

Grandmaternal Perinatal Serum DDT in Relation to Granddaughter Early Menarche and Adult Obesity

Three Generations in the Child Health and Development Studies

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CHE Webinar June 9, 2021



Outline

1. Significance
2. Power of a pregnancy cohort
3. About DDT
4. Study Methods
5. Results
6. Prior human and experimental literature
7. Integrating all DDT results in CHDS → Conclusions

1. Significance of this research

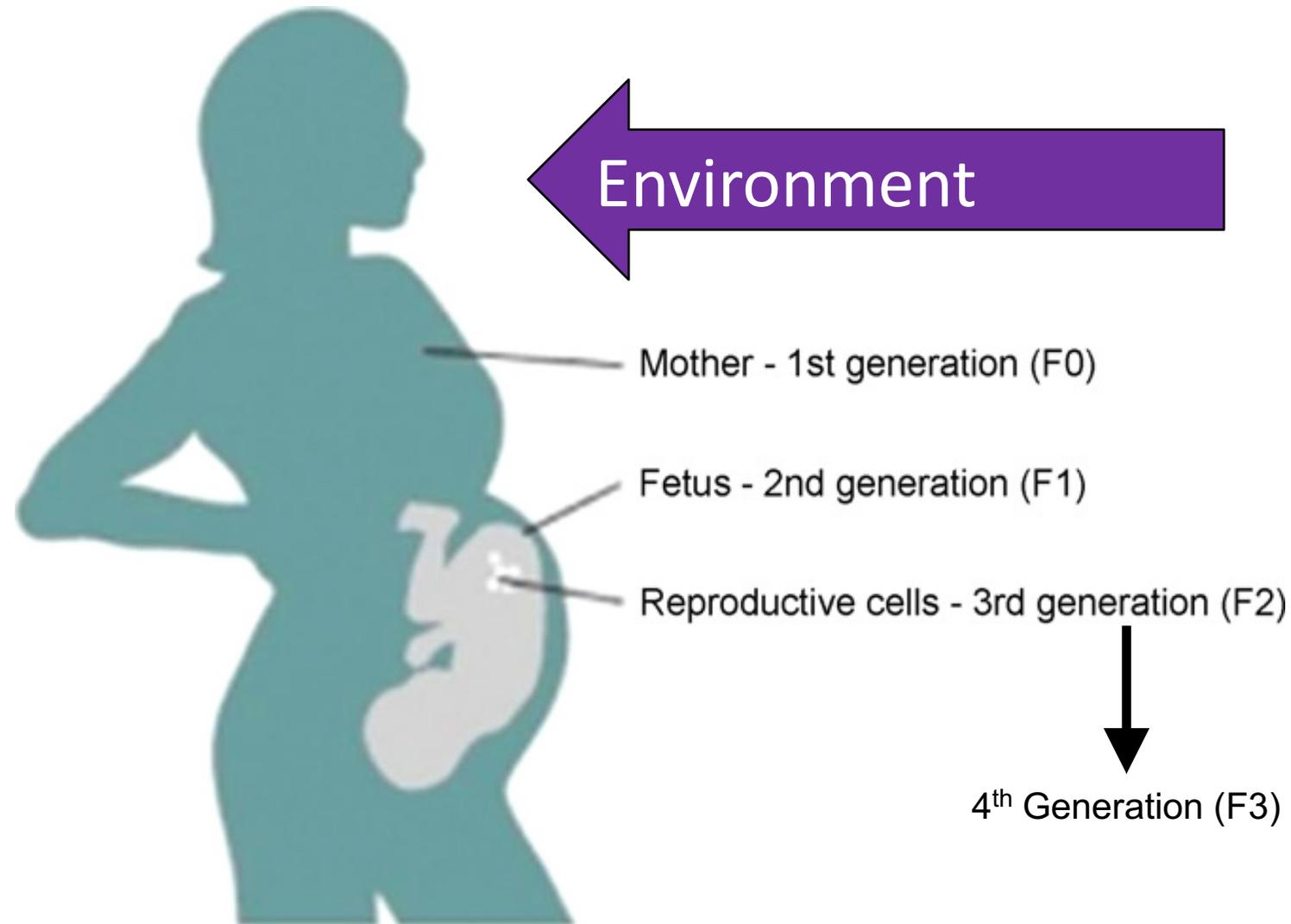
First article to report on human associations of grandmother exposures to a persistent organic pollutant like DDT with granddaughter health

Piera M. Cirillo, Michele A. La Merrill, Nickilou Y. Krigbaum and Barbara A. Cohn
Cancer Epidemiol Biomarkers Prev April 14 2021 **DOI:** 10.1158/1055-9965.EPI-20-1456

2. Power of a pregnancy cohort

What is the Child Health and Development Studies?

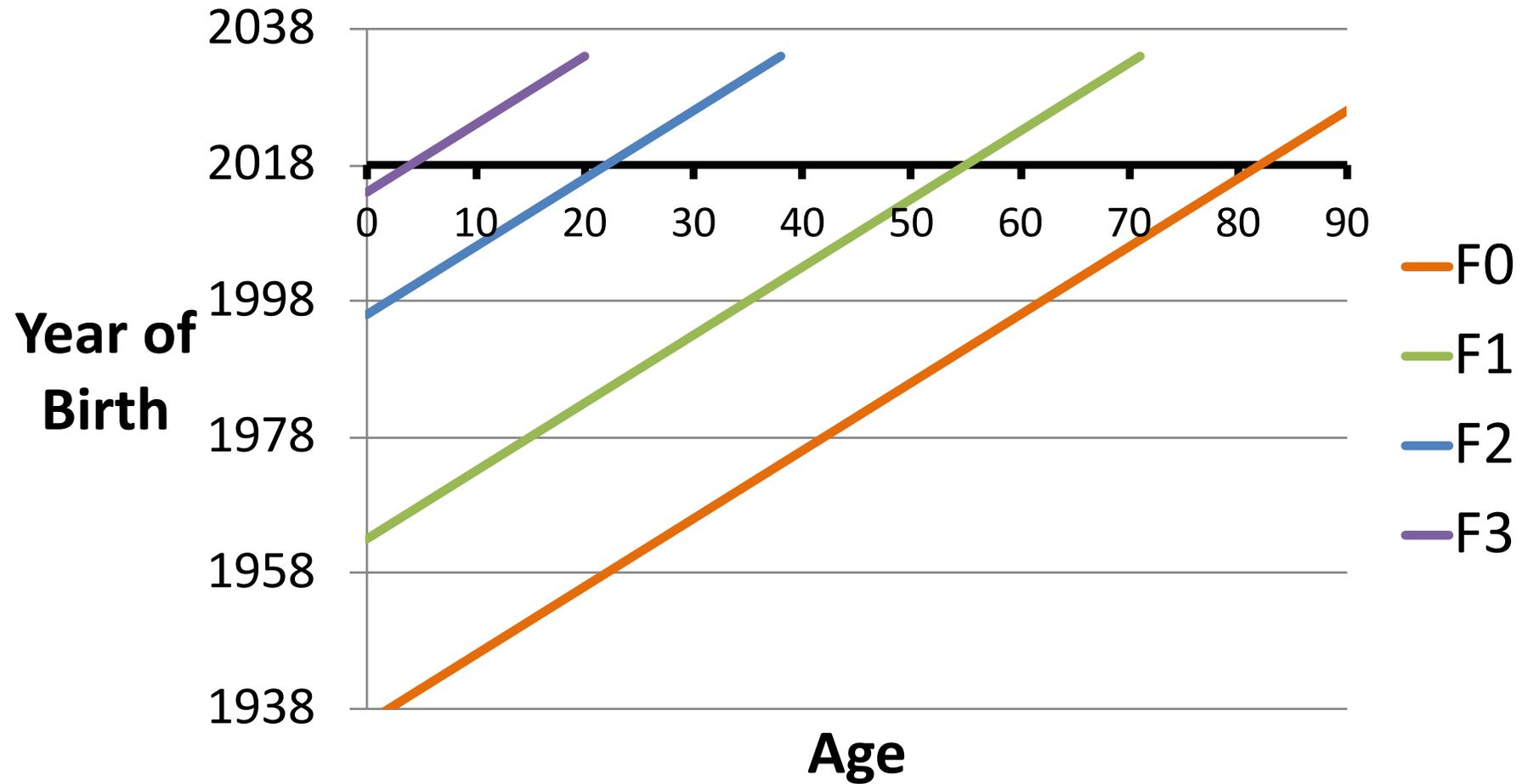
Exposures to pregnant women impact three generations simultaneously



- Initiated in 1959
- Enrolled ~ 20,000 pregnancies by 1967
- Partnership with Kaiser Foundation Health Plan, Oakland, California



Birth Year and Ages of CHDS Generations

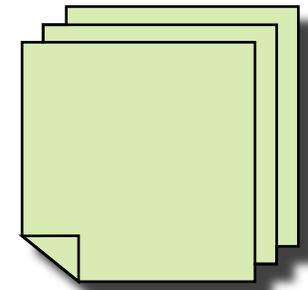


Recruitment success in the CHDS

- >98% of eligible families participated in the CHDS between 1959 and 1967.
- CHDS collected information on over 20,000 pregnancies, from 15,000 women

Interviews provide prospective predictors

- Socio-economic (F0, F1, F2)
- Demographics (F0, F1, F2)
- Behavior (F0, F1, F2)
- Pregnancy history (F0, F1, F2)
- Attitudes and stressors (F0, F1)



Medical records for accurate phenotype

- Medical conditions 6 months *before* and during pregnancy, and labor and delivery (F0)
- Prenatal weight and blood pressure, hemoglobin, albumin and urinary glucose (F0)
- Growth and development (F1)
- Cancer (F0, F1)



Examination studies provide further life-course perspective on F1 and F2

- Exams at ages 5, 9-11, 15-17, 30, 44, 50 (F1)
- Exam at age 20 (F2)
- Biospecimens at age 30, 50 (F1)
- Biospecimens at age 20 (F2)

Blood samples enable assays for biomarkers and environmental exposures

- Over 65,000 serum samples (F0+F1+F2)
- Drawn at each trimester, post-partum (F0)



3. About DDT

Why does DDT still matter?



PROTECT YOUR CHILDREN

Against Disease-Carrying Insects!



TRIMZ DDT
REG. U. S. PAT. OFF.
CHILDREN'S ROOM
WALLPAPER and Ceiling Paper

KILLS FLIES, MOSQUITOS, ANTS

... as well as moths, bedbugs, silverfish and other household pests after contact!

MEDICAL SCIENCE KNOWS many common insects breed in filth, live in filth and carry disease. Science also recognizes the dangers that are present when these disease-carrying insects invade the home. Actual tests have proved that one fly can carry as many as 6,600,000 bacteria! Imagine the health hazard—especially to children—from flies seriously suspected of transmitting such diseases as scarlet fever, measles, typhoid, diarrhea... even dread polio! Some types of mosquitos carry malaria and yellow fever. And any mosquito bite is painful and easily infected when scratched.

NON-HAZARDOUS to children or adults, to pets or clothes. Certified to be absolutely safe for home use. Tested and commended by *Parents' Magazine*.

GUARANTEED effective against disease-carrying insects for 1 year. Actual tests have proven the insect-killing properties still effective after 2 years of use.

NO SPRAYS! NO LIQUIDS! NO POWDERS! So convenient, so safe because the DDT is fixed to the paper. It can't rub off!

BEAUTIFUL! "Jack and Jill" or "Disney Favorites"—gay new patterns that protect as they beautify a child's room.

DDT CEILING PAPERS, TOO! Extra protection for your children's room—for every other room in the house. Choice of two tints.

TESTED AND
 COMMENDED
 by
PARENTS'
MAGAZINE
 CONSUMER
 SERVICE
 BUREAU

READY-PASTED! Just Dip in Water and Hang!

Anyone can put Trimz Wallpaper up without help or previous experience. Millions have done it—proved it's quick, clean, easy! Nothing to get ready—no tools, paste or muss. Just cut strips to fit, dip in water and hang. It's dry in 20 minutes! Guaranteed to stick—guaranteed to please or money back. And so **INEXPENSIVE!** You can protect your child for \$8 to \$12—depending on size of room.



Just Dip in Water and Apply

Trimz DDT Children's Room Wallpaper, Trimz DDT Cedar Closet Wallpaper now available at Department, Chain, Hardware, Paint, and Wallpaper stores everywhere.

Many beautiful new patterns also available in regular Trimz Ready-Pasted Wallpaper at \$1.98, \$2.49, \$2.99 per box.

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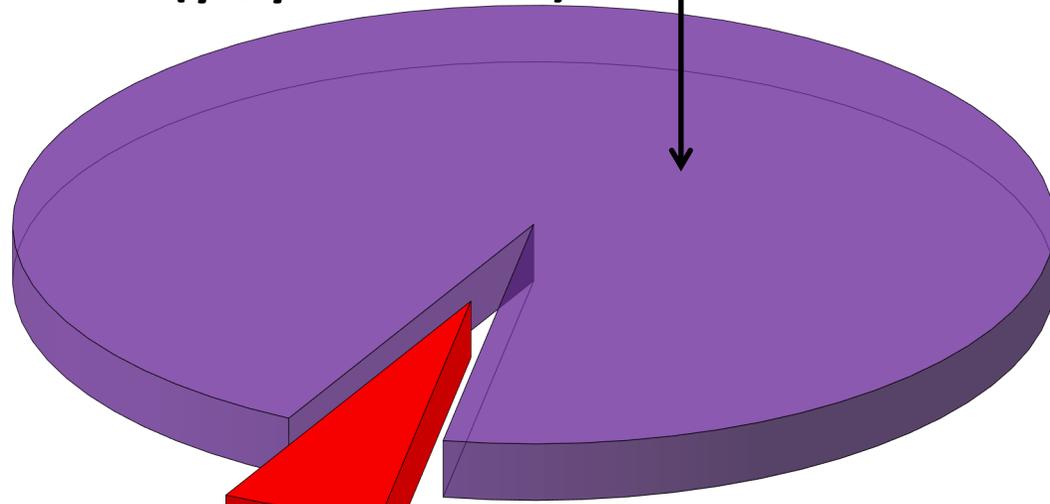
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Three “DDT” Compounds

Insecticide

(p,p'-DDT)



Contaminant

(o,p'-DDT)



TIME



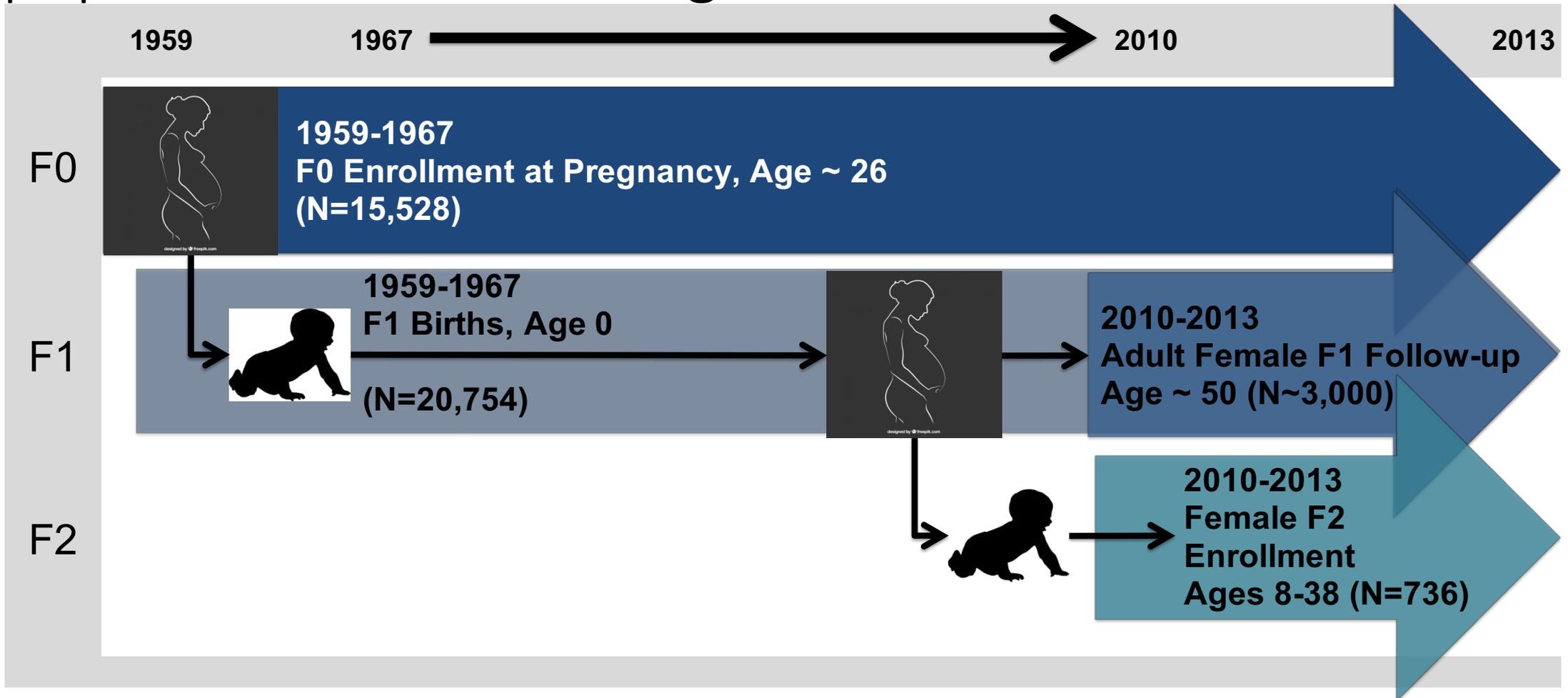
Metabolite

(p,p'-DDE)

4. Study methods

3 Generations Breast Cancer Study (3Gs) funded by the California Breast Cancer Research Program

Child Health and Development Studies (CHDS): population-based multi-generational cohort



Study Sample

- Adult granddaughters participated in a home visit, had available DDT measures from grandmothers' serum, and had available information on body mass index (BMI) in all three generations (258 triads).
- Information on age at menarche in all three generations (235 triads).
- Study sample was highly comparable on demographics for family background compared to those eligible
- Of note: 30% of the sample were Black women

How we defined granddaughter early menarche

- Age 11 or less because this was the bottom 25% of the menarche ages reported by granddaughters.

Other Factors We Considered

- Grandmother and mothers body mass index, race, and age at menarche
- Whether grandmother overweight modified the correlation of DDT with granddaughter obesity and menarche
 - DDTs are stored in fat
 - Adiposity may modify metabolism and/or transfer of pollutants to the fetus

5. Results

Comparing grandmothers and granddaughters

- Granddaughters were more likely to be obese ($BMI \geq 30 \text{ kg/m}^2$) than their grandmothers at a similar age (32% versus 9%).
- Granddaughters were younger at menarche than their grandmothers (median age of 12 versus 13).
- Health implications: Granddaughters at higher risk for reproductive problems, disability, heart disease, and some cancers over the life-course

Associations of grandmothers' perinatal *o,p'*-DDT with adult granddaughter obesity depended significantly ($p=0.028$) on grandmothers' overweight (BMI ≥ 25 kg/m²), $n=258$ triads

	Association of <i>o,p'</i> -DDT in grandmothers' perinatal serum with granddaughter obesity: Compares top tertile to bottom tertile of <i>o,p'</i> -DDT					
	For Grandmother NOT Overweight (n=182)			For Grandmother Overweight (n=76)		
Model Adjustment	Odds Ratio	(95% CI)	p-value	Odds Ratio	(95% CI)	p-value
All DDTs	3.6	(1.4, 9.6)	0.009	0.4	(0.1, 1.0)	0.055
+ Mother (F1) BMI	3.4	(1.5, 8.0)	0.004	0.4	(0.1, 1.1)	0.080
+ F1 BMI + Race	2.6	(1.0, 6.7)	0.050	0.3	(0.1, 1.0)	0.052

Associations of grandmothers' perinatal serum *o,p'*-DDT with granddaughter early menarche (\leq age 11), n=235 triads

	Estimated <i>o,p'</i> -DDT Association Compares top tertile vs. bottom tertile of <i>o,p'</i> -DDT		
Model Adjustment	Odds Ratio	(95% CI)	p-value
DDT congeners and Grandmother Age at Menarche	2.2	(1.2, 4.0)	0.007
+ Mother (F1) Age at Menarche	2.3	(1.2, 4.1)	0.008
+ Race Adjusted	2.1	(1.1, 3.9)	0.024
+ F1 BMI Adjusted	2.1	(1.1, 3.9)	0.022

Summary of Findings

- Grandmaternal serum *o,p'*-DDT during her pregnancy was associated with obesity in granddaughters when grandmother herself is of normal weight (70% of our 1960's pregnancies).
- Regardless of her weight, grandmaternal serum *o,p'*-DDT during her pregnancy was associated with earlier menarche in her granddaughter.
- Granddaughter findings were not explained by weight, timing of menarche in grandmother or mother.

Limitations and Strengths

- Other unknown exposures?
- Uncertainty regarding whether *o,p'*-DDT is a marker of recent exposure or is itself the primary toxic influence among the DDTs?
- Limited representation of Hispanics and Asians. However, our cohort represents in-migration from geographic areas of the U.S, where DDT was in heavy use and reflects racial/ethnic composition of Alameda County, CA in the 1960's.
- Strengths of this study are its prospective design, direct measurement of multiple DDTs in grandmother perinatal serum during active exposure, the ability to account for the contribution of grandmother and mother obesity and age at menarche, representation of Black families who had higher DDT exposures, likely due to migration of families from the South.

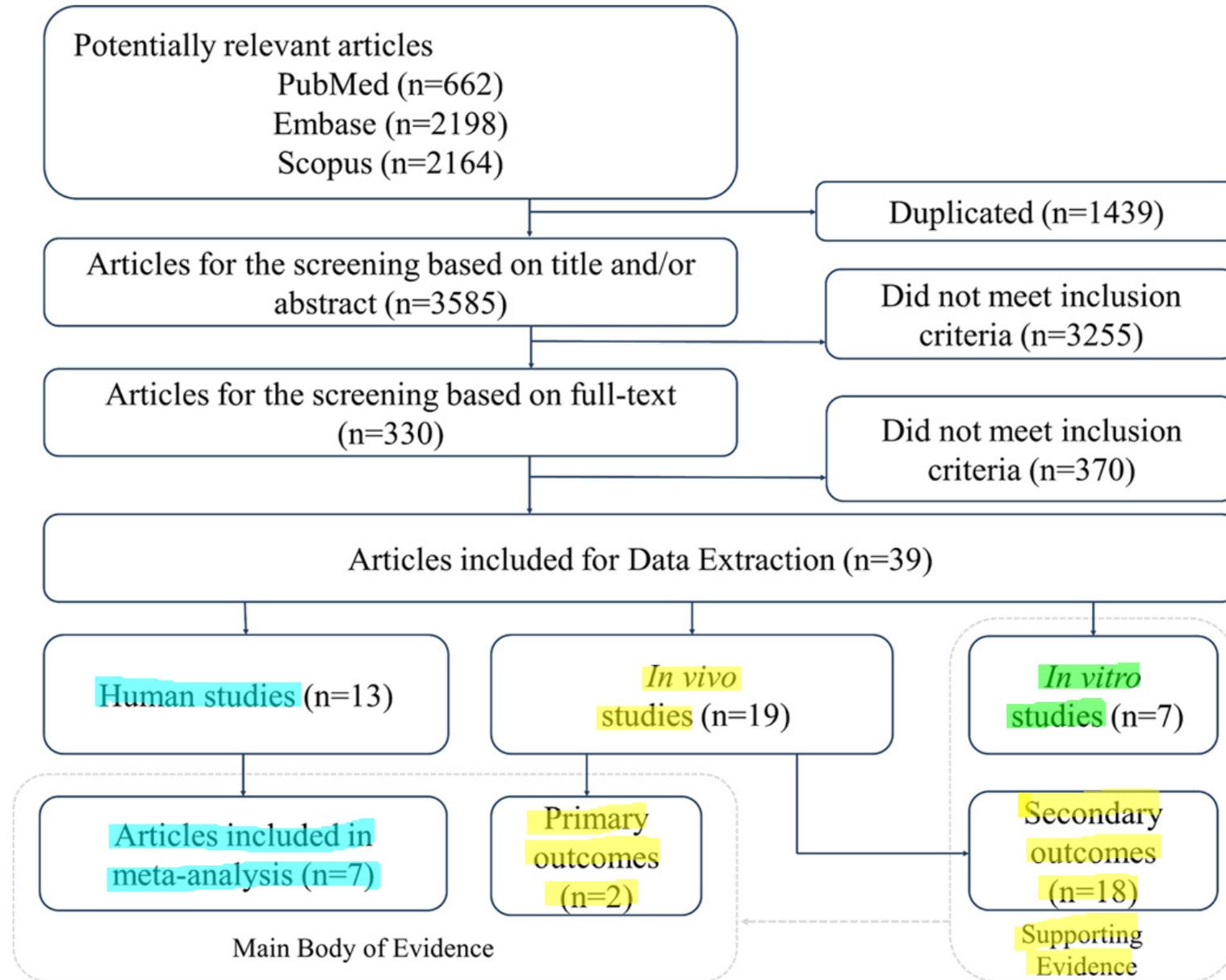
6. Previous human, animal and in vitro research on DDT and obesity

Association between Exposure to p,p-DDT and Its Metabolite p,p-DDE with Obesity: Integrated Systematic Review and Meta-Analysis

CONCLUSIONS: We classified p,p-DDT and p,p-DDE as “presumed” to be obesogenic for humans, based on a moderate level of primary human evidence, a moderate level of primary in vivo evidence, and a moderate level of supporting evidence from in vivo and in vitro studies.

German Cano-Sancho, Andrew G. Salmon, and Michele A. LaMerrill.

[https://doi.org/ 10.1289/EHP527](https://doi.org/10.1289/EHP527)



In vivo (animal studies) DDT/DDE Findings following prenatal exposure

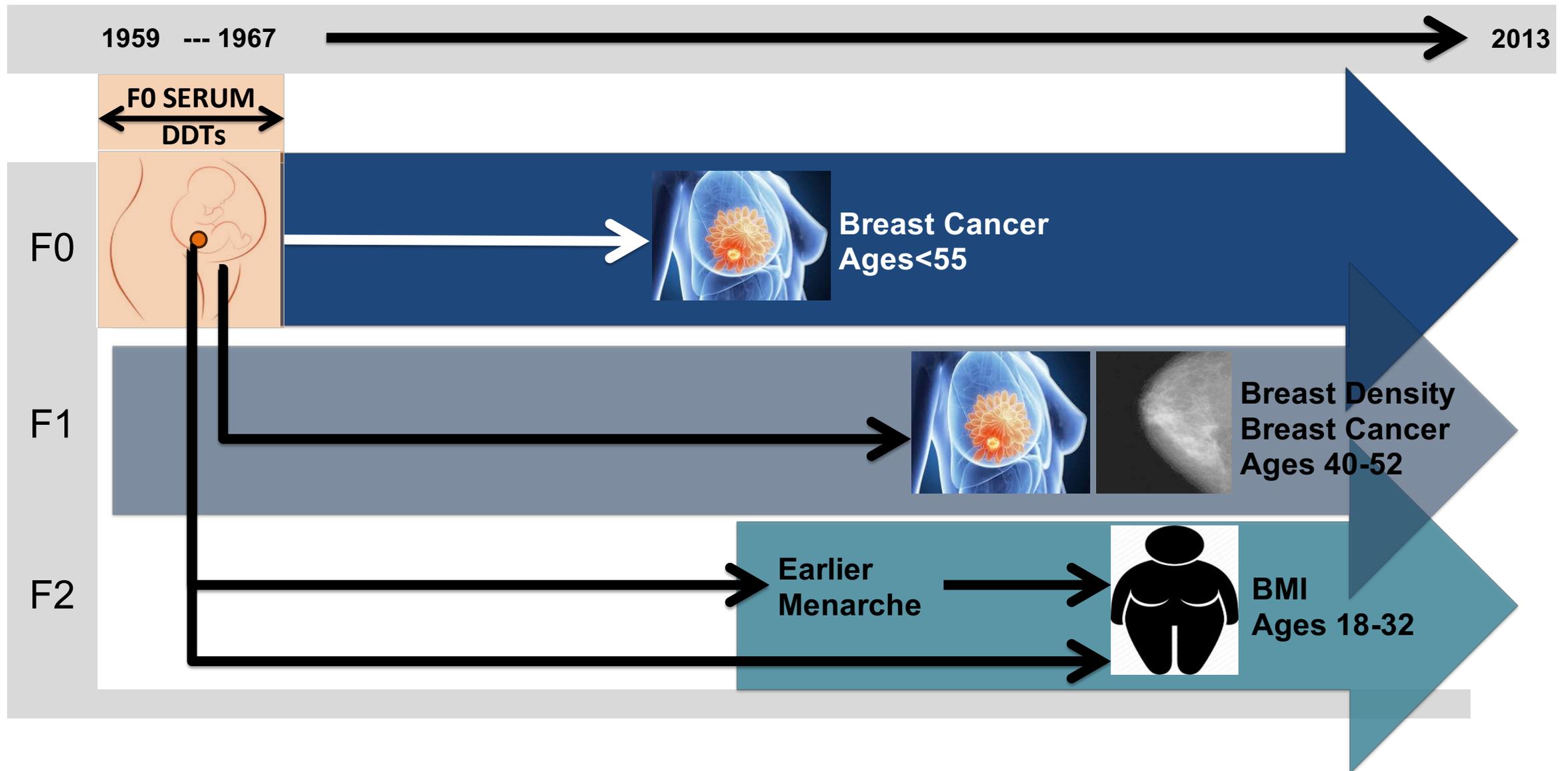
- Energy balance
- Adipose cell differentiation
- Adipokines
- Lipids
- Gene expression

Significant Gaps in Knowledge (not exhaustive)

- Human studies
 - p,p-DDT and o,p'-DDT not usually studied
 - Continuing follow-up across life-course and generations
 - Exposome measurement
- In vivo studies
 - Adiposity not measured
 - Endocrine mechanism/interaction not known
 - Transgenerational designs
- In vitro studies
 - Human cell studies needed to compare mouse cell results

7. Putting Granddaughter Results together with prior work on DDT in the CHDS

Pregnancy: a critical window of exposure for 3 human generations



Take Away Messages

- Exposure to compounds like DDT, which are endocrine disruptors, have potential for persistent effects on multiple, subsequent human generations—aligning with observations in animal studies.
- Ancestral exposure to endocrine disruptors may impact **current** generations long after they are banned and may have contributed to the current epidemic of obesity. Mitigation may depend on revealing mechanisms through trans-disciplinary research.
- Long-term health effects of endocrine disruptors may not be revealed for decades. Therefore, reduction of unnecessary and widespread exposures to such chemicals is warranted to protect the public health.

Future of CHDS

- CHDS is the **only** opportunity for 3 -4 generation research on impact of environmental chemicals **DURING THE CRITICAL WINDOWS OF PREGNANCY/AND IN THE WOMB**
- Seeking funds to secure the cohort for the future of science
 - to store biospecimens
 - communicate with CHDS members
 - enroll great-grandchildren
- Please contact me if you have ideas or can help

We Thank Funders

California Breast Cancer Research Program several critical awards most notably our Three Generations of Breast Cancer Study (15ZB-0186) and Germline EDC Exposure and Breast Cancer Risk in the Three Generations of Breast Cancer Study (22UB-5411)

National Institutes of Health (Multiple Institutes over 60 years but mainly NICHD)

State of California which created and supports the California Cancer Registry, The Vital Status and Department of Motor Vehicle Files –without which this birth cohort could not exist.

It takes a village... really more like a state and nation



Shuzhao Li



Dean Jones



CHDS Researchers



CHDS Participant Advisory Council



Piera Cirillo



Michele La Merrill



Mary Beth Terry



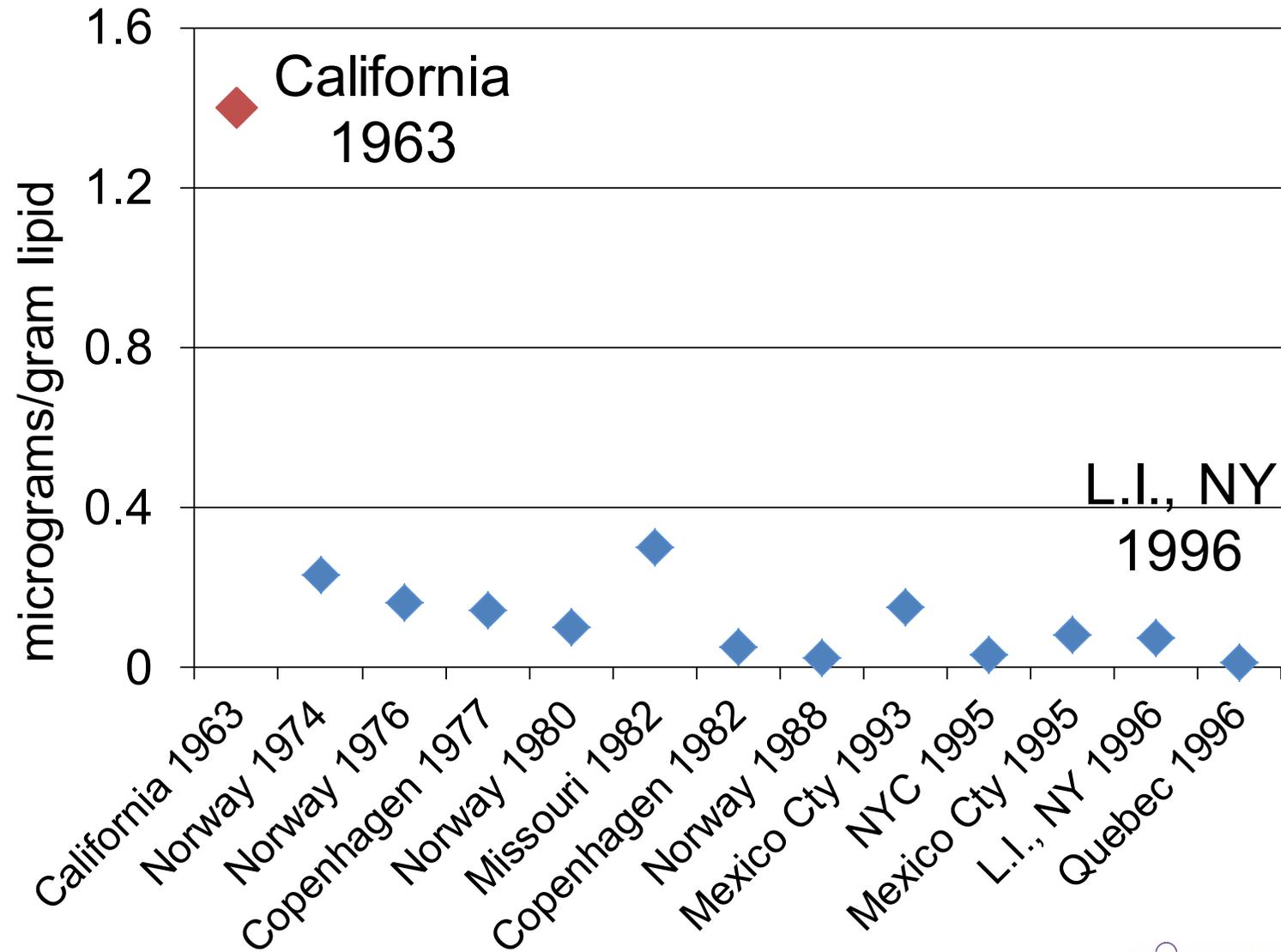
June-Soo Park



Myrto Petreas

END (extra slides after)

Median p,p' -DDT in 13 Studies



Measurements in Daughters (age ~50) and Granddaughters (age ~20)

Measurement		Units	Equipment/Notes
Measured at In-person Visit among F1/F2			
BMI		kg/m ²	
	Weight	kg	Seca 813 High-Capacity Floor Scale
	Height	cm	Seca 213 Stadiometer
Assessed via Questionnaire among F1/Adult F2 ages (18+)			
Age at Menarche		Years	Self-report
BMI age 30 for F1		kg/m ²	Self-report

In our 3 generation pregnancy cohort, CHDS, we found

- Previously
 - Pregnancy exposure to p,p' -DDT is associated with mother's breast cancer most strongly for the generations of women first exposed before puberty.
 - *in utero* exposure to o,p' -DDT was associated with breast density and breast cancer in daughters and with DNA methylation (epigenomic changes) in breast cancer and menarche related genes in daughters.
- First 3 generation human study
 - Grandmaternal o,p' -DDT associated with granddaughters' obesity and timing of menarche.

Pregnancy is a critical window of exposure for 3 generations humans.

Multi-generational DDT effects on breast cancer risk in the CHDS

