OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 09/30/2024)

BIOGRAPHICAL SKETCH

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

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| NAME: Von Holle, Ann |
| eRA COMMONS USER NAME (credential, e.g., agency login): ANNVONHOLLE |
| POSITION TITLE: Biostatistician |

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.)*

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| --- | --- | --- | --- |
| 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 | MOTH | 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 research interests, broadly focusing on capturing longitudinal patterns of exposure change, inform both the prevention and study of disease outcomes. My goals moving forward are to shift from a focus on single exposures ‌to capturing multiple exposures across time to help better understand mechanisms by which breast cancer occurs and, on a larger scale, steps we follow to prevent the occurrence of disease. To accomplish these goals, my plan is to investigate modifiable risk factors, such as the lifestyle change of postmenopausal women as they relate to breast cancer prevention and mortality reduction. I first began my work with, and interest in, body size change, a lifestyle measure figuring prominently in my K99/R00 proposal, as a biostatistician in an academic research center. One example of this collaboration is a work in which we assessed weight-for-length trajectories in infants of women reporting an eating disorder. My interest in assessing weight change over time scaffolded my next steps to pursue doctoral training in epidemiology and shaped my long-term goals to focus on a new area studying lifestyle exposures and health outcomes in public health research. During my doctoral training, I studied the role of infant anthropometric measure change within a life course perspective, and found that predictors of infant weight and its role as an exposure are not uniform across the age scale with unique characteristics occurring within the window of the first six months of growth. I leveraged my predoctoral experiences studying body size change, a shared modifiable lifestyle risk factor between chronic disease and cancer, to transition to a focus on breast cancer epidemiology in my postdoctoral work. My first project included characterizing familial correlation of age of onset in sisters. In this work, I focused on the change in breast cancer risk over age-time, which was essential when evaluating risk in relation to an affected sister’s age. We found evidence to support similarities in the age of onset of breast cancer, with implications for personalized medicine. I have continued my interest in studying body size change in critical windows of time with recent work in preparation that describes the associations between body size and breast cancer risk around the time of change in which women typically transition to menopause. My proposed K99/R00 research focuses on this critical window of change and studies lifestyle risk factors that are associated with chronic disease, mortality, and breast cancer risk. This work will combine my experience in longitudinal measures of lifestyle exposures with age-time dependence of breast cancer risk, and it provides a unique platform upon which I can expand my research expertise while meaningfully contributing to public health. Additional training will expand my knowledge of lifestyle factors besides body size during the postmenopausal period, and I will learn advanced joint modeling techniques so I can combine analyses of longitudinal exposures with risk of disease. This training creates a path for me to complete the proposed research and move toward an overarching goal to inform public health prevention measures to reduce breast cancer incidence and all-cause mortality.

1. Von Holle A, North K, Gahagan S, Blanco E, Burrows R, Lozoff B, Howard A, Justice A, Graff M, Voruganti S. Infant Growth Trajectories and Lipid Levels in Adolescence: Evidence From a Chilean Infancy Cohort. American Journal of Epidemiology. 2022 April 25; :-. Available from: https://academic.oup.com/aje/advance-article/doi/10.1093/aje/kwac057/6573816 DOI: 10.1093/aje/kwac057
2. 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.
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. 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. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

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| 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

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| 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 collaborated with lead authors in designing and conducting analyses. 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 over 100,000 pregnancies. Of the 20 MoBa publications in which I was a co-author, I was the lead statistician on 15 of them, many of which center on changes in body size as an exposure, which will be an exposure that features prominently in my K99/R00 aims. This body of work supports 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. In my collaborations, I trained myself to conduct longitudinal analyses to best understand weight change patterns, and this work motivated my dissertation work studying body size change as an exposure.

* 1. 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.
  2. 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.
  3. 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.
  4. 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.

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

My dissertation research, completed in 2018, informed how growth in early life can influence later life risk factors. The “Developmental Origins of Health and Disease” theoretical framework informed my three aims, examining associations between body size change over time during infancy and lipid levels in adolescence. To fund this dissertation work, I successfully applied for and received an individual two-year American Heart Association predoctoral fellowship (2016-2018). When determining the extent to which associations exist between infant growth before six months and lipid outcomes measured during adolescence, I assessed patterns of infant growth as an exposure through innovative statistical approaches. These approaches included nonlinear mixed effects models and latent class growth mixture modeling, which provided novel insights into infant growth as exposure associated with lipid biomarkers. 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 that socioeconomic position of an infant’s family can play a role in anthropometric growth even in the first five months, 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 before six months of age that have distinct growth profiles and unique associations that may not be consistent with other age periods. During graduate school, I further refined my knowledge of the application of advanced longitudinal methods as well as creating scientific bodies of work in which, as a first author, I refined my skills in developing concepts, writing manuscripts, and collaborating with co-authors. This work enforced my appreciation for windows of time with unique growth characteristics available through well-characterized temporal data, which may also show unexpected associations with health outcomes.

* 1. Von Holle A, North K, Gahagan S, Blanco E, Burrows R, Lozoff B, Howard A, Justice A, Graff M, Voruganti S. Infant Growth Trajectories and Lipid Levels in Adolescence: Evidence From a Chilean Infancy Cohort. American Journal of Epidemiology. 2022 April 25; :-. Available from: https://academic.oup.com/aje/advance-article/doi/10.1093/aje/kwac057/6573816 DOI: 10.1093/aje/kwac057
  2. 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.
  3. 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.

1. **Postdoctoral training at the National Institute of Environmental Health Sciences**

My postdoctoral experience has led me to several important findings that underline the importance of timing when considering risk factors for breast cancer occurrence. This work occurred as I learned best practices in breast cancer research, and I have received advanced training in both cancer and cardiovascular disease outcomes—two of the most frequently occurring diseases in the United States with shared lifestyle risk factors, including body size, physical activity, alcohol use, and smoking. My work also brought a shift in my methodological focus from mixed effects and latent class models to time-to-event models with time-dependent covariates. Using these methods, and with my collaborators at NIEHS, I found evidence supporting an increase in risk around the age of the affected sister’s diagnosis, and, if replicated, this original work offers the potential for diagnostic screening of women with affected sisters. I am also the lead author on a manuscript in preparation using data from an international breast cancer consortium with more than 10,000 breast cancer cases that describes age-dependent changes in the association between body mass index and breast cancer risk over age-time around 50 years, a point at which women typically transition to menopause. We have found little evidence for change ‌in associations across a ten-year range around age 50, and we expect future studies to provide more information about the expected shift to an adverse association between body mass index and breast cancer risk after menopause. The important window of time in which women enter and move through menopause accompanied by shifts in health status relevant to our findings–further motivated and informed the aging studies focus of my proposed research aims.

Several recent projects include a multi-pronged focus on serum iron biomarkers, which are considered both an outcome and risk factor for human health such as iron deficiency anemia and cancer. Our findings contradict prior studies that found a positive association between serum iron levels and the risk of breast cancer. Body iron status is also tightly linked to menopause status because of the cessation of menses, and, to best characterize these findings, we divided women into groups by menopause status. Similarly, in a manuscript I am preparing in which we describe predictors of iron status, postmenopause status is a powerful predictor of higher iron levels. This research underlines the importance of considering menopause status when estimating associations between exposures and disease, and this consideration underlies my proposed aims.

* 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.