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Do symptoms of depression predict telomere length? Evidence from the West of Scotland Twenty-07 Study.

Short title: Depressive symptoms and telomeres

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Abstract

Objective: Psychological factors such as the stress of caregiving are emerging as predictors of telomere length, an index of biological ageing. However, although lifetime major depressive disorder is associated with shorter telomeres, less is known about depression symptoms. Depression and depressive symptoms are associated with a range of morbidities and mortality, but the extent to which they predict biological ageing is unclear. The present study examined participants in the West of Scotland Twenty-07 Study across three age cohorts and four waves of data collection from 1992/93 to 2007/08. **Methods:** Participants were aged 37, 57, and 76 years old at final data collection. Depressive symptoms were measured using the Hospital Anxiety and Depression Scale at each time point. Telomere length was assessed from 1063 blood samples collected at the final wave in 2007/08 for respondents who also had depression data. **Results:** Average depression symptoms (β = -.12, p = .047) and their change over time (β = -.12, p = .031) were negatively associated with telomere length, but only in the youngest cohort . Depressive symptoms were not cross-sectionally associated with telomere length in 2007-08 (β = -.03, p = .45). In the youngest cohort only, depressive symptoms assessed in 1995-97 and 2000-04 were associated with shorter telomere length (β = .14, p = .046, and β = .18, p = .012, respectively), but not 1992-93 or 2007-08; associations in the middle and older aged cohorts were non-significant. **Conclusions:** Depressive symptoms predict shorter telomeres, but only in younger adults.

Keywords: ageing; depression; telomeres; cohort study;

Abbreviations:

AUC Area under the curve

CES-D Centre for Epidemiologic Studies Depression Scale

DNA Deoxyribonucleic acid

EDTA Ethylenediaminetetraacetic acid

GDS Geriatric Depression Scale

HADS Hospital Anxiety and Depression Scale

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MDD Major Depressive Disorder

NHS National Health Service

PBL Peripheral blood leukocyte

SE Standard error of the mean

T/S ratio Telomere repeat copy number to single copy gene number ratio

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Depression is a strong predictor of morbidity and mortality (see e.g., (1, 2), even when socio-demographic variables and health behaviours are taken into account. The prevalence of depression is high among individuals with ageing-related physical illnesses (3-5). Several underlying mechanisms have been proposed including telomere shortening as an index of biological ageing (6), which contributes to increased incidence of age-related diseases (7, 8). Telomeres are specialized nucleoprotein complexes at the end of chromosomes. They function to cap the chromosome, enabling recognition of the end of chromosomes as a break in DNA, thus preventing chromosomal fusions. Telomeres typically shorten during somatic cell division as a consequence of the 'end replication problem' (9, 10), as well as through various processes of genetic damage, with oxidative stress a potentially prominent driver of this telomere erosion. Thus, telomere length has been regarded as a biomarker of biological ageing that may help explain environmentally induced differences in rates of ageing, such as those associated with caregiving stress (11, 12) and childhood adversity (13, 14).

The presence of shorter telomeres is a feature of many age-related conditions and diseases, including: immunosenescence, cardiovascular disease, sarcopenia, osteoporosis, osteoarthritis and skin ageing (15). Moreover, there are plausible mechanisms by which telomere attrition might contribute to these diseases (15). However, it is also possible that telomere length may primarily be related to illness due to its strong association with chronic stress exposure rather than being a direct cause of illness (15). The use of telomere length as a marker of biological ageing has been criticized, and evidence linking telomere length to functional decline is somewhat equivocal (16, 17).

Over the past few years, a number of studies have found associations between MDD and telomere length; those with long-term MDD have been reported to have shorter telomeres than non-depressed controls. In a middle-aged sample with a variety of mood disorders including MDD, telomeres were significantly shorter among those with mood disorders versus age-matched controls (18). Similarly, in a large Taiwanese sample of all ages, presence of MDD was shown to be associated

with shorter telomeres compared to controls almost as strongly as age and more strongly than monoamine oxidase A genotype, both factors which have been associated with shortened telomeres (19). Finally, leukocyte telomeres were shorter among a sample of adults with recurrent MDD aged 21-97 years, particularly among those showing a hypocortisolaemic state (20);an association which was not altered by adjustment for BMI or anti-depressant medication. In each of these studies, the results survived adjustment for the age and sex of the participants. Additionally, the chronicity of the depression has been observed to be inversely related to telomere length; in a small study where no association between telomere length and current MDD was found, individuals aged 25-69 years with more chronic courses of depression had shorter telomeres (6). This would suggest that it is recurrent depression that accelerates biological ageing. However, another study found no association between telomere length and time since depression onset, although there was a negative relationship between telomere length and current MDD (21). Further, the middle-aged study above found no effect of chronicity (18), but average lifetime duration of illness was far longer than in the study reporting effects for those with the most chronic illness (6). MDD has also been associated with shorter baseline telomere length in older patients with certain disease conditions including coronary heart disease, although there was no relationship between MDD and the 5-year change in telomere length in these patients (22).

Less is known about telomere length and symptoms of depression in the general population or patients without a clinical diagnosis of MDD. Only two studies, both in older adults, have examined depressive symptoms in this context. One was a cohort of 890 older patients with chronic heart failure, where lower perceived mental health, but not depressive symptoms measured by the Centre for Epidemiologic Studies Depression Scale (CES-D), was associated with shorter telomere length; neither were there differences between groups with more or less severe depressive symptoms (23). The other study measured depressive symptoms, alongside optimism, cognitive functioning and loneliness, as part of an overall assessment of mental wellbeing in 326 elderly men; telomere length was not associated with depressive symptoms measured using the Geriatric Depression Scale (GDS-15) or, indeed, the other measures of wellbeing (24). However, as this latter study focused only on males and both were in elderly samples, it is not yet known whether

telomere length and depressive symptoms are linked in cohorts more varied in age and sex and more representative of the general population.

The present analyses of data from three cohorts in the West of Scotland Twenty-07 Study examined whether or not symptoms of depression were associated with telomere length. Firstly, it was examined, using area under the curve (AUC) whether the chronicity, i.e. the average level of depression over the waves, or the change over time, i.e., worsening of symptoms, are predictive of telomere length. A second set of analyses aimed to determine associations between depressive symptoms at each wave of measurement were associated with telomere length. In both sets of analyses, we also assessed whether any relationship between depressive symptoms and telomere length varied among the three different age cohorts that characterise the study.

Methods

Participants

Participants were resident in Glasgow and the surrounding areas in Scotland at the baseline survey of the West of Scotland Twenty-07 Study in 1987/8; with four subsequent follow-up interviews approximately every five years until the fifth wave of interviews in 2007/08 (25). The Twenty-07 Study has two subsamples: the regional sample, a two-stage stratified random sample of people of the appropriate ages living in and around the city of Glasgow, and the localities sample, a random sample of people of the appropriate ages from two specific areas of Glasgow. The region and localities samples had the same data collection instruments at all waves, except at wave 3 when the localities sample only received a postal questionnaire with a more restricted set of instruments. Unfortunately this meant the HADS was not administered to the localities sample at this wave. Consequently, this paper is based on the regional sample that was administered measures of depression at each follow-up. The achieved sample at baseline was 3036 (approximately 1000 per cohort); participants comprised three distinct age cohorts born in the early 1970s, 1950s and 1930s. Symptoms of depression were measured at each wave from wave 2 in 1990-92 to wave 5 in 2007/08. Telomere length was measured in blood samples taken at wave 5. Data were available for 1063 respondents who had both telomere data and depression data at each wave. Of these, 337

were aged 37 years, 441, were aged 57 years, and 285 were aged 76 years at the final follow-up in 2007/08. Data, including blood samples at wave 5, were collected by trained nurses in the homes of the study participants. NHS or University of Glasgow ethics committee approval was obtained for each wave of the study and all participants provided informed consent.

Measures

Demographics and health behaviours

Household social class (an accepted index of socio-economic position) was classified as manual or non-manual from the occupation of the head of household, using the Registrar General's (26) classification (26). Head of household was defined as either the participant or his/her spouse/partner, depending on which of the two held the highest occupational status. Smoking status, whether or not antidepressant medication was being taken, was measured at each wave. Presence of long-standing illnesses were measured at wave 5 through coding participants' physical health conditions using Royal College of General Practitioners morbidity codes. A comparison of the three cohorts at baseline with the same geographic area in the 1991 UK census revealed equivalence in terms of sex, social class, and home ownership (27). The sample was almost entirely White, reflecting the West Scotland population from which it was drawn. Household social class, anti-depressive medication status, number of long standing illnesses, and smoking status variables were used as covariates along with age cohort and sex.

Depression and anxiety

Symptoms of depression and anxiety were measured at each wave (except wave 1, hence analyses do not include this wave) using the Hospital Anxiety and Depression Scale (HADS) (28). The HADS is a well-recognised assessment instrument that comprises fourteen items, seven measuring depression and seven measuring anxiety; only the depression items were analysed in the present study. The depression subscale emphasises anhedonia (the inability to experience pleasure from activities previously viewed as enjoyable) and largely excludes somatic items (for example, concentration difficulties, fatigue and appetite disturbances). Items are scored on a 4-point scale, 0 to 3; the higher the score, the greater the depression and anxiety. For this analysis, if only one or

two items on a subscale were missing, the score was calculated as the mean of valid responses multiplied by seven (29). The HADS has good concurrent validity (30, 31), performs well as a psychiatric screening device (31, 32), and boasts acceptable psychometric properties; for example, a Cronbach's α of .90 for the depression items has been reported (33) and test-retest reliability coefficients as high as .85 for depression have been found over two weeks, and .70 for over periods greater than six weeks (31). Continuous depression score was used in all analyses. For the figures, however, the binary cut-off of ≥8 for possible depression caseness was used; this clinically relevant cut-off is derived from the original validation of the scale in medical outpatients against psychiatrists' ratings of caseness (28).

Procedure

At wave 5, respondents' blood was drawn by venepuncture from the median cubital vein (major arm vein) at the end of the interview. Whole blood (4ml) was collected in potassium EDTA vacutainer tubes (Becton Dickinson, New Jersey, USA). The tubes were were stored at 4 degrees centigrade until DNA extraction. DNA was extracted from peripheral blood leukocytes (PBLs) using the Maxwell® automated purification system according to the manufacturer's instructions (Promega, WI, USA). The DNA concentration and purity were quantified using the Nanodrop spectrophotometer (Thermo Fisher Scientific, MA, USA).

Telomere length

Telomere length was analysed at the Institute of Cancer Sciences, University of Glasgow. Telomere lengths in the DNA extracted from PBLs were determined by Q-PCR, following the method of Cawthon (34). Telomere length determination was performed blindly using a Roche Light Cycler LC480. Telomere length analyses were performed in triplicate for each sample, using a single-copy gene amplicon primer set (acidic ribosomal phosphoprotein, 36B4) and a telomere-specific amplicon primer set (35). Quality control parameters employed for the amplifications comprised using a cut off of 0.15 for the standard deviation (SD) of the threshold cycle (Ct) for sample replicates. At a SD above 0.15 the sample was reanalysed. The average SD across plates was 0.05. A control DNA sample was used to generate a standard curve on every plate to enable

absolute quantification analysis. Relative telomere length was estimated from Ct scores using the comparative Ct method after confirming that the telomere and control gene assays yielded similar amplification efficiencies. This method determines the ratio of telomere repeat copy number to single copy gene number (T/S) ratio in experimental samples relative to a control sample DNA. This normalised T/S ratio was used as the estimate of relative telomere length (Relative T/S). It should be noted that the same control DNA sample was used on every plate that was analysed. The intra-assay variation was assessed by comparing the relative telomere estimates (T/S ratio) across assays for the positive controls, which were assayed on every assay plate. The average intra-assay coefficient of variance was 0.56% for telomere and 0.19 % for 36B4 plates.

Data reduction and analyses

Differences in depressive symptom scores between age cohorts, sexes, and by social class were explored using ANOVA. The main analysis was by linear regression, where telomere length was the dependent variable. In order to examine the effects of average depressive symptoms and the change over time, an AUC approach was taken. First, to examine the impact of average depression, we calculated AUC relative to ground, using the trapezoid formula (36). We also calculated AUC relative to baseline – AUC_b, by subtracting depression score at wave 2 from each subsequent measure and again applying the trapezoid method; this provides an indication of the increase or change in symptoms over time. In fully adjusted analyses, assay plate number (a measure of the time order of the assays), age cohort, sex, social class, antidepressant medication and number of limiting longstanding physical illnesses at the time of telomere assessment, were entered first at step 1 as covariates. Tests for a linear trend using ANOVA polynomial contrasts indicates that there is a significant linear association between the plate variable and telomere length, $p = .002$. Depression score was then entered at step 2. In order to examine interactions with age, these models were run again with adjustment for covariates at step 1, mean-centred depression score and age cohort at step 2, and depression * age interaction effects at step 3. Bivariate associations between depression score at waves 2, 3, 4, and 5 and telomere length were examined with and without full adjustment for covariates as above, and interactions with age were tested similarly. Given the importance of age in predicting telomere length, we were also interested in depression and telomere effects within

each age cohort tested separately (coded as 1, 3, and 5, for the youngest, middle, and older groups, respectively). One participant's telomere length datum was removed from the analysis due to being an extreme outlier, thus the statistics presented throughout are based on those with both telomere data and HADS data at all of waves 2 to 5, which resulted in a sample of 1063. Variations in degrees of freedom reflect occasional missing data for some of the covariates. The computer program used for analysis was PASW (SPSS) version 18.

Results

Socio-demographics and depression

Socio-demographic and health behaviour data of the sample overall and for each age cohort at wave 5, when telomere length was measured are shown in Table 1, which illustrates that depression scores increased across the age cohorts. The overall means (SD) across the cohorts for depression scores at wave 2, 3, 4, and 5, were 3.5 (2.81) for the 37 year olds, 3.5 (2.77) for the 57 year olds, and 3.6 (3.06) for the 76 year olds. Depression scores did not significantly differ between males and females, $p = .29$, but were significantly higher among participants from manual occupational households, $p < .001$, with mean (SD)s of 4.7 (3.57) and 3.3 (2.79) for manual and non-manual, respectively. Depression was also significantly lower in the younger 37 year old cohort, $p = .002$, but did not differ between those aged 57 and 76 years, $p = .17$; the mean (SD)s at wave 5 are shown in Table 1.

[Insert Table 1 about here]

Telomere length

Mean (SD) telomere length (Relative T/S ratio) for the sample as a whole was 0.8 (0.20). Older respondents, $F(2,1060) = 41.84$, $p < .001$, $\eta^2 = .073$, and those from manual occupational groups at wave 5, $F(1,1061) = 6.92$, $p = .009$, $\eta^2 = .006$, had significantly shorter telomeres, although this

latter effect is attributable to a higher proportion of manual workers in the eldest 76 year old cohort ($p < .001$), and was rendered non-significant following adjustment for age ($p = .83$). Those with a greater number of limiting longstanding physical illnesses at the time of telomere assessment also had shorter telomeres, $r(1055) = -.13$, $p < .001$. Males, current smokers, and those currently taking anti-depressant medication did not significantly differ in telomere length from those who were female, previous or never smokers, or those not taking such medication.

Depression average and change over time

Using AUC to examine average depressive symptoms, i.e., their chronicity, the mean (SD) AUC was 53.4 (35.63). Unadjusted analyses showed that higher depressive symptoms on average related to shorter telomeres, $\beta = -.09$, $p = .005$. Fully adjusted regression models revealed no effect of symptoms on telomere length, $\beta = -.05$, $p = .15$. However, using the mean-centred interaction term, there was a significant depression * age cohort interaction effect, $\beta = .14$, $p = .047$, $\Delta R^2 = .003$. Analysis by age cohort revealed that a negative association between depression and telomere length was present only for the youngest 37 year old age cohort, $\beta = -.12$, $p = .038$, $\Delta R^2 = .013$, not the middle, $\beta = -.05$, $p = .33$, $\Delta R^2 = .002$, or oldest cohorts, $\beta = .04$, $p = .49$, $\Delta R^2 = .002$. The significant interaction model is shown in Table 2; Figure 1 shows the area under the curve for each age cohort separately.

The change in depression over time was modeled as AUC relative to baseline (AUC_b) in order to examine the impact of increases or decreases in symptom severity across all four waves of data collection. The mean (SD) AUC_b was 1.3 (25.98). In an unadjusted model, there was no association between change in depression over time and telomere length, $\beta = -.02$, $p = .42$. A fully adjusted regression model showed that AUC_b for depressive symptoms was not associated with telomere length, $\beta = -.05$, $p = .11$. However, again, a significant depression * age interaction was revealed, $\beta = .14$, $p = .031$, $\Delta R^2 = .004$, such that AUC_b depression was significantly associated with shortened telomeres, but only in the 37 year olds cohort, $\beta = -.12$, $p = .026$, $\Delta R^2 = .015$, not the middle, $\beta = -.04$, $p = .41$, $\Delta R^2 = .002$, or oldest cohorts, $\beta = .04$, $p = .49$, $\Delta R^2 = .002$. The

significant fully adjusted interaction model is shown in Table 2. The associations between depression AUC and AUC_b with telomere length for each age cohort separately are displayed in Figure 2.

[Insert Table 2 and Figures 1 and 2 about here]

Depression score and telomere length at each wave – unadjusted analyses

In unadjusted analyses, depression at wave 2 was not associated with reduced telomere length, although there was a trend for this association, β = -.05, *p* = .081. At wave 3, β = -.08, *p* = .006, and at wave 4, β = -.07, *p* = .028, greater depressive symptoms related to shorter telomeres years later. At wave 5, there was a cross-sectional negative association between depressive symptoms and telomere length, β = -.07, *p* = .031. For each wave where there was a significant association, analyses were repeated separately for each age cohort. At wave 3, the associations were significant for the youngest 37 year old cohort, β = -.11, *p* = .042, but not the middle, β = -.09, *p* = .070, or older cohorts, β = .05, *p* = .40. At wave 4, the associations were significant for the youngest 37 year old cohort, β = -.15, *p* = .004, but not the middle, β = -.04, *p* = .41, or older cohorts, β = .03, *p* = .58. Finally, at wave 5, the associations were not significant for the youngest, β = -.01, *p* = .79, middle, β = -.07, *p* = .14, or older cohorts, β < .001, *p* = .99.

Depression score and telomere length at each wave – adjusted analyses

In fully adjusted models, depression score at wave 2 was not associated with telomere length, β = .01, *p* = .65, neither was there a significant depression score*age interaction, β = -.02, *p* = .82. At wave 3, depression score was not associated with telomere length, β = -.04, *p* = .25. However, there was a significant depression * age interaction effect, β = .14, *p* = .046, ΔR^2 = .003, such that those with higher depressive symptoms had shorter telomeres 12 years later than those with lower depressive symptoms; this was observed in the younger 37 year old cohort only. For depression at

wave 4, there was similarly no significant effect of depression, $\beta = -.03$, $p = .28$, but there was a significant depression * age interaction, $\beta = .18$, $p = .012$, $\Delta R^2 = .005$, again such that within the youngest cohort only, those with higher depressive symptoms had shorter telomeres. The models were repeated, using depression score at wave 5; depression score was not associated with telomere length, $\beta = -.03$, $p = .45$, and there was no depression * age interaction effect, $\beta = .02$, $p = .72$. The models are shown in Table 2.

Similar analyses were conducted for the anxiety subscale of the HADS. There were no main effects or interactions with age for anxiety score at any follow-up. Analyses are available on request from the authors.

To create an illustrative figure, fully adjusted univariate ANOVAs were conducted using binary depression score variables created using the cut-off for possible clinical depression ($\geq$8) shown by 7-9% of the sample across the waves, as not many (<2%) of the participants reached the suggested cut-off for probable depression ($\geq$11) (28). In the model using depression caseness from wave 3, there was a significant depression * age interaction effect, $F(2,1046) = 3.49$, $p = .031$, $\eta^2 = .007$. Similarly, for wave 4 depression caseness, there was a marginally significant depression * age interaction effect, $F(2,1046) = 2.97$, $p = .052$, $\eta^2 = .006$. The fully adjusted models are displayed in Figure 3. Pairwise comparisons indicated that the significant differences in telomere lengths between those with and without possible depression were within the youngest 37 year old cohort only ($p = .013$ and .012 for waves 3 and 4, respectively). The non-significant effects at wave 5 are also shown in Figure 3.

[Insert Figure 3 about here]

Sensitivity Analysis

In order to correct for bias due to drop out, the above wave-specific regression analyses were repeated but based on those who took part in all five waves and were weighted to the living baseline sample using inverse probability weights (37). These analyses were conducted using the Complex Samples command in SPSS-19 GLM model for linear regression. Broadly the same results emerged. At waves 2 and 5, there were no significant depression score* age interactions, $p = .53$ and .67, respectively. At wave 3, as before, there was a significant depression*age interaction effect, Wald F = 4.47, $p = .035$, such that those with higher depressive symptoms had shorter telomeres 12 years later than those with lower depressive symptoms in the 37 year old cohort only. For depression at wave 4, there was also a significant interaction, Wald F = 4.83, $p = .028$.

Discussion

The present regression analysis of depressive symptoms and telomere length found no main effects of depressive symptoms at each wave. However, there were significant interaction effects with age for average depressive symptoms, change over time, and at two of the waves such that in the younger cohort only who were aged 37 years, those with higher depressive symptoms overall, worsening of symptoms over time, and higher scores at wave 3 in 1995/7 and wave 4 in 2001/04 had shorter telomeres than those with fewer depressive symptoms. These findings withstood adjustment for a range of covariates, but the effect sizes were small.

The lack of associations between average and change in depressive symptoms as well as symptoms at certain time points and telomere length in the older 76 year old group in the present findings are in line with those from studies of depressive symptoms that reported no association with telomere length in older populations (23, 24). However, they contrast with previous studies showing associations between the more stringent measure of MDD and shortened telomeres in individuals of a range of ages (18-21), likely due to the differences in severity between a diagnosis of MDD and depressive symptoms. Further, the HADS does not assess all of the symptoms of MDD, but rather anhedonia in the absence of physical symptoms, thus lack of concordance between the present results and those for MDD might be expected.

Most notably, the present significant interaction effects showed that associations between telomere length and depressive symptomatology overall, change from baseline, and at specific time points only emerged for the younger group, suggesting that for depressive symptoms, effects on telomere length are modest and may only be observable in younger groups where the impact of increasing age, the main predictor of telomere length, on telomere length is less strong. This is surprising, given that the effects of stress are expected to increase cumulatively, thus one might expect stronger effects at older ages. For example, in one study of telomere length and anxiety disorders, stronger associations were found in the older part of the sample aged 48-87 years (13), but DSM classified anxiety rather than symptoms were assessed, thus effects were more likely to be observed than in the present study of symptoms. Alternatively, it is possible that the cause and effects of depression differ greatly between younger and older adults; as early age of illness appears to have adverse effects on prognosis (38, 39), and indeed changed more for the worse in the younger cohort here, it might also be expected that depressive symptoms presenting relatively earlier in life might have stronger associations with markers of ageing, such as telomere length.

These explanations go no way towards determining why, even in the younger cohort, associations were only shown at two time points. However, that the depression AUC and AUC_b showed the same effects for the youngest cohort concurs with the notion that it is the chronicity and worsening of depression which is most strongly associated with telomere shortening (6), although this effect of chronicity has not been observed in all studies (21). In the individual time point analyses, the lack of association for contemporary symptoms might reflect the timing of chronic stress or distress effects on biological ageing, such that a certain time lag is needed before such effects on telomere attrition are observable as shorter telomeres (40). For example, childhood adversity was a stronger associate of shorter telomere length than *current* psychological distress in middle-aged participants (13). What is more surprising is that depressive symptoms approximately 16 years prior to telomere assessment were not associated with telomere length, given previous effects for childhood adversity (41, 42). However, it is perhaps the case that depressive symptoms alone rather than a diagnosis of MDD are not pervasive or severe enough to exert an effect over such a time period.

This might explain why associations were only found for the middle two time points. Alternatively, it is noticeable that the biggest increase in symptoms for the youngest cohort occurred between waves 2 and 3, and 3 and 4. It is possible that it was this surge in depressive symptoms that was driving the associations observed, as this would also influence the AUC and AUC_b values for each cohort.

Given that this study shows some, albeit modest, evidence of an association between depressive symptoms and telomere length in younger adults, what might be the explanation for this relationship? First, it is possible that early life is a sensitive period for telomere attrition to be affected by stress as the effects of other behavioural and socio-demographic variables on telomere length are not always consistent across age groups; in this sample, educational and childhood SES measures were associated with telomere length, but only in the younger cohort (43). Second, depression may not only impact on telomere length via biological pathways but also via negative health behaviours such as dietary fat consumption (44), smoking (45), alcohol consumption (46), and lack of physical activity (47). In the absence of full data on these variables, we were only able to show that smoking behaviour in our sample did not impact upon telomere length. However, it remains possible that these health behaviours differ between the age cohorts, which might explain why associations were only observed in our younger cohort. Certainly we observed that smoking was more common in the younger two cohorts than the 76 year olds. Third, depression is also a common consequence of chronic stress (48), which is known to result in disturbance of multiple systems including the immune system (49), and such processes are thought also to accelerate telomere shortening (14). Thus it is possible that both depressive symptoms and telomere shortening are effects of early life stress, as chronic stress is known to have a role in the aetiology of depression. Certainly, individuals undergoing the chronic stress of caregiving for a spouse with dementia show both higher depressive symptoms and shorter telomeres than matched controls (12); and caregiving mothers with higher perceived stress show shortened telomeres (11). However, in observational studies it is difficult to tease out causality and its direction.

The present study is not without limitations. First, as indicated above, telomere length was only measured at the final wave. However, given that assays for this are a relatively recent development, and the difficulties of collecting blood samples in large epidemiological studies, this is still one of the largest studies to examine telomere length across different age groups. Second, depressive symptoms were measured rather than a diagnosis of depression. However, as depressive symptoms are more common, it was felt important to assess the potential effects on biological ageing of less severe mental distress. However, one of the reasons for our lack of association between depression and telomere length in the older cohort might be our choice of depression assessment. The HADS excludes the physical symptoms of depression, and physical symptoms, such as fatigue, are linked to increased inflammation (50). Inflammation is thought to play a role in telomere attrition as well as increasing with age (51); thus, the absence of physical symptoms from our depression measure might underlie the lack of association with telomere attrition in our older cohort. Finally, as noted above, observational studies cannot determine the direction of causality. That depression results in biological ageing would appear to be the more parsimonious explanation than telomere shortening causing an increase in depressive symptomatology, given that symptoms prior to but not contemporary to telomere assessment related to shorter telomeres. However, it should be acknowledged that a third factor, like inflammation or indeed oxidative stress (52), might contribute to both depressive symptomatology and telomere shortening, and the present analysis suggests that depressive symptoms alone do not consistently relate to telomere length.

In conclusion, depressive symptoms were not consistently associated with shorter telomeres over time. The present modest associations for younger adults for average depression overall and change over time indexed by AUC and at two time points suggest that where associations are observed, the age of the sample and chronicity and worsening of symptoms may influence whether depression is seen to relate to telomere shortening. Replication, potentially with other psychometric measures of depressive symptoms would be needed to confirm this.

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Table 1: Descriptive statistics of the sample overall and by age cohort at wave 5

	Mean (SD) / N (%)				
Variable		Age cohort			*p*
	Overall	Youngest (37 years)	Middle (57 years)	Older (76 years)	
N	1063	337	441	285	-
Age	55.7 (15.12)	36.6 (0.67)	57.1 (111)	76.1 (0.84)	<.001[1]
Sex - male	482 (45)	157 (47)	198 (45)	127 (45)	.85[2]
Manual social class	263 (25)	44 (13)	108 (24)	111 (39)	<.001[3]
Current smoker	225 (21)	76 (23)	111 (25)	38 (13)	<.001[3]
No. longstanding physical illnesses	0.7 (1.12)	0.3 (0.56)	0.7 (1.07)	1.2 (1.43)	<.001[2]
Taking antidepressants	103 (10)	18 (5)	52 (12)	33 (12)	.005[3]
Depression score at wave 5	3.6 (3.06)	3.2 (4.54)	4.1 (4.66)	4.4 (4.50)	<.001[2]
Telomere length – T/S ratio	0.8 (0.20)	0.9 (0.21)	0.8 (0.19)	0.7 (0.19)	<.001[2]

[1] ANOVA
[2] Chi-squared test

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Table 2: Fully adjusted regressions predicting telomere length from depression score, age cohort, and their interaction at each wave, adjusted for sex, social class, assay plate, and medication use.

Depression measure		β	*p*	ΔR^2
Average (AUC)	Step 2: Depression score	-.05	.15	
	Age cohort	-.27	<.001	
	Step 3: Depression x Age cohort	.14	.047	.003
Change (AUC_b)	Step 2: Depression score	-.05	.11	
	Age cohort	-.28	<.001	
	Step 3: Depression x Age cohort	.14	.031	.015
Wave 2	Step 2: Depression score	.01	.65	
	Age cohort	-.28	<.001	
	Step 3: Depression x Age cohort	-.02	.82	.000
Wave 3	Step 2: Depression score	-.04	.25	
	Age cohort	-.27	<.001	
	Step 3: Depression x Age cohort	.14	.046	.003
Wave 4	Step 2: Depression score	-.03	.28	
	Age cohort	-.27	<.001	
	Step 3: Depression x Age cohort	.18	.012	.005
	Wave 5			
	Step 2: Depression score	-.03	.45	

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Age cohort	-.27	<.001	
Step 3: Depression x Age cohort	.02	.72	.000

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Figure 1: Depression scores by age cohort at each wave.

Figure 2: Telomere length against average depression (AUC) for (a) youngest (N = 337), (b) middle (N = 441), and (c) eldest (N = 285) age cohorts, and against change in depression (AUC relative to baseline) for (d) youngest, (e) middle, and (f) eldest age cohorts,. * $p < .05$. Error bars represent standard error of the mean (SE).

Figure 3: Telomere length for the youngest (N = 337), middle (N = 441), and eldest (N = 285) age cohorts for those with and without possible depression ($\geq$8) scores at the (a) wave 3, (b) wave 4, and (c) wave 5. * $p < .05$. Error bars represent standard error of the mean (SE).

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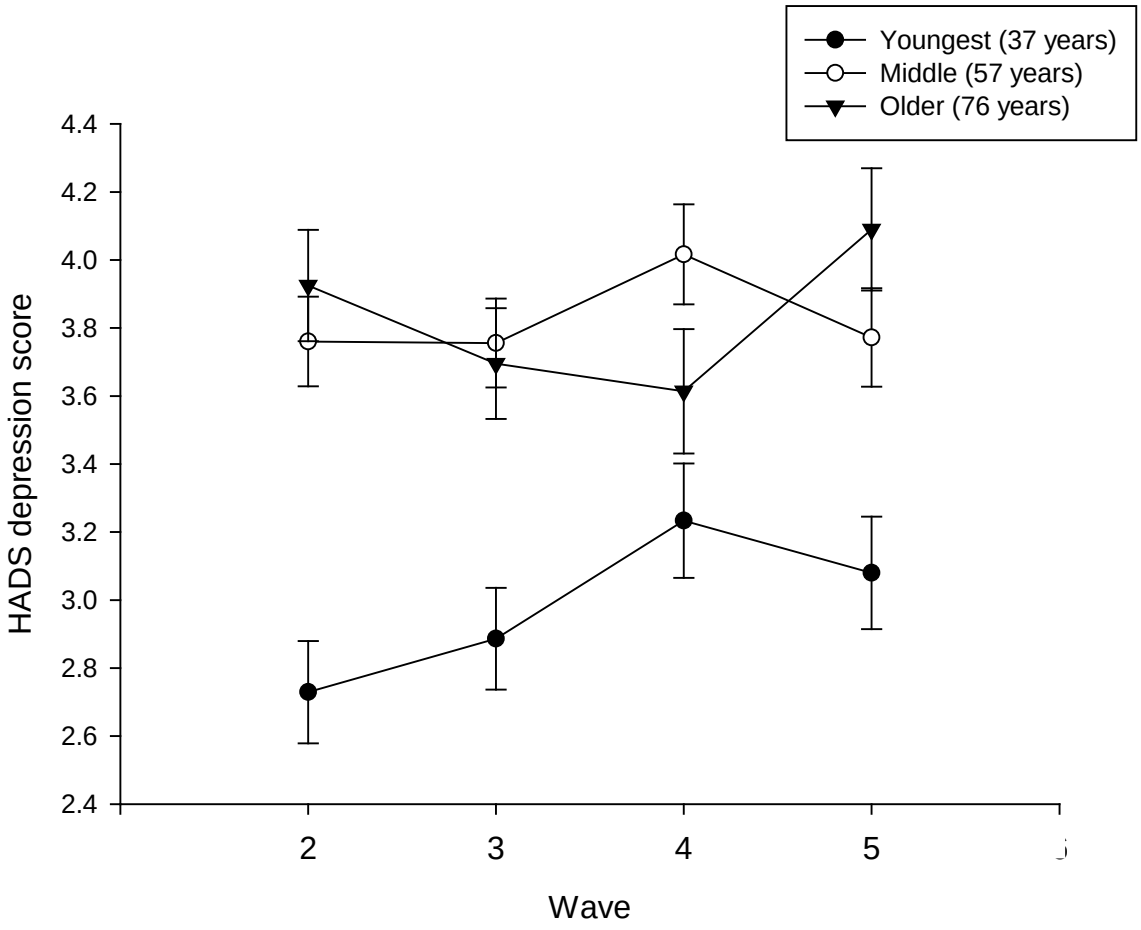

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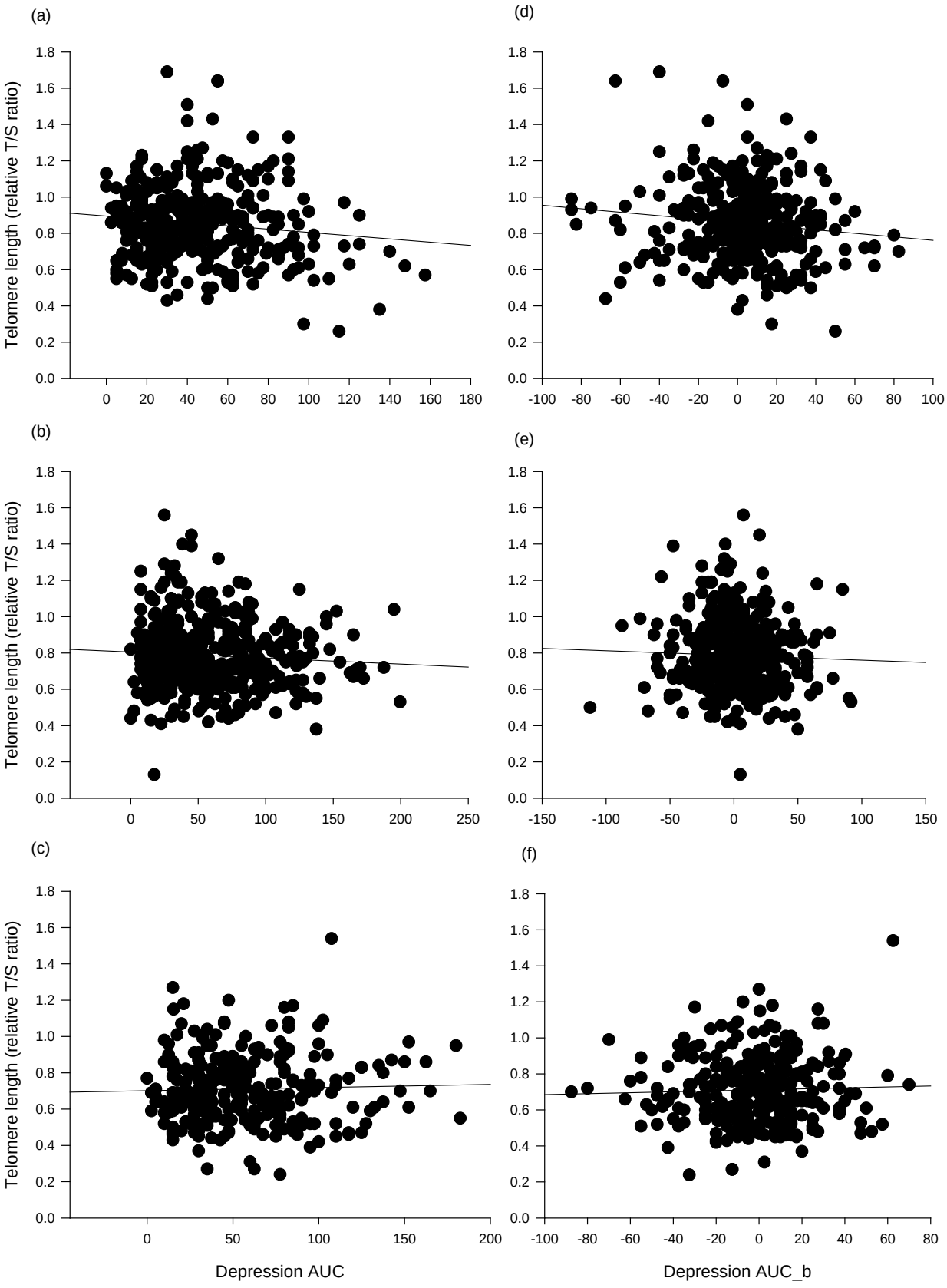

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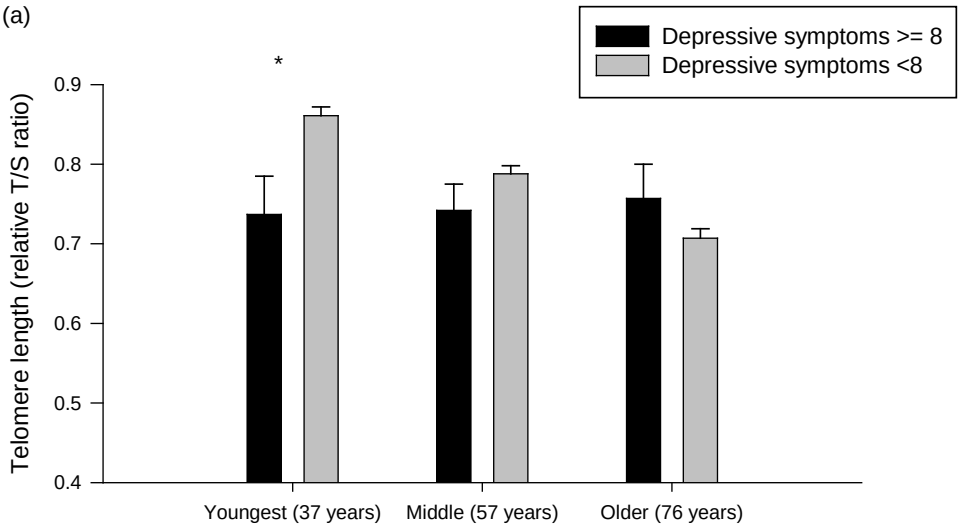

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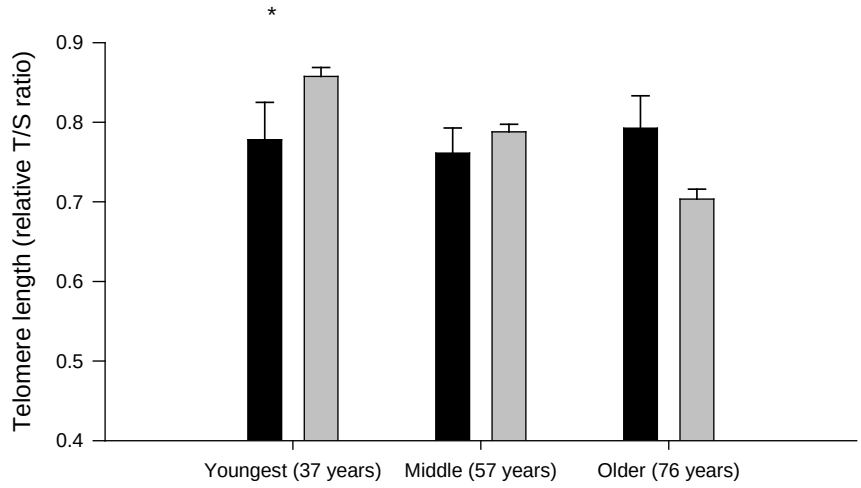

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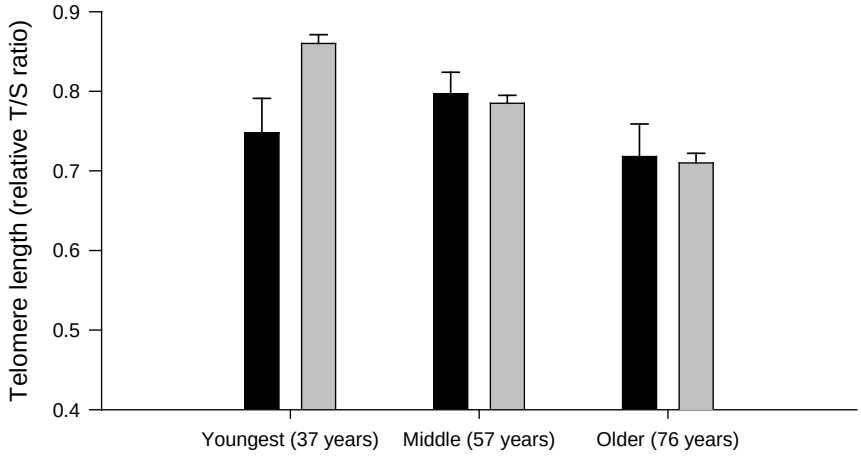

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