Lifespan Stressors and Alzheimer's Disease Study

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Effects of Psychosocial Stressors (PSS)

- PSS: significantly associated with poor health outcomes including CVD [1], T2D [2] and depression [3].
- Repeated stress: damage to the hippocampus via glucocorticoids and excitatory amino acid neurotransmitters released during stress, increasing risk for AD [4,5].
- The "Barker hypothesis": negative experiences during critical periods of development can have lifelong effects on structure or function of organs and body systems that "program" the individual for later susceptibility to chronic disease [6].
- The "accumulation of risk" hypothesis: insults gradually accumulate over the life course; biological and social risk factors at each life stage may combine to effect adult disease [7].

Impact of psychosocial stress on cognitive health

- "Subjective stress" (one's perception of the effect of life events and/or chronic stressors; influenced by personality, temperament)—*important, but not the focus of our work*
- "Objective stressors" -- type, timing, spacing, cumulative, interactions, resilience vs. increasing vulnerability
- Our research objective --is to examine strength of associations between objective stressors and cognitive health in late life with a powerful and comprehensive data resource
- Later studies (if consistent "signal") - examine mechanisms, moderators, relative effects of subjective vs. objective

The Cache County Study on Memory in Aging (R01-AG11380)

Utah State University

Duke University

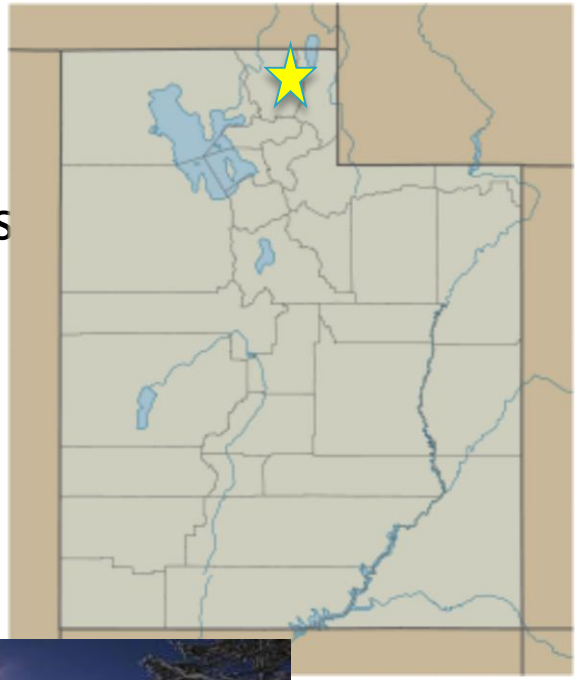
The Johns Hopkins University

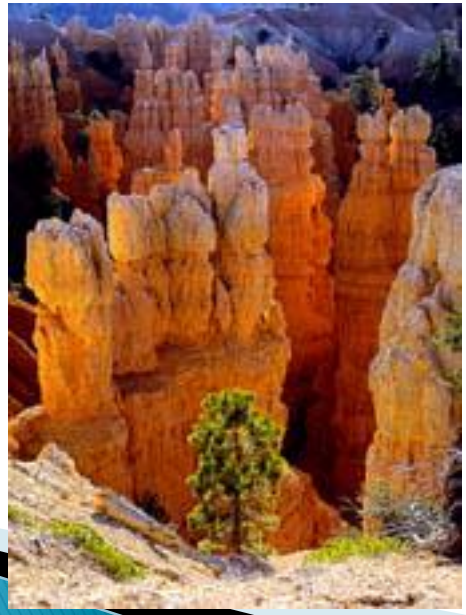
University of Utah
R01-AG11380:
1994-2011

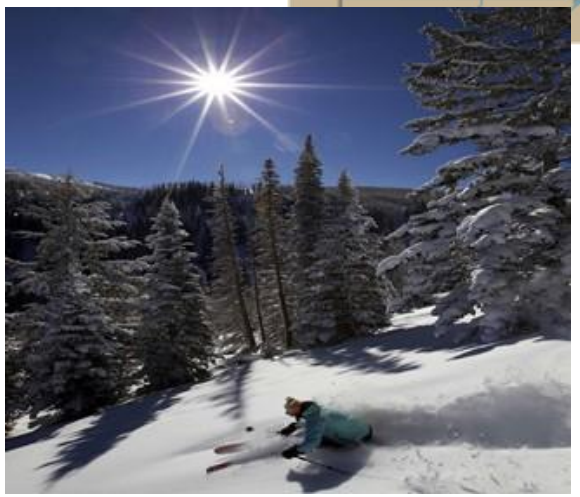
John Breitner (JHU); Bonita Wyse (USU) 1994-2000
Kathie Welsh-Bohmer (Duke); Maria Norton (USU) 2001-2011

Cache County, UT characteristics

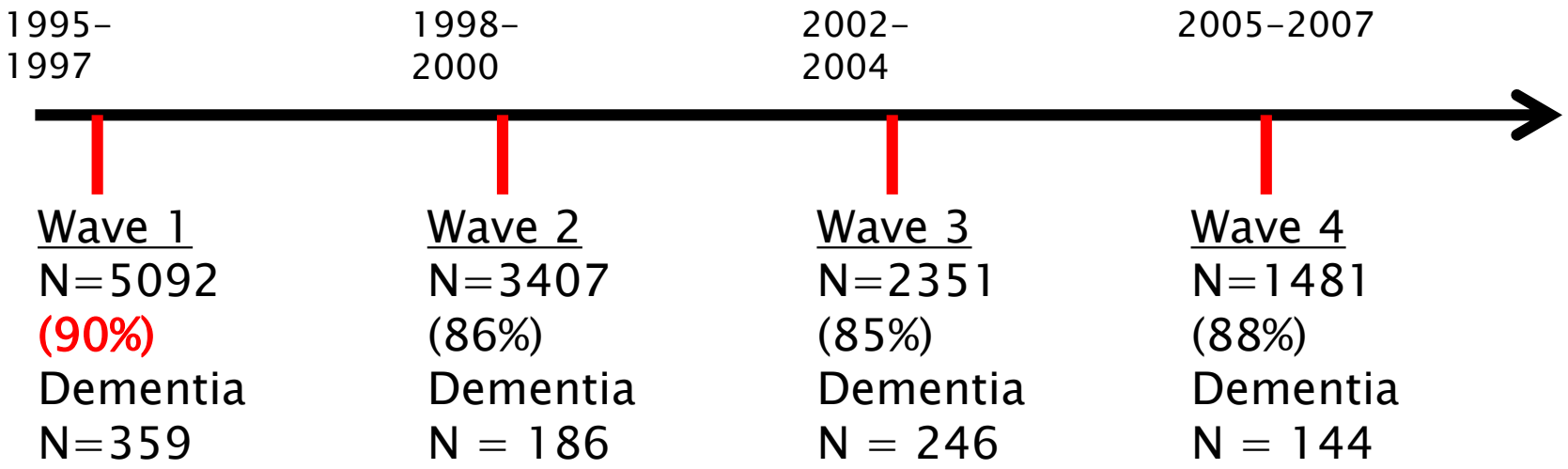
- Median life expectancy substantially exceeds US norms (by 10 years)
- Low rates of smoking and drinking
- 35% Lower rates of cardiovascular diseases
- Higher education than national norms
- Very high participation rate (90%)







Cache County Memory Study – 5092 participants



At each wave:
multi-stage dementia ascertainment w| expert consensus diagnosis

Total dementia = 942
AD = 612 (65%)

Traditional approach to measuring Psychological Stress

	Life Event	Value
1	Death of spouse	100
2	Divorce	73
3	Marital separation	65
4	Jail term	63
5	Death of close family member	63
6	Personal injury or illness	53
7	Marriage	50
8	Fired at work	47
9	Marital reconciliation	45
10	Retirement	45
	Etc…….	

Holmes TH & Rahe RH. The Social Readjustment Rating Scale. J of Psychosom Res, 11(2), 1967; 213-218

Self-report Retrospective Recall Bias

- Cognitive impairment so cannot remember all stressors
- Negative stigma/shame
- Cognitive reframing in later life
- Self preservation (*thinking about past* stressors *brings on depressed mood*)

Limitations of prior studies of stress/cognitive health--limitations

- Clinic-based samples *(may not generalize)*
- Smaller sample size *(under powered)*
- Modest participation rate *(non-responder bias)*
- Self-report *(recall bias)*

Prior studies--limitations (continued)

- Only a limited number of PSS were queried *(poor representation of intended domain, i.e. low content validity)*
- **Even though there is evidence that PSS effects accumulate over the lifespan……. no study has examined lifespan cumulative effects, nor compared salience of PSS across developmental stages of life, on risk for AD**

Lifespan Stressors and Alzheimer's Disease (R01-AG31272; PI: Norton)

- Utilize the in-depth, longitudinal dementia assessments in population-based study in Cache County
- Utilize objective records to code individual stressors
- Investigate associations between PSS and AD (individually and in aggregate over specific stages of the lifespan)

New approach to stress research

- Link participants in the CCMS study to the Utah Population Database
- Removes recall bias
- A greater variety of types of stressors
- Spanning entire lifespan

Norton MC et al. Cumulative Psychosocial Stressors Predict Alzheimer's Disease in Children of the Great Depression. Paper presentation at the Gerontological Society of America, New Orleans, LA, Nov. 2013.

Utah Population Database (UPDB)

- A statewide linked population-based data resource on 8+ million individuals
- Origins—Multi-generation family pedigrees from LDS Church's genealogical archives
- Later addition of data from:
  - Vital Statistics Bureau (birth, death, marriage, divorce)
  - Driver's license data (provides height, weight, geolocation)
  - Hospitalization inpatient records (ICD diagnosis codes)
  - US Military service registration records
  - US Census (occupation, education, household composition, primary language, etc)

A database that is continually growing….

http://www.hci.utah.edu/groups/ppr

Utah Population Database (UPDB)

- Multi-generational pedigrees: *subject, spouse, parents, children (can go farther than this, i.e. grandparents, grandchildren, nieces, nephews, etc)*
- Categories of stressors ***and their timing***:
  - Deaths of loved ones: *parents, siblings, spouses, offspring*
  - Fertility: *offspring births, spacing, weight, gestation (weeks)*
  - Marital history: *dates of marriage, divorce*

- The UPDB facilitates demographic, epidemiological and genetic studies
- Can derive psychosocial stressors
  - "primary" (experienced directly by target individual, e.g. *person experiences teen pregnancy or widowhood or divorce*)
  - "secondary" (experienced by family members and indirectly affecting the individual, e.g. *(a person's spouse is hospitalized, or person's child gets divorced*)
- 5,091 out of 5,092 CCMS subjects were linked to the UPDB, permitting derivation of stressor variables

Create PSS lifespan matrix for each subject

Year of age	Father death	Mother death	Marriage	Divorce	Child birth
0					
1					
2					
…					
105					

With PSS lifespan matrix:

- **Can aggregate multiple PSS within a broad domain**
  - Marital events *(marriage, divorce, re-marriage)*
  - Bereavement events *(death of parent, sibling, child)*
  - Fertility events *(# of children, low birthweight, premature)*
  - Miscellaneous *(e.g. English as second language; spouse military service)*
- **Can aggregate chronologically across:**
  - Entire lifespan,
  - Different developmental periods
  - Birth to start of AD study ("prevalent" exposures)
  - Start of AD study to death or right-censoring ("incident" exposures)
- **Can aggregate non-normative events** (offspring birth is normative at age 26 but is non-normative at age 15)
- **Can aggregate across all PSS for each year** (to identify "tragedy")

UPDB raw data utilized in Cache County

- Birth dates, gestation (weeks), birth weights, birth spacing
- Death dates and Causes of death
- Marriage, divorce dates
- Inpatient hospitalization records
- Socioeconomic status (from occupations)
- Link records to CCMS subject via relationship codes and unique identifiers within the UPDB
- Compare dates, aggregate across various relationship types
- Ignore events in UPDB ***before*** CCMS subject's birth, ***after*** CCMS subject's death date, or ***after*** subject's dementia onset

Results of studies reported today

1. (Childhood) Effect of Early Parental Death on Alzheimer's disease (AD) Risk
Norton et al. *American Journal of Geriatric Psychiatry* 2011 Sep;19(9):814-824.

2. (Young Adulthood) Effect of Offspring Death on Rate of Late-life Cognitive Decline
Greene et al. *American Journal of Geriatric Psychiatry, 2013*
http://dx.doi.org/10.1016/j.jagp.2013.05.002.

3. (Late-life). Having a spouse develop dementia—affect on one's own later dementia risk.
Norton et al. *Journal of the American Geriatrics Society*, 2010.

4. (Childhood). Effect of multiple family deaths during childhood—affect on late-life CRP.
Norton MC,et al. Presentation at the Alzheimer's Association International Conference on Alzheimer's Disease, July 2013, Boston, MA.

5. (Lifespan) . Effect of cumulative lifetime stressors on AD risk.
Norton et al. *American Journal of Geriatric Psychiatry, in revision.*

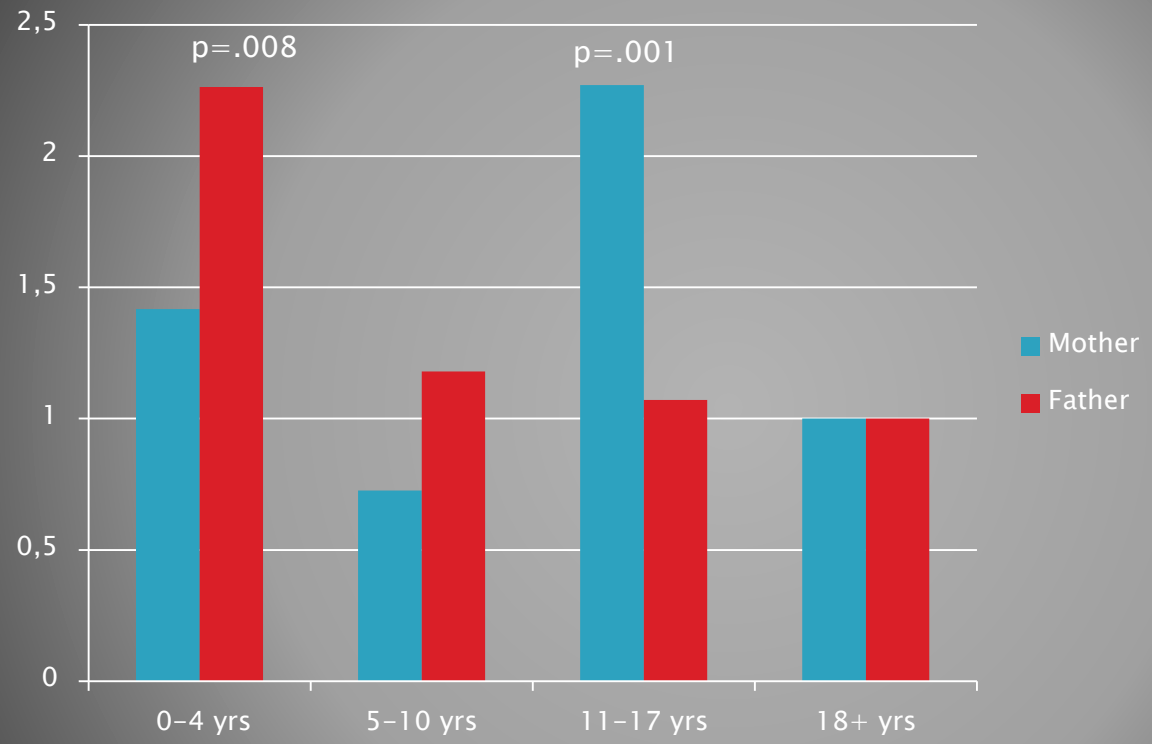
STUDY #1: Effect of Early Parental Death on AD Risk

- Code mother's and father's death during subject's age 0-4, 5-10, 11-17, 18+ years (ref. category)
- Effect of Early Mother/Father Death on AD risk, via Logistic Regression
- Models adjusted for age, gender, education, socio-economic status and APOE genotype
- Remarriage of widowed parent

Early Parental Death: Logistic regression OR (p-value) for AD vs. no dementia

MODEL	n	Mother Death	Father Death	Father & Mother Death
Maternal Death (ref=18+)	3814	(.005)		(.006)
0-4 yrs	87	1.452 (.207)		1.417 (.240)
5-10 yrs	99	0.735 (.346)		0.726 (.328)
11-17 yrs	108	2.266 (.001)		2.271 (.001)
Paternal Death (ref=18+)	3742		(.073)	(.064)
0-4 yrs	69		2.228 (.009)	2.263 (.008)
5-10 yrs	122		1.145 (.628)	1.180 (.554)
11-17 yrs	175		1.059 (.803)	1.071 (.767)

Stressor of early parental death predicts late-life AD risk



Models controlled for age, gender, education, APOE status, socioeconomic status
Neither gender nor APOE moderated these associations.

Norton MC, et al. Early parental death and remarriage of widowed parents as risk factors for Alzheimer's disease. *American Journal of Geriatric Psychiatry* 2011 Sep;19(9):814-824

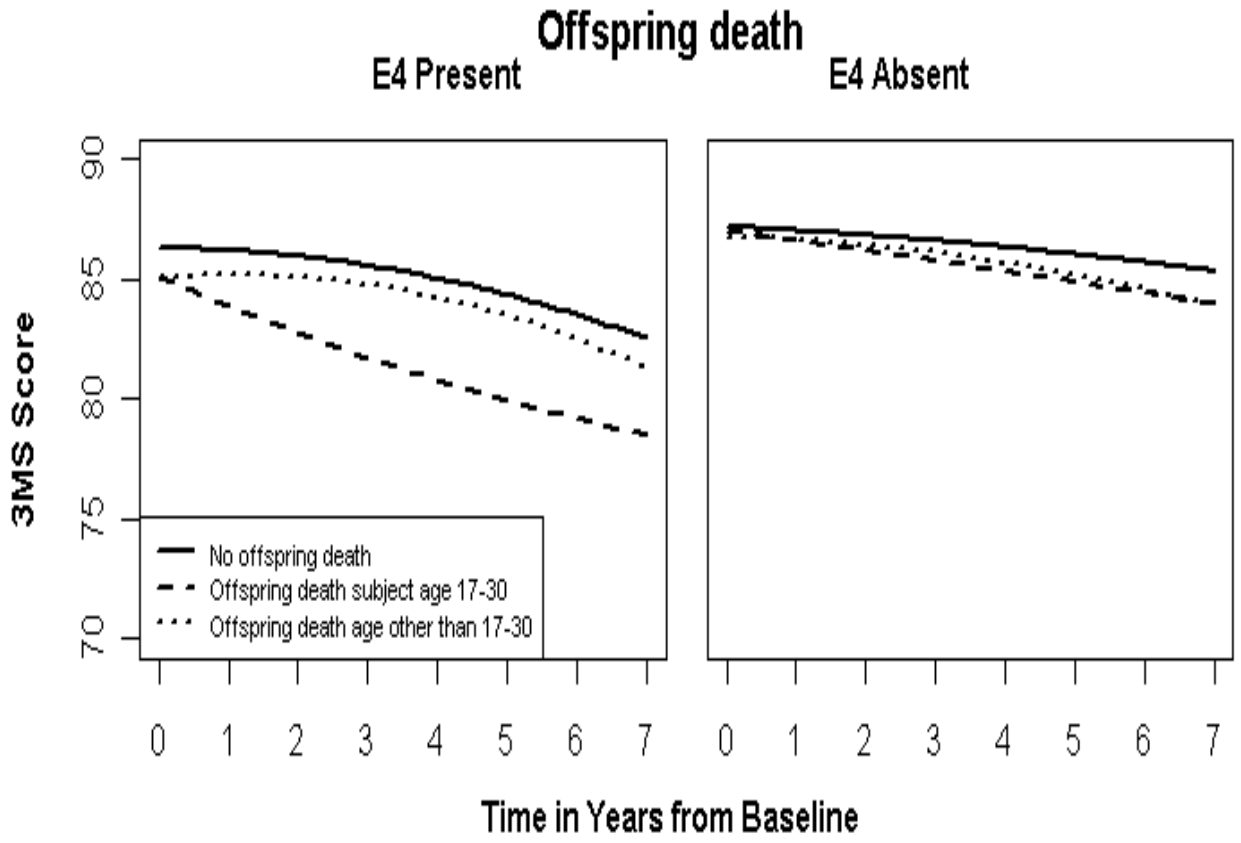
Early Parental Death: Logistic regression OR (p-value) for AD vs. no dementia)

MODEL	n	Mother Death	Father Death	Father &Mother Death
Maternal Death (ref=18+)	3814	(.035)		(.038)
0-4 yrs NO remarriage	41	1.664 (.201)		1.531 (.292)
0-4 yrs W/ remarriage	46	1.246 (.615)		1.292 (.557)
5-10 yrs NO remarriage	51	0.588 (.259)		0.567 (.228)
5-10 yrs W/ remarriage	48	0.926 (.865)		0.942 (.895)
11-17 yrs NO remarriage	79	2.390 (.003)		2.410 (.003)
11-17 yrs W/ remarriage	29	1.959 (.171)		1.943 (.178)
Paternal Death (ref=18+)	3742		(.284)	(.261)
0-4 yrs NO remarriage	49		2.402 (.017)	2.399 (.019)
0-4 yrs W/ remarriage	20		1.896 (.245)	1.999 (.207)
5-10 yrs NO remarriage	106		1.135 (.669)	1.167 (.604)
5-10 yrs W/ remarriage	16		1.219 (.803)	1.334 (.718)

STUDY #2: Effect of Offspring Death on Rate of Late-life Cognitive Decline

- Consider biological offspring who lived at least 1 day (not stillborn)
- Code offspring death (include deaths prior to and after CCMS baseline interview but ***before subject's dementia onset***)
- Model 3MS cognitive status with linear mixed models to assess impact of offspring death on:
  - Baseline level of cognitive status
  - Rate (& acceleration) of cognitive decline over time

Stressor of offspring death (when parent is age 17-30 years) and effect on late-life cognitive decline is moderated by APOE status



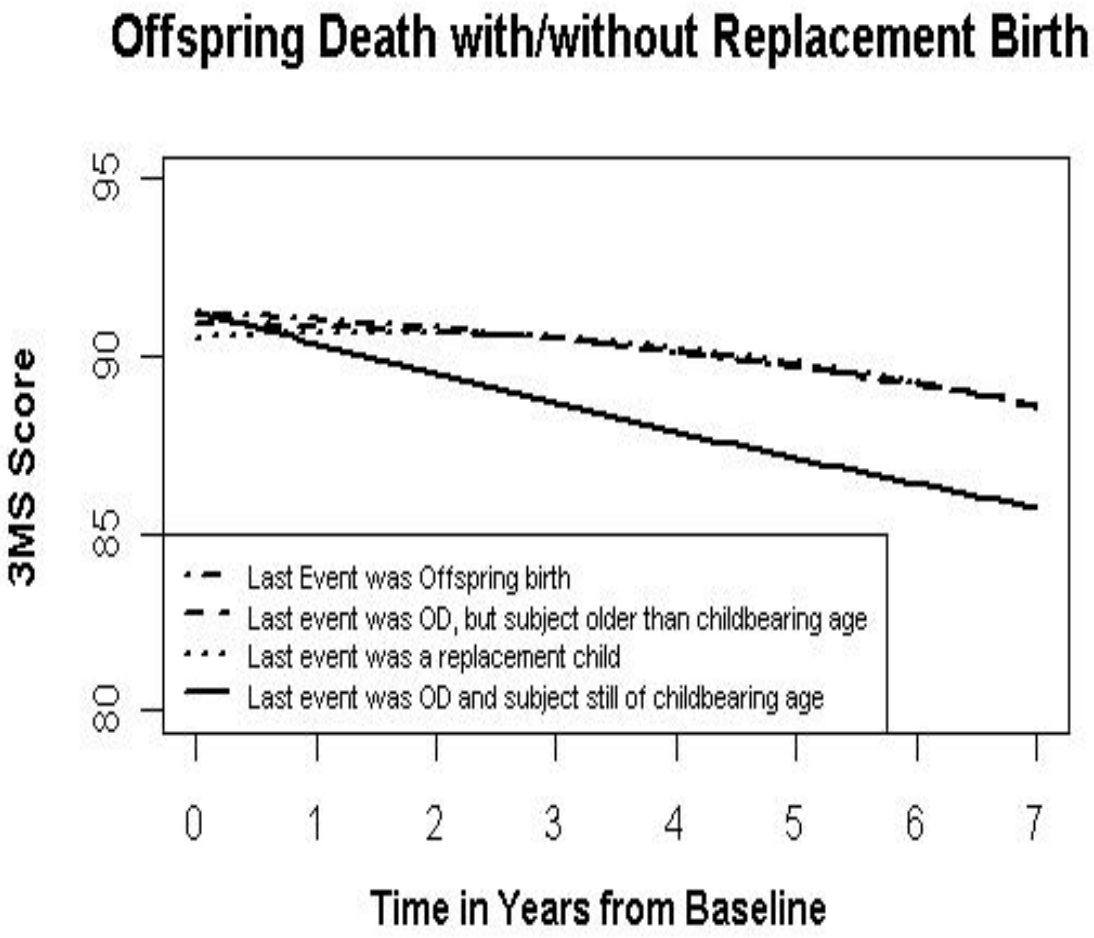
Linear Mixed Models

Ɛ4 Present
Linear p=0.006
Quadratic p=0.018
(1.2 pt/year faster; p=.003)

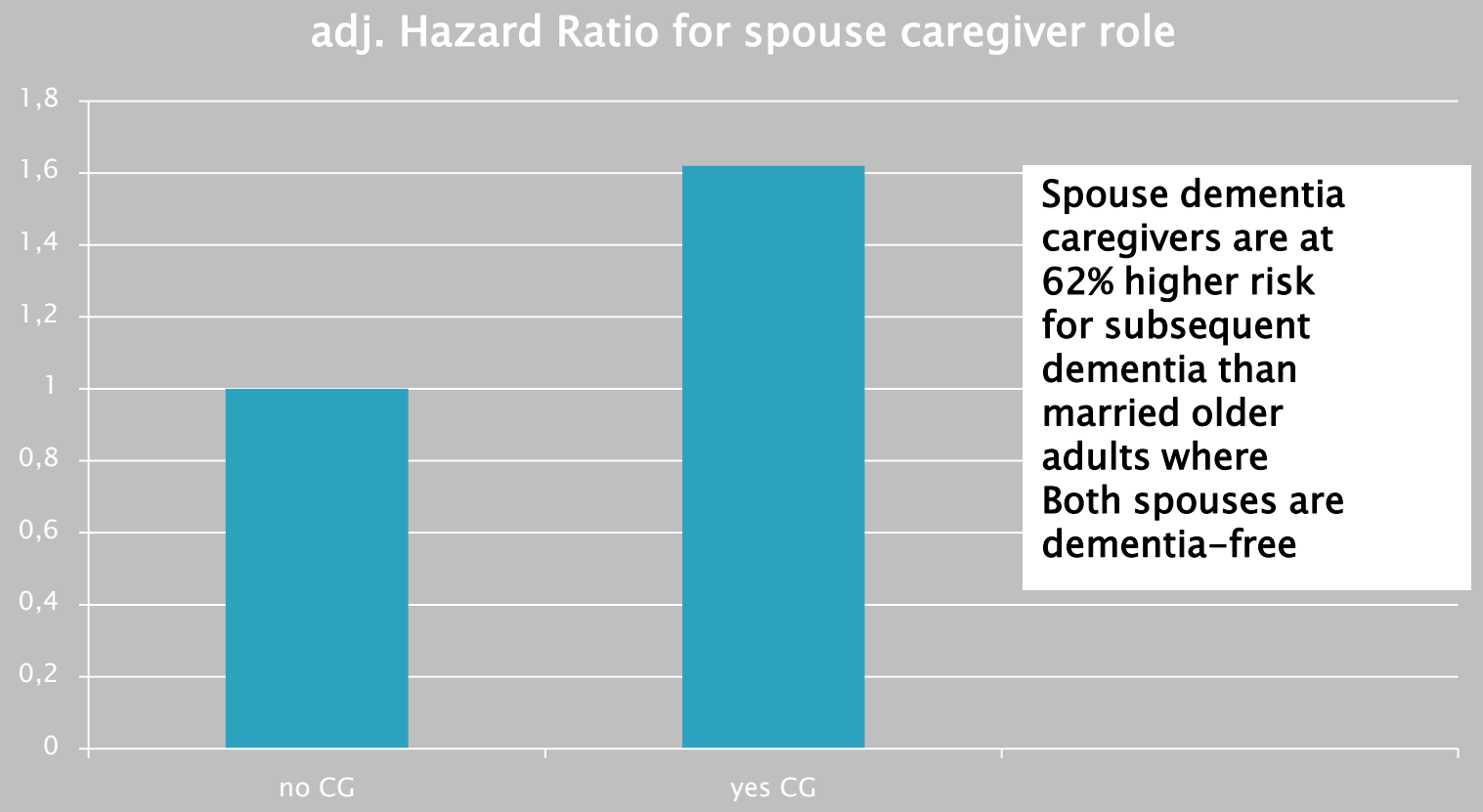
Ɛ4 Absent
Linear p=0.546
Quadratic p=0.342

Greene D, et al. American Journal of Geriatric Psychiatry. 2014 Nov;22(11):1307-15. doi: 10.1016/j.jagp.2013.05.002.

OD without replacement (during childbearing yrs) .8 pt/year faster decline than no OD (p=.009)

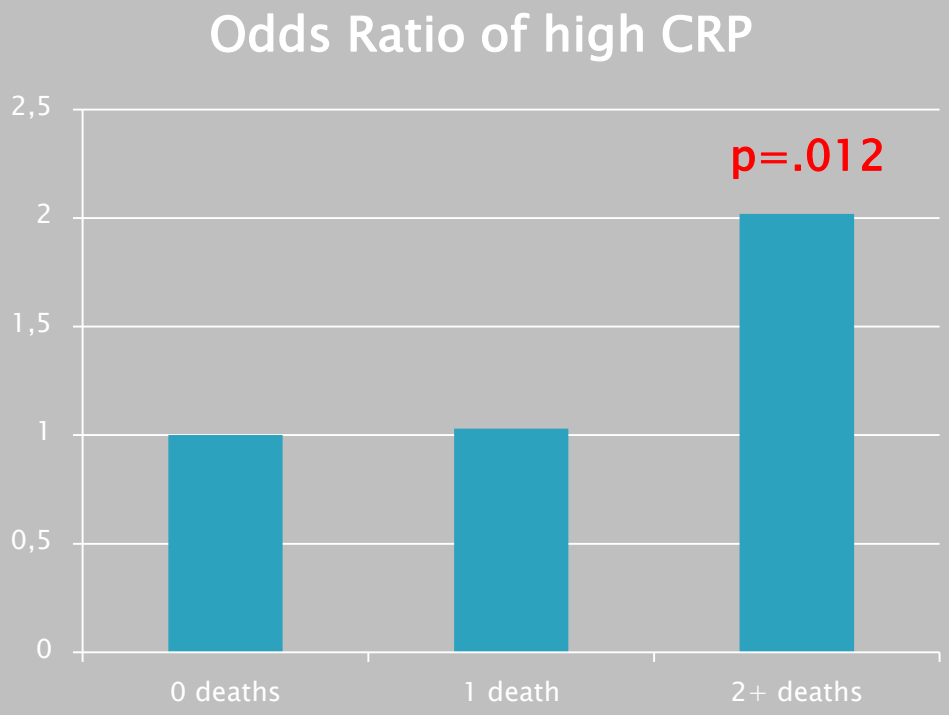


STUDY #3: Stressor of having a spouse with dementia predicts one's own dementia risk



Norton MC, et al. Journal of the American Geriatrics Society. 58:895-900, 2010 May.

STUDY #4: Multiple family deaths in childhood linked to double the risk of clinically elevated C-reactive protein in late life (n=2,176)



NOTE: Because neuroinflammation is associated with AD, we examined systemic inflammation (later models will test mediation, i.e. effect of chronic stress on AD via Inflammation).

Norton MC,et al. Presentation at the Alzheimer's Association International Conference on Alzheimer's Disease, July 2013, Boston, MA.

STUDY #5: Effect of cumulative lifetime stressors on AD risk

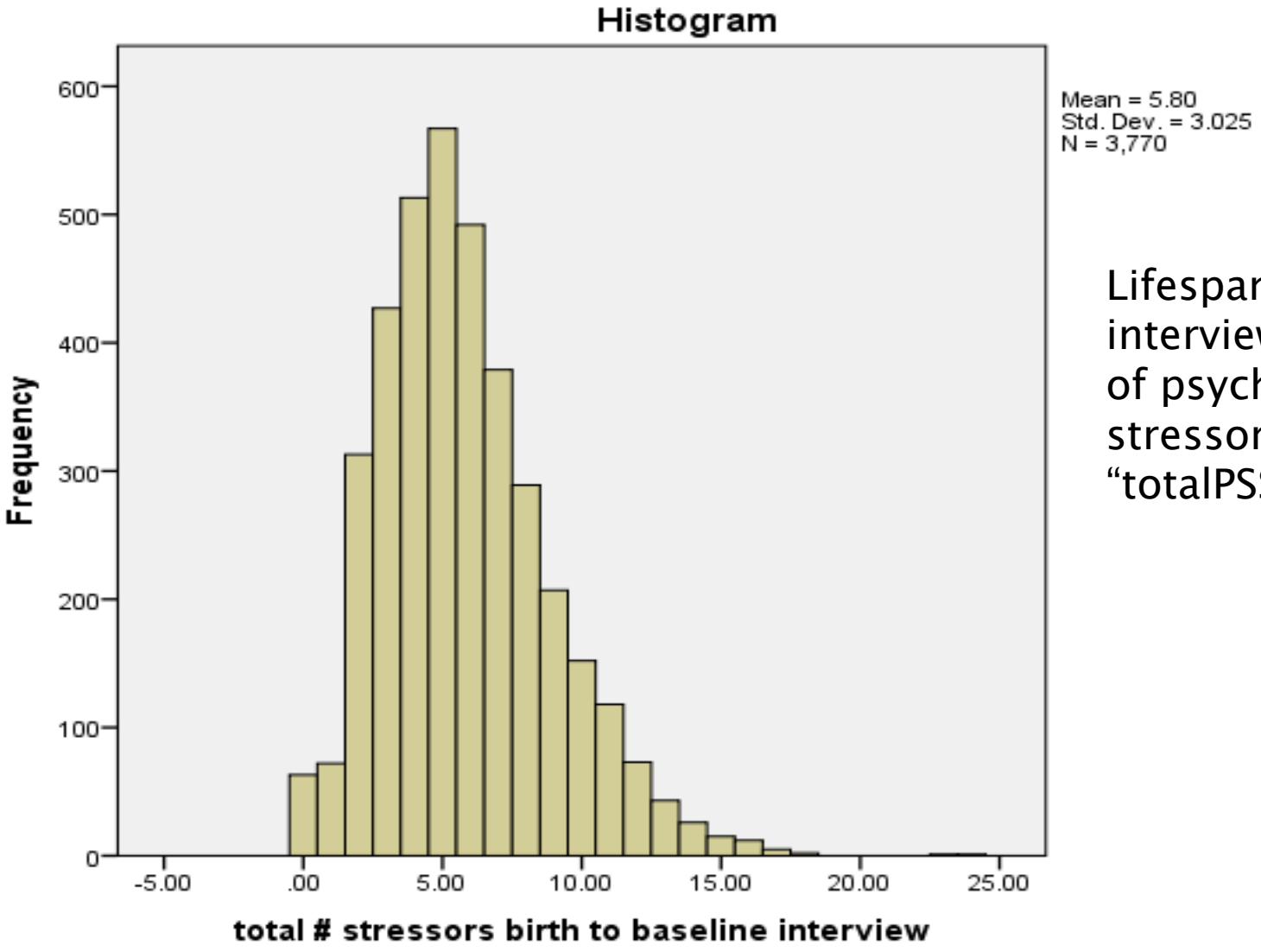
Hypothesis. The greater the cumulative lifespan PSS exposure , the greater the AD risk

- hospitalization(s) of mother, father, sibling(s), spouse(s), offspring
- death(s) of mother, father, sibling(s), spouse(s), offspring;
- never marrying, divorce(s), remarriage;
- nulliparity, 8+ offspring, stillborn/premature offspring, out-of-wedlock birth;
- high school or less education, low SES, and “blue collar” career.

Cox regression analysis

- Time to AD onset from baseline interview
- Key exposure variable: total # of stressors from birth to baseline interview
- Age groups: 65–69, 70–74, 75–79, and 80+ years
- Covariates: gender, # ε4 alleles at *APOE*

Subjects who died, dropped out, or for whom the study ended without a dementia dx were "right-censored" at last visit



Lifespan to baseline interview total # of psychosocial stressors "totalPSS"

Age 65-69 (birth years 1926-1930); n=983
18% higher AD risk *for each additional stressor*

Variables in the Equation

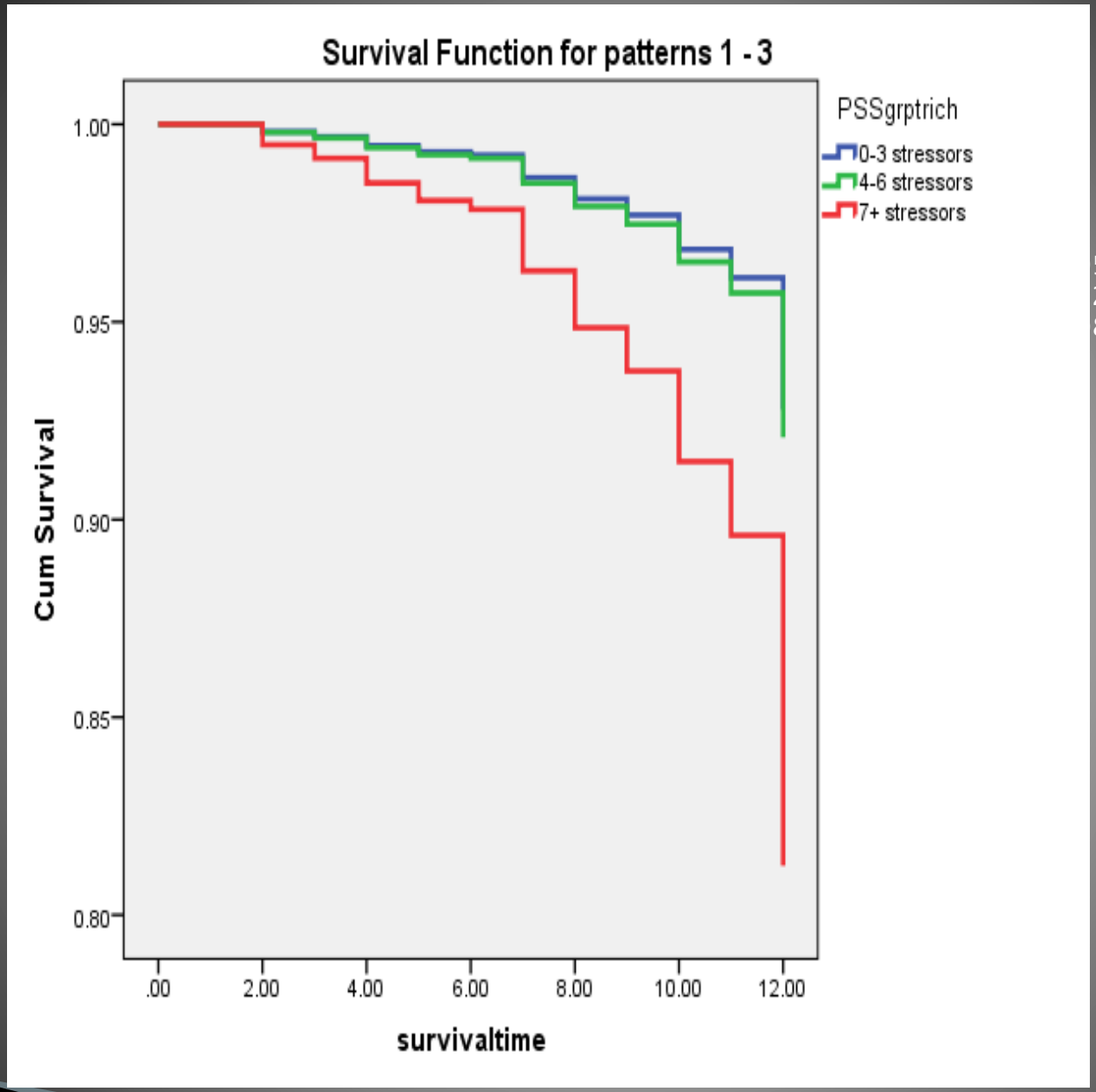
	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
TOTALPSS	.163	.060	7.460	1	.006	1.177	1.047	1.323
1+ e4 alleles	1.197	.316	14.312	1	.000	3.311	1.781	6.156
Female gender	-.167	.308	.293	1	.588	.847	.463	1.547
age	.031	.119	.070	1	.791	1.032	.818	1.302

NOTE: TotalPSS was n.s. related to AD-free survival time in those aged 70-74 years (p=0.123), 75-79 years (p=0.829), or 80+ years (p=0.675)

Age 65-69 (birth years 1926-1930); n=983
TotalPSS: 0-3 vs. 4-6 vs. 7+ PSS (tertiles)

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
1+ e4 alleles	1.182	.317	13.938	1	.000	3.261	1.753	6.066
Female gender	-.166	.308	.290	1	.590	.847	.463	1.549
PSS group			8.756	2	.013			
4-6 vs. 0-3 PSS	.097	.395	.060	1	.806	1.102	.508	2.390
7+ vs. 0-3 PSS	1.020	.411	6.157	1	.013	2.772	1.239	6.204
Age	.021	.119	.030	1	.862	1.021	.808	1.289


Survival Function for patterns 1 - 3
PSSgrptrich
0-3 stressors
4-6 stressors
7+ stressors
Cum Survival
1.00
0.95
0.90
0.85
0.80
.00
2.00
4.00
6.00
8.00
10.00
12.00
survivaltime

Summary

- Early parental death (esp. mother) is associated with double the risk for AD in late life—***but only among those whose widowed parent does not remarry***
- Offspring death is associated with significantly more rapid cognitive decline in late life—***but only among those who subsequently do not have any more children***
- **Having a spouse with dementia is associated with one's own later dementia risk**
- **Multiple family deaths during childhood linked to higher risk for systemic inflammation in late life**
- Cumulative number of PSS across the lifespan is linked to higher AD risk (18% higher risk with each additional PSS)—***but only among persons born 1926-1930, a cohort effect or survival bias?***

Conclusions

- PSS are linked to faster cognitive decline and higher risk for AD in late life
- UPDB provides an innovative way to assess PSS (*singly, multiply, and in various contexts*) without recall bias
- PSS effects do not appear to be universal, but are somewhat complex, suggesting more vulnerable sub-populations for whom risk may be greater
- PSS effects are likely moderated by many factors linked to context and coping (e.g. *remarriage, SES, social supports, mental health, personality, lifestyle behaviors*)

Acknowledgements

- National Institute on Aging AG-022095, AG-031272, and AG-011380.
- Partial support for all data sets within the Utah Population Database (UPDB) was provided by the University of Utah Huntsman Cancer Institute and the Huntsman Cancer
- Institute Cancer Center Support grant, P30 CA42014 from National Cancer Institute.

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Thank You!

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