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April 30, 2020

The Metabolic Consequences of Poor Sleep

Background

The last three decades have seen persistent declines in self-reported sleep duration and simultaneous increases in the prevalence of obesity and diabetes in the United States. There is a growing body of evidence for associations between sleep disturbances and the development of metabolic disorders. The pathophysiological mechanisms underlying this neuro-endocrine-metabolic connection are still poorly understood but involve overactivation of the sympathetic nervous system, oxidative stress and systemic inflammation, and abnormal hormone levels. Over time, these changes result in insulin resistance and dysfunction within the pancreas, causing problems with insulin secretion and glucose intolerance that eventually progresses to type 2 diabetes. Glucose tolerance is commonly assessed via a two-hour oral glucose tolerance test (OGTT), in which a blood glucose level > 140 mg/dl is abnormal and indicates insulin resistance.

The objective of the present study was to investigate the relationship between poor sleep (in quality or quantity) and glucose intolerance in a population of adolescents and adults in the United States. It was hypothesized that individuals who self-report poor sleep quantity or quality are at higher risk of having an abnormal OGTT result than individuals who self-report experiencing good sleep.

Methods

This retrospective cross-sectional study used data from the 2015-2016 National Health and Nutrition Examination Survey (NHANES). Subjects included in the present study (n = 1681) had the following data available: results of OGTT, completed Sleep Disorders Questionnaire, and diabetes diagnosis status. The exposure was a dichotomized version of results of the self-reported Sleep Disorders Questionnaire, splitting subjects into those reporting Good Sleep (n = 1165) and Poor Sleep (n = 516). The outcome of interest was the OGTT result, both as a binary (Normal/Abnormal) and continuous (in mg/dl) result.

A propensity score matched analysis was conducted to compare OGTT outcomes between similar subjects in the Poor Sleep and Good Sleep groups. The propensity score was modeled on 23 total covariates chosen to represent demographics, general health status, and lifestyle factors. Three matching techniques (1:1 greedy matching on the linear propensity score with and without replacement, and 1:1 caliper matching without replacement), as well as a weighted analysis, were performed to optimize covariate balance between groups. The analysis technique offering the best balance was used to model the effect of group on the binary and continuous OGTT outcomes.

Results

Of 516 subjects reporting Poor Sleep, 132 (26%) had an Abnormal OGTT result > 140 mg/dl, compared to 247 (21%) of subjects reporting Good Sleep. Using this binary outcome, an unadjusted logistic model yielded an estimated odds ratio of 1.23 (95% CI 1.00, 1.63) for subjects reporting Poor Sleep compared to those reporting Good Sleep. The mean OGTT result was 123.4 mg/dl (SD 53.9) among Poor Sleepers and 118.2 mg/dl (SD 49.5) among Good Sleeper. An unadjusted linear regression model yielded an effect estimate of a 5.24 mg/dl (95% CI -0.04, 10.53) higher OGTT result in the Poor Sleep group than the Good Sleep group.

The 1:1 greedy match on the linear propensity score with replacement offered the best balance of covariates between groups, matching all 516 Poor Sleep subjects with 332 Good Sleep subjects. The resulting adjusted analysis based on this match yielded an odds ratio of 0.84 (95% CI 0.64, 1.10) for the binary outcome and an effect estimate of -4.74 mg/dl (95% CI -11.52, 2.03) for the continuous outcome, in the direction of normal/lower OGTT results in the Poor Sleep group than the Good Sleep group.

Conclusions

The results of adjusted analyses following propensity matching techniques indicate that individuals who self-report Poor Sleep quality are not at a higher (or lower) risk of an abnormal OGTT result compared to those who self-report Good Sleep. Additional work is needed to assess the effects of other sleep metrics and to determine if sleep impacts other physiological processes upstream of glucose tolerance outcomes.

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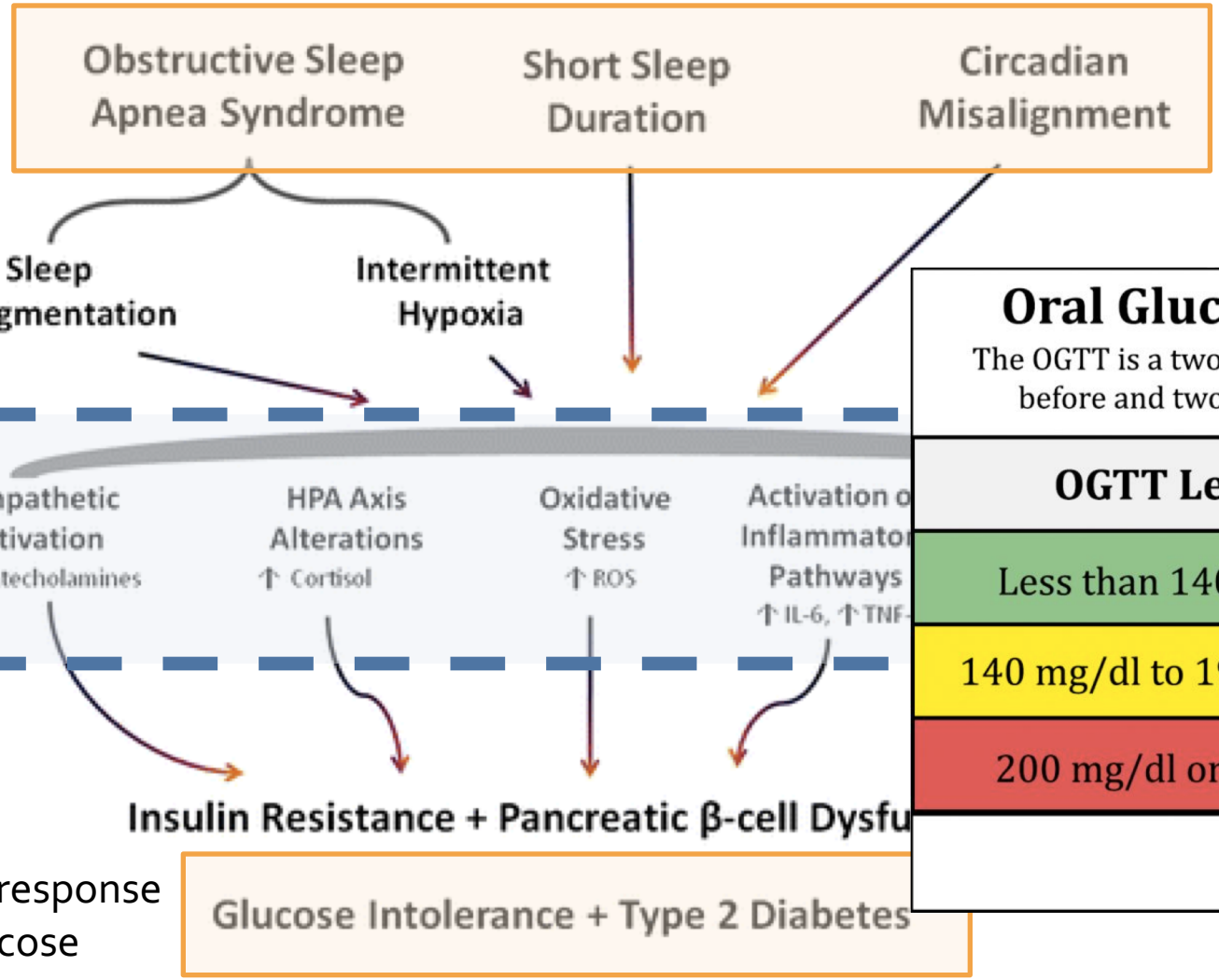
Background

↓ sleep quality and quantity



Oral Glucose Tolerance Test (OGTT)

The OGTT is a two-hour test that checks your blood glucose levels before and two hours after you drink a special sweet drink.

OGTT Level	Result
Less than 140mg/dl	Normal
140 mg/dl to 199 mg/dl	Prediabetes
200 mg/dl or higher	Diabetes

SOUTHWEST UTAH PUBLIC HEALTH DEPARTMENT

Background

Sleep Med Clin. Author manuscript; available in PMC 2009 Jun 16.

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Sleep and Glu

Mary Ip, MD[a,*] and Ba

Briançon-Marjollet *et al. Diabetology & Metabolic Syndrome* (2015) 7:25

DOI 10.1186/s13098-015-0018-3

DIABETOLOGY & METABOLIC SYNDROME

REVIEW

The impact metabolism mechanism

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Diane Godin-Ribuot[1,2†] ar

Psychoneuroendocrinology 1[illegible]0 (2019) 1[illegible]4444

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ELSEVIER

Associations between poor sleep and glucose intolerance in

Ibasaraboh D. Iyegha, Angela Y. Chieh, Bianca M. Bryant, Li Li*

Research Question

Among individuals age 16+ living in the United States in 2015-2016, does poor sleep increase the risk of glucose intolerance as measured by a 2 hour OGTT?

Hypothesis

Individuals who self-report poor sleep quantity or quality are at **higher risk** of having an abnormal OGTT result than individuals who self-report experiencing good sleep.

Data Source: 2015-2016 NHANES

- National Health and Nutrition Examination Survey
  - Funded by CDC, continuous survey program operating since 1999
  - 15 counties selected each year, ~ 5,000 total participants annually

- 2015-2016 was most recent year with data available for necessary variables

- Pulled from:
  - Demographics Data
  - Dietary Data
  - Physical Examination Data
  - Questionnaire Data (including Sleep Questionnaire)
  - Laboratory Data (OGTT results)

Exclusion Criteria for OGTT:
- Younger than 12
- Safety exclusions (e.g. hemophilia)
- Taking diabetes medications
- Self-reported weight loss
- Pregnancy
- Refusal
- Failure to comply with OGTT instructions

Study Population

- N = 1681 with OGTT, sleep disorders questionnaire, and non-missing diabetes diagnosis data available
- 840 male, 841 female
- Ages 16 to >80

- Original exclusion criterion: diagnosis of diabetes
  - n = 23 (diabetes) and n = 28 (borderline diabetes)
  - Likely affects outcome (OGTT) but may be unrelated to sleep
  - Decided to include as covariate instead

National Health and Nutrition Examination Survey

Exposure: Self-Reported Sleep

- From 7-question Sleep Disorders Questionnaire
- Dropped 2 questions: "Usual wake time on work days" and "Usual sleep time on work days"

Question	Answer Options
How much sleep do you usually get at night on workdays?	Numerical (hours) **(< 5 hours)**
In the past 12 months, how often did you snore while sleeping?	Never Rarely (1-2 nights/week) Occasionally (3-4 nights/week) **Frequently (5+ nights/week)**
In the past 12 months, how often did you snort, gasp, or stop breathing while you were asleep?	Never Rarely (1-2 nights/week) Occasionally (3-4 nights/week) **Frequently (5+ nights/week)**
Have you ever told a doctor or other health professional that you have trouble sleeping?	No **Yes**
In the past month, how often did you feel excessively or overly sleepy during the day?	Never Rarely (1x/month) Sometimes (2-4x/month) Often (5-15x/month) **Almost always (16-30x/month)**

Poor Sleep: at least one **RED** response

Good Sleep: no **RED** responses

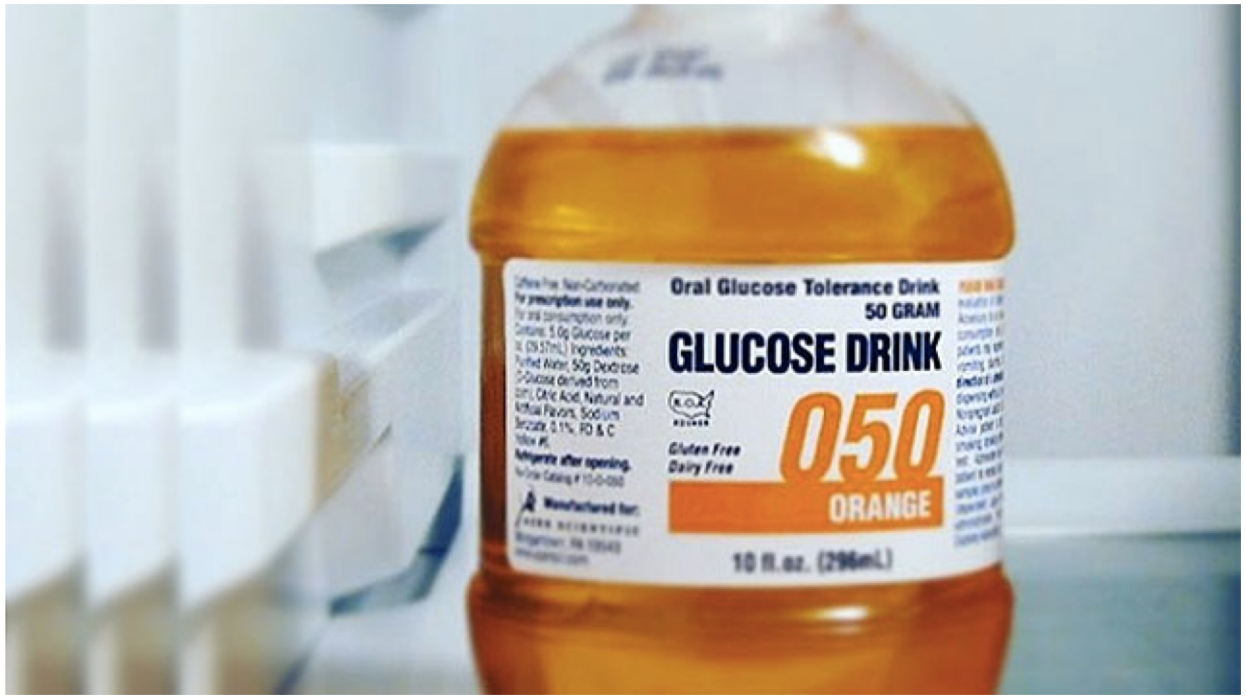
Poor Sleep = 516 (31%)

Good Sleep = 1165 (69%)

Outcome: Oral Glucose Tolerance Test Result

- **Binary:**
  - > 140 mg/dl → Abnormal
  - < 140 mg/dl → Normal

- **Continuous:** in mg/dl
  - Ranged from 35 mg/dl to 532 mg/dl



Covariates and Missingness

- **General demographic variables:**
  - Age, sex, race/ethnicity, insurance status, ratio of family income to poverty level, and general health status
- **Things that could affect sleep quantity/quality:**
  - Living with a partner, presence of young children in the household, feelings of anxiety, feelings of depression, and average # of alcoholic drinks/day
- **Things that could affect OGTT result:**
  - BMI, diabetes diagnosis, family history of diabetes, diet quality, # of meals not home-prepared/week, participating in physically vigorous work, and participating in physically vigorous recreation activities

How Missing Values Were Handled:

- Orange: only a few cases missing (< 10)
  - Used single imputation
- Blue: more substantial missingness (~ 50 – 220)
  - Used single imputation
  - Included imputation indicator variable
- Green: only 2 missing cases, but too important to outcome to impute
  - Dropped cases
- Red: 645 (almost 40%) missing
  - Dropped covariate entirely

Unadjusted Table One

	Good Sleep	Poor Sleep	*p*
n	1165	516	
Female (%)	563 (48.3)	278 (53.9)	0.041
Age (mean (SD))	42.12 (18.58)	48.08 (18.92)	<0.001
Race/Ethnicity (%)			<0.001
Hispanic	390 (33.5)	143 (27.7)	
White	398 (34.2)	231 (44.8)	
Black	206 (17.7)	107 (20.7)	
Other	171 (14.7)	35 (6.8)	
BMI (mean (SD))	28.23 (6.76)	29.23 (6.89)	0.005
Diabetes Diagnosis (%)			0.032
Diabetes Diagnosed	13 (1.1)	10 (1.9)	
No Diabetes Diagnosed	1138 (97.7)	492 (95.3)	
Borderline Diabetes Diagnosed	14 (1.2)	14 (2.7)	
Positive Family History of Diabetes (%)	352 (30.2)	209 (40.5)	<0.001
Lives With a Partner (%)	665 (57.1)	284 (55.0)	0.468
Young Kids in Household (%)	264 (22.7)	90 (17.4)	0.018
Ratio of Fam Income to Poverty (mean (SD))	2.48 (1.57)	2.46 (1.54)	0.846
Insured (%)	911 (78.2)	425 (82.4)	0.059
Diet Quality (%)			<0.001
Excellent	105 (9.0)	36 (7.0)	
Very Good	221 (19.0)	84 (16.3)	

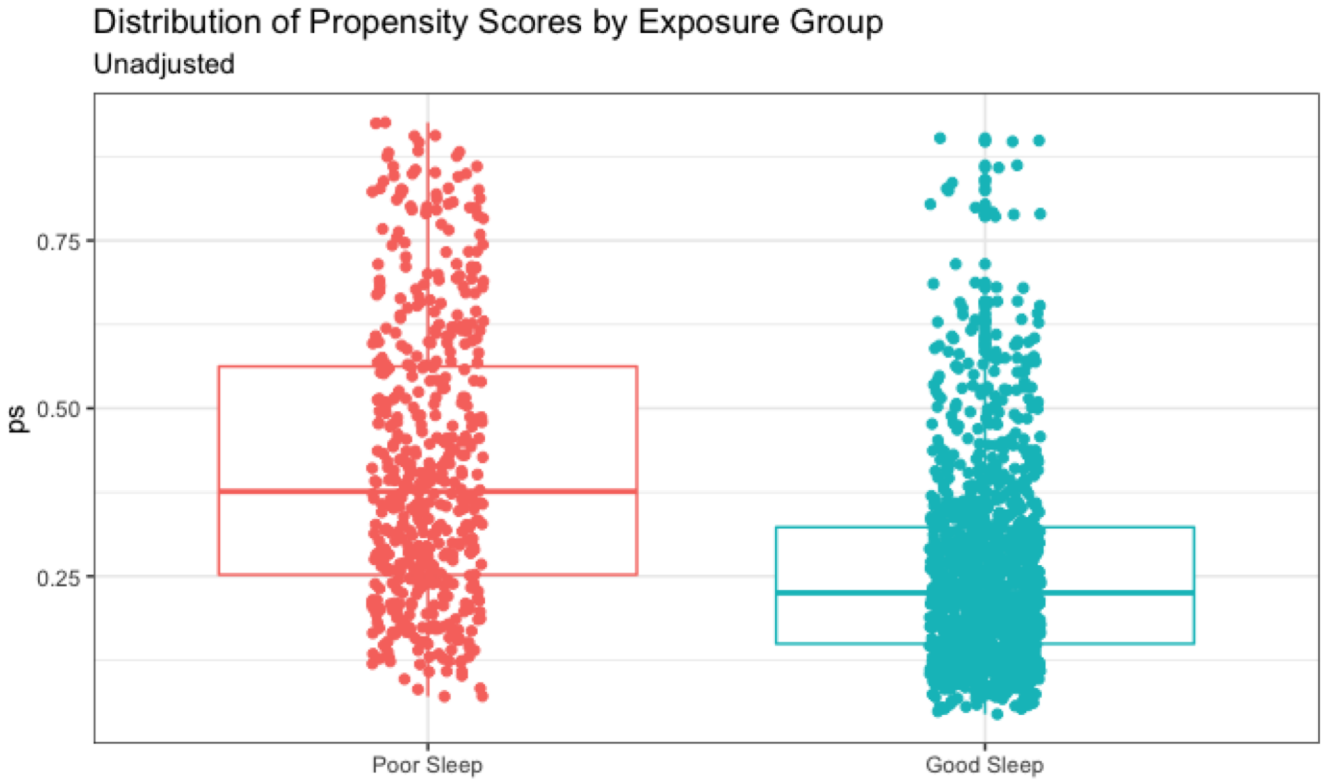
Analysis Plan

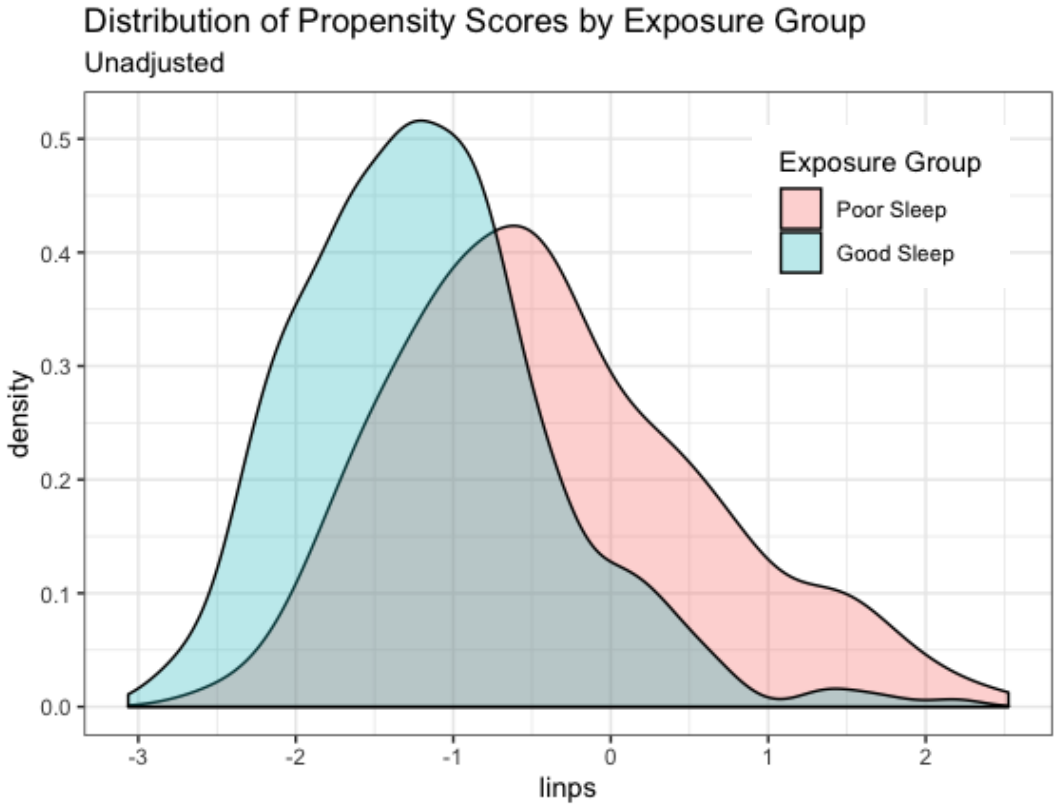
- Propensity Score Model
- Match 1: 1:1 Greedy Matching without Replacement
- Match 2: 1:1 Greedy Matching with Replacement
- Match 3: 1:1 Caliper Matching without Replacement
- Weighting
- Outcome Models

Propensity Score Model

- Total of **23** covariates included in model
- Models probability to be in Poor Sleep group

	Minimum PS	Maximum PS
Poor Sleep	0.071	0.926
Good Sleep	0.045	0.902

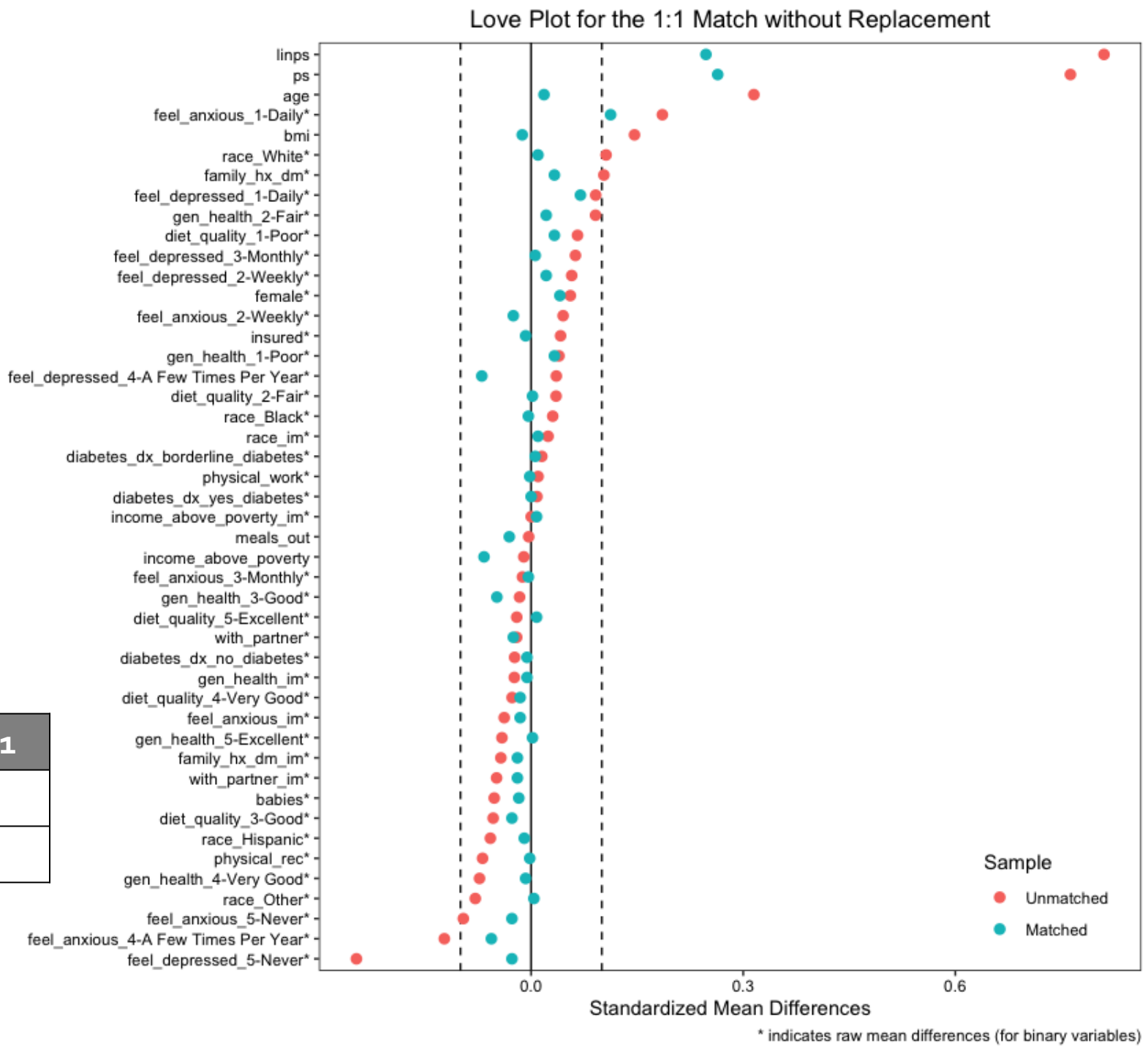




Match 1:
1:1 Greedy Match Without Replacement

- 516 matches:
- 516 Poor Sleep subjects
- 516 Good Sleep subjects (dropped 649 controls)

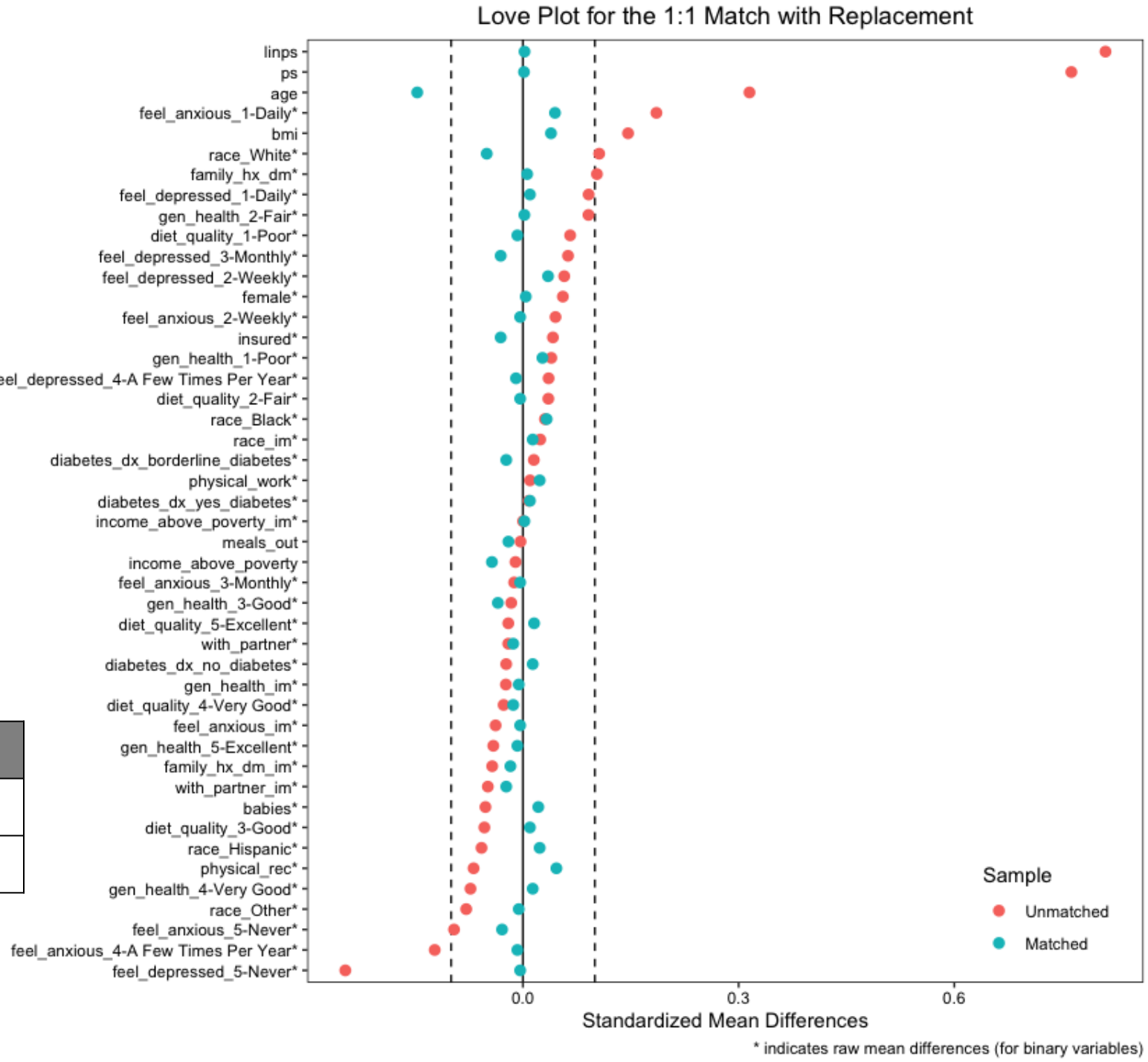
	Unadjusted	Match 1
Rule 1 (< 10%)	81%	25%
Rule 2 (0.8 – 1.25)	1.53	1.70



Match 2:
1:1 Greedy Match With Replacement

- 516 matches:
- 516 Poor Sleep subjects
- 332 Good Sleep subjects (dropped 833 controls)

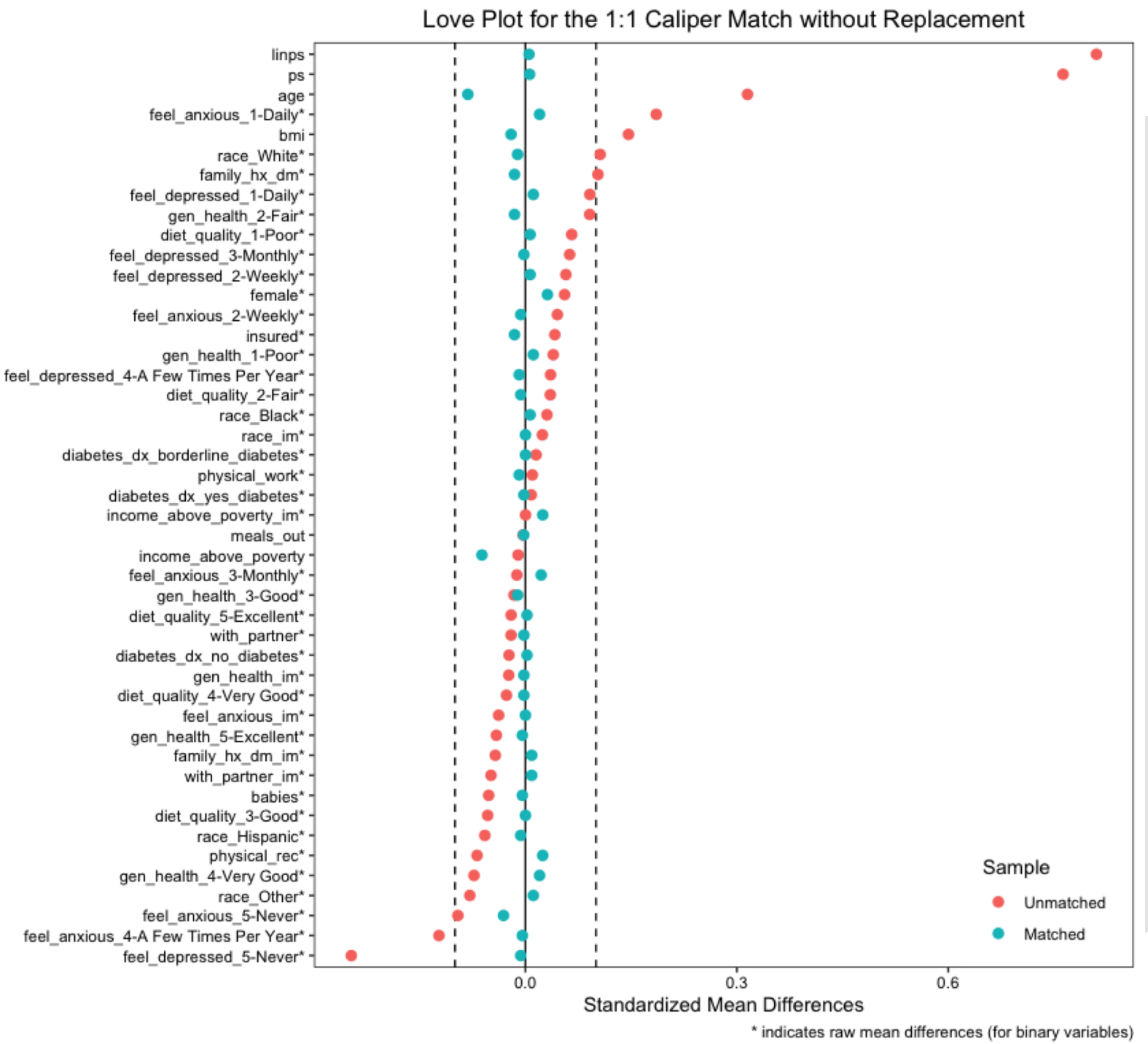
	Unadjusted	Match 1	Match 2
Rule 1	81%	25%	0.2%
Rule 2	1.53	1.70	1.01



Match 3:
1:1 Caliper Match Without Replacement

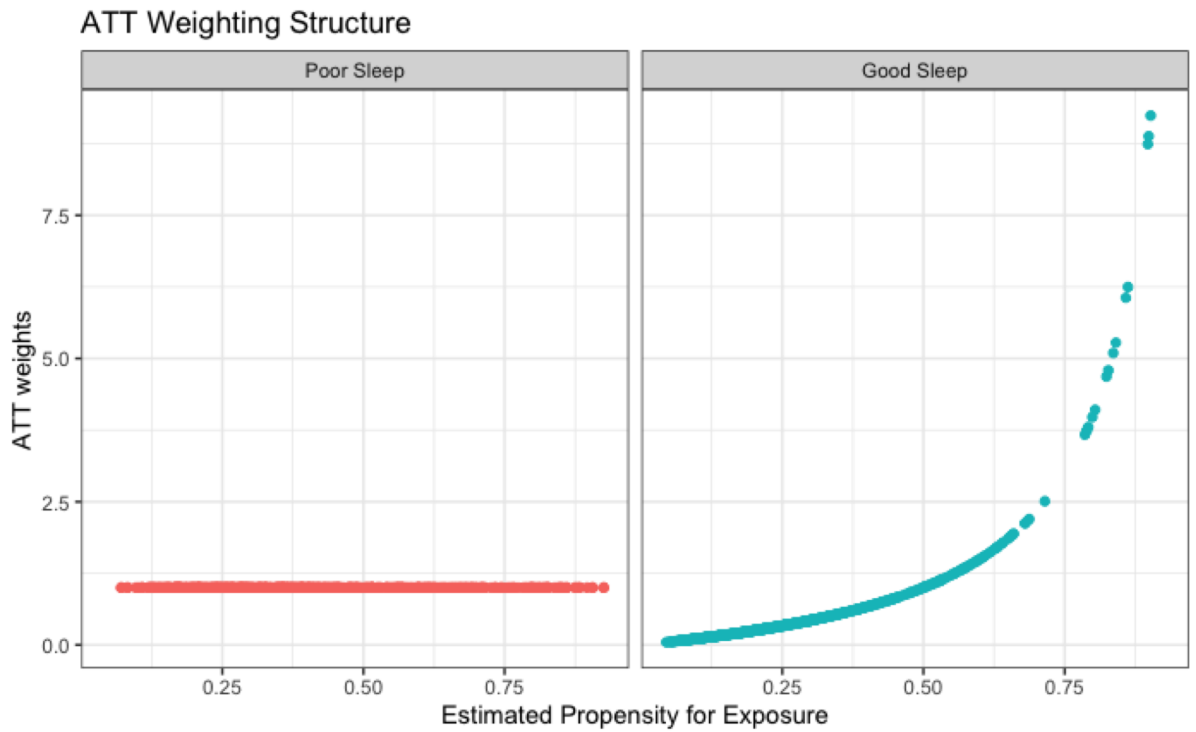
- 449 matches
- 449 Poor Sleep subjects (dropped 67 exposed)
- 449 Good Sleep subjects (dropped 716 controls)
- Caliper = 0.20

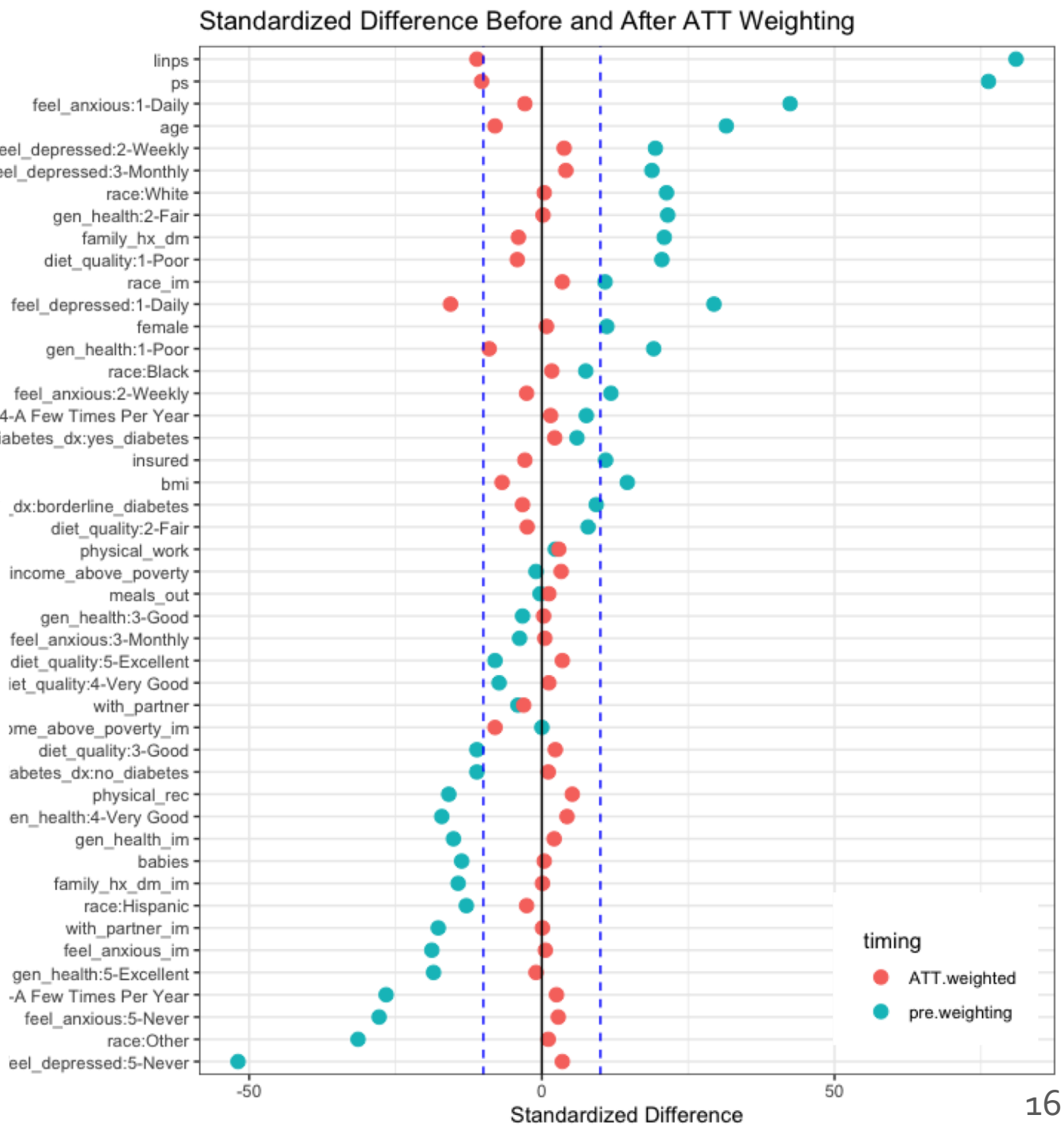
	Match 1	Match 2	Match 3
Rule 1	25%	0.2%	0.5%
Rule 2	1.70	1.01	1.01



ATT Weighting

	Unadjusted	Match 2	Weighting
Rule 1	81%	0.2%	11.1%
Rule 2	1.53	1.01	0.77





Outcomes

Primary Outcome: Binary

Normal vs. Abnormal OGTT (140 mg/dl cutoff)

	OR Estimate	95% CI
Unadjusted	1.23	(1.00, 1.63)
Match 2 (with replacement)	0.84	(0.64, 1.10)

After a 1:1 greedy match with replacement, subjects with Poor Sleep are 0.84 times as likely to have an abnormal OGTT result compared to subjects with Good Sleep.

Secondary Outcome: Continuous

OGTT result in mg/dl

	Estimate	95% CI
Unadjusted	5.24 mg/dl	(-0.04, 10.53)
Match 2 (with replacement)	-4.74 mg/dl	(-11.52, 2.03)

After a 1:1 greedy match with replacement, subjects with Poor Sleep are estimated to have an OGTT result that is 4.74 mg/dl lower than subjects with Good Sleep.

Clinical Conclusions

Among individuals age 16+ living in the United States in 2015-2016, does poor sleep increase the risk of glucose intolerance as measured by a 2 hour OGTT?

Results of analyses suggest poor sleep is <u>not</u> associated with risk of glucose intolerance in this population.

- Acute vs. chronic nature of this problem: need a better way to capture severity and duration of poor sleep characteristics
- Maybe blood glucose levels are an endpoint – could other outcomes (e.g. hormone changes) happen first?
- Relying on self-report data for exposure is never great: high risk of misclassification bias

Potential Stability Analyses & Other Statistical Considerations

- Use different criteria to dichotomize into Poor and Good Sleep groups
  - Maybe throw out "Have you EVER told a doctor you have trouble sleeping?"
  - Different analyses for sleep quantity and sleep quality
- Use different cutoff threshold for Normal vs. Abnormal OGTT
  - E.g. 200 mg/dl, used to distinguish pre-diabetic from diabetic
- Restrict age range of included subjects
  - Different sleep requirements for different age groups
- Handle missing data differently
  - E.g. drop cases, impute with new random seed, impute using different variables
- Additional covariates
  - Smoking status, blood pressure, other comorbidities

Questions

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