Gene-Environment Interplay in Adult Depression Symptomatology:
Initial Findings from iGEMS

The Consortium on Interplay of Genes and Environment across Multiple Studies

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PURPOSE OF iGEMS

Aim #1: Harmonize social phenotypes and aging outcomes to enable combined analysis.

Aim #2: Test hypotheses about the impact of early life experiences and mid- and late-life social contexts on late-life functioning using co-twin control methods.

Aim #3: Test whether social, intellectual, and physical engagement reflect active gene-environment (GE) correlational processes.

Aim #4: Test whether genetic influences on functioning in one area can be moderated by environmental factors that emerge from changes in other areas of functioning (i.e., GE interaction).

Aim #5: Identify specific biological and genetic factors (biomarkers, candidate genes) that may mediate observed genetic and environmental processes.

Studies included in iGEMS

DANISH TWIN REGISTRY
UNIVERSITY OF SOUTHERN DENMARK

MADT
Middle-Age Danish Twin study

LSADT
Longitudinal Study of Aging Danish Twins

MTSADA
Minnesota Twin Study of Adult Development and Aging

Swedish Twin Registry

TOSS
Twin Offspring Study in Sweden

SATSA
The Swedish Adoption/Twin Study of Aging

Gender
Health among Men and Women in Aging

OCTO Twin
Origins of Variance in the Old-Old

HARMONIZE PHENOTYPES

We established work groups to develop a common format for administrative files for each study and to identify phenotypes where there was overlapping item content. For specified phenotypes, in order to establish a common metric across different items and different response formats, we collected data from a new harmonization sample, who were administered each questionnaire measuring the target phenotype. For example, the Swedish and Minnesota studies measured depression with the 20-item Center for Epidemiologic Studies Depression (CES-D) scale, where items had 4 response options, whereas the Danish studies measured depression with the 17-item CAMDEX depression inventory, where most items had 3 response options.

HARMONIZATION SAMPLE: 635 respondents obtained through Amazon Mechanical Turk, USC Healthy Minds subject pool, and the Alzheimer's Association TrialMatch, with similar numbers of men and women, and of individuals younger than 60 and aged 60 and older.
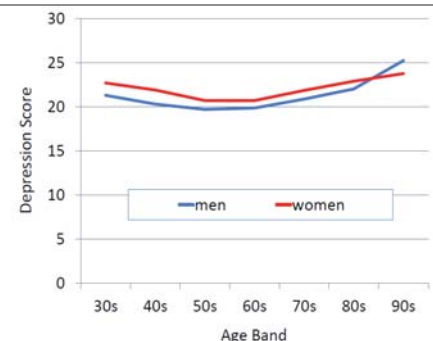
HARMONIZATION INSTRUMENT: Respondents were given a link to a Qualtrix survey of which there were 2 versions. one with CES-D first, the other with CAMDEX first. Between the two depression scales were three vocabulary items that should be common knowledge. Several demographic questions were included at the beginning or end of the survey. Those who did not answer the vocabulary items correctly were excluded.

HARMONIZATION ANALYSES: IRT random equivalence equating with WINSTEPS was applied to establish a measurement crosswalk. Person proficiency estimates were obtained from separate Rasch analyses on each test. Rescaling parameters were calculated by adjusting the difference between the means of the person estimates for the two scales and rescaling by the ratio of the person standard deviations. At this point, the two scales reported the same mean and standard deviation for person proficiency and a crosswalk between the raw scores of CES-D and CAMDEX was created. We found age differences on mean scores but not on the cross-walk. The resulting conversation table was then applied to the twin data to conduct a combined analysis of depression.

CONDUCT COMBINED DATA ANALYSIS

iGEMS SAMPLE: 14,190 with depression score (6229 men and 7961 women). The table shows number of pairs with complete depression data.

DESCRIPTIVE STATISTICS USING HARMONIZED DEPRESSION SCORE:
Mean scores by age and sex show the characteristic U-shaped pattern by age, greater depression among women than men, and a cross-over in the oldest years. Variance was greater in the two older age groups than in younger decades. 16% scored over 25 on harmonized depression, suggesting clinically significant symptoms.

Number of Pairs	under 50	50s	60s	70s	80 and up
MZ	504	419	492	408	190
DZ	571	453	488	581	235
OS	100	296	246	197	16

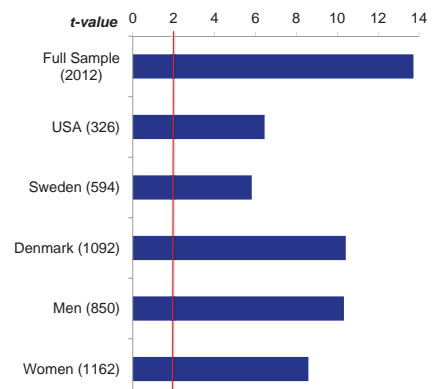## TWIN ANALYSES USING HARMONIZED DEPRESSION SCORE:

Shown below are intrapair correlations and results from an Mx 5-age group analysis of all twins, with DZ and OS combined, adjusted for age, sex, and country. Nonshared variance (Ve) significantly differed across age groups, and suggested increases into old-old age.

Absolute Variance Components
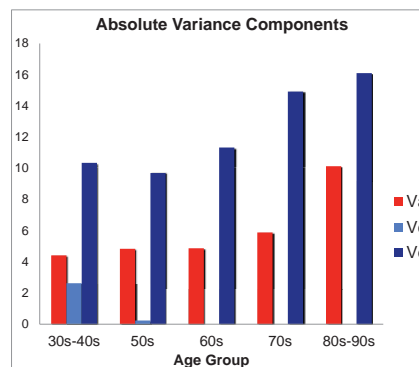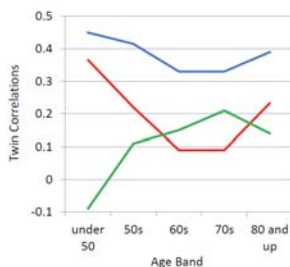
Age Group	A	C	E	Va	Vc	Ve	Total Var
30s-40s	0.25	0.15	0.60	4.41	2.63	10.35	17.39
50s	0.33	0.02	0.66	4.83	0.24	9.69	14.76
60s	0.30	0.00	0.70	4.87	0.00	11.33	16.20
70s	0.28	0.00	0.72	5.88	0.00	14.92	20.80
80s-90s	0.39	0.00	0.61	10.13	0.00	16.10	26.23

TEST OF GXE:

An initial test of GxE using MZ pairs (Fisher, 1925) was conducted, testing for heterogeneity of within-pair differences in depression scores, with scores adjusted for sex, age, age^2, and country, and rank-normalized. The tests were significant for the full MZ sample, within country, and within sex, suggesting possible GxE (p=9.64E-09 to 4.62E-41).