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"Moving from the Means to the Standard Deviations in Symptom Management Research"

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My Program of Research

- **Determine the deleterious effects of unrelieved pain**
- **Develop and test interventions to improve pain management**
  - Cancer pain associated with bone metastasis
  - Gender differences
  - Neuropathic pain following breast cancer surgery
  - CTX-induced neuropathy
- **Evaluate the inter-relationships among multiple symptoms and their impact on patient outcomes**

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Multiple Symptoms

- **Patients with cancer**
- **Family caregivers of patients with cancer**
- **Changes in symptoms over time**
  - Fatigue
  - Sleep disturbance
  - Pain
  - Anxiety
  - Depression
  - Attentional fatigue
- **Symptom clusters**
- **Inter-individual differences**

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Issue of Variability

- **Variability in research**
  - Attempt to reduce variability
    - Study design
    - Inclusion and exclusion criteria
- **Variability in clinical practice**
  - Rule rather than the exception
  - Large inter-individual differences are seen in patients' responses to treatments
    - 30% rule in pain management
- **Need to understand inter-individual variability**
  - Identify patients at higher risk for more severe symptoms and/or poorer outcomes
  - Determine the optimal treatment regimens for individual patients

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Purposes of This Presentation

- **Describe an approach to evaluate for inter-individual differences in initial levels of a symptom and the trajectories of that symptom**
  - Hierarchical linear modeling (HLM)
- **Describe an approach to identify distinct subgroups of patients with distinct symptom experiences**
  - Growth mixture modeling
- **Describe how to integrate molecular markers into symptom management research**

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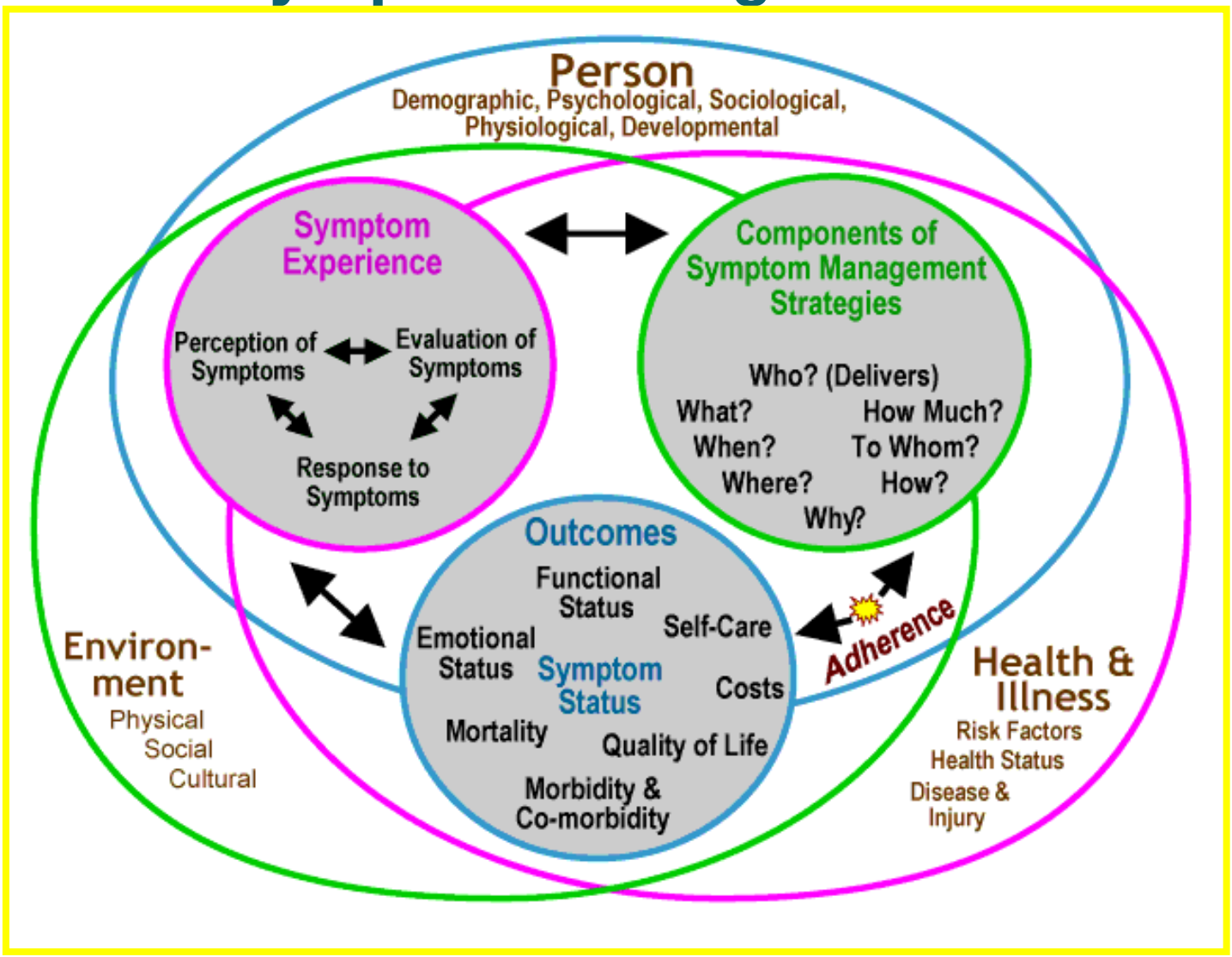
UCSF Theory of Symptom Management



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Humphreys, et al. 2008. A middle range theory of symptom management. In Smith & Liehr : *Middle range theory for nursing*; 145-158.

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Background

- **Sleep disturbance is a common problem in oncology patients**
  - Occurs in 30% to 88% of patients
  - Adversely effects their mood and quality of life (QOL)
- **Limited information exists on the trajectories of sleep disturbance**
- **Limited information exists on predictors of inter-individual variability in sleep disturbance**

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Breast Symptoms Study

- **Descriptive, longitudinal study**
- **Cancer centers in the San Francisco Bay area**
- **Inclusion criteria**
  - Over 18 years of age
  - Able to read, write, and understand English
  - Diagnosed with cancer of one breast
  - Scheduled to undergo surgery for breast cancer
- **Exclusion criteria**
  - Metastatic disease
  - Bilateral breast cancer
  - Undergoing a bilateral mastectomy (including prophylactic mastectomy)

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Study Procedures

- **Patients (n=398) were enrolled prior to surgery**
- **Patients were followed monthly for 6 months**
- **Main aims**
  - Evaluate for neuropathic pain
  - Evaluate for lymphedema

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General Sleep Disturbance Scale (GSDS)

- **Evaluated overall level of sleep disturbance in the past week (Lee, 1992)**
- **Total GSDS score ranges from 0 to 147**
  - Score of ≥43 indicates a clinically meaningful level of sleep disturbance
- **Seven subscales (i.e., quality of sleep, quantity of sleep, sleep onset latency, mid-sleep awakenings, early awakenings, medications for sleep, excessive daytime sleepiness)**
  - Scores can range from 0 to 7
  - Estimation of the number of days a patient experiences a significant problem
  - Scores of ≥3 indicate a clinically meaningful score

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Additional Questionnaires

- Demographic questionnaire
- Karnofsky Performance Status score
- Self-Administered Comorbidity Questionnaire (SCQ; 0 to 39)
- Pain and hot flash assessment
- State-Trait Anxiety Inventories (STAI-S, STAI-T; 20 to 80)
- Center for Epidemiological Studies – Depression Scale (CES-D; 0 to 60)
- Lee Fatigue Scale (LFS; 0 to 10)
- Attentional Function Index (AFI; 0 to 10)
- Multidimensional Quality of Life Scale – Patient Version (MQOLS-PV; 0 to 10)

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Demographic Characteristics of the Patients (n=398) Prior to Surgery

Characteristic	Mean (SD)
Age (years)	54.9 (11.6)
Education (years)	15.7 (2.7)
Lives alone	23.9%
Married (%)	41.5%
Non-white	35.4%
Employed	47.5%

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Clinical Characteristics of the Patients Prior to Surgery

Characteristic	Mean (SD)
KPS score	93.2 (10.3)
SCQ score	4.3 (2.8)
Body mass index (kg/m^2)	26.8 (6.2)
Gone through menopause	62.3%
Experiencing hot flashes	31.9%
Stage of disease	
0	18.3%
I	37.9%
IIA, IIB	35.4%
IIIA, IIIB, IIIC, IV	8.3%

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Treatment Characteristics

Characteristic	% (n)
Neoadjuvant chemotherapy received	19.8 (79)
Type of surgery	
Breast conservation	79.9 (318)
Mastectomy	20.1 (80)
Underwent reconstruction to breast at the time of surgery	21.6 (86)
Underwent sentinel node biopsy	82.4 (328)
Underwent axillary lymph node dissection	37.4 (149)

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Data Analysis

- **Descriptive statistics and frequency distributions were calculated**
- **Mean score for total sleep disturbance (i.e., GSDS total score) was calculated for each assessment**
  - 7 assessments
- **Rather than ANOVA - Hierarchical linear modeling (HLM) was used to evaluate for changes in sleep disturbance over time**
  - Based on regression analysis
  - Full maximum likelihood estimations
  - Software developed by Raudenbush and colleagues

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HLM Analysis

- **HLM analysis was done in two stages**
- **Stage 1 – examined intra-individual variability in GSDS scores over time**
  - Three level one models were tested
  - Identified the change parameters that best described individual changes in total GSDS scores
- **Stage 2 – examined inter-individual differences in the trajectories of GSDS scores (i.e., intercept, linear and quadratic slopes) as a function of proposed predictors at Level 2**
  - Predictors were based on a review of the literature

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HLM of GSDS Scores

- **Test the fit of the model**
  - Linear
  - Quadratic
  - Cubic
- **Test for significant inter-individual differences in intercept and slope parameters**
- **Exploratory analyses were done to evaluate a number of variables as predictors of inter-individual differences in the intercept and slope parameters**
  - t-value >2.0 was required for additional model testing
- **Predictors were based on a review of the literature**

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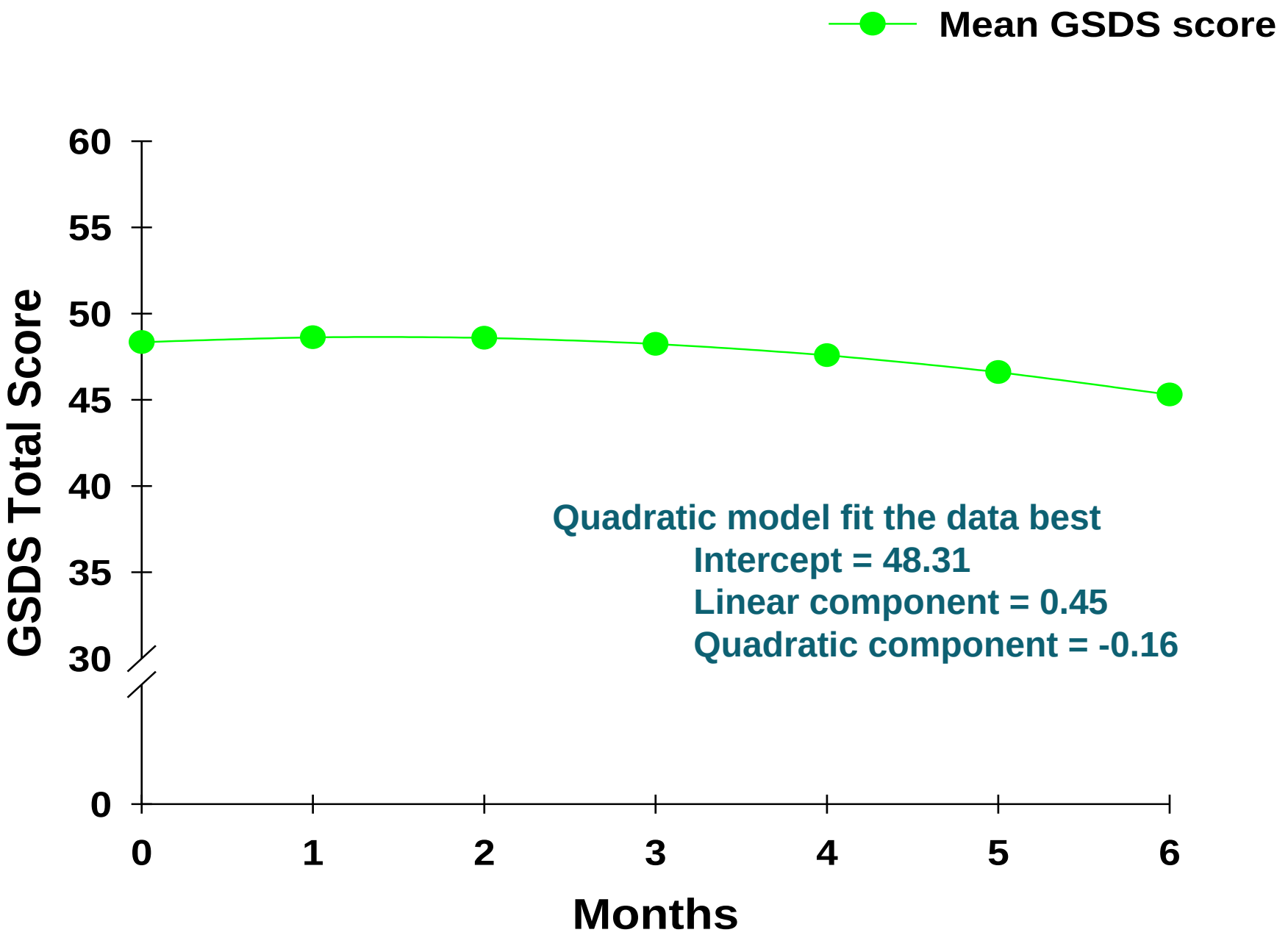
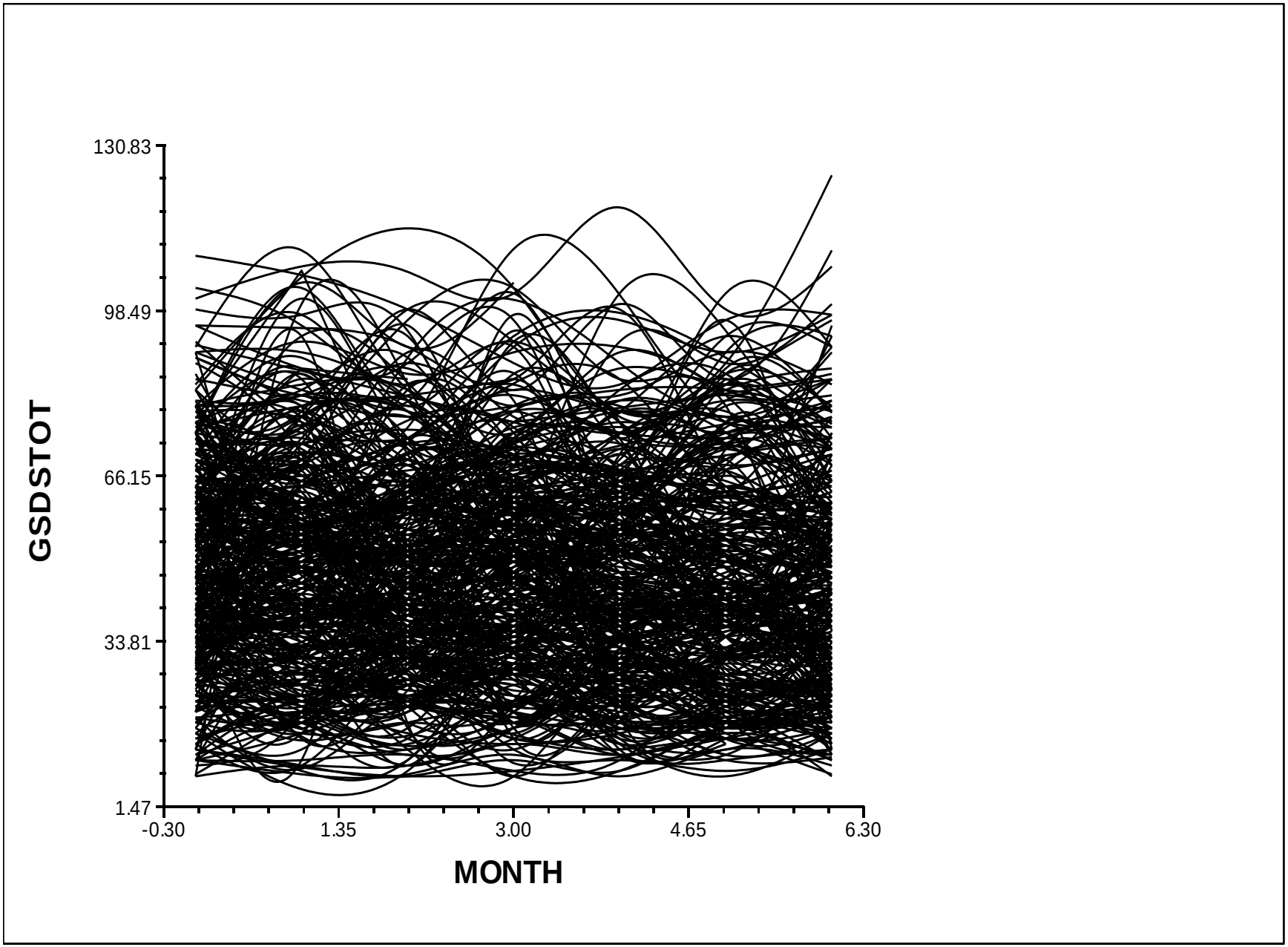
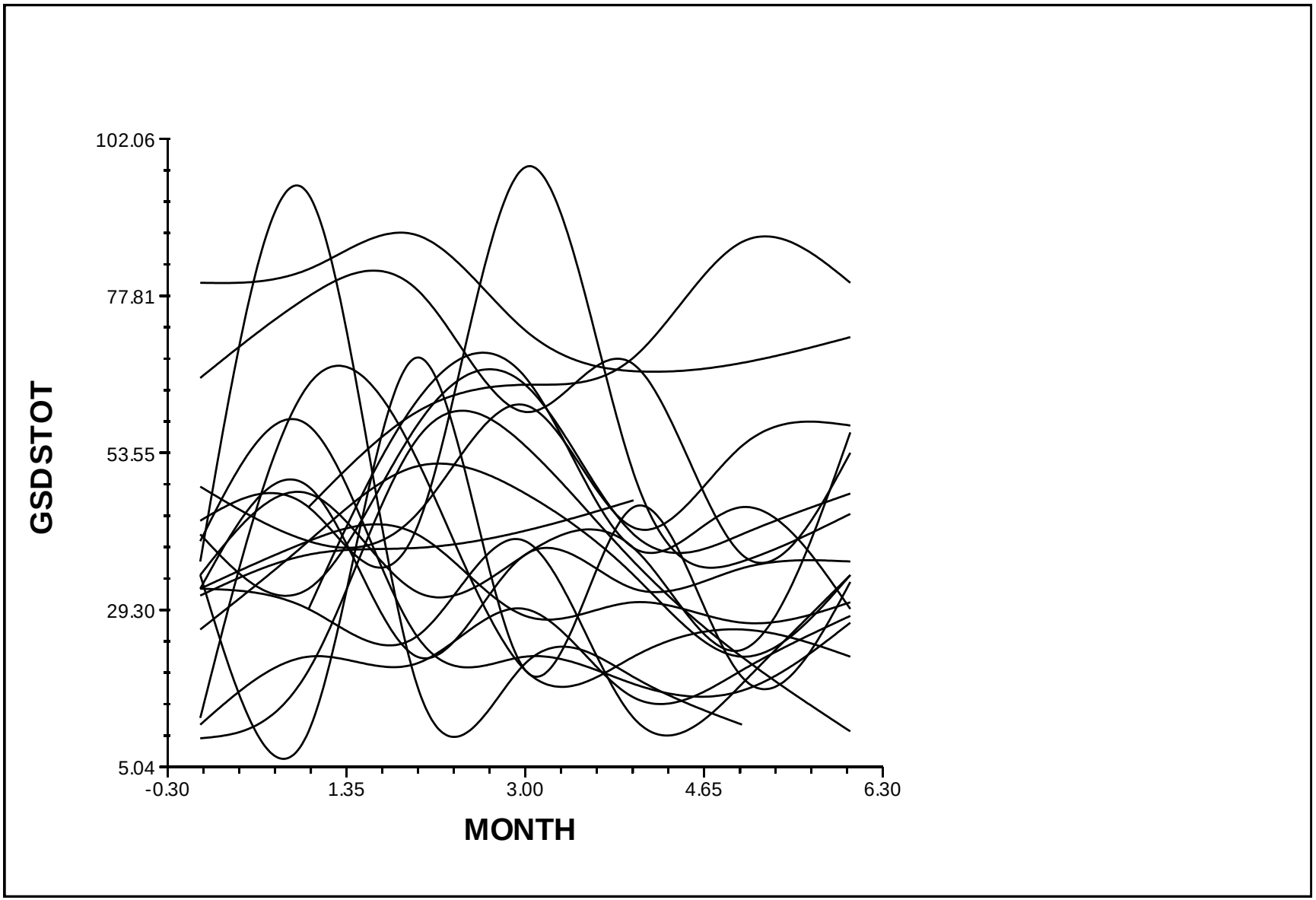

Mean GSDS score
GSDS Total Score
60
55
50
45
40
35
30
0
0
1
2
3
4
5
6
Months
Quadratic model fit the data best
Intercept = 48.31
Linear component = 0.45
Quadratic component = -0.16


130.83
98.49
66.15
33.81
1.47
GSDSTOT
-0.30
1.35
3.00
4.65
6.30
MONTH


102.06
77.81
53.55
29.30
5.04
GSDSTOT
-0.30
1.35
3.00
4.65
6.30
MONTH

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Exploratory Analyses

Potential Predictor	Intercept	Linear Coefficient	Quadratic Coefficient
Age			
White			
Lives alone			
Partnered			
Education		■	■
Employment status			

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■ - From exploratory analysis had t-value > 2.0

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Exploratory Analyses

Potential Predictor	Intercept	Linear Coefficient	Quadratic Coefficient
Body mass index			
SCQ score	■		
KPS score	■		
Stage of disease			
Neoadjuvant CTX	■		
Type of surgery			
SLNB			
ALND			
Reconstruction			
Menopausal status			

■ - From exploratory analysis had t-value > 2.0

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Exploratory Analyses

Potential Predictor	Intercept	Linear Coefficient	Quadratic Coefficient
Body mass index			
SCQ score	■		
KPS score	■		
Stage of disease			
Neoadjuvant CTX	■		
Type of surgery			
SLNB			
ALND			
Reconstruction			
Menopausal status			

■ - From exploratory analysis had t-value > 2.0

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Exploratory Analyses

Potential Predictor	Intercept	Linear Coefficient	Quadratic Coefficient
CES-D score	■	■	■
Trait anxiety	■		
State anxiety		■	■
Attentional fatigue	■		
Fatigue score	■	■	
Energy score			
Hot flashes (Y/N)	■		
Severity of hot flashes			
Distress of hot flashes			
Pain (Y/N)			

■ - From exploratory analysis had t-value > 2.0

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Predictors in the Final Quadratic Model

Intercept	Linear Coefficient	Quadratic Coefficient
KPS score	Education	Education
SCQ score	Adjuvant CTX	Adjuvant CTX
CES-D score	CES-D score	CES-D score
Physical fatigue		
Hot flash severity		
Attentional fatigue		

Van Onselen et al. J Pain Symptom Manage 45(2):244-260, 2013

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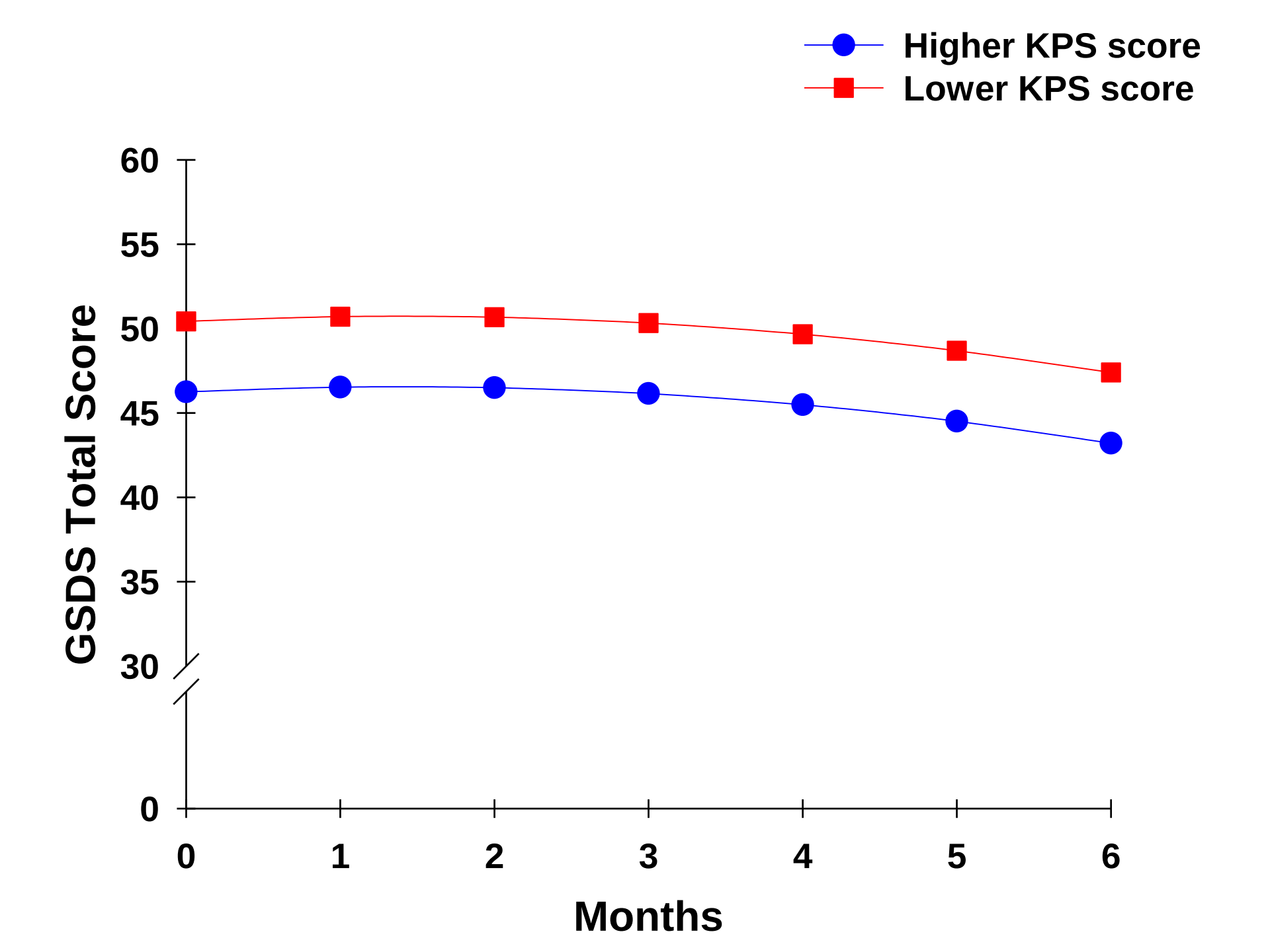
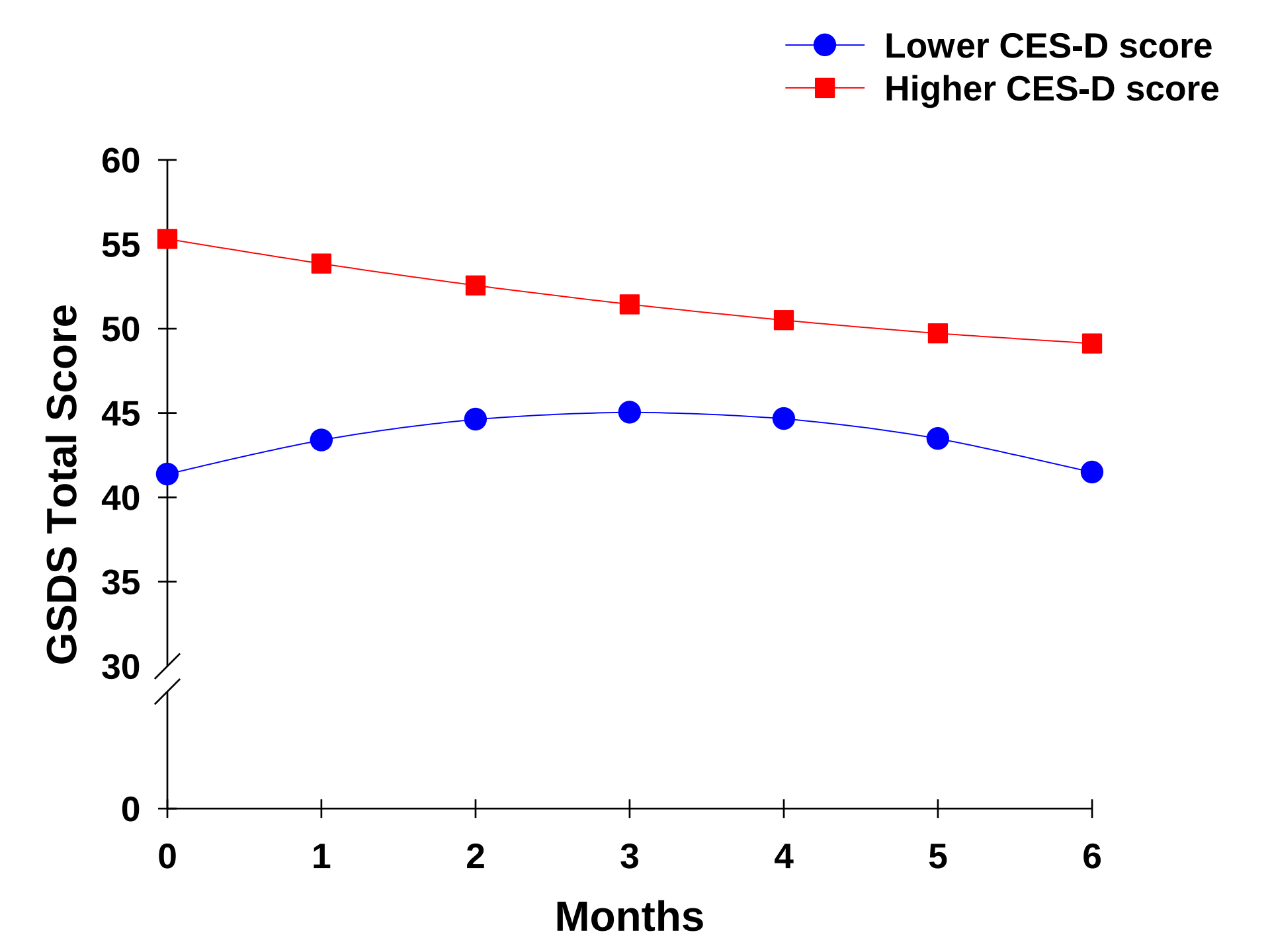

Higher KPS score
Lower KPS score
GSDS Total Score
60
55
50
45
40
35
30
0
0
1
2
3
4
5
6
Months


Lower CES-D score
Higher CES-D score
GSDS Total Score
60
55
50
45
40
35
30
0
0
1
2
3
4
5
6
Months

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Data Analysis Procedures

- **Identification of latent classes**
  - Unconditional Growth Mixture Modeling
    - Robust maximum likelihood estimation
- **Evaluate for differences in demographic and clinical characteristics and symptom severity scores among the GMM latent classes prior to surgery (i.e., enrollment)**
  - ANOVA
  - Chi-square analyses
  - Post hoc contrasts – Bonferroni correction

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Growth Mixture Modeling (GMM)

- Method for modeling (understanding) differences in change trajectories
- This method allows us to "discover" groups (classes) of individuals with different change profiles
- This new categorical variable can be used to understand differences between/among the latent classes on a variety of characteristics

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GMM ANALYSIS

- **GMM analysis was done using Mplus version 5.1**
- **GMM analysis with robust maximum likelihood estimation was used to identify the latent classes (i.e., subgroups of patients) with distinct sleep disturbance trajectories over the 6 months of the study**
  - Intercepts and linear and quadratic slopes were estimated for each latent class
- **Model fit was assessed by**
  - Lowest Bayesian Information Criteria (BIC)
  - Testing the K versus K-1 class models
  - Visual inspection of the plots of observed versus predicted values

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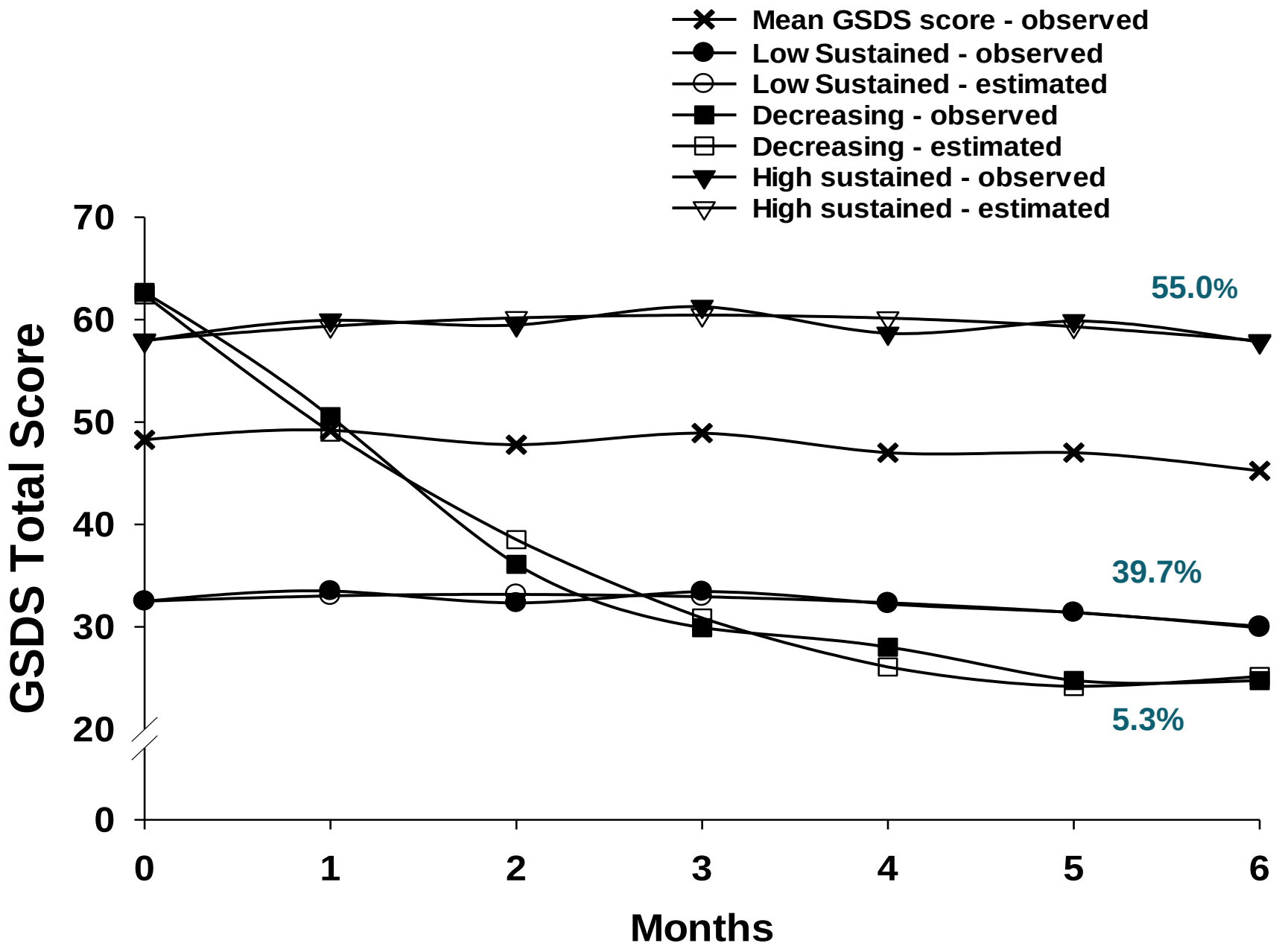
Mean GSDS score - observed
Low Sustained - observed
Low Sustained - estimated
Decreasing - observed
Decreasing - estimated
High sustained - observed
High sustained - estimated
55.0%
39.7%
5.3%
GSDS Total Score
70
60
50
40
30
20
0
0
1
2
3
4
5
6
Months

Fit Indices

GMM Solution	LL	AIC	BIC	Entropy	BLRT (df)	VLMR (df)
1-Class[a]	-4522.03	9076.05	9139.84	N/A	N/A	N/A
2-Class	-4488.48	9018.95	9102.67	0.56	67.10** (5)	67.10 (5)
3-Class[b]	**-4473.49**	**8998.99**	**9102.63**	**0.71**	**29.97[†] (5)**	**29.97** (5)**
4-Class	-4471.97	9007.93	9135.50	0.56	5.63[ns] (5)	5.63[ns] (5)

[ns] = not significant; * p ≥ .05; ** p ≥ .01; *** p ≥ .001; **** p ≥ .0001; [†] p < .00005

[a] Latent growth curve model with linear and quadratic components; Chi^2= 43.72, 19 df, p < .001, CFI = .99, RMSEA = .057. Note that entropy, BLRT, & VLMR are not relevant for the latent growth model.

[b] 3-class model was selected.

Van Onselen et al. Supportive Care Cancer 20:2611-2619, 2012

Demographic Differences

Characteristic	Low Sustained GSDS (39.7%) Mean (SD)	Decreasing GSDS (5.3%) Mean (SD)	High Sustained GSDS (55.0%) Mean (SD)	Statistics
Age (years)	57.7 (12.1)	53.8 (9.8)	53.0 (10.9)	F(2,395)=7.95; p=0.0004
Education (years)	15.5 (2.6)	15.5 (2.1)	15.9 (2.7)	F(2,390)=0.98; p=0.38
	n (%)	n (%)	n (%)	
White	102 (65.0)	17 (81.0)	136 (62.4)	χ^2=2.92; p=0.23
Married/partnered	62 (39.5)	11 (52.4)	92 (42.6)	χ^2=1.37; p=0.51
Work for pay	86 (54.4)	10 (47.6)	93 (43.1)	χ^2=4.73; p=0.09
Lives alone	37 (23.7)	8 (38.1)	50 (23.1)	χ^2=2.36; p=0.31

Van Onselen et al. Supportive Care Cancer 20:2611-2619, 2012

Clinical Differences

Characteristic	Low Sustained (39.7%) Mean (SD)	Decreasing (5.3%) Mean (SD)	High Sustained (55.0%) Mean (SD)	Statistics
KPS score	96.5 (6.8)	92.9 (10.1)	90.9 (11.7)	$F(2, 388)=14.20$; $p\leq0.0001$
SCQ score	3.7 (2.4)	3.9 (2.7)	4.8 (3.1)	$F(2, 394)=7.11$; $p=0.001$
Body mass index (kg/m^2)	26.5 (5.8)	24.5 (4.6)	27.2 (6.5)	$F(2, 389)=2.15$; $p=0.12$
	n (%)	n (%)	n (%)	
Gone through menopause	104 (68.0)	14 (66.7)	130 (61.0)	$\chi^2=1.93$; $p=0.38$
Stage of disease				
0	25 (15.8)	8 (38.1)	40 (18.3)	$\chi^2=11.83$; $p=0.07$
I	72 (45.6)	5 (23.8)	74 (33.8)	
IIA, IIB	50 (31.6)	7 (33.3)	84 (38.4)	
IIIA, IIIB, IIIC, IV	11 (7.0)	1 (4.8)	21 (9.6)	

Treatment Differences

Characteristic	Low GSDS Sustained (1) (39.7%)	Decreasing GSDS (2) (5.3%)	High Sustained GSDS (3) (55.0%)	Statistics
Surgical treatment				
Breast-conserving	131 (82.9)	10 (47.6)	177 (80.8)	χ^2=14.63; p=0.001 2>1,3
Mastectomy	27 (17.1)	11 (52.4)	42 (19.2)	
Sentinel node biopsy	138 (87.3)	16 (76.2)	174 (79.5)	χ^2=4.53; p=0.10
Axillary lymph node dissection	52 (32.9)	5 (23.8)	92 (42.2)	χ^2==5.15; p=0.08
Breast reconstruction at the time of surgery	30 (19.1)	11 (52.4)	45 (20.5)	χ^2=12.44; p=0.002 2>1,3
Neoadjuvant chemotherapy	27 (17.1)	4 (19.0)	48 (22.0)	χ^2=1.41; p=0.50
Adjuvant chemotherapy	43 (27.2)	4 (19.0)	86 (39.3)	χ^2=8.05; p<0.02 3>1
Adjuvant radiation therapy	99 (62.7)	8 (38.1)	117 (53.4)	χ^2=6.16; p<0.05

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REVIEWS

- Specific candidate cytokine genes are associated with sleep regulation and sleep disorders
- Cytokine dysregulation is associated with sleep disturbance in humans
- Limited studies
- Our recent Fatigue, Pain, and Sleep study identified an association between one candidate gene (i.e., IL6 rs35610689) and sleep disturbance

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Purposes of the Study

- **In a sample women following breast cancer surgery:**
  - Replicate the association found in our previous study of patients and family caregivers between **IL6** and **sleep disturbance**
  - Identify additional cytokine gene associations in a larger sample of breast cancer patients

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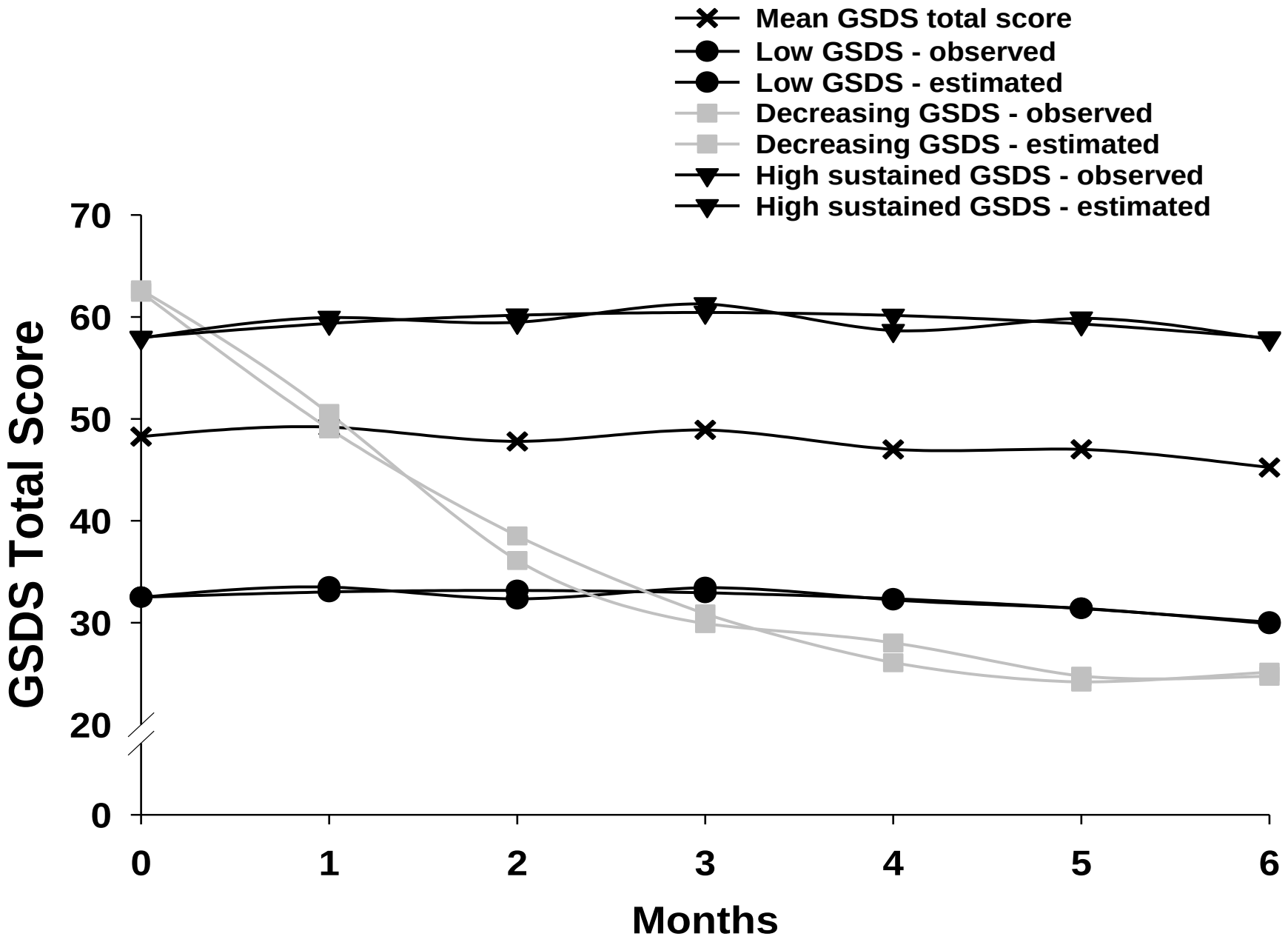
Mean GSDS total score
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Low GSDS - estimated
Decreasing GSDS - observed
Decreasing GSDS - estimated
High sustained GSDS - observed
High sustained GSDS - estimated
GSDS Total Score
70
60
50
40
30
20
0
0
1
2
3
4
5
6
Months

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Genetic Analysis

- **Genomic DNA isolated from banked peripheral blood mononuclear cells (PBMCs)**
- **SNPs selected required to be common (minor allele frequency ≥0.05)**
- **Quality control filtering of SNPs performed**
  - SNPs with call rates <95% or Hardy Weinberg <0.001 were excluded
- **82 SNPs among 15 cytokine genes were included in genetic association analyses**

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Phenotypic Data Analyses

- **Extreme phenotype approach**
  - Low sustained
  - High sustained
- **Differences between the latent classes in various demographic and clinical characteristics were evaluated at enrollment (prior to surgery)**
  - Independent-t tests for continuous variables
  - Mann-Whitney U tests for continuous variables not normally distributed
  - Chi-Square analyses for categorical variables
- **No adjustments were made for missing data**

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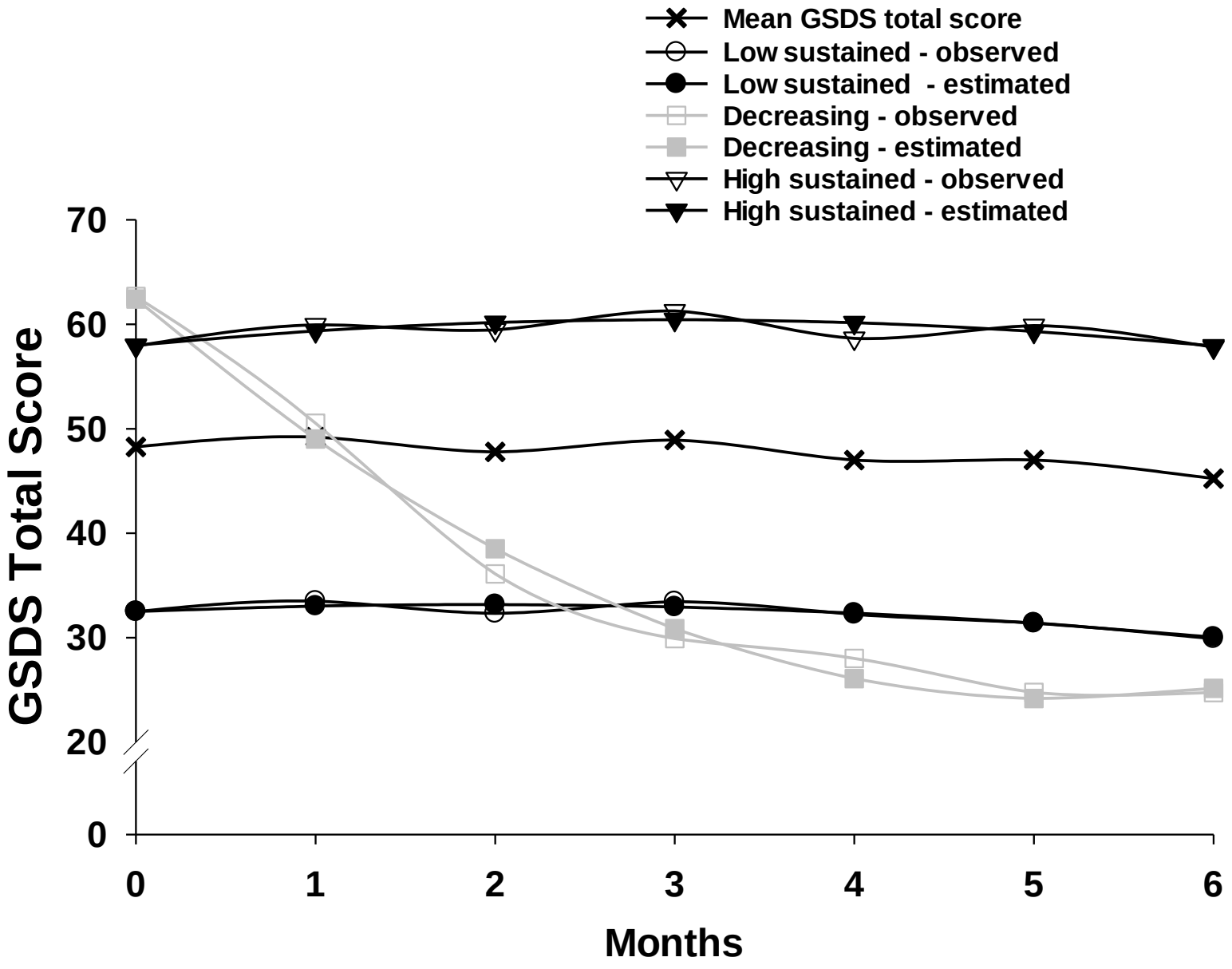
Mean GSDS total score
Low sustained - observed
Low sustained - estimated
Decreasing - observed
Decreasing - estimated
High sustained - observed
High sustained - estimated
GSDS Total Score
70
60
50
40
30
20
0
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2
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6
Months

Differences in Demographics

Characteristic	Low Sustained N=158 (41.9%) Mean (SD)	High Sustained N=219 (58.1%) Mean (SD)	Statistics
Age (years)	57.7 (12.1)	53.0 (10.9)	t=3.93, p<0.0001
KPS Score	96.5 (6.8)	90.9 (11.7)	t=5.76, p<0.0001
SCQ Score	3.7 (2.4)	4.8 (3.1)	t=-3.86, p<0.0001
	N (%)	N(%)	
Working for pay (% yes)	86 (54.4)	93 (43.1)	p=0.04
CTX during first 6 months (% yes)	43 (27.2)	86 (39.3)	p=0.02
SLNB (% yes)	138 (87.3)	174 (79.5)	p=0.053

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Genetic Analyses

- **Allele and genotype frequencies determined by gene counting**
- **Three genetic models assessed (additive, dominant, recessive) for each SNP**
- **Logistic regression analysis was used to evaluate the association between genotype and sleep disturbance group membership**
  - Controlling for significant covariates including genomic estimates of and self-reported race/ethnicity
  - Only those characteristics that were significant in the bivariate analyses were evaluated in the multivariate analyses
- **Backwards stepwise approach**
- **Excluding race/ethnicity only predictors with p-value of <0.05 were retained in final model**

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Covariates Retained in the Final Model

- **Age**
  - For each 5 year increase in age, the odds of belonging to the High Sustained sleep disturbance class decreased by 15% (OR=0.85, CI = 1.101,3.921)
- **KPS score**
  - For each 10 unit increase in KPS score, the odds of belonging to the High Sustained sleep disturbance class decreased by 48% (OR=0.52, CI = 0.362,0.744)
- **SCQ score**
  - Higher SCQ scores were associated with a 1.2 fold increase in the odds of belonging to the High Sustained sleep disturbance class (OR=1.15, CI = 1.025,1.298)
- **Adjuvant CTX**
  - Receipt of adjuvant CTX was associated with a 2.4 fold increase in the odds of belonging to the High Sustained sleep disturbance class (OR=2.43, CI = 1.330,4.427)
- **SLNB**
  - If the patient had a SLNB, the odds of belonging to the High Sustained sleep disturbance class decreased by 69% (OR=0.31, CI = 0.141,0.690)

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Cytokine Gene Associations

- **Three cytokine gene associations were found in this study of patients with breast cancer**
  - NFKB2 rs1056890
  - IL13 rs1800925
  - ILIR2 Haplotype A2 (composed of rs11674595-rs7570441)
- **We found an association with NFKB2 in our previous study of patients and family caregivers**
  - Different SNP in the same gene **(NKFB2 rs7897947)**

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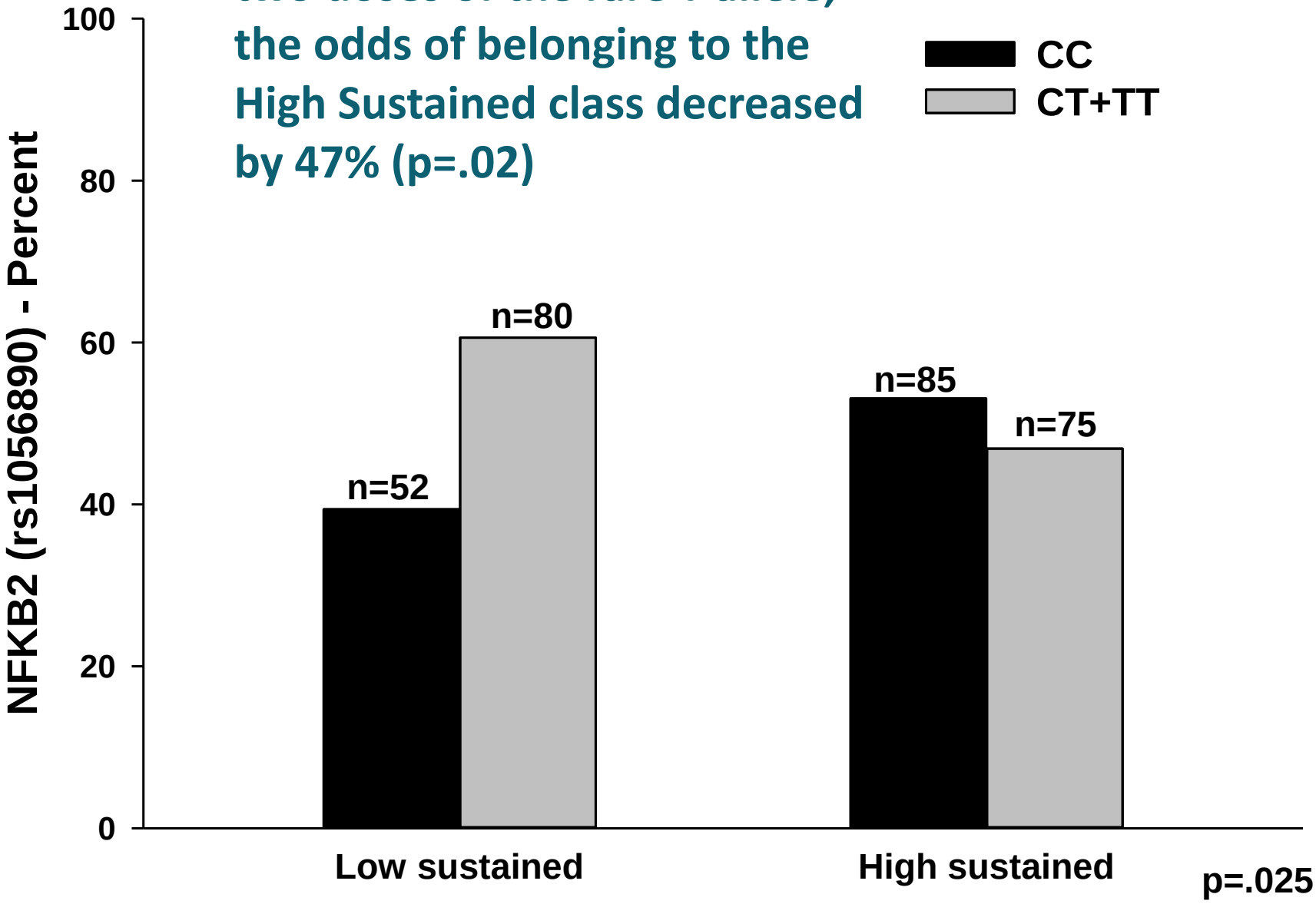
For patients who carried one or two doses of the rare T allele, the odds of belonging to the High Sustained class decreased by 47% (p=.02)



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Nuclear Factor Kappa Beta 2

- **Pro-inflammatory cytokine**
  - Part of the nuclear factor-kappa beta family
  - Made up of transcription factors that regulate various biological processes (e.g., immunity, stress responses, apoptosis, cellular differentiation)
- **Inappropriate activation of NFKB is linked to inflammatory processes (e.g., asthma, lung fibrosis, septic shock)**
- **NFKB2 rs1056890**
  - Located in the 3' untranslated region of the gene in an area that is evolutionarily conserved
  - No known function
  - May be in LD with a functional SNP

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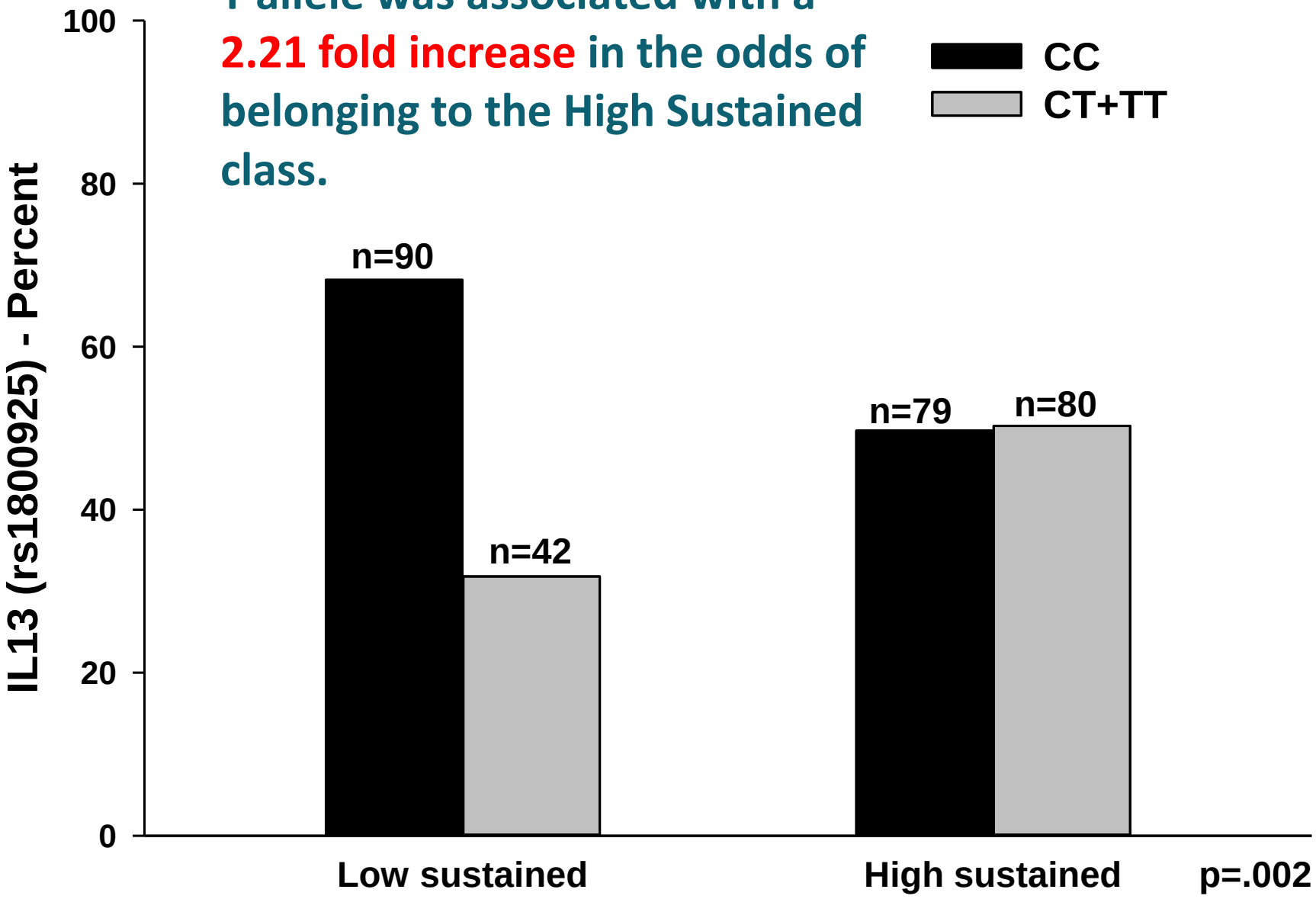
Carrying one or two doses of rare T allele was associated with a 2.21 fold increase in the odds of belonging to the High Sustained class.
CC
CT+TT
IL13 (rs1800925) - Percent
100
80
60
40
20
0
n=90
n=42
n=79
n=80
Low sustained
High sustained
p=.002

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Interleukin 13

- **IL 13 is an anti-inflammatory cytokine**
- **IL13 rs1800925**
  - Located in the promoter region of IL13
  - Occurs in an evolutionarily conserved region of the gene
  - This SNP has no known function
- **Previous studies demonstrated an association between this SNP and psoriasis**
- **IL13 is known to play a role in other inflammatory conditions**

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Interleukin 1 Receptor 2

- **IL1R2 Haplotype A2 is composed of two SNPs (rs11674595-rs7570441)**
  - Each additional dose of the haplotype was associated with a **2.08 fold increase** in odds of belonging to the higher sleep disturbance class
- **IL1R2 is an anti-inflammatory cytokine that blocks inflammatory signaling and inhibits pro-inflammatory IL1 activity by acting as a decoy receptor**
- **The two SNPs in the IL1R2 haplotype are located in introns in regions that are evolutionarily conserved**

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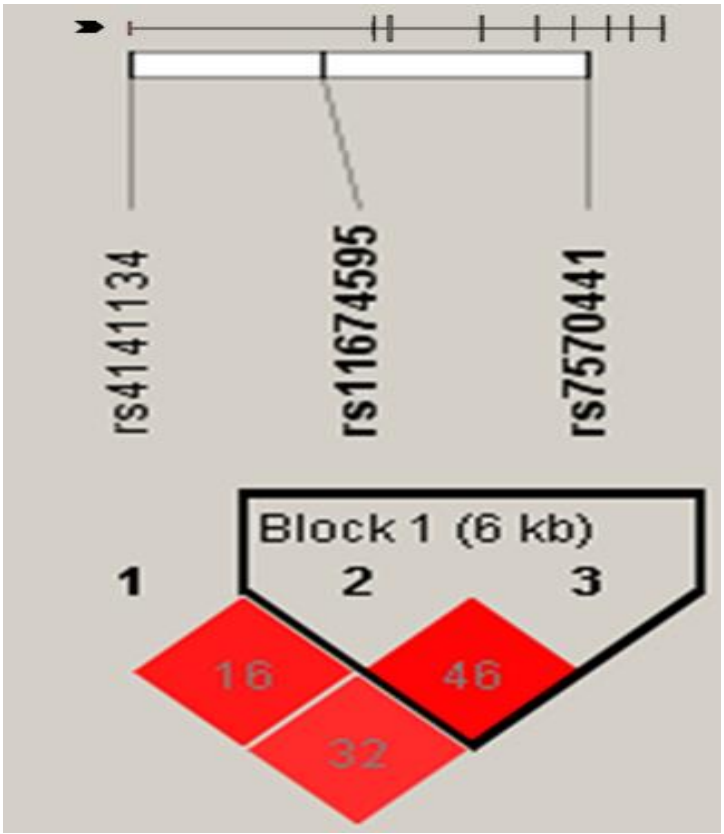

Haplotype	Low Sustained	High Sustained
A1: T-G	157 (59.5%)	183 (57.5%)
A2: T-A	*37 (14.0%)*	*63 (19.7%)*
A3: C-G	1 (<0.0%)	0 (0.0%)
A4: C-A	69 (26.1%)	74 (23.1%)

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Conclusion - Issue of Variability

- **Variability in research**
  - Attempt to reduce variability
    - Study design
    - Inclusion and exclusion criteria
- **Variability in clinical practice**
  - Rule rather than the exception
  - Large inter-individual differences are seen in patients' responses to treatments
    - 30% rule in pain management
- **Need to understand inter-individual variability**
  - Identify patients at higher risk for more severe symptoms and/or poorer outcomes
  - Determine the optimal treatment regimens for individual patients

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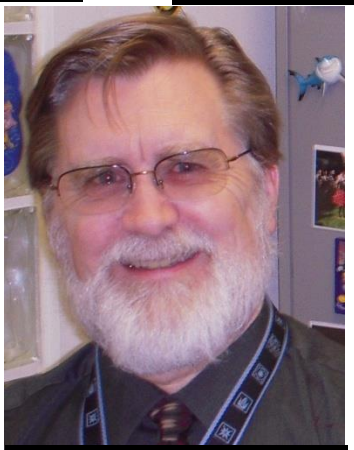
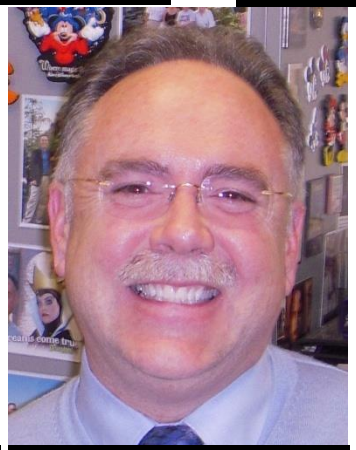

Bruce Cooper


Steve Paul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