STRESS AND SLEEP ASSOCIATIONS WITH MENTAL HEALTH:

A PSYCHONEUROIMMUNOLOGY AND PRECISION MEDICINE FRAMEWORK

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Student Declaration

I, Odessa S. Hamilton, confirm that the work presented in this thesis is my own and has not been submitted for any other academic award. Where information is from other sources, I confirm that this has been appropriately indicated, and work completed in collaboration with others is indicated as such.

Signature: [redacted] Date: **1 October 2024**

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Table of Contents

ACRONYMS

2SMR	Two-sample Mendelian randomization
ACTH	Adrenocorticotropic hormone
APC	Antigen-presenting cell
APP	Acute-phase proteins
AIC	Akaike information criterion
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AUTS2	Activator of transcription and developmental regulator gene
β	Standardised beta regression coefficient
B	Unstandardised beta regression coefficient
BBB	Blood-brain barrier
BBSRC	Biotechnology and Biological Sciences Research Council
BD	Bipolar disorder
BDNF	Brain-derived neurotrophic factor
bFGF	Basic fibroblast growth factor
aBIC	Adjusted Bayesian information criterion
BIC	Bayesian information criterion
BMI	Body mass index
CAPI	Computer-assisted personal interviews
CCA	Complete case analysis
CES-D	Centre for Epidemiological Studies Depression Scale
CI	95% confidence interval
Cortisol	Hair cortisol
COVID-19	Coronavirus disease (i.e., SARS-CoV-2)
CNS	Central nervous system
CRH	Corticotrophin releasing hormone
CRP	C-reactive protein
CTACK	Cutaneous T-cell attracting chemokine
DAG	Directed acyclic graph
DALY	Disability-adjusted life-years
DEPICT	Data-Driven Expression-Prioritized Integration for Complex Traits
DNA	Deoxyribonucleic acid
DSM	Diagnostic and Statistical Manual of Mental Disorders
ELSA	English Longitudinal Study of Ageing
ESRC	Economic and Social Research Council

Fb	Fibrinogen
fMRI	Functional magnetic resonance imaging
g/L	Grams per litre
GAMLSS	Generalized Additive Model for Location, Scale and Shape
GCSE	General Certificate of Secondary Education
GR	Glucocorticoid receptor
GWAS	Genome-wide association studies
$H_{\#}$	Hypotheses
HDL	High-density lipoprotein
HGF	Hepatocyte growth factor
HPA-axis	Hypothalamic-pituitary-adrenal-axis
hr	Hour
HR	Hazard ratio
hsCRP	High sensitivity C-reactive protein
i-n	Immune and neuroendocrine
ICD	International Classification of Diseases
IGF-1	Insulin growth factor-1
IMD	Index of Multiple Deprivation
KNN	K-nearest neighbours
IL-#	Interleukins (numbered by order of discovery)
IL-1ra	IL-1 receptor antagonist
IVs	Instrumental variables
IVW	Inverse-variance weighted estimate
IQR	Interquartile range
L	Liters
LDL	Low-density lipoprotein
log	Logarithmic transformation
LPA	Latent profile analysis
LRT	Likelihood ratio test
m	Independent markers in genotyping panel
M	Mean
MAF	Minor allele frequency
MAPKAP1	Mitogen-activated protein kinase associated protein 1 gene
MAR	Missing at random
MCID	Minimal clinically important difference
MCP3	Monocyte-specific chemokine 3
Md	Median

MDD	Major depressive disorder
mg/L	Milligrams per litre
MICE	Multiple Imputation by Chained Equations
MIDAS	Midlife in the United States
ML	Maximum likelihood
mmol/l	Millimoles per litre
mRNA	Messenger ribonucleic acid
MR	Mendelian randomization
N/n	Number of observations
NHS	National Health Service
NIHR	National Institute for Health and Care Research
NK	Natural killer cells
NRMSE	Normalized root mean squared error
OCD	Obsessive-compulsive disorder
OLS	Ordinary least squares
OSC	Occupational social class (abbreviated also to occupation)
OR	Odds ratio
p	Significance (alpha) level
PAX8	Paired Box 8 gene
PC	Principal components
PFC	Proportion of falsely classified
pg/mg	Picograms per milligram
PGC	Psychiatric Genomics Consortium
PGS	Polygenic score
PNI	Psychoneuroimmunology
PPAE	Percentage of the protective association explained
PSG	Polysomnography
P_T	p-value threshold
PTSD	Post-traumatic stress disorder
PYAR	Person-years at risk
r	Correlation statistic
RCT	Randomised controlled trial
Ref	Reference category
REM	Rapid eye movement
RQ	Research question
RRR	Relative risk ratio
S#	Supplementary materials number

SAM-axis	Sympathetic–adrenal–medullary-axis
SCZ	Schizophrenia
SD	Standard deviations (±)
SE	Standard errors
SES	Socioeconomic status
SNP	Single-nucleotide polymorphisms
SNS	Sympathetic nervous system
SWS	Slow-wave sleep
TNF-α	Tumor necrosis factor-alpha
TRAIL	TNF-related apoptosis-inducing ligand
UCL	University College London
UK	United Kingdom
UKB	UK Biobank
USA	United States of America
VRK2	Vaccinia Related Kinase 2 gene
W	Wave
WBC[C]	White Blood Cell [Counts] (i.e., leukocytes)
WHO	World Health Organization

GREEK LETTERS

α	Alpha
ε	Epsilon
K	Kappa
χ	Chi
μ	Mu
π	Pi
σ	Sigma

THESIS PUBLICATIONS

The work carried out as part of this thesis has contributed to the following publications, as formally declared in APPENDIX F:

1. Hamilton, O. S., Iob, E., Ajnakina, O., Kirkbride, J. B. & Steptoe, A. Immune-neuroendocrine patterning and response to stress. A latent profile analysis in the English longitudinal study of ageing. *Brain, Behavior, and Immunity* **15**, 600-608 (2023) https://doi.org/10.1016/j.bbi.2023.11.012.

2. Hamilton, O. S. & Steptoe, A. Socioeconomic determinants of inflammation and neuroendocrine activity: A longitudinal analysis of compositional and contextual effects. *Brain, Behavior, and Immunity* **107**, 276–285 (2022). https://doi.org/10.1016/j.bbi.2022.10.010

3. Hamilton, O. S. & Steptoe, A. Financial stress and sleep duration in immune and neuroendocrine patterning. An analytical triangulation in ELSA. Brain, Behavior, and Immunity S0889159125000911 (2025) doi:10.1016/j.bbi.2025.03.006.

4. Hamilton, O.S., Steptoe, A. & Ajnakina, O. Polygenic predisposition, sleep duration, and depression: evidence from a prospective population-based cohort. *Transl Psychiatry* **13**, 323 (2023). https://doi.org/10.1038/s41398-023-02622-z.

5. Hamilton, O.S., Cadar, D. & Steptoe, A. Systemic inflammation and emotional responses during the COVID-19 pandemic. *Transl Psychiatry* **11**, 626 (2021). https://doi.org/10.1038/s41398-021-01753-5

ABSTRACT

Stress has a well-documented role in mental health, but molecular mechanisms are uncertain. This thesis adopts a psychoneuroimmunological and precision medicine framework to explore likely sleep and biological pathways. **Chapter 1** reviews extant literature, providing a foundation for the multidisciplinary approach detailed in **Chapter 2** that uses English Longitudinal Study of Ageing data. The five following studies address different parts of the framework. **Chapter 3** ($STUDY_1$) compares compositional and contextual socioeconomic stressors in immune-neuroendocrine activity. **Chapter 4** ($STUDY_2$) explores immune-neuroendocrine patterning and its response to common stressors, considering genetic predisposition. **Chapter 5** ($STUDY_3$) tests independent, interactive, and genetic associations between stress and suboptimal sleep in latent categorisation of biological risk. **Chapter 6** ($STUDY_4$) investigates suboptimal sleep and depression directionality through polygenic predisposition. **Chapter 7** ($STUDY_5$) assesses inflammation and subclinical depression associations when experiencing pandemic-related stress. **RESULTS.** Stress was a key driver of immune-neuroendocrine processes in older adults. Financial factors, at the individual-level, were more salient than differences in neighbourhood deprivation. Financial stress was associated with short but not long sleep and was associated with distinct immune-neuroendocrine profiles. Suboptimal sleep was not associated with immune-neuroendocrine profiles, and it did not moderate associations. Phenotypic findings supported bidirectionality between suboptimal sleep and depression, but polygenic analyses showed a unidirectional association of short sleep on depression. Pre-pandemic inflammation increased vulnerability to subclinical depression during the pandemic. **CONCLUSIONS.** Those with fewer socioeconomic resources are more vulnerable to biological stability, which may contribute to risk of depression. Independently of neighbourhood deprivation, financial stress emerged as a potential target for reducing short sleep and offers a promising pathway for understanding immune-neuroendocrine changes. However, there is limited evidence that stress and sleep act synergistically in biological processes. Although sleep duration is a less persuasive target for immune-neuroendocrine changes in older adults, a more direct role in depression was identified.

CONCEPTUAL OVERVIEW

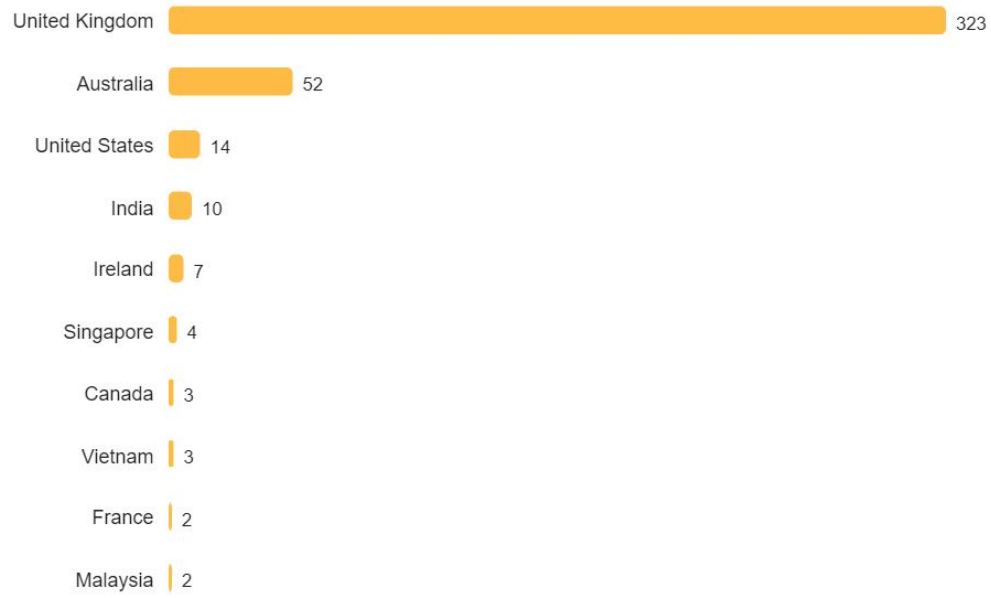
Accounting for approximately one-third of disability worldwide, mental ill-health comes at a tremendous personal and societal cost.[1] Many health care systems are overburdened by both subclinical forms of mental distress among the general population[2] and psychopathology in clinical populations.[3] Interestingly, mounting evidence has revealed the potential for a shared aetiology or common phenotypic expression across the mental health spectrum.[4,5] In spite of the distinct diagnostic classifications between common and severe mental disorders, there are noteworthy conceptual, clinical, and causal links that should prevent entirely distinct lines of study.[6,7] Moreover, mental ill-health is biologically complex, driven by a network of interdependent mechanisms. Thus, my interest is to establish whether mental illnesses share common antecedents using a single psychoneuroimmunological and precision medicine framework. Psychoneuroimmunology (PNI) being the connective pathway between cognition and the physiological response of the immune, nervous, and endocrine systems.[8] Precision medicine being the use of statistical and genomic strategies to enable a more precise targeting of subgroups with disease.[9] It is predicated on an increased understanding of the genetic and molecular mechanism of disease, to improve diagnostic sensitivity, and to make it possible to intervene earlier.[10] Both approaches consider variability in biology, behaviour, and environment. Together they offer an improved model for the prediction, prevention, and treatment of disease. The role of stress in mental health is well-documented, but the biological and genetic contributions to this dynamic remain unclear.[11] Evidence points to stress-induced suboptimal sleep and adverse immune-neuroendocrine responses,[12,13] as pathways through which stress leads to psychological dysfunction.[14–16] There is, however, the issue of directionality.[17–20] Stress, sleep, and immune-neuroendocrine activity have historically been thought of as epiphenomena of or secondary to mental ill-health, but a growing literature suggests that they may be prodromal.[21,22] For this reason, and to strengthen causal inference, I test associations within the present framework using advanced statistical techniques, and genetically informed designs.[23–25]

IMPACT STATEMENT

Leveraging advanced statistical, epidemiological, and genomic methods, in observational and summary-level data, I hope to advance the understanding of the synthesis between stress, sleep, immune, and neuroendocrine processes in maintaining mental health. I have generated evidence on how stress associated with material deprivation, and other psychosocial stressors, ultimately contributes to adverse mental states, through genetic, biological, and sleep mechanisms. In this respect, critical gaps in the literature and key methodological issues have been addressed.

The evidence generated has been disseminated through various channels, including peer-reviewed publications, academic articles, blogs, journalistic interviews, news articles, media appearances, social media, conferences, and lectures. The hope remains to raise awareness, broaden the reach of acquired knowledge, and pursue the sustainability of its impact. One paper, for example, captured more than 400 articles worldwide in a day of release (***Figure 1.1***) and was featured by The Guardian, The Independent, The Telegraph, The Washington Post, and elsewhere. Published work has received over 75,000 views, with a single blog reaching an audience of over 10,000.

Figure 1.1 Global article tracker coverage of doi.org/10.1038/s41398-023-02622-z on 20/10/23



I have led seven research projects for my PhD, four of which that have been published in journals of international standing, one that is under review, another that is being prepared for submission, and the final one that is in progress. The former five have been included in this thesis. Separately, I have published a systematic review and have an econometrics paper under review, with two other working papers. The work generated throughout my PhD has also led to a scholar award of monetary value from the Society for Biopsychosocial Science and Medicine (formerly known as the American Psychosomatic Society [APS]), remunerated consultancy requests, two tuition scholarships to attend the University of Venice and Harvard University respectively, a UKRI study grant, an call to attribute as a special edition Editor for the Sociological Review journal, and an invitation for an extended institutional visit to Harvard T. H. Chan School of Public Health, Harvard Medical School, and Massachusetts General Hospital.

For various reasons, the line of study in this thesis is important to the broader academic community, clinicians, pharmaceutical professionals, policy makers, and society at large. **First**, the exploration of stress-induced dysfunctional sleep across the psychological spectrum has the potential to reveal both disorder-specific and transdiagnostic psychophysiological mechanisms,[26] such that intervening on stress or dysfunctional sleep at an early stage, as modifiable targets for treatment,[27,28] could offer an evidence-based preventive strategy for the onset or prognosis of psychological disorders.[22] **Second**, the exploration of how molecular processes result in differences in mental health outcomes advances our relatively limited understanding of how biological systems interact, revealing, for example, whether specific biomarkers are independently related to changes in specific outcomes, or whether there are synergistic effects between a collection of biomarkers that contribute to symmetries in clinical outcomes, with differences underpinned by genetic vulnerabilities. These greatly benefit efforts to understand the genesis of mental health conditions, individualised care within a precision medicine setting, and how observational evidence can effectively translate to clinical trials. **Third**, while it is still very early

days to consider clinical utility, support is provided for the potential benefit of genetic-medical integration to improve diagnostics and the quality of care. This advocates the routine assessment of genetic and biological markers in clinic for patients who present with prodrome symptoms of mental ill-health. **Fourth**, there has been a rise in community-based social and behavioural prescriptions to coincide with pharmacological treatments,[29] but adherence to social prescriptions can be low, particularly for mental health complaints. An increase in the strategic generation and distribution of quality evidence may convince the public of the value of social prescriptions.[30] **Finally**, the findings serve to inform policy through the submission of evidence that could inform macro- and individual-level interventions. For instance, markedly raising the minimum wage could reduce the financial burden of low socioeconomic groups. As a result, lessening their stress exposure and leading to a greater prioritisation of sleep that is more consolidated. This in turn could confer salubrious effects on immunity, and thus, mental health. Such non-clinical interventions have the potential to improve mental health outcomes, reduce health inequalities, while lessening pressures on primary and secondary care systems.[31] Each leading to a lesser financial and social burden on society.

With valuable contributions from Professors Andrew Steptoe and Karoline Kuchenbäecker, my supervisors, I developed the structure of this thesis and led its efficient completion. Together we defined objectives, shaped the study designs, and made strategic decisions on the statistical approach. In time order, I have worked with Dr Philipp Frank, Dr Eleonora Iob, Dr Dorina Cadar, Dr Pamela Almeida-Meza, Johannes Wagner, Ramota Alaran, Professor Anne McMunn, Professor Yvonne Kelly, Esme Elsden, Tracy Odigie, Nathalie Rich, Dr Madelaine Davies-Kelloc, Dr Evangeline Tabor, Dr Olesya Ajnakina, Professor Paola Zaninotto, Dr Giorgio Di Gessa, Professor James Kirkbride, Dr Jennifer Dykxhoorn, Dr Victoria Garfield, Valentina Paz, Professor Neil Davies, Dr Isabelle Austin-Zimmerman, Dr Georgina Navoly, Diana Dunca, Dr Emma Anderson, Dr Luke Daves, Dr Shaun Scholes, Professor Aric Prather, Dr Bizu Gelaye, and Dr Diana Juvinao-Quintero. *Each in different ways have added to my knowledgebase in contribution to this thesis.*

CHAPTER 1. BACKGROUND

1.1 Chapter overview

This chapter reviews the literature on stress and sleep duration associations with mental ill-health, and the underlying genetic, immune, and neuroendocrine mechanisms. It has seven interrelated themes. **In the opening section**, the centrality of mental health to population health across life course is discussed, along with the individual and societal burden that arises from its absence. **In section two**, stress is described, with a focus on accumulative, chronic, psychosocial stressors, and special attention given to financial-related stress. Evidence of the physiological role of sleep in maintaining health is introduced. Then the known reciprocity between stress and poor sleep in the literature is reviewed. Next, we see how mental health is shaped by stress and maladaptive sleep experiences. **In section three**, the biological framework is outlined and offers evidence on the molecular basis of immune-neuroendocrine concentrations, with genomic contributions considered. Here, the role of stress and sleep in a biological context reviewed. **The penultimate section of this chapter** comprehensively details PNI pathways, with reflections on its role in mental ill-health. **In the final sections**, the way in which precision medicine underpins the thesis and gives it clinical relevance is outlined, before concluding on what is yet known and the gaps that this thesis seeks to fill, with research questions and hypotheses detailed. At each juncture, **limitations** of the existing literature are discussed.

1.1.2. Mental Ill-health

"*The energy of the mind is the essence of life*." **Aristotle**

Mental disorders are among the most intractable enigmas in medicine, and it is clear that mental ill-health comes at a tremendous personal and societal cost.[32,33] Age at onset maps across life-course, as revealed by a meta-analysis of 708,561 individuals across 192 epidemiological studies, with over a third of mental disorder detected before the age of 14.[34] It is unsurprising then that some health care systems are overburdened by both subclinical forms of mental distress among

the general population and psychopathology in clinical populations.[35] Further, meta-analytic findings, across 203 studies in 29 countries, reveal that individuals who suffer from mental illness have 2.22 times higher mortality rate than those without. This comes at an estimated an annual 8 million deaths worldwide attributable to mental ill-health.[36] Noted also as the leading worldwide cause of years lived with a disability, driven up by population growth and ageing,[37] mental illness is estimated to account for one-third of all disability worldwide.[38] A recent study estimated mental illness accounted for 970.1 million cases.[33] The global number of disability-adjusted life-years (DALY) due to mental illness[a] rose by 44.5 million between 1990-2019.[33] Depressive (37.3%) and anxiety disorders (22.9%) accounted for the largest proportion of mental illness DALYs, followed by schizophrenia at 12.2%, and bipolar disorder (BD) trailing at 6.8%.[33] These corroborate Whiteford and colleagues' (2013)[37] estimates where depressive disorders accounted for 40.5% (95% confidence intervals [CI]=31.7-49.2) of DALYs caused by mental illness, whereas, anxiety disorders were reported at 14.6% (CI=11.2-18.4), schizophrenia at 7·4% (CI=5.0-9.8), and BD at 7.0% (CI=4.4-10.3). The age-standardised DALY rate for mental illness was highest in The Americas and Australasia. It was also higher among females by 276.8 per 100,000 people. For these reasons, efforts must be made to understand, prevent, and manage both common and severe mental illness. An extensive body of evidence suggests an appropriate model is one of multifactorial causations. To this end, a PNI and precision medicine framework will be used to investigate the potentially causal sleep, genetic, and immune-neuroendocrine mechanisms through which stress affects mental health.

1.1.3. Stress

"*It's not stress that kills us, it is our reaction to it.*" **Hans Selye**

[a] Disability-adjusted life-years (DALY) are measured as the sum of years lived with and years of life lost to disability.[33]

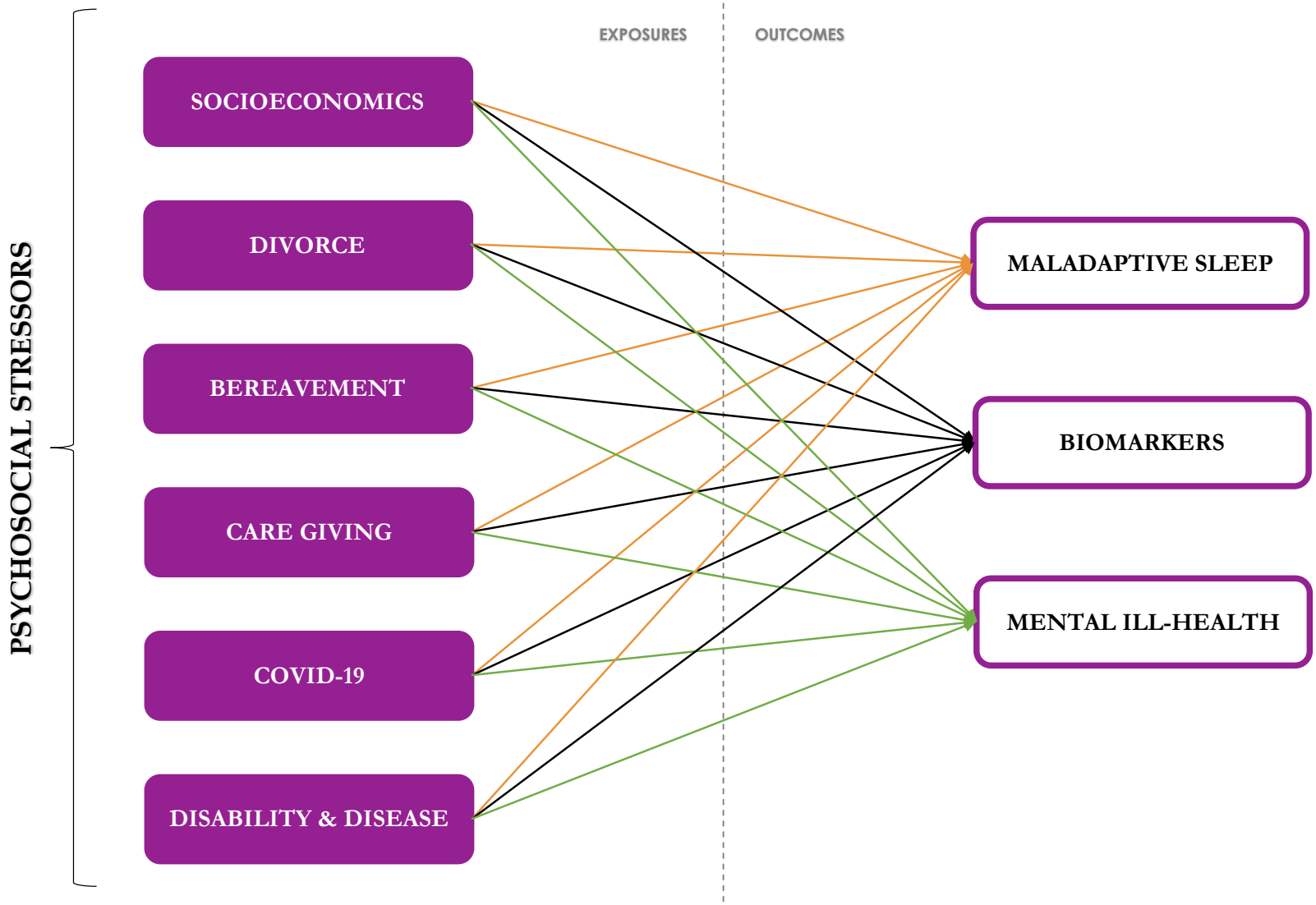
Although stress perception and reactivity varies by person and within person over time,[39] broadly speaking, there are physiological benefits to time-limited stress, such as that experienced during exams or public speaking. This type of *good stress* (in the vernacular) or eustress, is processed adaptively,[40] but chronic – repeated and prolonged – stress exposure is a key factor in the onset and progression of non-communicable[41] and chronic disease.[42,43] Stress can be imposed on us or we can think it into being. It is, however, notoriously difficult to define.[44] Though there are many classifications,[39,45–47] there is no single definitional consensus. Cohen and Prather (2019)[44] suggest that each classification represents different stages and facets of a single model, be it environmental, psychological, or biological, acute or chronic, actual or anticipatory, resistance to stress exposure is futile. This makes stress an especially attractive modifiable target for maintaining mental health. In this thesis, stress is represented using seven likely chronic psychosocial stressors (***Figure 1.2***), with special attention given to financial-related stress, as a long-acknowledged cross-cultural determinant of health. Financial-related is indexed by material deprivation, financial strain, and socioeconomic staus.[16,48,49] As such, it has been referred to as '*the status syndrome*',[50] which has been widely associated with a high prevalence of mental illness.[12,51,52] It is assessed also at contextual and compositional levels. Contextual factors refer to characteristics of the place in which people live, combining information from multiple domains, across education, employment, income, skills, training, housing, crime; health and disability.[53] It captures the multidimensional nature of deprivation and the poverty it signifies, while compositional factors relate to idiosyncratic characteristics of the individuals within a neighbourhood.

1.1.4. Maladaptive Sleep

"*Sleep is that golden chain that ties health and our bodies together.*" **Thomas Dekker**

Sleep, as a state of decreased arousal and responsiveness, occurs in repeating cycles controlled by the internal circadian clock.[54] Despite the ubiquity of sleep, its purpose and mechanistic function

Figure 1.2 **Psychosocial stressors known to be associated with sleep, inflammation, and mental illness**



in maintaining health remains an enigma.[55,56] Sleep macrostructure refers to the temporal organisation of sleep stages. It is based on successive epochs of conventional lengths during nighttime sleep, typically 60-90 minutes. It cycles through non-Rapid Eye Movement (NREM) sleep – stages 1-2 and slow wave sleep (SWS) – and Rapid Eye Movement (REM) sleep.[57] This differs from sleep microstructure that is measured on the basis of shorter, phasic events (e.g., sleep spindles[b]; alternate phases of arousal). Despite these differences, both are physiologically and clinically valuable.[59] Sleep architecture is the overall structure and sequence of the cyclic sleep stages that occur through the night. It is marked by clear transitions between sleep stages, with adequate time spent in deep sleep.[26] Sleep duration can influence the number of sleep cycles, affecting the quality of sleep events and the distribution of cycles. Short sleep can limit the number of cycles, with less time spent in restorative sleep stages like deep NREM sleep. A shorter sleep period can alter the structure, sequence, and balance of sleep, with certain stages, such as REM sleep, being prioritised to compensate for the sleep deficit. Conversely, long sleep can extend the number of sleep cycles, potentially leading to prolonged time in lighter sleep stages (such as NREM stages 1-2), which may reduce sleep efficiency, while long sleep may allow for more time in restorative stages, it is often associated with sleep fragmentation, so decreased sleep quality.[60]

According to one study, the UK prevalence of insufficient short sleep, defined as less than 5-6 hours per night,[61–63] has increased from 8.6% to 10.1% over a 10-year period.[64] During the same period, excessive long sleep, with thresholds greater than 8-10 hours a night,[61–63] reduced from 31.5% to 25.6%, although this is still exceptionally high from a population perspective.[64] Such rates raise concerns about a potential increase in the incidence of mental ill-health, particularly among older adults, given the purported downward trajectory of optimal sleep duration observed across life-course.[65] A meta-analysis by Ohayon and colleagues (2004)[66] found that total sleep time, sleep

[b] Sleep spindles are brief bursts of oscillatory electroencephalographic activity that occurs during non-rapid eye movement (NREM) sleep.[58]

efficiency, the percentage of SWS, REM sleep, and REM latency all decreased with age, while sleep latency, sleep disturbances, and the percentage of sleep stages 1-2 increased with age. The decrease in sleep efficiency was more evident from age 40, with a 3% decrease observed per decade, but only sleep efficiency continued to significantly decrease after 60, while sleep latency increased expeditiously with age, being more pronounced after 65. However, middle-aged individuals were not included in these analyses.[66] A subsequent cross-sectional population study was largely consistent with this earlier meta-analysis, such that there were significant alterations to sleep structure and duration across age in the general population.[67] However, a study of 198 participants from the general population, aged 20-95 had mixed results. There was little variation in sleep architecture with increasing age and, notably, older individuals did not necessarily need more time to fall asleep than their younger counterparts. Interindividual variation in sleep appeared to diminish with age, but total sleep time, sleep efficiency index, and the percentage of SWS and REM sleep decreased with age, as did the variability of these parameters. Authors surmise that the experimental nature of the study may lack ecological value. The artificial conditions of the study setting may influence sleep, key sleep events may occur outside of the 8 hours recording window, or it might not fully capture the variability or complexity of nighttime sleep.[68]

Many sleep studies solely focus on the physiopathological characteristics of sleep debt instead of its social properties.[69] In contrast, here the biopsychosocial aspects of sleep take the fore; tested as manifestation of stress; a potentiator of inflammation; and an upstream antecedent of mental ill-health. Research has not provided a complete understanding of the dynamic and multifactorial role of sleep architecture in maintaining mental health,[70] and studies have yielded mixed results, in part, due to the differences in sleep measures.[71] There are many aspects of sleep, but here, assessments of suboptimal sleep durations are the primary indication of risk, with additional attention given to dyssomnias where data permits. This is because sleep duration, as compared to sleep disturbance or quality, is a relatively consistent, widely available tool, that is easy to measure

(non-invasive, low burden, so inexpensive). It can offer relatively precise, quantifiable estimates through self-report or sleep diaries that are less influenced by perceptual bias, and it can be supported by actigraphy or polysomnography (PSG) techniques.[72] Granted, suboptimal sleep durations experienced with sleep disturbance, for example, is likely more problematic for mental health outcomes than each of these experienced singularly,[73] but an objective of this thesis is to generate evidence unencumbered by multiple lines of evidence on difference sleep measures.

1.1.5. Stress and Maladaptive Sleep

"*Sleep is the best cure for waking troubles.*" **Miguel de Cervantes**

Anecdotally, many of us struggle to sleep when stressed, and we experience stress more intensely after a bad night's sleep, but such conventional wisdom has been evidenced empirically.[74] Bidirectionality between them is problematic because cause and effect is unclear,[71,75] with both direct and indirect influences.[76] Several theoretical models have been proposed to give reason to this multiplicative relationship, of them, the Stress-Diathesis Model of Insomnia[77] and Cognitive Model of Insomnia are especially compelling.[78] The former model posits that those with a predisposing vulnerability from underlying pathogenic mechanisms, be it genetic, biological, or psychological, are more susceptible to sleep disorders when exposed to stress.[77] The latter submits that sleep disorders are perpetuated by distorted thinking, such as a hyperfocus on sleep loss or its consequences that increase cognitive valence and emotional arousal.[78] The suggestion is that stress interacts with predisposing (e.g., personality) and perpetuating factors (e.g., stimulus control) to predict the onset and maintenance of maladaptive sleep duration, timing, and efficiency, while sleep loss itself exacerbates stress perceptions.[71] That said, limited empirical support has emerged for these models, despite their intuitive explanatory power.[77]

As evidenced in animals, chronic stress reduces the duration of both SWS and REM sleep, but different stress modalities result in distinct sleep responses,[79] the pattern of change depending on

the nature of the stressful experience and the ability of the rats to leverage coping strategies.[80] In humans, stress can also indirectly contribute to poor sleep via unhealthy behaviours, such as smoking, heavy alcohol or coffee consumption, sedentary routines, and substance abuse.[81,82] Inversely, insufficient sleep has been linked to physiological stress responses, including hypothalamic-pituitary-adrenal-axis (HPA-axis) dysregulation and rapid autonomic activation.[80] The latter involves the rapid, involuntary activation of the autonomic nervous system (ANS) that consists of the sympathetic (SNS) and parasympathetic (PNS) nervous systems, respectively responsible for the counterbalancing of the *fight or flight* and *rest and digest* responses.[80,83,84]

On balance of evidence,[77,85,86] stress likely precedes poor sleep, initiating a downward cyclical trajectory between them. Sleep is plausibly the central biosocial factor linking everyday social events to biological processes, that when dysregulated result in states of mental ill-health.[87–89] This is especially troubling because modern-day stressors,[90] and mounting societal demands,[91] amid global health challenges,[92] have disrupted normative sleep routines, certainly for some demographics more than others, with sleep duration increasing for young adults but reducing for middle aged adults. This is notable given the finding that sleep was a mechanism through which stressors experienced during the 2019 coronavirus disease (COVID-19) had measurable impact on mental health.[94] More so, given earlier indications of a clear gradient across the number of adverse events experienced each week by socioeconomic groups during the pandemic, and a perpetuation of inequality; particularly as it relates to financial adversities.[95] However, it is still in debate as to whether stress has forced a gradual decline in the number of hours devoted to sleep or not.[96] Some studies have supported an increase in percentage incidence of suboptimal sleep,[61] while others have cast doubt on this increase.[64,96] It is conceivable that an increased awareness of sleep hygiene, along with the emergence of sleep medicine, may have contributed to the observed rises in self-reported sleep problems and clinical sleep disorder diagnoses.

1.1.6. Stress and Mental Ill-heath

Stress has a complex relationship with health. Psychosocial stressors have long been linked to poor health,[97,98] and those with limited socioeconomic resources, as a proxy for stress, tend to have worse mental and physical health,[99] with a shorter life expectancy than those who are not materially deprived. For example, in a Finnish and United Kingdon (UK) cohort prospective study, Kivimäki and colleagues (2020)[99] reported that being less advantaged was associated with an increased risk for 18 (32.1%) of the 56 conditions assessed (validated by replication), and area deprivation was associated with a further three. Of the 18 temporally sequenced, socioeconomically patterned illnesses, 16 (88.9%) of them were strongly interconnected with mental health problems. They revealed that a disease cascade began with psychomorbidity and was followed by diseases of the pancreas, liver, kidney, lungs, heart, vascular system, cancer, and dementia. Differences in health between socioeconomic groups have been attributed to variations in economic, social, educational, and psychological resources.[100] These socioeconomic determinants are correlated but their associations with mental health may differ, as each represents a different permutation of social and economic capital.[14] It is likely that each has a monotonic functional relationship with health.[16]

Of socioeconomic determinants, financial strain, as it has been conceptualised in the literature,[101] is of particular interest for three main reasons. First, it is predicated on a perceived (relative) or actual (absolute) inability to meet needs and fund financial obligations irrespective of the social stratum to which one belongs.[101] Second, it is a relatively underutilised socioeconomic construct in biosocial literature. Finally, it has escalated in saliency across populations because of the '*cost of living crisis*',[102] it can surreptitiously pervade every aspect of an individual's life, arguably, in a way that other stressors do not. For instance, congruent with material deprivation,[c] financial strain can contribute toward or be a single, proximal source for familial and social conflict, social exclusion

[c] Material deprivation reflects a lack of physical resources necessary for a standard quality of life, whereas financial strain refers to stress arising from perceived income insufficiency and difficulty meeting financial obligations.[103]

and isolation, *karoshi*,[d] hunger, reduced freedoms, restricted medical care, denied opportunity, and lost hope. It can also contribute to the erosion of personal resources, such as self-esteem and confidence.[11] Even as a direct correlate of disadvantage, individuals with a lack of resources may be vulnerable to and less able to cope with other chronic stressors, psychological distress, traumatic life events, and daily struggles.[16,105,106]

Therefore, health and well-being may be shaped by socioeconomic resources, but the biological and genetic mechanisms that contribute to this relationship are yet to be fully explicated.[11] Cellular and molecular contributions are biologically complex, and with few credible stress-related loci identified, there is no immediate avenue for assessing the genetic basis of stress and its role in mental health.[107,108] Still, the strong and consistent documented gradients between socioeconomic determinants and health using phenotypic data,[16,48,49,101] with a range of non-specific outcomes,[99] draw attention to possible biosocial pathways that may explain how financial stress leads to mental ill-health. Stress-induced sleep abnormalities and aberrant immune-neuroendocrine activity are two proposed pathways.[14–16] It is argued that the cumulative burden of stressors, particularly those associated with a lack of socioeconomic resources, could lead to a vulnerability of poor sleep and adverse biological reactivity that results in psychological dysfunction.[12,13]

1.1.7. Maladaptive Sleep and Mental Ill-health

Converging evidence has advanced maladaptive sleep as an underlying diathesis in subclinical and pathological expression of common[109] and severe mental disorders,[110] but only recently has it been recognised as a public health concern.[111] One study found that relative to healthy controls, participants with major depressive disorder (MDD) had prolonged sleep latency, increased REM density, but longer REM latency, with fewer arousals.[112] During the acute phase of illness, an early

[d] A Japanese phrase translated as "*death from overwork*".[104]

review revealed that 50-80% of psychiatric patients complained of poor sleep. This percentage averaged 40-47% in randomly selected community samples without mental illness.[113] However, sleep that is too little, too much, or too fragmented has also been implicated in the genesis of mental illness across a spectrum of severity.[22] This is concerning given that 260 million older adults are expected to experience suboptimal sleep durations by 2030,[63] as a result of ongoing epidemiologic transitions.[114] A meta-analysis of seven longitudinal studies that involved 25,271 participants for short sleep and 23,663 participants for long sleep duration, found that these suboptimal sleep durations were significantly associated with increased risk of depression in adults, with relative risk ratios (RRR) at 31% and 42% respectively.[115] A more recent meta-analysis across 154 studies (*n*=5,717) offered evidence that extended wakefulness, shortened sleep, and sleep disturbances adversely influenced emotional functioning. Authors explored experimental reductions in sleep (i.e, total sleep deprivation, partial sleep restriction, or sleep fragmentation) on multiple aspects of subclinical emotional experiences (i.e., positive and negative affect, mood disturbances, anxiety and depressive symptoms, and emotional reactivity). All forms of sleep loss led to lower positive affect, more anxiety symptoms and blunted emotional arousal. However, negative affect, emotional valence, and depressive symptoms depended on the type of sleep loss.[116] In fact, sleep has been offered as a central antecedent of interest in mental illness across experimental and epidemiological paradigms,[22] but no single sleep alteration has proved to be specific to a single mental health disorder.[26] Despite persuasive longitudinal and meta-analytic evidence, results from different studies have been contradictory. This calls into question the temporal sequence between maladaptive sleep and mental illness, which may be better examined using a combination of genetic and observational data, with sufficiently long follow-up periods. For instance, suboptimal sleep has received serious interest in the expression of mental ill-health.[117–119] It is implicated in the onset and persistence of psychological distress among the general population,[111,119] and it has emerged as a plausible causal factor in the genesis of various psychomorbidities of an affective, anxious, and psychotic nature.[26] However, this juxtaposes

evidence to suggest that maladaptive sleep is a common side effect of pharmacologic treatments, prescribed to treat mental illness; from antidepressants and antipsychotics to other sedative psychotropic medications. This would suggest that suboptimal sleep follows treatment for mental illness.[120] There is additional evidence proposing that maladaptive sleep is a non-specific epiphenomenon of mental illness[20] or that it is secondary to common and severe mental illness, implying that it follows mental illness.[61,110] Thus, we see that in spite of a large body of evidence that has explored prognostic sequencing between suboptimal sleep durations, specifically, and mental ill-health,[117,118,121,122] the directional role between them has been inconsistent, so these complex associations remain incompletely understood.

1.1.7.1. Genetics of Sleep and Mental Disorders

Efforts to unravel bidirectional associations between suboptimal sleep and mental ill-health has been obfuscated in part by the use of observational, phenotypic data. Environmental factors, such as stress, can contribute to overall sleep duration, but sleep is also heritable.[123] A twin study showed that genetic differences account for 35-40% of the variance in sleep, with no evidence of a decline in genetic predisposition over the life-course.[124] However, single nucleotide polymorphisms (SNP) heritability (viz. narrow-sense heritability) for overall sleep duration estimates at 9.8%, with short sleep at 7.9%, and long sleep at 4.7%.[125] Genetic instruments, arguably, offer the most parsimonious solution to resolving the direction of effects, given that they are not susceptible to confounding.[126] Disentangling the genetics of traits from the traits themselves in associations could enhance models involved in identifying disease risk. Polygenic scores integrate common genetic variant effects into a single risk metric, used to model genetic risk and helpful to reduce unobserved confounding.[126] However, Mendelian randomization (MR) presents as a powerful tool to make the assessment of causality possible, given its use of genetic variants as instrumental variables (IVs) with assumptions.[127] By focusing only on the genetically regulated component of exposures, MR can avoid reverse causality and estimates will not be biased by confounders because genotypes

minimally change from conception.[128] Clinical utility remains low but there is significant promise for future clinical applications as sample sizes and ancestral diversity of GWAS increase.[129] Although not formally tested in this thesis, earlier MR studies provide a useful benchmark to compare results from observational and polygenic analyses.

Using genome-wide association studies (GWAS) for self-reported sleep duration, Dashti and colleagues (2019)[125] derived a polygenic score (PGS) from 78 associated SNPs that explained 1.4% of the phenotypic variance. For observed PGS associations, authors went on to test causality using a two-sample MR (2SMR)[e] by looking at the per allele difference in disease outcomes. Authors found curvilinear phenotypic associations between sleep duration and depression, with long sleep being additionally associated with BD, but not schizophrenia in fully adjusted models, and there was no polygenic risk. Congruent with these findings, another recent study by Austin-Zimmerman and colleagues (2023)[131] used an inverse-variance weighted (IVW) estimate method in a MR study to support a positive, unidirectional causal effect of short sleep on depression, with bidirectionality seen between long sleep and depression. Elsewhere, Sun and colleagues (2022)[132] used insomnia, chronotype, and sleep duration associated SNPs in a bidirectional 2SMR analysis. They found a causal effect of overall sleep duration on the risk of BD but not for other psychiatric disorders; an effect of insomnia on MDD and post-traumatic stress disorder (PTSD); and a negative effect of *morningness* chronotype on MDD and schizophrenia. Curiously, the weakest evidence was for sleep duration, which may have been due to its quadratic quality. Results may have differed should it have been demarcated by short and long sleep parameters. Even so, a bidirectional causal effect of MDD and PTSD on insomnia was observed, along with a suggestive inverse association between MDD and sleep duration. There is stronger support here for the predictive effect of short sleep on mental health outcomes that infers unidirectional effects, but there appears to be

[e] A two-sample Mendelian randomization (2SMR) uses genetic variants as instruments to estimate causal effects by leveraging separate, non-overlapping datasets for the genetic association between the exposure and outcome traits.[130]

bidirectional effects between long sleep and said outcomes. Therefore, directionality may be predicated on the sleep measure. Stronger powered GWAS should be used to inform future MRs, with SNPs across multiple ancestries to add to the evidence on the generalisability. In addition, further information offered on the biological mechanisms between suboptimal sleep durations and a range of mental disorders would benefit our understanding of these processes.

1.1.8. Stress, Maladaptive Sleep, and Mental Ill-health

Studies have shown that stress is associated with anxiety, depression,[133] schizophrenia,[134] and BD,[135] but less have looked at the simultaneous role of stress and poor sleep in mental ill-health.[76] There is evidence of a reciprocal relationship between stress and maladaptive sleep,[74,136,137] and both are identified determinants of mental ill-health.[14120,137–139] Less clear is whether poor sleep is a mediator or moderator of associations between stress and mental ill-health. Merrill (2022)[76] found that stress was independently more strongly related to mental ill-health than sleep. However, the cumulative effect of both stress and sleep revealed the strongest associations, supporting effect modification between the two over additive effects. Curiously, schizophrenia was most prone to this interaction, plausibly due to the role of stress[140] and maladaptive sleep[141] in psychosis, with an influence on extreme mood swings (mania and depression), which is characteristic of BD.[142]

As it relates to socioeconomic stress, Steptoe, Emch, and Hamer (2020)[101] showed that financial strain, specifically, was positively related to maladaptive sleep and poorer reported mental health, while Moore, Adler, Williams, and Jackson (2002)[48] identified a mediating role of sleep in the association between socioeconomic status and mental health. Others have shown significant inter-individual variations in reported sleep patterns among general and clinical populations that are greatly influenced by an individual's socioeconomic profile.[69,143] The problem is that associations are not universally consistent,[76] and the type of measurement used is relevant to associations, such that different stressors and different sleep measurement techniques should be seen as

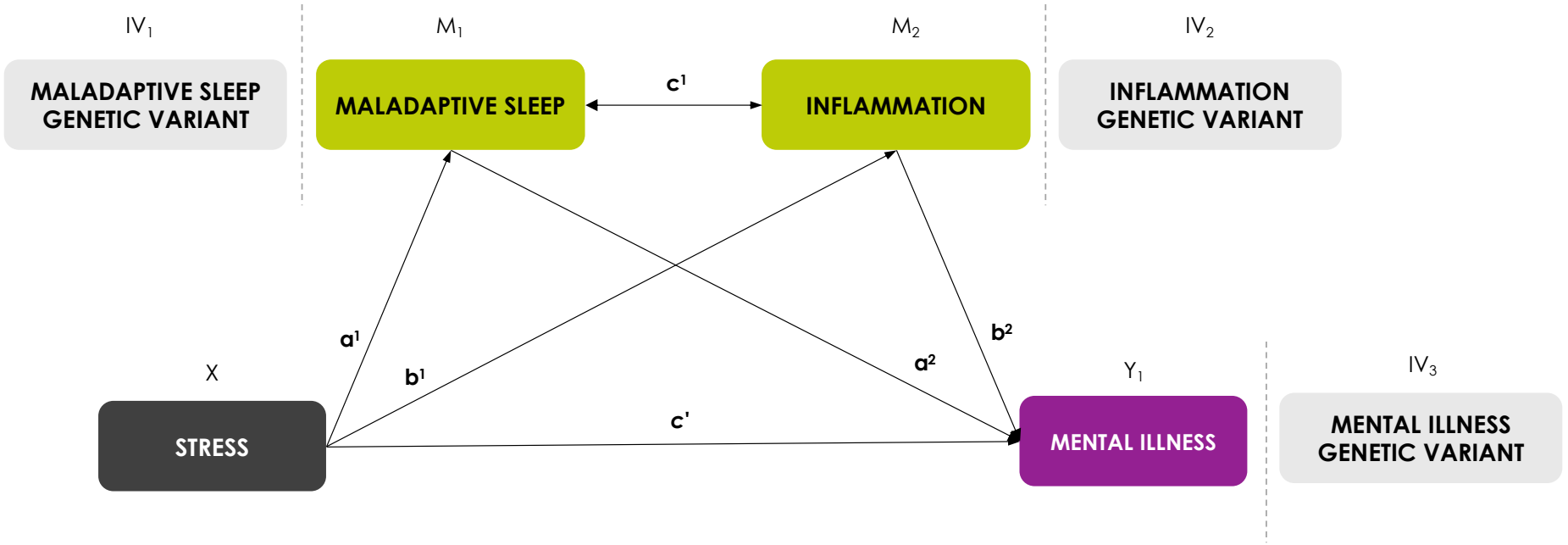
complementary, rather than redundant.[71] One study compared associations and tested interactions between stress and dyssomnias in various mental health conditions in 21,027 working-aged adults (mean [M]=46.42 standard deviations [±] 11.50). The risk of stress was significantly greater for those with a dyssomnia (2.36; CI=1.90-2.94), and stress was more strongly associated with mental disorder than dyssomnias, but contrary to other research, the combined risk of stress and dyssomnias was not exclusively worse for risk of mental disorder than stress and sleep independently. It was greater for anxiety, depression, obsessive-compulsive disorder (OCD), and schizophrenia, but not BD.[76]

1.2. The Biological Framework

"*The best and most efficient pharmacy is within your own system.*" **Robert C. Peale**

Scholars have warned against operationalising stress as a unilateral path to mental ill-heath, instead of giving salience to attributing mediators.[19] To uncover alternative pathways that capture the complexities of the association between stress and mental ill-health, interdisciplinary efforts are required, with complex, multivariate, transactional models that account for time, person and environment.[19] This approach underpins the rationale of this thesis, insofar as the need to focus on mechanisms, using advanced analytics, while taking an interdisciplinary approach. Thus, building on a PNI and precision medicine framework (later discussed), the stress-mental health relationship is viewed in the context of suboptimal sleep and immune-neuroendocrine biomarkers, while considering the role of genetics, as conceptualised in ***Figure 1.3***. Ultimately, immune and neuroendocrine responses are believed to be dependent on individual genetic architecture,[144–146] psychosocial stress exposure[147,148] and sleep.[56,87,149] This is notable given the suggestion that elevated levels of systemic inflammation is a risk factor for mental illness,[150–153] despite it not being a universal observation,[154,155] that is dependant on the biomarker tested.[150] The current evidence suggests more than a correlational effect, but the degree to which immune and neuroendocrine

Figure 1.3 **A conceptual psychoneuroimmunology and precision medicine framework**



Indirect effect of X on Y through M_i only = $a_i b_i$
Indirect effect of X on Y through M_1 and M_2 in serial = $a_1 d_{21} b_2$
Direct effect of X on Y = c'

dysregulation plays a role in the genesis and aetiology of mental illness, and how this differs between disorders is not absolute.[156]

1.2.1. The Molecular Basis of Immune-Neuroendocrine Activity

Haematological traits are important biomedical indicators that describe blood cells circulating in the body. Blood cell types are extremely diverse, with a wide range of functions central to health and disease, but they share a common progenitor cell type; the hematopoietic stem cell.[157] They are broadly classified into three distinct groups (i.e., leukocytes [white blood cell counts {WBCC}]; erythrocytes [red blood cell counts{RBCC}]; thrombocytes [platelets]). Each are integral to a plethora of physiological processes (***Figure 1.4***). The values of haematological traits are not distributed independently, but are significantly correlated, because of the processes through which they differentiate from hematopoietic stem cells and reside in peripheral blood. Haematological homeostasis, as it pertains to the counts and volume of peripheral blood cells, along with their biological activity, is tightly regulated within narrow physiological ranges. For this reason, abnormalities are closely linked to the development of disease and they serve as useful prognostic parameters.[158]

Cytokines are signalling molecules produced by immune cells that have been generated through haematopoiesis[f] (***Figure 1.4***).[159] With over 300 discovered, including chemokines, lymphokines, interferons, and tumor necrosis factors,[160] cytokines are marked by a complex series of physiological interactions that involve pleiotropy, redundancy, synergy, and antagonism (***Figure 1.5***). A common feature is their pleiotropic nature, insofar as a given cytokine triggering proliferation in one type of cell, but another cell type may respond to the same cytokine with growth arrest. This complexity is confounded by the fact that cytokines act in concert with other

[f] Haematopoiesis is the process of blood cell maturation and formation.[159]

Figure 1.4 **Haematopoiesis | Blood cell maturation and formation.**[159,161]

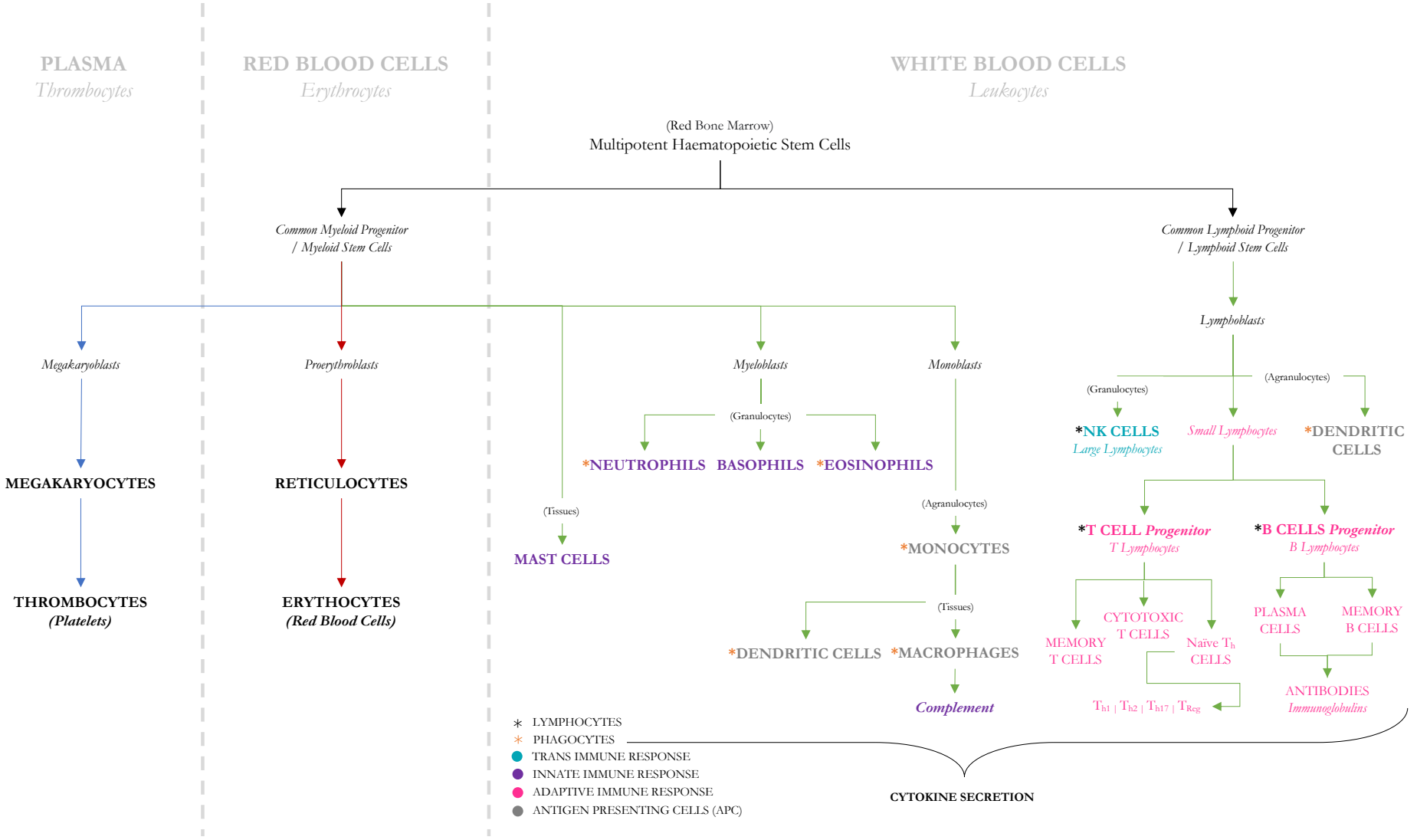


Figure 1.5 **An example conceptualisation of the complexity of cytokine action.**[162,163]

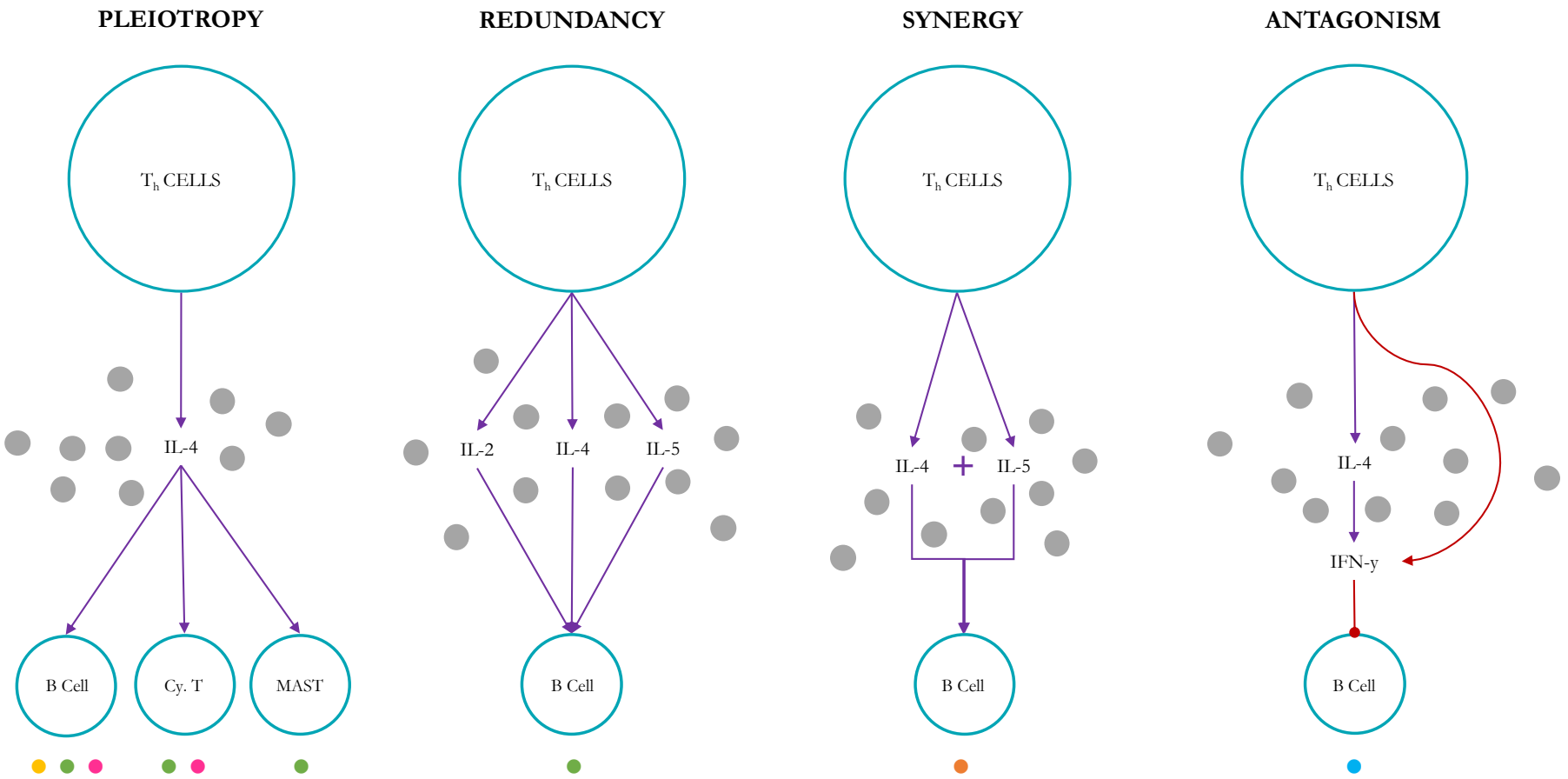


Figure 1.6 **A network of cytokine secretions.**[164,165]

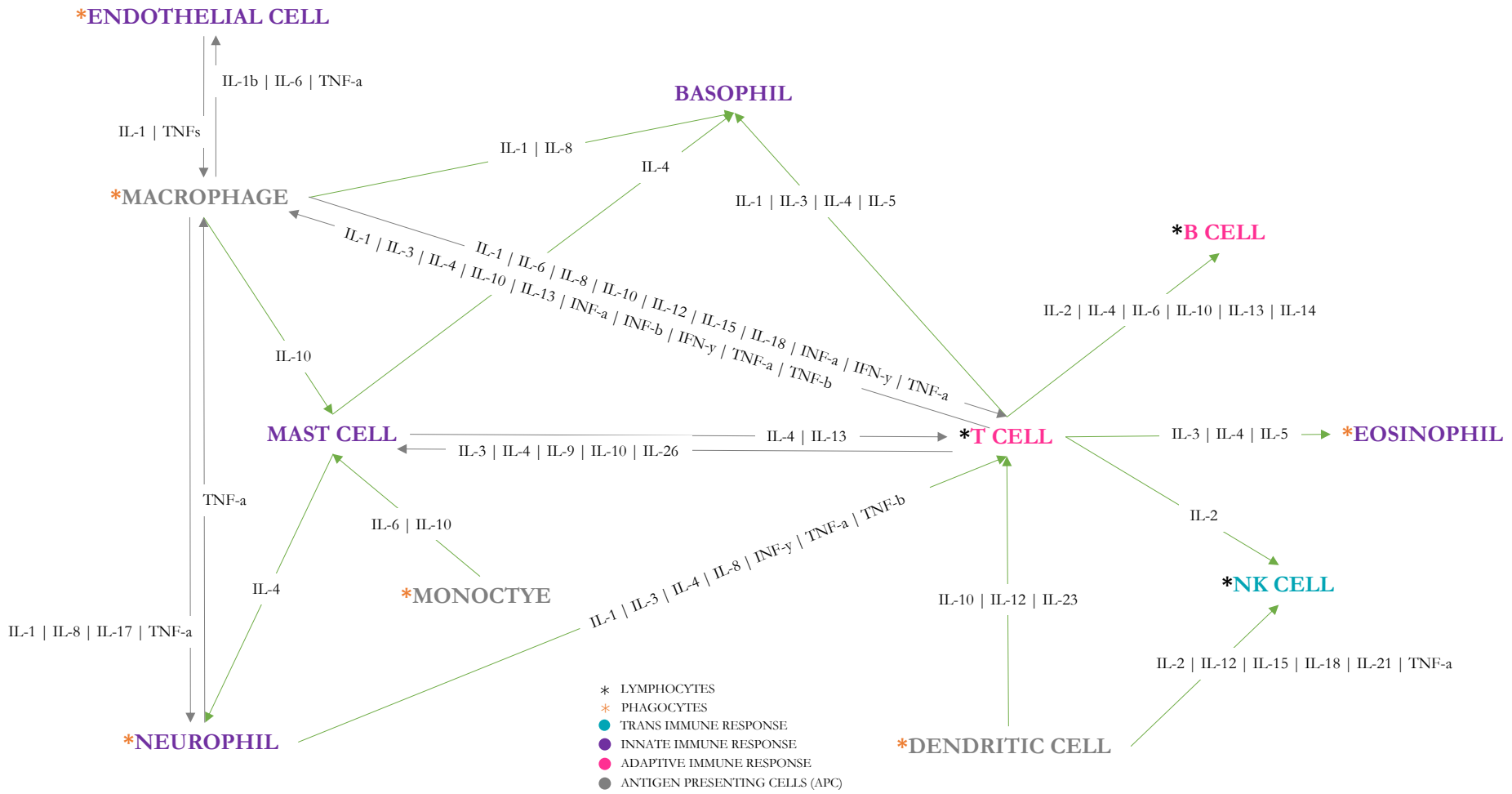
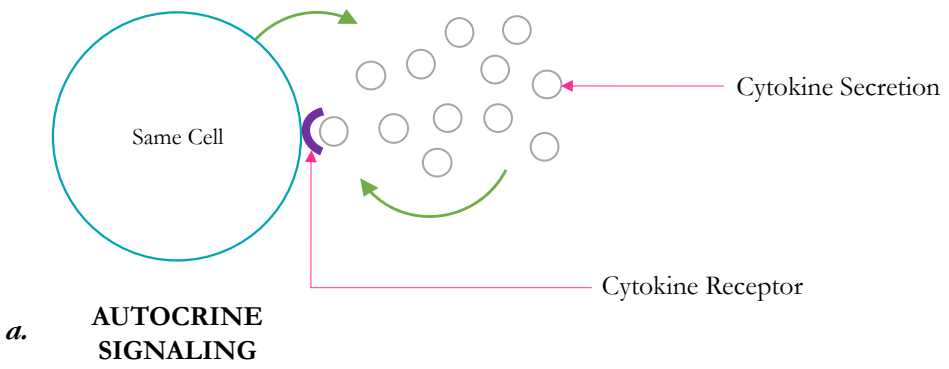
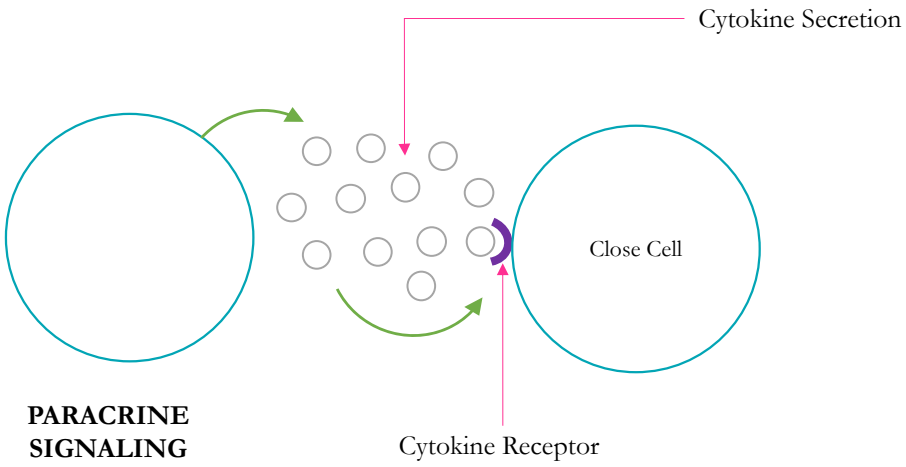


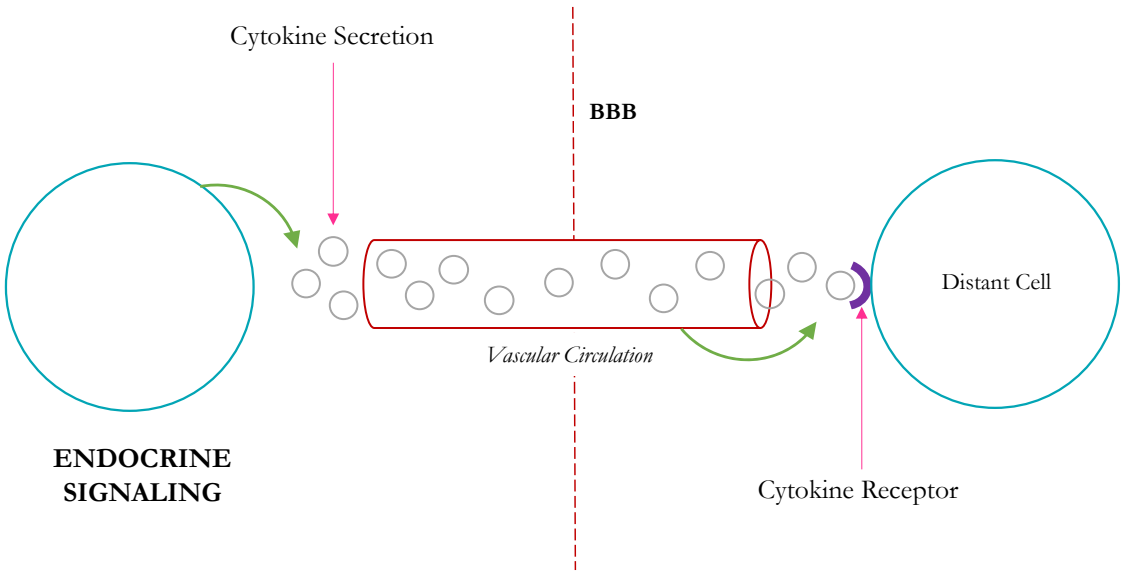
Figure 1.7 **A conceptual diagram of modes of cytokine signalling.**[160,166]



a. **AUTOCRINE SIGNALING**



b. **PARACRINE SIGNALING**



c. **ENDOCRINE SIGNALING**

contextual signals (***Figure 1.6***).[167] In addition, they play a critical role in immune response orchestration and coordination with neural and endocrine processes through autocrine, paracrine, and endocrine signalling (***Figure 1.7***). They traverse the blood-brain barrier (BBB) to modulate various molecular and cellular processes, including monoamines metabolism,[168] and signal directly to the brain via the autonomic nervous system (ANS). Released cytokines are detected by the afferent vagus nerve, which relays this information to the nucleus tractus solitarius (NTS) and the dorsal motor nucleus (DMN). This then activates the efferent vagus nerve, initiating the cholinergic anti-inflammatory pathway, which suppresses cytokine production via α7 nicotinic acetylcholine receptors (α7nAchR) on immune cells. This process contributes to abnormal psychological states across a continuum of severity.[28,87,169] It is why inflammation is conceptualised as a mediator of the association between stress-induced sleep abnormalities and a diverse set of mental health conditions.[170]

Locally, cytokine production triggers the release of biomarkers, such as CRP and fibrinogen, positive acute-phase proteins (APP)[171] that are synthesised by hepatocytes[g] in the liver. Where even minor APP elevations can represent prognostic implications for future disease, so they represent strong easily detectable markers of inflammation.[173] However, they have been inconsistently associated with mental illness across a spectrum of severity.[154,155]

Inflammation is a defence mechanism responsible for maintaining homeostatic equilibrium, as a cellular and molecular adaptive response to stimuli. This response can be acute, with a short lifecycle, accelerating rapidly in severity from trauma, infection, or injury. Whereas chronic inflammation, characterised by a prolonged and sustained release, can persist months, even years.[174–176] The regulation of inflammation involves a vast network of interacting molecules, cells

[g] Hepatocytes being the major parenchymal cells in the liver that are responsible for a variety of cellular functions, such as carbohydrate, lipid and protein metabolism, detoxification, and immune cell activation to maintain liver homeostasis.[172]

and proteins. Besides neural mediated actions, the endocrine system is an active participant in this regulation.[177] For this reason, there are numerous biomarkers involved in inflammatory processes that can be useful for diagnostic purposes. However, five were selected owing to data availability and because they reflect immune, neural, and endocrine pathways. These were C-reactive protein (CRP); fibrinogen (Fb); WBCC; insulin-like growth factor 1 (IGF-1); and hair cortisol (cortisol). Pro-inflammatory markers include CRP, fibrinogen, and WBCC. By contrast, IGF-1 is a key marker of the neuroendocrine function involved in anabolic processes and cortisol is a key neuroendocrine marker involved in catabolic processes. Inflammation has downregulation effects on IGF-1 secretion,[178] while the IGF-1-axis has anti-inflammatory effects on inflammation.[179]

More specifically, CRP, largely used as a marker of inflammation and infection, is produced under the transcriptional control of IL- (interleukin-) 6.[180] In normal state, it is present at low, even undetectable, concentrations, so high-sensitivity tests should be performed and analysed in a laboratory for greater accuracy. It has a rapid increase of up to 5-1,000-fold, or up to 50,000 fold in acute inflammatory processes, which is measurable within 4-6 hours of a single stimulus with a prompt return to baseline. With few exceptions, CRP is a positive correlate of IL-6, and is frequently used as a IL-6 surrogate.[181] Understanding CRP is important because it remains a widely studied marker of low-grade systemic inflammation linked to physical[182–184] and mental illness,[185–187] where even subtle elevations in baseline concentrations can significantly increase disease risk.[181] In addition, it is not merely a short-term marker of risk but has longer term consequences.[188]

By contrast, fibrinogen is a slow reacting APP involved in clot-formation, with approximately two-three fold increases in response to infection, inflammation, and trauma. Increases are apparent after approximately 8 hours and it remains elevated for 24-48 hours.[189,190] Fibrinogen is a soluble protein that is synthesised also by hepatocytes.[191] It is the end product of the coagulation cascade that is key to clot formation and is an active regulator of the inflammatory response, identified as

a significant risk factor for disease.[192] As an APP, fibrinogen range 2-4 g/L under normal physiological conditions, with a half-life of ~4 days.[191] The proinflammatory function of fibrinogen (and its derivative peptides) lies in its ability to bind to and activate a number of immune cells through distinct ligand–receptor interactions.[193] Its signalling has been shown to activate proinflammatory pathways, such as nuclear factor kappa-B (NF-ϰB), a complex protein that controls deoxyribonucleic acid (DNA) transcription.[194] It also regulates the local production of cytokines, such as tumor necrosis factor-α (TNF-α) and IL-1 beta (β),[192] along with leukocyte recruitment and cell survival.[195]

WBCC is a cellular component that plays a fundamental role in the innate and adaptive immune response. It releases inflammatory mediators that activate and regulate these responses. As the first line of defence against pathogens, detect and respond to foreign antigens,[196] leukocytes fight infections, and they promote apoptosis[h] and debris removal[198] to promote tissue regeneration. It originates from hematopoietic stem cells in the bone marrow, differentiating into granulocytes, lymphocytes, and monocyte-macrophage lineage cells (***Figure 1.4***). Neutrophils represent 50-70% of total WBCC, lymphocytes 20-30%, monocytes 5-10%, eosinophils 1-5%, and basophils 0.5-1%. Each have further narrower classifications.[158] In spite of their non-specificity, WBCC are useful indicators of inflammation that are frequently used in clinic. The proportional balance of each component likely presents better than single parameters the state and severity of inflammation, so that treatment decisions can be better informed.[199] WBCC are of additional interest because of their exchange with cytokines[190] and glucocorticoids.[200] They have receptors for stress hormones that are produced by the pituitary and adrenal glands, and when cytokines are released during the immune response, they have direct impact on the function and infiltration of WBCC.[190] These counter actions between cytokine signalling and leukocyte activity are key to immune function

[h] Apoptosis is programmed cell death that promotes monocyte and macrophage recruitment to sites of inflammation and facilitates later cell corpse clearance, a process known as efferocytosis that ultimately suppresses inflammation.[197]

(***Figure 1.6***) and their dual role in maintaining health. WBCC and CRP are also phenotypically[201] and genetically[202] correlated with the other. In whole-blood culture stimulation assays, CRP elicited a 2-fold activation of peripheral leukocytes on average from a 1-4 hour time-point, inducing proinflammatory changes. Of note, the increase in WBCC was entirely attributed to an increase in neutrophils. Circulating lymphocytes decreased by ~40% and there were no significant changes to monocyte counts [203]

Cortisol is a hormone and glucocorticoid steroid that has biphasic regulation of inflammation. Identified as an end product of HPA-axis activity, it has a central role in organising the stress response, so is deemed a reliable stress measure. Briefly, the hypothalamus secretes corticotrophin-releasing hormone (CRH) on stimulation, then adrenocorticotrophic hormone (ACTH) is secreted by the pituitary gland, which stimulates cortisol secretion from the cortex of the adrenal gland. In the main, the HPA-axis self-regulates through negative feedback, where elevated cortisol levels suppress CRH and ACTH release, thus reducing cortisol production. With a biological half-life of ~80 minutes, cortisol varies from anti-(suppressive) to pro-(stimulating) inflammatory in a time-dependent way. It can be assayed using hair, saliva, urine, or blood substrates, but the former, thought to reflect cortisol secretion from three months earlier, has been best established as a long-term, retrospective assessment of cumulative HPA axis activity. Cortisol levels peak prior to awakening, then progressively decrease throughout the day, reaching to low levels in the evening. Central to the stress response, glucocorticoids mobilise amino acids and fats for energy and synthesis into new compounds, They also exhibit mineralocorticoid activity, suppress the immune system, and exert anti-inflammatory effects on traumatised tissues.[142,204–207]

Macrophage-derived IGF-1 is a small anabolic peptide hormone or growth factor. It is principally produced by hepatocytes in the liver in response to growth hormone (GH), which is secreted by anterior pituitary somatotrophs, but it can be synthesised by most other somatic cells in response

to stress stimuli. Central to ageing, it is an endocrine mediator of growth and development but is also a prominent component of innate and acquired immunity in cooperation with cytokines. Together they regulate innate immunity by modulating differentiation and proliferation of myeloid lineage cells. As a single chain polypeptide consisting of 70 amino acids, it primarily exerts its effects though autocrine and paracrine interactions between growth factors and cytokines (***Figure 1.8***). IGF circulates at nanomolar levels and has a half-life of minutes, which can be extended up to 15 hours when complexed with one of seven known IGF-binding proteins (IGFBPs). Almost all immune cells, including lymphocytes, peripheral blood mononuclear cells (PBMC) and natural killer (NK) cells are susceptible to IGF-1 expression.[174,205–207175,206–208177,208–210] The precise mechanisms of how IGF-1 influences cytokine production are complex and are still an active area of research, but its role in immune regulation highlights the interconnectedness of the endocrine system and cytokine activity.[211] Although the growth hormone (GH) axis, of which IGF-1 is a mediator, exerts pro- and anti-inflammatory effects, relationships with the immune system are reported as mutual. This axis has a number of additional effects, including modulation of carbohydrate, lipid, protein and mineral metabolism, cancer development, and various other physiological processes related mainly to the cardiovascular and renal systems. [212]

Importantly, polymorphic variations[213] are known to significantly contribute to the inter-individual variance of circulating concentrations of these biomarkers.[146] Genes encoding biomarkers are candidate loci for diseases with an inflammatory basis,[213] and many common SNPs are linked to mental disorder,[1] but genetic contributions are rarely considered in phenotypic analyses.[146]

1.2.1.1. Heritability in Immune-Neuroendocrine Activity

Heritability measures the proportion of phenotypic variance that is explained by genetic factors in a population.[23] Broad-sense heritability, narrow-sense heritability, and SNP-based heritability are the prevailing types. Broad-sense heritability represents the proportion of phenotypic variance

explained by all genetic factors, including additive, dominant and epistatic effects. This estimation relies on pedigree-based designs involving monozygotic (MZ) and dizygotic (DZ) twins, or family-based designs involving full siblings. Narrow-sense heritability evaluates the proportion of phenotypic variance explained by additive genetic effects. It represents the degree to which genes transmitted by parents determine the phenotype of their children. It is determined by GWAS that perform association tests on millions of SNPs, assayed across the whole genome in distally related individuals who have been drawn from the general population.[23,214] However, narrow-sense heritability only explains a fraction of the heritability estimated from familial studies. Causal SNPs are thought to individually account for such a small proportion of variations that their effects do not reach statistical significance in GWAS studies. To resolve this, Yang and colleagues (2010)[215] developed SNP-based heritability. This method estimates the proportion of additive genetic variance that can be captured by considering all available SNPs simultaneously, without testing for the association of any individual SNP with the phenotype. Thus, most of the heritability is not missing but has not previously been detected because the individual effects are too small to pass stringent significance tests.[215]

Heritability of biomarkers is an important consideration because it indicates the role that genetic factors play in determining individual differences in these traits. Familiar and twin studies have consistently demonstrated a strong genetic component to these traits, and they are highly polygenic. Evidence suggests a substantial familial and genetic influence on CRP, fibrinogen, WBCC, cortisol, and IGF-1.[216] Each have relatively high heritability, which in brief can be understood as the proportion of the total variation of the trait that can be attributed to unobserved genetic effects.[216] IGF-1 is a polypeptide product of the *IGF-1* gene, with twin-based heritability estimates as high as 62%.[217] There have been hypotheses of age dependences, although, these have not been confirmed.[217,218] A twin study found a substantial proportion of variance in cortisol was attributable to genetic factors, with no significant contribution found for shared environment. This

corresponded to a heritability estimate of 72% (h_r^2=0.72) in a robustly adjusted multivariate model.[205] Comparatively, circulating fibrinogen concentrations have a relatively moderate heritability range of 34-46%.[145] Residual heritability estimates have been shown to be statistically greater than zero for CRP and WBCC (CRP h_r^2=0.40; WBCC h_r^2=0.35), indicating that major genes in other chromosomal regions, polygenes, and other familial factors may account for up to 35-40% of the variance in these traits.[216] Equally, twin studies reveal that there is a highly significant hereditable component in base-line CRP concentrations (20-52%), with associations between CRP production and genetic polymorphisms in IL-1 and IL-6 also suggested.[180,219] In addition, twin heritability estimates show a 2-fold variation for WBCC ranging 35-71%,[220] with twin heritability for neutrophils (67%), monocytes (66%), eosinophils (69%), and lymphocytes (71%) also being relatively high.[221] This is important because WBCC derives from myeloid lineage cells (***Figure 1.4***). Given their collective, fundamental role in the innate and adaptive immune response, they are important clinical indicators of inflammation.[158,220] Even a 10^9/L increment in WBCC has been associated with a 32% increased risk of coronary heart disease, 20% of all-cause mortality,[220] with greater symptom severity in BD,[222] and differences in the regulation of leukocytes seen in depression and schizophrenia.[200]

1.2.1.2. Genome-wide Association Studies (GWAS) in Immune-Neuroendocrine Activity

Biomarker GWAS have been successful in identifying novel biological pathways via thousands of biomarker-associated loci and their impact on disease.[223] For example, GWAS have identified 266 unique loci, said to explain 16.3% of the variation in CRP levels, with 42 biological pathways underpinning CRP regulation.[146] This supports a polygenic model for this trait.[224] Ligthart and colleagues (2018)[225] used Data-Driven Expression-Prioritized Integration for Complex Traits (DEPICT) analysis to offer further evidence that genes annotated to the associated CRP variants predominately cluster at genes linked to the immune and liver systems, which is consistent with CRP being a highly sensitive, prototypical APP. GWAS also identified independent signals in 23

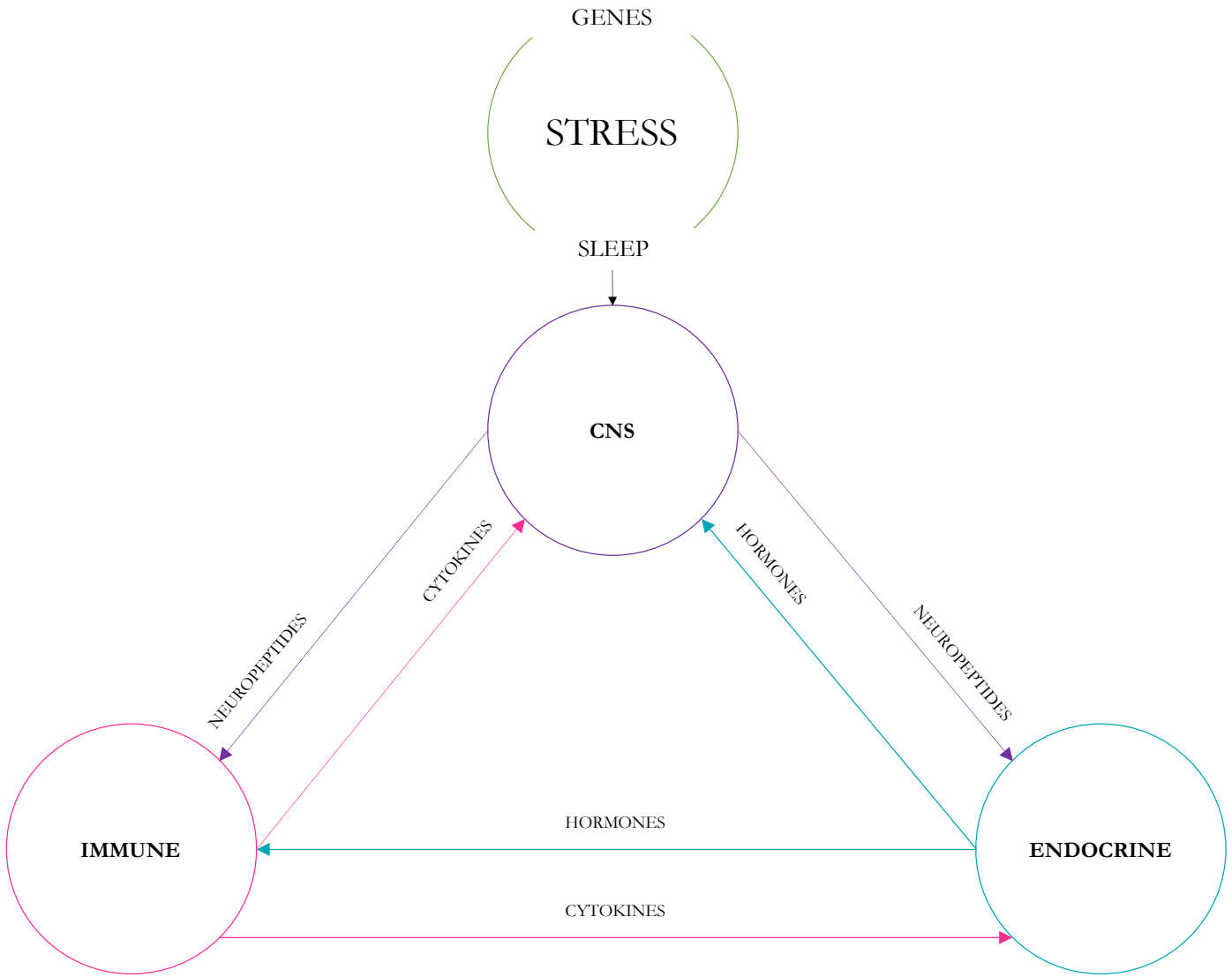
loci, 15 of which were unique, together explaining 3.7% of fibrinogen variation.[226] GWAS linked 145 genomic loci to traits that impact the formation of WBCC, RBCC, and platelets; predominantly reported in European ancestry (227 SNPs discovered in n>62,000 participants), then Asian (48 SNPs, n=16,000) and African (36 SNPs, n=14,000) cohorts.[227] Authors estimated common autosomal genotypes explained between 5-21% of the variance in white cell indices, compared to 10-28% in red cell and 18-30% in platelet indices.[228] In another GWAS, Kaplan and colleagues (2011)[229] showed that rs700752 was the only SNP associated with circulating IGF-1 concentrations at the level of genome-wide significance (p=4.9×10^{-9}). However, this association was attenuated (meta-analysis p=0.038) after adjustment for IGFBP-3 concentrations. Three additional SNPs for IGF-I concentrations achieved significance at p<10-6. The CORtisol NETwork (CORNET) consortium undertook GWAS meta-analysis for plasma cortisol in 12,597 European participants. Authors showed that <1% of variance in plasma cortisol was accounted for by genetic variation in a single region of chromosome 14.[230]

1.2.2. Psychoneuroimmunological Pathways

"*Our bodies are our gardens, to which our wills are gardeners.*" **Shakespeare (Othello).**

PNI, the scientific field centred on the integrative network between cognition, immunity, endocrinology and the central nervous system (CNS), provides a useful framework to understand how stress through sleep influences inflammation (***Figure 1.8***).[138,231,232] It looks at how psychological dynamics modulate physiological responses and influence overall health via cytokine-mediated communications, such that increased cytokine serum levels may lead to decreased availability of serotonin and other neurotransmitters.[150,171] In brief, the CNS innervates the immune and endocrine systems through neurotransmitters. Hormonal signals from the endocrine system modulate the CNS and immunity, while immune cells communicate through soluble proteins (cytokines) that are transported through the blood-brain interface or through

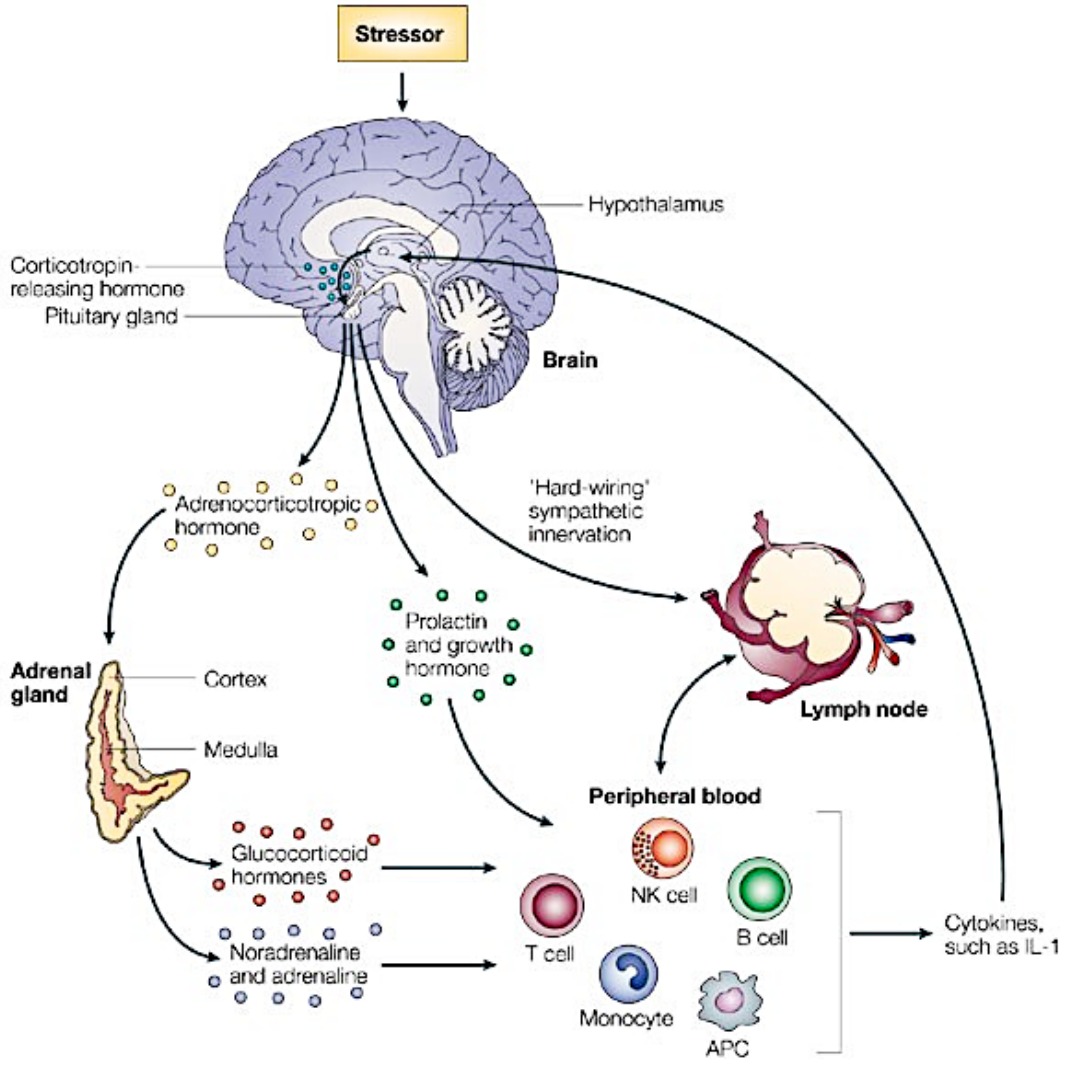
Figure 1.8 **A conceptual diagram of psychoneuroimmunological pathways**



neurotransmitter release to the endocrine and nervous systems[147] (***Figures 1.7c; 1.8***). As discussed, this dynamic, trilateral process can be dysregulated by stress or maladaptive sleep, with striking similarities of immuno-modulation seen between the two.[90] Stress can lead to a redistribution of immune cells in peripheral circulation, an upregulation in inflammatory genes, as well as an impairment in neuroendocrine activity that regulates inflammatory activity,[74] although, mechanisms underlying these processes are poorly understood. Abnormal sleep parameters are believed to more proximately stimulate downstream pathways from the CNS to the periphery, which alters cell gene expression and transcription that potentiates negative immune action.[233] In both instances, innate immune signalling pathways become activated towards dysregulation, with the release of innate proinflammatory cytokines.

Correspondingly, stress exposure, as perceived by the brain, can induce a cascade of neuroendocrine responses that impact upon cytokine production. This is said to transpire through the stimulation of two key pathways; the HPA[204] and sympathetic–adrenal–medullary (SAM) axes,[234] as crucial parts of the interface between stress and brain functioning (***Figure 1.9***). Notably, most immune cells have receptors for one or more 'stress hormones' associated with the HPA and SAM axes. Immune modulation can be either direct, through binding of the hormone to its cognate receptor, or indirect through cytokine production dysregulation.[235] Adrenocorticotropic hormone (ACTH) production by the pituitary gland promotes glucocorticoid hormones, the primary glucocorticoid of interest here being cortisol.[234] The suppressive role of cortisol in immune function is long known.[236,237] When functional, it exerts an inhibitory effect on pro-inflammatory cytokines by binding to glucocorticoid receptors on immune cells. This binding can suppress the transcription of pro-inflammatory cytokine genes, and alter the production of cytokines, including interferons, chemokines, interleukins, tumor necrosis factors, and transforming growth factors. The stress response, characterised by increased cortisol release, can then be seen as a regulatory mechanism of inflammation, that when perturbed fails in this important endeavour. Therefore, we

Figure 1.9 **Stress-associated modulation of the neuroendocrine response.**[234]



see that glucocorticoids play a key role in the upregulation of pro-inflammatory cytokines, such as TNF-α and IL-6, which have transcriptional control of APPs, such as CRP, through the liver,[180,238] on the immune system. It can stimulate the production of anti-inflammatory cytokines while inhibiting pro-inflammatory cytokines.[239]

1.2.2.1. Stress and Immune-Neuroendocrine Activity

Transient stress can be acutely immunoenhancing, supporting a rapid response to threats, but prolonged stress can lead to immunosuppression during later stages of the immune response.[142,240]

Still, meta-analytic results from 293 independent studies (n=18,941; M_{age}=34.8±15.9) over 30 years showed that different stressful events reliably associate with changes in multiple markers of the immune system in both general and clinical populations,[231] and a growing body of literature has supported associations between socioeconomic determinants of stress and inflammation,[241,242] despite variability across sample demographics.[16] Materially deprived individuals have shown higher levels of circulating inflammatory markers even in the general population.[243,244] However, a meta-analysis across 43 studies with non-patient samples (n=111,156; M_{age}range=9.96-74.26) found considerable variability in the strength of the estimated role of material deprivation in CRP and IL-6.[15] Certainly, this variability might be indicative of demographic differences, but a more nuanced consideration is variation arising from unobserved factors, such as suboptimal sleep and variations in genetic signature.

1.2.2.2. Maladaptive Sleep and Immune-Neuroendocrine Activity

Converging evidence has demonstrated the homeostatic role of sleep in the regulation of inflammatory processes.[141,245,246] More specifically, sleep architecture is a key component of the acute phase response (APR), central to host defence function,[56] and it is a critical modulator of hormonal release and glucose regulation.[247] Adaptive sleep supports neurally-integrated immunity.[87] In contrast, maladaptive sleep initiates and sustains activation of the inflammatory response,[149] as seen through marked elevations in systemic, cellular, and genomic markers of inflammation.[245] One systematic review and meta-analysis[73] of 72 studies (n>500,000) revealed some heterogeneity among studies that looked at sleep disturbance and duration in inflammation (indexed by CRP, IL-6, and TNF-α). On balance of evidence, authors found evidence for sleep disturbance and long sleep, but not short sleep, being associated with increased systemic inflammation. Notably, larger effect sizes were linked to younger age and a greater proportion of the sample were female. However, results largely depended on the biomarker tested, the method of data collection, and the sleep parameter used. For example, symptom reporting of sleep

disturbance was not associated with increased CRP levels, but it was with IL-6. Whereas sleep disturbance assessed by questionnaire was associated with CRP and IL-6. This remained true when symptom reporting, questionnaire, and diagnostic assessments were combined, such that sleep disturbance was associated with CRP and higher levels of IL-6, but not TNF-α. Notably, diagnosed assessments of sleep disturbance could only be investigated when combined because of a lack of power. As it relates to sleep duration, when treated continuously it was not associated with these inflammatory markers. When the extremes of sleep duration were compared to optimal sleep (i.e., 7-8 hours), short sleep was not associated with CRP, neither IL-6, nor TNF-α, but long sleep was associated with higher levels of CRP, IL-6, but not TNF-α.

Elsewhere, short sleep trajectories have been shown to be particularly relevant to inflammatory responses,[248] and a more salient concern to cohorts prone to age-related declines in sleep efficiency.[249] Even one night of sleep restricted to 4-hours can lead to over a three-fold increase in monocyte production of IL-6, TNF-α, and messenger RNA (mRNAs),[250] while a single hour of shorter sleep has been associated with CRP and IL-6 elevations.[251] In a randomised controlled trial (RCT), sleep-deprived adults had higher baseline cortisol levels and an exaggerated cortisol response to stress than well-rested adults.[252] Findings that suggest that sleep deprivation contributes to inflammatory processes by sensitising the brain to stress.[253] Although there are some consistencies, these studies highlights the difficultly in replicating results, comparing studies with different study designs, and making broad-stoke generalisations across different populations.

1.2.2.3. Psychoneuroimmunological Pathways and Mental-Ill-health

The acknowledgement that inflammatory processes may represent a common mechanism of disease has long been extended to psychiatric disorders.[254] Thus, it is fair to say that the exploration of immune and neuroendocrine mechanisms is key to understanding the genesis and pathophysiology of mental disorders, to improve diagnosis, stratification, and treatment.[255,256]

There are different proposed pathways through which this can occur. Higher levels of pro-inflammatory cytokines may influence neurotransmission, leading to altered production of neurotransmitters, such as serotonin, norepinephrine, dopamine, and brain-derived neurotrophic factor (BDNF). Each which have even been associated with specific psychiatric symptoms, such as anhedonia.[257] Cytokines may also influence neurocircuitry, leading to alterations in motivation status, anxiety, arousal, and alarm response.[258] Converging evidence from experimental, genomic, and epidemiological data, support that immune and neuroendocrine biomarkers underpin mental-ill-health across a spectrum of severity.[154,255,259–261] There is robust observational evidence for depression,[153,185,254] BD,[262–264] and schizophrenia,[152,168,265] but limited, less compelling evidence for anxiety,[266,267] and mixed support for causality in these conditions.[154,155,225] In a 2SMR study, Chen and colleagues (2022)[155] assessed the causal effects of 41 systemic inflammatory regulators on seven mental and neurodevelopmental disorders. The results found support for the genetically predicted concentrations of 15 unique systemic inflammatory regulators being causally associated with the risk of mental disorder. These included basic fibroblast growth factor (bFGF) and IL-1 receptor antagonist (IL-1Ra) for MDD, Eotaxin, bFGF, IL-8, and TNF-α for anorexia nervosa, cutaneous T-cell attracting chemokine (CTACK) and IL-18 for OCD, and monocyte-specific chemokine 3 (MCP3), hepatocyte growth factor (HGF), IL-17, IL-1Ra and TNF-related apoptosis-inducing ligand (TRAIL) for schizophrenia, with no support for BD.

Despite the aforementioned evidence, a fundamental issue is that associations have been reported in the opposite direction, suggesting that the presumed causal direction favours mental illness as an antecedent to inflammatory processes. This is conceivable. One study found a prospective association between agoraphobia and CRP over 5½ years, with no evidence of inflammation in any anxiety disorder.[268] Using multiple methodological approaches, Sumner and colleagues (2020)[269] concluded that elevated inflammation may increase risk of PTSD onset, but equally PTSD may lead to heightened inflammation. This inconsistency is seen with other severe mental

disorders.[270,271] In an experimental study, Juruena and colleagues (2006) found that depressed patients had higher cortisol levels compared with controls.[272] Another study found that baseline IL-6 did not predict a 6-year change in subclinical depression, with no evidence, in either direction, of a relationship between CRP and subclinical depression. On balance of evidence, authors supposed depression likely precedes inflammatory processes in older adults.[268] Yet in a systematic review, meta-analysis, and meta-regression, Mac Giollabhui and colleagues (2021)[273] found longitudinal associations, of small magnitude, in both directions, between depression and inflammatory markers, particularly for IL-6. However, the extent of these associations is likely obscured by the heterogeneity in depression and profound methodological differences between studies. Interestingly, severity may account for bidirectional associations. Strawbridge and colleagues (2019)[274] found that more severe, chronic or treatment-resistant depressive disorders were associated with dysregulated inflammatory activity. Still, the inconsistent associations suggest the need for a more nuanced, translational approach that considers genetic influence, biological clustering, and between-study comparisons in homogenous populations, with similar methodological strategies. Here it is proposed that mental disorders have a shared immune-neuroendocrinological basis, with environmental exposure and genetic signatures predisposing individuals to developing one psychopathological strand over another.

1.2.2.4. Psychoneuroimmunological Pathways | Unresolved Components

A substantial amount of knowledge has been generated to advance our understanding of how the integrative network between immunity, endocrinology and the neurology regulates homeostasis, and how a disruption to this dynamic, conceivably from factors such as stress and sleep, trigger the overproduction of proinflammatory cytokines[275] seen in mental illness.[81,97] However, there remains a number of unresolved components. First, the combined mechanisms, order of risk, and causality remain uncertain. Second, the type and level of stress exposure, plus the time that it takes for dysfunctional sleep to translate to inflammatory states is not often accounted for.[245] Third,

complexity arises from the diverse selection of biomarkers used across the integrative network of immune, endocrine, and nervous systems, leading to low specificity, with independent biomarkers being inconsistently implicated in different mental health conditions.[276] Fourth, genetic drivers of immune and neuroendocrine concentrations are rarely taken into account when assessing their antecedents in health and disease, which increases residual confounding and likely inflates effects. Finally, we lack an understanding of the complex ways in which these biomarkers interact, and their patterns of exchange are seldom considered in analytic designs. Thus, elucidating the role of genes, biomarkers, stress, and sleep in mental health remains a critical area of scientific exploration.

1.3. Precision Medicine

"*It is far more important to know what person the disease has than what disease the person has.*" **Hippocrates**

A peripheral focus of this thesis is to assess what populations are most at risk to PNI processes and subsequent disease, by bringing the importance of personalised medicine to the fore. Precision medicine is a transformative approach to healthcare that harnesses statistical and genomic evidence to better understand population risk,[9] such that treatments can be tailored, and interventions can be targeted to individuals rather than the inverse.[254] The premise of precision medicine is well-established, and can, for example, be easily understood through the now conventional practice of donor-recipient matching for blood transfusions, rather than transfusion by randomly selected donors.

Advanced statistical techniques, such as latent profile analysis (LPA), takes a precision medicine approach, by leveraging large-scale observational and health data, to uncover sub-populations of disease risk. Greater specificity in cohort characteristics and biological profiles that are relevant to disease risk can enhance clinical treatment responses and healthcare decisions. LPA is a model-based, structural equation modeling method for identifying and clustering individuals into

unobserved groups. It assumes individuals can be probabilistically classified into subpopulations with distinct attributes. Through model fit criteria, it identifies the optimal number of profiles by modelling the distribution of the observed data, and it estimates the proportional size and characteristics of each profile within the population. Once defined, latent profile membership can be used as a distinct variable in subsequent analyses.[277,278]

Equally, systematically recording information on the genomic signature of individuals, where the presence of genetic variants associated with disease risk and treatment response is identified, can offer insight into individuals' genetic predispositions and susceptibilities to disease with increased specificity.[10] We are a distance away from the population-level clinical utility of these genomic strategies in many areas, but notable progress has been made in fields like oncology, where these strategies are extensively used by the National Health Service (NHS) for routine practice to guide personalised treatments. Genetic-medical integration continues to hold great promise for clinicians to choose more effective, personalised treatment options, with the potential to improve diagnosis and therapeutic outcomes, while minimising adverse effects. By leveraging these approaches, precision medicine promises a new era of more effective, safer, and patient-centric medical interventions. All for the ultimate benefit of society in that it improves quality of care and, thus, improves the efficacy of health care provision overall.

1.4. Limitations of Extant Evidence

"*The only true wisdom is in knowing you know nothing.*" **Socrates**

Causation is a tenet of scientific inquiry, but the existing body of evidence on associations between stress, sleep, immune-neuroendocrine biomarkers, and mental ill-health, by large, lack the capacity to establish causal claims. This is for several reasons:

i. Much of the cumulated evidence has not been examined prospectively, and with cross-sectional evidence, directionality cannot be inferred because the temporal order cannot be established.[279]
ii. Causality is putatively made possible with the use of IVs, but genetic methods are predicated on strong assumptions[23,280] that are not always satisfied, which frustrates causal claims.[281]
iii. Research could benefit from a multifaceted approach that integrates self-reported, diagnostic, biological, and genomic data, as together they have the potential to offer greater objectivity.
iv. Too few studies take a systematic approach to covariate control. A DAG offers a logical structure to causal claims, based on the integration of multiple lines of evidence.
v. The link between stress and mental ill-health is widely acknowledged, but the mechanisms are not universally agreed nor understood.
vi. Capturing the extent and complexity of associations is further obfuscated by likely publication bias, as positive results are more likely to be published; plausibly skewing the available evidence.
vii. A shortage of syndicate studies have left a gap in knowledge. The use of standardised measures, comparative populations, and consistent methods allow for fairer comparison and an unambiguous synthesis of results.

1.5. Conclusion

Stress, particularly financial-related stress, has been implicated in mental health conditions,[48,99] although its effects vary across different segments of the population.[282] With consideration given to genetic predisposition, the overarching hypothesis of this thesis is that this association is linked through the mechanistic action of suboptimal sleep and aberrant immune and neuroendocrine activity. Compelling hypotheses have been put forward to explain these relationships, including the hypothalamic-pituitary stress system, a *hallmark* of the stress response.[283] However, low-grade systemic inflammation through PNI pathways, have been proposed as a more proximal mechanism, with changes seen to cellular, molecular, and epigenetic forms of plasticity.[97] For this reason, research efforts in PNI have shifted in part from neural-immune to immune-neural

signalling. Specifically, in how the activation of inflammatory networks shape mood, cognition and behaviour.[234,284–286] Research to elucidate the biological mechanisms underlying these associations are essential to reducing socioeconomic disparities in health.[287] There are various complications to understanding the relationships presented here, but a gallant step has been taken within this thesis to advance the understanding of stress, suboptimal sleep, and immune-neuroendocrine biomarkers in mental illness across a spectrum of severity, with considerable attention given to the underlying role of genetics.

1.6. Overarching Objectives

Overall, this thesis seeks to understand the biobehavioural mechanisms that link stress to the onset and progression of mental ill-health. It is intended to evoke novel interventions and improve treatment decisions. The thesis takes a structured, progressive, phased approach to the framework illustrated in ***Figure 1.10***. Each phase corresponds to a unique research question, and each research question has been assigned a chapter, as detailed below. Various advanced statistical techniques have been used to offer a nuanced response to each question and improve on earlier evidence.

1.7. Research Questions (RQ) and Hypotheses ($H_{\#}$)

CHAPTER 3. SOCIOECONOMIC STRESS AND IMMUNE-NEUROENDOCRINE ACTIVITY

| Cross-sectional and longitudinal analysis of compositional and contextual effects, with the percentage of the protective association explained in confounding structures.

RQ 2. What determinants are most strongly associated with variations in immune and neuroendocrine activity?

H_{2a}. Contextual socioeconomic determinants were expected to be stronger drivers of biomarker activity than compositional determinants cross-sectionally and longitudinally.

H_{2a}. Of all covariates, health behaviours were expected to account for the greatest variance.

CHAPTER 4. STRESS AND IMMUNE-NEUROENDOCRINE PATTERNING

| A latent profile analysis, longitudinal analysis, and polygenic risk prediction

RQ 1. Are common psychosocial stressors associated with immune and neuroendocrine latent profiles?

H_{1a}. Heterogeneous patterns of immune and neuroendocrine activity were expected, with two to three subgroups emerging from the data.

H_{1b}. Psychosocial stress was expected to be longitudinally associated with more adverse immune and neuroendocrine profiles, irrespective of genetic predisposition.

CHAPTER 5. FINANCIAL STRESS, SLEEP DURATION, AND IMMUNE-NEUROENDOCRINE PATTERNING

| An analytic triangulation, with latent profile analysis, effect modification, and polygenic risk prediction

RQ 3. Is financial stress and suboptimal sleep independently and interactively associated with adverse immune and neuroendocrine profiles.

H_{3a}. Financial stress and suboptimal sleep were expected to be independently and interactively associated with adverse immune and neuroendocrine profiles.

H_{3b}. Polygenic risk for short and long sleep were expected to be genetically associated with adverse immune and neuroendocrine profiles.

CHAPTER 6. POLYGENIC PREDISPOSITION, SLEEP DURATION, AND DEPRESSION

| Polygenic risk prediction, with longitudinal phenotypic associations

RQ 4. What is the directional association between sleep duration and depression?

H_{4}. A positive, unidirectional association between polygenic predisposition to overall sleep duration, short sleep, and long sleep were expected in the onset of subclinical depression.

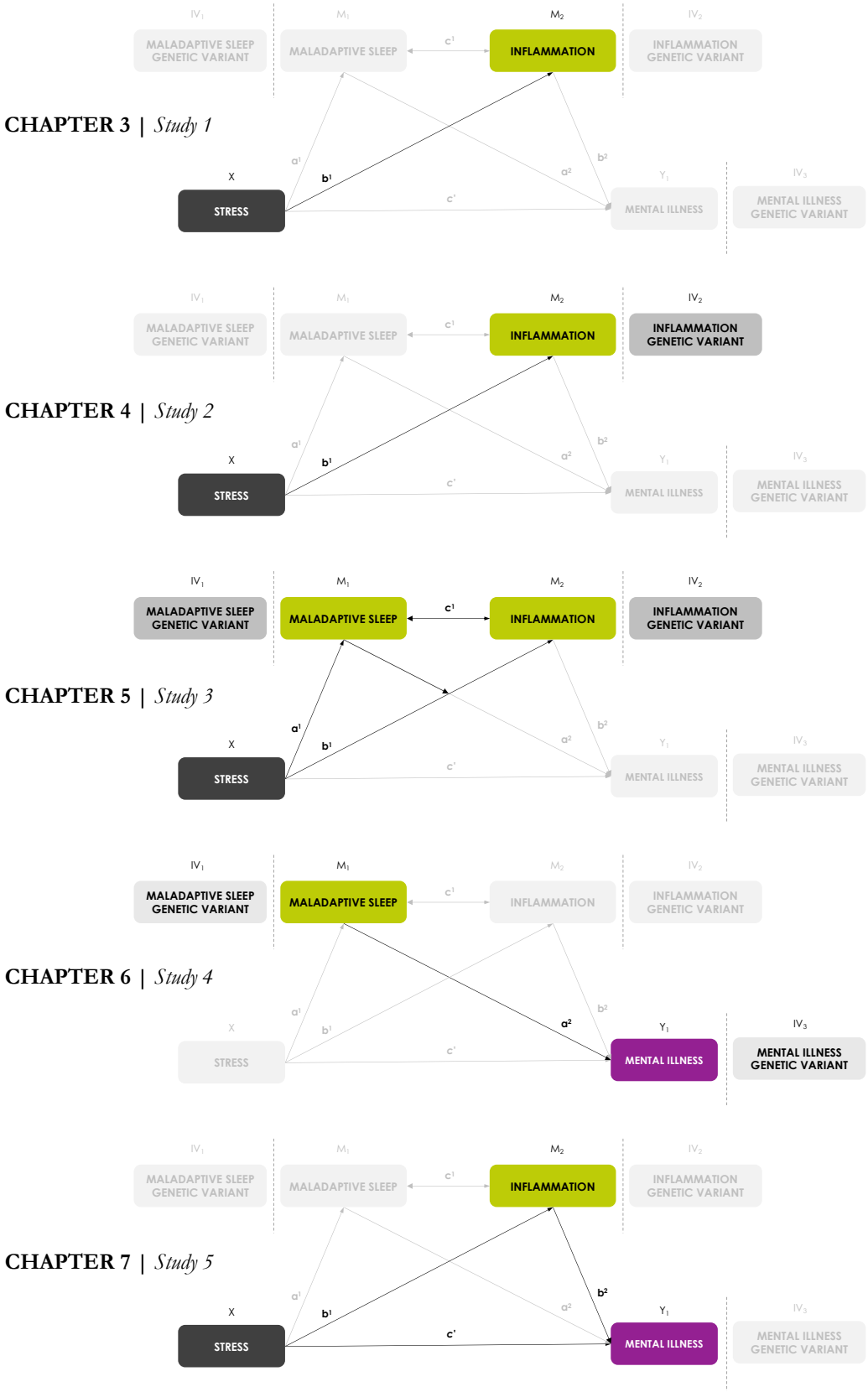
CHAPTER 7. COVID-19 STRESS, INFLAMMATION, AND DEPRESSION

| Longitudinal analysis

RQ 5. Is inflammation associated with depression in the presence of pandemic-related stress?

H_{5}. Greater inflammation was expected to be longitudinally associated with depression in the presence of stress during the pandemic.

Figure 1.10 **The Conceptual Framework by Chapter**



CHAPTER 2. METHODOLOGY

2.1. Data

Fully anonymised data were drawn from the English Longitudinal Study of Ageing (ELSA), an ongoing multidisciplinary, observational study, with a household response rate of ~70% at first wave.[288] Aligned with the National Census, ELSA is representative of the non-institutionalised general population aged ≥50 in England. Data collection is performed in participants' homes, via computer-assisted personal interviews (CAPI) and self-completed questionnaires biennially, then nurse visits quadrennially for biological samples. However, not all participants provided blood samples for assay, due to problems in scheduling visits from study nurses and ineligibility (e.g., being on anticoagulant medication; having a haematological disorder; having a history of convulsions). All participants provided written consent, and ethical approval was granted by the National Research Ethics Service (London Multicentre Research Ethics Committee).

2.2. Variable Construction

2.2.1. Stress Composite Score

Psychosocial stress was measured as a composite score on a scale from no stressful life events to the experience of six stressors. An ordinal score was estimated as the summation of the presence of six binary stressors, dichotomised (low versus high) at the median. Despite this median split, there was an unequal distribution of participants in each group due to the limited number of integer values of this score (0-6):

Financial Strain. The perceived chance of not having enough financial resources in the future to meet needs; categorised by 0; 1-39; 40-60; 61-99; 100% and dichotomised at >60%.

Care Giving. Being an informal caregiver to an adult who is sick or frail, in the past week, or during the last month while being in receipt of Carer's Allowance.

Disability. Has one or more difficulties mobilising (i.e., walking 100 yards; sitting 2-hours; rising from chairs after sitting long periods; climbing stairs; stooping, kneeling, crouching; reaching or extending arms above shoulders; pulling or pushing large objects; lifting or carrying objects over 10 pounds; picking-up a 5p coin).

Illness. Has a longstanding illness or health condition that limits activity.

Bereavement. Experienced the death of a parent, spouse, or partner in the past two years.

Divorce. experienced divorce or a long-term relationship breakdown in the past two years.

2.2.1. Socioeconomic Stress Indicators

2.2.1.1. Contextual (Neighbourhood-level)

Index of Multiple Deprivation for England (IMD). Due to the waves of data analysed throughout this thesis, the 2004 IMD (i.e., neighbourhood deprivation) was used. It is a relative measure of deprivation that combines multiple area-level socioeconomic indicators into a single deprivation score. It is predicated on 38 indicators, across seven domains: education; employment; income; skills and training deprivation; barriers to housing and services; living environment deprivation and crime; health and disability (**Table 2.1**). The seven domains were measured at the 'lower level super output area' (LSOA), a statistical unit introduced in the 2001 Census that contains 1,500 households on average. Details of both theoretical and practical implementation of this measure, including its reliability and validity, have been published elsewhere.[289] Neighbourhood deprivation was demarcated into tertiles; the first representing the most deprived on a gradient to the third that represents the least deprived (reference category).

2.2.1.2 Compositional (Individual-level)

Wealth. Calculated by summating total household wealth, as determined by net wealth from property, possessions, housing, liquid assets; cash, savings, investments, artwork, and

jewellery, net of debt, exclusive of pension wealth. Wealth was then divided into tertiles; the first representing the least wealth and the third representing the greatest wealth (reference category). Total wealth is a more reliable socioeconomic measure than income in older cohorts, owing to a greater reliance on accumulated capital as one ages, conferring income less salience.[290]

Education. Recoded from 7-items into four categories of higher education (i.e., degree or equivalent; reference category); primary and secondary school qualifications (i.e., A-level, higher education below degree, GCSE [General Certificate of Secondary Education] or equivalent); and no qualifications.

Occupational Social Class (Occupation). A three-category version of the National Statistics Socio-Economic Classification:[291] managerial and professional (reference category); intermediate; routine and manual. Occupation, in this context, is predicated on the individuals' last known career, rather than their current occupation.

2.2.4. Sleep Duration

Sleep duration was measured with an open-ended question, asking participants about the length of their sleep on an average weeknight. Outlier values greater than 3± from the M were excluded from the raw data. Following literature, to improve model fit, interpretability, and to avoid non-linear interaction complexity,[118,121] sleep duration was categorised into "≤5 hours (hrs)" (i.e., short sleep), ">5-<9hrs" (i.e., optimal-sleep), and "≥9hrs" (i.e., long sleep).

2.2.5. Subclinical Depression

The eight-item Centre for Epidemiologic Studies Depression Scale (CES-D)[292] was used to assess self-reported experiences of depression over the past week. The psychometric properties were excellent in validity and reliability to the original 20-item scale.[293] The eight-item scale included

Table 2.1 Components of the Index of Multiple Deprivation (IMD)

Domains	Indicators
Income Deprivation (5)	1. Adults and children in Income Support families 2. Adults and children in income-based Jobseeker's Allowance families 3. Adults and children in Pension Credit (Guarantee) families 4. Adults and children in Child Tax Credit families (who are not claiming Income Support, income-based Jobseeker's Allowance or Pension Credit) whose equivalised income (excluding housing benefits) is below 60% of the median before housing costs 5. Asylum seekers in England in receipt of subsistence support, accommodation support, or both
Employment Deprivation (7)	1. Claimants of Jobseeker's Allowance (both contribution-based and income-based) women aged 18-59 and men aged 18-64, averaged over four quarters 2. Claimants of Incapacity Benefit women aged 18-59 and men aged 18-64, averaged over four quarters 3. Claimants of Severe Disablement Allowance women aged 18-59 and men aged 18-64, averaged over four quarters 4. Claimants of Employment and Support Allowance (those with a contribution-based element) women aged 18-59 and men aged 18-64 5. Participants in New Deal for the 18-24s who are not in receipt of Jobseeker's Allowance, averaged over four quarters 6. Participants in New Deal for 25+ who are not in receipt of Jobseeker's Allowance, averaged over four quarters 7. Participants in New Deal for Lone Parents (after initial interview) aged 18 and over, averaged over four quarters
Health Deprivation and Disability (4)	1. Years of Potential Life Lost 2. Comparative Illness and Disability Ratio 3. Acute morbidity 4. Mood or anxiety disorders
Education Skills and Training Deprivation (7)	1. Key Stage 2 attainment 2. Key Stage 3 attainment 3. Key Stage 4 attainment 4. Secondary school absence 5. Staying on in education post 16 6. Entry to higher education 7. Adult skills
Barriers to Housing and Services (7)	1. Household overcrowding 2. Homelessness 3. Housing affordability 4. Road distance to a GP surgery 5. Road distance to a supermarket or convenience store 6. Road distance to a primary school 7. Road distance to a Post Office
Living Environment Deprivation (4)	1. Housing in poor condition 2. Houses without central heating 3. Air quality 4. Road traffic accidents
Crime (4)	1. Violence 2. Burglary 3. Theft 4. Criminal damage

whether, "*during past week",* participants felt:- "…*depressed much of the time*"; "…*everything was an effort*"; "…*happy much of the time*"; "…*felt sad much of the time*"; "…*lonely much of the time*"; "…*enjoyed life much of the time*"; "…*could not get going much of the time*"; and "*whether their sleep was restless during the past week*". The items were scored on a binary response scale (anchored at 1='*yes*'; 0='*no*'). Positively worded items were reversed scored. Higher scores indicated a greater experience of depression. Scores were summed to generate a total continuous score, ranging 0 ('*no depression*') to 7 ('*subclinical depression*'), then dichotomised at ≥4; a well-recognised clinically significant indicator of pathological depression.[293] The Cronbach's alpha (α) for the original and reduced score in this sample was 0.80, suggesting adequate internal consistency. This corresponds to the α computed by Steffick (2000) for the first three waves of data (i.e., 0.84; 0.83; 0.81).[293]

2.2.6. Biomarkers

Immune and neuroendocrine biomarkers included high-sensitivity plasma C-reactive protein (hsCRP/CRP; mg/L), plasma fibrinogen (Fb; g/L), plasma leukocytes/white blood cell counts (WBCC; 109/L), hair cortisol (cortisol; pg/mg), and serum insulin-like growth factor-1 (IGF-1; mmol/L). Selection was based on availability of immune and neuroendocrine-related biomarkers. Blood samples were discarded if deemed insufficient or unsuitable (e.g., haemolysed; received >5 days post-collection). Exclusion criteria included coagulation, haematological disorders, being on anticoagulant medication or having a history of convulsions. was normally distributed, but due to an initially skewed distribution, logarithmic (log) transformation was performed on CRP, WBCC, cortisol, and IGF-1 values. Correlations reported in each study between the biomarkers were as expected and in line with earlier evidence.[207,294–296]

C-reactive Protein. Plasma CRP (mg/L) was assayed using the N Latex CRP mono Immunoassay on the Behring Nephelometer II analyser (Dade Behring, Milton Keynes, UK). Intra and inter-assay coefficients of variation were <2%. The lower detection limit of the assay was 0.2mg/L. CRP values >20mg/L were excluded from analyses (*n*=116), as these were taken to

reflect acute inflammatory processes rather than chronic inflammation.[188] CRP was treated as continuous, with higher values indicating greater levels of inflammation.

Fibrinogen. Plasma fibrinogen (g/L) was analysed using a modification of the Clauss thrombin clotting method on the Organon Teknika MDA 180 coagulation analyser (Organon Teknika, Durham, USA). Intra and inter-assay coefficients of variation were <7%. The lower detection limit of the assay was 0.5 g/L. Fibrinogen was treated as continuous, with higher values indicating greater levels of inflammation.

Leukocytes **(White Blood Cell Counts).** Plasma leukocytes/WBCC were analysed as continuous counts per 109/L; measured on a haematology-automated analyser (Abbott Diagnostics Cell-Dyn 4000 and Sysmex XE), with higher values indicating greater levels of inflammation.

Hair Cortisol. Hair strands ~3cm in length, weighing ~10mg were collected from the posterior vertex, as close to the scalp as possible. Assuming an average hair growth of ~1cm per month,[297] the hair segment closest to the scalp is thought to provide a measure of the average cortisol output over the preceding three months prior to sampling. Exclusion criteria for hair sampling included pregnancy, breastfeeding, select scalp conditions, having <2cm of hair length, and an inability keep one's head still. Hair cortisol concentrations were analysed at the Technische Universität Dresden (Germany). Cortisol levels were assayed using high performance liquid chromatography-mass spectrometry (LC/MS) following a standard wash and steroid extraction procedure,[298] and were expressed in pg/mg. Data was log-transformed, as the distribution was positively skewed. Cortisol was treated as continuous, with higher values indicating greater levels of inflammation.

Insulin-like Growth Factor-1. Serum IGF-1 (nmol/L) was measured using the DPC Immulite 2000 method, by an electrochemiluminescent immunoassay on IDS ISYS analyser. Inter

and intra-assay coefficients of variation were <14%. IGF-1 was treated as continuous, with lower values indicating greater neuroendocrine activity.

2.2.7. Cross-study Covariates

Baseline outcomes, along with factors likely to confound analyses across studies were selected *a priori*. These included *demographic variables*: age (≥50 years); age^2 ([squared] to account for non-linearity); sex (male; female); smoking status (binary:- non-smokers/ex-smokers or smokers); weekly alcohol consumption (binary:- low <3 or high ≥3 day); weekly physical activity (binary:- sedentary or moderate/vigorous activity); *genetic variables*: PGS for CRP, WBCC, cortisol, and IGF-1, short sleep and long sleep, and 10 principal components (PCs) to account for population stratification (methods later explained); *clinical variables*: body mass index (BMI); calculated as weight in kilograms divided by height in meters squared [underweight:≤18.5; normal:18.6-24.9; overweight:25-29.9; obese:≥30kg/m2]); *health variables*: any self-reported clinician diagnosis (abnormal heart rhythm; angina; arthritis; asthma; cancer; chronic lung disease; congestive heart failure; coronary heart disease; diabetes; heart murmur; hypertension; osteoporosis; dementia; Parkinson's disease; or psychiatric disorder).

2.2.8. Genetic Data Derivation

The genome-wide genotyping was performed at University College London (UCL) Genomics in 2013-2014 with funding from the ESRC using the llumina HumanOmni2.5 BeadChips (HumanOmni2.5-4v1, HumanOmni2.5-8v1.3), which measures ~2.5 million markers that capture the genomic variation down to 2.5% minor allele frequency (MAF). Using PLINK and PRSice software, PGS for CRP, cortisol, and IGF-1 were calculated using summary statistics from GWAS from the UK Biobank.[299] Unless otherwise stated, a single *p*-value threshold of 0.001 was used for all PGSs to limit multiple testing, while maximising their potential predictive ability.

2.2.8.1. Quality Control

The methods employed for quality control of genomic data in the ELSA study are those outlined by the Health and Retirement Study (HRS).[300] This was done to harmonise the research across the age-related longitudinal studies by adopting a consistent methodology. SNPs were excluded if they were non-autosomal, MAF was <1%, if more than 2% of genotype data were missing and if the Hardy-Weinberg Equilibrium was $p<10^{-4}$. Samples were removed based on call rate (<0.99), heterozygosity, relatedness, and if the recorded sex phenotype was inconsistent with genetic sex. To identify ancestrally homogenous analytic samples the ELSA genomic samples use a combination of both self-reported ethnicity and analyses of genetic ancestry. To improve genome coverage, untyped quality-controlled genotypes to the Haplotype Reference Consortium were imputed[301] using the University of Michigan Imputation Server.[302] Post-imputation, variants were kept that were genotyped or imputed at INFO>0.80, in low linkage disequilibrium ($R^2<0.1$) and with Hardy-Weinberg Equilibrium p-value$>10^{-5}$. After the sample quality control 7,179,780 variants were retained for further analyses. To account for potentially biasing ancestry differences in genetic structures, a PCs analysis was conducted, retaining the top 10 PCs,[303] which were subsequently used to adjust for possible population stratification in the association analyses.[303,304] Genetic ancestry was estimated via comparison of participants' genotypes to global reference populations using principal component analyses (PCA) employing PLINK1.9. [303,304] PCA allows examining population structure in a cohort by determining the average genome-wide genetic similarities of individual samples. Therefore, derived PCs can be used to group individuals with shared genetic ancestry, to identify outliers, and as covariates, to reduce false positives due to population stratification. Although up to 98% of the ELSA participants self-described to be of European background, PCA highlighted the presence of ancestral admixture in 0.9% (n=65) individuals,[303] implying they had ancestors from two or more populations. Even though this type of labelling of ancestral populations oversimplifies the complexity of human genetic variation, accounting for systematic differences in allele frequencies is necessary for genetic analyses.

Therefore, these participants with ancestral admixture were removed from the analyses. The final sample includes all self-reported European participants that had PC loadings within 1± of the mean for eigenvectors one. PCs were then re-calculated to further account for population stratification, retaining the top 10 PCs,[303] which were subsequently used to adjust for possible population stratification in the association analyses.[303,304] Therefore, the analytic sample included the full ELSA sample that provided genetic samples and passed quality control. It is noteworthy that the methods employed for quality control of genomic data as described above are those outlined by the HRS.[305] This was done to harmonise the research across the age-related longitudinal studies by adopting a consistent methodology.

2.2.8.2. Polygenic Scores (PGS)

PGSs are indices of individuals' genetic propensity for a trait, derived as the sum of the total number of trait-associated alleles, otherwise known as SNPs, across the genome and weighted by their respective association effect size estimated through genome-wide association analysis.[306] To aid in the interpretability of the results, all PGSs were standardised by subtracting the mean and dividing by their corresponding standard deviations; this scaling ensured a comparison of results across models.

PGS for CRP. This PGS used results from two GWAS, based on both HapMap and 1,000 Genomes imputed data and encompassing data from 88 studies comprising 204,402 European individuals.[225] The GWAS meta-analyses of CRP revealed 58 distinct genetic loci ($p<5\times10^{-8}$). After adjustment for BMI in the regression analysis, the associations at all except three loci remained. The lead variants at the distinct loci explained up to 7.0% of the variance in circulating concentrations of CRP. Further, 66 gene sets that were organised in two substantially correlated clusters were identified, one mainly composed of immune pathways and the other characterised by metabolic pathways in the liver. The GWAS summary statistics for this phenotype contained

10,019,203 SNPs; of these, 1,301,076 SNPs overlapped with the ELSA genetic database and were included in the PGS for the CRP phenotype.

PGS for WBCC. This PGS in ELSA was calculated using summary statistics from GWAS meta-analyses that included data from the UKB and a largescale international collaborative effort, including data from 563,085 European ancestry participants. There were 27,090,932 genetic loci at a genome-wide significance of $p<5\times10^{-8}$, with 5,106 new genetic variants independently associated with 29 blood cell phenotypes covering a range of variation that impacts haematopoiesis. The WBCC phenotype (109/L), as an aggregate number of white blood cells per unit volume of blood, is one of several quantitative clinical laboratory measures that together reflect hematopoietic progenitor cell production, haemoglobin synthesis, maturation, release from the bone marrow, and clearance of mature or senescent blood cells from circulation.[307] Raw phenotypes were regressed on age, age^2, sex, PCs, and cohort specific covariates. WBCC related traits were log^{10} transformed before regression modelling. Residuals from the modelling were obtained and then inverse normalised. The cohort level association analyses were conducted using a linear mixed effects model to account for known or cryptic relatedness (e.g., BOLT-LMM, EPACTS https://github.com/statgen/EPACTS and rvtests with the additive genetic model). Linear mixed effects models have been shown to effectively account for both population structure and inter-individual relatedness within the UK Biobank cohort, along with having increased discovery power over simple linear regression with PCs.

PGS for IGF-1. This PGS was calculated using summary statistics from GWAS that included 10,280 men and women in the analyses, comprising 1,712 participants from the Cardiovascular Health Study (CHS), 3,507 from the Framingham Heart Study (FHS), 1,607 participants from the Cooperative Research in the Region of Augsburg (KORA) study, and 3,454 from the Study of Health in Pomerania (SHIP). Analyses of SNPs associated with IGF-1 concentrations revealed that rs700752 was associated with IGF-I concentrations ($p=4.9\times10^{-9}$), but this was attenuated (meta-analysis $p=0.038$) after adjustment for IGFBP-3 concentrations. Three

additional SNPs achieved $p<10^{-6}$ in relation to IGF-I concentrations: rs2153960 on chromosome 6q21, MAF=0.31, $p=5.1\times10^{-7}$; rs1245541 on chromosome 10q22.1, MAF=0.39, $p=5.0\times10^{-7}$; rs7780564 on chromosome 7p21.3, MAF=0.45, $p=3.9\times10^{-7}$.

PGS for Morning Plasma Cortisol. This PGS in ELSA was contracted using the results from the CORNET consortium, who undertook the GWAS meta-analysis for plasma cortisol in 12,597 White participants from 11 Western European population-based cohorts and replicated their results in 2,795 participants from three independent cohorts.[230] Cortisol was measured by immunoassay in blood samples collected from study participants between 07:00h and 11:00h. Each study performed single marker association tests, and study-specific linear regression models that used z-scores of log-transformed cortisol, and additive SNP effects, and were adjusted for age and sex (model 1); age, sex, and smoking (model 2); then age, sex, smoking and BMI (model 3). Imputation of the gene-chip results used the HapMap CEU population, build 36. The results indicate that <1% of variance in plasma cortisol was accounted for by genetic variation in a single region of chromosome 14. The CORNET GWAS summary statistics for this phenotype contained 2,660,191 SNPs; of these, 837,709 SNPs overlapped with the ELSA genetic database and were included in the PGS for 'Morning Plasma Cortisol' phenotype.

2.3. Methodological Techniques

2.3.1. Directed Acyclic Graph (DAG)

Research questions cannot be computed from the data alone, nor from the distributions that govern the data, control decisions should have a strong theoretical basis. There must also be a demonstrable dose-response relationship, that is, variation in the exposure must statistically explain changes in the magnitude of the outcome, and this explanation of change must remain statistically significant after controlling for likely rival explanations.[308] However, many of the available studies have a limited selection of covariates, so have considerable unobserved

confounding. Controlling for factors associated with both the exposure and outcome is essential for making fully justified inferences about causality, but there is some question as to whether some studies have inadvertently introduced bias by conditioning on a variable that serves as a mediator. This would be a collider, that is, a variable that itself is caused by two alternate variables, one that is (or is associated with) the exposure and another that is (or is associated with) the outcome.[309] For instance, BMI has previously been linked to both inflammation and mental illness. Therefore, conditioning on BMI in a study investigating these associations may have introduced collider stratification bias.[310] This type of endogenous selection bias gives reason for DAGs, a valuable technique to visually represent posited causal relationships among variables, while considering potential sources of bias and confounding. It helps to ensure that the tested associations are scientifically plausible and consistently observed across different study designs, populations, and contexts to support generalisability. This level of replication is central to establishing causality irrespective of contextual variation. Ultimately, the DAG was developed to trace causal pathways, mitigate bias, optimise parameter inferences, and improve estimate accuracy. Variables that were likely on the causal pathway were excluded from the main models, because conditioning on them would have introduced collider bias.[311] The DAG served as validation for the proper parameterisation of the models, to reduce overadjustment bias, and to ensure the adherence of assumptions, *inter alia* homoscedasticity and an absence of interactions.[312,313] It is important to note that while the DAG identifies the presence of bias, it does not explicitly specify the type nor the magnitude of the bias, whether there are competing biases, or whether the observed bias is clinically meaningful.[314] DAGs were conducted in DAGitty.net.

2.3.2. Multiple Imputation

Multiple imputation can reduce bias despite the proportion of missingness being substantial.[315] Thus, owing to a better powered sample, with greater precision, and a higher possibility of bias from case-wise deletion,[316] the main analyses were conducted using imputed datasets, except if

otherwise stated. Imputations were performed on data missing on exposures, covariates, and outcomes, with the exclusion of genetic data and entirely absent biological data. Imputation was performed using missForest; a Random Forests algorithm-based machine learning imputation method. Random forests is non-parametric, it works with high-dimensional data, and it has a built-in feature selection that evaluates entropy and information gain, so it is robust to noisy data and multicollinearity. In the presence of nonlinearity and interactions missForest outperformed prominent imputation methods, such as multiple imputation by chained equations (MICE) and k-nearest neighbours (KNN) in all metrics.[317] In ELSA, socioeconomic and health-related variables are the main drivers of attrition[288] but these variables were included in the imputation models, so the assumption that missingness was at random (MAR) was likely to be met. Imputed and observed data were homogenous in the early use of the study data, indicating that results deriving from imputed data aligned with those from complete case analyses (Chapters 3, 4, and 6). The imputation yielded minimal variable error across studies, with continuous variables measured as the normalized root mean squared error (NRMSE) and categorical variables measured as the proportion of falsely classified (PFC). Values lower than 0.5 for NRMSE and PFC are well within the range of accuracy.[317] Therefore, the error rates in all studies herein indicate excellent performance relative to these benchmarks. Multiple imputation was conducted in R v.4.2.0: RStudio v.2022.02.2.

2.3.3. Latent Profile Analysis (LPA)

Immune and neuroendocrine biomarkers, which varied across studies, were entered into the LPA. The LPA model for observed variable *A* can be expressed as:

$$\sigma \frac{2}{A} = \sum_{t=1}^{T} \pi_t (\mu_{At} - \mu_A)^2 + \sum_{t=1}^{T} \pi_t \sigma_{At}^2$$

where μ_{At} and σ_{At}^2 denote (*t*) class-specific means and variances for variable *A*, and π_t show the proportion of *N* participants that belong to class *t*. A stepwise approach was taken to identify the optimal number of latent profiles, while ensuring statistical saliency; starting with a single-profile model, additional profiles were added to improve model fit. The number of latent profiles was determined on the basis of the Akaike information criterion (AIC),[318] Bayesian information criterion (BIC),[319] and adjusted Bayesian information criterion (aBIC).[320] Further, the information criteria and the likelihood ratio tests (LRT) indicated the goodness of fit of different latent profile models, with the best model being the one with the lowest AIC, BIC, and aBIC values, with a significant LRT (p<0.05). The entropy statistic that provides the quality of the classification model, and the average posterior probabilities for each latent profile, indicating profile membership classification errors, were also taken into account.[321] The closer to 1 these indicators were, the better the classification quality,[322] although a common cut-off point for posterior probabilities is ≥0.70.[323] An entropy of ≥0.80 indicates clear profile separation.[324] Every profile needed to contain ≥5% of participants, with the profiles being of good theoretical interpretability.[325] Once the number of latent profiles was established, each individual within the sample was assigned to a cluster for which they had the largest posterior probability, reflecting the most likely affiliation. The *low-risk* profile was the reference in all cases. The LPA was conducted in Stata 18.1 (STATA CorpLP, USA).

2.3.4. Association Analyses

Baseline characteristics across studies were expressed as means and proportions, with Analysis of Variance (ANOVA) or Chi-squared (χ^2) comparisons on outcomes wherever useful. Where appropriate, the studies tested associations using linear, logistic, or multinomial regression. Respectively, results were reported as betas coefficients (unstandardised or standardised), odds ratios (OR), or RRR, with standard errors (SE) and CI. Analyses were two-tailed. All regression

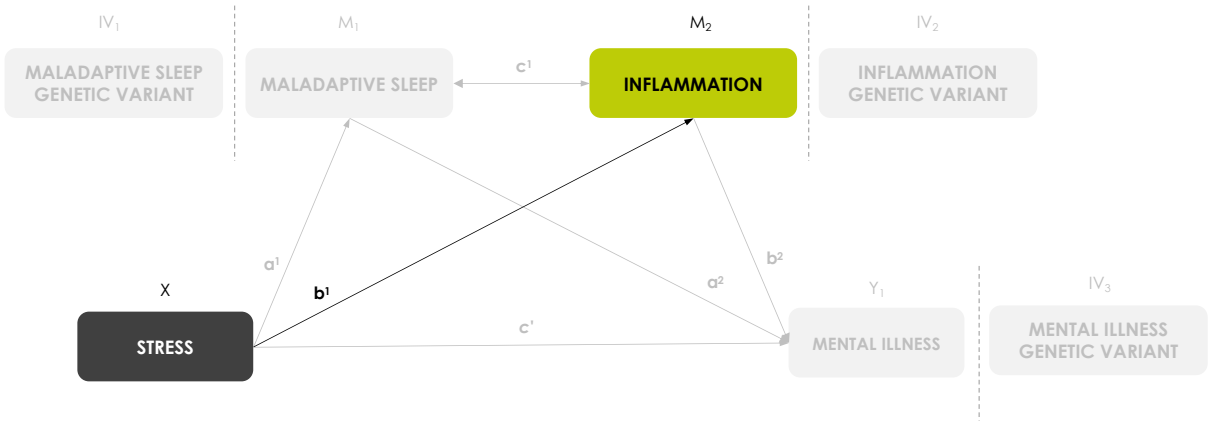
assumptions were met.[326,327] Different models were fitted to understand the role of covariates on associations**.** For stepwise model adjustments, changes in OR/RRR due to the inclusion of covariates were calculated using the equation $\exp(\beta_{j,\text{new}}-\beta_j)$, which represents the multiplicative change in the ratios for a given covariate X_j after adjusting for the effects of other covariates. Where β_j is the original coefficient associated with the covariate X_j in the model before the inclusion of additional covariates, and $\beta_{j,\text{new}}$ is the new coefficient associated with the covariate X_j after the inclusion of additional covariates, reflecting the adjusted effect of X_j in the presence of other covariates. Moreover, to test the extent to which different models explained associations, the B for outcomes were calculated using the percentage of the protective association explained (PPAE); a well-established epidemiological method[328] using the formula: PPAE = (B [crude model 1 and model X] – B [crude model 1] / (1-B [crude model 1]), where X is the model tested. Association analyses were all conducted in Stata 18.1 (STATA CorpLP, USA).

CHAPTER 3. SOCIOECONOMIC STRESS AND IMMUNE-NEUROENDOCRINE ACTIVITY

3.1. Chapter overview

With findings published in *Brain, Behavior, and Immunity* (Hamilton & Steptoe, 2022),[329] this chapter reviews the evidence on and draws a distinction between contextual and compositional socioeconomic determinants of inflammation and neuroendocrine activity. It examines how immune-neuroendocrine activity are cross-sectionally and longitudinally nested in these meso-level socioeconomic characteristics.

Figure 3.1 **The section of the conceptual framework (*Figure 1.10*) addressed in Chapter 3**



3.2. Introduction

Immune and neuroendocrine processes are of vital importance in health and disease.[98,171,330 331] The economic burden[332] and the gravity of these accumulative costs to health[183] have prompted a more in depth study of the factors contributing to inflammatory and neuroendocrine processes. One important determinant from a biobehavioural perspective is material deprivation.

Material deprivation can lead to psychological stress, and is known to actuate a systemic level response through PNI pathways.[333–335] Among developed countries, the UK has one of the largest gradients in deprivation,[336] with 7.8 million people in persistent poverty.[337] This is a concern for policy makers, not least, because of growing health disparities.[338] There is greater exposure to stress[339] and communicable disease in deprived areas, while individuals within those areas are, on average, more likely to engage in harmful health behaviours.[15,340] Still, they tend to have fewer educational, social, and psychological resources with which to cope,[339] with less availability of medical services and a reduced inclination to access care.[341]

An important distinction can be drawn between contextual and compositional socioeconomic indicators.[342] Deprived populations are disproportionately exposed to environments characterised as pro-inflammatory.[343] Compositional factors have been linked to inflammatory and neuroendocrine states.[15] However, given the multidimensional of deprivation, it is conceivable that contextual determinants are more proximal risk factors,[344] such that health and disease are shaped by social and spatial context. The interest here is in the relative strength of contextual and compositional factors and prospective nature of these associations, as well as the extent to which different sets of covariates account for the gradient in outcomes. Differentiating between contextual and compositional effects is key to understanding how the environment confers risk on health after accounting for individual-level risk factors.[345] This could help inform the focus, level, and magnitude of interventions targeted at narrowing the health divide. Ignoring this distinction increases the likelihood of an invalid transfer of results obtained at the ecological level to the individual level (the ecological fallacy), as is the case when failing to account for ecology or context (the individualistic fallacy). Overlooking their dependent nature, along with the source of the dependency, can lead to significant findings where none exist.[346]

Older cohorts are increasingly relevant to the understanding of socioeconomic determinants of immune and neuroendocrine activity because material deprivation is related to the acceleration of core phenotypic, functional, molecular, and cellular aging processes.[49,347] Also inflammaging[348] and somatopause[349] are aspects of ageing that contribute toward the gradual elevations of low-grade circulating inflammatory markers and decrements in the expression of circulating IGF-1 over time.

Misspecification of effects is possible when making isolated selections within a study,[350] given that biologics are pleiotropic, so associations were tested using CRP, fibrinogen, WBCC, and IGF-1.[351]

3.2.1. Hypotheses

Neighbourhood-contextual indicators were expected to be stronger drivers of biomarker activity cross-sectionally and longitudinally, because individual-compositional indicators are less salient at older ages,[290] and neighbourhood-contextual indicators have been more consistent predictors of poor health in this population.[352] In addition, modifiable health behaviours were expected to account for greater variance in associations than demographic or clinical factors.

3.3. Methods

All measure details and methods are described in Chapter 2, so are not repeated here.

3.3.1. Study Design

Data were drawn from ELSA.[288] Cross-sectional data and longitudinal exposures were taken from W4 (baseline; 2008) and longitudinal outcomes from W6 (follow-up; 2012). 7,568 participants had measures on all exposures and covariates at baseline. Though 6,466 participants had complete data on any of the biomarkers at baseline, 5,841 participants had complete data on all biomarkers at baseline, which was reduced to 3,562 at follow-up four years later. Each biomarker was analysed independently. After exclusions on CRP values >20mg/L (n=116),[188] the analytic sample for CRP

was 3,968 (36.92%), 3,932 (36.58%) for fibrinogen, 4,022 (37.42%) for WBCC, and 4,056 (37.73%) for IGF-1. There were no substantial differences in the characteristics and biomarker levels between participants included and excluded from analyses.

3.3.2. Study Variables

3.3.2.1 Exposures

Contextual (Neighbourhood-level) Socioeconomic Indicators. The IMD, that is neighbourhood deprivation, was assessed at W4 (2008). The measure was demarcated into tertiles; the first representing the most deprived on a gradient to the third that represents the least deprived (reference category).

Compositional (Individual-level) Socioeconomic Indicators. Compositional indicators were assessed at W4 (2008), and included, wealth, education, and occupational social class. Each were divided into tertiles. The first represented the lowest category, and the third the highest, which was the reference category.

3.3.2.2 Outcomes

Immune and Neuroendocrine Biomarkers. Immune and neuroendocrine biomarkers measured at W6 (2012) included CRP, fibrinogen, WBCC, and IGF-1. CRP, fibrinogen, and WBCC were treated as continuous, with higher values indicating greater levels of inflammation. IGF-1 was treated as continuous, with lower values indicating greater neuroendocrine activity.

3.3.2.3 Covariates

Factors likely to confound analyses were selected *a priori*, including *demographic variables*: age; sex; *clinical variables*: BMI; *health variables*: limiting longstanding illness; and mobility difficulties; *modifiable health behaviours*: smoking status; alcohol consumption; physical activity. Reference categories were

being male, of normal weight, not having a limiting longstanding illness, being fully mobile, a non-smoker/ex-smoker, having low alcohol consumption, and being physically active.

3.3.4. Statistical Analyses

3.3.4.1. Multiple Imputation

Missingness ranged from 0.00-52.33% (Table S3.1). The imputation of the missing values yielded a minimal error for continuous variables (NRMSE=0.02%) and categorical variables (PFC=0.20%). Imputed and observed data were homogenous (Table S3.1).

3.3.4.2. Association Analyses

Cross-sectional analyses used a series of linear regressions to assess associations between exposures and outcomes at W4 (2008). Longitudinal analyses extended this to outcomes at W6 (2012). Analyses were weighted using inverse probability weights to ensure national representation and to take account of differential nonresponse at follow-up.[353] The most deprived category was reported against the least deprived reference. Results were presented as B regression coefficients with SE. The basic model for the analysis can be expressed as: ($\hat{Y}_i = B_0 + B_1X_{1i} + B_2X_{2i} + ... + B_pX_{pi} + u_i$ where $\hat{Y}$ is the predicted value of the outcome; B_0 is the value of $\hat{Y}$ when all exposures equal zero; B_1 through B_p are the estimated regression coefficients, X_1-X_p are distinct covariates, and u is the error term). Each regression coefficient represents the change in $\hat{Y}$ relative to a one-unit change in the respective exposure. Independent multivariate models were fitted to understand the role of different sets of covariates on associations. Biomarkers were modelled independently as CRP was linearly correlated with fibrinogen (r=0.310), WBCC (r=0.262), and IGF-1 (r=0.158) at p<0.001. No further issues existed with collinearity and all models met regression assumptions. The unadjusted model (1), that conditioned on the baseline biomarker being measured, was included in all models. Model 2 adjusted for age and sex (*demographic variables*). Model 3 adjusted for BMI, limiting longstanding illness, and mobility difficulties (*clinical variables*); Model 4 adjusted for

smoking status, alcohol consumption, and physical activity (*modifiable health behaviours*); Model 5 adjusted for all covariates. To test the extent to which different models explained associations PPAE was used.

3.3.4.3. Sensitivity Analyses

Six sensitivity analyses were carried out on longitudinal associations. First, sets of covariates were added sequentially rather than independently. Second, due to the potentially confounding effects of inflammaging and somatopause, the moderating effect of age was tested (dichotomised by mean age [≥64.25 years]). Third, immune and neuroendocrine levels have been shown to be higher in men than women,[244,354] so the role of sex as an effect modifier was tested. Fourth the exclusion of CRP values thought to represent acute inflammatory processes (≥20mg/L) was reassessed on the basis of arguments put forward by Giollabhui et al. (2020),[355] so regressions were repeated including those values. Fifth, analyses used complete cases to compare the efficiency and coverage of CI for the estimated coefficients and to ensure results were not an artefact of the imputed data. Association analyses replicated that in imputed data. The analytical sample formation for the complete case analysis (CCA) is illustrated in *Figure S3.1*. Finally, changes in residence over time may have influenced the longitudinal role of neighbourhood-contextual and individual-compositional factors in immune and neuroendocrine responses, so analyses were redistricted to non-movers.

3.4. Results

3.4.1 Descriptive Statistics

Descriptive statistics for the exposures and outcomes are shown in **Table 3.1**. The sample comprised 3,562 individuals for whom total baseline data was available. Of these, 44.67% were male, 55.33% female, aged on average 64.26 years (±8.35; $_{range}$50-99). Participants were, on average,

Table 3.1 Sample characteristics

Variable		Baseline (N = 3,562)	
		N / Mean (SD)	% / Range
Age		64.26 (8.35)	50-99
Sex	Male	1,591	44.67
	Female	1,971	55.33
BMI (kg/m2)	Underweight (≤18.5)	21	0.59
	Normal (18.6-24.9)	963	27.04
	Overweight (25–29)	1,580	44.36
	Obese (≥30)	998	28.02
Limiting Longstanding Illness	No	2,571	72.18
	Yes	991	27.82
Mobility Difficulties	No	1,753	49.27
	Yes	1,807	50.73
Smoking Status	Non-smokers/Ex-smokers	3,125	87.73
	Smokers	437	12.27
Alcohol Consumption	<3 days a week	2,259	63.42
	≥3 days a week	1,303	36.58
Physically Activity	Moderately/Vigorously Active	2,699	75.77
	Sedentary	863	24.23
Change of Residence (2008-2013)	No	3,400	95.45
	Yes	162	4.55
IMD	Lowest Tertile	998	28.02
	Middle Tertile	1,598	44.86
	Highest Tertile	966	27.12
Wealth	Lowest Tertile	1,079	30.21
	Middle Tertile	1,537	43.15
	Highest Tertile	949	26.64
Education	Higher	1,263	35.46
	Primary/Secondary/Tertiary	1,174	32.96
	Alternative or None	1,125	31.58
OSC	Managerial/Professional	1,353	37.98
	Intermediate Occupations	919	25.80
	Routine/Manual	1,290	36.22
CRP* (mg/L; Baseline)		1.11 (0.63)	0.18-3.04
CRP* (mg/L; Follow-up)		1.03 (0.59)	0.10-3.05
Fb (g/L; Baseline)		3.31 (0.52)	1.30-5.40
Fb (g/L; Follow-up)		2.94 (0.50)	1.30-5.30
WBCC* (10^9/L; Baseline)		1.80 (0.29)	-0.22-3.92
WBCC* (10^9/L; Follow-up)		1.82 (0.28)	0.72-3.48
IGF-1* (nmol/L; Baseline)		2.72 (0.35)	1.39-4.17
IGF-1* (nmol/L; Follow-up)		2.74 (0.32)	1.39-4.04

Notes: ELSA, waves 4-6 (2008/09-2012/13); N = observations; % = percentage frequencies; SD = standard deviations; BMI = Body Mass Index; IMD = Index of Multiple Deprivation (i.e., Neighbourhood Deprivation); OSC = Occupational Social Class; CRP = C-reactive protein; Fb = Fibrinogen; WBC = White Blood Cell Counts (leukocytes); IGF-1 = Insulin-Growth Factor-1; * Log-transformed variable.

overweight (72.38%), moderately to vigorously active (75.77%), with no limiting longstanding illness (72.18%), and were non-smokers (87.73%), who consumed alcohol less than three days in a given week (63.42%), but there was an equal balance of those with and without mobility difficulties. Biomarkers were stable on average from baseline to follow-up, although individual trajectories varied widely.

3.4.2. Cross-sectional associations between compositional and contextual socioeconomic indicators and biomarkers

All associations between compositional and contextual socioeconomic indicators and biomarker activity were significant in the unadjusted model (**Table 3.2**). All in the fully adjusted model (Model 5), the association between IMD and IGF-1 was significant (β=-0.055, CI=-0.084-0.026), but the relationships with CRP (β=0.026, CI=-0.023-0.075), fibrinogen (β=0.001, CI=-0.044-0.045), and WBCC (β=-0.011, CI=-0.034-0.012) were no longer significant. Less wealth was associated with higher concentrations of CRP (β=0.104 CI=0.054-0.155), fibrinogen (β=0.086, CI=0.040-0.132), and WBCC (β=0.032 CI=0.008-0.056), and with lower IGF-1 (β=--0.065, CI=-0.095-0.035). With two exceptions; education and IGF-1 (β=-0.012, CI=-0.040-0.015); occupation and WBCC (β=0.010, CI=-0.010-0.028), associations between individual-compositional socioeconomic indicators and biomarkers were significant (Education: CRP β=0.050, CI=0.006-0.094; fibrinogen β=0.069, CI=-0.030-0.109; WBCC β=0.030, CI=0.010-0.051; Occupation: CRP β=0.061, CI=0.018-0.103; fibrinogen β=0.041, CI=0.002-0.080; IGF-1 β=-0.031, CI=-0.056--0.005).

3.4.3. Longitudinal associations between compositional and contextual socioeconomic indicators and biomarkers

Across the 4-year follow-up period, all compositional and contextual socioeconomic indicators were longitudinally associated with biomarker activity in basic models adjusted only for baseline biomarker levels (**Table 3.3**). Overall, being less advantaged was associated with greater future

Table 3.2 Cross-sectional relationships of compositional and contextual socioeconomic indicators with immune and neuroendocrine biomarkers

Adjustments		CRP* (*N* = 3,968)			Fb (*N* = 3,932)			WBCC* (*N* = 4,022)			IGF-1* (*N* = 4,056)		
		β (SE)	95% CI	*p*	β (SE)	95% CI	*p*	β (SE)	95% CI	*p*	β (SE)	95% CI	*p*
Contextual Indicators	**IMD**												
	Model 1: Crude model	0.131 (0.027)	0.078-0.183	<0.001	0.084 (0.023)	0.038-0.130	<0.001	0.038 (0.012)	-0.013-0.062	0.002	-0.060 (0.015)	-0.089--0.031	<0.001
	Model 5: Fully Adjusted [d]	0.026 (0.025)	-0.023-0.075	0.303	0.001 (0.023)	-0.044-0.045	0.972	-0.011 (0.012)	-0.034-0.012	0.358	-0.055 (0.015)	-0.084--0.026	<0.001
Compositional Indicators	**Wealth**												
	Model 1: Crude model	0.285 (0.026)	0.233-0.336	<0.001	0.230 (0.023)	0.185-0.275	<0.001	0.101 (0.012)	0.078-0.125	<0.001	-0.091 (0.015)	-0.120--0.062	<0.001
	Model 5: Fully Adjusted [d]	0.104 (0.026)	0.054-0.155	<0.001	0.086 (0.023)	0.040-0.132	<0.001	0.032 (0.012)	0.008-0.056	0.010	-0.065 (0.015)	-0.095--0.035	<0.001
	Education												
	Model 1: Crude model	0.114 (0.024)	0.067-0.161	<0.001	0.117 (0.021)	0.076-0.158	<0.001	0.049 (0.011)	0.027-0.071	<0.001	-0.067 (0.014)	-0.094--0.041	<0.001
	Model 5: Fully Adjusted [d]	0.050 (0.022)	0.006-0.094	0.025	0.069 (0.020)	-0.030-0.109	<0.001	0.030 (0.011)	0.010-0.051	0.004	-0.012 (0.014)	-0.040-0.015	0.375
	OSC												
	Model 1: Crude model	0.171 (0.023)	0.126-0.216	<0.001	0.139 (0.020)	0.099-0.178	<0.001	0.047 (0.011)	0.026-0.068	<0.001	-0.057 (0.014)	-0.085--0.030	<0.001
	Model 5: Fully Adjusted [d]	0.061 (0.022)	0.018-0.103	0.006	0.041 (0.020)	0.002-0.080	0.037	0.010 (0.010)	-0.010-0.028	0.341	-0.031 (0.013)	-0.056--0.005	0.018

Notes: IMD = Index of Multiple Deprivation (i.e., Neighbourhood Deprivation); OSC = Occupational Social Class; β = unstandardised regression coefficient; SE = standard error; CI = confidence interval; *p* = significance value.
* Log transformed variable
[a] Demographic variables: age and sex
[b] Clinical variables: BMI, limiting longstanding illness, and mobility difficulties
[c] Modifiable health behaviours: smoking status, alcohol consumption, and physical activity
[d] All variables: age, sex, BMI, limiting longstanding illness, mobility difficulties, smoking status, alcohol consumption, and physical activity

Table 3.3 Longitudinal relationships of compositional and contextual socioeconomic indicators with immune and neuroendocrine biomarkers

Adjustments		CRP* (*N* = 3,968)			Fb (*N* = 3,932)			WBCC* (*N* = 4,022)			IGF-1* (*N* = 4,056)		
		β (SE)	95% CI	*p*	β (SE)	95% CI	*p*	β (SE)	95% CI	*p*	β (SE)	95% CI	*p*
Contextual Indicators	**IMD**												
	Model 1: Crude model [a]	0.068 (0.020)	0.028-0.108	0.001	0.053 (0.019)	0.016-0.091	0.005	0.034 (0.009)	0.015-0.052	<0.001	-0.017 (0.009)	-0.034--0.001	0.050
	Model 5: Fully Adjusted [b]	0.042 (0.021)	0.002-0.082	0.039	0.029 (0.019)	-0.009-0.067	0.135	0.023 (0.010)	0.005-0.042	0.014	-0.015 (0.009)	-0.032-0.003	0.095
Compositional Indicators	**Wealth**												
	Model 1: Crude model [a]	0.076 (0.020)	0.037-0.116	<0.001	0.076 (0.019)	0.038-0.113	<0.001	0.050 (0.009)	0.032-0.069	<0.001	-0.029 (0.009)	-0.046--0.011	0.001
	Model 5: Fully Adjusted [b]	0.028 (0.021)	-0.014-0.070	0.194	0.031 (0.020)	-0.017-0.052	0.119	0.035 (0.010)	0.016-0.055	<0.001	-0.015 (0.009)	-0.034--0.003	0.099
	Education												
	Model 1: Crude model [a]	0.058 (0.018)	0.022-0.094	0.002	0.078 (0.017)	0.044-0.112	<0.001	0.030 (0.009)	0.013-0.047	<0.001	-0.026 (0.008)	-0.042--0.011	0.001
	Model 5: Fully Adjusted [b]	0.020 (0.019)	-0.018-0.058	0.298	0.034 (0.018)	0.001-0.070	0.050	0.020 (0.009)	0.002-0.037	0.029	0.002 (0.008)	-0.014-0.019	0.777
	OSC												
	Model 1: Crude model [a]	0.056 (0.018)	0.022-0.091	0.001	0.064 (0.016)	0.032-0.097	<0.001	0.033 (0.008)	0.017-0.049	<0.001	-0.021 (0.008)	-0.037--0.006	0.006
	Model 5: Fully Adjusted [b]	0.028 (0.018)	-0.007-0.063	0.118	0.034 (0.017)	0.001-0.067	0.045	0.024 (0.008)	0.008-0.041	0.003	-0.006 (0.008)	-0.021-0.009	0.449

Notes: IMD = Index of Multiple Deprivation (i.e., Neighbourhood Deprivation); OSC = Occupational Social Class; β = unstandardised regression coefficient; SE = standard error; CI = confidence interval; *p* = significance value.
* Log transformed variable
[a] Baseline neuroimmune biomarkers respectively controlled for: CRP = C-reactive protein; Fb = fibrinogen; WBC = white blood cell counts; IGF-I = insulin-like growth factor-1
[b] All variables: age, sex, BMI, limiting longstanding illness, mobility difficulties, smoking status, alcohol consumption, and physical activity

inflammation and lower IGF-1 concentration. Some attenuation was seen after full adjustment (Model 4), but IMD remained associated with CRP (β=0.042, CI=0.002-0.082) and WBCC (β=0.023, CI=0.005-0.042). As were individual-contextual factors, specifically wealth with WBCC (β=0.035, CI=0.016-0.055), education with fibrinogen (β=0.034, CI=0.001-0.070) and WBCC (β=0.020, CI=0.002-0.037), and occupation with fibrinogen (β=0.034, CI=0.001-0.067) and WBCC (β=0.024, CI=0.008-0.041). Other associations were lost after taking covariates into account ([IMD: fibrinogen β=0.029, CI=-0.009-0.067; IGF-1 β=-0.015, CI=-0.032-0.003]; [Wealth: CRP β=0.028, CI=-0.014-0.070; fibrinogen β=0.031, CI=-0.017-0.052; IGF-1 β=-0.015, CI=-0.034--0.003]; [Education: CRP β=0.020, CI=-0.018-0.058; IGF-1 β=0.002, CI=-0.014-0.019]; [Occupation: CRP β=0.028, CI=-0.007-0.063; IGF-1 β=-0.006, CI=-0.021-0.009]).

3.4.4. Associations between neighbourhood-contextual indicators and biomarkers after accounting for individual-compositional indicators

Table 3.4 details analyses testing the extent to which associations between IMD and biomarkers survived adjustment for individual-level indicators. In the unadjusted models, IMD was significantly associated with all immune and neuroendocrine biomarkers. After full adjustment (Model 4), IMD was longitudinally associated with higher CRP (β=0.042, CI=0.002-0.082) and WBCC (β=0.023, CI=0.005-0.042) over the four-year period. These associations remained robust to the inclusion of education (CRP β=0.041, CI=0.000-0.081; WBCC β=0.021, CI=0.002-0.040) and occupation (CRP β=0.040, CI=0.000-0.081; WBCC β=0.020, CI=0.001-0.039), but they were not longer significant after wealth and other covariates together were taken into account (CRP β=0.039, CI=-0.004-0.082; WBCC β=0.015, CI=-0.005-0.035).

3.4.5. Percentage of protective association explained (PPAE) for models assessing compositional and contextual socioeconomic indicators in biomarker activity

Covariates accounted for a varying degree of the association between socioeconomic indicators and biomarkers (**Table 3.5**). The three sets of covariates in combination, accounted for 11.76-92.31% of the PPAE. *Clinical variables* BMI; limiting longstanding illness; mobility difficulties) explained between 9.09-35.29% of the variance. *Modifiable health behaviours* (smoking status; alcohol consumption; physical activity) accounted for the greatest PPAE in CRP, fibrinogen, and WBCC (≤42.11%). However, *demographic variables* (age; sex) were most salient to IGF-1 (≤88.46%).

3.4.6. Sensitivity Analyses

First, there was a consistent pattern of results when covariates were added sequentially rather than independently to the longitudinal analyses, suggesting that findings were not biased by model strategy (Table S3.2). Second, there were no significant interactions between compositional and contextual socioeconomic indicators and age, suggesting that inflammaging and somatopause were not biasing results (Table S3.3). Third, sex did not relate to the pattern of results, as there were no significant interactions between compositional and contextual socioeconomic indicators and sex (Table S3.4). Fourth, results were materially unchanged when CRP values ≥20mg/L were included in analyses, suggesting that associations were robust to the inclusion of these very high values (Table S3.5). Fifth, there was a substantial overlap in CI between the analyses performed in complete cases versus imputed data in the main analyses, suggesting that the use of imputed data did not bias results (Table S3.6). Finally, when analyses were restricted to people who did not move their residence over the study period, results were again materially unchanged (Table S3.7).

3.5. Discussion

In this large longitudinal population study of UK older adults, neighbourhood contextual and individual compositional indicators of socioeconomic status were associated with heightened

Table 3.4 Differences in the relationship between neighbourhood factors and biomarkers explained by individual socioeconomic indicators

Adjustments	CRP* (*N* = 3,968)			Fb (*N* = 3,932)			WBCC* (*N* = 4,022)			IGF-1* (*N* = 4,056)		
	β (SE)	95% CI	*p*	β (SE)	95% CI	*p*	β (SE)	95% CI	*p*	β (SE)	95% CI	*p*
IMD												
Model 1: Crude model [a]	0.068 (0.020)	0.028-0.108	0.001	0.053 (0.019)	0.016-0.091	0.005	0.034 (0.009)	0.015-0.052	<0.001	-0.017 (0.009)	-0.034--0.001	0.050
Model 5: Fully Adjusted [b]	0.042 (0.021)	0.002-0.082	0.039	0.029 (0.019)	-0.009-0.067	0.135	0.023 (0.010)	0.005-0.042	0.014	-0.015 (0.009)	-0.032-0.003	0.095
IMD | Wealth												
Model 1: Crude model + Wealth [a]	0.047 (0.022)	0.004-0.090	0.031	0.028 (0.021)	-0.012-0.068	0.174	0.019 (0.010)	-0.001-0.039	0.067	-0.005 (0.010)	-0.024-0.014	0.612
Model 5: Fully Adjusted + Wealth [b]	0.039 (0.022)	-0.004-0.082	0.073	0.022 (0.020)	-0.019-0.062	0.294	0.015 (0.010)	-0.005-0.035	0.146	-0.010 (0.009)	-0.028-0.009	0.314
IMD | Education												
Model 1: Crude model + Education [a]	0.059 (0.021)	0.019-0.100	0.004	0.040 (0.019)	0.002-0.077	0.040	0.029 (0.010)	0.010-0.048	0.003	-0.012 (0.009)	-0.030-0.006	0.182
Model 5: Fully Adjusted + Education [b]	0.041 (0.021)	0.000-0.081	0.049	0.024 (0.019)	-0.014-0.062	0.216	0.021 (0.010)	0.002-0.040	0.030	-0.016 (0.009)	-0.033-0.002	0.085
IMD | OSC												
Model 1: Crude model + OSC [a]	0.060 (0.021)	0.019-0.100	0.004	0.039 (0.019)	0.000-0.077	0.047	0.027 (0.010)	0.008-0.046	0.005	-0.014 (0.009)	-0.032-0.004	0.128
Model 5: Fully Adjusted + OSC [b]	0.040 (0.021)	0.000-0.081	0.050	0.022 (0.020)	-0.017-0.060	0.270	0.020 (0.010)	0.001-0.039	0.043	-0.015 (0.009)	-0.033-0.003	0.102

Notes: IMD = Index of Multiple Deprivation (i.e., Neighbourhood Deprivation); OSC = Occupational Social Class; β = unstandardised regression coefficient; SE = standard error; CI = confidence interval; *p* = significance value.
* Log transformed variable
[a] Baseline neuroimmune biomarkers respectively controlled for: CRP = C-reactive protein; Fb = fibrinogen; WBC = white blood cell counts; IGF-I = insulin-like growth factor-1
[b] All variables: age, sex, BMI, limiting longstanding illness, mobility difficulties, smoking status, alcohol consumption, and physical activity

Table 3.5 The percentage of protective association between socioeconomic indicators and biomarkers by different sets of covariates

	Adjustments	CRP* (*N* = 3,968)	Fb (*N* = 3,932)	WBCC* (*N* = 4,022)	IGF-1* (*N* = 4,056)
Contextual Indicators	**IMD**				
	Model 1: Crude model [a]	-	-	-	-
	Model 2: Model 1 + demographic [b]	**-2.94**	**-5.66**	**-2.94**	**-17.65**
	Model 3: Model 1 + clinical [c]	**20.59**	**18.87**	**11.76**	**35.29**
	Model 4: Model 1 + health behaviours [d]	**26.47**	**39.62**	**23.53**	**29.41**
	Model 5: Fully Adjusted [e]	**38.24**	**45.28**	**32.35**	**11.76**
Compositional Indicators	**Wealth**				
	Model 1: Crude model [a]	-	-	-	-
	Model 2: Model 1 + demographic [b]	**3.95**	**2.63**	**2.00**	**24.14**
	Model 3: Model 1 + clinical [c]	**31.58**	**19.74**	**10.00**	**34.48**
	Model 4: Model 1 + health behaviours [d]	**38.16**	**42.11**	**18.00**	**31.03**
	Model 5: Fully Adjusted [e]	**63.16**	**59.21**	**30.00**	**48.28**
	Education				
	Model 1: Crude model [a]	-	-	-	-
	Model 2: Model 1 + demographic [b]	**17.24**	**19.23**	**0.00**	**88.46**
	Model 3: Model 1 + clinical [c]	**29.31**	**16.67**	**13.33**	**23.08**
	Model 4: Model 1 + health behaviours [d]	**32.76**	**29.49**	**20.00**	**26.92**
	Model 5: Fully Adjusted [e]	**65.52**	**56.41**	**33.33**	**92.31**
	OSC				
	Model 1: Crude model [a]	-	-	-	-
	Model 2: Model 1 + demographic [b]	**7.14**	**10.94**	**-3.03**	**47.62**
	Model 3: Model 1 + clinical [c]	**23.21**	**14.06**	**9.09**	**23.81**
	Model 4: Model 1 + health behaviours [d]	**30.36**	**31.25**	**18.18**	**28.57**
	Model 5: Fully Adjusted [e]	**50.00**	**46.88**	**27.27**	**71.43**

Notes: PPAE = percentage of protective association explained; IMD = Index of Multiple Deprivation (i.e., Neighbourhood Deprivation); OSC = Occupational Social Class.
* Log transformed variable
[a] Baseline neuroimmune biomarkers respectively controlled for: CRP = C-reactive protein; Fb = fibrinogen; WBC = white blood cell counts; IGF-I = insulin-like growth factor-1
[b] Demographic variables: age and sex
[c] Clinical variables: BMI, limiting longstanding illness, and mobility difficulties
[d] Health behaviours: smoking status, alcohol consumption, and physical activity
[e] All variables: age, sex, BMI, limiting longstanding illness, mobility difficulties, smoking status, alcohol consumption, and physical activity

inflammation and low IGF-1 concentrations in models adjusted for baseline biomarkers, implying a higher risk to the overall systemic status of individuals with fewer socioeconomic resources. It is striking that these socioeconomic effects were observed over a 4-year period, and that many remained independent of a comprehensive selection of covariates. In particular, associations between all four socioeconomic indicators and greater WBCC remained significant after taking demographic, clinical, and behavioural factors into account. Contrary to hypothesis, neighbourhood contextual indicators were weaker drivers of inflammation and neuroendocrine activity than were individual compositional indicators. Certainly, in the case of WBCC, neighbourhood effects survived individual differences in education and occupation, but significance was lost when wealth was taken into account. As expected, health behaviours accounted for a greater proportion of the variance in socioeconomic associations with inflammation than the other sets of covariates, but this was not so for concentrations of IGF-1 where demographics were more salient.

Interestingly, the variations in immune and neuroendocrine activity observed between the cross-sectional and longitudinal associations allude to possible socioeconomic differences in immune and neuroendocrine expression over time. Contexts and health can change over time,[346] but consistent UK geographical patterns of deprivation have been reported over a century,[356,357] with more stability in the deprivation profile seen in geographically larger areas.[356]

There are reciprocal relationships between the complex physiological processes aimed at homeostatic balance, that could explain differences in effect sizes, and the temporal changes seen in the biological pattern of results within the data cross-sectionally and longitudinally.[358] Fibrinogen is involved in processes other than inflammation, such as haemostasis and angiogenesis. CRP, by contrast, has high sensitivity to insult, as the major human APP, so the rapidity and magnitude of effects may be more substantial. IGF-1 in circulation is downregulated by inflammatory

cytokines[179], so cytokine expression may have attenuated the independent predictive value of socioeconomic determinants in IGF-1 at the cellular level. Interactions as crosstalk and antagonism are possible, since low IGF-1 also antagonises the CRP mechanism through the activation of a number of intracellular signalling pathways, which may have reduced CRP expression prospectively.[358]

A substantial literature support that where you live, over and above individual characteristics, shape individual health and health inequalities among populations.[244,335,342,344,359,360] However, the present results cast doubt on research that has implicated neighbourhood determinants in inflammation and neuroendocrine processes without consideration being given to individual effects in the study design. One study of patients with coronary artery disease found that neighbourhood deprivation was associated with lower cardiovascular stress reactivity with no differences in immune or neuroendocrine response.[360] These results were independent of individual-level factors, and after accounting for variation in the probability of residing in a deprived or affluent neighbourhood by using a propensity weighting scheme. Further research is needed to elucidate the exact contextual mechanisms for environmental factors that appear to modulate inflammation and neuroendocrine activity.

As is documented elsewhere,[335] socioeconomic differences in inflammation and neuroendocrine activity were mostly explained by variations in health behaviours; smoking status, alcohol consumption and physical activity specifically. This confirms the hypotheses. The PPAE for each model has not been described in this context before. Health behaviours explained up to a half of the variance in associations between socioeconomic factors and inflammation. Remarkably, the PPAE for the demographics model accounted for over four fifths of the association between socioeconomic indicators and neuroendocrine activity. This was an unexpected result but may be explained by the sensitivity of IGF-1 to the somatopause. Modifiable health behaviours have

previously been identified as mediators between neighbourhood-contextual factors and inflammatory markers such as CRP.[359]

3.5.1. Strengths and Limitations

This study uniquely explored how immune and neuroendocrine activity was cross-sectionally and longitudinally nested in meso-level socioeconomic characteristics. For the first time, to our knowledge, it also tested what factors accounted for the greatest variance in associations between socioeconomic indicators and inflammation. Information is provided on pre-disease mechanisms that allow for a richer understanding of the deprivation-health gradient before disease become evident.[338] As it relates to limitations that are specific to this study, the length of residence was not taken into account, although, whether participants had moved during the study period was assessed. Residential areas within the UK are not monolithic, so although the index of multiple deprivation is calculated at a detailed level of areas, typically with 1,000-3,000 residents, most areas are heterogenous.[289] Contextual indicators may therefore be underestimated for some and overestimated for others in the same area, leading to the ecological fallacy.[361] Other strengths and limitations of the present study are highlighted in the general discussion (Chapter 8).

3.5.2. Conclusion

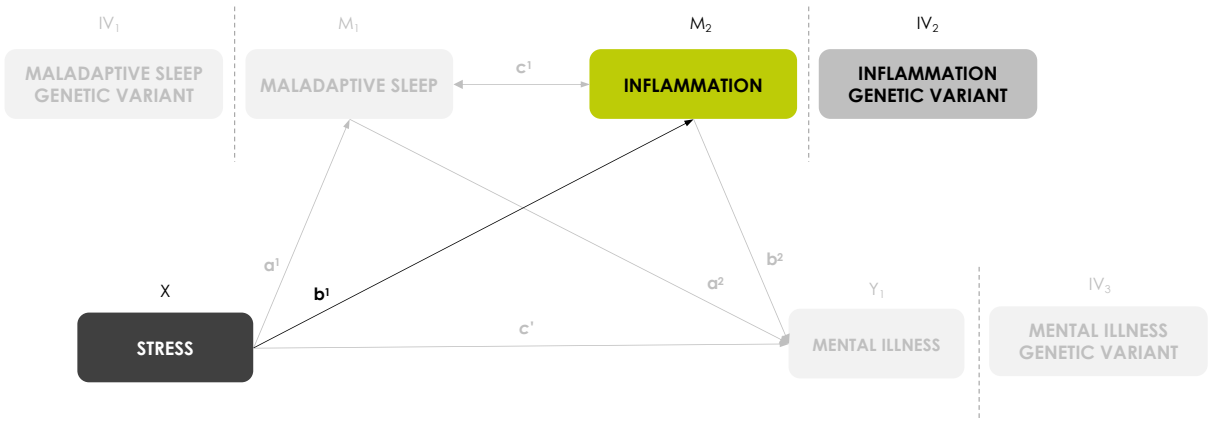
Several interesting findings emerged from this prospective population-based study that examined associations of socioeconomic determinants at the contextual and compositional level with immune and neuroendocrine activity, while taking into account the role of covariates. Neighbourhood associations were primarily dependent on the characteristics of people living in the area, rather than the area itself. Examining disparities in immune and neuroendocrine status through the lens of compositional factors can improve the surveillance of important equity issues[345] and steer interventions toward individual-level prescriptions, over a broader society approach.

CHAPTER 4. STRESS AND IMMUNE-NEUROENDOCRINE PATTERNING

4.1. Chapter overview

With findings published in *Brain, Behavior, and Immunity* (Hamilton et al., 2024),[362] on the back of Chapter 3, where differences in associations and effect sizes were observed between biomarkers, this chapter first explores patterns of immune-neuroendocrine activity through LPA. It then tests whether common life stressors are longitudinally associated with the derived profiles, after controlling for genetic predisposition and a broad selection of confounding factors.

Figure 4.1 **The section of the conceptual framework (*Figure 1.10*) addressed in Chapter 4**



4.2. Introduction

Communication between proinflammatory cytokines of the innate immune system with glucocorticoids and their analogs of the neuroendocrine system, is an active continuous process necessary to maintain homeostasis, even in healthy individuals.[358,363] Dysregulation of this network has negative implications in disease aetiology.[364,365] The high rates of chronic conditions associated with inflammatory and neuroendocrine dysregulation, along with the advancing age of the population, has provided the impetus to identify modifiable factors that could be leveraged to mitigate disease genesis; stress is one such factor.[287]

Stress has been implicated as a modulator of immune and neuroendocrine activity via PNI pathways.[178,366] However, the dominant position that stress disrupts immune and neuroendocrine integrity is an oversimplification of this biological pathway that fails to account for the reciprocal regulation of these transducing systems[364,367] and their variation among the population.[368] Immune and neuroendocrine interactions may be intensified in the presence of stress,[178] but individuals can have highly heterogeneous patterns of immune and neuroendocrine activity, which may conflate effects and give a partial explanation for the diverse and comorbid clinical outcomes associated with stress in the literature.[287,369,370,41,371]

Owing to interindividual and intraindividual variability in biomarkers,[372] genetic variation is another key consideration. As a major determinant of circulating immune and neuroendocrine function, genetic variation plays an important role in susceptibility to disease,[21] and these biomarkers are of high polygenic heritability.[213] It is, therefore, important that genetic markers are accounted for in analyses that explore immune and neuroendocrine traits.

Moreover, despite concerns of inflammaging and somatopause (i.e., age-related increases in plasma concentrations of inflammatory peptide biomarkers and the reduced expression of growth hormone secretion across age),[373] there remains a paucity of literature on stress and immune-neuroendocrine activity in older cohorts. This demographic group is increasingly relevant from a public health perspective because of the advancing age of the population.

Classifying the different patterns of immune and neuroendocrine activity in a population-based cohort of older adults, quantifying their prevalence, and identifying which profiles are most strongly associated with long-term stress exposure could be beneficial for three reasons. First, it may help to elucidate some of the present uncertainty about immune and neuroendocrine patterning.[276] Second, it could contribute to more targeted preventative treatments and novel

therapeutic strategies, such as the identification of biomarkers that characterise patients into subgroups most likely to benefit from cytokine-mediated pharmacological treatments, or the design of more personalised clinical trials through targeted recruitment. Third, it could be a resource for the formulation of more robust hypotheses for future research exploring stress models in immune and neuroendocrine activity, and their subsequent roles in human health and behaviour.

These issues were addressed in a UK cohort of community-dwelling older adults, to classify and quantify distinct immune and neuroendocrine profiles, and to investigate the longitudinal association between psychosocial stress and the revealed profiles. To represent these interrelated, molecular pathways, two acute-phase reactants (i.e., CRP and fibrinogen) were selected, along with two hormones; one catabolic (i.e., cortisol), the other anabolic (i.e., IGF-1).

4.2.1. Hypotheses

Heterogeneous patterns of immune and neuroendocrine activity were expected, with two to three subgroups emerging from the data. Psychosocial stress was also expected to be longitudinally associated with more adverse immune and neuroendocrine patterns four years later.

4.3. Methods

All measure details and methods are described in Chapter 2, so are not repeated here.

4.3.1. Study Design

The present study used data from ELSA participants at wave (W) 4 (2008), who were followed up four years later at W6 (2012).[288]

4.3.2. Study Variables

4.3.1.1. Exposures

Psychosocial Stress. Each proposed stressor was assessed at W4 (2008). This composite score comprised:- Financial Strain; Care Giving; Disability; Illness; Bereavement; and Divorce.

4.3.1.2. Outcomes

Immune and Neuroendocrine Biomarkers. Each of the biomarkers were measured at W6 (2012) included CRP (mg/L), fibrinogen (g/L), IGF-1 (mmol/L) and cortisol (pg/mg).

4.3.1.3. Covariates

Factors likely to confound analyses were selected *a priori* (see ***Figure 4.2*** for the DAG), including *demographic variables*: age; sex; *socioeconomic variables*: education; occupational social class; *health behaviours*: smoking status; alcohol consumption; physical activity; *genetic variables*: PGSs for CRP, cortisol, and IGF-1 and 10 PCs; *biomarkers*: baseline (W4) CRP, fibrinogen, and IGF-1 entered into the LPA; *binary health indicator*: any self-reported physician diagnosis.

4.3.4. Statistical Analyses

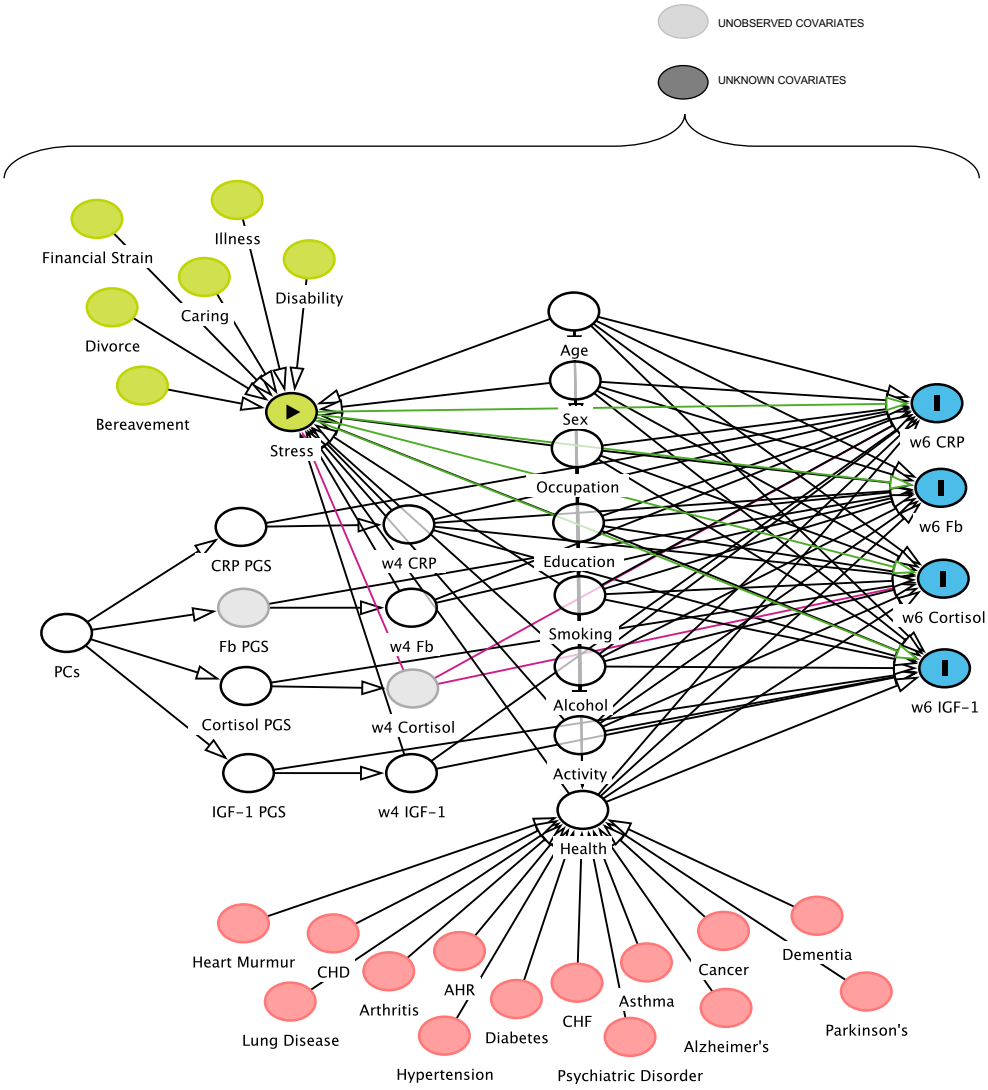
4.3.4.1. Polygenic Scores (PGS)

A single *p*-value threshold of 0.001 was used for PGS for CRP, cortisol, and IGF-1 to limit multiple testing, while maximising their potential predictive ability.

4.3.4.2. Multiple Imputation

Missingness ranged from 0.00-52.26%, with cortisol having the greatest proportion of missingness, and other variables having less than 37% missing (Table S4.1). Given the possibility of bias in the complete case analyses,[316] missing values on exposures, covariates, and outcomes were imputed using missForest.[317] Participants without genetic information were excluded from the analyses,

Figure 4.2 **DAG conceptually representing associations between study variables**



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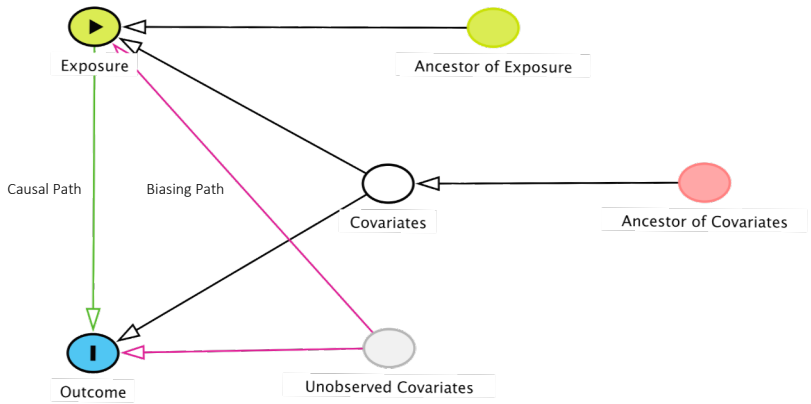


rather than imputed. The imputation of the missing values yielded minimal error for continuous variables (NRMSE=0.02%) and categorical variables (PFC=0.07%). Imputed and observed data were comparable in terms of participant characteristics summary distributions (Table S4.1).

4.3.4.3. Latent Profile Analysis (LPA)

An LPA was conducted on CRP, fibrinogen, IGF-1, and cortisol to uncover patterns of immune and neuroendocrine activity at both waves.

4.3.4.4. Association Analyses

Multinomial logistic regression was used to investigate the association between psychosocial stress at W4 (2008) and the probability of immune and neuroendocrine profile membership at W6 (2012). Models with different sets of covariates were fitted to understand their role in the association between stress and immune and neuroendocrine profiles. Model 1 was unadjusted. Model 2 adjusted for baseline immune and neuroendocrine profiles. Model 3 additionally adjusted for *demographic* and *genetic* variables. Model 4 adjusted for all covariates. Results were presented as RRR, with SE and CI.

4.3.5. Sensitivity Analyses

Six sensitivity analyses were conducted to examine the robustness of the findings. First, to ensure associations were not dependent on the binary classification of stress, analyses were repeated using an ordinal score of stress (reported as unstandardised [B] regression coefficients with SE). Second, to reveal any differences in stress exposure on profile membership, regressions were repeated using each of the six psychosocial stressors independently. Third, individuals who were disabled or with longstanding limiting illness were more likely to be immunosuppressed given anti-inflammatory prescriptions, thus altering immune and neuroendocrine activity. Therefore, the stress index was reconstructed, excluding these measures, before rerunning the analyses to quantify the extent to

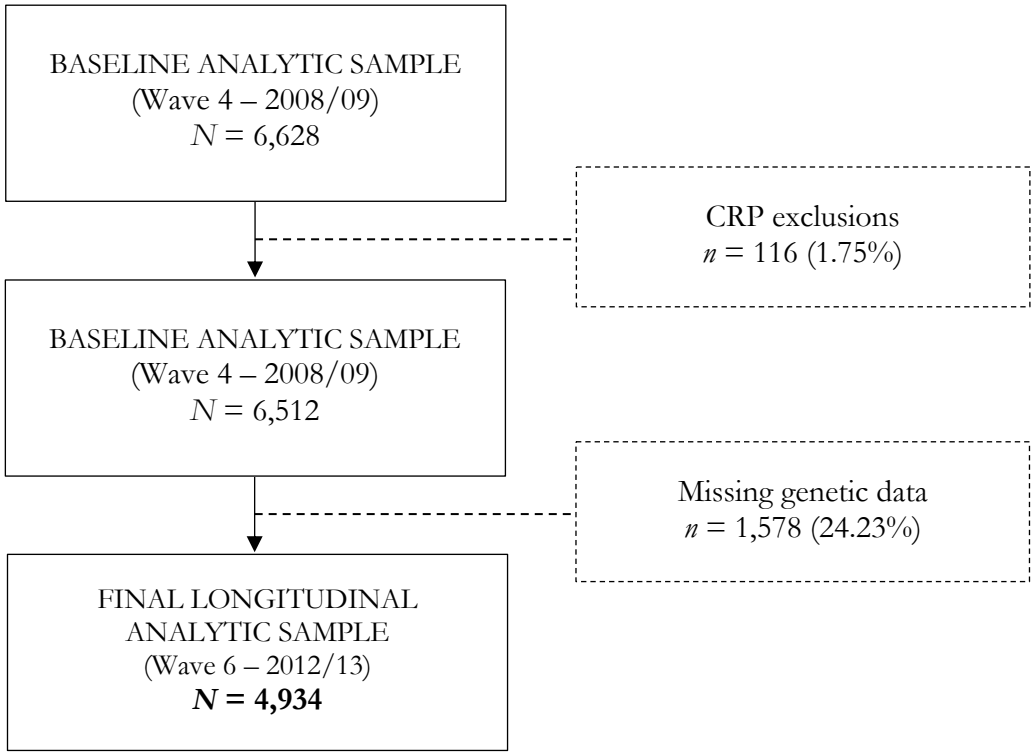
which they could have biased the results. Fourth, due to the potentially confounding effects of inflammaging and somatopause,[373] along with known differences in stress associations across age,[374] the moderating effect of age was tested (dichotomised by mean age [≥65 years]). Fifth, because of known sex differences in biomarker activity,[375] effect modification by sex was tested. Finally, results were compared from the imputed analyses with a CCA to understand the potential impact of different approaches to deal with missing data on the results. The analytical sample formation for CCA is illustrated in *Figure S4.1*.

4.4. Results

4.4.1. Descriptive Statistics

Of the 6,512 core respondents, 1,578 had missing genetic data, leaving a final analytic sample of 4,934 (***Figure 4.3***). Participant characteristics are shown in **Table 4.1.** Those from the analytic sample were materially unchanged from participants in the core sample (Table S4.1). CRP was linearly correlated with fibrinogen (r=0.706); cortisol (r=0.273); and IGF-1 (r=-0.163), as fibrinogen was with cortisol (r=0.176; all at p<0.001; Table S4.2). Participants, male (~45%) and female (~55%), with a median age of 65 years old (interquartile range: 59-72; M_{age}=66.31; ±9.35; $_{range}$50-99) were followed over a four year period (2008-2012). Most were non-smokers (87.27%) and consumed alcohol less than three days a week (64.27%), and almost two thirds were sedentary (72.88%). There was a fairly equal educational (Higher - 32.12%; Primary/Secondary/Tertiary - 31.29%; Alternative/None - 36.58%) and occupational social class divide (Managerial/Professional - 36.28%; Intermediate Occupations - 25.62%; Routine/Manual - 38.10%). There were 8,083 unique documented stress experiences (***Figure 4.4***). Approximately 13% of the sample experienced a high level of stress, and this high stress group tended to be younger, female, smokers, who drank less than three alcoholic drinks a week (**Table 4.1**). As it pertains to each independent stressor, 17.02% of the sample experienced financial strain, 7.01%

Figure 4.3 **Flow chart of missingness and the analytic sample for imputed data**



were informal carers, 45.80% had difficulty mobilising, 31.46% had a limiting longstanding illness, 40.86% were bereaved, and 9.18% were divorcees (***Figure 4.5***).

4.4.2. Latent Profile Analysis of Immune and Neuroendocrine Biomarkers

A three-profile model of immune and neuroendocrine biomarkers provided the most parsimonious fit to biomarker data at W6 (Table S4.3; *Figures S4.2* [a-g]), after which there were limited returns in AIC and BIC value (***Figure 4.6***); entropy was above 0.80 (***Figure 4.7***); the mean posterior probabilities did not exceed 0.70; each profile comprised more than 5% of participants (***Figure 4.8***); and each profile was theoretically meaningful. The most common profile was 2 (40%), followed by profile 1 (36%), then profile 3 (24%; ***Figure 4.9***). Profile 1 (M_{age}=64.16; ±7.77; 36% of the sample) was defined as '*low-risk*' as it was characterised by those having low CRP, low fibrinogen, low cortisol, and high IGF-1. Profile 2 (M_{age}=66.59; ±9.38; 40% of the sample) was

Table 4.1 Sample characteristics

Variable		Baseline (N=4,934)			
		N / M (SD)	% / Range	*t*	χ^2
Age		66.31 (9.35)	50-99	<0.001	
Age (Binary)	< M	2,437	49.39		<0.001
	≥ M	2,497	50.61		
Sex	Male	2,235	45.30		<0.001
	Female	2,699	54.70		
Education	Higher	1,585	32.12		0.961
	Primary/Secondary/Tertiary	1,544	31.29		
	Alternative/None	1,805	36.58		
Occupational Social Class	Managerial/Professional	1,790	36.28		0.708
	Intermediate Occupations	1,264	25.62		
	Routine/Manual	1,880	38.10		
Smoking Status	Non-smokers/Ex-smokers	4,306	87.27		<0.001
	Smokers	628	12.73		
Alcohol Consumption	<3 days a week	3,171	64.27		0.004
	≥3 days a week	1,763	35.73		
Physical Activity	Moderately/Vigorously Active	1,338	27.12		0.335
	Sedentary	3,596	72.88		
PGS for CRP	Low	3,945	79.96		0.421
	High	989	20.04		
PGS for cortisol	Low	3,969	80.44		0.482
	High	965	19.56		
PGS for IGF-1	Low	3,929	79.63		0.180
	High	1,005	20.37		
Stress Score (Ordinal)		1.51(.90)	0-6	-	
Stress Score (Binary)	No	4,318	87.52		-
	Yes	616	12.48		
CRP* (mg/L; Baseline)		1.19 (.68)	.18-3.04	0.915	
CRP* (mg/L; Follow-up)		1.37 (.73)	.10-3.05	0.998	
Fb (g/L; Baseline)		3.38 (.56)	1.30–5.90	0.728	
Fb (g/L; Follow-up)		3.12 (.54)	1.50–5.80	0.984	
Cortisol* (pg/mg; Follow-up)		2.93 (1.34)	.13-6.49	0.999	
IGF-1* (nmol/L; Baseline)		2.78 (.34)	1.10-4.19	0.393	
IGF-1* (nmol/L; Follow-up)		2.78 (.27)	1.61-4.06	0.309	

Notes: ELSA, waves 4-6 (2008/09-2012/13); N = observations; M = mean; % = percentage frequencies; SD = standard deviations; *t* = t-test significance between the exposed and unexposed for continuous variables; χ^2 = Pearson Chi square test significance between the exposed and unexposed for categorical variables; < = less than; ≥ = greater than or equal to; OSC = occupational social class; CRP = C-reactive protein; Fb = Fibrinogen; IGF-1 = Insulin-growth factor-1; * Log-transformed variable; I-N = immune and neuroendocrine.

Figure 4.4. **Percentage of total stress experienced (N=8,083)**

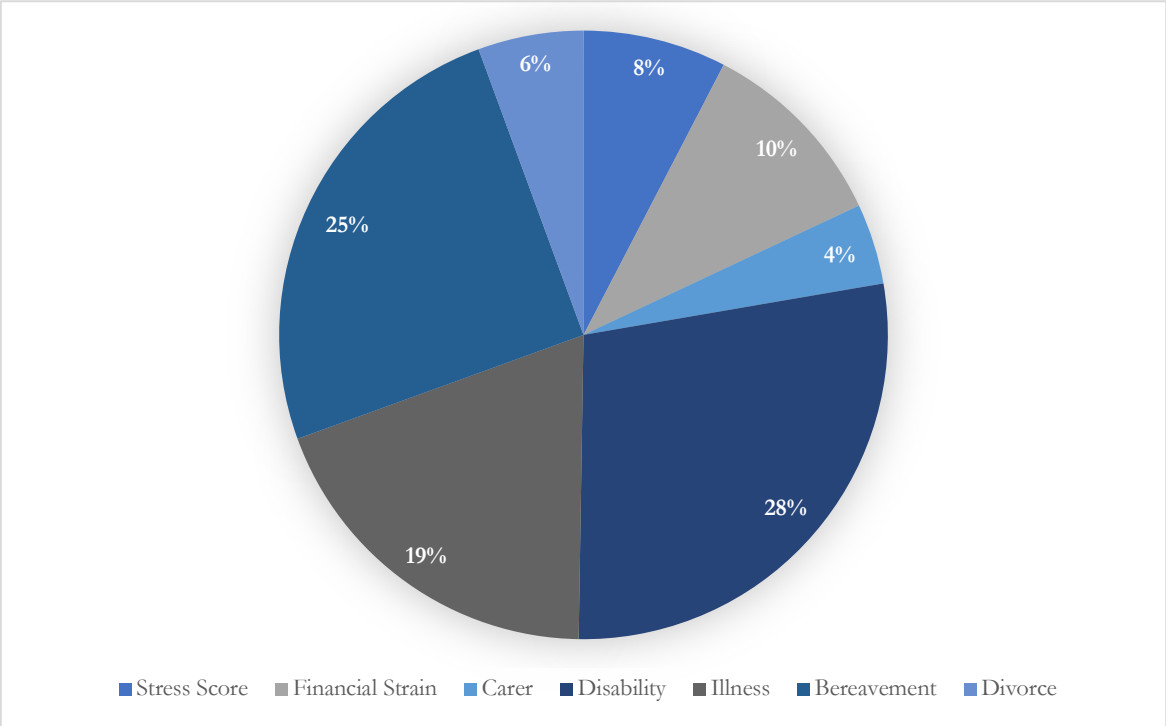


Figure 4.5 **Independent stress experiences of the sample (N=8,083)**

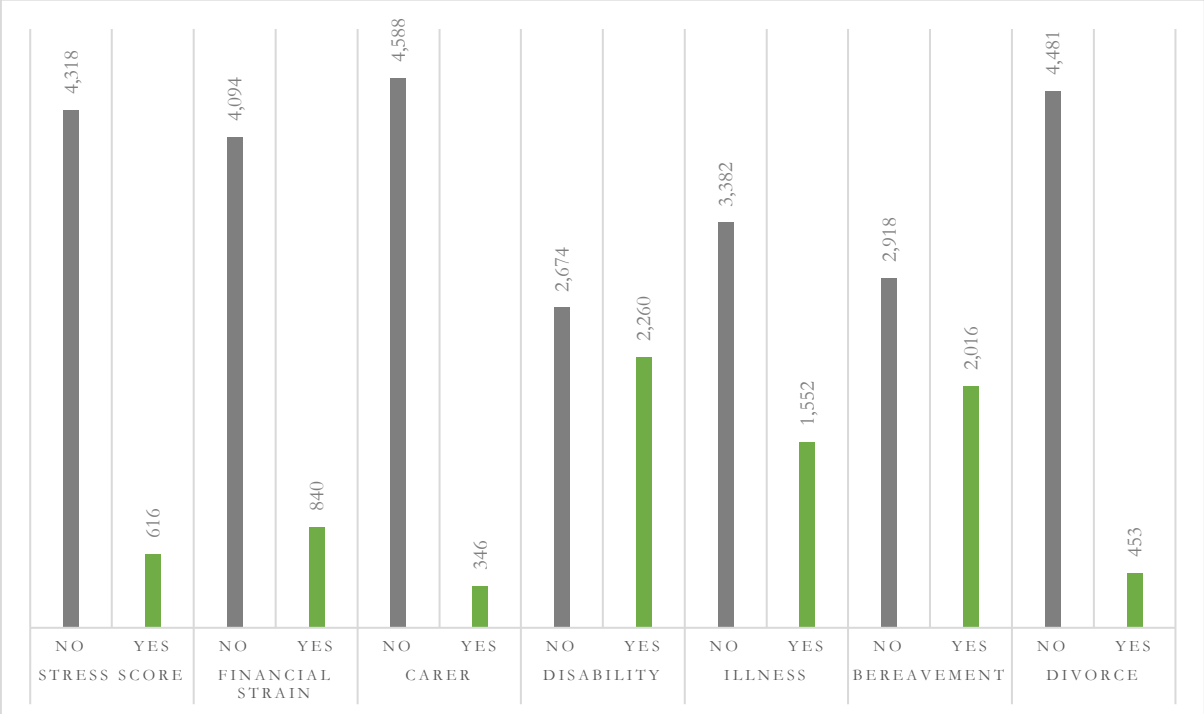


Figure 4.6 **The Akaike information criterion (AIC), Bayesian information criterion (BIC) for seven profiles**

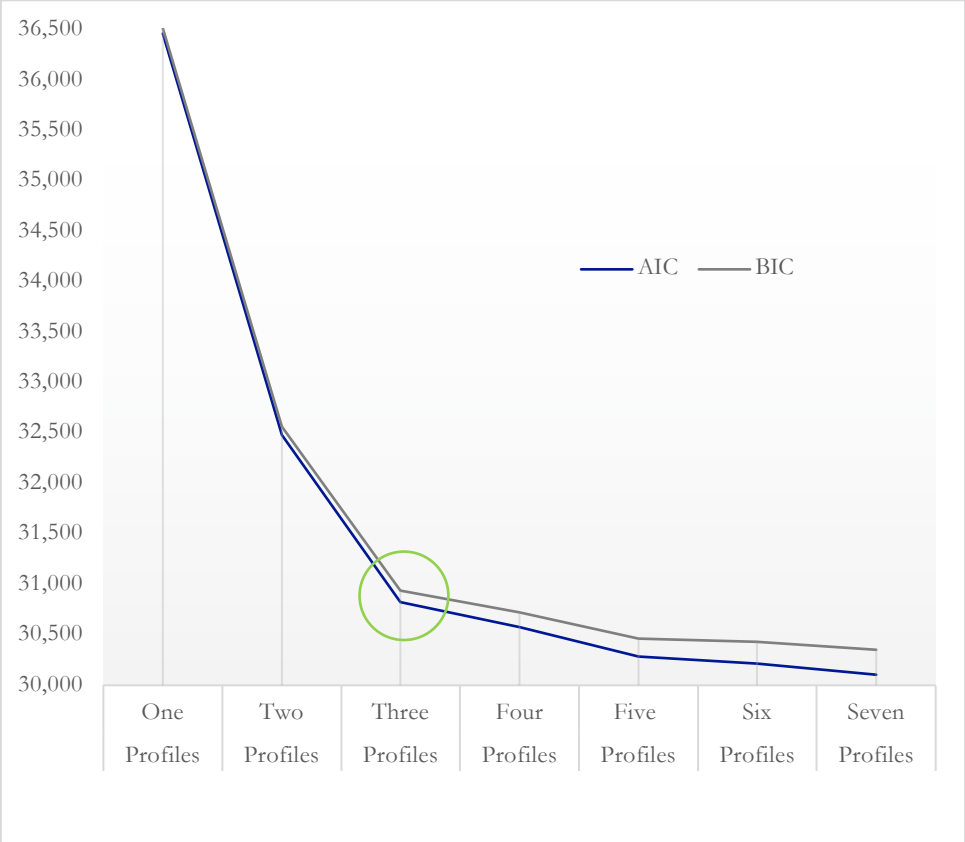


Figure 4.7 **The entropy and normalised entropy statistic for the seven profile LPA model**

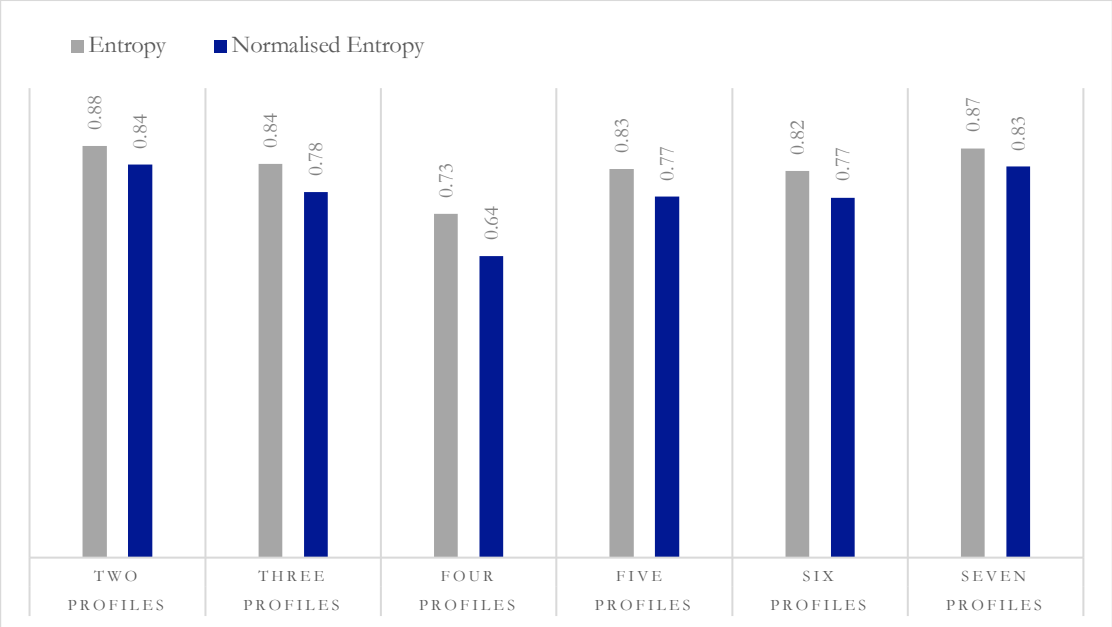


Figure 4.8 **The mean posterior probabilities for the seven profile LPA model fit**

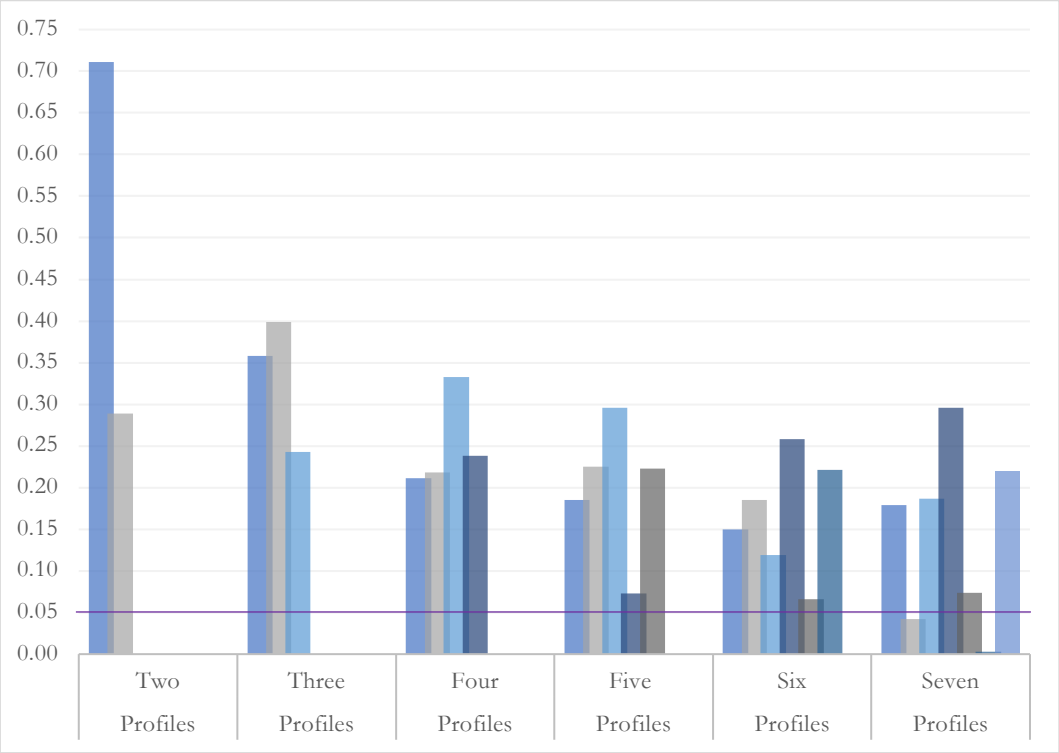


Figure 4.9 **The percentage of participants belonging to each immune and neuroendocrine profile**

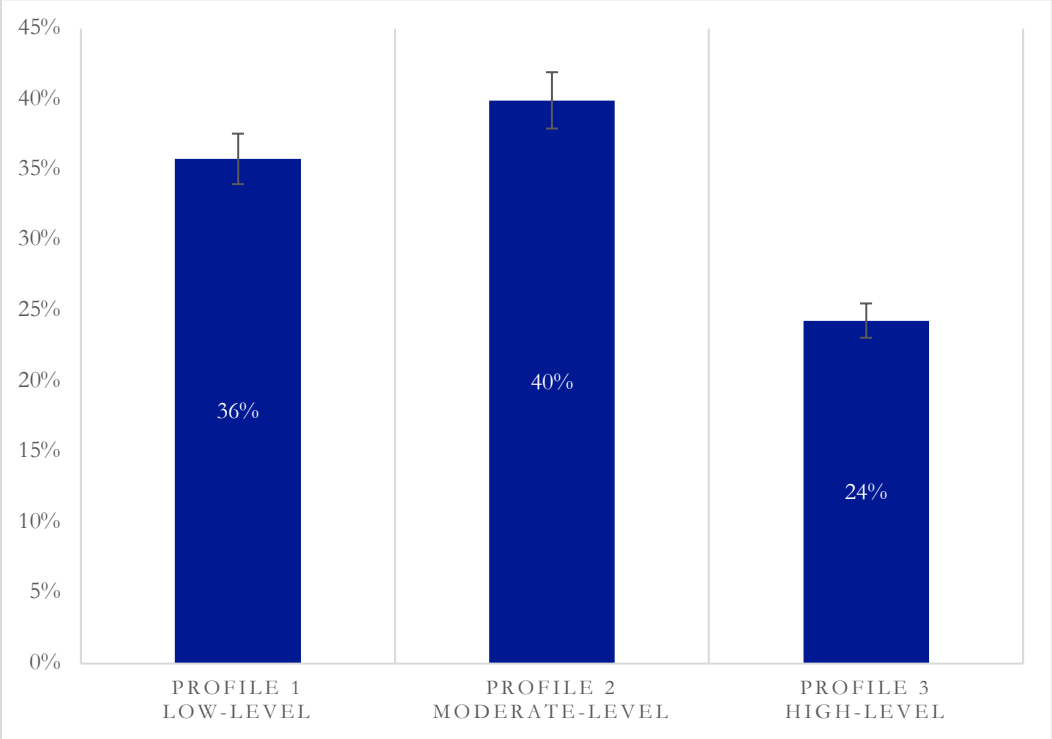
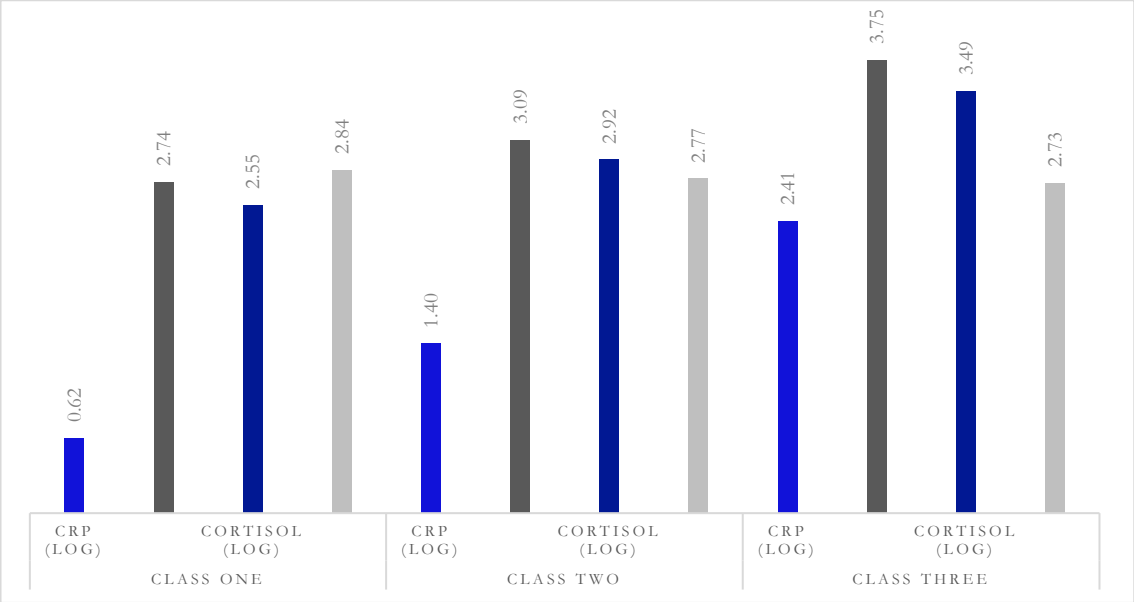


Figure 4.10 **The mean levels of immune and neuroendocrine biomarkers for a three-profile solution**



the modal group, and consisted of individuals with moderate CRP, fibrinogen, cortisol, and IGF-1 levels, which was defined as '*moderate-risk*'. Finally, profile 3 (M_{age}=69.03; ±10.62; 24% of the sample) was marked by a high probability of high CRP, high fibrinogen, high cortisol, and low IGF-1, so this group was defined as '*high-risk*' (***Figure 4.10***).

4.4.3. Stress and Profile Membership of Immune and Neuroendocrine Biomarkers

In **Table 4.2**, the unadjusted model shows that greater stress was associated with the probability of being in the *high-risk* profile versus *low-risk* profile. This persisted after adjustment for baseline immune and neuroendocrine profiles and further adjustment for *demographic* and *genetic variables*. In the fully adjusted model, the risk of a *high*-immune and neuroendocrine profile (was *low-risk* profile) was 1.6 times higher in the group exposed to high levels of stress compared with participants with lower stress exposure (Model 4: RRR=1.61, CI=1.23-2.12). In the fully adjusted model, however, stress was not associated with the probability of being in the *moderate-risk* profile versus *low-risk* profile (Model 4: RRR=1.10, CI=0.89-1.35). To understand the role of specific confounding factors with greater nuance, results with incremental model adjustment can be found in the

supplement (Table S4.4). There was evidence of suppression by *demographic* and *genetic variables,* which increased the RRR by 38% (Model 3: RRR=1.80, CI=1.39-2.35, $p<0.001$), and by *health* variables, which increased the RRR by 20% (Model 3c: RRR=1.81, CI=1.39-2.36, $p<0.001$).

Table 4.2 Longitudinal associations of stress with immune and neuroendocrine biomarker profiles (N=4,934)

Adjustments	Binary Stress Score				
	RRR	SE	95% CI		*p*
***Moderate-risk* Profile**					
Model 1: *Unadjusted*	0.98	0.10	0.81	1.20	0.870
Model 2: *Model 1 + baseline biomarkers* [a]	1.01	0.11	0.83	1.24	0.898
Model 3: *Model 2 + demographics & genetics* [b]	1.14	0.12	0.93	1.41	0.213
Model 4: *Fully Adjusted* [c]	1.10	0.12	0.89	1.35	0.401
***High-risk* Profile**					
Model 1: *Unadjusted*	1.34	0.15	1.08	1.66	0.008
Model 2: *Model 1 + baseline biomarkers* [a]	1.42	0.18	1.10	1.83	0.007
Model 3: *Model 2 + demographics & genetics* [b]	1.80	0.24	1.39	2.35	<0.001
Model 4: *Fully Adjusted* [c]	1.61	0.22	1.23	2.12	0.001

Notes: The *low-risk* group is the reference; RRR = relative risk ratio; SE = standard errors; CI = confidence interval; *p* = significance value.
a Baseline biomarkers: C-reactive protein (CRP); fibrinogen; insulin-growth factor-1 (IGF-1).
b Demographic and genetic variables: age; sex; 10 principal components (PCs); CRP polygenic score (PGS); cortisol PGS; IGF-1 PGS.
c All variables: CRP; fibrinogen; IGF-1; age; sex; 10 PCs; CRP PGS; cortisol PGS; IGF-1 PGS; education; occupational social status; smoking status; alcohol consumption; physical activity; health (i.e., chronic lung disease; coronary heart disease; abnormal heart rhythm; heart murmur; congestive heart failure; angina; hypertension; diabetes; cancer; Parkinson's; Alzheimer's; dementia; asthma; arthritis; osteoporosis; psychiatric disorder).

4.4.4. Sensitivity Analyses

First, results were consistent when a continuous classification of psychosocial stress was used. For each single increase in the stress score, individuals were 19% more likely to be in the *high-risk* immune and neuroendocrine profile versus the *low-risk* profile in the fully adjusted model (Model 4: RRR=1.19, CI=1.23-2.12, $p=0.001$; Table S4.5). Second, when individual stressors were tested against immune and neuroendocrine profile membership, financial strain (Model 4: RRR=1.59, CI=1.25-2.01, $p<0.001$), limiting longstanding illness (Model 4: RRR=1.34, CI=1.10-1.65,

p=0.005), and bereavement (Model 4: RRR=1.26, CI=1.04-1.52, *p*=0.016) were each associated with belonging to the *high-risk* profile, as compared with the *low-risk* profile in fully adjusted models. Financial strain and bereavement showed gradients in risk, as each were associated with *high-* and *moderate-risk* profile membership. Caregiving and divorce were not associated with differences in profile membership, while disability was associated with a 30% lower risk of belonging to the *high-risk* profile (Tables S4.6[a-f]). Third, the stress index that excluded both disability and limiting long standing illness had higher relative risk coefficients than the primary composite score (Model 4: RRR=1.71, CI=1.32-2.22, *p*<0.001), consistent with the previous observation with respect to disability (Table S4.7). Fourth, there was no evidence of differences in the association between stress and biomarker profile membership between younger and older age groups (interaction *p*=0.913), although relative risk coefficients were substantially larger for those aged 65 and older (Table S4.8a-b). Fifth, similar to age, there was no interaction (*p*=0.239) nor difference in the risk profile between the sexes when results were stratified by sex (Tables S4.9a-b). Finally, similar mean levels of immune and neuroendocrine biomarkers for a three-profile solution in a CCA were observed (*Figures S4.3-4*) as compared with the main imputed data (*Figure S4.2c*). Re-analysis of the association between stress and profile membership in the CCA sample yielded similar results (Table S4.10).

4.5. Discussion

In a large nationally representative sample of UK older adults, we used multiple biomarkers in a LPA to provide a comprehensive characterisation of physiological activity across the integrative network of the immune, nervous, and endocrine systems. We found longitudinal evidence of an overall association between stress and the risk of high versus low immune and neuroendocrine profile membership four years later. Associations remained significant after accounting for polygenic markers of immune and neuroendocrine activity, and a range of demographic, socioeconomic, behavioural, and health factors. There was, however, no consistent gradient in risk

as there was no significant difference in stress levels between *low-* and *moderate-risk* profiles, nor were there differences in the association between stress and immune-neuroendocrine profile activity by age or sex. Stress associated with financial strain was the strongest independent determinant of belonging to the *high-risk* immune and neuroendocrine profile, followed by limiting longstanding illness and bereavement. Furthermore, financial strain and bereavement showed gradients in risk. In contrast, disability was associated with a lower risk for *moderate-* and *high-risk* profile membership (vs *low-risk*).

As noted elsewhere,[376] the biological responses to stress exposure are multiphasic, where we see the stimulation or suppression of immune and neuroendocrine activity, or both simultaneously,[377] with the direction of effect depending on the biomarker being evaluated.[378] The complexity of immune and neuroendocrine interconnectivity was addressed by using latent profile analyses to identify distinct typologies of activity. Variability was revealed within the derived profiles, and highlights why the evaluation of single biomarkers can obfuscate understanding of stress exposure.

The incremental rise in mean fibrinogen and cortisol levels from profile one to three, aligns with increases in mean CRP, which is consistent with earlier evidence on the synchronised physiological exchange between their respective systems to maintain homeostasis.[363] However, the unexpected moderate decline in IGF-1 between each of the derived profiles is notable. The reasons for this is unclear given the well documented covariance between each represented system in the LPA.[179,358,378] As part of a coordinated systemic regulatory mechanism that facilitates a dynamic cellular microenvironment, proinflammatory cytokines can induce a state of resistance in hormonal secretion, including in IGF-1.[378] This can attenuate the mitogenic effect of IGF-1, but can also have anti-proliferative effects on IGF-1,[358] which should be reflected here. The reason for the blunted effect of IGF-1 seen in the present study, is conceivably because IGF-1 secretion is sensitive to nutritional and endocrine control, such that hormonal resistance is rendered

maladaptive by pharmacologic use and dietary choices;[212] neither of which were measured here. In addition, O'Connor and colleagues (2008)[358] suggest that cellular responses can vary tremendously depending on ligand origin and concentration, the number of cell receptors, and signalling kinetics post receptor activation, not to mention extracellular control of IGF-1, which is a second mode of regulation.

It is also clear from converging lines of evidence that different stressors have different predictive power.[178,231,368,371] There was some evidence to support this in the present study, with the largest effect sizes observed following financial stress, but given the overlap of CI, there is not strong associative differentiation. Part of the challenge is in establishing a '*hierarchy of stress*' to determine which psychosocial stressors are most problematic; distinguishing between rare acute stressors that have high clinical risk and everyday stressors that create chronic risk and contribute more to overall disease burden in the population. The present study takes a step toward this purpose, and while an LPA was used to look at immune and neuroendocrine patterning, future study would benefit from a more comprehensive stress score that is also submitted to LPA to see how stress clusters in the population.

4.5.1. Strengths and Limitations

This study has several strengths. To our knowledge this is the first study to explore how common stressors are related to immune and neuroendocrine profile membership. Dichotomising the ordinal stress score reduced the influence of its non-normality, quasi-continuous quality, and limited the chance of underestimated correlations and an inflation of Type II errors (i.e., false negatives). Therefore, it offered more meaningful results, despite the potential loss of power. However, it is important to caveat that the self-reported nature of each item of the stress score may have introduced some measurement error to the results, and there is an assumption in the stress measure that different exposures carry equal weight, but this is typically not so. Further

limitations of this study map across other studies in this thesis, so are reflected on in the general discussion (Chapter 8).

4.5.2. Conclusion

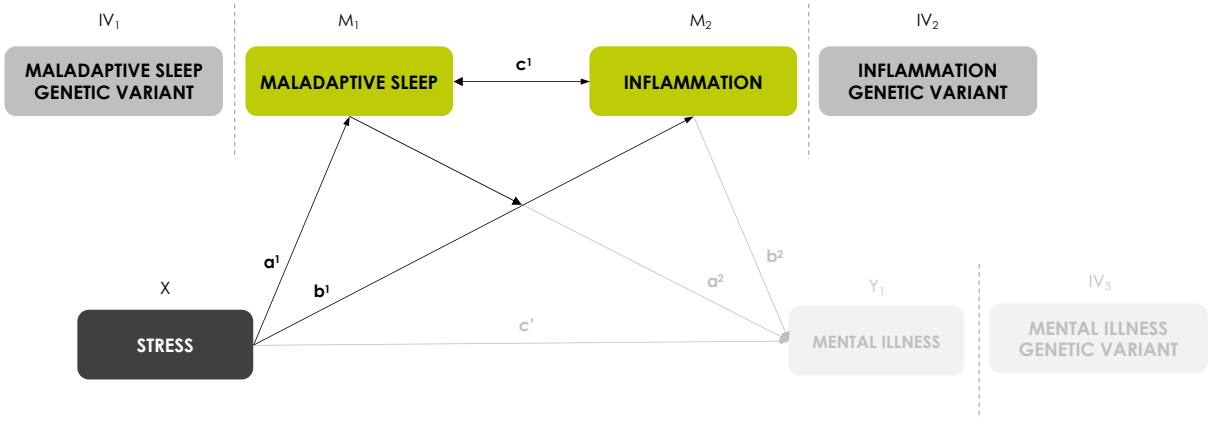
The synergistic immune and neuroendocrine response to stress represents an important target for secondary clinical intervention. Intervening on these processes could alter the course of disease.[379] Multivariate biomarkers were examined, including CRP, fibrinogen, cortisol, and IGF-1, using empirically derived data reduction techniques to uncover subgroup differences in how immune and neuroendocrine biomarkers pattern together. It proved an effective method to explore the complex series of reactions across the immune, nervous, and endocrine systems. Because stress was positively associated with the derived immune and neuroendocrine profiles, the results support that exposure to high levels of stress can actuate a cascade of complex central and peripheral physiological events that has previously been linked to pathology, sub-clinical illness, and debility.

CHAPTER 5. FINANCIAL STRESS, SLEEP DURATION, AND IMMUNE-NEUROENDOCRINE PATTERNING

5.1. Chapter overview

This chapter takes learnings from Chapters 3 and 4, then explores the independent and interactive risk of financial-related stress and suboptimal sleep durations in adverse immune and neuroendocrine latent profile membership. In Chapter 3, compositional factors were more salient to biological risk, than were contextual factors, so efforts to elucidate individual-level factors were reflected here. Analyses were expanded to include suboptimal sleep, as a factor not earlier explored in this context. However, the focus was narrowed to financial stress, as the strongest independent determinant of belonging to the *high-risk* immune and neuroendocrine profile, with a gradient in risk, in Chapter 4. For results less encumbered by confounding, this study also uses polygenic risk prediction to test short and long sleep associations with profile membership. The full manuscript is under review and is available on *medRxiv* (Hamilton & Steptoe, 2024).[380]

Figure 5.1 **The section of the conceptual framework (*Figure 1.10*) addressed in Chapter 5**



5.2. Introduction

The most intriguing aspect of inflammation is the plurality of its modulators and its breadth of effects that support health or contribute to morbidity, both physical and mental, and mortality

worldwide.[381,98] Human, animal, and *in vitro* studies converge to the understanding that exogenous acute and chronic stress directs adverse effects on immunologic mechanisms.[382] In humans, material deprivation is ubiquitous and among the strongest indicators of stress.[15,46] When sleep deprived, alterations can also be seen to major effector systems, including the HPA-axis and the SNS. This corresponds to catecholamine elevations that drive abnormal inflammatory responses, with shifts seen to the levels and temporal profile of the response. In addition, there are functional alterations in the expression of pro-inflammatory cytokines that then interact with the brain through humoral, neural, and cellular pathways.[87,250,383]

It is equally important to consider whether stress is as antithetical to good sleep as poor sleep is to stress, with evidence that they co-occur and are reciprocally reinforcing.[384] Stress has been implicated as a predisposing factor for shorter actigraphy-determined total sleep time. In turn worse sleep has been associated with greater stress perception.[71] In another study, a one unit increase in self-reported stress was associated with a 3min decrease in actigraphic and self-reported total sleep, but there were no significant associations between sleep parameters and next-day stress.[75] On balance of evidence, it is likely that stress precedes poor sleep. Still, results have been difficult to unravel, with inconsistencies between and within studies. On one side, findings have largely depended on the type, acuteness and chronicity of stress On the other side, findings have depended on the type and degree of sleep abnormality, along with whether it is assessed by self-report, actigraphy, or polysomnography.[71,385]

A better understanding of the interaction between financial stress and suboptimal sleep may clarify how they independently and collectively influence immune-neuroendocrine biomarkers as a clinically relevant pathway to disease. It is possible that the impact of experiencing both is synergistic rather than additive or multiplicative. Therefore, reflecting worse combined effects on biological processes. One study found that stress was associated with total serum brain-derived

neurotrophic factor (BDNF), determined by an Analysis of Covariance (ANCOVA). A significant interaction was also found between stress and self-reported insomnia on levels of BDNF. In the same data, a mediation analysis showed that insomnia mediated the association between stress and BDNF.[386] This dual role of insomnia suggests that sleep influences the strength and direction of stress on BDNF (moderation) and interrupts the pathway through which stress influences BDNF (mediation). However, in another study that used a repeated measures Analysis of Variance (ANOVA), no interaction between stress and sleep deprivation was detected. Authors surmised that sleep loss instead lowers the threshold at which an event is perceived as a stressful.[137] Methods and measures likely account for these differences.[387] This raises the question of whether the nature of the relationship between financial stress and inflammatory processes is altered by the presence of suboptimal sleep. Particularly, having controlled for genetic predisposition and a rich selection of confounders.

When results from different approaches, across disciplines, with unrelated source of bias, point to the same conclusion it strengthens confidence in the finding.[388] For this reason, in this study, several statistical, genomic, and epidemiological techniques were used to address this research question. First, an LPA, described in earlier chapters, was used to capture the heterogeneity and latent structure of all five immune and neuroendocrine biomarkers (i.e., CRP; fibrinogen; WBCC; cortisol; IGF-1) that decomposed the population into a small number of groups.[389] Second, PGS were taken into account in the analyses to index genetic predisposition and to understand genetic risk for immune-neuroendocrine profile membership. Third, the construction of a DAG served to identify sources of bias and visually represent the complex causal pathways between variables.[314] Fourth, an observational, longitudinal design allowed for temporal associations to be traced in a way that points to directionality. Finally, effect modification between financial stress and suboptimal sleep was evaluated to uncover subgroup differences in patterning of immune-neuroendocrine processes.

5.2.1. Hypotheses

Given findings from Chapter 4, similar heterogeneous patterns of immune and neuroendocrine activity were expected, with three clusters emerging from the data. In addition, financial stress and suboptimal sleep were hypothesised to be independently associated with belonging to the highest risk latent profile of immune-neuroendocrine biomarkers. Moreover, an interaction between financial stress and suboptimal sleep in this association was anticipated.

5.3. Methods

All measure details and methods are described in Chapter 2, so are not repeated here.

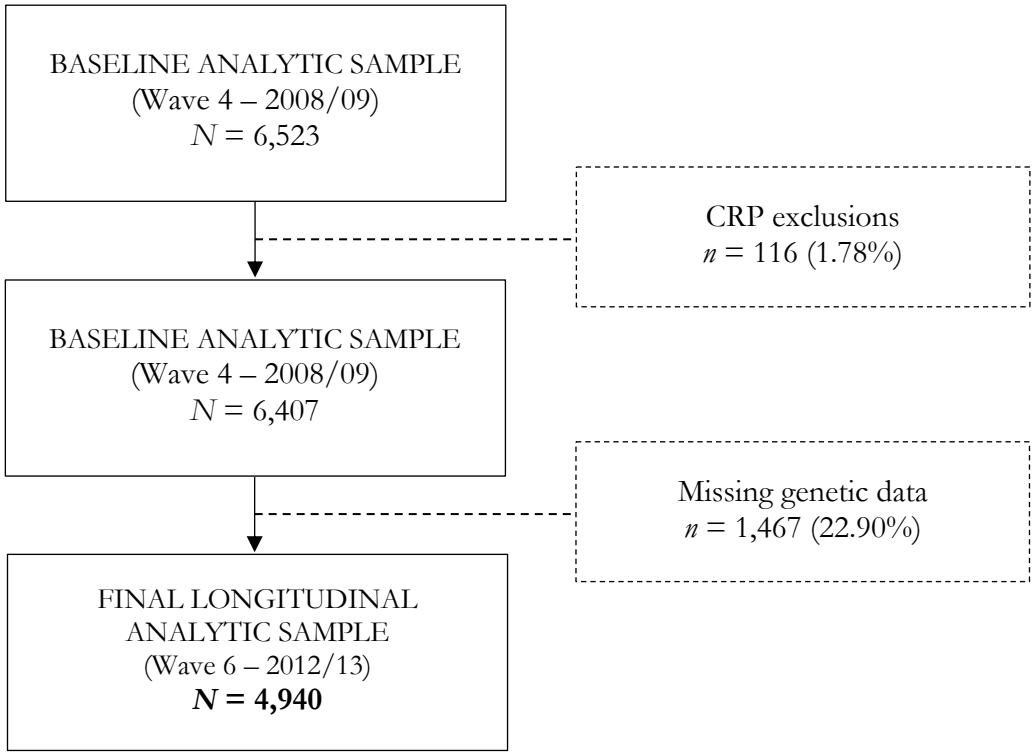
5.3.1. Study Design

Fully anonymised data were drawn from ELSA.[288] Here, longitudinal sample derivation is from W4 (2008) and W6 (2012). Analyses were weighted using longitudinal survey weights. A total of 6,523 participants had complete measures and at least one biomarker at baseline. The sample was 6,407, after exclusions of CRP values >20mg/L (n=116; as these values reflect acute, rather than chronic inflammation). Of these, 1,467 had missing genetic data, leaving an analytic sample of 4,940 (***Figure 5.2***).

5.3.1.1. Exposure

Financial Stress. Financial stress was assessed at W4 (2008), as indexed by financial strain, a binary measure of the perceived chance of not having enough financial resources to meet needs (dichotomised at >60% chance). The higher the percentage, the higher the belief of having insufficient resources and, thus, the higher the stress experience.

Figure 5.2. **Flow chart of missingness and the analytic sample for imputed data**



5.3.1.2. Moderator

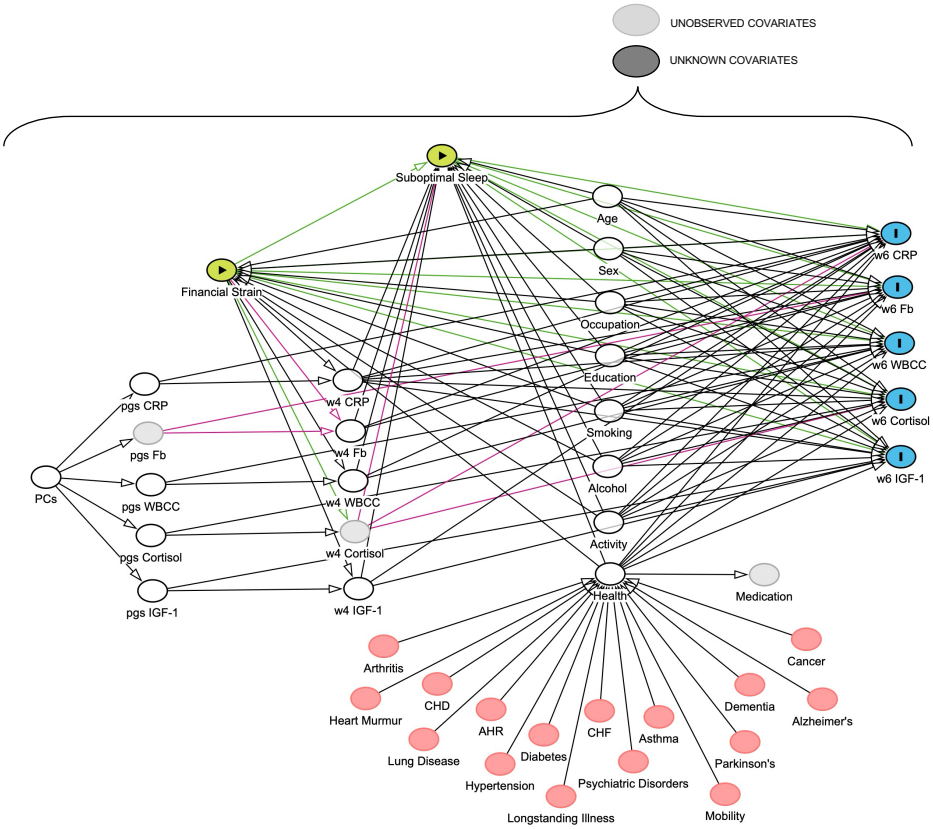
Sleep Duration. Sleep duration was assessed at W4 (2008) and was demarcated by "≤5hrs" (i.e., short sleep), ">5-<9hrs" (i.e., optimal-sleep), and "≥9hrs" (i.e., long sleep).

5.3.1.3. Outcomes

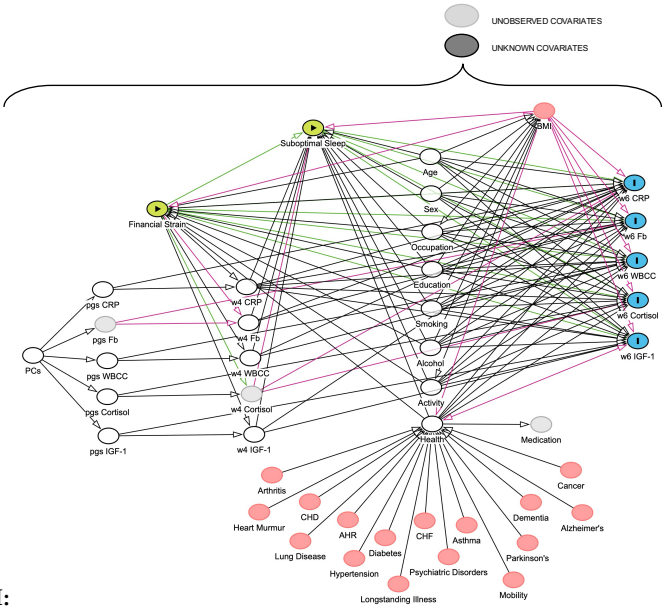
Immune and Neuroendocrine Biomarkers. Each of the biomarkers were measured at W6 (2012) included CRP, fibrinogen, WBCC, cortisol, and IGF-1. CRP, fibrinogen, WBCC, and cortisol were treated as continuous, with higher values indicating greater levels of inflammation. IGF-1 was treated as continuous, with lower values indicating greater neuroendocrine activity.

Figure 5.3 **DAG conceptually representing causal effects between study variables**

Final Model:



Including BMI:



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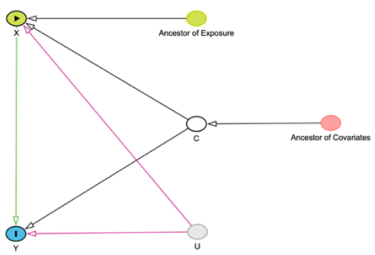


Notes: X = Exposure; Y = Outcome; C = Covariates; U = Unobserved Variables; ------ = Causal Path; ------ = Biasing Path

5.3.1.4. Covariates

Covariates were built into the model *a priori,* on the basis of a DAG (***Figure 5.3***). All measured at W4, covariates included *demographics*: age; age^2; sex; *genetic variables*: 10 PCs, PGS for CRP, WBCC, cortisol, IGF-1, and sleep duration; *socioeconomic variables*: education; wealth; *health behaviours*: smoking status; weekly alcohol consumption; weekly physical activity; *health variables*: limiting longstanding illness; any self-reported clinician diagnosis; difficulty with mobility.

5.3.2. Statistical Analyses

5.3.2.1. Polygenic Score (PGS)

Z-scores were used to standardise all PGSs for CRP, WBCC, IGF-1, cortisol, and sleep duration in these analyses, so values from different distributions could be equitably compared and to improve interpretability.

5.3.2.2. Multiple Imputation

Owing to attrition and item non-response missingness ranged 0.00-61.0% (Table S5.1). Imputation yielded a minimal error for continuous variables (NRMSE=0.07%) and categorical variables (PFC=0.05%).

5.3.2.3. Latent Profile Analysis (LPA)

To cluster the sample according to concentrations of CRP, fibrinogen, WBCC, cortisol, and IGF-1, an LPA was conducted.

5.3.2.4. Association Analyses

Baseline characteristics were expressed as means and proportions, with ANOVA and $\chi 2$ comparisons on biomarkers. Logarithmic transformation was performed on CRP, WBCC, cortisol, and IGF-1 values because of their originally skewed distribution, but fibrinogen was normally

distributed. There was no evidence of attrition bias due to systematic differences in missing data or differential loss-to-follow-up (Table S5.1). Multinomial regressions were used to test several key associations. First, the cross-sectional association between financial stress and suboptimal sleep at W4 (2008). Second, the longitudinal association of financial stress at W4 on suboptimal sleep, then immune-neuroendocrine profile membership at W6 (2012). Third, the association between suboptimal sleep at W4 and immune-neuroendocrine profile membership at W6. Finally, a multiplicative interaction term was applied between financial stress and suboptimal sleep at W4 on immune-neuroendocrine profiles at W6; expressed by an ordinary least squares (OLS) regression equation:

$$Y = \mu + \eta X + \alpha D + \beta(D \cdot X) + Z\gamma + \epsilon.$$

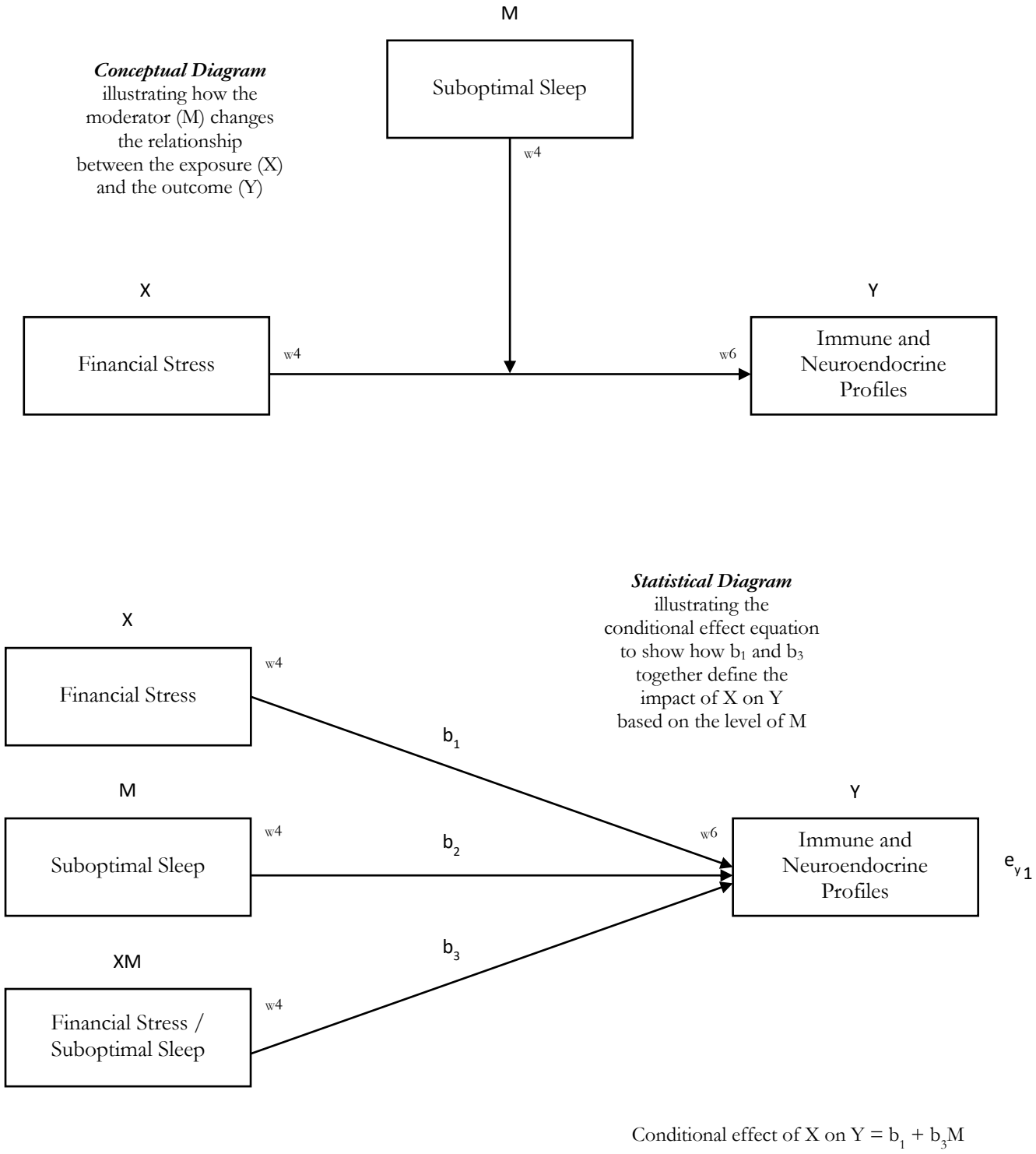
where Y represents immune-neuroendocrine profile membership (W6 *outcome*); D represents financial stress (W4 *exposure*); X represents suboptimal sleep (W4 *moderator*); $D{\cdot}X$ is the interaction term with its constituent first-order terms (D and X); Z is a vector of covariates, while μ and ϵ represent the constant and error terms, respectively. The magnitude of the interaction coefficient represents the estimated change in the effect of the focal exposure D on the outcome Y for a single unit change in the moderator X (conceptual and statistical illustration in ***Figure 5.4***). All regression assumptions were met.[326,327] The highest risk category was reported against the lowest risk reference. Results were reported as RRR, with SE and CI. Different models were fitted to understand the role of covariates on associations: Model 1 was unadjusted; model 2 adjusted for baseline immune-neuroendocrine profiles; model 3 controlled for demographic and genetic variables; model 4 was fully adjusted.

5.3.2.5. Sensitivity Analyses

To test the robustness of the results, nine additional analyses were performed. First, owing to known changes in stress perception[390] and sleep trajectories as we age,[249] it is conceivable that these

factors are a less salient risk to biological processes in later adulthood, so associations were stratified by median age (≥65). Second, sex-stratified analyses were performed because individuals who experience short sleep are more likely to be men, while women are more likely to experience long sleep,[248,391] with sex differences also reported in stress experience.[392] Third, excess adipose tissue, as measured by BMI, is a likely mediator because of its shared genetic basis with suboptimal sleep,[393] along with its known roles in stress[394] and inflammation,[395] so independent analyses controlled for BMI. Fourth, caseness of suboptimal sleep durations were low. Thus, to ensure that results were not contingent on power nor the extremities of short and long sleep, the thresholds were changed to "≤6hrs" (i.e., short sleep), ">6-<8hrs" (i.e., optimal-sleep), and "≥8hrs" (i.e., long sleep) on the basis of an umbrella review of 85 meta-analyses.[396] Fifth, while longitudinal analyses are more informative for understanding temporal relationships, cross-sectional analyses may highlight associations that might have been obscured by time-based fluctuations or noise. Thus, cross-sectional findings between financial stress and the biological profiles may serve as a useful contrast to longitudinal patterns. Sixth, a stepwise regression of each confounder would be helpful to better understand associations between stress, sleep, and immune-neuroendocrine profiles. Seventh, longitudinal associations were tested between the immune and neuroendocrine biomarkers and suboptimal sleep durations to test whether associations were hypothesised in the right direction. Eighth, to ensure the temporal stability of the latent profiles across waves, a Cohen's Kappa statistic and $\chi 2$ between waves was tested. Finally, PGSs can detect a common genetic basis between traits and provide a prediction of an individual's genetic risk for a particular disease, or in this case a biological outcome.[397] PGSs for short and long sleep were, therefore, used to test associations with immune-neuroendocrine profile membership, for results less encumbered by confounding, and to provide stronger evidence of a possible causal effect between the two. There are no GWAS from which a PGS for stress could be derived. The final analysis for sensitivity tested for possible reverse causality between the immune-neuroendocrine latent profiles and suboptimal sleep durations.

Figure 5.4 **Conceptual and Statistical Diagrams Illustrating Effect Modification**



Notes: Wave = W; X = Exposure; M = Moderator; b_1 = Main Effect; b_2 = Moderator Main Effect; b_3 = Interaction Coefficient; e_{Y1} = Residual Error. The conditional effect of X at W4 on Y at W6 is represented by b_1+b_3M, where b_1 is the main effect of X on Y, and $b_3$captures how this effect changes based on the moderator M. If M≠0, the impact of X on Y varies according to the level of M, indicating effect modification.

5.4. Results

5.4.1. Descriptive Statistics

Sample characteristics are described in **Table 5.1**. Participants were male (45.3%) and female (54.7%), aged 66.3 years on average (±9.35; range50-99). Of these, 17.0% experienced financial strain, 12.7% short sleep, and 1.7% long sleep. Although individual trajectories varied widely, biomarkers were relatively stable from baseline to follow-up. CRP was linearly correlated with fibrinogen (r=0.707); WBCC (r=0.448); cortisol (r=0.281); and IGF-1 (r=-0.167; all p=<0.001). All other correlations can be found in Table S5.2. Participants were, on average, overweight (73.4%), but active (72.9%), most consumed alcohol less than three days a week (64.3%) and were non-smokers (87.3%). The majority were without disorder (67.2%), and most had no limiting longstanding illness (68.5%), but similar proportions were with and without mobility difficulties (45.8/54.2%). Financial stress declined 3.22 percentage points (pp) between baseline and follow-up, short sleep declined 2.2pp, but long sleep increased 3.56pp (Table S5.3).

5.4.2. Latent profile analysis of immune and neuroendocrine biomarkers

Similar to the earlier chapter, a three-profile model of the immune-neuroendocrine biomarkers offered the most parsimonious fit to the data (Table S5.4; *Figures S5.1-2a-g*). After which there were limited returns in AIC, BIC, and aBIC value. The lowest values offered the most optimal balance between model fit and simplicity (***Figure 5.5***). The significant LRT indicated that this model was statistically preferable to the simpler model. Entropy was 0.67 (***Figure 5.6***) and the mean posterior probabilities did not exceed 0.70, together signalling clear profile separation and good classification quality. Each profile had ≥5% of participants (***Figure 5.7***); and there was theoretical meaning to the profiles. The predicted marginal mean margins of the profiles can be seen in ***Figure 5.8***. Profile 1, defined as '*low-risk*', included 35.2% of the sample (M_{age}=64.05; ±7.72; $_{male}$47.44/$_{female}$52.56%), characterised by individuals with low CRP, fibrinogen, WBCC, cortisol, and high IGF-1.

Table 5.1 Sample characteristics

Variable		Baseline (N= 4,940)			
		N / M (SD)	% / Range	ANOVA	χ^2
Age		66.3 (9.35)	50-99	<0.001	
Age (Binary)	<65 Md	2,436	49.31		<0.001
	≥65 Md	2,504	50.69		
Sex	Male	2,237	45.3		0.073
	Female	2,703	54.7		
Education	Higher	1,589	32.2		<0.001
	Lower	1,543	31.2		
	Alternative/No	1,808	36.6		
Wealth	Lowest	1,573	31.8		<0.001
	Middle	2,014	40.8		
	Highest	1,353	27.4		
Smoking Status	Never/Ex-Smokers	4,312	87.3		<0.001
	Current Smoker	628	12.7		
Alcohol Consumption	<3 days a week	3,175	64.3		<0.001
	≥3 days a week	1,765	35.7		
Physical Activity	Sedentary	1,340	27.1		<0.001
	Active	3,600	72.9		
Mobility	Mobile	2,678	54.2		<0.001
	Not Mobile	2,262	45.8		
Limiting Longstanding Illness	None	3,386	68.5		<0.001
	Present	1,554	31.5		
Health	No health condition	3,319	67.2		<0.001
	At least one health condition	1,621	32.8		
BMI	<25, Underweight/Normal	1,312	26.6		<0.001
	25-30, Overweight: Pre-obese	2,213	44.8		
	30 or over, Obese	1,415	28.6		
PGS for CRP		0.00 (1.00)	-3.50 (3.76)	0.235	
PGS for WBCC		0.00 (1.00)	-4.03 (2.58)	0.123	
PGS for IGF-1		0.00 (1.00)	-3.69 (3.83)	0.411	
PGS for cortisol		0.00 (1.00)	-3.47 (3.28)	0.928	
PGS for Sleep Duration		0.00 (1.00)	-4.09 (2.87)	0.449	
CRP* (mg/L; Baseline)		0.28 (0.46)	-0.70-1.30	<0.001	
CRP* (mg/L; Follow-up)		0.40 (0.48)	-1.00-1.30	<0.001	
Fb (g/L; Baseline)		3.38 (.56)	1.30-5.90	<0.001	
Fb (g/L; Follow-up)		3.12 (0.52)	1.50-5.80	<0.001	
WBCC* (nmol/L; Baseline)		0.79 (0.13)	-0.10-1.50	0.062	
WBCC* (nmol/L; Follow-up)		0.81 (0.11)	0.34-1.51	<0.001	
IGF-1* (nmol/L; Baseline)		1.18 (0.16)	0.30-1.81	<0.001	
IGF-1* (nmol/L; Follow-up)		1.18 (0.13)	0.60-1.76	<0.001	
Cortisol* (nmol/L; Follow-up)		1.23 (0.65)	-0.85-2.82	0.158	
Stress (indexed by Financial Strain)	No Strain (0-60%)	4,099	83.0		<0.001
	Strain (61-100%)	841	17.0		
Sleep Duration	Short Sleep	627	12.7		<0.001
	Optimal Sleep	4,227	85.6		
	Long Sleep	86	1.7		
I-N Profiles (Baseline)	*Low-risk*	2,590	52.4		<0.001
	Moderate-risk	1,773	35.9		
	High-risk	577	11.7		
I-N Profiles (Follow-up)	*Low-risk*	1,739	35.2		-
	Moderate-risk	1,951	39.5		
	High-risk	1,250	25.3		

Notes: ELSA, waves 4-6 (2008-2012); N = observations; M = mean; Md = median; % = percentage frequencies; SD = standard deviations; ANOVA = analysis of variance between the exposed and unexposed for continuous variables with a 3-level categorical variable; χ^2 = Pearson chi square test significance between the exposed and unexposed for categorical variables with a 3-level categorical variable; < = less than; ≥ = greater than or equal to; BMI = body mass index; PGS = polygenic score; CRP = C-reactive protein; Fb = fibrinogen; WBCC = white blood cell counts; IGF-1 = insulin-growth factor-1; Cortisol = hair cortisol; * Log-transformed variable; I-N = immune and neuroendocrine.

Figure 5.5. **Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) Values of Immune and Neuroendocrine Profiles to Assess Model Fit for wave 6**

The modal profile 2, defined as '*moderate-risk*', included 39.5% of the sample (M_{age}=66.53; ±9.31; $_{male}$43.77/$_{female}$56.23%) and consisted of individuals with moderate CRP, fibrinogen, WBCC, cortisol, and IGF-1 levels. Finally, profile 3, defined as '*high-risk*', included 25.3% of the sample (M_{age}=69.13; ±10.60; $_{male}$44.68/$_{female}$55.32%;) and was marked by a high probability of high CRP, fibrinogen, WBCC, cortisol, and low IGF-1 (***Figure 5.8***). The number of individuals within the *low-risk* group fell by 17.2% from baseline (W4; 2008) to follow-up (W6; 2012), with the *moderate-risk* group increasing by 3.6%, and the *high-risk* group increasing by 13.6% (**Table 5.1**).

Figure 5.6. **Entropy and Normalised Entropy Values of Immune and Neuroendocrine Biomarker Profiles to Assess Profile Quality for wave 6**

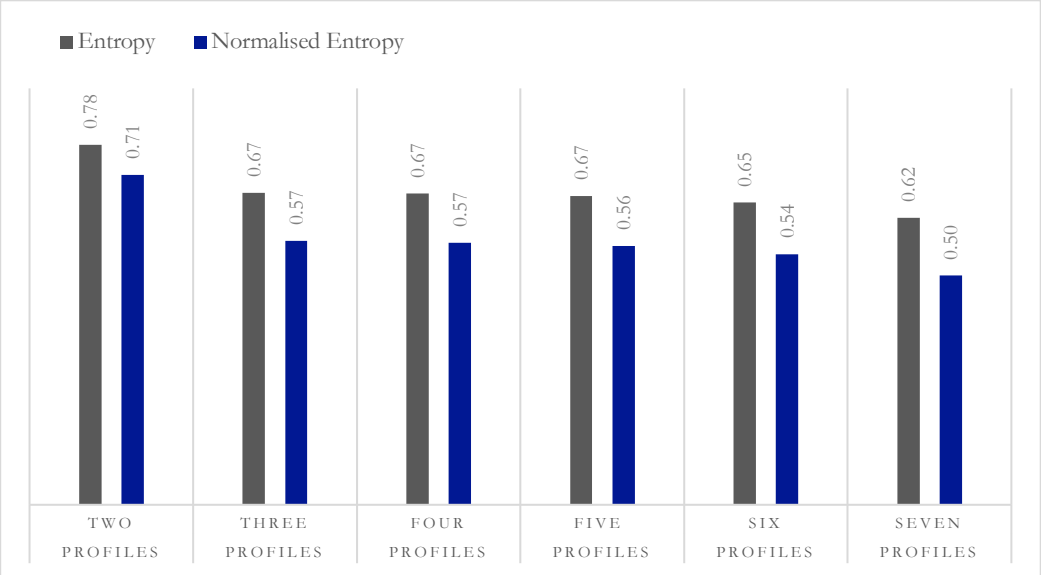


Figure 5.7. **Mean Posterior Probabilities of Immune and Neuroendocrine Biomarker Profiles to Assess Membership Confidence (≥5%) for wave 6**

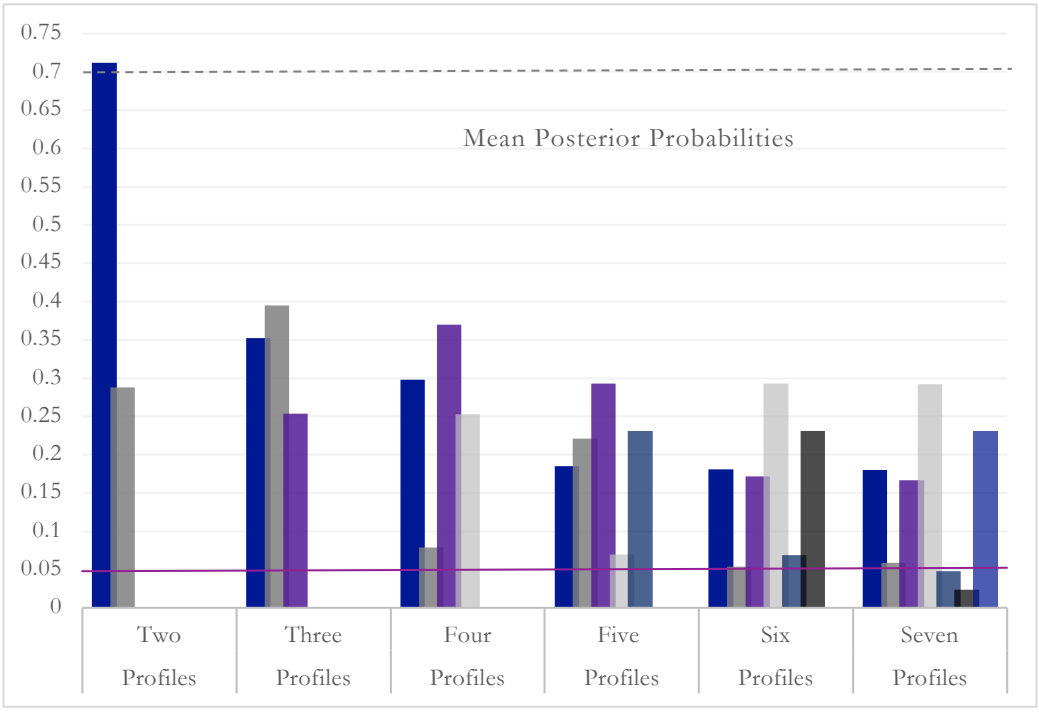
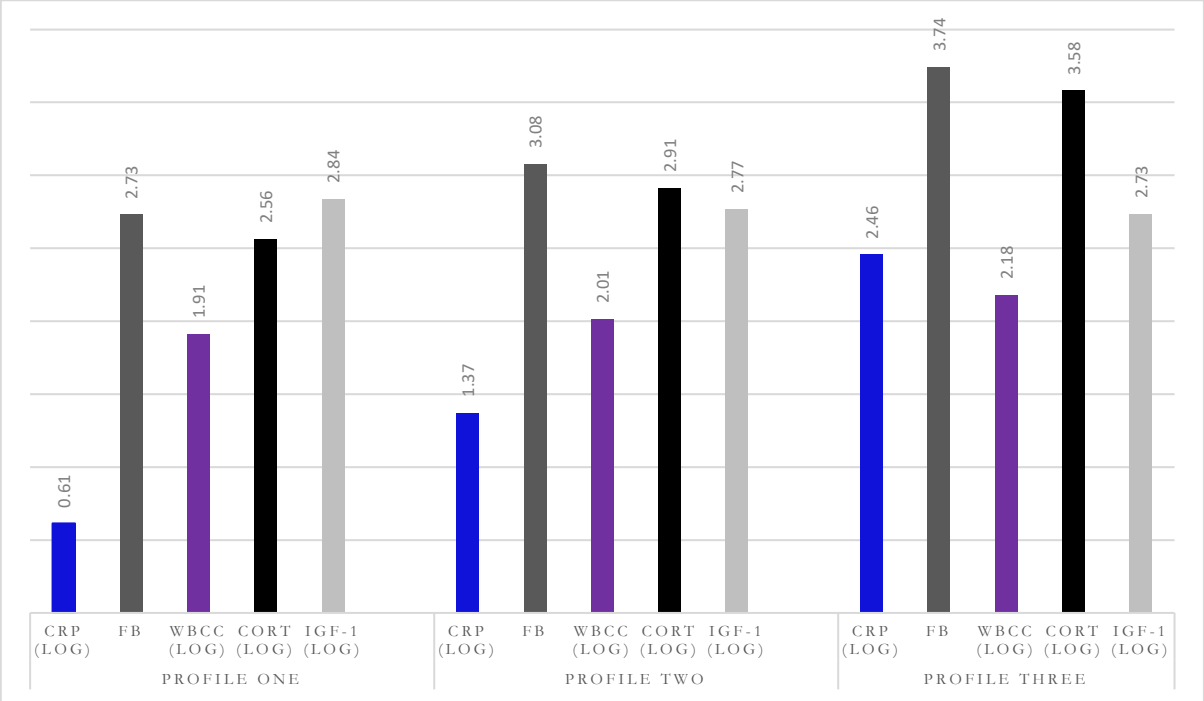


Figure 5.8. **Predicted Marginal Mean Margins of Immune and Neuroendocrine Profiles**



5.4.3. Cross-sectional associations of financial stress with suboptimal sleep

As shown in **Table 5.2**, after adjustment for, age, sex, and genetic predisposition to adverse immune-neuroendocrine biological signatures, the experience of financial-related stress was cross-sectionally associated with an 80% greater risk of experiencing short sleep (Model 3: RRR=1.80; CI=1.47-2.20), but not long sleep (Model 4: RRR=1.24; CI=0.70-2.19). Associations held after full adjustment, with financial stress being associated with a 45% greater risk of short sleep (RRR=1.45; CI=1.18-1.79).

5.4.4. Longitudinal associations of financial stress with suboptimal sleep

In models adjusted for baseline suboptimal sleep, age, sex, and genetic predisposition (**Table 5.3**), financial stress was longitudinally associated with a greater risk of experiencing short sleep (Model 3: RRR=1.46; CI=1.14-1.86), but not long sleep (Model 3: RRR=1.22; CI=0.86-1.72). When fully adjusted, financial stress was associated with a 31% greater risk of experiencing short sleep 4 years later (Model 4: RRR=1.31; CI=1.02-1.68).

Table 5.2 Cross-sectional associations between stress and suboptimal sleep

Adjustments	Stress				
	RRR	SE	95% CI		*p*
Short Sleep					
Model 1: *Unadjusted*	1.80	0.18	1.47	2.19	<0.001
Model 2: *Model 2 + demographics & genetics* [a, b]	1.80	0.19	1.47	2.20	<0.001
Model 3: *Fully Adjusted* [c]	1.45	0.15	1.18	1.79	<0.001
Long Sleep					
Model 1: *Unadjusted*	1.13	0.32	0.64	1.98	0.680
Model 2: *Model 2 + demographics & genetics* [a, b]	1.24	0.36	0.70	2.19	0.463
Model 3: *Fully Adjusted* [c]	1.11	0.33	0.62	1.98	0.721

Notes: The *low-risk* group is the reference; RRR = relative risk ratio; SE = standard errors; CI = confidence interval; *p* = significance value.
a Demographic variables: age; sex
b Genetic variables: 10 principal components (PCs); C-reactive protein (CRP) polygenic score (PGS); white blood cell counts (WBCC) PGS; insulin growth factor-1 (IGF-1) PGS; cortisol PGS; sleep duration PGS.
c All variables: age; sex; 10 PCs; CRP PGS; WBCC PGS; IGF-1 PGS; cortisol PGS; education; wealth; occupational social status; smoking status; alcohol consumption; physical activity; mobility; limiting longstanding illness; health (i.e., chronic lung disease; coronary heart disease; abnormal heart rhythm; heart murmur; congestive heart failure; angina; hypertension; diabetes; cancer; Parkinson's; Alzheimer's; dementia; asthma; arthritis; osteoporosis; psychiatric disorder).

Table 5.3 Longitudinal associations between stress and suboptimal sleep

Adjustments	Stress				
	RRR	SE	95% CI		*p*
Short Sleep					
Model 1: *Unadjusted*	1.80	0.20	1.45	2.23	<0.001
Model 2: *Model 1 + baseline sleep duration* [a]	1.47	0.18	1.15	1.87	0.002
Model 3: *Model 2 + demographics & genetics* [b]	1.46	0.18	1.14	1.86	0.003
Model 4: *Fully Adjusted* [c]	1.31	0.17	1.02	1.68	0.035
Long Sleep					
Model 1: *Unadjusted*	1.06	0.18	0.76	1.48	0.729
Model 2: *Model 1 + baseline sleep duration* [a]	1.09	0.19	0.78	1.53	0.628
Model 3: *Model 2 + demographics & genetics* [b]	1.22	0.22	0.86	1.72	0.265
Model 4: *Fully Adjusted* [c]	1.05	0.19	0.74	1.50	0.773

Notes: The *low-risk* group is the reference; RRR = relative risk ratio; SE = standard errors; CI = confidence interval; *p* = significance value.
a Baseline sleep duration.
b Demographic and genetic variables: age; sex; 10 principal components (PCs); C-reactive protein (CRP) polygenic score (PGS); white blood cell counts (WBCC) PGS; insulin growth factor-1 (IGF-1) PGS; cortisol PGS; sleep duration PGS.
c All variables: baseline immune and neuroendocrine profiles; baseline suboptimal sleep; age; sex; 10 PCs; CRP PGS; WBCC PGS; IGF-1 PGS; cortisol PGS; sleep duration PGS; education; wealth; occupational social status; smoking status; alcohol consumption; physical activity; mobility; limiting longstanding illness; health (i.e., chronic lung disease; coronary heart disease; abnormal heart rhythm; heart murmur; congestive heart failure; angina; hypertension; diabetes; cancer; Parkinson's; Alzheimer's; dementia; asthma; arthritis; osteoporosis; psychiatric disorder).

5.4.5. Longitudinal associations between financial stress with immune and neuroendocrine profiles

Having adjusted for baseline profiles, along with demographic and genetic factors, as shown in **Table 5.4**, financial stress experience was longitudinally associated with 28% increased likelihood of being classified into the *moderate-risk* profile, as compared to the *low-risk* profile (Model 3: RRR=1.28; CI=1.06-1.54). This was reduced to null after full adjustment as other factors introduced into the model explained associations (Model 4: RRR=1.18; CI=0.97-1.43). By contrast, with membership of the *high-risk* profile across the same models, financial stress was associated with a 65% greater risk of belonging to this group (Model 3: RRR=1.65; CI=1.31-2.07), which fell to 42% after full adjustment (Model 4: RRR=1.42; CI=1.12-1.80).

5.4.6. Longitudinal associations between suboptimal sleep with immune and neuroendocrine profiles

At any level of adjustment, suboptimal sleep durations were not prospectively associated with a greater risk of belonging to the *moderate-risk* profile compared with the *low-risk* profile (**Table 5.5**). Short sleep was not associated with future risk of *high-risk* immune-neuroendocrine profile membership in adjusted models. There were indications that long sleep was associated with a two-fold increase in the likelihood of *high-risk* profile membership when adjusted for baseline profiles, demographic, and genetic factors (Model 3: RRR=2.02; CI=1.02-3.98), but this association was attenuated to null after full adjustment (Model 4: RRR=1.48; CI=0.73-2.98).

5.4.7. Effect modification between financial stress and suboptimal sleep in immune and neuroendocrine profile membership

There was no moderating effect of suboptimal sleep on the association between financial stress and immune-neuroendocrine profile membership (**Table 5.6**). The coefficients of interaction

terms were close to zero for short sleep. The magnitude of effects was large for long sleep but with large confidence intervals. Thus, there was insufficient evidence to reject the null hypothesis.

5.4.8. Sensitivity Analyses

First, when associations were stratified by age, financial stress was associated with a 70% higher relative risk of belonging to the *high-risk* immune-neuroendocrine profile in younger individuals (RRR=1.70; CI=1.20-2.41; p=0.003), with indications of a gradient in risk, such that the *moderate-risk* profile showed an intermediate pattern (RRR=1.30; CI=1.00-1.70; p=0.050). However, there were no associations in the older age category (Table S5.5). As it relates to the suboptimal sleep associations with immune-neuroendocrine profile membership, effect sizes did not differ by age (Table S5.6). In the second sensitivity analysis, sex-stratified analyses revealed that men, but not

Table 5.4 Longitudinal associations of stress with immune and neuroendocrine profiles

Adjustments	Stress				
	RRR	SE	95% CI		*p*
***Moderate-risk* Profile**					
Model 1: *Unadjusted*	1.26	0.12	1.05	1.50	0.012
Model 2: *Model 1 + baseline profiles* [a]	1.23	0.12	1.03	1.48	0.025
Model 3: *Model 2 + demographics & genetics* [b]	1.28	0.12	1.06	1.54	0.010
Model 4: *Fully Adjusted* [c]	1.18	0.12	0.97	1.43	0.093
***High-risk* Profile**					
Model 1: *Unadjusted*	1.57	0.15	1.30	1.90	<0.001
Model 2: *Model 1 + baseline profiles* [a]	1.52	0.17	1.21	1.90	<0.001
Model 3: *Model 2 + demographics & genetics* [b]	1.65	0.19	1.31	2.07	<0.001
Model 4: *Fully Adjusted* [c]	1.42	0.17	1.12	1.80	0.004

Notes: The *low-risk* group is the reference; RRR = relative risk ratio; SE = standard errors; CI = confidence interval; p = significance value.
a Baseline immune and neuroendocrine profiles.
b Demographic and genetic variables: age; sex; 10 principal components (PCs); C-reactive protein (CRP) polygenic score (PGS); white blood cell counts (WBCC) PGS; insulin growth factor-1 (IGF-1) PGS; cortisol PGS; sleep duration PGS.
c All variables: baseline immune and neuroendocrine profiles; age; sex; 10 PCs; CRP PGS; WBCC PGS; IGF-1 PGS; cortisol PGS; education; wealth; occupational social status; smoking status; alcohol consumption; physical activity; mobility; limiting longstanding illness; health (i.e., chronic lung disease; coronary heart disease; abnormal heart rhythm; heart murmur; congestive heart failure; angina; hypertension; diabetes; cancer; Parkinson's; Alzheimer's; dementia; asthma; arthritis; osteoporosis; psychiatric disorder).

Table 5.5 Longitudinal associations of suboptimal sleep with immune and neuroendocrine profiles

Adjustments	Short Sleep				
	RRR	**SE**	**95% CI**		***p***
Moderate-risk **Profile**					
Model 1: *Unadjusted*	1.15	0.12	0.94	1.41	0.171
Model 2: *Model 1 + baseline profiles* [a]	1.08	0.11	0.88	1.33	0.447
Model 3: *Model 2 + demographics & genetics* [b]	1.01	0.11	0.82	1.25	0.907
Model 4: *Fully Adjusted* [c]	0.90	0.10	0.72	1.12	0.335
High-risk **Profile**					
Model 1: *Unadjusted*	1.45	0.16	1.17	1.80	0.001
Model 2: *Model 1 + baseline profiles* [a]	1.26	0.16	0.98	1.62	0.075
Model 3: *Model 2 + demographics & genetics* [b]	1.19	0.16	0.92	1.54	0.192
Model 4: *Fully Adjusted* [c]	0.87	0.12	0.67	1.14	0.323
Adjustments	**Long Sleep**				
	RRR	**SE**	**95% CI**		***p***
Moderate-risk **Profile**					
Model 1: *Unadjusted*	1.55	0.48	0.85	2.84	0.152
Model 2: *Model 1 + baseline profiles* [a]	1.43	0.45	0.77	2.66	0.254
Model 3: *Model 2 + demographics & genetics* [b]	1.16	0.37	0.62	2.16	0.650
Model 4: *Fully Adjusted* [c]	1.05	0.34	0.55	1.98	0.893
High-risk **Profile**					
Model 1: *Unadjusted*	3.52	1.03	1.98	6.24	<0.001
Model 2: *Model 1 + baseline profiles* [a]	2.78	0.94	1.43	5.41	0.003
Model 3: *Model 2 + demographics & genetics* [b]	2.02	0.70	1.02	3.98	0.043
Model 4: *Fully Adjusted* [c]	1.48	0.53	0.73	2.98	0.277

Notes: The *low-risk* group is the reference; RRR = relative risk ratio; SE = standard errors; CI = confidence interval; *p* = significance value.

a Baseline immune and neuroendocrine profiles.

b Demographic and genetic variables: age; sex; 10 principal components (PCs); C-reactive protein (CRP) polygenic score (PGS); white blood cell counts (WBCC) PGS; insulin growth factor-1 (IGF-1) PGS; cortisol PGS; sleep duration PGS.

c All variables: baseline immune and neuroendocrine profiles; age; sex; 10 PCs; CRP PGS; WBCC PGS; IGF-1 PGS; cortisol PGS; education; wealth; occupational social status; smoking status; alcohol consumption; physical activity; mobility; limiting longstanding illness; health (i.e., chronic lung disease; coronary heart disease; abnormal heart rhythm; heart murmur; congestive heart failure; angina; hypertension; diabetes; cancer; Parkinson's; Alzheimer's; dementia; asthma; arthritis; osteoporosis; psychiatric disorder).

Table 5.6 Effect modification between stress and suboptimal sleep in immune and neuroendocrine profile membership

Adjustments	Stress × Short Sleep				
	RRR	SE	95% CI		*p*
***Moderate-risk* Profile**					
Model 1: *Unadjusted*	0.90	0.22	0.55	1.45	0.660
Model 2: *Model 1 + baseline profiles* [a]	0.95	0.24	0.58	1.57	0.852
Model 3: *Model 2 + demographics & genetics* [b]	0.95	0.24	0.58	1.57	0.841
Model 4: *Fully Adjusted* [c]	0.95	0.24	0.57	1.57	0.827
***High-risk* Profile**					
Model 1: *Unadjusted*	0.77	0.20	0.46	1.28	0.309
Model 2: *Model 1 + baseline profiles* [a]	0.78	0.24	0.43	1.42	0.408
Model 3: *Model 2 + demographics & genetics* [b]	0.83	0.26	0.45	1.53	0.557
Model 4: *Fully Adjusted* [c]	0.85	0.27	0.46	1.58	0.602
Adjustments	**Stress × Long Sleep**				
	RRR	**SE**	**95% CI**		***p***
***Moderate-risk* Profile**					
Model 1: *Unadjusted*	4.07	4.57	0.45	36.79	0.211
Model 2: *Model 1 + baseline profiles* [a]	4.23	4.81	0.45	39.30	0.205
Model 3: *Model 2 + demographics & genetics* [b]	4.64	5.30	0.49	43.60	0.179
Model 4: *Fully Adjusted* [c]	4.02	4.64	0.42	38.62	0.228
***High-risk* Profile**					
Model 1: *Unadjusted*	2.11	2.36	0.24	18.86	0.503
Model 2: *Model 1 + baseline profiles* [a]	2.08	2.51	0.20	22.16	0.545
Model 3: *Model 2 + demographics & genetics* [b]	2.97	3.59	0.28	31.61	0.366
Model 4: *Fully Adjusted* [c]	2.28	2.81	0.21	25.50	0.502

Notes: The *low-risk* group is the reference; RRR = relative risk ratio; SE = standard errors; CI = confidence interval; *p* = significance value.

a Baseline immune and neuroendocrine profiles.

b Demographic and genetic variables: age; sex; 10 principal components (PCs); C-reactive protein (CRP) polygenic score (PGS); white blood cell counts (WBCC) PGS; insulin growth factor-1 (IGF-1) PGS; cortisol PGS; sleep duration PGS.

c All variables: baseline immune and neuroendocrine profiles; age; sex; 10 PCs; CRP PGS; WBCC PGS; IGF-1 PGS; cortisol PGS; education; wealth; occupational social status; smoking status; alcohol consumption; physical activity; mobility; limiting longstanding illness; health (i.e., chronic lung disease; coronary heart disease; abnormal heart rhythm; heart murmur; congestive heart failure; angina; hypertension; diabetes; cancer; Parkinson's; Alzheimer's; dementia; asthma; arthritis; osteoporosis; psychiatric disorder).

women, stressed from a lack of resources had a greater risk of belonging to the *high-risk* immune-neuroendocrine profile (RRR=1.68; CI=1.16-2.43; p=0.006; Table S5.7) despite an overlap of confidence intervals. However, this pattern between the sexes was not replicated in suboptimal sleep associations with immune-neuroendocrine profile membership (Table S5.8). The third sensitivity analysis included BMI as an additional covariate in Model 4, with no substantive change seen in the magnitude of effects (Tables S5.9-10). The fourth sensitivity analysis used less stringent thresholds for short and long sleep (≤6 hr [n=2,095; 19.29%]; ≥8 hr [n=4,788; 44.08%] respectively) and results were materially unchanged (Table S5.11). The fifth sensitivity analysis showed that financial stress was cross-sectionally associated with the immune and neuroendocrine profiles in the minimally adjusted model (Model 2: *moderate-risk*: RRR=1.24; CI=1.05-1.45; p=0.010; *high-risk*: RRR=1.30; CI=1.03-1.64; p=0.028). This was true also in model 3 (*moderate-risk*: RRR=1.25; CI=1.07-1.47; p=0.006; *high-risk*: RRR=1.32; CI=1.04-1.67; p=0.021), but associations were reduced to null by other competing factors in the final model (Model 4: *moderate-risk*: RRR=1.07; CI=0.90-1.26; p=0.446; *high-risk*: RRR=1.01; CI=1.79-1.29; p=0.951). This suggests that financial stress might have delayed effects on immune and neuroendocrine systems that are better captured prospectively. In the sixth sensitivity analyses, a stepwise regression of each confounder along with their discrete contributions provided a clearer understanding of their individual contributions to the associations between stress, sleep, and immune-neuroendocrine profiles (Tables S5.12a-b; 13a-b). The seventh analysis for sensitivity, longitudinal associations were revealed between the immune and neuroendocrine biomarkers and long sleep durations, but not short sleep. This suggests a possible reversal of roles between biological processes and long sleep (Table S5.14). The eighth sensitivity analysis, the Kappa suggests fair class stability over time, with a significant value that supports the presence of a genuine relationship beyond chance (κ=0.263, SE=0.0087, Z=30.08, p<0.001). The statistically significant relationship between profile assignments across waves show that participant classifications were meaningfully associated, rather than shifting randomly over time (χ^2[4]=1400, p<0.001). In the final sensitivity analysis, a 1±

increase in genetic liability for short sleep and long sleep was not associated with immune-neuroendocrine profile membership (Table S5.15).

5.5. Discussion

In a large, population-representative, prospective cohort study of older adults, cross-sectional, longitudinal, and multiplicative associations were tested between financial stress and suboptimal sleep in immune-neuroendocrine profile membership. Financial stress was cross-sectionally and longitudinally associated with short sleep, but not long sleep. Associations held having controlled for genetic predisposition and a broad selection of covariates. Financial stress was additionally associated with *high-risk* profile membership four years later. It is worth noting that there was no change in the magnitude of effects when accounting for BMI. In addition, against expectations, suboptimal sleep was not associated with immune-neuroendocrine profile membership, nor did it modify the relationship between financial stress and said profiles.

The unexpected finding that suboptimal sleep was not prospectively associated with immune-neuroendocrine profile membership is an important contribution to understanding the role of sleep in immune-neuroendocrine processes. It challenges compelling evidence elsewhere that sleep is integral to endocrine, metabolic, and immune integrity, and where sleep loss, even acutely, perturbs gene expression and the functional cellular response.[250,383] Meta-analytic evidence substantiates cross-sectional associations between suboptimal sleep and heightened inflammatory levels,[398] with further evidence that associations are longitudinal.[251,399] Even when modelled curvilinearly, sleep duration remained associated with inflammatory processes.[391] Still, in all cases, results depended on the biomarkers measured and the temporal relationship between exposures and outcomes.

Polygenic risk prediction is a useful tool in observational studies to confirm the less confounded role of traits in outcomes, albeit limited to genetic contribution.[23] Results arising from the PGSs for short and long sleep, support the phenotypic findings that suboptimal sleep durations are not prospectively associated with immune-neuroendocrine profiles. These corresponding results raise the possibility of reverse causality. First, having considered the previously reported role of immune-neuroendocrine biomarkers in diurnal variations,[84,87] with much of the evidence on sleep duration and inflammation being cross-sectional, limiting inferences on directionality.[398,400] Second, because PGSs point to directionality given they are largely unconfounded; predicated on inherited DNA differences from birth that increase the predictive facility of complex traits in unrelated individuals among the population.[401,402] Still, the current predictive facility of PGSs is insufficient for clinical implementation. This is due to the aetiological complexity of common disorders, like sleep duration, that are influenced by gene-environment interactions, with polygenic architecture that has contributions from multiple SNPs of small effect, rather than a dominant genetic variant of large effect that can be isolated.[403] Owing to this complexity, the ecological value of PGSs is reduced and the immediate scope to dismiss the credibility of sleep-related policy from these findings is narrow. Thus, results can be considered preliminary and hypothesis-generating.

It is, nonetheless, important to control for genetic influence in analyses, given the stability of genetic sequence across the lifespan and genetic variation that accounts for a notable proportion of individual difference in health and disease.[404] Our adjustment for a comprehensive selection of confounders, notably genetic predisposition for adverse biomarker levels, has rarely been reported elsewhere. We show that the longitudinal role of financial stress on suboptimal sleep and immune-neuroendocrine profiles is independent of genetic predisposition, but the role of suboptimal sleep on profile membership was not robust enough to withstand this genetic influence. The contrast with earlier evidence linking suboptimal sleep to inflammatory markers, may, in part, be attributable to statistically less controlled analyses that increase the likelihood of Type I error.[405]

In the absence of moderation, results putatively contradict anecdotal and empirical evidence[406] that stress exposure compounded with suboptimal sleep durations increase risk to biological signatures. Analyses can be considered preliminary, owing to the modest cell sizes of suboptimal sleep cases, and other common power attenuating factors, including exposure-mediator intercorrelations, scale coarseness, the artificial categorisations of continuous variables, or the transformation of non-normal outcomes.[407] These may have restricted the detection of interactions, with unstable parameter estimates and inflated standard errors, but given the sizeable alphas, it is unlikely that a greater powered sample would have detected moderating effects with reliable estimates. Results point to financial stress being a more proximate risk factor to immune-neuroendocrine processes than suboptimal sleep, so much so that financial stress may reach a threshold beyond which suboptimal sleep has limited additional returns. The lack of interaction is consistent with the limited influence of sleep duration in this cohort.[408]

5.5.1. Strengths and Limitations

This was the first study, to our knowledge, to triangulate evidence across multiple fields of study to advance PNI knowledge, by revealing how inflammation and neuroendocrine markers cluster in older cohorts and respond to financial stress and suboptimal sleep over time. There are many other strengths to this study and, invariably, findings must be interpreted in light of some limitations. As these span across multiple studies within this thesis, they are discussed more broadly in the general discussion (Chapter 8).

5.5.2. Conclusion

Immune and neuroendocrine activity has a highly complex aetiology due to multisystem exchanges and exogenous influences. We capitalise on converging methods of estimation to unravel a portion of this complexity. Results show the distinct and interactive roles of financial stress and suboptimal

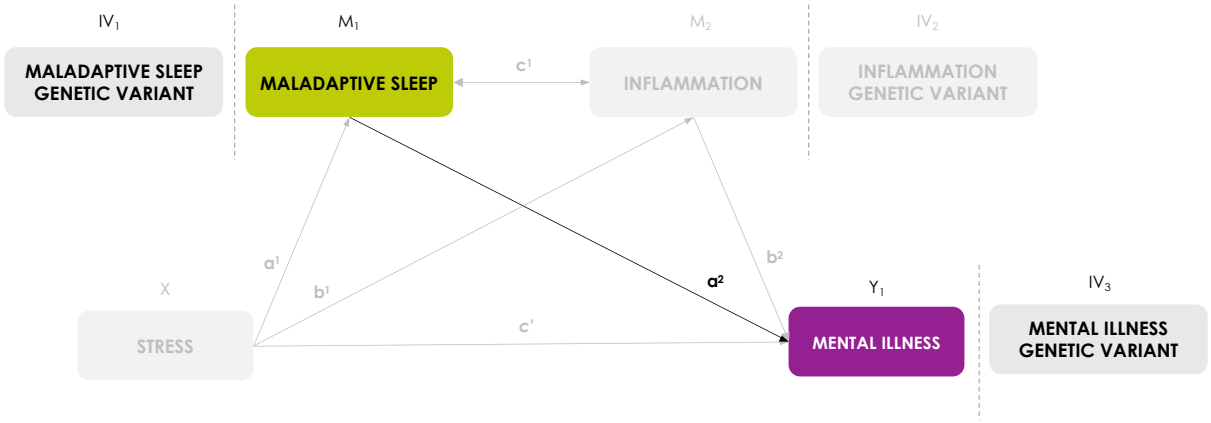
sleep in determining immune-neuroendocrine latent profile membership. Suboptimal sleep has long been recognised as a prime factor in biological processes. However, its inconsistent findings in the present study make it a less compelling target for immune-neuroendocrine patterning, certainly in older adults. This is especially true because there was no evidence to support that the combined experience of financial stress and suboptimal sleep was worse for immune-neuroendocrine patterning than financial stress alone. This study underscores several potential areas of interest for future research while emphasising the need for translational investigations. Key areas among them are the need to assess whether results hold in a younger cohort, whether associations are causal, and whether these immune-neuroendocrine profiles mediate associations between stress and disease. Addressing these questions will contribute to an improved understanding of biosocial mechanisms to disease.

CHAPTER 6. POLYGENIC PREDISPOSITION, SLEEP DURATION, AND DEPRESSION

6.1. Chapter overview

This chapter investigates the prospective direction of suboptimal sleep durations and subclinical depression, with findings published in *Translational Psychiatry* (Hamilton et al., 2023).[409] It uses PGS of short sleep, long sleep, and depression to understand associations less confounded by other factors. It also looks at phenotypic associations longitudinally to compare with the genetic results.

Figure 6.1 **The section of the conceptual framework (*Figure 1.10*) addressed in Chapter 6**



6.2. Introduction

Short sleep (typically <5-6hrs) and long sleep (typically >8-10hrs)[61–63] are suboptimal sleep durations that, along with depression, are major contributors to public health burden among community-dwelling older adults. Cai and colleagues' (2023)[410] meta-analysis of 55 studies revealed that over a third of older populations globally had depression (*n*=59,851). Elsewhere, depression prevalence was found to increase with age but plateau in adults aged 55-74.[411] Older adults also tend to experience a downward trajectory of optimal sleep duration as they age.[66] Given the

worldwide phenomenon of population ageing, an emergent need has arisen for a better understanding of the mechanism driving the nexus of suboptimal sleep durations and depression onset in older adults.

Clinical and epidemiological evidence have demonstrated the comorbid nature of suboptimal sleep durations and depression,[115] with longitudinal associations shown in both directions.[61,121] Specifically, some evidence suggests that short sleep[119] and long sleep[117] precedes the onset of depression, whereas others have suggested that depression precedes the onset of suboptimal sleep durations.[61] Inconsistencies observed between results may be due to methodological constraints, such as the use of different measures for sleep and depression,[61,117] cross-sectional designs,[412,413] relatively small sample sizes, and participant pools with a diverse range of characteristics, including military personnel[121] and adolescents,[414] across clinical and sub-clinical populations.[121,415] One compelling study on bidirectionality revealed that sleep disorders predict depression more consistently than depression predicts sleep disorders over a 20-year period.[415] However, the absence of genetic information may be an important factor that contributes to the uncertainty of directionality between suboptimal sleep durations and depression in adults. PGSs are thought to be key in beginning to understand the nature of sleep duration[416] and depression.[417] As earlier discussed, PGSs can detect whether a common genetic basis exists between related traits or diseases, and can provide prediction of an individuals' genetic risk for a particular disease or outcome.[418] This approach, therefore, can be used to investigate whether suboptimal sleep durations and depression possess underlying shared genetic aetiology.

Using a large, phenotypically well-defined sample of UK population-representative older adults, PGSs were used across an average course of 8 years. First, to ascertain the role of polygenic predisposition to overall sleep duration, short sleep, and long sleep in the development of depression. Second, to test the role of polygenic predisposition to depression in overall sleep

duration, and the onset of short sleep and long sleep. Despite substantial variation in thresholds defining short sleep and long sleep in the literature, a meta-analysis of prospective studies supported a curvilinear risk of short sleep (<5-7hrs) and long sleep (>8-9hrs) sleep on depression that did not differ substantially by age.[115] The extremes of these durations informed the sleep thresholds used in the present study.

6.2.1. Hypotheses

As sleep disorders have been found to be stronger and more persistent longitudinal predictors of future depression than the inverse,[415] a significant, unidirectional association was hypothesised between polygenic predisposition to overall sleep duration, short sleep, and long sleep duration in the onset of depression during an average 8-year period.

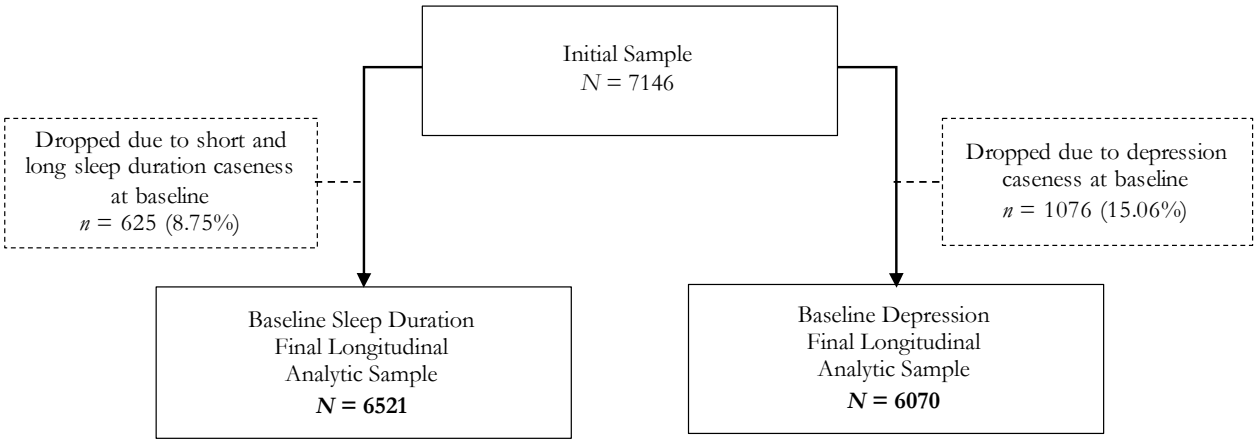
6.3. Methods

All measure details and methods are described in Chapter 2, so are not repeated here.

6.3.1. Study Design

Data were derived from ELSA.[288] Data from combined waves 2 and 4 (2004-2008) were used as baseline as genetic data were first introduced across this period. Data for outcomes on sleep duration and depression were derived from combined waves 6 and 8 (2012-2016), given that depression and sleep duration may fluctuate within subjects over time. When testing the role of sleep at baseline on depression onset at follow-up, the sample of 7,146 was reduced by 625 (8.8%) participants who experienced depression at baseline. Correspondingly, when testing the role of depression at baseline in the onset of suboptimal sleep durations at follow-up, 1,076 (15.1%) participants who experienced short sleep or long sleep at baseline were excluded from the sample of 7,146. This left two analytic samples of 6,521 and 6,070, respectively (***Figure 6.2***).

Figure 6.2 **Flow chart of the analytic sample for imputed data**



6.3.2. Study variables

6.3.2.1. Sleep Duration

Sleep duration was assessed at combined waves 2-4 (2004-2008) and waves 6-8 (2012-2016). These were demarcated by "≤5hrs" (i.e., short sleep), ">5-<9hrs" (i.e., optimal-sleep), and "≥9hrs" (i.e., long sleep).

6.3.2.2. Subclinical Depression

The CES-D[292] was used to assess self-reported experiences of depression over the past week. The scale was reduced by a single item (i.e., "*whether their sleep was restless during the past week*"), as this item iterated sleep estimations. Scores were summed to generate a total discrete score, ranging 0-7 ('*no depression*' to '*depression*'), then dichotomised by ≥4.

6.3.2.3. Covariates

Covariates for the genetic analyses included age; age^2; sex; and 10 PCs.

6.3.4. Statistical Analyses

6.3.4.1. Genetic Analyses

The genome-wide genotyping was performed at UCL Genomics in 2013-2014 with ESRC funding.

6.3.4.2. Quality Control

SNPs were excluded if they were non-autosomal, had MAF <1%, more than 2% missing genotype data, or Hardy-Weinberg Equilibrium $p<^{10-4}$. Samples were removed based on call rate (<0.99), heterozygosity, relatedness, or inconsistencies between recorded sex phenotype and genetic sex. To ensure ancestral homogeneity, self-reported ethnicity was combined with genetic ancestry analyses, estimating ancestry via PCA, and removed participants with ancestral admixture (n=65). Post-imputation, variants with INFO>0.80, low linkage disequilibrium (R^2<0.1), and Hardy-Weinberg p>10−5 were retained, with 179,780 variants kept for further analyses.

6.3.4.3. Polygenic Scores (PGS)

PGS for sleep duration, short sleep, and long sleep were calculated using summary statistics from UK Biobank GWAS.[412,419] To calculate PGS for depression, summary statistics from GWAS of MDD was conducted by the Psychiatric Genomics Consortium (PGC) encompassing n=1331010 participants.[417] All PGSs here were calculated using a six p-value threshold (P_T; i.e., 0.001, 0.01, 0.05, 0.1, 0.3, and 1) using PRSice (Table S6.1).[420] To estimate the strength of the polygenic score, information was used on sample size (n; total size of the training and target samples in case/control studies, n is the sum of the number of cases and number of controls), total number of independent markers in the polygenic score (m), lower and upper P-values to select markers into polygenic score, proportion of variance explained by genetic effects in the training sample, and the genetic variance for each trait included in the analyses as reported in the original articles.[412,417,419] The strength of the PGSs was estimated for each trait across all P_T using the Additive Variance Explained and Number of Genetic Effects Method of Estimation (AVENGEME) package

implemented in R (Table S6.1).[421,422] This is a widely used tool to estimate the statistical power of PGSs.[403,423] Because the same traits in the training and testing samples were included, estimating of cov12 is not required, as it is the same as the genetic variance (*vg*1); thus, cov12 was omitted from the polygenescore function of this approach. AVENGEME further requires pi0 as an input in the calculations of the power of PGSs. In the present study, the default value of pi0, that is zero, was used, which may give lower power than other values. These estimates allowed selection with P_T to for each polygenic score to use in the analyses. Analyses showed that the ultimate P_T was 0.001 for the PGSs for sleep duration (m=39476, R^2=0.003, P=2.12×10^{-5}), short sleep (m=52197, R^2=0.004, P=6.52×10^{-08}), long sleep (m=24262, R^2=0.011, P=6.47×10^{-18}), and depression (m=63824, R^2=0.001, P=0.003). Although the PGSs for sleep duration, short sleep and depression at the chosen thresholds followed a normal distribution, the PGS for long sleep followed a multimodal distribution at the 0.001 P_T. This is not uncommon as PGS derived using the P_T+ clump approach will often include only a small number of SNPs when using a stringent p value threshold and may therefore not fit a normal distribution.[397] Thus, the PGS for long sleep at the 0.01 P_T (m=127099, R^2=0.003, P=5.79×10^{-06}) was used, which did not violate the assumption of normality.[424] The estimated predictive accuracy for PGSs can be found in Table S6.1. All PGSs were standardised. Correlations between PGSs and phenotypic data ranged $^{-}$-0.057-$^{+}$0.048 (Table S6.2).

6.3.4.4. Multiple Imputation

Missingness from baseline to follow-up, ranged 0.0-46.7% across all variables. As with all earlier studies, the imputation of the missing values yielded a minimal error for continuous (NRMSE=0.09%) and categorical (PFC=0.14%) variables, and a comparison of imputed and observed data indicated homogeneity between samples (Table S6.3).

6.3.4.5. Association Analyses

Logistic regressions, reported as OR with CI, were used to test whether PGSs for sleep duration, short sleep, and long sleep were associated with the onset of depression during an average 8-year follow-up period. Using multilinear and multinomial regressions, associations were investigated between PGS for depression and overall sleep duration, and onset of short sleep and long sleep during follow-up. Here, standardised regression coefficients (β) and RRR, respectively, with SE and CI, denote the unit increase in overall sleep duration and the relative risk of short sleep and long sleep, as compared to optimal-sleep (the reference category). Sleep duration was modelled continuously with quadratic (squared) terms to account for nonlinearity. When significant linear and quadratic effects were detected, the linear effect took lower-order and was subsumed under the quadratic effect. Models were fitted to understand the role of covariates on associations: Model 1 was unadjusted; Model 2 controlled for baseline age, age^2, sex and 10 PCs.

6.3.4.6. Sensitivity Analyses

Five sets of sensitivity were performed to measure the robustness of the main results. First, to test whether associations were dependent on the categorisation of depression, so analyses were repeated using continuous scores. Second, phenotypic associations, using self-reported sleep duration, short sleep, long sleep, and depression, were tested to assess consistency with the genetic findings. Due to the likelihood of socioeconomic, environmental, and behavioural confounding in phenotypic studies, these sensitivity analyses were additionally adjusted for education, wealth, smoking status, physical activity, BMI, triglycerides, and limiting longstanding illness. The breakdown of the analytic sample for phenotypic associations with missingness, exclusions, and attrition across waves can be found in the supplement (2). Third, although exploratory studies do not strictly require multiplicity adjustment, confirmatory studies do, so analyses were corrected for the total number of regressions per outcome measure (i.e., two tests for each, resulting in an *p*-value threshold change from 0.05 to 0.025).[425] Fourth, to ensure consistency with results from

imputed data, analyses were repeated using complete cases. Finally, since the clinically significant CES-D is based on an eight-item scale with a cut-off threshold of 4,[292] it was important to ensure that results from the reduced score were consistent with the original.

6.4. Results

6.4.1. Descriptive Statistics

The details of the sample at baseline are given in **Table 6.1**. There were no notable differences in participant characteristics between the analytic samples when the exposures were overall sleep duration, short sleep, and long sleep (*n*=6,521) versus depression (*n*=6,070). Participants, with an average age of 65 years (±9), were followed up to 12 years (M=8; range=4-12). At baseline, mean sleep duration was 6.97 hours a night (±1.24); 10.47% (*n*=755) of participants reported ≤5 hours a night, and 4.49% (*n*=321) reported sleeping ≥9 hours a night, whereas 15.27% (*n*=625) of all older adults reported depression. At the end of the follow-up period, mean sleep duration was 6.92 (±1.14); 15.27% (*n*=1,091) of participants reported sleeping ≤5 hours a night, and 4.76% (*n*=340) reported sleeping ≥9 hours a night, while 11.47% (*n*=820) of all older adults reported the experience of depression.

6.4.2. PGSs for sleep duration, short sleep, and long sleep in depression onset

Relationships between PGSs for sleep duration, short sleep, and long sleep in onset of depression during the average 8-year follow-up are presented in **Table 6.2**. One standard deviation increase in PGS for short sleep was associated with an average increase of 14% in odds of developing depression during the follow-up period in the fully adjusted model (Model 2: OR=1.40; CI=1.03-1.25). However, there was no significant association of the PGS for sleep duration (Model 2: OR=0.92, CI=0.84-1.00) and long sleep (Model 2: OR=0.97, CI=0.89=-1.06) and the onset of depression during the same follow-up period.

Table 6.1 Sample characteristics

Variable		Complete Sample (N = 7,146)		Analytic Samples: Longitudinal depression sample (N = 6,521)		Analytic Samples: Longitudinal sleep duration sample (N = 6,070)	
		N / Mean (SD)	% / Range	N / Mean (SD)	% / Range	N / Mean (SD)	% / Range
Age (years)		64.83 (9.52)	50-99	64.66 (9.39)	50-99	64.72 (9.52)	50-99
Sex	Male	3,296	46.12	3100	47.54	2873	47.33
	Female	3,850	53.88	3421	52.46	3197	52.67
Sleep Duration	Short Sleep ≤5 hrs	755	10.57	639	9.80	-	-
(Baseline)	Optimal Sleep >5 - <9 hrs	6,070	84.94	5592	85.75	6070	84.94
	Long Sleep ≥9 hrs	321	4.49	290	4.45	-	-
Sleep Duration	Short Sleep ≤5 hrs	1,091	15.27	951	14.58	629	10.36
(Follow-up)	Optimal Sleep >5 - <9 hrs	5,715	79.98	5263	80.71	5206	85.77
	Long Sleep ≥9 hrs	340	4.76	307	4.71	235	3.87
Depression	No	6,521	91.25	6521	91.25	5592	92.13
(Baseline)	Yes	625	8.75	-	-	478	7.87
Depression	No	6,326	88.53	5986	91.80	5494	90.51
(Follow-up)	Yes	820	11.47	535	8.20	576	9.49

Notes: ELSA, waves 2–8; N = observations; M = mean; SD = standard deviation; % = percentage frequencies.

Table 6.2 Relationships of polygenic scores for sleep duration, short sleep, and long sleep with onset of depression during an average 8-year follow-up

Models	Depression		
	OR (*SE*)	**95% CI**	***p***
Polygenic score for sleep duration			
Model 1: Unadjusted model [a]	0.914 (0.041)	0.838-0.997	0.044*
Model 2: Model 1 + age, age^2, sex, and 10 PCs	0.916 (0.041)	0.839-1.001	0.053
Polygenic score for short sleep			
Model 1: Unadjusted model [a]	1.122 (0.051)	1.027-1.226	0.011*
Model 2: Model 1 + age, age^2, sex, and 10 PCs	1.140 (0.056)	1.035-1.255	0.008*
Polygenic score for long sleep			
Model 1: Unadjusted model [a]	0.968 (0.043)	0.887-1.057	0.466
Model 2: Model 1 + age, age^2, sex, and 10 PCs	0.973 (0.044)	0.890-1.063	0.544

Note. PCs = principal components; OR = (odds ratio); SE = standard error; CI = confidence interval; p = significance value.
[a] Baseline caseness of outcomes were omitted from analyses. Alpha values have been adjusted to account for multiple testing. * denotes significance at <0.001.

6.4.3. PGS for depression in overall sleep duration, and short sleep and long sleep onset

Relationships between PGS for depression in overall sleep duration, and onset of short sleep and long sleep during an 8-year follow-up are presented in **Table 6.3**. In the fully adjusted model (2), no significant associations were observed between PGS for depression and future overall sleep duration (β=-0.02; CI=-0.04-0.00), or short sleep (RRR=1.05, CI=0.97-1.15), and long sleep (RRR=0.97, CI=0.85-1.10) by the end of the follow-up period.

A conceptual diagram of all PGSs and phenotypic associations are illustrated in ***Figure 6.3***.

Table 6.3 Relationships of polygenic score for depression with overall sleep duration, and onset of short sleep and long sleep during an average 8-year follow-up

Models	Sleep duration			Short sleep[c]			Long sleep[c]		
	β (*SE*)	95% CI	*p*	RRR (*SE*)	95% CI	*p*	RRR (*SE*)	95% CI	*p*
Polygenic score for depression									
Model 1: Unadjusted model [a b]	-0.001 (0.002)	-0.005-0.002	0.452	1.043 (0.044)	0.960-1.133	0.324	0.972 (0.065)	0.854-1.108	0.675
Model 2: Model 1 + age, age^2, sex, and 10 PCs	-0.002 (0.002)	-0.005-0.002	0.407	1.055 (0.045)	0.970-1.148	0.212	0.966 (0.065)	0.846-1.103	0.607

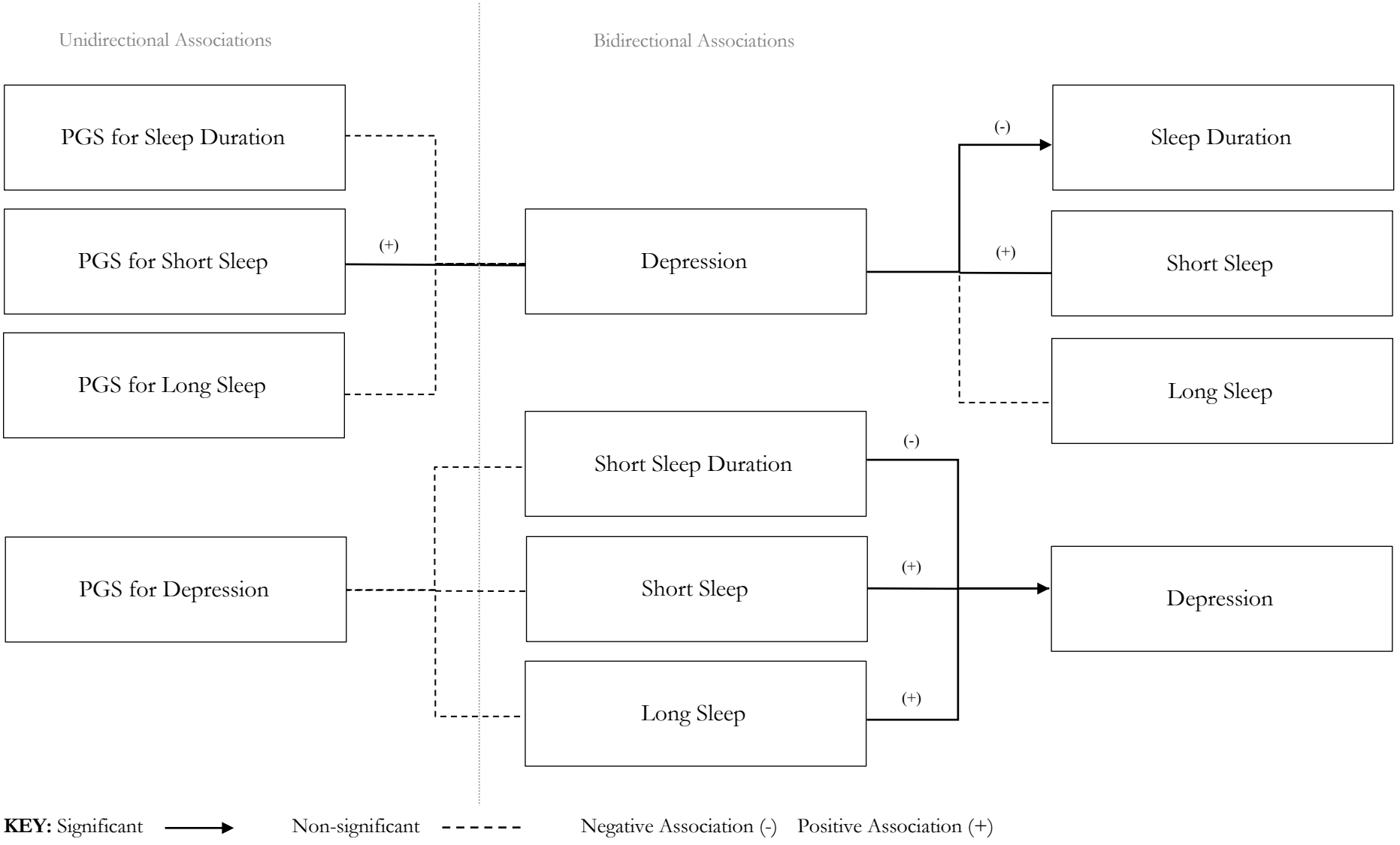
Note. PCs = principal components; β = standardised regression coefficient; RRR = relative risk ratios; SE = standard error; CI = confidence interval; p = significance value. Alpha values have been adjusted to account for multiple testing.

[a] Baseline caseness of outcomes were omitted from analyses.

[b] Sleep duration squared was included in sleep duration models to account for non-linearity.

[c] Baseline comparison was optimal sleep.

Figure 6.3 **Conceptual diagram of relationships between polygenic score for sleep duration, short sleep, long sleep or depression and phenotypic overall sleep duration, short sleep, long sleep, and depression**



6.4.4. Sensitivity Analyses

The results from the first set of sensitivity analyses that used continuous scores for depression followed the same pattern as those found in the main analyses, therefore, the categorisation of depression did not bias results (Table S6.4). The second set of sensitivity analyses between phenotypic associations showed that overall sleep duration was associated with lower odds of depression onset (Model 2: OR=0.79, CI=0.74-0.84, p<0.001). However, short sleep (Model 2: OR=2.58, CI=2.05-3.26, p<0.001) and long sleep (Model 2: OR=1.58, CI=1.07-2.33, p=0.022) were associated with higher odds of depression onset (Table S6.5). Depression was associated with overall sleep duration (Model 2: β=-0.02, CI=-0.03- -0.00, p=0.012) and short sleep onset (Model 2: RRR=1.31, CI=0.98-1.75, p=0.050), but not long sleep onset (Model 2: RRR=1.02, CI=0.62-1.66, p=0.944; Table S6.6). The third set of sensitivity analyses correcting for multiple testing did not influence the results. The fourth set of sensitivity analyses that used complete cases followed the same pattern as those in the main analyses (Table S6.7-8; the analytic sample formation for this study can be found in *Figure S6.1*). The final set of analyses that assessed consistency between the original and reduced CES-D scores revealed that results were materially unchanged (Tables S6.9-10).

6.5. Discussion

To our knowledge, this is the first study to use polygenic predisposition to prospectively investigate directionality between suboptimal sleep durations and depression, in a large population-representative sample of older adults. Results show that genetic predisposition to short sleep was strongly associated with the onset of depression over an average 8-year period, but genetic predisposition to overall sleep duration and long sleep was not. During the same follow-up period, polygenic predisposition to depression was not associated with overall sleep duration, short sleep, or long sleep among older adults, suggesting that different mechanisms underlie the relationship between depression and the subsequent onset of suboptimal sleep durations in older adults.

Findings were, by and large, upheld in a comprehensive set of sensitivity analyses highlighting their robustness.

Results showed that suboptimal sleep durations were experienced by 15% or less of an otherwise healthy, non-clinical sample of English older adults. Although there was no change to the average sleep time of seven hours per night, the 43% increase in percentage incidence of short sleep echoes earlier evidence.[61] This within-person change may reflect age-related changes in sleep patterns,[66] but it is inconsistent with reviews that have cast doubt on the proliferation of suboptimal sleep durations among the general population.[64,96] It is conceivable that an increased awareness of poor sleep, along with the emergence of sleep medicine, have led to observed rises in self-reported sleep problems and clinical sleep disorder diagnoses.

Corresponding to earlier observational evidence,[61] levels of depression also increased over the average follow-up period of 8 years. In line with hypotheses, results showed that polygenic predisposition to short sleep was related to between-person variation in depression. This contradicts a MR study,[426] that found no causal relationship between short sleep (nor overall, or long sleep duration) and depression in either direction using IVW, weighted median (WM), and MR Egger methods. However, the definitional cut-off point was <7hrs, as compared to ≤5hrs in the present study. Although the use of polygenic risk prediction is a methodological advancement, results are consistent with twin studies,[414] and findings highlighting a positive genetic correlation between short sleep and depression in adults aged 40-69.[412] Several mechanisms have been theorised to translate short sleep to depression, including electroencephalogram abnormalities (e.g., prolonged time spent in REM sleep), abnormal circadian rhythms,[427] and HPA-axis hyperactivity, which is closely linked to impaired sleep continuity and reduction of SWS.[428] Evidence is extended by demonstrating that common genetic markers for short sleep also play an important role the incidence of depression in older adults. Owing to the nature of genetic risk,

coupled with high rates of depression and suboptimal sleep durations among the population, the modest effect sizes found in the present study are plausibly of clinical and public health importance.

In agreement with meta-analytic results that combined data on 23,663 participants from seven prospective studies,[115] table five in the supplementary shows that phenotypic self-reported long sleep was a risk factor for the onset of depression during the average 8-year follow-up in older adults. In addition, overall phenotypic sleep duration was negatively associated with depression, which aligns with earlier work.[119] However, contrary to hypotheses, these relationships were not replicated in the genetic analyses, nor were they in two MR studies that focused on overall sleep duration.[132,429] The first that found that overall sleep duration was not causally associated with depression, the second that found it had a 19% protective effect. It is plausible that these discrepancies between phenotypic and genetic associations are attributable to the strength of the genetic instruments. Specifically, in the present study no significant relationships were found of polygenic predisposition for overall sleep duration or long sleep with onset of depression. Congruently, no associations were observed between polygenic predisposition to depression in onset of long sleep during the same follow-up period. Together, these results suggest that other underlying factors drive the nexus of overall sleep duration, long sleep, and depression in older adults. Inflammation and metabolic abnormalities are two such potential factors that could account for increases in long sleep[87] and depression.[153]

Polygenic predisposition to depression was not associated with overall sleep duration, nor short sleep or long sleep onset, but on the same basis in phenotypic data, the present study echoes earlier assertions[122,430] that depression is a risk factor for the expression of short sleep, and is negatively associated with overall sleep duration. However, in line with the genetic findings, depression did not precede long sleep. This contrasts observational evidence put forward that depression has a

curvilinear association with sleep duration, so is salient to both short sleep and long sleep.[118,121] An appropriate next step for future study is to test causal sequences using MR for observed polygenic associations.

6.5.1. Strengths and Limitations

This was a novel study that explored directionality between suboptimal sleep durations and depression in older adults, using polygenic risk prediction and phenotypic evidence. There are several other strengths and non-specific limitations to the present study that apply also to the syndicate of studies in this thesis. These are, therefore, more extensively discussed in Chapter 8. However, it is important to note here that the phenotypic sensitivity analyses did not account for physical or mental comorbidities, nor relevant medications that can affect sleep duration and depression. This is because of limited data availability across a broader number of waves in this study. Additionally, classical depression, typically associated with reduced sleep, and atypical depression, often linked to increased sleep, were analysed within the same sample.[431] This may have introduced heterogeneity into the analyses, potentially attenuating associations between sleep duration and depression by masking distinct underlying biological or behavioural mechanisms.

6.5.2. Conclusion

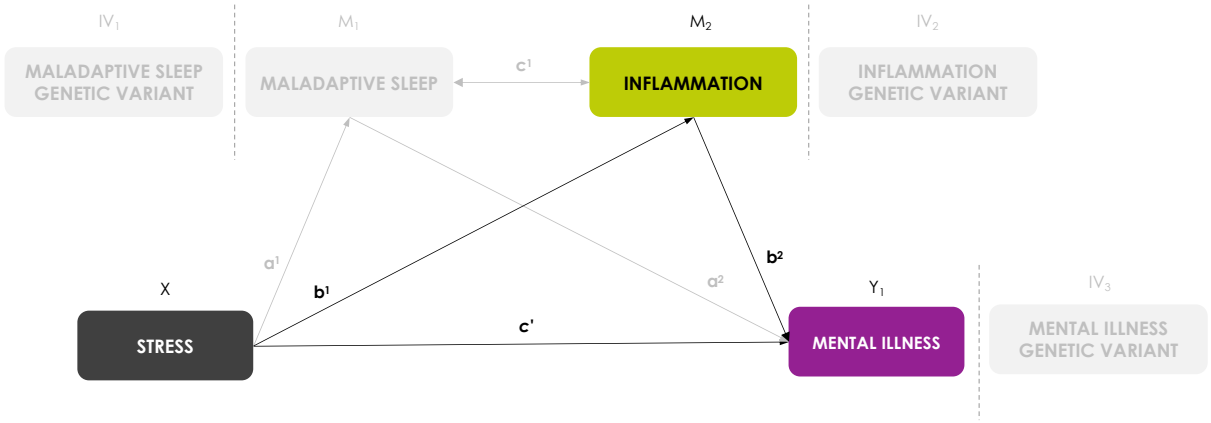
Here, important groundwork is laid for future investigations using polygenic risk prediction to understand associations between suboptimal sleep durations and depression. Polygenic predisposition to short sleep was associated with onset of depression, but polygenic predisposition to sleep duration and long sleep were not. Polygenic predisposition to depression was also not associated with overall sleep duration, short sleep, or long sleep onset. Evidence is provided of molecular mechanisms involved, with an indication of the direction of effects. Future research should focus on the clinical utility of these results, with genetic-medical integration used to improve the quality of care.

CHAPTER 7. COVID-19 STRESS, INFLAMMATION, AND DEPRESSION

7.1. Chapter overview

This chapter explores whether elevated inflammatory biomarkers measured pre-pandemic would be positively associated with increased symptoms of depression experienced during the COVID-19 pandemic. It also examines the incidence of depression in English older adults during this period. Findings have been published in *Translational Psychiatry* (Hamilton et al., 2021).[432] It is positioned last as it completes the framework, by showing clearly how inflammatory processes can influence mental health, with a stressor that is clearly defined in time, (i.e., COVID-19 did not exist when the inflammatory markers were measured), so there can be no doubt about temporality.

Figure 7.1 **The section of the conceptual framework (*Figure 1.10*) addressed in Chapter 7**



7.2. Introduction

The outbreak of Sars-CoV-2 (COVID-19) infection led to over 7,600,000 infections within the UK, 231,550,000 cases worldwide, and a mortality rate among the infected exceeding 2%.[433] The mental health sequelae of the pandemic became a distinct public health concern.[434,435] Older adults were among those most vulnerable to fatal incidence of COVID-19,[436] which led to intense fears of contagion and a heightened awareness of individual fragility. Reports of affective responses

were diverse, from emotional distress, depression, irritability and insomnia to fear, anxiety, despair, guilt and anger.[437] The population worldwide was subjected to intrusive pandemic containment measures intended to limit pathogen transmission, reduce prognostic severity, and minimise mortality. Containment measures limited daily routines such that social and economic activity were substantially reduced, with access to healthcare and care provisions being interrupted.[438,439] These mitigation efforts came at the expense of psychological wellbeing,[440] with a rise in psychosocial stressors ranging from social isolation and financial insecurity[441] to increased rates of domestic discord.[442] Equally, harmful behaviours such as high-risk alcohol consumption,[443] dysfunctional eating,[444] and medical care avoidance[438] were on the rise, with Buss and colleagues (2023)[340] reporting an increase in the prevalence of smoking and high-risk drinking, at 17.7% and 32.2% respectively, from pre-pandemic levels (n=47,799). The proliferation of pandemic-related stress raised concerns over the psychological vulnerability of older individuals.[445,446]

COVID-19 resulted in a dislocation of people lives that had very broad effects. Studies on the emotional responses to earlier epidemics offered insight into the deleterious impact of highly virulent infectious disease on community mental health that impacts sectors of the population differently.[447,448] Further, given the pre-pandemic inequalities in mental wellbeing, similar disproportionate patterns of vulnerability were anticipated during COVID-19.[449] Research on responses to the COVID-19 pandemic exposed disparities in the distribution of distress, the severity of mental illness, and variation in the magnitude of change from pre-pandemic status.[450] Demographic factors contributing to effects were found to explain this variation, with less advantaged groups, females, ethnic minorities, the disabled, and those with pre-existing physical or mental conditions being at greatest risk to adverse emotional responses.[436,437,449,451]

CRP and fibrinogen have been found to predict poor course of depression,[452,453] and both are established markers of inflammation in relation socioeconomic status, social isolation, loneliness,

and other factors.[15,454,455] However, meta-analytic surveys of existing evidence have concluded that links between CRP concentration and future depression in both adults and children are weak and inconsistent.[273,456] Such associations may be more likely to emerge under conditions of severe stress. It is plausible, therefore, that heightened antecedent inflammation primes vulnerable individuals to increased depression in the face of pandemic-related challenges, particularly when those psychosocial stressors are perceived as unpredictable and uncontrollable. The pandemic may function as a catalyst for neuroimmune dysregulation to increase risk of depressive symptoms, but our understanding of these processes is limited by a lack of studies linking pre-pandemic inflammation to mental health outcomes during the pandemic. The current study is, therefore, aimed to examine the incidence of depression in older adults during the COVID-19 pandemic considering inflammatory levels and depression before the pandemic.

7.2.1. Hypotheses

We postulated that individuals with higher systemic inflammation pre-pandemic would present higher depression during the pandemic.

7.3. Methods

All measure details and methods are described in Chapter 2, so are not repeated here.

7.3.1. Study Design

Fully anonymised data were drawn from ELSA.[288] The COVID-19 Substudy started in June 2020 to capture a robust selection of psychosocial experiences during the pandemic, using an online platform or computer-assisted telephone interviews (CATI). The present study used data from the COVID-19 Substudy (2020), and ELSA W8 (2016/17) and W9 (2018/19). The COVID-19 Substudy had a 75% response rate (n=7,040), of which 5,820 were core respondents, while the remaining were non-core (younger partners of the core respondents from whom data was

collected). There were no missing data on depression. Of the 5,820 core respondents, 3,830 had measures of CRP and 3,591 of fibrinogen in waves 8 and 9. After exclusions on missing data for covariates, the analytic samples were 3,574 for CRP analyses and 3,314 for fibrinogen (***Figure 7.2***).

7.3.2. Study Variables

7.3.2.1. Exposures

Inflammatory Biomarkers. Two inflammatory markers were analysed, CRP (mg/L) and fibrinogen (g/L). Samples were collected for half of the participants in W8 and the remaining half during W9, then data were combined. CRP values >20mg/L were excluded from analyses (*n*=79). Using a well-recognised clinical demarcation of inflammation in the adult population,[457] CRP was dichotomised low (<3mg/L) and high [≥3mg/L]. CRP and fibrinogen were treated as continuous variables, with higher values indicating greater levels of inflammation.

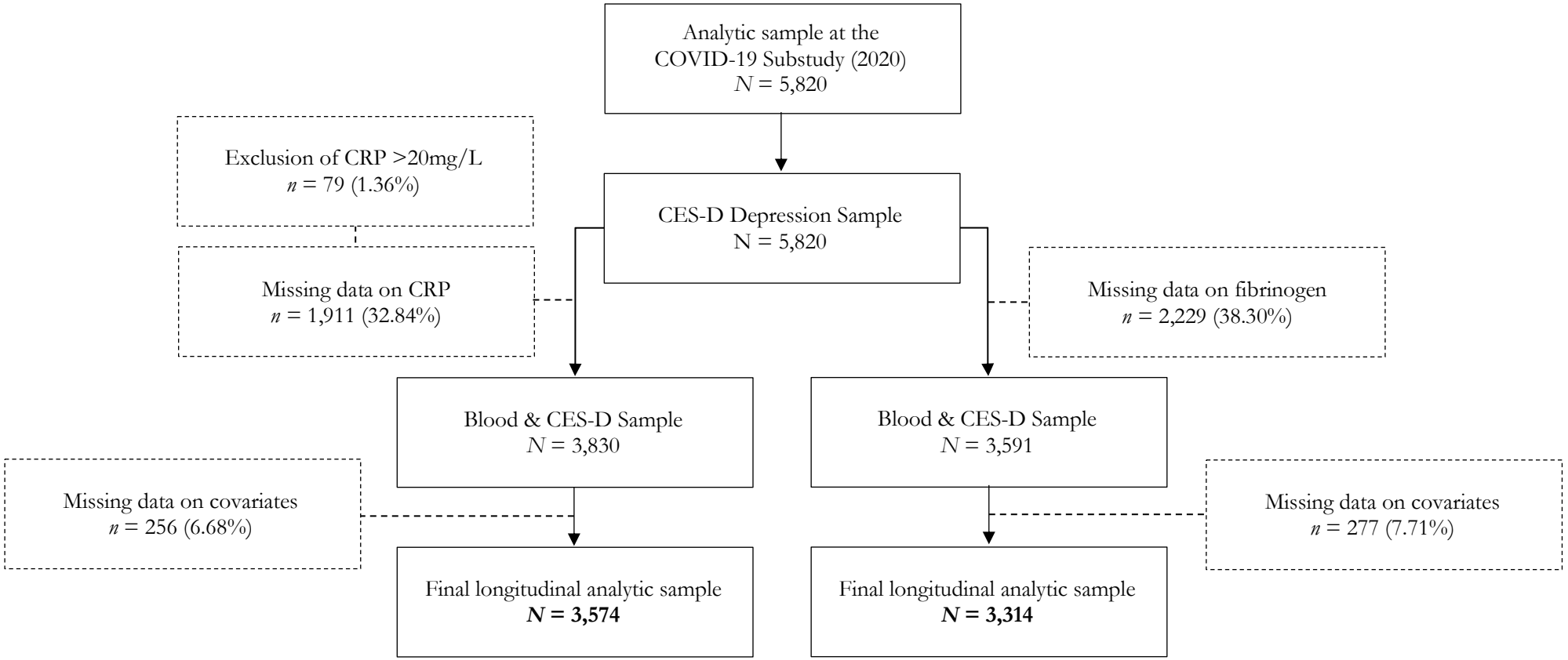
7.3.2.2. Outcome

Subclinical Depression. The CES-D[292] was used to assess depression '*over the past week*' in the COVID-19 Substudy and ELSA W8 and W9. However, one item (i.e., "*felt sad much of the time*…") was unintentionally omitted from the COVID-19 Substudy, so for comparability, an analogous seven-item scale was calculated for pre-pandemic waves (8/9). The internal consistency (α) in this sample was 0.75 across waves 8 and 9, and 0.80 in the COVID-19 Substudy, indicating good scale reliability. A threshold of ≥4 was used to indicate subclinical depression caseness, which produces comparative results to the 16-symptom cut-off in the 20-item CES-D scale.[293]

7.3.1.3. Covariates

Variables considered likely to confound the analyses were selected *a priori,* comprising: *demographic variables*: age and sex; *socioeconomic variables*: education, and wealth; *health behaviours*: smoking status,

Figure 7.2 **Flow Chart of the COVID-19 Substudy Analytic Sample**



alcohol consumption, and physical activity; *clinical variables*: plasma triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and limiting longstanding illness.

7.3.3. Statistical Analyses

7.3.3.1 Association Analyses

Longitudinal associations between inflammatory markers at baseline (combined waves 8-9; 2016/19) and depression during the COVID-19 Substudy (2020) were assessed with logistic regressions. Separate analyses were carried out for each inflammatory marker. ORs were computed with CI for the presence of depression among people with high CRP, with the reference category being low CRP. The analyses of fibrinogen report the OR of depression per unit increase in fibrinogen concentration. The basic model (1) adjusted for pre-pandemic depression only. Subsequent models additionally adjusted for *demographic variables* (Model 2), *socioeconomic variables* (Model 3), *health behaviours* (Model 4), and *clinical variables* (Model 5). The final model (6) included all covariates.

7.3.3.2. Sensitivity Analyses

The first sensitivity analysis tested whether the associations found in the main analyses depended on the binary classification of depression (using the CES-D threshold); instead, continuous CES-D scores were analysed. The results are presented as β coefficients with SE. Exposure to COVID-19 may have led to an overestimation of emotional responses,[458–460] so the second sensitivity analysis tested whether the results remained unchanged when participants with possible COVID-19 infection were excluded. We assessed exposure to COVID-19 in two ways. First, participants were asked whether they had been hospitalised for COVID-19. Second, the presence of at least two of the three core coronavirus symptoms was evaluated, as defined by the UK NHS: "*high temperature*"; "*new continuous cough*"; and "*loss of sense of smell or taste*". Those hospitalised or those meeting the NHS criteria for core symptoms were categorised as possible COVID-19 cases. In

the third sensitivity analysis, the exclusion of very high CRP values was reassessed on the basis of arguments put forward by Giollabhui et al. (2020).[355] The regression models were therefore repeated, including individuals with CRP values ≥20mg/L in the depression group. The fourth sensitivity analysis evaluated whether associations between CRP and later depression depended on the binary division of CRP into normal and high categories. Therefore, continuously distributed CRP values were included into the regression models. Fifth, BMI was added as an additional covariate. BMI was not included in the primary analyses because conditioning on BMI may have introduced collider stratification bias,[309,310] and because the sample size was reduced through missing data on height and weight. The sixth sensitivity analysis repeated the analyses with alcohol intake modelled across the full range of consumptions (8 points from '*almost daily*' to '*not at all in the past 12 months*') instead of binary categorisation. The seventh analysis, it was considered that individual's exposure to different types of stress during the pandemic may be responsible for the results. Therefore a suite of measures of personal exposure to the coronavirus was identified (i.e., a combined measure of NHS core symptoms; personal hospitalisation; or household member hospitalisation and/or death due to coronavirus), together with the financial impact of the pandemic (current personal financial circumstance on a 5-point scale ["*much worse off*" to "*much better off*", as compared to pre-pandemic status), and a difficulty in accessing services during the pandemic (including access to a bank/cashpoint, supermarket, hospital, and/or pharmacy on a 4-point scale ["*easy*"; "*difficult*"; "*unable*"; "*unwilling*"]). These variables were controlled for to test whether the association between pre-pandemic inflammation and depression during the pandemic was reduced when these factors were taken into account.

7.4. Results

7.4.1. Descriptive Statistics

Participant baseline characteristics are displayed in **Table 7.1**. CRP and fibrinogen were positively correlated (r=0.481, p<0.001). There were no notable differences in participant characteristics

Table 7.1. Sample characteristics for the CRP and fibrinogen analyses

Variable		CRP (*n* = 3,574)			Fb (*n* = 3,314)		
		Obs.	Mean (SD) / N (%)	Range	Obs.	Mean (SD) / N (%)	Range
Age		3,574	67.91 (8.38)	52-90	3,314	67.87 (8.42)	52-90
Sex	Male	1,548	43.31%		1,439	43.42%	
	Female	2,026	56.69%		1,875	56.58%	
Education	Higher Education	1,492	41.75%		1,362	41.10%	
	Tertiary Education	413	11.56%		389	11.74%	
	Secondary/Primary Education	910	25.46%		850	25.65%	
	Alternative or No Education	759	21.24%		713	21.51%	
Wealth	Lowest Quintile (1)	428	11.98%		411	12.40%	
	2nd Quintile	558	15.61%		514	15.51%	
	3rd Quintile	805	22.52%		747	22.54%	
	4th Quintile	917	25.66%		848	25.59%	
	Highest Quintile (5)	866	24.23%		794	23.96%	
Smoking Status	Non-smoker	2,916	81.59%		2,701	81.50%	
	Smoker	658	18.41%		613	18.50%	
Alcohol Consumption	Less than daily	2,886	80.75%		2,680	80.87%	
	Daily (5-7 per week)	688	19.25%		634	19.13%	
Physical Activity	Sedentary (0)	443	12.40%		418	12.61%	
(Vigorous/Moderate)	1	479	13.40%		443	13.37%	
	2	1,116	31.23%		1,042	31.44%	
	3	652	18.24%		603	18.20%	
	Active (4)	884	24.73%		808	24.38%	
Triglyceride (mmol/l)		3,574	1.43 (0.69)	0.3-4.5	3,314	1.43 (0.69)	0.4-4.5
HDL (mmol/l)		3,574	1.60 (0.47)	0.4-4	3,314	1.59 (0.47)	0.4-4
LDL (mmol/l)		3,574	2.91 (0.98)	0.4-7.6	3,314	2.91 (0.98)	0.4-7.6
Limiting Longstanding Illness	No	2,534	70.90%		2,329	70.28%	
	Yes	1,040	29.10%		985	29.72%	
COVID-19 NHS CORE Symptoms	No	3,491	97.71%		3,231	97.52%	
	Yes	82	2.29%		82	2.48%	
Hospitalisation for COVID-19	No	3,561	99.66%		3,301	99.64%	
	Yes	12	0.34%		12	0.36%	
CRP (log, ≤20 mg/L)		3,574	0.96 (0.60)	0.01-3.01	-	-	-
CRP (≤20 mg/L)	<3 mg/L	2,732	76.44%		-	-	-
	≥3 mg/L	842	23.56%		-	-	-
Fb (g/L)		-	-	-	3,314	3.23 (0.56)	1.6-6.5
Depression (Baseline CES-D)		3,574	1.02 (1.41)	0-7	3,314	0.08 (0.26)	0-1
Depression (Pandemic CES-D)		3,574	1.56 (1.88)	0-7	3,314	0.16 (0.37)	0-1
Depression (Baseline CES-D)	<4	3,317	92.81%		3,067	92.55%	
	≥4	257	7.19%		247	7.45%	
Depression (Pandemic CES-D)	<4	3,001	83.97%		2,773	83.68%	
	≥4	573	16.03%		541	16.32%	

Note. CRP = C-reactive protein; Fb = Fibrinogen; SD = standard deviation; NHS = National Health Service.

between the CRP (*n*=3,574) and fibrinogen (*n*=3,314) samples. Participants were ~43% male and ~57% female, with an average age of ~69.89 (±8.40; range=52-90). In both samples, the majority of participants were non-smokers (81.59%/81.50%), and only around one in five drank alcohol on most days of the week. Two-thirds reported no longstanding limiting illness (70.90%/70.28%), while over a third were engaged in moderate to vigorous physical activity (42.97%/42.58%). A small number of participants had been exposed to the coronavirus; 82 were symptomatic (2.29%/2.48%); 12 had been hospitalised (0.34%/0.36%). Before the pandemic 7.19% (CRP analysis) and 7.45% (fibrinogen analysis) had depression above threshold, and this increased to 16.03%/16.32% during the pandemic, confirming a large increase in incidence of depression.

7.4.2. Associations between inflammation and depression during the pandemic

Analyses are summarised in **Table 7.2**. CRP was positively associated with the incidence of depression. The crude odds ratio of 1.69 in model 1, adjusted for baseline depression (Model 1: OR=1.69; CI=1.38-2.08), was reduced to 1.40 (Model 6: OR=1.40 CI=1.12-1.73) after full adjustment. This indicates that the odds of depression during the COVID-19 crisis were increased by 40% among participants with high CRP concentrations pre-pandemic. Plasma fibrinogen was also associated with depression when unadjusted, and remained significant after adjusting for baseline depression, age, sex, education, wealth (Model 3: OR=1.23, CI=1.04-1.46), and clinical variables (Model 5: OR=1.22, CI=1.03-1.45). However, associations were attenuated and no longer significant after adjustment of health behaviours (Model 4: OR=1.16, CI=0.98-1.38), suggesting that these factors accounted substantially for the relationship between fibrinogen and depression. The odds for depression for every unit increase in fibrinogen were 12% , but it was not significant in the fully adjusted model (Model 6: OR=1.12, CI=0.94-1.34). The largest reduction in odds was observed in models 3 and 4, with an indication that wealth, physical activity, and smoking may partially explain the association between inflammation and depression during the pandemic.

Table 7.2. Longitudinal associations between pre-pandemic inflammatory markers and depression during the pandemic

Adjustments	CRP (*n* = 3,574)			Fb (*n* = 3,314)		
	OR (*SE*)	95% CI	*p*	OR (*SE*)	95% CI	*p*
Model 1: *adjusted for baseline depressive symptoms*	1.69 (0.18)	1.38-2.08	<0.001	1.29 (0.11)	1.09-1.52	0.003
Model 2: *Model 1 + adjustment for age and sex*	1.65 (0.17)	1.34-2.03	<0.001	1.26 (0.11)	1.07-1.50	0.007
Model 3: *Model 1 + adjustment for education and wealth*	1.57 (0.17)	1.27-1.93	<0.001	1.23 (0.11)	1.04-1.46	0.019
Model 4: *Model 1 + adjustment for health behaviours* [a]	1.50 (0.16)	1.22-1.85	<0.001	1.16 (0.10)	0.98-1.38	0.085
Model 5: *Model 1 + adjustment for clinical variables*[b]	1.59 (0.17)	1.29-1.97	<0.001	1.22 (0.11)	1.03-1.45	0.025
Model 6: *adjusted for all covariates*[c]	1.40 (0.16)	1.12-1.73	0.003	1.12 (0.10)	0.94-1.34	0.180

Note. CRP = C-reactive protein; Fb = Fibrinogen; OR = odds ratio; *SE* = standard error; CI = confidence interval; *p* = significance value
a *Health behaviours* = smoking status; alcohol consumption; physical activity.
b *Clinical variables* = triglyceride; high-density lipoprotein (HDL); low-density lipoprotein (LDL); limiting longstanding illness.
c All covariates = depression (CES-D ≥4); age; sex; education; wealth; smoking status; alcohol consumption; physical activity; triglyceride; high-density lipoprotein (HDL); low-density lipoprotein (LDL); limiting longstanding illness.

7.4.3. Sensitivity Analyses

The first sensitivity analysis modelled depression as continuous scores. Findings did not substantially deviate from the results of the main analyses (Table S7.1). The β adjusted for baseline depression, age, and sex (Model 1: β=0.23, CI=0.10-0.36, p<0.001) was 0.14 in the fully adjusted CRP model (Model 6: β=0.14, CI=0.01-0.27, p=0.034). The results for the prospective associations between fibrinogen and depression were significant in models 1-5 but no longer robust in the fully adjusted model (Model 6: β=0.07, CI=-0.04-0.17, p=0.202). The second sensitivity analysis showed that the associations between CRP and depression were mostly unaffected by additional

adjustment for coronavirus exposure (Table S7.2). Estimates of the relationship between fibrinogen and depression remained broadly similar after exposure to the coronavirus was taken into account. In the third sensitivity analysis, the magnitude of associations remained unchanged when analyses included very high CRP values. The fourth sensitivity analysis modelled CRP as a continuous measure. The association with depression during the pandemic remained significant in the fully adjusted model (Model 6: OR=1.18, CI=1.00-1.39, p=0.046; Table S7.3). The fifth sensitivity analysis introduced BMI as an additional covariate (Table S7.4). The sample size was reduced both for the CRP and fibrinogen analyses, resulting in reduced power. However, the association between CRP and depression (Model 5: OR=1.41, CI=1.12-1.79, p=0.004) and fibrinogen and depression (Model 5: OR=1.24, CI=1.03-1.50, p=0.026) remained significant when BMI was added to the models. In sensitivity analysis six alcohol consumption was modelled across 8 categories. The results were mostly unchanged from those of the primary analysis (Table S7.5). Finally, in the seventh sensitivity analysis, personal exposure to the coronavirus, the financial impact of the pandemic, and a difficulty in accessing services during the pandemic was conditioned on. The relationship between CRP and depression (Model 6: OR=1.70, CI=1.38-2.09, p<0.001; Table S7.6), and fibrinogen and depression (Model 6: OR=1.29, CI=1.09-1.52, p=0.003) was independent of these COVID-19 impact factors.

7.5. Discussion

This study sought to relate the magnitude of change in depression during the pandemic in older adults with earlier levels of systemic inflammation while taking into consideration pre-pandemic levels of depression. The results revealed that pre-pandemic CRP concentrations were positively associated with depression in the early months of the COVID-19 pandemic in England, independently of pre-pandemic depression, sociodemographic factors, behavioural, and health-related factors. Pre-pandemic fibrinogen concentration was also related to depression during the pandemic, but these associations were explained by covariates, notably health behaviours.

Infection with COVID-19 has been linked to subsequent severe psychiatric conditions,[435,461] but even in the general population without COVID-19 infection, increases in psychological distress have been substantial.[449,462–464] Inflammation is relevant to this dynamic for two reasons. First, psychological stress modulates immunity at cellular and molecular levels, as has been established in experimental and observational studies, which can lead to prolonged endocrine and immune dysregulation with deleterious health consequences.[178] Second, systemic inflammation is an important determinant of depression, and this association has been established in animal models,[364] studies of affective responses to pro-inflammatory medication,[465] along with population and clinical studies.[150,466–469]

Results suggest that the background level of systemic inflammation measured before the pandemic is associated with heightened depression during the stressful early phase of the pandemic. In the analytic models adjusted for age, sex and baseline depression, the odds of depression during June/July 2020 increased to 69% for high CRP and 29% for each unit increase in fibrinogen. Stress-induced sensitisation of the neuroimmune microenvironment,[178] neuroendocrine pathways[469] and inflammasomes[470] have been identified as potential mechanisms contributing to these findings. Although CRP and fibrinogen are positively correlated and both are reliable indicators of inflammation, each represent different aspects of inflammation. CRP is known to be a more sensitive neuroimmune biomarker, since patterns of change in plasma fibrinogen concentrations are rather more moderate.[296,471] This is likely due to fibrinogen being additionally involved in other physiological processes, such as haemostasis and angiogenesis.[472]

The origin of differences in pre-pandemic inflammatory levels governed the selection of covariates in these analyses. Systemic inflammation is inversely associated with socioeconomic status,[15] physical health,[457] and behavioural factors, such as smoking and sedentary behaviour.[473] Smoking

and sedentary behaviours are known to have increased in a subset of the population during the COVID-19 pandemic,[474,475] and during this same period, being less advantaged and having lower physical health were shown to predict greater psychological distress.[450,476] This health inequality during this period is unsurprising as in the years before the pandemic (2013-2019), Kock and colleagues (2021)[477] reported that the most disadvantaged occupational social grade, with children, experienced the highest smoking prevalence among groups. There is additional evidence that smoking[478] and physical inactivity[473] are related to inflammation and depression. Within the sample, modifiable health behaviours (i.e., smoking, inactivity, alcohol consumption) had the largest impact on the association between inflammation and depression during the pandemic, but even when these and other factors were taken into account, the relationship for CRP remained significant.

Sensitivity analyses confirmed that depression as continuous scores did not substantially deviate from the results of the main analyses. In addition, the magnitude of effects remained unchanged when analyses were performed after including individuals with CRP values of 20mg/L and above. The regression coefficients were only minimally affected by the additional adjustment of subjects who were exposed to the coronavirus. Modelling CRP as a continuous variable provided a similar pattern of results to those of the main findings. When testing also tested whether personal experiences during the pandemic affected the pattern of results. Exposure to stressors such as financial hardship, restricted access to services and COVID-19 infection among friends and family did not modify the primary results. This is not to imply that these factors do not contribute to psychological distress during the pandemic, but that their influence was independent of the links between inflammation and depression that were identified. Overall, these sensitivity analyses suggest that the conclusions have not been biased by the way that variables have been categorised.

Further research is needed to develop a complete picture of other psychological outcomes experienced during the pandemic due to neuro-immune persistence. In addition, an exploration

into other possible biomarkers could offer insight into the extent of biological mechanisms involved. This could confer targets for treatment in inflammation-induced psychiatric conditions and could be especially advantageous in reducing psychological burden during pandemics. Public health systems could become better equipped to manage population distress in the face of potential future widescale virulent outbreaks, and in doing so, the healthcare burden and public spending could be reduced.[479]

7.5.1. Strengths and Limitations

To the best of our knowledge, this was the first study to prospectively address inflammatory conditions prior to the COVID-19 pandemic in relation to depression during the pandemic while considering earlier levels of depression. In addition, few studies have explored the role of both CRP and fibrinogen in the experience of depression in this context. Pre-pandemic measures of inflammation were measured as part of routine data collection before COVID-19 emerged, so prior expectations could not bias results. The response rate for data collection during June/July 2020 (75%) was higher than in most studies of mental health during the pandemic. Despite concerns that the inclusion of participants who had been exposed to the coronavirus may lead to an overestimation of emotional responses, the inclusion of their data did not bias results. Nevertheless, conclusions should be interpreted with respect to limitations, three that are more critical in the current study. Depression was measured early in the pandemic, and it has been shown to fluctuate over time.[480] It is also not possible to be certain of inflammatory levels immediately before the pandemic since measures were taken 1-3 years earlier. However, other studies have demonstrated that inflammation is relatively stable over several years in the ELSA cohort.[481] Finally, research has shown that early life stress, unaccounted for in these analyses, can have long-lasting effects on immune function and may have contributed to raised inflammatory levels in later life.[481,482] This could represent an important factor for understanding the persistence of inflammation and its association with depression during the pandemic.

7.5.2. Conclusion

In a cohort of UK older adults, findings show that those with heightened inflammation before the pandemic were at most risk of developing depression in the early months of the COVID-19 crisis. Earlier immune dysfunction may be a key consideration in the development of depression during pandemics where psychosocial stressors are pervasive. The high prevalence of population distress has implications for community mental ill-health, public resources, national recovery and preparedness in the face of future virulent outbreaks.

CHAPTER 8. GENERAL DISCUSSION

Five empirical studies have been included to further the evidence and scientific understanding of the biobehavioural and genetic mechanisms that link stress to mental ill-health in older adults. Each study responded to a section of the overarching PNI and precision medicine framework (***Figure 1.10***). The emerging core piece was to understand the mechanistic role of the immune, endocrine, and neural systems, how this occurs in the face of genetic vulnerability, and how this can improve diagnostic sensitivity, in a way that could make it possible to intervene earlier.[10] Thus, this thesis was able to speak to combined mechanisms of mental ill-health, over cross-sectional and longitudinal timepoints, in a non-clinical population of older men and women in England. A number of methodologies were used, with a view to enabling a more precise targeting of groups for the better prediction, prevention, and treatment of disease. It combines techniques and principles across epidemiology, statistics, biology, genetics, behavioural science, economics, and precision medicine.

8.1. Biological Considerations

The molecular and mathematical drivers of immune and neuroendocrine communications have been long studied.[364,381,483] Results across studies one to three confirm that the evaluated biomarkers are, on average, temporally stable, despite individual trajectories varying widely, also shown elsewhere.[481] Critically, studies two and three within this thesis were able to provide an important characterisation of physiological activity across the integrative network through LPA. It revealed a pattern of multisystem dysregulation, with biological subgroups and gradients of risk identified. Each that were not formally considered together in this context. Study two and three reveal that stress has systemic influences on biology, and not just on isolated biomarkers alone was shown in study one. For this reason, uniform impacts on health across a population cannot then be assumed. Mechanistic precision medicine approaches should be exploited to further develop this line of enquiry. The findings from the LPA may give partial reason to the inconsistent findings in the

literature that explore biological processes in disease.[484,485] Particularly as it relates to the often irreconcilable findings between observational studies and randomised control trials, that this thesis offers a theorised method to resolve.[486,487] This also underscores the importance of considering the complex crosstalk between these systems in maintaining homeostasis,[358,363] rather than fixations on single biomarkers that can be fundamentally misleading from a biological perspective when used exclusively.[381] In this way it biomarker panels avoid relatively arbitrary single selections, based on ease of collection, assay, and analysis. Still, it is important to note the value of independent biomarkers, which helps to reduce noise, by isolating the most relevant biomarkers involved in maintaining health. Independent biomarker analyses, as in study one, serve as a foundation for validating latent profiles and other integrative models. Ultimately, both are mutually reinforcing. The LPA reveals systemic patterns and identifies holistic risk panel, while independent biomarker analyses deepen biological understanding. Together, they form a powerful toolkit for advancing PNI research and its application in personalised care.

Each biomarker has a unique role in maintaining health, but functionally they are involved in proliferation, differentiation, migration, and apoptosis of targeted cells.[488] Some biomarkers are more resistant to exogenous factors that are typically not controlled for in analyses.[489] They are characterised by interrelated pleiotropic, synergistic, and redundant actions that have afferent and efferent functional components.[365] Such factors should be among the various considerations when making biomarker selections. When this dynamic process is dysregulated, as supported by the results here, it contributes toward to varying concentrations of circulating biomarkers[367] that can contribute to diversity in disease sequelae.[178,490] This can make prediction more challenging and the interpretation of single biomarkers less intuitive. Particularly because the multicollinearity assumption in regressions mean that biomarkers are best modelled independently.[491] The latent variable modelling approach taken in studies two and three, similar to an earlier study of American adults,[492] allowed for a synchronised assessment of a diverse set of biomarkers. Three profiles

emerged in across these studies, but the results here are otherwise not directly comparable, as the selection of biomarkers differed rather considerably. Even so, the derived profiles here lend support to study one within this thesis, along with earlier research that reflects symmetry between biomarkers of the immune, nervous, and endocrine systems.[358,378,493,494]

8.2 Genetic Considerations

The findings across the first three studies extend previous evidence on PNI processes,[178,231,368] by showing that stress exposure is associated with immune and neuroendocrine biomarkers independently, and a greater probability of *high-risk* immune and neuroendocrine profile membership, irrespective of the genetic contribution of the PGS included in the model. The latter is a particularly important feature of this thesis. It is also a methodological advance over previous observational research where genetic contribution is rarely considered. It is well-established that genetic factors affect the magnitude of the immune and neuroendocrine response.[213] Inter-individual variability in biomarker concentrations and their respective binding proteins are partly the result of polymorphic variations in respective genes, while genes encoding biomarkers are candidate loci for diseases with an inflammatory basis.[213] Moreover, CRP,[495] fibrinogen,[495] cortisol,[496] WBCC,[220] and IGF-1[497] each have high heritability. Still, the role of genes in the circulation of these biomarkers in blood is complex and multiphasic,[498] insofar as genetic influences on these biomarkers varying across different biological stages or in response to environmental and physiological stimuli. Take cortisol for example, it is implicated in the elevation of inflammation, but it can paradoxically bind the glucocorticoid receptor (GR) and repress the expression of genes encoding pro-inflammatory cytokines.[499]All things considered, while SNPs associated with each biomarker only explained a small proportion of the variance in our phenotypic associations, where the magnitude or strength of associations was small, it is plausible that they confounded earlier evidence, such that their omission modestly inflated effect sizes or widened confidence intervals. It is, thus, clear from extant literature that genetic variation plays an important role in immune,

endocrine, and neural function and circulating levels in blood.[216,223,500] This thesis supports that immune and neuroendocrine coding genes influence these traits across studies one, two, and three. In studies two and three, the relative risk ratios were reduced by between 1-89 percent with the inclusion of demographic and genetic variables. As is common with narrow-sense heritability,[215] the genetic contribution to these traits tended to be small. When included in models independently for sensitivity, genetic variables accounted for up to one percent of the variance, but each reached statistical significance, indicating a relationship with the respective phenotypes that could bias results if unaccounted for. These values were small, but they represented cumulative explanatory power, reflecting aggregate genetic contribution, and in one instance, the role of suboptimal sleep on immune-neuroendocrine profiles was not robust enough to withstand genetic influence. Thus, results support the supposition that the inclusion of these genetic substructures remains key to increasing the ecological validity of observational studies. Therefore, controlling for them is a strength of this thesis.

Polygenic risk prediction using genetic scores in studies three and four proved a useful tool to point to directionality, and the phenotypic and genetic differences between suboptimal durations and subclinical depression associations in study four are persuasive in explaining why directionality between indices of sleep and depression has been obfuscating. However, these results could not speak to causality in the same way that MR does because of directional pleiotropy.[23] The method used in polygenic risk prediction could not be used to isolate SNPs exclusively associated with the exposure of interest, but it is a strong step toward unravelling issues of directionality. Although polygenic risk prediction has its limitations when compared to MR, the two approaches share several methodological similarities and often yield comparable results. Both exploit GWAS summary statistics and can be performed using individual-level or summary-level data. However, most polygenic risk applications, require individual-level data, except when estimating shared genetic aetiology. Importantly, both methods can estimate the effect of liability to an exposure on

an outcome, and PGS can even be utilised in a one-sample MR framework. When heterogeneity is low and the PGS is appropriately scaled to the exposure, as in studies three and four here, both methods should yield equivalent results. Furthermore, both rely on the variance explained (R^2) as a metric of the instrument's total strength.[501] Given these overlapping principles, the methods applied in this thesis offer a robust basis for inferring causal directionality. Moreover, although we are far from universal clinical utility, PGSs hold promise as a useful diagnostic tool for the early detection of disorders broadly,[502] and certainly of subclinical depression. With this in mind, intervening on short sleep at an early stage could be a preventative strategy for the risk of depression symptomology in the future. The presence of both should be routinely assessed in clinic, since independent conditions that cooccur can be treated as a way to attenuate the synergistic effects seen between them.

8.3. Stress Considerations

In study two, over 12 percent of older adults experienced a high level of stress, with more than 8,000 unique stress experiences reported. Results from studies one and two show that there was a difference in the type and level of stress chronicity, which in associations with biological processes, was not previously known. Stress linked to financial strain, illness, and bereavement in study two was the strongest prospective determinants of adverse biological profiles. There was also a clear dose effect, with each additional stressor experience leading to worse immune and neuroendocrine activity, and of the common life stressors evaluated, financial stress emerged as an important modulator of these biological processes in this thesis, and results held in study three. Financial stress was associated with adverse immune and neuroendocrine activity overall in study one, but immune and neuroendocrine changes depended on individual-compositional factors, over and above neighbourhood-contextual factors. In some cases, neighbourhood effects survived individual differences in education and occupation, but not when wealth was taken into account. These results together give weight to the view that wealth in older cohorts[290] is especially

meaningful to biological stability and mental health, particularly when considering study five results, which indicate that biological instability was associated with depression amidst pandemic-related stress. Moreover, results from study three support that financial stress is a reliable target to reduce short sleep, while also offering a promising pathway to understand the stratification of immune-neuroendocrine activity among the general population. The cumulative results suggest that policies designed to alleviate the financial burden on the population could be effective in reducing adverse biological and physiological processes. This is with the view that such policies could mitigate the burden on an already stretched public health system. Still, the magnitude of associations between socioeconomic stress and inflammation has varied widely across earlier studies.[15,242] This is attributable in part to variations in sample characteristics and study design, including principles used to limit confounding bias,[503] which gave reason for the intentional congruence in study design within this thesis. At the same time, meta-analytic findings by Muscatell and colleagues (2020)[15] from 43 papers in 111,156 individuals revealed that the less advantaged, defined by income, education, and occupation, experienced higher levels of systemic inflammation, indexed by CRP and IL-6. However, this was less consistent for fibrinogen and WBCC in study two, this was echoed by the cross-sectional findings for CRP and IGF-1, and additional evidence was provided on the upregulation of WBCC longitudinally in a sample of community-dwelling older adults. In other words, deprivation can set individuals on an adverse immune-neuroendocrine trajectory that can even be observed among non-clinical populations. Extant literature has shown that CRP is higher among those with less wealth,[242,243,504] lower education,[505,506] and lower occupation,[505,507] while wealth,[243,508] education,[243,339,508,509] and occupation[339,505,508] have been identified as correlates of change in circulating fibrinogen. In addition, lower education and occupation are known to be associated with elevated WBCC.[339,505] However, unlike the evidence produced here, most other studies are cross-sectional, so no inferences can be made on the direction of these results. Still, although unadjusted longitudinal neighbourhood-contextual effects have been observed with CRP and fibrinogen, only associations with fibrinogen remained

statistically significant after full adjustment.[359] This has been echoed at the individual-compositional level,[510,511] with larger effects also seen in WBCC over CRP.[510]

Curiously, caregiving and divorce as stressors in study two were not independently associated with differences in profile membership. Then contrary to expectations, disability was associated with a 30 percent lower risk of belonging to the *high-risk* profile. These findings sit in direct contrast to financial strain, bereavement, and longstanding illness. The former two which also revealed gradients in risk. The reasons for these results are uncertain. As it relates to caregiving, Roth and colleagues' (2019) meta-analysis in an older population revealed that caregivers had greater inflammation than those without caring responsibilities, with small reductions in immune functioning too. However, associations were weak, with questionable clinical significance. In addition, authors raised concerns of possible selection bias.[512] It is conceivable that caregiving, as an act of altruism, fosters purpose and fulfilment. Reinforcing one's self-view and beliefs about one's own morality, goodness, usefulness, and values. It can also be a way to maintain social connectiveness with another human being. In these ways, caregiving may build psychological resources that become protective, despite the inevitable pressure that comes with it.[513–515] Divorce is paradoxical in that it can create[516] or alleviate stress,[517] with intraindividual variation over time. Divorce has accelerated among adults 50 or older. A population who are now more likely to experience marital dissolution than widowhood.[518] This aligns with prognostications about this group being more accepting of divorce than their predecessors,[519] although, it is perhaps the enduring attachment to an ex-spouse that can be biologically problematic. Under these circumstances, one study found impairments in the cellular immune response, but it remains one of the few studies that explores ways in which psychological responses to divorce may be associated with immunological changes.[520] Finally disability, granted as a non-specific, broad designation, can be a protective factor in immune-neuroendocrine processes for several reasons. Individuals with disabilities tend to have valuable access to social support, whether from family,

friends, or community resources, and social support is a well-documented candidate for reducing stress.[521] Living with a disability can promote higher reserves of resiliency as a compensatory hallmark to cope with normative losses. This, coupled with greater variation in stress-reactivity among older adults.[522] Equally, disability can lead to physical and psychological adaptation and flexibility that may mitigate against stress.[523] Certainly in England, social provisions have been developed to lessen the additional burden associated with disability,[524] albeit an imperfect system. Perhaps it is the societal barriers to access, rather than the disability itself that increases stress and poses greater risk to one's biological status. Given that this group is wealthier on average, participants may have greater resources with which to overcome these barriers, thus mitigate stress.

Beyond a binary interpretation of statistical significance, the interpretation of estimates must consider whether effect sizes are meaningful from a public health perspective. An evaluation that is contingent on exposure and outcome prevalence, together with the Minimal Clinically Important Difference (MCID), which captures the magnitude of the issue and its ecological value.[525] Given the ubiquity of financial stress exposure[526] and the far-reaching impacts that biological processes have on health,[98] a 42-59 percent increase in relative risk identified in studies two and three is meaningful. This is in spite of a more comprehensive biomarker matrix included into the LPA in study three, with more exhaustive controls used to mitigate confounding. Although there are notable complications to drawing policy conclusions from a single study,[527] the same was true across studies both studies, and financial stress associations with immune-neuroendocrine profile memberships echoes study one results in the same longitudinal dataset. The findings from these three studies can, therefore, be treated as scientific replication that underscores the robustness and consistency of the observed relationships. Together making results more persuasive.

8.4. Suboptimal Sleep Considerations

Suboptimal sleep durations did not moderate associations between stress and biological processes in study three. Mediation is improbable since neither short nor long sleep were associated with the profiles of immune and neuroendocrine activity. It is conceivable that immune and neuroendocrine interactions compensate for sleep deficits (at least in the short term), but these compensatory mechanisms are thought to be overwhelmed by chronic suboptimal sleep durations.[87,88,391] So these results were unexpected. In study four, phenotypic analyses showed that short and long sleep was associated with depression, with large effect sizes and narrow confidence intervals. This supports that there was sufficient power to detect a signal in this dataset with a similar sample size. Thus, the null results in study three are likely true. It is possible that associations are underestimated without multiple assessments and a sufficiently long follow-up period for suboptimal sleep to translate to inflammatory states. However, it is more likely that the effect of suboptimal sleep is not sufficiently strong to influence a set of biomarkers within a profile. Instead, it may have specific influences over select markers of inflammation,[250,383] as has been seen elsewhere, where results depended on the biomarkers measured.[251,391,399] In this respect, results could also depend on the sleep type and combination. One study found that insomnia was associated with CRP, but only in participants who slept equal to or less than six hours.[528] The self-reporting nature of measurement may have influenced results, but subjective reports of total sleep time and sleep efficiency have not previously differed from actigraphy and PSG.[529]

All this said, there are strong indications of reverse causality. When investigating CRP and IL-6 independently, a study of 147,478 individuals from the UKB and 2,905 from the Netherlands Study of Depression and Anxiety (NESDA), found that CRP was associated with a 5 percent odds increase in sleep problems. Both biomarkers were respectively associated with a 27 and 26 percent odds increase in sleep duration. Congruent with these results, the authors found that genetically predicted IL-6 was associated with an increased risk of sleep problems. This was determined through a MR, fixed-effects IVW meta-analysis per exposure-outcome combination, and results

held after False-Discovery Rate (FDR) correction for multiple testing.[267] Study three confirms these results, insofar as the biological profiles being associated with long sleep, although not short sleep, in the sensitivity analyses. In addition, there a gradient in risk was identified that has not earlier been seen. Ultimately, results suggest that the sleep mechanism may be further downstream from stress and more proximate to mental illness in the framework.

Still, the age composition of the cohort has important implications to sleep.[67,530] There is suggestive evidence of age-related effects from the first sensitivity analyses in study three that warrants replication in a younger sample. One notion that merits consideration is survivor bias (viz. left truncation), where selective attrition led to a healthier, more resilient older group upon stratification, who are not characteristic of the general population.[531] Certainly, suboptimal sleep may be just a less prominent risk factor for immune and neuroendocrine processes in older adults. Equally, results could be attributed to the confounding effects of inflammaging and the somatopause.[373] Hence, why system-wide investigations in this demographic group is important from a public health perspective. Differences in age by stratification and effect modification was tested, but they were not found to bias results. The age range may need to be broader to effectively differentiate between groups.

From a behavioural point of view, the practice of napping in this group might serve as a protective factor for immune and neuroendocrine processes. One study found that cortisol decreased immediately after a midday nap of up to 30 minutes, which was accompanied by a return to baseline leukocytes counts.[532] In a later randomised, polysomnography-monitored study, an increase in norepinephrine and cytokine values after a sleep-restricted night was not observed after the countermeasure of a nap.[533] Given the higher prevalence of napping among older cohorts,[249] this practice may have mitigated the influence of sleep duration on the inflammatory status of this population by acting on homeostatic processes. Equally, this cohort may not expend as much

energy as younger cohorts,[534] with insufficient sleep debt corresponding to lesser homeostatic pressure[i].[535] This pressure accumulates exponentially during wakefulness and dissipates during sleep. Striking a balance between sleep-promoting and wake-promoting neurons that control the volume and amplitude of slow-wave activity.[408]

Overall, extant evidence supports a growing view that short sleep is more salient to the experience of biological processes[248,250,251] and depression[119,536] than long sleep, and that this is true across lifespan. The former could not be confirmed in study three, but findings from study four confirm the latter. In either case, different molecular mechanisms are said to underlie associations at either end of the sleep duration distribution.[416,537] Dashti and colleagues found a negative genetic correlation between short sleep and long sleep (r_g=-0.28). Correspondently, Garfield (2021) found that of the two novel SNPs at the PAX8 signal, the one associated with short sleep was near the activator of transcription and developmental regulator (AUTS2) gene, but the one associated with long sleep was near the mitogen-activated protein kinase associated protein 1 (MAPKAP1) gene. Mutations at each gene have been implicated in different disorders, so this variation in gene expression could underlie the suboptimal sleep differences observed in this thesis. Although robustly replicated common variants of sleep duration are at the Vaccinia Related Kinase 2 (VRK2) and Paired Box 8 (PAX8) genes,[416] there may be unidentified markers of large effects that drive the risk for long sleep. Important also is that the genic basis of sleep duration is known to be pleiotropic, with the presence of the same SNPs but different risk alleles reacting in a multiplicity of ways.[538] This could additionally explain differences seen between short sleep and long sleep associations.

[i] Homeostatic pressure refers to the compensatory increases in essential sleep duration, sleep consolidation, and sleep intensity that mounts in response to an extended period of wakefulness.[535]

8.5. Mental Ill-health Considerations

Owing to the collection of studies, much can be said of the mechanisms but less can be said of mental ill-health broadly. Further evidence, in the same population, is necessary to understand the symmetries across the mental health spectrum. Study five closes the loop of the framework, insofar as linking stress, inflammation, and mental ill-health. There we see pre-pandemic inflammation is associated with heightened depression during the pandemic. The implication being that inflammation makes us more prone to mental illness when stressed. Further, there was a striking dose-response, with the odds increasing by up to 69 percent for each unit increase in inflammatory concentrations. This is plausibly of clinical consequence.[525] Without the broader context of the pandemic, results are supported, in part, by a persuasive study of over 150,000 adults, across two samples, insofar as inflammation being associated with core depressive symptoms of low mood and anhedonia. However, the magnitude of associations was small, there were less consistent associations with anxiety, and only IL-6 was thought to be causally linked to depression. Moreover, unlike the evidence presented here, there was no account of stress in this study.[267] Still, this thesis would have benefitted from the formal testing of causality and the mediation of inflammation in stress and multiple mental health outcomes using predictive methods, which should also resolve directionality.

Study four is especially helpful to unravel directionality between sleep and depression. Here, the contrasting results from phenotypic and polygenic analyses was an important contribution to the literature. There is much uncertainty in the literature about whether suboptimal sleep precedes depression, or whether depression is an antecedent of sleep. Prognostic sequencing has been shown in both directions.[61,121] Even in study four, with large effect sizes, short and long sleep were associated with depression eight years later, and depression was associated with overall sleep duration and short sleep over the same time period. Moreover, the genetic basis of depression was

not associated with suboptimal sleep durations, but on the same basis in phenotypic data, earlier assertions were echoed.[122,430] Again, corresponding to earlier literature where associations are observed in both directions,[121,539] with similar results observed in younger populations too.[413,540] For the first time, we see that having a polygenic risk for short sleep makes individuals more prone to depression, which credibly initiates the bidirectional cycle between the two. Overall, results go against accepted clinical lore[j] about sleep as it is incongruent with notions of short and long sleep primarily being a symptom of mental illness.[22]

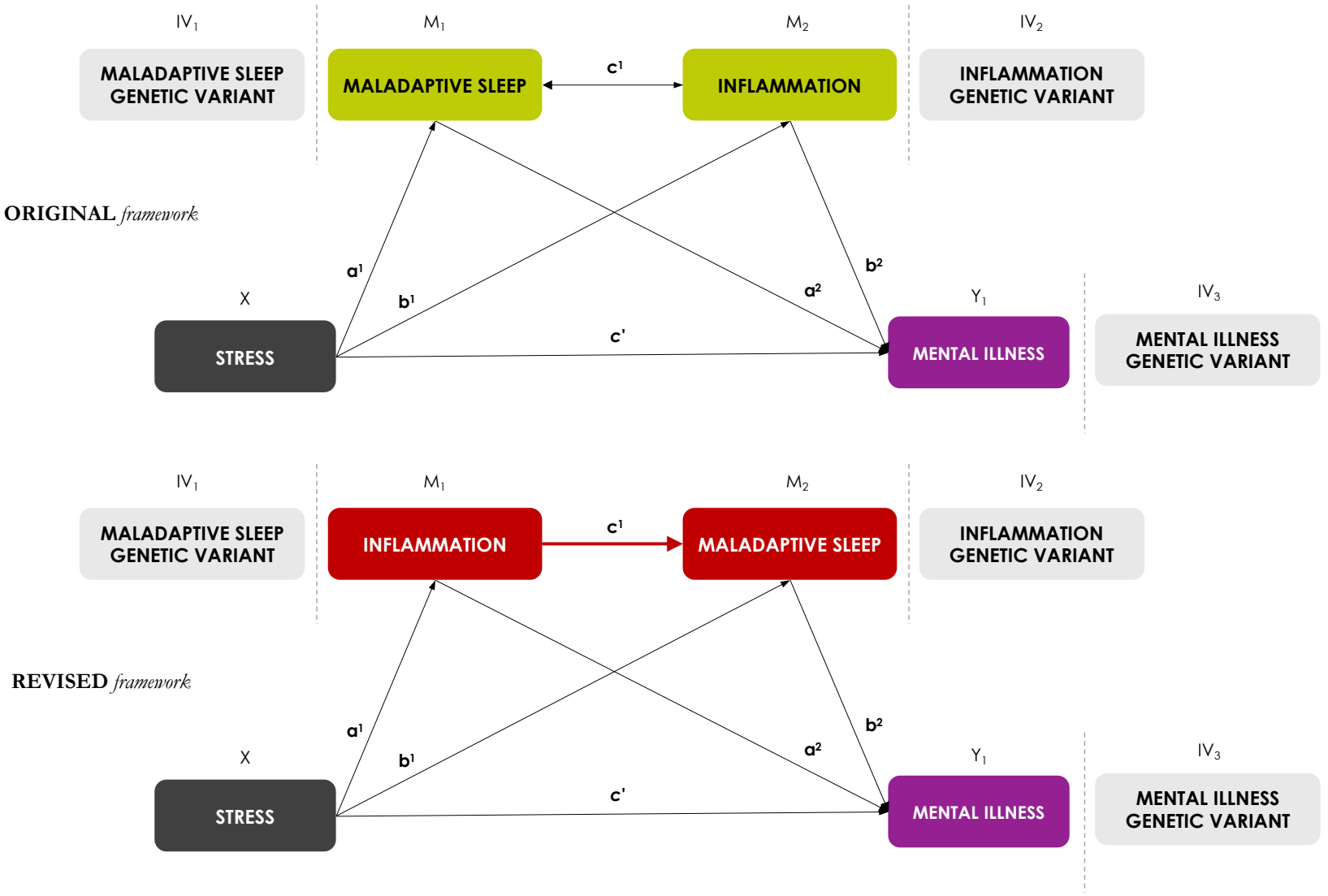
Considerations were also given to depression incidence, where an increase in caseness was seen overtime. This aligns with a study of almost 17,000 individuals that found a high prevalence of depression likelihood in 64 percent of an international convenience sample. A further 69 percent of those did not meet the recommended 7-9 hours of nighttime sleep.[118] Depression has been described as one of the most prevalent psychiatric conditions, with a point prevalence rate estimated at 5 percent and a lifetime prevalence at circa 15 percent.[541] However, it is also comorbid with a range of other psychomorbidities,[22,541,542] albeit rarely primary risk factor,[541] so exploring it in isolation misses an opportunity to see the broader matrix of mental health.

8.6. Framework Considerations

Taken together, results suggest that the ordering of the framework may need to be revisited **(Figure 8.1).** As postulated, it is most likely that stress is the starting point. Owing to the results, stress is now thought to more proximately dysregulate immune-neuroendocrine processes, while also directly driving changes in sleep durations. A testable theory is that immune-neuroendocrine processes connect stress to suboptimal sleep, where each of these are now believed to have an influence on mental ill-health through this multifactorial pathway.

[j] Clinical lore being the conventional understanding of diagnostic order among clinicians.

Figure 8.1 A comparison of the original and revised conceptual frameworks



Consequently, a reordering is proposed of suboptimal sleep durations and immune-neuroendocrine processes in the framework. This is said with caution given that directionality has not explicitly been tested between all variables of interest in a single study. Although stress is positioned as the origin of this dynamic, feedback loops occurring between them could mean that once provoked they influence each another in complex, cyclic ways rather than following a single, linear, unidirectional path. This was demonstrated in study four, where phenotypic associations indicated bidirectionality, but polygenic associations revealed both unidirectionality and a likely starting point in this dynamic. A more nuanced framework should account for feedback loops and consider group variability to fully capture the complexity of these relationships.

8.7. Directionality

Directionality is an important consideration in this thesis because relationships between stress, sleep duration, biomarkers, and mental illness are complex and multidirectional. The findings across the eight chapters of this thesis provide valuable insights into the likely direction of these relationships, adding empirical weight to the final theoretical framework **(Figure 8.1)**. In the first study, results supported a stress-induced immune activation model, given that financial stress, at the individual and neighbourhood level, was associated with heightened inflammatory responses. The cross-sectional nature of the first analysis limited inferences being made on the temporal order, but this was resolved through longitudinal analyses that confirmed this prospective sequence. The same was corroborated in the second study, where a selection of commonly experienced stressors, including financial stress, were independently and collectively tested against profiles of the biomarkers and results were significant with increased odds reaching 71 percent. The third study replicated this ordering between financial stress and profiles of the biomarkers. This study also offered additional information on the likely placement of sleep on this hypothesised pathway, insofar as suboptimal sleep durations did not precede inflammatory risk in phenotypic nor genetic models. In addition, study three reinforced the hypothesis that stress is a

precursor to suboptimal sleep, even though suboptimal sleep was neither a mediator nor moderator of the association between stress and the immune-neuroendocrine markers. The fourth study was especially helpful in unravelling directionality between sleep and depression given its primary use of genetic data. Here, the contrasting results between the phenotypic and polygenic analyses provided an important contribution to the literature on directionality in observational analyses. There has been much uncertainty regarding whether suboptimal sleep precedes depression or whether depression is an antecedent of suboptimal sleep given that sequences have been observed in both directions. However, the polygenic analyses here supported a unidirectional relationship of short sleep duration increasing the risk of depression. This lends credence to short sleep being an early marker for depressive symptomatology, rather than a consequence or side effect of depression. The final study provided evidence that stress-induced inflammation temporally precedes depression. This supports the idea that systemic inflammation may be a vulnerability factor that interacts with stress to give rise to mental illness. These final results were particularly beneficial to the thesis in that it supported the proposed ordering between inflammatory markers and depression in the overall framework.

8.8. Precision Medicine Considerations

The analytical strategy leveraged much more than a convenient device with which to model individual differences. Semiparametric, finite mixture models, such as the LPA used here, offered a principled way to identify heterogeneity based on observed patterns within empirical data.[543] It proves useful when the normality assumption of the maximum likelihood (ML) fitting function, used to estimate the model, is unwittingly violated.[544] These models avoid the need for *ad hoc* classifications. Instead they are estimated in the service of more flexibly modelling characteristics of the aggregate population as a whole.[389] Studies that isolate individual biomarkers offer important mechanistic insights, but studies that aggregate profiles contribute to a more comprehensive understanding of system-level activity. Distinct biological groups in the population have been

identified across studies. Where stress was an antecedent, differences in the risk of belonging to the *moderate-* or *high-risk* groups, as compared to the *low-risk* group, emerged. This emphasis on group-level differences highlights the importance of considering the biological context and complexity. LPA was chosen over other traditional clustering methods because it identifies subgroups of individuals with similar biomarker activity,[545] with population-level configurations of immune and neuroendocrine biomarker activity with increased specificity. Although it is not yet a mechanistic development with clinical utility, results advance a precision medicine approach[9] that paves the wave for predictive strategies built on high-performance computing (HPC) and artificial intelligence (AI).[546] Technologies that can be trained to assimilate the LPA model in order to predict risk groups with greater accuracy, such that remedies can be directed toward identified subgroups, rather than indiscriminate treatments ascribed across heterogeneous populations.[389]

8.9. Methodological Considerations

It was important that the design and population did not vary widely between each study for sake of evaluating the proposed framework without introducing unnecessary bias, as has been earlier reported as being problematic elsewhere.[547] Still, the intricacies of these relationships warrant careful interpretation because it has been tested in a relatively affluent, older cohort of the general population in England. Extrapolations to other groups is probable but not absolute. ELSA is a demographically representative cohort but the majority of the sample, circa 99 percent are of White European origin and are of older age.[288] A broader demographic representation would have improved generalisability, and given that ethnic groups are said to experience higher levels of stress,[548] their absence in each study is perhaps a considerable limitation. Still, this data is linked to census indicators of objectively measured contextual and compositional characteristics, and offers precise estimates of objective, systematically measured, interrelated biomarkers. Notably, each study also benefited from a comprehensive calculation of wealth that is unavailable in most studies. Wealth was computed on the basis of precise information on multiple individual components

rather than a broad categorisation of assets. Certainly, this makes deriving evidence more compelling.

As in all cohort studies, the confounding structure was limited to the data available at each wave. However, the sheer scope of data allowed for discriminative decisions to be made variables. In this respect, the DAGs offered a visual representation of the likely covariates. Following epidemiological principles, confounding variables that were included in the model had a strong theoretical basis,[314,549] with a data-driven approach used in parallel to arrive at the most optimal model formation. One that sought to limit unobserved confounding, while avoiding over-adjustment, or introducing unnecessary bias. To this point, conditioning on possible mediators was carefully considered to mitigate the likelihood of collider stratification bias.[309–311] By and large, associations held having accounted for genetic vulnerabilities, and results were also generally independent of the comprehensive selection of confounders identified through the DAGs. At the same time, study two, aligned with study five, found that health behaviours accounted for the greatest variance in associations. First, between socioeconomic stress and inflammation (at the individual-compositional and neighbourhood-contextual level). Second, between inflammation and depression when exposed to pandemic-related stress. However, it should be noted that age, sex, and genetic factors were more salient to neuroendocrine activity when evaluating biomarkers independently. Still, variation in these exposures was statistically associated with changes in the magnitude of these outcomes and remained significant after controlling for these rival explanations Nonetheless, the causal DAG represented a particular set of assumptions, but its complexity does not explicitly reflect real-world concerns about reciprocity or sources of bias, and it does not specify the estimate magnitude, nor its interplay with random errors.[314].

Complete case analysis remains the dominant method for handling missing data in biosocial research,[489] but evidence can be skewed by missingness,[316] so the preferred method adopted in this

thesis was multiple imputation. It is a common feature of this thesis, and comparisons between complete cases and imputations have consistently converged, with results being materially unchanged. Invariably, confidence intervals were narrower, and the magnitude of effects were larger in the imputed data. Chatzi and colleagues (2024)[489] revealed similar findings, in that cortisol and cortisone levels among the most deprived groups were smaller in the complete case analysis than in the imputed set. As it relates to the applied imputation method, missForest in all metrics has been shown to outperform other prominent imputation methods, such as MICE and KNN. This is in the presence of nonlinearity and interactions.[317] There are some promising newer methods, such as deep learning,[550] but one study[550] found that missForest outperformed deep generative models, particularly in imputing categorical variables. Concluding that there is no gain with deep learning where the sample size is limited. Moreover, the number of hyperparameters to tune for deep generative models is typically much larger than in missForest. The training time and memory size needed for the hyperparameter search on big data can also be prohibitive in some applications. Finally, the stability and convergence of the deep generative models were questionable for data of a small or moderate size, or even when the number of observations was relatively large, that is, less than 30,000.[550]Therefore, benefits to deep learning typically manifest when using big data.

As persuasive as results are, the present syndicate of results cannot speak to causality. Predictive facility cannot be claimed, but this is with all observational studies that cannot yield definitive conclusions on cause and effect, particularly in the face of reverse causality.[551] It is not without limitations, but MR and machine learning (later discussed) offer a promising avenue to overcome this challenge. Nonetheless, each study adds much value to the understanding of mechanisms that connect stress to mental illness. The evidence has been examined prospectively in all studies, so directionality can be inferred through the temporal order of events.[552]Arguably, the most promising approach is to triangulate evidence across multiple techniques to improve inferences,

as was borne out in this thesis.[388] The systematic approach taken provides a logical structure from which to later test causal claims. Future hypotheses can be based on theory submitted here and the triangulation of multiple lines of scientific evidence. This translational approach helps to ensure that the tested associations are empirically credible and observable across different lines of enquiry. Again, why the use of standardised measures, in the same population, with converging methods was necessary to allow for an unambiguous synthesis of results, less encumbered by bias.

8.10. General Strengths

In addition to study-specific strengths earlier detailed, this thesis benefits from several broader strengths across studies. One is in the use of a large, well-powered, well-characterised, nationally representative, longitudinal cohort of older adults.[288] Furthermore, the prospective and polygenic nature of the studies facilitated an exploration into the temporal direction of associations using polygenic and phenotypic data. The LPA solved statistical complications not previously feasible in this context.[553] Wherever used, the multiple imputation strategy was consistent with CCA. Genetic predisposition is accounted for, which while normative in clinical trials through natural random assignment,[554] is an underutilised approach in observational research. Given the triangulation of evidence, diverse analytic strategy, and inclusion of objective genetic and biological measures, there was not an overreliance of self-reported measures that can be susceptible to a number of biases. Finally, all associations were tested in a sizeable sample, and the PGSs were constructed using the results from most recent and largest GWAS meta-analyses, so analyses were not constrained by the sample size.

8.11. General Limitations

Invariably there are several weaknesses across the studies that could not be overcome. Models based on nested counterfactuals rest on strong assumptions about confounding,[555] but as with all observational studies, results might be subject to over-adjustment, unobserved confounding, or

residual confounding. In Chapters 3, 4, and 5, a four-year period may be insufficient to establish causal directionality, especially in light of the chronic nature of stress and suboptimal sleep. However, the longitudinal nature of the study allows for the inference of temporal relationships. In this respect, Mendelian randomization (MR) offers a promising avenue to overcome these challenges, although it is not without limitations.[554,556] Still, this thesis supports that the most promising approach is to triangulate evidence across multiple sources to improve causal claims.[388]. Concerns have been raised about the under-reporting of depression in older adults.[557] The CES-D is an established, commonly used measure, but Steffick (2000) raises its shortcomings in evaluating depressive disorders.[293] Among them is that it is indicative of subclinical depression, and not major depressive disorder as a psychiatric diagnosis, which is the GWAS the PGS was based upon. It, thus, captures genetic risk for clinical depression that may be biologically different to the symptoms captured by the CES-D.[417] Financial stress and sleep duration are self-reported and time varying, so individuals may experience changes throughout the course of the study that are subject to recall bias. Future study may benefit from objective measures in a time-varying effect model.[558] Moreover, financial stress was measured with a single item, so it may not have captured its multidimensionality. There are many aspects of sleep, so assessments of sleep duration offer only one indication of risk, and while participants provided single sleep duration estimates, there are likely intra-individual differences in sleep duration that were not assessed. Independently, each study may have benefited from a more extended follow-up period and the use of time-stratified survival analysis to strengthen inferences. Additionally, covariates were measured at baseline without time-varying assessments. Immune and neuroendocrine activation involves a constellation of cells that interact and create a microenvironment that promotes disease. Many of which are further upstream than those tested here.[483] but here a relatively small number of biomarkers are included to represent this complex network. Biomarker measurement can be challenging, more so on a large scale. The confounding structure in each study was carefully designed, guided by DAGs, to ensure informed adjustments, but the absence of information about medication that may have

influenced the biomarkers of interest remains a limitation. Summary statistics for fibrinogen was not available from existing GWAS, so the PGS could not be developed and included in the models. However, a strong genetic correlation with CRP has been documented elsewhere,[495] and PGS for CRP was accounted for in analyses. Similarly, baseline cortisol was unavailable, but follow-up cortisol was correlated with CRP, fibrinogen, and WBCC; each adjusted for at baseline where relevant. A consistent number of profiles derived from analysis across waves despite its omission. As it relates to power, heterogeneity in the GWAS discovery sampling may have influenced the predictive power of the derived PGSs. Incidence for suboptimal sleep outcomes is low, particularly for long sleep, limiting power and perhaps suppressing associative signals. In addition, as the default pi0 parameter was used, which is zero, the estimated power for each polygenic score might have been lower than it would have been if other values for this parameter were used. Then owing to the non-random nature of the studies, no claim can be made on prevalence. Genomic strategies assume lifetime exposure to the risk factor,[127] as a common epidemiological limitation of longitudinal investigations, but the present study would have benefited from the retrospective subclinical and pathological episode records of participants from birth.

8.12. Literature Contributions

This thesis contributes to the literature in several ways. First, much of the existing literature on stress, suboptimal sleep, immune-neuroendocrine biomarkers is cross-sectional and in small samples, which limits generalisability and the ability to infer temporality. Moreover, older adults remain an understudied population in this area, despite being disproportionately impacted due to age-related biological changes. Given these physiological vulnerabilities associated with ageing, it was important to focus analyses on this population. This thesis addresses these gaps by integrating a collection of longitudinal analyses, in a well-defined, large dataset of community-dwelling older adults. In addition, this thesis combines self-reported and objective measures, alongside biological and genetic data, ensuring a multifaceted, comprehensive approach. Through the application of

consistent measures across studies within the same population, this thesis enables a clearer synthesis of findings, addressing a common shortfall in previous research. There are also few studies where genetic contributions are accounted for in analyses, despite their known importance in sleep, biological processes, and mental illness. This thesis revealed that their inclusion in models was important, so it is important to account for heritable factors that have been largely overlooked in observational studies. The genetic markers used in analyses were also helpful in pointing to the causal direction between suboptimal sleep, immune-neuroendocrine activity, and depression. DAGs, though increasingly used in epidemiological research, remain a relatively novel methodological tool to systematically adjust for confounders to reduce bias. The extensive literature review undertaken through this process allowed for various critical discussions on inconsistencies observed in the existing body of literature, ensuring a balanced view and interpretation that acknowledges null findings when applicable and considers the likely influence of publication bias. Finally, this thesis puts forward a structured framework through which stress may lead to mental ill-states, which has not previously been reported. By shedding light on these pathways, particularly within an ageing population, this research advances the understanding of the genetic, biological, and behavioural mechanisms linking stress to mental health, with important implications for both prevention and intervention strategies.

8.13. Future Research Prospects

Time and space did not allow for the inclusion of other studies in this thesis. However, there are several other lines of enquiry, and five methodological advancements that would have been helpful to more completely elucidate mechanisms that connect stress to mental ill-health. Among them is understanding the prevalence and severity of stress, suboptimal sleep durations, and mental illness within older cohorts. As earlier discussed, there is reason to believe that age is a key consideration in these relationships, so comparisons with other age groups may benefit the scientific community, clinicians, and society at large. In this respect, it would be interesting to explore trajectories of

stress exposure and how its relationship with biological processes evolves across the lifespan. This could identify critical periods, hypothetically during adolescence or menopause, that heighten vulnerability to adverse outcomes. In addition, testing the entire framework across a broader range of mental health conditions would clarify whether findings hold across disorders.

From a methodological perspective, the identification of causal effects between suboptimal sleep, inflammation, and mental disorder across a spectrum of severity would also have been enlightening. A mediated MR would allow for the estimation of the magnitude of that causal effect. It would also determine whether inflammatory markers mediate that effect. However, it comes with strong assumptions that must be met to conclude causality. Second, though not assessed here, it is important to note that the experience of stress in later life may differ from that in early or mid-life due to physical and psychological resources,[339,559] behavioural,[560] and other salient factors that are characteristic of this group.[249] To this end, a multi-cohort case-control study stratified by age that spans the life course would be of value. Third, it is important to assess whether latent profiles of immune and neuroendocrine biomarkers are associated with mental disorder. Whether this differs from associations with physical disorder, and whether there are differences in efficacy between biomarker profiles and independent biomarkers. This would reveal whether a biomarker-wide approach offers greater insight into outcome-wide disease risk, compared to assessing biomarkers independently. A cox proportional hazards regression could be used to model time-to-event. This would facilitate a comparison of the hazard ratios for outcome-wide disorders based on these biomarker profiles. It would also allow for time-varying covariates to be included in the model. However, a violation of the assumption of proportional hazards (viz., the relative risk between groups is not constant over time) could lead to erroneous conclusions, and Cox models may not appropriately capture complex, non-linear relationships as would be intended. Fourth, Generalized Estimating Equations (GEE) would be a powerful statistical tool to analyse repeated measures and longitudinal, correlated data such as these. It would provide robust estimates of

population-averaged effects, but its inability to model subject-specific effects moves us away from the intended precision medicine approach. Fifth, a Random Forest machine learning approach could be applied to identify key drivers of mental disorder. Specifically, assessing the relative contributions of stress, suboptimal sleep, biological markers and genetic scores, along with other peripheral factors. Random Forests would make predictions by constructing decision trees on different bootstrap samples of the data, reducing overfitting and variance through aggregation, while improving predictive accuracy through averaging or majority voting. Unfortunately, machine learning is often seen as a *black box* model because it is difficult to understand how predictors interact or contribute to outcomes in a meaningful way. For that reason among others, interpretation is difficult, which can make it less translatable to policy and practice than traditional statistical methods.[561] Moreover, these methods are data-hungry and require large, well-structured datasets to yield reliable, robust results. Without appropriate tuning and validation, biased predictions or unstable importance rankings are likely. Sixth, associations between stress, suboptimal sleep, inflammatory biomarkers, and mental illness likely involve variation in means as well as distributions. Interventions that shift the outcome mean, while reducing variability are more optimal solutions than those that impact the mean only.[562] Therefore, the Generalized Additive Model for Location, Scale and Shape (GAMLSS)[563] approach may be particularly advantageous to the ongoing aims of this thesis. It is a flexible, data-driven statistical model that allows for associations and interactions to be fit without assuming linearity or homoscedasticity.[k] GAMLSS models associations by the mean (location) as is typical in regressions, but also by the variance (scale), skewness (shape), and kurtosis (tail) of the outcome. Understanding if and how the exposures influence variability in mental health has aetiological significance. Especially since these exposures could feasibly affect mental health variability but not affect the mean.[563] Finally, a structural equation modeling (SEM) approach could be taken to test the full model, that is,

[k] The assumption of homoscedasticity is that the variability of the outcome is unrelated to the exposure, but this is not always the case.[562]

simultaneous assessment of all exposures and outcomes, with direct and indirect effects between all variables. This is a hybrid approach combines factor analysis among latent variables and multiple regression via simultaneous equation modeling; an econometrics approach.[564] It maintains several advantages over regression and other multivariate techniques. Specifically it allows for the specification of a complex, *a priori* theory-driven models that can be tested with empirical data, such as that proposed here.[565] Together, these seven additional studies would enhance understanding and predictive accuracy over that which has already been established in this thesis.

8.14. Final Conclusion

As has been earlier found, [63,64] stress remains a compelling target to reduce suboptimal sleep, inflammatory status, and mental ill-health.[48,99] A lack of socioeconomic resources has emerged as a key stressor, credibly because of its rare ability to impress upon a diverse set of life experiences,[566] but the path to mental-ill health does not appear to be linear, nor unidimensional. The role of sleep in biological processes is less absolute, certainly in older cohorts. Conceivably as a result of naturally occurring behaviours that are mitigating. Yet, suboptimal sleep seems to have a more direct path to mental ill-health. Genetic contributions are important, and findings here suggest that evidence not accounting for genetic inheritance may have been moderately overinflated. Still, the studies included in this thesis support the notion that inflammatory processes across the integrative network[97,283] are the lynchpin that connects psychosocial factors to mental ill-health.[234,284–286] As underpinned by PNI. Strides have been taken to understand the sub-populations most at risk to PNI processes and subsequent disease, which brings the importance of personalised medicine to the fore. Further study will help to confirm these conclusions with clinical relevance. Yet as intended, the insights from this thesis on the biopsychosocial mechanisms of mental ill-health are proposed to be key to reducing socioeconomic disparities in health.[287] By advancing our understanding of the interplay between stress, suboptimal sleep, immune and neuroendocrine

activity, and genetic predisposition in mental ill-health, this work contributes to scientific discourse in a meaningfully way.

APPENDICES

APPENDIX A

CHAPTER 3 | Supplementary Material

Figure S3.1 Flow chart of the analytic sample *for* complete cases

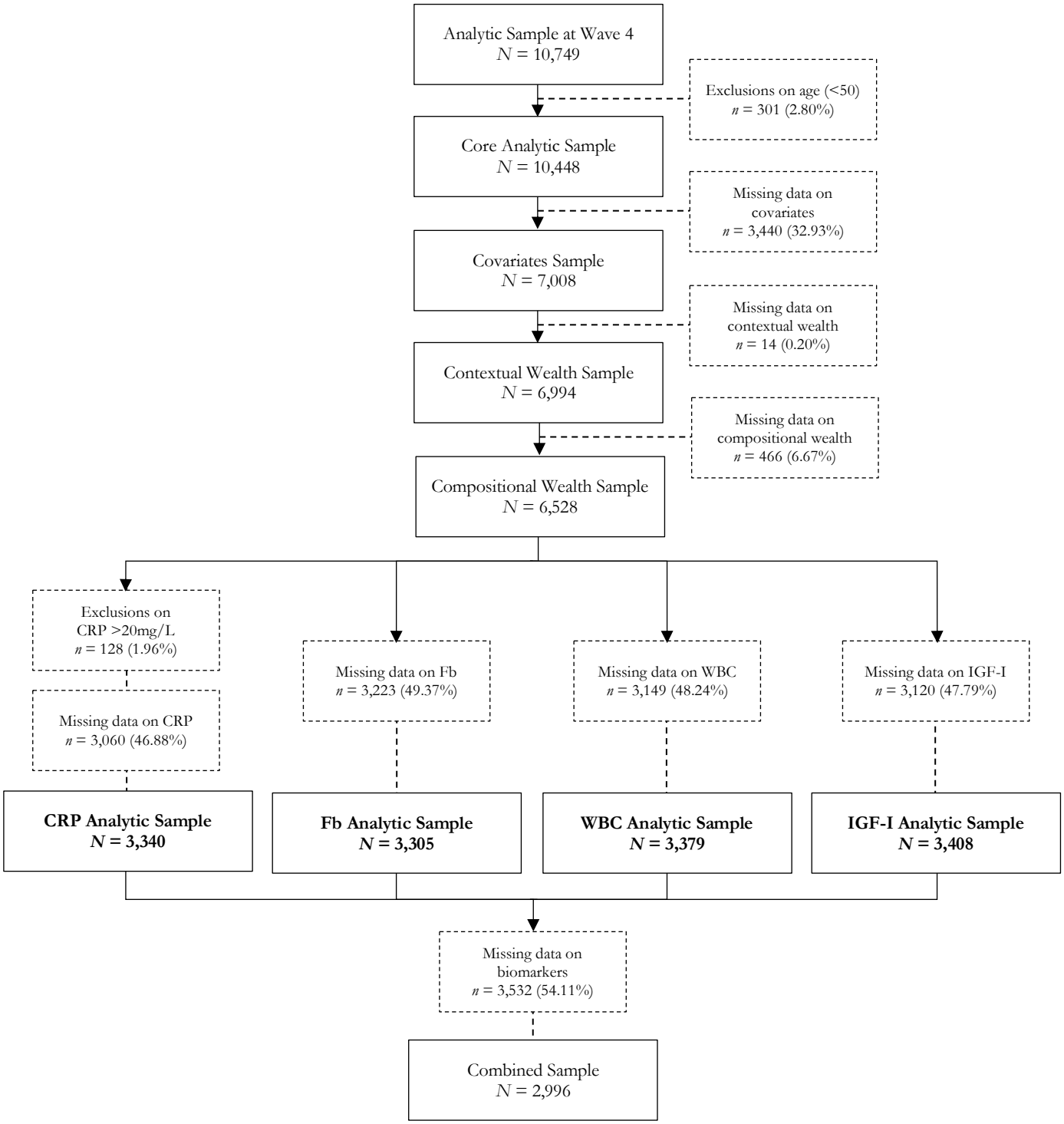


Table S3.1 A comparison of imputed and observed sample characteristics, with missing data

Variable		Missing Data N | %	Complete Cases (N = 2,996)		Imputed (N = 3,562)	
			N / Mean (SD)	% / Range	N / Mean (SD)	% / Range
Age		0 | 0.00%	64.41 (8.18)	50-99	64.26 (8.35)	50-99
Sex	Male	0 | 0.00%	1,334	44.53	1,591	44.67
	Female		1,662	55.47	1,971	55.33
BMI (kg/m2)	Underweight (≤18.5)	2,474 | 23.02%	17	0.57	21	0.59
	Normal (18.6-24.9)		800	26.70	963	27.04
	Overweight (25–29)		1,327	44.29	1,580	44.36
	Obese (≥30)		852	28.44	998	28.02
Limiting Longstanding Illness	No	8 | 0.07%	2,178	72.70	2,571	72.18
	Yes		818	27.30	991	27.82
Mobility Difficulties	No	141 | 1.31%	1,454	48.53	1,753	49.27
	Yes		1,542	51.47	1,807	50.73
Smoking Status	Non-smokers/Ex-smokers	203 | 1.89%	2,655	88.62	3,125	87.73
	Smokers		341	11.38	437	12.27
Alcohol Consumption	<3 days a week	1,956 | 18.20%	1,811	60.45	2,259	63.42
	≥3 days a week		1,185	39.55	1,303	36.58
Physically Activity	Moderately/Vigorously Active		2,326	77.64	2,699	75.77
	Sedentary	179 | 1.67%	670	22.36	863	24.23
IMD	Lowest Tertile	23 | 0.21%	860	28.70	998	28.02
	Middle Tertile		1,339	44.69	1,598	44.86
	Highest Tertile		797	26.60	966	27.12
Wealth	Lowest Tertile	1,160 | 10.79%	878	29.31	1,079	30.21
	Middle Tertile		1,308	43.66	1,537	43.15
	Highest Tertile		810	27.04	949	26.64
Education	Higher	100 | 0.93%	1,072	35.78	1,263	35.46
	Primary/Secondary/Tertiary		991	33.08	1,174	32.96
	Alternative or None		933	31.14	1,125	31.58
OSC	Managerial/Professional	534 | 4.97%	1,149	38.35	1,353	37.98
	Intermediate		788	26.30	919	25.80
	Routine/Manual		1,059	35.35	1,290	36.22
CRP* (mg/L; Baseline)		4,502 | 41.88%	1.10 (0.63)	0.18-3.03	1.11 (0.63)	0.18-3.04
CRP* (mg/L; Follow-up)		5,625 | 52.33%	1.02 (0.59)	0.10-3.05	1.03 (0.59)	0.10-3.05
Fb (g/L; Baseline)		4,535 | 42.19%	3.31 (0.52)	1.30-5.40	3.31 (0.52)	1.30-5.40
Fb (g/L; Follow-up)		5,620 | 52.28%	2.94 (0.49)	1.30-5.30	2.94 (0.50)	1.30-5.30
WBCC* (10^9/L; Baseline)		4,471 | 41.59%	1.79 (0.29)	-0.22-3.92	1.80 (0.29)	-0.22-3.92
WBCC* (10^9/L; Follow-up)		5,571 | 51.83%	1.81 (0.28)	0.72-3.48	1.82 (0.28)	0.72-3.48
IGF-1* (nmol/L; Baseline)		4,441 | 41.32%	2.72 (0.35)	1.39-4.14	2.72 (0.35)	1.39-4.17
IGF-1* (nmol/L; Follow-up)		5,519 | 51.34%	2.74 (0.32)	1.39-4.04	2.74 (0.32)	1.39-4.04

Notes: ELSA, waves 4-6 (2008/09-2012/13); N = observations; % = percentage frequencies; M = mean; SD = standard deviations; BMI = Body Mass Index; IMD = Index of Multiple Deprivation (i.e., Neighbourhood Deprivation); OSC = Occupational Social Class; CRP = C-reactive protein; Fb = Fibrinogen; WBC = White Blood Cell Counts (leukocytes); IGF-1 = Insulin-Growth Factor-1; * Log-transformed variable.

Table S3.2 Relationships of compositional and contextual socioeconomic indicators with immune and neuroendocrine biomarkers, adding covariates sequentially

	Adjustments	CRP* (*N* = 3,968)			Fb (*N* = 3,932)			WBCC* (*N* = 4,022)			IGF-1* (*N* = 4,056)		
		β (SE)	95% CI	*p*	β (SE)	95% CI	*p*	β (SE)	95% CI	*p*	β (SE)	95% CI	*p*
Contextual Indicators	**IMD**												
	Model 1: Crude model [a]	0.068 (0.020)	0.028-0.108	0.001	0.053 (0.019)	0.016-0.091	0.005	0.034 (0.009)	0.015-0.052	<0.001	-0.017 (0.009)	-0.034-0.001	0.050
	Model 2: Model 1 + demographic [b]	0.070 (0.020)	0.031-0.110	0.001	0.056 (0.019)	0.018-0.093	0.003	0.035 (0.009)	0.017-0.054	<0.001	-0.020 (0.009)	-0.037-0.003	0.023
	Model 3: Model 2 + clinical [c]	0.057 (0.020)	0.018-0.097	0.005	0.047 (0.019)	0.010-0.085	0.013	0.032 (0.009)	0.013-0.050	0.001	-0.017 (0.009)	-0.034-0.001	0.060
	Model 4: Model 3 + health behaviours [d]	0.042 (0.021)	0.002-0.082	0.039	0.029 (0.019)	-0.009-0.067	0.135	0.023 (0.010)	0.005-0.042	0.014	-0.015 (0.009)	-0.032-0.003	0.095
Compositional Indicators	**Wealth**												
	Model 1: Crude model [a]	0.076 (0.020)	0.037-0.116	<0.001	0.076 (0.019)	0.038-0.113	<0.001	0.050 (0.009)	0.032-0.069	<0.001	-0.029 (0.009)	-0.046-0.011	0.001
	Model 2: Model 1 + demographic [b]	0.073 (0.020)	0.033-0.112	<0.001	0.074 (0.019)	0.037-0.112	<0.001	0.049 (0.009)	0.031-0.068	<0.001	-0.022 (0.009)	-0.039-0.005	0.011
	Model 3: Model 2 + clinical [c]	0.052 (0.021)	0.011-0.092	0.012	0.061 (0.019)	0.023-0.099	0.002	0.045 (0.010)	0.026-0.064	<0.001	-0.018 (0.009)	-0.035-0.000	0.046
	Model 4: Model 3 + health behaviours [d]	0.028 (0.021)	-0.014-0.070	0.194	0.031 (0.020)	-0.017-0.052	0.119	0.035 (0.010)	0.016-0.055	<0.001	-0.015 (0.009)	-0.034-0.003	0.099
	Education												
	Model 1: Crude model [a]	0.058 (0.018)	0.022-0.094	0.002	0.078 (0.017)	0.044-0.112	<0.001	0.030 (0.009)	0.013-0.047	<0.001	-0.026 (0.008)	-0.042-0.011	0.001
	Model 2: Model 1 + demographic [b]	0.048 (0.019)	0.011-0.085	0.012	0.063 (0.018)	0.028-0.097	<0.001	0.030 (0.009)	0.012-0.047	0.001	-0.003 (0.008)	-0.019-0.013	0.726
	Model 3: Model 2 + clinical [c]	0.035 (0.019)	-0.002-0.072	0.063	0.053 (0.018)	0.018-0.088	0.003	0.027 (0.009)	0.009-0.044	0.003	-0.000 (0.008)	-0.016-0.016	0.978
	Model 4: Model 3 + health behaviours [d]	0.020 (0.019)	-0.018-0.058	0.298	0.034 (0.018)	0.001-0.070	0.050	0.020 (0.009)	0.002-0.037	0.029	0.002 (0.008)	-0.014-0.019	0.777
	OSC												
	Model 1: Crude model [a]	0.056 (0.018)	0.022-0.091	0.001	0.064 (0.016)	0.032-0.097	<0.001	0.033 (0.008)	0.017-0.049	<0.001	-0.021 (0.008)	-0.037--0.006	0.006
	Model 2: Model 1 + demographic [b]	0.052 (0.018)	0.017-0.086	0.003	0.057 (0.017)	0.024-0.089	0.001	0.034 (0.008)	0.017-0.050	<0.001	-0.011 (0.008)	-0.026-0.004	0.163
	Model 3: Model 2 + clinical [c]	0.041 (0.018)	0.007-0.076	0.019	0.050 (0.017)	0.018-0.083	0.002	0.031 (0.008)	0.015-0.047	<0.001	-0.008 (0.008)	-0.023-0.007	0.297
	Model 4: Model 3 + health behaviours [d]	0.028 (0.018)	-0.007-0.063	0.118	0.034 (0.017)	0.001-0.067	0.045	0.024 (0.008)	0.008-0.041	0.003	-0.006 (0.008)	-0.021-0.009	0.449

Notes: IMD = Index of Multiple Deprivation (i.e., Neighbourhood Deprivation); OSC = Occupational Social Class; β = unstandardised regression coefficient; SE = standard error; CI = confidence interval; *p* = significance value.
* Log transformed variable
[a] Baseline neuroimmune biomarkers respectively controlled for: CRP = C-reactive protein; Fb = fibrinogen; WBC = white blood cell counts; IGF-I = insulin-like growth factor-1
[b] Demographic variables: age and sex
[c] Clinical variables: BMI, limiting longstanding illness, and mobility difficulties
[d] Health behaviours: smoking status, alcohol consumption, and physical activity

Table S3.3 Relationships of compositional and contextual socioeconomic indicators with biomarkers, with age interactions

	Adjustments	CRP* (*N* = 3,968)			Fb (*N* = 3,932)			WBCC* (*N* = 4,022)			IGF-1* (*N* = 4,056)		
		β (SE)	95% CI	*p*	β (SE)	95% CI	*p*	β (SE)	95% CI	*p*	β (SE)	95% CI	*p*
IMD													
Main Effect	Model 1: Crude model [a]	0.079 (0.027)	0.027-0.131	0.003	0.061 (0.025)	0.011-0.111	0.016	0.043 (0.013)	0.019-0.068	0.001	-0.013 (0.012)	-0.036-0.010	0.252
	Model 5: Fully Adjusted [b]	0.049 (0.027)	-0.003-0.102	0.066	0.032 (0.025)	-0.018-0.082	0.206	0.030 (0.013)	0.005-0.055	0.017	-0.008 (0.012)	-0.032-0.015	0.487
Interaction [c] IMD * Age	Model 1: Crude model [a]	-0.026 (0.041)	-0.106-0.054	0.528	-0.017 (0.038)	-0.092-0.058	0.662	-0.022 (0.019)	-0.059-0.016	0.254	-0.010 (0.018)	-0.045-0.025	0.585
	Model 5: Fully Adjusted [b]	-0.013 (0.041)	-0.093-0.066	0.744	-0.006 (0.038)	-0.080-0.069	0.880	-0.016 (0.019)	-0.053-0.021	0.407	-0.010 (0.018)	-0.045-0.025	0.561
Wealth													
Main Effect	Model 1: Crude model [a]	0.066 (0.026)	0.014-0.118	0.011	0.059 (0.025)	0.010-0.107	0.018	0.051 (0.012)	0.027-0.075	<0.001	-0.022 (0.012)	-0.045-0.000	0.055
	Model 5: Fully Adjusted [b]	0.024 (0.027)	-0.029-0.077	0.481	0.018 (0.026)	-0.033-0.068	0.488	0.037 (0.013)	0.012-0.062	0.004	-0.014 (0.012)	-0.038-0.009	0.229
Interaction [c] Wealth * Age	Model 1: Crude model [a]	0.024 (0.041)	-0.055-0.104	0.550	0.044 (0.038)	-0.030-0.119	0.245	-0.008 (0.019)	-0.045-0.029	0.666	-0.010 (0.018)	-0.045-0.025	0.575
	Model 5: Fully Adjusted [b]	0.012 (0.040)	-0.067-0.091	0.764	0.032 (0.038)	-0.043-0.106	0.403	-0.006 (0.019)	-0.043-0.031	0.752	-0.009 (0.018)	-0.044-0.026	0.614
Education													
Main Effect	Model 1: Crude model [a]	0.048 (0.025)	-0.002-0.097	0.058	0.051 (0.024)	0.005-0.098	0.032	0.024 (0.012)	0.001-0.047	0.043	-0.017 (0.011)	-0.039-0.005	0.126
	Model 5: Fully Adjusted [b]	0.018 (0.025)	-0.032-0.068	0.480	0.019 (0.024)	-0.028-0.066	0.434	0.016 (0.012)	-0.007-0.040	0.169	-0.011 (0.011)	-0.022-0.011	0.320
Interaction [c] Education * Age	Model 1: Crude model [a]	0.019 (0.037)	-0.054-0.092	0.609	0.046 (0.035)	-0.022-0.115	0.186	0.002 (0.017)	-0.032-0.037	0.896	-0.002 (0.016)	-0.034-0.031	0.924
	Model 5: Fully Adjusted [b]	0.011 (0.037)	-0.062-0.083	0.776	0.036 (0.035)	-0.033-0.104	0.305	0.007 (0.017)	-0.027-0.041	0.702	-0.000 (0.016)	-0.032-0.032	0.994
OSC													
Main Effect	Model 1: Crude model [a]	0.048 (0.023)	0.003-0.093	0.035	0.044 (0.022)	0.002-0.087	0.040	0.033 (0.011)	0.012-0.054	0.002	-0.029 (0.010)	-0.049-0.009	0.004
	Model 5: Fully Adjusted [b]	0.019 (0.023)	-0.027-0.064	0.423	0.015 (0.022)	-0.028-0.058	0.483	0.026 (0.011)	0.005-0.048	0.017	-0.023 (0.010)	-0.043-0.003	0.023
Interaction [c] OSC * Age	Model 1: Crude model [a]	0.018 (0.035)	-0.052-0.087	0.614	0.042 (0.033)	-0.023-0.107	0.209	-0.005 (0.017)	-0.038-0.027	0.754	0.025 (0.016)	-0.005-0.056	0.105
	Model 5: Fully Adjusted [b]	0.028 (0.035)	-0.041-0.097	0.424	0.045 (0.033)	-0.019-0.110	0.169	-0.003 (0.016)	-0.035-0.030	0.876	0.026 (0.016)	-0.005-0.056	0.099

Notes: IMD = Index of Multiple Deprivation (i.e., Neighbourhood Deprivation); OSC = Occupational Social Class; β = unstandardised regression coefficient; SE = standard error; CI = confidence interval; *p* = significance value.
* Log transformed variable
[a] Baseline neuroimmune biomarkers respectively controlled for: CRP = C-reactive protein; Fb = fibrinogen; WBC = white blood cell counts; IGF-I = insulin-like growth factor-1
[b] All variables: age, sex, BMI, limiting longstanding illness, mobility difficulties, smoking status, alcohol consumption, and physical activity
[c] Age (>=64.25)

Table S3.4 Relationships of compositional and contextual socioeconomic indicators with biomarkers, with sex interactions

	Adjustments	CRP* (*N* = 3,968)			Fb (*N* = 3,932)			WBCC* (*N* = 4,022)			IGF-1* (*N* = 4,056)		
		β (SE)	95% CI	*p*	β (SE)	95% CI	*p*	β (SE)	95% CI	*p*	β (SE)	95% CI	*p*
IMD													
Main Effect	Model 1: Crude model [a]	0.095 (0.030)	0.036-0.154	0.002	0.054 (0.029)	-0.002-0.110	0.060	0.047 (0.014)	0.019-0.075	0.001	-0.015 (0.013)	-0.041-0.011	0.247
	Model 5: Fully Adjusted [b]	0.069 (0.030)	0.010-0.129	0.021	0.030 (0.029)	-0.027-0.086	0.301	0.038 (0.014)	0.010-0.065	0.008	-0.013 (0.013)	-0.038-0.013	0.332
Interaction [c] IMD * Sex	Model 1: Crude model [a]	-0.050 (0.041)	-0.129-0.030	0.221	-0.001 (0.038)	-0.076-0.074	0.986	-0.024 (0.019)	-0.061-0.014	0.215	-0.004 (0.018)	-0.039-0.031	0.815
	Model 5: Fully Adjusted [b]	-0.050 (0.040)	-0.128-0.029	0.218	-0.001 (0.038)	-0.076-0.073	0.972	-0.026 (0.019)	-0.063-0.011	0.173	-0.004 (0.017)	-0.038-0.030	0.824
Wealth													
Main Effect	Model 1: Crude model [a]	0.075 (0.030)	0.015-0.134	0.014	0.048 (0.029)	-0.008-0.104	0.091	0.058 (0.014)	0.030-0.086	<0.001	-0.031 (0.013)	-0.057-0.005	0.018
	Model 5: Fully Adjusted [b]	0.032 (0.031)	-0.029-0.092	0.306	0.012 (0.029)	-0.045-0.069	0.681	0.044 (0.014)	0.015-0.072	0.002	-0.024 (0.013)	-0.050-0.003	0.079
Interaction [c] Wealth * Sex	Model 1: Crude model [a]	0.002 (0.040)	-0.077-0.081	0.954	0.052 (0.038)	-0.023-0.126	0.173	-0.010 (0.019)	-0.047-0.027	0.582	0.011 (0.018)	-0.024-0.045	0.537
	Model 5: Fully Adjusted [b]	-0.007 (0.040)	-0.086-0.071	0.860	0.034 (0.038)	-0.039-0.108	0.362	-0.016 (0.019)	-0.052-0.021	0.402	0.016 (0.017)	-0.018-0.050	0.366
Education													
Main Effect	Model 1: Crude model [a]	0.058 (0.028)	0.003-0.113	0.040	0.043 (0.027)	-0.009-0.096	0.103	0.028 (0.013)	0.002-0.053	0.036	-0.006 (0.012)	-0.030-0.018	0.610
	Model 5: Fully Adjusted [b]	0.023 (0.028)	-0.032-0.079	0.414	0.010 (0.027)	-0.042-0.063	0.702	0.012 (0.013)	-0.014-0.038	0.365	0.007 (0.012)	-0.017-0.031	0.560
Interaction [c] Education * Sex	Model 1: Crude model [a]	0.006 (0.038)	-0.068-0.080	0.870	0.060 (0.035)	-0.009-0.130	0.089	0.021 (0.018)	-0.013-0.056	0.232	-0.015 (0.016)	-0.047-0.017	0.356
	Model 5: Fully Adjusted [b]	0.000 (0.037)	-0.073-0.074	0.991	0.050 (0.035)	-0.019-0.119	0.156	0.018 (0.017)	-0.016-0.052	0.300	-0.010 (0.016)	-0.042-0.022	0.550
OSC													
Main Effect	Model 1: Crude model [a]	0.047 (0.025)	-0.003-0.097	0.065	0.054 (0.024)	0.007-0.101	0.023	0.030 (0.012)	0.006-0.053	0.012	-0.024 (0.011)	-0.045-0.002	0.034
	Model 5: Fully Adjusted [b]	0.022 (0.025)	-0.028-0.072	0.380	0.034 (0.024)	-0.014-0.081	0.162	0.019 (0.012)	-0.004-0.042	0.112	-0.016 (0.011)	-0.038-0.006	0.153
Interaction [c] OSC * Sex	Model 1: Crude model [a]	0.017 (0.035)	-0.052-0.085	0.637	0.013 (0.033)	-0.052-0.077	0.702	0.014 (0.016)	-0.018-0.046	0.403	0.017 (0.015)	-0.014-0.047	0.281
	Model 5: Fully Adjusted [b]	0.010 (0.035)	-0.058-0.078	0.777	0.000 (0.033)	-0.064-0.064	0.998	0.011 (0.016)	-0.021-0.043	0.502	0.019 (0.015)	-0.011-0.049	0.206

Notes: IMD = Index of Multiple Deprivation (i.e., Neighbourhood Deprivation); OSC = Occupational Social Class; β = unstandardised regression coefficient; SE = standard error; CI = confidence interval; *p* = significance value.
* Log transformed variable
[a] Baseline neuroimmune biomarkers respectively controlled for: CRP = C-reactive protein; Fb = fibrinogen; WBC = white blood cell counts; IGF-I = insulin-like growth factor-1
[b] All variables: age, sex, BMI, limiting longstanding illness, mobility difficulties, smoking status, alcohol consumption, and physical activity
[c] Sex (Male [reference group] & Female)

Table S3.5 Relationships of compositional and contextual socioeconomic indicators with CRP, including values ≥20mg/L

	Adjustments	CRP* (*N* = 3,968)		
		β (SE)	95% CI	*p*
Contextual Indicators	**IMD**			
	Model 1: Crude model [a]	0.068 (0.020)	0.028-0.108	0.001
	Model 5: Fully Adjusted [e]	0.042 (0.021)	0.002-0.082	0.039
Compositional Indicators	**Wealth**			
	Model 1: Crude model [a]	0.076 (0.020)	0.037-0.116	<0.001
	Model 5: Fully Adjusted [e]	0.028 (0.021)	-0.014-0.070	0.194
	Education			
	Model 1: Crude model [a]	0.058 (0.018)	0.022-0.094	0.002
	Model 5: Fully Adjusted [e]	0.020 (0.019)	-0.018-0.058	0.298
	OSC			
	Model 1: Crude model [a]	0.056 (0.018)	0.022-0.091	0.001
	Model 5: Fully Adjusted [e]	0.028 (0.018)	-0.007-0.063	0.118

Notes: IMD = Index of Multiple Deprivation (i.e., Neighbourhood Deprivation); OSC = Occupational Social Class; β = unstandardised regression coefficient; SE = standard error; CI = confidence interval; *p* = significance value.
* Log transformed variable
[a] Controlled for baseline CRP = C-reactive protein
[b] Demographic variables: age and sex
[d] Clinical variables: BMI, limiting longstanding illness, and mobility difficulties
[c] Health behaviours: smoking status, alcohol consumption, and physical activity
[e] All variables: age, sex, BMI, limiting longstanding illness, mobility difficulties, smoking status, alcohol consumption, and physical activity

Table S3.6 Relationships of compositional and contextual factors with immune and neuroendocrine biomarkers (2008/09-2012/13), using complete cases

Adjustments		CRP* (*N* = 3,340)			Fb (*N* = 3,305)			WBCC* (*N* = 3,379)			IGF-1* (*N* = 3,408)		
		β (SE)	95% CI	*p*	β (SE)	95% CI	*p*	β (SE)	95% CI	*p*	β (SE)	95% CI	*p*
Contextual Indicators	**IMD**												
	Model 1: Crude model [a]	0.064 (0.022)	0.020-0.108	0.004	0.036 (0.021)	-0.004-0.076	0.079	0.027 (0.010)	0.007-0.048	0.008	-0.011 (0.010)	-0.030-0.008	0.247
	Model 2: Model 1 + demographic [b]	0.066 (0.022)	0.022-0.110	0.003	0.039 (0.020)	0.002-0.079	0.060	0.029 (0.010)	0.008-0.049	0.006	-0.014 (0.009)	-0.032-0.005	0.142
	Model 3: Model 1 + clinical [d]	0.050 (0.022)	0.006-0.093	0.026	0.026 (0.021)	-0.014-0.067	0.205	0.023 (0.010)	0.003-0.043	0.027	-0.006 (0.010)	-0.025-0.012	0.505
	Model 4: Model 1 + health behaviours [c]	0.049 (0.023)	0.005-0.094	0.029	0.019 (0.021)	-0.022-0.060	0.356	0.019 (0.010)	-0.001-0.040	0.065	-0.007 (0.010)	-0.026-0.012	0.499
	Model 5: Fully Adjusted [c]	0.040 (0.023)	-0.004-0.085	0.074	0.014 (0.021)	-0.026-0.055	0.490	0.016 (0.010)	-0.004-0.037	0.119	-0.009 (0.010)	-0.028-0.010	0.338
Compositional Indicators	**Wealth**												
	Model 1: Crude model [a]	0.073 (0.022)	0.029-0.116	0.001	0.084 (0.020)	0.044-0.124	<0.001	0.047 (0.010)	0.027-0.067	<0.001	-0.025 (0.010)	-0.044-·0.006	0.009
	Model 2: Model 1 + demographic [b]	0.069 (0.022)	0.025-0.113	0.002	0.080 (0.020)	0.040-0.120	<0.001	0.046 (0.010)	0.025-0.066	<0.001	-0.019 (0.009)	-0.037-·0.000	0.045
	Model 3: Model 1 + clinical [d]	0.047 (0.023)	0.003-0.091	0.037	0.068 (0.021)	0.027-0.109	0.001	0.041 (0.011)	0.020-0.062	<0.001	-0.016 (0.010)	-0.035-0.003	0.093
	Model 4: Model 1 + health behaviours [c]	0.048 (0.023)	0.002-0.093	0.041	0.056 (0.021)	0.014-0.098	0.009	0.037 (0.011)	0.016-0.058	0.001	-0.017 (0.010)	-0.037-0.003	0.092
	Model 5: Fully Adjusted [c]	0.027 (0.023)	-0.011-0.069	0.249	0.043 (0.022)	0.000-0.085	0.048	0.030 (0.011)	0.009-0.052	0.005	-0.013 (0.010)	-0.032-0.007	0.208
	Education												
	Model 1: Crude model [a]	0.053 (0.020)	0.013-0.093	0.009	0.073 (0.019)	0.037-0.110	<0.001	0.029 (0.009)	0.010-0.047	0.002	-0.026 (0.009)	-0.043-·0.009	0.003
	Model 2: Model 1 + demographic [b]	0.044 (0.021)	0.003-0.085	0.036	0.059 (0.019)	0.022-0.097	0.002	0.028 (0.010)	0.009-0.047	0.003	-0.003 (0.009)	-0.020-0.014	0.747
	Model 3: Model 1 + clinical [d]	0.036 (0.020)	-0.004-0.076	0.077	0.061 (0.019)	0.024-0.098	0.001	0.024 (0.009)	0.006-0.043	0.010	-0.020 (0.009)	-0.037-·0.003	0.024
	Model 4: Model 1 + health behaviours [c]	0.037 (0.021)	-0.004-0.078	0.074	0.054 (0.019)	0.017-0.092	0.005	0.022 (0.010)	0.004-0.041	0.019	-0.020 (0.009)	-0.038-·0.003	0.024
	Model 5: Fully Adjusted [c]	0.021 (0.021)	-0.021-0.062	0.333	0.034 (0.020)	-0.005-0.072	0.085	0.018 (0.010)	-0.001-0.037	0.064	0.001 (0.009)	-0.016-0.019	0.878
	OSC												
	Model 1: Crude model [a]	0.056 (0.019)	0.018-0.094	0.004	0.054 (0.018)	0.019-0.088	0.003	0.035 (0.009)	0.017-0.053	<0.001	-0.019 (0.008)	-0.035-·0.003	0.023
	Model 2: Model 1 + demographic [b]	0.052 (0.019)	0.014-0.090	0.007	0.046 (0.018)	0.011-0.081	0.010	0.035 (0.009)	0.018-0.053	<0.001	-0.008 (0.008)	-0.025-0.008	0.301
	Model 3: Model 1 + clinical [d]	0.043 (0.019)	0.005-0.081	0.027	0.045 (0.018)	0.010-0.080	0.012	0.031 (0.009)	0.014-0.049	0.001	-0.014 (0.008)	-0.030-0.003	0.105
	Model 4: Model 1 + health behaviours [c]	0.042 (0.020)	0.004-0.081	0.032	0.036 (0.018)	0.000-0.071	0.049	0.028 (0.009)	0.010-0.046	0.002	-0.014 (0.008)	-0.030-0.003	0.109
	Model 5: Fully Adjusted [c]	0.032 (0.020)	-0.007-0.070	0.109	0.026 (0.018)	-0.010-0.061	0.158	0.025 (0.009)	0.007-0.043	0.006	-0.004 (0.008)	-0.021-0.012	0.593

Notes: IMD = Index of Multiple Deprivation (i.e., Neighbourhood Deprivation); OSC = Occupational Social Class; β = unstandardised regression coefficient; SE = standard error; CI = confidence interval; *p* = significance value.
* Log transformed variable
[a] Baseline neuroimmune biomarkers respectively controlled for: CRP = C-reactive protein; Fb = fibrinogen; WBC = white blood cell counts; IGF-I = insulin-like growth factor-1
[b] Demographic variables: age and sex
[c] Clinical variables: BMI, limiting longstanding illness, and mobility difficulties
[d] Health behaviours: smoking status, alcohol consumption, and physical activity
[e] All variables: age, sex, BMI, limiting longstanding illness, mobility difficulties, smoking status, alcohol consumption, and physical activity

Table S3.7 Longitudinal relationships of compositional and contextual socioeconomic indicators with immune and neuroendocrine biomarkers, having restricted the sample to non-movers

	Adjustments	CRP* (*N* = 3,794)			Fb (*N* = 3,753)			WBCC* (*N* = 3,847)			IGF-1* (*N* = 3,877)		
		β (SE)	95% CI	*p*	β (SE)	95% CI	*p*	β (SE)	95% CI	*p*	β (SE)	95% CI	*p*
Contextual Indicators	**IMD**												
	Model 1: Crude model [a]	0.069 (0.020)	0.028-0.109	0.001	0.056 (0.020)	0.018-0.094	0.004	0.035 (0.010)	0.016-0.054	<0.001	-0.014 (0.009)	-0.032-0.004	0.116
	Model 5: Fully Adjusted [b]	0.044 (0.021)	0.003-0.085	0.036	0.033 (0.020)	-0.005-0.072	0.091	0.025 (0.010)	0.006-0.044	0.011	-0.012 (0.009)	-0.030-0.006	0.180
Compositional Indicators	**Wealth**												
	Model 1: Crude model [a]	0.065 (0.020)	0.025-0.106	0.002	0.067 (0.020)	0.031-0.108	<0.001	0.049 (0.010)	0.030-0.068	<0.001	-0.028 (0.009)	-0.046--0.010	0.002
	Model 5: Fully Adjusted [b]	0.018 (0.021)	-0.025-0.061	0.408	0.026 (0.021)	-0.015-0.066	0.213	0.034 (0.010)	0.014-0.054	0.001	-0.015 (0.009)	-0.033-0.004	0.125
	Education												
	Model 1: Crude model [a]	0.059 (0.018)	0.022-0.096	0.002	0.073 (0.018)	0.039-0.108	<0.001	0.030 (0.009)	0.012-0.047	0.001	-0.026 (0.008)	-0.042--0.010	0.002
	Model 5: Fully Adjusted [b]	0.021 (0.019)	-0.017-0.060	0.284	0.033 (0.019)	-0.003-0.070	0.073	0.019 (0.009)	0.001-0.037	0.040	0.003 (0.009)	-0.014-0.020	0.711
	OSC												
	Model 1: Crude model [a]	0.062 (0.018)	0.026-0.097	0.001	0.068 (0.017)	0.035-0.101	<0.001	0.032 (0.008)	0.016-0.049	<0.001	-0.023 (0.008)	-0.038--0.007	0.004
	Model 5: Fully Adjusted [b]	0.034 (0.018)	-0.001-0.070	0.060	0.040 (0.017)	0.006-0.074	0.021	0.024 (0.009)	0.007-0.041	0.005	-0.007 (0.008)	-0.023-0.008	0.348

Notes: IMD = Index of Multiple Deprivation (i.e., Neighbourhood Deprivation); OSC = Occupational Social Class; β = unstandardised regression coefficient; SE = standard error; CI = confidence interval; *p* = significance value.
* Log transformed variable
[a] Baseline neuroimmune biomarkers respectively controlled for: CRP = C-reactive protein; Fb = fibrinogen; WBC = white blood cell counts; IGF-I = insulin-like growth factor-1
[b] All variables: age, sex, BMI, limiting longstanding illness, mobility difficulties, smoking status, alcohol consumption, and physical activity

APPENDIX B

CHAPTER 4 | Supplementary Material

Figure S4.1 **Flow chart of missingness and the analytic sample for complete cases**

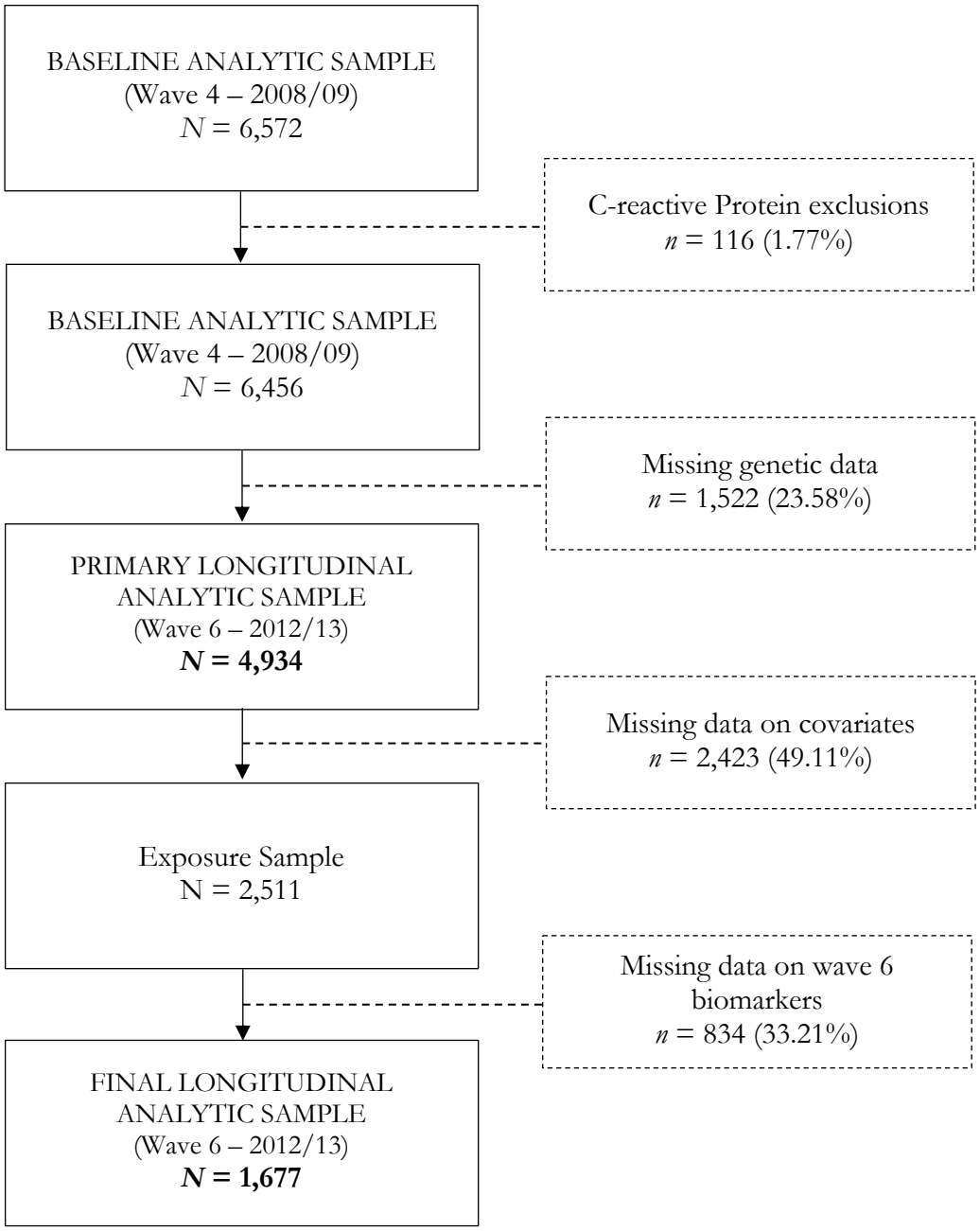
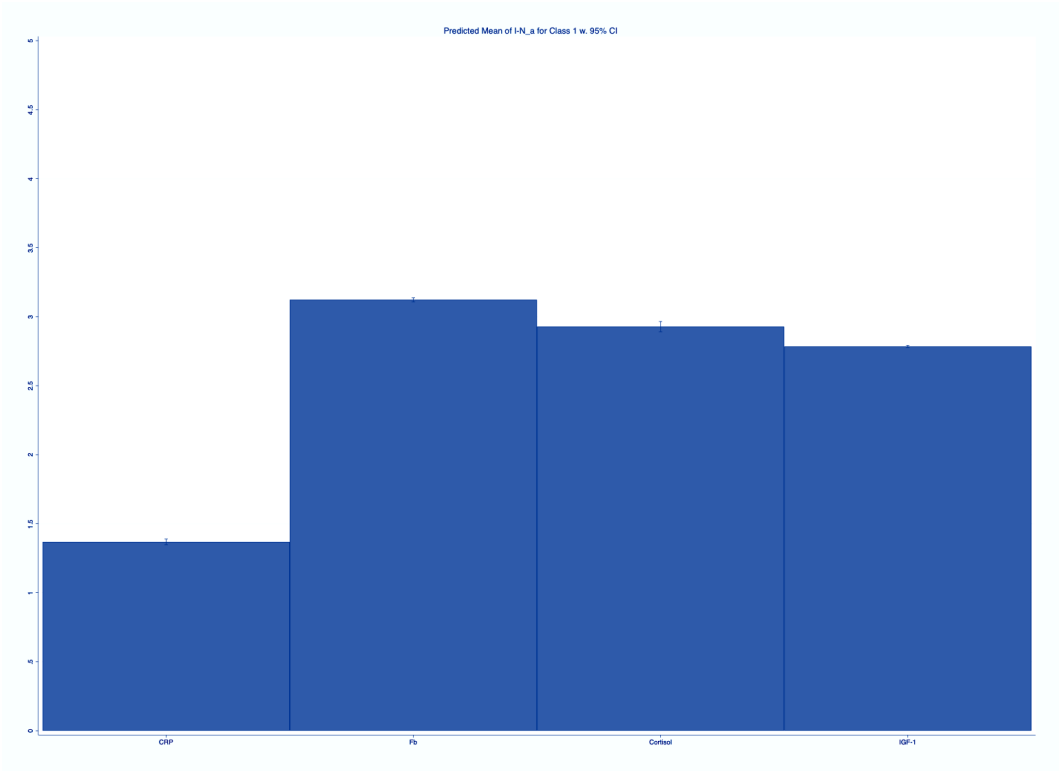
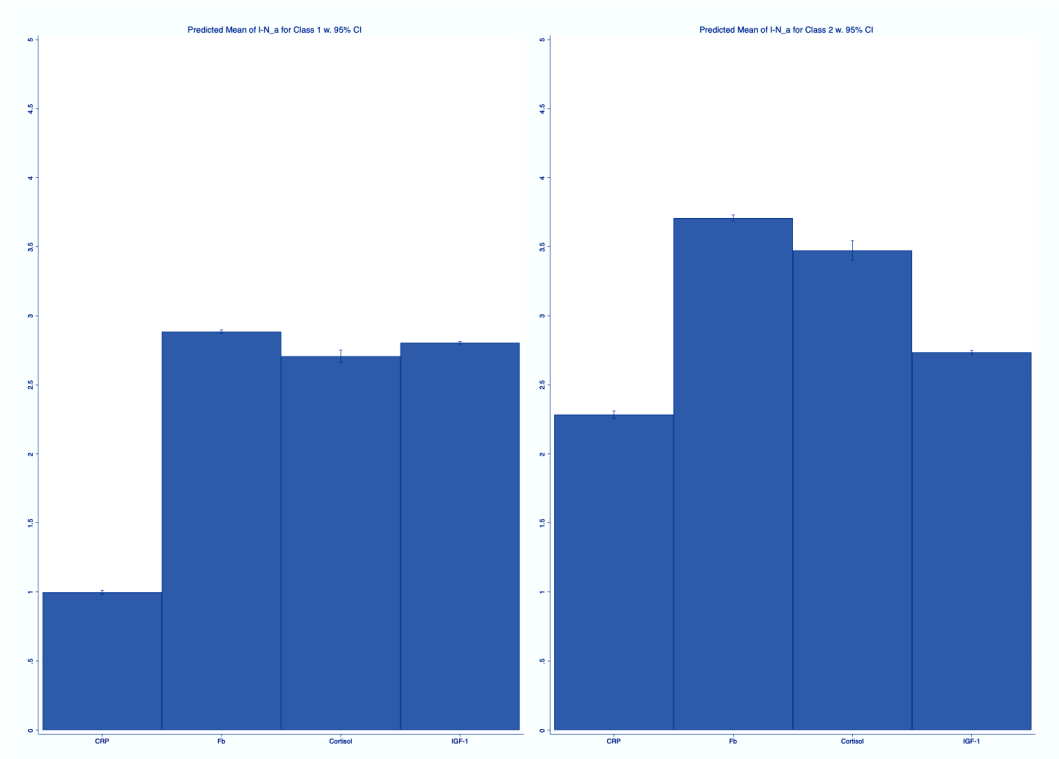


Figure S4.2 **[a-g] Mean immune and neuroendocrine biomarker levels for a one to seven profile solution (N = 4,934)**

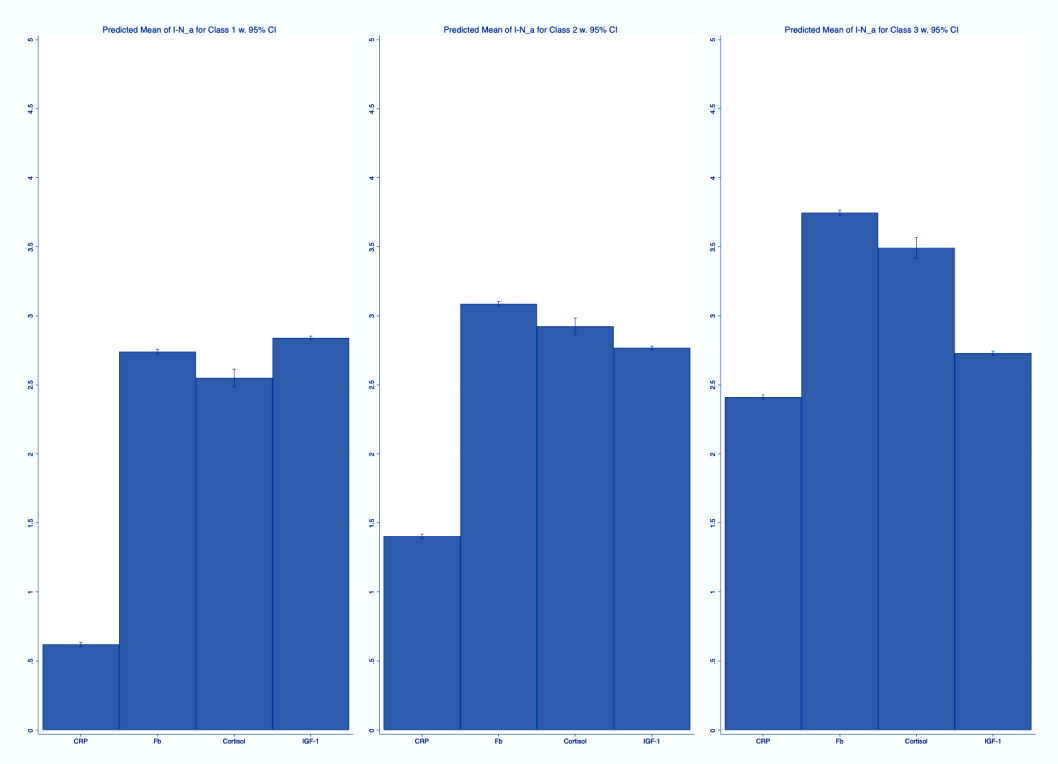
a



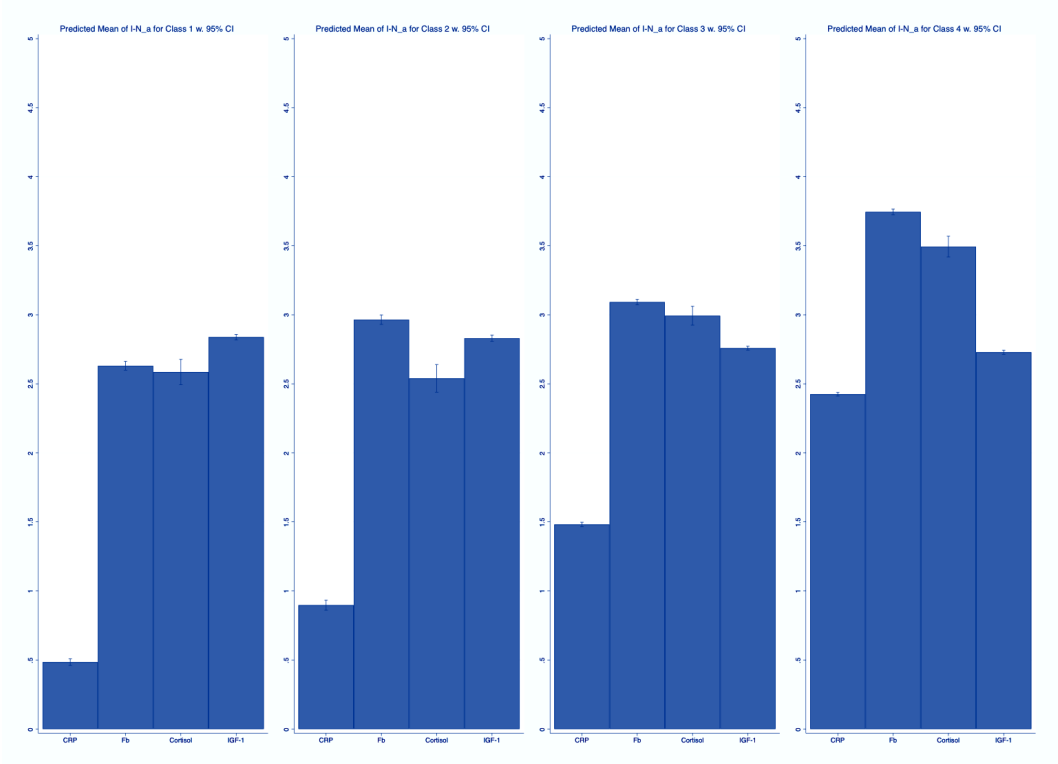
b



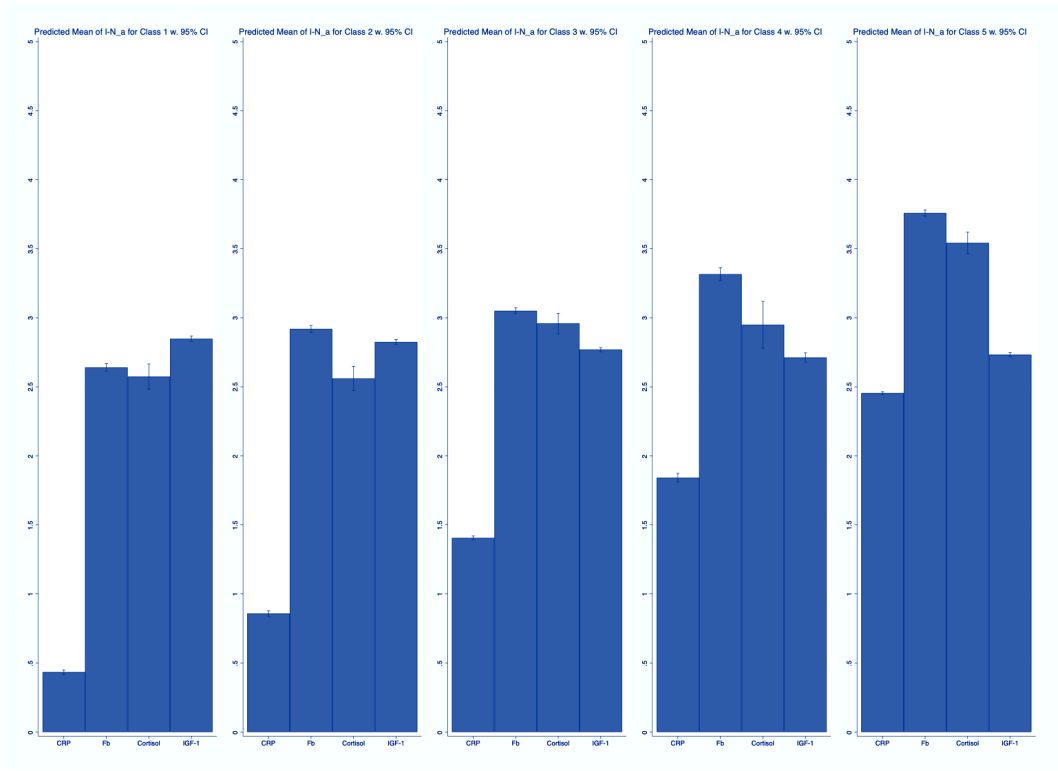
c


Predicted Mean of I-N_a for Class 1 w. 95% CI
Predicted Mean of I-N_a for Class 2 w. 95% CI
Predicted Mean of I-N_a for Class 3 w. 95% CI
CRP
Fb
Cortisol
IGF-1

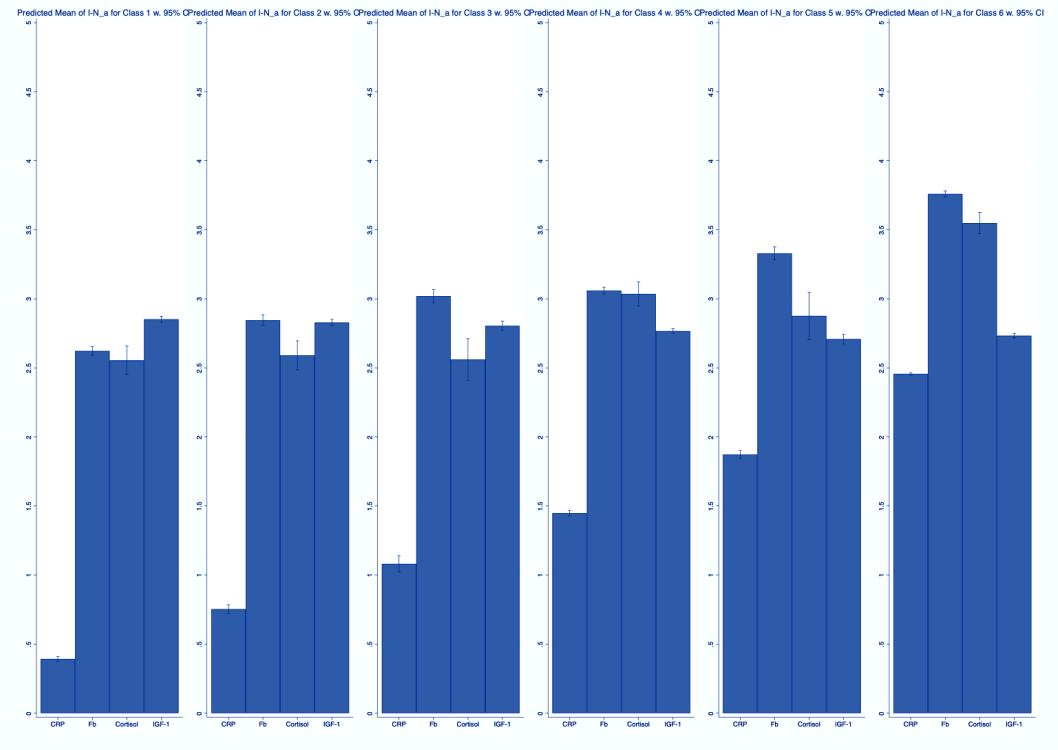
d


Predicted Mean of I-N_a for Class 1 w. 95% CI
Predicted Mean of I-N_a for Class 2 w. 95% CI
Predicted Mean of I-N_a for Class 3 w. 95% CI
Predicted Mean of I-N_a for Class 4 w. 95% CI
CRP
Fb
Cortisol
IGF-1

e


Predicted Mean of I-N_a for Class 1 w. 95% CI
Predicted Mean of I-N_a for Class 2 w. 95% CI
Predicted Mean of I-N_a for Class 3 w. 95% CI
Predicted Mean of I-N_a for Class 4 w. 95% CI
Predicted Mean of I-N_a for Class 5 w. 95% CI
CRP
Fb
Cortisol
IGF-1

f


Predicted Mean of I-N_a for Class 1 w. 95% CI
Predicted Mean of I-N_a for Class 2 w. 95% CI
Predicted Mean of I-N_a for Class 3 w. 95% CI
Predicted Mean of I-N_a for Class 4 w. 95% CI
Predicted Mean of I-N_a for Class 5 w. 95% CI
Predicted Mean of I-N_a for Class 6 w. 95% CI
CRP
Fb
Cortisol
IGF-1

g

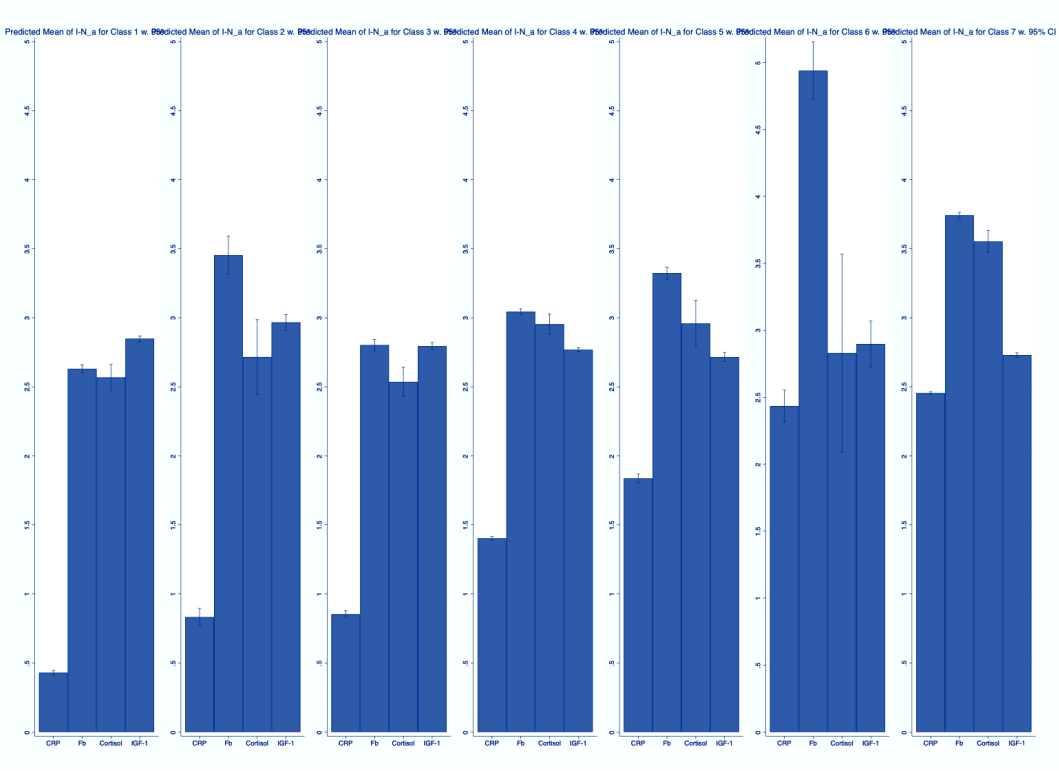

Predicted Mean of I-N_a for Class 1 w. 95% CI
Predicted Mean of I-N_a for Class 2 w. 95% CI
Predicted Mean of I-N_a for Class 3 w. 95% CI
Predicted Mean of I-N_a for Class 4 w. 95% CI
Predicted Mean of I-N_a for Class 5 w. 95% CI
Predicted Mean of I-N_a for Class 6 w. 95% CI
Predicted Mean of I-N_a for Class 7 w. 95% CI
CRP
Fb
Cortisol
IGF-1

Figure S4.3 **The predicted mean values of immune and neuroendocrine biomarker profiles for the three-profile solution using complete case data (N = 1,677)**

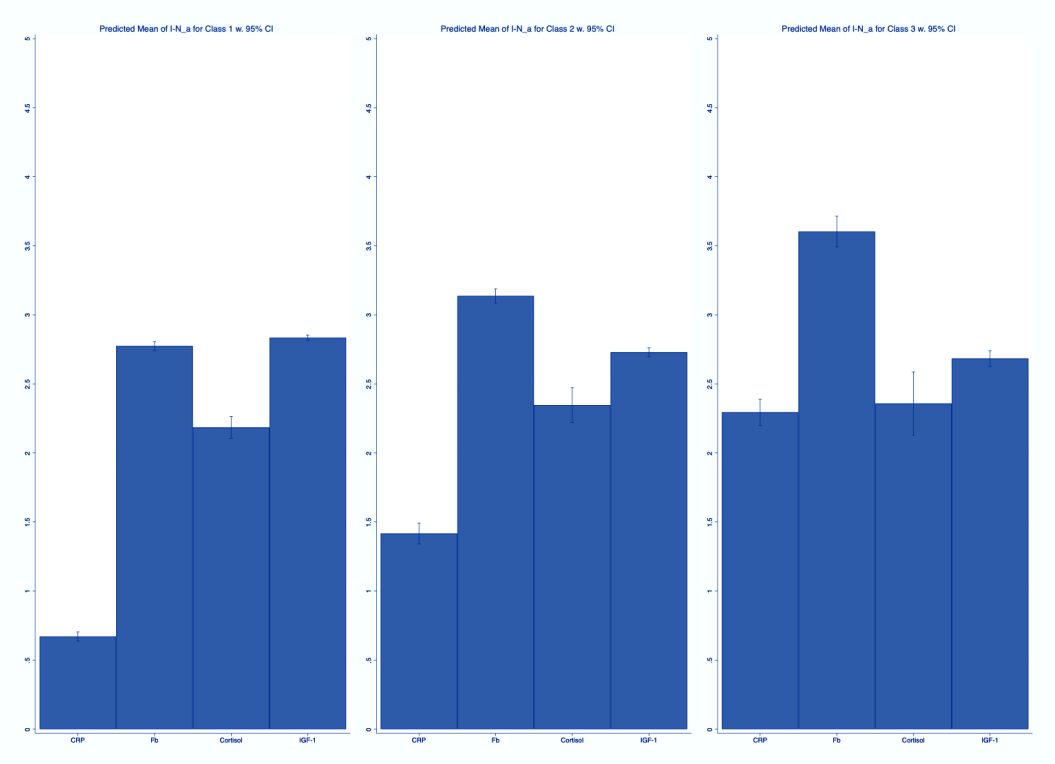
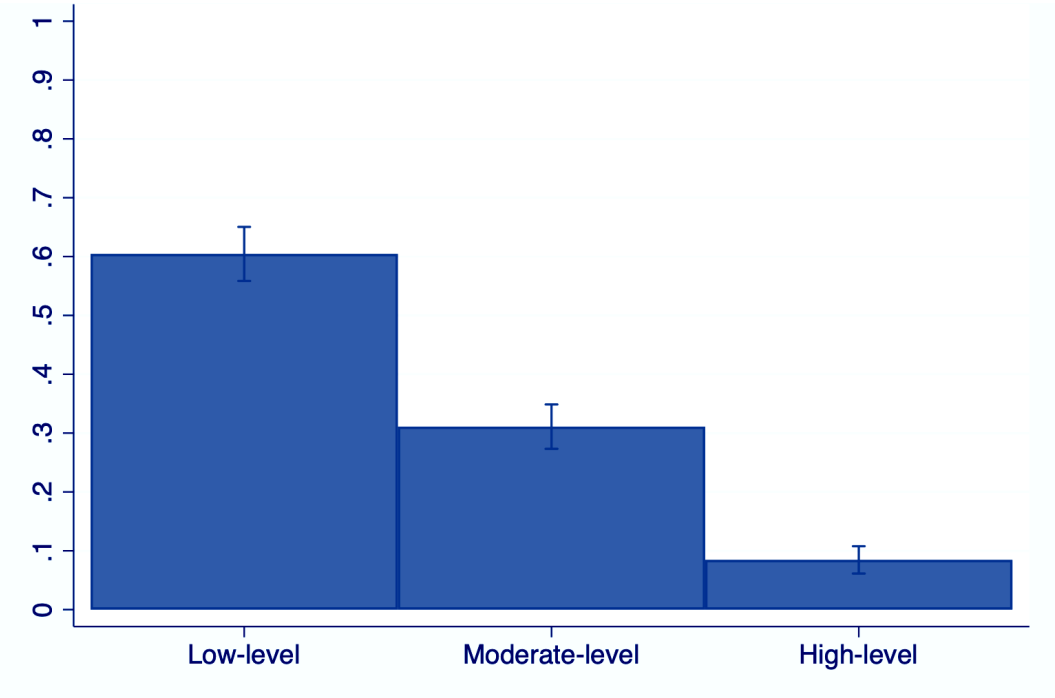


Figure S4.4 **The percentage of participants belonging to each immune and neuroendocrine biomarker profile with 95% confidence intervals for the three-profile solution using complete case data (N = 1,677)**



Profile	N	%
1	1,028	61.30
2	517	30.83
3	132	7.87

Table S4.1 A comparison of core, imputed, and observed sample characteristics, with missing data

Variable		Missing Data	Core Sample (N=6,456)		Imputed (N=4,934)		Complete Cases (N=1,677)	
		N | %	N / Mean (SD)	% / Range	N / Mean (SD)	% / Range	N / Mean (SD)	% / Range
Age		0 | 0	65.40 (9.42)	50-99	66.31 (9.35)	50-99	65.04 (8.01)	50-99
Age (Binary)	< Median	0 | 0	3,684	56.57	2,437	49.39	826	49.25
	≥ Median		2,828	43.43	2,497	50.61	851	50.75
Sex	Male	0 | 0	2,941	45.16	2,235	45.30	540	32.20
	Female		3,571	54.84	2,699	54.70	1,137	67.80
Education	Higher	15 | 0.23	2,111	32.42	1,585	32.12	567	33.81
	Primary/Secondary/Tertiary		2,075	31.86	1,544	31.29	562	33.51
	Alternative or None		2,326	35.72	1,805	36.58	548	32.68
Occupational Social Class	Managerial/Professional	149 | 2.31	2,430	37.32	1,790	36.28	598	35.66
	Intermediate Occupations		1,639	25.17	1,264	25.62	455	27.13
	Routine/Manual		2,443	37.52	1,880	38.10	624	37.21
Smoking Status	Non-smokers/Ex-smokers	44 | 1.68	5,663	86.96	4,306	87.27	1,485	88.55
	Smokers		849	13.04	628	12.73	192	11.45
Alcohol Consumption	<3 days a week	548 | 8.49	4,253	65.31	3,171	64.27	1,029	61.36
	≥3 days a week		2,259	34.69	1,763	35.73	648	38.64
Physical Activity	Moderately/Vigorously Active	34 | 0.53	1,781	27.35	1,338	27.12	383	22.84
	Sedentary		4,731	72.65	3,596	72.88	1,294	77.16
PGS for CRP	Low	1,522 | 23.57	3,945	79.96	3,945	79.96	1,353	80.68
	High		989	20.04	989	20.04	324	19.32
PGS for cortisol	Low	1,522 | 23.57	3,969	80.44	3,969	80.44	1,377	82.11
	High		965	19.56	965	19.56	300	17.89
PGS for IGF-1	Low	1,522 | 23.57	3,929	79.63	3,929	79.63	1,345	80.20
	High		1,005	20.37	1,005	20.37	332	19.80
Stress Score		0 | 0	1.56 (.90)	0-6	1.51(.90)	0-6	1.50 (.89)	0-6
Binary Stress Score	No	0 | 0	5,655	86.84	4,318	87.52	1,487	88.67
	Yes		857	13.16	616	12.48	190	11.33
CRP* (mg/L; Baseline)		159 | 2.46	1.18 (.68)	.18-3.05	1.19 (.68)	.18-3.04	1.13 (.65)	.18–3.03
CRP* (mg/L; Follow-up)		2,374 | 36.77	1.35 (.71)	.10-3.05	1.37 (.73)	.10-3.05	1.04 (.60)	.10-3.03
Fb (g/L; Baseline)		188 | 2.91	3.37 (.56)	1.30-5.90	3.38 (.56)	1.30–5.90	3.32 (.52)	1.70–5.30
Fb (g/L; Follow-up)		2,373 | 36.76	3.11 (.51)	1.30-5.80	3.12 (.54)	1.50–5.80	2.96 (.50)	1.60–5.20
Cortisol* (pg/mg; Follow-up)		3,374 | 52.26	2.76 (1.35)	.13-6.49	2.93 (1.34)	.13-6.49	2.50 (1.22)	.13-6.49
IGF-1* (nmol/L; Baseline)		95 | 1.47	2.77 (.34)	1.10-4.19	2.78 (.34)	1.10-4.19	2.78 (.32)	1.61–3.85
IGF-1* (nmol/L; Follow-up)		2,297 | 35.58	2.78 (.27)	1.61-4.06	2.78 (.27)	1.61-4.06	2.79 (.30)	1.61–4.06

Notes: ELSA, waves 4-6 (2008/09-2012/13); N = observations; % = percentage frequencies; SD = standard deviations; OSC = occupational social class; CRP = C-reactive protein; Fb = Fibrinogen; IGF-1 = Insulin-growth factor-1; * Log-transformed variable; I-N = immune and neuroendocrine.

Table S4.2 Correlations between immune and neuroendocrine biomarkers

	CRP	Fb	Cortisol	IGF-1
CRP	1 -			
Fb	0.706* <0.001	1		
Cortisol	0.273* <0.001	0.176* <0.001	1	
IGF-1	-0.163* <0.001	-0.011 0.438	0.005 0.752	1

Notes: C-reactive protein (CRP); Fb = Fibrinogen; IGF-1 = insulin-growth factor-1; * Significant at $p<0.001$ level

Table S4.3 Seven Profile LPA model fit indices and predicted probability of profile membership (N = 4934)

Criteria	One Profile	Two Profiles	Three Profiles	Four Profiles	Five Profiles	Six Profiles	Seven Profiles
AIC	36460.95	32478.36	30823.00	30574.08	30283.37	30214.23	30105.23
AIC Difference (N)	-	3982.59	1655.36	248.92	290.71	69.14	109.00
AIC Difference (%)	-	12.26	5.37	0.81	0.96	0.23	0.36
BIC	36512.98	32562.92	30940.07	30723.67	30465.48	30428.86	30352.38
BIC Difference (N)	-	3950.06	1622.85	216.40	258.19	36.62	76.48
BIC Difference (%)	-	12.13	5.25	0.70	0.85	0.12	0.25
aBIC	36487.56	32521.61	30882.87	30650.59	30376.51	30324.00	30231.63
aBIC Difference (N)	-	3965.95	1638.73	232.29	274.08	52.51	92.37
aBIC Difference (%)	-	12.19	5.31	0.76	0.90	0.17	0.31
Entropy	-	0.88	0.84	0.73	0.83	0.82	0.87
Normalised Entropy	-	0.84	0.78	0.64	0.77	0.77	0.83
M Posterior Probabilities (SE)	-	0.711 (.007)	0.358 (.008)	0.211 (.012)	0.185 (.008)	0.150 (.008)	0.179 (.008)
	-	0.289 (.007)	0.399 (.008)	0.218 (.011)	0.225 (.008)	0.185 (.010)	0.042 (.009)
	-	-	0.243 (.006)	0.333 (.009)	0.296 (.008)	0.119 (.010)	0.187 (.011)
	-	-	-	0.238 (.006)	0.073 (.006)	0.258 (.010)	0.296 (.008)
	-	-	-	-	0.223 (.006)	0.066 (.005)	0.074 (.006)
	-	-	-	-	-	0.221 (.006)	0.003 (.001)
	-	-	-	-	-	-	0.219 (.006)
N classes >5%	Yes	Yes	Yes	Yes	Yes	Yes	No

Notes: AIC = Akaike information criterion; BIC = Bayesian information criterion; aBIC = adjusted Bayesian information criterion; N = number of observations; M = mean; SE = standard errors.

Table S4.4 Longitudinal associations of the stress score with immune and neuroendocrine biomarker profiles, with incremental model adjustment (N=4,934)

Adjustments	Binary Stress Score				
	RRR	SE	95% CI		*p*
***Moderate-risk* Profile**					
Model 1: *Unadjusted*	0.98	0.10	0.81	1.20	0.870
Model 2: *Model 1 + baseline biomarkers* [a]	1.01	0.11	0.83	1.24	0.898
Model 3: *Model 2 + demographics & genetics* [b]	1.14	0.12	0.93	1.41	0.213
Model 3a: *Model 3 + socioeconomics* [b1]	1.14	0.12	0.92	1.40	0.232
Model 3b: *Model 3 + health behaviours* [b2]	1.09	0.12	0.88	1.35	0.412
Model 3c: *Model 3 + health* [b3]	1.15	0.12	0.93	1.41	0.206
Model 4: *Fully Adjusted* [c]	1.10	0.12	0.89	1.35	0.401
***High-risk* Profile**					
Model 1: *Unadjusted*	1.34	0.15	1.08	1.66	0.008
Model 2: *Model 1 + baseline biomarkers* [a]	1.42	0.18	1.10	1.83	0.007
Model 3: *Model 2 + demographics & genetics* [b]	1.80	0.24	1.39	2.35	<0.001
Model 3a: *Model 3 + socioeconomics* [b1]	1.77	0.24	1.36	2.31	<0.001
Model 3b: *Model 3 + health behaviours* [b2]	1.61	0.22	1.22	2.11	0.001
Model 3c: *Model 3 + health* [b3]	1.81	0.25	1.39	2.36	<0.001
Model 4: *Fully Adjusted* [c]	1.61	0.22	1.23	2.12	0.001

Notes: The *low-risk* group is the reference; RRR = relative risk ratio; SE = standard errors; CI = confidence interval; *p* = significance value.

a Baseline biomarkers: C-reactive protein (CRP); fibrinogen; insulin-growth factor-1 (IGF-1).

b Demographic and genetic variables: age; sex; 10 principal components (PCs); CRP polygenic score (PGS); cortisol PGS; IGF-1PGS.

b1 Socioeconomics: education; occupational social status.

b2 Health behaviours : smoking status; alcohol consumption; physical activity.

b3 Health: chronic lung disease; coronary heart disease; abnormal heart rhythm; heart murmur; congestive heart failure; angina; hypertension; diabetes; cancer; Parkinson's; Alzheimer's; dementia; asthma; arthritis; osteoporosis; psychiatric disorder.

c Fully adjusted: CRP; fibrinogen; IGF-1; age; sex; 10 PCs; CRP PGS; cortisol PGS; IGF-1 PGS; education; occupational social status; smoking status; alcohol consumption; physical activity; health (i.e., chronic lung disease; coronary heart disease; abnormal heart rhythm; heart murmur; congestive heart failure; angina; hypertension; diabetes; cancer; Parkinson's; Alzheimer's; dementia; asthma; arthritis; osteoporosis; psychiatric disorder).

Table S4.5 Longitudinal associations of the stress score with immune and neuroendocrine biomarker profiles (N=4,934)

Adjustments	Stress Score				
	RRR	SE	95% CI		*p*
***Moderate-risk* Profile**					
Model 1: *Unadjusted*	1.08	0.05	1.00	1.18	0.766
Model 2: *Model 1 + baseline biomarkers* [a]	1.11	0.05	1.01	1.22	0.942
Model 3: *Model 2 + demographics & genetics* [b]	1.25	0.06	1.13	1.38	0.080
Model 4: *Fully Adjusted* [c]	1.19	0.06	1.07	1.31	0.175
***High-risk* Profile**					
Model 1: *Unadjusted*	1.08	0.05	1.00	1.18	0.050
Model 2: *Model 1 + baseline biomarkers* [a]	1.11	0.05	1.01	1.22	0.031
Model 3: *Model 2 + demographics & genetics* [b]	1.25	0.06	1.13	1.38	0.000
Model 4: *Fully Adjusted* [c]	1.19	0.06	1.07	1.31	0.001

Notes: The *low-risk* group is the reference; RRR = relative risk ratio; SE = standard errors; CI = confidence interval; *p* = significance value.
a Baseline biomarkers: C-reactive protein (CRP); fibrinogen; insulin-growth factor-1 (IGF-1).
b Demographic and genetic variables: age; sex; 10 principal components (PCs); CRP polygenic score (PGS); cortisol PGS; IGF-1 PGS.
c All variables: CRP; fibrinogen; IGF-1; age; sex; 10 PCs; CRP PGS; cortisol PGS; IGF-1 PGS; education; occupational social status; smoking status; alcohol consumption; physical activity; health (i.e., chronic lung disease; coronary heart disease; abnormal heart rhythm; heart murmur; congestive heart failure; angina; hypertension; diabetes; cancer; Parkinson's; Alzheimer's; dementia; asthma; arthritis; osteoporosis; psychiatric disorder).

Table S4.6a Longitudinal associations of financial strain with immune and neuroendocrine biomarker profiles (N=4,934)

Adjustments	Binary Financial Stress Score				
	RRR	SE	95% CI		*p*
***Moderate-risk* Profile**					
Model 1: *Unadjusted*	1.28	0.12	1.07	1.53	0.007
Model 2: *Model 1 + baseline biomarkers* [a]	1.27	0.12	1.06	1.53	0.010
Model 3: *Model 2 + demographics & genetics* [b]	1.32	0.12	1.09	1.58	0.004
Model 4: *Fully Adjusted* [c]	1.23	0.12	1.02	1.48	0.033
***High-risk* Profile**					
Model 1: *Unadjusted*	1.66	0.16	1.37	2.01	<0.001
Model 2: *Model 1 + baseline biomarkers* [a]	1.66	0.19	1.33	2.09	<0.001
Model 3: *Model 2 + demographics & genetics* [b]	1.79	0.21	1.42	2.26	<0.001
Model 4: *Fully Adjusted* [c]	1.59	0.19	1.25	2.01	<0.001

Notes: The *low-risk* group is the reference; RRR = relative risk ratio; SE = standard errors; CI = confidence interval; *p* = significance value.
a Baseline biomarkers: C-reactive protein (CRP); fibrinogen; insulin-growth factor-1 (IGF-1).
b Demographic and genetic variables: age; sex; 10 principal components (PCs); CRP polygenic score (PGS); cortisol PGS; IGF-1 PGS.
c All variables: CRP; fibrinogen; IGF-1; age; sex; 10 PCs; CRP PGS; cortisol PGS; IGF-1 PGS; education; occupational social status; smoking status; alcohol consumption; physical activity; health (i.e., chronic lung disease; coronary heart disease; abnormal heart rhythm; heart murmur; congestive heart failure; angina; hypertension; diabetes; cancer; Parkinson's; Alzheimer's; dementia; asthma; arthritis; osteoporosis; psychiatric disorder).

Table S4.6b Longitudinal associations of care giving with immune and neuroendocrine biomarker profiles (N=4,934)

Adjustments	Binary Care Giving Stress Score				
	RRR	SE	95% CI		*p*
***Moderate-risk* Profile**					
Model 1: *Unadjusted*	1.05	0.14	0.82	1.36	0.685
Model 2: *Model 1 + baseline biomarkers* [a]	1.02	0.14	0.79	1.33	0.866
Model 3: *Model 2 + demographics & genetics* [b]	1.07	0.14	0.83	1.40	0.598
Model 4: *Fully Adjusted* [c]	1.10	0.15	0.84	1.43	0.484
***High-risk* Profile**					
Model 1: *Unadjusted*	1.05	0.15	0.79	1.40	0.726
Model 2: *Model 1 + baseline biomarkers* [a]	1.02	0.17	0.73	1.42	0.930
Model 3: *Model 2 + demographics & genetics* [b]	1.17	0.21	0.83	1.65	0.371
Model 4: *Fully Adjusted* [c]	1.29	0.23	0.91	1.83	0.153

Notes: The *low-risk* group is the reference; RRR = relative risk ratio; SE = standard errors; CI = confidence interval; *p* = significance value.
a Baseline biomarkers: C-reactive protein (CRP); fibrinogen; insulin-growth factor-1 (IGF-1).
b Demographic and genetic variables: age; sex; 10 principal components (PCs); CRP polygenic score (PGS); cortisol PGS; IGF-1 PGS.
c All variables: CRP; fibrinogen; IGF-1; age; sex; 10 PCs; CRP PGS; cortisol PGS; IGF-1 PGS; education; occupational social status; smoking status; alcohol consumption; physical activity; health (i.e., chronic lung disease; coronary heart disease; abnormal heart rhythm; heart murmur; congestive heart failure; angina; hypertension; diabetes; cancer; Parkinson's; Alzheimer's; dementia; asthma; arthritis; osteoporosis; psychiatric disorder).

Table S4.6c Longitudinal associations of disability with immune and neuroendocrine biomarker profiles (N=4,934)

Adjustments	Binary Disability Stress Score				
	RRR	SE	95% CI		*p*
***Moderate-risk* Profile**					
Model 1: *Unadjusted*	0.59	0.04	0.51	0.67	<0.001
Model 2: *Model 1 + baseline biomarkers* [a]	0.65	0.04	0.57	0.75	<0.001
Model 3: *Model 2 + demographics & genetics* [b]	0.74	0.05	0.64	0.85	<0.001
Model 4: *Fully Adjusted* [c]	0.80	0.06	0.69	0.92	0.002
***High-risk* Profile**					
Model 1: *Unadjusted*	0.33	0.03	0.28	0.39	<0.001
Model 2: *Model 1 + baseline biomarkers* [a]	0.46	0.04	0.39	0.55	<0.001
Model 3: *Model 2 + demographics & genetics* [b]	0.55	0.05	0.45	0.66	<0.001
Model 4: *Fully Adjusted* [c]	0.70	0.07	0.58	0.86	<0.001

Notes: The *low-risk* group is the reference; RRR = relative risk ratio; SE = standard errors; CI = confidence interval; *p* = significance value.
a Baseline biomarkers: C-reactive protein (CRP); fibrinogen; insulin-growth factor-1 (IGF-1).
b Demographic and genetic variables: age; sex; 10 principal components (PCs); CRP polygenic score (PGS); cortisol PGS; IGF-1 PGS.
c All variables: CRP; fibrinogen; IGF-1; age; sex; 10 PCs; CRP PGS; cortisol PGS; IGF-1 PGS; education; occupational social status; smoking status; alcohol consumption; physical activity; health (i.e., chronic lung disease; coronary heart disease; abnormal heart rhythm; heart murmur; congestive heart failure; angina; hypertension; diabetes; cancer; Parkinson's; Alzheimer's; dementia; asthma; arthritis; osteoporosis; psychiatric disorder).

Table S4.6d Longitudinal associations of limiting longstanding illness with immune and neuroendocrine biomarker profiles (N=4,934)

Adjustments	Binary Limiting Longstanding Illness Stress Score				
	RRR	SE	95% CI		*p*
***Moderate-risk* Profile**					
Model 1: *Unadjusted*	1.46	0.11	1.26	1.69	<0.001
Model 2: *Model 1 + baseline biomarkers* [a]	1.34	0.10	1.15	1.55	<0.001
Model 3: *Model 2 + demographics & genetics* [b]	1.25	0.10	1.07	1.46	0.004
Model 4: *Fully Adjusted* [c]	1.14	0.09	0.97	1.34	0.112
***High-risk* Profile**					
Model 1: *Unadjusted*	2.64	0.21	2.26	3.10	<0.001
Model 2: *Model 1 + baseline biomarkers* [a]	2.01	0.19	1.67	2.42	<0.001
Model 3: *Model 2 + demographics & genetics* [b]	1.81	0.18	1.50	2.18	<0.001
Model 4: *Fully Adjusted* [c]	1.34	0.14	1.10	1.65	0.005

Notes: The *low-risk* group is the reference; RRR = relative risk ratio; SE = standard errors; CI = confidence interval; *p* = significance value.
a Baseline biomarkers: C-reactive protein (CRP); fibrinogen; insulin-growth factor-1 (IGF-1).
b Demographic and genetic variables: age; sex; 10 principal components (PCs); CRP polygenic score (PGS); cortisol PGS; IGF-1 PGS.
c All variables: CRP; fibrinogen; IGF-1; age; sex; 10 PCs; CRP PGS; cortisol PGS; IGF-1 PGS; education; occupational social status; smoking status; alcohol consumption; physical activity; health (i.e., chronic lung disease; coronary heart disease; abnormal heart rhythm; heart murmur; congestive heart failure; angina; hypertension; diabetes; cancer; Parkinson's; Alzheimer's; dementia; asthma; arthritis; osteoporosis; psychiatric disorder).

Table S4.6e Longitudinal associations of bereavement with immune and neuroendocrine biomarker profiles (N=4,934)

Adjustments	Binary Bereavement Stress Score				
	RRR	SE	95% CI		*p*
***Moderate-risk* Profile**					
Model 1: *Unadjusted*	1.06	0.07	0.93	1.21	0.397
Model 2: *Model 1 + baseline biomarkers* [a]	1.07	0.07	0.93	1.22	0.354
Model 3: *Model 2 + demographics & genetics* [b]	1.16	0.08	1.01	1.33	0.040
Model 4: *Fully Adjusted* [c]	1.18	0.08	1.02	1.36	0.022
***High-risk* Profile**					
Model 1: *Unadjusted*	1.11	0.08	0.96	1.29	0.178
Model 2: *Model 1 + baseline biomarkers* [a]	1.10	0.10	0.93	1.31	0.273
Model 3: *Model 2 + demographics & genetics* [b]	1.25	0.12	1.04	1.50	0.016
Model 4: *Fully Adjusted* [c]	1.26	0.12	1.04	1.52	0.016

Notes: The *low-risk* group is the reference; RRR = relative risk ratio; SE = standard errors; CI = confidence interval; *p* = significance value.
a Baseline biomarkers: C-reactive protein (CRP); fibrinogen; insulin-growth factor-1 (IGF-1).
b Demographic and genetic variables: age; sex; 10 principal components (PCs); CRP polygenic score (PGS); cortisol PGS; IGF-1 PGS.
c All variables: CRP; fibrinogen; IGF-1; age; sex; 10 PCs; CRP PGS; cortisol PGS; IGF-1 PGS; education; occupational social status; smoking status; alcohol consumption; physical activity; health (i.e., chronic lung disease; coronary heart disease; abnormal heart rhythm; heart murmur; congestive heart failure; angina; hypertension; diabetes; cancer; Parkinson's; Alzheimer's; dementia; asthma; arthritis; osteoporosis; psychiatric disorder).

Table S4.6f Longitudinal associations of divorce with immune and neuroendocrine biomarker profiles (N=4,934)

Adjustments	Binary Divorce Stress Score				
	RRR	SE	95% CI		*p*
***Moderate-risk* Profile**					
Model 1: *Unadjusted*	1.03	0.12	0.82	1.29	0.810
Model 2: *Model 1 + baseline biomarkers* [a]	1.05	0.13	0.83	1.32	0.698
Model 3: *Model 2 + demographics & genetics* [b]	1.10	0.13	0.87	1.39	0.441
Model 4: *Fully Adjusted* [c]	0.98	0.12	0.77	1.25	0.886
***High-risk* Profile**					
Model 1: *Unadjusted*	1.27	0.16	0.99	1.62	0.060
Model 2: *Model 1 + baseline biomarkers* [a]	1.31	0.20	0.98	1.76	0.069
Model 3: *Model 2 + demographics & genetics* [b]	1.52	0.23	1.13	2.05	0.006
Model 4: *Fully Adjusted* [c]	1.20	0.19	0.88	1.64	0.243

Notes: The *low-risk* group is the reference; RRR = relative risk ratio; SE = standard errors; CI = confidence interval; *p* = significance value.
a Baseline biomarkers: C-reactive protein (CRP); fibrinogen; insulin-growth factor-1 (IGF-1).
b Demographic and genetic variables: age; sex; 10 principal components (PCs); CRP polygenic score (PGS); cortisol PGS; IGF-1 PGS.
c All variables: CRP; fibrinogen; IGF-1; age; sex; 10 PCs; CRP PGS; cortisol PGS; IGF-1 PGS; education; occupational social status; smoking status; alcohol consumption; physical activity; health (i.e., chronic lung disease; coronary heart disease; abnormal heart rhythm; heart murmur; congestive heart failure; angina; hypertension; diabetes; cancer; Parkinson's; Alzheimer's; dementia; asthma; arthritis; osteoporosis; psychiatric disorder).

Table S4.7 Longitudinal associations of stress with immune and neuroendocrine biomarker profiles, excluding measures for disability and limiting longstanding illness (N=4,934)

Adjustments	Reduced Binary Stress Score				
	RRR	SE	95% CI		*p*
***Moderate-risk* Profile**					
Model 1: *Unadjusted*	1.04	0.10	0.86	1.26	0.698
Model 2: *Model 1 + baseline biomarkers* [a]	1.05	0.11	0.86	1.28	0.646
Model 3: *Model 2 + demographics & genetics* [b]	1.17	0.12	0.95	1.43	0.141
Model 4: *Fully Adjusted* [c]	1.11	0.12	0.90	1.36	0.335
***High-risk* Profile**					
Model 1: *Unadjusted*	1.47	0.15	1.19	1.80	<0.001
Model 2: *Model 1 + baseline biomarkers* [a]	1.52	0.19	1.19	1.94	0.001
Model 3: *Model 2 + demographics & genetics* [b]	1.89	0.24	1.47	2.43	<0.001
Model 4: *Fully Adjusted* [c]	1.71	0.23	1.32	2.22	<0.001

Adjustments	Reduced Stress Score				
	RRR	SE	95% CI		*p*
***Moderate-risk* Profile**					
Model 1: *Unadjusted*	1.10	0.05	1.01	1.21	0.029
Model 2: *Model 1 + baseline biomarkers* [a]	1.11	0.05	1.01	1.21	0.033
Model 3: *Model 2 + demographics & genetics* [b]	1.18	0.06	1.07	1.30	0.001
Model 4: *Fully Adjusted* [c]	1.15	0.06	1.04	1.27	0.004
***High-risk* Profile**					
Model 1: *Unadjusted*	1.25	0.06	1.13	1.38	<0.001
Model 2: *Model 1 + baseline biomarkers* [a]	1.25	0.08	1.11	1.41	<0.001
Model 3: *Model 2 + demographics & genetics* [b]	1.42	0.09	1.26	1.61	<0.001
Model 4: *Fully Adjusted* [c]	1.35	0.09	1.19	1.53	<0.001

Notes: The *low-risk* group is the reference; RRR = relative risk ratio; SE = standard errors; CI = confidence interval; *p* = significance value.
a Baseline biomarkers: C-reactive protein (CRP); fibrinogen; insulin-growth factor-1 (IGF-1).
b Demographic and genetic variables: age; sex; 10 principal components (PCs); CRP polygenic score (PGS); cortisol PGS; IGF-1 PGS.
c All variables: CRP; fibrinogen; IGF-1; age; sex; 10 PCs; CRP PGS; cortisol PGS; IGF-1 PGS; education; occupational social status; smoking status; alcohol consumption; physical activity; health (i.e., chronic lung disease; coronary heart disease; abnormal heart rhythm; heart murmur; congestive heart failure; angina; hypertension; diabetes; cancer; Parkinson's; Alzheimer's; dementia; asthma; arthritis; osteoporosis; psychiatric disorder).

Table S4.8a Longitudinal associations of stress with immune and neuroendocrine biomarker profiles stratified by median age (65 years)

Adjustments	Binary Stress Score | < Mdn Age (N=2,437)					Binary Stress Score | ≥ Mdn Age (N=2,497)				
	RRR	**SE**	**95% CI**		***p***	**RRR**	**SE**	**95% CI**		***p***
***Moderate-risk* Profile**										
Model 1: *Unadjusted*	1.06	0.13	0.83	1.35	0.660	1.10	0.21	0.76	1.59	0.624
Model 2: *Model 1 + baseline biomarkers* [a]	1.13	0.15	0.88	1.45	0.350	1.08	0.21	0.74	1.58	0.687
Model 3: *Model 2 + demographics & genetics* [b]	1.13	0.15	0.88	1.46	0.343	1.16	0.23	0.79	1.70	0.458
Model 4: *Fully Adjusted* [c]	1.08	0.14	0.83	1.39	0.583	1.12	0.22	0.76	1.65	0.581
***High-risk* Profile**										
Model 1: *Unadjusted*	1.26	0.18	0.95	1.67	0.117	2.05	0.38	1.43	2.95	<0.001
Model 2: *Model 1 + baseline biomarkers* [a]	1.40	0.24	0.99	1.96	0.056	1.98	0.42	1.31	3.00	0.001
Model 3: *Model 2 + demographics & genetics* [b]	1.37	0.24	0.96	1.93	0.079	2.29	0.51	1.49	3.53	<0.001
Model 4: *Fully Adjusted* [c]	1.18	0.22	0.83	1.69	0.354	2.13	0.49	1.36	3.34	0.001

Notes: The *low-risk* group is the reference; < = less than; ≥ = greater than or equal to; Mdn = Median; RRR = relative risk ratio; SE = standard errors; CI = confidence interval; *p* = significance value.

a Baseline biomarkers: C-reactive protein (CRP); fibrinogen; insulin-growth factor-1 (IGF-1).

b Demographic and genetic variables: age; sex; 10 principal components (PCs); CRP polygenic score (PGS); cortisol PGS; IGF-1 PGS.

c All variables: CRP; fibrinogen; IGF-1; age; sex; 10 PCs; CRP PGS; cortisol PGS; IGF-1 PGS; education; occupational social status; smoking status; alcohol consumption; physical activity; health (i.e., chronic lung disease; coronary heart disease; abnormal heart rhythm; heart murmur; congestive heart failure; angina; hypertension; diabetes; cancer; Parkinson's; Alzheimer's; dementia; asthma; arthritis; osteoporosis; psychiatric disorder).

Table S4.8b The moderated effective of age on longitudinal associations between stress and immune and neuroendocrine biomarker profiles (N=4,934)

Adjustments	Stress Score | Age				
	RRR	SE	95% CI		*p*
***Moderate-risk*: Profile**					
Model 1: *Unadjusted*	1.00	0.00	0.99	1.01	0.445
Model 2: *Model 1 + baseline biomarkers* [a]	1.00	0.00	0.99	1.00	0.229
Model 3: *Model 2 + demographics & genetics* [b]	0.99	0.01	0.99	1.00	0.202
Model 4: *Fully Adjusted* [c]	0.99	0.01	0.99	1.00	0.172
***High-risk*: Profile**					
Model 1: *Unadjusted*	1.01	0.01	1.00	1.02	0.205
Model 2: *Model 1 + baseline biomarkers* [a]	1.00	0.01	0.99	1.01	0.829
Model 3: *Model 2 + demographics & genetics* [b]	1.00	0.01	0.99	1.01	0.801
Model 4: *Fully Adjusted* [c]	1.00	0.01	0.99	1.01	0.913

Table S4.9a Longitudinal associations of stress with immune and neuroendocrine biomarker profiles stratified by sex

Adjustments	Binary Stress Score | Male (N=2,235)					Binary Stress Score | Female (N=2,699)				
	RRR	SE	95% CI		*p*	RRR	SE	95% CI		*p*
***Moderate-risk* Profile**										
Model 1: *Unadjusted*	0.90	0.15	0.66	1.25	0.540	1.01	0.13	0.78	1.31	0.922
Model 2: *Model 1 + baseline biomarkers* [a]	0.96	0.16	0.69	1.33	0.790	1.03	0.14	0.79	1.35	0.818
Model 3: *Model 2 + demographics & genetics* [b]	1.09	0.19	0.78	1.53	0.611	1.16	0.16	0.89	1.52	0.280
Model 4: *Fully Adjusted* [c]	0.97	0.17	0.69	1.37	0.857	1.16	0.16	0.88	1.53	0.289
***High-risk* Profile**										
Model 1: *Unadjusted*	1.32	0.23	0.94	1.84	0.112	1.34	0.19	1.01	1.76	0.042
Model 2: *Model 1 + baseline biomarkers* [a]	1.46	0.30	0.97	2.18	0.069	1.41	0.24	1.02	1.97	0.040
Model 3: *Model 2 + demographics & genetics* [b]	1.82	0.39	1.19	2.77	0.006	1.78	0.31	1.26	2.50	0.001
Model 4: *Fully Adjusted* [c]	1.48	0.33	0.95	2.29	0.080	1.66	0.30	1.17	2.37	0.005

Notes: The *low-risk* group is the reference; RRR = relative risk ratio; SE = standard errors; CI = confidence interval; *p* = significance value.

a Baseline biomarkers: C-reactive protein (CRP); fibrinogen; insulin-growth factor-1 (IGF-1).

b Demographic and genetic variables: age; sex; 10 principal components (PCs); CRP polygenic score (PGS); cortisol PGS; IGF-1 PGS.

c All variables: CRP; fibrinogen; IGF-1; age; sex; 10 PCs; CRP PGS; cortisol PGS; IGF-1 PGS; education; occupational social status; smoking status; alcohol consumption; physical activity; health (i.e., chronic lung disease; coronary heart disease; abnormal heart rhythm; heart murmur; congestive heart failure; angina; hypertension; diabetes; cancer; Parkinson's; Alzheimer's; dementia; asthma; arthritis; osteoporosis; psychiatric disorder).

Table S4.9b The moderated effective of sex on longitudinal associations between stress and immune and neuroendocrine biomarker profiles (N=4,934)

Adjustments	Stress Score | Sex				
	RRR	**SE**	**95% CI**		***p***
***Moderate-risk* Profile**					
Model 1: *Unadjusted*	1.03	0.08	0.89	1.19	0.704
Model 2: *Model 1 + baseline biomarkers* [a]	1.05	0.08	0.91	1.23	0.495
Model 3: *Model 2 + demographics & genetics* [b]	1.11	0.09	0.95	1.29	0.189
Model 4: *Fully Adjusted* [c]	1.09	0.09	0.93	1.27	0.299
***High-risk* Profile**					
Model 1: *Unadjusted*	1.03	0.09	0.87	1.21	0.742
Model 2: *Model 1 + baseline biomarkers* [a]	1.08	0.11	0.89	1.31	0.469
Model 3: *Model 2 + demographics & genetics* [b]	1.15	0.12	0.94	1.41	0.163
Model 4: *Fully Adjusted* [c]	1.13	0.12	0.92	1.39	0.239

Table S4.10 Longitudinal associations of stress with immune and neuroendocrine biomarker profiles (N=4,934)

Adjustments	Binary Stress Score				
	RRR	SE	95% CI		*p*
***Moderate-risk* Profile**					
Model 1: *Unadjusted*	0.98	0.10	0.81	1.20	0.870
Model 2: *Model 1 + baseline biomarkers & demographics* [a]	1.14	0.12	0.92	1.40	0.225
Model 3: *Model 2 + genetics* [b]	1.14	0.12	0.93	1.41	0.213
Model 4: *Fully Adjusted* [c]	1.10	0.12	0.89	1.35	0.401
***High-risk* Profile**					
Model 1: *Unadjusted*	1.34	0.15	1.08	1.66	0.008
Model 2: *Model 1 + baseline biomarkers & demographics* [a]	1.79	0.24	1.38	2.33	<0.001
Model 3: *Model 2 + genetics* [b]	1.80	0.24	1.39	2.35	<0.001
Model 4: *Fully Adjusted* [c]	1.61	0.22	1.23	2.12	0.001

Notes: The *low-risk* group is the reference; RRR = relative risk ratio; SE = standard errors; CI = confidence interval; *p* = significance value.
a Baseline biomarkers and genetic variables: C-reactive protein (CRP); fibrinogen; insulin-growth factor-1 (IGF-1); age; sex.
b Demographic: 10 principal components (PCs); CRP polygenic score (PGS); cortisol PGS; IGF-1 PGS.
c All variables: CRP; fibrinogen; IGF-1; age; sex; 10 PCs; CRP PGS; cortisol PGS; IGF-1 PGS; education; occupational social status; smoking status; alcohol consumption; physical activity; health (i.e., chronic lung disease; coronary heart disease; abnormal heart rhythm; heart murmur; congestive heart failure; angina; hypertension; diabetes; cancer; Parkinson's; Alzheimer's; dementia; asthma; arthritis; osteoporosis; psychiatric disorder).

Table S4.11 Longitudinal associations of stress with immune and neuroendocrine biomarker profiles, with complete case data (N=1,677)

Adjustments	Binary Stress Score				
	RRR	SE	95% CI		*p*
***Moderate-risk* Profile**					
Model 1: *Unadjusted*	1.23	0.20	0.89	1.70	0.210
Model 2: *Model 1 + baseline biomarkers* [a]	1.33	0.25	0.93	1.91	0.117
Model 3: *Model 2 + demographics & genetics* [b]	1.38	0.26	0.96	1.99	0.084
Model 4: *Fully Adjusted* [c]	1.33	0.25	0.91	1.93	0.136
***High-risk* Profile**					
Model 1: *Unadjusted*	1.22	0.34	0.71	2.11	0.473
Model 2: *Model 1 + baseline biomarkers* [a]	1.35	0.41	0.74	2.46	0.330
Model 3: *Model 2 + demographics & genetics* [b]	1.44	0.45	0.78	2.65	0.239
Model 4: *Fully Adjusted* [c]	1.23	0.40	0.65	2.32	0.524

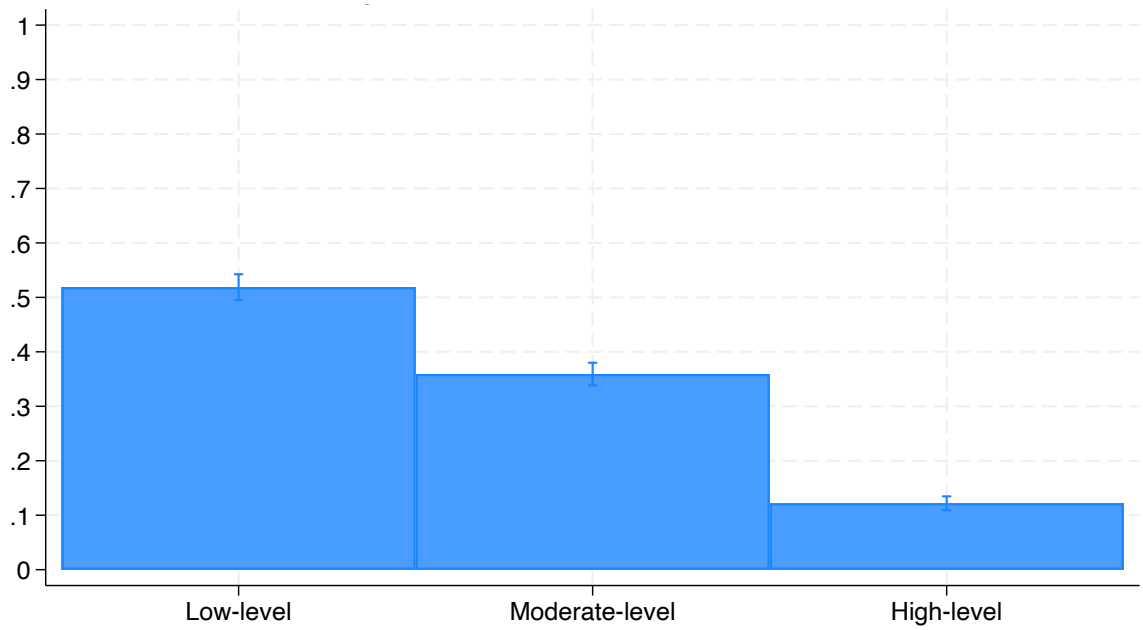
Adjustments	Stress Score				
	RRR	SE	95% CI		*p*
***Moderate-risk* Profile**					
Model 1: *Unadjusted*	1.09	0.07	0.97	1.23	0.141
Model 2: *Model 1 + baseline biomarkers* [a]	1.11	0.07	0.97	1.26	0.125
Model 3: *Model 2 + demographics & genetics* [b]	1.13	0.08	0.99	1.29	0.071
Model 4: *Fully Adjusted* [c]	1.12	0.08	0.98	1.29	0.096
***High-risk* Profile**					
Model 1: *Unadjusted*	1.13	0.12	0.92	1.38	0.236
Model 2: *Model 1 + baseline biomarkers* [a]	1.14	0.13	0.92	1.43	0.241
Model 3: *Model 2 + demographics & genetics* [b]	1.19	0.14	0.95	1.49	0.141
Model 4: *Fully Adjusted* [c]	1.09	0.13	0.86	1.38	0.492

Notes: The *low-risk* group is the reference; RRR = relative risk ratio; SE = standard errors; CI = confidence interval; *p* = significance value.
a Baseline biomarkers: C-reactive protein (CRP); fibrinogen; insulin-growth factor-1 (IGF-1).
b Demographic and genetic variables: age; sex; 10 principal components (PCs); CRP polygenic score (PGS); cortisol PGS; IGF-1 PGS.
c All variables: CRP; fibrinogen; IGF-1; age; sex; 10 PCs; CRP PGS; cortisol PGS; IGF-1 PGS; education; occupational social status; smoking status; alcohol consumption; physical activity; health (i.e., chronic lung disease; coronary heart disease; abnormal heart rhythm; heart murmur; congestive heart failure; angina; hypertension; diabetes; cancer; Parkinson's; Alzheimer's; dementia; asthma; arthritis; osteoporosis; psychiatric disorder).

APPENDIX C

CHAPTER 5 | Supplementary Material

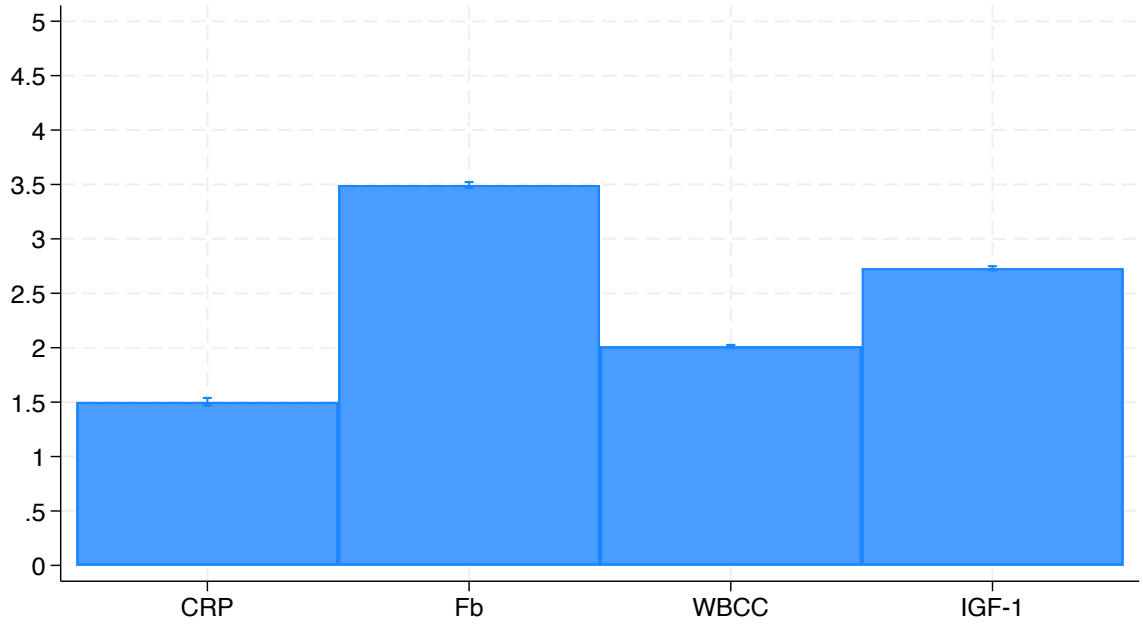
Figure S5.1 **The percentage of participants belonging to each immune and neuroendocrine biomarker profile with 95% confidence intervals for the wave 4 three-profile solution (N = 4,940)**



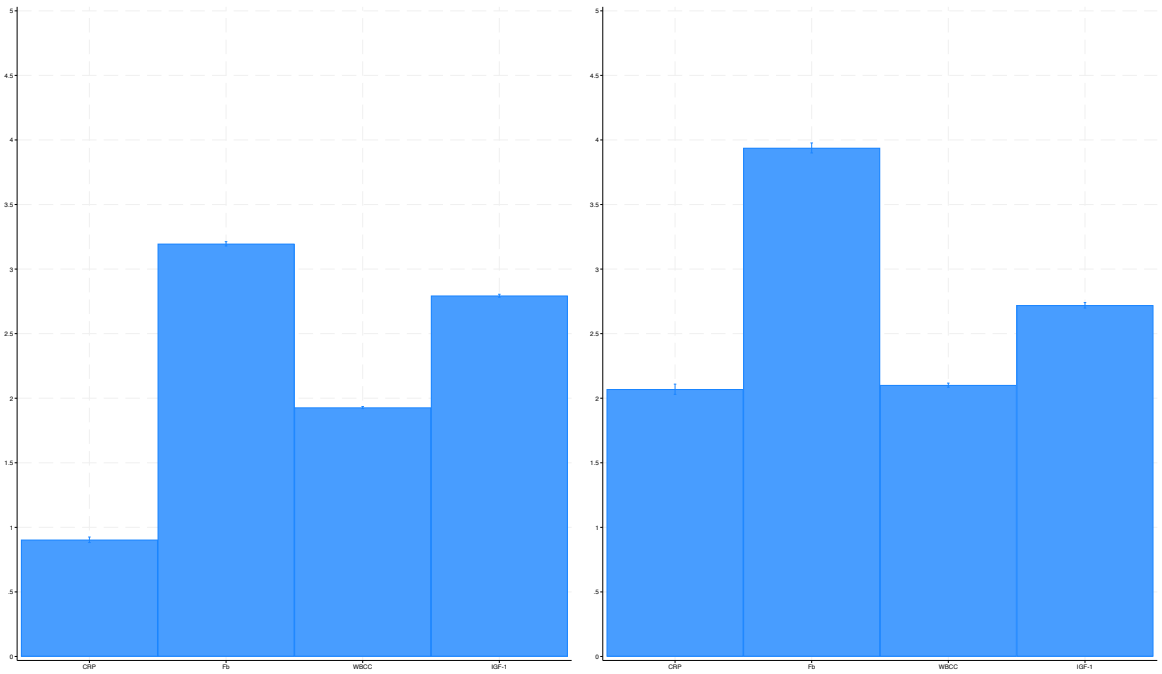
Profile	N	%
1	2,590	52.43
2	1,773	35.89
3	577	11.68

Figure S5.2 **[a-g] Predicted mean of immune and neuroendocrine biomarker levels for a one to seven profile solution for wave 6 (N = 4,940)**

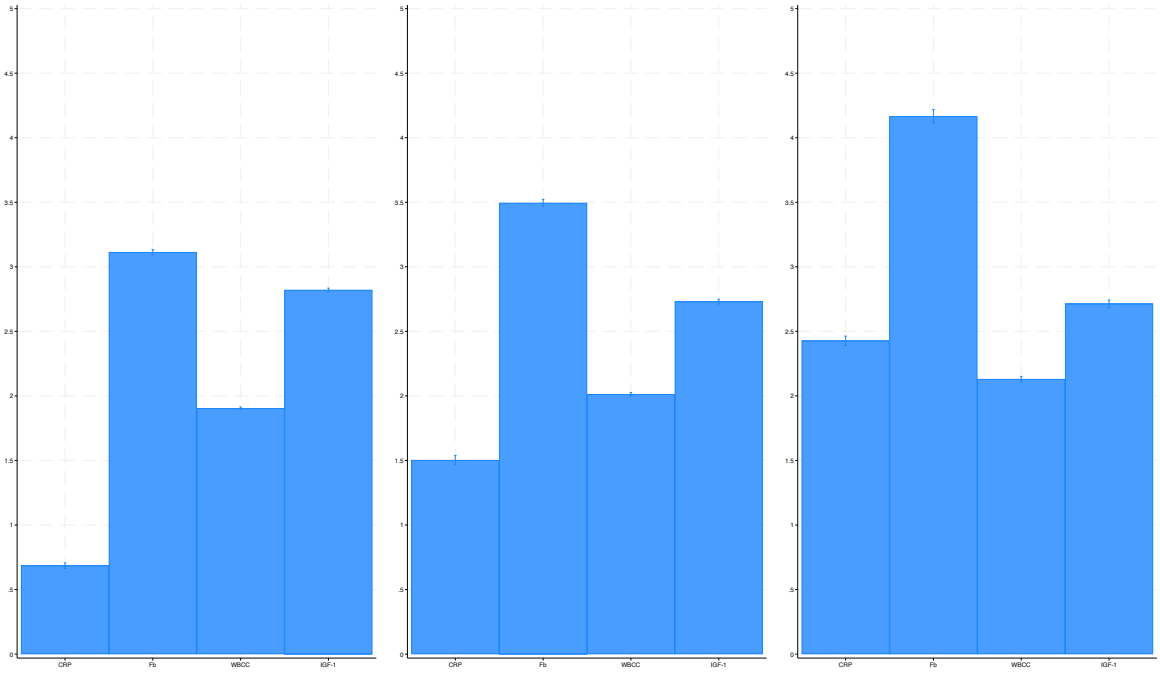
a



b



c


5
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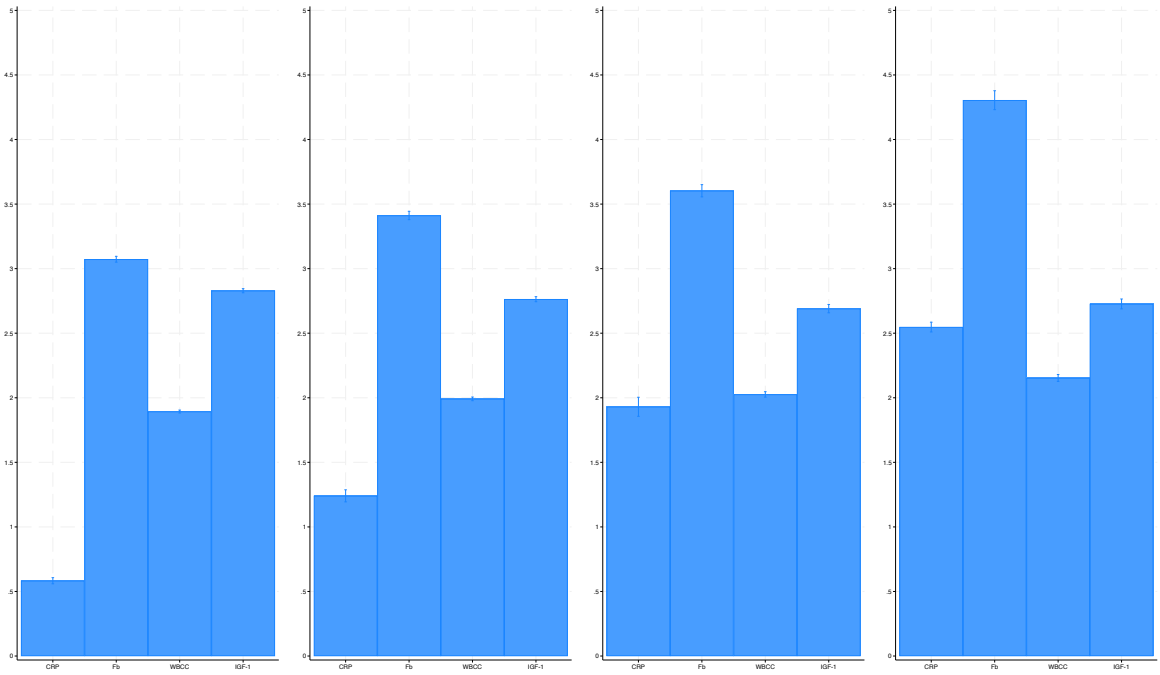
4
3.5
3
2.5
2
1.5
1
.5
0
CRP
Fb
WBCC
IGF-1

d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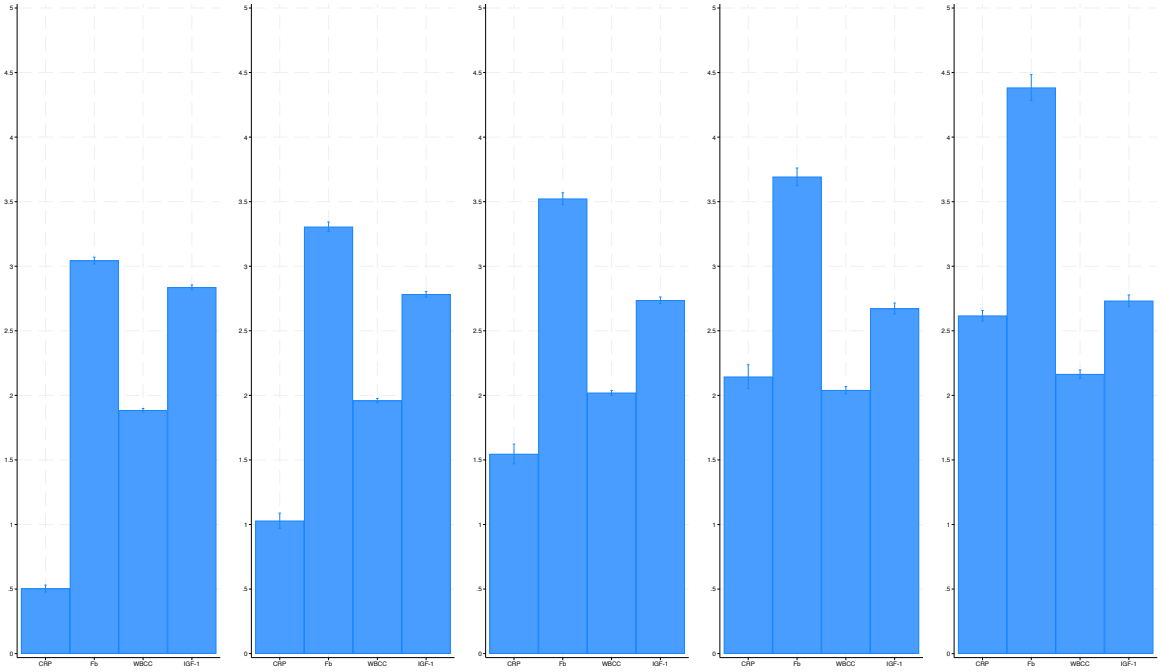
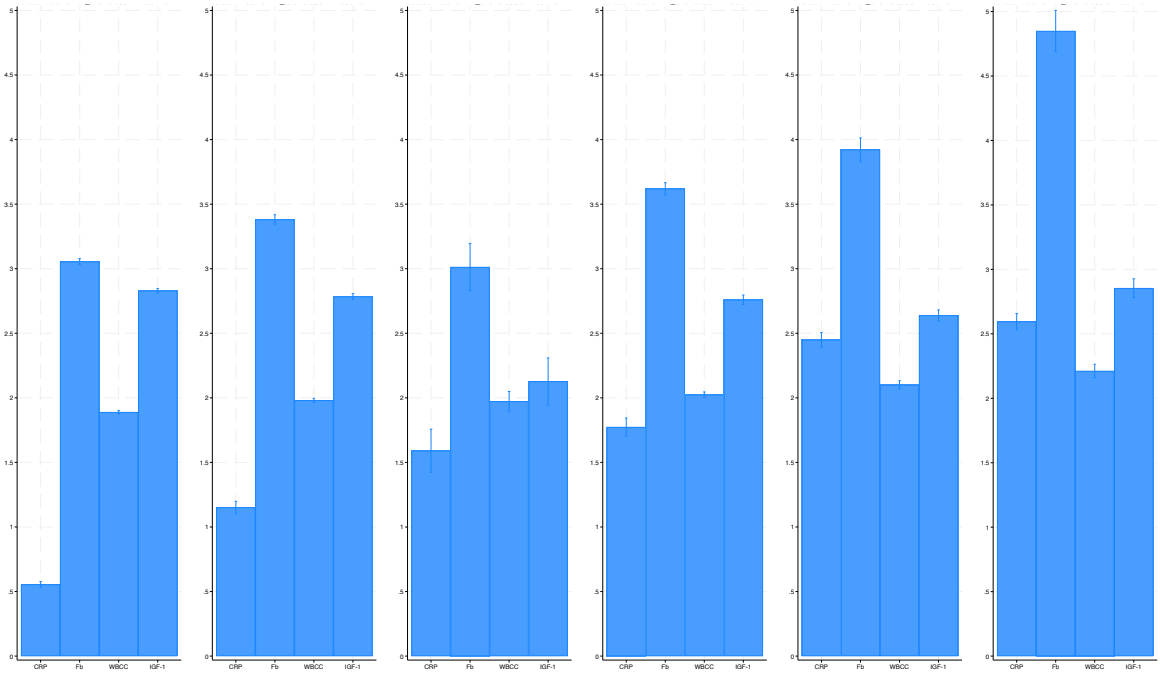
4
3.5
3
2.5
2
1.5
1
.5
0
CRP
Fb
WBCC
IGF-1

e



f



g

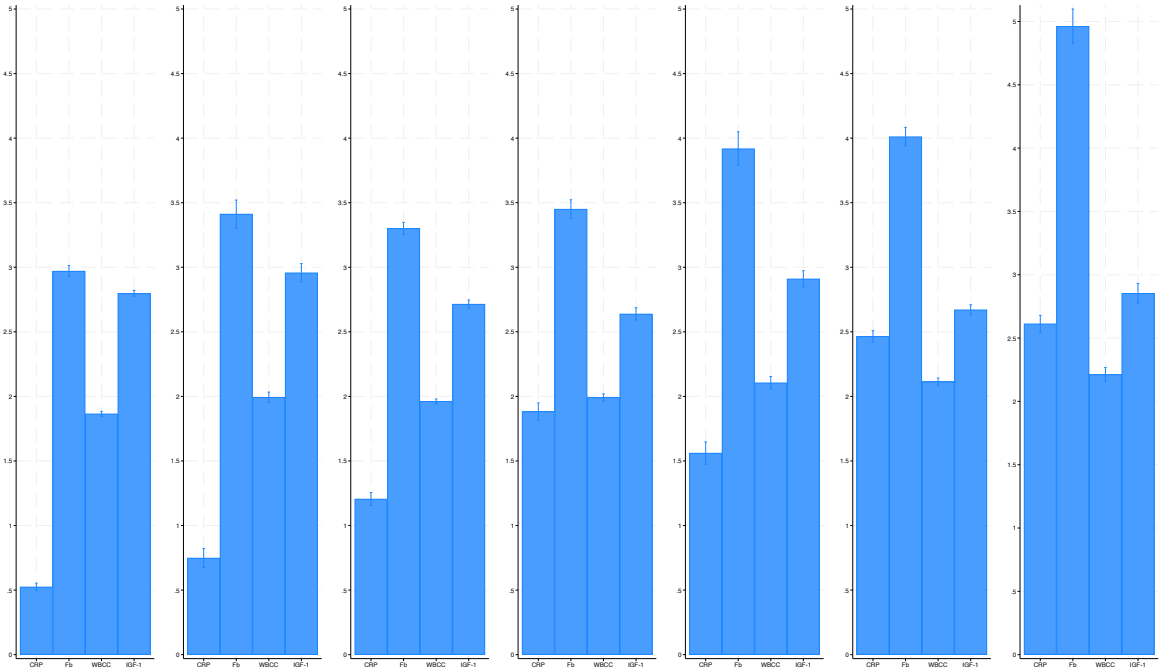


Table S5.1 The distribution of missing data, with a comparison between imputed, core, and complete case sample characteristics

Variable		Missing Data	Imputed (N = 4,940)		Core (N = 6,523)		Complete Case (N = 1,305)	
		N | %	N / M (SD)	% / Range	N / M (SD)	% / Range	N / M (SD)	% / Range
Age		0 | 0	66.3 (9.35)	50-99	65.4 (9.43)	50-99	64.53 (7.85)	50-99
Age (Binary)	< Md	0 | 0	2,436	49.31	3,205	49.13	628	48.12
	≥ Md		2,504	50.69	3,318	50.87	677	51.88
Sex	Male	0 | 0	2,237	45.3	2,945	45.15	410	31.42
	Female		2,703	54.7	3,578	54.85	895	68.58
Education	Higher	100 | 0.93	1,589	32.2	2,116	32.44	445	34.10
	Primary/Secondary/Tertiary		1,543	31.2	2,075	31.81	436	33.41
	Alternative/No		1,808	36.6	2,332	35.75	424	32.49
Wealth	Lowest	1,160 | 10.79	1,573	31.8	2,082	31.92	399	30.57
	Middle		2,014	40.8	2,581	39.57	565	43.30
	Highest		1,353	27.4	1,860	28.51	341	26.13
OSC	Managerial/Professional	534 | 4.97	1,793	36.3	2,434	37.31	475	36.40
	Intermediate		1,264	25.6	1,641	25.16	352	26.97
	Routine/Manual		1,883	38.1	2,448	37.53	478	36.63
Smoking Status	Never/Ex-Smokers	203 | 1.89	4,312	87.3	5,673	86.97	1,146	87.82
	Current Smoker		628	12.7	850	13.03	159	12.18
Alcohol Consumption	<3 days a week	1,597 | 14.86	3,175	64.3	4,262	65.34	815	62.45
	≥3 days a week		1,765	35.7	2,261	34.66	490	37.55
Physical Activity	Sedentary	179 | 1.67	1,340	27.1	1,786	27.38	304	23.30
	Active		3,600	72.9	4,737	72.62	1,001	76.70
Mobility	Mobile	141 | 1.31	2,678	54.2	3,422	52.46	687	52.64
	Not Mobile		2,262	45.8	3,101	47.54	618	47.36
Limiting Longstanding Illness	None	8 | 0.07	3,386	68.5	4,535	69.52	923	70.73
	Present		1,554	31.5	1,988	30.48	382	29
Health	No health condition	132 | 1.23	3,319	67.2	4,640	71.13	866	66.36
	At least one health condition		1,621	32.8	1,883	28.87	439	33.64
BMI (kg/m2)	<25, Underweight/Normal	2,474 | 23.02	1,312	26.6	1,769	27.12	354	27.13
	25-30, Overweight: Pre-obese		2,213	44.8	2,917	44.72	564	43.22
	30 or over, Obese		1,415	28.6	1,837	28.16	387	29.66
CRP* (mg/L; Baseline)		4,502 | 41.88	0.28 (0.46)	-0.70-1.30	0.28 (0.46)	-0.70-1.30	0.24 (0.46)	-0.70-1.29
CRP* (mg/L; Follow-up)		5,625 | 52.33	0.40 (0.48)	-1.00-1.30	0.39 (0.47)	-1.00-1.30	0.19 (0.43)	-1.00-1.29
Fb (g/L; Baseline)		4,535 | 42.19	3.38 (0.56)	1.30-5.90	3.37 (0.56)	1.30-5.90	3.32 (0.53)	1.70-5.30
Fb (g/L; Follow-up)		5,620 | 52.28	3.12 (0.52)	1.50-5.80	3.10 (0.52)	1.30-5.80	2.95 (0.49)	1.60-4.70
WBCC* (nmol/L; Baseline)		4,471 | 41.59	0.79 (0.13)	-0.10-1.50	0.79 (0.13)	-0.10-1.70	0.78 (0.13)	0.15-1.50
WBCC* (nmol/L; Follow-up)		5,571 | 51.83	0.81 (0.11)	0.34-1.51	0.81 (0.11)	0.31-1.51	0.79 (0.13)	0.39-1.51
IGF-1* (nmol/L; Baseline)		4,441 | 41.32	1.18 (0.16)	0.30-1.81	1.17 (0.16)	0.30-1.81	1.18 (0.15)	0.60-1.66
IGF-1* (nmol/L; Follow-up)			1.18 (0.13)	0.60-1.76	1.18 (0.13)	0.60-1.76	1.19 (0.14)	0.70-1.76
Cortisol* (nmol/L; Follow-up)		6,556 | 60.99	1.23 (0.65)	-0.85-2.82	0.39 (0.47)	-1.00-1.30	0.89 (0.59)	-0.85-2.82
Stress (indexed by Financial Strain)	No Strain (0-60%)	676 | 6.29	4,099	83.0	5,407	82.89	1,049	80.38
	Strain (61-100%)		841	17.0	1,116	17.11	256	19.62
Sleep Duration	Short Sleep	0 | 0	627	12.7	828	12.69	181	13.72
	Optimal Sleep		4,227	85.6	5,575	85.47	1,126	85.37
	Long Sleep		86	1.70	120	1.84	12	0.91

Notes: ELSA, waves 4-6 (2008/09-2012/13); N = observations; M = mean; Md = median; % = percentage frequencies; SD = standard deviations; < = less than; ≥ = greater than or equal to; OSC = occupational social class; BMI = body mass index; CRP = C-reactive protein; Fb = fibrinogen; WBCC = white blood cell counts; IGF-1 = insulin-growth factor-1; Cortisol = hair cortisol; * Log-transformed variable; I-N = immune and neuroendocrine.

Table S5.2 Correlations between immune and neuroendocrine biomarkers

	CRP	Fb	WBCC	Cortisol	IGF-1
CRP	1				
Fb	**0.7065*** <0.001	1			
WBCC	**0.4477*** <0.001	**0.4122*** <0.001	1		
Cortisol	**0.2811*** <0.001	**0.1893*** <0.001	**0.2317*** <0.001	1	
IGF-1	**-0.1671*** <0.001	-0.011 0.356	-0.006 0.627	0.004 0.755	1

Notes: CRP = C-reactive protein; Fb = fibrinogen; WBCC = white blood cell counts; IGF-1 = insulin growth factor-1; Cortisol = hair cortisol; * Significant at $p<0.001$ level

Table S5.3 Change in financial stress and suboptimal sleep cases across waves

Variable		*n*	%
Financial Stress (W4)	No Strain (0-60%)	4,114	83.28
	Strain (61-100%)	826	16.72
Financial Stress (W5)	No Strain (0-60%)	4,179	84.60
	Strain (61-100%)	761	15.40
Financial Stress (W6)	No Strain (0-60%)	4,273	86.50
	Strain (61-100%)	667	13.50
Sleep Duration (W4)	Short Sleep	627	12.69
	Optimal Sleep	4,227	85.57
	Long Sleep	86	1.74
Sleep Duration (W6)	Short Sleep	518	10.49
	Optimal Sleep	4,160	84.21
	Long Sleep	262	5.30

Notes: W = wave; *n* = number of observations; % = percentage of observations. Wave 5 sleep duration was unavailable.

Table S5.4 Seven profile LPA model fit indices and predicted probability of profile membership

Criteria	One Profile	Two Profiles	Three Profiles	Four Profiles	Five Profiles	Six Profiles	Seven Profiles
AIC	35960.37	30398.85	28688.66	28428.96	28023.89	27852.44	27662.91
AIC Difference (N)	-	5561.52	1710.19	259.70	405.07	171.45	189.53
AIC Difference (%)	-	18.30	5.96	0.91	1.45	0.62	0.69
BIC	36025.42	30502.93	28831.77	28611.10	28245.06	28112.65	27962.14
BIC Difference (N)	-	5522.49	1671.16	220.67	366.04	132.41	150.51
BIC Difference (%)	-	18.10	5.80	0.77	1.30	0.47	0.54
aBIC	35993.64	30452.09	28761.86	28522.13	28137.02	27985.54	27815.97
aBIC Difference (N)	-	5541.55	1690.23	239.74	385.11	151.48	169.57
aBIC Difference (%)	-	18.20	5.88	0.84	1.37	0.54	0.61
Entropy	-	0.91	0.83	0.79	0.83	0.86	0.86
Normalised Entropy	-	0.88	0.77	0.71	0.77	0.82	0.81
M Posterior Probabilities (SE)	-	.712 (.007)	.352 (.008)	.298 (.013)	.185 (.008)	.181 (.008)	.180 (.008)
		.288 (.007)	.395 (.008)	.079 (.014)	.221 (.008)	.054 (.012)	.059 (.011)
			.254 (.006)	.370 (.009)	.293 (.008)	.172 (.114)	.167 (.013)
				.253 (.006)	.070 (.005)	.293 (.008)	.292 (.008)
					.231 (.006)	.069 (.005)	.048 (.006)
						.231 (.006)	.024 (.004)
							.230 (.006)
N classes >5%	Yes	Yes	Yes	Yes	Yes	No	No

Notes: AIC = Akaike information criterion; BIC = Bayesian information criterion; aBIC = adjusted Bayesian information criterion; N = number of observations; M = mean; SE = standard errors.

Table S5.5 Longitudinal associations of stress with immune and neuroendocrine biomarker profiles stratified by median age (65 years)

Adjustments	Binary Stress Score | < Md Age (N=2,436)					Binary Stress Score | ≥ Md Age (N=2,504)				
	RRR	SE	95% CI		*p*	RRR	SE	95% CI		*p*
***Moderate-risk* Profile**										
Model 1: *Unadjusted*	1.39	0.17	1.09	1.78	0.008	1.12	0.15	0.86	1.46	0.383
Model 2: *Model 1 + baseline biomarkers* [a]	1.39	0.18	1.08	1.80	0.011	1.10	0.15	0.84	1.43	0.498
Model 3: *Model 2 + demographics & genetics* [b]	1.38	0.18	1.07	1.79	0.014	1.19	0.17	0.90	1.56	0.221
Model 4: *Fully Adjusted* [c]	1.30	0.18	1.00	1.70	0.050	1.08	0.15	0.81	1.42	0.614
***High-risk* Profile**										
Model 1: *Unadjusted*	1.97	0.28	1.50	2.60	<0.001	1.31	0.18	0.99	1.72	0.056
Model 2: *Model 1 + baseline biomarkers* [a]	1.98	0.33	1.43	2.75	<0.001	1.24	0.20	0.91	1.69	0.176
Model 3: *Model 2 + demographics & genetics* [b]	1.97	0.33	1.42	2.75	<0.001	1.40	0.23	1.02	1.93	0.040
Model 4: *Fully Adjusted* [c]	1.70	0.30	1.20	2.41	0.003	1.23	0.21	0.88	1.71	0.232

Notes: The *low-risk* group is the reference; < = less than; ≥ = greater than or equal to; Md = Median; RRR = relative risk ratio; SE = standard errors; CI = confidence interval; *p* = significance value.

a Baseline biomarkers: C-reactive protein (CRP); fibrinogen; insulin-growth factor-1 (IGF-1).

b Demographic and genetic variables: age; sex; 10 principal components (PCs); CRP polygenic score (PGS); cortisol PGS; IGF-1 PGS.

c All variables: CRP; fibrinogen; IGF-1; age; sex; 10 PCs; CRP PGS; cortisol PGS; IGF-1 PGS; education; occupational social status; smoking status; alcohol consumption; physical activity; health (i.e., chronic lung disease; coronary heart disease; abnormal heart rhythm; heart murmur; congestive heart failure; angina; hypertension; diabetes; cancer; Parkinson's; Alzheimer's; dementia; asthma; arthritis; osteoporosis; psychiatric disorder).

Table S5.6 Longitudinal associations of suboptimal sleep with immune and neuroendocrine biomarker profiles stratified by median age (65 years)

Adjustments	Short Sleep | < Md Age (N=2,436)					Short Sleep | ≥ Md Age (N=2,504)				
	RRR	**SE**	**95% CI**		***p***	**RRR**	**SE**	**95% CI**		***p***
***Moderate-risk* Profile**										
Model 1: *Unadjusted*	1.09	0.16	0.82	1.45	0.547	1.17	0.17	0.88	1.56	0.281
Model 2: *Model 1 + baseline biomarkers* [a]	0.95	0.15	0.70	1.29	0.745	1.15	0.17	0.86	1.54	0.335
Model 3: *Model 2 + demographics & genetics* [b]	0.93	0.14	0.69	1.26	0.636	1.07	0.16	0.79	1.44	0.664
Model 4: *Fully Adjusted* [c]	0.87	0.14	0.64	1.19	0.387	0.93	0.15	0.68	1.26	0.629
***High-risk* Profile**										
Model 1: *Unadjusted*	1.61	0.26	1.18	2.21	0.003	1.29	0.20	0.96	1.75	0.093
Model 2: *Model 1 + baseline biomarkers* [a]	1.15	0.23	0.79	1.69	0.471	1.29	0.22	0.92	1.81	0.148
Model 3: *Model 2 + demographics & genetics* [b]	1.14	0.23	0.77	1.69	0.504	1.16	0.21	0.82	1.65	0.410
Model 4: *Fully Adjusted* [c]	0.89	0.19	0.59	1.35	0.594	0.84	0.16	0.58	1.21	0.351
	Long Sleep | < Md Age (N=2,436)					**Long Sleep | ≥ Md Age (N=2,504)**				
***Moderate-risk* Profile**										
Model 1: *Unadjusted*	1.98	1.01	0.73	5.38	0.180	1.22	0.47	0.57	2.60	0.604
Model 2: *Model 1 + baseline biomarkers* [a]	1.54	0.83	0.53	4.43	0.426	1.20	0.47	0.56	2.57	0.648
Model 3: *Model 2 + demographics & genetics* [b]	1.53	0.83	0.53	4.43	0.437	0.94	0.38	0.43	2.06	0.876
Model 4: *Fully Adjusted* [c]	1.39	0.77	0.47	4.11	0.554	0.86	0.35	0.38	1.92	0.706
***High-risk* Profile**										
Model 1: *Unadjusted*	3.70	1.92	1.34	10.25	0.012	2.80	1.00	1.39	5.63	0.004
Model 2: *Model 1 + baseline biomarkers* [a]	1.79	1.14	0.52	6.23	0.358	2.68	1.07	1.22	5.88	0.014
Model 3: *Model 2 + demographics & genetics* [b]	2.00	1.28	0.58	6.99	0.275	1.78	0.75	0.78	4.07	0.173
Model 4: *Fully Adjusted* [c]	1.44	0.95	0.40	5.22	0.575	1.35	0.59	0.57	3.20	0.502

Notes: The *low-risk* group is the reference; < = less than; ≥ = greater than or equal to; Md = Median; RRR = relative risk ratio; SE = standard errors; CI = confidence interval; *p* = significance value.

a Baseline biomarkers: C-reactive protein (CRP); fibrinogen; insulin-growth factor-1 (IGF-1).

b Demographic and genetic variables: age; sex; 10 principal components (PCs); CRP polygenic score (PGS); cortisol PGS; IGF-1 PGS.

c All variables: CRP; fibrinogen; IGF-1; age; sex; 10 PCs; CRP PGS; cortisol PGS; IGF-1 PGS; education; occupational social status; smoking status; alcohol consumption; physical activity; health (i.e., chronic lung disease; coronary heart disease; abnormal heart rhythm; heart murmur; congestive heart failure; angina; hypertension; diabetes; cancer; Parkinson's; Alzheimer's; dementia; asthma; arthritis; osteoporosis; psychiatric disorder).

Table S5.7 Longitudinal associations of stress with immune and neuroendocrine biomarker profiles stratified by sex

Adjustments	Binary Stress Score | Male (N=2,237)					Binary Stress Score | Female (N=2,703)				
	RRR	SE	95% CI		*p*	RRR	SE	95% CI		*p*
***Moderate-risk* Profile**										
Model 1: *Unadjusted*	1.18	0.17	0.88	1.57	0.267	1.28	0.15	1.02	1.62	0.033
Model 2: *Model 1 + baseline biomarkers* [a]	1.20	0.18	0.90	1.60	0.225	1.23	0.15	0.97	1.56	0.093
Model 3: *Model 2 + demographics & genetics* [b]	1.25	0.19	0.93	1.67	0.145	1.27	0.16	0.99	1.61	0.058
Model 4: *Fully Adjusted* [c]	1.18	0.18	0.87	1.60	0.289	1.15	0.15	0.90	1.48	0.275
***High-risk* Profile**										
Model 1: *Unadjusted*	1.78	0.27	1.32	2.40	<0.001	1.42	0.18	1.10	1.83	0.006
Model 2: *Model 1 + baseline biomarkers* [a]	1.91	0.34	1.35	2.69	<0.001	1.31	0.20	0.97	1.76	0.074
Model 3: *Model 2 + demographics & genetics* [b]	2.02	0.36	1.42	2.87	<0.001	1.41	0.22	1.04	1.91	0.027
Model 4: *Fully Adjusted* [c]	1.68	0.32	1.16	2.43	0.006	1.23	0.20	0.90	1.68	0.203

Notes: The *low-risk* group is the reference; < = less than; ≥ = greater than or equal to; RRR = relative risk ratio; SE = standard errors; CI = confidence interval; *p* = significance value.

a Baseline biomarkers: C-reactive protein (CRP); fibrinogen; insulin-growth factor-1 (IGF-1).

b Demographic and genetic variables: age; sex; 10 principal components (PCs); CRP polygenic score (PGS); cortisol PGS; IGF-1 PGS.

c All variables: CRP; fibrinogen; IGF-1; age; sex; 10 PCs; CRP PGS; cortisol PGS; IGF-1 PGS; education; occupational social status; smoking status; alcohol consumption; physical activity; health (i.e., chronic lung disease; coronary heart disease; abnormal heart rhythm; heart murmur; congestive heart failure; angina; hypertension; diabetes; cancer; Parkinson's; Alzheimer's; dementia; asthma; arthritis; osteoporosis; psychiatric disorder).

Table S5.8 Longitudinal associations of suboptimal sleep with immune and neuroendocrine biomarker profiles stratified by sex

Adjustments	Short Sleep | Male (N=2,237)					Short Sleep | Female (N=2,703)				
	RRR	**SE**	**95% CI**		***p***	**RRR**	**SE**	**95% CI**		***p***
***Moderate-risk* Profile**										
Model 1: *Unadjusted*	1.04	0.17	0.75	1.43	0.837	1.20	0.16	0.93	1.55	0.162
Model 2: *Model 1 + baseline biomarkers* [a]	1.00	0.17	0.72	1.40	0.981	1.12	0.15	0.85	1.46	0.427
Model 3: *Model 2 + demographics & genetics* [b]	0.95	0.16	0.68	1.33	0.766	1.06	0.15	0.81	1.38	0.694
Model 4: *Fully Adjusted* [c]	0.83	0.15	0.58	1.18	0.293	0.94	0.13	0.71	1.24	0.669
***High-risk* Profile**										
Model 1: *Unadjusted*	1.41	0.25	1.00	1.99	0.050	1.46	0.21	1.10	1.92	0.008
Model 2: *Model 1 + baseline biomarkers* [a]	1.33	0.27	0.89	1.97	0.166	1.23	0.21	0.89	1.71	0.212
Model 3: *Model 2 + demographics & genetics* [b]	1.21	0.25	0.80	1.82	0.365	1.17	0.20	0.84	1.63	0.362
Model 4: *Fully Adjusted* [c]	0.77	0.17	0.50	1.19	0.233	0.93	0.17	0.66	1.32	0.697
	Long Sleep | Male (N=2,237)					**Long Sleep | Female (N=2,703)**				
***Moderate-risk* Profile**										
Model 1: *Unadjusted*	1.46	0.77	0.52	4.12	0.476	1.56	0.59	0.75	3.28	0.237
Model 2: *Model 1 + baseline biomarkers* [a]	1.41	0.76	0.49	4.03	0.522	1.38	0.54	0.64	2.99	0.415
Model 3: *Model 2 + demographics & genetics* [b]	1.13	0.61	0.39	3.27	0.821	1.11	0.45	0.51	2.44	0.796
Model 4: *Fully Adjusted* [c]	1.02	0.56	0.35	3.01	0.969	0.99	0.41	0.44	2.21	0.982
***High-risk* Profile**										
Model 1: *Unadjusted*	4.19	2.02	1.63	10.78	0.003	3.12	1.15	1.52	6.43	0.002
Model 2: *Model 1 + baseline biomarkers* [a]	4.51	2.41	1.58	12.86	0.005	2.01	0.89	0.85	4.79	0.114
Model 3: *Model 2 + demographics & genetics* [b]	3.45	1.88	1.19	10.06	0.023	1.47	0.66	0.61	3.56	0.395
Model 4: *Fully Adjusted* [c]	2.49	1.43	0.81	7.65	0.111	1.11	0.51	0.45	2.75	0.820

Notes: The *low-risk* group is the reference; < = less than; ≥ = greater than or equal to; RRR = relative risk ratio; SE = standard errors; CI = confidence interval; *p* = significance value.

a Baseline biomarkers: C-reactive protein (CRP); fibrinogen; insulin-growth factor-1 (IGF-1).

b Demographic and genetic variables: age; sex; 10 principal components (PCs); CRP polygenic score (PGS); cortisol PGS; IGF-1 PGS.

c All variables: CRP; fibrinogen; IGF-1; age; sex; 10 PCs; CRP PGS; cortisol PGS; IGF-1 PGS; education; occupational social status; smoking status; alcohol consumption; physical activity; health (i.e., chronic lung disease; coronary heart disease; abnormal heart rhythm; heart murmur; congestive heart failure; angina; hypertension; diabetes; cancer; Parkinson's; Alzheimer's; dementia; asthma; arthritis; osteoporosis; psychiatric disorder).

Table S5.9 Longitudinal associations of stress with immune and neuroendocrine profiles, adjusted for BMI

Adjustments	Stress				
	RRR	SE	95% CI		*p*
***Moderate-risk* Profile**					
Model 1: *Unadjusted*	1.26	0.12	1.05	1.50	0.012
Model 2: *Model 1 + baseline biomarkers* [a]	1.23	0.12	1.03	1.48	0.025
Model 3: *Model 2 + demographics & genetics* [b]	1.28	0.12	1.060	1.54	0.010
Model 4: *Fully Adjusted* [c]	1.18	0.12	0.97	1.43	0.099
***High-risk* Profile**					
Model 1: *Unadjusted*	1.57	0.15	1.30	1.90	<0.001
Model 2: *Model 1 + baseline biomarkers* [a]	1.52	0.17	1.21	1.90	<0.001
Model 3: *Model 2 + demographics & genetics* [b]	1.65	0.19	1.308	2.07	<0.001
Model 4: *Fully Adjusted* [c]	1.42	0.17	1.12	1.80	0.004

Notes: BMI = body mass index; The *low-risk* group is the reference; RRR = relative risk ratio; SE = standard errors; CI = confidence interval; *p* = significance value.

a Baseline immune and neuroendocrine profiles.

b Demographic and genetic variables: age; sex; 10 principal components (PCs); C-reactive protein (CRP) polygenic score (PGS); white blood cell counts (WBCC) PGS; insulin growth factor-1 (IGF-1) PGS; cortisol PGS; sleep duration PGS.

c All variables: baseline immune and neuroendocrine profiles; age; sex; 10 PCs; CRP PGS; WBCC PGS; IGF-1 PGS; cortisol PGS; education; wealth; occupational social status; smoking status; alcohol consumption; physical activity; mobility; limiting longstanding illness; health (i.e., chronic lung disease; coronary heart disease; abnormal heart rhythm; heart murmur; congestive heart failure; angina; hypertension; diabetes; cancer; Parkinson's; Alzheimer's; dementia; asthma; arthritis; osteoporosis; psychiatric disorder); BMI.

Table S5.10 Longitudinal associations of suboptimal sleep with immune and neuroendocrine profiles, adjusted for BMI

Adjustments	Short Sleep				
	RRR	SE	95% CI		*p*
***Moderate-risk* Profile**					
Model 1: *Unadjusted*	1.15	0.12	0.94	1.41	0.171
Model 2: *Model 1 + baseline biomarkers* [a]	1.08	0.11	0.88	1.33	0.447
Model 3: *Model 2 + demographics & genetics* [b]	1.01	0.11	0.82	1.25	0.907
Model 4: *Fully Adjusted* [c]	0.89	0.10	0.71	1.10	0.281
***High-risk* Profile**					
Model 1: *Unadjusted*	1.45	0.16	1.17	1.80	0.001
Model 2: *Model 1 + baseline biomarkers* [a]	1.26	0.16	0.98	1.62	0.075
Model 3: *Model 2 + demographics & genetics* [b]	1.19	0.16	0.92	1.54	0.192
Model 4: *Fully Adjusted* [c]	0.86	0.12	0.66	1.13	0.280
Adjustments	**Long Sleep**				
	RRR	**SE**	**95% CI**		***p***
***Moderate-risk* Profile**					
Model 1: *Unadjusted*	1.55	0.48	0.85	2.84	0.152
Model 2: *Model 1 + baseline biomarkers* [a]	1.43	0.45	0.77	2.66	0.254
Model 3: *Model 2 + demographics & genetics* [b]	1.16	0.37	0.62	2.16	0.650
Model 4: *Fully Adjusted* [c]	1.05	0.34	0.55	1.98	0.893
***High-risk* Profile**					
Model 1: *Unadjusted*	3.52	1.03	1.98	6.24	<0.001
Model 2: *Model 1 + baseline biomarkers* [a]	2.78	0.94	1.43	5.41	0.003
Model 3: *Model 2 + demographics & genetics* [b]	2.02	0.70	1.02	3.98	0.043
Model 4: *Fully Adjusted* [c]	1.48	0.53	0.73	2.99	0.277

Notes: The *low-risk* group is the reference; RRR = relative risk ratio; SE = standard errors; CI = confidence interval; *p* = significance value.

a Baseline immune and neuroendocrine profiles.

b Demographic and genetic variables: age; sex; 10 principal components (PCs); C-reactive protein (CRP) polygenic score (PGS); white blood cell counts (WBCC) PGS; insulin growth factor-1 (IGF-1) PGS; cortisol PGS; sleep duration PGS.

c All variables: baseline immune and neuroendocrine profiles; age; sex; 10 PCs; CRP PGS; WBCC PGS; IGF-1 PGS; cortisol PGS; education; wealth; occupational social status; smoking status; alcohol consumption; physical activity; mobility; limiting longstanding illness; health (i.e., chronic lung disease; coronary heart disease; abnormal heart rhythm; heart murmur; congestive heart failure; angina; hypertension; diabetes; cancer; Parkinson's; Alzheimer's; dementia; asthma; arthritis; osteoporosis; psychiatric disorder); BMI.

Table S5.11 Longitudinal associations between suboptimal sleep durations at less stringent thresholds (≤6 hr; >6-<8 hr; and ≥8 hr) and immune and neuroendocrine profile membership

Adjustments	Short Sleep				
	RRR	SE	95% CI		*p*
***Moderate-risk* Profile**					
Model 1: *Unadjusted*	1.21	0.09	1.05	1.39	0.010
Model 2: *Model 1 + baseline biomarkers* [a]	1.13	0.09	0.98	1.31	0.098
Model 3: *Model 2 + demographics & genetics* [b]	1.08	0.08	0.93	1.25	0.329
Model 4: *Fully Adjusted* [c]	0.99	0.08	0.85	1.15	0.885
***High-risk* Profile**					
Model 1: *Unadjusted*	1.46	0.12	1.24	1.71	<0.001
Model 2: *Model 1 + baseline biomarkers* [a]	1.26	0.12	1.05	1.52	0.014
Model 3: *Model 2 + demographics & genetics* [b]	1.20	0.12	0.99	1.46	0.058
Model 4: *Fully Adjusted* [c]	0.97	0.10	0.79	1.18	0.736
Adjustments	**Long Sleep**				
	RRR	**SE**	**95% CI**		***p***
***Moderate-risk* Profile**					
Model 1: *Unadjusted*	1.10	0.16	0.83	1.45	0.507
Model 2: *Model 1 + baseline biomarkers* [a]	1.00	0.15	0.75	1.34	0.982
Model 3: *Model 2 + demographics & genetics* [b]	0.88	0.13	0.65	1.17	0.367
Model 4: *Fully Adjusted* [c]	0.85	0.13	0.63	1.14	0.282
***High-risk* Profile**					
Model 1: *Unadjusted*	2.09	0.30	1.58	2.76	<0.001
Model 2: *Model 1 + baseline biomarkers* [a]	1.61	0.27	1.16	2.24	0.005
Model 3: *Model 2 + demographics & genetics* [b]	1.31	0.23	0.94	1.84	0.116
Model 4: *Fully Adjusted* [c]	1.18	0.21	0.83	1.67	0.354

Notes: The *low-risk* group is the reference; RRR = relative risk ratio; SE = standard errors; CI = confidence interval; *p* = significance value.

a Baseline immune and neuroendocrine profiles.

b Demographic and genetic variables: age; sex; 10 principal components (PCs); C-reactive protein (CRP) polygenic score (PGS); white blood cell counts (WBCC) PGS; insulin growth factor-1 (IGF-1) PGS; cortisol PGS; sleep duration PGS.

c All variables: baseline immune and neuroendocrine profiles; age; sex; 10 PCs; CRP PGS; WBCC PGS; IGF-1 PGS; cortisol PGS; education; wealth; occupational social status; smoking status; alcohol consumption; physical activity; mobility; limiting longstanding illness; health (i.e., chronic lung disease; coronary heart disease; abnormal heart rhythm; heart murmur; congestive heart failure; angina; hypertension; diabetes; cancer; Parkinson's; Alzheimer's; dementia; asthma; arthritis; osteoporosis; psychiatric disorder).

Table S5.12a Longitudinal associations of stress with immune and neuroendocrine profiles, with stepwise adjustments

Adjustments	Stress				
	RRR	SE	95% CI		*p*
Moderate-risk **Profile**					
Model 1: Unadjusted	1.26	0.12	1.05	1.50	0.012
Model 2: Baseline profiles [a] + Model 1 [a]	1.23	0.12	1.03	1.48	0.025
Model 3a: Genetics [b] + Model 2	1.23	0.12	1.03	1.48	0.025
Model 3b: Demographics [c] + Model 3a	1.28	0.12	1.06	1.54	0.010
Model 3c: Socioeconomics [d] + Model 3b	1.22	0.12	1.01	1.47	0.041
Model 3d: Health behaviours [e] + Model 3c	1.20	0.12	0.99	1.45	0.067
Model 4: Health [f] + Model 3d	1.18	0.12	0.97	1.43	0.093
High-risk **Profile**					
Model 1: Unadjusted	1.57	0.15	1.30	1.90	<0.001
Model 2: Baseline profiles [a] + Model 1 [a]	1.52	0.17	1.21	1.90	<0.001
Model 3a: Genetics [b] + Model 2	1.51	0.17	1.20	1.89	<0.001
Model 3b: Demographics [c] + Model 3a	1.65	0.19	1.31	2.07	<0.001
Model 3c: Socioeconomics [d] + Model 3b	1.49	0.18	1.18	1.88	0.001
Model 3d: Health behaviours [e] + Model 3c	1.45	0.18	1.14	1.83	0.002
Model 4: Health [f] + Model 3d	1.42	0.17	1.12	1.80	0.004

Notes: The *low-risk* group is the reference; RRR = relative risk ratio; SE = standard errors; CI = confidence interval; *p* = significance value.
a Baseline immune and neuroendocrine profiles.
b Genetics: 10 principal components (PCs); C-reactive Protein (CRP) polygenic score (PGS); White Blood Cell Counts (WBCC) PGS; Insulin Growth Factor-1 (IGF-1) PGS; [Hair] Cortisol PGS; Sleep Duration PGS.
c Demographics: age; sex.
d Socioeconomics: education; wealth; occupational social status.
e Health behaviours : smoking status; alcohol consumption; physical activity.
e Health: mobility; limiting longstanding illness; health (i.e., chronic lung disease; coronary heart disease; abnormal heart rhythm; heart murmur; congestive heart failure; angina; hypertension; diabetes; cancer; Parkinson's; Alzheimer's; dementia; asthma; arthritis; osteoporosis; psychiatric disorder).

Table S5.12b Longitudinal associations of stress with immune and neuroendocrine profiles, with discrete covariate contributions

Adjustments	Stress				
	RRR	SE	95% CI		*p*
***Moderate-risk* Profile**					
Model 1: Unadjusted	1.26	0.12	1.05	1.50	0.012
Model 2: Baseline profiles [a]	1.23	0.12	1.03	1.48	0.025
Model 3a: Genetics [b] + Model 2	1.23	0.12	1.03	1.48	0.025
Model 3b: Demographics [c] + Model 2	1.28	0.12	1.06	1.54	0.010
Model 3c: Socioeconomics [d] + Model 2	1.16	0.11	0.96	1.40	0.123
Model 3d: Health behaviours [e] + Model 2	1.18	0.11	0.98	1.42	0.081
Model 3e: Health [f] + Model 2	1.20	0.11	1.00	1.45	0.053
***High-risk* Profile**					
Model 1: Unadjusted	1.57	0.15	1.30	1.90	<0.001
Model 2: Baseline profiles [a]	1.52	0.17	1.21	1.90	<0.001
Model 3a: Genetics [b] + Model 2	1.51	0.17	1.20	1.89	<0.001
Model 3b: Demographics [c] + Model 2	1.66	0.19	1.32	2.09	<0.001
Model 3c: Socioeconomics [d] + Model 2	1.35	0.16	1.07	1.69	0.010
Model 3d: Health behaviours [e] + Model 2	1.40	0.16	1.11	1.76	0.004
Model 3e: Health [f] + Model 2	1.42	0.17	1.13	1.78	0.003

Notes: The *low-risk* group is the reference; RRR = relative risk ratio; SE = standard errors; CI = confidence interval; *p* = significance value.
a Baseline immune and neuroendocrine profiles.
b Genetics: 10 principal components (PCs); C-reactive Protein (CRP) polygenic score (PGS); White Blood Cell Counts (WBCC) PGS; Insulin Growth Factor-1 (IGF-1) PGS; [Hair] Cortisol PGS; Sleep Duration PGS.
c Demographics: age; sex.
d Socioeconomics: education; wealth; occupational social status.
e Health behaviours : smoking status; alcohol consumption; physical activity.
e Health: mobility; limiting longstanding illness; health (i.e., chronic lung disease; coronary heart disease; abnormal heart rhythm; heart murmur; congestive heart failure; angina; hypertension; diabetes; cancer; Parkinson's; Alzheimer's; dementia; asthma; arthritis; osteoporosis; psychiatric disorder).

Table S5.13a Longitudinal associations of suboptimal sleep with immune and neuroendocrine profiles, with stepwise adjustments

Adjustments	Short Sleep				
	RRR	SE	95% CI		*p*
***Moderate-risk* Profile**					
Model 1: Unadjusted	1.15	0.12	0.94	1.41	0.171
Model 2: Baseline profiles [a] + Model 1 [a]	1.08	0.11	0.88	1.33	0.447
Model 3a: Genetics [b] + Model 2	1.08	0.11	0.88	1.33	0.479
Model 3b: Demographics [c] + Model 3a	1.16	0.11	0.82	1.25	0.883
Model 3c: Socioeconomics [d] + Model 3b	0.96	0.10	0.77	1.18	0.686
Model 3d: Health behaviours [e] + Model 3c	0.94	0.10	0.78	1.16	0.75
Model 4: Health [f] + Model 3d	0.90	0.10	0.72	1.12	0.335
***High-risk* Profile**					
Model 1: Unadjusted	1.45	0.16	1.17	1.80	0.001
Model 2: Baseline profiles [a] + Model 1 [a]	1.26	0.16	0.98	1.62	0.075
Model 3a: Genetics [b] + Model 2	1.27	0.16	0.99	1.64	0.063
Model 3b: Demographics [c] + Model 3a	1.19	0.16	0.919	1.54	0.187
Model 3c: Socioeconomics [d] + Model 3b	1.02	0.14	0.79	1.33	0.869
Model 3d: Health behaviours [e] + Model 3c	0.93	0.13	0.71	1.21	0.57
Model 4: Health [f] + Model 3d	0.87	0.12	0.67	1.14	0.323
Adjustments	**Long Sleep**				
	RRR	**SE**	**95% CI**		***p***
***Moderate-risk* Profile**					
Model 1: Unadjusted	1.55	0.48	0.85	2.84	0.152
Model 2: Baseline profiles [a] + Model 1 [a]	1.43	0.45	0.77	2.66	0.254
Model 3a: Genetics [b] + Model 2	1.41	0.45	0.76	2.62	0.279
Model 3b: Demographics [c] + Model 3a	1.16	0.37	0.62	2.16	0.618
Model 3c: Socioeconomics [d] + Model 3b	1.12	0.10	0.59	2.09	0.742
Model 3d: Health behaviours [e] + Model 3c	1.04	0.34	0.55	1.96	0.551
Model 4: Health [f] + Model 3d	1.05	0.34	0.55	1.98	0.893
***High-risk* Profile**					
Model 1: Unadjusted	3.52	1.03	1.98	6.24	<0.001
Model 2: Baseline profiles [a] + Model 1 [a]	2.78	0.94	1.43	5.41	0.003
Model 3a: Genetics [b] + Model 2	2.82	0.97	1.45	5.52	0.002
Model 3b: Demographics [c] + Model 3a	2.02	0.70	1.02	1.54	0.043
Model 3c: Socioeconomics [d] + Model 3b	1.83	0.64	0.92	3.63	0.085
Model 3d: Health behaviours [e] + Model 3c	1.50	0.53	0.74	3.01	0.744
Model 4: Health [f] + Model 3d	1.48	0.53	0.73	2.98	0.277

Notes: The *low-risk* group is the reference; RRR = relative risk ratio; SE = standard errors; CI = confidence interval; *p* = significance value.
a Baseline immune and neuroendocrine profiles.
b Genetics: 10 principal components (PCs); C-reactive Protein (CRP) polygenic score (PGS); White Blood Cell Counts (WBCC) PGS; Insulin Growth Factor-1 (IGF-1) PGS; [Hair] Cortisol PGS; Sleep Duration PGS.
c Demographics: age; sex.
d Socioeconomics: education; wealth; occupational social status.
e Health behaviours : smoking status; alcohol consumption; physical activity.
e Health: mobility; limiting longstanding illness; health (i.e., chronic lung disease; coronary heart disease; abnormal heart rhythm; heart murmur; congestive heart failure; angina; hypertension; diabetes; cancer; Parkinson's; Alzheimer's; dementia; asthma; arthritis; osteoporosis; psychiatric disorder).

Table S5.13b Longitudinal associations of suboptimal sleep with immune and neuroendocrine profiles, with discrete covariate contributions

Adjustments	Short Sleep				
	RRR	SE	95% CI		*p*
***Moderate-risk* Profile**					
Model 1: Unadjusted	1.15	0.12	0.94	1.41	0.171
Model 2: Baseline profiles [a]	1.08	0.11	0.88	1.33	0.447
Model 3a: Genetics [b] + Model 2	1.08	0.11	0.88	1.33	0.479
Model 3b: Demographics [c] + Model 2	1.02	0.11	0.83	1.26	0.835
Model 3c: Socioeconomics [d] + Model 2	1.00	0.11	0.81	1.23	0.965
Model 3d: Health behaviours [e] + Model 2	1.01	0.11	0.82	1.24	0.958
Model 3e: Health [f] + Model 2	0.96	0.10	0.79	1.19	0.715
***High-risk* Profile**					
Model 1: Unadjusted	1.45	0.16	1.17	1.80	0.001
Model 2: Baseline profiles [a]	1.26	0.16	0.98	1.62	0.075
Model 3a: Genetics [b] + Model 2	1.27	0.16	0.99	1.64	0.063
Model 3b: Demographics [c] + Model 2	1.18	0.16	0.92	1.53	0.916
Model 3c: Socioeconomics [d] + Model 2	1.04	0.14	0.81	1.35	0.746
Model 3d: Health behaviours [e] + Model 2	1.02	0.14	0.79	1.33	0.873
Model 3e: Health [f] + Model 2	0.94	0.13	0.73	1.23	0.65
Adjustments	**Long Sleep**				
	RRR	**SE**	**95% CI**		***p***
***Moderate-risk* Profile**					
Model 1: Unadjusted	1.55	0.48	0.85	2.84	0.152
Model 2: Baseline profiles [a]	1.43	0.45	0.77	2.66	0.254
Model 3a: Genetics [b] + Model 2	1.41	0.11	0.76	2.62	0.279
Model 3b: Demographics [c] + Model 2	1.17	0.37	0.63	2.18	0.623
Model 3c: Socioeconomics [d] + Model 2	1.35	0.43	0.73	2.52	0.344
Model 3d: Health behaviours [e] + Model 2	1.26	0.40	0.68	2.35	0.465
Model 3e: Health [f] + Model 2	1.24	0.40	0.67	2.32	0.497
***High-risk* Profile**					
Model 1: Unadjusted	3.52	1.03	1.98	6.24	<0.001
Model 2: Baseline profiles [a]	2.78	0.94	1.43	5.41	0.003
Model 3a: Genetics [b] + Model 2	2.82	0.97	1.44	5.52	0.002
Model 3b: Demographics [c] + Model 2	1.98	0.68	1.01	3.89	0.047
Model 3c: Socioeconomics [d] + Model 2	2.39	0.83	1.22	4.70	0.012
Model 3d: Health behaviours [e] + Model 2	2.04	0.70	1.04	4.01	0.039
Model 3e: Health [f] + Model 2	1.94	0.67	0.99	3.83	0.055

Notes: The *low-risk* group is the reference; RRR = relative risk ratio; SE = standard errors; CI = confidence interval; *p* = significance value.

a Baseline immune and neuroendocrine profiles.

b Genetics: 10 principal components (PCs); C-reactive Protein (CRP) polygenic score (PGS); White Blood Cell Counts (WBCC) PGS; Insulin Growth Factor-1 (IGF-1) PGS; [Hair] Cortisol PGS; Sleep Duration PGS.

c Demographics: age; sex.

d Socioeconomics: education; wealth; occupational social status.

e Health behaviours : smoking status; alcohol consumption; physical activity.

e Health: mobility; limiting longstanding illness; health (i.e., chronic lung disease; coronary heart disease; abnormal heart rhythm; heart murmur; congestive heart failure; angina; hypertension; diabetes; cancer; Parkinson's; Alzheimer's; dementia; asthma; arthritis; osteoporosis; psychiatric disorder).

Table S5.14 Longitudinal associations of immune and neuroendocrine profiles with suboptimal sleep

Adjustments	*Moderate-risk* Profile				
	RRR	**SE**	**95% CI**		***p***
Short Sleep					
Model 1: *Unadjusted*	1.51	0.15	1.24	1.84	<0.001
Model 2: *Model 1 + baseline profiles* [a]	1.38	0.15	1.11	1.71	0.003
Model 3: *Model 2 + demographics & genetics* [b]	1.38	0.15	1.11	1.72	0.004
Model 4: *Fully Adjusted* [c]	1.21	0.14	0.96	1.51	0.103
Adjustments	***High-risk* Profile**				
	RRR	**SE**	**95% CI**		***p***
Model 1: *Unadjusted*	1.33	0.20	0.99	1.79	0.059
Model 2: *Model 1 + baseline profiles* [a]	1.13	0.19	0.82	1.57	0.454
Model 3: *Model 2 + demographics & genetics* [b]	1.11	0.19	0.80	1.54	0.539
Model 4: *Fully Adjusted* [c]	0.86	0.15	0.61	1.22	0.388
Adjustments	***Moderate-risk* Profile**				
	RRR	**SE**	**95% CI**		***p***
Long Sleep					
Model 1: *Unadjusted*	2.14	0.31	1.61	2.83	<0.001
Model 2: *Model 1 + baseline profiles* [a]	2.11	0.31	1.58	2.80	<0.001
Model 3: *Model 2 + demographics & genetics* [b]	1.91	0.28	1.43	2.56	<0.001
Model 4: *Fully Adjusted* [c]	1.66	0.25	1.23	2.23	0.001
Adjustments	***High-risk* Profile**				
	RRR	**SE**	**95% CI**		***p***
Model 1: *Unadjusted*	2.93	0.53	2.06	4.18	<0.001
Model 2: *Model 1 + baseline profiles* [a]	2.81	0.52	1.96	4.03	<0.001
Model 3: *Model 2 + demographics & genetics* [b]	2.30	0.43	1.59	3.33	<0.001
Model 4: *Fully Adjusted* [c]	1.81	0.35	1.24	2.64	0.002

Notes: The *low-risk* group is the reference; RRR = relative risk ratio; SE = standard errors; CI = confidence interval; *p* = significance value.

a Baseline immune and neuroendocrine profiles.

b Demographic and genetic variables: age; sex; 10 principal components (PCs); C-reactive Protein (CRP) polygenic score (PGS); White Blood Cell Counts (WBCC) PGS; Insulin Growth Factor-1 (IGF-1) PGS; [Hair] Cortisol PGS; Sleep Duration PGS.

c All variables: Baseline immune and neuroendocrine profiles; age; sex; 10 PCs; CRP PGS; WBCC PGS; IGF-1 PGS; Cortisol PGS; education; wealth; occupational social status; smoking status; alcohol consumption; physical activity; mobility; limiting longstanding illness; health (i.e., chronic lung disease; coronary heart disease; abnormal heart rhythm; heart murmur; congestive heart failure; angina; hypertension; diabetes; cancer; Parkinson's; Alzheimer's; dementia; asthma; arthritis; osteoporosis; psychiatric disorder).

Table S5.15 The longitudinal role of PGS for suboptimal sleep durations in immune and neuroendocrine profile membership

Adjustments	PGS for Short Sleep				
	RRR	**SE**	**95% CI**		***p***
***Moderate-risk* Profile**					
Model 1: *Unadjusted*	1.01	0.03	0.95	1.08	0.818
Model 2b: *Model 1 + demographics & genetics* [a]	0.99	0.04	0.92	1.07	0.831
***High-risk* Profile**					
Model 1: *Unadjusted*	1.04	0.04	0.97	1.12	0.300
Model 2b: *Model 1 + demographics & genetics* [a]	1.00	0.05	0.91	1.10	0.992
Adjustments	**PGS for Long Sleep**				
	RRR	**SE**	**95% CI**		***p***
***Moderate-risk* Profile**					
Model 1: *Unadjusted*	0.99	0.03	0.93	1.05	0.694
Model 2b: *Model 1 + demographics & genetics* [a]	0.97	0.03	0.91	1.04	0.439
***High-risk* Profile**					
Model 1: *Unadjusted*	1.06	0.04	0.99	1.15	0.097
Model 2b: *Model 1 + demographics & genetics* [a]	1.03	0.05	0.94	1.13	0.555

Notes: The *low-risk* group is the reference; RRR = relative risk ratio; SE = standard errors; CI = confidence interval; *p* = significance value.
a Demographic and genetic variables: age; age^2; sex; 10 principal components (PCs).

APPENDIX D

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Figure S6.1 **Flow chart of the analytic sample for complete case analyses**

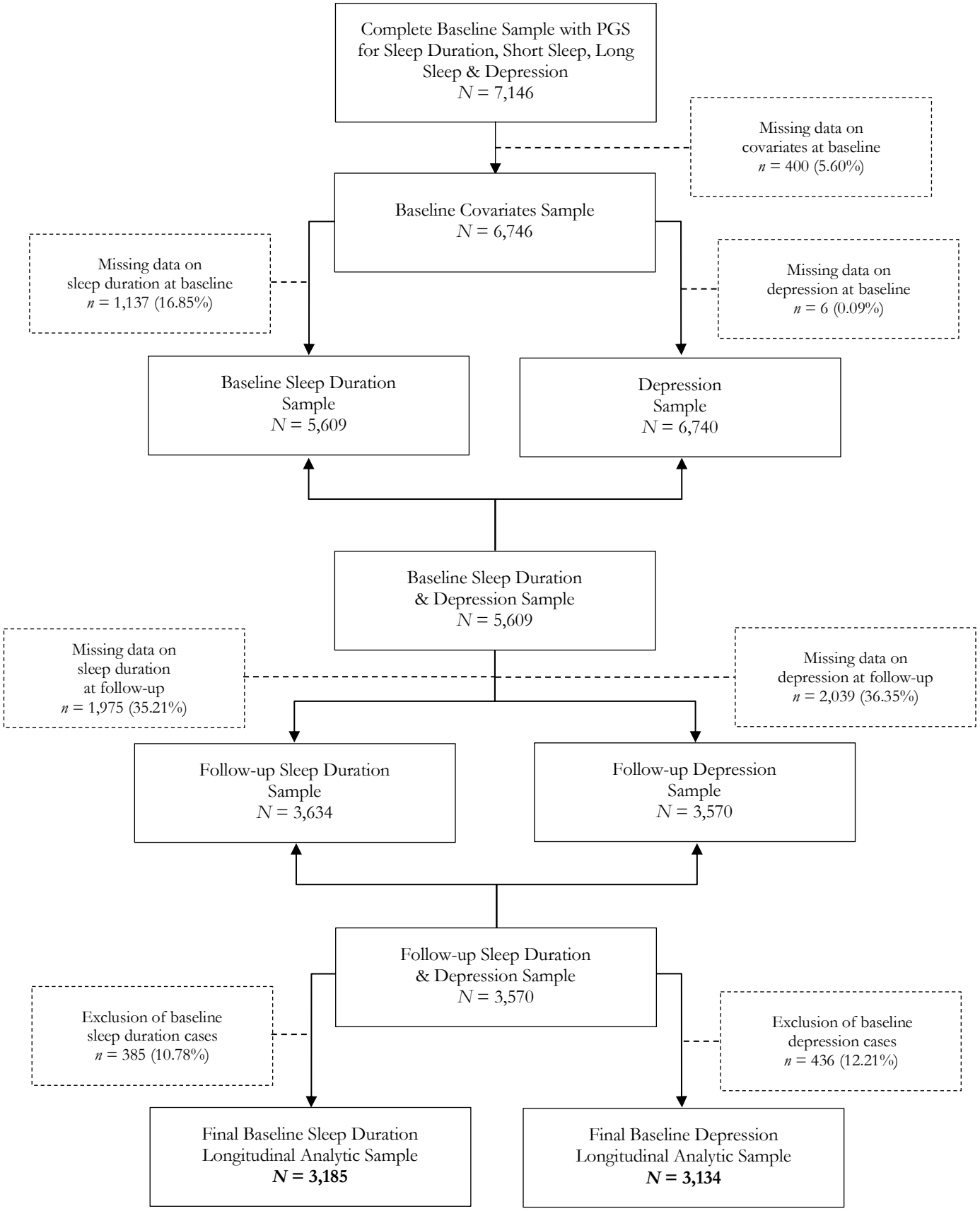

Table S6.1 Estimated the predictive accuracy (R^2, P-value) for polygenic scores

Variable		*P*-value threshold for polygenic scores (P_T)					
		0.001	**0.01**	**0.05**	**0.1**	**0.3**	**1**
Polygenic score for sleep duration	m	39,476	106,361	384,317	384,317	836,823	2,092,574
	R^2	0.003	0.002	0.002	0.002	0.002	0.001
	P	2.12×10^{-5}	1.09×10^{-4}	1.11×10^{-4}	1.37×10^{-4}	4.60×10^{-4}	9.12×10^{-3}
Polygenic score for short sleep	m	52,197	191,839	569,428	988,019	229,2361	6,227,565
	R^2	0.004	0.002	0.002	0.002	0.001	0.001
	P	6.52×10^{-08}	6.82×10^{-05}	0.0002	0.001	0.002	0.026
Polygenic score for long sleep	m	24,262	127,099	448,761	837,119	2,125,346	6,246,221
	R^2	0.011	0.003	0.002	0.002	0.039	0.001
	P	6.47×10^{-18}	5.79×10^{-06}	0.0002	0.001	0.004	0.039
Polygenic score for depression	m	63,824	213,672	579,538	925,255	2,049,803	5,356,042
	R^2	0.001	0.001	0.001	0.001	0.001	0.0004
	P	0.003	0.005	0.005	0.005	0.011	0.056

Notes: m = total number of independent markers in genotyping panel; R^2 = the predictive accuracy; *P* = p-value

Table S6.2 Correlations between polygenic scores for sleep duration, short sleep, long sleep and depression and phenotypic sleep duration, short sleep, long sleep, and depression

	Polygenic score for depression	Polygenic score for sleep duration	Polygenic score for short sleep	Polygenic score for long sleep	Depression phenotype	Sleep duration phenotype
Polygenic score for depression	1.000					
Polygenic score for sleep duration	0.160**	1.000				
Polygenic score for short sleep	0.031*	-0.500**	1.000			
Polygenic score for long sleep	0.047*	0.620**	-0.033*	1.000		
Depression phenotype	0.048**	-0.009	0.039*	0.003	1.000	
Sleep duration phenotype	-0.025*	0.043*	-0.057**	-0.003	-0.147**	1.000

Notes = Significant at *** $p<0.001$; ** $p<0.05$

Table S6.3 A comparison of imputed and observed sample characteristics

Variable		Imputed (*N* = 7,146)		Complete Case (*N* = 3,494)	
		%	Mean (SD) Range	%	Mean (SD) Range
Age		100	64.83 (9.52) 50-99	100	61.93 (7.24) 50-89
Sex	Male	46.12		44.36	
	Female	53.88		55.64	
Sleep Duration		100	6.97 (1.24) 1-13		6.85 (1.23) 1.5-12
(Baseline)	Short Sleep ≤5 hrs	10.57		12.22	
	Optimal Sleep >5 - <9 hrs	84.94		86.55	
	Long Sleep ≥9 hrs	4.49		1.23	
Sleep Duration		100	6.92 (1.14) 1-14		3,494 (6.84) 1-14
(Follow-up)	Short Sleep ≤5 hrs	15.27		6.58	
	Optimal Sleep >5 - <9 hrs	79.97		89.58	
	Long Sleep ≥9 hrs	4.76		3.84	
Depression	No	91.25		91.16	
(Baseline)	Yes	8.75		8.84	
Depression	No	88.53		86.81	
(Follow-up)	Yes	11.47		13.19	

Notes: ELSA, waves 2–8; % = N = observations; percentage frequencies; M = mean; SD = standard deviations.

Table S6.4 Relationships of polygenic scores for sleep duration, short sleep, and long sleep with onset of depression during an average 8-year follow-up, using continuous values for depression

Models	Depression		
	β (SE)	95% CI	*p*
Polygenic score for sleep duration			
Model 1: Unadjusted model [a]	-0.023 (0.014)	-0.051-0.005	0.109
Model 2: Model 1 + age, age², sex, and 10 PCs	-0.021 (0.013)	-0.047-0.006	0.121
Polygenic score for short sleep			
Model 1: Unadjusted model [a]	0.037 (0.014)	0.009-0.065	0.010*
Model 2: Model 1 + age, age², sex, and 10 PCs	0.044 (0.015)	0.016-0.073	0.002*
Polygenic score for long sleep			
Model 1: Unadjusted model [a]	-0.008 (0.014)	-0.036-0.019	0.553
Model 2: Model 1 + age, age², sex, and 10 PCs	-0.002 (0.013)	-0.028-0.025	0.909

Note. PCs = principal components; β = standardised regression coefficient; SE = standard error; CI = confidence interval; p = significance value. Alpha values have been adjusted to account for multiple testing. * denotes significance at <0.001.

[a] Baseline caseness of outcomes were omitted from analyses.

Table S6.5 Relationships of phenotypic overall sleep duration, short sleep, and long sleep with onset of depression during an average 8-year follow-up

Models	Depression		
	OR (*SE*)	95% CI	*p*
Sleep duration phenotype			
Model 1: Unadjusted model [a]	0.736 (0.026)	0.688-0.788	<0.001*
Model 2: Model 1 + age, age², sex, and 10 PCs	0.744 (0.026)	0.694-0.796	<0.001*
Model 3: Adjustment for all baseline covariates [b]	0.788 (0.028)	0.736-0.844	<0.001*
Short sleep phenotype			
Model 1: Unadjusted model [a]	3.364 (0.380)	2.695-4.199	<0.001*
Model 2: Model 1 + age, age², sex, and 10 PCs	3.173 (0.364)	2.535-3.972	<0.001*
Model 3: Adjustment for all baseline covariates [b]	2.583 (0.306)	2.048-3.257	<0.001*
Long sleep phenotype			
Model 1: Unadjusted model [a]	1.776 (0.342)	1.218-2.590	0.003*
Model 2: Model 1 + age, age², sex, and 10 PCs	1.729 (0.336)	1.181-2.532	0.005*
Model 3: Adjustment for all baseline covariates [b]	1.578 (0.313)	1.069-2.328	0.022*

Note. PCs = principal components; OR = (odds ratio); SE = standard error; CI = confidence interval; p = significance value.

[a] Baseline caseness of outcomes were omitted from analyses. Alpha values have been adjusted to account for multiple testing. * denotes significance at <0.001.

[b] Baseline covariates controlled for: age, age², sex, 10 PCs, education, wealth, smoking status, physical activity, body mass index, triglyceride and limiting longstanding illness.

Table S6.6 Relationships of phenotypic depression with overall sleep duration, and onset of short sleep and long sleep during an average 8-year follow-up

Models	Sleep duration			Short sleep[d]			Long sleep[d]		
	β (*SE*)	95% CI	*p*	RRR (*SE*)	95% CI	*p*	RRR (*SE*)	95% CI	*p*
Depression phenotype									
Model 1: Unadjusted model [a b]	-0.028 (0.007)	-0.041--0.014	<0.001*	1.468 (0.205)	1.117-1.930	0.006	1.146 (0.274)	0.716-1.832	0.571
Model 2: Model 1 + age, age^2, sex, and 10 PCs	-0.026 (0.007)	-0.040--0.012	<0.001*	1.452 (0.206)	1.099-1.918	0.009	1.036 (0.251)	0.644-1.667	0.885
Model 3: Adjustment for all baseline covariates [c]	-0.018 (0.007)	-0.032--0.004	0.012*	1.310 (0.193)	0.982-1.749	0.050	1.018 (0.254)	0.624-1.659	0.944

Note. PCs = principal components; RRR = relative risk ratio; SE = standard error; CI = confidence interval; p = significance value. Alpha values have been adjusted to account for multiple testing. * denotes significance at <0.001.

[a] Baseline caseness of outcomes were omitted from analyses.

[b] Sleep duration squared was included in sleep duration models to account for non-linearity.

[c] Baseline covariates controlled for: age, age^2, sex, 10 PCs, education, wealth, smoking status, physical activity, body mass index, triglyceride and limiting longstanding illness.

[d] Baseline comparison was optimal sleep.

Table S6.7 Relationships of polygenic scores for sleep duration, short sleep, and long sleep with onset of depression during an average 8-year follow-up in complete case data (N=3185)

Models	Depression		
	OR (*SE*)	95% CI	*p*
Polygenic score for sleep duration			
Model 1: Unadjusted model [a]	0.915 (0.053)	0.816-1.025	0.123
Model 2: Model 1 + age, age^2, sex, and 10 PCs	0.916 (0.054)	0.815-1.028	0.136
Polygenic score for short sleep			
Model 1: Unadjusted model [a]	1.113 (0.065)	0.992-1.249	0.067
Model 2: Model 1 + age, age^2, sex, and 10 PCs	1.136 (0.073)	1.002-1.289	0.047*
Polygenic score for long sleep			
Model 1: Unadjusted model [a]	0.963 (0.055)	0.861-1.078	0.516
Model 2: Model 1 + age, age^2, sex, and 10 PCs	0.969 (0.057)	0.864-1.087	0.591

Note. PCs = principal components; OR = (odds ratio); SE = standard error; CI = confidence interval; p = significance value. Alpha values have been adjusted to account for multiple testing. * denotes significance at <0.001.

[a] Baseline caseness of outcomes were omitted from analyses.

Table S6.8 Relationships of polygenic scores for depression with overall sleep duration, and onset of short sleep and long sleep during an average 8-year follow-up in complete case data (N=3134)

Models	Sleep duration			Short sleep[c]			Long sleep[c]		
	β (*SE*)	95% CI	*p*	RRR (*SE*)	95% CI	*p*	RRR (*SE*)	95% CI	*p*
Polygenic score for depression									
Model 1: Unadjusted model [a b]	-0.018 (0.021)	-0.058-0.022	0.376	1.055 (0.129)	0.830-1.340	0.661	0.985 (0.108)	0.794-1.220	0.887
Model 2: Model 1 + age, age^2, sex, and 10 PCs	-0.024 (0.021)	-0.065-0.016	0.238	1.090 (0.136)	0.854-1.392	0.489	0.963 (0.107)	0.775-1.197	0.737

Note. PCs = principal components; RRR = relative risk ratio; SE = standard error; CI = confidence interval; p = significance value. Alpha values have been adjusted to account for multiple testing.

[a] Baseline caseness of outcomes were omitted from analyses.

[b] Sleep duration squared was included in sleep duration models to account for non-linearity.

[c] Baseline comparison was optimal sleep.

Table S6.9 Relationships of polygenic scores for sleep duration, short sleep, and long sleep with onset of depression during an average 8-year follow-up using a cut-off threshold of 3 for the Centre for Epidemiologic Studies Depression Scale (CES-D)

Models	Depression		
	OR (*SE*)	**95% CI**	***p***
Polygenic score for sleep duration			
Model 1: Unadjusted model [a]	0.944 (0.039)	0.870-1.024	0.162
Model 2: Model 1 + age, age^2, sex, and 10 PCs	0.938 (0.040)	0.863-1.019	0.938
Polygenic score for short sleep			
Model 1: Unadjusted model [a]	1.159 (0.049)	1.067-1.259	<0.001*
Model 2: Model 1 + age, age^2, sex, and 10 PCs	1.200 (0.055)	1.096-1.313	<0.001*
Polygenic score for long sleep			
Model 1: Unadjusted model [a]	1.001 (0.042)	0.922-1.087	0.985
Model 2: Model 1 + age, age^2, sex, and 10 PCs	1.012 (0.044)	0.931-1.101	0.773

Note. PCs = principal components; OR = (odds ratio); SE = standard error; CI = confidence interval; p = significance value. Alpha values have been adjusted to account for multiple testing. * denotes significance at <0.001.

[a] Baseline caseness of outcomes were omitted from analyses.

Table S6.10 Relationships of polygenic scores for sleep duration, short sleep, and long sleep with onset of depression during an average 8-year follow-up using the 8-item CES-D

Models	Depression		
	OR (*SE*)	95% CI	*p*
Polygenic score for sleep duration			
Model 1: Unadjusted model [a]	0.932 (0.044)	0.849-1.024	0.142
Model 2: Model 1 + age, age^2, sex, and 10 PCs	0.932 (0.045)	0.848-1.025	0.147
Polygenic score for short sleep			
Model 1: Unadjusted model [a]	1.129 (0.055)	1.027-1.241	0.012*
Model 2: Model 1 + age, age^2, sex, and 10 PCs	1.148 (0.060)	1.036-1.271	0.008*
Polygenic score for long sleep			
Model 1: Unadjusted model [a]	1.020 (0.049)	0.928-1.121	0.682
Model 2: Model 1 + age, age^2, sex, and 10 PCs	1.027 (0.050)	0.933-1.130	0.592

Note. PCs = principal components; OR = (odds ratio); SE = standard error; CI = confidence interval; p = significance value. Alpha values have been adjusted to account for multiple testing. * denotes significance at <0.001.

[a] Baseline caseness of outcomes were omitted from analyses.

APPENDIX E

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Table S7.1 Longitudinal associations between pre-pandemic inflammatory markers and depression during the pandemic modelled as continuous scores

Adjustments	CRP (*n* = 3 574)			Fb (*n* = 3 314)		
	Coef. (SE)	95% CI	*p*	Coef. (SE)	95% CI	*p*
Model 1: *adjusted for baseline depressive symptoms*	0.25 (0.07)	0.12-0.38	<0.001	0.14 (0.05)	0.04-0.24	0.005
Model 2: *Model 1 + adjustment for age and sex*	0.23 (0.07)	0.10-0.36	<0.001	0.13 (0.05)	0.03-0.23	0.013
Model 3: *Model 1 + adjustment for education and wealth*	0.21 (0.07)	0.08-0.34	0.001	0.13 (0.05)	0.03-0.23	0.014
Model 4: *Model 1 + adjustment for health behaviours* [a]	0.20 (0.07)	0.07-0.33	0.003	0.11 (0.05)	0.00-0.21	0.044
Model 5: *Model 1 + adjustment for clinical variables*[b]	0.21 (0.07)	0.08-0.34	0.001	0.11 (0.05)	0.01-0.22	0.028
Model 6: *adjusted for all covariates*[c]	0.14 (0.07)	0.01-0.27	0.034	0.07 (0.05)	-0.04-0.17	0.202

Notes. CRP = C-reactive protein; Fb = Fibrinogen; Regression coefficient (X) = a one-unit increase in inflammation is associated with an X unit increase in depressive symptoms; SE = standard error; CI = confidence interval; *p* = significance value.

a H*ealth behaviours* = smoking status; alcohol consumption; physical activity.

b *Clinical variables* = triglyceride; high-density lipoprotein (HDL); low-density lipoprotein (LDL); limiting longstanding illness.

c All covariates = depression (CES-D); age; sex; education; wealth; smoking status; alcohol consumption; physical activity; triglyceride; high-density lipoprotein (HDL); low-density lipoprotein (LDL); limiting longstanding illness.

Table S7.2 Longitudinal associations between pre-pandemic inflammatory markers and depression during the pandemic, accounting for participant exposure to the coronavirus

Adjustments		CRP (*n* = 3 573)			Fb (*n* = 3 313)		
		Coef. (SE)	**95% CI**	***p***	**Coef. (SE)**	**95% CI**	***p***
Model 1:	*adjusted for baseline depressive symptoms*	0.25 (0.07)	0.12-0.38	<0.001	0.14 (0.05)	0.04-0.24	0.005
Model 2:	*Model 1 + adjustment for age and sex*	0.23 (0.07)	0.10-0.36	<0.001	0.13 (0.05)	0.03-0.23	0.014
Model 3:	*Model 1 + adjustment for education and wealth*	0.21 (0.07)	0.08-0.34	0.001	0.13 (0.05)	0.02-0.23	0.016
Model 4:	*Model 1 + adjustment for health behaviours* [a]	0.20 (0.07)	0.07-0.32	0.003	0.10 (0.05)	0.00-0.21	0.047
Model 5:	*Model 1 + adjustment for clinical variables*[b] *and COVID-19 variables*[c]	0.21 (0.07)	0.08-0.34	0.001	0.11 (0.05)	0.01-0.22	0.029
Model 6:	*adjusted for all covariates*[d]	0.14 (0.07)	0.01-0.27	0.034	0.07 (0.05)	-0.04-0.17	0.216

Notes. CRP = C-reactive protein; Fb = Fibrinogen; Regression coefficient (X) = one-unit increase in inflammation is associated with an X unit increase in depressive symptoms; *SE* = standard error; CI = confidence interval; *p* = significance value.

a *Health behaviours* = smoking status; alcohol consumption; physical activity.

b *Clinical variables* = triglyceride; high-density lipoprotein (HDL); low-density lipoprotein (LDL); limiting longstanding illness.

c *COVID-19 variables* = hospitalized for COVID-19; two of three National Health Service (NHS) core coronavirus symptoms.

d All covariates = depression (CES-D); age; sex; education; wealth; smoking status; alcohol consumption; physical activity; triglyceride; high-density lipoprotein (HDL); low-density lipoprotein (LDL); limiting longstanding illness; hospitalized for COVID-19; two of three National Health Service (NHS) core coronavirus symptoms.

Table S7.3 Longitudinal associations between inflammatory markers (continuous logarithmic transformed CRP) and depression during the pandemic

Adjustments	CRP (*n* = 3 574)		
	OR (*SE*)	95% CI	*p*
Model 1: *adjusted for baseline depressive symptoms*	1.39 (0.11)	1.19-1.61	<0.001
Model 2: *Model 1 + adjustment for age and sex*	1.35 (0.10)	1.16-1.57	<0.001
Model 3: *Model 1 + adjustment for education and wealth*	1.30 (0.10)	1.12-1.52	0.001
Model 4: *Model 1 + adjustment for health behaviours* [a]	1.26 (0.10)	1.08-1.47	0.004
Model 5: *Model 1 + adjustment for clinical variables*[b]	1.32 (0.11)	1.13-1.55	<0.001
Model 6: *adjusted for all covariates*[d]	1.18 (0.10)	1.00-1.39	0.046

Notes. CRP = C-reactive protein; OR = odds ratio; *SE* = standard error; CI = confidence interval; *p* = significance value.

a *Health behaviours* = smoking status; alcohol consumption; physical activity.

b *Clinical variables* = triglyceride; high-density lipoprotein (HDL); low-density lipoprotein (LDL); limiting longstanding illness.

c All covariates = depression (CES-D ≥4); age; sex; education; wealth; smoking status; alcohol consumption; physical activity; triglyceride; high-density lipoprotein (HDL); low-density lipoprotein (LDL); limiting longstanding illness.

Table S7.4 Longitudinal associations between pre-pandemic inflammatory markers and depression during the pandemic, accounting for BMI.

Adjustments		CRP (*n* = 3 120)			Fb (*n* = 2 880)		
		OR (*SE*)	95% CI	*p*	OR (*SE*)	95% CI	*p*
Model 1:	*adjusted for baseline depressive symptoms*	1.56 (0.18)	1.24-1.95	<0.001	1.33 (0.12)	1.11-1.60	0.002
Model 2:	*Model 1 + adjustment for age and sex*	1.52 (0.18)	1.22-1.91	<0.001	1.29 (0.12)	1.08-1.56	0.006
Model 3:	*Model 1 + adjustment for education and wealth*	1.45 (0.17)	1.16-1.82	<0.001	1.27 (0.12)	1.06-1.53	0.010
Model 4:	*Model 1 + adjustment for health behaviours* [a]	1.38 (0.16)	1.10-1.74	0.006	1.21 (0.12)	1.00-1.46	0.046
Model 5:	*Model 1 + adjustment for clinical variables*[b] *and BMI*[c]	1.41 (0.17)	1.12-1.79	0.004	1.24 (0.12)	1.03-1.50	0.026
Model 6:	*adjusted for all covariates*[d]	1.26 (0.16)	0.99-1.61	0.056	1.14 (0.11)	0.94-1.39	0.189

Notes. BMI = Body Mass Index; CRP = C=reactive protein; Fb = Fibrinogen; OR = (odds ratio); *SE* = standard error; CI = confidence interval; *p* = significance value.

a *Health behaviours* = smoking status; alcohol consumption; physical activity.

b *Clinical variables* = triglyceride; high-density lipoprotein (HDL); low-density lipoprotein (LDL); limiting longstanding illness; BMI.

c All covariates = depression (CES-D ≥4); age; sex; education; wealth; smoking status; alcohol consumption; physical activity; triglyceride; high-density lipoprotein (HDL); low-density lipoprotein (LDL); limiting longstanding illness; BMI.

Table S7.5 Longitudinal associations between pre-pandemic inflammatory markers and depression during the pandemic, conditioned on an 8-point classification of alcohol consumption

Adjustments	CRP (*n* = 3 574)			Fb (*n* = 3 331)		
	OR (*SE*)	95% CI	*p*	OR (*SE*)	95% CI	*p*
Model 1: *adjusted for baseline depressive symptoms*	1.69 (0.18)	1.38-2.08	<0.001	1.29 (0.11)	1.09-1.52	0.003
Model 2: *Model 1 + adjustment for age and sex*	1.65 (0.17)	1.34-2.03	<0.001	1.26 (0.11)	1.07-1.50	0.007
Model 3: *Model 1 + adjustment for education and wealth*	1.57 (0.17)	1.27-1.93	<0.001	1.23 (0.11)	1.04-1.46	0.019
Model 4: *Model 1 + adjustment for health behaviours* [a]	1.49 (0.16)	1.21-1.84	<0.001	1.14 (0.10)	0.96-1.36	0.136
Model 5: *Model 1 + adjustment for clinical variables*[b]	1.59 (0.17)	1.29-1.97	<0.001	1.22 (0.11)	1.03-1.45	0.025
Model 6: *adjusted for all covariates*[c]	1.40 (0.16)	1.13-1.75	0.002	1.12 (0.10)	0.93-1.34	0.224

Notes. CRP = C=reactive protein; Fb = Fibrinogen; OR = (odds ratio); *SE* = standard error; CI = confidence interval; *p* = significance value.

a *Health behaviours* = smoking status; alcohol consumption; physical activity.

b *Clinical variables* = triglyceride; high-density lipoprotein (HDL); low-density lipoprotein (LDL); limiting longstanding illness.

c All covariates = depression (CES-D ≥4); age; sex; education; wealth; smoking status; alcohol consumption; physical activity; triglyceride; high-density lipoprotein (HDL); low-density lipoprotein (LDL); limiting longstanding illness.

Table S7.6 Longitudinal associations between pre-pandemic inflammatory markers and depression during the pandemic, accounting for participant exposure to the coronavirus, financial impact of the pandemic and a difficulty in accessing services during the pandemic

Adjustments	CRP (*n* = 3 572)			Fb (*n* = 3 312)		
	OR (*SE*)	95% CI	*p*	OR (*SE*)	95% CI	*p*
Model 1: *adjusted for baseline depressive symptoms*	1.70 (0.18)	1.38-2.08	<0.001	1.29 (0.11)	1.09-1.53	0.003
Model 2: *Model 1 + adjustment for age and sex*	1.65 (0.17)	1.34-2.03	<0.001	1.27 (0.11)	1.07-1.50	0.007
Model 3: *Model 1 + adjustment for education and wealth*	1.57 (0.17)	1.28-1.94	<0.001	1.23 (0.11)	1.04-1.46	0.016
Model 4: *Model 1 + adjustment for health behaviours* [a]	1.51 (0.16)	1.22-1.86	<0.001	1.16 (0.10)	0.98-1.38	0.084
Model 5: *Model 1 + adjustment for clinical variables*[b]	1.60 (0.17)	1.29-1.97	<0.001	1.23 (0.11)	1.03-1.46	0.020
Model 6: *Model 1 + COVID-19 impact variables*[c]	1.70 (0.18)	1.38-2.09	<0.001	1.29 (0.11)	1.09-1.52	0.003
Model 7: *adjusted for all covariates*[d]	1.40 (0.16)	1.13-1.74	0.003	1.12 (0.10)	0.94-1.34	0.215

Notes. CRP = C=reactive protein; Fb = Fibrinogen; OR = (odds ratio); *SE* = standard error; CI = confidence interval; *p* = significance value.

a *Health behaviours* = smoking status; alcohol consumption; physical activity.

b *Clinical variables* = triglyceride; high-density lipoprotein (HDL); low-density lipoprotein (LDL); limiting longstanding illness.

c *COVID-19 impact variables* = exposure to the coronavirus, the financial impact of the pandemic and a difficulty in accessing services during the pandemic.

d All covariates = depression (CES-D ≥4); age; sex; education; wealth; smoking status; alcohol consumption; physical activity; triglyceride; high-density lipoprotein (HDL); low-density lipoprotein (LDL); limiting longstanding illness.

APPENDIX F

CHAPTERS 3-7 | Research Paper Declaration Forms

UCL Research Paper Declaration Form

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Immune-neuroendocrine patterning and response to stress. A latent profile analysis in the English longitudinal study of ageing

b) **Please include a link to or doi for the work**

https://doi.org/10.1016/j.bbi.2023.11.012

c) **Where was the work published?**

Brain, Behavior, and Immunity

d) **Who published the work?** (e.g. OUP)

Elsevier

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Odessa S. Hamilton, MSc (OSH), Eleonora Iob, PhD (EI), Olesya Ajnakina, PhD (OA), James B. Kirkbride, PhD (JK), Andrew Steptoe, DSc (AS)

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Study funding was secured by AS. Conception and planning by OSH and AS. OSH and EI designed the statistical analysis plan. OSH and OA prepared the data. OSH performed data analyses, then interpreted results with input from all authors. All authors had access to the data, take responsibility for data integrity, the accuracy of analysis, and its interpretation. All authors act as guarantors, and critically appraised the manuscript drafted by OSH for submission.

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Socioeconomic determinants of inflammation and neuroendocrine activity: A longitudinal analysis of compositional and contextual effects

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https://doi.org/10.1101/2024.07.23.24310898

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Study funding was secured by AS. Conception and planning by both authors. OSH designed the statistical analysis plan, prepared the data, performed the analyses, and drafted the manuscript. Both authors interpreted results and act as guarantors, taking responsibility for integrity of the data, the accuracy of analyses, its interpretation, and the critical appraisal the manuscript.

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Polygenic predisposition, sleep duration, and depression: evidence from a prospective population-based cohort

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https://doi.org/10.1038/s41398-023-02622-z

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Springer Nature

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a) **What is the title of the manuscript?**

Systemic inflammation and emotional responses during the COVID-19 pandemic

b) **Please include a link to or doi for the work**

https://doi.org/10.1038/s41398-021-01753-5

c) **Where was the work published?**

Translational Psychiatry

d) **Who published the work?** (e.g. OUP)

Springer Nature

e) **When was the work published?**

December 2021

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Date
29 November 2024

APPENDIX G

Additional Academic Contributions

Non-PhD Publications

Publication	Journal	Date
Hamilton, O. S. & Lordan, G. Ability or luck: A systematic review of interpersonal attributions of success. *Front. Psychol.* **13**, 1035012 (2023).	Frontiers Organisational Psychology · DOI	Jan 2023

Papers Under Review

Paper	Pre-print Server	Date
Hamilton, O. S., Jolles, D., & Lordan, G. *Quiet Quitting. A macroeconomic analysis of 4 million people*	IZA Institute of Labour Economics DOI	Jun 2023

Working Papers

Paper
Hamilton, O. S., Ajnakina, O., Frank, P., Scholes, S., & Steptoe, A. | A Comparative Study of Immune and Neuroendocrine Protein Biomarkers with Latent Profiles in All-Cause Hospitalisation: A Time-To-Event Analysis.
Hamilton, O. S., Ajnakina, O., Austin-Zimmerman, I., … Prather, A., Steptoe, A., & Kuchenbäcker, K. | The Causal Effect of Suboptimal Sleep on Risk of Mental Disorder and the role of Inflammation: A Two Sample Mendelian Randomization Study.
Hamilton, O. S., Juvinao-Quintero, D., Ajnakina, O., Steptoe, A., Kuchenbäcker, K., & Gelaye, B. | Stress, Sleep Disturbances, and Neuroinflammation in Obstetric Outcomes: A Machine Learning and Network Analysis.

Thought Leadership *(a selection)*

Publication	Publisher	Date
Hamilton, O. S. Stress, the Brain, and Immunity | Psychology Today United Kingdom. *Psychology Today*	Psychology Today	Nov 2023
Hamilton, O. S. When Money Worries Keep You Up at Night | Psychology Today United Kingdom. *Psychology Today*	Psychology Today	Dec 2022
Hamilton, O. S. In Sickness and Wealth: Financial Stress Can Make Us Sick | Psychology Today United Kingdom. *Psychology Today*	Psychology Today	Nov 2022
Hamilton, O. S. & Meadows, G. Five Reasons Why You Need to Improve Your Employees' Sleep to Improve Their Mental Health.	The Sleep School	Nov 2022
Hamilton, O. S., Kohler, L., Cox, E. B. & Lordan, G. How to Make Your Organization's Language More Inclusive. *Harvard Business Review* (2022).	Harvard Business Review	Mar 2022
Hamilton, O. S. Night Owls Aren't Lazy: Rethinking Sleep Variation | Psychology Today United Kingdom. *Psychology Today*	Psychology Today	Mar 2022
Hamilton, O. S. Work. Stress. Sleep. Repeat. Breaking the cycle of mutually reinforcing work stress and sleep deprivation. *London School of Economics (LSE) Business Review*	LSE Business Review	Feb 2022
Hamilton, O. S. Older Adults Have Been Primed for Pandemic-Related Mental Illness | Psychology Today United Kingdom. *Psychology Today*	Psychology Today	Jan 2022
Hamilton, O. S. Beneath the Skin: The Problems Chronic Stress Can Cause | Psychology Today United Kingdom. *Psychology Today*	Psychology Today	Dec 2021

Publication	Publisher	Date
Hamilton, O. S. Beneath the skin: from occupational stress to mental illness. *London School of Economics (LSE) Business Review*	LSE Business Review	May 2021

Conference Presentations & Invited Talks *(a selection)*

Event	Host	Date
Hamilton, O. S., Ajnakina, O., Frank, P., Scholes, S., & Steptoe, A. (2024). THELANCET-D-24-02841R1 A Comparative Study of Immune and Neuroendocrine Protein Biomarkers with Latent Profiles in All-Cause Hospitalisation: A Time-To-Event Analysis. 922	The Lancet Public Health Science DOI	Nov 2024
Hamilton, O. S., Iob, E., Ajnakina, O., Kirkbride, J. B., & Steptoe, A. (2024). P53 Immune-neuroendocrine patterning and response to stress. A latent profile analysis in the English longitudinal study of ageing. *J Epidemiol Community Health*, *78*(Suppl 1), A72–A72.	Journal of Epidemiology & Community Health DOI	Aug 2024
Hamilton, O. S., Iob, E., Ajnakina, O., Kirkbride, J. B., & Steptoe, A. (2024). OP922 Immune-neuroendocrine patterning and response to stress. A latent profile analysis in the English longitudinal study of ageing.	Society for Biopsychosocial Science and Medicine (a.k.a. APS)	Mar 2024
Hamilton, O. S., & Steptoe, A. (2024). P2 Socioeconomic determinants of inflammation and neuroendocrine activity: A longitudinal analysis of compositional and contextual effects. *Psychoneuroendocrinology*, *160*, 106788.	Psychoneuroendocrinology DOI	Feb 2024

Hamilton, O. S., & Steptoe, A. (2023). OP4.2. Socioeconomic determinants of inflammation and neuroendocrine activity: A longitudinal analysis of compositional and contextual effects. *Psychoneuroendocrinology*, *160*, 106788.	Health Studies User Conference	Jun 2023
Hamilton, O. S. & Lordan, G., (2022). Luck vs. Skill	Human Risk	Nov 2022
Hamilton, O. S., Steptoe, A., & Ajnakina, O. (2022). OP54 Polygenic predisposition, sleep duration, and depression: Evidence from a prospective population-based cohort*. *J Epidemiol Community Health*, *76*(Suppl 1), A26–A26.	Journal of Epidemiology & Community Health DOI	Nov 2022
Hamilton, O. S., Dalman, C., Hollander, A., Khandaker, G., & Kirkbride, J. OP10 The Association Between Dyssomnias and Non-Affective Psychosis and the Mediating Role of Inflammation and Common Mental Disorders in the Swedish National Patient Register, with Data Linkage	KaBris	Sep 2022
Hamilton, O. S., Steptoe, A. & Ajnakina, O. OP54 Polygenic Predisposition, Sleep Duration, and Depression: Evidence from a Prospective Population-Based Cohort. *Journal Epidemiology Community Health* A26 (2022).	Society for Social Medicine	Sep 2022

Registrations & Memberships

MBPsS | British Psychological Society	Fellow | Royal Society for Public Health

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