Telomere length in individuals with and without major depression and adverse childhood experiences

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Highlights

- Healthy and depressed individuals with and without childhood trauma were tested
- The sample had a good physical health status and no use of antidepressants
- Telomere length (TL) of leukocytes did not differ between groups
- TL was not associated with severity of depression or childhood trauma
- TL was not associated with subjective current stress

Abstract

Major depressive disorder (MDD) and adverse childhood experiences (ACE) are associated with poor physical and mental health in adulthood. One underlying mechanism might be accelerated cellular aging. For example, both conditions, MDD and ACE, have been related to a biological marker of cellular aging, accelerated shortening of telomere length (TL). Since MDD and ACE are confounded in many studies, we aimed with the current study to further disentangle the effects of MDD and ACE on TL using a full-factorial design including four carefully diagnosed groups of healthy participants and MDD patients with and without ACE (total N= 90, all without use of antidepressants). As dependent variable, TL was assessed in leukocytes. We found no group differences based on MDD and ACE exposure in TL. While TL was negatively associated with age and male sex, TL was not associated with any measure of severity of MDD, ACE or current stress. One possible explanation for our null result may be the comparatively good physical health status of our sample. Future research is needed to elucidate the relation of TL, MDD and ACE, taking potential effect modification by medication intake and physical health status into account.

Keywords: telomere length, major depressive disorder, childhood trauma, early life stress, stress

1 Introduction

Major depressive disorder (MDD) is a severe mental disorder with increased risk for premature biological aging and age-related disorders in adults such as cardiovascular and metabolic diseases (Han et al., 2019; Otte et al., 2016). Early life stress, as resulting from adverse childhood experiences (ACE) e.g. physical or sexual abuse, is a major risk factor for both depression and age-related disease and premature death (Bellis et al., 2015; Otte et al., 2016). One underlying mechanism might be accelerated cellular aging as indicated by telomere length (TL) shortening. Telomere biology plays a crucial role in genome integrity and chromosomal stability (Blackburn et al., 2015). Telomeres consist of a deoxyribonucleic-acid (DNA)-protein-complex that forms the protective caps at the ends of chromosomes. Telomeres shorten with every cell division cycle, constituting a well-established indicator for cellular aging processes (Blackburn et al., 2015). Both, MDD and ACE, are associated with shortened TL (Epel et al., 2018; Rentscher et al., 2020). Furthermore, shorter TL is associated with several physical, particularly age-related diseases (D'Mello et al., 2015; Epel et al., 2018), and accelerated TL shortening has even been suggested as a causal mechanism of the increased risk for age- related diseases in MDD (Epel et al., 2018).

While there is evidence that MDD as well as ACE are associated with shortened TL (Epel et al., 2018; Rentscher et al., 2020), studies investigating both, ACE and MDD, reveal ambiguous results. For example, one study reports an association of ACE and with TL in healthy controls, but not in MDD patients (Chen et al., 2014). In another study, shorter TL was found to be associated with more stressful life events in the past five years, but not with ACE or depression (Verhoeven et al., 2015). Osler and colleagues, however, reported a negative association of TL and ACE that was partly mediated by depressive mood (Osler et al., 2016).

Together, the role of ACE for TL shortening in MDD remains inconclusive. As ACE is common in MDD, with almost half of all adult MDD patients reporting a history of ACE (Nelson et al.,

2017), observed TL shortening in MDD may have been confounded by effects of ACE in some earlier studies. On the other hand, ACE may have differential effects in TL shortening in patients suffering from MDD compared to healthy individuals.

To further disentangle effects of MDD and ACE on TL, we used a systematic approach in which the factors ACE and MDD were fully crossed. We recruited four carefully diagnosed groups of MDD patients and healthy participants with and without a history of ACE, who were screened for potentially confounding variables and did not take antidepressant medication. We hypothesized that 1) individuals with MDD and individuals with ACE have shorter TL compared healthy controls and that 2) this effect would be most pronounced in MDD patients with ACE.

2 Material and Methods

2.1 Participants

Patients and healthy participants were recruited from our specialized affective disorder unit at the Department of Psychiatry and Psychotherapy, Campus Benjamin Franklin, Charité - Universitätsmedizin Berlin and by public postings. All patients and participants provided written informed consent. Healthy participants and outpatients received monetary compensation for their participation. The study was approved by the local ethical committee and addressed a secondary research question of a larger research project, which has been reported elsewhere (e.g., Kuehl et al., 2020).

Inclusion criteria for depressed patients were an acute MDD as assessed with the Structured Clinical Interview for DSM-IV axis I (SCID-I) to validate psychiatric diagnoses. Current depressive symptom severity was assessed with the Montgomery Asberg Depression Rating Scale (MADRS) and the Beck Depression Inventory (BDI).

ACE was defined as repeated physical or sexual abuse at least once a month over one year or more before the age of 18 adapted from the definition of Heim and colleagues from a study indicating long-lasting changes in the biological stress systems after ACE (Heim et al., 2000). We used a comparably strict inclusion criterion to ensure that we could hypothesize persistent biological changes. The inclusion criterion of "repeated physical or sexual abuse at least once a month over one year or more before the age of 18" was checked by a detailed semi-structured interview (Early Trauma Inventory; ETI) conducted by a trained clinical researcher. In addition, we used the shorter, but established Childhood Trauma Questionnaire (CTQ) to quantify ACE in a way that is easy to compare to other studies.

Exclusion criteria for depressed patients were schizophrenia, schizoaffective disorder, bipolar disorder, depressive disorder with psychotic features, dementia, panic disorder and alcohol or drug dependence. Healthy participants with and without ACE had to be free of any current mental disorder. Additional exclusion criteria for all were CNS relevant diseases, neurological diseases, severe somatic diseases, diabetes type 1 and 2, steroid diseases, hypertonia, current infections, pregnancy and use of antidepressant medication. Physical health was checked by physical examination and a clinical interview.

The study sample consisted of 23 MDD patients with ACE (MDD+/ACE+), 24 MDD patients without ACE (MDD+/ACE-), 22 participants with ACE but no current or lifetime MDD (MDD-/ACE+) and 21 participants with no current or lifetime MDD and no ACE (MDD-/ACE-).

2.2 Procedure

All patients and participants underwent one study visit including psychological and medical diagnostics by physical examination (including blood entake) and clinical interviews (including

SCID-I and MADRS) as well as ACE assessment (ETI). Afterwards they filled out questionnaires regarding MDD and ACE (BDI, CTQ) and a questionnaire regarding perceived current stress (Perceived Stress Questionnaire, PSQ).

2.3 Measurement of telomere length

Average relative leukocyte TL was quantified at the laboratory of the Centre for Environmental Sciences, University Hasselt, Belgium, by a modified quantitative real-time polymerase chain reaction (qPCR) protocol as described previously (Martens et al., 2016). DNA was extracted from whole blood using the QIAamp DNA Mini Kit (Qiagen, Inc., Venlo, The Netherlands). DNA quantity and purity was assessed by a Nanodrop 1000 spectrophotometer (Isogen, Life Science, Belgium). DNA integrity was assessed by agarose gel-electrophoresis. All TL measurements were performed in triplicate on a 7900HT Fast Real-Time PCR System (Applied Biosystems) in a 384-well format. The single-copy gene (36B4, acidic ribosomal phosphoprotein P0) reaction mixture contained 1x QuantiTect SYBR Green PCR master mix, 300 nM 36B4u primer (CAGCAAGTGGGAAGGTGTAATCC) and 500 nM 36B4d primer (CCCATTCTATCATCAACGGGTACAA). Used cycling conditions for the single copy gene were: 1 cycle at 95°C for 10 min, followed by 40 cycles at 95°C for 15 sec, and 58°C for 1 min and 20 sec. The telomere reaction mixture contained 1x QuantiTect SYBR Green PCR master mix, 2 mMdithiothreitol (DTT), 300 nMtelg primer (ACACTAAGGTTTGGGTTTGGGTTTGGGTTTGGGTTAGTGT) and 900 nMtelc primer (TGTTAGGTATCCCTATCCCTATCCCTATCCCTATCCCTAACA). Used cycling conditions were: 1 cycle at 95°C for 10 min, followed by 2 cycles at 94°C for 15 sec and 49°C for 2 min and 30 cycles at 94°C for 15 sec, 62°C for 20 sec, and 74°C for 1 min and 40 sec. Relative average TL was expressed as the ratio of telomere copy number to single-copy gene number (T/S) relative to the average T/S ratio of the entire sample set. Coefficients of variation

within triplicates of the telomere runs, single-copy gene runs, and T/S ratios were achieved of 0.51 %, 0.35 %, and 6.8 %, respectively.

2.4 Statistical analysis

Univariate ANOVAs and $\chi 2$ tests were used to compare groups regarding demographic characteristics. Post hoc tests were conducted when applicable.

Differences in TL between the four groups (MDD+/ACE+, MDD+/ACE-, MDD-/ACE+, MDD-/ACE-) were analyzed by univariate ANOVA. We controlled for sex, age, BMI and smoking in an additional ANCOVA because effects of these factors on TL have been reported in previous studies (Epel et al., 2018). As TL data and residuals were normally distributed, no further data transformation was necessary. In addition, we used bivariate (Pearson) correlation analysis to analyze associations between TL and severity of depression and childhood adversity using BDI, MADRS, ETI and CTQ scores and perceived current stress using PSQ score as well as linear regression models to predict TL by BDI, MADRS, ETI, CTQ and PSQ scores controlling for age, sex, BMI and smoking.

For some variables, there was missing data: BDI sum score: N=1 (MDD+/ ACE-), MADRS sum score: N=1 (MDD+/ ACE+), ETI sum score (MDD+/ ACE+), PSQ sum score: N=5 (4 x MDD+/ ACE+, 1 x MDD-/ ACE+).

Data analysis was performed using the SPSS statistical software (SPSS 27.0, Inc., Chicago, IL, USA). The significance level was set at $p < .05$ for all applied analysis.

3 Results

3.1 Sample characteristics

Group demographics and clinical characteristics are summarized in *Table 1*. In accordance with our recruitment criteria, both MDD groups did not differ in depressive symptom severity (see MADRS and BDI), but scores were higher compared to healthy individuals with and without ACE. Both groups with ACE had significantly higher ETI and CTQ scores compared to the groups without ACE. Abuse frequencies as assessed by the ETI had a range between daily and monthly experiences in both ACE groups (physical abuse (MDD+/ ACE+): daily: N=1, weekly: N=10, monthly: N=7; sexual abuse (MDD+/ ACE+): daily: N= 2, weekly: N= 2, monthly: N= 5; physical abuse (MDD-/ ACE+): daily: N=2, weekly: N= 8, monthly: N=8; sexual abuse (MDD-/ ACE+): daily: N= 1, weekly: N= 1 , monthly: N= 3).

Regarding perceived current stress, both MDD groups showed higher PSQ scores compared to healthy participants with and without ACE. There were no significant group differences in age, sex and educational level. However, MDD patients with ACE had a higher BMI compared to MDD patients without ACE and were more often smokers. In further analyzes of TL, we controlled for BMI and smoking as well as for age and sex. There were no differences between groups regarding blood pressure and pulse as well as in most measures of complete blood counts apart from white blood cells with higher amounts in MDD+/ACE+ compared to MDD+/ACE-. All measures of blood pressure, pulse and complete blood count were within a normal range.

Table 1: Sample characteristics of MDD patients with and without ACE and healthy participants with and without ACE

	MDD+ / ACE+ N = 23	**MDD+ / ACE- N = 24**	**MDD- / ACE+ N = 22**	**MDD- / ACE- N = 21**	**statistics**
Sex (f/m)	14/9	17/7	15/7	12/9	p= .76
Age (years; SD)	38.1 (11.4)	32.7 (11.5)	34.7 (10.7)	36.1 (11.4)	p= .39
Education(years; SD)	11.3 (1.6)	12.0 (1.4)	11.8 (1.4)	12.1 (1.3)	p= .17
Body Mass Index (kg/m²; SD)	25.1 (2.9)	22.0 (3.5)	23.9 (3.4)	23.5 (3.6)	p= .02, MDD+/ACE+ > MDD+/ ACE-
Smoking (y/n)	14/9	7/17	6/16	5/16	p= .03, MDD+/ACE+: p= .004
Use of hormonal contraceptives (women, y/n)	3/11	5/12	5/10	2/10	p= .75
Systolic blood pressure (mm/Hg; SD)	118 (12)	114 (11)	115 (14)	116 (11)	p= .77
Diastolic blood pressure (mm/Hg; SD)	70 (11)	68 (8)	68 (11)	68 (9)	p= .81
Pulse (bpm; SD)	72 (15)	77 (14)	72 (11)	70 (8)	p= .29
Relative leukocyte TL (SD)	1.03 (0.20)	1.04 (0.17)	1.02 (0.18)	0.98 (0.17)	p= .74
First MDD episode (y/n)*	1/21	3/21	_	_	p= .85
Number of previous MDD episodes (SD)*	5.1 (4.8)	3.5 (3.0)			p= .19
Length of current MDD episode (months, SD)*	10.9 (13.4)	11.0 (11.9)			p= .99
Depressive symptoms					
MADRS (SD)	27.4 (8.0)	28.0 (5.8)	1.6 (1.8)	0.8 (1.4)	p < .001, MDD+/ACE+ = MDD+/ACE- > MDD- /ACE+ = MDD-/ACE-
BDI (SD)	26.8 (8.6)	26.1 (8.3)	4.5 (4.7)	1.3 (1.6)	p < .001, MDD+/ACE+ = MDD+/ACE- > MDD- /ACE+ = MDD-/ACE-
Adverse childhood experiences					
ETI (SD)	752 (483)	191 (201)	612 (365)	15 (22)	p < .001, MDD+/ACE+ = MDD- /ACE+ > MDD+/ACE- = MDD- /ACE-
CTQ (SD)	71.8 (16.3)	41.0 (10.1)	60.7 (17.2)	31.3 (4.7)	p < .001, MDD+/ACE+ > MDD- /ACE+ > MDD+/ACE- =MDD-/ACE-
Perceived stress					
PSQ (SD)	69.5 (14.7)	64.6 (12.9)	34.3 (20.7)	26.6 (14.0)	p < .001, MDD+/ACE+ = MDD+/ACE- > MDD- /ACE+ = MDD-/ACE-

Abbreviations: MDD = Major depressive disorder; ACE = Adverse childhood experiences; MDD+/ACE+ = MDD patients with ACE, MDD+/ACE- = MDD patients without ACE, MDD-/ACE+ = participants with ACE but no MDD, MDD-/ACE- = participants without MDD and without ACE; SD = Standard deviation; MADRS = Montgomery Asberg Depression Rating Scale, BDI = Beck Depression Inventory, ETI = Early Trauma Inventory, CTQ = Childhood Trauma Questionnaire, PSQ: Perceived Stress Questionnaire, TL = telomere length
* only MDD groups included in analyses

3.2 Telomere length

There was no significant effect of group on TL, neither in the unadjusted ($F_{3,86}$= .43, p= .735, see *Figure 1*) or adjusted (controlling for age, sex, BMI, smoking) model ($F_{3,72}$= .66, p= .580). However, in the adjusted model, age ($F_{1,72}$= 9.54, p= .003, partial eta²= .117) and sex ($F_{1,72}$= 5.40, p= .023, partial eta²= .070) were significantly associated with TL, indicating shorter TL in men compared to women (T_{82}= 3.84, p< .001) and showing that older age was associated with shorter TL (r= - .40, p< .001). None of the other covariate was significantly associated with TL.

Bivariate (Pearson) correlation analysis revealed no significant association between TL with MADRS (r= .06, p= .558), BDI (r= .15, p= .154), ETI (r= - .04, p= .748), CTQ (r= .04, p= .710) or PSQ (r= .15, p= .168) scores, showing that severity of MDD and ACE as well as perceived current stress were not significantly related to TL.

In line with these results, additional linear regression models controlling for age, sex, BMI and smoking revealed no significant prediction of MADRS, BDI, ETI, CTQ and PSQ for TL, either (please see supplements for detailed results). Age and sex, but not BMI and smoking, significantly predicted TL in all models (MADRS: age: ß= - .36, p < .001; sex: ß= - .30, p= .004; BDI: age: ß= - .36, p < .001; sex: ß= - .30, p= .004; ETI: age: ß= - .35, p= .001; sex: ß= - .31, p= .004 ; CTQ: age: ß= - .36, p < .001; sex: ß= - .30, p= .004; PSQ: age: ß= - .36, p= .001; sex: ß= - .31, p = .004).

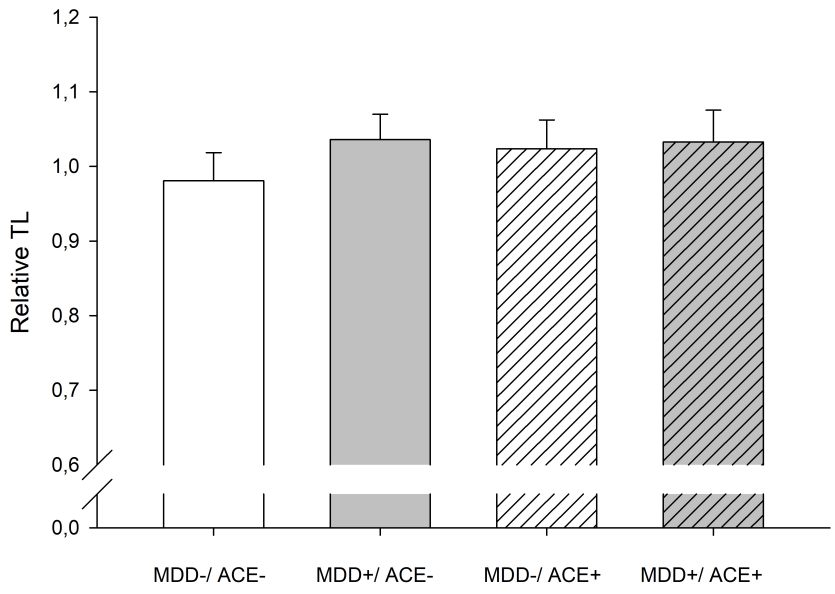

Fig. 1. Relative leukocyte telomere length (TL) in individuals with and without major depressive disorder (MDD) and adverse childhood experiences (ACE). There were no significant differences in TL between groups.

4 Discussion

In contrast to our hypothesis, we found no effects of MDD or ACE on TL. There were no significant differences in TL between the four groups (MDD+/ACE+, MDD+/ACE-, MDD-/ACE+, MDD-/ACE-) in either the adjusted and unadjusted models and no significant associations between severity of MDD or ACE and TL. As expected, TL was shorter in males and negatively associated with age.

Our hypothesis was based on previous literature, including meta-analyses (see Epel et al., 2018), which suggest shorter TL for MDD and ACE. Overall, previous meta-analyses on effects either of MDD (e.g., Darrow et al., 2016; Ridout et al., 2016) or ACE (e.g., Hanssen et al., 2017; Pepper et al., 2018) on TL show small to medium effects, even though not all included studies tend in the same direction. In the current study, we used a systematic approach in which the factors ACE and MDD were fully crossed to overcome potential confounding of the factors

MDD and ACE, but did not find any significant results. Therefore, other factors might contribute to our diverging results and help understand the heterogeneity observed in literature. To the null finding in our study might have contributed that all patients and participants of our study were relatively young, non-obese, physical healthy as assessed by clinical interview, medical examination, blood pressure, pulse and complete blood count and were free of antidepressant medication. We used strict inclusion criteria to minimize influence of potential confounders, however they also reduce the generalizability of our results to MDD patients in general who often use antidepressant medication and have an increased risk for several somatic comorbidities. Somatic comorbidity increases the unfavorable impact of MDD on TL (Ridout et al., 2016), thus, TL shortening might be more pronounced in subsamples of MDD patients who show physical abnormalities or even somatic comorbidities. This would be in line with a previous finding which demonstrates that TL is negatively associated with several biomarkers of cardiovascular and metabolic risk (Rehkopf et al., 2016). Antidepressant medication may affect TL as well, however potentially even in a protective way (Epel et al., 2018).

Another important explanation for diverging results might be due to different definitions of ACE that have been used in previous research. However, we used a rather strict criterion in our definition of ACE and thus we do not assume that inclusion of more severe cases compared to other studies explains our null results.

Important limitations of our study are the relatively small sample size and the cross sectional design. Importantly, a prospective study in chronic MDD patients (Vance et al., 2018) found no differences between MDD patients and healthy controls at baseline, but accelerated TL shortening in MDD patients two years later. Of note, that study investigated only chronic MDD patients, but further inclusion criteria were comparable to ours. However, range and mean of age were somewhat higher and only unstable cardiovascular comorbidities were excluded. That makes it plausible that also in our sample differences in TL could occur over time with shorter TL in MDD (and ACE) groups. Importantly, the shorter MDD duration in average of our sample

compared to the chronic course of MDD in patients of the study by Vance and colleagues might contribute to the diverging results as well.

Although we found no effect of the covariates BMI and smoking on TL, the highest BMI and most smokers were found in the MDD group with ACE. Such behavioral factors might also contribute to worse physical health outcomes as time progresses.

The small sample size is a major limitation of our study, however we believe that there is scientific value in examine the research question in this cohort because of the strength of the study design and approach. Particular strengths of our study are the following: Proposed hypotheses were based on biological plausibility and evidence from previously-published studies. The stringent set of inclusion and exclusion criteria resulted in a full-factorial 2x2 design with four carefully diagnosed groups of MDD patients and healthy participants with and without a history of ACE, who were screened for potentially confounding variables. The use of antidepressant medication that could have an effect on telomere length was excluded. The methods to assess telomere length fully conform with the standards developed by the NIH funded Telomere Research Network (https://trn.tulane.edu/resources/lab-protocols/).

In conclusion, our results suggest that MDD and ACE might not be independently associated with TL shortening. Future research should take potential associations with medication, life style factors and physical health markers into account and use prospective designs to further elucidate the relation of TL, MDD and ACE.

Conflict of interest

The authors declare no conflicts of interest.

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Supplementary material

Results of linear regression models of telomere length prediction by measures of severity of major depressive disorder, adverse childhood experiences and current stress (controlled for age, sex, body mass index and smoking) are presented.

For some variables there was missing data: MADRS sum score: N=1 (MDD+/ ACE+), BDI sum score: N=1 (MDD+/ ACE-), ETI sum score (MDD+/ ACE+), PSQ sum score: N=5 (4 x MDD+/ ACE+, 1 x MDD-/ ACE+).

MADRS = Montgomery Asberg Depression Rating Scale; BDI = Beck Depression Inventory; ETI = Early Trauma Inventory; PSQ = Perceived Stress Questionnaire; MDD= Major depressive disorder; ACE = Adverse childhood experiences

Prediction of telomere length

variable	unstandardized	standardized	standard error
constant	1.278***		.127
MADRS	.001	.107	.001
Age	- .006***	- .360***	.002
Sex	- .113**	-.301**	.038
BMI	.004	.072	.005
Smoking	- .019	- .052	.038
R^2	.252		
Corr R^2	.207		
$F_{5,83}$	5.597***		

* p < .05; ** p < .01; *** p < .001
MADRS = Montgomery Asberg Depression Rating Scale; BMI = Body mass index

Prediction of telomere length

variable	unstandardized	standardized	standard error
constant	1.247***		.127
BDI	.002	.178	.001
Age	- .006**	- .341**	.002
Sex	- .111**	- .297**	.037
BMI	.004	.082	.005
Smoking	- .031	- .082	.038
R^2	.270		
Corr R^2	.227		
$F_{5,83}$	6.154***		

* p < .05; ** p < .01; *** p < .001
BDI = Beck Depression Inventory; BMI = Body mass index

Prediction of telomere length

variable	unstandardized	standardized	standard error
constant	1.307***		.125
ETI	< .001	- .023	< .001
Age	- .006**	- .354**	.002
Sex	- .114**	- .305**	.039
BMI	.003	.064	.005
Smoking	- .010	- .026	.039
R^2	.242		
Corr R^2	.196		
$F_{5,83}$	5.292***		

* p < .05; ** p < .01; *** p < .001
ETI = Early Trauma Inventory; BMI = Body mass index

Prediction of telomere length

Variable	unstandardized	standardized	standard error
Constant	1.300***		.127
CTQ	< .001	.023	.001
Age	- .006***	- .362***	.002
Sex	- .114**	-.303**	.038
BMI	.003	.062	.005
Smoking	- .010	- .028	.038
R^2	.249		
Corr R^2	.205		
$F_{5,84}$	5.576***		

* p < .05; ** p < .01; *** p < .001
CTQ = Childhood Trauma Questionnaire; BMI = Body mass index

Prediction of telomere length

variable	Unstandardized	standardized	standard error
constant	1.278***		.127
PSQ	.001	.148	.001
Age	- .006**	- .355**	.002
Sex	- .118**	-.309**	.040
BMI	.003	.048	.005
Smoking	- .004	- .010	.039
R^2	.254		
Corr R^2	.207		
$F_{5,79}$	5.374***		

* p < .05; ** p < .01; *** p < .001
PSQ = Perceived Stress Questionnaire; BMI = Body mass index