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AWARD NUMBER: W81XWH-16-1-0753

TITLE: Prenatal Polyunsaturated Fatty Acid Levels and Risk of Autism Spectrum Disorders

PRINCIPAL INVESTIGATOR: Kristen Lyall

RECIPIENT: Drexel University

REPORT DATE: October 2018

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release; Distribution Unlimited

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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

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1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2018	Annual	30 Sep 2017 - 29 Sep 2018

4. TITLE AND SUBTITLE
Prenatal Polyunsaturated Fatty Acid Levels and Risk of Autism Spectrum Disorders

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-16-1-0753

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

DREXEL UNIVERSITY
3141CHESTNUT ST PHILADELPHIA
PA 19104-2816

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT The causes of autism spectrum disorder (ASD) are not well understood, but research suggests that factors influencing early brain development may be involved. Polyunsaturated fatty acids (PUFAs), which include omega 3 fatty acids, are fats obtained from the diet that play key roles in early fetal brain development. It is not known whether levels of these crucial fats during pregnancy influence risk of ASD. This project will examine the relationship between PUFA levels and ASD, addressing the role of environmental risk factors in ASD (a FY15 priority Area of Interest. Specifically, the goal of this project is to determine whether levels of PUFAs measured from maternal blood samples collected during pregnancy, and in a subgroup group, from newborn blood spots, differ between children with ASD and those without ASD. We will also explore whether the relationship between PUFAs and ASD differs in certain subgroups, such as by race/ethnicity, preterm birth, or child gender. Based on the importance of PUFAs in neurodevelopment, we suspect that lower levels of PUFAs may be related to ASD.

In order to address these questions, we will use data from routine screening programs in the state of California. Children with ASD (cases) will be selected from the California Department of Developmental Services (DDS), a statewide program that coordinates services for children with autism and other disabilities. Children without ASD (controls)will be selected from California birth certificates in the same year as children with ASD. PUFAs will be measured in the previously collected blood samples from pregnancy(500 cases and 500 controls), and in newborn blood spots from a subgroup (200 cases and 200 controls) using sensitive, state-of-the-art technology. Statistical analyses will examine differences in levels of maternal and newborn PUFAs between children with and without ASD, adjusting for demographic and other factors that may influence the association. Subgroup analyses will explore potential differences by major categories of race/ethnicity, gender, preterm birth, and others. Because the samples used in this study were collected during the time when PUFAs may have the greatest influence on the developing brain, associations seen here will inform on the role of PUFAs in risk of ASD.

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	34	19b. TELEPHONE NUMBER *(include area code)*

TABLE OF CONTENTS

1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

The purpose of this project is to determine whether prenatal levels of polyunsaturated fatty acids (PUFAs), as classes (omega 3, omega 6, and total PUFA) as well as individual fatty acids, are associated with offspring autism spectrum disorder (ASD). These fats are critical in neurodevelopmental processes with evidence for disruption in ASD, and thus we hypothesize that altered levels of them during critical windows of neurodevelopment may influence risk. To address this hypothesis, we are conducting a population-based case control study, including 500 cases with ASD identified through the California Department of Developmental Services (DDS) and 500 general population controls identified through state birth certificates and matched by birth year (2011-2013), birth month, and sex, after excluding DDS clients. Using banked prenatal serum specimens collected through routine prenatal screening in California, levels of PUFAs are measured using liquid chromatography-mass spectrometry/high resolution mass spectrometry (LC-MS/MHMS). In a subset of participants (n=400), we will also examine measured levels of PUFAs in neonatal blood spots. Results from this work will provide novel information about the relationship between PUFAs and ASD, in the first study with measured levels of PUFAs during pregnancy.

2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

Autism, etiology, epidemiology, polyunsaturated fatty acids, prenatal risk factors, nutrition

3. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Major goals included in the SOW, and information on target and actual dates and percent completion, are listed below:

1. **Procurement of Maternal and Neonatal Stored Blood Samples (relevant to Aims 1, 2, and 3)**

   Target completion: Year 1, quarter 3-4

   Actual completion/% complete: Year 1, quarter 4- all maternal and neonatal samples have been obtained; thus, this task is 100% complete.

   Description: We have obtained all maternal prenatal serum samples (n=1002; an additional 2 were obtained due to unexpected differences in availability of samples and the need to balance case-control birth years) neonatal blood spots (n=400). This major goal included the following sub-tasks: completing and submitting IRB and vital record use applications (completed by the second quarter of our first year, slightly later than expected due to California review board meeting dates); selecting cases and controls from California databases (projected for quarter 1; completed slightly later than anticipated, due to waiting for approvals); obtaining approval

from the Genetic Disease Screening Program (GDSP) for use of samples (completed as projected); requesting and obtaining samples from GDSP and sample shipment to the Snyder laboratory (obtaining of samples completed approximately one quarter later than expected, due to delays in the California Biobank queue process.)
Major milestones sought and achieved: Local and CPHS IRB approvals; HRPO approval; procurement of samples.

2. **Measurement of PUFAs in maternal serum and newborn blood spots (relevant to Aims 1 and 3)**
   Target completion: Year 1, quarter 4- year 2, quarter 2
   Actual completion/% complete: We have completed laboratory analyses of all samples (100% complete).
   Description: Measurement of PUFAs in maternal samples was completed in the Spring of 2018. Measurement of PUFAs in newborn spots was just recently completed. There had been some delay in shipment of newborn blood spots due to California Biobank administrative delays.
   Major milestones sought and achieved: Completion of biosample assays for PUFAs.

3. **Data analysis of PUFAs in association with ASD (relevant to Aims 1, 2, and 3)**
   Target completion: (Year 2, quarters 2-4.)
   Actual completion/% complete: 75% complete; we have completed analyses of maternal PUFA levels and ASD and have recently begun analyses of newborn PUFAs and ASD. Analyses of newborn levels will parallel those conducted for maternal levels, and thus can be efficiently conducted given statistical programming is already in place.
   Description: Substantial progress towards this major goal has occurred over the past year. Subtask 1 (analyses of maternal levels) has been completed and we are finalizing the presentation of results; subtask 2 (examination of modifiers and subgroups) has also been conducted; and subtask 3 (analyses of newborn levels) is beginning. Results relevant to Aim 1 are presented in Appendix 1.
   Milestone achieved: Completion of statistical analyses.

4. **Presentation of findings (relevant to Aims 1, 2, and 3)**
   Target completion: (Year 3, quarters 1-4)
   Actual completion/% complete: 40%
   Description: We have presented results based on maternal serum PUFAs as an oral presentation at an International conference this year: the International Meeting for Autism Research (INSAR) in Rotterdam, Netherlands May 2018. The abstract (submitted based on preliminary results) was provided in the Appendix of our Year 1 Annual Report. In addition, we are planning to submit preliminary results based on newborn levels for the 2019 INSAR conference (abstract submission deadline of 11/30/18); thus, subtask 2 of this major task will be completed shortly. We are preparing the maternal serum results manuscript presently, and expect to have a draft ready for submission for publication in the third quarter of this year. A manuscript of newborn results will be prepared following completion of newborn level analyses, anticipated for the third quarter.
   Milestone achieved: Presentation of findings.

What was accomplished under these goals?
For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Major accomplishments under these goals (since the last report) include: completion of laboratory analyses of newborn blood spots using liquid chromatography tandem mass spectrometry, which represents a relatively novel assay and demonstrates success in ability to measure PUFA levels in archived bloodspot samples. An additional major accomplishment is the completion of data analysis for maternal PUFA levels and presentation of these findings at the 2018 INSAR meeting. Specifically, we conducted crude and multivariate adjusted logistic regression to examine the association between maternal PUFA levels in quantiles and offspring ASD. These results, summarized in Appendix Tables 1 and 2 and Figure 1, suggest there may be increases in risk associated with certain levels and in certain subgroups (e.g, those with comorbid intellectual disability), but that these associations do not follow a clear linear or dose-response pattern.
Results of newborn PUFAs will yield novel information about how maternal and neonatal PUFA levels correlate, and whether associations differ based on these time periods.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Under funding from this project, the PI attended the 2018 meeting of the International Society for Autism Research (INSAR), where she presented findings from this study. This presentation was part of a panel on prenatal nutrition and ASD, and Dr. Lyall was one of three presenters in the panel.

The laboratory analyst supported by this project has gained additional expertise and training in measurement of PUFAs in two biological matrices using mass spectrometry, under the guidance of Co-Investigator Dr. Snyder. In addition, this work is providing training opportunities for two masters-level students who will be assisting in analyses PUFAs and ASD. Dr. Lyall will be mentoring these two students with an interest in how biomarkers during pregnancy may predict autism.

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Results from maternal PUFA analyses from this work were presented at the INSAR meeting as described above. As the premiere autism conference, findings were disseminated to professionals in the field. We also plan to disseminate findings through publishing in peer reviewed journals; the manuscript based on associations with maternal PUFA levels is currently being prepared.

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

The majority of our major goals have been accomplished; during the final year of our project, our primary focus will be on finalizing results and preparing them for presentation and publication. Analyses of newborn PUFA levels are currently in beginning stages and thus we plan to complete these analyses during the next reporting period. We will also conduct secondary and sensitivity analyses to test the robustness of our findings. As stated, we also plan to prepare and submit manuscripts for both the maternal and the neonatal PUFA levels in association with ASD during this reporting period. We may also seek publication of the laboratory methods for analyzing PUFA levels in archived newborn blood spot samples, given the relative novelty of this method.

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Our study provides the first results on the association between measured levels of maternal and newborn PUFA levels in association with ASD diagnosis. Because there was some suggestion of increased risk for having a child with ASD with comorbid intellectual disability among mothers with low levels of certain PUFAs, our work may have potential impact on dietary recommendations. The majority of pregnant women do not eat recommended levels of fish, which are a key source of these PUFAs. If our findings are further supported in work seeking to replicate these results, there is thus the potential for risk reduction with dietary modifications for certain subgroups. Furthermore, because few studies have measured levels of these fatty acids in newborn blood spot samples, our study has provided novel information on methods to conduct such measurements, which could be applied in other studies.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

The suggestion of potentially increased risk with certain PUFA levels for ASD with comorbid intellectual disability suggests the need to further examine these associations in study populations with detailed information on broader neurodevelopmental outcomes in order to tease apart specificity of associations and better understand how risk may differ for different neurodevelopmental conditions and for individuals with comorbid conditions. Thus, our findings could have an impact on other fields of specialty focused on other, non-ASD neurodevelopmental disorders. In addition, as stated above, the measurement of PUFAs in newborn blood spots may have an impact on other disciplines seeking to measure these fatty acids in novel and more readily available matrices.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:
- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to Report

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Findings here should be replicated and further studied prior to making wide-scale public health recommendations. However, there is evidence that PUFA intake is below recommended levels for pregnant women in the US; thus, if there is further support for increased risk to certain subgroups with levels outside of average ranges, risk reduction strategies based on dietary recommendations could ultimately be created, and this may have an impact on risk of ASD.

5. CHANGES/PROBLEMS: The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

No significant changes in approach have been made.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

We have not experienced any major problems during this reporting period. We did have an issue with having one less case than planned, due to lack of biospecimen availability. We will therefore have an analysis sample size including 499 ASD cases, rather than 500 as planned. This loss will not impact our statistical power to detect associations, and analyses will be run comparing statistical modeling strategies using complete matched sets (e.g., conditional logistic regression) as well as using logistic regression accounting for matching factors to ensure there is also no impact on effect estimates.

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

None

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

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

None

Significant changes in use or care of vertebrate animals.

Not applicable

Significant changes in use of biohazards and/or select agents

Not applicable

6. PRODUCTS: List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: Author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

None

Other publications, conference papers, and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Conference presentation: INSAR, Rotterdam, NL, May 2018.
Lyall K, Windham GC, Snyder N, Carver J, Newschaffer C. "Prenatal levels of polyunsaturated fatty acids in association with autism spectrum disorder." Oral presentation given on May 10th, 2018.
Acknowledgement of federal support was given in the presentation slides.

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to report

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. In addition to a description of the technologies or techniques, describe how they will be shared.

Nothing to report

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. State whether an application is provisional or non-provisional and indicate

the application number. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

- **Other Products**

Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment, and/or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

Nothing to report

- *data or databases;*
- *biospecimen collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change."

(NO CHANGES)

Name: Dr. Kristen Lyall
Project Role: Principle Investigator
Researcher Identifier
Nearest person month worked: 2
Contribution to Project: Oversaw all project activities, obtained appropriate approvals, and conducted data analyses.

Name: Dr. Nathaniel Snyder
Project Role: Co-Investigator
Researcher Identifier
Nearest person month worked: 1
Contribution to Project: Performed laboratory analysis of PUFAs in maternal serum samples and newborn blood spots.

Name: Dr. Gayle Windham
Project Role: Co-Investigator
Researcher Identifier
Nearest person month worked:1
Contribution to Project: Oversaw data linkage and aided in preparation of data files; helped to coordinate case control selection process.

Name: Jasmine Carver
Project Role: Data Analyst
Researcher Identifier
Nearest person month worked: 1
Contribution to Project: Under supervision of Co-I, Gayle Windham, performed data management, and data linkage.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Please see attached appendix. Active support has changed for some investigators, but there is no overlap and support changes do not impact effort on the current project.

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.
Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

(NO CHANGE)
Organization name: California Department of Public Health (CDPH)
Location: Richmond, CA
Contribution: Collaboration- Co-Investigator Dr. Gayle Windham and her study staff at CDPH collaborated with the study PI to ensure data linkage and study sample selection necessary for this project. As noted in the previous annual report for this project, Dr. Windham and her team have extensive experience with California birth certificate and DDS data, and conducting data linkages for similar projects. Dr. Windham and her staff have maintained close communication with the PI of this project, Dr. Lyall, including through attending project meetings via conference calls. Facilities have not been exchanged.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating PI and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ers.amedd.army.mil*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.*

N/A

9. APPENDICES: *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*

Please see attached. Appendix 1: Results Summary. Appendix 2: Other support documentation.

ADDITIONAL NOTES:

Appendices provided include other support documents for all key investigators (PI and Co-Investigators with support from this project) as well as results summaries.

MARKING OF PROPRIETARY INFORMATION: Data that was developed partially or exclusively at private expense shall be marked as "Proprietary Data" and Distribution Statement B included on the cover page of the report. Federal government approval is required before including Distribution Statement B. The recipient/PI shall coordinate with the COR/GOR to obtain approval. **REPORTS NOT PROPERLY MARKED FOR LIMITATION WILL BE DISTRIBUTED AS APPROVED FOR PUBLIC RELEASE.** It is the responsibility of the Principal Investigator to advise the COR/GOR when restricted limitation assigned to a document can be downgraded to "Approved for Public Release." **DO NOT USE THE WORD "CONFIDENTIAL" WHEN MARKING DOCUMENTS. DO NOT USE WATERMARKS WHEN MARKING DOCUMENTS.**

PUFA	Median ng/ml	Case/control n	AOR (95%CI)[1]	P for trend[2]
n-3 fatty acids				
ALA (18:3)				
Q1	0.3	109/128	1.0	0.66
Q2	0.79	132/119	1.29 (0.89, 1.86)	
Q3	1.48	125/125	1.16 (0.80, 1.69)	
Q4	2.73	124/122	1.17 (0.81, 1.71)	
SA (18:4)				
Q1	0.11	90/101	1.0	0.88
Q2	0.14	138/135	1.09 (0.74, 1.60)	
Q3	0.17	122/115	1.11 (0.75, 1.66)	
Q4	0.22	149/151	1.01 (0.69, 1.47)	
EPA (20:5)				
Q1	0.12	107/133	1.0	0.86
Q2	0.22	136/117	1.25 (0.86, 1.82)	
Q3	0.34	116/130	0.84 (0.57, 1.25)	
Q4	0.71	140/122	1.10 (0.73, 1.64)	
DPA				
Q1	9.64	125/125	1.0	0.67
Q2	13.5	120/131	0.82 (0.57, 1.19)	
Q3	17.7	127/123	0.88 (0.60, 1.27)	

Q4	24.5	127/123	0.88 (0.61, 1.28)	
DHA (22:6)				
Q1	1.05	118/120	1.0	0.78
Q2	1.31	132/126	0.97 (0.67, 1.40)	
Q3	1.58	118/136	0.79 (0.54, 1.15)	
Q4	2.11	131/120	0.96 (0.65, 1.44)	
AA (20:4)				
Q1	4.94	118/131	1.0	0.89
Q2	5.92	123/127	0.97 (0.67, 1.40)	
Q3	6.94	127/123	0.97 (0.67, 1.41)	
Q4	8.44	131/121	1.02 (0.70, 1.48)	
n-6 fatty acids				
LA (18:2)				
Q1	21.9	125/124	1.0	0.09
Q2	31.7	132/120	0.96 (0.66, 1.39)	
Q3	42.0	123/126	0.83 (0.56, 1.21)	
Q4	58.2	119/132	0.74 (0.50, 1.09)	
GLA (18:3)				
Q1	1.1	121/122	1.0	0.71
Q2	1.91	118/137	0.79 (0.55, 1.14)	
Q3	2.8	126/123	0.99 (0.68, 1.43)	
Q4	4.45	134/117	0.98 (0.68, 1.43)	
DGLA (20:3)				
Q1	0.93	121/125	1.0	0.16
Q2	1.42	131/123	1.03 (0.71, 1.48)	
Q3	1.92	126/123	0.90 (0.62, 1.31)	
Q4	2.76	121/131	0.78 (0.53, 1.15)	
ECA (20:2)	(detect/non-detect)[3]		1.03 (0.75, 1.42)	NA

Abbreviations for individual fatty acids as listed in Table 1.
[1]Adjusted for: *matching factors* (child sex, child month and year of birth), as well as maternal education, race/ethnicity, pre-pregnancy BMI, maternal age, and insurance status.
[2]P-value for test of trend from Wald test for score variable defined using median values within each quartile.
[3]Analyzed as a binary variable comparing those with detected levels of this fatty acid to those with values below the limit of detection (LOD), given the high proportion of participants with values <LOD (79%).

Table 2B: Associations between maternal mid-pregnancy PUFA levels and offspring ASD (adjusted ORs and 95% CIs): Summed classes of fatty acids

PUFA	Median ng/ml	Case/control n	AOR (95%CI) [1]	P for trend[2]
Total PUFA				
Q1	44.1	123/125	1.0	0.14
Q2	60.0	140/126	1.08 (0.75, 1.56)	
Q3	75.4	116/125	0.77 (0.53, 1.14)	
Q4	101	120/126	0.80 (0.55, 1.13)	
Total n6				
Q1	41.3	124/127	1.0	0.11
Q2	57.1	142/125	1.13 (0.78, 1.62)	
Q3	71.4	118/125	0.81 (0.55, 1.19)	
Q4	96.2	115/125	0.79 (0.54, 1.17)	
Total n3				

Q1	1.99	124/135	1.0	0.92
Q2	2.81	131/124	1.10 (0.77, 1.58)	
Q3	3.7	119/122	0.94 (0.65, 1.35)	
Q4	5.41	125/121	1.02 (0.71, 1.48)	
DHA+EPA				
Q1	1.21	116/121	1.0	0.80
Q2	1.55	132/127	0.95 (0.65, 1.37)	
Q3	1.95	110/127	0.75 (0.51, 1.10)	
Q4	2.75	141/127	0.95 (0.64, 1.41)	

Summed classes were created by summing levels for individual fatty acids within these categories (as defined in Table 1); ECA was not included in sums given the high proportion of <LOD.

[1]Adjusted for: *matching factors* (child sex, child month and year of birth), as well as maternal education, race/ethnicity, pre-pregnancy BMI, maternal age, and insurance status.

[2]P-value for test of trend from Wald test for score variable defined using median values within each quartile.

Table 3A: Associations between maternal mid-pregnancy PUFA levels and offspring ASD with and without comorbid intellectual disability (ID): Individual fatty acids

	ASD with ID		ASD without ID	
PUFA	case n	Adjusted OR (95% CI)	case n	Adjusted OR (95% CI)
ALA (18:3)				
Q1	13	1.0	95	1.0
Q2	20	1.36 (0.63, 2.97)	116	1.24 (0.84, 1.82)
Q3	18	1.21 (0.56, 2.64)	106	0.98 (0.66, 1.44)
Q4	14	0.93 (0.41, 2.15)	108	1.10 (0.74, 1.63)
SA (18:4)				
Q1	16	1.0	74	1.0
Q2	13	0.59 (0.26, 1.32)	125	1.21 (0.81, 1.81)
Q3	22	1.01 (0.47, 2.16)	100	1.14 (0.75, 1.75)
Q4	16	0.57 (0.27, 1.25)	133	1.12 (0.75, 1.66)
EPA (20:5)				
Q1	17	1.0	90	1.0
Q2	17	0.90 (0.42, 1.93)	119	1.34 (0.91, 1.98)
Q3	18	0.72 (0.32, 1.62)	98	0.92 (0.61, 1.39)
Q4	15	0.67 (0.28, 1.59)	125	1.26 (0.83, 1.91)
DHA (22:6)				
Q1	16	1.0	102	1.0
Q2	21	1.05 (0.50, 2.18)	111	0.94 (0.64, 1.38)
Q3	14	0.64 (0.28, 1.44)	104	0.82 (0.56, 1.21)
Q4	16	0.74 (0.32, 1.70)	115	1.01 (0.67, 1.54)
LA (18:2)				
Q1	17	1.0	108	1.0
Q2	12	0.58 (0.25, 1.35)	120	1.03 (0.70, 1.51)
Q3	22	1.06 (0.49, 2.26)	101	0.78 (0.53, 1.17)
Q4	16	0.78 (0.35, 1.76)	103	0.74 (0.49, 1.12)
GLA (18:3)				
Q1	19	1.0	102	1.0
Q2	12	0.57 (0.26, 1.26)	106	0.89 (0.61, 1.30)
Q3	19	1.16 (0.56, 2.42)	107	0.98 (0.67, 1.44)
Q4	17	0.93 (0.44, 1.97)	117	1.01 (0.69, 1.49)
DGLA (20:3)				
Q1	15	1.0	106	1.0
Q2	19	1.24 (0.59, 2.63)	112	0.98 (0.67, 1.44)
Q3	17	0.97 (0.44, 2.15)	109	0.89 (0.60, 1.31)
Q4	16	0.96 (0.43, 2.17)	105	0.77 (0.52, 1.16)
AA (20:4)				
Q1	18	1.0	100	1.0
Q2	18	0.85 (0.41, 1.77)	105	0.94 (0.64, 1.37)
Q3	13	0.70 (0.31, 1.57)	114	1.03 (0.70, 1.51)
Q4	18	1.00 (0.47, 2.14)	113	1.00 (0.68, 1.51)
ECA (detect/non)	14	1.02 (0.53, 1.96)	101	1.04 (0.74, 1.46)

AOR presented are adjusted as in Table 2. 67 ASD cases had comorbid intellectual disability (ID), while 432 did not. Control numbers for these analyses are as presented in Table 2A.

Table 3B: Associations between maternal mid-pregnancy PUFA levels and offspring ASD with and without comorbid intellectual disability (ID): Summed classes of fatty acids

	ASD with ID		ASD without ID	
PUFA	Case n	AOR (95%CI)	Case n	AOR (95%CI)
Total PUFA				
Q1	17	1.0	107	1.0
Q2	15	0.77 (0.35, 1.68)	125	1.09 (0.75, 1.60)
Q3	17	0.89 (0.41, 1.96)	98	0.75 (0.50, 1.12)
Q4	18	0.96 (0.44, 2.09)	102	0.79 (0.52, 1.18)
Total n6				
Q1	17	1.0	107	1.0
Q2	15	0.83 (0.38, 1.81)	127	1.17 (0.80, 1.72)
Q3	17	0.95 (0.43, 2.10)	101	0.80 (0.54, 1.20)
Q4	18	1.03 (0.47, 2.24)	97	0.78 (0.52, 1.17)
Total n3				
Q1	21	1.0	104	1.0
Q2	18	0.80 (0.40, 1.62)	115	1.20 (0.82, 1.75)
Q3	11	**0.40 (0.18, 0.93)**	106	1.02 (0.69, 1.49)
Q4	17	0.63 (0.30, 1.33)	107	1.06 (0.72, 1.56)
DHA+EPA				
Q1	16	1.0	100	1.0
Q2	21	1.03 (0.49, 2.17)	111	0.92 (0.63, 1.36)
Q3	11	0.48 (0.20, 1.15)	99	0.80 (0.54, 1.20)
Q4	19	0.79 (0.35, 1.82)	122	1.00 (0.66, 1.52)

AOR presented are adjusted as in Table 2; sums calculated as described in Table 2B footnote.
67 ASD cases had comorbid intellectual disability (ID), while 432 did not. Control numbers for these analyses are as presented in Table 2B.

	PUFA name	Lipid name/type	Primary dietary sources
ALA	Alpha-linolenic acid	18:3 n-3	Chia, flaxseed, walnuts, canola oil
SA	Stearidonic acid (SDA)	18:4 n-3	Seafood
EPA	Eicosapentaenoic acid	20:5 n-3	Fish/seafood, fish oils
DPA	Docosapentaenoic acid	22:5 n-3	Meats, fish
DHA	Docosahexaenoic acid	22:6 n-3	Fish/seafood, fish oils, (particularly salmon, herring, mackerel, tuna, halibut)
LA	Linoleic acid	18:2 n-6	Grains, nuts, seeds,
GLA	Gamma-linolenic acid	18:3 n-6	Plant seed oils
ECA	Eicosadienoic acid	20:2 n-6	Flaxseed oil, pork
DGLA	Di-homo-gamma linolenic acid	20:3 n-6	Plant seed oils
AA	Arachidonic acid	20:4 n-6	Chicken, eggs, meats

Appendix 1: Results summary

Table 1: Summary of PUFAs examined

	PUFA name	Lipid name/type	Primary dietary sources
ALA	Alpha-linolenic acid	18:3 n-3	Chia, flaxseed, walnuts, canola oil
SA	Stearidonic acid (SDA)	18:4 n-3	Seafood
EPA	Eicosapentaenoic acid	20:5 n-3	Fish/seafood, fish oils
DPA	Docosapentaenoic acid	22:5 n-3	Meats, fish
DHA	Docosahexaenoic acid	22:6 n-3	Fish/seafood, fish oils, (particularly salmon, herring, mackerel, tuna, halibut)
LA	Linoleic acid	18:2 n-6	Grains, nuts, seeds,
GLA	Gamma-linolenic acid	18:3 n-6	Plant seed oils
ECA	Eicosadienoic acid	20:2 n-6	Flaxseed oil, pork
DGLA	Di-homo-gamma linolenic acid	20:3 n-6	Plant seed oils
AA	Arachidonic acid	20:4 n-6	Chicken, eggs, meats

Table 2A: Associations between maternal mid-pregnancy PUFA levels and offspring ASD (adjusted ORs and 95% CIs): Individual fatty acids

PUFA	Median ng/ml	Case/control n	AOR (95%CI)[1]	P for trend[2]
n-3 fatty acids				
ALA (18:3)				
Q1	0.3	109/128	1.0	0.66
Q2	0.79	132/119	1.29 (0.89, 1.86)	
Q3	1.48	125/125	1.16 (0.80, 1.69)	
Q4	2.73	124/122	1.17 (0.81, 1.71)	
SA (18:4)				
Q1	0.11	90/101	1.0	0.88
Q2	0.14	138/135	1.09 (0.74, 1.60)	
Q3	0.17	122/115	1.11 (0.75, 1.66)	
Q4	0.22	149/151	1.01 (0.69, 1.47)	
EPA (20:5)				
Q1	0.12	107/133	1.0	0.86
Q2	0.22	136/117	1.25 (0.86, 1.82)	
Q3	0.34	116/130	0.84 (0.57, 1.25)	
Q4	0.71	140/122	1.10 (0.73, 1.64)	
DPA				
Q1	9.64	125/125	1.0	0.67
Q2	13.5	120/131	0.82 (0.57, 1.19)	
Q3	17.7	127/123	0.88 (0.60, 1.27)	
Q4	24.5	127/123	0.88 (0.61, 1.28)	
DHA (22:6)				
Q1	1.05	118/120	1.0	0.78
Q2	1.31	132/126	0.97 (0.67, 1.40)	
Q3	1.58	118/136	0.79 (0.54, 1.15)	
Q4	2.11	131/120	0.96 (0.65, 1.44)	
AA (20:4)				
Q1	4.94	118/131	1.0	0.89
Q2	5.92	123/127	0.97 (0.67, 1.40)	
Q3	6.94	127/123	0.97 (0.67, 1.41)	
Q4	8.44	131/121	1.02 (0.70, 1.48)	
n-6 fatty acids				
LA (18:2)				
Q1	21.9	125/124	1.0	0.09
Q2	31.7	132/120	0.96 (0.66, 1.39)	
Q3	42.0	123/126	0.83 (0.56, 1.21)	
Q4	58.2	119/132	0.74 (0.50, 1.09)	
GLA (18:3)				
Q1	1.1	121/122	1.0	0.71
Q2	1.91	118/137	0.79 (0.55, 1.14)	
Q3	2.8	126/123	0.99 (0.68, 1.43)	
Q4	4.45	134/117	0.98 (0.68, 1.43)	
DGLA (20:3)				
Q1	0.93	121/125	1.0	0.16
Q2	1.42	131/123	1.03 (0.71, 1.48)	
Q3	1.92	126/123	0.90 (0.62, 1.31)	

Q4	2.76	121/131	0.78 (0.53, 1.15)	
ECA (20:2)	(detect/non-detect)[3]		1.03 (0.75, 1.42)	NA

Abbreviations for individual fatty acids as listed in Table 1.
[1]Adjusted for: *matching factors* (child sex, child month and year of birth), as well as maternal education, race/ethnicity, pre-pregnancy BMI, maternal age, and insurance status.
[2]P-value for test of trend from Wald test for score variable defined using median values within each quartile.
[3]Analyzed as a binary variable comparing those with detected levels of this fatty acid to those with values below the limit of detection (LOD), given the high proportion of participants with values <LOD (79%).

Table 2B: Associations between maternal mid-pregnancy PUFA levels and offspring ASD (adjusted ORs and 95% CIs): Summed classes of fatty acids

PUFA	Median ng/ml	Case/control n	AOR (95%CI) [1]	P for trend[2]
Total PUFA				
Q1	44.1	123/125	1.0	0.14
Q2	60.0	140/126	1.08 (0.75, 1.56)	
Q3	75.4	116/125	0.77 (0.53, 1.14)	
Q4	101	120/126	0.80 (0.55, 1.13)	
Total n6				
Q1	41.3	124/127	1.0	0.11
Q2	57.1	142/125	1.13 (0.78, 1.62)	
Q3	71.4	118/125	0.81 (0.55, 1.19)	
Q4	96.2	115/125	0.79 (0.54, 1.17)	
Total n3				
Q1	1.99	124/135	1.0	0.92
Q2	2.81	131/124	1.10 (0.77, 1.58)	
Q3	3.7	119/122	0.94 (0.65, 1.35)	
Q4	5.41	125/121	1.02 (0.71, 1.48)	
DHA+EPA				
Q1	1.21	116/121	1.0	0.80
Q2	1.55	132/127	0.95 (0.65, 1.37)	
Q3	1.95	110/127	0.75 (0.51, 1.10)	
Q4	2.75	141/127	0.95 (0.64, 1.41)	

Summed classes were created by summing levels for individual fatty acids within these categories (as defined in Table 1); ECA was not included in sums given the high proportion of <LOD.
[1]Adjusted for: *matching factors* (child sex, child month and year of birth), as well as maternal education, race/ethnicity, pre-pregnancy BMI, maternal age, and insurance status.
[2]P-value for test of trend from Wald test for score variable defined using median values within each quartile.

Table 3A: Associations between maternal mid-pregnancy PUFA levels and offspring ASD with and without comorbid intellectual disability (ID): Individual fatty acids

	ASD with ID		ASD without ID	
PUFA	case n	Adjusted OR (95% CI)	case n	Adjusted OR (95% CI)
ALA (18:3)				
Q1	13	1.0	95	1.0
Q2	20	1.36 (0.63, 2.97)	116	1.24 (0.84, 1.82)
Q3	18	1.21 (0.56, 2.64)	106	0.98 (0.66, 1.44)
Q4	14	0.93 (0.41, 2.15)	108	1.10 (0.74, 1.63)
SA (18:4)				
Q1	16	1.0	74	1.0
Q2	13	0.59 (0.26, 1.32)	125	1.21 (0.81, 1.81)
Q3	22	1.01 (0.47, 2.16)	100	1.14 (0.75, 1.75)
Q4	16	0.57 (0.27, 1.25)	133	1.12 (0.75, 1.66)
EPA (20:5)				
Q1	17	1.0	90	1.0
Q2	17	0.90 (0.42, 1.93)	119	1.34 (0.91, 1.98)
Q3	18	0.72 (0.32, 1.62)	98	0.92 (0.61, 1.39)
Q4	15	0.67 (0.28, 1.59)	125	1.26 (0.83, 1.91)
DHA (22:6)				
Q1	16	1.0	102	1.0
Q2	21	1.05 (0.50, 2.18)	111	0.94 (0.64, 1.38)
Q3	14	0.64 (0.28, 1.44)	104	0.82 (0.56, 1.21)
Q4	16	0.74 (0.32, 1.70)	115	1.01 (0.67, 1.54)
LA (18:2)				
Q1	17	1.0	108	1.0
Q2	12	0.58 (0.25, 1.35)	120	1.03 (0.70, 1.51)
Q3	22	1.06 (0.49, 2.26)	101	0.78 (0.53, 1.17)
Q4	16	0.78 (0.35, 1.76)	103	0.74 (0.49, 1.12)
GLA (18:3)				
Q1	19	1.0	102	1.0
Q2	12	0.57 (0.26, 1.26)	106	0.89 (0.61, 1.30)
Q3	19	1.16 (0.56, 2.42)	107	0.98 (0.67, 1.44)
Q4	17	0.93 (0.44, 1.97)	117	1.01 (0.69, 1.49)
DGLA (20:3)				
Q1	15	1.0	106	1.0
Q2	19	1.24 (0.59, 2.63)	112	0.98 (0.67, 1.44)
Q3	17	0.97 (0.44, 2.15)	109	0.89 (0.60, 1.31)
Q4	16	0.96 (0.43, 2.17)	105	0.77 (0.52, 1.16)
AA (20:4)				
Q1	18	1.0	100	1.0
Q2	18	0.85 (0.41, 1.77)	105	0.94 (0.64, 1.37)
Q3	13	0.70 (0.31, 1.57)	114	1.03 (0.70, 1.51)
Q4	18	1.00 (0.47, 2.14)	113	1.00 (0.68, 1.51)
ECA (detect/non)	14	1.02 (0.53, 1.96)	101	1.04 (0.74, 1.46)

AOR presented are adjusted as in Table 2. 67 ASD cases had comorbid intellectual disability (ID), while 432 did not. Control numbers for these analyses are as presented in Table 2A.

Table 3B: Associations between maternal mid-pregnancy PUFA levels and offspring ASD with and without comorbid intellectual disability (ID): Summed classes of fatty acids

	ASD with ID		ASD without ID	
PUFA	Case n	AOR (95%CI)	Case n	AOR (95%CI)
Total PUFA				
Q1	17	1.0	107	1.0
Q2	15	0.77 (0.35, 1.68)	125	1.09 (0.75, 1.60)
Q3	17	0.89 (0.41, 1.96)	98	0.75 (0.50, 1.12)
Q4	18	0.96 (0.44, 2.09)	102	0.79 (0.52, 1.18)
Total n6				
Q1	17	1.0	107	1.0
Q2	15	0.83 (0.38, 1.81)	127	1.17 (0.80, 1.72)
Q3	17	0.95 (0.43, 2.10)	101	0.80 (0.54, 1.20)
Q4	18	1.03 (0.47, 2.24)	97	0.78 (0.52, 1.17)
Total n3				
Q1	21	1.0	104	1.0
Q2	18	0.80 (0.40, 1.62)	115	1.20 (0.82, 1.75)
Q3	11	**0.40 (0.18, 0.93)**	106	1.02 (0.69, 1.49)
Q4	17	0.63 (0.30, 1.33)	107	1.06 (0.72, 1.56)
DHA+EPA				
Q1	16	1.0	100	1.0
Q2	21	1.03 (0.49, 2.17)	111	0.92 (0.63, 1.36)
Q3	11	0.48 (0.20, 1.15)	99	0.80 (0.54, 1.20)
Q4	19	0.79 (0.35, 1.82)	122	1.00 (0.66, 1.52)

AOR presented are adjusted as in Table 2; sums calculated as described in Table 2B footnote.
67 ASD cases had comorbid intellectual disability (ID), while 432 did not. Control numbers for these analyses are as presented in Table 2B.

Figure 1: Association between deciles of maternal total PUFA levels and offspring ASD with and without comorbid ID

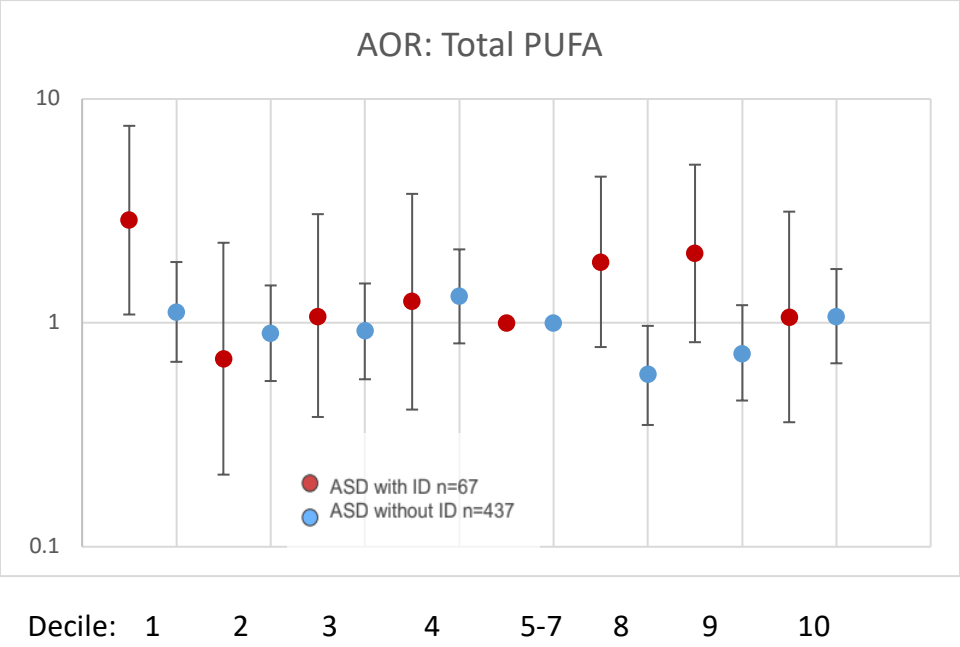

Figure legend: Graph shows adjusted ORs (adjusted as in Tables above) for a given decile of total PUFA levels, relative to the 5th-7th deciles as the referent. Odds ratios were elevated for the lowest decile of total PUFA, as well as the 8th and 9th deciles, for odds of ASD with ID only; only the former reached statistical significance (AOR= 0.59, 95% CI 0.35-0.97).

Figure 2: Association between deciles of maternal n-3 PUFA levels and offspring ASD with and without comorbid ID

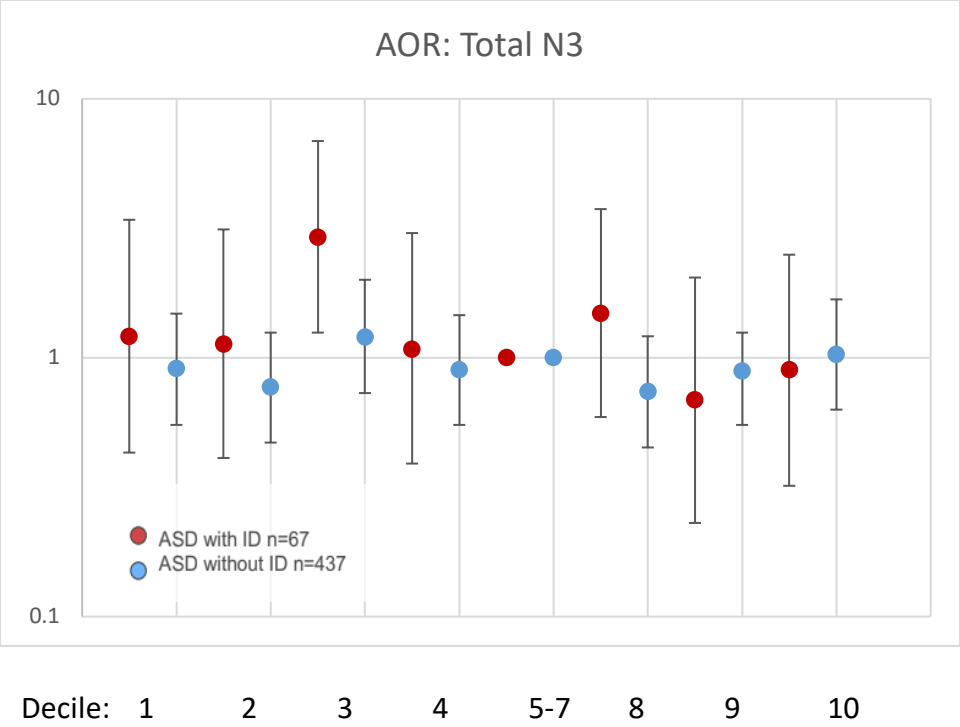

Figure legend: Graph shows adjusted ORs (adjusted as in Tables above) for a given n-3 decile, relative to the 5th-7th deciles as the referent. Odds ratios were elevated for the 3rd and 8th deciles for odds of ASD with ID only; with the former reaching statistical significance (AOR= 2.93, 95% CI 1.25-6.87).

APPENDIX 2: OTHER SUPPORT DOCUMENTATION

OTHER RESEARCH SUPPORT: LYALL, KRISTEN

Research Support: Since the last reporting period, Dr. Lyall has received additional support from grants U2COD023375-02 and R21 HD096356-01; full support information is provided below.

CURRENT SUPPORT

TITLE: N/A - New Investigator Start-up Funding
FON: N/A
ROLE: PI
EFFORT: N/A
SUPPORTING AGENCY: Drexel University
GRANTS OFFICER: N/A
PERFORMANCE PERIOD: 07/01/2015-06/29/2018
FUNDING AMOUNT: $30,000
GOALS: Funding to be used for generation of preliminary data and associated costs to enable research program start-up.
SPECIFIC AIMS: N/A
OVERLAP: None

TITLE: An ASD Enriched (ASD-ER) ECHO Cohort (Grant # UG3OD023342)
EFFORT: 15%
SUPPORTING AGENCY: NIH
GRANTS OFFICER: N/A
PERFORMANCE PERIOD: 09/01/2016-08/31/2023
FUNDING AMOUNT: $11,378,719
PROJECT GOALS: In order to facilitate the study of environmental risk factors for ASD and related developmental delays in ECHO, this proposes to assemble a cohort of cohorts from 14 sites that include more than 1,000 siblings of confirmed ASD cases who are at markedly higher risk for ASD. Approximately 500 lower risk subjects will also be enrolled. Subjects were either pre- or postnatally enrolled and prospectively followed.
SPECIFIC AIMS: UG3 Phase (Years 1-2) 1. Establish and implement initial processes supporting both the overall ECHO initiative and the specific ASD ER aims, including: i. develop participant re-contact and consent procedures; ii. create a protocol for the collection of shed deciduous teeth; iii. re-contact ASD-ER subjects; and iv. collect shed deciduous teeth. 2. Validate quantification of prenatal deposition of selected (organochlorine pesticides, PCBs, and phthalates) persistent organic pollutants (POPs) in dental tissues as an exposure biomarker.
UH3 Phase (Years 3-7) For the ASD-ER Cohort: 3. Estimate associations of individual POP exposure levels and POP mixture exposure as measured in dental tissue with continuous, dichotomous, and trajectory ASD-related phenotypes. The Aim 2 validation study can be used for exposure measurement error correction, if the needed. 4. Estimate associations of individual metal exposure levels and metal mixture exposure with continuous, dichotomous, and trajectory ASD-related phenotypes. 5. Use polygenic risk scores (PRS) to explore the role of genetic susceptibility in modifying the effect of prenatal POP and metal and exposure on the expression of ASD-related phenotypes. For the full ECHO cohort (in the Neurodevelopmental Focus Area)
6. Screen a range of environmental exposures for indications that exposure effects are magnified by specific susceptibility genotypes in the enriched risk ASD-ER cohort (using gene-environment wide interaction study, GEWIS, approaches) then replicate GEWIS analyses for exposures flagged in ASD-ER in the remaining ECHO cohort. The approach can be used for ASD and broader developmental delay outcomes.
ROLE: Co-Investigator
OVERLAP: None

TITLE: Prenatal exposure to metals and risk for ASD in MARBLES and EARLI (Grant # R01ES025531)
EFFORT: 4.7%
SUPPORTING AGENCY: NIH, Subcontract to Drexel; Prime Institution: Johns Hopkins

GRANTS OFFICER: N/A
PERFORMANCE PERIOD: 07/01/2016-06/30/2021
FUNDING AMOUNT: $181,845
PROJECT GOALS: Estimate the prospective associations between directly measured prenatal and birth exposure to five metals (Pb, Hg, Cd, Se, Mn) and subsequent risk for ASD and related quantitative phenotypes. Examine the utility of epigenetic DNA methylation measurement in characterizing the ASD risk associated with prenatal metals exposure.
SPECIFIC AIMS: 1) Estimate prospective associations between directly measured prenatal and birth exposure to each of five metals (Pb, Hg, Cd, Se, Mn), and to pooled metals, and subsequent risk for ASD and related quantitative phenotypes; 2) Maximize ability to detect risk due to metals exposure by incorporating maternal and child genetic susceptibility; 3) Integrate epigenetic DNA methylation in the examination of prenatal metals exposure ASD risk.
ROLE: Co-Investigator
OVERLAP: None

TITLE: Prenatal Exposure to Endocrine Disrupting Chemical Mixtures and ASD Risk (Grant # R01ES026903)
EFFORT: 7.5%
SUPPORTING AGENCY: NIEHS
GRANTS OFFICER: Molly E. Puente; Puentem@mail.nih.gov; 919-541-1373
PERFORMANCE PERIOD: 9/15/2017-8/31/2021
FUNDING AMOUNT: $242,276
GOALS: Prenatal brain development is heavily influenced by hormonal mechanisms, and endocrine disrupting chemicals (EDCs) cross the placenta to reach the particularly vulnerable fetus. In this project, we measure EDC exposure from blood and urine samples collected from pregnant women to study the effect of a woman's exposure to complex mixtures of these chemicals on the behaviors in their child that are related to autism spectrum disorders (ASD). We will determine whether and how much exposure to EDC mixtures increases ASD behaviors and will identify any particular EDCs that are driving effects we observe, in order to inform possible approaches to reduce pregnant women's exposure to EDCs that may be increasing their children's ASD risk.
SPECIFC AIMS: Aim 1: (a) characterize the cumulative effect of prenatal exposure to complex EDC mixtures on ASD related phenotype and (b) identify specific EDCs driving any observed mixture effect. Aim 2: Explore whether EDC mixture effects vary across subgroups defined by sibling ASD status, sex, and cognitive status. Aim 3: Explore whether prenatal exposure to complex EDC mixtures affects maternal prenatal thyroid hormone levels, biomarkers for one candidate mechanism by which EDCs may influence ASD risk.
OVERLAP: None.
Role: Co-Investigator
OVERLAP: None

(NEW)
TITLE: Optimizing social communication measurement with the Social Responsiveness Scale (Grant #1U2COD023375-02)
ROLE: Principal Investigator
EFFORT: 15%
SUPPORTING AGENCY: NIH
GRANTS OFFICER: N/A
PERFORMANCE PERIOD: 04/01/2018-03/31/2020
FUNDING AMOUNT: $46,090 (Drexel Subcontract)
PROJECT GOALS: The major goals of this project are to compare the validity of the newly proposed "short scale" 16-item version of the Social Responsiveness Scale (SRS) to the original 65-item scale, using existing data from ECHO cohorts. We will compare the distributional properties of these scales, assess their performance in established risk factor analysis, and also optimize the SRS for computer-adaptive-testing (CAT) administration for use in a validation sub-study, which will also compare performance to the existing short and full SRS. Results across these analyses will help to guide use of the SRS for social communication research.

(NEW)
TITLE: Oxidative stress pathways and placental pathology in association with autism spectrum disorder and neurodevelopment (Grant # R21 HD096356-01)

ROLE: Principal-Investigator
EFFORT: 20%
SUPPORTING AGENCY: NIH
GRANTS OFFICER: N/A
PERFORMANCE PERIOD: 7/1/2018-6/30/2023
FUNDING AMOUNT: $ 331,488
PROJECT GOALS: Oxidative stress (OS, the state of imbalance between antioxidants and reactive oxidant species) can cause damage to proteins, lipids, and DNA; with both the developing brain and placenta particularly susceptible to such imbalance, OS may have lasting impacts on the developing fetus. The proposed project, which uses data from a high-risk pregnancy cohort of mothers who have had a child with an autism spectrum disorder (ASD), will examine prenatal levels of key oxidative stress biomarkers as well as placental measures in association with ASD phenotype and neurodevelopment as captured by validated continuous scales (the Social Responsiveness Scale and the Mullen Scales of Early Learning). By using biomarkers of OS-induced DNA damage (8-OHdG), protein oxidation (tyrosines), and lipid peroxidation (8-isoprostane), antioxidant balance (glutathione and the GSH/GSSG ratio), and exploring mediation through placental morphology and vascular pathology, this study will provide novel information about potential OS pathways that may lead to adverse neurodevelopmental outcomes.
SPECIFIC AIMS:

1. Examine associations between prenatal maternal OS biomarkers and ASD/neurodevelopment
2. Examine placental morphology in association with OS and ASD/neurodevelopment
3. Examine placental vascular pathology in association with OS and ASD/neurodevelopment

OVERLAP: None

OTHER RESEARCH SUPPORT: Craig Newschaffer

Research Support: Since the last reporting period, Dr. Newschaffer has received additional support from two grants (U2COD023375-02 and R21 HD096356-01); full support information is provided below.

CURRENT SUPPORT

TITLE: Early Detection of Autism Spectrum Disorder (Robins)
EFFORT: 3%
SUPPORTING AGENCY: NIH
GRANTS OFFICER: Saiyda Khan; Email: khansa@mail.nih.gov; Phone: (301) 496-5001
PERFORMANCE PERIOD: 09/25/2014-05/31/2015
FUNDING AMOUNT: $3,029,559 total costs
PROJECT GOALS: To examine the optimal schedule for routine ASD screening, and the integration of screening with surveillance and other strategies to detect autism.
SPECIFIC AIMS: 1) Determine the most appropriate schedule for ASD screening (12, 15, or 18 mos); 2) Examine the effect of a brief training on the accuracy of physician surveillance in identifying ASD during pediatric well-child care visits; 3) Identify factors that influence ASD screening and surveillance
OVERLAP: None

TITLE: Mobilizing Community Systems to Engage Families in Early ASD Detection & Services
EFFORT: 5%
SUPPORTING AGENCY: NIH; Subaward to Drexel, Prime Institution: Florida State University
GRANTS OFFICER: Jackie Chia; Email: Jackie.Chia@nih.gov; Phone: 301-443-1341
PERFORMANCE PERIOD: 08/25/2014-06/30/2019
FUNDING AMOUNT: $10,439,836 total costs
PROJECT GOALS: the overarching purpose of this collaborative research investigation is to document the effectiveness of an online automated universal screen for communication delay and autism initially at 18 months of age and decision rule for referral to an ASD evaluation and study an evidence-based intervention to increase family engagement and expedite receipt of screening, diagnosis, eligibility for early intervention (EI), and EI services.
SPECIFIC AIMS: 1) Test effectiveness of universal ASD screening at 18mos and referral for evaluation; 2) Test effectiveness of family engagement intervention; 3) Explore mediators and moderators of intervention; 4) monitor implementation of evidence-based EI; 5) improve uptake of evidence-based EI.
OVERLAP: None.

TITLE: Perspective Evaluation of Air Pollution, Cognition, and Autism from Birth Onward (Volk)
EFFORT: 5%
SUPPORTING AGENCY: NIH; Subaward to Drexel, Prime Institution: Johns Hopkins University
GRANTS OFFICER: N/A
PERFORMANCE PERIOD: 06/10/2014-04/30/2016
FUNDING AMOUNT: $88,627 total costs
PROJECT GOALS: Determine if air pollutant exposure is associated with ASD risk.
SPECIFIC AIMS: 1) Assign air pollution exposure using modeling techniques; 2) Examine effects of exposure on cognative development; 3) Evaluate the effect of pollutant exposures on ASD traits and diagnoses.
OVERLAP: None (Directly complementary project that will provide air pollutant measures to be used to develop exposure response biomarkers here)

TITLE: Prenatal Antimicrobial Agent Exposure, Fetal Androgens and ASD Risk

EFFORT: 1%
SUPPORTING AGENCY: NIH
GRANTS OFFICER: James R Williams; Email: williamsjr@niehs.nih.gov; Phone: 919-541-1403
PERFORMANCE PERIOD: 08/01/2015-06/30/2017 (1 year NCE)
FUNDING AMOUNT: $430,375
PROJECT GOALS: Investigate the association between prenatal antimicrobial exposure and ASD risk.
SPECIFIC AIMS: 1) Estimate the association between biomarkers of prenatal maternal TCS/TCC exposure and sibling ASD-related outcomes at 12 and 36 months; 2) Assess whether fetal testosterone levels mediate and/or modify the association between prenatal maternal TCS/TCC exposure and sibling ASD-related outcomes at 12 and 36 months
OVERLAP: None.

TITLE: Folic Acid Prevention Pathways for ASD in High Risk Families
EFFORT: 5%
SUPPORTING AGENCY: NIH
GRANTS OFFICER: E-mail: Cindy Lawler lawler@niehs.nih.gov
PERFORMANCE PERIOD: 8/1/15-7/30/20
FUNDING AMOUNT: $172,790
PROJECT GOALS: Examine pathways for prevention of ASD through folate intake.
SPECIFIC AIMS: 1) Examine association between folate intake and ASD; 2) Investigate whether associations between periconceptional folate and ASD risk is altered by methylation-altering genotypes.
OVERLAP: None.

TITLE: Lipidomics of meconium in neurodevelopment (Snyder)
EFFORT: 5%
SUPPORTING AGENCY: NIH/NICHD
GRANTS OFFICER: Saiyda Khan; Telephone: 301-496-5001; E-mail: khansa@mail.nih.gov
PERFORMANCE PERIOD: 04/22/2016-03/31/2018
FUNDING AMOUNT: $275,000 Direct Costs
PROJECT GOALS: This proposal will quantify and compare the lipid content of meconium in typically developing versus neurodevelopmentally delayed children from a prospective enriched risk cohort of early events in autism spectrum disorder.
SPECIFIC AIMS: Specific Aim 1. Identify unknown chromatographic features with differential abundance between ASD and controls in a prospective enriched risk cohort. Specific Aim 2. Structurally elucidate the putative biomarkers of ASD and compare the lipid content of meconium, placenta, and cord blood. Specific Aim 3. Develop and validate a targeted method for the quantitation of putative biomarkers of ASD.
OVERLAP: No overlap.

TITLE: Component A: MD CADDRE: Study to Explore Early Development, SEED Phase III (Grant # U01DD001214)
EFFORT: 3%
SUPPORTING AGENCY: NIH, Subcontract to Drexel; Prime Institution: Johns Hopkins
GRANTS OFFICER: N/A
PERFORMANCE PERIOD: 07/01/2016-06/30/2017
FUNDING AMOUNT: $11,540
PROJECT GOALS: Continue SEED 2 recruitment at Maryland Site – conducted primary and other approved analyses using SEED 1 data.
SPECIFIC AIMS: Build a large multisite case-control ASD study. Evaluate association between a range of risk factors and ASD occurrence.

OVERLAP: None

TITLE: Prenatal Exposure to Endocrine Disrupting Chemical Mixtures and ASD Risk (Grant # R01ES026903)
EFFORT: 5%
SUPPORTING AGENCY: NIH
GRANTS OFFICER: Molly E. Puente; Puentem@mail.nih.gov; 919-541-1373
PERFORMANCE PERIOD: 09/15/2017 – 08/31/2021
FUNDING AMOUNT: $242,276
GOALS: Prenatal brain development is heavily influenced by hormonal mechanisms, and endocrine disrupting chemicals (EDCs) cross the placenta to reach the particularly vulnerable fetus. In this project, we measure EDC exposure from blood and urine samples collected from pregnant women to study the effect of a woman's exposure to complex mixtures of these chemicals on the behaviors in their child that are related to autism spectrum disorders (ASD). We will determine whether and how much exposure to EDC mixtures increases ASD behaviors and will identify any particular EDCs that are driving effects we observe, in order to inform possible approaches to reduce pregnant women's exposure to EDCs that may be increasing their children's ASD risk.
SPECIFC AIMS: Aim 1: (a) characterize the cumulative effect of prenatal exposure to complex EDC mixtures on ASD related phenotype and (b) identify specific EDCs driving any observed mixture effect. Aim 2: Explore whether EDC mixture effects vary across subgroups defined by sibling ASD status, sex, and cognitive status. Aim 3: Explore whether prenatal exposure to complex EDC mixtures affects maternal prenatal thyroid hormone levels, biomarkers for one candidate mechanism by which EDCs may influence ASD risk.
OVERLAP: None.

TITLE: An ASD Enriched (ASD-ER) ECHO Cohort (Grant # UG3OD023342)
EFFORT: 20%
SUPPORTING AGENCY: NIH
GRANTS OFFICER: N/A
PERFORMANCE PERIOD: 09/01/2016-08/31/2023
FUNDING AMOUNT: $11,378,719
PROJECT GOALS: In order to facilitate the study of environmental risk factors for ASD and related developmental delays in ECHO, this proposes to assemble a cohort of cohorts from 14 sites that include more than 1,000 siblings of confirmed ASD cases who are at markedly higher risk for ASD. Approximately 500 lower risk subjects will also be enrolled. Subjects were either pre- or postnatally enrolled and prospectively followed.
SPECIFIC AIMS: UG3 Phase (Years 1-2) 1. Establish and implement initial processes supporting both the overall ECHO initiative and the specific ASD ER aims, including: i. develop participant re-contact and consent procedures; ii. create a protocol for the collection of shed deciduous teeth; iii. re-contact ASD-ER subjects; and iv. collect shed deciduous teeth. 2. Validate quantification of prenatal deposition of selected (organochlorine pesticides, PCBs, and phthalates) persistent organic pollutants (POPs) in dental tissues as an exposure biomarker.
UH3 Phase (Years 3-7) For the ASD-ER Cohort: 3. Estimate associations of individual POP exposure levels and POP mixture exposure as measured in dental tissue with continuous, dichotomous, and trajectory ASD-related phenotypes. The Aim 2 validation study can be used for exposure measurement error correction, if the needed. 4. Estimate associations of individual metal exposure levels and metal mixture exposure with continuous, dichotomous, and trajectory ASD-related phenotypes. 5. Use polygenic risk scores (PRS) to explore the role of genetic susceptibility in modifying the effect of prenatal POP and metal and exposure on the expression of ASD-related phenotypes. For the full ECHO cohort (in the Neurodevelopmental Focus Area)
6. Screen a range of environmental exposures for indications that exposure effects are magnified by specific susceptibility genotypes in the enriched risk ASD-ER cohort (using gene-environment wide interaction study, GEWIS, approaches) then replicate GEWIS analyses for exposures flagged in ASD-ER in the remaining ECHO cohort. The approach can be used for ASD and broader developmental delay outcomes.

OVERLAP: None

TITLE: Prenatal exposure to metals and risk for ASD in MARBLES and EARLI (Grant # R01ES025531)
EFFORT: 4%
SUPPORTING AGENCY: NIH, Subcontract to Drexel; Prime Institution: Johns Hopkins
GRANTS OFFICER: N/A
PERFORMANCE PERIOD: 07/01/2016-06/30/2021
FUNDING AMOUNT: $181,845
PROJECT GOALS: Estimate the prospective associations between directly measured prenatal and birth exposure to five metals (Pb, Hg, Cd, Se, Mn) and subsequent risk for ASD and related quantitative phenotypes. Examine the utility of epigenetic DNA methylation measurement in characterizing the ASD risk associated with prenatal metals exposure.
SPECIFIC AIMS: 1) Estimate prospective associations between directly measured prenatal and birth exposure to each of five metals (Pb, Hg, Cd, Se, Mn), and to pooled metals, and subsequent risk for ASD and related quantitative phenotypes; 2) Maximize ability to detect risk due to metals exposure by incorporating maternal and child genetic susceptibility; 3) Integrate epigenetic DNA methylation in the examination of prenatal metals exposure ASD risk.
OVERLAP: None

(NEW)
TITLE: Optimizing social communication measurement with the Social Responsiveness Scale (Grant #1U2COD023375-02)
ROLE: Co-Investigator
EFFORT: 3.3%
SUPPORTING AGENCY: NIH
GRANTS OFFICER: N/A
PERFORMANCE PERIOD: 04/01/2018-03/31/2020
FUNDING AMOUNT: $46,090 (Drexel Subcontract)
PROJECT GOALS: The major goals of this project are to compare the validity of the newly proposed “short scale” 16-item version of the Social Responsiveness Scale (SRS) to the original 65-item scale, using existing data from ECHO cohorts. We will compare the distributional properties of these scales, assess their performance in established risk factor analysis, and also optimize the SRS for computer-adaptive-testing (CAT) administration for use in a validation sub-study, which will also compare performance to the existing short and full SRS. Results across these analyses will help to guide use of the SRS for social communication research.

(NEW)
TITLE: Oxidative stress pathways and placental pathology in association with autism spectrum disorder and neurodevelopment (Grant # R21 HD096356-01)
ROLE: Co-Investigator
EFFORT: 3.3%
SUPPORTING AGENCY: NIH
GRANTS OFFICER: N/A
PERFORMANCE PERIOD: 7/1/2018-6/30/2023
FUNDING AMOUNT: $ 331,488
PROJECT GOALS: Oxidative stress (OS, the state of imbalance between antioxidants and reactive oxidant species) can cause damage to proteins, lipids, and DNA; with both the developing brain and placenta particularly susceptible to such imbalance, OS may have lasting impacts on the developing fetus. The proposed project, which uses data from a high-risk pregnancy cohort of mothers who have had a child with an autism spectrum disorder (ASD), will examine prenatal levels of key oxidative stress biomarkers as well as placental measures in

association with ASD phenotype and neurodevelopment as captured by validated continuous scales (the Social Responsiveness Scale and the Mullen Scales of Early Learning). By using biomarkers of OS-induced DNA damage (8-OHdG), protein oxidation (tyrosines), and lipid peroxidation (8-isoprostane), antioxidant balance (glutathione and the GSH/GSSG ratio), and exploring mediation through placental morphology and vascular pathology, this study will provide novel information about potential OS pathways that may lead to adverse neurodevelopmental outcomes.

SPECIFIC AIMS:

1. Examine associations between prenatal maternal OS biomarkers and ASD/neurodevelopment
2. Examine placental morphology in association with OS and ASD/neurodevelopment
3. Examine placental vascular pathology in association with OS and ASD/neurodevelopment

OTHER SUPPORT
ROBINSON, LUCY F.

Research Support: Since the last reporting period, Dr. Robinson has received additional support from one grant; full support information is provided below.

CURRENT SUPPORT

TITLE Structure and Growth of the Thoracolumbar Spine and Ribs in Normative Pediatric and AIS subjects - A Comprehensive Multi-Center and multi-Modal Validation Study
EFFORT: 3%
SUPPORTING AGENCY: Scoliosis Research Society
GRANTS OFFICER: N/A
PERFORMANCE PERIOD: Jan 1, 2015 – Dec 31, 2017
FUNDING AMOUNT: $50,000
PROJECT GOALS: Describe growth of lumbar spine (vertebrae and intervertebral discs) 4%for normative and adolescent idiopathic scoliosis (AIS) subjects.
SPECIFIC AIMS: 1. Quantify the 3D geometry of the lumbar spine (vertebrae and intervertebral discs) and growth rates based on retrospective abdominal computed tomography (CT) scans from 100 normative male and female subjects, ages 1 – 18 years. All the subjects will be within the 5th and 95th percentiles of height, weight, and body mass index (BMI). Hypothesis 1: Structural morphology and growth rates of the lumbar spine will vary with age and gender in the pediatric population.2. Characterize the 3D thoracolumbar vertebra morphology, 3D rib position and geometry, and 3D geometric morphology of the costovertebral articulations at each thoracic level using biplanar radiographic image-based reconstructions obtained using EOS (EOS imaging Inc, Cambridge, MA) from 120 AIS subjects (ages 10-18 years) displaying a right curvature, with varying Lenke curve types and Cobb angle. The total number of subjects will be evenly distributed among the six Lenke curve types, with each group further sub-divided by Cobb angle of greater than and less than 45 degrees. 3. Use Generalized Procrustes Analysis (GPA) and Multi-level Functional Principal Component Analysis (MFPCA) based regression to create average shape models and predictive equations that describe Lenke curve type and Cobb angle-dependent spine and rib cage shape changes in AIS subjects.
OVERLAP: None.

TITLE: Prenatal Exposure to Endocrine Disrupting Chemical Mixtures and ASD Risk (Grant # R01ES026903)
EFFORT: 5%
SUPPORTING AGENCY: NIH
GRANTS OFFICER:
PERFORMANCE PERIOD: 09/15/2017 – 08/31/2021
FUNDING AMOUNT: $242,276
GOALS: Prenatal brain development is heavily influenced by hormonal mechanisms, and endocrine disrupting chemicals (EDCs) cross the placenta to reach the particularly vulnerable fetus. In this project, we measure EDC exposure from blood and urine samples collected from pregnant women to study the effect of a woman's exposure to complex mixtures of these chemicals on the behaviors in their child that are related to autism spectrum disorders (ASD). We will determine whether and how much exposure to EDC mixtures increases ASD behaviors and will identify any particular EDCs that are driving effects we observe, in order to inform possible approaches to reduce pregnant women's exposure to EDCs that may be increasing their children's ASD risk.
SPECIFC AIMS: Aim 1: (a) characterize the cumulative effect of prenatal exposure to complex EDC mixtures on ASD related phenotype and (b) identify specific EDCs driving any observed mixture effect. Aim 2: Explore whether EDC mixture effects vary across subgroups defined by sibling ASD status, sex, and cognitive status. Aim 3: Explore whether prenatal exposure to complex EDC mixtures affects maternal prenatal thyroid hormone levels, biomarkers for one candidate mechanism by which EDCs may influence ASD risk.

OVERLAP: None.

(NEW)

TITLE Molecular, Cancer-Specific, Intraoperative Imaging of Breast Surgical Margin
EFFORT: 3%
SUPPORTING AGENCY: NIH STTR
GRANTS OFFICER: N/A
PERFORMANCE PERIOD: Jun 1, 2018 – May 31, 2019
FUNDING AMOUNT: $90,000
PROJECT GOALS: To evaluate the effectiveness of a novel biomarker for intraoperative classification of tissue type (normal vs. malignant) in tumor margins.
OVERLAP: None

OTHER RESEARCH SUPPORT: SNYDER, NATHANIEL

Research Support: Since the last reporting period, Dr. Snyder has received additional support from a NARSAD young investigator grant and two subcontracts from unrelated R01s; full support information is provided below.

CURRENT SUPPORT

TITLE: Prenatal biomarkers of exposure and individual susceptibility to endocrine disrupting compounds
EFFORT: 75%
SUPPORTING AGENCY: NIH/NIEHS
GRANTS OFFICER: James R. William; Telephone: 919-541-1403; E-mail: williamsjr@niehs.nih.gov
PERFORMANCE PERIOD: 02/01/2016-01/31/2019
FUNDING AMOUNT: $149,750 Direct Costs
PROJECT GOALS: This project will overcome major challenges in quantitation of exposure during gestation and develop the independent research career of a young investigator focused on environmental health sciences.
SPECIFIC AIMS: Specific Aim 1. Quantify internal dose of prototypical EDC exposures (BPA, methylparaben, bis (2-ethylhexyl) phthalate, and vinclozolin) in controlled exposures in mice and human variable population exposures using developmentally relevant blood, urine, placenta, meconium and fetal tissue. Specific Aim 2. Elucidate the influence of endogenous metabolic mediators of EDC exposure (sex hormones and folates) on a known biologically relevant exposure response (DNA methylation) during critical neurodevelopmental windows in EDC exposed mice and humans. Exploratory Aim. Identify additional candidate biomarkers of biological response to EDC exposure.
OVERLAP: No overlap.

TITLE: Metabolism of propionic acid (Grant # R03HD092630)
EFFORT: 2.5%
SUPPORTING AGENCY: NIH
GRANTS OFFICER: Saiyda Khan; lhansa@mail.nih.gov; 301-496-5001
PERFORMANCE PERIOD: 09/01/2017-08/31/2019
FUNDING AMOUNT: $50,000 Direct Costs
PROJECT GOALS: Propionic acidemia (PA) is the manifestation of a set of inborn errors of metabolism that still result in significant morbidity and mortality despite detection by newborn screening. The recent discovery of a metabolite of excess propionic acid indicates that biomarkers with diagnostic, prognostic, and therapeutic potential may be possible. This research will quantify and describe the metabolism of this new metabolite for further investigation in PA patients and model systems.
SPECIFIC AIMS: Specific Aim 1. Characterize and quantify metabolites of propionate through 2M2PE.
Specific Aim 2. Identify cellular localization and putative enzymology of metabolism through 2M2PE.
Specific Aim 3. Establish and validate a quantitative method for biomarkers of dysregulated propionate metabolism in urine, saliva and serum.
OVERLAP: No overlap.

(**NEW**)
TITLE: Steroid metabolism in a high-risk autism spectrum disorder prospective pregnancy cohort
EFFORT: 5%
SUPPORTING AGENCY: Brain & Behavior Research Foundation
GRANTS OFFICER: N/A
PERFORMANCE PERIOD: 01/15/2018-01/14/2020
FUNDING AMOUNT: $35,000 (Y1 total cost)
ROLE: Principal Investigator
PROJECT GOALS: Steroid metabolism in a high-risk autism spectrum disorder prospective pregnancy cohort

This study will quantify and characterize the molecular lipid content of meconium from a high-risk autism spectrum disorder (ASD) pregnancy cohort to identify biomarkers of risk for ASD.
OVERLAP: No overlap.

(**NEW**)
TITLE: Defining an acetyl-CoA-sensing mechanism as a form of intraorganelle communication in cancer (R01 CA228339)
EFFORT: 5%
SUPPORTING AGENCY: NIH
GRANTS OFFICER: N/A
PERFORMANCE PERIOD: 07/01/2018-06/30/2023
FUNDING AMOUNT: $16,741 (Drexel Subcontract)
ROLE: Co-Investigator
PROJECT GOALS: The goals of this proposal are to quantify the dynamics of mitochondrial, cytoplasmic and nuclear acetyl-CoA in cancer.
OVERLAP: No overlap.

(**NEW**)
TITLE: The role of the placenta in mediating the exposure and the hormonal effects of phthalates on fetal development
EFFORT: 2.5%
SUPPORTING AGENCY: NIH
GRANTS OFFICER: N/A
PERFORMANCE PERIOD: 03/01/2018-02/28/2023
FUNDING AMOUNT: $88,735 (Drexel Subcontract)
ROLE: Co-Investigator
PROJECT GOALS: In completing the aims of the project, we will generate novel urinary biomarkers that can be applied prospectively and retrospectively to birth cohort studies to increase precision in estimating associations of prenatal exposures and postnatal outcomes, adjusting for the role of the placenta. We will develop a human-specific in vitro model to test biologic placental mediation of fetal endocrine disrupting effects, and use statistical mediation analysis to evaluate these relationships in pregnancy. With this, we will develop the potential to identify high-risk pregnancies earlier and within a timeframe to reduce long-term risks to the reproductive health of the child.
OVERLAP: No overlap.