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Insomnia symptoms as long-term predictors of anxiety symptoms in middle-aged and older adults from the English Longitudinal Study of Ageing (ELSA), and the role of systemic inflammation

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ABSTRACT

Insomnia, i.e., difficulties in sleep onset and sleep maintenance, may increase the risk of anxiety symptoms, although long-term follow-up studies are rarely reported. Here, we examined whether insomnia symptoms may predict anxiety symptoms in a 9-year follow-up, and whether inflammation may play a mediating role. Data from 1355 participants (63.44 ± 7.47 years, 55.1 % females) from the English Longitudinal Study of Ageing (ELSA) were analysed. Insomnia symptoms were assessed in 2012/13. High-sensitivity C-reactive protein (hs-CRP), a marker of systemic inflammation, was measured in 2016/17. Anxiety symptoms were assessed in 2020/21. After adjusting for confounders and baseline levels, structural equation modelling (SEM) revealed that insomnia symptoms significantly predicted anxiety symptoms ($\beta = 0.357$, $p < .001$) but not hs-CRP ($\beta = -0.016$, $p = .634$). Similarly, hs-CRP was not related to anxiety symptoms ($\beta = -0.024$, $p = .453$). The hs-CRP mediation hypothesis was therefore rejected ($\beta = 0.0004$; 95 % BCI -0.001 to 0.005), and multi-group SEM showed that sex did not moderate these paths. However, baseline diagnoses of anxiety disorders prospectively predicted higher hs-CRP ($B = 0.083$, $p = .030$). Results of the current study suggest that individuals with baseline anxiety disorders may be at higher risk of developing low-grade chronic inflammation. Several alternative psychophysiological mechanisms linking insomnia and anxiety symptoms should be explored, including autonomic and cortical pre-sleep arousal, cortisol reactivity, and pro-inflammatory cytokines. Finally, insomnia symptoms may be a treatment target to lower the risk of anxiety symptoms in elderly.

1. Introduction

The prevalence of insomnia in adults (i.e., persistent difficulties in sleep onset and/or sleep maintenance, [1]) is remarkably high, with estimates ranging from 5.8 to 19 % in Western societies for clinically diagnosed insomnia [2,3], and up to 48 % for insomnia symptoms (i.e., occurring ≤3 nights per week; [4]). Insomnia is associated with poorer quality of life [5] and dysregulated affect dynamics including high emotional reactivity and affect variability [6] and emotion dysregulation [7,8].

The co-occurrence of insomnia and anxiety has long received attention in psychopathology. Adult individuals with anxiety disorders show longer sleep onset latency and night-time wakefulness compared to controls with large effect sizes in meta-analyses of polysomnographic data [9] and subjective sleep measures [10]. While sleep problems are traditionally considered a consequence of anxiety states (e.g., pre-sleep worries may disrupt subsequent sleep in adults; [11]), evidence exists that insomnia itself may exacerbate anxiety across the lifespan [12,13], so that the two conditions may eventually be bidirectionally connected and reinforcing one another (e.g., Ref. [14]). Considering the temporal dynamics of the insomnia-anxiety connection, longitudinal epidemiological studies highlighted that individuals with insomnia without anxiety at baseline had higher risk of developing anxiety disorders compared to healthy sleepers, with large effect sizes at short-to medium-term follow-ups (OR: 3.23, CI: 1.52–6.85, [15]). Consistent evidence from ecological momentary assessment studies shows that poorer sleep was associated with increased anxiety symptoms the next day in adult samples [16,17]. Indirect evidence that insomnia may even *cause* anxiety derives from experimental sleep manipulation studies showing that partial and total sleep deprivation may lead to increased anxiety in individuals of all ages [18], while insomnia resolution leads to improvement in anxiety symptoms in middle adults and elderly (Benz et al.,

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2019; [19]). However, long-term longitudinal studies of insomnia and anxiety are lacking [20], despite being particularly necessary considering the age-dependent linear increase of insomnia [4], and the high prevalence of anxiety symptoms in older adults [21].

Several physiological and biological variables have been hypothesised to play a mediatory role between insomnia and anxiety, including dysregulation of corticolimbic brain circuits (e.g., Ref. [22]), and hypothalamic-pituitary-adrenal (HPA) axis hyperarousal (e.g., Ref. [23]). Most recently, the activation of the inflammatory immune system has been invoked as a possible mediator (e.g., Ref. [24]).

Inflammation is a biological process orchestrated by the innate immune system as a response to physical damage, pathogen exposure, and psychosocial threats [25]. Chronic stress conditions are usually associated with increased peripheral inflammatory markers concentrations, including cytokines and acute-phase proteins such as C-reactive protein (CRP) [26]. Notably, sleep is believed to be a key modulator of the inflammatory response (e.g., Ref. [27,28]). Experimental sleep deprivation has been associated with the activation of nuclear factor-kappaB, a key transcriptional control pathway in the inflammatory response [29], while prolonged experimental sleep disturbance (i.e., chronic manipulation of sleep onset and nocturnal wake), may lead to the down-regulation of D-series resolvins, which are inflammatory resolution mediators [30]. Moreover, individuals with self-reported insomnia tend to show an inflammatory profile characterised by increased proinflammatory cytokines (i.e., interleukin[IL]-6, IL-1β, TNF-α), and CRP [31,32]. Importantly, upregulation of inflammatory response has also been cross-sectionally observed in individuals with anxiety disorders, who show on average a rise in CRP when compared to controls (e.g., Ref. [33–35]). Interesting evidence also suggests that inflammatory activation may be aetiologically involved in the development of affective symptoms including depressive and anxiety symptoms (e.g., Ref. [36,37]). For example, innate immune activation through simulated bacterial infection (i.e., lipopolysaccharide (LPS-)induced inflammation) is associated with state anxiety and low mood in experimental human [38,39] and animal models [40], although contrasting evidence was also reported (e.g., Ref. [41,42]). Van Eeden et al. [43] recently reported that LPS-induced inflammation was associated with somatic symptoms of anxiety and agoraphobia.

In this context, the English Longitudinal Study of Ageing (ELSA) is a population-based panel study conducted in Britain since 2002 [44], including periodic assessment of health variables and inflammatory markers. Using ELSA data, we recently showed that insomnia symptoms assessed in 2008/09 (wave 4) were predictive of depressive symptoms in 2016/17 (wave 8) through the mediation of high sensitivity CRP (hs-CRP) assessed in 2012/13 (wave 6) in women [45]. In 2023, data on wave 10 of ELSA was released and included the first assessment of anxiety symptoms in this cohort. This allowed us to estimate the longitudinal association between insomnia symptoms and anxiety symptoms using a long-term (9 years) follow-up, and to further test the potential mediatory role of inflammation. In this study, we hypothesised that baseline insomnia symptoms would be associated with higher hs-CRP in the mid-term assessment and higher anxiety symptoms at follow-up, and that hs-CRP would partially mediate the association between insomnia and anxiety symptoms.

2. Methods

2.1. Procedure and participants

This research used data from the English Longitudinal Study of Aging (ELSA; Zaninotto and Steptoe, 2019; Banks et al., 2019). ELSA participants provided written informed consent, and ethical approval was obtained from the National Research Ethics Service (see Ref. [46] for detailed study procedures). For the aims of the present investigation, three waves of data collection were considered: insomnia symptoms were assessed in 2012/2013 (wave 6); hs-CRP protein was assessed in 2016/2017 (wave 8); and anxiety symptoms were assessed in 2020/2021 (wave 10).

We analysed an analytical sample of 1355 participants who provided complete data for the main variables under investigation (i.e., key data at all three waves; see Supplementary Fig. 1). The main reasons for missing data in ELSA include non-respondents (i.e., those who lack contact, refuse to participate, or cannot be traced) and non-eligibility (i.e., deaths or relocation outside of Great Britain) (see Cheshire et al., 2011). At baseline, the sample was predominantly composed of females (55.1 %). The mean age was 63.44 years (SD = 7.47). Regarding marital status, 72.5 % were married, 5.8 % cohabited, and 21.8 % were single. Moreover, 29.2 % of the sample performed vigorous sports more than once a week, 12.3 % once a week, 12.3 % one to three times a month, and 46.2 % hardly ever/never. A small percentage of the respondents (8.3 %) did not have an alcoholic drink during the last 12 months. Mean Body Mass Index (BMI) was 27.91 kg/m2 (SD = 4.89), with values ranging from 16.9 to 53.3 kg/m2. Descriptive statistics are summarised in Supplementary Table 1.

2.2. Measures

2.2.1. Insomnia symptoms

Insomnia symptoms were assessed using three items derived from the Jenkins Sleep Problems Scale [47]. These items assess difficulties falling asleep, the frequency of nocturnal awakenings, and the frequency of waking up feeling tired and worn out over the preceding month. Respondents rated each item on a four-point scale, ranging from 0 (not during the last month) to 3 (three or more times a week). The resulting item scores were summed to create a total score (range 0–9), with higher scores indicative of more severe insomnia symptoms. The Jenkins Sleep Scale has been previously used in longitudinal cohort studies (e.g., Ref. [48–50]). Cronbach's alpha in the present sample was 0.60; however, measurement error was partialled out in further analysis through a latent variable approach.

2.2.2. Inflammation

hs-CRP (mg/L), a marker of systemic inflammation [51], was assessed from blood drawn from participants' forearms during a nurse visit. Participants were instructed to refrain from eating, smoking, consuming alcohol, or engaging in vigorous exercise for 30 min preceding the nurse visit. hs-CRP levels were quantified using the N Latex CRP mono immunoassay on the Behring nephelometer analyser II. Blood samples were processed and analysed at the Royal Victoria Infirmary laboratory in Newcastle upon Tyne, UK.

2.2.3. Anxiety symptoms

Anxiety symptoms at follow-up were assessed using the 7-item Generalized Anxiety Disorder (GAD-7) scale [52]. The scale is composed of seven items corresponding to symptoms based on the criteria for GAD in the Diagnostic and Statistical Manual of Mental Disorders, such as "Feeling nervous, anxious or on edge", "Not being able to stop or control worrying", "Being so restless that it is hard to sit still", and "Worrying too much about different things". Participants were asked to rate how often they have been bothered by the aforementioned symptoms on a 4-point scale, ranging from 1 ("Not at all") to 4 ("Nearly every day"). The resulting item scores were summed to create a composite score, where higher scores indicate more pronounced anxiety. Cronbach's alpha in the present sample was 0.89.

2.2.4. Covariates

Several covariates measured at baseline (wave 6) were included in the analysis due to their associations with insomnia, inflammation and/or anxiety symptoms (see Ref. [8,41,45]): age; BMI; income; alcohol drinking frequency over the last 12 months (ranging from "not at all in the last 12 months to "almost every day"); smoking (dummy variable: 0 = no and 1 = yes); frequency of vigorous sports activity (ranging from

"never" to "more than once a week"); diagnosis of depressive disorders (dummy variable: 0 = no and 1 = yes); and newly diagnosed cardiovascular diseases (i.e., high blood pressure, angina, heart attack, congestive heart failure, heart murmur, abnormal heart rhythm, diabetes, stroke diagnosis, high cholesterol). Furthermore, baseline levels of hs-CRP were considered as a control variable to disentangle the longitudinal component of the mediation effect (Jose, 2016). Similarly, the presence of anxiety disorder diagnosis at wave 6 was considered as a control measure in the absence of another measure of anxiety levels. At each ELSA wave, participants were asked if a doctor had ever diagnosed them with 'any emotional, nervous or psychiatric problems.' Participants responding "yes" to this screening item were then asked to identify which problems they had, including "anxiety".

2.3. Data analysis

Data were analysed using IBM SPSS v.25 (IBM Corporation, Armonk NY; USA) and Mplus v. 8.6 [53]. Preliminarily, descriptive statistics and bivariate Pearson's correlations for the main variables under investigation were calculated. Due to the substantial non-normality of hs-CRP, we computed its logarithm to normalise the variable as recommended by Tabachnick and Fidell [54]. However, considering the 4-point scoring of the Jenkins Sleep Problems Scale and non-negligible deviations from univariate normality (i.e., skewness and kurtosis $> |1|$; [55]), items were treated as categorical and weighted least square parameter estimates with robust standard errors and mean and variance-adjusted chi-square test statistics (WLSMV; [53]) were employed to deal with non-normal and ordinal indicators.

Afterwards, the mediating role of hs-CRP in the relationship between insomnia symptoms and inflammation was examined within a structural equation modelling (SEM) framework. Firstly, the factorial validity and empirical distinctiveness of the latent dimensions of insomnia and anxiety were analysed using a confirmatory factor analysis (CFA; [56]). Insomnia symptoms were defined through their three items as manifest indicators. Concerning anxiety symptoms, we relied on a parcelling approach, which has several advantages over using single indicators (e.g., higher reliability, and fewer parameter estimates; see Ref. [57]). Specifically, three parcels were constructed by sequentially assigning items on the basis of their corrected item-total correlations (i.e., *balancing approach*; [57]). Discriminant validity between the two dimensions was further examined through the *phi* method (see Ref. [58]). After providing empirical evidence of validity for the set of latent constructs, we specified a partial mediation model linking insomnia to anxiety symptoms via hs-CRP (see Fig. 1). The significance of the indirect effect was formally tested by calculating 95 % bias-corrected bootstrap confidence intervals (5000 resamples; [59]). Indirect effects whose confidence intervals did not encompass zero were considered statistically significant. According to a multifaceted approach to the assessment of model fit (Tanaka, 1993), several indices were considered to evaluate the fit of the models to the observed data [60,61]: Comparative Fit Index and Tucker-Lewis index (CFI and TLI; >0.90 indicates reasonable fit), Root Mean Square Error of Approximation (RMSEA; <0.08 indicates reasonable fit), and Standardized Root Mean Square Residual (SRMR; <0.08 indicates reasonable fit).

As a further step, we examined whether sex moderated the relationships between insomnia symptoms, hs-CRP, and anxiety symptoms by employing multi-group structural equation modelling and considering sex as a grouping variable [62,63]. This allowed us to examine both the mediating role of inflammation in the relationship between insomnia symptoms and anxiety symptoms, as well as the moderating role of sex on such paths, in light of current evidence suggesting sex differences in insomnia symptoms and anxiety symptoms in older females [64,65]. From a practical standpoint, we constrained the main structural paths to be equal across the two sex groups. Constraints that were found to be untenable through the nested chi-square difference test pointed out the presence of a moderating effect, i.e., a statistically significant difference in the effect of a variable on another between males and females (e.g., Ref. [66]). In order to properly examine the moderation hypothesis, we preliminarily performed factorial invariance tests to examine whether the latent dimensions under investigation were measured consistently across sexes [67]. Specifically, configural (i.e., same pattern of free and fixed loadings), metric (i.e., equivalence of factor loadings), and scalar (i.e., equivalence of items' thresholds) invariance models were specified. To evaluate and compare the fit of these nested models, we calculated the differences in CFI (ΔCFI) and RMSEA (ΔRMSEA). As suggested by Wang & Wang [61], CFI and RMSEA differences larger than 0.01 and 0.15, respectively, would indicate a meaningful worsening in model fit.

3. Results

3.1. Preliminary analyses

Means, standard deviations, and zero-order correlations for the main

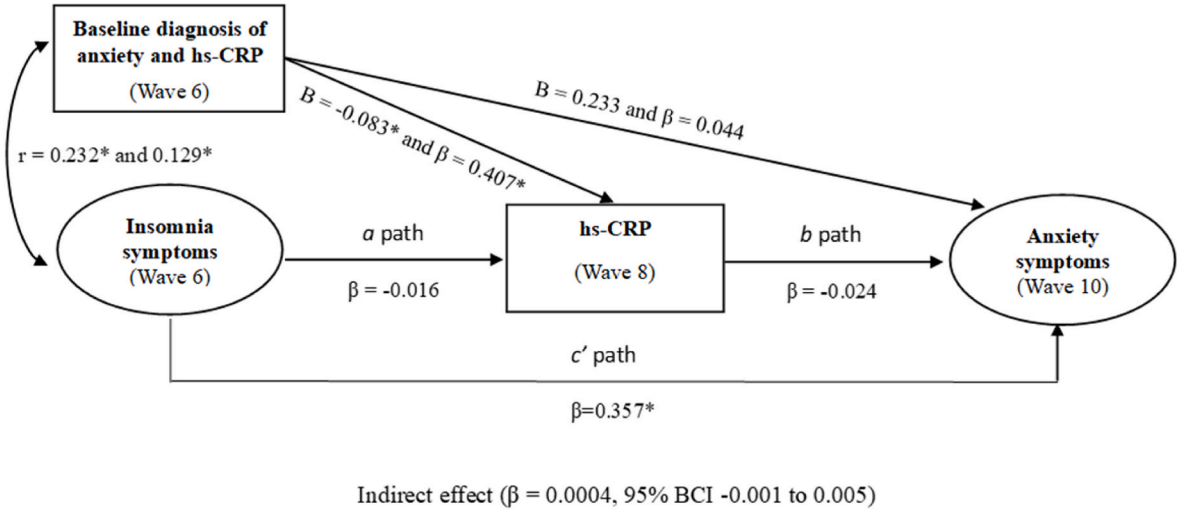

Fig. 1. Longitudinal mediation model. Note: hs-CRP was log-transformed due to a substantial deviation from univariate normality (see Ref. [54]). *β* represents completely standardised beta coefficients, *B* represents unstandardised structural coefficients, and *r* represents bivariate correlations. Covariates were not reported to avoid clutter (i.e., age, BMI, income, alcohol drinking frequency, smoking, sports activity, diagnosis of depressive disorders, and cardiovascular diseases). *p < .05.

study variables are reported in Table 1. More specifically, insomnia symptoms at wave 6 were cross-sectionally ($r = 0.102$, $p < .001$) but not longitudinally ($r = 0.050$, $p = .068$) correlated with hs-CRP. Also, insomnia symptoms at wave 6 were significantly correlated with anxiety symptoms at wave 10 ($r = 0.259$, $p < .001$). Conversely, hs-CRP at wave 8 was not significantly associated with anxiety symptoms at wave 10 ($r = 0.031$, $p = .249$). As expected, baseline diagnosis of anxiety (wave 6) was significantly related to anxiety symptoms at wave 10 ($r = 0.180$, $p < .001$). Similarly, hs-CRP correlated across wave 6 and 8, highlighting a medium-to-high relative stability ($r = 0.470$, $p < .001$).

3.2. Structural equation models

3.2.1. Measurement model

Initially, we conducted a CFA examining the latent factors of insomnia symptoms and anxiety symptoms, with each dimension defined by its corresponding items/parcels serving as manifest indicators. The CFA model demonstrated satisfactory fit indices: $\chi2(8) = 53.698$, $p < .001$; RMSEA = 0.065 (90 % CI 0.049–0.082); CFI = 0.996, TLI = 0.993, SRMR = 0.026. As reported in Supplementary Table 2, standardised item loadings on the intended factors ranged from 0.520 to 0.944 ($M = 0.780$, $SD = 0.147$). Notably, the latent correlation between insomnia symptoms and anxiety symptoms was 0.382 ($p < .001$), and fixing this correlation to 1 resulted in a significant chi-square difference test, providing discriminant validity evidence: $\Delta\chi2\ (1) = 700.410$, $p < .001$. Overall, these findings underscored the factorial validity and empirical distinctiveness of the two latent dimensions.

3.2.2. Unadjusted structural model

After confirming the validity of the measurement model, we proceeded to estimate a longitudinal mediation model, positing an indirect relationship between insomnia symptoms (wave 6) to anxiety symptoms (wave 10) via hs-CRP (wave 8). Baseline diagnosis of anxiety disorders and levels of hs-CRP (wave 6) were accounted for to disentangle the longitudinal component of the mediation effect (Jose, 2016). The model exhibited an excellent fit to the data: $\chi2(20) = 71.594$, $p < .001$; RMSEA = 0.044 (90 % CI 0.033–0.055); CFI = 0.996, TLI = 0.993, SRMR = 0.023. Findings showed a direct effect of insomnia symptoms on anxiety symptoms ($\beta = 0.359$, $p < .001$), i.e., higher levels of insomnia symptoms at wave 6 predicted increased anxiety symptoms at wave 10, eight years later. Insomnia symptoms at wave 6 were not associated with hs-CRP at wave 8 ($\beta = -0.006$, $p = .847$), which in turn was not associated with anxiety symptoms at wave 10 ($\beta = -0.028$, $p = .362$). Accordingly, the mediation hypothesis was rejected ($\beta = 0.0002$; 95 % BCI -0.002 to 0.006). Baseline diagnosis of anxiety disorder (wave 6) significantly predicted higher levels of hs-CRP at wave 8 ($B = 0.073$, $p = .037$), even after adjusting for baseline inflammation.

3.2.3. Adjusted structural model

Relevant potential confounders such as age, BMI, income, alcohol drinking frequency, smoking (0 = no and 1 = yes), frequency of vigorous sports activity, diagnosis of depressive disorders (0 = no and 1 = yes), and cardiovascular diseases (0 = no and 1 = yes) were further included in the analysis as covariates. The model exhibited an excellent fit to the observed data: $\chi2(52) = 246.940$, $p < .001$; RMSEA = 0.053 (90 % CI 0.046–0.059); CFI = 0.986, TLI = 0.963, SRMR = 0.025. Findings confirmed that insomnia symptoms were directly associated with anxiety ($\beta = 0.357$, $p < .001$), such that higher levels of insomnia symptoms at wave 6 were predictive of increased anxiety symptoms at wave 10, eight years later. Insomnia symptoms at wave 6 were not related to hs-CRP at wave 8 ($\beta = -0.016$, $p = .634$), which in turn was not associated with anxiety symptoms at wave 10 ($\beta = -0.024$, $p = .453$). Consistently, the mediation hypothesis was rejected ($\beta = 0.0004$; 95 % BCI -0.001 to 0.005). Baseline diagnosis of anxiety disorder (wave 6) confirmed its positive association with hs-CRP at wave 8 ($B = 0.083$, $p = .030$). As expected, hs-CRP was relatively stable across wave 6 and wave 8 ($\beta = 0.407$, $p < .001$). With respect to the covariates, BMI was positively associated with hs-CRP ($\beta = 0.140$, $p < .001$), whilst alcohol exerted a negative albeit negligible influence on hs-CRP ($\beta = -0.046$, $p = .031$). Overall, the model explained 25 % of the variance in hs-CRP and 16 % of the variance in anxiety symptoms (see Fig. 1).

3.2.4. Sex-stratified model

Sex differences in the structural paths were investigated by relying on a multigroup approach. Within multi-group SEM, the interaction effects between a categorical variable (sex) and continuous predictors are examined by imposing equality constraints on the structural paths (e.g., Ref. [62,63]). As a prerequisite for testing the moderating role of sex, factorial invariance tests were conducted to ensure that the two latent dimensions of insomnia symptoms and anxiety symptoms were measured consistently across sexes. Specifically, the configural two-factor model fitted well when tested simultaneously on males and females, suggesting that the same pattern of free and fixed loadings held for the two groups: $\chi2(16) = 67.646$, $p < .001$; RMSEA = 0.069 (90 % CI 0.053–0.086); CFI = 0.996, TLI = 0.993, SRMR = 0.030. Similarly, both metric (ΔCFI = −0.002; ΔRMSEA = 0.008) and scalar (ΔCFI = −0.002; RMSEA improved by 0.018) invariance models were fully supported, highlighting the equivalence of factor loadings and items' thresholds, respectively. Invariance constraints were consistently retained for further analyses.

Thereafter, a multigroup SEM analysis was conducted based on the previously estimated mediation model, and the three main structural parameters were constrained to be equal across sexes (i.e., *a, b,* and *c' paths*; see Fig. 1). The hypothesised model, with the structural parameters constrained to equality across males and females, exhibited an excellent fit to the data: $\chi2(133) = 357.727$, $p < .001$; RMSEA = 0.050 (90 % CI 0.044–0.056); CFI = 0.982, TLI = 0.964, SRMR = 0.029. A comparison between this model and an alternative unconstrained model yielded a non-significant chi-square difference test: $\Delta\chi2\ (3) = 4.061$, $p = .255$. Thus, the multigroup analysis indicated that all structural parameters were invariant across sexes. Consistent with the analysis conducted on the overall sample, hs-CRP did not mediate the longitudinal relationship between insomnia symptoms and anxiety symptoms in males ($\beta = 0.001$; 95 % BCI -0.002 to 0.013) nor in females ($\beta = 0.001$; 95 % BCI -0.002 to 0.013).

Table 1
Descriptive statistics and zero-order correlations for the main variables. Note: CRP was log-transformed due to a substantial deviation from univariate normality [54]. *p < .05.

Variable	Mean (SD)/%	1	2	3	4	5
1. Insomnia symptoms (wave 6)	6.79 (2.56)					
2. Anxiety disorder diagnosis (wave 6)	5.2 % yes	0.185*				
3. hs-CRP_Log (wave 6)	0.42 (0.29)	0.102*	0.026			
4. hs-CRP_Log (wave 8)	0.41 (0.31)	0.050	0.062*	0.470*		
5. Anxiety symptoms (wave 10)	10.15 (3.84)	0.259*	0.180*	0.084*	0.031	

4. Discussion

The aim of this study was to test the long-term association between insomnia symptoms and anxiety symptoms, exploring the potential mediatory role of hs-CRP, a marker of systemic inflammation. Results highlighted that baseline insomnia symptoms were significantly associated with anxiety symptoms at 9-year follow-up. The standardised effect size appeared robust ($\beta = 0.361$, $p < .001$), even after controlling for the presence of clinically defined anxiety conditions at baseline and other potential confounders. This result extends previous evidence on

the short- and medium-term predictive role of insomnia on anxiety in young and middle aged adult populations (e.g., Ref. [68–70]).

Baseline insomnia symptoms were associated with later hs-CRP in correlation analysis but not in structural models, and as a consequence, CRP did not mediate the association between baseline insomnia symptoms and follow-up anxiety symptoms. Previous meta-analytic investigations detected significantly higher CRP in adult individuals with insomnia disorder compared to controls (e.g., Ref. [31,32]), and up to 22 % of those with insomnia display CRP>3 mg/L, as indicative of possible low-grade chronic inflammation. Indeed, we previously found that insomnia symptoms were slightly associated with hs-CRP in ELSA [45]. Several explanations may account for these results. First, ELSA includes individuals from the general population of older adults rather than clinically defined patients with insomnia disorder. Moreover, in Ballesio et al. [45], we were not able to control for the baseline assessment of hs-CRP. Therefore, it is possible that after controlling for the baseline, statistical significance might be lost. Consistent with this, a recent Mendelian randomisation study, an analytic procedure which overcomes the influence of confounders, suggested the lack of causality between genetically defined insomnia and inflammation [32]. Research on the directionality of insomnia/inflammation link remains, however, in its youth [28], and experimental studies in adult samples still suggest that insomnia may drive inflammation [30]. Putatively, a wide range of alternative biological and physiological mechanisms other than hs-CRP may underlie the association between insomnia and anxiety symptoms. For instance, which specific inflammatory marker may be relevant in anxiety remains debated [34]. A recent mice model showed that IL-6 had a detrimental effect on transcriptional signature of monocytes in peripheral and central circulation after stress induction that was associated with anxiety [71]. In adults, the association between insomnia and IL-6 may also be stronger than that with CRP [31], and IL-6 may also be more strongly affected by circadian rhythm variations [72], which are frequent among individuals experiencing insomnia [73]. Unfortunately, the data collection protocol for ELSA prevented cytokines such as IL-6 from being assessed, so the mediatory role of cytokines between insomnia and anxiety remains to be tested. Also, heightened cortisol reactivity throughout the 24 h has been reported in individuals with insomnia disorder [74], and may be associated with anxiety symptoms in adults [75] and elderly [76]. Cortical and autonomic hyperarousal may also be involved. For instance, increased fast frequency EEG activity during non-rapid eye movement sleep in adult individuals with insomnia disorder as compared to healthy sleepers has been reported and proposed to reflect excessive sensory processing which may predispose to anxiety symptoms [77]. Similarly, sympathetic hyperarousal has been observed in both insomnia disorder and anxiety disorders [78,79]. Future studies may enrich this field examining the potential mediatory role of these factors.

Importantly, while hs-CRP did not longitudinally predict follow-up anxiety symptoms in our sample, the presence of a diagnosis of anxiety disorder at baseline was significantly associated with higher hs-CRP in the mid-term assessment, even after controlling for baseline inflammation. This result is consistent with a previous population-based study in middle aged and older adults [41] showing that anxiety disorders at baseline were associated with an increase of hs-CRP in follow-up period, independent of confounders such as smoking, physical activity, BMI, and anti-inflammatory drugs, while baseline hs-CRP was not prospectively associated with anxiety disorders at follow-up. Again, a possible explanation of these findings may involve the autonomic nervous system. For instance, low resting state heart rate variability, which is frequently detected in those with anxiety conditions [80], has been associated with heightened inflammation across the lifespan [81].

Clinically, the results of the current study support the role of sleep onset and sleep maintenance as potential targets for reducing anxiety symptoms in older adults. Guideline-recommended treatment for insomnia in adults is cognitive behavioural therapy for insomnia (CBT-I), which is a multi-component treatment aiming at rebuilding sleep-related physiological processes and restructuring sleep-related cognitions [65]. Numerous meta-analyses of randomised controlled trials unequivocally demonstrated that CBT-I is robustly effective in improving subjective sleep and daytime functioning of middle aged and older adult patients with insomnia with moderate to large effect sizes (Ballesio et al., 2018; [82]). Moreover, meta-analyses also demonstrated that CBT-I may reduce anxiety symptoms and worry [19,83]. Our results suggest that reducing insomnia symptoms may potentially lower the risk of anxiety symptoms in elderly. Older adults would benefit from being screened for insomnia symptoms, and being referred for evidence-based treatments accordingly.

4.1. Limitations

Several limitations of the present study should be acknowledged. First, insomnia symptoms were evaluated using three items derived from the Jenkins Sleep Problems Scale, which covered nighttime insomnia symptoms such as difficulties falling asleep, nocturnal awakenings, and waking up tired. However, this precluded the assessment of daytime consequences of insomnia (e.g., fatigue, cognitive difficulties), as well as satisfaction with sleep patterns or sleep-related worry. Future studies may benefit from the inclusion of self-report scales with greater content validity (e.g., Ref. [84]). Relatedly, in order to overcome the limitations of retrospective self-report scales, future studies may consider integrating objective sleep assessments, such as polysomnography, along with semi-structured clinical interviews for anxiety symptoms (e.g., Structured Clinical Interview for DSM-5; [85]). This multifaceted approach would provide a more comprehensive understanding of the interplay between sleep, inflammation, and anxiety. Furthermore, it is worth noting that the participants enrolled in the ELSA study were adults aged over 50, and that the majority of our sample (98.5 %) were of White ethnicity. Therefore, caution should be exercised when generalising findings to a broader population, and future replication studies involving adolescents and young adults are warranted. The anxiety assessment procedure coincided with the post pandemic period (2020/2021), and this could have somewhat influenced the results. Nearly 65 % of older adults perceived an increase in anxiety during the pandemic [86]. However, our results are in line with Meaklim et al. [69] study demonstrating that insomnia predicted persistent anxiety even during the pandemic. Additionally, it is worth noting that CRP shows significant intra-individual variations [87] and may vary depending on the time of year [88]. Thus, alternative longitudinal designs, such as ecological momentary assessment, may be better suited to examine daily variations and relationships between sleep, anxiety and inflammation. It is also plausible to hypothesise a bidirectional relationship between insomnia and anxiety symptoms, with the two conditions reinforcing one another (see Ref. [14] for a systematic review). Unfortunately, the assessment of anxiety symptoms through a standardised continuous measure was first included in wave 10 of ELSA, preventing the assessment of the bi-directionality of the posited model. Related to this, we were only able to include the control of anxiety disorder diagnosis at the baseline, rather than the levels of anxiety symptoms. Future studies are needed to examine a complete longitudinal mediation model that allows for the exploration of all potential pathways between sleep, inflammation, and anxiety over time. Finally, personality traits such as neuroticism, arousability predisposition or maladaptive perfectionism were not investigated although their possible role predicting insomnia symptoms and/or anxiety symptoms [89–91].

5. Conclusions

The current study highlighted insomnia symptoms as long-term predictors of anxiety symptoms in older adults from the general population. Results did not differ between men and women, and remained significant after controlling for anxiety disorders diagnosis at the baseline. Notably, the presence of baseline anxiety disorders was associated

with a prospective increase in hs-CRP, suggesting that the biological features of anxiety disorders may involve innate immune system activation. Contrary to our hypotheses, we found no robust evidence that insomnia symptoms were prospectively associated with hs-CRP. Therefore, the current study does not support the mediatory role of CRP in the association between insomnia and anxiety symptoms. Several alternative psychophysiological mechanisms may link insomnia and anxiety symptoms, including vegetative (i.e., autonomic) and cortical pre-sleep arousal [24,69], and cortisol reactivity [74], and the role of pro-inflammatory cytokines such as IL-6 should be further tested in future investigations [24]. Putatively, current results suggest that insomnia symptoms may be a potential target for evidence-based interventions in older adults, which may reduce the risk of anxiety symptoms in this population.

Declaration of generative AI in scientific writing

Authors did not use generative AI or AI-assisted technologies in writing this manuscript.

CRediT authorship contribution statement

Andrea Zagaria: Writing – review & editing, Writing – original draft, Visualization, Software, Formal analysis, Data curation. **Andrea Ballesio:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization.

Declaration of competing interest

With respect to the manuscript entitled: "**Insomnia as a long-term predictor of anxiety symptoms in the English Longitudinal Study of** Ageing **(ELSA), and the role of systemic inflammation**".

Authors have no conflict of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2024.09.020.

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