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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 (F2) by linking to the California Birth Records, which was slightly greater than our original estimate of 20,000. Using address history files, we verified 18,371 CHDS grandchildren births. 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 second generation (F1) women. This comparison supported the validity of our matching efforts to identify our CHDS F2. By linking the verified births to the California Department of Developmental Services records we have successfully identified 116 autism cases in our cohort which exceeds our initial estimate of 72. We will use a prospective study of 18,371 CHDS grandchildren (F2) with 116 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

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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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 18,317 verified CHDS grandchildren (F2) with 116 autism cases to explore the effect of grandparental (F0) exposures. The CHDS study population is a 50+ year follow-up of 20,020 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. COMPLETED
7. Analysis of grandparental peri-conceptual and prenatal risk factors for grandchild autism. IN PROGRESS
8. Investigate relation of grandparental risk factors for autism to growth and development in the parent. IN PROGRESS

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.
    d. Using past address history and other CHDS data we were able to verify 18,317 births from 1989 to 2014.
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. Using past address history and other CHDS data we were able to verify 18,317 births and 116 autism causes in the CHDS F2 generation.
6. Using the 18,317 verified F2 identified births which contain the 116 autism cases we have created a data set that contains archived CHDS data on grandparents (F0) and parents (F1). We also appended the DDS data and variables available for the 116 identified autism cases.
7. This process has started and is currently in progress
8. This process has started and is currently in progress.

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?

7. Continue to conduct analysis of grandparental peri-conceptual and prenatal risk factors for grandchild autism.
8. Continue to 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.

What was the impact on other disciplines?

Nothing to report

What was the impact on technology transfer?

Nothing to report

What was the impact on society beyond science and technology?

Nothing to report

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to report

Actual or anticipated problems or delays and actions or plans to resolve them

We had a delay and difficulty was finalizing the Data Use Agreement (DUA) with the California Department of Developmental Services (DDS). The DDS DUA for the CDPH was in place in the originally anticipated time but DDS wanted a separate DUA from the Public Health Institute. After months of discussion, they reversed their position allowing the DUA to cover both entities, but this was not signed and approved until May 2018. We requested a 12 month no cost extension in June 2018, to complete the work and make up for the delay in our original grant timeline.

Changes that had a significant impact on expenditures

We had a delay was finalizing the Data Use Agreement (DUA) with the California Department of Developmental Services (DDS). The DDS DUA for the CDPH was in place in the originally anticipated time but DDS wanted a separate DUA from the Public Health Institute. After months of discussion, they reversed their position allowing the DUA to cover both entities, but this was not signed and approved until May 2018. We could not proceed with the planned data file building and data analysis until this agreement was complete and did not spend the funds allocated to that process. We requested a 12 month no cost extension to complete the work and make up for the delay in our original grant timeline. Expenditures will be the same as the original grant and it is only the timeline for spending them that has changed.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report

Significant changes in use or care of human subjects

Nothing to report

Significant changes in use or care of vertebrate animals

Nothing to report

Significant changes in use of biohazards and/or select agents

Nothing to report

6. PRODUCTS:

- **Publications, conference papers, and presentations**

  Nothing to report

- **Journal publications.**

  Nothing to report

- **Books or other non-periodical, one-time publications.**

  Nothing to report

- **Other publications, conference papers, and presentations.**

  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

Nickilou Krigbaum- No change

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 began July 1, 2018
1R01AG058704 (Suglia) 07/01/18-02/28/22
0.4 calendar
NIH
Stress, Epigenetics and Aging

The following support began July 1, 2019

1R01MH118545-01A1 (Ellman) 07/01/19-06/30/24
1.2 calendar
NIH
Maternal Inflammation During Pregnancy: Clinical and Neurocognitive Outcomes in Adult Offspring

What other organizations were involved as partners?

Nothing to report

5. SPECIAL REPORTING REQUIREMENTS
COLLABORATIVE AWARDS:

QUAD CHARTS:

6. APPENDICES: