it is 10/01/2019 – 9/30/2020

Pending: **None**

Current Research Support

Mentor Last Name, First Name, MI: Sandler, Dale P.

Mentor eRA Commons Username: DPSAND

Position Title: Senior Investigator

Laboratory or Branch name: Epidemiology Branch

Group name: Chronic Disease Epidemiology

Current Projects:

Project Number	Description or Title	Current Fiscal Year Dates*	Amount
1 ZIA ES044005-22	ENVIRONMENTAL AND GENETIC RISK FACTORS FOR BREAST CANCER: THE SISTER STUDY	10/1/2019 – 09/30/2020	\$1,330,456
1 ZIA ES049028-24	ENVIRONMENTAL EXPOSURES AND RISK FOR CANCER AND CHRONIC DISEASES IN ADULTS	10/1/2019 – 09/30/2020	\$32,165
1 ZIA ES049030-24	HEALTH EFFECTS OF EXPOSURES IN AGRICULTURE	10/1/2019 – 09/30/2020	\$2,924
1 ZIA ES102945-11	GULF LONGITUDINAL FOLLOW-UP (GULF) STUDY	10/1/2019 – 09/30/2020	\$17,544
	<i>Contracts used</i>	<i>Same</i>	\$9,938,232
	<i>Core Lab Support</i>	<i>Same</i>	\$38,309

* Fiscal Years always begin Oct 1 and end Sept 30. So, for the CURRENT year, it is 10/01/2019 – 9/30/2020

Pending: **None**

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.)
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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.)
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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 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.

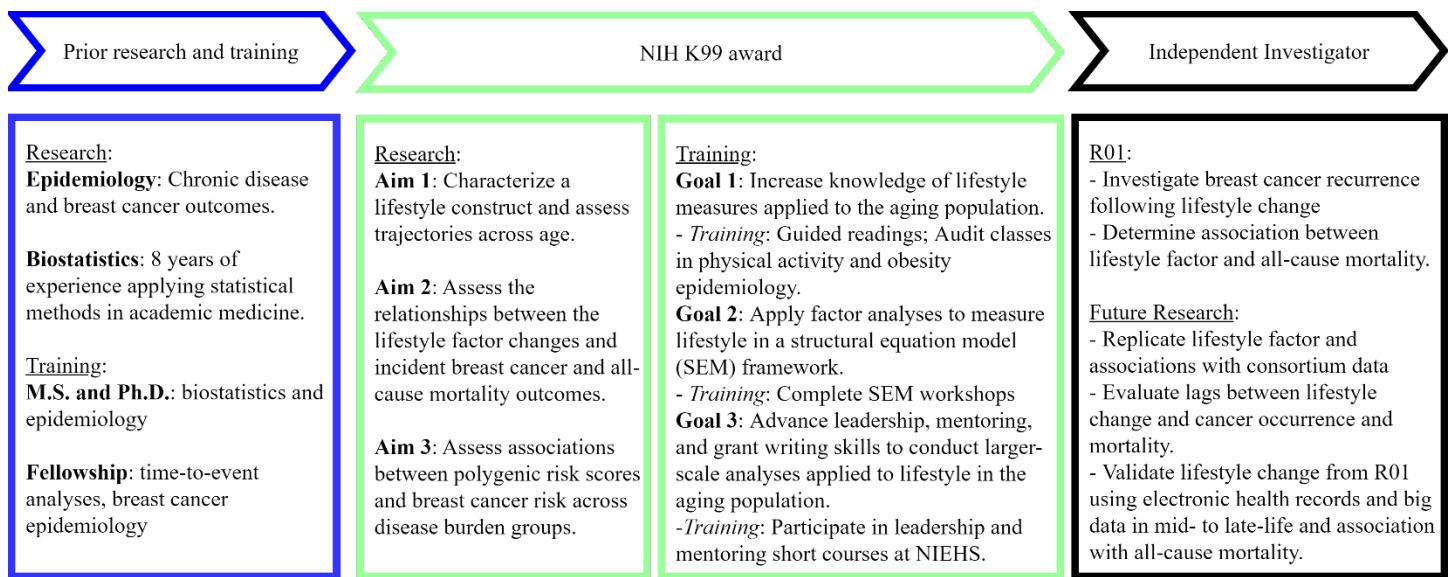


Figure 1. Career Timeline

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%)	
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.

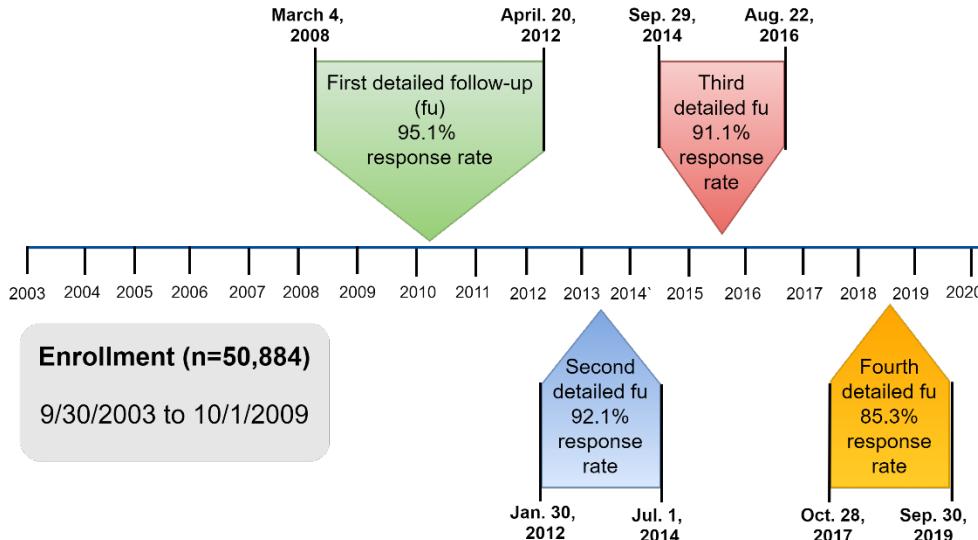


Figure 1. Follow-up information for the Sister Study

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

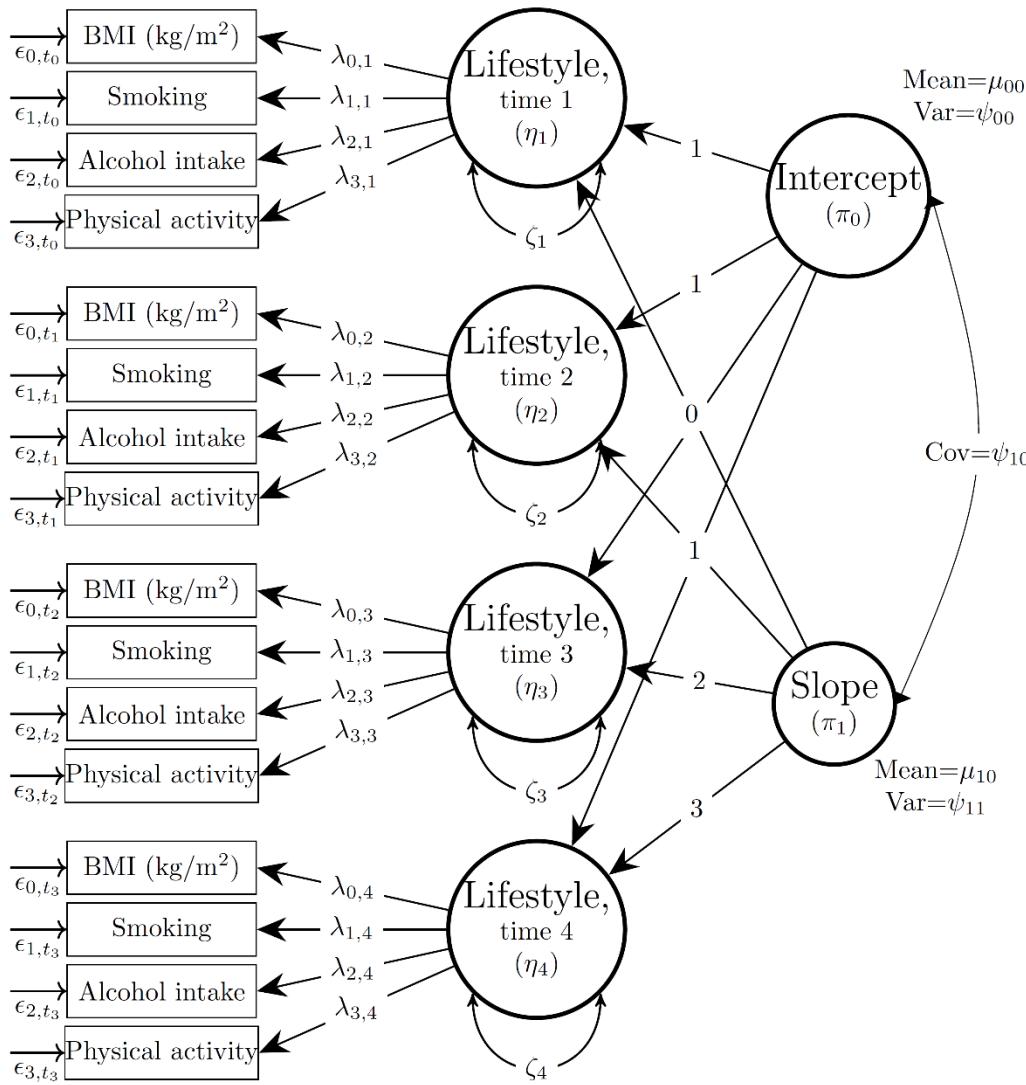


Figure 2. Curve-of-Factors Model for three key lifestyle indicators in postmenopausal women across four follow-up times.

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,

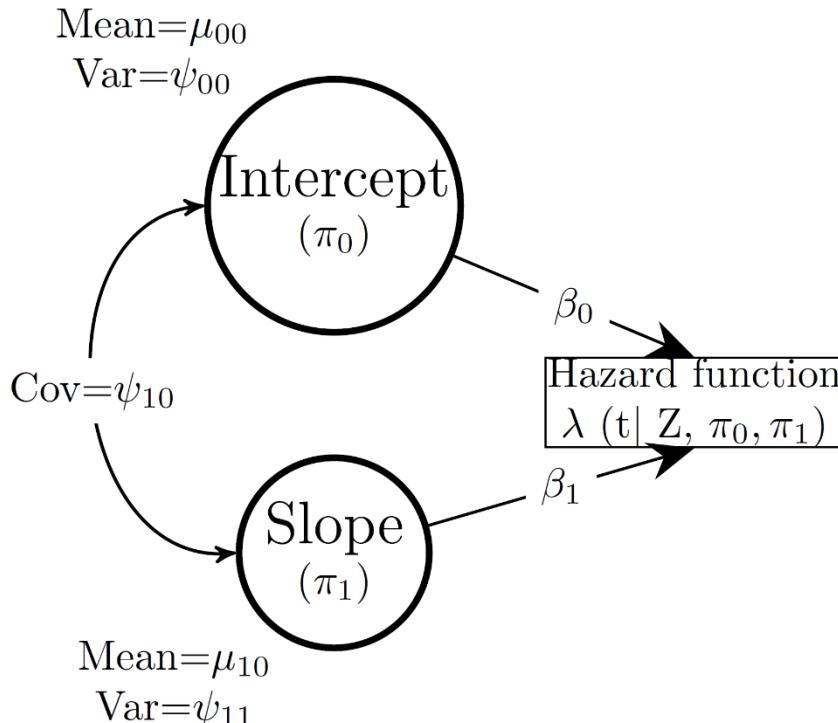


Figure 3. Model for joint analysis of factors and time to event models.

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.

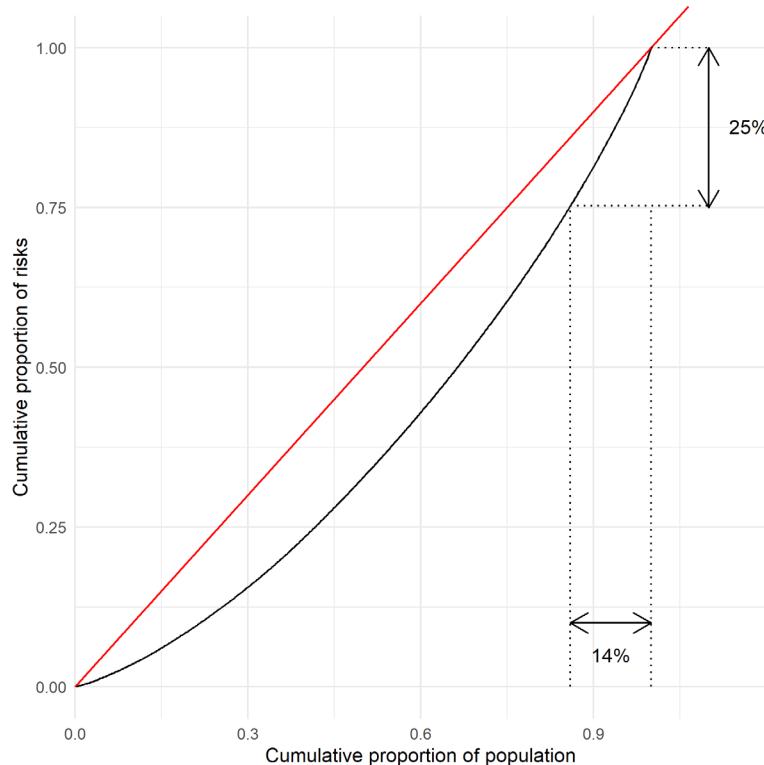


Figure 4. Sample Lorenz curve for lifestyle factors and risk.

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.

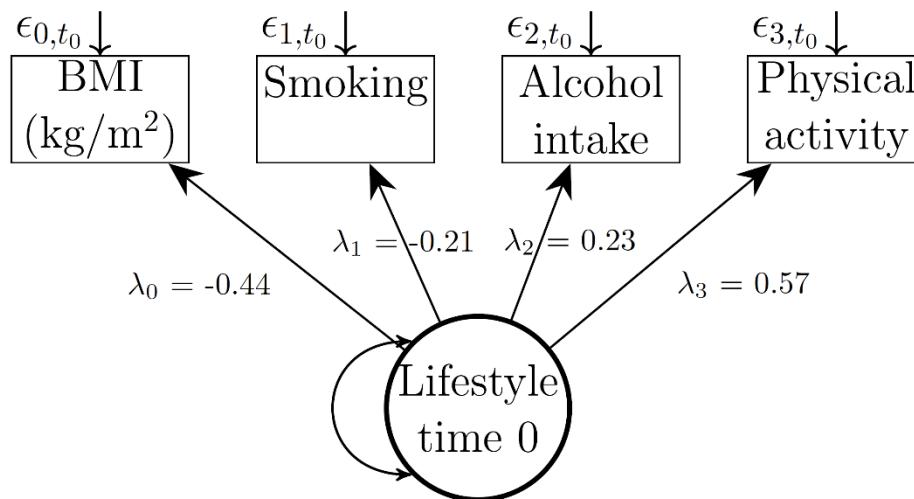


Figure 5. Factor analysis demonstration for three key lifestyle indicators in postmenopausal women at study entry.

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.



National Institutes of Health
National Institute of
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Research Triangle Park, NC 27709
Website: www.niehs.nih.gov

May 28, 2021

Dear Review Committee:

I am delighted to provide this letter to support Dr. Von Holle's K99/R00 proposal, "**Lifestyle change over time and postmenopausal breast cancer risk**". The proposed work would characterize lifestyle and change in lifestyle over time in novel applications of structural equation methods to assess associations between modifiable factors and both breast cancer risk and all-cause mortality in a large U.S. cohort of postmenopausal women. The proposed work will fill a research gap needed to assess effects of patterns of lifestyle and changes, in ways that could inform prevention practices. As her primary mentor, I am excited to guide Dr. Von Holle in the planned research and help her to be successful in her affiliated career development goals.

Dr. Von Holle already had a broad body of academic research experience when I recruited her as a postdoctoral trainee at the National Institute of Environmental Health Sciences (NIEHS) in 2018. Her work as a masters-level biostatistician helped her develop the ability to plan, design and write statistical methods for peer-reviewed research papers. This experience will continue to serve her well as she organizes the statistical analyses for her three proposed aims. She leveraged that work experience in her doctoral-level studies in epidemiology in her pursuit to become an independent investigator. During her time developing her dissertation on growth, which integrated chronic disease and life course epidemiology research areas, she advanced her knowledge of structural equation modeling and longitudinal data analysis applications, a background which will be key to support the analytic parts of her work in assessing lifestyle factors and their relationships with time-to-event outcomes. Overall, this unusually strong background in research environments will be essential to organize her work, complete aims on time, and plan effective approaches around her aims to address hypotheses regarding modifiable lifestyle factor combinations and change over time during the postmenopausal years.

I have known Dr. Von Holle since 2018, when she began her postdoctoral fellowship in my research group. During this time, I have observed her strong interest in collaboration, her diligence, and her creative scientific strategies when applying methods to unsolved epidemiological problems in age-time dependence of risk and cancer biomarker research. In her time as a trainee at NIEHS, Ann has developed a solid understanding of breast cancer epidemiology and how age can play an effect-modifying role in breast cancer incidence. She will expand her focus on age, and specifically risk during the postmenopausal years, as she pursues her proposed K99/R00 aims. In our first publication together, we investigated familial correlation of breast cancer age of onset in families and found evidence supporting a higher relative risk when a woman is closer in age to the onset-age of her previously affected sister, even when the proband onset is late in life. Breast cancer risk is different for early versus later age of onset, and this underlying concept was essential to acknowledge before correctly identifying evidence for familial correlation. When working on our second publication covering iron as a biomarker for

breast cancer incidence, we again maintained a focus on the important split between pre- and postmenopausal years in the Sister Study. Iron stores begin to increase after menopause, with the cessation of regular menses, and Ann had to split analyses by these groups to best understand the role that circulating and stored iron may play in breast cancer incidence. Having based both of these projects on Sister Study data, Ann now has a strong understanding of this data source. This knowledge she acquired during her trainee time will support her work on the proposed K99/R00 aims based on data from the Sister Study, and there would be no barrier to her continued access to these data. During our collaborations, she worked independently when developing and implementing our research strategy and showed a remarkable level of independence, initiative, and resourcefulness. She was at the same time open to the guidance that I provided during our weekly meetings. These weekly meetings served several purposes, including to check in during her process of creating projects for publication, to develop some new research directions, if needed, and to evaluate her progress. Besides her creativity in coming up with new approaches to extend her prior work with the Sister Study, she showed an extraordinary level of diligence and drive in completing these projects. These are strong indicators that she will be successful in completing her proposed research and training and will progress to develop an outstanding long-term independent career in epidemiology.

The three proposed aims in Ann's K99/R00 plan build upon her work experience, dissertation development, and postdoctoral training. Her K99 aim focuses on a novel approach to characterizing common lifestyle factors that are considered leading causes of mortality and are also important determinants of breast cancer risk. Once she completes the first aim, she can use this carefully characterized measure to estimate associations with breast cancer risk and all-cause mortality, devising novel joint modeling approaches that combine longitudinal lifestyle assessments and time-to-event methods. Considering that few if any observational studies to date have had both longitudinal and event measures combined with adequate approaches to estimate their associations, her work with the Sister Study will bring fresh approaches to a research area that is lacking in large-scale evidence. Her focus on factors that are particularly relevant to the postmenopausal years for the women in the Sister Study will also support a NIA research strategy to understand individual effects on aging from a life-course perspective and promote areas to target when developing intervention policies. Completing these aims will move her closer towards her overarching goal to become an independent investigator with a focus on breast cancer prevention and mortality reduction in postmenopausal women.

My own research as a principal investigator in the Biostatistics and Computational Biology Branch at the National Institute of Environmental Health Sciences spans research areas and includes methods development, reproductive epidemiology and cancer epidemiology. I initially proposed and am a founding co-investigator for the Sister Study and was principal investigator of the "Two Sister Study", an ancillary study (funded by Susan G. Komen for the Cure) that focused on young-onset (under age 50) breast cancer. Since the early 1990s, the Sister Study has prospectively followed over 50,000 women who have at least one sister diagnosed with breast cancer and themselves had no breast cancer diagnosis at enrollment. The median age at baseline in this cohort exceeded 55, so the majority are now elderly, and this cohort will provide Ann with a substantial sample size to follow women entering and progressing through their postmenopausal years. We have collected information on lifestyle factors over four detailed follow-up periods while maintaining low drop-out rates. This unique and comprehensive information will support Ann's proposed aims to understand the function of lifestyle change in relation to breast cancer and mortality risk. Once completed, the findings could direct researchers towards areas of lifestyle change in postmenopausal women that will yield the strongest favorable outcomes.

My mentoring experience is extensive. I hold adjunct professor appointments in both the Epidemiology Department and the Biostatistics Department in the School of Public Health at

UNC, Chapel Hill. I have served on Ph.D. committees for 25 students in those two departments and I currently serve as primary mentor for two students in the Biostatistics Department, and for two postdoctoral fellows at NIEHS, including Dr. Von Holle. Including those, I have worked with 11 postdoctoral trainees in all, two of whom are now tenured faculty (one at Duke and one at UNC). Almost all of my trainees secured research positions in academic, government, and industry institutions.

The career development plan Ann has developed will play an integral part in her plans for the K99/R00 as well as her transition into an independent investigator role with plans for future R01 applications. As part of that plan, Ann will tightly integrate my mentorship into her week-to-week research activities. Foremost, she will continue to meet with me each week as we work together on immediate analytic and research aims, discuss responsible conduct of research, and plan her future grant applications and research ideas. Similar to our mentoring relationship for these past three years, I will also discuss and point her towards relevant conferences, symposia, and local discussion groups and opportunities to teach short courses. Her career development and training plan includes attendance and presentations at national conferences relevant to her three proposed aims and, as a postdoctoral fellow at the Biostatistics and Computational Biology Branch, she is encouraged and has financial support to attend these types of meetings. Within this plan and my mentoring scope, my expectation for Ann during the two-year K99 phase is to publish at least two manuscripts per year.

Supplementing my role as her primary mentor, Ann will rely on her mentoring team and advisory committee to accomplish her aims and transition to an independent investigator's position. As mentioned above, I will function as the primary mentor alongside Dr. Dale Sandler as a co-mentor. I have had a working relationship with Dale as a collaborating colleague for 37 years and as a founding co-investigator of the Sister Study. With this mature working relationship, we can provide a coordinated mentoring relationship with Ann when she launches the K99 phase of her project. Dr. Sandler's epidemiological focus on risk factors, including lifestyle, and their impact on chronic disease and breast cancer outcomes, will complement my areas of expertise when applied to Ann's three proposed research aims. Together, we can also guide her transition to an independent investigator position through networking and career development opportunities present at NIEHS.

Outside our roles as primary and co-mentors, Ann has assembled a diverse and talented advisory committee to address the particular components of her proposed research. One member of the advisory group, Dr. Nisha Gottfredson, is a professor at the University of North Carolina, Chapel Hill, Department of Health Behavior. She is expert in structural equation modeling as it applies to public health settings. She will advise Ann on best practices in performing the lifestyle factor analysis, which forms the foundation of the first and second proposed aims. Besides this guidance, Dr. Gottfredson will provide directed readings to Ann that relate to aspects of the physical activity, alcohol use, and body fatness characteristics of the factor and their relationship to the proposed health outcomes. Dr. Shanshan Zhao, a principal investigator at the National Institutes of Environmental Health Sciences, is another member of her advisory committee. Dr. Zhao is an expert in time-to-event statistical modeling, and she will provide guidance to Ann as she starts her second aim involving joint survival analysis. Another member of the advisory group, Dr. Mary Beth Terry, is a professor of epidemiology at Columbia University. Her expertise in genetic and cancer epidemiology will supplement my own expertise and will be of particular relevance to the third aim focusing on gene-environment associations in relation to breast cancer and lifestyle characteristics. Ann and I have agreed that biannual group meetings of the team (perhaps by Zoom) would offer a practical starting point with additional as-needed meetings to be scheduled as she proceeds with her training plan that includes a combination of didactic training, conference attendance, individual mentoring and guided

readings. As shown in her letters of support, all members of the mentoring committee are enthusiastic about this project and Ann's prospects as an independent investigator.

Following the first two years and K99 phase of her proposed career development and training plan, I will support Ann in her R00 phase of the development plan as she steps towards her goal to be an independent investigator. First, Ann will seek advice, guidance and networking support from members of her mentorship team as she engages in the job search process. This support will include thorough and in-depth discussions as she enters the R01 idea development phase starting in her second year of the proposed grant. She will also continue accessing the excellent programming put forward by the Office of Fellows' Career Development at NIEHS and Office of Intramural Training and Education at NIH. For example, one of her training objectives includes taking part in the "Management Bootcamp" offered by NIH for fellows. Outside of the NIEHS experience, she will also seek support from her advisors on the mentorship team, all of whom have success in grant-writing and can offer invaluable advice to structure her R01 grant application.

Ann's prior research with Sister Study data has informed her proposed aims, and her familiarity with the data source will serve her well as she moves forward in a new research area, independent of her prior work. To conduct her investigations of a composite lifestyle factor, its changes over time and associations with risk of breast cancer and all-cause mortality, she will need to continue her data sharing agreement with the Sister Study she has had since 2018. As a co-investigator of this study, I will ensure that she continues to maintain the data sharing agreement she has in place to access Sister Study data.

While conducting her research at NIEHS as a Postdoctoral Intramural Research Trainee, Ann has spent almost all her time in her full-time position devoted to research and career development activities. The exception to this rule is her valuable service activities as a member of the NIEHS trainee steering committee. Ann will continue her full-time appointment in the BCBB and will be able to commit 100% of her effort to her research training and career development during the K99 mentorship phase. Postdoctoral fellows in this branch do not have teaching, administrative or clinical obligations, though they are encouraged as part of their training to take on voluntary teaching roles in our short-term biannual biostatistics short courses. My well-established tenure as an independent investigator in the Biostatistics and Computational Biology Branch ensures that we will be able to cover any additional unanticipated programming needs that arise over the duration of this proposed research. Moreover, I commit to written progress evaluations in the K99 phase for the first two years.

I would like to conclude with a resounding endorsement of Ann's capabilities as a researcher in my group. She came into my research group with strong analytic capabilities and epidemiological training from her work and doctoral training experiences. In my group she has shown a passion for epidemiological principles and novel methodological applications resulting in a growing publication record. Her work in my group combined with her past work experience leads me to trust in her capabilities to transform this experience and training into a new research direction investigating changes in modifiable lifestyle factors and health outcomes. I look forward to promoting this career path for Ann and fully expect her to thrive as an independent investigator.

Sincerely,



Clarice Weinberg
Senior Investigator
Biostatistics and Computational Biology Branch



DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health
National Institute of
Environmental Health Sciences
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June 6, 2021

K99/R00 Review Committee
National Institutes of Health

RE: Letter of Support for K99/R00 application (FOA PA-20-188) – Dr. Ann Von Holle

Dear colleagues:

It is my pleasure to convey my support for and be part of Dr. Ann Von Holle's proposed K99/R00 project titled, "**Lifestyle change over time and postmenopausal breast cancer risk**". The common modifiable lifestyle characteristics that Ann proposes to consider are important because they are leading causes of both mortality and breast cancer risk. To capture these variables in a single risk measure and examine how longitudinal changes in this measure are related to health outcomes is a novel approach to lifestyle research with an eye towards improving the health of women as they age beyond menopause. Much of my research has concerned the impact of lifestyle factors on cancer and non-cancer health outcomes. I am thus well suited and committed to supporting Dr. Von Holle as she progresses in her career development and carries out this novel line of work.

My experience as Chief of the Epidemiology Branch at the National Institute of Environmental Health Science (NIEHS) since 2003, leader of the Chronic Disease Epidemiology Group, and as founding Principal Investigator of the Sister Study positions me well to serve as co-mentor to Dr. Von Holle in pursuit of her research aims, training goals, and transition to career independence. In addition to my work on the Sister Study, I participate in many research consortia that are relevant to Dr. Von Holle's work. The connections I have made through these consortia will be useful in guiding her to future career opportunities. My research interests over the years have been broad, covering a range of environmental and lifestyle exposures in relation to both cancer and non-cancer chronic diseases. My research group uses the Sister Study cohort to examine risk factors for breast cancer and other chronic diseases, including many of the factors that Dr. Von Holle proposes to address – but our work has considered potential risk factors singly and not in combination. I thus am thrilled to be part of her plans to advance the field and facilitate disease prevention by treating these factors as a single concurrent exposure in relation to disease risk and accounting for how longitudinal changes in the combined lifestyle factor may alter risk over time. I am very excited to have Ann apply novel analytic techniques to richly defined Sister Study data on participant characteristics and push us closer to being able to improve population health -- specifically related to a population of women in their post-reproductive years.

Mentoring at all levels is of great importance to me. During my time as Branch Chief I have greatly expanding the mentoring program in our Branch. I was named the 2013 *NIEHS Mentor of the Year* and was recognized as NIH Graduate Partnerships Program Outstanding Mentor in 2019. I have been the primary or co-mentor for 19 postdoctoral trainees at NIEHS since 2002, am primary mentor for 4 current and 2 past tenure-track investigators and have taken 4 investigators to tenure at NIEHS. I have also been secondary mentor to trainees working in other Branches, including those working with Dr. Weinberg who is Dr. Von Holle's primary mentor. Most of my former fellows now hold research positions at NIH and major academic or governmental Institutions. I continue to collaborate with and mentor many of these former trainees. Having been in a position to observe the outstanding trainees who have spent time in our Branch over the years, I have every expectation that Dr. Von Holle will follow in the footsteps of the best of these trainees who have become successful independent researchers and themselves hold positions of leadership.

Dr. Von Holle started as a postdoctoral Intramural Research Trainee at NIEHS in 2018. I first collaborated with her on a novel analysis of familial concordance in breast cancer risk which led to her paper, "Evidence for familial clustering in breast cancer age of onset" (*Int J Epidemiol* 2021). With this work, she began her training in breast

cancer epidemiology, gained a strong understanding of the Sister Study cohort, and developed a foundation of knowledge of the complexities of changing breast cancer risk as women age. In this work she learned of the differences in characteristics between women with early versus later onset of breast cancer and how these factors could affect her analyses. I was also a co-author on her most recent paper evaluating the associations between serum iron biomarkers and breast cancer risk (*Cancer Epidemiol Biom Prev* 2021) in which potential differences in the pre- and postmenopausal periods factored strongly in her analyses. She is integrating this concept into her research proposal focusing on the postmenopausal period, with its distinct combination of lifestyle characteristics that can influence both breast cancer and all-cause mortality. In a recent attempt to understand the disparate effects of obesity in pre-and post-menopausal breast cancer, Dr. Von Holle discovered that the relationship between body mass index (BMI) and breast cancer varied by both menopause status and age-time. I facilitated her access to data from a large consortium so that she could explore this further by focusing on the peri-menopausal transition. She has already presented her preliminary results at the annual meeting of this group, expanding her professional network. In these and other collaborative projects, Dr. Von Holle has shown an ability to take on methodologically challenging projects and work independently while also considering the advice of her mentors. She can draw on these experiences as she carries out the K99 phase of her proposed research and transitions to independence.

During the K99 phase of her research work, Dr. Von Holle will rely on her mentorship team, including me as a co-mentor, to set herself on course to achieve her goal of becoming an independent investigator. I am prepared to co-mentor Ann during her K99 phase as described in her training plan. As PI of the Sister Study cohort I will make sure that the data she needs are readily available and I will encourage her to participate in the many training opportunities we provide, including twice-month Sister Study working group meetings. I will also encourage her to participate in a variety of Epidemiology Branch seminar series, working groups, and journal clubs, as well as to meet with my research group when we discuss work that is relevant to her project. Second, I will direct Dr. Von Holle to relevant readings on prospective cohorts and the risk factors she plans to include as well as to opportunities to expand her understanding of the design and conduct of prospective field studies, including how aspects of data collection could affect study outcomes or interpretation. Third, as the Epidemiology Branch Chief, I will make sure she has opportunity participate and present her research during our Branch meetings where she will find a collegial atmosphere and investigators and trainees who can offer constructive feedback as she develops her analyses, writes her manuscripts, and presents her work. With the varied resources and opportunities available in the Epidemiology Branch, we can provide Dr. Von Holle with a rich mentoring experience that will facilitate her training and career development goals.

I look forward to active engagement with Dr. Von Holle's mentorship committee. She plans biannual steering committee meetings, with additional meetings as needed. I also plan to meet individually with her to review research progress and advise on career planning and future research.

Dr. Von Holle brings a unique background in biostatistics to her work in epidemiology that she will leverage to develop novel solutions to public health problems. She is hardworking and tenacious in the pursuit of solutions to thorny problems. These characteristics will serve her well as she works on her proposed K99/R00 aims. She holds great promise as an independent researcher. As she begins her R00, I see her ability to execute her research in an efficient and organized manner, nurture collaborations, and use her creative vision to develop novel hypotheses as a strong sign of her future success as an independent investigator studying modifiable risk factors relating to the health of postmenopausal women. She has my enthusiastic support for her research and training proposal.

Sincerely,



Dale P. Sandler, Ph.D.
Chief, Epidemiology Branch



May 24, 2021

Dear Members of the Review Committee,

It is my great pleasure to serve as part of the mentorship team for Dr. Ann Von Holle's proposed K99/R00 project titled, "Lifestyle change over time and postmenopausal risk of breast cancer". Modifiable lifestyle factors play an important role in breast cancer risk, and more largely, all-cause mortality. Her proposed project addressing these research areas is exciting as it leverages novel methods applications to investigate simultaneous longitudinal risk and exposure changes. To facilitate her success in completing her proposed aims, I am thrilled to serve as a member of her mentorship team especially as she starts her third aim, which covers the role of lifestyle as an effect modifier of the genetic association with breast cancer -- a topic also more broadly identified as gene-environment associations.

As a Professor of epidemiology at Columbia University focusing on genetic and cancer epidemiology, my extensive research on lifestyle-related factors for cancer risk, such as body mass index and physical activity, overlaps with Dr. Von Holle's proposed K99/R00 aims. Having published in this area and as a principal investigator in many studies focusing on environmental exposures and breast cancer risk, I am well positioned to serve as a mentor for Ann for this research project. Besides time spent with the advisory group meetings, I can provide guided readings relating to topics as they relate to her third aim, assessing the gene-environment associations, and direct her to national and international meetings that can support her research and career development. The field of gene-environment associations is rapidly changing and my advanced epidemiological expertise will keep this project in line with the newest concepts.

Besides my many scientific contributions, I have an extensive record of mentorship, including more than 12 postdoctoral candidates in my research lab during my tenure. My background enables me to provide a high-level of guidance, which will enable her to finish her proposed project in as efficient and innovative manner as possible. Also, I will provide feedback as she develops her R01 topics in the third and fourth years of the K99/R00 period.

In closing, this research project offers a creative angle to understanding the role of lifestyle and its change in relation to breast cancer incidence and all-cause mortality in a

sample of postmenopausal women. I offer my strong support to Dr. Von Holle in her training goals when she starts this new and innovative work so she can move into the next phase of her career: investigating modifiable risk factors in women in their post-reproductive years. Her comprehensive and well-developed training plan alongside her promising proposed aims will position her to be a successful epidemiologist focusing on the connection between lifestyle and health for postmenopausal women. I look forward to supporting Ann during this project as a part of her mentorship team.

Sincerely,



Mary Beth Terry, PhD
Professor of Epidemiology
Mailman School of Public Health, Columbia University
722 W. 168th Street, Room 1607
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May 19, 2021

To the NIH Review Committee:

I am writing to offer my enthusiastic support of Dr. Ann Von Holle's K99 application, "Lifestyle change over time and postmenopausal breast cancer risk." I was first acquainted with Dr. Von Holle in 2013, when we collaborated on a manuscript to evaluate the relationship between longitudinal trajectories of internalizing during childhood and adolescent eating disorder status. Although my role on that project was to provide guidance on longitudinal modeling, it was clear that Dr. Von Holle was a very gifted and capable statistician who needed little support to learn the modeling technique. Given this experience, I am confident that Dr. Von Holle will easily meet her training objectives with the plan that she has laid out.

Specifically, my role on Dr. Von Holle's training advisory committee is to provide guidance to her as she learns how to apply latent variable models (factor analysis, structural equation modeling, and growth curve modeling) to address her research questions. Given what I know about her aptitude and work ethic, along with the importance of her research, I am excited to have the opportunity to participate in Dr. Von Holle's training plan. I commit to meeting with Dr. Von Holle as needed, and at least bi-annually, as she has specified in her training timeline. On an individual-level, I will provide her guided readings as she progresses through analyses for her first aim in the mentored K99 phase. Towards the latter half of her K99 phase, I can provide her career-related guidance during her job search and grant writing advice during the R01 application phase.

In conclusion, Dr. Von Holle will innovate with her K99/R00 proposal when she applies the factor analysis concept to important lifestyle characteristics, which number among the top causes of all-cause mortality and breast cancer. I am excited to be an advisor on her mentorship team when she begins her research, and these efforts, in combination with her career development and training plan, will allow her to achieve her goals. I look forward to advising Ann through each phase of her K99/R00 grant, with a public health goal to address the role of lifestyle change in health outcomes of postmenopausal women.

Sincerely,

Misha Gottfredson

Nisha Gottfredson, PhD
Assistant Professor of Health Behavior
UNC Gillings School of Global Public Health



National Institutes of Health
National Institute of
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Dear members of the review committee,

I am writing to express my strong and enthusiastic support for Dr. Ann Von Holle's K99/R00 proposal titled, "Lifestyle change over time and postmenopausal breast cancer risk." It will be a pleasure to serve on her advisory committee as she starts work on her second aim to assess the relationships between the lifestyle factor changes and incident breast cancer and all-cause mortality outcomes. She will apply joint analysis methods to modifiable lifestyle risk factors and risk -- a novel approach in this research area -- and it will improve our understanding of which factors may best match successful lifestyle interventions specific to populations of women past reproductive age.

As a principal investigator in the Biostatistics and Computational Biology Branch at the National Institute of Environmental Health Sciences, my expertise encompasses many aspects of statistical methods for survival analysis. For example, in 2019 I published a book titled, "The Statistical Analysis of Multivariate Failure Time Data: A Marginal Modeling Approach". I will rely on this experience when I serve as an advisor on Ann's mentorship team and advise her should any problems arise during the analytic components of the second aim, which employs joint analytic methods. With joint longitudinal methods, new papers are coming out with increasing frequency and having an expert such as myself for her mentoring team will be essential to help her accomplish her analytic work and build upon this research as she determines the best statistical approaches during the R01 application phase.

In addition to my scientific accomplishments, I have mentored or co-mentored 8 trainees in my first 6 years as a principal investigator. With this mentoring experience, I can help structure her second training objectives to advance her knowledge of joint longitudinal and survival analyses. I plan to direct her towards scientific conferences and additional workshops. These activities as well as guided readings can enhance her expertise in applying these methods.

In summary, this K99/R00 proposal applies several new and innovative statistical approaches to the important lifestyle factors that number in the top causes of all-cause mortality and breast cancer. I enthusiastically support Dr. Von Holle as she starts her training goals and then moves into the R00 phase of her proposed project with the goal to transition into an independent investigator role. I believe that the combination of her career development and training plans with her research strategy will place her on a successful track to achieve her goals. Similarly, I look forward to advising Ann as she moves through these milestones with an overarching goal to improve the health of women as they age past their reproductive years.

Sincerely,
Shanshan Zhao, Ph.D.

Principal Investigator
Biostatistics and Computational Biology Branch
NIEHS/NIH

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.



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
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Website: <http://www.niehs.nih.gov>

Dear Review Committee:

It is my great pleasure to offer support for Dr. Ann Von Holle's application for a K99/R00 award. Dr. Von Holle is currently a postdoctoral trainee in the Biostatistics and Computational Branch, Division of Intramural Research at NIEHS. Ann works in the research group of Clarice R. Weinberg, Ph.D., an eminent and established expert in epidemiological methods and genetic epidemiology.

Dr. Von Holle's K99/R00 proposal incorporates her rich research experiences from both her graduate and postdoctoral training. She will combine longitudinal and time-to-event analyses using novel techniques when studying modifiable lifestyle exposures in the Sister Study, an ongoing prospective cohort study of women led by NIEHS researchers who also will be her mentors. In her first aim, she will characterize combinations of lifestyle characteristics and their change over time that are unique to women who have aged past menopause. Completion of her proposed aims can address gaps in research informing public health interventions in women who are aging past menopause. Upon successful completion of these aims, Ann's proposed research will set her on a path to research independence, including a successful R01 application.

The NIEHS has a very strong intramural research program with extensive and leading work in the epidemiological research of common complex disease within the Sister Study, Dr. Von Holle's chosen area of study. Ann's career development and training plan specifies Dr. Clarice R. Weinberg as her primary mentor and Dr. Dale P. Sandler as her co-mentor, leaders of the Sister Study with expertise that is uniquely suited to Dr. Von Holle's K99 mentored phase of her research. Dr. Shanshan Zhao, a principal investigator at NIEHS and expert in statistical methods, will also be part of her mentorship team. We acknowledge and will support this excellent mentoring team within NIEHS to ensure the completion of Ann's aims and goals for training and career development. On an institutional level, NIEHS has programs in place to support trainees in their career development. First, mentors conduct annual reviews of their trainee's progress prior to their reappointment for additional year(s). Outside of their time dedicated to research within the Division, we encourage trainees to attend our extensive weekly seminar offerings and attend career-related workshops in areas such as communication, leadership, and teaching. As mentioned in Dr. Von Holle's career development and training plan, the NIEHS Office of Fellows Career Development, under my supervision, will assist Ann in her job search for which this award will be invaluable. Also, during her K99 mentored phase, Ann will not have requirements to teach or have clinical or administrative responsibilities. Last, we will support Dr. Von Holle during the K99 phase through normal financial support mechanisms in the Division of Intramural Research.

In short, the NIEHS offers enthusiastic support of Dr. Von Holle's career development and goals to become an independent investigator through her K99/R00 proposal. As she advances towards her goals, we are committed to offering her our institutional support through the effective programs we have structured to train outstanding researchers. In committing this support, we are confident that she will excel in her career to promote a better understanding of the role of modifiable factors in breast cancer and all-cause mortality outcomes.

Sincerely,

Paul W. Doetsch, M.S., Ph.D.
Deputy Scientific Director, NIH/NIEHS

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.