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TITLE: Grandparental Exposures and Risk of Autism in the Third Generation

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13. SUPPLEMENTARY NOTES

14. ABSTRACT
In the second year, we identified 21,772 Child Health and Development Studies grandchildren by linking to the California Birth Records, which was slightly greater than our original estimate of 20,000. We were able to support our matching results by using self-reported child bearing (births of F2) data collected from a subset of our cohort F1 women. This comparison supported the validity of our matching efforts to identify our CHDS F2. By linking these births to the California Department of Developmental Services records we have successfully identified 131 autism cases in our cohort which exceeds our initial estimate of 72. We will use a prospective study of 21,772 CHDS grandchildren (F2) with 131 autism cases to explore the effect of grandparental (F0) exposures. This will be the first study of its kind in the United States, linking three generations from the 1960's through the 2010's and will establish a platform for studying germline exposures and risk of autism.

15. SUBJECT TERMS
Autism, Prospective Study, Germline Exposures, Multi-generation Cohort, Grand-parental Risk Factors

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1. INTRODUCTION:

This study will test the hypothesis that Grandparental exposures during peri-conception and pregnancy predict increased risk of autism in the grandchildren. This study will identify cases of autism spectrum disorder (ASD) and unaffected controls in the grandchildren of The Child Health and Development Studies (CHDS) multigenerational cohort. We will use a prospective study of 21,772 CHDS grandchildren (F2) with 131 autism cases to explore the effect of grandparental (F0) exposures. The CHDS study population is a 50+ year follow-up of 20,000 pregnancies that occurred in the 1960's. Significantly, the 1960's was a period when maternal pregnancy exposures to a wide variety of endocrine active compounds were high, including prescription drugs, cigarette smoking, alcohol and coffee. We identified CHDS grandchildren by linking to California birth records. We identified grandchildren with autism by linking to California Department of Developmental Services (CA-DDS) files. Risk factors include grandmaternal and grandpaternal age, smoking, alcohol, coffee, and grandmaternal prescription drugs (tranquilizers, sedatives, amphetamines, diuretics, antihistamines hormones) during pregnancy.

2. KEYWORDS:

Autism, Prospective Study, Germline Exposures, Multi-generation Cohort, Grand-parental Risk Factors

3. ACCOMPLISHMENTS:

What were the major goals of the project?

1. Submit for Local IRB (PHI) & CPHS approval. COMPLETED
2. Submit for DDS and Vital Records approval. COMPLETED
3. Submit for HRPO approvals. COMPLETED
4. Perform CHDS linkage to California Vital Statistics Birth Records to identify CHDS grandchild births. COMPLETED
5. Link CHDS grandchild birth records to the Department of Developmental Services records to identify cases of autism in grandchildren. COMPLETED
6. Link archive CHDS data on grandparents and parents to data generated on grandchildren. IN PROGRESS
7. Analysis of grandparental peri-conceptual and prenatal risk factors for grandchild autism. BEGIN IN YEAR 3
8. Investigate relation of grandparental risk factors for autism to growth and development in the parent. BEGIN INYEAR 3

What was accomplished under these goals?

1. We have submitted and received approval from both Local IRB (Public Health Institute) & California Committee of Human Subjects (CPHS) approval.

2. We have submitted and received approval from the California Department of Health Information and Research Section to receive access to birth files from 1975 to 2014.

3. We have submitted and received approval from HRPO.

4. We have received the physical files containing the birth records from 1975 to 2014.

    a. We matched our cohort members (F1) to the California birth records and have completed this process.

    b. During the process we develop and refined our matching protocol and methods.

    c. We identified 21,772 F2, which was slightly greater than our original estimate of 20,000.

5. We had identified DDS variables we needed for the match and for analysis. We applied and received DDS approval and we have successfully run our CHDS state record file numbers against DDS records. By matching state record numbers (F2) to Department of Developmental Services we have successfully identified 131 autism cases in our cohort which exceeds our initial estimate of 72.

6. Using the 21,772 F2 identified births which contain the 131 autism cases we have started to build our data set that contains our archived CHDS data on grandparents (F0) and parents (F1). We are also appending the DDS data and variables available for the 131 identified autism cases.

7. This will start in Year 3.

8. This will start in Year 3.

What opportunities for training and professional development has the project provided?

Nothing to report

How were the results disseminated to communities of interest?

We have discussed this project at our quarterly Participant Advisory Council (PAC) meetings. Our PAC is a diverse group of CHDS mothers, sons and daughters who have partnered with us to help guide our research. They have expressed interest in studying Autism on multiple occasions and are eager to hear updates on our progress and findings in this study. We have reported and discussed our success with linking to the birth files. Our PAC is excited for the potential of this

data and linkage for autism research, appreciates the increased scientific potential this linkage has built for the CHDS cohort.

What do you plan to do during the next reporting period to accomplish the goals?

6. Finish linking our archive of CHDS data on grandparents (F0) and parents (F1) to data generated on grandchildren (F2).

7. Conduct analysis of grandparental peri-conceptual and prenatal risk factors for grandchild autism.

8. Investigate relation of grandparental risk factors for autism to growth and development in the parent.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Applying for and being granted IRB approval and linkage approval at Institutional, State and Federal levels, for linkage to public records sets a precedent for future linkages. This is an expansion of the permissions and linkages the CHDS already routinely conducts (DMV, CA death and CA cancer). Proving the feasibility and process of linking grand-parental health to grandchild health information will advance multigenerational and transgenerational research possibilities.

We are creating a matching procedure that CHDS and other researchers can use in conducting data linkages, especially for matching to California Vital Statistics data (California Birth Record Files). Briefly, birth record data available for matching in California has changed and expanded over the years requiring year-specific matching protocols. For example, before 1989, birthdate for mothers and fathers, and father's first name were not included in the electronic birth record files. This made the matches less reliable than matches done after 1989 where those variables were available to improve the matching integrity. We were able to support our matching results by using self-reported child bearing (births of F2) data collected from a subset of F1 women in our cohort. This comparison supported the validity of our matching to identify F2 births in our cohort. When comparing F1 women who previously self-reported having a child (n=2,029), 91% matched to the California Birth Record Files as mothers of an identified CHDS F2s. We would not expect a 100% match because not women who self-reported having children resided in California and our birth match was limited to California births.

By linking to our F2 we now have the possibility to expand our multigenerational and transgenerational research. We now have the link (state file record number) that will enable us to identify and obtain blood spots for our cohort offspring that were collected and archived by the state of California. These blood spots would allow for environmental analysis of contaminants, genetic, and epigenetic markers.

Nothing to report

- **Website(s) or other Internet site(s)**

  Nothing to report

- **Technologies or techniques**

  Nothing to report

- **Inventions, patent applications, and/or licenses**

  Nothing to report

- **Other Products**

  Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Barbara Cohn – No change

Name:	*Nickilou Krigbaum*
Project Role:	Researcher
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*2*
Contribution to Project:	*Krigbaum compiled and submitted all submissions to IRBs and for linkage approval renewals. She conducted the linkages to the California Birth Record Files to the CHDS cohort to identify the CHDS grandchildren that will be used in this study.*
Funding Support:	

Gayle Windham – No change

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

The following support ended February 28, 2018:
21UB-8002 (Cohn) 03/01/15 – 2/28/2018 1.44 calendar months
California Breast Cancer Research Program
Chemical Safety during Breast Cancer Susceptible Windows

22AB-1200 (Cohn) 09/01/16 – 02/28/18 1.20 calendar months
California Breast Cancer Research Program
ReThink Plastic

The following support began December 1, 2017:
23UB-9452 (Cohn) 12/01/17 – 11/30/20 1.20 calendar months
California Breast Cancer Research Program
Linking Neighborhood and Individual ACEs to Breast Cancer

The following support began April 1, 2018:
554297 (Marcus) 04/01/18-03/31/21 0.6 calendar months
Tobacco-Related Disease Research Program
Tobacco Smoke Exposure and Atrial Fibrilation

What other organizations were involved as partners?

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS:

Nothing to Report

9. APPENDICES:

Nothing to Report