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Posttraumatic Stress Disorder, Depression, and Accelerated Aging: Leukocyte Telomere Length in the Nurses' Health Study II

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ABSTRACT

BACKGROUND: Exposure to trauma, posttraumatic stress disorder (PTSD), and depression have been independently associated with leukocyte telomere length (LTL), a cellular marker of aging associated with mortality and age-related diseases. However, the joint contributions of trauma and its psychological sequelae on LTL have not been examined.

METHODS: We conducted an analysis of LTL in a subset of women from the Nurses' Health Study II (N = 1868). Lifetime exposure to traumatic events, PTSD, and depression was assessed with validated measures. DNA was extracted from peripheral blood leukocytes and telomere repeat copy number to single gene copy number was determined by quantitative real-time polymerase chain reaction telomere assay. Linear regression models assessed the association of trauma, PTSD, and depression with LTL after adjustment for health behaviors and medical conditions.

RESULTS: Trauma, PTSD, and depression were not independently associated with LTL in mutually adjusted models. However, individuals with severe psychological distress—characterized by comorbid PTSD and depression—had shorter LTL equivalent to being 7.62 years older (95% CI, 0.02 to 17.97) than participants who had never experienced a traumatic event and were not depressed. Further examination found only an association among individuals with the highest number of PTSD symptoms and comorbid depression equivalent to 9.71 additional years of aging (95% CI, 1.36 to 20.49). No effect was found among individuals meeting the minimum threshold for probable PTSD with comorbid depression.

CONCLUSIONS: Severe psychological distress, as indicated by the presence of comorbid PTSD and depression, may be associated with shorter LTL.

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Previous studies have found that lifetime stress is associated with shorter telomere length, indicating that telomere length may be a marker of psychosocial stress exposure (1,2). Telomeres are repetitive noncoding sequences of TTAGGG at the end of chromosomes that protect chromosomes from deterioration during cell division (3). The erosion or shortening of telomeres, which occurs naturally during aging and as a response to toxic environmental exposures such as cigarette smoke (4), leads to reproductive senescence and apoptosis of cells (5). Shorter telomeres have been associated with chronic diseases, including cardiovascular disease (6–8) and type 2 diabetes (9–12), as well as with mortality (6,13,14), and are considered a marker of biological age (15). Recent meta-analyses have found that posttraumatic stress disorder (PTSD) (16,17) and depression (16,18) are each associated with shorter telomere length. For example, one meta-analysis comprising 5 studies of PTSD and telomere length found that individuals with versus without PTSD had shorter telomeres equivalent to a standardized mean difference of −1.27 (95% CI, −2.12 to −0.43), while individuals with versus without depression had a standardized mean difference of −0.21 (95% CI, −0.29 to −0.12) (16). However, while both forms of psychological distress commonly occur following exposure to trauma, previous studies have generally focused on PTSD and depression independently.

These meta-analyses have reported substantial heterogeneity in effects across studies (e.g., PTSD I^2 = 94%; depression I^2 = 96%) (16) as well as indicated the inconsistency of associations between PTSD or depression with telomere length across study designs (17). There are 3 plausible reasons for inconsistency in the findings. First, meta-analyses of both forms of distress included studies with relatively small sample sizes [e.g., a mean of 44 participants per study (16,19–21); or half the studies with <60 participants (16)]. Second, despite findings that 52% of individuals with PTSD report co-occurring depression (22), previous studies have generally examined

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these forms of distress independently without accounting for either overlap between them or shared effects, which may result in obscuring their associations with telomere length (20,21). Third, variations in the prevalence of comorbid PTSD and depression across studies could further explain differing associations. Previous studies have found that depression severity, but not timing of depression onset (e.g., time since onset and leukocyte telomere length [LTL] measurement), has been associated with shorter LTL (18). Because individuals who meet criteria for both PTSD and depression report higher levels of depressive symptoms than those with depression alone (23,24), variation in the prevalence of PTSD and the accompanying severe distress (either comorbid PTSD and depression or higher depression severity) could account for some of the observed variation in associations.

To date, no study has examined the joint effects of both disorders, as large sample sizes with sufficient comorbidity are needed to disentangle these relationships (22). Of note, in our own previous work in the same cohort used in the present study, the Nurses' Health Study II (NHS II), we found in sensitivity analyses some initial suggestion that women with comorbid PTSD and depression had shorter telomeres than those with either disorder alone (25). However, our previous study was underpowered (N = 116), there was only 1 participant in the group with trauma and depression but no PTSD, and the interaction analyses did not reach statistical significance (25). Fourth, prior studies vary widely in the confounders included. For example, few studies consider possible effects of childhood abuse in these associations, even though child abuse has been associated with shorter telomere length and PTSD/depression (17,18,26–28). As a result, child abuse may be a confounder or PTSD and depression may serve to mediate the observed associations with telomere length. Some recent studies following up on these meta-analyses have failed to replicate associations of PTSD or depression with telomere length, finding either no effect (29) or an effect only among subgroups of participants [e.g., Whites vs. African Americans or Hispanics (30), females (31), and males (32)].

In the current article, we build on our previous analysis by using a sample over 10 times larger to address these limitations and disentangle the contributions of trauma, PTSD, and depression to telomere length. We also address the limitations of prior work by conducting sensitivity analyses accounting for childhood abuse and by capitalizing on the rich, longitudinal data of the NHS II to adjust for a wide range of potential covariates. We hypothesized that while trauma, PTSD, and depression would each be independently associated with shorter telomere length after mutual adjustment, comorbid PTSD and depression would be associated with shorter telomere length as compared with trauma alone or each disorder independently.

METHODS AND MATERIALS

Participants for the current study included women from the NHS II, an ongoing cohort of 116,430 female nurses recruited in 1989 and assessed every 2 years via questionnaires assessing health-related factors. Participants were ages 24 to 44 years at baseline. Across follow-up, women are invited to complete additional questionnaires and substudies. Blood samples from a subset of the full cohort were collected at 2 time points, between 1996 and 1999 (blood draw 1) or between 2010 and 2012 (blood draw 2). A total of 92,888 women who had completed the 1995 biennial questionnaire and had no previous diagnoses of cancer were invited to participate in the first blood draw, 29,611 (31.9%) of whom participated. All women who completed the first blood draw were invited to participate in the second blood draw, 16,424 (55.5%) of whom participated. For both draws, women were mailed collection kits with all necessary supplies and blood sample–related questionnaires. Samples were returned to the NHS II laboratory via overnight courier and were processed by the lab; separated into plasma, red blood cell, and white blood cell components; and stored in liquid nitrogen freezers. Prior studies with these data suggest that women who participated in the blood sample collection were similar to the whole NHS II cohort (33,34). Our sample included women who participated in a PTSD substudy of NHS II (2008), which assessed trauma, PTSD, and depression symptoms (35), and had LTL measured as part of their participation in additional NHS II substudies including ones on childhood abuse (36), religion and spirituality (Spirituality Study) (37), or lifetime stress (Mind-Body Study) (38). Mailed return of the questionnaires implied consent. This study was approved by the Partners HealthCare Human Research Committee.

Lifetime Trauma

Lifetime trauma was assessed using the Brief Trauma Questionnaire, which listed 15 types of traumatic events plus a 16th "other" option, with participants asked to endorse any event they experienced (35,39). Participants were then asked which traumatic event happened first, which traumatic event they considered their worst, and at what ages each occurred. Participants were considered trauma exposed if they endorsed any type of traumatic event, including an event identified via the other category. Informed consent was received from all participants and the study protocol was approved by the Institutional Review Boards of Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health.

Posttraumatic Stress Disorder

The Short Screening Scale for DSM-IV Posttraumatic Stress Disorder was used to assess 5 PTSD avoidance symptoms (criterion C) and 2 hyperarousal symptoms (criterion D) in relation to a participant's worst trauma (40). Participants that reported a history of 4 or more symptoms in relation to their worst traumatic event were considered to have a probable diagnosis of PTSD, with onset identified according to the date of their worst traumatic event. Prior work has demonstrated that a cutoff of 4 symptoms on this measure classified PTSD cases with a sensitivity of 85%, a specificity of 93%, a positive predictive value of 68%, and a negative predictive value of 98% in a validation study (41). In the NHS II, the reliability of self-reported age of onset of trauma and PTSD has been excellent when comparing the screener with the reported age of onset in an interview within a subset of participants (intraclass correlation coefficient = 0.95) (42).

History of Depression

Two different classification algorithms for lifetime history of depression were used, based on available measures. For the first blood collection (1996–1999), following prior work, participants with a score ≤60 on the 5-item Mental Health Index in the survey prior to their blood collection (either 1993 or 1997) were considered to have a history of depression (42). For the second blood collection (2010–2012), we used 3 indicators for history of depression: 1) whether participants experienced 2 or more weeks of depressive symptoms (asked every 2 years starting in 2001); 2) if they were ever diagnosed with depression by a doctor (asked every 2 years starting in 2003); and 3) the Center for Epidemiologic Studies Depression Scale, 10-Item Version (asked in 2008) (43). Participants answering yes to either question or scoring ≥10 on the Center for Epidemiologic Studies Depression Scale, 10-Item Version were classified as having probable depression (43).

Co-occurrence of Trauma, PTSD, and Depression

Based on the dichotomous lifetime trauma, lifetime PTSD, and depression variables, joint occurrence of trauma, PTSD, and depression was coded as follows: 1) no trauma, no depression (reference); 2) no trauma, depression; 3) trauma, no depression, no PTSD; 4) trauma, depression, no PTSD; 5) trauma, no depression, PTSD; and 6) trauma, depression and PTSD.

Leukocyte Telomere Length

LTL was assessed in batches of assays across the 3 NHS II substudies (childhood abuse substudy, Spirituality Study, Mind-Body Study) with all assays conducted at the same laboratory using the same procedures, which have been described elsewhere (44). Briefly, genomic DNA was extracted from peripheral blood leukocytes using the QIAmp (Qiagen) 96-spin blood protocol. PicoGreen DNA quantitation was conducted using a Molecular Devices 96-well spectrophotometer. Genomic DNA was subsequently dried down and resuspended. The telomere repeat copy number to single gene copy number (T/S) ratio was determined by a modified version of the quantitative real-time polymerase chain reaction telomere assay run on the Applied Biosystems 7900HT PCR System. Triplicate reactions of each assay were done on each sample. As previously reported in the childhood abuse substudy, the coefficient of variation (CV) for the exponentiated T/S ratio of blinded quality control (QC) samples across batches ranged from 23% to 33%, while within-replicate CVs for participants and blinded QC samples were lower within plates (range, 10.7%–19.4%), further dropping to 14% to 26% after excluding QC samples with within-triplicate CVs >20%. When nonblinded laboratory QC samples were included across plates, CVs in these samples averaged 11.5% (25). Based on these results, we concluded that most variation occurred between batches.

LTL, reported as the exponentiated T/S ratio, was log transformed, as values deviated significantly from normality. The Rosner batch-correction method (45) was used to correct for possible batch effects by first regressing the log-LTL on indicators for laboratory batch and potential predictors of LTL that might vary by batch, including participant's year of birth; father's age at birth; and age, smoking status, and body mass index (BMI) at time of blood draw. A correction parameter for each batch was estimated by subtracting the average of all batch parameter estimates from the parameter estimate for each individual batch. A batch-adjusted log-LTL for each sample was then created by adjusting the log-LTL by subtracting that batch's correction parameter. Although quantitative real-time polymerase chain reaction method is known to introduce variation in LTL measurement, the variation is nondifferential across outcomes, as assays were conducted blinded to PTSD and depression status.

Covariates

Age at blood draw was determined by self-reported birthdate and the date of the blood draw. Self-reported BMI was collected at the time of the blood draw (46). Lifetime smoking status from the preceding survey was coded as never versus ever. Participants' diets from the most recent survey prior to the blood draw were classified into quintiles of healthiness based on a validated food frequency questionnaire (47) and the Alternative Healthy Eating Index (48). Past month alcohol consumption was coded as 0 drinks/mo, 1 to 3 drinks/mo, 1 drink/wk, 2 to 4 drinks/wk, or 5+ drinks/wk. Frequency of exercising heavily enough to sweat was assessed in the closest biennial questionnaire prior to blood draws as <1, 1, 2 to 3, or 4+ times/wk. Self-reported physician diagnoses of high cholesterol, high blood pressure, and type 2 diabetes were assessed in the biennial survey prior to blood draw. Childhood physical and emotional abuse before age 12 was assessed using 5 questions from the physical and emotional abuse subscales of the Childhood Trauma Questionnaire included as part of the violence substudy in 2001 (49). The frequency of family members 1) hitting so hard it left bruises, 2) punishing in a way that seemed cruel, 3) insulting, 4) screaming and yelling, and 5) punishing with a belt or other hard object was queried. Following prior work in this sample (50), responses of never (scored as 0), rarely (scored as 1), sometimes (scored as 2), often (scored as 3), or very often (scored as 4) were summed, and then overall scores were divided into quartiles. Sexual abuse was assessed with the Sexual Maltreatment Scale of the Conflict Tactics Scales (51), which consists of 2 questions regarding unwanted sexual touching and forced or coerced sexual contact by an adult or older child before age 12 years and 2 questions about experiences between ages 12 and 17. Participants could respond, "No this never happened" (scored as 0), "Yes this happened once" (scored as 1), or "Yes this happened more than once" (scored as 2). Responses were summed and individuals were then classified as having experienced no sexual abuse (score = 0), infrequent sexual abuse (score = 1 or 2), moderately frequent sexual abuse (score = 3 or 4), or frequent sexual abuse (score ≥ 5).

Statistical Analyses

We examined the distribution of LTL and prevalence of covariates by the joint trauma, PTSD, and depression exposure. Differences in the means and standard deviations of age and BMI by exposure group were examined using Kruskal-Wallis tests. Prevalence of smoking, diet, alcohol use, high cholesterol, high blood pressure, type 2 diabetes, and frequency of

exercise in each group was calculated, and group differences were assessed using χ^2 tests.

We fit a series of linear regressions estimating the association of each level of trauma, PTSD, and depression with log-transformed, batch-corrected LTL, adjusting for 1) demographics (e.g., age, race) and substudy; 2) demographics plus health behaviors including BMI, smoking, alcohol use, exercise, and diet; and 3) demographics, health behaviors, and health risk factors, including type 2 diabetes, high blood pressure, and the use of cholesterol-lowering drugs. We expanded on this main analysis in 3 additional analyses outlined in Table 1. First, we assessed whether the effect of trauma, PTSD, or depression varied by the participant's age by fitting an additional model including an interaction between age and trauma, PTSD, depression, and their joint effects. Second, to assess whether the severity of PTSD was associated with shorter LTL and not just probable PTSD, we recategorized participants as having no PTSD symptoms, 1 to 3 PTSD symptoms (subclinical), 4 to 5 PTSD symptoms (moderate), and 6 to 7 PTSD symptoms (high). The joint contribution of trauma, depression, and PTSD severity was assessed by creating indicator variables as follows: no trauma/no depression (reference), trauma/no depression/no PTSD symptoms, trauma/no depression/1 to 3 PTSD symptoms, trauma/no depression/4 to 5 PTSD symptoms, trauma/no depression/6 to 7 PTSD symptoms, no trauma/depression, trauma/depression/no PTSD symptoms, trauma/depression/1 to 3 PTSD symptoms, trauma/depression/4 to 5 PTSD symptoms, and trauma/depression/6 to 7 PTSD symptoms. We also conducted a test of trend across levels of PTSD exposure by creating a continuous variable of PTSD severity (range, 0–3) among individuals with and without depression to assess a possible dose-response association with PTSD severity. Third, we similarly assessed whether severity of depression symptoms was associated with shorter LTL by categorizing individuals into quartiles of either 5-item Mental Health Index scores (for LTL assessed in blood draw 1) or the 2008 Center for Epidemiologic Studies Depression Scale, 10-Item Version (for LTL assessed in blood draw 2). We then stratified depression quartile by trauma and probable PTSD status resulting in 12 categories of exposure. Models were fit as above, and we also conducted a test of trend across levels of depression exposure separately among individuals with and without trauma and PTSD to assess a possible dose-response association.

To aid the interpretation of our results, we estimated the equivalent number of years of aging for each level of joint trauma, PTSD, and depression variable by dividing their β coefficients by the β coefficient for age, which reflects the effect of 1 year of aging, from a model fit without trauma, PTSD, or depression (52). A set of 1000 bootstraps was conducted to estimate a 95% confidence interval. To estimate the degree to which unmeasured confounders could account for the associations between trauma, PTSD, depression, and their joint effects on LTL, we calculated the minimum associations that the confounder would need to have in order to fully account for the association of trauma, PTSD, and depression with LTL using the E-value (53).

We conducted 4 sensitivity analyses to assess the robustness and of our findings as well as the potential selection bias. First, the history of depression of participants whose blood was collected in 1996 to 1999 may have been underdiagnosed, as the 5-item Mental Health Index assessed depressive symptoms in the last 4 weeks only. At the time of this blood collection, participants were ages 31 to 51, and 12% met thresholds for probable depression. Nationally representative studies have found a lifetime prevalence of 23.2% for depression, with the onset of 90% of cases by age 55 (54). While differences in prevalence between our sample and other studies could be due to real differences between the NHS II cohort and the general U.S. population, we nevertheless tested the effect of misclassifying 9% of the sample as not having a depression diagnosis by randomly assigning 9% of these participants (n = 73) to have depression, refitting our models, and pooling results across 1000 iterations.

Second, as childhood abuse has been associated with PTSD (26), depression (55), and LTL (16,18) and represents a potential common cause, we fit a model further adjusted for childhood physical, emotional, and sexual abuse to assess potential confounding. Third, we excluded participants (n = 116) who were included in the previous NHS II analysis conducted by Roberts *et al.* (25) to assess whether our results were driven primarily by this previous sample. Fourth, the childhood abuse substudy selected participants based on cardiovascular disease status, which previous studies have found to be associated with both PTSD and shorter telomere length (56,57). Thus, using participants from the childhood abuse substudy may artificially induce an association between PTSD/depression and LTL. To address whether the selection

Table 1. Trauma, Depression, and PTSD Categories and Number of Exposure Groups Across Analyses

Analysis	Trauma	Depression	PTSD	No. of Categories
Main	Exposed	Probable depression	Probable PTSD	6
	Unexposed	No probable depression	No probable PTSD	
Age Interaction	Exposed	Probable depression	Probable PTSD	11
	Unexposed	No probable depression	No probable PTSD	
PTSD Severity	Exposed	Probable depression	No PTSD symptoms	10
	Unexposed	No probable depression	1–3 PTSD symptoms	
			4–5 PTSD symptoms	
			6–7 PTSD symptoms	
Depression Severity	Exposed	Depression quartiles	Probable PTSD	12
	Unexposed		No probable PTSD	

PTSD, posttraumatic stress disorder.

criteria used to recruit participants into the different substudies affected our results, we fit models stratified by substudy (e.g., childhood abuse substudy, Mind-Body Study, and Spirituality Study).

RESULTS

Significant differences in age, BMI, smoking status, exercise, high blood pressure, type 2 diabetes, and cholesterol drug use were found by PTSD/depression exposure status (Table 2). Women who experienced trauma and reported PTSD and/or depression were more likely to have been lifetime smokers ($p < .001$) and have higher BMI ($p < .001$) than women without PTSD/depression regardless of trauma history. Women with both PTSD and depression were more likely to report high blood pressure ($p < .001$) and type 2 diabetes than women who reported only PTSD or depression.

In the model adjusting for age, race, and substudy, women with comorbid PTSD and depression had shorter LTL ($\beta = -0.05$; 95% CI, −0.10 to −0.01) compared with women with no trauma exposure, PTSD, or depression (see model 1 in Table 3). This association remained after further adjustment for health behaviors (model 2) or for additional health risk factors (model 3). This difference in LTL was equivalent to women with trauma exposure, PTSD, and depression being 7.62 years older (95% CI, 0.02 to 17.97) than women without trauma or depression. In E-value analyses, we calculated that an unmeasured confounder would have to be equally associated with the joint distress variable and LTL at a relative risk of 1.69 to account for the observed association. No significant interaction was found between age and any PTSD/depression category (see Table S1).

In analyses examining PTSD severity, participants with the highest number of PTSD symptoms (i.e., 6–7 symptoms) and

Table 2. Descriptive Statistics by Trauma, PTSD, and Depression Status

	T–P–D–, *n* = 294	T+P–D–, *n* = 834	T–P–D+, *n* = 62	T+P+D–, *n* = 238	T+P–D+, *n* = 265	T+P+D+, *n* = 175	Total, *N* = 1868	*p* Value
Age at Blood Draw, Years, Mean (SD)	49.69 (7.39)	50.59 (7.14)	54.12 (6.74)	48.48 (6.57)	55.12 (6.67)	54.02 (6.83)	51.26 (7.32)	<.001
Race, *n* (%)								.723
Other[a]	15 (5.1%)	38 (4.6%)	1 (1.6%)	13 (5.5%)	9 (3.4%)	9 (5.1%)	85 (4.6%)	
White	279 (94.9%)	796 (95.4%)	61 (98.4%)	225 (94.5%)	256 (96.6%)	166 (94.9%)	1783 (95.4%)	
Substudy, *n* (%)								<.001
Childhood abuse	152 (51.7%)	408 (48.9%)	20 (32.3%)	143 (60.1%)	49 (18.5%)	44 (25.1%)	816 (43.7%)	
Mind-Body Study	24 (8.2%)	81 (9.7%)	2 (3.2%)	31 (13.0%)	10 (3.8%)	9 (5.1%)	157 (8.4%)	
Spirituality Study	118 (40.1%)	345 (41.4%)	40 (64.5%)	64 (26.9%)	206 (77.7%)	122 (69.7%)	895 (47.9%)	
BMI, Mean (SD)	25.65 (5.33)	25.93 (5.26)	25.14 (3.25)	26.63 (5.98)	27.18 (5.93)	27.58 (6.24)	26.28 (5.55)	<.001
Lifetime Smoker, *n* (%)	71 (24.1%)	264 (31.7%)	20 (32.3%)	97 (40.8%)	84 (31.7%)	77 (44.0%)	613 (32.8%)	<.001
Past Month Alcohol Use, *n* (%)								.589
0 drinks/mo	113 (38.4%)	321 (38.5%)	16 (25.8%)	86 (36.1%)	105 (39.6%)	65 (37.1%)	706 (37.8%)	
1–3 drinks/mo	67 (22.8%)	175 (21.0%)	14 (22.6%)	67 (28.2%)	51 (19.2%)	33 (18.9%)	407 (21.8%)	
1 drink/wk	30 (10.2%)	85 (10.2%)	7 (11.3%)	26 (10.9%)	24 (9.1%)	22 (12.6%)	194 (10.4%)	
2–4 drinks/wk	46 (15.6%)	129 (15.5%)	15 (24.2%)	29 (12.2%)	40 (15.1%)	27 (15.4%)	286 (15.3%)	
5+ drinks/wk	38 (12.9%)	124 (14.9%)	10 (16.1%)	30 (12.6%)	45 (17.0%)	28 (16.0%)	275 (14.7%)	
Exercise, *n* (%)								.025
<1 time/wk	71 (24.1%)	194 (23.3%)	14 (22.6%)	75 (31.5%)	70 (26.4%)	41 (23.4%)	465 (24.9%)	
1 time/wk	45 (15.3%)	124 (14.9%)	12 (19.4%)	39 (16.4%)	20 (7.5%)	29 (16.6%)	269 (14.4%)	
2–3 times/wk	94 (32.0%)	284 (34.1%)	18 (29.0%)	73 (30.7%)	82 (30.9%)	61 (34.9%)	612 (32.8%)	
4+ times/wk	84 (28.6%)	232 (27.8%)	18 (29.0%)	51 (21.4%)	93 (35.1%)	44 (25.1%)	522 (27.9%)	
Diet Quintile, *n* (%)								.375
1	58 (19.7%)	138 (16.5%)	11 (17.7%)	37 (15.5%)	41 (15.5%)	20 (11.4%)	305 (16.3%)	
2	59 (20.1%)	155 (18.6%)	16 (25.8%)	35 (14.7%)	48 (18.1%)	29 (16.6%)	342 (18.3%)	
3	58 (19.7%)	167 (20.0%)	8 (12.9%)	60 (25.2%)	59 (22.3%)	45 (25.7%)	397 (21.3%)	
4	62 (21.1%)	166 (19.9%)	9 (14.5%)	50 (21.0%)	55 (20.8%)	34 (19.4%)	376 (20.1%)	
5	57 (19.4%)	208 (24.9%)	18 (29.0%)	56 (23.5%)	62 (23.4%)	47 (26.9%)	448 (24.0%)	
High Blood Pressure, *n* (%)	46 (15.6%)	126 (15.1%)	13 (21.0%)	25 (10.5%)	55 (20.8%)	48 (27.4%)	313 (16.8%)	<.001
Type 2 Diabetes, *n* (%)	5 (1.7%)	9 (1.1%)	3 (4.8%)	4 (1.7%)	14 (5.3%)	11 (6.3%)	46 (2.5%)	<.001
Cholesterol Drug Use, *n* (%)	34 (11.6%)	120 (14.4%)	14 (22.6%)	24 (10.1%)	80 (30.2%)	36 (20.6%)	308 (16.5%)	<.001
LTL, Mean (SD)	−0.62 (0.28)	−0.62 (0.26)	−0.61 (0.23)	−0.62 (0.27)	−0.61 (0.24)	−0.65 (0.25)	−0.62 (0.26)	.712

Plus or minus signs indicate presence of each condition (e.g., T+P+D– indicates participants who were trauma exposed, met criteria for lifetime PTSD, and did not have probable depression). Kruskal-Wallis tests were used to compare means of continuous variables across groups and χ^2 tests for categorical variables.

BMI, body mass index; D, depression; LTL, leukocyte telomere length; P, posttraumatic stress disorder; PTSD, posttraumatic stress disorder; T, trauma.

[a]"Other" includes participants identifying as American Indian, Asian, Black, Hawaiian, Multiracial, or Other/Unknown.

Table 3. Linear Association of Trauma, PTSD, and Depression With Leukocyte Telomere Length

	n	Model 1 (95% CI)[a]	Model 2 (95% CI)[b]	Model 3 (95% CI)[c]
No Trauma or Depression	294	Reference	Reference	Reference
Trauma, No PTSD or Depression	834	0.00 (−0.03 to 0.03)	0.00 (−0.03 to 0.03)	0.00 (−0.04 to 0.03)
Depression, No Trauma or PTSD	62	−0.01 (−0.08 to 0.06)	−0.01 (−0.08 to 0.06)	−0.01 (−0.08 to 0.06)
Trauma and PTSD, No Depression	238	0.02 (−0.03 to 0.06)	0.02 (−0.02 to 0.06)	0.02 (−0.02 to 0.06)
Trauma and Depression, No PTSD	265	−0.02 (−0.06 to 0.02)	−0.02 (−0.06 to 0.03)	−0.02 (−0.06 to 0.03)
Trauma, PTSD, and Depression	175	−0.05 (−0.10 to −0.01)[d]	−0.05 (−0.1 to 0.00)[d]	−0.05 (−0.1 to 0.00)[d]

All models mutually adjusted for trauma, depression, and PTSD status.
PTSD, posttraumatic stress disorder.
[a]Adjusted for age, race, and substudy.
[b]Model 1 further adjusted for body mass index, smoking, alcohol use, exercise, and diet.
[c]Model 2 further adjusted for blood pressure, diabetes, and cholesterol drug use.
[d]$p < .05$.

depression had shorter LTL equivalent to 9.71 years of aging (95% CI, 1.37 to 20.49) (Figure 1) versus participants with no lifetime trauma, depression, or PTSD (Table 4). Trend analyses of PTSD symptom severity were not significant among either those with ($p = .11$) or without ($p = .97$) depression. In analyses examining depression severity, no significant association was found between those with higher levels of depression symptoms with or without comorbid PTSD or experience of trauma compared with those with the lowest level of depression severity and no experience of trauma or PTSD (see Table S2). Results from sensitivity analyses were consistent with those from the main results (see Figure S1 and Table S3). When considering effects of potentially underestimating prevalence of depression history, the association of comorbid PTSD and depression with LTL was consistent with the primary analysis (β = −0.04; 95% CI, −0.09 to 0.00). Similarly, after adjusting the experience of childhood physical, emotional, and sexual abuse, the association between comorbid PTSD and depression compared with no experience of trauma, depression, or PTSD remained consistent though not significant (β = −0.04; 95% CI, −0.10 to 0.01). Analyses excluding participants in the prior NHS II publication (25), and stratified by substudy, also led to attenuation in the effect estimates, but the direction of effects was consistent with findings from the main analyses.

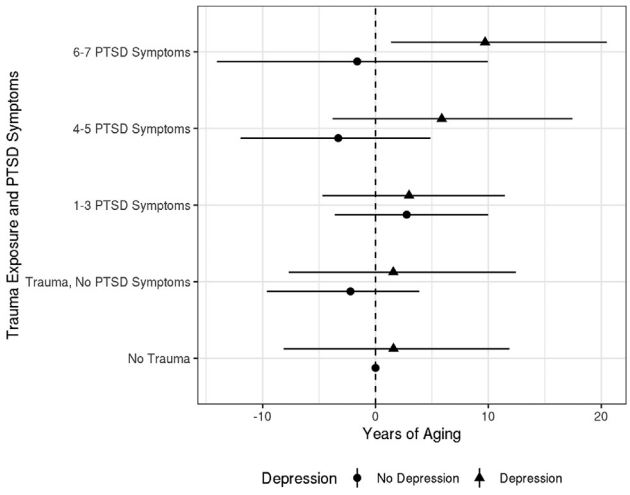

Figure 1. Equivalent number of years of aging associated with trauma and posttraumatic stress disorder (PTSD) symptom severity, stratified by lifetime depression status. Years of aging were estimated by weighting the effect of each trauma, PTSD, and depression variable with the effect of age from a model fit without trauma, PTSD, or depression. A set of 1000 bootstraps was conducted to estimate the 95% confidence interval.

DISCUSSION

We report here that PTSD with comorbid depression is associated with shorter LTL, equivalent to 7.62 years of aging, compared with women with no trauma exposure or depression. When adjusted for the other conditions, trauma, PTSD, and depression were not associated with shorter LTL (Table 3). Prior studies have mixed findings regarding the association of PTSD and depression with LTL, with recent studies finding either no effect (58) or an effect only for a subgroup of participants [e.g., older participants (59) or males (32,59) for depression; severely trauma-exposed participants for PTSD (60)]. Our results indicate that severe distress as indicated by comorbid PTSD and depression is associated with shorter LTL specifically among women with the highest number of PTSD symptoms (6–7 symptoms; equivalent years of aging = 9.71), but more severe depression symptoms even in the presence of PTSD was not associated with shorter LTL (Table S2). These results were consistent even after adjusting for the experience of childhood physical, emotional, and sexual abuse, which have been associated both with psychological distress and shorter LTL (17,18,26–28). If only severely symptomatic individuals have shorter LTL, as PTSD and depression are highly comorbid (20,21,61), previous results in the literature of PTSD and depression alone being associated with shorter LTL may be capturing the comorbidity implicitly when classifying cases by only one disorder. Furthermore, individuals with comorbid PTSD and depression may also represent those with the greatest severity for each disorder (22,62), which supports previous findings that depression severity is associated with shorter LTL (18).

These results are subject to several limitations. First, the data are cross-sectional, which precludes testing direction of effect. It may be that shorter LTL leads to increased risk for PTSD or depression rather than the reverse, though prospective studies of PTSD and depression indicate that prior PTSD/

Table 4. Linear Association of the Joint Occurrences of Trauma, Depression, and PTSD Symptoms With Leukocyte Telomere Length

	n	Model 1 (95% CI)[a]	Model 2 (95% CI)[b]	Model 3 (95% CI)[c]
No Trauma or Depression	294	Reference	Reference	Reference
Depression, No Trauma	62	−0.01 (−0.08 to 0.06)	−0.01 (−0.08 to 0.06)	−0.01 (−0.08 to 0.06)
Trauma, No Depression, PTSD Sx = 0	427	0.02 (−0.02 to 0.05)	0.02 (−0.02 to 0.05)	0.02 (−0.02 to 0.05)
Trauma, No Depression, PTSD Sx = 1–3	407	−0.02 (−0.06 to 0.02)	−0.02 (−0.06 to 0.02)	−0.02 (−0.06 to 0.02)
Trauma, No Depression, PTSD Sx = 4–5	165	0.02 (−0.03 to 0.07)	0.02 (−0.03 to 0.07)	0.02 (−0.03 to 0.07)
Trauma, No Depression, PTSD Sx = 6–7	73	0.01 (−0.06 to 0.07)	0.01 (−0.05 to 0.08)	0.01 (−0.05 to 0.08)
Trauma, Depression, PTSD Sx = 0	95	−0.01 (−0.07 to 0.05)	−0.01 (−0.07 to 0.05)	−0.01 (−0.07 to 0.05)
Trauma, Depression, PTSD Sx = 1–3	170	−0.02 (−0.07 to 0.02)	−0.02 (−0.07 to 0.03)	−0.02 (−0.07 to 0.03)
Trauma, Depression, PTSD Sx = 4–5	97	−0.04 (−0.10 to 0.02)	−0.04 (−0.10 to 0.02)	−0.04 (−0.10 to 0.02)
Trauma, Depression, PTSD Sx = 6–7	78	−0.07 (−0.13 to −0.01)[d]	−0.07 (−0.13 to −0.00)[d]	−0.06 (−0.13 to 0.00)[d]

All models mutually adjusted for trauma, depression, and PTSD status.
PTSD, posttraumatic stress disorder; Sx, symptoms.
[a]Adjusted for age, race, and substudy,
[b]Model 1 further adjusted for body mass index, smoking, alcohol use, exercise, and diet.
[c]Model 2 further adjusted for blood pressure, diabetes, and cholesterol drug use.
[d]$p < .05$.

depression is associated with subsequent shortened LTL (16,18). Second, LTL was assessed in multiple batches across several substudies. While we adjusted for substudy in our models, residual differences may remain. Third, PTSD was assessed retrospectively and incompletely for participants whose blood was drawn after 2008, while current and not lifetime depression was assessed for participants in first blood draw. In our sensitivity analysis of depression misclassification, we found an effect of comorbid PTSD and depression on LTL consistent with our main analysis, even with 9% of participants' depression status misclassified. These results imply that the associations between comorbid PTSD and depression are robust to underreporting of depression. Fourth, while the NHS II sample size would be one of the largest studies of LTL and PTSD/depression conducted, some levels of the exposure had a relatively small number of women in them (e.g., lifetime depression, no trauma/PTSD group had $n = 62$). Fifth, while we examined increasing PTSD symptoms stratified across depression status (Table 4) and vice versa, our screening measures assessed only seven PTSD symptoms and half of the DSM-IV depression symptoms, which limited our ability to assess whether severity of PTSD or depression alone accounted for LTL shortening. Our use of screening measures also prevents us from examining the association of PTSD symptom dimensions with telomere length.

Further research explicating the relationship between PTSD and depression with LTL would provide important insight into how PTSD and depression affect physical health. Prospective studies, which can directly address issues of temporality, should be conducted and assess all PTSD and depression symptoms to determine whether joint distress, severe symptoms of a single disorder, or a shared component is associated with shortened LTL. Untangling the association between PTSD/depression and LTL would aid in the identification of at-risk groups based on specific symptomology for poorer physical health outcomes with implications for both treatment and prevention.

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REFERENCES

1. Mathur MB, Epel E, Kind S, Desai M, Parks CG, Sandler DP, *et al.* (2016): Perceived stress and telomere length: A systematic review,

meta-analysis, and methodologic considerations for advancing the field. Brain Behav Immun 54:158–169.
2. Willis M, Reid SN, Calvo E, Staudinger UM, Factor-Litvak P (2018): A scoping systematic review of social stressors and various measures of telomere length across the life course. Ageing Res Rev 47:89–104.
3. Moyzis RK, Buckingham JM, Cram LS, Dani M, Deaven LL, Jones MD, *et al.* (1988): A highly conserved repetitive DNA sequence, (TTAGGG) n, present at the telomeres of human chromosomes. Proc Natl Acad Sci U S A 85:6622–6626.
4. Valdes AM, Andrew T, Gardner JP, Kimura M, Oelsner E, Cherkas LF, *et al.* (2005): Obesity, cigarette smoking, and telomere length in women. Lancet 366:662–664.
5. Wong LM, van der Harst P, de Boer R, Huzen J, van Gilst W, van Veldhuisen D (2010): Aging, telomeres and heart failure. Heart Fail Rev 15:479–486.
6. Le Carolyn MH, Neylan TC, Na B, Regan M, Zhang Q, Cohen BE (2013): Lifetime trauma exposure and prospective cardiovascular events and all-cause mortality: Findings from the Heart and Soul Study. Psychosom Med 75:849–855.
7. Edmondson D, Kronish IM, Shaffer JA, Falzon L, Burg MM (2013): Posttraumatic stress disorder and risk for coronary heart disease: A meta-analytic review. Am Heart J 166:806–814.
8. Van der Kooy K, Van Hout H, Marwijk H, Marten H, Stehouwer C, Beekman A (2007): Depression and the risk for cardiovascular diseases: Systematic review and meta analysis. Int J Geriatr Psychiatry 22:613–626.
9. Knol M, Twisk JW, Beekman AT, Heine R, Snoek FJ, Pouwer F (2006): Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. Diabetologia 49:837.
10. Mezuk B, Eaton WW, Albrecht S, Golden SH (2008): Depression and type 2 diabetes over the lifespan: A meta-analysis. Diabetes Care 31:2383–2390.
11. Vancampfort D, Rosenbaum S, Ward PB, Steel Z, Lederman O, Lamwaka AV, *et al.* (2016): Type 2 diabetes among people with posttraumatic stress disorder: Systematic review and meta-analysis. Psychosom Med 78:465–473.
12. Zhao J, Miao K, Wang H, Ding H, Wang DW (2013): Association between telomere length and type 2 diabetes mellitus: A meta-analysis. PLoS One 8:e79993.
13. Chwastiak LA, Rosenheck RA, Desai R, Kazis LE (2010): The association of psychiatric illness and all-cause mortality in the national department of Veterans Affairs Health Care System. Psychosom Med 72:817–822.
14. Cuijpers P, Vogelzangs N, Twisk J, Kleiboer A, Li J, Penninx BW (2014): Comprehensive meta-analysis of excess mortality in depression in the general community versus patients with specific illnesses. Am J Psychiatry 171:453–462.
15. Aviv A (2006): Telomeres and human somatic fitness. J Gerontol A Biol Sci Med Sci 61:871–873.
16. Darrow SM, Verhoeven JE, Révész D, Lindqvist D, Penninx BW, Delucchi KL, *et al.* (2016): The association between psychiatric disorders and telomere length: A meta-analysis involving 14,827 persons. Psychosom Med 78:776.
17. Li X, Wang J, Zhou J, Huang P, Li J (2017): The association between post-traumatic stress disorder and shorter telomere length: A systematic review and meta-analysis. J Affect Disord 218:322–326.
18. Ridout KK, Ridout SJ, Price LH, Sen S, Tyrka AR (2016): Depression and telomere length: A meta-analysis. J Affect Disord 191:237–247.
19. Boks MP, van Mierlo HC, Rutten BP, Radstake TR, De Witte L, Geuze E, *et al.* (2015): Longitudinal changes of telomere length and epigenetic age related to traumatic stress and post-traumatic stress disorder. Psychoneuroendocrinology 51:506–512.
20. Wolf EJ, Morrison FG, Sullivan DR, Logue MW, Guetta RE, Stone A, *et al.* (2019): The goddess who spins the thread of life: Klotho, psychiatric stress, and accelerated aging. Brain Behav Immun 80:193–203.
21. Connolly SL, Stoop TB, Logue MW, Orr EH, De Vivo I, Miller MW, *et al.* (2018): Posttraumatic stress disorder symptoms, temperament, and the pathway to cellular senescence. J Trauma Stress 31:676–686.
22. Rytwinski NK, Scur MD, Feeny NC, Youngstrom EA (2013): The co-occurrence of major depressive disorder among individuals with posttraumatic stress disorder: A meta-analysis. J Trauma Stress 26:299–309.
23. Gros DF, Price M, Magruder KM, Frueh BC (2012): Symptom overlap in posttraumatic stress disorder and major depression. Psychiatry Res 196:267–270.
24. Shalev AY, Freedman S, Peri T, Brandes D, Sahar T, Orr SP, *et al.* (1998): Prospective study of posttraumatic stress disorder and depression following trauma. Am J Psychiatry 155:630–637.
25. Roberts AL, Koenen KC, Chen Q, Gilsanz P, Mason SM, Prescott J, *et al.* (2017): Posttraumatic stress disorder and accelerated aging: PTSD and leukocyte telomere length in a sample of civilian women. Depress Anxiety 34:391–400.
26. Brewin CR, Andrews B, Valentine JD (2000): Meta-analysis of risk factors for posttraumatic stress disorder in trauma-exposed adults. J Consult Clin Psychol 68:748–766.
27. Nanni V, Uher R, Danese A (2012): Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: A meta-analysis. Am J Psychiatry 169:141–151.
28. Ridout KK, Levandowski M, Ridout SJ, Gantz L, Goonan K, Palermo D, *et al.* (2018): Early life adversity and telomere length: A meta-analysis. Mol Psychiatry 23:858–871.
29. Wium-Andersen MK, Ørsted DD, Rode L, Bojesen SE, Nordestgaard BG (2017): Telomere length and depression: Prospective cohort study and Mendelian randomisation study in 67 306 individuals. Br J Psychiatry 210:31–38.
30. Wignall ND, Deschner M, Evans HM, Brown ES (2017): Relationship between current depressive symptoms and telomere length in a large, multiethnic sample. J Clin Psychiatry 78:1331–1336.
31. Liu JJ, Wei YB, Forsell Y, Lavebratt C (2017): Stress, depressive status and telomere length: Does social interaction and coping strategy play a mediating role? J Affect Disord 222:138–145.
32. Whisman MA, Richardson ED (2017): Depressive symptoms and salivary telomere length in a probability sample of middle-aged and older adults. Psychosom Med 79:234–242.
33. Sumner JA, Chen Q, Roberts AL, Winning A, Rimm EB, Gilsanz P, *et al.* (2017): Cross-sectional and longitudinal associations of chronic posttraumatic stress disorder with inflammatory and endothelial function markers in women. Biol Psychiatry 82:875–884.
34. Sumner JA, Chen Q, Roberts AL, Winning A, Rimm EB, Gilsanz P, *et al.* (2018): Posttraumatic stress disorder onset and inflammatory and endothelial function biomarkers in women. Brain Behav Immun 69:203–209.
35. Koenen KC, De Vivo I, Rich-Edwards J, Smoller JW, Wright RJ, Purcell SM (2009): Protocol for investigating genetic determinants of posttraumatic stress disorder in women from the Nurses' Health Study II. BMC Psychiatry 9:29.
36. Mason SM, Prescott J, Tworoger SS, DeVivo I, Rich-Edwards JW (2015): Childhood physical and sexual abuse history and leukocyte telomere length among women in middle adulthood. PLoS One 10:e0124493.
37. Spence ND, Farvid MS, Warner ET, VanderWeele TJ, Tworoger SS, Argentieri MA, *et al.* (2020): Religious service attendance, religious coping, and risk of hypertension in women participating in the Nurses' Health Study II. Am J Epidemiol 189:193–203.
38. Huang T, Trudel-Fitzgerald C, Poole EM, Sawyer S, Kubzansky LD, Hankinson SE, *et al.* (2019): The Mind–Body Study: Study design and reproducibility and interrelationships of psychosocial factors in the Nurses' Health Study II. Cancer Causes Control 30:779–790.
39. Roberts AL, Dohrenwend BP, Aiello A, Wright RJ, Maercker A, Galea S, *et al.* (2012): The stressor criterion for posttraumatic stress disorder: Does it matter? J Clin Psychiatry 73:264–270.
40. Breslau N, Peterson EL, Kessler RC, Schultz LR (1999): Short screening scale for DSM-IV posttraumatic stress disorder. Am J Psychiatry 156:908–911.
41. Lee YC, Agnew-Blais J, Malspeis S, Keyes K, Costenbader K, Kubzansky LD, *et al.* (2016): Post-traumatic stress disorder and risk for incident rheumatoid arthritis. Arthritis Care Res (Hoboken) 68:292–298.

42. McCabe C, Thomas K, Brazier J, Coleman P (1996): Measuring the mental health status of a population: A comparison of the GHQ–12 and the SF–36 (MHI–5). Br J Psychiatry 169:517–521.
43. Irwin M, Artin KH, Oxman MN (1999): Screening for depression in the older adult: Criterion validity of the 10-item Center for Epidemiological Studies Depression Scale (CES-D). Arch Int Med 159:1701–1704.
44. McGrath M, Wong JY, Michaud D, Hunter DJ, De Vivo I (2007): Telomere length, cigarette smoking, and bladder cancer risk in men and women. Cancer Epidemiol Biomarkers Prev 16:815–819.
45. Rosner B, Cook N, Portman R, Daniels S, Falkner B (2008): Determination of blood pressure percentiles in normal-weight children: Some methodological issues. Am J Epidemiol 167:653–666.
46. Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC (1990): Validity of self-reported waist and hip circumferences in men and women. Epidemiology 1:466–473.
47. Willett W, Sampson L, Browne M, Stampfer MJ, Rosner B, Hennekens CH, *et al.* (1988): The use of a self-administered questionnaire to assess diet four years in the past. Am J Epidemiol 127:188–199.
48. McCullough ML, Feskanich D, Stampfer MJ, Giovannucci EL, Rimm EB, Hu FB, *et al.* (2002): Diet quality and major chronic disease risk in men and women: Moving toward improved dietary guidance. Am J Clin Nutr 76:1261–1271.
49. Bernstein DP, Fink L, Handelsman L, Foote J, Lovejoy M, Wenzel K, *et al.* (1994): Initial reliability and validity of a new retrospective measure of child abuse and neglect. Am J Psychiatry 151:1132–1136.
50. Roberts AL, Chen Y, Slopen N, McLaughlin KA, Koenen KC, Austin SB (2015): Maternal experience of abuse in childhood and depressive symptoms in adolescent and adult offspring: A 21-year longitudinal study. Depress Anxiety 32:709–719.
51. Straus MA, Hamby SL, Finkelhor D, Moore DW, Runyan D (1998): Identification of child maltreatment with the Parent-Child Conflict Tactics Scales: Development and psychometric data for a national sample of American parents. Child Abuse Neglect 22:249–270.
52. Monroe DM, Goldstein RL, Teylan MA, Hart JE, DeVivo I, Orr EH, *et al.* (2019): Clinical associations with telomere length in chronic spinal cord injury. Spinal Cord 57:1084–1093.
53. VanderWeele TJ, Ding P (2017): Sensitivity analysis in observational research: introducing the E-value. Ann Intern Med 167:268–274.
54. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE (2005): Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 62:593–602.
55. Norman RE, Byambaa M, De R, Butchart A, Scott J, Vos T (2012): The long-term health consequences of child physical abuse, emotional abuse, and neglect: A systematic review and meta-analysis. PLoS Med 9:e1001349.
56. Sumner JA, Kubzansky LD, Elkind MS, Roberts AL, Agnew-Blais J, Chen Q, *et al.* (2015): Trauma exposure and posttraumatic stress disorder symptoms predict onset of cardiovascular events in women. Circulation 132:251–259.
57. Weischer M, Bojesen SE, Cawthon RM, Freiberg JJ, Tybjærg-Hansen A, Nordestgaard BG (2012): Short telomere length, myocardial infarction, ischemic heart disease, and early death. Arterioscler Thromb Vasc Biol 32:822–829.
58. Vincent J, Hovatta I, Frissa S, Goodwin L, Hotopf M, Hatch SL, *et al.* (2017): Assessing the contributions of childhood maltreatment subtypes and depression case-control status on telomere length reveals a specific role of physical neglect. J Affect Disord 213:16–22.
59. Wang X, Sundquist K, Hedelius A, Palmér K, Memon AA, Sundquist J (2017): Leukocyte telomere length and depression, anxiety and stress and adjustment disorders in primary health care patients. BMC Psychiatry 17:148.
60. Kim TY, Kim SJ, Choi JR, Lee S-T, Kim J, Hwang IS, *et al.* (2017): The effect of trauma and PTSD on telomere length: An exploratory study in people exposed to combat trauma. Sci Rep 7:4375.
61. Monsees GM, Tamimi RM, Kraft P (2009): Genome-wide association scans for secondary traits using case-control samples. Genet Epidemiol 33:717–728.
62. Kendler KS, Gardner CO, Prescott CA (2005): Toward a comprehensive developmental model for major depression in women. Focus 159:1133–1197.