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The association between stress and multiple long-term conditions: A cohort study

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ABSTRACT

Background: Stress is an important predictor of long-term conditions. We examine whether hair cortisol (a biomarker of stress) is associated with incidence and accumulation of multiple long-term conditions (MLTC).
Methods: We included data from 4295 individuals aged ≥50 years within the English Longitudinal Study of Ageing dataset with data on hair cortisol, sociodemographic and health behaviour variables. Cox proportional hazards models were used to quantify the association between hair cortisol at baseline and accumulation of MLTC between 2012/2013 and 2018/2019, both for individuals with and without MLTC at baseline.
Results: Our cohort included 1458 (34.0%) individuals who accumulated MLTC between 2012/2013 and 2018/2019. The proportion of individuals with zero, 1, and ≥ 2 conditions at baseline who accumulated MLTC were 12.0% (n = 127), 40.4% (n = 520), and 41.7% (n = 811), respectively. Higher cortisol levels were associated with higher risk of accumulation of MLTC in both unadjusted [HR:1.15(1.05–1.25)] and models adjusted for sociodemographic and health behaviours [HR:1.12(1.02–1.22)]. For individuals without MLTC at baseline, higher cortisol levels were significantly associated with higher risk of developing MLTC in unadjusted [HR: 1.20 (1.05–1.36)] and adjusted models [HR: 1.16(1.02–1.32)].
Conclusion: The study provides the first evidence of the role of stress in the development and accumulation of MLTC. This modifiable risk factor could be targeted to reduce the risk of MLTC. However, further work is needed to better understand the mechanisms and pathways that link stress and accumulation of MLTC.

1. Introduction

In England in 2019, approximately 53% of primary care adults had two or more multiple long-term conditions (MLTC) (multimorbidity) and 33% had three or more multiple long-term conditions. [1] This is an increase of 66% between 2004 and 2019 and prevalence is expected to increase further due to the ageing population. [2] MLTC are defined as the co-existence of two or more chronic conditions in the same individual. [3,4] MLTC are associated with increased risk of premature death, significant reductions in functioning and quality of life, and increased health and social care utilisation and costs. [5–9] Given the growing burden of MLTC, understanding risk factors that could ameliorate the accumulation of MLTC is a high priority research area. The role of stress in the development and worsening of individual chronic disease including cardiovascular disease, diabetes, cancer, obesity and depression is well documented. [10–12] Stress occurs when demands from life events (for example, losing a loved one or losing employment) are greater than an individual's ability to cope with those demands. [13] This results in cognitive appraisals which may influence health through different pathways. First, this appraisal may trigger negative emotions (anxiety, worry or fear) which may result in unhealthy lifestyle behaviours such as smoking, drinking alcohol, or overeating. [14,15] Second, the stress response activates the body's neuroendocrine system, known as the hypothalamic–pituitary–adrenal (HPA) axis, stimulates production of hormones such as adrenaline and cortisol. Chronic exposure to stress results in dysregulation of the HPA and other regulatory systems which may result in the development of chronic diseases. [16–19]

Abbreviations: MLTC, Multiple long-term conditions; ELSA, English Longitudinal Study of Ageing.

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Despite extensive previous research on the role of stress in the development of individual disease, its contribution to MTLC has been poorly examined with previous studies limited by lack of availability of objective measures of stress, as well as small study sample size and short follow-up period. Previous studies have examined the link between perceived stress and MTLC. [20–25] All of these studies were cross-sectional designs. One study reported that perceived stress was increased with MTLC in 238 patients living in Canada. [20] Three studies were based on adults living in low- and middle-income countries and found that perceived stress was associated with MTLC. [22–24] However, measures of perceived stress may be susceptible to self-report bias, do not capture chronic experiences of stress, and have weak correlations with physiological indicators of stress. [15] More recently, studies have assessed stress using cortisol levels in hair samples as an indication of exposure to stress over a prolonged period of up to 6 months. [26–28] Hair cortisol levels have been linked to stress exposures and single diseases, but not to the development or progression of MLTC. [29,30] To address these gaps in the literature, we aimed to quantify the association between stress (measured using the biomarker cortisol) and the risk of accumulation of MLTC over a six-year follow-up period.

2. Methods

This study is reported in line with the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) guidelines.

2.1. Ethics

Ethical approval for the survey was obtained from the National Health Service (NHS) Research Ethics Committees under the National Research and Ethics Service (NRES). Ethical approval for this study was obtained from the University of Southampton Faculty of Medicine Research Committee (67496).

2.2. Data source

The English Longitudinal Study of Ageing (ELSA) is a prospective population-based cohort study of 11,391 individuals aged ≥50 years living in private households in England. Data was collected from 2002 onwards with biennial follow-up in 'waves' denoting data collection periods. At each wave, data on demographic, economic, physical health, mental health and well-being, lifestyle behaviours and psychosocial variables were collected through in-person interviews and self-report questionnaires. Data on clinical variables (e.g.: anthropometric measures, blood pressure readings, blood tests) were additionally collected every four years during a nurse visit. Full details of the sampling design and data collection methodology can be found elsewhere. [31–33] The data has been collated in a database which we accessed to conduct secondary data analysis.

2.3. Follow-up period

We used data from 2012 to 2013 (referred to as wave 6 in the ELSA database) to 2018–2019 (wave 9). Our baseline period was 2012–2013 (wave 6) as this was the first wave to collect measurement data on stress.

2.4. Stress

Hair samples were collected by researchers during the ELSA nurse visit. Hair length of 3 cm closest to the scalp was collected during the nurse visit. Following a wash and steroid extraction procedure, liquid chromatography-mass spectrometry was performed to quantify cortisol levels. [34] Cortisol measures were positively skewed and therefore log-transformed. Values >660 pg/ml were excluded from the analyses, as these were considered extreme values. This approach has been taken by other studies assessing cortisol, including in the ELSA dataset. [35,36] Hair samples were not collected from individuals who were pregnant, breast-feeding, unable to sit with head remaining still, had a scalp condition or hair length of <2 cm at the posterior vertex.

2.5. MLTC

MLTC was defined as the presence of two or more of the following self-reported clinician-diagnosed conditions including: hypertension, diabetes, cancer, chronic lung disease (chronic bronchitis or emphysema), asthma, angina, myocardial infarction, congestive heart failure, heart murmur, arrhythmia, stroke, mental health disorders (depression, anxiety, emotional problems, hallucinations, schizophrenia, psychosis), arthritis, osteoporosis, Parkinson's disease, Alzheimer's disease, dementia, cancer. These conditions were selected based on previous research and Delphi consensuses defining MLTC. [37,38] An additional variable indicating whether two or more conditions were reported at any follow-up wave (for individuals without MLTC at baseline) or an increase of one or more conditions since baseline were reported at any follow-up wave (for individuals with MLTC at baseline) was created. Accumulation of MLTC was therefore defined as an increase from zero or 1 condition at baseline to ≥2 conditions or any increase in number of conditions from ≥2 conditions at baseline. [39] For individuals with zero or 1 condition at baseline, an additional variable indicating whether they reported ≥2 chronic conditions (i.e., newly-formed MLTC) at any follow-up wave was created.

2.6. Covariates

Baseline data on sociodemographic and health behaviour variables were included as these have been shown to be associated with stress and health. [40,41] Sociodemographic variables were age (continuous), sex (male, female), ethnicity (white/non-white), marital status (single, married, cohabitating, widowed, divorced or separated), educational attainment (no qualification, education below degree, degree level education), occupation type (managerial and professional, intermediate, routine and manual). Health behaviour variables were smoking (non-smoker, ex-smoker, current smoker), physical activity levels (low/sedentary, moderate, high) and alcohol consumption (not at all in last 12 months, 1–2 times a year or every couple of months, once or twice a month, once or twice a week, 3–6 days a week, almost daily). Hair characteristics (hair colour, treatment (dyed or chemically treated) and assay phase), were also included as covariates as studies have found that these factors may alter cortisol levels and therefore need to be accounted for. [42,43]

2.7. Statistical analysis

Descriptive statistics were used to summarise baseline characteristics. A series of Cox proportional hazard models were fitted on the analytical sample to quantify the association between cortisol level at baseline and time to accumulation of MLTC (censoring for end of study or loss of follow-up, whichever occurred first). Study wave was used as a proxy of time to accumulation of MLTC where year of diagnoses was not available. Proportional hazards assumptions were checked visually using plots of Schoenfeld residuals. Model 1 included cortisol level, hair characteristics (hair colour, whether treated (and if so, treatment type), assay phase). Model 2 additionally adjusted for sociodemographic variables (age, sex, ethnicity, marital status, educational attainment, occupation type as an indicator of socioeconomic status, and employment status). Model 3 additionally adjusted for health behaviours (smoking status, physical activity levels, and alcohol consumption). A similar set of models were fitted to assess the association between cortisol level at baseline and incidence of MLTC in individuals without MLTC at baseline, both for individuals with <2 conditions at baseline and individuals with zero or 1 condition separately. All analyses were conducted unweighted in STATA 17.0.

3. Results

A total of 10,601 individuals completed the baseline (ELSA wave 6) interview, of whom 4911 (46.3%) provided hair samples, and 4761 (44.9%) individuals had plausible values of cortisol. Our analytical sample included 4295 (40.5%) individuals aged ≥50 years old and with data on all covariates (Fig. 1). Baseline characteristics of our analytical sample were similar to the full sample (Table 1 and Supplementary Table 1). Mean age of the study sample was 67.4 (9.1) years of age, 2878 (67.0%) were female, and 54.7% (2348/4295) individuals did not have MLTC at baseline. One thousand four hundred and fifty-eight individuals (34.0%) accumulated MLTC between 2012/2013 and 2018/2019. The proportion of individuals with zero, 1, and ≥ 2 conditions at baseline who accumulated MLTC were 12.0% (n = 127), 40.4% (n = 520), and 41.7% (n = 811), respectively. Two hundred and fifty (17.1%; 250/1458) individuals experienced an increase in number of conditions at more than one wave and 48 (3.3%) individuals experienced an increase in number of conditions at non-consecutive waves. The proportion of individuals who accumulated MLTC between 2012/2013–2014/2015, 2014/2015–2016/2017, 2016/2017–2018/2019 were 16.2% (621/3842), 14.3% (536/3760), and 13.7% (517/3764), respectively. The proportion of individuals with incident MLTC between 2012/2013–2014/2015, 2014/2015–2016/2017, 2016/2017–2018/2019 were 12.2% (258/2117), 11.8% (245/2073), 11.4% (241/2106), respectively.

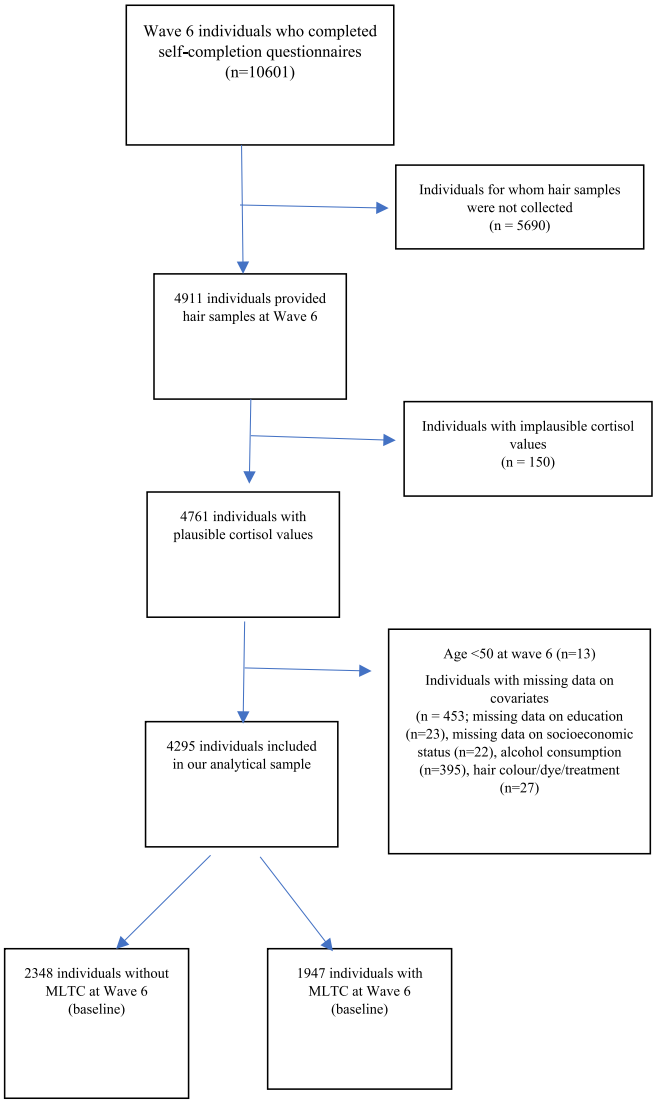

Fig. 1. Selection of the study sample.

3.1. Stress and accumulation of MLTC

Higher cortisol levels were associated with higher odds of accumulation of MLTC during the follow-up period, both in unadjusted [HR (95% CI): 1.15(1.05–1.25)] (p < .01) and models adjusting for sociodemographic variables [HR (95% CI): 1.13(1.04–1.23)] (p = .01) (Table 2). Cortisol levels remained significantly associated with accumulation of chronic conditions, even after additionally adjusting for health behaviours [HR (95% CI): 1.12(1.02–1.22)] (p = .01).

3.2. Stress and incident MLTC

Higher hair cortisol levels were significantly associated with higher odds of developing MLTC in unadjusted models [HR (95% CI): 1.20 (1.05–1.36)] (p < .01). This association remained significant after adjusting for sociodemographic covariates alone [HR (95% CI): 1.17 (1.03–1.33)] (p = .02) as well as after adjusting for sociodemographic and health behaviours [HR (95% CI): 1.16 (1.02–1.32)] (p = .02) (Table 2). A stronger association between cortisol level and risk of incident MLTC was observed for a subsample of individuals with zero conditions at baseline [unadjusted HR: 1.48 (1.11–1.97) (p = .01) and fully-adjusted HR: 1.46 (1.08–1.97) (p = .01)]. However, for individuals with 1 condition at baseline, higher cortisol levels were not significantly associated with risk of incident MLTC [unadjusted HR: 1.08 (0.93–1.24) (p = .31) and fully-adjusted HR: 1.05 (0.91–1.21)] (p = .53).

4. Discussion

To our knowledge, this is the first study to examine the association between stress (measured objectively using hair cortisol) and the accumulation of MLTC over an extended follow-up of six years. We found that higher hair cortisol levels were associated with higher risk of accumulation of MLTC overall, as well as higher risk of incidence of MLTC in those without MLTC at baseline. The association between cortisol level and MLTC was not explained by health behaviours. In our analysis of a subsample of individuals with 1 condition at baseline, cortisol level was not significantly associated with risk of incident MLTC. This may be due to individual differences as well as differences in the proportion of individuals with specific conditions at baseline; In our sample, hypertension, diabetes, stroke and arthritis were significantly correlated with cortisol levels. Compared to individuals with 1 condition at baseline, a higher proportion of individuals with 2 or more conditions had hypertension (31.2% vs 65.1%), diabetes (3.5% vs 19.7%), stroke (0.9% vs 8.0%) and arthritis (35.1% vs 65.3%).

4.1. Comparison to existing literature

Our findings are consistent with previous studies examining the association between stress (measured using objective markers) and single diseases. [27] For example, Jackson et al. (2017) reported that high levels of hair cortisol were associated with obesity in a study of 2527 individuals in the ELSA dataset. [27] A growing body of studies (sample sizes ranging from 32 to 3675) have found that high levels of hair cortisol were associated with incidence and prognosis of cardiovascular diseases. [30] In a study of 102 workers, Janssens et al. (2017) reported higher mean levels of hair cortisol in workers with depressive symptoms compared to those without. [44] A study of 9222 Australian adults used life events as a proxy for stress and found that work-related and personal and family-related stress contributed to the development of individual diseases such as depression, circulatory diseases, and type 2 diabetes. [45]

Our findings are also consistent with the limited existing studies that have examined the link between stress and MLTC, albeit using self-

Table 1
Baseline characteristics of study sample.

Characteristic	Total sample (n = 4295)	Zero or 1 condition at baseline (n = 2348)	Zero conditions at baseline (n = 1062)	1 condition at baseline (n = 1286)	≥2 conditions at baseline (n = 1947)
Mean age	67.4 (9.1)	65.2 (8.4)	63.5 (7.9)	66.5 (8.5)	70.1 (9.1)
Female, n (%)	2878 (67.0)	1514 (64.5)	663 (62.4)	851 (66.2)	1364 (70.1)
White Ethnicity, n (%)	4211 (98.0)	2297 (97.8)	1037 (97.6)	1260 (98.0)	1914 (98.3)
Education, n (%)					
No qualifications	998 (23.2)	440 (18.7)	174 (16.4)	266 (20.7)	558 (28.7)
Intermediate	1987 (46.3)	1106 (47.1)	516 (48.6)	590 (45.9)	881 (45.3)
Degree level or higher	777 (18.1)	520 (22.2)	246 (23.2)	274 (21.3)	257 (13.2)
Foreign/other	533 (12.4)	282 (12.0)	126 (11.9)	156 (12.1)	251 (12.9)
Marital status*, n (%)					
Married	2841 (66.1)	1672 (71.2)	755 (71.1)	917 (71.3)	1169 (60.0)
Cohabitating	15 (0.4)	11 (0.5)	6 (0.6)	5 (0.4)	4 (0.2)
Single, never married	240 (5.6)	135 (5.7)	72 (6.8)	63 (4.9)	105 (5.4)
Widowed	684 (15.9)	248 (10.6)	80 (7.5)	168 (13.1)	436 (22.4)
Separated/Divorced	515 (12.0)	282 (12.0)	149 (14.0)	133 (10.3)	233 (12.0)
Socioeconomic status (NS-SEC3 classification), n (%)					
Managerial and professional occupation	1522 (35.4)	914 (38.9)	433 (40.8)	481 (37.4)	608 (31.2)
Intermediate occupation	1184 (27.6)	666 (28.4)	301 (28.3)	365 (28.4)	518 (26.6)
Routine and manual occupation	1553 (36.2)	752 (32.0)	322 (30.3)	430 (33.4)	801 (41.1)
Other	36 (0.8)	16 (0.7)	6 (0.6)	10 (0.8)	20 (1.0)
Currently working, n (%)	1341 (31.2)	971 (41.4)	532 (50.1)	439 (34.1)	370 (19.0)
Smoking status					
Non-smoker	1730 (40.3)	1008 (42.9)	462 (43.5)	546 (42.5)	722 (37.1)
ex-smoker	2127 (49.5)	1082 (46.1)	465 (43.8)	617 (48.0)	1045 (53.7)
Smoker	438 (10.2)	258 (11.0)	135 (12.7)	123 (9.6)	180 (9.2)
Physical activity level, n (%)					
No activity	252 (5.9)	72 (3.1)	25 (2.4)	47 (3.7)	180 (9.2)
Mild activity	655 (15.3)	223 (9.5)	75 (7.1)	148 (11.5)	432 (22.2)
Moderate activity	2073 (48.3)	1159 (49.4)	502 (47.3)	657 (51.1)	914 (46.9)
Vigorous activity	1315 (30.6)	894 (38.1)	460 (43.3)	434 (33.7)	421 (21.6)
Alcohol consumption, n (%)					
not at all last 12 months	576 (13.4)	205 (8.7)	82 (7.7)	123 (9.6)	371 (19.1)
Once/twice a year/every couple months	772 (18.0)	373 (15.9)	173 (16.3)	200 (15.6)	399 (20.5)
Once or twice a month	513 (11.9)	272 (11.6)	121 (11.4)	151 (11.7)	241 (12.4)
Once/twice a week	973 (22.7)	582 (24.8)	262 (24.7)	320 (24.9)	391 (20.1)
3–6 days a week	858 (20.0)	558 (23.8)	261 (24.6)	297 (23.1)	300 (15.4)
Almost daily	603 (14.0)	358 (15.2)	163 (15.3)	195 (15.2)	245 (12.6)
Hair treated, n (%)	1711 (39.8)	943 (40.2)	434 (40.9)	509 (39.6)	768 (39.4)
Phase					
1	2380 (55.4)	1311 (55.8)	553 (52.1)	758 (58.9)	1069 (54.9)
2	1915 (44.6)	1037 (44.2)	509 (47.9)	528 (41.1)	878 (45.1)
Cortisol level (pg/ml)	0.9 (0.6)	0.9 (0.6)	0.8 (0.5)	0.9 (0.6)	0.9 (0.6)
Accumulated MLTC by 2018–2019, n (%)	1458 (34.0)	647 (27.6)	127 (12.0)	520 (40.4)	811 (41.7)

reported perception of stress. [20–25,46,47] Two of these studies were longitudinal studies – one study assessing the link between perceived stress and use of primary care services in individuals with MLTC over a 1-year follow-up period and a separate study investigating the association of perceived stress with hospitalization and all-cause mortality (30 days following hospitalization) in individuals with MLTC over an almost 4-year follow-up period. [46,47] The longitudinal nature, longer follow-up period, and use of biomarkers in the present study extends previous studies in this field and provides further evidence for the role of stress in the accumulation of MLTC.

4.2. Strengths and limitations

Strengths of the study include a relatively large cohort, the availability of a range of measures (including biomarker of stress), and longitudinal study design which allowed us to examine prospective associations whilst accounting for relevant confounders. However, the study has some limitations. Firstly, the study uses self-report measures of health variables (as well as covariates) which may not be accurate due to recall or memory-related issues and social desirability bias. Secondly, we used selected health conditions and were not able to include certain conditions such as chronic kidney or liver disease which were not collected as part of the survey. Similarly, we were not able to adjust for medication data such as use of steroids or cardiovascular medication,

Table 2
Unadjusted and adjusted associations of hair cortisol with accumulation (n = 4295) and incidence of MLTC (n = 2348).

	Unadjusted model*	Model adjusted for sociodemographic characteristics	Model adjusted for sociodemographic + health behaviour variables
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Accumulation of MLTC			
Hair cortisol	**1.15 (1.05–1.25)**	**1.13 (1.04–1.23)**	**1.12 (1.02–1.22)**
Incident MLTC			
Hair cortisol	**1.20 (1.05–1.36)**	**1.17 (1.03–1.33)**	**1.16 (1.02–1.32)**

* Unadjusted model additionally included hair characteristics and diabetes. Bold font = statistically significant.

which have been found to be associated with cortisol levels in hair samples. [43] Thirdly, our analyses did not use sampling weights to account for non-response. Although the ELSA dataset includes sampling weights, these were not appropriate for individuals who provided hair samples and responded at waves 6 to 9. Fourthly, the majority of our sample were of white ethnicity. It is therefore possible that our findings may not be generalisable to other ethnic groups. However, it is likely that stronger associations may be found for ethnic minority groups as they have been found to report higher levels of stress. [48]

4.3. Implications for clinical practice and future research

Accumulating evidence suggests that stress may be causally implicated in development of chronic diseases, and this study further suggests the need to examine whether stress might be a target for interventions that could reduce the subsequent risk of developing or accumulating MLTC. More broadly, the study emphasises the importance of assessing non-biological factors in the primary care setting. Understanding the holistic care needs of patients can improve the quality of care and allow development of more tailored and effective interventions for patients. To date, there has been little evidence for the effectiveness of interventions targeting MLTC, including those using a 'whole person' approach. A model of care which additionally assesses patients' responses to stress (resulting from health as well as social situation and life events) and stratifies patients based on their stress response levels may improve care and outcomes for patients. However, further work is needed to better understand the mechanisms and pathways that link stress and MLTC, as we did not find evidence for a role of health behaviours in the link between stress and MLTC. Future research is also needed to determine how best to capture and incorporate stress data into routine primary care (and primary care data collection) and intervention strategies.

Consent for publication

Not applicable.

Role of the funding source

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Declaration of Competing Interest

The authors declare that they have no competing interests to report.

Data availability

The English Longitudinal Study of Ageing (ELSA) data can be publicly accessed through UK Data Service portal. Data and supporting documents are available from: https://www.elsa-project.ac.uk/accessing-elsa-data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychores.2023.111566.

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