



Trinity College Dublin

Coláiste na Tríonóide, Baile Átha Cliath

The University of Dublin

An evaluation of the Allostatic Load framework for quantifying differences in health and longevity.

Sinéad McLoughlin

2023

A thesis submitted to the University of Dublin, Trinity College,
for the Degree of Doctor of Philosophy in the School of Medicine

Supervisor: Dr Cathal McCrory

DECLARATION

I declare that this thesis has not been submitted as an exercise for a degree at this or any other university and it is entirely my own work.

I agree to deposit this thesis in the University's open access institutional repository or allow the library to do so on my behalf, subject to Irish Copyright Legislation and Trinity College Library conditions of use and acknowledgement.

I consent to the examiner retaining a copy of the thesis beyond the examining period, should they so wish (EU GDPR May 2018).



Sinéad McLoughlin

Date: 29/08/2022

ACKNOWLEDGEMENTS

Firstly, I would like to thank my exceptional supervisor, Dr Cathal McCrory. Your unwavering support, guidance and encouragement made navigating this PhD possible, despite challenging life events and a global pandemic. You have spent countless hours engaging with this body of work, and I have learned from each and every interaction. From a personal and professional perspective, you have been such a great mentor, and I will always feel privileged to have been your student.

I would also like to thank the TILDA team, both past and present, who have provided treasured support over the years. The feedback and words of encouragement I received during internal seminars have been truly appreciated. Specifically, I must acknowledge Dr Siobhan Scarlett, who has gone above and beyond the call of duty as a mentor since supervising my MSc thesis all those years ago. I would also like to acknowledge the great contribution to knowledge and research made by all participants of TILDA. This research would not have been possible without their commitment. I am also extremely thankful to Professor Rose Anne Kenny, and co-authors Dr Aisling M. O'Halloran, Professor Mel Bartley, and Professor Patrick Präg for insightful discussions on some of the studies included in this thesis.

On a personal note, I must thank my parents, Carmel and Gerry, for the endless support and love they have given me. Somehow you have always managed to ensure we had the opportunities to choose the paths in life that we saw fit. Thanks to my siblings, Róisín and Ciarán, for always being there for me and for keeping me humble. You have both accomplished great things in recent years, and I'm excited to see where life takes you both. To my "*crazy aunties*", you have been to hell and back in recent years, yet you are the strongest women I know. How you have stuck together in the tough times and continued to love, and laugh is inspiring. Your bond is beautiful. To my dear friends, both at home and abroad, thank you for loyal friendship despite the distance at times. You'll all be relieved to hear that I'm finished college now. Count me in for all future nights out, nights in, trips away and babysitting duties.

To Sam, you have lived this journey with me. Thank you for keeping me going, keeping me sane, and keeping me silly. You have shown such patience and understanding as I pursued this PhD, and you have never failed to help me put things into perspective during the challenging moments. I love you, and I can't wait for our next adventure - who knows where we'll end up. Finally, it would be remiss of me not to acknowledge our non-human best friend, Smudge, for his unswerving companionship and entertainment. We don't deserve dogs.

This thesis was supported by the Health Research Board (HRB) of Ireland under an Emerging Investigator Award to Dr Cathal McCrory (EIA- 2017-012).

CONTENTS

1	Chapter 1: Introduction	18
1.1	A brief history of the evolution of stress research	20
1.2	Modern concepts of stress physiology: allostasis	22
1.3	Allostatic load	23
1.3.1	Operationalisation of allostatic load	29
1.3.2	The issue of various scoring methods	30
1.3.3	The issue of various biomarker panels	31
1.4	Allostatic load and poor health outcomes	33
1.5	Stress exposure as a precursor to allostatic load	34
1.5.1	Inter-individual differences	36
1.6	Ageing and allostatic load	38
1.7	Social gradient in health	39
1.8	Measuring socio-economic position	40
1.8.1	Education	40
1.8.2	Income	41
1.8.3	Occupation	42
1.9	The life course approach to health	43
1.10	Socio-economic position and allostatic load: life course models	45
1.10.1	Methodological considerations	48
1.11	Summary and the established gaps in the literature	49
2	Chapter 2: Methods	51
	Chapter summary	51
2.1	Purpose of the study	51
2.1.1	Study 1: Does the choice of Allostatic Load scoring algorithm matter for predicting age-related health outcomes?	52
2.1.2	Study 2: Psychosocial adversity and Allostatic Load	52
2.1.3	Study 3: Intergenerational social mobility and Allostatic Load burden	52
2.1.4	Study 4: The association of allostatic load biomarkers with stress and all-cause mortality	53
2.2	The Irish Longitudinal Study on Ageing (TILDA)	53
2.2.1	TILDA sampling design	54
2.2.2	TILDA Wave 1 data collection	54

2.3	Measures	55
2.3.1	Physiological parameters	55
2.3.2	Socio-economic position.....	57
2.3.3	Outcome variables	57
2.4	Statistical analysis	58
2.5	Research paradigm.....	59
3	Chapter 3: Does the choice of Allostatic Load scoring algorithm matter for predicting age-related health outcomes?	61
	Chapter 3: Published work list.....	62
3.1	Introduction.....	63
3.1.1	Different scoring systems for AL	63
3.1.2	Does the choice of AL scoring method matter for predicting health?	65
3.1.3	Should we incorporate sex differences in the calculation of the AL index?	66
3.1.4	Should we incorporate medications in the calculation of the AL index?	66
3.2	The present study	67
3.3	Methods.....	67
3.3.1	Sample.....	67
3.3.2	Physiological parameters	68
3.3.3	Calculation of summary measures	69
3.3.4	Health outcomes.....	72
3.4	Statistical analysis	73
3.5	Results.....	75
3.5.1	Walking speed.....	78
3.5.2	Grip strength	79
3.5.3	Self-rated health	80
3.5.4	Area under the receiver operating characteristic curve (AUC)	81
3.6	Discussion	83
3.6.1	Use of one vs two-tailed risk	85
3.6.2	The importance of considering sex differences	85
3.6.3	The importance of considering medications	86
3.7	Strengths and limitations.....	86
3.8	Conclusion	87
4	Chapter 4: Psychosocial adversity and Allostatic Load burden in Mid-Life and Older Ages	93

CHAPTER 4: PUBLISHED WORK LIST	94
4.1 Introduction.....	95
4.2 Methods.....	96
4.2.1 Data	96
4.2.2 Measures	96
4.2.3 Analytical approach	98
4.2.4 Missing cases	99
4.3 Results.....	100
4.4 Discussion	101
4.5 Conclusion	103
5 Chapter 5: Intergenerational social mobility and allostatic load burden: a diagonal reference modelling approach.....	111
CHAPTER 5: PUBLISHED WORK LIST	112
5.1 Introduction.....	113
5.2 The present study	117
5.2.1 Methods.....	118
5.3 Results.....	125
5.3.1 Diagonal Reference Models.....	128
5.3.2 Linear models.....	132
5.4 Discussion	134
5.4.1 Relation to other studies.....	135
5.4.2 Differences in biomarker composition.....	136
5.4.3 Differences in sample composition.....	136
5.4.4 Differences in class schema	137
5.4.5 Different levels of social mobility	137
5.5 Strengths and limitations.....	138
5.6 Conclusion	139
6 Chapter 6: The association of allostatic load biomarkers with stress and all-cause mortality	153
6.1 Introduction.....	154
6.2 Heterogeneity of biomarkers used to define allostatic load.....	155
6.3 In search of an optimal panel of biomarkers for allostatic load.....	155
6.4 Allostatic load and stress	156
6.5 The utility of allostatic load as a predictor of mortality.....	156

6.6	Physiological sub-systems	158
6.7	Rationale and present study	159
6.8	Methods.....	159
6.8.1	Data source.....	159
6.8.2	Measurements	160
6.8.3	Statistical approach	165
6.8.4	Missing cases	165
6.9	Results.....	169
6.9.1	Correlation of biomarkers and sub-systems with PSS.....	169
6.9.2	Association of biomarkers with risk of all-cause mortality	172
6.9.3	Association of physiological sub-systems with risk of all-cause mortality	174
6.9.4	Association of allostatic load burden with risk of all-cause mortality.....	174
6.9.5	Sensitivity analyses	174
6.10	Discussion.....	175
6.10.1	Which AL biomarkers were most strongly associated with mortality?	176
6.10.2	Which AL sub-systems were most strongly associated with mortality?	179
6.10.3	Is the overall AL index greater than the sum of its parts?	180
6.10.4	Implications.....	182
6.11	Strengths and limitation	183
6.12	Conclusion	183
7	Chapter 7: Discussion and conclusion	188
7.1	Discussion of principle findings and their implications	188
7.1.1	Comparing the predictive utility of various operational definitions of AL on health	188
7.1.2	Life course adversity and AL.....	189
7.1.3	Life course socio-economic position and AL	192
7.1.4	AL and its component biomarkers	193
7.2	Summary of key strengths and limitations.....	195
7.3	Future research directions	196
7.3.1	Medications.....	196
7.3.2	Sex differences.....	197
7.3.3	Dynamic and longitudinal measures of AL	199
7.3.4	Inter-individual differences.....	201
7.3.5	Alternate measures of multi-system physiological dysregulation	203

7.3.6	AL as a mediator on the SEP-mortality relationship	204
7.4	Clinical implications	205
7.4.1	Clinimetrics	207
7.4.2	Personal reflections	207
7.5	Conclusion	208

LIST OF TABLES

Table 3.1:	Sample characteristics.....	75
Table 3.2:	Univariate descriptives of individual biomarkers by sex.....	77
Table 3.3:	Model Fit Statistics for different Allostatic Load Scoring Algorithms predicting Walking Speed.....	78
Table 3.4:	Model Fit Statistics for different Allostatic Load Scoring Algorithms predicting Grip Strength.....	80
Table 3.5:	Model Fit Statistics for different Allostatic Load Scoring Algorithms predicting self-rated health.....	81
Table 5.1:	Sample characteristics according to origin and destination social class position and intergenerational social class mobility	120
Table 5.2:	Conditional means for allostatic load resulting from the cross-classification of origin and destination social class position	127
Table 5.3:	Parameter estimates from diagonal reference models estimating mobility effects on Allostatic Load burden.....	129
Table 5.4:	Independent and mutually adjusted associations of origin and destination social class with Allostatic Load burden.....	133
Table 6.1:	Details of the 25 biomarkers included in this study.....	163

Table 6.2 Descriptive statistics of the 25 biomarkers (n= 3588)	166
Table 6.3: Sample characteristics by a) mortality status and (b) inclusion status.....	167
Table 6.4: Correlations of all biomarkers and physiological sub-systems with the Perceived Stress Scale	171

LIST OF SUPPLEMENTARY TABLES

Supplementary Table 3.1: Biomarker panel.....	89
Supplementary Table 3.2: Clinically defined risk cut-points for each biomarker	90
Supplementary Table 3.3: Correlations between the AL scoring algorithms and age	90
Supplementary Table 3.4: Distributional statistics for each AL scoring algorithm (n = 4477)	91
Supplementary Table 3.5: Area Under the Curve and associated 95% confidence intervals for different AL scoring algorithms in predicting poor health outcomes	92
Supplementary Table 4.1: Sample characteristics.....	105
Supplementary Table 4.2: Prevalence of adverse events, and rates of missing cases.....	106
Supplementary Table 4.3: Independent and multivariable adjusted associations of each adversity type with Allostatic Load (n= 4477)	107
Supplementary Table 4.4: Independent and multivariable adjusted associations of each adversity type with Allostatic Load, derived from clinical cut points (n= 4477).....	108
Supplementary Table 4.5: Independent and multivariate associations of each adversity type and Allostatic Load on non-imputed data.....	110
Supplementary Table 5.1: Overview of supplementary analyses	141
Supplementary Table 5.2: Biomarker descriptives, and high risk cut points for generating the supplemental clinical risk allostatic load index	142
Supplementary Table 5.3: Parameter estimates from diagonal reference models on allostatic load, interactions.....	143

Supplementary Table 5.4: Parameter estimates from diagonal reference models estimating mobility effects on the allostatic load sub-systems	144
Supplementary Table 5.5: Parameter estimates from diagonal reference models estimating mobility effects on allostatic load (clinical cut-points incorporating medication usage).....	145
Supplementary Table 5.6: Parameter estimates from diagonal reference models estimating educational mobility effects on allostatic load.....	146
Supplementary Table 5.7: Parameter estimates from diagonal reference models estimating mobility effects on allostatic load (5-level SEP)	147
Supplementary Table 5.8: Parameter estimates from diagonal reference models (biomarkers based on prior Understanding Society study)	148
Supplementary Table 5.9: Sample characteristics by category of social mobility.....	149
Supplementary Table 5.10: Parameter estimates from diagonal reference models estimating mobility effects on allostatic load burden, controlling for lifestyle confounders.....	150
Supplementary Table 5.11: Parameter estimates from diagonal reference models estimating mobility effects on allostatic load burden, taking a conservative maximum bias approach to missing data (n=5,153).....	152
Supplementary Table 6.1: Hazard ratio (HR) and 95% confidence intervals (CI) of biomarkers on mean 8-year mortality (multiple imputation analysis, n= 3855).....	185
Supplementary Table 6.2: Hazard ratio (HR) and 95% confidence intervals (CI) of biomarkers on mean 8-year mortality (complete case analysis, n= 3332).....	186
Supplementary Table 6.3:	187

LIST OF FIGURES

Figure 1.1: Four types of allostatic load	26
Figure 1.2: Biological mechanisms of allostatic load	29
Figure 3.1: AUC estimates for different scoring algorithms, predicting slow walking speed	82
Figure 3.2: AUC estimates for different scoring algorithms, predicting weak grip strength.....	82
Figure 3.3: AUC estimates for different scoring algorithms, predicting poor self-rated health	83
Figure 4.1: Independent association of each adversity type with AL in the minimally (A) and full multivariable (B) adjusted models	101
Figure 5.1: Conditional means for Allostatic Load according to intergenerational social class trajectory, adjusting for age, sex, and childhood health.....	126
Figure 6.1: Zero-order biomarker inter-correlation matrix	170
Figure 6.2: Forest plot of hazard ratios (HRs) and 95% confidence intervals (CI) of biomarkers on mean 8-year mortality (multiple imputation analysis, n=3855).....	173

LIST OF SUPPLEMENTARY FIGURES

Supplementary Figure 3.1: Sample flow chart	88
Supplementary Figure 4.1: Sample flow chart	104
Supplementary Figure 5.1: Sample flow chart	140
Supplementary Figure 6.1: Histogram (untransformed) graph matrix for the allostatic load biomarkers.....	184

LIST OF APPENDICES

Appendix 1: Letter to the editor in response to the publication of Chapter 3.....	253
Appendix 2: Author response to the letter to the editor	254
Appendix 3: Publication of Chapter 4	255
Appendix 4: Publication of Chapter 5	259
Appendix 5: Copyright permission from Psychoneuroendocrinology	272
Appendix 6: Copyright permission from Health Psychology	272
Appendix 7: Copyright permission from Journals of Gerontology: Series B.....	273

THESIS SUMMARY

The Allostatic Load (AL) framework posits that chronic or repeated exposure to stressors can cause dysregulation of multiple interrelated physiological systems, which if prolonged, may ultimately lead to deteriorations in health. Since its conceptualisation in the early 1990s, research on AL has grown steadily, showing promise as a sub-clinical predictor of poor health outcomes, and is known to be patterned by socio-economic position (SEP). AL is typically indexed using a composite index of biomarkers across multiple systems, yet no gold standard operational definition exists. This has brought about a large heterogeneity of biomarkers and techniques to instantiate the concept, complicating comparisons of results across studies and stunting the development of the framework. This thesis addresses several of the limitations within the extant literature using the rich psychosocial and biological data from Wave 1 of The Irish Longitudinal Study on Ageing (TILDA). Specifically, it addresses: (1) whether the method of calculating composite biomarker indices impacts the predictive utility AL on health outcomes, (2) the extent of the association of life course stress exposure with AL, (3) whether mobility in/ out of social disadvantage across the life course moderates AL burden, and (4) the association of a large suite of biomarkers with stress and all-cause mortality. The results of this evaluation can be used to help inform the development of AL indices. Recommendations for future research to develop the AL framework include longitudinal analysis to further understand the causal mechanisms underlying the pathway to poor health from exposure to adverse events over the life course. Additionally, researchers in the field should attempt to broaden the measures applied in relation to the AL index and incorporate dynamic measures of physiological functioning.

PUBLICATIONS

- **McLoughlin, S.**, Präg, P., Bartley, M., Kenny, R. A. & McCrory, C. Intergenerational Social Mobility and Allostatic Load in Midlife and Older Ages: A Diagonal Reference Modeling Approach. *Journals Gerontol. Ser. B* **78**, 154–166 (2022).
- **McLoughlin, S.**, Kenny, R. A., & McCrory, C. (2021). Psychosocial adversity and allostatic load burden in midlife and older ages. *Health Psychology*, *40*(7), 468–471.
<https://doi.org/10.1037/hea0001098>
- **McLoughlin, S.**, Kenny, R. A., & McCrory, C. (2021). Critiquing a study or a paradigm?: In response to: The Promise of Allostatic Load Rests Upon Strategic Operationalization, Scoring, and Targeted Interventions. *Psychoneuroendocrinology*, *123*, 104881.
<https://doi.org/https://doi.org/10.1016/j.psyneuen.2020.104881>
- **McLoughlin, S.**, Kenny, R. A., & McCrory, C. (2020). Does the choice of Allostatic Load scoring algorithm matter for predicting age-related health outcomes? *Psychoneuroendocrinology*, *120*, 104789.
<https://doi.org/https://doi.org/10.1016/j.psyneuen.2020.104789>
- McCrory, C., Fiorito, G., **McLoughlin, S.**, Polidoro, S., Cheallaigh, C. N., Bourke, N., Karisola, P., Alenius, H., Vineis, P., Layte, R., & Kenny, R. A. (2020). Epigenetic Clocks and Allostatic Load Reveal Potential Sex-Specific Drivers of Biological Aging. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, *75*(3), 495–503.
<https://doi.org/10.1093/gerona/glz241>
- McCrory, C., **McLoughlin, S.** & O'Halloran, A.M. *Socio-Economic Position Under the Microscope: Getting 'Under the Skin' and into the Cells*. *Current Epidemiological Reports* *6*, 403–411 (2019). <https://doi.org/10.1007/s40471-019-00217-1>

Chapter summary

This thesis is motivated by an interest in how the social world and exposures to adversity can impact on health, with a specific interest in the long run effects of stress exposure on morbidity and mortality. This first chapter introduces the research topic, describes the life course approach to health, and provides a brief review of the literature preparatory to the more nuanced reviews included in each of the empirical chapters. A theoretical framework for understanding the possible mechanisms underlying the intersection of social and biological research is discussed, and the central and specific aims of this thesis are presented.

Rationale

A consistent finding across cultures and populations is that individuals from more disadvantaged backgrounds will develop diseases earlier and will die earlier compared with their more advantaged counterparts. A seminal paper by Krieger and colleagues in 1997 used the general term “*social position*” to refer one’s class and status, and “*socio-economic position*” to include income or difference in wealth across groups in society ¹. These components can be measured at the individual, household or neighbourhood level, and are commonly quantified by indicators of education, income and occupation ². Socio-economic status (SES) is often used in health inequalities research, somewhat interchangeably to socio-economic position. Although there is no consensus on the distinction between these two terms, SES tends to capture social prestige rather than class which taps into more economic resources ¹. This thesis adopts the term “*socio-economic position*” (SEP) to capture how individuals and groups are socially stratified within society by virtue of their position based on both resourced-based and prestige-based measures ¹. SEP is now accepted as a fundamental

cause of disease ³, making the inverse relationship between SEP and health one of the most important issues in social policy. Indicators of SEP, and how it is typically assessed, is explored later in this chapter.

Although prior studies have established SEP as an overarching determinant of health, the biological mechanisms explaining this link remain poorly understood. One candidate mechanism is Allostatic Load (AL), a psychosocial framework and quantitative measure of biomarkers across multiple physiological systems posited to capture the biological effects of stress. It is postulated that those growing up in more disadvantaged environments are subjected to a greater number of stressors over the life course ⁴. The term “*life course*” denotes the sequence of activities, states or events across domains or areas of life spanning from birth, or in utero, to death ⁵. AL offers a framework wherein cumulative exposure to social, psychological, and environmental stressors increase the risk of diseases in later life by disrupting the physiological regulatory systems that are involved in initiating, maintaining and inhibiting the stress response ⁶. Individuals at socio-economic disadvantage are hypothesised to experience a faster accumulation of AL ⁷, yet this complex relationship has not been researched in the Irish context; the current older population was born and raised in the early and mid-20th century, a period of great social, economic and cultural revolution which shaped the lives and futures across a multitude of domains.

1.1 A brief history of the evolution of stress research

The French physiologist Claude Bernard's (1813–1878) experimental medicine brought him international recognition through the development of the theory of a self-regulating physiological interior. His early work on the role of the liver in secreting glucose, and studies of heat regulation led to the development of the concept that the body is constantly working to maintain a stable internal environment, of which is necessary for survival. He coined the “*Milieu Interieur*” (the environment within) as sustaining a balance through compensatory changes across physiological systems ⁸. Physiologists at the time believed that the organs functioned independently, resulting in Bernard's forward-thinking concepts not gaining popularity until Walter Canon (1871-1945) expanded on physiological mechanisms in response to noxious insults decades later ⁹.

Canon introduced the phrase “*fight or flight*” in the early 1900s to capture how animals react to threats with a release of hormones from the sympathetic nervous system, and additionally coined “*homeostasis*” as how the body maintains a stable internal state. His scientific advances attempted to capture how the body seemed to stabilise physiological parameters not by chance, but in a coordinated fashion, particularly via the sympathetic nervous system and the adrenal glands ¹⁰. He noted that any deviation from the strict pre-defined parameters, or failed regulation, was antecedent to pathology. These deviations could be caused not only by environmental threats, but also by emotional or psychosocial threats, positing that equilibrium was brought about by both *sense* organs and by negative feedback loops of the autonomic nervous system. According to this classic concept of physiological control, the role of feedback mechanisms was to reduce variability as a function of healthy systems ¹¹. The primary shortfall to this original definition of homeostasis, however, was the lack of recognition of the ability of the body and mind to anticipate regular or likely threats and mitigate responses. Nonetheless, homeostasis was accepted by Western biologists in the early 20th

century, who typically studied physiological systems in isolation, regardless of what is occurring throughout the rest of the body.

However, it was Hans Selye (1907-1982) who was credited as the first to use the term “stress” in biology, referring to it as “*a nonspecific deviation from the normal resting state*”¹² (pg. 500). Stating that stress is “*caused by function or damage and it stimulates repair*”, and defining stress as “*essentially the rate of wear and tear in the body caused by life*”, Selye was the first to describe the idea that chronic stress could result in cumulative damage on the body through his three-stage process, “*general adaptation syndrome*” (GAS)¹²:

- The “*Alarm Reaction*” was the response to a stressor, where the body enters a state of arousal, categorised by increased blood pressure and heart rate
- The “*Stage of Resistance*” occurs if the stressor continues, and sees the body enter a state of resistance, wherein an individual could be vulnerable to “*diseases of adaptation*”, as the immune system is impacted
- The “*Stage of Exhaustion*”, where resistance cannot be sustained any longer, adaptation fails, leading to damage to internal compensatory mechanisms and organs

While Selye’s GAS framework was the first to link stress with illness, his work focused purely on the internal stressors that impact physiology of the body. Since that time, researchers have discovered that stress is the product of mind and body and can cause psychological responses in both short term and long-term situations. The research of Bernard, Cannon and Selye laid the foundations for decades of further research towards understanding the physiological basis and indeed consequences of stress exposure on health.

1.2 Modern concepts of stress physiology: allostasis

Elaborating on the existing paradigm of homeostasis, which depicted the necessity of physiological set points to exist within certain parameters, Peter Sterling and Joseph Eyer proposed the concept of “*allostasis*”, defined as an adaptive process for actively maintaining “*stability through change*”¹³. The advancement of the theory of allostasis brought about the acknowledgment that any deviation beyond the homeostatic set points does not necessarily indicate pathology. It appreciates the brain and body to be dynamic, highly interdependent, and predictive organisms that require continuous re-evaluation of need for the readjustment of operational setpoints, including actively returning them to homeostasis as required. The duo describes the adaptability of allostasis as a highly efficient feedback loop, stating that “*the only possible link between sociopsychological and physiological phenomena is the brain*” (pg. 631), and advocated for the adoption of a new conceptual model with the central nervous system at the core of somatic physiology¹³.

Although allostasis may seem a similar concept to homeostasis, homeostasis can be seen as a function within allostasis. Homeostasis’ feedback system aims to reduce variability and maintain constancy within systems¹¹, while variability is favourable within the concept of allostasis as it allows internal adaptation to environmental demands. Allostasis can therefore be acknowledged as the primary process in the adaptation to stress exposure, as it involves changes across physiological systems to allow an individual to react and cope with any imminent threat to the organism. Healthy allostatic functioning requires systems such as the autonomic nervous system (ANS) and immune system to adjust in response to external stressors, and is therefore a key element to survival in acute circumstances of threat^{14,15}. The ANS, which is the division of the peripheral nervous system responsible for controlling the function of a broad range of organs and glands, responds to internal and external challenges. The two branches of the ANS, the sympathetic (SNS) and parasympathetic nervous systems (PNS) are highly coordinated yet provide contrasting functions; the former

increases heart rate, enhancing blood supply to the lungs and muscles, suppresses digestion while the latter aids the return of these parameters to baseline, and promotes digestion once again ¹⁶.

Acute stress is adaptive, it can increase blood pressure and heart rate to meet the challenge, and aid in memorizing the threat for when/ if it reoccurs. Recovery of the baseline state is as important a part of coping, adaptation, and resilience as is the capacity to mount an effective stress response in the first place ¹⁷. For instance, the release of stress hormones can signal the release of anti-inflammatory cytokines, which dampen the immune system temporarily to allow for the organism to focus efforts on the immediate threat. This concept has been visually conceptualised as a “*domino effect*” by Juster (2011) wherein constant or repeated stress inexorably strains interconnected biological systems that collectively collapse like domino pieces as biomarkers topple and trail towards pathophysiological consequences. This collapse due to overexposure can result in multi-system, multi-dimensional “*wear and tear*” across interrelated physiological systems, known as allostatic load ¹⁸.

1.3 Allostatic load

Internationally recognised authority in neuroendocrinology, the late Bruce McEwen wrote that the widespread use of the term ‘*stress*’ in modern culture has made it a very ambiguous word to describe the ways in which the body copes with psychosocial, environmental, and physical challenges ¹⁹. McEwen was a key figure in the conceptualization of AL, acknowledging the usefulness of allostasis, yet conceding that it only accounted for present state adaptations, and not the consequences of such adaptation. He postulated that when the challenge is long-term, recovery of baseline state may be impeded. It is this long-term chronic and repeated activation of the stress response that potentially poses risk to health, as inefficient activation/ deactivation of the response

can lead to an overexposure to stress hormones. He pinpointed the brain as the central mediator of the stress response, as it determines what is threatening and what requires physiological responses to a given stressor ⁶. Co-ordination of allostasis therefore depends on the brain's evaluation of threat and execution of physiological responses, which are fundamentally shaped by individual genetic, behavioural and social and environmental exposures ^{14,20}.

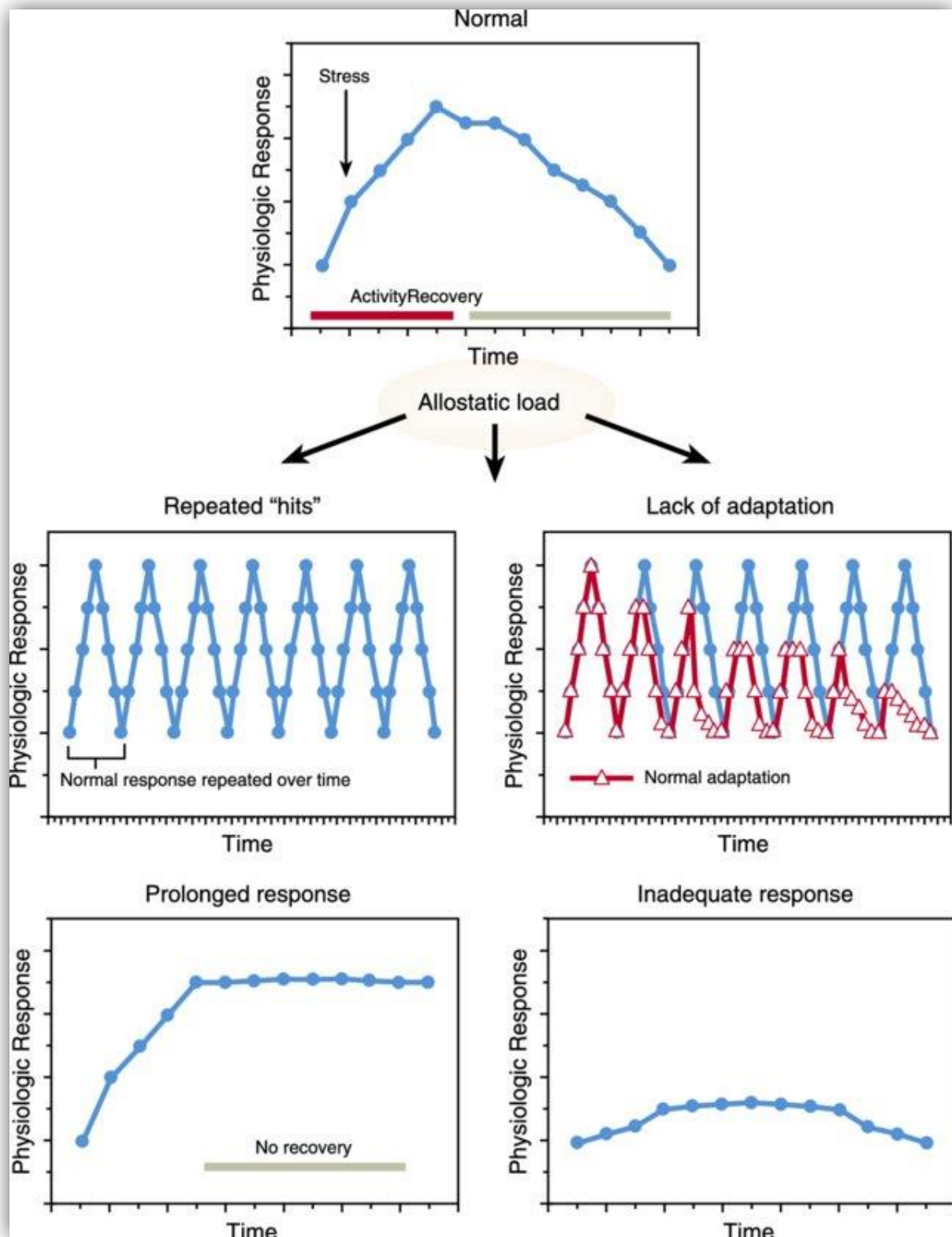
McEwen proposed that the body's response to challenge usually involves two steps; the first step requires turning on an allostatic response, while the second is switching off the response when the challenge has passed. The normal allostatic response is depicted in Figure 1.1, alongside four hypothesised profiles that can occur separately or in combination to describe how the release of stress hormones deviate from the healthy response ¹⁸. These profiles, or allostatic states, alter the typical production of such hormones, which as time progresses modifies normal physiological parameters, after which they continue to be produced at an increased or inadequate level (Figure 1.1) ¹⁹.

- “*repeated hits*” refers to the experience of frequent stressors, where the repeated surges of the stress response lead to allostatic load.
- “*lack of adaptation*” involves a failure to habituate to a chronic/ re-occurring stressors. As a result, each exposure involves a heightened release of hormones, contributing to physiological dysregulation
- “*prolonged response*” involves a failure of the responses to stress to shut off once the stressor has passed and adaptation is no longer necessary.
- “*inadequate response*” refers to the failure to respond adequately to the stressors, which can lead to hyperactivity of other allostatic systems, such as the inflammatory

system to compensate for the inadequate hypothalamic pituitary adrenal (HPA) regulation.

The HPA axis is a major hormone system that responds to stress, and has a central role in regulating many homeostatic systems in the body, including the metabolic system, cardiovascular system, immune system, reproductive system and central nervous systems ²¹. While the primary function of the HPA axis is to help the body cope with stress by increasing energy levels, suppressing the immune system, and enhancing memory and cognitive function, chronic activation of the HPA axis can play a contributory factor in the development of multi-system dysregulation ²². Anatomically, the hypothalamus detects stress and sends a signal to the pituitary gland which releases adrenocorticotrophic hormone (ACTH). ACTH then travels to the adrenal glands, located on top of the kidneys, and triggers the release of cortisol, which aids in the mobilisation of energy to help the body react to the stressor. Dysregulation of this central system, driven by chronic or repeated exposure to stressors, is hypothesised to be one of the primary drivers of AL burden ²³.

Figure 1.1: Four types of allostatic load



Note: Adapted from McEwen, B. (1998). Protective and damaging effects of stress mediators. *The New England Journal of Medicine*, 338(3), 171–179. <https://doi.org/10.1056/NEJM199801153380307>¹

¹ [copyright 1998 Massachusetts Medical Society]

McEwen & Seeman (1999) added to the original conceptualization of AL. They present the following stages of allostasis and allostatic load, each of which plays a different role in the cascade of reactions and effects involved in allostasis.

- Primary mediators refer to the substances released as part of allostasis and include catecholamines and cytokines.
- Primary outcomes comprise physiologic parameters that are directly impacted from the repeat fluctuations of allostasis, alongside elevated activity of biological systems that are under challenge, such as blood pressure or lipids.
- Secondary outcomes² capture dysregulation across the metabolic, cardiovascular, and immune systems.
- Finally, tertiary outcomes refer to the disease states caused by allostatic load burden ³
²³.

In essence, the concept of AL describes the cumulative physiological damage resulting from these profiles: it is the consequence of the over or underactivity of systems impacted as a result of the stress response ²³. Its critical assumption is that various threats, and their interpretation as threats although they may be non-lethal, is thought to trigger the fight or flight reaction. Underlying driving characteristics of the allostasis process is that the physiological mediators are interconnected, interdependent and have non-linear effects ^{24,25}.

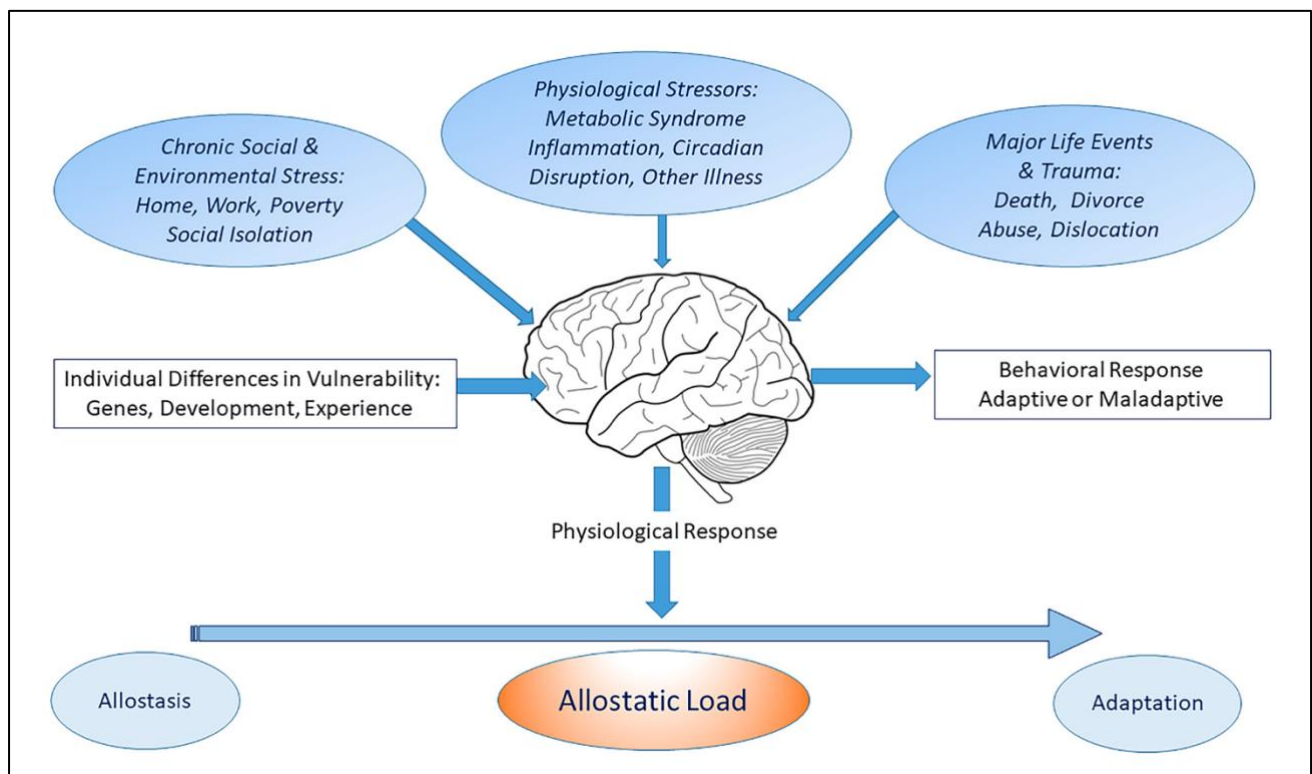
² The literature sometimes combines primary outcomes and secondary outcomes, with the assumption that they are caused by the expression of primary mediators and their interactions.

³ Allostatic load and allostatic overload are terms often used interchangeably throughout the literature. This thesis adopts the term allostatic load burden

The concept of AL is rooted in the theory of stress and adaptation, and is operationalised through a multisystem framework that aims to provide a comprehensive pathway for understanding psychosocial and physiological predictors of health risk than the more common approach of concentrating on risks associated with individual systems, and exploring the complex interplay between psychological and physiological processes. It refers to the cumulative wear and tear on the body that results from ongoing efforts to adapt to stressors, and has been linked to a variety of negative health outcomes ²⁶. The theoretical underpinnings of this thesis on AL therefore draw from a range of disciplines, including physiology, psychology, and epidemiology, to provide a comprehensive understanding of the complex interactions between stress, physiological response, and health outcomes ²⁷. The thesis will also draw on broader social and cultural theories to explore the ways in which social determinants of health, such as SEP, which have been shown to influence the development of AL burden ²⁸. By grounding the research in a range of theoretical frameworks, the thesis aims to provide a nuanced and comprehensive understanding of the complex interplay between stress, physiology, and health.

Figure 1.2 additionally presents the notion that stress exposure can affect the body indirectly, such as through social environments and health behaviours ²⁹. Both perceived stress and traumatic stress is a significant risk factor for cigarette smoking ³⁰, as smoking is often used to self-medicate to ease feeling of stress. The acute response of nicotine, the main psychoactive ingredient in tobacco products, is a sense of relaxation, yet smoking activates the stress response, raising blood pressure and heart rate and can lead to greater anxiety and overall tension. Such damaging lifestyle behaviours may be embodied within the overall notion of AL, i.e. how an individual copes with a stressor ⁶, or recognised as confounders on the relationship of AL with tertiary health outcomes ³¹.

Figure 1.2: Biological mechanisms of allostatic load



Note: Illustration taken from McEwen, B. S. & Akil, H. Revisiting the stress concept: Implications for affective disorders. *Journal of Neuroscience* . 40, 12–21 (2020)

1.3.1 Operationalisation of allostatic load

The operationalisation of AL has been a bone of contention within the literature since its conception. Operationalisation refers to the process by which a concept is quantified into a measurable observation. Higher AL indicates an individual has experienced greater stress induced wear and tear and is consequently likely to be at risk of poor health or disease states and succumb to early mortality at a higher rate than their contemporaries. However, AL cannot be quantified directly, and can only be estimated through the measurement of physiological parameters, and is typically indexed using a composite index of biomarkers across multiple systems^{32–36}. Seeman et al. (1997) using *The MacArthur Studies of Successful Aging* offered the first operationalisation of AL, by summing a panel of at-risk multi-system biomarkers, such that higher scores indicated higher AL burden. High risk was determined using 75th percentiles with respect to the sample's biomarker

distributions (lowest 25th percentile represented risk for appropriate markers), and dysregulated biomarkers were summed to create an index (0-10). Biomarkers included in this first operational definition of AL were systolic blood pressure, diastolic blood pressure, waist-hip ratio, ratio of total to HDL serum cholesterol, glycosylated haemoglobin, DHEAS, cortisol, epinephrine, and norepinephrine. Seeman et al. (2001) acknowledged that this original index was not intended to serve as a fixed or comprehensive method of estimating AL, yet has become somewhat of a default measure internationally³⁷⁻³⁹. To date, there is no gold standard panel method of calculating indices of AL, nor a gold standard panel of biomarkers recommended for the quantification of AL. These two overarching issues surrounding the measurement of AL will be discussed in turn.

1.3.2 The issue of various scoring methods

AL, as originally defined, captures dysregulation that can occur with deviation from the normal range in either direction, high or low. However, as established above, the original scoring method was created by summing dysregulated biomarkers³². This “*classic*” measure of AL is commonly employed, yet it is not without its limitations. Dichotomising biomarkers assumes linear risk, and results in a huge loss of data, pooling individuals of intermediate risk with those of extreme risk and excluding individuals who may be on the precipice of risk. This has led to the use of measures capturing both ends of the distribution, known as two-tail risk, or indeed eschewing cut points and utilising continuous measures, such as z-scores. These z-score measures represent the absolute value of the standardised distance between their level of a given biomarker and the population mean of that biomarker. This is particularly relevant for biomarkers such as cortisol, as increasing evidence suggests that low cortisol (hypocortisolism), as well as high cortisol (hypercortisolism) are reflective of chronic stress and indeed predictive of poor outcomes. However, few studies have incorporated this methodology as their primary AL measure^{40,41}, with a slew of alternate methods used across studies. This is encapsulated by a recent examination of the *National*

Health and Nutrition Examination Survey (NHANES) publications utilising AL indices which found that 18 different calculations were used across 21 studies. This heterogeneity is a result of limited empirical guidelines available to researchers in the field, and limited evidence on whether the calculation impacts on the predictive utility of the measure itself. Juster et al. (2010) describes over 10 methods that have been used to formulate allostatic load measures, including the classic method, alongside correlational and data reduction techniques. However, there are problems with such approaches as they move away from the theoretical bedrock of AL, and towards a measure more akin to biological dysregulation or biological ageing.

Operationalizing the theory of allostatic load into a measurable index has therefore posed a challenge to researchers in this area across the globe, with little to no guidelines provided by the empirical literature, other than to include multi-system parameters. This makes direct comparison of results difficult and hampered true advancements, including inspiring health promotion policy and interventions ²⁸. Despite this variability in measures used, few have investigated whether the choice in measure employed relates to the predictive utility of AL. **Chapter 3 will therefore consider whether the choice of AL scoring algorithm impacts on predictions of age-related health outcomes, using an older sample of Irish residents.**

1.3.3 The issue of various biomarker panels

In addition to notable heterogeneity in the calculations employed to generate summary measures of AL, there is major inconsistencies in biomarkers employed in these measures ²⁸. AL, as established, is typically indexed using a composite index of biomarkers across multiple systems ^{32–36}. The composition of biological measures from various systems is supported by the robust evidence of shared variance across biomarkers from multiple systems ^{35,42}, yet which systems and which

biomarkers from these systems provide the best account of AL has yet to be established. Studies since the “*original 10*” composition among the MacArthur Studies of Successful Ageing⁴³, have included or excluded biomarkers as a function of availability or ease of data collection. While debate remains around what biomarkers to include in the measure, few have assessed whether certain biomarkers have better predictive utility than a composite score in predicting specific clinical hard end-points, such as mortality^{44,45}.

The issue surrounding the choice of biomarkers was first highlighted when Seeman et al. (2001) noted that the original panel resembled that of Metabolic Syndrome (Syndrome X). However, when the overall AL measure was deconstructed into neuroendocrine and metabolic sub-scores, the panel of neuroendocrine biomarkers were two fold stronger predictors of mortality than the metabolic panel of biomarkers³². A recent review of 11 papers examining the relationship of discrimination with AL burden found that AL scores were calculated using 9 different sets of biomarkers, ranging from 7 to 24 across studies – c-reactive protein and systolic blood pressure were most prevalent in these studies⁴⁶. A recent meta-analysis has shown AL shows great promise in predicting both all-cause and CVD mortality⁴⁷. Studies of single biomarkers as predictors of mortality, however, are limited in scope and can produce inconsistent results⁴⁸. Similarly, few have assessed whether certain biomarkers have stronger predictive utility than a composite score in predicting specific clinical hard end points, such as mortality^{44,45}. Which systems and which biomarkers from these systems provide the best account of AL is yet to be explored. This is of interest due to varying results across studies to date; Castagne et al. (2018) found that degraded inflammation and cardiovascular systems drove the associations with mortality, whilst Goldman et al. (2006) found the neuroendocrine and immune markers to hold more explanatory power than typical clinical markers such as BMI and blood pressure. Quantifying the theory of allostatic load

into a measurable index has therefore posed a challenge to research in this area across the globe, with debate remaining around what biomarkers to include in the measure. Understanding how allostatic load relates to mortality is important, as it is the ultimate hard clinical endpoint and allows an opportunity to understand whether particular markers or organ systems are driving the association.

How and if medications should be included, incorporated, or ignored when it comes to using a measure of physiological dysregulation also remains unidentified. On the one hand, evidence of medication use/ prescription indicates an underlying physiological deterioration at a subsystem level, and therefore individuals should be assigned “*at risk*” for a given biomarker if they take medications to treat a condition measured by said biomarker ⁴⁹. However, correcting for medication use may be overestimating the current state of dysregulation. This is a particularly important issue in older populations such as the TILDA sample, as polypharmacy and its complex interactions with biological systems exists in a much higher level associated with increased age ⁵⁰. However, capturing medication use, dosage and its consequent impact on biomarker values is a complex process, especially without access to biomarker data prior to the prescription of medication. **These issues are addressed in Chapter 3 by comparing the predictive utility of indices including/ excluding medication use on health outcomes, and in Chapter 6, which scrutinises the relevant association of a range of biological markers with mortality and perceived stress.**

1.4 Allostatic load and poor health outcomes

Understanding how allostatic load relates to disease states and early mortality is important, as it could aid in the advancement of the framework not only for research purposes, but for clinical interventions. The first validation of AL as a predictor of tertiary health outcomes was in the seminal MacArthur Studies of Successful Aging. This cohort of high-functioning older adults were aged

between 70-79⁵¹. Initial findings reported higher AL was associated with lower baseline cognitive and physical functioning, while at 3 year follow-up, higher AL burden was associated with greater declines in cognitive and physical functioning⁴³. These findings were substantiated with a 7 year follow-up study which found that AL predicted mortality³². Since these early studies, others have directly evaluated the association between AL and mortality outcomes. The results have been consistent; higher AL is associated with increased risk of all-cause mortality^{32,36,45,52-55}. Each one-unit increase in AL was associated with a 24% higher risk of all-cause mortality using data from the Reasons for Geographic and Racial Difference in Stroke (REGARDS). Mathew et al. (2020) consolidated findings on the link between AL and cancer-specific mortality from 30,769 participants over 4 studies^{36,41,56,57}, and found that a one-unit increase in AL was associated with a 9% increased risk of cancer-specific mortality⁵⁸. Another study not included in this meta-analysis found that a one-unit increase in AL score was associated with a 7% higher risk of cancer-specific mortality, while CRP was the only biomarker included in the 10-item index of AL that predicted this outcome⁴⁴. The utility of AL as a predictor of poor health outcomes is now evident, yet its utilization is hampered by the current inconsistencies in operationalisation.

1.5 Stress exposure as a precursor to allostatic load

An individual's biopsychosocial system is affected by insults across the life course, and those living in less advantaged positions are posited to endure more insults through pathways of material resources (e.g., housing), environmental exposures (e.g., allergens) and behavioural choices (e.g., smoking)⁵⁹. Psychological stress occurs when an individual perceives the environmental demands to exceed adaptive capacity⁶⁰. This is a dynamic view on stress, wherein stress is viewed as a process rather than a static entity, that disrupts the body's physiological regulatory processes. For this reason, exposure to stress can be examined as a potentially important initial exposure on a pathway towards ill health. Guided by Barker's biological programming hypothesis, adversity, or exposure to stressors

during early life can damage the development of biological systems and impair the development of adaptive coping mechanisms ⁶¹. Childhood is an important period for generating an individual's health trajectory, and is a critical period of complex physiological development ⁶². A critical period refers to a time or period during which biological or environmental events are required for normal development to occur ⁶¹. Although often used interchangeably in the literature, there are subtle differences between critical periods and sensitive periods. A sensitive period is defined a limited time window within the life course during which the effects of experiences or exposures on a particular physiological system are particularly strong, or the organism may be particularly plastic than other time points.

Exposure to stressful events during critical periods, including prenatal alcohol exposure, can create functional disruption of the foetus that lead to later life disease ^{62 63}. There is evidence to also suggest that exposure in the formative years can alter neural architecture, thus increasing stress reactivity to later insults ⁶². Indeed, evidence suggests that early life stress exposure can recalibrate the HPA axis, which is one of the main stress response systems, with individuals who have suffered childhood maltreatment presenting higher overall diurnal cortisol levels ⁶⁴. As a result, the experience of adversity during these time windows may exert disproportionately larger effects on physiological systems compared with adversity experienced during later time periods. Despite this, a number of studies have not included data on childhood adversities when assessing the impact of adversity on AL.

That the experience of adversity during childhood may be more deleterious to AL burden than adulthood exposure is highlighted by a retrospective Danish study, which investigated composite familial and economic indices of adverse events across the lifespan: the experience of two or more adversities in childhood, or three or more adversities in adulthood, was significantly

associated with increased AL in men, but not women ⁶⁵, whilst the experience of adversity in childhood potentiated the effects of adversity in later life for men, challenging the notion that the biological embedding of stress is primarily cumulative. In addition, disadvantaged socio-economic circumstances are known to be a risk factor for increased risk of adversities ⁶⁶, and evidence is emerging for the association of poverty with clusters of adverse childhood events ⁶⁷. This suggests that the link with AL may be caused by distal (i.e., poverty) events rather than the experience of more proximal stress-related events *per se*, yet very few studies control for the experience of poverty when examining links between the experience of individual adverse events and AL.

AL as a predictor of poor health is well established ⁶⁸. Yet, it is to be convincingly demonstrated that higher stress leads directly to higher AL burden ⁶⁹. Heterogenous measures of both stress and AL across studies complicate this matter, and it is yet to be elucidated whether varying domains of stress exposure at different stages of the life course are equally detrimental to AL burden. Further disentanglement of the relative impact of individual adversities on AL burden in different ecological contexts is warranted. **Chapter 4 assesses the relationship of a number of self-reported stress exposures from both childhood and adulthood on AL burden to understand the link between life course stress and multi-system physiological dysregulation.**

1.5.1 Inter-individual differences

Within the AL framework, the brain is the master controller of the primary mediators, and is also the target of these systems, subject to both protection and damage ¹⁵. Thus, stress research has highlighted that perceptions of stress are intimately entwined with the biological response to stress ⁶. Similarly, both allostasis and allostatic load are affected by damaging health behaviours. These forms of behaviour are integral to the overall notion of allostasis, as the use of substances to improve the perceptions of stress are indicative of how one deals with a stressor or a challenge, as well as

contributing to allostatic load through known pathways. Health behaviours play a strong role in shaping population health outcomes for most major diseases throughout the world, with the most common diseases in the US (e.g., heart disease, stroke, cancers) preventable with the adoption of healthier lifestyle choices ⁷⁰. A systematic review of 55 studies examining the influence of stress on physical activity found that the experience of stress impairs efforts to be physically active ⁷¹. However, similar to many health behaviours, this is a double edged sword, as the empirical data supporting a positive impact of exercise on health outcomes is abundant ⁷². Rodriquez et al. (2019) found that unhealthy behaviours did not modify the relationship of AL and depressive disorders ⁷³. Suvarna and colleagues (2020) recently published a systematic review of 26 studies exploring health risk behaviours and AL ³¹. Interestingly, this review found that socially disadvantaged individuals were at a higher risk of developing multiple health-risk behaviours, including poor sleep, poor diet, and limited physical activity.

The male-female health-mortality paradox results from females living longer than males but spending a higher proportion of their later lives in poor health. Such sex differences exist with respect to certain diseases, with men more prone to coronary heart diseases, while women suffer more often from autoimmune disorders. This differential tends to change over time, as well as across the life course, with data from Germany suggesting that women have overtaken men in terms of cardiovascular mortality prevalence ⁷⁴. Not only is a sex differential noted across health outcomes, but recent findings have also reported a distinct correlation between biological sex, sex hormones, gender, and stress physiology. McEwen discussed sex differences across HPA and the autonomic nervous system, which is the physiological seesaw that controls homeostasis of the body, in mice ⁷⁵. However, the basis of this sex dimorphism circumstance remains little understood. Furthermore, sex

differences in circulating biomarkers have been noted, with varying clinical guidelines established for men and women across biomarkers including BMI and DHEAS.

In respect to AL, a recent systematic review by Kerr et al. (2020) demonstrated that higher AL burden is experienced by men ⁷⁶. Women show higher mean levels of inflammatory markers and overall burden, but slower rates of increase in inflammation with age, according to a study from NHANES ⁷⁷. However, such differences could be muted in composite biological indices, including AL. Dysregulation across biomarkers may vary according to sex, yet the count of dysregulated biomarkers could be comparable, leading to similar mean scores of AL burden at initial glance ⁷⁸. Women appear to reach similar levels of risk to men within 5-10 years post-menopause, in line with increased fat storage, particular abdominal fat storage ⁷⁷. However, the sex differential in mortality is more pronounced in young adulthood and decreases in postmenopausal ages as this life stage in women coincides with a faster pace of mortality rates. The production of estrogen has been hypothesised as a protective anti-inflammatory hormone in women ⁷⁹. While a thorough investigation into biological sex differences in AL is outside the remit of this thesis, the potential confounding must not be disregarded in relation to both the generation of AL indices and the differential incidence of health outcomes experienced by sex.

1.6 Ageing and allostatic load

Ageing is an experience shared by all, yet the experience of ageing is heterogeneous across individuals, groups, and cultures, with a series of putative causes for these differences. One such mechanism is exposure to psychosocial stress. Stress is a universal experience, yet socio-economically disadvantaged groups experience a higher number of stressful events across their life course than those in more advantaged circumstances. Successful ageing can be conceptualised as

one's ability to adapt and effectively respond to the dynamic challenges they are exposed to throughout the life course. Research on this concept aims to increase the proportion of healthy life years, or time spent in a healthy state in accordance with the increase in life expectancy. Therefore, the concepts of allostasis and successful ageing are intertwined, fostering measures of allostatic load to be presented and utilised as a measure of biological ageing. Pre-disease states, as measured using AL indices, cannot be assessed without information regarding the mechanisms leading to diseases that are prevalent with age ¹⁵. To understand the life course implications of stress on health, a mid-life to older cohort, such as The Irish Longitudinal Study on Ageing (TILDA), seems well suited.

1.7 Social gradient in health

The social gradient in health refers to the graded relationship between a measure of socio-economic position and health in a population; generally, the most socially disadvantaged have the highest levels of morbidity, those who are less disadvantaged have better health than their disadvantaged counterparts, and those who are most advantaged in terms of socio-economic circumstances have the best health outcomes. Indeed, disadvantaged SEP is associated with almost every cause of premature mortality ^{80,81}. In fact, a meta-analysis of almost two million people residing among seven high income countries has shown that low SEP translates to an approximate reduction of 2 years in life span ⁸². The tumultuous relationship of unhealthy lifestyle behaviours (i.e., smoking) with disease outcomes is well established, while prospective research supports socio-economic disadvantage as a determinant of such behaviours, alongside providing an independent association with poor health. For instance, a recent meta-analysis found that low socio-economic position, measured via area deprivation, was associated with an increased risk for 32% (18 out of 54) of physical and mental conditions examined, independent of lifestyle factors and obesity ⁸³. This study, which mapped morbidity from electronic health records in Finland and the UK, also found that an interconnectedness of diseases (i.e., multi-morbidity) was evident in low socio-economic

groups; mental health and substance use were strongly connected with diseases of the liver, cardiovascular and dementias.

1.8 Measuring socio-economic position

There is a longstanding debate on how best to measure the rank of individuals in society. Measures of SEP are wide ranging, and no single measure captures the full influence of SEP on health outcomes “*at all time points, in all settings*”⁸⁴. Various measures of SEP tend only to be moderately correlated⁸⁵, and are differentially related to mortality risk⁸⁶. This suggests that although the social gradient is evident across indicators, the aetiological pathways may differ depending on the indicator used as they connote different life course influences on health¹. A full debate on the minutiae of the many viewpoints and efficacy of the various SEP measures is beyond the scope of this thesis. However, the following section expands on the most commonly employed measures, with commentary on the potential impact that the choice of indicator may have on the observed health inequalities amongst older adults specifically.

1.8.1 Education

Education is a powerful predictor of health outcomes. This relationship was first noted by Kitigawa and Hauser in their study on mortality differentials in the US⁸⁷, and established internationally across a variety of health measures since⁸⁸. Typically, higher levels of schooling are protective for health, and while the relationship is complex, a number of mechanisms have been proposed to understand this link⁸⁹. Much of the research on the education-health relationship has been grounded in fundamental cause theory, wherein education is seen as a fundamental cause of health because it determines access to income, environment, and lifestyle behaviours⁹⁰. This is based on the causal model that education is the portal to occupation, thus predicting income, with higher

education associated with higher earnings. Health literacy develops with schooling, referring to the ability to seek out, read, process, and understand basic health information which can be utilised to manage health related decisions for oneself⁹¹. Beyond having such knowledge, other mechanisms include the cognitive resources and knowledge related assets of an individual that develop alongside education, including reasoning and effectiveness skills that can be utilised to “*acquire, evaluate, and use information*”⁹² to prevent poor health⁹³. A large systematic review investigating the relationship between education and cognition found that 51/88 studies reported significant effects, such that lower education was associated with higher risk of dementia, 37/88 reported null effects⁹⁴.

Unlike other indicators of SEP, education is unlikely to succumb to issues around reverse causation. Education tends to be established in early life, prior to the onset of chronic health conditions, and it is generally fixed by the time of entry into work in early adulthood⁹⁵. Education can be operationalised both as a continuous variable (i.e., years of schooling completed) or a categorical variable (i.e., level of education attained; primary, secondary, third level and above), but it is not without its limitations as an indicator of SEP. Education does not measure class, status, or income, but instead gives an indication of what these may be using probabilistic terms. Additionally, it is sensitive to cohort effects, as educational systems tend to vary highly across populations, countries, and cultures. For example, educational attainment lacks discriminatory power in Ireland, as it is age-related, due to the introduction of free secondary level education after 1968.

1.8.2 Income

Income refers to wages or any flow of earnings received as a result of employment and is easy to capture. Current income, both individual and household, provides access to material resources and opportunities, including housing, food, and health care, which may influence health. It is a highly unstable measure of SEP, due to its ability to change on a short-term basis⁹⁶.

Additionally, income is very sensitive to issues of reverse causation; higher income enables better access to the means to produce good health (e.g., health care) poor health impinges on the ability to work, thereby reducing income. To add complexity to the relationship between money and health, it is typically confounded by a number of external factors, including early life or parental SEP. Wealth considers assets such as car and home ownership and is also considered an important measure that shares characteristics with income but tends to be more stable over time. Wealth accumulation is considered desirable across societies as it involves economic stability. The prevalence of home ownership is high in Ireland relative to other countries, with ~85% of TILDA participants reporting owning at least one property ⁹⁷. This high prevalence of home ownership in older adults reduces the sensitivity of assets as an indicator of SEP. However, individuals could have high levels of wealth, yet low income or immediate access money. Income is also an age dependent indicator of SEP. For example, the utility of income amongst older cohorts is poor, as retirement and pension's mask much of the earnings experienced by an individual. Some evidence also suggests that collecting accurate financial data is more complex in more advantaged households, due to multiple streams of income, such as pensions, savings and, in some countries, age-related welfare ⁹⁸.

1.8.3 Occupation

While income and education represent the resources available to an individual and imply status, occupation captures prestige and is more often employed in European studies. While not a measure of social status *per se*, it does capture aspects of economic class, and is believed to be a valid measure of social stratification or socially constructed inequality ⁹⁹. Occupation arguably reflects educational attainment, provides income and signals social standing ¹⁰⁰, and some have argued that it is not necessary if information on income and education is available ¹⁰¹. This argument is refuted with evidence suggesting a distinct gradient in health beyond income and education. Interestingly, the relationship of occupation as an indicator of SEP with health is complex, as it could capture work

related stress exposure. Such exposures could be psychosocial, or environmental for those who hold hazardous jobs (e.g., construction site workers) ²⁹.

Occupational groups are often categorised into different social class groupings, and although the lack of single agreed way of measuring occupation, the most commonly employed measure in Ireland is that of the Central Statistics Office, coded using the International Standard Classification of Occupations (1988). Individuals of similar occupational skill and social standing are grouped together:

- i. Professional
- ii. Managerial and technical
- iii. Non-manual
- iv. Skilled manual
- v. Semi-skilled
- vi. Unskilled
- vii. All others gainfully occupied and unknown

These three commonly employed indicators of SEP all have overlapping properties yet have varying and distinct underlying mechanisms related to health. Galobardes (2007) suggested that if the purpose of including a measure of socio-economic position in modelling as a covariate, researchers should use composite measures to control for as much socio-economic variance as possible ⁹⁶. While this approach could be attractive to control for the varying aspects that the different indicators capture without falling foul to multicollinearity, it could mask the underlying mechanisms of how the varying indicators independently and distinctly contribute to health. The choice of SEP indicator should therefore be theoretically based.

1.9 The life course approach to health

Life course approaches to health, which integrate biological, social and behavioural mechanisms, suggest that an individual's life experiences are precursors to later health outcomes ¹⁰².

A life course approach enables a more dynamic view on the impact of SEP on physiological functioning, wherein the important yet complex pathways between early life and later health are recognised ^{61,103}. One of the most important contributions to understanding the pervasive impact of social inequalities over space and time comes from Nancy Krieger and forms a central tenet of her eco-social theoretical framework. She is credited with coining the term ‘*embodiment*’ to describe how organisms “*literally incorporate, biologically, the world in which we live, including our societal and ecological circumstances*” [pg. 351] ¹⁰⁴. It is a dynamic, adaptive response occurring continually across the life course, and is influenced through social structures.

Life course perspectives are critical for understanding the differential impact of SEP on health. Does the timing of exposure of socio-economic disadvantage matter in the context of AL, such that childhood exposure results in “*permanent and irreversible*” scarring effects on biological systems ⁶¹ [pg. 286], or do the negative impacts of SEP disadvantage compound over time, with each additional life stage spent in low SEP adding to an ever-growing health disadvantage ¹⁰⁵? Perhaps the negative effects of low SEP are reversible and mitigated through intergenerational or intragenerational systematic changes, as implied by the social mobility model ^{106,107}. While these models are closely interrelated, and difficult to disentangle statistically ¹⁰⁸, they have the potential to expand our understanding of the impact of life course SEP on biological risk.

In this light, children born into more disadvantaged socio-economic positions are faced with conditions that have been shown to affect health at all ages and set constraints on the likelihood of adopting a higher social class later in life ¹⁰⁵. This theory of divergence is rooted in the Matthew effect, stating that disadvantage increases exposure to risk, whilst advantage increases opportunity ¹⁰⁹. Cumulative dis/advantage suggests a process wherein the relationship between SEP and

dysregulation is initiated in early life and continues over the life course to become magnified in later life in the form of poor health outcomes ¹⁰⁵. Social mobility refers to transitions in SEP across the life course which can be intergenerational, intragenerational or both. The social mobility model posits that upward mobility will be beneficial to physiological functioning compared to downward mobility or stable low SEP across the life course ⁵⁹. A key empirical question to be answered by this model is whether any physiological effects of early life SEP can be moderated by later life mobility ^{106,107}. These life course models, which denote the sequence of activities, states or events across domains or areas of life spanning from birth, or in utero, to death ⁵, will be expanded on in a later section.

1.10 Socio-economic position and allostatic load: life course models

Allostatic load offers one conceptual framework by which we can try to better understand the impact of the social environment on health outcomes. Research suggests that the likelihood of being exposed to a stressor is patterned by socio-economic context, and therefore, individuals who grow up in poor environments are at greater risk of being exposed to multiple stressors ¹¹⁰. Several reviews have linked socio-economic differences with the prevalence of disease and mortality ^{111,112}, and while researchers have long engaged with the social gradients in the distribution of AL burden ^{113,114}, few studies have utilised the aforementioned life course models to examine how AL develops over time, and those that have, employed a variety of data sources and statistical techniques which have contributed to disparate findings ^{115–118}. Understanding how this comes to be may lie in examining how these different sorts of dis/advantages combine across the whole life course ⁹⁰.

Exposure to both beneficial and adverse events over the life course varies, ultimately constituting a unique life exposure trajectory that manifests as different expressions of health and longevity ¹¹⁰. It is well accepted that the experience of childhood poverty has substantial effects on multiple aspects of children's development, ranging from cognition to social and emotional development. Children born into lower socio-economic positions are faced with conditions that have been shown to affect health at all ages and decrease the possibility of upward mobility to a higher social class later in life ¹⁰⁵. Adverse childhood experiences (ACEs) have emerged over the past two decades as an important factor that negatively alters physical health outcomes, with early life disadvantage seen as the "*launch pad for a lifetime of health problems*" ¹¹⁹, wherein a chain of risk is initiated that may increase the risk of subsequent experiences that are detrimental for health. One such chain of risk could involve lifestyle choices which are shaped by structural factors in society. Poverty imposes a cognitive burden, present bias (i.e., the tendency to settle for a smaller reward than to wait for a larger reward in the future), and stress, which can then encourage poverty-perpetuating behaviour, such as lower educational attainment. This could be one explanation of how low socio-economic position reciprocally feeds back into behaviour, to preproduce poverty intergenerationally ¹²⁰.

The social mobility model focuses on the importance of change in social position to adulthood health. The "*null hypothesis*" in social mobility research refers to the notion that mobility does not exert a direct or unique effect on health ¹²¹. Absolute and relative mobility measures separate phenomenon; absolute social mobility refers to ending up in a different SEP from origin, while relative mobility measures how a person's ranking in SEP compares to that of their inherited position. The view that social mobility has negative and disruptive effects on individuals and groups has a history dating back to the dissociative thesis of Sorokin (1959), who put forward the idea that

social mobility places a strain on individuals ¹²². The notion of “*falling from grace*” ¹²³ refers to the experience of intergenerational downward mobility elevating feelings of distress and loss of control. Therefore, it has been proposed that downward mobility may influence health through stress-related factors, alongside lifestyle and social circumstances ¹²⁴. This is somewhat reflected in Sorokin’s dissociative thesis. Houle and Martin (2011) found little evidence for Sorokin’s hypothesis however when analysing data from the Wisconsin Longitudinal Survey (n= 4557). Lower psychological distress was reported in the sons of farmers who moved to non-manual positions (i.e., upward mobility), when accounting for origin and destination class, alongside control variables (e.g., adolescent depression, teenage cognition, teen marriage, father’s education etc.) ¹²⁵. No other forms of mobility, including other upwardly mobile groups, were associated with distress in this study of men, suggesting a small beneficial effect of mobility out of farming. In contrast, the “*rags to riches*” perspective suggests that movement upward from origin SEP could lead to positive health outcomes. In essence, it could be a joint determination, as an individual with poor health is more likely to be downwardly mobile than an individual who enjoys good health, and this poor health may govern both downward social mobility and higher rates of morbidity and mortality in later life. To complicate the matter, manual occupations, more often than non-manual occupations require physically fit individuals. Following mobility theory, an individual’s characteristics, behaviours and health outcomes are affected by both origin and destination SEP ¹²⁶. The acculturation hypothesis asserts that mobile individuals come to resemble those in their destination class, in terms of their health. It posits that the health implications of social mobility are not due to the movement itself but attributed to the class contexts in which people find themselves. Rather than being influenced by the movement, this theory posits that mobile people’s health is primarily a result of being in different social contexts. However, social causation may be at play here, wherein the health risks that an individual is exposed to are associated with the culture and the environment of the socio-economic position ¹²⁷.

1.10.1 Methodological considerations

The complexity of models generated by the life course approach, which necessitates the inclusion of proximal and distal factors, and their interactions require sophisticated data analysis techniques. It is important to account not only for the psychological processes of social mobility (net mobility effects), but also to account for the resources associated with status attainment (level effects). A discussion over how best to model the effects of intergenerational social mobility has been enduring since the 1967, with Blau and Duncan arguing that the influence of origin and destination position must be separated from the effect of mobility to begin to understand any direct influence inter/intragenerational mobility ¹²⁶. The “*square additive model*” was proposed to separate these effects yet was flawed as it assumed that the effect of the same class was the same in origin and destination. The “*diamond additive model*” followed, which was superior in isolating a mobility effect based on the use of one status parameter that represented individuals who did not change class across time (non-mobile). However, Sobel (1981) argued that this model failed to parametrise the status effect of these non-mobile individuals.

Sobel, arguing that the key to accurately estimating the influence of mobility, proposed the “*diagonal reference model*” (DRM) ¹²⁸. Based on sociological theory, these models allow for a simultaneous modelling of origin, destination, and mobility effects, breaking the linear dependency. They additionally assume that non-mobile individuals constitute the core of a social position, representing the true characteristics of any given SEP. DRM treats origin, destination, and the indicators for upward and downward mobility differently to previous methods. They are designed for contingency tables, wherein the cell means are modelled as a function of the diagonal effects, wherein individuals in the diagonal of the table represent the mobile ¹²⁹. The weights are constrained

to be non-negative, and to sum to one. To date, methodologic and conceptual issues across studies made direct comparison difficult. While the literature on SEP and AL is vast, including a number of systematic reviews, which model accounts for the link between SEP and AL remains little understood. **The relationship of socio-economic position across the life course with AL, with a specific interest in intergenerational social mobility, is examined in Chapter 5.**

1.11 Summary and the established gaps in the literature

In summary, the potential utility of allostatic load as a subclinical predictor of poor health outcomes has been established ^{26,68}, yet major restraints to its advancement remain outstanding. First, while prior research has often criticised the large heterogeneity of AL indices utilised across studies, few have attempted to understand or scrutinise whether this issue has a direct impact on the results. Hence, it is necessary to investigate the extent to which differential methods of generating indices of AL from the same set of biomarkers impacts on the prediction of poor health outcomes.

Second, the theory underpinning the AL framework suggests that stress exposure drives AL burden, with greater exposure to stress precipitating a greater burden of AL, yet this premise is lacking in empirical support and construct validity remains to be established. Despite this, AL has assumed an increasingly prominent position in research addressing the health consequences of stress exposure in recent years. Given the absence of universal measures of both stress, adversity and AL used across studies ²⁸, it is not yet known whether exposure to different domains of stress across the life course are equally detrimental for AL, or if specific domains are more deleterious to AL burden.

Third, the relationship of social disadvantage with AL burden has been established ²⁸. What remains theoretically opaque however, is whether changes in socio-economic circumstances across the life course can compensate for disadvantage in childhood. Thus far, the sparse literature on the effects of social mobility on AL burden has failed to come to a consensus. With the high rates of

upward mobility in Ireland as a result of rapid industrialization ¹³⁰, Ireland offers an optimal testing ground for such an important issue, which will feed directly into policy discourse surrounding the potential effects of childhood intervention.

Finally, a common issue throughout the review of the vast literature on AL continuously arises; what biomarkers are best suited to measure and reflect stress induced physiological dysregulation? To date, researchers appear to use the biological data available to them, primarily due to the lack of consensus and support for a universal panel of biomarkers. I aim to move towards a more refined measurement of biomarkers, which will prove useful for researchers and studies intending to measure and assess AL burden.

Chapter summary

This chapter describes the research aims of the overall thesis, the data used, and the measures and analysis strategies employed.

2.1 Purpose of the study

The purpose of this PhD study was to address the research gaps highlighted in section 1.11 by investigating and evaluating the allostatic load framework for quantifying difference in health and longevity. Allostatic load is increasingly applied as an objective measure of chronic stress, and has been shown to be consistently associated with poor health outcomes, and socially patterned. Despite the widespread application of AL in research, issues remain about the reproducibility and generalisability of results due to methodological inconsistencies and limited conceptual validation. While offering suggestions to change the AL framework could lead to a better understanding of the complex interplay between stress and health, and could indeed help to inform the development of interventions that effectively reduce the negative impact of chronic stress on health and well-being, three decades of research has been conducted based off the original conceptual framework and therefore suggestions to improve the operationalisation and predictive utility for researchers and clinicians may be more beneficial. The presence of this problem translates into an excessive number of research questions, therefore requires some delineation; the intention of this thesis is to address some of the most frequently declared limitations in studies utilising measures of AL, through four empirical studies, described below. Insight from the results should therefore be utilised to improve the AL measures used, or indeed contribute to a consensus to move away from the conceptual framework if limited support is found here and in other studies.

2.1.1 Study 1: Does the choice of Allostatic Load scoring algorithm matter for predicting age-related health outcomes?

Several composite measures of AL have been proposed and utilised in the literature. The aim of this paper is to examine and compare the effects of a number of AL scoring algorithms in a community dwelling cohort of older persons. This study will therefore add to the existing literature by incorporating sex-specific and clinical risk definitions, and utilising objective measures of physical health functioning. Based on previous studies, I hypothesis that each AL scoring algorithm will be associated with these health outcomes.

2.1.2 Study 2: Psychosocial adversity and Allostatic Load

This study applies a life course approach to investigate the relationship of adversity and AL that does not limit experiences of stress exposure to adulthood or recent events, and expands measured adversities to include possible psychosocial, physical and environmental experiences. Furthermore, these measures vary in terms of subjective and objective measurement. I hypothesise that both childhood and adulthood adversity is associated with later life AL burden.

2.1.3 Study 3: Intergenerational social mobility and Allostatic Load burden

This paper assesses whether social mobility, i.e., the movement between socio-economic position across the life course, is associated with AL burden. I will establish whether the social patterning of physiological dysregulation that has been found in other studies²⁸ exists in my data. I will investigate whether upward/ downward social mobility from childhood SEP is associated with lower/higher burden of AL in later life. I take advantage of the unique characteristics of the Irish

context, i.e., high prevalence of upward mobility, to assess the association of mobility with AL burden.

2.1.4 Study 4: The association of allostatic load biomarkers with stress and all-cause mortality

There remains little consensus as to what biomarkers should be employed to represent the multi-system physiological dysregulation proposed by the AL framework. This study aims to assess the correlation of a broad battery of biomarkers, composite system indices and AL measures with stress, and subsequently their association with all-cause mortality. This study is strengthened by its prospective design, as it utilises mortality data for up to 10 years since collection of the biological data.

2.2 The Irish Longitudinal Study on Ageing (TILDA)

This thesis employs data from The Irish Longitudinal Study on Ageing (TILDA) to evaluate the Allostatic Load framework and its utility in quantifying differences in health and longevity. TILDA is a nationally representative study of the community-dwelling over 50s population in Ireland, which collects data on the social, biological, economic and health circumstances of the sample. Established in 2006, TILDA completed its primary wave of data collection in 2009. To date, TILDA has been harmonized with a number of international scale longitudinal studies, such as the Health and Retirement Study (HRS) in the United States, and the English Longitudinal Study on Ageing (ELSA). TILDA is currently completing its sixth wave of data collection, with a detailed nurse led health assessment captured at Wave 1, Wave 3 and Wave 6. Ethics for TILDA has been granted by the Trinity College Dublin Research Ethics Committee, and all participants provide written consent.

2.2.1 TILDA sampling design

Sampling for TILDA was conducted using the RANSAM random sampling procedure ¹³¹, with the Irish Geodirectory as a sampling frame. The Irish Geodirectory is a comprehensive listing of all residential addresses in the Republic of Ireland, compiled by the Irish postal service, *An Post* and *Ordnance Survey Ireland*. A three-stage sampling process was adopted to identify any adult aged 50 years or older, and their spouse of any age, living in a residential address in the Republic of Ireland. The first stage involved identifying 3,155 clusters which comprised of between 50 and 1,180 addresses, stratified by socio-economic status, age and geographical location. Of these, 640 clusters, and 40 addresses within each cluster were randomly selected, identifying 25,600 addresses ¹³². Interviewers were required to identify the eligibility of each selected address by determining whether a member of the household was aged 50 years or older. The effective response rate was defined as the proportion of households including an eligible participant from whom an interview was successfully obtained – 62%. Additional detail on the sampling design is described further elsewhere ^{132,133}.

2.2.2 TILDA Wave 1 data collection

Wave 1 interviews were completed between October 2009 and February 2011, and there are three components to data collection. Firstly, a Computer Assisted Personal Interviews (CAPI) are administered by trained social interviewers in the participant's own home. The CAPI gathers detailed information on demographics, economic status, lifestyle behaviors and self-reported health. Participants were also asked to complete a self-completion questionnaire (SCQ) and return it to the TILDA office in a pre-paid envelope provided by the interviewer (n = 6139: 85%). The SCQ contained questions on life course stress exposure, and other sensitive items. The third component involved a clinical health assessment. The health centers (Dublin and Cork) were designed to allow nurses to assess three participants at any one time, as there were four different stations corresponding

to one of more test types (i.e., cognitive measures, vision, gait, cardiovascular). Participants who preferred not to travel to attend a health assessment due to mobility or other issues were offered a health assessment at home. Home health assessments measured a reduced number of health measures due to the practicalities of completing the assessment at home. All health assessments were carried out by trained research nurses, and included anthropometric measures such as height and weight, physical function measures such as Timed-Up-and-Go and grip strength, and cognitive measures. All participants who completed their assessment at home completed the cognitive tests before the other physical measures are taken. The in-center health assessment also collected more detailed measures of cardiovascular, bone and eye health ¹³⁴. During Wave 1, a total of 5,894 participants aged over 50 completed a health assessment (72.1%), 860 of which completed a health assessment at home.

2.3 Measures

Whilst full details of all measures used are provided in each paper's methodology, in this chapter, I provide background on the data and the design of each paper. All equipment used to collect biological and physical data are calibrated as per manufacturer's protocols, and TILDA enlisted support for any equipment issues through collaboration with St. James's Hospital Medical Physics and Bioengineering department ¹³².

2.3.1 Physiological parameters

The following outlines the biological parameters that are employed across each study. The average of two measurements of seated systolic blood pressure, diastolic blood pressure and resting heart rate were obtained separated by a 1-minute interval using an automatic digital oscillometric blood pressure monitor (OMRONTM, M10-IT). An average of two measurements between the carotid and femoral arteries was obtained using a Vicorder[®] system (Skidmore Medical Ltd, Bristol,

UK), a non-invasive gold standard method of measuring arterial stiffness and pulse wave velocity¹³³. Metabolic system biomarkers included waist-hip ratio, body mass index (BMI) glycosylated hemoglobin (HbA1c), total cholesterol, and high-density lipoprotein. Weight was measured using a SECA electronic floor scales, and height was measured using a SECA 240 wall mounted measuring rod. BMI was calculated by dividing weight in kilograms by height in meters squared. SECA measuring tapes were used to record WHR with measurements taken to the nearest millimeter. Blood collection procedures were approved after consultation and peer review from the scientific community in Ireland, the UK and the US. Ethics constrained the collection of blood to 25ml per participant. Total cholesterol is a measure of the amount of lipoproteins in the bloodstream, and was obtained from non-fasting blood samples. Venepuncture was performed with a butterfly and a green 21-gauge Vacutainer needle, and stored in EDTA tubes. A direct determination of high-density lipoprotein was performed using PEG-modified enzymes and dextran sulphate. HbA1c reflects blood sugar levels and metabolic functioning in the 8-12 weeks prior to blood sampling and were analyzed by reverse-phase action exchange chromatography using an ADAMS A1c HA-8180V analyzer.

C-Reactive Protein (CRP) serves as our singular marker of immunological dysregulation as it was the only inflammatory marker available in the full TILDA cohort at baseline. It was measured in non-fasting blood serum on a Roche Cobas c 701 analyser using an immunoturbidimetric assay for the in vitro quantitative determination of CRP. Detection limits ranged from 0.3-350 mg/l. The two renal markers included Creatinine and cystatin-c, which were measured simultaneously from frozen plasma. Creatinine was measured using an enzymatic method traceable to isotope-dilution mass spectrometry (Roche Creatinine plus ver.2, Roche Diagnostics, Basel Switzerland), whilst cystatin-c was measured using a second-generation particle enhanced immunoturbidimetric assay (Roche Tina-quant™) on a Roche Cobas 701 analyzer. This assay has a measuring range of 0.40–6.80 mg/L and is traceable to the European reference standard material (ERM-DA471/IFCC).

2.3.2 Socio-economic position

The introductory chapter outlined the popular indicators of socio-economic position (SEP).

This thesis primarily employs occupational class to represent SEP; childhood SEP is drawn from retrospective data on father's occupation from childhood (age 14), and current occupation, or highest paid job if retired, was used to estimate contemporaneous SEP. Education was not chosen as the primary SEP measure due to the potential influence of the educational reforms introduced in Ireland in the late 20th century, while income is a less useful indicator in older cohorts as it may be affected by retirement status. However, sensitivity checks are carried out throughout this thesis using these alternative measures of SEP. Following the Irish Central Statistics Office (CSO) social class coding schema, occupations for both time points were classified into five categories: professional/managerial, non-manual, skilled manual/ semi-skilled, unskilled and parent never worked. Participants who reported farming as origin/ destination occupation were asked to provide acreage, and if they had any other paid work, and were coded into the appropriate categories above as a result. Farmers with unknown acreage were coded as missing.

2.3.3 Outcome variables

Among the outcome variables utilized in this thesis are composite biomarker indices (allostatic load), physical function (walking speed, grip strength) and all-cause mortality. Spatiotemporal gait analysis was captured at the TILDA health center assessments using a 4.88 meter computerized GAITRite® mat with pressure sensors which is placed in the center of a room. Participants are asked to walk for 2.5 meters before the beginning of the mat, and a further 2 meters beyond the mat to ensure that acceleration and deceleration is not accounted for in the measurement, and it can be used as a steady state walking speed measure ¹³⁵. Data from two walks were averaged, and walking speed is defined as the distance covered by the body per unit time (cm/second). Grip strength was

captured using a handheld Baseline® dynamometer, where participants are asked to squeeze the device as hard as possible for a few seconds. Two attempts from the dominant hand are averaged (kilograms). An objective health outcome which has been relatively well supported by the literature is mortality. Mortality was identified from calls/ emails from family members to the TILDA office, fieldwork interviewers and from official death registration data from the General Register Office (GRO) and linked to individual level survey data from TILDA. Follow up within the study is ongoing but was censored for respondents without a death at Wave 5 (December 2018).

2.4 Statistical analysis

Statistical analyses were conducted using Stata 15.1¹³⁶. As a range of analysis strategies are used throughout this thesis, they are described individually in each chapter. The respective analyses are summarized next. Chapter 3 analyses 14 variations of AL scoring algorithms and their association with three age related health outcomes (walking speed, grip strength, and self-rated health). I regressed each score separately (adjusting for age and sex), using ordinary least squares regression with respect to walking speed and grip strength, and ordinal logistic regression for self-rated health (SRH). Model fit was examined using from R^2 , Bayesian Information Criterion (BIC), and the area under the Receiver Operating Characteristic curve (AUC). Higher values of R^2 and lower values of BIC indicate better model fit.

Chapter 4 analyses the association of psychosocial adversities with AL. I use negative binomial regression to model the association of a number of life course adversities, adjusting for age and sex. Further analyses adjusted for behavioural and lifestyle confounders. Unstandardized coefficients were exponentiated and reported as incidence rate ratios (IRR), which can be interpreted as the percentage change in AL associated with the experience of each adversity. Little's test of missing completely at random (MCAR) was conducted to test the assumption of missing completely

at random for multivariate, partially observed quantitative data. The test statistic takes a form similar to the likelihood-ratio statistic for multivariate normal data and is asymptotically χ^2 distributed under the null hypothesis that there is no difference between the means of different missing value patterns (Li, 2013). Therefore, if the p value is greater than 0.05, one can conclude that the data are missing at random. Multiple imputation accounted for any bias from missing data.

Chapter 5 analyses the life course association of socioeconomic position and AL via three statistical models. Firstly, AL was regressed on childhood SEP, adjusting for adulthood SEP to distinguish whether childhood represented a critical period for the embedding of SEP. Secondly, AL was regressed on life course SEP, with the inclusion of a categorical interaction of childhood * adulthood SEP to test for the existence of a cumulative nature of socioeconomic disadvantage. Thirdly, Diagonal Reference Models (DRM) were estimated to test whether the effects of childhood SEP are modified by adulthood circumstance. This method allows for the investigation of movement effects across levels of categorical variables ¹³⁷.

Chapter 6 analyses include logistic regression, and Cox survival analyses. The inter-correlations of 25 biomarkers using Pearson correlation matrices. The correlation of these biomarkers with the Perceived Stress Scale (PSS) are also examined. Cox proportional hazards regression models are utilised to estimate the relationship of each biomarker, system and overall AL score with mortality. Schoenfeld residuals are examined to ensure the data meets the proportional hazard's assumption.

2.5 Research paradigm

While I believe that I am an objective researcher, I also acknowledge that to have an interest in a topic there may be an underlying subconscious bias that may influence some aspects of the research design, research questions and the eventual interpretation of the data. Every researcher has their own subliminal view on what constitutes truth and knowledge, which may guide and bias the

direction in which research is conducted. In order to conduct research, it is therefore important to know what these biases are. Approaching the research questions within this thesis, I bring to the table the assumption that truth is singular and confirmatory, and that quantitative research designs allow the researcher to minimise the variation by controlling for factors that may lie outside the remit of the researchers beliefs or experiences. This approach is therefore separate to that of qualitative research designs, wherein a research may believe and allow for multiple truths to exist, accepting the influence of varying perspectives between individuals. While my research is focused on objective biomarker data, it also incorporates self-reported survey data. I acknowledge the importance of subjective knowledge and the potential limitations of quantitative methods, and therefore, I intend to interpret the findings with caution and in the context of broader social and cultural factors.

Chapter 3: Does the choice of Allostatic Load scoring algorithm matter for predicting age-related health outcomes?

Chapter summary

Background: Allostatic Load (AL) is posited to provide a measure of cumulative physiological dysregulation across multiple biological systems and demonstrates promise as a sub-clinical marker of overall health. Despite the large heterogeneity of measures employed in the literature to represent AL, few studies have investigated the impact of different AL scoring systems in predicting health.

Methods: This study uses data for 4477 participants aged 50+ years participating in the Irish Longitudinal Study on Ageing (TILDA) to compare the utility of 14 different scoring algorithms that have been used to operationalise AL (i.e., count-based high-risk quartiles, deciles, and two-tailed cut-points, z-scores, system-weighted indices, clinical cut-points, sex-specific scores, and incorporating medication usage). Model fit was assessed using R², Bayesian Information Criterion (BIC), and the area under the Receiver Operating Characteristic curve (AUC).

Results: The measure incorporating medications predicted walking speed and self-rated health (SRH) marginally better than others. In general, AL was not predictive of grip strength.

Conclusion: Overall, the results suggest that the choice of AL scoring algorithm exerts a relatively modest influence in predicting a number of important health outcomes.

Chapter 3: Published work list

The following chapter was published in *Psychoneuroendocrinology*:

McLoughlin, S., Kenny, R. A., & McCrory, C. (2020). Does the choice of Allostatic Load scoring algorithm matter for predicting age-related health outcomes? *Psychoneuroendocrinology*, 120, 104789. <https://doi.org/https://doi.org/10.1016/j.psyneuen.2020.104789>

The following tables and figures included in this chapter were published as part of this paper:

- Table 3.1: Sample characteristics
- Table 3.2: Univariate descriptives of individual biomarkers by sex
- Table 3.3: Model Fit Statistics for different Allostatic Load Scoring Algorithms predicting Walking Speed
- Table 3.4: Model Fit Statistics for different Allostatic Load Scoring Algorithms predicting Grip Strength
- Table 3.5: Model Fit Statistics for different Allostatic Load Scoring Algorithms predicting self-rated health
- Supplementary Table 3.1: Biomarker panel
- Supplementary Table 3.2: Clinically defined risk cut-points for each biomarker
- Supplementary Table 3.3: Correlations between the AL scoring algorithms and age
- Supplementary Table 3.4: Distributional statistics for each AL scoring algorithm (n = 4477)
- Supplementary Table 3.5: Area Under the Curve and associated 95% confidence intervals for different AL scoring algorithms in predicting poor health outcomes
- Figure 3.1: AUC estimates for different scoring algorithms, predicting slow walking speed
- Figure 3.2: AUC estimates for different scoring algorithms, predicting weak grip strength
- Figure 3.3: AUC estimates for different scoring algorithms, predicting poor self-rated health
- Supplementary Figure 3.1: Sample flow chart

3.1 Introduction

Allostatic Load (AL) is posited to represent a sub-clinical measure of physiological wear and tear resulting from chronic exposure to life course stressors (McEwen & Stellar, 1993). In recent decades, the framework has contributed to an enhanced interdisciplinary understanding of how social, environmental, and psychological factors impact physiological functioning and shape health disparities^{26,138,139}. Despite this apparent utility, AL is beset by a number of methodological and conceptual difficulties that have hampered its potential clinical utility. These include: (1) the ongoing failure to agree a core set of biomarkers that define the construct, and (2) a plethora of different AL scoring algorithms, limiting our ability to compare results across studies. The former issue, concerning the heterogeneity of biomarkers used across studies, has been discussed at length in a number of recent reviews^{24,28}, but the latter issue has received rather less attention in the literature, and is arguably just as important.

3.1.1 Different scoring systems for AL

Seeman et al. (1997) provided the first operational definition of AL using a high-functioning sample of adults aged 60 years and older. They employed 10 biomarkers across the neuroendocrine, immune, metabolic and cardiovascular systems, and summed the number of parameters for which an individual had values in the highest risk quartile, based on the sample distribution⁴³. This measure predicted physical and cognitive decline within the MacArthur Studies of Successful Ageing in the US, and greater incidence of cardiovascular disease over a three-year follow-up. The authors concluded that AL might perform even better in general population studies. The original scoring algorithm for AL remains a popular method today, with the aforementioned systematic review²⁸ reporting that 73% of included studies utilised this approach, despite the potential loss of information from the full risk spectrum.

Lack of consensus around an agreed biomarker panel ^{24,28,140} and scoring system ^{26,141} has led to a proliferation of different means for characterising AL. Considerable heterogeneity in AL calculation exists across studies utilising the MacArthur cohort alone, including: the original count of high-risk quartiles ^{38,43,142}, recursive partitioning ³³, and use of second-order terms ⁵⁵. Alternate AL formulations from other international studies include: a sum of z-scores, which may be considered more informative as it retains the continuous properties of the data ^{53,143}, or the use of decile cut-points which consider only the top end of the risk distribution. Two-tailed approaches (i.e., top and bottom quartiles or deciles) for some ^{41,144} or for all biomarkers ^{16,145} have also been employed to account for the fact that biological risk may be non-linear.

Canonical correlation, a technique that measures the associations between sets of inter-connected variables ³⁷, and recursive partitioning, a decision-tree technique ^{33,146}, have been criticised for incorporating information on health outcomes in their derivation, which can result in the over-fitting of models and limits replication across other datasets ¹⁴¹. Clinical cut-points have also been used ^{52,113,147–149}; but, the lack of universally agreed values (e.g. cut-points for parasympathetic or immunological markers) potentially limits their application. In addition, such definitions of risk remove the potential utility of AL as a sub-clinical disease measure for identifying risk prior to the emergence of the clinical phenotype. More sophisticated attempts to develop AL measures include multivariate methods, such as grade of membership (GOM) which assesses how well an individual's scores on the set of biomarkers used to define AL correspond to a set of predefined archetypal profiles ^{145,150}. Interestingly, the predictive utility of AL measures calculated using GOM and count based methods are not dissimilar ¹⁵⁰. These dissimilarities, and also how the use of such complex algorithms would not be practical in clinical settings, may explain why more elaborate measures have not been adopted more widely.

3.1.2 Does the choice of AL scoring method matter for predicting health?

Methodological disparities in the scoring of the AL index across studies not only makes comparison of results challenging, but also hampers progress towards the use of AL as an early diagnostic screener and / or therapeutic target. This is an important theoretical and empirical matter that has not been subjected to the type of systematic investigation one might expect. Our review of the literature identified only two studies to date ^{141,150} that have explicitly examined this issue.

Seplaki et al. (2005) compared the predictive utility of 9 different AL scoring algorithms (including count of high-risk quartiles/deciles, GOM, z-scores, and two-tailed quartiles/deciles, derived from two biomarker panels) in identifying poor health outcomes. Results were remarkably similar irrespective of the method used to calculate AL. They did, however, suggest that two-tailed formulations, or measures that retain the continuous properties of the biological variables, might be preferred going forward. A separate investigation by Li et al. (2019) involving the NHANES cohort compared the utility of 5 scoring algorithms (i.e., count of high-risk quartiles, z-scores, logistic regression, factor analysis, GOM) in predicting self-reported health, diabetes, and hypertension. The best predictive performance was provided by a measure utilising the standardised coefficients from multivariable logistic regressions to weight individual biomarkers. However, similar to canonical correlation, health outcomes were used in the development of the scoring algorithm, which hampers replication across other populations. Li et al. (2019) recommended the original method of high-risk quartiles as a good alternative.

3.1.3 Should we incorporate sex differences in the calculation of the AL index?

To date, despite evidence of sex differences within the stress response ^{151,152}, and in the downstream biological parameters associated with the stress response ^{77,153–156}, there is no consensus regarding the incorporation of sex-specific risk values in the calculation of AL measures. Seplaki et al. (2006) were the first to suggest deriving an AL score using sex-specific risk definitions, with a number of others adopting this approach since ^{45,54,157–160}. Notwithstanding the potential import of biological sex differences, a recent review of NHANES revealed that only 1/21 AL studies incorporated sex-specific risk definitions ¹⁶¹, and to date, no study has compared the predictive utility of an AL measures including and excluding sex-specific risk definitions with alternate calculations.

3.1.4 Should we incorporate medications in the calculation of the AL index?

Whether and how doctor-prescribed medication should be incorporated into the development of the AL index is another bone of contention ¹⁶². Medications can act on the biological systems to reduce observed values, reducing risk of disease ^{142,163}. On the other hand, wear and tear may already have occurred if there is a need to medicate, and this excess risk should be accounted for when calculating the score. Varied approaches to the resolution of this problem exist including: scoring an individual at high risk if taking a medication which deflates values on the biomarker ¹⁶⁴; adding ‘medication use’ as a covariate in regression models ¹⁶⁵; or increasing individual biomarker values in an attempt at increasing prediction accuracy (e.g. systolic and diastolic blood pressure adjusted by adding 10mmHG and 5mmHG, respectively if taking anti-hypertensives) ¹⁶⁶. To date, no study has compared the predictive utility of AL measures including medication use compared with alternate formulations.

3.2 The present study

The present study builds upon the work of Seplaki et al. (2005) and Li et al. (2019) in several important ways. Firstly, we use a sample from a nationally representative cohort of community-dwelling older persons, whereas Seplaki et al. (2005) used a militaristic sample with heavy male bias, and Li et al. (2019) used an all-female sample. Secondly, we use a number of objective measures of physical health functioning (i.e., walking speed, grip strength) as the criterion variables in the analysis. Thirdly, we incorporate sex-specific and clinical risk definitions. Finally, we examine whether included medication usage improves the predictive accuracy of AL.

3.3 Methods

3.3.1 Sample

This analysis used data from the first wave of The Irish Longitudinal Study on Ageing (TILDA), a nationally representative prospective study of over 8,175 persons aged 50 years and over living in the Republic of Ireland. Sampling involved a three-stage selection process with the Irish Geodirectory as the sampling frame, where residential addresses were divided into geographical clusters, of which 640 were selected based on area level socio-economic status and location. Additional information on the sampling frame and study design is available in detail elsewhere ¹³³. Data was collected through computer assisted personal interview (CAPI) carried out by a trained interviewer, a leave behind self-completion questionnaire (SCQ), and a comprehensive clinic-based, nurse-administered health assessment. These assessments included the collection of blood samples for biomarker assessment and a battery of cognitive and physical tests. Ethical approval for the study was provided by the Faculty of Health Science Research Ethics board in Trinity College Dublin, while informed consent is obtained from all respondents during data collection. In total, 5,894 people completed either the centre or home-based health assessment. Respondents who were missing on any of the biomarkers

were excluded for this study, leaving a total analytical case base of 4,477. A flow chart summarising inclusion criterion for analysis is provided in Supplementary Figure 3.1.

3.3.2 Physiological parameters

A total of 12 biomarkers across the cardiovascular, metabolic, renal, and immune systems were used to construct the various AL indices examined in this study. Biomarkers were selected to reflect the most commonly chosen systems in the AL literature ²⁴. Two of the biomarkers - pulse wave velocity (PWV) and cystatin C (Cysc) - are relatively novel with respect to AL formulation but their inclusion was theoretically motivated. For example, there is evidence to suggest that acute and chronic stress may induce arterial dysfunction as indexed using PWV ^{167,168}. Similarly, Cysc may serve as a preferred/complementary biomarker of kidney functioning compared with creatinine in older cohorts as it is less affected by declining muscle mass ¹⁶⁹. The component biomarkers and a description of their primary function is provided in **Error! Reference source not found..**

In terms of the cardiovascular system, the average of two measurements of seated Systolic Blood pressure (SBP), Diastolic Blood pressure (DBP) and Resting Heart Rate (RHR) were obtained separated by a 1-minute interval using an automatic digital oscillometric blood pressure monitor (OMRONTM, M10-IT). An average of two measurements between the carotid and femoral arteries was obtained using a Vicorder system, representing PWV (Skidmore Medical Ltd, Bristol, UK), a non-invasive gold standard method ¹³³. Metabolic system biomarkers included waist-hip ratio (WHR), body mass index (BMI) glycosylated haemoglobin (HbA1c), total cholesterol (TChol), and high-density lipoprotein (HDL). Weight was measured using a SECA electronic floor scales, and height was measured using a SECA 240 wall mounted measuring rod. BMI was calculated by dividing weight in kgs by height in metres squared. SECA measuring tapes were used to record

WHR with measurements taken to the nearest millimetre. TChol was obtained from non-fasting blood samples, with venepuncture performed with a butterfly and a green 21-gauge Vacutainer needle and stored in EDTA tubes. A direct determination of HDL was performed using PEG-modified enzymes and dextran sulphate. HbA1c reflects blood sugar levels and metabolic functioning in the 8-12 weeks prior to blood sampling and were analysed by reverse-phase action exchange chromatography using an ADAMS A1c HA-8180V analyser.

C-Reactive Protein (CRP) serves as our singular marker of immunological dysregulation as it was the only inflammatory marker available in the full TILDA cohort at baseline. It was measured in non-fasting blood serum on a Roche Cobas c 701 analyser using an immunoturbidimetric assay for the in vitro quantitative determination of CRP. Detection limits ranged from 0.3-350 mg/l. The two renal markers included Creatinine (Crea) and Cysc, which were measured simultaneously from frozen plasma. Crea was measured using an enzymatic method traceable to isotope-dilution mass spectrometry (Roche Creatinine plus ver.2, Roche Diagnostics, Basel Switzerland), whilst Cysc was measured using a second-generation particle enhanced immunoturbidimetric assay (Roche Tina-quant™) on a Roche Cobas 701 analyser. This assay has a measuring range of 0.40–6.80 mg/L and is traceable to the European reference standard material (ERM-DA471/IFCC). Log transformations were applied to CRP and PWV to account for right-skewed distributions.

3.3.3 Calculation of summary measures

High-risk quartiles (Classic Method): To re-create the original and most commonly employed scoring algorithm across studies ⁴³, dichotomous indicator variables were created for each biomarker. This will herein be referred to as the “*classic*” method, as it was the first operationalisation of AL, and remains the most popular method for generating AL across studies ¹⁷⁰. HDL was reverse coded

such that higher values represented increased risk. Empirically defined high-risk thresholds were distinguished based on the distribution of that biomarker in the sample; “1” was assigned to values falling above the 75th percentile of the distribution for each marker, and “0” was assigned to values below this threshold. These biomarkers were summed to create an index, with higher scores reflecting higher AL burden. **Two-tailed high-risk quartiles:** Seplaki et al. (2005) suggested that including risk factors at both high and low ends of the risk continuum may be more informative than simply using high-risk quartiles. To re-create this score, a value of “1” was assigned to values above the 75th percentile and below the 25th percentile of the distribution, and a value of “0” was assigned for values that fell intermediate of these thresholds. A sum of these biomarkers represented two-tailed physiological dysregulation.

Following the above methodologies, two further algorithms were created employing decile cut-points, to measure risk at more extreme levels of the distribution. **High-risk Deciles:** “1” was assigned for values above the 90th percentile, “0” was assigned to all values below this threshold, and all biomarkers were then summed. **Two-tailed high-risk deciles:** “1” was assigned for values above the 90th percentile and below 10th percentile for the measure incorporating both ends of the distribution, and “0” assigned to all values that lay intermediate between these thresholds, and scores on the individual biomarkers were then summed.

Z-scores: To create a score that retained the continuous properties of each physiological variable, each biomarker was standardised to a mean of 0 and a standard deviation of 1, and then summed to generate an overall AL score expressed in standard deviation units ^{53,143,171}. In other terms, a z-score is calculated by for each biomarker by subtracting the sample mean from the individual’s value and diving the result by the sample standard deviation. Higher values on the summed score indicate a

greater degree of multi-system dysregulation. **System Weighted:** It is common in the AL literature for some biological systems to be more heavily represented than others, of which metabolic system biomarkers tend to be most populous ²⁴. A system-weighted score was therefore created to reduce this bias. Firstly, biomarkers were dichotomised following the classic methodology ⁴³. Secondly, each dysregulated biomarker was weighted according to the total number of biomarkers per system. System risk indices were computed as the proportion of individual biomarkers for each system for which participant values fell into high-risk quartiles ¹¹⁵. For example, in the present study, the cardiovascular system was comprised of four biomarkers (SBP, DBP, RHR, PWV). Therefore, the sum of dysregulated biomarkers within this system were divided by 4 and expressed as a proportion ranging from 0.0-1.0. As CRP is the only immunological biomarker, no scaling occurred, hence “0” indicated no risk, whilst “1” indicated high risk. Finally, an AL score was computed as the sum of these weighted systems. This methodology has been used previously and ensures that each system is equally represented in the overall AL index ^{115,165,172}.

Sex-specific cut-points: To account for variability in biomarker values according to sex, each of these 6 scoring algorithms were re-created using sex-specific cut-points (Table 3.2). Therefore, to create the sex-specific count of high-risk quartiles measure, individuals falling above the 75th percentile were identified using the sample distributions for men and women separately, and scores were then pooled.

High-risk quartiles (incorporating medications): To allow for the possibility that medication use was masking high values, prescription drugs were incorporated into an additional algorithm based on the classic methodology, with individuals taking medication automatically reclassified as high-risk across affected biomarkers. In TILDA, medication usage was ascertained as part of the household

interview, where respondents were asked to retrieve the medicinal packaging of any regularly taken medications and interviewers transcribed the brand/generic name of the prescription medication. The medications data was then coded in-house by pharmacologists according to Anatomic Therapeutic Classification (ATC) codes¹³³. HbA1c was coded as high risk if individuals were currently prescribed medications of codes for insulin or analogues (A10), SBP was classified as high risk if individuals were taking anti-hypertensive medication (C02, C03, C09). RHR was recoded as high risk if taking beta-blockers (C07) or calcium blockers (C08) and finally, HDL was recoded as high risk if prescribed lipid modifying agents (C10).

Clinical: Finally, we derived a measure of AL using recognised risk definitions according to clinical guidelines^{52,115,117,147}. Clinical cut-points for each biomarker are provided in Supplementary Table 3.2.

3.3.4 Health outcomes

We utilised two objectively measured health outcomes – walking speed and grip strength (described below). Additionally, to enable comparison with Seplaki et al. (2005), a general self-reported health measure was included.

3.3.4.1 Walking speed

In older adults, walking speed has been shown to be a good indicator of overall physical function¹⁷³, and a predictor for hospitalisation¹⁷⁴ and higher morbidity¹⁷⁵. In TILDA, gait measurements were taken using a 4.88-metre computerised walkway with embedded pressure sensors (GAITRite, CIR Systems Inc., New York, NY). Participants completed two walks at their normal walking speed. The

average of the two readings represents the overall walking speed expressed in centimetres travelled per second (cm/s).

3.3.4.2 Grip strength

Low grip strength has been robustly associated with functional decline and mortality in older adults¹⁷⁶ and serves as a proxy for the overall strength of the musculoskeletal system. Two measures were taken from the dominant hand using a Baseline® Hydraulic Hand Dynamometer, and the highest of the two readings in kilograms (kgs) per square inch represented the measure of grip strength used in the analysis.

3.3.4.3 Self-rated health

Self-rated health (SRH) is a commonly assessed item in health surveys¹⁷⁷, and can provide insight into the perceptions that an individual has of their own health status relevant to their peers. SRH has previously been associated with decreased physical performance¹⁷⁸ and increased mortality risk¹⁷⁹. Previous studies have reported that lower SRH predicts higher AL^{180,181}. SRH was obtained during the CAPI with the item *“In general, compared to other people your age, would you say your health is...”* rated on a five-point scale of excellent, very good, good, fair, and poor.

3.4 Statistical analysis

All analyses were conducted in Stata (v.15; StataCorp, 2017), using TILDA dataset v.1.8.0. The outcome measures were regressed separately on each of the 14 AL scoring algorithms, adjusting for age and sex, using ordinary least squares regression with respect to walking speed and grip strength, and ordinal logistic regression for SRH. Overall model fit was assessed using the proportion of variance explained (R^2 for OLS, pseudo R^2 for ordinal logistic regression) and the Bayesian

Information Criterion (BIC). An obvious advantage of using information measures is that one can compare the goodness of fit of non-nested models ¹⁸², as the different AL scoring algorithms are essentially just reformulations of the same underlying set of 12 component biomarkers. The extent to which one model is preferred over another depends on the magnitude of the difference between the information measures. Higher values of R^2 and lower values of BIC indicate better model fit. BIC values were obtained using the FITSTAT package in Stata ¹⁸³. Following guidelines proposed by Raftery (1995), we noted a BIC difference >10 to indicate a better fitting model than the standard scoring algorithm ¹⁸⁴. To reduce the large number of potential contrasts between the different AL scoring algorithms, we take as our reference, the overall (i.e., non-sex-specific) quartile-based risk score (hereinafter referred to as classic method) as it is the one that has been predominantly used in the AL literature.

In order to provide a comparison with Seplaki et al. (2005), binary indicator variables were created for each of the health outcomes using cut-points guided by previous literature. Grip strength was dichotomised at $<37\text{kg}$ for men, and $<21\text{kg}$ for women ¹⁸⁵. Walking speed was dichotomised at $<120\text{cm/s}$ ¹⁷⁴. SRH was recoded as “1” if respondents rated their health as fair/poor, “0” otherwise ¹⁴¹. Each of the binary health outcomes were treated as dependent variables in separate logistic regression models, controlling for age and sex. The area under the Receiver Operator Characteristic curve (AUC) was calculated for each health outcome for each of the 14 different AL scoring algorithms using the ROCTAB procedure ¹⁸⁶. Higher AUC values indicate greater classification accuracy. Comparison of AUC estimates to test the statistical significance of the difference between the classic AL algorithm and all alternative algorithms were investigated using the ROCCOMP procedure ¹⁸⁷. Finally, as age is the strongest predictor of health, we also examined which of the AL algorithms was most strongly correlated with chronological age.

3.5 Results

Table 3.1 reports sample characteristics. The mean age of the sample was 61.8 years and female respondents accounted for 53.7% of the sample. Mean walking speed was 136.1 cm/s (SD= 20.4), and mean grip strength was 27.5 kgs (SD = 9.88). 89.0% of the sample reported that they were in excellent/very good/good health. In total, 45.4% of the sample were taking prescribed medications that potentially impacted values of biomarkers included in this study. Respondents included in the study were younger than those who were missing biomarker data, more educated and had, on average, a lower average count of chronic diseases. No sampling weights were applied however, as the primary focus of this study was to compare the predictive utility of various AL scoring algorithms and not to infer the relationship of AL and the health outcomes to the population. The relationship between age and each of the AL scoring algorithms was assessed using Spearman's correlations, reported in Supplementary Table 3.3. The measure incorporating medications was most strongly correlated with age ($r = 0.34$), whilst the two-tailed measures revealed weak correlations with age (e.g., overall quartile ($r = 0.05$), overall decile based ($r = 0.06$)).

Table 3.1: Sample characteristics

Variable	In sample (N=4477)		Missing (N=3697)	
	Mean	SD	Mean	SD
Sex (n, %)				
Male	2071	46.3	1673	45.3
Female	2406	53.7	2024	54.7
Age	61.8	8.4	66.3	10.8
Education (n, %)				
Primary	959	21.4	1545	41.8
Secondary	1882	42.1	1381	37.4
Tertiary	1635	36.5	768	20.8
Chronic diseases	1.6	1.4	1.8	1.5
Medications (n, %)	2033	45.4	697	18.85
Walking speed	136.1	20.4	132.5	22.0
Grip strength	27.5	9.88	25.59	9.59
SRH (n, %)				
Excellent, very good, good	3978	89.0	2922	79.2
Fair, poor	494	11.1	766	20.8

Note: This table was published in McLoughlin et al. (2020)

Univariate statistics and percentile cut-points for each of the 12 component biomarkers defining the AL construct are presented in Table 3.2. Two-sample t-tests revealed marked differences in biomarker values according to sex. Specifically, male respondents were characterised by significantly higher mean values for 9/12 biomarkers, whilst female respondents had significantly higher mean values for the latter 3 (RHR, CRP, Total Cholesterol). Supplementary Table 3.4 presents univariate statistics in respect of each of the 14 AL scoring algorithms used in the present study. Table 3.3, Table 3.4 and Table 3.5 report the model fit statistics for each AL scoring algorithm and the difference in model fit relative to the classic scoring algorithm for walking speed, grip strength and SRH, respectively. In this context, higher values for R^2 and lower values for BIC indicate a better fitting model compared with the standard model. In general, the results indicate that the choice of scoring algorithm has relatively modest effects on the proportion of variance explained in the health outcomes.

Table 3.2: Univariate descriptives of individual biomarkers by sex

Biomarker	Mean	SD	Min	10 th p	25th p	Median	75th p	90 th p	Max	p
Systolic blood pressure	134.67	19.49	78.50	111.00	121.00	133.50	146.50	159.50	220.00	
Male	138.95	18.28	83.00	117.50	126.50	137.00	150.00	162.00	220.00	
Female	130.99	19.75	78.50	107.50	117.00	129.00	143.00	158.00	208.50	<0.001
Diastolic blood pressure	82.30	11.06	51.50	68.50	75.00	82.00	89.50	96.50	132.00	
Male	83.72	10.88	53.50	70.50	76.50	83.50	90.50	97.00	132.00	
Female	81.09	11.06	51.50	67.00	73.50	80.50	88.00	95.50	125.50	<0.001
Resting heart rate	68.78	11.37	33.00	55.50	60.50	67.50	75.50	83.50	135.50	
Male	67.81	12.00	33.00	54.00	59.50	66.50	74.50	83.50	135.50	
Female	69.62	10.73	35.00	56.50	62.00	68.50	76.00	83.50	116.50	<0.001
Pulse wave velocity *	2.33	0.19	1.67	2.09	2.20	2.32	2.45	2.58	2.99	
Male	2.37	0.18	1.82	2.14	2.25	2.37	2.49	2.61	2.99	
Female	2.29	0.19	1.67	2.05	2.15	2.28	2.42	2.54	2.94	<0.001
High density lipoprotein (reversed)	-1.56	0.44	-3.82	-2.13	-1.80	-1.49	-1.23	-1.07	-0.48	
Male	-1.36	0.34	-3.50	-1.80	-1.54	-1.31	-1.11	-0.99	-0.63	
Female	-1.72	0.44	-3.82	-2.30	-1.98	-1.66	-1.41	-1.22	-0.48	<0.001
Cholesterol	5.15	1.05	1.80	3.80	4.50	5.10	5.80	6.50	12.20	
Male	4.88	1.05	1.80	3.50	4.20	4.90	5.60	6.20	9.10	
Female	5.39	1.00	2.20	4.10	4.70	5.30	6.00	6.70	12.20	<0.001
Glycosylated haemoglobin	33.06	5.45	16.00	28.00	30.00	32.00	35.00	38.00	94.00	
Male	33.47	5.72	17.00	28.00	30.00	32.00	35.00	39.00	88.00	
Female	32.72	5.18	16.00	28.00	30.00	32.00	34.00	37.00	94.00	<0.001
BMI	28.51	4.82	17.08	23.00	25.24	27.99	31.12	34.58	61.86	
Male	29.10	4.33	18.33	24.16	26.28	28.69	31.45	36.50	59.28	
Female	28.00	5.15	17.08	22.33	24.47	27.24	30.69	34.66	61.86	<0.001
Waist hip ratio	0.90	0.09	0.63	0.79	0.84	0.90	0.96	1.01	1.29	
Male	0.96	0.07	0.74	0.77	0.92	0.96	1.00	1.07	1.28	
Female	0.85	0.07	0.63	0.77	0.81	0.85	0.90	0.94	1.29	<0.001
Cystatin C	0.97	0.21	0.46	0.77	0.84	0.93	1.05	1.18	3.95	
Male	0.99	0.22	0.56	0.79	0.86	0.95	1.06	1.19	3.95	
Female	0.95	0.20	0.46	0.76	0.83	0.92	1.03	1.18	2.97	<0.001
Creatinine	79.21	19.90	40.00	59.00	66.00	77.00	88.00	101.00	486.00	
Male	89.09	20.21	49.00	71.00	78.00	86.00	96.00	109.00	486.00	
Female	70.71	15.13	40.00	56.00	61.00	68.00	77.00	87.00	231.00	<0.001
C-Reactive protein *	0.69	0.77	0.00	0.00	0.00	0.47	1.17	1.79	6.28	
Male	0.65	0.75	0.00	0.00	0.00	0.43	1.12	1.68	5.73	
Female	0.72	0.78	0.00	0.00	0.00	0.51	1.22	1.84	6.28	0.003

Note: Total sample n= 4477; male = 2071, female = 2406. p = significance level determined from two sample t-test, comparisons of mean values within biomarkers between male and female respondents. * = log transformed. This table was published in McLoughlin et al., (2020)

3.5.1 Walking speed

Looking first at the results for walking speed, Table 3.3 shows that the proportion of variance explained by the classic AL scoring algorithm (including age and sex) was 20.3%, compared with 17.8% for the worst (overall two-tailed quartiles and overall two-tailed deciles) and 21.2% for the best (high-risk quartiles incorporating medications) fitting models. The sex-specific high-risk quartiles, high-risk decile measures, weighted measures, sex-specific z-scores, and the algorithm incorporating medications led to a strong improvement in model fit relative to the classic AL scoring algorithm, according to the BIC guidelines proposed by Raftery (1995). However, it should be acknowledged that the gain in R^2 was typically very modest and amounted to, at most, +0.9%. The measures calibrated according to sex performed marginally better when predicting walking speed than the overall measures. The two-tailed measures by contrast performed poorly, with lower values of R^2 and large increases in BIC compared with the classic algorithm.

Table 3.3: Model Fit Statistics for different Allostatic Load Scoring Algorithms predicting Walking Speed

	R^2	$DIFF R^2$	BIC	$DIFF BIC$
High-risk quartiles				
Overall	0.203***	<i>REF</i>	38344.70	<i>REF</i>
Sex-specific	0.209***	0.006	38310.73	-33.97 ^a
Two-tailed quartiles				
Overall	0.178***	-0.025	38479.84	135.14
Sex-specific	0.182***	-0.021	38449.62	113.30
High-risk deciles				
Overall	0.205***	0.002	38329.40	-10.51 ^a
Sex-specific	0.207***	0.004	38322.91	-20.94 ^a
Two-tailed deciles				
Overall	0.178***	-0.025	38467.57	136.23
Sex-specific	0.180***	-0.023	38458.66	124.48
System weighted				
Overall	0.207***	0.004	38304.19	-22.17 ^a
Sex-specific	0.208***	0.005	38328.90	-27.40 ^a
Continuous				
Overall	0.204***	0.001	38337.43	-7.27
Sex-specific	0.205***	0.002	38331.71	-12.99 ^a
Medications	0.212***	0.009	38296.41	-48.29 ^a
Clinical	0.199***	-0.004	38362.26	17.56

Note: Adjusted for age and sex. R^2 = proportion of variance explained. R^2 Diff = gain in R^2 compared with the classic AL scoring algorithm. BIC = Bayesian Information Criterion. BIC Diff = Difference in BIC compared with the classic AL

scoring algorithm. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$. ^a = Substantial decrease in BIC compared with the classic AL scoring algorithm.

3.5.2 Grip strength

For grip strength, Table 3.4

Table 3.4 shows that the proportion of variance explained by the classic AL scoring algorithm (including age and sex) was 60.8%, and this value did not vary substantially across the other measures; +0.06% for the best fitting model (overall two-tailed deciles) compared with the classic model. Two-tailed decile measures, clinical and z-scores were the only AL scoring algorithms that exhibited statistically significant associations with grip strength independently of age and sex. The strength of these relationships were small, however, and the direction of these relationships differed; negative associations were noted for overall ($\beta = -0.16$, 95% CI: -0.27, -0.06) and sex-specific ($\beta = -0.11$, 95% CI: -0.02, -0.01) two-tailed deciles, whilst positive associations were noted for the clinical measure ($\beta = 0.13$, 95% CI: 0.02, 0.23), as well as the overall ($\beta = 0.05$, 95% CI: 0.01, 0.09) and sex-specific ($\beta = 0.05$, 95% CI: 0.01, 0.09) z-score measures.

Table 3.4: Model Fit Statistics for different Allostatic Load Scoring Algorithms predicting Grip Strength

	R^2	$DIFF R^2$	BIC	$DIFF BIC$
High-risk quartiles				
Overall	0.6078	<i>REF</i>	28968.53	<i>REF</i>
Sex-specific	0.6077	-0.0001	28968.90	0.37
Two-tailed quartiles				
Overall	0.6078	0.0000	28967.96	-0.57
Sex-specific	0.6078	0.0000	28968.06	-0.46
High-risk deciles				
Overall	0.6077	-0.0001	28969.34	0.82
Sex-specific	0.6076	-0.0002	28969.86	1.33
Two-tailed deciles				
Overall	0.6084**	0.0006	28960.84	-7.68
Sex-specific	0.6080*	0.0002	28965.64	-2.89
System weighted				
Overall	0.6077	-0.0001	28969.43	0.90
Sex-specific	0.6076	-0.0002	28969.74	1.21
Continuous				
Overall	0.6082*	0.0004	28963.277	-5.25
Sex-specific	0.6082**	0.0004	28963.083	-5.44
Medications	0.6077	-0.0001	28969.45	0.92
Clinical	0.6081*	0.0003	28964.77	-3.76

Note: Adjusted for age and sex. R^2 = proportion of variance explained. R^2 Diff = gain in R^2 compared with the classic AL scoring algorithm. BIC = Bayesian Information Criterion. BIC Diff = Difference in BIC compared with the classic AL scoring algorithm. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. ^a = Substantial decrease in BIC compared with the classic AL scoring algorithm. This table was published in McLoughlin et al., (2020)

3.5.3 Self-rated health

Table 3.5 shows that the classic AL measure accounted for 1.1% of the variance in SRH, compared with 0.02% for the worst fitting models (overall high-risk deciles, two-tailed high-risk decile measures) and 1.9% for the best fitting model (high-risk quartiles incorporating medications). The sex-specific high-risk quartile measure, overall weighted measure, the measure incorporating medications, and the clinical measure led to strong improvements in BIC values compared to the classic AL index, whilst the two-tailed measures performed substantially worse.

Table 3.5: Model Fit Statistics for different Allostatic Load Scoring Algorithms predicting self-rated health

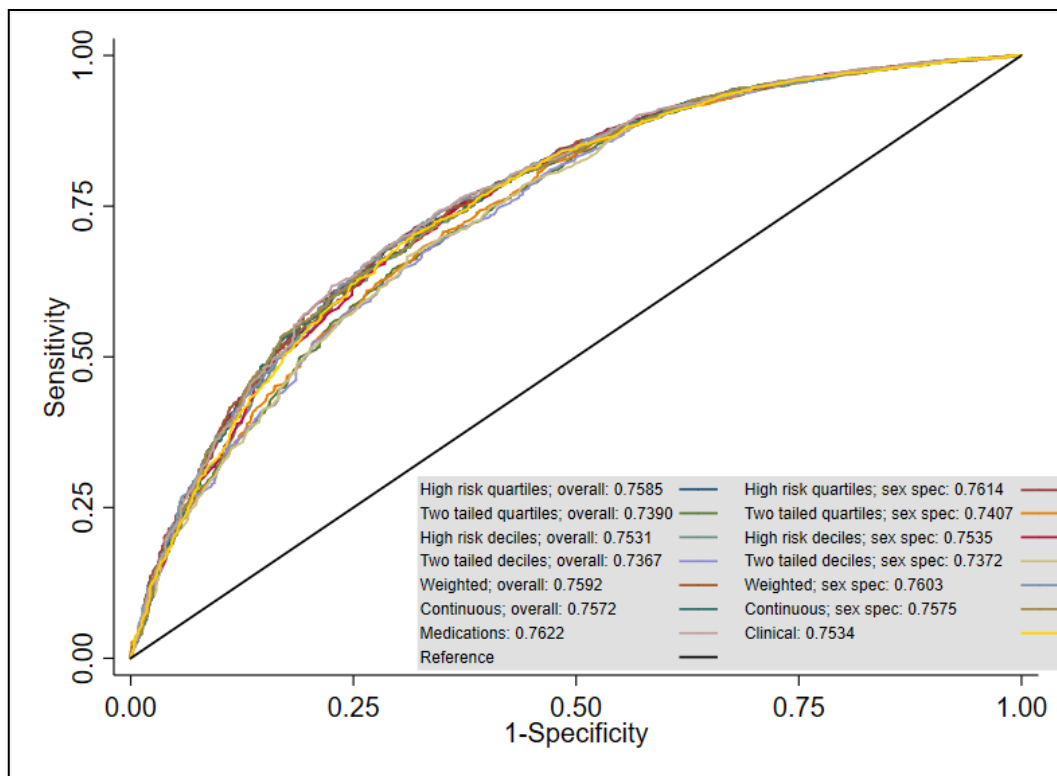
	R^2	$DIFF R^2$	BIC	$DIFF BIC$
High-risk quartiles				
Overall	0.011***	REF	12156.79	REF
Sex-specific	0.013***	0.002	12133.15	-23.65 ^a
Two-tailed quartiles				
Overall	0.002***	-0.009	12256.37	99.58
Sex-specific	0.003***	-0.008	12248.24	91.44
High-risk deciles				
Overall	0.011***	0.000	12149.79	-7.00
Sex-specific	0.011***	0.000	12158.46	1.67
Two-tailed deciles				
Overall	0.002***	-0.009	12262.80	106.00
Sex-specific	0.002***	-0.009	12262.81	106.02
System weighted				
Overall	0.012***	0.001	12139.15	-17.64 ^a
Sex-specific	0.011***	0.000	12149.24	-7.56
Continuous				
Overall	0.010***	0.001	12163.989	7.20
Sex-specific	0.010***	0.001	12158.346	1.55
Medications	0.019***	0.008	12052.43	-104.37 ^a
Clinical	0.008***	-0.003	12183.01	26.21

Note: Adjusted for age and sex. R^2 = proportion of variance explained. R^2 Diff = gain in R^2 compared with the classic AL scoring algorithm. BIC = Bayesian Information Criterion. BIC Diff = Difference in BIC compared with the classic AL scoring algorithm. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. ^a = Substantial decrease in BIC compared with the classic AL scoring algorithm. This table was published in McLoughlin et al., (2020)

3.5.4 Area under the receiver operating characteristic curve (AUC)

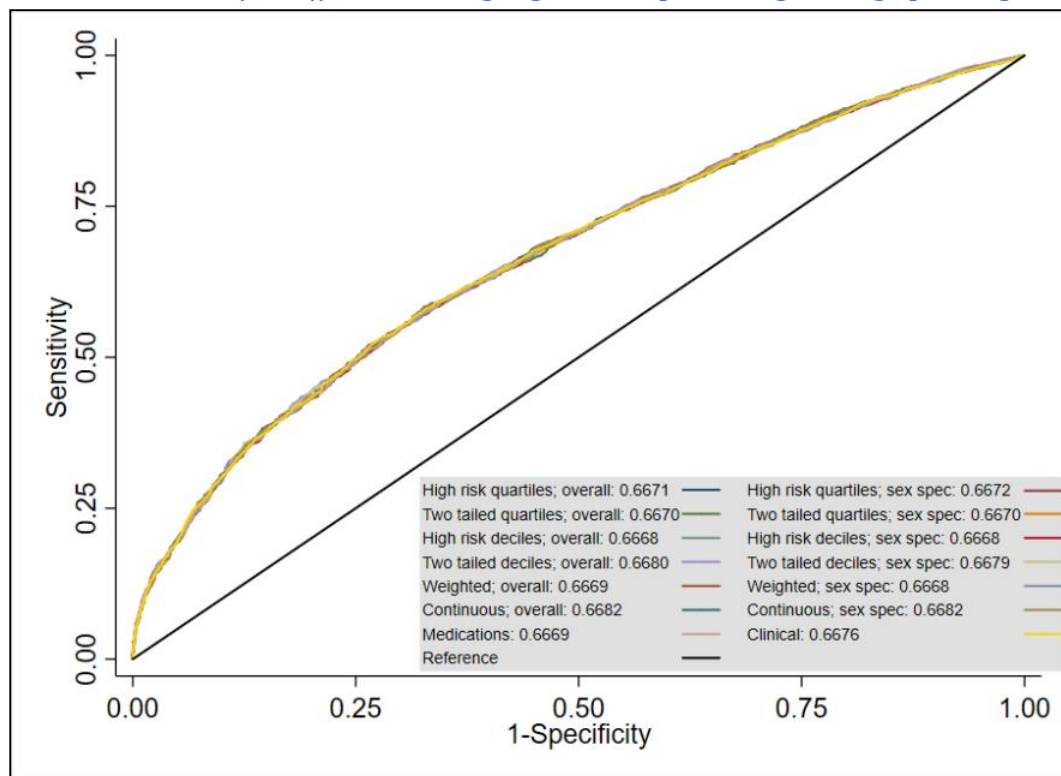
Supplementary Table 3.5 reports the AUC estimates for each of the AL scoring algorithms separately for each of the three binary health outcomes. Results were consistent with what was observed when using the continuous measures. Notably, the two-tailed measures (quartiles and deciles) performed worse than the classic algorithm when predicting walking speed (Figure 3.1) and SRH (Figure 3.3), whilst all measures predicted poor grip strength to the same degree of accuracy as the classic score (Figure 3.2). Although a minority of AL algorithms reached statistical significance with grip strength, no substantial differences in AUC were noted between these and the classic algorithm. In addition, the count of high-risk quartiles measure incorporating medications predicted fair/ poor SRH better than the classic measure.

Figure 3.1: AUC estimates for different scoring algorithms, predicting slow walking speed



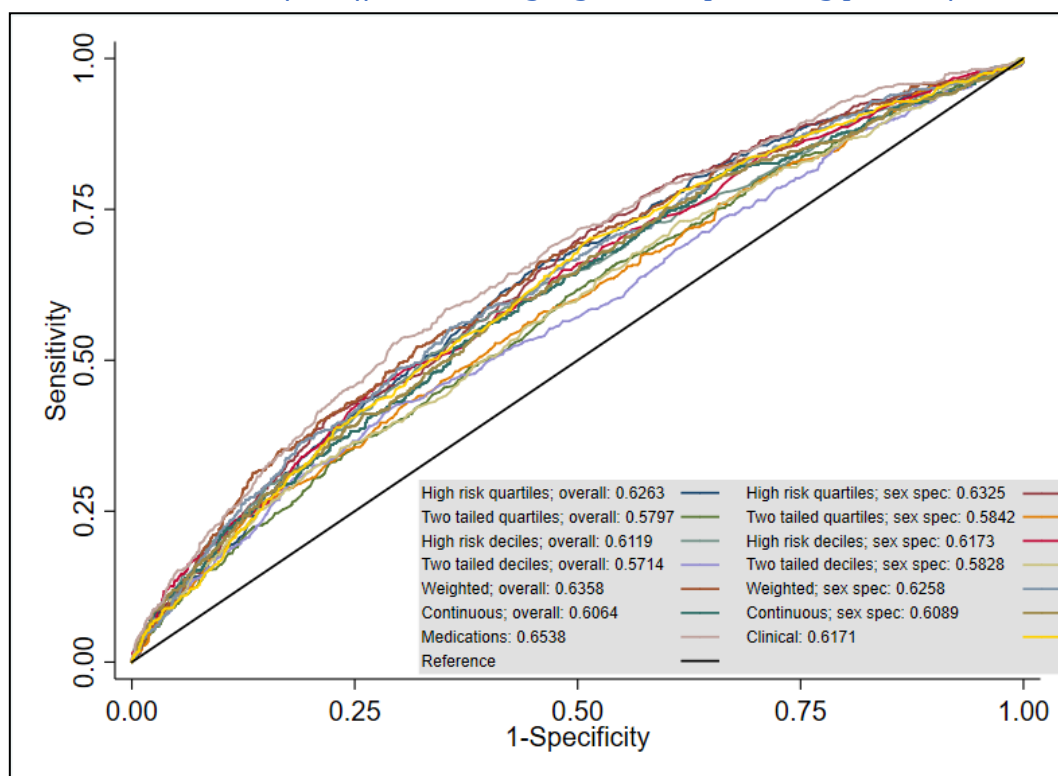
Note: this figure was published in McLoughlin et al., (2020)

Figure 3.2: AUC estimates for different scoring algorithms, predicting weak grip strength



Note: this figure was published in McLoughlin et al., (2020)

Figure 3.3: AUC estimates for different scoring algorithms, predicting poor self-rated health



Note: this figure was published in McLoughlin et al., (2020)

3.6 Discussion

The present study assessed the explanatory utility of a multitude of AL scoring algorithms for predicting a number of objective and subjective age-related health outcomes in an older adult population residing in Ireland. In accordance with the findings from a previous study involving a Taiwanese sample ¹⁴¹, we found that the choice of AL scoring algorithm has a relatively modest impact in terms of variance explanation and classification accuracy in the prediction of a number of important health outcomes. Although the differences between the 14 scoring algorithms were not pronounced in this study, there were, nevertheless, some subtle nuances observed.

AL was strongly associated with walking speed across all 14 scoring algorithms independently of age and sex, supporting prior findings regarding the predictive utility of AL for functional decline

^{37,140,146,172}. Although the differences were small when compared to the classic scoring algorithm, the count of high-risk quartiles incorporating medications performed marginally better. In contrast, few significant associations were observed between measures of AL and grip strength, and no algorithm fit the data significantly better than the classic method. Although few have investigated this relationship directly, grip strength shows strong age-related decline and is an important component of many frailty indices that have been found to be negatively associated with AL ^{115,140}. The null associations of the majority of AL scoring algorithms, and the varied direction of the relationship noted for those algorithms which did statistically predict grip strength is surprising, but not without precedent. Freire et al. (2020) for example, arrived at the rather counter-intuitive conclusion that higher AL burden (classic measure) was associated with higher grip strength in a small sample of older community-dwelling adults in Brazil (n=256), yet they hypothesised this contradictory result was due to survival bias ¹⁵³. Perhaps the predominantly null results arise as there are other potential confounders that we are not controlling for in this analysis, which may help preserve muscle strength at older ages (e.g., height, occupational class etc).

In respect of SRH, results were more variable across scoring algorithms, although differences were small in absolute terms. Similar to walking speed, the algorithm incorporating medication use was the best predictor of SRH in terms of model fit. This pattern of results begs the obvious question as to whether the better predictive performance of a measure incorporating medication when using a SRH measure is simply a reflection of the individual being more aware of their “*health state*” by virtue of consciously taking prescribed medications on a regular basis.

3.6.1 Use of one vs two-tailed risk

Notably, the AL scoring algorithms incorporating risk in both tails of the distribution of each biomarker underperformed relative to the classic one-tailed measure in this study. These findings align with results from the Hawaii Personality and Health Cohort (n=470), where two-tailed measures of AL were less effective than one-tailed measures in predicting SRH and depressive symptoms. In stark contrast, however, Seplaki et al. (2005) found that two-tailed measures of risk accounted for more variance across self-reported health measures than the classic AL index. This discrepant pattern of results across studies could be explained by differences in the biomarker panels employed to represent AL. Seplaki et al.'s (2005) study included primary mediators of the stress response such as cortisol, in which both high and low values can characterise certain syndromes and diseases¹⁸⁸, whereas, similar to the present study, Hampson et al. (2019) did not include any markers of neuroendocrine dysregulation. Moreover, in the context of the current study, it is difficult to see how low scores for HbA1c or cystatin C would increase risk of disease, which reinforces the need to think critically about whether risk on particular biomarkers is best conceptualised as linear or curvilinear when developing AL indices.

3.6.2 The importance of considering sex differences

Beyond the objective of comparing the predictive utility of various AL algorithms, this study found significant differences across mean biomarker values between male and female individuals. Furthermore, the AL algorithms which were calibrated relative to sex generally performed marginally better in terms of model fit than those derived from the pooled sample with respect to walking speed and SRH. Acknowledging that men and women may react differently to stress, both psychologically and biologically¹⁸⁹; we recommend that future investigations continue to examine the use of sex-specific cut-points, particularly where the distributions on the component biomarkers

differ according to sex, or indeed, where there might be large sex differences ¹⁹⁰, in the outcome measure (e.g., depression).

3.6.3 The importance of considering medications

The vexed question of whether to include medications in the calculation of the AL measure is a recurring feature in many critiques of the AL literature ^{73,161,191}. This issue has not always been afforded the attention it arguably deserves in many empirical studies, presumably because many studies either do not capture this information, rely on self-report, or perhaps due to operational difficulties in how to treat the data if using continuous measures (e.g., z-scores). We found that including medications led to small improvements in performance relative to the classic measure with respect to walking speed and SRH. It was also the algorithm which was most strongly correlated with age. Nevertheless, we applied only one of a number of potential techniques for including medications in the development of the AL index, and future studies may wish to consider alternative approaches such as including medications as a covariate ¹⁶⁵, or adjusting biomarker values upward to adjust for their deflationary effect on the biomarker of interest ¹⁶⁶.

3.7 Strengths and limitations

This study is among the first to examine and compare the effects of various AL scoring algorithms in a community-dwelling cohort of older persons. It benefits from having a large sample pulled from a nationally representative cohort, and gold standard measures of objective physiological functioning measured using trained nurses according to standard operating protocols. It advances the current knowledge base through the inclusion of these objective markers of physical fitness, by considering sex as an important variable in the determination of AL scores, and by accounting for medication use as a potential indicator of physiological wear and tear. Despite these strengths, this study does not

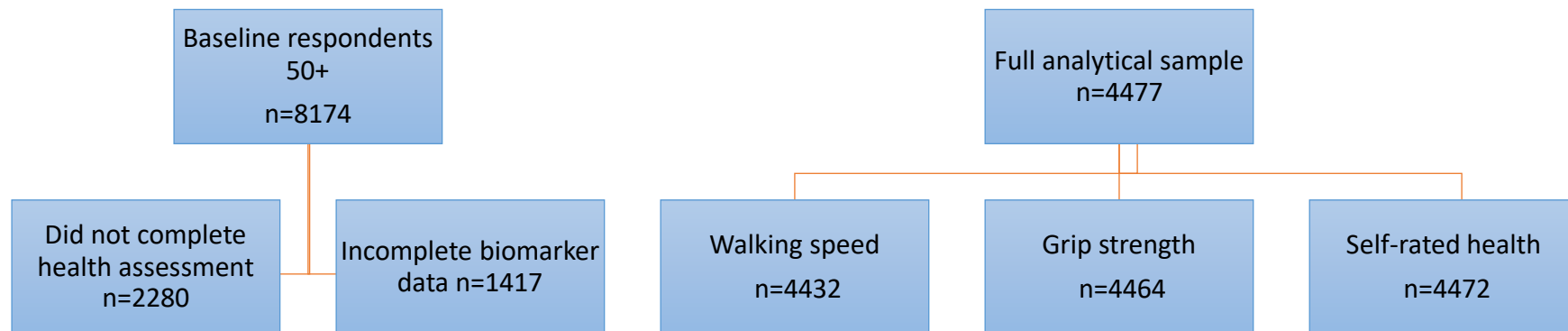
have any neuroendocrine markers at baseline which is an important limitation as they are hypothesised to play a central role in the stress response. Furthermore, whilst TILDA is a nationally representative cohort study, the sample employed in this paper is not generalisable to other populations. Similarly, the results from this study are not generalisable to studies employing biomarkers different to those used here. It should also be acknowledged that although significant associations were found between measures of AL and objective health outcomes in this study, the estimated models control only for the effects of age and sex. Instead, this study provides evidence for the construction of a summary score from individual biological components to predict poor health outcomes, without assuming a causal or directional relationship.

3.8 Conclusion

This study was motivated by the lack of empirical insight into the effects the choice of AL scoring algorithm has on the predictive utility of poor health outcomes. Seeman et al. (2010) claimed that their original method did not represent a gold standard, yet the results of this study suggest that this classic method performs well. We therefore echo the conclusion of others^{150,192}, and recommend that given that this is the technique used in the vast majority of papers, perhaps the notion of harmonising international work around this scoring algorithm should be considered. Nonetheless, the findings of this paper can help allay researchers concerns that the choice of scoring algorithm makes a large difference to the results, as associations of 14 measures of AL with two objective age-related health outcomes, and one subjective measure, did not vary substantially. These findings were supported by little differences across model fit statistics across models. However, whether the composition of biomarkers employed to reflect physiological dysregulation does remains to be elucidated.

CHAPTER 3 SUPPLEMENTARY MATERIAL

Supplementary Figure 3.1: Sample flow chart



Note: This figure was published in McLoughlin et al., (2020)

Supplementary Table 3.1: Biomarker panel

Biomarker	Acronym	Physiological function	System
Systolic blood pressure (mm Hg)	SBP	Measure of pressure when the heart pumps	Cardiovascular
Diastolic blood pressure (mm Hg)	DBP	Measure of pressure when the heart at rest	Cardiovascular
Pulse wave velocity	PWV	Measure of atherosclerosis	Cardiovascular
Resting heart rate	RHR	Number of palpitations made by the heart in a period of time	Cardiovascular
Wait hip ratio (cm)	WHR	Measure of central fat	Metabolic
Body mass index (kg/m ²)	BMI	Measure of lean fat mass	Metabolic
Glycated haemoglobin (mmol/mol)	HbA1c	Glucose metabolism	Metabolic
Total cholesterol (mmol/L)	TChol	Arteriole substance that contributes to development of plaques	Metabolic
HDL cholesterol (mmol/L)	HDL	Good cholesterol	Metabolic
Creatinine (umol/L)	Crea	Waste product from breakdown of muscle	Renal
Cystatin C (mg/L)	Cysc	Small protein produced by cells in the body	Renal
C-reactive protein (mg/L)	CRP	Acute phase inflammatory protein	Immune

Note: this figure was published in McLoughlin et al., (2020)

Supplementary Table 3.2: Clinically defined risk cut-points for each biomarker

Biomarker	Cut-point	Reference	
Systolic blood pressure (mm Hg)	≥ 140	(Chobanian et al., 2003)	193
Diastolic blood pressure (mm Hg)	≥ 90	(Chobanian et al., 2003)	193
Pulse wave velocity	≥ 12	(Mancia et al., 2013)	194
Resting heart rate	≥ 90	(Chobanian et al., 2003)	193
Waist hip ratio (cm)	≥ 1.00 for men, ≥ 0.9 for women	(World Health Organisation, 2011)	195
Body mass index (kg/m ²)	≥ 30	(World Health Organisation, 2020)	196
Glycated haemoglobin (mmol/mol)	≥ 48	(National Medicines Information Centre, 2012)	197
Total cholesterol (mmol/L)	≥ 6.2	(Expert Panel on Detection and Treatment of High Blood Cholesterol in Adults, 2001)	198
HDL cholesterol (mmol/L)	≤ 1 for men, ≤ 1.3 for women	(Expert Panel on Detection and Treatment of High Blood Cholesterol in Adults, 2001)	198
Creatinine (umol/L)	$<45 / \geq 90$	(Donnelly et al., 2014)	199
Cystatin C (mg/L)	≥ 1.55	(Brown et al., 2018)	200
C-reactive protein (mg/L)	≥ 3	(Ridker, 2003)	201

Note: this figure was published in McLoughlin et al., (2020)

Supplementary Table 3.3: Correlations between the AL scoring algorithms and age

AL scoring algorithm	Correlation
High-risk quartiles	
Overall	0.2670***
Sex-specific	0.2762***
Two-tailed quartiles	
Overall	0.0512***
Sex-specific	0.0628***
High-risk deciles	
Overall	0.2223***
Sex-specific	0.2182***
Two-tailed deciles	
Overall	0.0589***
Sex-specific	0.0554***
System weighted	
Overall	0.2651***
Sex-specific	0.2986***
Continuous	
Overall	0.2581***
Sex-specific	0.2727***
Medications	0.3423***
Clinical	0.2267***

*Note: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. This figure was published in McLoughlin et al., (2020)*

Supplementary Table 3.4: Distributional statistics for each AL scoring algorithm (n = 4477)

	Mean	SD	Min	25th p	Median	75th p	Max
High-risk quartiles							
Overall	2.89	2.08	0.00	1.00	3.00	4.00	10.00
Sex-specific	2.91	2.07	0.00	1.00	3.00	4.00	10.00
Two-tailed quartiles							
Overall	6.08	1.96	0.00	5.00	6.00	7.00	12.00
Sex-specific	6.10	1.96	0.00	5.00	6.00	7.00	12.00
High-risk deciles							
Overall	1.16	1.35	0.00	0.00	1.00	2.00	8.00
Sex-specific	1.16	1.36	0.00	0.00	1.00	2.00	8.00
Two-tailed deciles							
Overall	2.63	1.70	0.00	1.00	2.00	4.00	9.00
Sex-specific	2.64	1.70	0.00	1.00	2.00	4.00	10.00
System weighted							
Overall	0.97	0.78	0.00	0.25	0.85	1.45	3.60
Sex-specific	0.97	0.81	0.00	0.25	0.85	1.45	3.80
Continuous							
Overall	0.00	5.41	-14.75	-3.42	-0.26	3.27	41.89
Sex-specific	0.00	5.28	-15.82	-3.42	-0.29	2.95	37.28
Medications	3.48	2.35	0.00	2.00	3.00	5.00	11.00
Clinical	2.27	1.73	0.00	1.00	2.00	3.00	9.00

Note: this figure was published in McLoughlin et al., (2020)

Supplementary Table 3.5: Area Under the Curve and associated 95% confidence intervals for different AL scoring algorithms in predicting poor health outcomes

	Walking speed (n= 4432)			Grip strength (n = 4494)			SRH (n = 4472)		
	AUC	95% CI	Diff AUC	AUC	95% CI	Diff AUC	AUC	95% CI	Diff AUC
High-risk quartiles									
Overall	0.759	0.74-0.78	REF	0.667	0.65-0.68	REF	0.626	0.60-0.65	REF
Sex-specific	0.761	0.74-0.78	0.003	0.667	0.65-0.68	0.000	0.633	0.61-0.66	0.007
Two-tailed quartiles									
Overall	0.739	0.72-0.76	-0.020***	0.667	0.65-0.68	0.000	0.580	0.55-0.61	-0.046***
Sex-specific	0.741	0.72-0.76	-0.018***	0.667	0.65-0.68	0.000	0.584	0.56-0.61	-0.042**
High-risk deciles									
Overall	0.753	0.73-0.77	-0.006	0.667	0.65-0.68	0.000	0.612	0.59-0.64	-0.014
Sex-specific	0.754	0.74-0.77	-0.005	0.667	0.65-0.68	0.000	0.617	0.59-0.64	-0.009
Two-tailed deciles									
Overall	0.737	0.72-0.76	-0.022***	0.668	0.65-0.68	0.001	0.571	0.54-0.60	-0.055***
Sex-specific	0.737	0.72-0.76	-0.022***	0.668	0.65-0.68	0.001	0.583	0.56-0.61	-0.043**
System weighted									
Overall	0.759	0.74-0.78	0.000	0.667	0.65-0.68	0.000	0.636	0.61-0.66	0.010
Sex-specific	0.760	0.74-0.78	0.001	0.667	0.65-0.68	0.000	0.626	0.60-0.65	0.000
Continuous									
Overall	0.757	0.74-0.78	-0.002	0.668	0.65-0.68	0.001	0.606	0.58-0.64	-0.020*
Sex-specific	0.758	0.74-0.78	-0.001	0.668	0.65-0.68	0.001	0.609	0.58-0.64	-0.017
Medications	0.762	0.74-0.78	0.003*	0.667	0.65-0.68	0.000	0.654	0.63-0.68	0.028***
Clinical	0.753	0.74-0.77	-0.006*	0.668	0.65-0.68	0.001	0.617	0.59-0.64	-0.009**

Note: Adjusted for age and sex. 95% CI: 95% Confidence intervals. AUC: Area under the receiver operating curve. Diff AUC: gain in AUC compared with the classic AL scoring algorithm. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ significantly different from the classic AL scoring algorithm. This figure was published in McLoughlin et al., (2020)

Chapter 4: Psychosocial adversity and Allostatic Load burden in Mid-Life and Older Ages

Chapter summary

Objective: To investigate the individual and cumulative impact of childhood and adulthood adversity on Allostatic Load (AL) burden.

Methods: Retrospective cross-sectional study design data came from 4165 participants from the first wave of The Irish Longitudinal Study on Ageing (TILDA). AL was operationalised using 12 biomarkers across four physiological systems (cardiovascular, metabolic, renal, and immune). Measures of psychosocial adversity included poverty, abuse, loss, and illness. Negative binomial regression models estimated the relationship of individual adversities and a cumulative count of adversities with AL burden, controlling for age and sex. Multivariable models adjusted additionally for a range of other socio-demographic and lifestyle factors.

Results: Childhood physical abuse, childhood poverty, and having a spouse/partner/child experience a life-threatening illness/ accident were associated with 10% [95% CI= 1.04, 1.16], 9% [95% CI= 1.01, 1.18], and 6% [95% CI= 1.01, 1.12] greater AL burden respectively. Cumulative adversity was associated with 3% [95% CI= 1.01, 1.05] higher AL burden. Adjusting for socio-demographic and lifestyle covariates rendered the association of childhood poverty [IRR= 1.04, 95% CI= 0.98, 1.09; $p= .172$] and childhood physical abuse [IRR= 1.06, 95% CI= 0.99, 1.15; $p=0.118$] with AL burden non-significant, while the association of having an ill spouse/partner/child on AL persisted [IRR= 1.06, 95% CI= 1.01, 1.12; $p= 0.015$].

Conclusions: This study provided limited support for the idea that psychosocial stress leads to higher AL, with just 3/11 adversities associated with AL.

CHAPTER 4: PUBLISHED WORK LIST

This paper was published in *Health Psychology*:

McLoughlin, S., Kenny, R. A., & McCrory, C. (2021). Psychosocial adversity and allostatic load burden in midlife and older ages. *Health Psychology, 40*(7), 468–471.

<https://doi.org/10.1037/hea0001098>.

The following tables and figures were published as part of this paper:

- Figure 4.1: Independent association of each adversity type with AL in the minimally (A) and full multivariable (B) adjusted models
- Supplementary Figure 4.1: Sample flow chart
- Supplementary Table 4.1: Sample characteristics
- Supplementary Table 4.2: Prevalence of adverse events, and rates of missing cases
- Supplementary Table 4.3: Independent and multivariable adjusted associations of each adversity type with Allostatic Load (n= 4477)
- Supplementary Table 4.4: Independent and multivariable adjusted associations of each adversity type with Allostatic Load, derived from clinical cut points (n= 4477)
- Supplementary Table 4.6: Independent and multivariate associations of each adversity type and Allostatic Load on non-imputed data

4.1 Introduction

Trauma, maltreatment, and socio-economic adversity are all recognised as having a profound impact on risk of chronic disease ²⁰² and accelerated ageing ²⁰³. Although the mechanisms underlying this relationship remain to be fully elucidated, the Allostatic Load (AL) framework represents a plausible biological intermediary between psychosocial stress exposure and health. Whilst stress is known to protect under acute circumstances, repeated or chronic activation of the stress response may lead to physiological “*wear and tear*”, predisposing an individual to disease ⁴³. Nevertheless, research to date has not been conclusive in establishing that major repeated or prolonged exposure to adverse events leads to higher burden of AL in later life. While AL is conceptualised within a life course framework, studies linking adverse experiences with dysregulation have mainly focused on isolated life stages ^{38,204,205}, or specific life events ^{65,206}. Furthermore, early life may represent a critical period for the development of stress-response systems ²⁰⁷, but many studies do not include data on childhood adversities when assessing the cumulative impact of psychosocial adversity on AL.

Further scrutiny of the relative impact of individual adversities on AL burden, in lieu of the commonly employed crude counts of adversities, is warranted. This is suggested by the heterogeneity of findings across studies examining the association of isolated adverse events and AL. For example, work stress, financial strain, relationship stress and caregiving stress were positively associated with AL in a sample of Mexican-American women, yet no association was reported between health, housing, or relationship stress and AL ²⁰⁶. The purpose of this study was to examine the relationship of childhood and adulthood adversities with AL. We hypothesise that the experience of these stressors will be positively correlated with AL at mid-life and older ages.

4.2 Methods

4.2.1 Data

This analysis uses data from the first wave (2009-2011) of The Irish Longitudinal Study on Ageing (TILDA), a nationally representative prospective study of over 8,175 persons aged 50+ and their spouses living in the Republic of Ireland. Information on the sampling frame, study design and methods of data collection are described in detail elsewhere ¹³³. Standard errors of estimates were adjusted to account for the clustered design effect and stratification, and data were weighted using survey weights to account for the fact that respondents who attended the health centre were younger, better educated, and in better health. Ethical approval for the study was provided by the Faculty of Health Science Research Ethics board in Trinity College Dublin, while informed consent was obtained from all respondents during data collection.

4.2.2 Measures

4.2.2.1 *Allostatic Load*

Twelve biomarkers were used to create the summary AL index encompassing 4 physiological systems ²⁰⁸. This includes *the cardiovascular system*; systolic blood pressure, diastolic blood pressure, resting heart rate, pulse wave velocity, *the metabolic system*; waist-hip ratio, body mass index, glycosylated haemoglobin, high-density lipoprotein, total cholesterol, *the renal system*; creatinine, Cystatin-C, and the *immune system*; C-reactive protein. Log transformations were applied to C-reactive protein and pulse wave velocity to account for right-skewed distributions, and high-density lipoprotein was reverse coded such that higher values represented increased risk. Empirically defined high-risk thresholds were distinguished based on the distribution of that biomarker in the sample, separately for men and women. Biomarkers were dichotomised at the 75th percentile of risk and summed to create an index (range = 0-12) with higher scores reflecting higher AL.

4.2.2.2 *Psychosocial stressors*

Items adapted from the lifetime trauma list and administered as part of a self-completion questionnaire (SCQ) ²⁰⁹ were used to retrospectively measure adverse events experienced in childhood (i.e. parental alcohol/drug issues, physical abuse, sexual abuse and death of a parent) and adulthood (i.e. experience of a fire/flood or natural disaster, spouse/ child drug addiction, serious assault, personal life threatening illness, familial life threatening illness, and death of a child). These variables were coded 'no' / 'yes'. In addition, a subjectively measured question was included relating to the circumstances of the household prior to the age of 14, on a three-point scale; pretty well off financially, about average, and poor, represented as a binary variable (not poor/ poor). Cumulative counts, often preferred as they take account of the fact that adversities frequently co-occur, were calculated by summing the number of adversities reported, separately for childhood events (0-5) and adulthood events (0-6), as well as overall exposure (0-11).

4.2.2.3 *Covariates*

Covariates were chosen on the basis of their association with adversity and AL in the literature. Any association between the experience of an adverse event and AL could be due to common correlation with demographic or lifestyle factors. We therefore undertook a covariate analysis to help understand the potential life course pathways through which the experience of adversity leads to higher AL burden. Education was chosen as AL is highly patterned by SEP ¹⁰⁹. Educational attainment was represented as a three-level variable: primary education or less, secondary education, tertiary education. Risky health behaviours have been implicated as a potential mechanism for how adversities can impact AL burden ²⁶. The respondent's smoking status was captured using pack years, which was calculated via number of daily smoked / 20, *years of smoking. Problematic alcohol consumption was measured using the CAGE screening test ²¹⁰, where <2 items indicates a clinically significant profile ²¹¹. The scale comprises four items and follows a dichotomous yes/no response format, captured in the self-completion questionnaire. Answering yes

to two or more questions indicates a clinically significant profile and constitutes potentially hazardous drinking. The instrument has a sensitivity of 93% and a specificity of 76% for identification of problematic drinking ²¹². Physical activity was assessed using the 8-item International Physical Activity Questionnaire (IPAQ) ²¹³, which measures the amount of time spent walking and engaged in moderate and vigorous physical activity, and the amount of time spent sedentary. This information was used to derive a categorical variable for analysis representing low, medium, and high levels of physical activity using the International Physical Activity Questionnaire protocol (www.ipaq.ki.se). Respondents were asked to report all income resulting from full or part-time employment, private or public pensions, and income from other social welfare transfers. As income is heavily skewed, we use log income in this analysis. Social connectedness was indexed using the 4 item Berkman-Syme Social Network Index (SNI) ²¹⁴ derived from marital status; sociability (number and frequency of contacts with children, close relatives, and close friends); church group membership and membership in other community organizations. The SNI score is categorical, and ranges from 1 (low social connectedness) to 4 (high social connectedness).

4.2.3 Analytical approach

To reduce any potential bias arising from item non-response, we imputed for individuals missing on any of the individual adversity components and for whom we had an AL score. As the outcome variable (AL) was zero inflated and over dispersed (mean= 2.9, variance= 4.3), we modelled the association of each adversity type with AL using negative binomial regression. Unstandardised coefficients were exponentiated and reported as incidence rate ratios (IRR), which can be interpreted as the percentage change in AL associated with the experience of each adversity type. In the base models we adjust for age and sex (Model 1) as the experience of adversity may differ between age cohorts and sexes. In secondary models we adjust additionally for a broader set of socio-demographic and lifestyle factors using hierarchical entry of covariates, with variables entered with

respect to their approximate temporal experience across the life course. Even though it is not possible to unequivocally establish relative timing for most of these variables as they were measured contemporaneously, nor are they seen as a complete set of putative covariates, it might still be informative to examine the degree to which their common correlation attenuates the association of adversity with AL in an exploratory way to help inform future hypothesis generation. Covariates include: educational attainment (primary, secondary, tertiary) (Model 2) smoking pack years, problematic alcohol consumption, which was measured using the 4-item CAGE, and physical activity (low, medium, high) which was assessed using the 8-item International Physical Activity Questionnaire (Model 3). Respondents were asked to report all income resulting from full or part-time employment, private or public pensions, and income from other social welfare transfers. As income is heavily skewed, we use log income in this analysis (Model 4). Social connectedness was indexed using the 4-item Berkman-Syme Social Network Index (SNI) (Model 5). All analyses were conducted in Stata v.15 ¹³⁶, using TILDA dataset v.1.8.0.

4.2.4 Missing cases

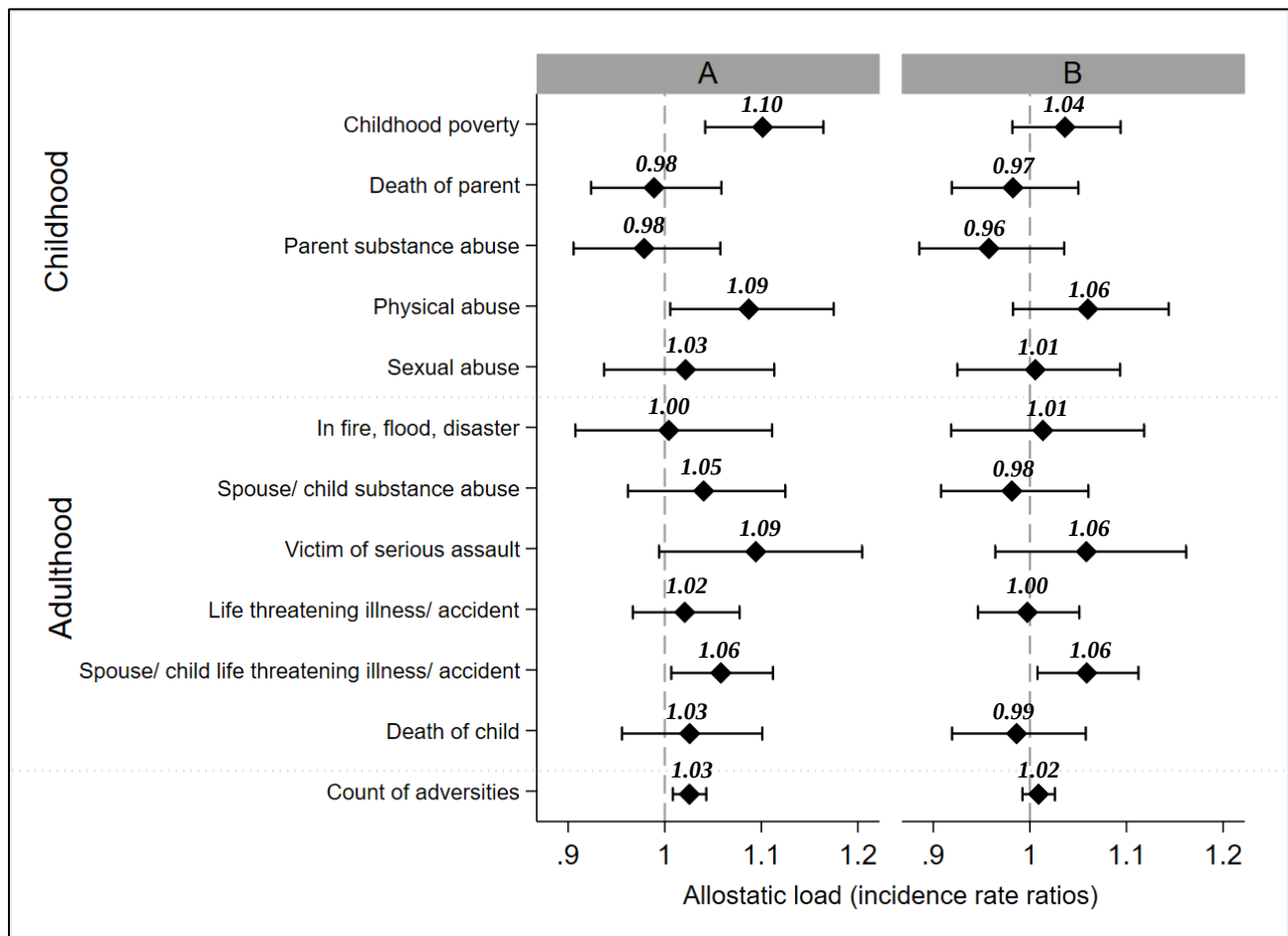
6914 respondents (84.6%) returned the SCQ and form the initial case base for the analysis. Further exclusions included 2248 respondents who did not take part in the nurse led health assessment, and 501 missing on one or more of the AL biomarkers (Supplementary Table 4.1). Full biomarker data was available for 4165 participants. The percentage of cases for which we imputed on any individual adversity ranged from 0.2% to 5.9% (Supplementary Table 4.2). Multiple imputation by chained equations was conducted to estimate missing values based on observed information, assuming all data were missing at random. The imputation model included all variables used in the final analysis, including those chosen based on prior knowledge of associations with psychosocial adversity, including the socio-demographic and lifestyle variables described in the supplementary material. A total of 20 datasets were imputed with random seed to facilitate replication.

4.3 Results

Supplementary Table 4.1 reports the sample characteristics; mean age of participants was 61.7 years (SD= 8.6), and 49.1% were male. Average AL was 3.0 (SD= 2.1). Supplementary Table 4.2 reports the number of cases and survey weighted prevalence for each adversity type. Figure 4.1A displays the age and sex adjusted independent association of each adversity type with AL, while Figure 4.1B reports the full multivariable adjusted estimates. In the base models (Supplementary Table 4.3, Model 1), participants who reported childhood poverty had significantly higher AL burden [IRR= 1.10, 95% CI= 1.04, 1.16; $p= 0.001$], as did those who reported childhood physical abuse [IRR= 1.09, 95% CI= 1.01, 1.18; $p= 0.026$]. Participants who reported having an ill spouse or child had a 6% higher AL burden [IRR= 1.06, 95% CI= 1.01, 1.12; $p= 0.026$]. No other individual adversity was significantly associated with AL. The cumulative count of psychosocial adversities was associated with a 3% increase in AL burden [IRR= 1.03, 95% CI= 1.01, 1.05; $p= 0.003$]. The inclusion of all covariates rendered the association of childhood poverty [IRR= 1.04, 95% CI= 0.98, 1.09; $p= 0.172$] and childhood physical abuse [IRR= 1.06, 95% CI= 0.99, 1.15; $p= 0.118$] with AL burden non-significant, while the association of having an ill spouse/partner/child with AL persisted [IRR= 1.06, 95% CI= 1.01, 1.12; $p= 0.015$] (Supplementary Table 4.3, Model 5).

As a sensitivity check, analyses were repeated using clinical cut-points as opposed to high-risk thresholds, but results were not appreciably different (Supplementary Table 4.4). However, when measures of parasympathetic functioning were included, which were available for a subset of participants, being a victim of serious assault was now associated with higher AL burden in the base but not the multivariable adjusted models (Supplementary Table 4.6 **Error! Reference source not found.**).

Figure 4.1: Independent association of each adversity type with AL in the minimally (A) and full multivariable (B) adjusted models



Note: Model A adjusts for age and sex. Model B = Model A + education, lifestyle factors (alcohol abuse, smoking pack years and physical activity), income, social network index. This figure was published in McLoughlin et al., (2021)

4.4 Discussion

This study examined the association of a number of childhood and adulthood adversities with AL in a large, community-based sample of older Irish adults. We found that the experience of adversity is common throughout life, with 66.7% experiencing at least one adversity; however, only 3/11 adversities (childhood poverty, childhood physical abuse and reporting that your spouse/partner/child experienced a serious or life-threatening illness or accident) were associated with higher AL, albeit merely a select few from the spectrum of adversities that could be experienced by a person during their lifetime. These findings elicit the obvious question as to why we observe linkages between

some adversity types and higher AL burden but not others. Although the majority of associations were in the positive direction, most adversities examined in this study were not significantly related to AL burden. It could be conceded that these null findings may result from crude measurement of the exposure (never vs. ever), which fails to capture variation in the timing, duration, or severity of the event, which would be expected to moderate the impact of the stressor on AL burden. There may also be respondent censoring of responses to some of the items, such as the experience of childhood sexual abuse. Moreover, the lack of correlation between many of the adulthood adversities and AL may arise because these exposures occur ‘more proximal’ in time to the measurement of AL, and the biological consequences of exposure may only appear with a lag. In accordance with the simplistic “*multiple matter*” paradigm ²¹⁵, cumulative adversity was positively associated with greater physiological dysregulation, with each additional adversity contributing to an 3% increase in AL. However, the addition of a number of socio-demographic and behavioural factors attenuated the relationship of childhood poverty, childhood physical abuse and cumulative adversity with AL burden, indicating potential pathways whereby exposure to psychosocial adversity becomes biologically embedded.

Strengths include the fact that the sample was drawn from a large nationally representative sample of the community-dwelling older population of Ireland and included a number of different measures of adversity in childhood and adulthood. Limitations include the fact that the adverse events were retrospectively reported and subject to recall bias. In addition, the AL measure may be less sensitive for capturing the direct effects of HPA-axis and SAM dysregulation as it does not include measures of the ‘primary mediators’ in McEwen’s and Seeman’s parlance ²¹⁶.

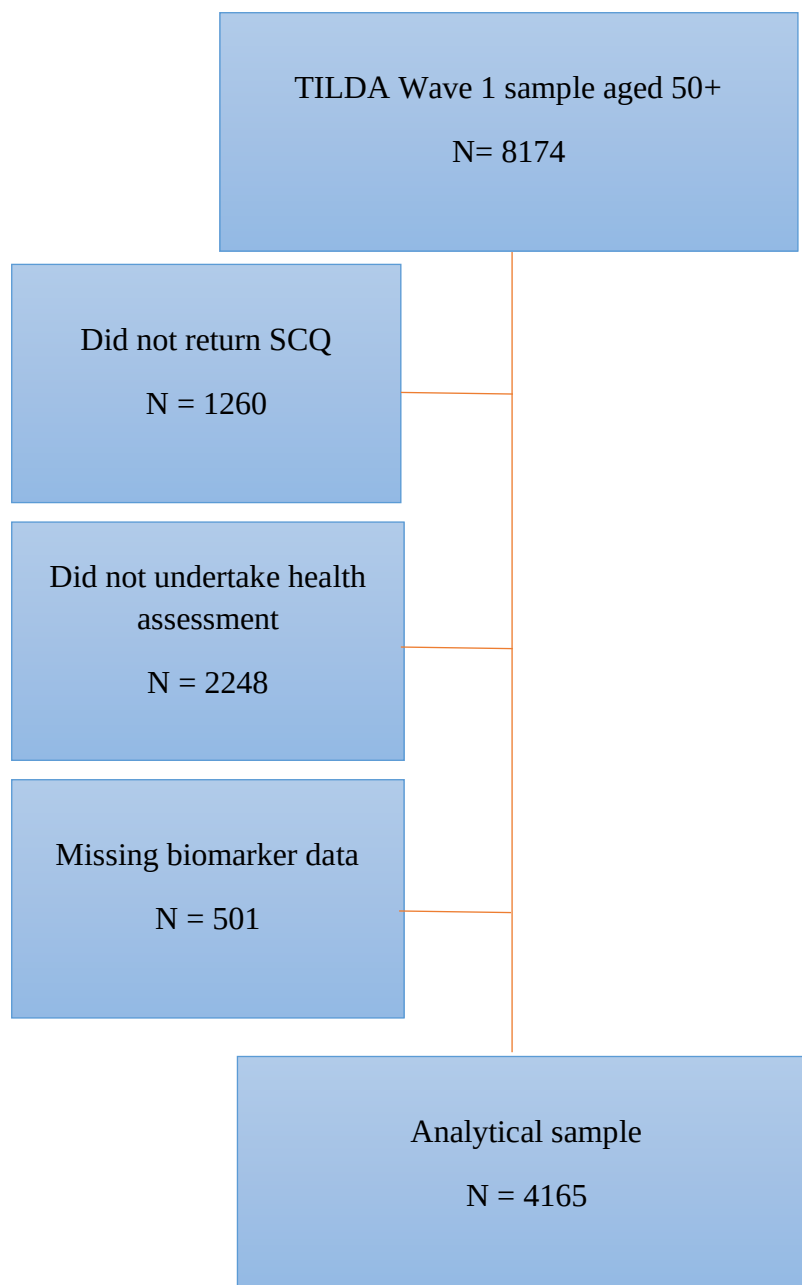
4.5 Conclusion

Overall, this study provides rather limited support for the idea that psychosocial stress causes physiological dysregulation, at least as indexed using the measure of AL as defined in this study.

Future work should seek to broaden the variety and type of adverse events examined in the context of AL and go beyond simple dichotomies of ever vs never exposed to develop a more nuanced understanding of how timing, duration, and severity impact upon one's biological health in the long run.

CHAPTER 4: SUPPLEMENTARY MATERIAL

Supplementary Figure 4.1: Sample flow chart



Note: This figure was published in McLoughlin et al., (2021)

Supplementary Table 4.1: Sample characteristics

Variable	Sample (4165)		Missing (3697)	
	n	% (mean)	n	% (mean)
Age	4165	(61.7)	3697	(66.7)
Gender				
Male	1913	49.1	1673	46.3
Female	2252	50.9	2024	53.7
Allostatic Load		(3.0)		-
Marital status				
Married	3203	77.5	2215	58.0
Not married	565	12.8	723	19.6
Widowed	397	9.65	759	22.5
Education				
Primary	868	30.6	1545	50.2
Secondary	1760	47.3	1381	37.6
Tertiary	1536	22.0	768	12.2
Missing	1	0.02	3	0.07
Smoking pack years		(13.7)		(16.9)
Problematic drinker				
Yes	574	14.3	240	8.81
Missing	90	2.3	1015	27.5
Physical activity level				
Low	1212	27.3	1384	38.7
Medium	1509	35.4	1177	31.0
High	1502	36.5	1091	29.1
Missing	33	0.8	45	1.25
Subjective health (contemporaneous)				
Excellent / very good	2491	57.5	1798	47.3
Good	1225	30.6	1124	30.7
Fair / poor	445	11.8	766	21.8
Missing	4	0.1	9	0.26

Note: unweighted n, and weighted % are shown. This table was published in McLoughlin et al., (2021)

Supplementary Table 4.2: Prevalence of adverse events, and rates of missing cases

Variable	Adversity experienced		Missing	
	n	%	n	%
Childhood				
Childhood poverty	828	22.6	6	0.2
Death of parent	558	14.7	213	5.9
Parental substance abuse	424	10.0	83	2.2
Physical abuse	344	7.9	2	0.03
Sexual abuse	312	6.9	68	2.7
Adulthood				
Natural disaster	191	4.4	83	2.0
Spouse/ child addicted	326	8.0	167	4.1
Victim of serious assault	245	6.2	106	2.8
Life threatening illness/ accident	758	18.4	93	2.3
Spouse/ child life threatening illness/ accident	958	23.4	176	4.5
Death of child	403	11.0	183	4.5
Childhood adversities			95	2.3
0	2682	56.4		
1	1026	30.0	-	-
2+	362	13.5		
Adulthood adversities			341	8.2
0	1997	53.1		
1	1193	30.4	-	-
2+	634	16.5		
Count of adversities			361	8.7
0	1385	31.3		
1	1263	33.7	-	-
2+	1156	35.1		

Note: unweighted n, and weighted % are shown. This table was published in McLoughlin et al., (2021)

Supplementary Table 4.3: Independent and multivariable adjusted associations of each adversity type with Allostatic Load (n= 4477)

	Model 1		Model 2		Model 3		Model 4		Model 5	
	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI
Childhood										
Childhood poverty	1.10***	(1.04, 1.16)	1.05	(1.00, 1.11)	1.04	(1.02, 1.02)	1.04	(0.98, 1.10)	1.04	(0.98, 1.09)
Death of parent	0.98	(0.92, 1.04)	0.97	(0.91, 1.03)	0.97	(0.91, 1.03)	0.97	(0.91, 1.03)	0.97	(0.91, 1.03)
Parent substance abuse	0.98	(0.91, 1.06)	0.98	(0.91, 1.06)	0.97	(0.89, 1.04)	0.97	(0.89, 1.04)	0.96	(0.89, 1.04)
Physical abuse	1.09*	(1.01, 1.18)	1.10*	(1.02, 1.19)	1.08	(1.00, 1.16)	1.08	(1.00, 1.16)	1.06	(0.99, 1.15)
Sexual abuse	1.03	(0.94, 1.12)	1.04	(0.96, 1.13)	1.02	(0.94, 1.11)	1.02	(0.94, 1.11)	1.01	(0.93, 1.10)
Adulthood										
In fire, flood, disaster	1.00	(0.90, 1.11)	1.02	(0.92, 1.13)	1.01	(0.92, 1.12)	1.01	(0.92, 1.12)	1.01	(0.92, 1.12)
Spouse, child addicted	1.05	(0.96, 1.13)	1.04	(0.96, 1.12)	1.00	(0.92, 1.08)	1.00	(0.92, 1.08)	0.98	(0.91, 1.06)
Victim of serious assault	1.09	(0.97, 1.22)	1.09	(0.99, 1.20)	1.07	(0.97, 1.18)	1.07	(0.97, 1.18)	1.06	(0.96, 1.17)
Life-threatening illness, accident	1.02	(0.97, 1.08)	1.02	(0.97, 1.08)	1.00	(0.95, 1.06)	1.00	(0.95, 1.06)	1.00	(0.95, 1.05)
Spouse/child life threat. illness, accident	1.06*	(1.01, 1.12)	1.06*	(1.01, 1.12)	1.06*	(1.01, 1.12)	1.06*	(1.01, 1.12)	1.06*	(1.01, 1.12)
Child died	1.03	(0.95, 1.12)	1.01	(0.94, 1.08)	1.00	(0.93, 1.07)	1.00	(0.93, 1.07)	0.99	(0.92, 1.07)
Count of adversities	1.03**	(1.01, 1.05)	1.03**	(1.01, 1.05)	1.02*	(1.00, 1.04)	1.01	(0.99, 1.03)	1.02	(1.00, 1.04)

Note: Model 1 = age and sex. Model 2 = Model 1 + education. Model 3 = Model 2 + lifestyle factors (alcohol abuse, smoking pack years and physical activity). Model 4 = Model 3 + income. Model 5 = Model 4 + social network index. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. This table was published in McLoughlin et al., (2021)

Supplementary Table 4.4: Independent and multivariable adjusted associations of each adversity type with Allostatic Load, derived from clinical cut points (n= 4477)

	Model 1		Model 2		Model 3		Model 4		Model 5	
	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI
Childhood										
Childhood poverty	1.12***	(1.05, 1.18)	1.07*	(1.01, 1.13)	1.06*	(1.00, 1.12)	1.06*	(1.00, 1.12)	1.06	(1.00, 1.12)
Death of parent	0.98	(0.92, 1.05)	0.97	(0.90, 1.04)	0.97	(0.91, 1.04)	0.97	(0.91, 1.04)	0.97	(0.91, 1.04)
Parent substance abuse	0.99	(0.91, 1.07)	0.99	(0.91, 1.07)	0.97	(0.90, 1.05)	0.97	(0.89, 1.05)	0.97	(0.89, 1.05)
Physical abuse	1.07	(0.98, 1.16)	1.08	(1.00, 1.17)	1.06	(0.98, 1.15)	1.06	(0.98, 1.15)	1.05	(0.97, 1.14)
Sexual abuse	1.02	(0.93, 1.12)	1.03	(0.94, 1.13)	1.01	(0.93, 1.11)	1.01	(0.93, 1.11)	1.01	(0.92, 1.10)
Adulthood										
Natural disaster	0.97	(0.87, 1.07)	0.99	(0.90, 1.09)	0.98	(0.89, 1.09)	0.98	(0.89, 1.09)	0.98	(0.89, 1.09)
Spouse/ child addicted	1.06	(0.97, 1.16)	1.05	(0.96, 1.14)	1.02	(0.93, 1.11)	1.02	(0.93, 1.11)	1.01	(0.93, 1.11)
Victim of serious assault	1.05	(0.94, 1.17)	1.04	(0.94, 1.15)	1.03	(0.92, 1.14)	1.02	(0.92, 1.14)	1.02	(0.91, 1.13)
Life threatening illness/ accident	0.99	(0.93, 1.05)	0.99	(0.93, 1.05)	0.97	(0.92, 1.04)	0.97	(0.92, 1.03)	0.97	(0.91, 1.03)
Spouse/ child life threatening illness/ accident	1.06*	(1.00, 1.12)	1.07*	(1.01, 1.12)	1.07*	(1.01, 1.12)	1.07*	(1.01, 1.12)	1.06*	(1.01, 1.12)
Death of child	1.05	(0.97, 1.13)	1.02	(0.94, 1.10)	1.01	(0.94, 1.10)	1.01	(0.94, 1.09)	1.01	(0.94, 1.09)
Count of adversities	1.02*	(1.00, 1.04)	1.02	(1.00, 1.04)	1.01	(0.99, 1.03)	1.01	(0.99, 1.03)	1.01	(0.99, 1.03)

Note: Model 1 = age and sex. Model 2 = Model 1 + education. Model 3 = Model 2 + lifestyle factors (alcohol abuse, smoking pack years and physical activity). Model 4 = Model 3 + income. Model 5 = Model 4 + social network index. *p<0.05, **p<0.01, ***p<0.001. Clinical cut points: Systolic blood pressure (mm Hg) ≥ 140 , Diastolic blood pressure (mm Hg) ≥ 90 , Pulse wave velocity ≥ 12 , Resting heart rate ≥ 90 , Waist hip ratio (cm) ≥ 1 , 00 for men, ≥ 0.9 for women, Body mass index (kg/m²) ≥ 30 , Glycated haemoglobin (mmol/mol) ≥ 48 , Total cholesterol (mmol/L) ≥ 6.2 , HDL cholesterol (mmol/L) ≤ 1 for men, ≤ 1.3 for women, Creatinine (umol/L) < 45 / ≥ 90 , Cystatin C (mg/L) ≥ 1.55 , C-reactive protein (mg/L) ≥ 3 . This table was published in McLoughlin et al., (2021)

Supplementary Table 4.5: Independent and multivariate associations of each adversity type and Allostatic Load, derived with additional markers of the parasympathetic system (n= 3672)

	Model 1		Model 2		Model 3		Model 4		Model 2	
	<i>IRR</i>	<i>95% CI</i>	<i>IRR</i>	<i>95% CI</i>	<i>IRR</i>	<i>95% CI</i>	<i>IRR</i>	<i>95% CI</i>	<i>IRR</i>	<i>95% CI</i>
Childhood										
Childhood poverty	1.11***	(1.04, 1.17)	1.06*	(1.00, 1.13)	1.05	(0.99, 1.12)	1.05	(0.99, 1.11)	1.05	(0.99, 1.11)
Death of parent	1.01	(0.94, 1.09)	1.00	(0.93, 1.08)	1.01	(0.93, 1.08)	1.00	(0.93, 1.08)	1.01	(0.94, 1.08)
Parent substance abuse	0.98	(0.89, 1.07)	0.98	(0.90, 1.07)	0.96	(0.88, 1.05)	0.96	(0.88, 1.05)	0.95	(0.87, 1.04)
Physical abuse	1.08	(0.99, 1.18)	1.09	(0.99, 1.19)	1.07	(0.97, 1.17)	1.07	(0.97, 1.17)	1.06	(0.96, 1.16)
Sexual abuse	1.00	(0.90, 1.11)	1.01	(0.91, 1.12)	0.99	(0.90, 1.09)	0.99	(0.89, 1.09)	0.98	(0.88, 1.08)
Adulthood										
Natural disaster	1.05	(0.94, 1.18)	1.07	(0.96, 1.20)	1.07	(0.95, 1.19)	1.07	(0.95, 1.19)	1.07	(0.95, 1.19)
Spouse/ child addicted	1.04	(0.94, 1.14)	1.03	(0.94, 1.12)	0.99	(0.91, 1.09)	0.99	(0.90, 1.08)	0.98	(0.89, 1.07)
Victim of serious assault	1.14*	(1.03, 1.26)	1.13*	(1.02, 1.25)	1.11*	(1.00, 1.23)	1.11	(1.00, 1.23)	1.10	(0.99, 1.21)
Life threatening illness/ accident	1.06	(0.99, 1.13)	1.06	(0.99, 1.13)	1.04	(0.98, 1.11)	1.04	(0.98, 1.11)	1.04	(0.97, 1.10)
Spouse/ child life threatening illness/ accident	1.05	(0.99, 1.11)	1.05	(1.00, 1.11)	1.06	(1.00, 1.12)	1.05	(1.00, 1.12)	1.05	(0.99, 1.11)
Death of child	1.03	(0.95, 1.11)	1.07	(0.93, 1.09)	0.99	(0.91, 1.07)	0.99	(0.91, 1.07)	0.98	(0.91, 1.07)
Count of adversities	1.03**	(1.01, 1.05)	1.03**	(1.01, 1.05)	1.02*	(1.00, 1.04)	1.02	(1.00, 1.04)	1.02	(1.00, 1.03)

*Note: Model 1 = age and sex. Model 2 = Model 1 + education. Model 3 = Model 2 + lifestyle factors (alcohol abuse, smoking pack years and physical activity). Model 4 = Model 3 + income. Model 5 = Model 4 + social network index. *p<0.05, ** p<0.01, ***p<0.001.*

Supplementary Table 4.6: Independent and multivariate associations of each adversity type and Allostatic Load on non-imputed data

	Model 1		Model 2		Model 3		Model 4		Model 5	
	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI
Childhood										
Childhood poverty	1.08*	(1.01, 1.15)	1.04	(0.97, 1.10)	1.01	(0.95, 1.07)	1.01	(0.95, 1.07)	1.01	(0.95, 1.07)
Death of parent	0.98	(0.91, 1.05)	0.97	(0.91, 1.04)	0.96	(0.90, 1.03)	0.96	(0.90, 1.03)	0.96	(0.89, 1.03)
Parent substance abuse	1.01	(0.94, 1.10)	1.01	(0.94, 1.10)	1.02	(0.94, 1.10)	1.02	(0.94, 1.10)	1.01	(0.93, 1.10)
Physical abuse	1.09	(1.00, 1.18)	1.09	(1.00, 1.19)	1.07	(0.98, 1.17)	1.07	(0.98, 1.17)	1.06	(0.97, 1.16)
Sexual abuse	0.96	(0.88, 1.06)	0.98	(0.89, 1.08)	0.97	(0.88, 1.07)	0.97	(0.88, 1.06)	0.96	(0.87, 1.06)
Adulthood										
Natural disaster	1.00	(0.89, 1.12)	1.02	(0.91, 1.15)	1.02	(0.91, 1.14)	1.02	(0.91, 1.15)	1.02	(0.91, 1.14)
Spouse/ child addicted	1.04	(0.96, 1.14)	1.04	(0.95, 1.13)	1.01	(0.92, 1.10)	1.00	(0.92, 1.10)	0.99	(0.91, 1.08)
Victim of serious assault	1.09	(0.97, 1.22)	1.09	(0.97, 1.22)	1.06	(0.95, 1.19)	1.06	(0.94, 1.19)	1.06	(0.94, 1.18)
Life threatening illness/ accident	1.02	(0.96, 1.08)	1.02	(0.97, 1.09)	1.01	(0.95, 1.07)	1.01	(0.95, 1.07)	1.01	(0.95, 1.07)
Spouse/ child life threatening illness/ accident	1.06*	(1.01, 1.12)	1.07*	(1.01, 1.12)	1.07*	(1.01, 1.13)	1.07*	(1.01, 1.13)	1.07*	(1.01, 1.13)
Death of child	1.03	(0.95, 1.12)	1.01	(0.93, 1.10)	1.01	(0.92, 1.09)	1.00	(0.92, 1.09)	1.00	(0.92, 1.09)
Count of adversities	1.03**	(1.01, 1.05)	1.02*	(1.00, 1.04)	1.02	(1.00, 1.04)	1.02	(0.99, 1.04)	1.01	(0.99, 1.03)

Note: Model 1 = age and sex. Model 2 = model 1 + education. Model 3 = model 2 + lifestyle factors (alcohol abuse, smoking pack years and physical activity). Model 4 = model 3 + income. Model 5 = model 4 + social network index. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. This table was published in McLoughlin et al., (2021)

Chapter 5: Intergenerational social mobility and allostatic load burden: a diagonal reference modelling approach

Chapter summary

Objectives: This study aims to understand the association of life course intergenerational social mobility with Allostatic Load burden in mid-life and older ages in Ireland.

Methods: The study involved biological data for 3,987 older adults participating in The Irish Longitudinal Study on Ageing (TILDA). Intergenerational social mobility was characterised using the cross-classification of origin socio-economic position (SEP) (i.e., father's occupation) and destination SEP (i.e., own occupation). AL was operationalised using 12 biomarkers tapping cardiovascular, metabolic, renal, and immune system dysregulation. Diagonal reference modelling (DRM) and ordinary least square regression (OLS) techniques were applied to explore the effect of social mobility on AL burden.

Results: 55.5% experienced intergenerational mobility: 37.5% were upwardly mobile, 18.0% were downwardly mobile. A social gradient in AL was observed among the socially non-mobile. Destination SEP ($b = 0.74$, 95% CI = 0.57, 0.92) predominated in influence over origin, although both life stages exerted significant influence on later life AL. Social mobility in either direction was not associated with AL burden. Mobility coefficients were substantially small across a large variety of model specifications.

Discussion: Findings provide evidence for an accumulation model of social inequalities in which disparities in health are diluted rather than increased by social mobility (i.e., gradient constraint), with the socially mobile having an AL score that is intermediate between their origin class and

destination class. This implies that the effects of origin SEP on health are not immutable but are instead responsive to changing socio-economic circumstances across the life course.

CHAPTER 5: PUBLISHED WORK LIST

This paper has been accepted for publication at *The Journals of Gerontology, Series B: Social Sciences*

McLoughlin, S., Präg, P., Bartley, M., Kenny, R. A., & McCrory, C. (2022). Intergenerational Social Mobility and Allostatic Load in Midlife and Older Ages: A Diagonal Reference Modeling Approach. *The Journals of Gerontology: Series B*, 78(1), 154–166. <https://doi.org/10.1093/geronb/gbac122>

The following tables and figures have been published as part of this paper:

- Figure 5.1: Conditional means for Allostatic Load according to intergenerational social class trajectory, adjusting for age, sex, and childhood health
- Supplementary Figure 5.1: Sample flow chart
- Supplementary Table 5.1: Overview of supplementary analyses
- Supplementary Table 5.2: Biomarker descriptives, and high risk cut points for generating the supplemental clinical risk allostatic load index
- Supplementary Table 5.4: Parameter estimates from diagonal reference models estimating mobility effects on the allostatic load sub-systems
- Supplementary Table 5.5: Parameter estimates from diagonal reference models estimating mobility effects on allostatic load (clinical cut-points incorporating medication usage)

- Supplementary Table 5.6: Parameter estimates from diagonal reference models estimating educational mobility effects on allostatic load
- Supplementary Table 5.7: Parameter estimates from diagonal reference models estimating mobility effects on allostatic load (5-level SEP)
- Supplementary Table 5.8: Parameter estimates from diagonal reference models (biomarkers based on prior Understanding Society study)
- Supplementary Table 5.9: Sample characteristics by category of social mobility
- Supplementary Table 5.10: Parameter estimates from diagonal reference models estimating mobility effects on allostatic load burden, controlling for lifestyle confounders
- Supplementary Table 5.11: Parameter estimates from diagonal reference models estimating mobility effects on allostatic load burden, taking a conservative maximum bias approach to missing data (n=5,153)

5.1 Introduction

There exists a gradient in health across socio-economic groups, such that the most disadvantaged experience the highest risk of morbidity and mortality ⁸⁰. It has been proposed that this social gradient in health comes about in large part because persons of less advantaged socio-economic position (SEP) experience greater stress exposure than their more advantaged SEP counterparts ²¹⁷, with the long-term effects of such insults culminating in a multi-system physiological burden known as allostatic load (AL) ¹⁴. AL has been posited as a potential explanatory framework for understanding the biological embedding of SEP over the life course. Despite the consistent link between less advantaged SEP and high AL burden demonstrated to date ²⁸, the relationship is complex, and how the experience of socio-economic dis/advantage moderates trajectories of physiological dysregulation remains to be determined.

Although life course models are closely interrelated and difficult to disentangle statistically¹⁰⁸, a life course approach enables a more dynamic view of the impact of SEP on physiological functioning, recognizing the complex pathways between early life and later health⁶¹. For instance, does the timing of socio-economic disadvantage matter in the context of AL, such that childhood exposure results in “permanent and irreversible” scarring effects on biological systems as implied by the critical period model⁶¹ [pg. 286]; or do the negative impacts of SEP disadvantage compound over time, with each additional life stage spent in less advantaged SEP adding to an ever growing health disadvantage, as suggested by the accumulation model?¹⁰⁵. Perhaps the negative effects of disadvantaged SEP are reversible and mitigated through intergenerational or intragenerational changes, as suggested by the social mobility model^{106,107}. The classic “*dissociation*” hypothesis stipulates that social mobility – irrespective of upwards or downwards - is disruptive and detrimental to the well-being of individuals, leading to reduced social integration, weakened social ties and feelings of alienation²¹⁸. These relational rifts may be experienced as stressful, thus exerting negative health implications. The “*falling from grace*” thesis argues that the experience of downward mobility is a more distressing experience than upward mobility, as failing to maintain the educational or occupational attainment of their parents leads to feelings of insecurity¹²³. On the other hand, the “*rising from rags*” thesis suggests that the positive effects of upward mobility may outweigh any negative consequences^{219,219}. “*Acculturation*” similarly suggests that the influence of destination class on health will be stronger than that of origin²²⁰. These theories have the potential to expand our understanding of how SEP impacts on biological risk over the life course.

Research to date examining the relation of different life course models with AL has shown mixed findings, especially regarding whether origin SEP (i.e., SEP in early life), is directly

associated with later life AL. For instance, data from a Northern Swedish cohort (n= 855; 51.8% male) found that life course socio-economic disadvantage was related to a greater burden of AL. This study also revealed that origin SEP, measured using parental occupation at age 16, was a particularly sensitive period for the embedding of socio-economic disadvantage on AL at midlife (age 43) amongst women, but not men after controlling for contemporaneous lifestyle behaviours and incorporating medication use ¹¹⁶. Data from the Midlife in the United States (MIDUS) (n= 1008; 45.2% male; age range: 35-85) supported an independent effect of a composite origin SEP variable on later life AL, adjusting for destination SEP, although the magnitude of the association was almost twice that for destination, holding age, sex and race/ethnicity constant ¹¹⁵. In line with this, results from a longitudinal analysis of the Multi-Ethnic Study of Atherosclerosis (MESA) (n= 6135; 47.8% male; age range 45-84) reported that the association of SEP and AL was primarily driven by destination SEP, after adjusting socio-demographic confounders and medication use ²²¹.

One factor that may play a role in the observed nuances across studies relates to the choice of statistical model. To date, investigations of the relative contribution of origin and destination SEP on AL have been dominated by simple linear models, estimated in a stepwise fashion. Typically, a baseline model estimates the direct effect of origin SEP on AL, and a second model controls for destination SEP ^{115,116}. However, Green and Popham (2019) caution that it may be problematic to compare the effects for multiple measures of SEP on AL as independent effects, as the possible causal effects of distal SEP measures may be biased with adjustment for proximate SEP measures. The effect estimates from these models are often presented simultaneously in one table, giving the impression of equivalent interpretation, leading to the so-called “*Table 2 fallacy*” ²²².

Eschewing the multiple adjustment method, Robertson and colleagues (2014) utilised a structural modelling approach to compare the fit of different life course models linking SEP with AL across three age cohorts (ages 35, 55, 75) using data from the West of Scotland study. When allowing effect sizes to vary between life stages, it was the accumulation model that provided the best fit to the data ¹¹⁸. In relation to the social mobility model, they found that intergenerational upward mobility was associated with higher AL burden in early (n=740), but not in mid (n=817) or late adulthood (n=483) (Robertson et al., 2014), possibly due to survival bias. However, neither linear models nor SEM techniques are able to isolate the relative effects of origin and destination SEP on AL, as the influence of social mobility cannot be estimated unless the effects of past and current SEP can be separated from mobility itself ²²³.

Diagonal Reference Models (DRM) ¹²⁸ were developed to overcome the linear dependency between origin and destination SEP. The notable feature of these models is their attempt to examine the independent effect of *moving* between SEP groups after accounting for *being* in different SEP's across the life course, with the guiding assumption that socially immobile individuals constitute the core of a social position and therefore best reflect its characteristics ¹²². Prag and Richards (2019) employed this technique to explicitly examine the effects of intergenerational social mobility on AL using data from *Understanding Society*, the UK Household Longitudinal Study (n= 9851; mean age 52.6, 44.4% male). They reported no significant associations of mobility with AL burden; a result which suggests that mobility in and of itself does not directly impact physiological dysregulation, and the weighting led to a conclusion that neither origin nor destination SEP predominate in their impact on AL ¹¹⁷. A recent US based study of young adults aged 25-32 that also used DRM's arrived at a similar conclusion regarding the relative weight to be afforded to origin and destination SEP

(measured using a composite of education and occupational attainment), but contrary to the UK study, there was some evidence of a mobility effect for the upwardly mobile ²²⁴.

5.2 The present study

Aside from methodological differences, the association of social mobility with AL may differ in varying social-economic-historic environments. The Republic of Ireland provides an interesting test case for the examination of social mobility effects on physiological dysregulation as it has a strong class-based structure ^{225,226}. The country has undergone radical economic development in recent decades, resulting in high levels of absolute social mobility as Ireland transitioned from a predominantly agrarian to a post-industrial economy. The 1950s saw a peak in emigration and virtual stagnation of real national income, yet the decade that followed saw rapid growth as economic policy incorporated a more export-oriented strategy, attracting foreign investment and leading to the ‘*Celtic Tiger*’ era at the start of the twenty-first century ²²⁶. Opportunities for middle-class and skilled-manual work increased concomitant with diminishing agricultural trade, which impacted on the occupational structure of the country ²²⁷. Analysing trends in social mobility, Layte and Whelan (2002) noted that the proportion of smallholders in Ireland, or individuals who owned small farms, decreased from 20% to 10% between 1973-1987 ¹³⁰. While the economy underperformed relative to its European counterparts who were experiencing the “*Golden Age*” up until the 1970s, Irish national income grew more rapidly and more dramatically, catching up with the performance of neighbouring economies by the 1980s. Gross National Income (GNI) growth averaged 1.1% between 1938-1950, rising to 3.9% between 1960-1973.

Educational achievement continues to be a key mechanism in the transmission of intergenerational disadvantage ¹³⁰. The educational system in Ireland went through a general

restructure around the time that the current older generation of individuals were navigating their own educational attainment, including the introduction of free secondary education. This notable reform, alongside the demand for employees with higher levels of education as the economy transformed to one based on skills and educational attainment, increased educational participation ²²⁸, assisting individuals from less advantaged SEP background to be socially mobile. From 1973 to 2000, the proportion of individuals with secondary school education who held non-manual positions increased two-fold, indicating a reduced capacity of higher qualifications to guarantee more advantaged positions ²²⁶. The high levels of upward mobility within an aging cohort therefore allows an in-depth investigation of the long run implications of transitioning out of origin dis/advantage for AL in later life.

5.2.1 Methods

5.2.1.1 Data source

The Irish Longitudinal Study on Ageing (TILDA) is a nationally representative prospective cohort study of community-dwelling older persons aged 50 years or more and their spouses living in the Republic of Ireland. The sample was generated using a 2-stage clustered sampling process and the Irish Geodirectory as the sampling frame, which comprises all addresses in the Republic of Ireland. The primary sampling units were 640 geographic regions selected by random selection, stratified on proportion of head of households in the professional class, proportion of the population aged ≥ 65 years, and geographical location. The second stage involved the selection of a random sample of 40 addresses from within each primary sampling unit, resulting in an initial sample of 25,600 addresses which were assessed for eligible participants aged ≥ 50 years. A response rate of 62.0% was achieved at the household level, which was defined as the proportion of sampled households, including an eligible participant from whom an interview was successfully obtained. The sampling fraction is approximately 1/150 of all community-dwelling adults aged 50 years and over

resident in the Republic of Ireland. Baseline data were collected between 2009 and 2011, via computer-assisted personal interviews (CAPI), leave-behind paper and pen self-completion questionnaires (SCQ) (response rate = 84.6%), and a health assessment (response rate = 61.6%) comprising the collection of blood samples (n= 5655) and other physiological parameters. Additional details of the study design are available elsewhere ¹³³. Ethical approval for this study was approved by the Faculty of Health Science Research Ethics board in Trinity College Dublin, while informed consent was obtained from all participants during data collection. TILDA data is publicly available from the Irish Social Sciences Data Archive (ISSDA) (<https://www.ucd.ie/issda/data/tilda/>) while access to the restricted researcher microdata file is available upon application (<https://tilda.tcd.ie/data/accessing-data/>).

Table 5.1: Sample characteristics according to origin and destination social class position and intergenerational social class mobility

	Included (n= 3987)		Excluded (n= 4186)	
	<i>n</i>	%	<i>n</i>	%
Age (mean, SD)	61.8	8.3	65.8	10.7
Female	2,134	53.5	2,296	54.9
Allostatic Load Index (mean, SD)	0.0	1.0	-	-
<i>Childhood health</i>				
Excellent	2249	56.4	2194	52.4
Very good	1009	25.3	1187	28.4
Good	497	12.5	531	12.7
Fair	172	4.3	195	4.66
Poor	60	1.50	77	1.84
Origin socio-economic position				
Professional / managerial	871	21.9	474	14.7
Non-manual / skilled manual	1,738	43.6	1,298	40.3
Semi-skilled / unskilled / never worked	1,378	34.6	1,452	45.0
Destination socio-economic position				
Professional / managerial	1,378	34.6	818	21.8
Non-manual / skilled manual	1,785	44.8	1,509	40.1
Semi-skilled / unskilled / never worked	824	20.7	1,434	38.1
Social mobility trajectories				
Downwardly mobile	716	18.0	571	19.5
<i>Non-mobile</i>				
Stable professional/ managerial	478	12.0	197	6.7
Stable non-manual/ skilled manual	881	22.1	545	18.7
Stable semi-skilled/ unskilled/ never worked	417	10.5	654	22.4
Upwardly mobile	1495	37.5	956	32.7
Degree of intergenerational social mobility				
Upwardly mobile 1 position	84	2.1	65	2.2
Upwardly mobile 2 positions	632	15.9	506	17.3
Downwardly mobile 1 position	1129	28.3	786	26.9
Downwardly mobile 2 positions	366	9.2	170	5.8

Note: SD = standard deviation. This table has been published in my paper McLoughlin et al. (2022)

5.2.1.2 Measurements

5.2.1.2.1 Outcome variable – Allostatic Load

Consensus is lacking regarding the optimal biomarker panel for use in the generation of AL indices, leading to large heterogeneity in biomarkers employed to date ²⁸. This study incorporates twelve biomarkers selected from available data based upon their representation of multiple physiological systems pertinent to disease risk, and their known association with age-related health outcomes in this cohort ²⁰⁸. This includes the *cardiovascular system*; systolic blood pressure, diastolic blood pressure, resting heart rate, pulse wave velocity, the *metabolic system*; waist–hip ratio, body mass index, glycosylated haemoglobin, high-density lipoprotein, total cholesterol, the *renal system*; creatinine, Cystatin-C, and the *immune system*; C-reactive protein. Log transformations were applied to C-reactive protein and pulse wave velocity to account for right-skewed distributions, and high-density lipoprotein was reverse coded such that higher values represented increased risk. Detailed measurement techniques for each biomarker are available elsewhere ²⁰⁸. Each biomarker was standardised to a mean of 0 and a standard deviation of 1 and summed to generate an overall AL score expressed in standard deviation units. Finally, this overall AL score was standardised to a mean of 0 and a standard deviation of 1.

5.2.1.2.2 Exposure variable

Occupational class was drawn from retrospective data on father’s occupation from childhood (age 14), and used to estimate origin SEP. Current occupation, or highest paid job if retired, was used to estimate contemporaneous or destination SEP. Following the Irish Central Statistics Office (CSO) social class coding schema and in line with previous research on Irish data, occupations for both time points were classified into five categories: professional/managerial, non-manual, skilled manual/semi-skilled, unskilled and parent never worked. Participants who reported farming as origin or destination occupation were asked to provide acreage, and if they had any other paid work, and were coded into the appropriate occupation categories based on CSO criteria: farmers with 0-29

acres were assigned to the semi-skilled group, 30-49 acres were assigned to the skilled manual group, 5-99 acres were assigned to the non-manual group, 100+ acres were assigned to the professional/managerial group. Farmers with unknown acreage were coded as missing. Due to small cell sizes, class was further collapsed into three categories: (i) professional/managerial, (ii) non-manual/skilled manual, and (iii) semi-skilled/unskilled/never worked. A series of dummy variables were generated to capture mobility trajectories (i.e., upwardly mobile, downwardly mobile, one step up, two steps up, one step down, two steps down).

Irish sociological research has a long tradition of using occupation to measure SEP because Ireland has a strong underlying social class structure ^{225,226}, which is correlated with other socio-economic indicators (i.e. income, education). Occupation is often favoured in social mobility research because it is an individual-level measure of SEP. Occupation serves as a key determinant of life chances and is also a measure that is in some sense transferable. As such, parental social class can be used to characterise the likely socio-economic circumstances of children within the household growing up ²²⁹. Although income has been used in studies elsewhere ^{115,230}, it is a less useful indicator in older cohorts as it may be affected by retirement status. Moreover, obtaining reliable information on the income status of the parent's generation is problematic. Education has also been used to characterise intergenerational mobility in many US-based studies ^{147,231,232}, but is arguably a less sensitive indicator in the Irish context because Ireland experienced massive educational upgrading between the 1960's and 1970's as a consequence of two educational reform acts, meaning that later-born cohorts generally have more education than earlier born cohorts. Nevertheless, we perform robustness checks on our results using education as an alternative measure of intergenerational social mobility.

5.2.1.3 Sample exclusions

Of the baseline sample over the age of 50 ($n = 8175$), 5655 of these participants successfully provided blood samples, and 4477 participants had complete biological data on the biomarkers needed to construct the AL index. Of these, 490 were missing on life course SEP variables; 319 were missing on origin SEP (including 174 farmers with unknown acreage) while 171 were missing destination SEP (including 15 farmers with unknown acreage), while 30 participants were missing SEP data on both life stages. The final analytical sample comprised 3987 respondents. A flow chart detailing eligibility criteria and final analytical sample is detailed in Supplementary Figure 5.1. Individuals excluded from the analyses differed to the extent that they tended to be older, with higher proportions within less advantaged SEP groups.

5.2.1.4 Analytical strategy

5.2.1.4.1 Diagonal Reference Models (DRMs)

DRMs were estimated to test whether AL is affected by social mobility besides origin and destination²³³. DRMs model the outcome of interest (AL) as the weighted sum of the estimated mean values in the socially immobile origin group and the socially immobile destination group. We adjust in the models for age (years) and sex (male, female) as patterns of intergenerational mobility and AL burden may vary across these important demographic characteristics. We also control for a childhood self-reported health indicator (excellent, very good, good, fair, poor), as poor childhood health could set restraints on social mobility and directly affect later life AL burden²³⁴.

For ease of interpretation in the DRM analysis, age was centred around the sample mean. The constant represents the average AL burden for male respondents of average age, while the class coefficients represent the deviations from that constant. The weight parameters express the relative importance of origin and destination on AL and are constrained to range between 0 and 1. A high

value of the destination weight value indicates that the relative importance of one's current SEP is greater than origin SEP with respect to AL. To test for mobility effects in DRMs, we created a series of dummy variables to represent (i) upward and downward mobility (ii) the magnitude of mobility (i.e., number of positions by which the respondent was mobile relative to origin class). For the sake of uniformity in nomenclature with the extant social mobility literature, we make use of the term "*mobility effects*". Note that this term is used to describe a statistical association rather than imply the existence of any causal relationships. We compared the fit of these nested models with the base model using the Akaike and Bayesian Information Criteria (AIC and BIC). The DRM models were implemented in Stata using the "drm" module developed by Kaiser ²³⁵.

5.2.1.4.2 Ordinary Least Square (OLS) models

DRMs are a relatively novel modelling approach within the AL literature. In light of this, we also estimated a series of ordinary least square models as both robustness checks and to allow comparison with prior research, bearing in mind the interpretation concerns as highlight via the table two fallacy. In separate models, we estimate first the independent associations of origin SEP and destination SEP with AL burden while adjusting for age, sex, and childhood self-reported health. We then include origin and destination SEP in the same model to test for mediation (i.e., mutual adjustment). We fit a two-way interaction term between origin and destination SEP to determine whether the relationship with AL over the life course is additive or multiplicative. We examined mobility effects in OLS models using the method typified by Luo & Waite (2005) by characterizing the study population into 5 social mobility trajectories: stable professional/managerial, stable non-manual/skilled manual, stable semi-skilled/unskilled, upwardly mobile, downwardly mobile; and comparing the conditional mean AL scores across groups ²³⁶. All analyses were conducted in Stata (V.15; ¹³⁶).

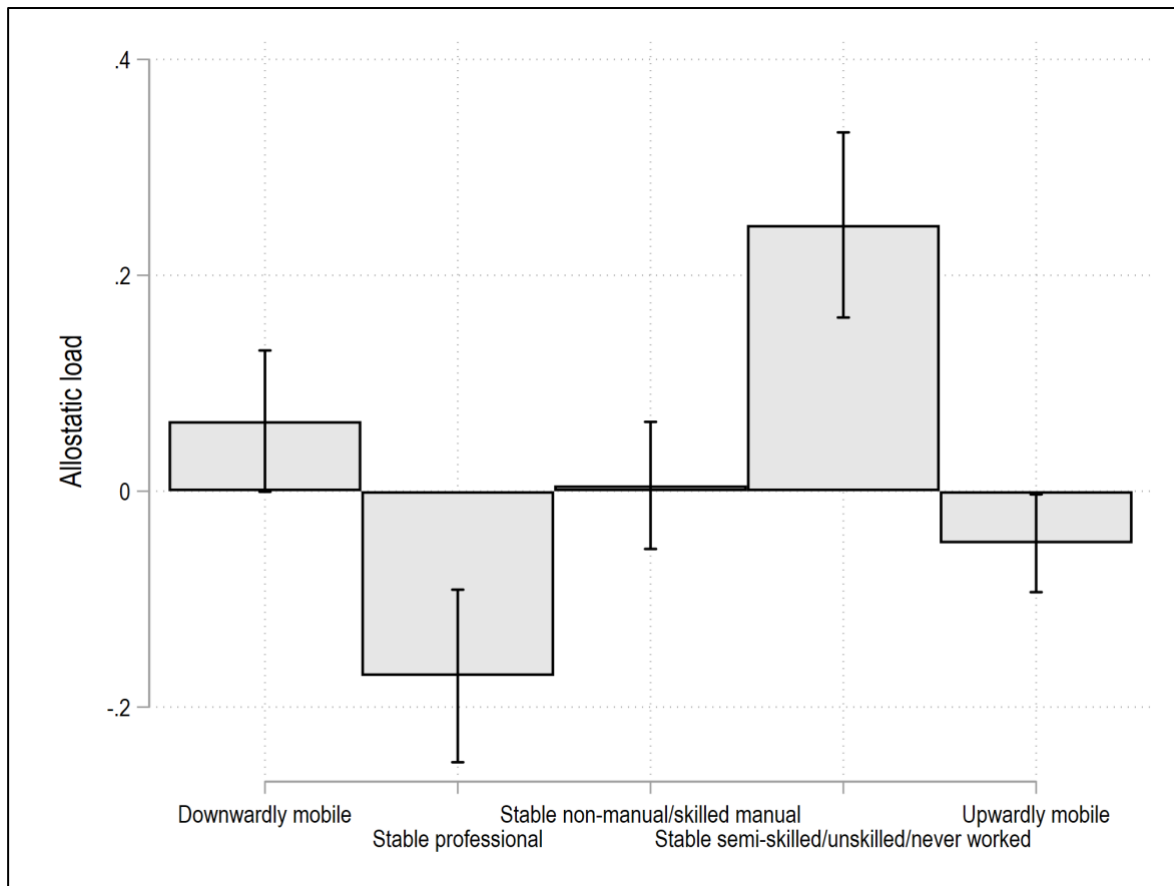
5.3 Results

The mean and SD values for each of the 12 biomarkers comprising the AL index are described in **Error! Reference source not found..**

Table 5.1 reports the characteristics of the sample and the degree of intergenerational social mobility within the TILDA cohort. The mean age of the sample (n= 3987) was 61.8 (SD= 8.3), and 53.5% were female. The majority of the sample reported their childhood health to be excellent (56.4%), very good (25.3%) or good (12.7%), with <6% reporting fair or poor health.

Table 5.1 also shows that the experience of intergenerational social mobility was common, with 37.5% of the sample upwardly mobile and 18.0% of the sample downwardly mobile, leaving 44.5% non-mobile. In general, those who were mobile tended to be mobile within ± 1 occupational position around their destination, with smaller proportions mobile by ± 2 occupational positions, suggesting origin places some constraints on destination. Table 5.2 shows the conditional means resulting from the cross-classification of origin and destination. Cells on the diagonal describe performance for individuals who were non-mobile across generations, cells below the diagonal describe those who were upwardly mobile, and cells above the diagonal describe those who were downwardly mobile. Upward mobility is associated with lower AL scores compared with class of origin, and downward mobility is associated with higher AL scores compared with class of origin.

Figure 5.1: Conditional means for Allostatic Load according to intergenerational social class trajectory, adjusting for age, sex, and childhood health



Note: This figure was published in McLoughlin et al., (2021)

Table 5.2: Conditional means for allostatic load resulting from the cross-classification of origin and destination social class position

	Destination		
	Professional/Managerial	Non-manual/skilled manual	Semi-skilled/unskilled/never worked
Origin	<i>Conditional Mean</i>	<i>Conditional Mean</i>	<i>Conditional Mean</i>
Professional/Managerial	-0.10	-0.01 (DM)	0.08 (DM)
Non-manual/skilled manual	-0.11 (UM)	0.06	0.10 (DM)
Semi-skilled/unskilled/never worked	0.03 (UM)	0.18 (UM)	0.23

Note: Adjusting for age, sex, and childhood self-reported health. UM = upwardly mobile; DM = Downwardly mobile. Diagonal cells reference the socially non-mobile. This table was published in McLoughlin et al., (2022)

5.3.1 Diagonal Reference Models

Table 5.3 reports the parameter estimates from the DRM analysis estimating mobility effects on AL burden. The baseline model reveals that the coefficients for AL burden are smaller for people in the higher social classes, reflecting the social gradient in health amongst the socially immobile. The coefficients for the confounding variables reveal that AL burden is lower for women than men and is positively associated with age. Poorer childhood health was associated with greater AL burden, but these effects were not significant. The subsequent models test for the effects of intergenerational mobility over and above the effects of origin and destination, allowing mobility effects to be separated from level effects. The weight parameters from Table 5.3 indicate that the level of AL burden is closer to their non-mobile counterparts in the destination group. No significant associations of mobility trajectories with AL are reported, which is in line with the AIC and BIC values indicating that the parsimonious base model fits the data best.

Table 5.3: Parameter estimates from diagonal reference models estimating mobility effects on Allostatic Load burden

	<i>Base model</i>		<i>Upward mobility</i>		<i>Downward mobility</i>		<i>Upward steps</i>		<i>Downward steps</i>	
	<i>b</i>	<i>95% CI</i>	<i>b</i>	<i>95% CI</i>	<i>b</i>	<i>95% CI</i>	<i>b</i>	<i>95% CI</i>	<i>b</i>	<i>95% CI</i>
Constant	1.14***	(1.05, 1.24)	1.16***	(1.05, 1.26)	1.14***	(1.04, 1.24)	1.15***	(1.05, 1.26)	1.14***	(1.04, 1.24)
Socially immobile										
Professional / managerial	-0.19***	(-0.24, -0.14)	-0.19***	(-0.24, -0.13)	-0.19***	(-0.24, -0.14)	-0.19***	(-0.24, -0.13)	-0.19***	(-0.24, -0.14)
Non-manual /skilled manual	-0.00	(-0.05, 0.04)	-0.01	(-0.06, 0.04)	-0.00	(-0.05, 0.04)	-0.00	(-0.07, 0.07)	-0.00	(-0.05, 0.04)
Semi-skilled/unskilled/never worked	0.19***	(0.13, 0.25)	0.20***	(0.14, 0.25)	0.19***	(0.13, 0.25)	0.19***	(0.13, 0.26)	0.19***	(0.13, 0.25)
Controls										
Female	-0.74***	(-0.80, -0.68)	-0.74***	(-0.80, -0.68)	-0.74***	(-0.80, -0.68)	-0.74***	(-0.79, -0.68)	-0.74***	(-0.79, -0.68)
Age*	0.03***	(0.03, 0.03)	0.03***	(0.03, 0.03)	0.03***	(0.03, 0.03)	0.03***	(0.03, 0.03)	0.03***	(0.03, 0.03)
<i>Childhood health</i>										
Excellent		<i>Ref</i>		<i>Ref</i>		<i>Ref</i>		<i>Ref</i>		<i>Ref</i>
Very good	0.01	(-0.06, 0.07)	0.01	(-0.06, 0.07)	0.01	(-0.06, 0.07)	0.01	(-0.06, 0.07)	0.01	(-0.06, 0.07)
Good	0.03	(-0.06, 0.11)	0.03	(-0.06, 0.11)	0.03	(-0.06, 0.11)	0.03	(-0.06, 0.11)	0.03	(-0.06, 0.11)
Fair	-0.03	(-0.17, 0.10)	-0.03	(-0.17, 0.10)	-0.03	(-0.17, 0.10)	-0.03	(-0.17, 0.10)	-0.03	(-0.17, 0.10)
Poor	0.21	(-0.02, 0.44)	0.21	(-0.02, 0.44)	0.21	(-0.02, 0.44)	0.21	(-0.02, 0.44)	0.21	(-0.02, 0.44)
Weights										
Origin	0.26**	(0.08, 0.43)	0.37*	(0.06, 0.69)	0.25*	(0.01, 0.49)	0.33	(-0.15, 0.80)	0.24*	(0.00, 0.49)
Destination	0.74***	(0.57, 0.92)	0.63***	(0.31, 0.94)	0.75***	(0.51, 0.99)	0.67**	(0.20, 1.15)	0.76***	(0.51, 1.00)
Mobility status										
Upward			-0.05	(-0.16, 0.06)						
One-step upward					-0.01	(-0.11, 0.10)				
Two steps upward							-0.04	(-0.17, 0.09)		
Downward							-0.02	(-0.28, 0.25)		
One step downward									-0.00	(-0.11, 0.10)
Two steps downward									-0.03	(-0.25, 0.20)
AIC		10392.8		10394.1		10394.8		10396.1		10396.8
BIC		10462.0		10469.6		10470.3		10477.8		10478.5
Degrees of freedom		11		12		12		13		13

Note: 95% confidence intervals in brackets. Age is centred around the sample mean. AIC: Akaike Information Criteria. BIC: Bayesian Information Criteria. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. This table was published in McLoughlin et al., (2022)

5.3.1.1 Sensitivity analyses

We undertook a series of sensitivity analyses to test the robustness of the DRM findings, the rationale for which is summarised in detail in **Error! Reference source not found.**, and briefly described here. We tested for interactions of the origin weight with age, sex, and mobility status in the DRM's (**Error! Reference source not found.**) but none of the interaction terms were statistically significant at conventional levels, suggesting that origin plays a similar role for AL burden across the life course, for the two sexes, and for those who experience mobility in their lives. To examine whether particular physiological systems were driving the observed associations and to enable comparison with previous studies, a series of separate DRM models were estimated across each of the sub-systems comprising the AL composite score (i.e., cardiovascular, immune, renal, metabolic). Destination SEP exerted more influence than origin on later life dysregulation across all systems (**Error! Reference source not found.**). Parameter estimates from DRMs estimating intergenerational mobility effects on a clinically derived AL index are reported in **Error! Reference source not found.**. This alternate index was generated by summing the number of high-risk biomarkers using clinical-risk cut-points and standardizing the overall index (**Error! Reference source not found.**). This measure incorporated medication usage in the AL score by manually scoring a biomarker as high risk if individual is taking a doctor diagnosed medication as ascertained at time of interview. Comparison of estimates with Table 5.3 revealed little difference, although the weights for origin were larger in magnitude when using this alternative AL index.

Educational attainment was introduced as an alternative measure of SEP to examine whether results were dependent on the socio-economic measure used in the analysis ²³⁷. Results were ostensibly similar, although the weights for destination were slightly larger in magnitude when examining

education over occupational in Table 5.3 (**Error! Reference source not found.**). Additionally, to assess the robustness of the 3-level SEP measure, parallel analyses were undertaken using a 5-level measure (i.e., professional/managerial, non-manual, skilled manual/ semi-skilled, unskilled, never worked) (**Error! Reference source not found.**). On this occasion, a significant negative association was observed for each step upward from origin, suggesting that results may be sensitive to the manner in which social class groups are aggregated.

To allow a more accurate comparison to results from *Understanding Society*¹¹⁷, and to allay suspicion that the choice of biomarkers used to generate the AL index were responsible for the different pattern of results observed between studies, an alternate measure of AL was constructed using a sum of standardised biomarkers comparable to the *Understanding Society* measure (systolic blood pressure, diastolic blood pressure, resting heart rate, waist circumference, BMI, triglycerides, total cholesterol, high density lipoprotein, HbA1c, C-reactive protein – missing fibrinogen). Destination SEP continued to exert approximately three times the influence of origin SEP on later life AL, and no significant associations of mobility trajectories with AL are reported (Supplementary Table 5.8).

To examine whether results were biased due to unmeasured confounding, additional contemporaneous socio-demographic and behavioural health variables potentially associated with both social mobility and AL burden were adjusted for in **Error! Reference source not found.** These included the Berkman-Syme social network index (0-4, higher values indicate higher social connectedness, derived from: marital status, sociability (number and frequency of contacts with children, close relatives, and close friends); church group membership and membership in other

community organizations)²¹⁴. Behavioural health variables included smoking status (never smoked, former smoker, current smoker), alcohol consumption frequency, and physical activity (low, moderate, high), measured using the international physical activity questionnaire (IPAQ)²¹³. The weights for destination were larger in magnitude with the inclusion of these contemporaneous variables, and there was no association of social mobility with AL burden.

Finally, we test the robustness of our findings by taking a conservative approach to the missing biomarker data. This alternate index was generated by summing the number of high-risk biomarkers based on the 75th percentile of risk based on the sample distribution and standardizing the overall index. Participants who attended the health assessment but who were missing on <7/12 of the biomarkers were manually coded as not at risk. Supplementary Table 5.11 illustrates that destination SEP continued to predominate over origin SEP in terms of AL burden, and no significant associations of mobility trajectories with AL are reported.

5.3.2 Linear models

The OLS models reveal a social gradient in AL burden according to both origin (Table 4, panel A) and destination (Table 4, column panel B) class. The mutually adjusted model (Table 4, panel C) reveals that destination mediates a substantial proportion of the effect of origin on AL burden. We examined whether the effects of origin and destination social class on AL burden were additive or multiplicative by fitting an origin*destination interaction term, but none of the individual contrasts nor the overall interaction term were significant ($F(4, 3972) = 0.61; p = 0.656$). This result suggests that the linear combination of origin and destination social class is sufficient to describe the effects of life course

social class position on AL burden in later life. This is consistent with what we observe when we examine the conditional mean AL score for the upwardly and downwardly mobile compared with those who remained intergenerationally stable in their class position in OLS models. Figure 5.1 shows that the upwardly mobile (M= -0.05) rank intermediate between the stable professional/managerial class (M= -0.17) and the stable non-manual/skilled manual class (M= 0.01), while the downwardly mobile (M= 0.06) rank intermediate between the stable non-manual/skilled manual class (M= 0.01) and the stable semi-skilled/unskilled class (M= 0.24).

Table 5.4: Independent and mutually adjusted associations of origin and destination social class with Allostatic Load burden

	Panel A		Panel B		Panel C	
	<i>b</i>	95% CI	<i>B</i>	95% CI	<i>b</i>	95% CI
<i>Origin class</i>						
Professional/ Managerial		<i>ref</i>	-		<i>ref</i>	
Non-manual/skilled manual	0.04	(-0.03, 0.11)	-		-0.01	(-0.08, 0.07)
Semi-skilled/ unskilled/ never worked	0.15** *	(0.08, 0.23)	-		0.08*	(0.01, 0.16)
<i>Destination class</i>						
Professional/ Managerial	-		<i>ref</i>		<i>Ref</i>	
Non-manual/ skilled manual	-		0.16** *	(0.10, 0.23)	0.16** *	(0.10, 0.22)
Semi-skilled/ unskilled/ never worked	-		0.30** *	(0.22, 0.38)	0.28** *	(0.20, 0.36)

*Note. All models adjust for age, sex, and childhood self-reported health. Panel A: the association of origin class with allostatic load. Panel B: the association of destination class with allostatic load. Panel C: mutually adjusted associations of origin and destination class with allostatic load. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. This table was published in McLoughlin et al., (2022)*

5.4 Discussion

This study sought to examine the association of intergenerational social mobility with AL burden at mid-life and older ages using a methodological technique – diagonal reference models – that has been underutilised in public health research despite its obvious advantages relative to alternative approaches such as mutual adjustment ²²², or differentiating groups based on combinations of their origin and destination social class positions ²³³. In line with previous studies using this technique ^{117,224}, we observed a pronounced social gradient in AL burden among the socially immobile. The professional/managerial group had the lowest burden of AL, while the unskilled/ never worked group had the highest burden of AL, with the semi-skilled/ non-manual group intermediate between the two. We found significant weights of both origin and destination SEP with AL burden, indicating independent influences from both life stages on later life physiological dysregulation. However, the relative importance of destination SEP on AL burden predominated, as approximately three times as much variance in AL burden was explained by destination compared with origin class. Social mobility was not associated with AL burden when accounting for SEP at both time points. The model fit statistics confirmed that the base model, that is, the one containing no mobility effects, provided the best fit to the data. A finding which implies that the linear combination of origin and destination is sufficient to characterise the impact of differing intergenerational social class trajectories on later life physiological dysregulation. This interpretation is supported by the lack of a significant interaction between origin and destination in the OLS models.

The higher weights for destination compared with origin class in the DRMs, the absence of mobility effects, the stronger associations of destination compared with origin in the OLS models, and the fact that the upwardly and downwardly mobile have AL burden intermediate between their class of

origin and class of destination in OLS are all consistent with an accumulation model of social inequalities in AL burden and the concept of ‘gradient constraint’²³⁸. Gradient constraint refers to a process of assortment whereby social mobility moderates rather than creates or amplifies, the size of the social class differential²³⁸. The central idea is that mobile individuals rank somewhere intermediate between the class they left and the class they join as they share characteristics in common with both. The fact that the downwardly mobile have higher AL burden than the upwardly mobile may simply reflect the greater number of years spent at a more disadvantaged level relative to class of origin, although they are still in better health than those stable at less advantaged social class positions across the span. Consistent with this interpretation, Supplementary Table S8 shows that the health-related characteristics of the upwardly mobile is comparable to those in the stable managerial/ professional groups, while the health profile of the downwardly mobile is more akin to those stable at less advantaged social class positions. These mobile individuals appear to adopt characteristics of their destination group, yet carry some of the legacy of origin, which serves to dilute the destination effect.

5.4.1 Relation to other studies

Our results are consistent with the extant literature documenting that individuals of less advantaged SEP experience higher AL burden²⁸. Findings from the UK Household Longitudinal Study, *Understanding Society*¹¹⁷ found approximately equal influence from both origin and destination on later life AL burden. This equal influence is echoed by recent results from the *National Longitudinal Study of Adolescent Health (Add Health)* of the US²²⁴, although a significant and positive mobility effect was reported in this study for those who experienced upward movement from origin. Our study however, found that a higher weight was afforded to destination SEP. These disparate findings between studies regarding whether origin or destination holds more influence in determining later life AL provoke the

obvious question as to why these differences arise, as methodological disparities cannot be held responsible for inconsistencies in results across studies in this case, as all studies utilised DRM. Alternate explanations will therefore be addressed in turn, including: (1) differences in biomarker composition between studies (2) differences in cohort characteristics, (3) differences in class schema and (4) varying patterns of social mobility.

5.4.2 Differences in biomarker composition

One of the longstanding criticisms of allostatic load as a concept is that there is no standard definition of the measure^{24,28} and investigators have tended to use the battery of biomarkers that are available to them in any given study to construct the index. Could the differences that we have observed regarding the relative weight to be afforded to origin as opposed to destination be due to the differing composition of the AL index between studies? This seems unlikely given the substantial overlap in the biomarkers used to define AL, with TILDA sharing 9/12 biomarkers in common with *Understanding Society*. Nevertheless, to address this possibility, we compared results for allostatic load subsystems – cardiovascular, metabolic, glucose – for which we substantially or entirely overlapped, and found that destination continued to predominate in terms of influence on later life AL in the present study (Supplementary Table 5.8).

5.4.3 Differences in sample composition

Another possibility is that the disparity in the relative weights afforded to origin and destination across studies arise due to differences in cohort characteristics. The mean age of the TILDA sample is 61.8 years, while *Understanding Society* and *Add Health* participants have a considerably younger age profile with a mean of 52.6 years and 29 years, respectively. Allostatic load is posited to represent a measure of

cumulative physiological dysregulation, so it may well be the case that the relative weights to be attached to origin and destination shift in balance over the life course as participants age ²³⁹.

5.4.4 Differences in class schema

Of course, it is entirely tenable that differences in results may arise due to the use of different occupational coding schemas. The present study uses the Irish Central Statistic's Office (CSO) occupational social class schema which is comparable to the British Registrar General's Social Class (RGSC). This schema assumes a linear ranking of occupations according to skill, whereas Prag & Richard (2018) use the National Statistics-Socio-Economic Classification (NS-SEC), which focuses more on the relational aspects of class, operationalizing a non-linear social class on the basis of employment relations and conditions ²⁴⁰. Despite these differences, it should be acknowledged that both studies documented a pronounced social gradient in AL among the socially immobile, so contrasts in the occupational coding are an unlikely explanation for the differences in the relative weight to be afforded origin as opposed to destination observed between studies. Moreover, rates of mobility have been compared using both classification schemes using English census data and observed strong correspondence between the two measures ¹²⁷.

5.4.5 Different levels of social mobility

The final consideration is different levels of social mobility across countries. We acknowledged previously that Ireland experienced tremendous structural mobility over the last 50 years with over half of the cohort experiencing mobility across generations. Given that the direction of mobility was predominantly in the upward direction, it is entirely plausible that the extent of structural mobility dwarves relative mobility, making it more difficult to isolate pure mobility effects on physiological

dysregulation. Indeed, it has been alleged that the upgrading of Ireland's class structure in the latter half of the 20th Century masked a persistent and deepening problem of blocked relative mobility ²⁴¹. The same accusation could be levelled against using intergenerational educational transitions as our measure of mobility as Ireland introduced two educational reform acts during this period, with the 1967 Act introducing free-secondary level schooling for all children, and the 1972 act introducing an additional year of schooling ²²⁸. This means that later born cohorts have more education than earlier born cohorts due to a structural policy change, not necessarily mobility effects per se. An alternative possibility is that the stronger origin effects observed in *Understanding Society* reflect an older and more ingrained class system. It may also represent a cohort or period effect, as Bartley and Plewis (2007) acknowledge that the relative importance of father's social class on a person's destination has become more pronounced in the UK over recent decades ¹²⁷. Future research should endeavour to compare results with more diverse populations, to provide insight into the potential impact of varying social mobility patterns.

5.5 Strengths and limitations

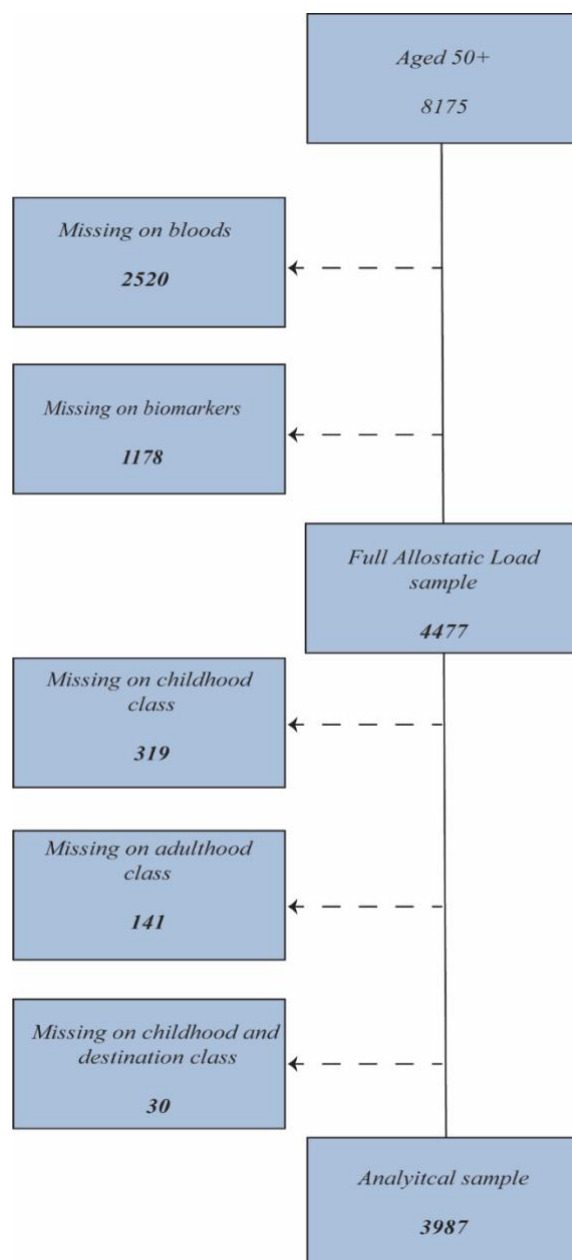
The study has several strengths, including the use of objective biological data from an Irish sample of mid-life and older adults, who grew up in an era of great social and economic change that enabled a large proportion of the population to climb the social ladder. We have already touted the advantage of DRMs over alternative approaches such as mutual adjustment or comparing different mobility groups as they allow one to isolate pure mobility effects and allow one to parameterise the relative importance of origin and destination class regarding their impact on health.

The primary limitation of the current study is that the analyses are cross-sectional, and causal relationships cannot be assessed. Indeed, any causal effect of intergenerational social mobility would be difficult to establish, as there is no counterfactual understanding of mobility effects. When comparing individuals with the same origin and destination SEP, mobility can only go in one direction, a world in which it would go into a different direction is not conceivable. While we can assess the impact of origin and destination SEP on AL, it is outside the remit of DRMs to assess more than two generations ²³³, and as such may not be sensitive to detecting subtle changes in the influence of origin and destination on physiological dysregulation at varying stages of the life course. It is of course possible that this study has underestimated levels of mobility, wherein individuals have been classed as socially immobile by virtue of ending up in the same class as their origin yet were mobile between these two very broad life stages. Misclassification of class categories could also be an issue as origin class was based on a retrospective report of father's occupation. On a similar note, there has been considerable debate about the extent to which a woman's own occupation is captured as a result of traditional parental responsibilities ¹²⁷.

5.6 Conclusion

Tracing the imprint of disadvantage offers a powerful tool to comprehend histories of vulnerability, and thus to inform policy on health inequalities ²⁴². These results imply that moving up or down the social ladder does not directly influence AL burden, although individuals tend to adopt similar AL burden to those in the socio-economic position of their destination. This does not refute the possible lasting impact of origin SEP on later life health but offers promise that interventions channelling individuals out of early life disadvantage to more advantageous socio-economic circumstances may lead to a lessening of AL burden within a population.

Supplementary Figure 5.1: Sample flow chart



Note: This figure was published in McLoughlin et al., (2022)

Supplementary Table 5.1: Overview of supplementary analyses

Name	Label	Rationale	Overview of findings
Supplementary Figure 5.1	Sample flow chart	Illustration of inclusion criteria and n of cases	Analytical sample comprises 3987 individuals who took part in the health assessment module of TILDA, and for whom we have full socio-economic position data
Supplementary Table 5.2	Biomarker descriptives, and high risk cut points for generating the supplemental clinical risk allostatic load index	Information required to generate the clinical AL index used in Supplementary Table S4	n/a
Supplementary Table 5.4	Parameter estimates from diagonal reference models on allostatic load burden, interactions	To test whether the origin weight varied by age, sex, or mobility status	Interaction terms were not statistically significant
Supplementary Table 5.5	Parameter estimates from diagonal reference models estimating mobility effects on the allostatic load sub-systems	To assess whether the influence of origin and destination varied across the physiological sub-systems that comprise the AL index.	Destination predominated over origin in influence on all sub-systems.
Supplementary Table 5.6	Parameter estimates from diagonal reference models estimating mobility effects on allostatic load burden (clinical cut-points incorporating medication usage)	The cut points used to generate AL indices could impact on the results. Here, we use clinical cut points often used in the AL literature, and coded certain biomarkers at risk if individuals reported taking medications that alter biomarker values.	Destination predominated over origin in influence on AL, and social mobility was not associated with AL.
Supplementary Table 5.7	Parameter estimates from diagonal reference models estimating educational mobility effects on allostatic load burden	To assess whether the impact of social mobility on AL was sensitive to the choice of SEP indicator employed.	Destination weights were slightly larger than the primary analysis (Table 3), and social mobility was not associated with AL.
Supplementary Table 5.8	Parameter estimates from diagonal reference models estimating mobility effects on allostatic load burden (5 level SEP)	The 3-level occupational schema was expanded to 5-level to assess whether the aggregation of occupations could impact on results.	Destination predominated over origin in influence on AL. Upward mobility was associated with lower burden of AL.
Supplementary Table 5.9	Intergenerational social mobility and AL based on alternate set of biomarkers	To test whether the findings were a result of the biomarker panel, an alternate biomarker panel based of that used in a previous study using the Understanding Society cohort.	Destination predominated over origin in influence on all sub-systems.
Supplementary Table 5.10	Sample characteristics by social mobility status	To explore the sample characteristics by lifestyle factor, which were entered as confounders in Supplementary Table S10	n/a
Supplementary Table 5.11	Parameter estimates from diagonal reference models estimating mobility effects on allostatic load burden, controlling for lifestyle confounders	To control for additional contemporaneous confounders on the relationship of social mobility with AL.	Destination predominated over origin in influence on AL, and social mobility was not associated with AL.
Supplementary Table 5.11	Parameter estimates from diagonal reference models estimating mobility effects on allostatic load burden, taking a conservative maximum bias approach to missing data	To assess whether the large proportion of data missing across biomarkers impact on the findings	Destination predominated over origin in influence on AL, and social mobility was not associated with AL.

Note: n/a = not applicable. This table was published in McLoughlin et al., (2022)

Supplementary Table 5.2: Biomarker descriptives, and high risk cut points for generating the supplemental clinical risk allostatic load index

Biomarker	Mean	SD	Clinical risk cut point
Systolic blood pressure	134.9	19.5	≥140.0 (or taking anti-hypertensives)
Diastolic blood pressure	82.4	11.0	≥90.0
Resting heart rate	68.8	11.4	≥90.0
Pulse wave velocity	2.3	0.2	≥12.0
HbA1c	33.1	5.5	≥48.0 (or taking diabetes medication)
Total cholesterol	5.2	1.1	≥6.2 (or taking statins)
BMI	28.6	4.8	≥30
Waist-height ratio	0.9	0.1	men ≥1.0, female ≥0.9
Cystatin C	1.0	0.2	≥1.6
Creatinine	79.1	19.8	≥90.0 or <49.0
C-reactive protein	0.7	0.8	≥3.0
High density lipoprotein*	-1.6	0.4	men <1, female <1.29 (or taking lipid modifying agents)
<i>Allostatic load index</i>	0.0	1.00	

*Note. *High density lipoprotein reverse coded. SD = standard deviation. Allostatic load index generated through a summation of standardised biomarkers. This table was published in McLoughlin et al., (2022)*

Supplementary Table 5.3: Parameter estimates from diagonal reference models on allostatic load, interactions

	<i>Female</i>		<i>Age</i>		<i>Upward mobility</i>		<i>Downward mobility</i>	
	<i>b</i>	<i>95% CI</i>	<i>b</i>	<i>95% CI</i>	<i>b</i>	<i>95% CI</i>	<i>b</i>	<i>95% CI</i>
Interaction term	0.06	(-0.26, 0.38)	-0.01	(-0.03, 0.01)	-0.08	(-0.60, 0.45)	0.08	(-0.45, 0.60)
Weights								
Origin	0.23	(-0.02, 0.48)	0.26*	(0.09, 0.43)	0.31	(-0.08, 0.70)	0.23	(-0.01, 0.47)
Destination	0.77***	(0.52, 1.02)	0.74***	(0.57, 0.91)	0.69**	(0.30, 1.08)	0.77**	(0.53, 1.01)
AIC	10390.7		10389.8		10390.7		10390.7	
BIC	10441.0		10440.1		10441.0		10441.0	
Degrees of freedom	8		8		8		8	

Note. 95% confidence intervals in brackets. AIC: Akaike Information Criteria. BIC: Bayesian Information Criteria. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. This table was published in McLoughlin et al., (2022)

Supplementary Table 5.4: Parameter estimates from diagonal reference models estimating mobility effects on the allostatic load sub-systems

	<i>Cardiovascular</i>		<i>Metabolic</i>		<i>Renal</i>		<i>Inflammatory</i>	
	<i>b</i>	<i>95% CI</i>	<i>b</i>	<i>95% CI</i>	<i>b</i>	<i>95% CI</i>	<i>b</i>	<i>95% CI</i>
Constant	0.50***	(0.40, 0.60)	1.00***	(0.90, 1.10)	0.99***	(0.89, 1.09)	-0.14**	(-0.25, -0.04)
Socially immobile								
Professional / managerial	-0.07*	(-0.12, -0.01)	-0.17***	(-0.22, -0.12)	-0.09***	(-0.14, -0.04)	-0.17***	(-0.23, -0.11)
Non-manual /skilled manual	-0.04	(-0.10, 0.01)	0.01	(-0.04, 0.06)	0.01	(-0.04, 0.05)	0.03	(-0.02, 0.08)
Semi-skilled/unskilled/never worked	0.11***	(0.05, 0.17)	0.16***	(0.09, 0.22)	0.08**	(0.02, 0.14)	0.13***	(0.07, 0.20)
Controls								
Female	-0.33***	(-0.39, -0.27)	-0.65***	(-0.71, -0.60)	-0.63***	(-0.68, -0.57)	0.08**	(0.02, 0.14)
Age	0.03***	(0.03, 0.03)	0.00	(-0.00, 0.00)	0.04***	(0.04, 0.05)	0.01***	(0.00, 0.01)
<i>Childhood health</i>								
Excellent		<i>ref</i>		<i>ref</i>		<i>ref</i>		<i>ref</i>
Very good	0.05	(-0.02, 0.12)	0.02	(-0.05, 0.09)	-0.08*	(-0.14, -0.01)	0.03	(-0.05, 0.10)
Good	0.02	(-0.08, 0.11)	0.03	(-0.06, 0.12)	-0.03	(-0.12, 0.05)	0.10	(-0.00, 0.19)
Fair	-0.07	(-0.22, 0.07)	0.00	(-0.14, 0.15)	-0.03	(-0.17, 0.10)	0.06	(-0.09, 0.22)
Poor	0.12	(-0.13, 0.36)	0.19	(-0.05, 0.43)	0.04	(-0.18, 0.27)	0.26*	(0.00, 0.51)
Weights								
Origin	0.31	(-0.04, 0.66)	0.30**	(0.09, 0.51)	0.24	(-0.15, 0.63)	0.18	(-0.06, 0.43)
Destination	0.69***	(0.34, 1.04)	0.70***	(0.49, 0.91)	0.76***	(0.37, 1.15)	0.82***	(0.57, 1.06)
AIC	10954.8		10860.3		10328.8		11262.6	
BIC	11024.0		10929.5		10398.0		11331.8	
Degrees of freedom	11		11		11		11	

Note. Age is centred around the sample mean. Cardiovascular system: systolic blood pressure, diastolic blood pressure, resting heart rate, pulse wave velocity. Metabolic system: BMI, waist-hip ratio, total cholesterol, HbA1c, high density lipoprotein. Renal system: Creatinine, cystatin-c. Inflammatory: C-reactive protein. AIC: Akaike Information Criteria. BIC: Bayesian Information Criteria. * $p < .05$, ** $p < .01$, *** $p < .001$. This table was published in McLoughlin et al., (2022)

Supplementary Table 5.5: Parameter estimates from diagonal reference models estimating mobility effects on allostatic load (clinical cut-points incorporating medication usage)

	<i>Base model</i>		<i>Upward mobility</i>		<i>Downward mobility</i>		<i>Upward Steps</i>		<i>Downward steps</i>	
	<i>b</i>	<i>95% CI</i>	<i>b</i>	<i>95% CI</i>	<i>b</i>	<i>95% CI</i>	<i>b</i>	<i>95% CI</i>	<i>b</i>	<i>95% CI</i>
Constant	0.59***	(0.50, 0.69)	0.61***	(0.51, 0.71)	0.61***	(0.51, 0.71)	0.62***	(0.51, 0.72)	0.61***	(0.51, 0.71)
Socially immobile										
Professional / managerial	-0.16***	(-0.22, -0.11)	-0.16***	(-0.21, -0.10)	-0.16***	(-0.22, -0.11)	-0.15***	(-0.21, -0.09)	-0.16***	(-0.22, -0.11)
Non-manual /skilled manual	-0.02	(-0.07, 0.03)	-0.02	(-0.08, 0.03)	-0.02	(-0.06, 0.03)	-0.04	(-0.09, 0.02)	-0.01	(-0.06, 0.03)
Semi-skilled/unskilled/never worked	0.18***	(0.12, 0.24)	0.18***	(0.12, 0.24)	0.18***	(0.12, 0.24)	0.19***	(0.13, 0.24)	0.18***	(0.12, 0.24)
Controls										
Female	-0.37***	(-0.43, -0.31)	-0.37***	(-0.43, -0.31)	-0.37***	(-0.43, -0.31)	-0.37***	(-0.43, -0.31)	-0.37***	(-0.43, -0.31)
Age	0.04***	(0.03, 0.04)	0.04***	(0.03, 0.04)	0.04***	(0.03, 0.04)	0.04***	(0.03, 0.04)	0.04***	(0.03, 0.04)
<i>Childhood health</i>										
Excellent		<i>ref</i>		<i>ref</i>		<i>ref</i>		<i>ref</i>		<i>ref</i>
Very good	-0.04	(-0.10, 0.03)	-0.04	(-0.10, 0.03)	-0.04	(-0.10, 0.03)	-0.04	(-0.10, 0.03)	-0.04	(-0.10, 0.03)
Good	-0.01	(-0.10, 0.08)	-0.01	(-0.10, 0.08)	-0.01	(-0.10, 0.08)	-0.01	(-0.10, 0.08)	-0.01	(-0.10, 0.08)
Fair	-0.09	(-0.23, 0.06)	-0.09	(-0.23, 0.06)	-0.08	(-0.23, 0.06)	-0.09	(-0.23, 0.06)	-0.08	(-0.23, 0.06)
Poor	0.12	(-0.12, 0.35)	0.11	(-0.12, 0.35)	0.11	(-0.12, 0.35)	0.11	(-0.12, 0.35)	0.12	(-0.12, 0.35)
Weights										
Origin	0.37***	(0.18, 0.56)	0.50**	(0.17, 0.84)	0.24	(-0.02, 0.51)	0.64***	(0.28, 1.00)	0.25	(-0.02, 0.52)
Destination	0.63***	(0.44, 0.82)	0.50**	(0.16, 0.83)	0.76***	(0.49, 1.02)	0.36	(-0.00, 0.72)	0.75***	(0.48, 1.02)
Mobility status										
Upward			-0.05	(-0.16, 0.06)						
Downward					-0.07	(-0.18, 0.03)				
One-step upward							-0.07	(-0.17, 0.03)		
Two steps upward							-0.16	(-0.34, 0.02)		
One step downward									-0.07	(-0.18, 0.03)
Two steps downward									-0.03	(-0.27, 0.20)
AIC	10680.1		10681.2		10680.3		10681.7		10682.2	
BIC	10749.3		10756.7		10755.8		10763.5		10764.0	
Degrees of freedom	11		12		12		13		13	

Note. Age is centred around the sample mean. Clinical cut points: systolic blood pressure ≥ 140 (or taking anti-hypertensives), diastolic blood pressure ≥ 90 , resting heart rate ≥ 90 , pulse wave velocity ≥ 12 , HbA1c ≥ 48 (or taking diabetes medication), High density lipoprotein men < 1 , female < 1.29 (or taking lipid modifying agents), total cholesterol ≥ 6.2 (or

taking statins), body mass index ≥ 30 , waist hip ratio men ≥ 1 , female ≥ 0.90 , cystatin c ≥ 1.55 , creatinine ≥ 90 or < 49 , c reactive protein ≥ 3 . AIC: Akaike Information Criteria. BIC: Bayesian Information Criteria. * $p < .05$, ** $p < .01$, *** $p < .001$. This table was published in McLoughlin et al., (2022)

Supplementary Table 5.6: Parameter estimates from diagonal reference models estimating educational mobility effects on allostatic load

	Base model		Upward mobility		Downward mobility		Upward Steps		Downward steps	
	<i>b</i>	95% CI	<i>b</i>	95% CI	<i>b</i>	95% CI	<i>b</i>	95% CI	<i>b</i>	95% CI
Constant	1.09***	(0.99, 1.19)	1.11***	(1.01, 1.21)	1.08***	(0.98, 1.19)	1.11***	(1.01, 1.22)	1.09***	(0.98, 1.19)
Socially immobile										
Primary	0.15***	(0.09, 0.21)	0.16***	(0.10, 0.22)	0.16***	(0.09, 0.22)	0.16***	(0.10, 0.22)	0.16***	(0.09, 0.22)
Secondary	0.01	(-0.03, 0.06)	0.01	(-0.04, 0.06)	0.01	(-0.04, 0.06)	0.01	(-0.04, 0.06)	0.01	(-0.04, 0.06)
Tertiary	-0.17***	(-0.22, -0.11)	-0.17***	(-0.22, -0.11)	-0.17***	(-0.22, -0.11)	-0.17***	(-0.22, -0.11)	-0.17***	(-0.22, -0.11)
Controls										
Female	-0.72***	(-0.78, -0.66)	-0.72***	(-0.78, -0.67)	-0.72***	(-0.78, -0.67)	-0.72***	(-0.78, -0.67)	-0.72***	(-0.78, -0.67)
Age	0.03***	(0.02, 0.03)	0.03***	(0.02, 0.03)	0.03***	(0.02, 0.03)	0.03***	(0.02, 0.03)	0.03***	(0.02, 0.03)
<i>Childhood health</i>										
Excellent		<i>ref</i>		<i>ref</i>		<i>ref</i>		<i>ref</i>		<i>ref</i>
Very good	0.01	(-0.06, 0.08)	0.01	(-0.06, 0.08)	0.01	(-0.06, 0.08)	0.01	(-0.06, 0.08)	0.01	(-0.06, 0.08)
Good	0.04	(-0.05, 0.13)	0.04	(-0.05, 0.13)	0.04	(-0.05, 0.13)	0.04	(-0.05, 0.13)	0.04	(-0.05, 0.13)
Fair	-0.03	(-0.18, 0.11)	-0.03	(-0.18, 0.11)	-0.03	(-0.18, 0.11)	-0.03	(-0.18, 0.11)	-0.03	(-0.18, 0.11)
Poor	0.17	(-0.08, 0.42)	0.17	(-0.08, 0.41)	0.17	(-0.08, 0.42)	0.17	(-0.08, 0.41)	0.17	(-0.08, 0.42)
Weights										
Origin	0.16	(-0.10, 0.42)	0.22	(-0.04, 0.47)	0.19	(-0.07, 0.45)	0.21	(-0.05, 0.47)	0.19	(-0.07, 0.45)
Destination	0.84***	(0.58, 1.10)	0.78***	(0.53, 1.04)	0.81***	(0.55, 1.07)	0.79***	(0.53, 1.05)	0.81***	(0.55, 1.07)
Mobility status										
Upward			-0.05	(-0.11, 0.01)						
Downward					0.05	(-0.02, 0.13)				
One-step upward							-0.06	(-0.12, 0.01)		
Two steps upward							-0.03	(-0.14, 0.07)		
One step downward									0.05	(-0.03, 0.13)
Two steps downward									0.08	(-0.13, 0.29)
AIC		9647.1		9646.4		9647.4		9648.3		9649.3
BIC		9715.5		9721.0		9721.9		9729.1		9730.1
Degrees of freedom		11		12		12		13		13

Note. Age is centred around the sample mean. Origin education is derived from highest level of education obtained by fathers. AIC: Akaike Information Criteria. BIC: Bayesian Information Criteria. * $p < .05$, ** $p < .01$, *** $p < .001$. This table was published in McLoughlin et al., (2022)

Supplementary Table 5.7: Parameter estimates from diagonal reference models estimating mobility effects on allostatic load (5-level SEP)

	<i>Base model</i>		<i>Upward mobility</i>		<i>Downward mobility</i>		<i>Upward Steps</i>		<i>Downward steps</i>	
	<i>b</i>	<i>95% CI</i>	<i>b</i>	<i>95% CI</i>	<i>b</i>	<i>95% CI</i>	<i>b</i>	<i>95% CI</i>	<i>b</i>	<i>95% CI</i>
Constant	1.17***	(1.06, 1.28)	1.18***	(1.07, 1.29)	1.16***	(1.04, 1.27)	1.21***	(1.10, 1.32)	1.12***	(1.00, 1.25)
Socially immobile										
Professional / managerial	-0.26***	(-0.33, -0.19)	-0.23***	(-0.31, -0.15)	-0.25***	(-0.32, -0.17)	-0.22***	(-0.30, -0.15)	-0.23***	(-0.32, -0.13)
Non-manual	-0.15***	(-0.23, -0.07)	-0.18***	(-0.27, -0.09)	-0.16***	(-0.24, -0.08)	-0.25***	(-0.33, -0.16)	-0.18***	(-0.27, -0.09)
Skilled manual / semi-skilled	0.05	(-0.03, 0.13)	0.07	(-0.01, 0.14)	0.06	(-0.02, 0.14)	0.04	(-0.03, 0.11)	0.09	(-0.00, 0.19)
Unskilled	0.20**	(0.06, 0.34)	0.19**	(0.07, 0.31)	0.20**	(0.07, 0.33)	0.17***	(0.08, 0.26)	0.18**	(0.06, 0.30)
Never worked	0.16*	(0.02, 0.30)	0.15*	(0.02, 0.29)	0.15*	(0.01, 0.29)	0.26***	(0.12, 0.40)	0.14	(-0.02, 0.29)
Controls										
Female	-0.72***	(-0.77, -0.66)	-0.72***	(-0.77, -0.66)	-0.72***	(-0.77, -0.66)	-0.71***	(-0.77, -0.66)	-0.71***	(-0.77, -0.66)
Age	0.03***	(0.03, 0.03)	0.03***	(0.03, 0.03)	0.03***	(0.03, 0.03)	0.03***	(0.03, 0.03)	0.03***	(0.03, 0.03)
<i>Childhood health</i>										
Excellent		<i>ref</i>		<i>ref</i>		<i>ref</i>		<i>ref</i>		<i>ref</i>
Very good	0.00	(-0.06, 0.07)	0.00	(-0.06, 0.07)	0.00	(-0.06, 0.07)	0.00	(-0.06, 0.07)	0.00	(-0.06, 0.07)
Good	0.03	(-0.06, 0.11)	0.03	(-0.06, 0.11)	0.03	(-0.06, 0.11)	0.03	(-0.06, 0.11)	0.02	(-0.06, 0.11)
Fair	-0.03	(-0.17, 0.10)	-0.04	(-0.17, 0.10)	-0.04	(-0.17, 0.10)	-0.04	(-0.18, 0.10)	-0.04	(-0.17, 0.10)
Poor	0.22	(-0.01, 0.44)	0.21	(-0.02, 0.44)	0.22	(-0.01, 0.44)	0.21	(-0.02, 0.44)	0.22	(-0.01, 0.45)
Weights										
Origin	0.30***	(0.13, 0.47)	0.47***	(0.23, 0.72)	0.36**	(0.13, 0.60)	0.75***	(0.48, 1.01)	0.47**	(0.17, 0.77)
Destination	0.70***	(0.53, 0.87)	0.53***	(0.28, 0.77)	0.64***	(0.40, 0.87)	0.25	(-0.01, 0.52)	0.53***	(0.23, 0.83)
Mobility status										
Upward			-0.08	(-0.16, 0.01)						
Downward					0.04	(-0.05, 0.14)				
One-step upward							-0.10*	(-0.18, -0.01)		
Two steps upward							-0.15*	(-0.28, -0.03)		
Three steps upward							-0.25*	(-0.45, -0.05)		
Four steps upward							-0.41**	(-0.68, -0.14)		
One step downward									0.11	(-0.02, 0.24)
Two step downward									0.04	(-0.13, 0.20)
Three steps downward									0.03	(-0.35, 0.40)
Four steps downward									0.14	(-0.29, 0.56)
AIC	10386.1		10385.2		10387.3		10387.5		10391.2	
BIC	10467.8		10473.3		10475.4		10494.5		10498.2	
Degrees of freedom	14		15		15		17		17	

Note. AIC: Akaike Information Criteria. BIC: Bayesian Information Criteria. * $p < .05$, ** $p < .01$, *** $p < .001$. This table was published in McLoughlin et al., (2022)

Supplementary Table 5.8: Parameter estimates from diagonal reference models (biomarkers based on prior Understanding Society study)

	<i>Base model</i>		<i>Upward mobility</i>		<i>Downward mobility</i>		<i>Upward Steps</i>		<i>Downward steps</i>	
	<i>b</i>	<i>95% CI</i>	<i>b</i>	<i>95% CI</i>	<i>b</i>	<i>95% CI</i>	<i>b</i>	<i>95% CI</i>	<i>b</i>	<i>95% CI</i>
Constant	0.75***	(0.65, 0.85)	0.76***	(0.65, 0.87)	0.75***	(0.64, 0.85)	0.75***	(0.64, 0.86)	0.75***	(0.64, 0.85)
Socially immobile										
Professional / managerial	-0.18***	(-0.23, -0.12)	-0.17***	(-0.23, -0.12)	-0.18***	(-0.23, -0.12)	-0.18***	(-0.23, -0.13)	-0.18***	(-0.23, -0.12)
Non-manual /skilled manual	-0.00	(-0.05, 0.05)	-0.01	(-0.08, 0.05)	-0.01	(-0.06, 0.05)	0.01	(-0.06, 0.08)	-0.01	(-0.06, 0.05)
Semi-skilled/unskilled/never worked	0.18***	(0.12, 0.24)	0.19***	(0.12, 0.25)	0.18***	(0.12, 0.24)	0.17***	(0.09, 0.25)	0.18***	(0.12, 0.25)
Controls										
Female	-0.52***	(-0.58, -0.46)	-0.52***	(-0.58, -0.46)	-0.52***	(-0.58, -0.46)	-0.52***	(-0.58, -0.46)	-0.52***	(-0.58, -0.46)
Age	0.00	(-0.00, 0.01)	0.00	(-0.00, 0.01)	0.00	(-0.00, 0.01)	0.00	(-0.00, 0.01)	0.00	(-0.00, 0.01)
<i>Childhood health</i>										
Excellent		<i>ref</i>		<i>ref</i>						<i>ref</i>
Very good	0.03	(-0.04, 0.10)	0.03	(-0.04, 0.10)	0.03	(-0.04, 0.10)	0.03	(-0.04, 0.10)	0.03	(-0.04, 0.10)
Good	0.04	(-0.05, 0.13)	0.04	(-0.05, 0.13)	0.04	(-0.05, 0.13)	0.04	(-0.05, 0.13)	0.04	(-0.05, 0.13)
Fair	-0.00	(-0.15, 0.14)	-0.00	(-0.15, 0.14)	-0.00	(-0.15, 0.14)	-0.00	(-0.15, 0.14)	-0.00	(-0.15, 0.14)
Poor	0.16	(-0.08, 0.41)	0.16	(-0.08, 0.41)	0.16	(-0.08, 0.41)	0.16	(-0.08, 0.41)	0.16	(-0.08, 0.41)
Weights										
Origin	0.25*	(0.05, 0.45)	0.36	(-0.03, 0.75)	0.29*	(0.01, 0.56)	0.18	(-0.40, 0.76)	0.28*	(0.00, 0.56)
Destination	0.75***	(0.55, 0.95)	0.64**	(0.25, 1.03)	0.71***	(0.44, 0.99)	0.82**	(0.24, 1.40)	0.72***	(0.44, 1.00)
Mobility status										
Upward			-0.04	(-0.17, 0.09)						
Downward					0.02	(-0.09, 0.13)				
One-step upward							-0.01	(-0.15, 0.14)		
Two steps upward							0.06	(-0.22, 0.34)		
One step downward									0.02	(-0.09, 0.14)
Two steps downward									-0.01	(-0.25, 0.23)
AIC	10973.5		10975.1		10975.4		10976.8		10977.3	
BIC	11042.7		11050.6		11050.9		11058.5		11059.0	
Degrees of freedom	11		12		12		13		13	

Note. Sum of high risk biomarkers based off previous study¹¹⁷, including total cholesterol, high density lipoprotein, triglycerides, HbA1c, C-reactive protein, systolic blood pressure, resting heart rate, body mass index and waist circumference. Age is centred around the sample mean. AIC: Akaike Information Criteria. BIC: Bayesian Information Criteria. * $p < .05$, ** $p < .01$, *** $p < .001$. This table was published in McLoughlin et al., (2022)

Supplementary Table 5.9: Sample characteristics by category of social mobility

	Downwardly mobile		Stable professional/ managerial		Stable non-manual/ skilled manual		Stable semi-skilled/ unskilled/ never worked		Upwardly mobile	
	N	%	N	%	N	%	N	%	N	%
<i>Self-rated health in childhood</i>										
Excellent	661	51.4	436	64.6	814	57.1	476	44.5	1365	55.7
very good	345	26.8	134	19.9	375	26.3	337	31.5	649	26.5
Good	196	15.2	63	9.3	165	11.6	169	11.6	287	11.7
Fair	61	4.7	30	4.44	48	3.37	58	3.37	117	4.8
Poor	24	1.86	12	1.78	24	1.68	30	2.80	33	1.35
<i>Berkman-Syme Social Network Index</i>										
Most isolated	54	7.54	22	4.60	30	3.4	36	8.6	56	3.75
Moderately isolated	193	27.0	91	19.0	210	23.8	122	29.3	327	21.9
Moderately integrated	286	39.9	210	43.9	358	40.6	182	43.7	622	41.6
Most integrated	183	25.6	155	32.4	283	32.1	77	18.5	490	32.8
<i>Smoking status</i>										
Never	328	45.8	228	47.7	412	46.8	151	36.2	707	47.3
Past smoker	264	36.9	197	41.2	342	38.9	163	39.1	618	41.3
Current smoker	124	17.3	53	11.1	126	14.3	103	24.7	170	11.4
<i>Physical activity</i>										
Low	187	26.4	108	22.7	266	30.4	125	30.4	387	26.1
Moderate	254	35.8	191	40.1	291	33.2	131	31.9	560	37.7
High	268	37.8	177	37.2	319	36.4	155	37.7	538	36.2
<i>Alcohol consumption frequency</i>										
Do not drink alcohol	152	23.4	53	11.7	173	21.4	109	30.2	275	19.8
Almost every day	31	3.7	54	11.9	40	5.0	13	3.6	115	8.3
Five or six days a week	31	4.8	35	7.7	30	3.7	7	1.9	64	4.6
Three or four days a week	79	12.1	77	17.0	107	13.2	28	7.8	218	15.7
Once or twice a week	186	28.6	132	29.1	268	33.2	103	28.5	427	30.8
Once or twice a month	86	13.2	58	12.8	113	14.0	50	13.9	161	11.6
Less than once a month	71	10.9	42	9.3	64	7.9	44	12.2	110	7.9
Not at all in the last 6 months	15	2.3	2	0.4	13	1.6	7	1.9	17	1.2

Note: Physical activity was measured using The International Physical Activity Questionnaire (IPAQ), which captures the amount of time (minutes) spent walking and engaged in moderate and vigorous physical activity, and the amount of time spent sedentary. Protocol available at www.ipaq.ki.se. The 4 item Berkman-Syme Social Network Index (SNI) (L. F. Berkman, 1979) derived from marital status; sociability (number and frequency of contacts with children, close relatives, and close friends); church group membership and membership in other community organizations. This table was published in McLoughlin et al., (2022)

Supplementary Table 5.10: Parameter estimates from diagonal reference models estimating mobility effects on allostatic load burden, controlling for lifestyle confounders

	<i>Base model</i>		<i>Upward mobility</i>		<i>Upward steps</i>		<i>Downward mobility</i>		<i>Downward steps</i>	
	<i>b</i>	<i>95% CI</i>	<i>b</i>	<i>95% CI</i>	<i>b</i>	<i>95% CI</i>	<i>b</i>	<i>95% CI</i>	<i>b</i>	<i>95% CI</i>
Constant	1.62***	(1.42, 1.81)	1.61***	(1.42, 1.81)	1.61***	(1.42, 1.81)	1.60***	(1.41, 1.80)	1.61***	(1.42, 1.81)
Socially immobile										
Professional / managerial	-0.16***	(-0.21, -0.10)	-0.16***	(-0.21, -0.10)	-0.16***	(-0.21, -0.10)	-0.16***	(-0.21, -0.10)	-0.16***	(-0.21, -0.10)
Non-manual /skilled manual	0.02	(-0.03, 0.06)	0.02	(-0.03, 0.07)	0.02	(-0.03, 0.06)	0.03	(-0.01, 0.07)	0.02	(-0.03, 0.07)
Semi-skilled/unskilled/never worked	0.14***	(0.08, 0.20)	0.14***	(0.07, 0.20)	0.14***	(0.08, 0.20)	0.13***	(0.06, 0.19)	0.14***	(0.08, 0.20)
Controls										
Female	-0.78***	(-0.84, -0.72)	-0.78***	(-0.84, -0.72)	-0.78***	(-0.84, -0.72)	-0.78***	(-0.84, -0.72)	-0.78***	(-0.84, -0.72)
Age	0.03***	(0.03, 0.03)	0.03***	(0.03, 0.03)	0.03***	(0.03, 0.03)	0.03***	(0.03, 0.03)	0.03***	(0.03, 0.03)
Self-rated health in childhood										
Excellent		ref		ref		ref		ref		ref
Very good	-0.01	(-0.08, 0.06)	-0.01	(-0.08, 0.06)	-0.01	(-0.08, 0.06)	-0.01	(-0.07, 0.06)	-0.01	(-0.08, 0.06)
Good	-0.00	(-0.09, 0.09)	-0.00	(-0.09, 0.09)	-0.00	(-0.09, 0.09)	-0.01	(-0.10, 0.08)	-0.00	(-0.09, 0.09)
Fair	0.02	(-0.13, 0.16)	0.02	(-0.13, 0.16)	0.02	(-0.13, 0.16)	0.02	(-0.13, 0.16)	0.02	(-0.13, 0.16)
Poor	0.19	(-0.05, 0.44)	0.19	(-0.05, 0.44)	0.19	(-0.05, 0.44)	0.19	(-0.05, 0.44)	0.19	(-0.05, 0.44)
Berkman-Syme Social Network Index										
Most isolated		ref		ref		ref		ref		ref
Moderately isolated	-0.17*	(-0.32, -0.02)	-0.17*	(-0.32, -0.02)	-0.17*	(-0.32, -0.02)	-0.17*	(-0.32, -0.03)	-0.17*	(-0.32, -0.02)
Moderately integrated	-0.20**	(-0.34, -0.06)	-0.20**	(-0.34, -0.06)	-0.20**	(-0.34, -0.06)	-0.20**	(-0.34, -0.06)	-0.20**	(-0.34, -0.06)
Most integrated	-0.31***	(-0.46, -0.17)	-0.31***	(-0.46, -0.17)	-0.31***	(-0.46, -0.17)	-0.31***	(-0.46, -0.17)	-0.31***	(-0.46, -0.17)
Smoking status										
Never		ref		ref		ref		ref		ref
Past smoker	0.08*	(0.01, 0.14)	0.08*	(0.01, 0.14)	0.08*	(0.01, 0.14)	0.08*	(0.01, 0.14)	0.08*	(0.01, 0.14)
Current smoker	0.12**	(0.03, 0.21)	0.12**	(0.03, 0.21)	0.12**	(0.03, 0.21)	0.12**	(0.03, 0.21)	0.12**	(0.03, 0.21)
Physical activity										
Low										
Moderate	-0.15***	(-0.22, -0.08)	-0.15***	(-0.22, -0.08)	-0.15***	(-0.22, -0.08)	-0.15***	(-0.22, -0.08)	-0.15***	(-0.22, -0.08)
High	-0.22***	(-0.30, -0.15)	-0.23***	(-0.30, -0.15)	-0.22***	(-0.30, -0.15)	-0.22***	(-0.30, -0.15)	-0.22***	(-0.30, -0.15)
Alcohol frequency										
Do not drink alcohol		ref		ref		ref		ref		ref
Almost every day	-0.28***	(-0.41, -0.15)	-0.28***	(-0.41, -0.16)	-0.28***	(-0.41, -0.15)	-0.28***	(-0.41, -0.15)	-0.28***	(-0.41, -0.15)
Five or six days a week	-0.17*	(-0.32, -0.02)	-0.17*	(-0.32, -0.02)	-0.17*	(-0.32, -0.02)	-0.17*	(-0.32, -0.02)	-0.17*	(-0.32, -0.02)

Three or four days a week	-0.17***	(-0.28, -0.07)	-0.18***	(-0.28, -0.07)	-0.17***	(-0.28, -0.07)	-0.18***	(-0.28, -0.07)	-0.18***	(-0.28, -0.07)
Once or twice a week	-0.17***	(-0.25, -0.09)	-0.17***	(-0.25, -0.09)	-0.17***	(-0.25, -0.09)	-0.17***	(-0.25, -0.09)	-0.17***	(-0.25, -0.09)
Once or twice a month	-0.05	(-0.15, 0.05)	-0.05	(-0.15, 0.06)	-0.05	(-0.15, 0.06)	-0.05	(-0.15, 0.05)	-0.05	(-0.15, 0.06)
Less than once a month	0.06	(-0.06, 0.17)	0.05	(-0.06, 0.17)	0.06	(-0.06, 0.17)	0.06	(-0.06, 0.17)	0.06	(-0.06, 0.17)
Not at all in the last 6 months	-0.05	(-0.29, 0.20)	-0.05	(-0.29, 0.20)	-0.05	(-0.29, 0.20)	-0.05	(-0.29, 0.19)	-0.05	(-0.29, 0.20)
Weights										
Origin	0.20	(-0.04, 0.44)	0.14	(-0.30, 0.59)	0.21	(-0.11, 0.53)	0.00	(-0.50, 0.50)	0.21	(-0.11, 0.54)
Destination	0.80***	(0.56, 1.04)	0.86***	(0.41, 1.30)	0.79***	(0.47, 1.11)	1.00***	(0.50, 1.50)	0.79***	(0.46, 1.11)
Mobility status										
Upward			0.02	(-0.09, 0.13)						
Downward					0.01	(-0.10, 0.11)				
One-step upward							0.03	(-0.07, 0.13)		
Two steps upward							0.10	(-0.08, 0.28)		
One step downward									0.00	(-0.10, 0.11)
Two steps downward									0.03	(-0.21, 0.26)
AIC	9384.0		9385.9		9386.0		9387.0		9387.9	
BIC	9538.9		9547.0		9547.1		9554.3		9555.3	
Degrees of freedom	25		26		26		27		27	

*Note. N=3,632. Physical activity was measured using The International Physical Activity Questionnaire (IPAQ), which captures the amount of time (minutes) spent walking and engaged in moderate and vigorous physical activity, and the amount of time spent sedentary. Protocol available at www.ipaq.ki.se. The 4 item Berkman-Syme Social Network Index (SNI)²¹⁴ derived from marital status; sociability (number and frequency of contacts with children, close relatives, and close friends); church group membership and membership in other community organizations. Age is centred around the sample mean. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. This table was published in McLoughlin et al., (2022)*

Supplementary Table 5.11: Parameter estimates from diagonal reference models estimating mobility effects on allostatic load burden, taking a conservative maximum bias approach to missing data (n=5,153)

	<i>Base model</i>		<i>Upward mobility</i>		<i>Downward mobility</i>		<i>Upward steps</i>		<i>Downward steps</i>	
	<i>b</i>	<i>95% CI</i>	<i>b</i>	<i>95% CI</i>	<i>b</i>	<i>95% CI</i>	<i>b</i>	<i>95% CI</i>	<i>b</i>	<i>95% CI</i>
Constant	0.63***	(0.54, 0.71)	0.63***	(0.54, 0.71)	0.61***	(0.53, 0.70)	0.62***	(0.53, 0.71)	0.61***	(0.52, 0.70)
Socially immobile										
Professional / managerial	0.13***	(0.08, 0.18)	0.13***	(0.08, 0.18)	0.13***	(0.08, 0.17)	0.12***	(0.07, 0.17)	0.12***	(0.08, 0.17)
Non-manual /skilled manual	0.03	(-0.02, 0.07)	0.03	(-0.02, 0.07)	0.03	(-0.01, 0.07)	0.03	(-0.02, 0.08)	0.04	(-0.00, 0.08)
Semi-skilled/unskilled/never worked	-0.15***	(-0.20, -0.11)	-0.15***	(-0.20, -0.11)	-0.16***	(-0.20, -0.11)	-0.16***	(-0.21, -0.11)	-0.16***	(-0.21, -0.11)
Controls										
Female	-0.28***	(-0.32, -0.23)	-0.28***	(-0.32, -0.23)	-0.28***	(-0.32, -0.23)	-0.28***	(-0.32, -0.23)	-0.28***	(-0.33, -0.23)
Age	0.01***	(-0.01, 0.01)	0.01***	(-0.01, 0.01)	-0.01***	(-0.01, -0.01)	-0.01***	(-0.01, -0.01)	0.01***	(-0.01, 0.01)
<i>Childhood health</i>										
Excellent		<i>ref</i>		<i>ref</i>		<i>ref</i>		<i>ref</i>		<i>ref</i>
Very good	-0.03	(-0.09, 0.02)	-0.03	(-0.09, 0.02)	-0.03	(-0.09, 0.02)	-0.03	(-0.09, 0.02)	-0.03	(-0.09, 0.02)
Good	-0.04	(-0.11, 0.04)	-0.04	(-0.11, 0.04)	-0.04	(-0.11, 0.04)	-0.04	(-0.11, 0.04)	-0.04	(-0.12, 0.04)
Fair	-0.16**	(-0.27, -0.04)	-0.16**	(-0.27, -0.04)	-0.16**	(-0.27, -0.04)	-0.16**	(-0.27, -0.04)	-0.16**	(-0.27, -0.04)
Poor	-0.17	(-0.35, 0.02)	-0.17	(-0.35, 0.02)	-0.17	(-0.35, 0.02)	-0.17	(-0.35, 0.02)	-0.17	(-0.35, 0.02)
Weights										
Origin	0.36***	(0.16, 0.55)	0.35*	(0.01, 0.70)	0.27	(-0.00, 0.54)	0.46*	(0.09, 0.83)	0.22	(-0.05, 0.48)
Destination	0.64***	(0.45, 0.84)	0.65***	(0.30, 0.99)	0.73***	(0.46, 1.00)	0.54**	(0.17, 0.91)	0.78***	(0.52, 1.05)
Mobility status										
Upward			-0.00	(-0.09, 0.09)						
Downward					0.04	(-0.05, 0.13)				
One-step upward							0.00	(-0.09, 0.09)		
Two steps upward							0.08	(-0.06, 0.23)		
One step downward									0.04	(-0.05, 0.13)
Two steps downward									0.20	(-0.00, 0.40)
AIC	13481.3		13483.3		13482.5		13483.3		13481.6	
BIC	13553.4		13561.9		13561.1		13568.4		13566.7	
Degrees of freedom	11		12		12		13		13	

Note: Age is centred around the sample mean, i.e., TILDA participants who attended the health assessment module, and provided life course SEP data. AIC: Akaike Information Criteria. BIC: Bayesian Information Criteria. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. This table was published in McLoughlin et al., (2022)

Chapter 6: The association of allostatic load biomarkers with stress and all-cause mortality

Chapter summary

Introduction: Allostatic load (AL) is posited to capture physiological dysregulation resulting from cumulative stress exposure, which is typically measured using composite panels of biomarkers, but there is a lack of consensus regarding which biomarkers are sufficient for its measurement.

Methods: This study explores the relation of 25 different allostatic load biomarkers encompassing 6 different physiological systems (inflammatory, cardiovascular, metabolic, anthropometric, parasympathetic, renal) with self-reported stress and hazard of all-cause mortality over a mean 8-year follow-up among a community dwelling sample of 3855 individuals aged 50 years and over to inform the development of an AL index that is built by selecting biomarkers that are correlated with stress *and* anticipate hard clinical endpoints.

Results: 9/25 biomarkers were significantly correlated with the Perceived Stress Scale (PSS), while 5/29 biomarkers and 2/6 sub-systems were significantly associated with increased hazard of all-cause mortality. C-reactive protein (HR= 1.36, 95% CI= 1.18, 1.56), Interleukin-6 (HR=1.34, 95% CI = 1.17, 1.54), Cystatin C (HR= 1.34, 95% CI= 1.18, 1.51), Interleukin-8 (HR= 1.21, 95% CI= 1.07, 1.40), and resting heart rate (HR= 1.21, 95% CI= 1.04, 1.40) were associated with increased risk of mortality. The renal (HR = 1.25, 95% CI= 1.09, 1.42) and inflammatory (HR= 1.31, 95% CI: 1.17, 1.53) sub-systems performed best in terms of predicting mortality risk. A composite index including all 25 biomarkers underperformed relative to individual biomarkers and physiological sub-systems (HR= 1.22, 95% CI = 1.02, 1.44).

Conclusion: This study can help inform the choice of biomarkers to define an AL index and may prompt some reappraisal regarding whether a multi-system AL measure predicts mortality better than the sum of its parts.

6.1 Introduction

Allostatic Load (AL) refers to the conceptual framework devised by McEwen & Stellar (1993) to capture the wear and tear on interrelated biological systems as a result of repeat and chronic adaptation to stressors²³. Allostasis is the ability of the body's physiological systems to maintain stability by successfully adapting to acute stressors¹³, while AL refers to the damage incurred on interrelated biological systems as a result of repeat and chronic adaptation¹⁸. Both the hypothalamic-pituitary-adrenal axis (HPA) and the sympathetic-adrenal-medullary (SAM) system are activated in response to stress, and the downstream result is the release of hormones and cytokines which, if prolonged, exacerbate dysregulation or AL burden across organ systems. According to the AL framework, these systems can become taxed and dysregulated, exhibiting imbalances across the *primary mediators* of the stress response (i.e., glucocorticoids, catecholamines and pro-inflammatory cytokines). *Secondary mediators* of the stress response refer to the sub-clinical disturbances across downstream organ systems caused by the hormonal imbalances (e.g., blood pressure, cholesterol, immune function etc.), which consequently lead to disease states, or *tertiary health outcomes*.

A number of common operational definitions of AL exist^{141,208}, yet it is typically represented as a multi-system index of dysregulated, or high-risk (e.g. highest quartiles of clinical risk), biomarkers derived from the sample distribution⁴³. Three decades have passed since the original operationalisation of AL: 10 biomarkers (i.e., epinephrine, norepinephrine, cortisol, DHEAS, systolic blood pressure (SBP), diastolic blood pressure (DBP), waist-hip ratio (WHR), total cholesterol

(TChol), high density lipoprotein (HDL), glycosylated haemoglobin (HbA1c)) were chosen to define AL, based on available biological data within the MacArthur Studies of Successful Ageing. This multi-system measure predicted physical and cognitive decline and greater incidence of cardiovascular disease over a three-year follow-up, establishing AL as a sub-clinical predictor ⁴³. However, there remains little consensus regarding which biomarkers should be used to instantiate the concept.

6.2 Heterogeneity of biomarkers used to define allostatic load

The notable diversity in biomarker panels employed to define AL across studies was first highlighted over a decade ago with a review depicting the use of 51 distinct biomarkers across 58 AL-related publications ²⁴. This variability was underscored by a systematic review of studies examining socio-economic position (SEP) and AL which reported the use of 59 distinct biomarkers across 26 studies ²⁸. The widespread inconsistencies in biomarker panels used is not just found *across* studies, but also *within* studies. In the *National Health and Nutritional Examination Survey (NHANES)*, 26 distinct biomarkers were used across 21 AL related publications ¹⁶¹. The lack of an agreed definition of AL remains problematic as AL is assuming an increasingly prominent position in research addressing how the social environment comes to impact health across populations ^{26,28}. AL is hypothesised to represent a pre-clinical measure of health ⁴³, yet the applicability of the measure is undermined by the absence of a gold standard panel of biomarkers, and lack of universally accepted guidelines for the quantification of the purported stress-related dysregulation.

6.3 In search of an optimal panel of biomarkers for allostatic load

Further, the search for an optimal panel of biological markers to define AL comes with a danger of straying too far from the conceptual underpinnings of the AL framework, which denote stress as the

root driver of multi-system dysregulation. As such, the purpose of the measurement developed by McEwen and Stellar (1993) was to capture the downstream multi-system physiological consequences of adaptations to the environment via stress response pathways, yet little attention has been given to the role of stress when it comes to calibrating a measure of AL. There is, after all, many non-stress related pathways through which the social environment may come to affect health (e.g., lifestyle behaviours, pollution etc.). To remain faithful to the original theory, it would be helpful if biomarkers included in AL indices were correlated with stress and associated with hard clinical endpoints.

6.4 Allostatic load and stress

The relationship of greater stress with declining health is well established ⁴, yet the relationship of stress exposure with AL burden remains inconsistent, and appears to be dependent on how stress is conceptualised. For instance, work stress, financial strain, relationship stress and caregiving stress were associated with AL in a sample of Mexican-American women (n= 301; mean age= 49.8), yet no association was reported of personal or familial health problems, housing or relationship stress with AL ²⁰⁶. Indeed, it has been argued that subjective reports of stress and objective stress measure distinct mechanisms ¹⁵⁸, and perceived stress may be more strongly related to AL than an objective count of stressors ²⁰⁵. Perhaps the disparate findings are reflective of the diverse biomarker panels utilised across studies, as a recent systematic review of 27 papers assessing the relationship of early life stress with AL burden noted the number of biomarkers employed ranged between 5 and 24 ²⁴³.

6.5 The utility of allostatic load as a predictor of mortality

Despite the inconsistent application of biomarker panels across studies, AL indices are consistently associated with hard clinical endpoints, including mortality (for review, see Parker et al., 2022), yet

the relationship of the component items of AL with mortality is less clear cut. For instance, peak flow, creatinine clearance, and c-reactive protein (CRP) were independently associated with all-cause mortality after controlling for age, sex, race and education in the MacArthur Study of Successful Aging, but not systolic (SBP) or diastolic blood pressure (DBP), HbA1c, high density lipoprotein (DHL), ratio of high to total cholesterol, waist hip ratio (WHR), cortisol, DHEAS, norepinephrine, epinephrine, albumin, Interleukin-6, fibrinogen)¹⁴². However, it was high risk quartiles of pulse rate, HDL, WHR, HbA1c and CRP, and scoring in the lowest quartiles of DBP and total cholesterol, but not SBP, that independently predicted all-cause mortality in the 2003 *Scottish Health Survey (SHeS)*³⁶. Direct comparison of results is difficult however, as the type of biomarkers employed differs across studies, while the units of measurement are rarely normalised to the same scale within (or between) studies to allow direct comparison of effect sizes. A further complexity to comparisons across studies includes the operationalisation the biomarkers. While some studies retain the continuous properties of the biomarkers, others dichotomise observed biomarkers values using risk cut points (e.g., clinical risk, sample derived risk and/or sex specific risk), possibly introducing measurement error and reducing variability.

Aside from the issue of which physiological parameters should be represented in AL indices, the number of biomarkers required to meet the requirements of a multi-system measure of dysregulation remains unknown. A recent editorial suggested that AL should be simplified to a single marker of HPA function, such as hair cortisol, as a solution to overcoming the wide array of biomarkers that have been used to define the concept²⁴⁴. This challenges the extant findings that suggest that single measures of biomarkers are not typically sufficient in capturing the global physiological dysregulation in which the concept of AL is rooted^{32,33,41}. The aforementioned study involving the SHeS cohort observed that HbA1c, HDL and WHR independently matched the predictive ability of a

composite AL index comprising SBP, DBP, WHR, heart rate, HDL, cholesterol, HbA1c, and CRP in predicting risk of mortality ³⁶, which is in contrast to many who report the composite AL index outperforms its components ^{32,41,45,142}.

6.6 Physiological sub-systems

A related question pertains to whether some physiological systems predominate in terms of their association with health. While grouping together multiple physiological sub-systems inevitably leads to a loss of biological specificity, these composite measures are purportedly useful for identifying the system-wide physiological impacts of stress that shape health outcomes, and in turn, risk of mortality ²⁴⁵. However, if one sub-system predicts as well or better than the composite index then this might prompt some reappraisal of the construct validity of the AL concept. For instance, Cornman et al. (2017) examined four composite sub-system scores (i.e., cardiovascular/ metabolic (0-7) ²⁴⁶, inflammation (0-6), HPA/SNS (0-4) and other (0-4)) derived from the 80th percentile of risk for 24 biomarkers from Social Environment and Biomarkers of Aging Study (SEBAS) ²⁴⁶. The cardiovascular/metabolic and inflammation sub-systems were predictive of mortality over a 4.5 year period, and performed as well as a composite AL index, while the HPA/ SNS and ‘other’ sub-score were not significantly associated with risk of mortality ²⁴⁶. Similarly, Castagné et al. (2018) generated physiological sub-system indices from 14 biomarkers representing inflammatory, metabolic, cardiovascular, and neuroendocrine function. Although the inflammatory and cardiovascular indices were significantly associated with risk of mortality, they marginally underperformed relative to the composite AL index ⁴⁵.

6.7 Rationale and present study

The Irish Longitudinal Study on Ageing (TILDA) collects a vast array of physiological, anthropometric, and blood-based biomarkers encompassing multiple organ systems, making it possibly one of the most extensive biomarker panels available worldwide for distilling an optimal AL index from the wide array of biomarkers that have been used to define the concept. In total, TILDA have substantial data on 25 of the 51 and 59 biomarkers captured in Juster et al. (2010) and Johnston et al.'s (2017) reviews, respectively. An additional strength is its prospective design, which means it has mortality data for up to 10 years since collection of the baseline biomarker data, affording us the opportunity to look at the predictive ability of the biomarker set over a long time-window. Stress is a central feature of the AL framework, but few studies have considered the correlation of component biomarker with stress when developing their AL indices. We address this deficit in the literature by simultaneously examining the correlation of the individual biomarkers with perceived stress and their association with mortality at up to 10-year follow-up amongst a population of community dwelling older people.

6.8 Methods

6.8.1 Data source

TILDA is a nationally representative prospective cohort study of over 8175 persons aged 50+ and their spouses living in the Republic of Ireland. The sampling fraction is approximately 1/156 of all community-dwelling adults aged 50 years and over resident in the Republic of Ireland, and details of the study design are available elsewhere¹³³. Baseline data were collected between 2009 and 2011, via computer-assisted personal interviews (CAPI), leave-behind paper and pen self-completion questionnaires (SCQ) (response rate = 84.6%), and a health assessment (response rate = 61.6%) which comprises the collection of blood samples and other cognitive and physiological parameters. If respondents were unable to attend the designated health assessment centre, a trained nurse

administered a subset of cognitive and physical tests in the respondent's home. Ethical approval for the study was provided by the Faculty of Health Science Research Ethics board in Trinity College Dublin, while informed consent was obtained from all respondents during data collection.

6.8.2 Measurements

6.8.2.1 Biomarkers and physiological sub-systems

Biomarkers are objectively measured physiological parameters. Details of the 25 biomarkers considered in this study and their relative physiological functions are reported in Table 1. Table 2 reports the descriptive statistics of each biomarker. Some biomarkers were characterised by marked skew and were log transformed to create a more symmetric distribution of the data. Supplementary Figure 6.1 illustrates the distribution of these biomarkers prior to transformation. For several of the biomarkers (standard deviation of the average n-n intervals calculated over 5 minutes (SDNN), Root mean square of successive RR interval differences (RMSSD), low frequency heart rate variability (LFHRV), high frequency heart rate variability (HFHRV) and high-density lipoprotein (HDL)), lower scores equate to higher risk for worse clinical outcomes and were reversed by multiplying the values by -1, so that higher values indicate higher risk. All biomarkers were standardised to a mean of 0 and a standard deviation of 1 to ensure meaningful comparison of effect sizes.

Physiological sub-system scores were calculated by summing standardised scores of system-specific biomarkers, and included (i) inflammatory: c-reactive protein (CRP), Interleukin-1 receptor antagonist (IL1RA), Interleukin-6 (IL6), Interleukin-8 (IL8), Interleukin-10 (IL10), Tumour necrosis factor alpha (TNFa); (ii) cardiovascular: systolic blood pressure (SBP), diastolic blood pressure (DBP), resting heart rate (RHR), Pulse pressure (pulse) and pulse wave velocity (PWV), (iii) parasympathetic: Standard deviation of the average n-n intervals calculated over 5 minutes (SDNN),

Root mean square of successive RR interval differences (RMSSD), low frequency heart rate variability (LFHRV), high frequency heart rate variability (HFHRV), (iv) metabolic: body mass index (BMI), waist hip ratio (WHR), waist circumference (Waist) and glycosylated haemoglobin (HbA1c), (v) lipids: high density lipoprotein (HDL), low density lipoprotein (LDL), Triglycerides, total cholesterol (TChol), and (vi) renal: creatinine and cystatin c (Cysc) sub-systems. A composite AL index was derived from summing all 25 biomarkers. The resulting sub-systems and composite AL index were then standardised a mean of 0 and a standard deviation of 1.

6.8.2.2 *Perceived stress*

A subjective measure of psychological stress over the previous month was measured using the well-validated Perceived Stress Scale (PSS) measured on a 0-4 response scale in the SCQ ²⁴⁷. Individual items refer to the degree to which respondents perceive their lives to be “*uncontrollable, unpredictable and overloading*” ²⁴⁷. Responses were summed to create a score of 0-16, with positive items reverse coded, such that higher scores indicated greater perceived stress. To reduce right skew, a square root transformation was applied to the PSS index. Missing data rate was $\leq 10\%$ for each item. The stress scale was found to be reliable (4 items: $\alpha = 0.63$).

6.8.2.3 *All-cause mortality*

Mortality status was ascertained through administrative record linkage to the national death registry (NDR) and linked to individual-level survey data from TILDA. Linking was performed for all individuals who died between Wave 1 and Wave 5, a maximum of 9.2 years of follow-up. Matching was conducted based on names, ages and addresses, and was successful for approximately 90% of the records - detailed procedures employed to perform this linkage are available elsewhere ²⁴⁸. Time to death was calculated from initial interview date through to date of death recorded on the NDR. Non-deceased respondents and those who were lost to follow-up were right censored at the end of

the follow-up period, 1st January 2019. The follow-up time was transformed to years by dividing these time frames by 365.25.

6.8.2.4 Demographic and lifestyle covariates

Any observed association between biomarkers and mortality could be due to common correlation with demographic or lifestyle factors. Therefore, a suite of confounders was controlled for in secondary models. Education (primary, secondary, tertiary attainment) was chosen as a demographic covariate, as AL burden and early mortality are highly patterned by socio-economic position ¹¹³. The Berkman-Syme social network index (SNI: 0-4, higher values indicate higher social connectedness) was employed to account for the effect of social connectedness, as loneliness was found to predict mortality amongst this cohort previously ²⁴⁹. The SNI was derived from: marital status, sociability (number and frequency of contacts with children, close relatives, and close friends); church group membership and membership in other community organizations) ²¹⁴. Smoking status (never, current, past), problematic alcohol consumption (no/ yes), and physical activity (low, med, high) were chosen to represent lifestyle factors, as risky health behaviours have been implicated as a potential mechanism through which stress can impact AL burden ³¹. Problematic alcohol use was derived from scoring ≥ 2 on the CAGE index ²¹¹, and physical activity was assessed using the 8-item International Physical Activity Questionnaire (IPAQ) ²¹³, following the IPAQ protocol (www.ipaq.ki.se).

Table 6.1: Details of the 25 biomarkers included in this study

System	Biomarker acronym	Biomarker name	Units	Physiological function
Inflammatory	CRP	C-reactive protein	mg/L	Acute phase pro-inflammatory protein synthesised mainly in the liver. It is activated by cytokines IL6, IL1 and TNFa and is elevated in response to inflammation and infection. Low CRP indicates less inflammation in the body
	IL1ra	Interleukin-1 receptor antagonist	pM	An anti-inflammatory protein, it competitively binds to IL-1 receptors and inhibits pro-inflammatory signalling by the cytokines IL1alpha and IL1beta
	IL6	Interleukin-6	pM	A potent pro-inflammatory cytokine produced by macrophages and T-cells in response to infection and tissue damage, responsible for stimulating acute phase proteins e.g., CRP
	IL8	Interleukin-8	pM	A chemokine, also called CXCL8, that is released early post-injury by macrophages, and plays a key role in the recruitment of neutrophils, phagocytosis, and angiogenesis. Widely used as a diagnostic and prognostic marker for infectious and other inflammatory conditions
	IL10	Interleukin-10	pM	Typically classified as anti-inflammatory and immunosuppressive cytokine that plays a central role in limiting immune responses to pathogens and damage signals. The effects of IL-10 are highly context-dependent and in some scenarios can lead to release of pro-inflammatory cytokines
	TNFa	Tumour necrosis factor alpha	pM	A pro-inflammatory cytokine mainly produced monocytes/macrophages during acute inflammation and with pleiotropic effects on various cell types. It activates signalling cascades involved in apoptosis and necrosis.
Cardiovascular	SBP	Systolic blood pressure	mmHg	Represents the maximum force exerted by blood against arterial walls when your heart beats
	DBP	Diastolic blood pressure	mmHg	Represents the minimum force exerted by blood against arterial walls when your heart rests between beats.
	RHR	Resting heart rate	bpm	The number of palpitations made by the heart when at rest
	Pulse	Pulse pressure	mmHg	Difference between SBP and DBP
	PWV	Pulse wave velocity	m/sec	Measure of arterial stiffness
Parasympathetic	SDNN	Standard deviation of the average n-n intervals calculated over 5 minutes.	m/sec	Captures differences in cardiac variability reflecting contributions from both parasympathetics and sympathetic nervous systems.
	RMSSD	Root mean square of successive RR interval differences	m/sec	Reflects the beat-to-beat variance in HR and is the primary time-domain measure used to estimate the vagally mediated changes reflected in HR
	LF-HRV	Low frequency heart rate variability – absolute (0,04-0.15)	Hz	Relative power of the low frequency band (0.04-0.15 Hz). In resting conditions, the LF band reflects baroreflex activity and not cardiac sympathetic innervation
	HF-HRV	High frequency heart rate variability (0.15-0.50)	Hz	Relative power of the high frequency band (0.15-0.40 Hz). The HF band reflects parasympathetic activity and is called the respiratory band because it corresponds to the HR variations related to the respiratory cycle.

Metabolic	BMI	Body mass index	Kg/m ²	Weight divided by height, represented on an index as a proxy measure of an individual's relative body fat percentage
	WHR	Waist hip ratio	ratio	Ratio of waist measurement to hip measurement. Higher levels indicate greater adipose fat distribution of concern for obese individuals.
	Waist	Waist circumference	Cm	Estimation of visceral fat. Higher levels indicate greater adipose fat distribution of concern for obesity and metabolic syndrome
	HBA1c	Glycated haemoglobin	mmol/mol	Average haemoglobin-bound blood glucose levels over 8-12 weeks, a measure of insulin sensitivity/resistance, high levels indicate risk of diabetes
Lipids	HDL	High density lipoprotein	mmol/L	Transports cholesterol from tissues to the liver, where they are removed from the body. Higher levels of HDL are favoured
	LDL	Low density lipoprotein	mmol/L	Known as the bad cholesterol, as high levels indicate a build-up of cholesterol in the arteries, thus lower levels are favoured
	Trig	Triglycerides	mmol/L	Fats from the food we eat that are carried in the blood and may be stored in fat cells for future energy release, low levels are favoured
	TChol	Total cholesterol	mmol/L	Critical for the production of a number of critical hormones, including cortisol. High cholesterol is a risk factor for heart disease
Renal	Creatinine	Creatinine	umol/L	Waste by-product of normal muscle function removed from kidneys and released into urine. High levels indicate poor kidney function
	Cysc	Cystatin C	mg/L	Produced by all nucleated cells. High levels indicate poor kidney function. It is also linked to cardiovascular disease and mortality. It's constitutive expression in most tissues suggests it additional homeostatic metabolic functions independent of the kidney. It has proteinase and protease activities

Note: CM= centimetre. mmHG=millimetre of mercury. Umol/L= micromole/litre. Kg/m² = kilogram/metre². Mg/l= milligram/litre. Ms= milliseconds. Hz=hertz. Pm= picomoles. Bpm = beats per minute. IBI = interbeat interval. Δ = change.

6.8.3 Statistical approach

We first examine the zero-order correlations between the battery of 25 AL biomarkers to explore the extent of inter-relatedness between the different measures. We then explore the zero-order correlation of the constellation of separate biomarkers with the PSS score to determine whether they are in fact correlated. Because self-reports of stress may vary across age group and sex, we also report the partial correlation of each biomarker with PSS partialling out age and sex. Cox proportional hazards regression models are then estimated for each biomarker, each sub-system, and the composite AL index with risk of all-cause mortality. The minimally adjusted models controlled for age and sex, while the multivariable models included adjustment for a broader array of demographic and lifestyle-related factors to determine whether there was a direct effect after adjusting out variance shared with these covariates. Inspection of scaled Schoenfeld residuals revealed a violation of the proportional hazard's assumption for age ($p < 0.001$), so all models were estimated including age as a time-varying covariate (age*log of survival time). All analyses were conducted using Stata 15.0 ¹³⁶.

6.8.4 Missing cases

The sample was set to individuals who attended the health centre assessment, contributed blood samples, and were not missing on the inflammatory and heart rate variability (HRV) panels ($n = 3855$). Of this sample, 3332 had complete biomarker and covariate data (Table 11). The case base for each biomarker and covariate varied for several reasons, including technical artefacts with respect to the HRV metrics, and sample quality and yield with respect to the blood-based biomarkers, while missing covariate data pertains to CAPI/ SCQ item non-response. Multiple imputation by chained equations was conducted using Stata (v.15) (StataCorp, 2017) to estimate missing values based on observed information, assuming all data were missing at random. 176 biomarker observations and 388 covariate observations were imputed to increase the sample to 3855. The imputation model

included all variables used in the final analysis (i.e., smoking, education, alcohol use, urban/rural status, age, sex, social network). A total of 20 datasets were imputed with a random seed to facilitate replication.

Table 6.2 Descriptive statistics of the 25 biomarkers (n= 3588)

System	Biomarker	Mean	SD	25 th percentile	50 th percentile	75 th percentile	Missing	Transformation
Inflammatory	CRP	3.1	10.7	1.0	1.6	3.2	0	Log
	IL1ra	592.4	753.0	221.2	353.3	622.2	0	Log
	IL6	1.2	3.7	0.5	0.7	1.1	0	Log
	IL8	7.8	24.1	4.2	5.6	7.8	0	Log
	IL10	0.7	5.9	0.2	0.3	0.4	0	Log
	TNFa	3.7	5.4	2.3	3.2	4.3	0	Log
Cardiovascular	SBP	134.1	19.1	120.5	133.0	146.0	15	Log
	DBP	82.2	10.9	75.0	81.5	89.0	15	
	RHR	68.7	11.2	61.0	67.5	75.0	15	
	Pulse pressure	51.9	13.0	42.5	50.5	59.5	15	
	PWV	10.3	2.0	42.5	50.5	59.5	100	
Parasympathetic	SDNN	38.0	17.7	25.8	34.5	46.9	0	Log, Reversed
	RMSSD	27.9	18.1	16.1	23.3	34.8	0	Log, Reversed
	LF-HRV	31.5	13.4	21.8	29.8	39.5	0	Log, Reversed
	HF-HRV	18.0	12.8	8.9	14.6	23.9	0	Log, Reversed
Metabolic	BMI	28.5	4.9	25.3	28.0	31.1	4	Log
	WHR	0.9	0.1	0.8	0.9	1.0	11	
	Waist	94.6	13.5	85.0	94.2	103.5	11	
	HBA1c	32.9	5.3	0.5	0.8	0.9	27	
Lipids	HDL	1.6	0.4	1.2	1.5	1.8	4	Reversed
	LDL	3.0	0.9	2.3	2.9	3.6	4	Log
	Trig	0.4	0.6	0.0	0.4	0.8	4	
	TChol	5.2	1.0	4.5	5.2	5.9	4	
Renal	Creatinine	78.6	19.5	66.0	76.0	88.0	0	Log
	Cysc	0.96	0.2	0.8	0.9	1.0	0	Log

Note: Values extracted prior to data transformations. SD = standard deviation. CRP = c-reactive protein. IL1ra = Interleukin-1 receptor antagonist. IL6 = Interleukin-6. IL8= Interleukin-8. IL10 = Interleukin-10. TNFa= Tumour necrosis factor alpha. SBP = systolic blood pressure. DBP = diastolic blood pressure. RHR = Resting heart rate. Pulse = pulse pressure. PWV = pulse wave velocity. SDNN = Standard deviation of the average n-n intervals calculated over 5 minutes. RMSSD = Root mean square of successive RR interval differences. LF-HRV = Low frequency heart rate variability HF-HRV = High frequency heart rate variability. BMI = body mass index. WHR= waist hip ratio. Waist = waist circumference. HDL = high density lipoprotein. LDL = low density lipoprotein. Trig = triglycerides. TChol = total cholesterol. Cysc = cystatin c.

Table 6.3: Sample characteristics by a) mortality status and (b) inclusion status

A			
	Died (n= 145)	Censored (n= 3710)	Chi ² / t-test
	% (mean)	% (mean)	P value
Age	(69.2)	(60.8)	***
Male	58.8	44.6	**
Marital status			***
Married	64.8	76.7	
Not married	13.8	14.5	
Widowed	22.4	8.8	
Smoking status			***
Never	31.7	46.4	
Current	40.7	38.8	
Past	27.6	14.7	
Alcohol problem	15.9	13.0	-
Missing	13.8	9.3	
Exercise			**
Low	37.9	26.9	
Moderate	35.9	35.8	
High	25.5	36.7	
Missing	0.7	0.7	
Education			***
Primary	35.2	20.5	
Secondary	35.2	42.1	
Tertiary	29.7	37.5	
Berkman-Syme social network			
Most isolated	6.9	4.9	-
Moderately isolated	25.5	24.0	
Moderately integrated	42.1	41.5	
Most integrated	24.8	29.3	

B			
	In sample (n= 3855)	Missing health assessment + bloods (n= 4319)	Chi2 (t test)
	<i>% (mean)</i>	<i>% (mean)</i>	<i>P value</i>
Deceased	3.7 (n=145)	14.4 (n= 622)	***
Cause of death			
Cancers	55.2	32.3	-
Cardiovascular	23.5	35.1	-
Respiratory	8.3	16.1	-
Other	13.0	16.6	-
Age	(61.2)	(66.2)	***
Male	45.2	46.4	-
Marital status			***
Married	76.2	62.5	
Not married	14.5	18.1	
Widowed	9.3	19.4	
Smoking status			***
Never	45.9	41.6	
Current	38.9	37.5	
Past	15.2	20.9	
Alcohol problem	13.1	7.2	***
Missing	9.4	24.4	
Exercise			***
Low	27.3	35.7	
Moderate	35.8	32.6	
High	36.3	30.5	
Missing	0.7	1.3	
Education			***
Primary	21.0	39.3	
Secondary	41.8	38.3	
Tertiary	37.2	22.5	
Berkman-Syme social network			***
Most isolated	5.0	9.0	
Moderately isolated	24.1	31.0	
Moderately integrated	41.5	39.5	
Most integrated	29.1	20.4	

Note: *P-values were calculated using a chi-squared test for all categorical variables, and t test for continuous variables. *** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$

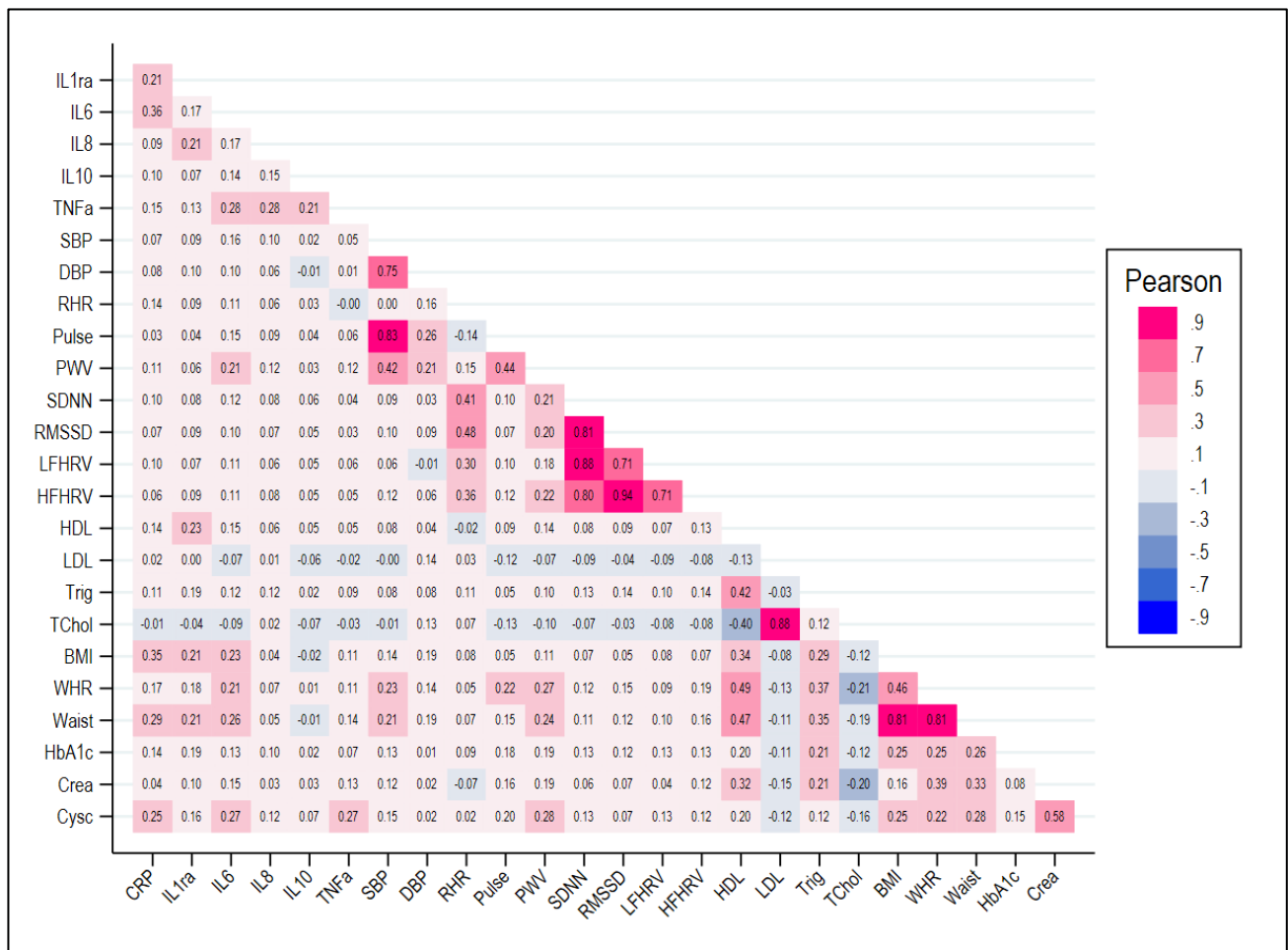
6.9 Results

The mean age of the respondents at entry into the study was 61.1 (SD = 7.9). 145/ 3855 (3.8%) of this sample died within the 10-year follow up period, with an average of 8.3 (SD = 1.0) years spent in the study, equating to more than 32,144 person-years. XXX presents the sample characteristics by mortality status and study inclusion status, respectively. Compared with their surviving counterparts, decedents were significantly older, more likely to be male, more likely to be widowed, to engage in limited exercise and report primary school education as their highest level of education achieved. These groups did not differ significantly in terms of social connectedness. Compared with those who did not attend the health centre assessment, participants included in this sample had lower rates of mortality, were younger, and were more likely to be married.

6.9.1 Correlation of biomarkers and sub-systems with PSS

XXX illustrates the zero-order correlations for all biomarkers. The range of correlations ranged from -0.40 to 0.94. As expected, positive correlations were evident among biomarkers from the same physiological sub-systems. For instance, the renal markers, Creatinine and Cysc were more heavily correlated with each other ($r = 0.58$) than they were with biomarkers comprising the other sub-systems. LDL and TChol were negatively correlated with many other biomarkers. The strongest inverse correlation was evident for TChol and HDL ($r = -0.40$). Figure 6.1 reports zero-order and partial coefficients (controlling for age and sex) of each of the 25 biomarkers with the PSS. 9/25 biomarkers were significantly correlated with stress in the expected direction with age and sex partialled out. Parasympathetic nervous system biomarkers were most consistently and strongly associated with the PSS, and to a lesser extent the inflammatory panel. With the notable exception of WHR and cystatin C, the cardiovascular, metabolic, renal and lipid sub-systems were not significantly related with self-evaluations of stress. The overall AL index was significantly and positively correlated with the PSS, although the magnitude of the relationship was small ($r = 0.05$).

Figure 6.1: Zero-order biomarker inter-correlation matrix



Note: Pairwise Pearson correlation coefficients. CRP = c-reactive protein. IL1ra = Interleukin-1 receptor antagonist. IL6 = Interleukin-6. IL8 = Interleukin-8. IL10 = Interleukin-10. TNFa = Tumour necrosis factor alpha. SBP = systolic blood pressure. DBP = diastolic blood pressure. RHR = Resting heart rate. Pulse = pulse pressure. PWV = pulse wave velocity. SDNN = Standard deviation of the average n-n intervals calculated over 5 minutes. RMSSD = Root mean square of successive RR interval differences. LF-HRV = Low frequency heart rate variability HF-HRV = High frequency heart rate variability. BMI = body mass index. WHR = waist hip ratio. Waist = waist circumference. HDL = high density lipoprotein. LDL = low density lipoprotein. Trig = triglycerides. TChol = total cholesterol. Cysc = cystatin c. HDL, SDNN, RMSSD, LFHRV and HFHRV are reverse coded.

Table 6.4: Correlations of all biomarkers and physiological sub-systems with the Perceived Stress Scale

System	Biomarker	Zero order correlation	Partial correlation (age, sex)
Inflammatory	CRP	0.04*	0.05**
	IL1ra	0.04*	0.04*
	IL6	0.02	0.04*
	IL8	0.01	0.02
	IL10	-0.02	-0.02
	TNFa	0.00	0.02
	Inflammatory index	0.03	0.04*
Cardiovascular	SBP	-0.05**	-0.03
	DBP	-0.02	-0.01
	RHR	0.02	0.02
	Pulse pressure	-0.06**	-0.02
	PWV	-0.04*	0.00
	Cardiovascular index	-0.05**	-0.02
Parasympathetic	SDNN	0.03	0.05**
	RMSSD	0.03	0.04*
	LF-HRV	0.05**	0.07***
	HF-HRV	0.02	0.03*
	Parasympathetic index	0.04*	0.05**
Metabolic	BMI	0.02	0.02
	Waist-hip ratio	0.03	0.06***
	Waist circumference	0.02	0.03
	HbA1c	-0.02	-0.00
	Metabolic index	0.02	0.03
Lipids	HDL	0.01	0.02
	LDL	0.02	0.00
	Triglycerides	0.03	0.03
	Total cholesterol	0.02	0.00
	Lipid's index	0.04*	0.02
Renal	Creatinine	-0.02	0.00
	Cystatin C	0.01	0.05**
	Renal index	-0.01	0.03
Allostatic load		0.02	0.05*

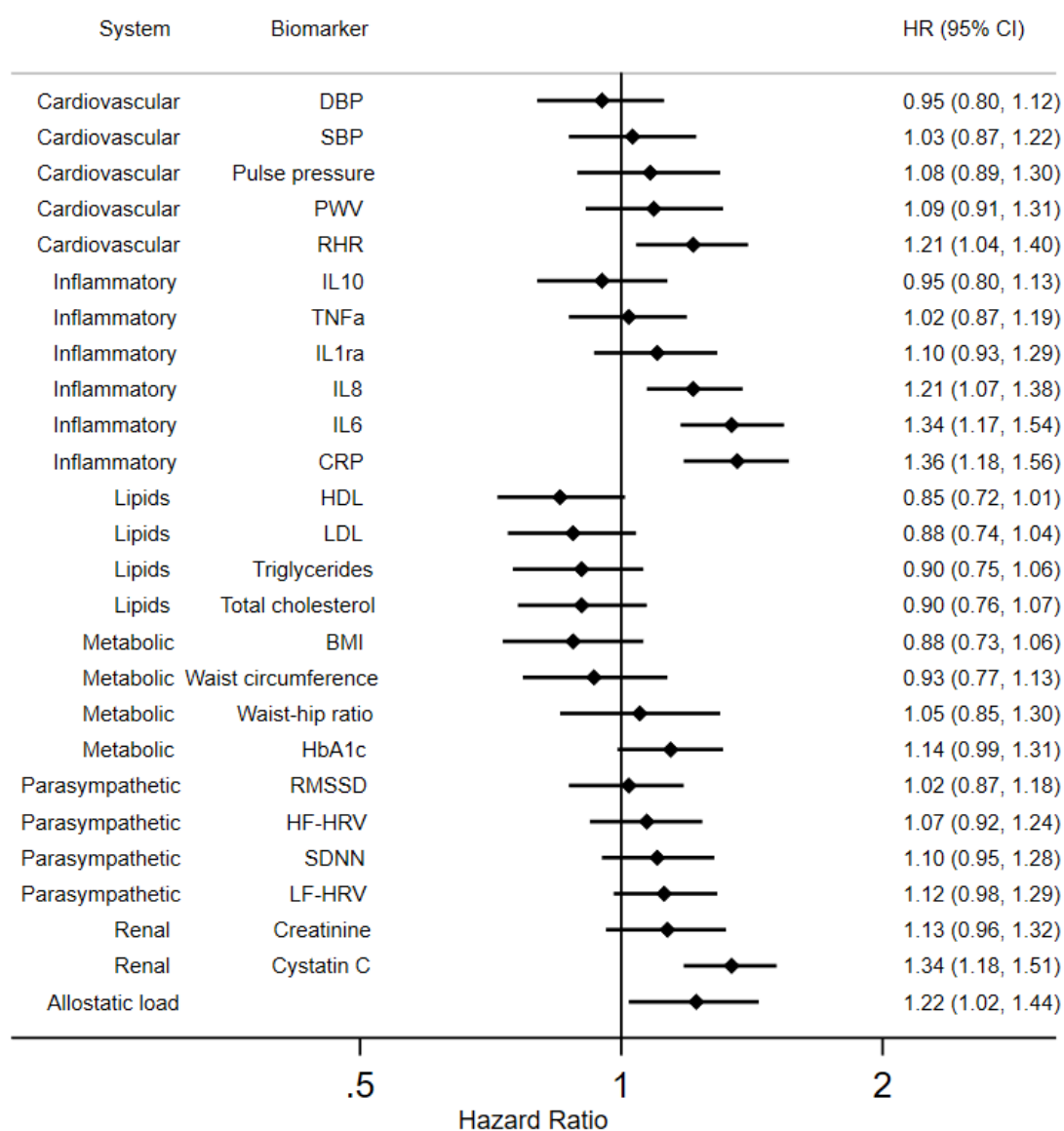
Note: n= 3339 (381 missing on PSS). CRP = c-reactive protein. IL1ra = Interleukin-1 receptor antagonist. IL6 = Interleukin-6. IL8= Interleukin-8. IL10 = Interleukin-10. TNFa= Tumour necrosis factor alpha. SBP = systolic blood pressure. DBP = diastolic blood pressure. RHR = Resting heart rate. Pulse = pulse pressure. PWV = pulse wave velocity. SDNN = Standard deviation of the average n-n intervals calculated over 5 minutes. RMSSD = Root mean square of successive RR interval differences. LF-HRV = Low frequency heart rate variability HF-HRV = High frequency heart rate variability. BMI = body mass index. WHR= waist hip ratio. Waist = waist circumference. HDL = high density lipoprotein. LDL = low density lipoprotein. Trig = triglycerides. TChol = total cholesterol. Cysc = cystatin c. *** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$

6.9.2 Association of biomarkers with risk of all-cause mortality

Figure 6.2 reports the Hazard Ratios (HRs) and associated 95% confidence intervals of each biomarker with risk of all-cause mortality over a mean 8.3 years of follow-up in the minimally adjusted models using multiple imputation. Overall, 5/25 biomarkers were associated with significantly increased hazard of all-cause mortality: CRP (HR= 1.36, 95% CI= 1.18, 1.56), Cysc (HR= 1.34, 95% CI= 1.18, 1.51), IL6 (HR= 1.34, 95% CI=1.17, 1.54), IL8 (HR= 1.21, 95% CI= 1.07, 1.40) and RHR (HR= 1.21, 95% CI= 1.04, 1.40). The lipid biomarkers were found, counter-intuitively, to be inversely related to risk of mortality, although these relationships were not statistically significant. Within each physiological sub-system, CRP (inflammatory), RHR (cardiovascular), LFHRV (parasympathetic), HbA1c (metabolic) and Cysc (renal) performed best in terms of predicting mortality.

Supplementary Table 6.1 summarises the multivariable Cox models. The association of CRP (HR= 1.30, 95% CI= 1.12, 1.50), IL6 (HR= 1.31, 95% CI= 1.14, 1.50), IL8 (HR= 1.19, 95% CI = 1.04, 1.36) and Cysc (HR= 1.29, 95% CI= 1.12, 1.47) with risk of mortality remained robust to adjustment for a broad array of socio-demographic and lifestyle-related factors. RHR was no longer associated significantly with risk of mortality in multivariable adjusted models.

Figure 6.2: Forest plot of hazard ratios (HRs) and 95% confidence intervals (CI) of biomarkers on mean 8-year mortality (multiple imputation analysis, n=3855)



*= reverse coded

6.9.3 Association of physiological sub-systems with risk of all-cause mortality

In terms of the physiological sub-systems, 2/6 were associated with significantly increased risk of mortality in the minimally adjusted models: the inflammatory (HR= 1.31, 95% CI: 1.13, 1.53) and renal systems (HR= 1.25, 95% CI: 1.09, 1.42) (). These relationships remained robust to multivariable adjustment. In line with the pattern of results from the independent associations of biomarkers with mortality, each unit increase in the lipid sub-system was associated with significantly reduced risk of mortality (HR= 0.81, 95% CI: 0.68, 0.97). The cardiovascular, anthropometric and PNS sub-systems were not significantly associated with risk of mortality.

6.9.4 Association of allostatic load burden with risk of all-cause mortality

A composite measure comprising all 25 biomarkers was associated significantly with increased risk of mortality. Each standard unit increase in the composite AL score was associated with increased risk of mortality (HR = 1.22, 95% CI = 1.02, 1.44). This relationship was significantly attenuated in multivariable adjustment (HR = 1.14, 95% CI = 0.96, 1.36).

6.9.5 Sensitivity analyses

Complete case analysis was also performed, restricting the sample to respondents with full biomarker and covariate information (n= 3332). The general pattern of results was similar (XXX) although the hazard ratio for RHR was smaller while those for SBP and pulse pressure were substantially larger.

A significant proportion of the TILDA sample are taking prescribed medications that could impact the observed values across many of the biomarkers examined here ⁵⁰. To account for this potential effect, medications were included as a covariate for a select number of biomarkers. In

TILDA, medication usage was ascertained as part of the household interview, where respondents were asked to retrieve the medicinal packaging of any regularly taken medications and interviewers transcribed the brand/ generic name of the prescription medication. The medications data was then coded in-house by pharmacologists according to Anatomic Therapeutic Classification (ATC) codes¹³³. HbA1c was adjusted for insulin or analogues (A10), SBP was adjusted for anti-hypertensive medication (C02, C03, C09). RHR was adjusted for beta-blockers (C07) or calcium blockers (C08) and finally, HDL was adjusted for lipid modifying agents (C10). Associations of these biomarkers with mortality, before and after controlling for this medication use, are reported in XXX. The relationships of these biomarkers with mortality after controlling for medication use were not appreciably different.

6.10 Discussion

Allostatic Load offers a multi-system index for quantifying the impact of stress on the body; however, the framework has been beset by the lack of construct validity as its composition varies across studies. Indeed, in many population-based studies, the definition of AL appears to be driven more by the availability of biomarkers rather than by any strict adherence to the theoretical and conceptual underpinnings of the AL framework, which placed a heavy premium on the role of neuroendocrine and inflammatory biomarkers in the physiological cascade that leads to organ system dysregulation, and ultimately, disease states¹⁵. It has been argued that researchers working under a set framework must not be tempted to stray too far from the featured causal pathways⁶⁹, which reinforces the necessity to re-examine the fundamentals of how AL is defined. This study investigated the association of 25 commonly employed biomarkers from 6 physiological sub-systems with stress and all-cause mortality in an attempt to advance the goal of calibrating a measure of AL that satisfies Delpierre's call for a measure that achieves "*theoretical consensus and empirical rigor*"⁶⁹.

The analysis was insightful. Overall, 9/25 biomarkers were significantly correlated with a contemporaneous measure of subjective stress, and 5/25 were significantly associated with increased risk of all-cause mortality. Surprisingly, only three of the battery of 25 biomarkers which are commonly used to define AL in the literature (CRP, IL6, Cysc) were correlated with stress *and* predictive of mortality. Additionally, markers of parasympathetic nervous system functioning were most strongly correlated with the PSS, although were not significantly associated with risk of mortality. A blunted cardiac-vagal modulation of heart rate variability has been noted previously amongst individuals with higher perceived stress ²⁵⁰, suggesting that this system is sensitive to psychosocial perturbations. Despite the low correlations between the individual biomarkers and the PSS, greater AL burden was correlated with greater PSS. It should be acknowledged that the stress measure employed here was circumscribed as it was based on a short-form (4-item) instrument and was designed to tap contemporaneous as opposed to long-run stress. Interestingly, a previous paper employing the TILDA cohort found rather limited support for long-run effects of life course stress on AL burden ²⁵¹, as did Gleib et al. (2007), which reinforces the need for more work in this vein.

6.10.1 Which AL biomarkers were most strongly associated with mortality?

Chronic stress has been shown to impact on immune system functioning ²⁵², and indeed inflammatory biomarkers appear to be the most consistent predictors of mortality across studies. Despite the expanded inflammatory panel assessed here, the commonly utilised inflammatory biomarker, CRP, was the best performing biomarker within this sub-system with respect to mortality, increasing the hazard of all-cause mortality by 36%. Indeed, CRP outperformed all biomarkers in relation to risk of mortality. CRP is an acute phase protein produced in the liver and secreted into the bloodstream during an inflammatory episode, largely in response to IL6 signalling ²⁵³. It is perhaps unsurprising therefore that the other primary cytokines such as IL6 and IL8 were also positively

associated with the hazard of all-cause mortality. Other studies have also concluded that CRP is the best individual predictor of mortality among the wide array of biomarkers that have been used to define AL^{44,45} as it seems to perform as a non-specific indicator of risk for many age-related diseases, including cardiovascular and Alzheimer's diseases²⁵⁴.

Cystatin C was one of the strongest predictors of mortality in this study: each log standardised unit increase in Cystatin C was associated with a 34% increase in the hazard of mortality, while creatinine was not significantly associated with mortality. Cystatin C has previously been proven to be a more sensitive marker than creatinine for the estimation of glomerular filtration rate²⁵⁵, and cardiovascular disease²⁵⁶ and is found in every tissue and bodily fluid, making it a more robust predictor of health risk.

Cardiovascular measures are the most commonly employed biomarkers in AL studies^{24,243}, and are often overrepresented relative to other systems due to the ease of data collection (e.g., blood pressure, pulse rate). Yet, with the notable exception of RHR, these markers were not related to all-cause mortality in this study. Indeed, RHR was one of better performing biomarkers in this analysis, with each standardised unit increase associated with a 21% increase in the hazard of mortality. This is a marker that does not appear often within the AL literature²⁴, despite its ease of measurement and the availability of evidence attesting to the strong prognostic value of RHR for identifying adverse cardiovascular events²⁵⁷. Pulse pressure performed better than the classical measures of SBP and DBP, possibly because SBP tends to increase with age, while DBP decreases with age, so a measure which captures the differential may be more informative. Interestingly, despite their inclusion in most operational definitions of AL, SBP and DBP tend to be poor predictors of mortality across studies^{36,45,142,258}. Notwithstanding these results, our study, and others⁴⁵ have shown that RHR

outperforms the other cardiovascular measures and hence, it may be preferable to include RHR and/or pulse pressure as markers of dysregulation in the cardiovascular system going forward.

Turning next to the metabolic system, no single marker was significantly associated with risk of mortality, although HbA1c was the best performing biomarker within this system increasing the hazard of mortality by 14% (95% CI: 0.99, 1.31). This is consistent with findings from the MacArthur studies, which reported poor performance across metabolic markers in respect to mortality (i.e., HbA1c, WHR) ¹⁴², and the NCDS, which found that the relationship of HbA1c with mortality was attenuated with multivariable adjustment ⁴⁵. However, these findings are inconsistent with findings from SHeS, wherein both HbA1c and WHR matched the predictive utility of the composite AL index ³⁶. It is perhaps surprising that the other anthropometric measures of metabolic system dysregulation including BMI, WHR and waist circumference were not more predictive of mortality. BMI, for example, is one of most commonly collected biomarkers in clinical settings and is often adopted as the basis of policy recommendations and public health campaigns yet is an indirect measure of body fat that fails to consider fat distribution, bone structure or age. This is particularly imperative when assessing older populations, as ageing is associated with a decrease in muscle mass and an increased risk of conditions that can increase fluid mass such as inflammation, greatly hampering the diagnostic accuracy of BMI amongst older people. The lack of signal for waist circumference and waist-hip ratio might be related to differences in mean values between men and women as we did not stratify separately by sex in this study. It should be acknowledged that prior studies that have done so among older age groups have found a signal with mortality for WHR, but not waist circumference or BMI ²⁵⁹.

Similarly, the poor performance of lipid markers with risk of mortality is consistent with previous findings ^{44,45,142}, although surprising in respect to findings from SHeS, which found that HDL matched the predictive utility of the composite AL ³⁶. However, while our analytic strategy was based on risk being linear as very few studies employing these biomarkers define risk as being two-tailed, although non-linear relationships of cholesterol with mortality have been reported previously ²⁶⁰. Medication use represents another confounding factor as 33% of TILDA respondents are taking lipid-modifying medications ⁵⁰. We attempted to determine whether this was a factor by adjusting the models for medication usage in supplementary models, but the predictive performance of total and HDL cholesterol with mortality did not increase appreciably.

6.10.2 Which AL sub-systems were most strongly associated with mortality?

We have seen that some specific AL biomarkers are more strongly correlated with mortality than others, but are some systems more strongly associated with mortality than others? This is potentially an important insight as some studies have investigated the performance of composite sub-systems over and above individual biomarkers to understand the mechanisms at play ^{45,142,246,261}. In our study, the inflammatory and renal sub-systems were most strongly associated with mortality, increasing the hazard of all-cause mortality by 31% and 25%, respectively. Similarly, Cornman et al., (2017) found that the inflammatory sub-system, comprising seven biomarkers (CRP, soluble intercellular adhesion molecule-1, sE-selectin, soluble IL-6 receptor, white blood cell count, neutrophils, and homocysteine), alongside a composite cardiovascular/metabolic index, was predictive of 4.5-year all-cause mortality in SEBAS ²⁴⁶. Interestingly, inflammation is highly sensitive to lifestyle factors, especially smoking ²⁶², with an extant literature demonstrating that inflammation lies on the causal pathway between smoking and cardiovascular disease ²⁶³. Despite this, the composite inflammation index remained robust to controlling for smoking status, suggesting that physiological mechanisms

other than those directly impacted by lifestyle factors are at play and life course stress remains a plausible exogenous influence.

In line with results from the individual biomarkers, the metabolic, cardiovascular and lipid systems were not associated with increased risk of mortality. Again, direct appraisal of sub-system indices across studies are complex, especially in relation to these three sub-systems due to the varying organisation of biomarkers into composite indices. For example, Cornman et al. (2017) examined a cardio-metabolic sub-system, rather than isolating cardiovascular markers from metabolic and lipid markers, and found it was predictive of mortality in SEBAS. In the same vein, similarities have been drawn between AL and metabolic syndrome (i.e., Syndrome X), as the two indices contain many of the same components (i.e., blood pressure, WHR, HDL, glucose). However, there is evidence that the two are conceptually distinct ²⁶⁴, and multi-system indices of AL have been shown to predict health outcomes better than metabolic syndrome ³², and indeed predict functional outcomes independent of the metabolic syndrome components ³⁷. Few studies include more than one marker of renal function so comparison of results across studies is difficult. However, Chadeau-Hyam and collaborators (2020) reported that renal dysregulation (i.e., creatinine) was not associated with incidence of cardiovascular related mortality in the UK biobank, while metabolic, inflammation, liver, and cardiovascular dysregulation were.

6.10.3 Is the overall AL index greater than the sum of its parts?

Our overall composite measure of AL, which was constructed as the sum of 25 biomarkers, was predictive of all-cause mortality. A standard unit increase in AL burden was associated with 22% increase in the hazard of all-cause mortality in the minimally adjusted models, but the association was rendered non-significant after controlling for socio-demographic factors and lifestyle-related

behaviours. We found that CRP, IL6 and Cysc all individually outperform the composite AL index in predicting all-cause mortality. Moreover, the inflammatory and renal sub-system indices also predicted risk of mortality more strongly than the overall AL index and were only marginally attenuated in multivariable adjustment. Nevertheless, an enduring limitation of AL research relates to the difficulty in comparing results due to the high variation in biomarker panels across studies. It should be acknowledged that of the studies which have examined whether biomarkers, systems, or the overall AL index predict mortality better, the majority have found that the composite AL index outperforms singular biomarkers and sub-systems ^{41,44,45}. For instance, Castagne et al. (2018) study involving the NCDS data found that high AL ($\geq 5/14$ biomarkers, based on sex-specific quartiles), comprising inflammatory, neuroendocrine, metabolic, and cardiovascular sub-systems outperformed all individual biomarkers and sub-systems in terms of mortality risk. Both TILDA and NCDS had a similar follow up time (10 vs. 11 years, respectively), and a similar number of recorded deaths (145 vs. 136, respectively). One considerable difference between the studies is the different scoring systems used; Castagne et al. (2018) dichotomised all biomarkers, sub-systems and AL indices into sex-specific quartiles of risk (highest quartile = high risk), while the current study employed z-scores to explore the full spectrum of risk. This seems an unlikely explanation for the differences though as Seeman et al. (2004) and Robertson et al., (2017) also dichotomised their biomarkers via risk quartiles and found that AL underperformed relative to the individual biomarkers. In addition to differences in biomarker composition, differences in age distribution between the cohorts might help account for some the discrepant pattern of results. The NCDS involved a younger age cohort (mean age = 44), while SHeS (mean age = 51), MacArthur studies (mean age = 74) and TILDA (mean age = 61) may be more affected by survivor bias due to assessment at older ages.

6.10.4 Implications

The predictive utility of AL for many clinical endpoints is now well established ⁶⁸, yet whether such measures are tapping stress-related dysregulation or an alternate causal pathway remains to be elucidated. On this basis of these results, and others ³⁶, one might question whether the use of large composite biomarker panels is superfluous. Perhaps AL ‘works’ simply because it comprises biomarkers that are strongly predictive of mortality even if not strongly related to stress, *per se*. There is, after all, many non-stress related pathways through which elevated levels of these biomarkers may increase risk for adverse outcomes (i.e., diet, infectious diseases, environmental toxins) ²⁶⁵. Hence stress may deserve no special status in contemporary theorising regarding the relationship of AL with disease risk. Initially conceived as a measure of the downstream biological response to stress exposure, which placed a heavy emphasis on the role of primary stress mediators, a notable shift in the use of AL indices has occurred in the epidemiological literature. Choice of biomarker panels has been based more on availability of data, rather than applying theoretical guidelines ²⁸. Some have stepped away from this framework yet adopted the operational methods it utilises, assuming terms such as “multi-system physiological dysregulation” ³⁵ and “biological health score” ^{261,266} in place of allostatic load.

In mitigation, it should be acknowledged that stress responses are not static ²³, and the AL framework relies on the non-linear and dynamic regulation of physiological parameters, and reducing these to a fixed point in time measure may be masking the true physiological impact of stress exposure. As biomarkers become increasingly common in large population-based studies, resolution of these ongoing theoretical and empirical concerns regarding what AL is, and what it is measuring, should prove possible. For *de novo* studies, our results might help inform decision making regarding which biomarkers work best within each system.

6.11 Strengths and limitation

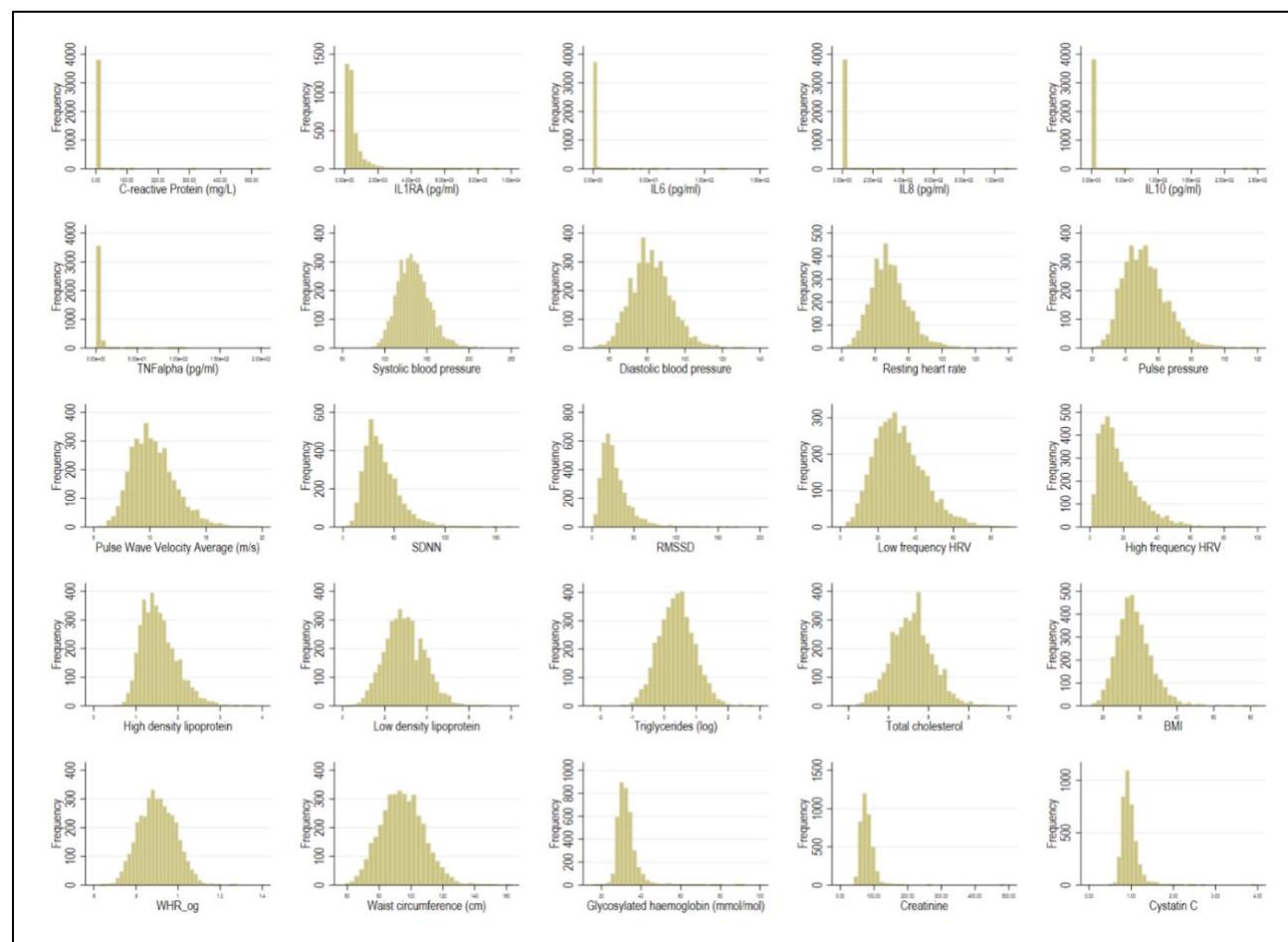
The primary aim of this paper was to establish the relationship of a broad suite of biomarkers with stress and mortality. TILDA, as a longitudinal study, has been following this cohort for over a decade, affording the opportunity to examine the long-run implications of biomarker dysregulation with risk of all-cause mortality using a large panel of biomarkers commonly employed in the AL literature. This study is not without its limitations, however. Firstly, those who partook in the health assessments tended to be the healthiest of the TILDA cohort, which may have led to conservative estimates due to survival bias. Measures of neuroendocrine function (e.g., catecholamines, cortisol, DHEA etc.) are limited in TILDA at baseline, and therefore we were not in a position to examine the relationship of these important stress biomarkers with mortality. In mitigation, some studies have found markers of neuroendocrine function are not strongly predictive of mortality^{45,246,258}. It should also be acknowledged that these markers are more sensitive to circadian rhythm and acute environmental challenges than secondary mediators, making their collection more complex. As already alluded to, our measure of subjective stress has a construct validity of 4-8 weeks, after which the predictive validity is expected to fall off rapidly²⁴⁷. However, the lag that exists between assessment of stress during the CAPI interview and the health assessment during which time the biomarker data was collected, averaged 15.7 (SD = 10.9) weeks, which may account for the relatively weak associations of the PSS measure with many of the biomarkers.

6.12 Conclusion

This study examined the association of 25 distinct biomarkers commonly employed in the AL literature and their association with stress and mortality among a large community-dwelling cohort of older people. Taken in conjunction, the results provide limited support for a strong relationship of subjective stress with AL and may provoke some reappraisal of why AL predicts mortality.

CHAPTER 6 SUPPLEMENTARY MATERIAL

Supplementary Figure 6.1: Histogram (untransformed) graph matrix for the allostatic load biomarkers



Note: CRP = c-reactive protein. IL1ra = Interleukin-1 receptor antagonist. IL6 = Interleukin-6. IL8 = Interleukin-8. IL10 = Interleukin-10. TNFa = Tumour necrosis factor alpha. SBP = systolic blood pressure. DBP = diastolic blood pressure. RHR = Resting heart rate. Pulse = pulse pressure. PWV = pulse wave velocity. SDNN = Standard deviation of the average n-n intervals calculated over 5 minutes. RMSSD = Root mean square of successive RR interval differences. LF-HRV = Low frequency heart rate variability HF-HRV = High frequency heart rate variability. BMI = body mass index. WHR = waist hip ratio. Waist = waist circumference. HDL = high density lipoprotein. LDL = low density lipoprotein. Trig = triglycerides. TChol = total cholesterol. Cysc = cystatin c.

Supplementary Table 6.1: Hazard ratio (HR) and 95% confidence intervals (CI) of biomarkers on mean 8-year mortality (multiple imputation analysis, n= 3855)

System	Biomarker	Minimally adjusted		Multivariable adjusted	
		HR	(95% CI)	HR	(95% CI)
Inflammatory	CRP	1.36***	(1.18, 1.56)	1.30***	(1.12, 1.50)
	IL1ra	1.10	(0.93, 1.29)	1.05	(0.89, 1.24)
	IL6	1.34***	(1.17, 1.54)	1.31***	(1.14, 1.50)
	IL8	1.21**	(1.07, 1.40)	1.19*	(1.04, 1.36)
	IL10	0.95	(0.80, 1.13)	0.97	(0.82, 1.16)
	TNFa	1.02	(0.87, 1.19)	0.99	(0.84, 1.17)
	Inflammatory sub-system	1.31***	(1.13, 1.53)	1.27**	(1.09, 1.48)
Cardiovascular	SBP	1.03	(0.87, 1.21)	1.03	(0.88, 1.22)
	DBP	0.95	(0.80, 1.12)	0.94	(0.80, 1.11)
	RHR	1.21*	(1.04, 1.40)	1.15	(0.99, 1.33)
	Pulse pressure	1.08	(0.89, 1.30)	1.09	(0.91, 1.32)
	PWV	1.09	(0.91, 1.31)	1.06	(0.86, 1.27)
	Cardiovascular sub-system	1.11	(0.93, 1.33)	1.10	(0.92, 1.30)
Parasympathetic	SDNN	1.10	(0.95, 1.28)	1.07	(0.92, 1.24)
	RMSSD	1.02	(0.87, 1.18)	1.00	(0.86, 1.16)
	LF-HRV	1.12	(0.98, 1.29)	1.09	(0.95, 1.25)
	HF-HRV	1.07	(0.92, 1.24)	1.05	(0.90, 1.22)
	Parasympathetic sub-system	1.08	(0.94, 1.25)	1.06	(0.91, 1.22)
Metabolic	BMI	0.88	(0.73, 1.06)	0.90	(0.75, 1.08)
	Waist-hip ratio	1.05	(0.85, 1.30)	0.97	(0.79, 1.21)
	Waist circumference	0.93	(0.77, 1.13)	0.91	(0.75, 1.11)
	HbA1c	1.14	(0.99, 1.31)	1.09	(0.94, 1.27)
	Metabolic sub-system	1.01	(0.84, 1.21)	0.96	(0.80, 1.15)
Lipids	HDL	0.86	(0.72, 1.01)	0.84	(0.72, 0.99)
	LDL	0.88	(0.74, 1.04)	0.86	(0.73, 1.08)
	Triglycerides	0.90	(0.75, 1.06)	0.86	(0.72, 1.02)
	Total cholesterol	0.90	(0.76, 1.07)	0.88	(0.75, 1.05)
	Lipid sub-system	0.81*	(0.68, 0.97)	0.79*	(0.66, 0.94)
Renal	Creatinine	1.13	(0.96, 1.32)	1.15	(0.98, 1.35)
	Cystatin C	1.34***	(1.18, 1.51)	1.29***	(1.12, 1.47)
	Renal sub-system	1.25**	(1.09, 1.42)	1.22**	(1.06, 1.40)
Allostatic load index		1.22*	(1.02, 1.44)	1.14	(0.96, 1.36)

Note: Bold highlight refers to the best performing biomarker within physiological system. Refer to Table 6.2 for data transformations. CRP = c-reactive protein. IL1ra = Interleukin-1 receptor antagonist. IL6 = Interleukin-6. IL8 = Interleukin-8. IL10 = Interleukin-10. TNFa = Tumour necrosis factor alpha. SBP = systolic blood pressure. DBP = diastolic blood pressure. RHR = Resting heart rate. Pulse = pulse pressure. PWV = pulse wave velocity. SDNN = Standard deviation of the average n-n intervals calculated over 5 minutes. RMSSD = Root mean square of successive RR interval differences. LF-HRV = Low frequency heart rate variability HF-HRV = High frequency heart rate variability. BMI = body mass index. WHR = waist hip ratio. Waist = waist circumference. HDL = high density lipoprotein. LDL = low density lipoprotein. Trig = triglycerides. TChol = total cholesterol. Cysc = cystatin c. Minimally adjusted models include age and sex. Covariates from multivariable models include educational status (primary, secondary, tertiary), alcohol abuse (CAGE), physical activity (eight-item International Physical Activity Questionnaire; low, medium, high), smoking status (never, current, past) years. *** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$.

Supplementary Table 6.2: Hazard ratio (HR) and 95% confidence intervals (CI) of biomarkers on mean 8-year mortality (complete case analysis, n= 3332)

System	Biomarker	Minimally adjusted model		Multivariable adjusted model	
		HR	(95% CI)	HR	(95% CI)
Inflammatory	CRP	1.29**	(1.10, 1.51)	1.25**	(1.06, 1.47)
	IL1ra	0.99	(0.82, 1.19)	0.96	(0.79, 1.16)
	IL6	1.32***	(1.13, 1.54)	1.29***	(1.10, 1.50)
	IL8	1.18*	(1.02, 1.37)	1.17*	(1.01, 1.37)
	IL10	0.95	(0.78, 1.15)	0.98	(0.81, 1.18)
	TNFa	0.98	(0.82, 1.18)	0.97	(0.80, 1.16)
	Inflammatory sub-system	1.23*	(1.04, 1.46)	1.20*	(1.01, 1.43)
Cardiovascular	SBP	1.17	(0.98, 1.40)	1.17	(0.98, 1.40)
	DBP	1.02	(0.85, 1.23)	1.02	(0.85, 1.22)
	RHR	1.11	(0.93, 1.32)	1.07	(0.90, 1.27)
	Pulse pressure	1.24*	(1.01, 1.52)	1.24*	(1.01, 1.53)
	PWV	1.10	(0.90, 1.35)	1.07	(0.88, 1.31)
	Cardiovascular sub-system	1.20	(0.99, 1.45)	1.17	(0.97, 1.41)
Parasympathetic	SDNN	1.07	(0.90, 1.27)	1.04	(0.88, 1.24)
	RMSSD	0.97	(0.82, 1.15)	0.96	(0.81, 1.14)
	LF-HRV	1.08	(0.92, 1.28)	1.07	(0.90, 1.27)
	HF-HRV	1.02	(0.86, 1.21)	1.01	(0.84, 1.21)
	Parasympathetic sub-system	1.03	(0.87, 1.23)	1.02	(0.86, 1.21)
Metabolic	BMI	0.91	(0.74, 1.12)	0.94	(0.77, 1.15)
	Waist-hip ratio	1.01	(0.80, 1.27)	0.95	(0.75, 1.21)
	Waist circumference	0.92	(0.74, 1.14)	0.91	(0.74, 1.13)
	Hba1c	1.14	(0.97, 1.34)	1.12	(0.94, 1.32)
	Metabolic sub-system	0.99	(0.80, 1.22)	1.00	(0.82, 1.24)
Lipids	HDL	0.88	(0.73, 1.06)	0.87	(0.72, 1.06)
	LDL	0.98	(0.81, 1.18)	0.96	(0.79, 1.15)
	Triglycerides	0.92	(0.76, 1.12)	0.90	(0.74, 1.09)
	Total cholesterol	0.97	(0.80, 1.17)	0.95	(0.79, 1.15)
	Lipid sub-system	0.90	(0.74, 1.09)	0.87	(0.72, 1.06)
Renal	Creatinine	1.13	(0.94, 1.36)	1.15	(0.96, 1.38)
	Cystatin C	1.34***	(1.16, 1.54)	1.30**	(1.12, 1.52)
	Renal sub-system	1.26**	(1.09, 1.45)	1.23**	(1.06, 1.44)
Allostatic load index		1.22	(0.99, 1.48)	1.16	(0.95, 1.42)

Note: Bold highlight refers to the best performing biomarker within physiological system. Refer to Table 2 for data transformations CRP = c-reactive protein. IL1ra = Interleukin-1 receptor antagonist. IL6 = Interleukin-6. IL8 = Interleukin-8. IL10 = Interleukin-10. TNFa = Tumour necrosis factor alpha. SBP = systolic blood pressure. DBP = diastolic blood pressure. RHR = Resting heart rate. Pulse = pulse pressure. PWV = pulse wave velocity. SDNN = Standard deviation of the average n-n intervals calculated over 5 minutes. RMSSD = Root mean square of successive RR interval differences. LF-HRV = Low frequency heart rate variability HF-HRV = High frequency heart rate variability. BMI = body mass index. WHR = waist hip ratio. Waist = waist circumference. HDL = high density lipoprotein. LDL = low density lipoprotein. Trig = triglycerides. TChol = total cholesterol. Cysc = cystatin c. Minimally adjusted models include age and sex. Covariates from multivariable models include educational status (primary, secondary, tertiary),

alcohol abuse (CAGE), physical activity (eight-item International Physical Activity Questionnaire; low, medium, high), smoking status (never, current, past). *** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$.

Supplementary Table 6.3: The impact of medications on biomarkers and their association with risk of mortality (multiple imputation analysis, n=3855)

	Minimally adjusted		+Medication	
	HR	95% CI	HR	95% CI
SBP	1.03	(0.87, 1.22)	1.03	(0.87, 1.22)
RHR	1.21*	(1.04, 1.40)	1.22*	(1.05, 1.41)
HbA1c	1.14	(0.99, 1.31)	1.14	(0.97, 1.35)
TChol	0.90	(0.76, 1.07)	0.92	(0.76, 1.11)
HDL ^a	0.85	(0.72, 1.01)	0.85	(0.72, 1.01)

Note: ^aHDL is reverse coded. HbA1c was coded as high risk if individuals were currently prescribed medications of codes for insulin or analogues (A10), SBP was classified as high risk if individuals were taking anti-hypertensive medication (C02, C03, C09). RHR was recoded as high risk if taking beta-blockers (C07) or calcium blockers (C08) and finally, HDL was recoded as high risk if prescribed lipid modifying agents (C10). *** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$

Chapter 7: Discussion and conclusion

Chapter summary

Allostatic load (AL) has gained momentum as a quantifiable measure of stress-related physiological wear and tear in recent decades. This thesis sought to advance the field by addressing some of the identified methodological and conceptual gaps relating to AL and its utility for understanding differences in health and mortality. This final chapter provides a brief synopsis of the findings from my 4 papers and discusses their relative contribution to the literature.

7.1 Discussion of principle findings and their implications

7.1.1 Comparing the predictive utility of various operational definitions of AL on health

A consistent finding in the literature is the association of AL burden, typically measured using composite multi-system indices, with poor health outcomes^{26,68}. My first contribution relates to one of the enduring shortcomings of AL, specifically, the heterogeneity of scoring algorithms used to quantify AL across studies which has hampered direct comparison of results across studies to date^{28,145}. Using the same panel of 12 biomarkers, 14 different scoring algorithms that have been used to operationalise AL were compared. The classic method involves a summation of biomarkers based on the highest risk quartiles of the sample distribution, while alternate scoring algorithms include deriving separate risk quartiles by sex, utilizing clinical risk thresholds, risk deciles rather than quartiles, summing standardised biomarkers, and incorporating medication use. Bivariate correlations revealed that all 14 indices were positively correlated with age in the expected direction, supporting findings from previous studies that found that AL burden increases with chronological age^{267,268}. I utilised ordinary least squares and logistical regression techniques to compare explained variance, model fit, and the Area Under the Curve (AUC), accounting for the effects of age and sex. Multivariate models investigating the association of each AL index with 3 age-related health

outcomes revealed that increasing AL burden was associated with slower walking speed and poorer self-rated health. AL burden and grip strength were not associated at conventional levels of significance. Compared with the classic scoring algorithm, differences in performance across indices were small. This was in line with findings from SEBAS ¹⁴¹ and NHANES ¹⁵⁰, and should therefore mitigate concerns surrounding the heterogeneity of approaches employed to date, as little differences were noted in the predictive utility across measures.

This study has been impactful and other researchers have adopted the findings to inform their choice of AL scoring algorithm ^{269,270}. Additionally, this study elicited an exchange with another research group in the form of a Letter to the Editor of *Psychoneuroendocrinology* ²⁷¹ (Appendix 1). We responded (Appendix 2) by debunking some of their criticisms that seemed to relate more to AL as a framework rather than a specific critique of the paper. Specifically, they commented on the absence of a clear consensus of which biomarkers should be used to generate AL indices, which is addressed in Chapter 6.

7.1.2 Life course adversity and AL

My second contribution was conceptual. As established, the theory underpinning the AL framework pertains to the damaging effects of repeat or chronic stressors exposure over time. Surprisingly, empirical evidence supporting this framework was lacking ²⁰⁵. Interestingly, I found modest support for the theory underpinning the framework of AL, adding to the heterogenous conclusions across studies investigating adverse events and their relationship with AL burden ^{204,206}. The association of cumulative stress exposure was associated with AL, yet the effect sizes were small, and were attenuated via socio-demographic and lifestyle factors. The majority of adversities examined in this study were unrelated to AL burden, which is perhaps surprising as some of these adversities, such as

the death of a parent during childhood, or the experience of childhood sexual abuse have been linked with worse health outcomes previously ²⁷². With just 3/ 11 adversities significantly related to AL burden, the findings of this study further highlight that not all types of stressors are equivalent with respect to their impact on AL. However, this study did not investigate duration, intensity, or timing of exposure.

A related topical research question pertains to the timing of the stress exposure. While childhood is well accepted to be a critical period for the embedding of disease ⁶², Lupien et al. (2009) proposed that the consequences of stress exposure and subsequent hormonal surges may be dependent on which brain regions are undergoing development at the time of exposure ¹⁰². Future studies should therefore also attempt to capture the timing of stressor exposure to aid the understanding of time-sensitive trajectories to AL burden. Finally, there is evidence to suggest that the HPA axis reacts differently to different stressors, with recent work identifying threat and deprivation as distinct underlying dimensions of early life adversities ^{273,274}. Threat involves the presence of an atypical environmental input, while deprivation involves the absence of expected environmental inputs ²⁷⁴. Both threat and deprivation can occur in isolation, or they can co-occur, differentially influencing the neurodevelopment in childhood.

Several lines of research highlight the potent effects of socio-economic adversity in childhood on health ^{63,275,276}. This was supported by way of a significant association of self-reported childhood poverty with later life AL burden in Chapter 4. Children living in poverty have previously been shown to have heightened stress reactivity ²⁷⁷, yet childhood material deprivation is not explicitly considered as an adverse childhood event (ACE) in the WHO's ACE-International Questionnaire. This is despite the fact that in this study and others, there is suggestive evidence that

childhood socio-economic adversity may serve as a distal factor influencing risks for the other adversities ⁴. However, educational attainment attenuated the association of childhood poverty and AL, suggesting that a primary way of overcoming childhood socio-economic poverty may be by achieving higher levels of education across the life course.

Exposure to childhood physical abuse was also associated with AL burden, yet once I accounted for the effects of smoking, the relationship of childhood physical abuse with AL burden was attenuated and no longer significant at conventional levels. This finding is interesting in the wider context of the literature on AL and health behaviours, as smoking plays a role in regulating negative mood and emotion, and is associated with greater burden of AL ³¹. The experience of trauma can lead to the development of maladaptive coping mechanisms that are irreparably damaging over time ^{278,279}.

The limitations of retrospective data collection should be expounded upon and carefully considered when interpreting the results, however. Recall bias can significantly impact the conclusions drawn from a study, and the time between the event and the reporting here should be acknowledged; the mean age of the sample was 61, meaning that adverse childhood events would have occurred approximately 5 decades prior. It is possible that individuals may not accurately remember past events, resulting in inaccuracies or inconsistencies in the data used in this thesis. In addition, retrospective recalled events are subject to the influence of current mood and experiences, which may affect the accuracy of recall. Retrospective accounts of previous events might also be desirable reconstructions and narratives that are more consistent with current behaviour, as has been discussed in relation to family violence ²⁸⁰. However, it is likely that the adversities reported here are underestimations, as false positives are rare ²⁸¹. Finally, although this study adjusted for relevant

covariates, it is possible that other unmeasured factors may have influenced the relationship between life course adversities and mental health or cognition, for example. The development of depression and increases in chronic stress and psychological distress were also associated with reduced likelihood of ‘forgetting’ a previously reported event ²⁸². Future studies using similar data should aim to remove such biases by using validated and reliable measures, and considering external sources and data linkages to triangulate the findings.

7.1.3 Life course socio-economic position and AL

Socio-economic position (SEP) is one of the most established and persistent determinants of health across the globe, shaping one’s material, behavioural, psychosocial, and environmental exposures across the lifespan. Indeed, the social gradient in AL burden has been well documented ^{7,26,28}, yet few studies have examined how this physiological dysregulation develops over the life course, and whether early life disadvantage leaves a scarring effect on later life AL irrespective of later life SEP. Chapter 5 employed a novel statistical technique, diagonal reference models (DRM), to examine the relationship of intergenerational social mobility with AL in later life in Ireland. This under-utilised approach has been touted to have the capability to disaggregate the direct effect of social mobility from origin and destination SEP ²³³. In line with the extant literature, individuals amongst the stable low group exhibited the highest AL burden, the lowest AL burden was exhibited by the stable high group, with mobile individuals exhibiting AL intermediate to those prevailing in their origin and destination groups. Furthermore, no independent association of social mobility in any direction with AL burden was revealed, mirroring the null associations of mobility on a wide range of outcomes, including well-being ²⁸³.

Identifying individuals and groups at risk of sub-clinical physiological dysregulation is essential for policymakers, allowing them to design and deliver key interventions to prevent disease manifestation. Certainly, the results of this study indicate that although childhood disadvantage may cast a long shadow on later life AL, modification of later life physiological dysregulation is possible with efforts that support social mobility. An outstanding issue relates to whether the improved AL amongst the upwardly mobile is related to psychological or material factors ^{219,237}. Indeed, a more thorough understanding of the life course pathways through which differences in AL burden arise may aid in the development of intervention strategies designed to ameliorate AL burden amongst the high-risk groups.

Zang et al. (2022) suggest some useful extensions of DRMs, including the ability to employ continuous SEP variables (i.e., income, years of schooling), and the ability of assessing more than two life stages, which will allow for a longitudinal examination of social mobility and its relationship with AL burden ¹³⁷. Despite the sophisticated methodology employed to investigate the impact of social mobility on AL, criticisms of DRMs exist. Fosse and Pfeffer in particular have argued that DRMs fail to capture the true effects of mobility, unless the linear effect of mobility is zero in the population, suggesting that the null effect of mobility on outcomes is an artifact of the models ²⁸³. These recent criticisms suggest that additional work may be needed to determine the validity of DRMs as a statistically sound method of disentangling mobility effects from net level effects.

7.1.4 AL and its component biomarkers

Disagreement over which biomarkers and which physiological systems to include in AL indices remain a bone of contention. There has been colossal variation in biomarkers employed over the past 25 years to define AL ^{24,26,28}. Regarding my final contribution, Chapter 6 examined the

association of 25 biomarkers across 6 biological systems with 10-year all-cause mortality. While taking somewhat of an atheoretical view to which biomarkers were included in the study, I attempted to ground the study within the AL framework by assessing the association of each biomarker with a measure of perceived stress and with mortality. 9/25 biomarkers were correlated with stress, while 5/25 were significantly associated with increased risk of mortality, with just 3/ 25 biomarkers correlated with both stress and risk of mortality. A composite measure of the 25 biomarkers, reflecting dysregulation across the cardiovascular, metabolic, lipid, parasympathetic, inflammation and renal systems, was correlated with stress, although this relationship was attenuated after adjustment for socio-demographic and lifestyle factors. I found that individual biomarkers of C-reactive protein, Interleukin-6 and Cystatin C exceeded the predictive utility of the composite AL index on risk of mortality. McCrory, McLoughlin et al. (forthcoming) employed data across 13 cohorts to perform individual participant data meta-analysis of biomarkers from 12 physiological systems on walking speed, grip strength and self-rated health. This study similarly found 5 biomarkers (C-reactive Protein, resting heart rate, high-density lipoprotein, waist-height ratio, HbA1c) that were available across all 13 cohorts investigated that matched or exceeded the predictive utility of a composite AL index on mortality. In the future, newer methodological approaches such as network analysis could be utilised to identify a biomarker panel that best predicts poor health outcomes and mortality. However, such methodologies take an atheoretical approach, moving away from the framework of AL and towards an atheoretical approach that suggests a series of biomarkers that predict adverse outcomes.

If AL were to be conceptualised today, in a world with statistical advances and increasing intricacies in the knowledge on the associations of individual biomarkers with health outcomes, would Seeman and colleagues have chosen the same suite of biomarkers to instantiate the concept ³²?

Perhaps not. Despite the examination of a large suite of multi-system biomarkers within TILDA, the optimal biomarker panel to instantiate the concept of AL remains to be agreed upon. One of the most topical points of contention within the AL literature relates to the lack of fidelity in the biomarkers used to generate AL indices. The creation of an expert working group who consolidate research findings across studies and crystallise a gold standard quantification of AL is now required. The development of a standardised AL index is critical in order to ensure research is valid and reproducible ²⁸.

7.2 Summary of key strengths and limitations

Specific strengths and weaknesses are described in each relevant chapter. The main strength of this work was the extensive information available through the TILDA study, which provides data on many aspects pertinent to the study of AL. The collection of biological data, coupled with detailed information on the social, economic and health status of each participant, enabled examination of the utility of AL as a predictor of health and mortality. Limitations were also present. Although TILDA is a nationally representative longitudinal cohort study, the studies in this thesis did not set out to determine causal associations between allostatic load and other variables, including socio-economic position, health outcomes or adverse experiences. Despite the random sampling strategy employed by TILDA to ensure a nationally representative cohort, there are exclusions to the sample. TILDA does not recruit institutionalised individuals or members of the travelling community, who may have different life experiences and health profiles to those captured in this study.

Additionally, there are other biological systems that could play a role in linking stress with poor health that were not assessed here. There is a consensus, despite the lack of application, that AL indices should include neuroendocrine biomarkers due to their involvement in stress adaptation ²⁸, yet this system is not represented in this study. Difficulties in measuring these primary mediators

may be at the root of their absence across studies. The regulation of cortisol for example is highly complex, as it is generally accepted that cortisol levels are highest shortly after awakening, declining throughout the day ^{112,284}, and the best approach of capturing reliable data on this biomarker remains under debate (i.e., blood, hair, saliva etc.). Cortisol was measured at Wave 3 of TILDA from the hair shaft of a small proportion of the sample as a retrospective indicator of average cortisol exposure in recent months and may offer promise for inclusion in future AL work with this cohort.

7.3 Future research directions

AL has been touted as “*an exemplar of transdisciplinarity*” ²⁸⁵, as it combines knowledge across disciplines, including biology, sociology, psychology and epidemiology. The advent of the international collection of biomarkers through longitudinal human population studies, alongside the push for open data and open science has provided expanded opportunities to understand the pathways in which social forces get “*under the skin*”. However, these datasets have only become available in the past decade or so, suggesting that our understanding of how the social becomes biological is only beginning. It is therefore timely to reflect on the current outstanding issues regarding the AL framework. While not prescriptive or exhaustive, the following section highlights some outlying issues that require additional insight to advance the field of AL.

7.3.1 Medications

Pharmaceuticals are designed to prevent or treat diseases by altering the physiological parameters of a biomarker; medication use can therefore contribute to low observed levels of a biomarker. However, medication use is likely to indicate underlying dysregulation, and may influence immune system functioning ²⁸⁶, yet has been disregarded in many studies investigating AL. Additionally, medication use may be a confounder on the relationship of stress and health, impacting both stress

reactivity and observed biomarker values. For example, anti-hypertensive medications are known to affect sympathetic reactivity to stress²⁸⁷, while corticosteroids may alter the HPA axis, resulting in reduced cortisol secretion²⁸⁸. Additionally, diuretics are often prescribed to treat hypertension, which would lower observed blood pressure values, but this medication may elevate observed glucose and cholesterol¹³. Indeed, McCrory, McLoughlin et al. (forthcoming) found that manually indicating a biomarker as high risk improved the association of biomarkers with mortality within a meta-analysis including TILDA data. However, this thesis found that accounting for medication use did not greatly impact on the relationship of AL with health outcomes, although its consideration improved model fit and strengthened the correlation of AL burden with age (pg. 86).

There are alternate methods of including medications in the development of AL indices that was not tested, such as utilising medication use as a covariate¹⁶⁵, or manually adjusting biomarker values relative to the difference the medication would have made to the biomarker of interest¹⁶⁶. Further investigation on the relative adjustments of biomarkers per dosage of medications taken could improve the knowledge of how medication use impacts on AL burden. Until this is established, any effects of medication on either the systems involved in stress response reactivity, AL burden or the outcome variable in question cannot be discounted. Indeed, a systematic assessment of the various approaches to account for medication could prove informative to many interested in the field of multi-system dysregulation.

7.3.2 Sex differences

The life course is highly gendered, referring to the normative life histories of men and women in relation to social organisation of career paths. Additionally, there have been reports that men and women's physiological stress response is inherently different¹⁸⁹, and these differences are found at

all stages of the life course ²⁸⁹. Why, and to what extent these differences play in the development of AL burden is complex and requires an understanding of whether the mechanisms relate to social and psychological factors, genetics and hormones, or their interactions. Juster et al. summarise evidence describing biomarker clustering of different AL components for men and women and argue that these biological signatures: “*demonstrate that there are multiple sex-specific routes whereby exacerbated biomarkers lead to AL and mortality risk*” (pg. 9) ²⁴. It is possible that men and women experience varying patterns of dysregulation without changing the overall score on an AL index, as sex-specific nuances in dysregulation cannot be extracted from an overall score ²⁹⁰. Whether this is related to changes in hormones that decrease post-menopause (i.e., estrogen), or alternate exogenous social factors associated with gender remains enigmatic, such as social networks, SEP, or lifestyle behaviours. A recent study examining trajectories of AL by sex between America and England found that while AL increased for both men and women with age, the rate of change differed and closed at the mid-60s in ELSA, but remained linear in HRS ²⁹¹. The effects of the menopause on AL are currently understudied and could be considered a confounder of the relationship of psychosocial stress with health. Certainly, age is one of the most important predictors of AL ²⁶⁷, and there may exist a complicated non-linear interplay of sex, age and biomarker functioning ²⁹².

A relevant finding from this study relates to how the utilisation of sex-specific cut points led to an improvement in model fit relative to the classical method generating risk cut points based on distribution of the pooled sample (Chapter 3: Table 3.3, Table 3.4, Table 3.5). Indeed, the mean values of many biomarkers differed between men and women (Chapter 3: Table 3.2), and averaging these groups observed value could lead to loss of biological specificity within an AL index, masking potential organ specific pathways in terms of how AL develops between the sexes. In sum, the aetiology of sex differences in AL remains little understood, and a thorough and systematic

investigation into the importance of such differences across physiological biomarkers is warranted, as biomarkers may be sensitive to changing hormones across the life course.

7.3.3 Dynamic and longitudinal measures of AL

The AL framework provides an integrative approach to characterise dynamic and non-linear influences across biological regulatory systems, yet researchers have attempted to capture this process of adaptation through a series of static biological measures. Bodily processes are not binary and gauging the fluctuations and dynamic divergences from the norm that homeostasis relies on could be where the future of AL measures lie. Perhaps the time has come to disengage from such static point-in-time measures and assess allostasis and the mechanisms underlying the development of AL. Below, I discuss a handful of dynamic measures that exist currently within TILDA.

Near-infrared spectroscopy (NIRS) is a non-invasive imaging method measures changes in the concentration of haemoglobin based on the principle of absorption of light as described by the modified Beer-Lambert law ²⁹³, which can be utilised to examine cerebral oxygenation. The output of the NIRS measure provides dynamic data, which could be assessed in relation to stress exposure. Indeed, Balters et al. (2021) recently reported a relationship of hemodynamic responses captured using a NIRS device with stress exposure ²⁹⁴. Little training is needed to use NIRS, and is relatively cheap in comparison to MRI, making it more accessible for use in research settings. Recently, Knight et al. (2020) examined disorder in neuro-cardiovascular systems with frailty via entropy, which is defined by irregularity and unpredictability in observed signals within TILDA, measured using a Finometer device ²⁹⁵. This measure of disorder was found to predict frailty. Interestingly, AL was associated with 10% greater odds of developing frailty over 3 years in the MacArthur Study of Successful Aging cohort ²⁹⁶, suggesting the utility of dynamic entropy measures in relation to predict

physiological dysregulation. The PNS withdraws vagal control of the heart, resulting in a greater ability to engage with the stressor. While static markers of PNS functioning were employed in the current thesis, the dynamic data that is captured during heart rate variability tests could be utilised over the static measures employed here. However, this system is rarely incorporated within AL studies ²⁴.

Another related limitation of many current epidemiological studies, including the present one, is that biomarkers of AL are collected at one time point only. Priorities for future research include repeat biological measures which will enable researchers to trace the imprint of stress-related dysregulation over time. Such data could help inform the relationship of stress with physiological dysregulation, and also provide insight into whether changes in AL and its component biomarkers moderate disease and mortality risk ⁶⁹. TILDA conducted magnetic resonance imaging (MRI) scans on a subset of individuals at Wave 3 of data collection and repeat measures to assess changes in varying areas of the brain known to be associated with the stress response (i.e., amygdala, hippocampus) would be invaluable to understanding how the brain is impacted by repeat and chronic stress exposure. Models including latent class growth modelling can be applied to these repeat datapoints to identify individuals with similar patterns of change across the life course. Indeed, one of the few longitudinal investigations of AL found that decreases in AL were associated with a reduction in risk of mortality within the high-functioning MacArthur cohort ⁵⁵, with changes in waist-hip ratio and norepinephrine driving this reduction in risk. While this study assessed repeat measures of AL to track risk of mortality over time, additional work is needed to understand moderators of the relationship of AL with health outcomes in population representative samples.

7.3.4 Inter-individual differences

The brain is the central mediator of stress responses, as it determines what is threatening and oversees the regulation of physiological and behavioural reactions ⁶. Perceptions, emotions, personality, self-efficacy and many other psychological mechanisms can moderate the cascade of responses from the neuroendocrine system to physiological stress responses in various biological systems ¹⁰². There is certainly evidence to support the view that high levels of control or self-efficacy buffers the impact of stress on health ²⁹⁷. Interestingly, personality has been shown to structure the likelihood of experiencing stressful events and to have poor social relationships, which are known to impact health outcomes ²⁹⁸. In terms of AL, Christensen et al. examined the cross-sectional associations of The Big Five personality traits (neuroticism, extraversion, conscientiousness, agreeableness, and openness) amongst the Copenhagen Aging and Midlife Biobank study. Openness and conscientiousness were inversely associated with AL in the overall sample, while extraversion was positively associated with AL in men only ¹⁵⁸. This supports a common finding that conscientiousness has a positive influence on health, and indeed this study reported partial mediation of the conscientiousness-AL relationship via health behaviours (i.e., smoking, alcohol, and physical activity). Personality is rather stable prior to mid-life ²⁹⁹, yet personality can change in response to trauma and through therapeutic intervention in adulthood³⁰⁰. Nevertheless, personality may be a relatively stable influence on health behaviours.

Resilience is “*achieving a positive outcome in the face of adversity*” ³⁰¹, and consists of several conceptual aspects, including biological (i.e., how quickly systems return to baseline after stress response activation) and psychological mechanisms (i.e., the ability to cope and avoid stress-induced mental health disorders). But the factors that determine resiliency and vulnerability to stress and adversity remain intertwined. McEwen and colleagues previously noted that the body can exhibit a profile indicative of growth after stress exposure, or “*physical thriving*” ³⁰², with evidence that

individuals with the ability to “*shift and persist*” was associated with resilience to AL after childhood poverty ²⁷⁹. A shift and persist approach consists of reframing cognitive appraisals of stressors more positively while persisting with a focus on hopes for the future ²⁷⁹. In line with the AL framework, moderate stress exposure may facilitate health benefits as there exists evidence of an inverted U-shaped relationship between stressor exposure and adaptation ⁷⁵. Changes to the structure of the brain further compound this relationship between individual coping mechanisms and allostatic load ³⁰³. Neuroplasticity refers to the development and modification of the brain structure that is ongoing in response to development, experiences and associated environmental changes, and the advent of technologies such as magnetic resonance imaging (MRI) may offer a means of better understanding the neurological implications of stress and AL. McEwen noted that dysregulation as a result of prolonged exposure to stressors may be exacerbated by genetic risk factors, in addition to early childhood events ¹⁵. Indeed, allostatic responses necessitate a physiological balance that can change and shift over time in response to stress exposure ³⁰⁴.

However, is it such that those with adaptive coping mechanisms and resilience manage and cope well with moderate stress, or is it such that adaptation to moderate stress promotes resilience? Environmental and social factors inherent to SEP can significantly shape one’s behaviour and resilience, and a thorough investigation of resilience profiles with AL is warranted, specifically to assess whether social prescribing can help promote resiliency and mediate the impact of adversity on multi-system physiological dysregulation, as suggested elsewhere ^{305,306}. This is a complex area of research however, as there is evidence to show that coping mechanisms change across the life course, in line with age-related emotional maturity ³⁰⁷. This question requires a multi-disciplinary approach, involving a thorough examination of biological and psychological mechanisms and their interactions before, during and after various forms of stress exposure.

7.3.5 Alternate measures of multi-system physiological dysregulation

Thus far, the assumed common correlation among AL biomarkers warrants their treatment of summation into a unidimensional construct. This is supported by McCaffery et al. (2012) who utilised confirmatory factor analysis (CFA) to explore this question amongst a mid-life sample in the US ²⁶⁴, and King et al. (2019) who utilised SEM to compare several factor structures amongst adolescents from NHANES ³⁰⁸. However, Booth et al. (2013) refuted these results by reporting different factor loadings relative to whether participants were medicated ⁴², which replicated findings by Seeman et al. (2010). Furthermore, results from Chapter 6 suggest that the inter-correlations of biomarkers vary, even within systems. Additional research is required to understand whether latent AL indices are indeed a unitary construct, or whether the factor structure underlying the panels of biomarkers would be better represented by several sub-dimensions.

Surveying the literature, there is growing interest in omics technologies to build conceptual links between the psychosocial and biological landscapes, including epigenomics, which captures gene-environment interactions. For example, telomere attrition is highly correlated with age and is associated with increased risk of age-related chronic disease and mortality ³⁰⁹. Telomeres are found at the ends of chromosomes in a nucleic-acid protein complex called shelterin and are repeating sequences of between 5 and 15 thousand base-pairs, and their function is akin to the plastic caps on the end of shoelaces, to protect chromosomes. Similar to AL, research to date has shown that telomere length is sensitive to stress ³¹⁰, SEP and perceived social support ³¹¹. Additionally, DNA methylation is one epigenetic process that refers to the addition of a methyl group to cytosine nucleotides on the genome at CpG (cytosine phosphate guanine) sites. Epigenetic clocks, which are

estimated based on methylation at specific CpG sites, are strongly correlated with chronological age³¹², with links between SEP and epigenetic ageing emerging³¹³.

The fact that there was just modest evidence to show that stress exposure was associated with the multi-system measure of biological markers in Chapter 4, and the weak associations of its component biomarkers with stress in Chapter 6, sparks the question of whether there is a true distinction between AL and other indices of biological dysregulation. While AL indices are process orientated and utilised to reflect physiological dysregulation theoretically as an outcome of exposure to life course risk factors, biological indices are goal orientated and developed primarily to predict poor health outcomes on processes of ageing³¹⁴. Additional research is needed into how these measures relate and intersect overtime, delineating the mechanisms by which the social world comes to exert effects on multi-system physiological dysregulation and health outcomes.

7.3.6 AL as a mediator on the SEP-mortality relationship

This thesis established the relationship of AL with age-related health outcomes and mortality, and SEP with AL. The next obvious step would be to examine AL as a mediator of the SEP-mortality relationship. Mediation is conceived as a causal phenomenon, whereby the relationship between two variables is accounted for by a variable that is conceptually on the causal pathway between the exposure and the outcome³¹⁵. Structural equation modelling can be utilised to investigate whether allostatic load mediates the association of socio-economic position with all-cause and cause-specific mortality. Attempts at examining AL as a mediator of the relationship of SEP with mortality have documented varying results thus far. Seeman et al. (2004) identified that AL mediates the relationship between SEP and mortality in a high functioning sample of older adults aged 70-79, explaining around 35.4% of the difference in mortality attributable to educational

differences amongst the MacArthur cohort ¹⁴². Kim et al. (2018) similarly assessed the role of AL burden in explaining the social patterning of mortality amongst the Korean Metabolic Syndrome Mortality Study, yet found a lower mediating effect of AL on the SEP-mortality relationship than Seeman and colleagues, reporting that AL accounted for just 6.6% of the SEP differential ³¹⁶. Gleib et al. (2013) reported that AL accounted for 19% of the educational differences in general health amongst a Moscow cohort ³¹⁷, while Hu et al. (2007) found no evidence to support AL as a mediator on the relationship of SEP with health (i.e., self-rated health, disability) using data from SEBAS ³¹⁸. Data from NHANES similarly found limited support for AL as mediator of the SEP effect on cognition, with AL accounting for just up to 4.5% of this relationship ³¹⁹. Many of these studies were cross-sectional in nature, and therefore less suited to assess mediation. Whether these differences are a result of statistical methods employed, differential biomarker panels or an alternate mechanism remains to be elucidated.

7.4 Clinical implications

AL researchers have suggested that AL indices may be clinically useful, with Seeman et al. arguing that they may “*provide the basis for a more comprehensive assessment of major risks in the aging process*” [pg. 2259] ⁴³. Clinicians routinely incorporate many of the biomarkers included in AL studies, however, attention is largely placed on values reaching clinically relevant levels. The AL framework incorporates sub-clinical cut points, allowing investigation and tracing of dysregulation prior to the onset of clinical symptomology and disease manifestation. This thesis utilised a non-clinical sample of community dwelling older adults and found that AL burden predicted poor physiological functioning and risk of mortality. Although the results may not be generalisable to clinical samples, AL may offer a unified orientation for clinicians to assess changes across body systems relative to the patient over time ³²⁰. However, as the typical method of operationalisation utilises the sample distribution to assign risk categories, *a priori* clinical cut points are advisable to

allow uniformity in risk assessments using this framework. This thesis has advanced the utility of AL as a clinically useful tool in two specific aspects. I have tackled one of the most prevalent limitations regarding the operationalisation of the conceptual framework of AL by comparing a multitude of measures comprising the same biomarker panel, and secondly investigated the individual relationship of 25 multi-system biomarkers with mortality. Both of these studies can help inform the establishment of AL as a measure in clinical settings, although this will require the development and acceptance of a universal index.

Additional research questions that require longitudinal AL measures include whether lowering relative AL burden reduces disease risk in the long run. Indeed, questions surround the reversibility of AL, and whether this reversibility impacts on the existing burden on the healthcare system. Rosenberg et al. (2020) performed a scoping review of AL related intervention articles, with intervention times ranging from 1.75 months to 5 years. 4/6 articles showed potential and promise for the ability to modify AL burden over time ³²¹. Interestingly, a multipronged lifestyle overhaul could be more effective for health than targeting individual health behaviours ³²², as the two nutritional based intervention programs did not manage to reduce AL burden ³²³. However, promising strategies to prevent and reduce AL include cognitive behavioural therapy (CBT) ³²⁴, and antipsychotics ¹⁹². Indeed, evidence for the potential impact of yoga practise on perceived stress is emerging ³²⁵, which is interesting in light of the potential importance of mindfulness and yoga practise on many biomarkers used within AL indices, including blood pressure, lipids and cytokines ³²⁶; and may be useful tools for moderating the impact of stress on AL. As outlined by Juster et al., future studies should assess what combinations of health-promoting activities and therapies are best suited across SEP groups, age cohorts and sex ³²⁷.

7.4.1 Clinimetrics

Despite its well-established limitations, evidence is mounting for the clinical relevance of AL, with the recent publication of clinimetric criteria for the diagnosis of allostatic overload. Clinimetrics refers to a domain concerned with indices and rating scales to measure symptoms and clinical phenomena. These metrics for the clinical diagnosis of allostatic load were first suggested by Fava et al. (2010)³²⁸, with a revision incorporated in the 2019 Diagnostic Criteria for Psychosomatic Research³²⁹. This approach intends to diagnose AL through psychosomatic criteria opposed to the traditional biological approach, which could increase the number of people screened and act as somewhat of a pre-cursor to assessing the impact of toxic stress on health outcomes through biomarkers. Peng et al. (2021) demonstrated that capturing this clinimetric AL alongside the classical physiological AL derived from biomarkers would provide a much more nuanced assessment over the long term in longitudinal cohorts³³⁰. Indeed, the triangulation of sub-clinical, clinical, and neuropsychological testing may advance the AL framework. Additional transdisciplinary research is required to answer McEwen's concern regarding whether top-down therapies (e.g., physical activity, social engagement) have the capability to lower AL burden and its associated risks, or whether pharmacological and target clinical interventions is most advantageous³⁰³.

7.4.2 Personal reflections

The results of the studies included in this thesis adds to that body of evidence surrounding the predictive utility of indices of composite biomarkers with poor health and early mortality. Improving the operationalisation of AL can feed indirectly into social policy changes – improving the accuracy and precision of the AL index can help identify populations that are at higher risk of chronic stress and associated poor health problems. This information could be used to guide social policy interventions that target these populations, such as providing additional resources and support to disadvantaged communities. Additionally, AL and its changes over time can serve as a useful

outcome measure for evaluating the effectiveness of such social policy interventions aimed at reducing chronic stress and improving health outcomes. Despite these opportunities, a consensus surrounding how best to measure AL needs to be understood.

However, there remains a number of outstanding limitations, particularly relating to the theoretical underpinnings of the AL framework. The inconsistent findings of the association of stress with multisystem dysregulation, along with evidence suggesting that stressors outside the psychosocial, such as environmental toxins. Moving away from individual level associations, the combination of a wide range of external factors and their internal biological responses, that is, the “*totality of environmental exposures from conception onwards*”, is known as the exposome³³¹. New opportunities to understand the impact of the exposome are emerging, with technologies including wearable devices to gather information about local and person-based concentrations of environmental stressors gaining importance and offering insight into how the exposome can influence multi-system dysregulation³³². By taking a holistic approach to health policy that addresses the underlying social and environmental factors contributing to chronic stress, we can create a healthier and more equitable society for all.

7.5 Conclusion

This thesis has sought to evaluate the utility of the allostatic load (AL) framework in quantifying differences in health and longevity in Ireland. This body of work has consolidated the view that AL is a robust predictor of health and mortality, yet further work is needed to advance the framework to establish interventions targeting sub-clinical dysregulation.

References

1. Krieger, N., Williams, D. R. & Moss, N. E. Measuring social class in US public health research: concepts, methodologies, and guidelines. *Annu. Rev. Public Health* **18**, 341–378 (1997).
2. Galobardes, B., Shaw, M., Lawlor, D. A., Lynch, J. W. & Smith, G. D. Indicators of socioeconomic position (part 2). *J. Epidemiol. Community Health* **60**, 95–101 (2006).
3. Link, B. & Phelan, J. Social conditions as fundamental causes of health inequalities. *Handb. Med. Sociol. Sixth Ed.* 3–17 (1995) doi:10.2307/j.ctv16h2n9s.4.
4. Thoits, P. A. Stress and Health: Major Findings and Policy Implications. *J. Health Soc. Behav.* **51**, S41–S53 (2010).
5. Mayer, K. U. Whose Lives? How History, Societies, and Institutions Define and Shape Life Courses. *Res. Hum. Development* **1**, 161–187 (2004).
6. McEwen, B. S. & Gianaros, P. Central role of the brain in stress and adaptation: links to socioeconomic status, health, and disease. *Ann N Y Acad Sci* **1186**, 190–222 (2010).
7. Seeman, T. E., Epel, E., Gruenewald, T., Karlamangla, A. & McEwen, B. S. Socio-economic differentials in peripheral biology: cumulative allostatic load. *Ann N Y Acad Sci* **1186**, 223–239 (2010).
8. Goldstein, D. S. & Kopin, I. J. Evolution of concepts of stress. *Stress* **10**, 109–120 (2007).
9. Robinson, A. *Let's Talk About Stress: History of Stress Research*. (2018). doi:10.1037/gpr0000137.
10. Cannon, W. B. *The wisdom of the body. The wisdom of the body*. (W W Norton & Co, 1932).
11. Carlson, E. D. & Chamberlain, R. M. Allostatic load and health disparities: A theoretical

- orientation. *Res. Nurs. Health* **28**, 306–315 (2005).
12. Selye, H. Stress and disease. *Journal of Psychosomatic Research* vol. 16 500–514 at <https://doi.org/10.1288/00005537-195507000-00002> (1955).
 13. Sterling, P. & Eyer, J. Allostasis: A new paradigm to explain arousal pathology. in *Handbook of life stress, cognition and health*. (ed. Fisher S, R. J.) 629–649 (John Wiley & Sons, 1988).
 14. McEwen, B. S. Protective and damaging effects of stress mediators. *N. Engl. J. Med.* **338**, 171–179 (1998).
 15. McEwen, B. S. Interacting mediators of Allostasis and Allostatic Load: Towards an Understanding of Resilience in Aging. *Metabolism* **52**, 10–16 (2003).
 16. Sapolsky, R. M., Romero, L. M. & Munck, A. U. How Do Glucocorticoids Influence Stress Responses? Integrating Permissive, Suppressive, Stimulatory, and Preparative Actions*. *Endocr. Rev.* **21**, 55–89 (2000).
 17. Friedman, M. J. & McEwen, B. S. Posttraumatic stress disorder, allostatic load, and medical illness. in *Trauma and health: Physical health consequences of exposure to extreme stress*. 157–188 (American Psychological Association, 2004). doi:10.1037/10723-007.
 18. McEwen, B. S. Stress, adaptation, and disease. Allostasis and allostatic load. *Ann N Y Acad Sci* **840**, 33–44 (1998).
 19. McEwen, B. S. Allostasis and allostatic load: implications for neuropsychopharmacology. *Neuropsychopharmacology* **22**, 108–124 (2000).
 20. McEwen, B. S. Physiology and neurobiology of stress and adaptation: Central role of the brain. *Physiol. Rev.* **87**, 873–904 (2007).
 21. Juruena, M. F., Bourne, M., Young, A. H. & Cleare, A. J. Hypothalamic-Pituitary-Adrenal

Axis Dysfunction by Early Life Stress. *Neurosci. Lett.* **759**, 136037 (2021).

22. Rodrigues, S. M., LeDoux, J. E. & Sapolsky, R. M. The influence of stress hormones on fear circuitry. *Annu. Rev. Neurosci.* **32**, 289–313 (2009).
23. McEwen, B. S. & Stellar, E. Stress and the individual. Mechanisms leading to disease. *Arch Intern Med* **153**, 2093–2101 (1993).
24. Juster, R. P., McEwen, B. S. & Lupien, S. J. Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neurosci. Biobehav. Rev.* **35**, 2–16 (2010).
25. McEwen, B. S. & Gianaros, P. J. Stress- and allostasis-induced brain plasticity. *Annu. Rev. Med.* **62**, 431–445 (2011).
26. Beckie, T. M. A systematic review of allostatic load, health, and health disparities. *Biol Res Nurs* **14**, 311–346 (2012).
27. Yang, L., Rosemberg, M. A. S. & Seng, J. S. Allostatic load: A theoretical model for understanding the relationship between maternal posttraumatic stress disorder and adverse birth outcomes. *Midwifery* **62**, 205–213 (2018).
28. Johnson, S. C., Cavallaro, F. L. & Leon, D. A. A systematic review of allostatic load in relation to socioeconomic position: Poor fidelity and major inconsistencies in biomarkers employed. *Soc. Sci. Med.* **192**, 66–73 (2017).
29. Adler, N. & Newman, K. Socioeconomic Disparities In Health: Pathways And Policies. (2002).
30. Gallo, L. C. *et al.* Associations of chronic stress burden, perceived stress, and traumatic stress with cardiovascular disease prevalence and risk factors in the HCHS/SOL Sociocultural Ancillary Study Linda. *Psychosom. Med.* **76**, 468–475 (2014).

31. Suvarna, B. *et al.* Health risk behaviours and allostatic load: A systematic review. *Neurosci. Biobehav. Rev.* **108**, 694–711 (2020).
32. Seeman, T. E., McEwen, B. S., Rowe, J. W. & Singer, B. H. Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. *Proc Natl Acad Sci U S A* **98**, 4770–4775 (2001).
33. Gruenewald, T. L., Seeman, T. E., Ryff, C. D., Karlamangla, A. S. & Singer, B. H. Combinations of biomarkers predictive of later life mortality. *Proc Natl Acad Sci U S A* **103**, 14158–14163 (2006).
34. Ryff, C. D. *et al.* Psychological Well-Being and Ill-Being: Do They Have Distinct or Mirrored Biological Correlates? *Psychother. Psychosom.* **75**, 85–95 (2006).
35. Wiley, J. F., Gruenewald, T. L., Karlamangla, A. S. & Seeman, T. E. Modeling Multisystem Physiological Dysregulation. *Psychosom. Med.* **78**, 290–301 (2016).
36. Robertson, T., Beveridge, G. & Bromley, C. Allostatic load as a predictor of all-cause and cause-specific mortality in the general population: Evidence from the Scottish Health Survey. *PLoS One* **12**, e0183297 (2017).
37. Karlamangla, A. S., Singer, B. H., McEwen, B. S., Rowe, J. W. & Seeman, T. E. Allostatic load as a predictor of functional decline. MacArthur studies of successful aging. *J Clin Epidemiol* **55**, 696–710 (2002).
38. Weinstein, M., Goldman, N., Hedley, A., Yu-Hsuan, L. & Seeman, T. Social linkages to biological markers of health among the elderly. *J. Biosoc. Sci.* **35**, 433–453 (2003).
39. Dowd, J. B. & Goldman, N. Do biomarkers of stress mediate the relation between socioeconomic status and health? *J. Epidemiol. Community Health* **60**, 633–639 (2006).

40. Goldman, N., Kimbro, R. T., Turra, C. M. & Pebley, A. R. Socioeconomic gradients in health for white and Mexican-origin populations. *Am J Public Heal.* **96**, 2186–2193 (2006).
41. Hwang, A. C. *et al.* Predicting all-cause and cause-specific mortality by static and dynamic measurements of allostatic load: a 10-year population-based cohort study in Taiwan. *J Am Med Dir Assoc* **15**, 490–496 (2014).
42. Booth, T., Starr, J. M. & Deary, I. Modeling multisystem biological risk in later life: allostatic load in the Lothian birth cohort study 1936. *Am J Hum Biol* **25**, 538–543 (2013).
43. Seeman, T. E., Singer, B. H., Rowe, J. W., Horwitz, R. I. & McEwen, B. S. Price of adaptation--allostatic load and its health consequences. MacArthur studies of successful aging. *Arch Intern Med* **157**, 2259–2268 (1997).
44. Akinyemiju, T. *et al.* Association of Allostatic Load with All-Cause and Cancer Mortality by Race and Body Mass Index in the REGARDS Cohort. *Cancers (Basel)*. **12**, (2020).
45. Castagné, R. *et al.* Allostatic load and subsequent all-cause mortality: which biological markers drive the relationship? Findings from a UK birth cohort. *Eur. J. Epidemiol.* **33**, 441–458 (2018).
46. Miller, H. N., Lafave, S., Marineau, L., Stephens, J. & Thorpe, R. J. The impact of discrimination on allostatic load in adults: An integrative review of literature. *J. Psychosom. Res.* (2021) doi:10.1016/j.jpsychores.2021.110434.
47. Parker, H. W., Abreu, A. M., Sullivan, M. C. & Vadiveloo, M. K. Allostatic Load and Mortality: A Systematic Review and Meta-Analysis. *Am. J. Prev. Med.* (2022) doi:10.1016/j.amepre.2022.02.003.
48. Johnson, T. E. Recent results : Biomarkers of aging. *Exp. Gerontol.* **41**, 1243–1246 (2006).

49. Geronimus, A. T., Hicken, M., Keene, D. & Bound, J. ‘Weathering’ and age patterns of allostatic load scores among blacks and whites in the United States. *Am J Public Heal.* **96**, 826–833 (2006).
50. Richardson, K. *et al.* *Polypharmacy in adults over 50 in Ireland: Opportunities for cost saving and improved healthcare.* (2012).
51. Berkman, L. F. *et al.* High, usual and impaired functioning in community-dwelling older men and women: findings from the MacArthur Foundation Research Network on Successful Aging. *J. Clin. Epidemiol.* **16**, 1129–1140 (1993).
52. Borrell, L. N., Dallo, F. J. & Nguyen, N. Racial/ethnic disparities in all-cause mortality in U.S. adults: the effect of allostatic load. *Public Heal. Rep* **125**, 810–816 (2010).
53. Levine, M. E. & Crimmins, E. M. A comparison of methods for assessing mortality risk. *Am J Hum Biol* **26**, 768–776 (2014).
54. Duru, O. K., Harawa, N. T., Kermah, D. & Norris, K. C. Allostatic load burden and racial disparities in mortality. *J. Natl. Med. Assoc.* **104**, 89–95 (2012).
55. Karlamangla, A. S., Singer, B. H. & Seeman, T. E. Reduction in allostatic load in older adults is associated with lower all-cause mortality risk: MacArthur studies of successful aging. *Psychosom Med* **68**, 500–507 (2006).
56. Beydoun, H. A., Huang, S., Beydoun, M. A., Hossain, S. & Zonderman, A. B. Mediating-Moderating Effect of Allostatic Load on the Association between Dietary Approaches to Stop Hypertension Diet and All-Cause and Cause-Specific Mortality: 2001-2010 National Health and Nutrition Examination Surveys. *Nutrients* **11**, (2019).
57. Acheampong, T., Jiang, L., Ziogas, A. & Odegaard, A. O. Multi-Systemic Biological Risk and Cancer Mortality: The NHANES III Study. *Sci. Rep.* **10**, 5047 (2020).

58. Mathew, A. *et al.* Allostatic Load in Cancer: A Systematic Review and Mini Meta-Analysis. *Biol. Res. Nurs.* (2020) doi:10.1177/1099800420969898.
59. Vanhoutte, B. & Nazroo, J. Life Course Pathways to Later Life Wellbeing: A Comparative Study of the Role of Socio-Economic Position in England and the U.S. *J. Popul. Ageing* **9**, 157–177 (2016).
60. Cohen, S., Kessler, R. C. & Gordon, L. U. Strategies for measuring stress in studies of psychiatric and physical disorders. in *Measuring stress: A guide for health and social scientists*. 3–26 (Oxford University Press, 1995).
61. Ben-Shlomo, Y. & Kuh, D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. *Int. J. Epidemiol.* **31**, 285–293 (2002).
62. Shonkoff, J. P., Boyce, W. T. & McEwen, B. S. Neuroscience, molecular biology, and the childhood roots of health disparities: building a new framework for health promotion and disease prevention. *Jama* **301**, 2252–2259 (2009).
63. Shonkoff, J. P. *et al.* The lifelong effects of early childhood adversity and toxic stress. *Pediatrics* **129**, (2012).
64. Marques-Feixa, L. *et al.* Childhood maltreatment disrupts HPA-axis activity under basal and stress conditions in a dose-response relationship in children and adolescents. *Psychol. Med.* (2021) doi:10.1017/S003329172100249X.
65. Dich, N. *et al.* Early life adversity potentiates the effects of later life stress on cumulative physiological dysregulation. *Anxiety, Stress. Coping* **28**, 372–390 (2015).
66. Walsh, D., McCartney, G., Smith, M. & Armour, G. Relationship between childhood socioeconomic position and adverse childhood experiences (ACEs): A systematic review.

Journal of Epidemiology and Community Health at <https://doi.org/10.1136/jech-2019-212738> (2019).

67. Lacey, R. E. *et al.* Adverse childhood experiences and early life inflammation in the Avon Longitudinal Study of Parents and Children. *Psychoneuroendocrinology* 104914 (2020) doi:<https://doi.org/10.1016/j.psyneuen.2020.104914>.
68. Guidi, J., Lucente, M., Sonino, N. & Fava, G. A. Allostatic Load and Its Impact on Health: A Systematic Review. *Psychother. Psychosom.* (2020) doi:10.1159/000510696.
69. Delpierre, C. *et al.* Origins of health inequalities: The case for allostatic load. *Longit. Life Course Stud.* 7, 79 (2016).
70. Danaei, G. *et al.* The Preventable Causes of Death in the United States: Comparative Risk Assessment of Dietary, Lifestyle, and Metabolic Risk Factors. *PLoS Med* 6, (2009).
71. Stults-Kolehmainen, M. A. & Sinha, R. *The effects of stress on physical activity and exercise.* *Sports Medicine* vol. 44 (2014).
72. Posadzki, P. *et al.* Exercise/physical activity and health outcomes: an overview of Cochrane systematic reviews. *BMC Public Health* 20, 1–12 (2020).
73. Rodriguez, E. J., Kim, E. N., Sumner, A. E., Nápoles, A. M. & Pérez-Stable, E. J. Allostatic Load: Importance, Markers, and Score Determination in Minority and Disparity Populations. *J. Urban Heal.* 96, 3–11 (2019).
74. Regitz-Zagrosek, V. Sex and gender differences in health. Science & Society Series on Sex and Science. *EMBO Rep.* 13, 596–603 (2012).
75. McEwen, B. S. Sex, stress and the hippocampus: allostasis, allostatic load and the aging process. *Neurobiol. Aging* 23, 921–939 (2002).

76. Kerr, P., Kheloui, S., Rossi, M., Désilets, M. & Juster, R.-P. Allostatic load and women's brain health: A systematic review. *Front. Neuroendocrinol.* 100858 (2020)
doi:<https://doi.org/10.1016/j.yfrne.2020.100858>.
77. Yang, Y. & Kozloski, M. Sex differences in age trajectories of physiological dysregulation: inflammation, metabolic syndrome, and allostatic load. *J. Gerontol. A. Biol. Sci. Med. Sci.* **66**, 493–500 (2011).
78. Kezios, K. L. *et al.* Comparing different operationalizations of allostatic load measured in mid-life and their patterning by race and cumulative life course socioeconomic status. *Psychoneuroendocrinology* 105689 (2022) doi:10.1016/j.psyneuen.2022.105689.
79. Eskes, T. & Haanen, C. Why do women live longer than men? *Eur. J. Obstet. Gynecol. Reprod. Biol.* **133**, 126–133 (2007).
80. Snyder-mackler, N. *et al.* Social determinants of health and survival in humans and other animals. *Science* (80-.). **368**, 37–39 (2020).
81. Smith, G. D., Neaton, J. D., Wentworth, D., Stamler, R. & Stamler, J. Socioeconomic differentials in mortality risk among men screened for the multiple risk factor intervention trial: I. White men. *Am. J. Public Health* **86**, 486–496 (1996).
82. Stringhini, S. *et al.* Socioeconomic status and the 25 × 25 risk factors as determinants of premature mortality: a multicohort study and meta-analysis of 1·7 million men and women. *Lancet* **389**, 1229–1237 (2017).
83. Kivimäki, M. *et al.* Association between socioeconomic status and the development of mental and physical health conditions in adulthood: a multi-cohort study. *Lancet Public Heal.* **5**, e140–e149 (2020).
84. Galobardes, B., Shaw, M., Lawlor, D. A., Lynch, J. W. & Smith, G. D. Indicators of

- socioeconomic position (part 1). *J. Epidemiol. Community Health* **60**, 7–12 (2006).
85. Geyer, S., Hemstrom, O., Peter, R. & Vagero, D. Education, income, and occupational class cannot be used interchangeably in social epidemiology. Empirical evidence against a common practice. *J Epidemiol Community Heal.* **60**, 804–810 (2006).
 86. Torssander, J. & Erikson, R. Stratification and mortality – A comparison of education, class, status and income. *Eur. Sociol. Rev.* **26**, 265–474 (2010).
 87. Kitigawa, E. & Hauser, P. *Differential mortality in the United States: a study in socioeconomic epidemiology*. (Harvard University Press, 1973).
 88. Raghupathi, V. & Raghupathi, W. The influence of education on health: An empirical assessment of OECD countries for the period 1995-2015. *Arch. Public Heal.* **78**, 1–18 (2020).
 89. Card, D. Estimating the return to schooling: Progress on some persistent econometric problems. *Econometrica* **69**, 1127–1160 (2001).
 90. Bartley, M. *Health Inequality: An introduction to concepts, theories and methods*. (Polity Press, 2017).
 91. Berkman, N. D., Sheridan, S. L., Donahue, K. E., Halpern, D. J. & Crotty, K. Low health literacy and health outcomes: An updated systematic review. *Ann. Intern. Med.* **155**, 97–107 (2011).
 92. Mirowsky, J. & Ross, C. E. *Education, social status, and health. Education, social status, and health*. (Aldine de Gruyter, 2003).
 93. Mirowsky, J. & Ross, C. E. *Education, Social Status, and Health*. (Routledge, 2017).
 94. Sharp, E. S. & Gatz, M. Relationship between education and dementia: An updated systematic review. *Alzheimer Dis. Assoc. Disord.* **25**, 289–304 (2011).

95. Glymour, M. M., Avendano, M. & Kawachi, I. Socioeconomic status and health. in *Social Epidemiology* (eds. Berkman, L. F., Kawachi, I. & Glymour, M. M.) 17–62 (Oxford University Press, 2014).
96. Galobardes, B., Lynch, J. & Smith, G. D. Measuring socioeconomic position in health research. *Br Med Bull* **81–82**, 21–37 (2007).
97. Mosca, I. & McCrory, C. Personality and wealth accumulation among older couples: Do dispositional characteristics pay dividends? *J. Econ. Psychol.* **56**, 1–19 (2016).
98. Frick, J. R. & Grapka, M. M. Missing income data in the German SOEP : Incidence, imputation and its impact on the income distribution. *SOEP Surv. Pap.* (2014).
99. Bartley, M. & Blane, D. Inequality and social class. in *Sociology as applied to medicine* (ed. Scambler, G.) (Saunders, 2008).
100. Fujishiro, K., Xu, J. & Gong, F. What does ‘occupation’ represent as an indicator of socioeconomic status?: Exploring occupational prestige and health. *Soc. Sci. Med.* **71**, 2100–2107 (2010).
101. Nam, C. B. & Boyd, M. Occupational status in 2000: Over a century of census-based measurement. *Popul. Res. Policy Rev.* **23**, 327–358 (2004).
102. Lupien, S. J., McEwen, B. S., Gunnar, M. R. & Heim, C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nat Rev Neurosci* **10**, 434–445 (2009).
103. Shaefer, H. L., Lapidos, A., Wilson, R. & Danziger, S. Association of income and adversity in childhood with adult health and well-being. *Soc. Serv. Rev.* **92**, 69–92 (2018).
104. Krieger, N. A glossary for social epidemiology. *Epidemiol. Bull.* **23**, 7–11 (2002).
105. Shuey, K. M. & Willson, A. E. Economic hardship in childhood and adult health trajectories:

- An alternative approach to investigating life-course processes. *Adv. Life Course Res.* **22**, 49–61 (2014).
106. Iveson, M. H. & Deary, I. J. Intergenerational social mobility and subjective wellbeing in later life. *Soc. Sci. Med.* **188**, 11–20 (2017).
 107. Pudrovska, T. & Anikputa, B. Early-life socioeconomic status and mortality in later life: an integration of four life-course mechanisms. *Journals Gerontol. Ser. B* **69**, 451–460 (2014).
 108. Hallqvist, J., Lynch, J., Bartley, M., Lang, T. & Blane, D. Can we disentangle life course processes of accumulation, critical period and social mobility? An analysis of disadvantaged socio-economic positions and myocardial infarction in the Stockholm Heart Epidemiology Program. *Soc. Sci. Med.* **58**, 1555–1562 (2004).
 109. Merton, R. K. *Social theory and social structure*. (Free Press, 1968).
 110. Hertzman, C. & Power, C. Child development as a determinant of health across the life course. *Curr. Paediatr.* **14**, 438–443 (2004).
 111. Beckie, T. M., Duffy, A. & Groer, M. W. The Relationship between Allostatic Load and Psychosocial Characteristics among Women Veterans. *Womens. Health Issues* **26**, 555–563 (2016).
 112. Dowd, J. B., Simanek, A. M. & Aiello, A. E. Socio-economic status, cortisol and allostatic load: a review of the literature. *Int J Epidemiol* **38**, 1297–1309 (2009).
 113. Crimmins, E. M., Kim, J. K. & Seeman, T. E. Poverty and biological risk: the earlier ‘aging’ of the poor. *J Gerontol A Biol Sci Med Sci* **64**, 286–292 (2009).
 114. Seeman, T. E. *et al.* Modeling multisystem biological risk in young adults: The Coronary Artery Risk Development in Young Adults Study. *Am J Hum Biol* **22**, 463–472 (2010).

115. Gruenewald, T. L. *et al.* History of socioeconomic disadvantage and allostatic load in later life. *Soc. Sci. Med.* **74**, 75–83 (2012).
116. Gustafsson, P. E., Janlert, U., Theorell, T., Westerlund, H. & Hammarstrom, A. Socioeconomic status over the life course and allostatic load in adulthood: results from the Northern Swedish Cohort. *J. Epidemiol. Community Heal.* **65**, 986–992 (2011).
117. Präg, P. & Richards, L. Intergenerational social mobility and allostatic load in Great Britain. *J. Epidemiol. Community Heal.* **73**, 100–105 (2019).
118. Robertson, T., Popham, F. & Benzeval, M. Socioeconomic position across the lifecourse & allostatic load: data from the West of Scotland Twenty-07 cohort study. *BMC Public Health* **14**, 184 (2014).
119. Raphael, D. Poverty in childhood and adverse health outcomes in adulthood. *Maturitas* **69**, 22–26 (2011).
120. Brady, D. Theories of the Causes of Poverty. *Annu. Rev. Sociol.* **45**, 155–175 (2019).
121. Halaby, C. N. & Sobel, M. E. Mobility Effects in the Workplace. *Am. J. Sociol.* **85**, 385–416 (1979).
122. Sorokin, P. A. *Social and cultural mobility*. (Free Press, 1959).
123. Newman, K. S. *Falling from grace: downward mobility in the age of affluence*. vol. 319 (University of California Press, 1999).
124. Rosvall, M., Chaix, B., Lynch, J., Lindström, M. & Merlo, J. Similar support for three different life course socioeconomic models on predicting premature cardiovascular mortality and all-cause mortality. *BMC Public Health* **6**, 1–17 (2006).
125. Houle, J. N. & Martin, M. A. Does intergenerational mobility shape psychological distress ?

- Sorokin revisited. *Res. Soc. Stratif. Mobil.* **29**, 193–203 (2011).
126. Blau, P. M. & Duncan, O. D. *The American occupational structure*. (John Wiley & Sons, 1967).
 127. Bartley, M. & Plewis, I. Increasing social mobility: An effective policy to reduce health inequalities. *J. R. Stat. Soc. Ser. A Stat. Soc.* **170**, 469–481 (2007).
 128. Sobel, M. E. Diagonal Mobility Models: A Substantively Motivated Class of Designs for the Analysis of Mobility Effects. *Am. Sociol. Rev.* **46**, 893–906 (1981).
 129. Billingsley, S., Drefahl, S. & Ghilagaber, G. Diagonal reference models in longitudinal analyses of fertility and mortality. in *Modelling fertility* 1–14 (2016).
 130. Whelan, C. T. & Layte, R. Late Industrialization and the Increased Merit Selection Hypothesis: Ireland as a Test Case. *Eur. Sociol. Rev.* **18**, 35–50 (2002).
 131. Whelan, B. J. RANSAM: A Random Sample Design for Ireland. *Econ. Soc. Rev.* **10**, 169–174 (1979).
 132. Cronin, H., Kamiya, Y., Kearney, P., Barrett, A. & Timonen, V. The Design of the Irish Longitudinal Study on Ageing.
 133. Whelan, B. J. & Savva, G. M. Design and methodology of the Irish Longitudinal Study on Ageing. *J. Am. Geriatr. Soc.* **61 Suppl 2**, S265-8 (2013).
 134. Cronin, H., O'Regan, C., Finucane, C., Kearney, P. & Kenny, R. A. Health and aging: Development of the Irish Longitudinal Study on Ageing health assessment. *J. Am. Geriatr. Soc.* **61**, 269–278 (2013).
 135. Donoghue, O. & Kenny, R. A. AMBER CROSS CODE - Walking speed in middle-aged and older Irish adults and the implications for pedestrian traffic signals. (2015).

136. StataCorp. Stata Statistical Software: Release 15. at (2017).
137. Zang, E., Sobel, M. E. & Lying, L. The Mobility Effects Hypothesis: Past, Present, and Future. *SocArXiv* **06520**, (2022).
138. Merkin, S. S. *et al.* Neighborhoods and cumulative biological risk profiles by race/ethnicity in a national sample of U.S. adults: NHANES III. *Ann Epidemiol* **19**, 194–201 (2009).
139. Upchurch, D. M. *et al.* A Longitudinal Investigation of Race, Socioeconomic Status, and Psychosocial Mediators of Allostatic Load in Midlife Women: Findings From the Study of Women’s Health Across the Nation. *Psychosom Med* **77**, 402–412 (2015).
140. Szanton, S. L., Gill, J. M. & Allen, J. K. Allostatic load: a mechanism of socioeconomic health disparities? *Biol Res Nurs* **7**, 7–15 (2005).
141. Seplaki, C. L., Goldman, N., Gleib, D. A. & Weinstein, M. A comparative analysis of measurement approaches for physiological dysregulation in an older population. *Exp. Gerontol.* **40**, 438–449 (2005).
142. Seeman, T. E. *et al.* Cumulative biological risk and socio-economic differences in mortality: MacArthur Studies of Successful Aging. *Soc. Sci. Med.* **58**, 1985–1997 (2004).
143. Hawkley, L. C., Lavelle, L. A., Berntson, G. G. & Cacioppo, J. T. Mediators of the relationship between socioeconomic status and allostatic load in the Chicago Health, Aging, and Social Relations Study (CHASRS). *Psychophysiology* **48**, 1134–1145 (2011).
144. LeBron, A. M. W., Schulz, A. J., Mentz, G. B., Israel, B. A. & Stokes, C. A. Social relationships, neighbourhood poverty and cumulative biological risk: findings from a multi-racial US urban community. *J Biosoc Sci* 1–18 (2019) doi:10.1017/s002193201900004x.
145. Seplaki, C. L., Goldman, N., Weinstein, M. & Lin, Y. H. Measurement of cumulative

- physiological dysregulation in an older population. *Demography* **43**, 165–183 (2006).
146. Singer, B., Ryff, C. D. & Seeman, T. Operationalizing allostatic load. in *Allostasis, homeostasis, and the costs of physiological adaptation*. 113–149 (Cambridge University Press, 2004). doi:10.1017/CBO9781316257081.007.
 147. Allen, A. M. *et al.* Racial discrimination, educational attainment, and biological dysregulation among midlife African American women. *Psychoneuroendocrinology* **99**, 225–235 (2019).
 148. Gleib, D. A. *et al.* Perceived stress and biological risk: is the link stronger in Russians than in Taiwanese and Americans? *Stress* **16**, 411–420 (2013).
 149. Petrovic, D. *et al.* Sociodemographic, behavioral and genetic determinants of allostatic load in a Swiss population-based study. *Psychoneuroendocrinology* **67**, 76–85 (2016).
 150. Li, Y., Rosemberg, M. S., Dalton, V. K., Lee, S. J. & Seng, J. S. Exploring the optimal allostatic load scoring method in women of reproductive age. *J Adv Nurs* **75**, 2548–2558 (2019).
 151. Juster, R. P. *et al.* Sex Differences and Gender Diversity in Stress Responses and Allostatic Load Among Workers and LGBT People. *Curr Psychiatry Rep* **21**, 110 (2019).
 152. Verma, R., Balhara, Y. P. S. & Gupta, C. S. Gender differences in stress response: Role of developmental and biological determinants. *Ind. Psychiatry J.* **20**, 4–10 (2011).
 153. Freire, A. do N. F., Barbosa, J. F. de S., Pereira, D. S., Gomes, C. dos S. & Guerra, R. O. Allostatic load and stress biomarkers in a sample of community-dwelling older adults. *Arch Gerontol Geriatr* **87**, 104006 (2020).
 154. Goldman, N. *et al.* Sex differentials in biological risk factors for chronic disease: estimates from population-based surveys. *J Womens Heal.* **13**, 393–403 (2004).

155. Santos-Lozada, A. R. & Howard, J. T. Using Allostatic Load to Validate Self-rated Health for Racial/Ethnic Groups in the United States. *Biodemography Soc. Biol.* **64**, 1–14 (2018).
156. Stoney, C. M., Matthews, K. A., McDonald, R. H. & Johnson, C. A. Sex differences in lipid, lipoprotein, cardiovascular, and neuroendocrine responses to acute stress. *Psychophysiology* **25**, 645–656 (1988).
157. Christensen, D. S. *et al.* Early life predictors of midlife allostatic load: A prospective cohort study. *PLoS One* **13**, e0202395 (2018).
158. Christensen, D. S. *et al.* Objective and subjective stress, personality, and allostatic load. *Brain Behav* (2019) doi:10.1002/brb3.1386.
159. Gustafsson, P. E., Janlert, U., Theorell, T., Westerlund, H. & Hammarstrom, A. Social and material adversity from adolescence to adulthood and allostatic load in middle-aged women and men: results from the Northern Swedish Cohort. *Ann Behav Med* **43**, 117–128 (2012).
160. Robertson, T., Benzeval, M., Whitley, E. & Popham, F. The role of material, psychosocial and behavioral factors in mediating the association between socioeconomic position and allostatic load (measured by cardiovascular, metabolic and inflammatory markers). *Brain. Behav. Immun.* **45**, 41–49 (2015).
161. Duong, M. T., Bingham, B. A., Aldana, P. C., Chung, S. T. & Sumner, A. E. Variation in the Calculation of Allostatic Load Score: 21 Examples from NHANES. *J Racial Ethn Heal. Disparities* **4**, 455–461 (2017).
162. Lipowicz, A., Szklarska, A. & Malina, R. M. Allostatic load and socioeconomic status in Polish adult men. *J Biosoc Sci* **46**, 155–167 (2014).
163. Seeman, T. E., Singer, B. H., Ryff, C. D., Dienberg Love, G. & Levy-Storms, L. Social relationships, gender, and allostatic load across two age cohorts. *Psychosom. Med.* **64**, 395–

406 (2002).

164. Seeman, M., Stein Merkin, S., Karlamangla, A., Koretz, B. & Seeman, T. Social status and biological dysregulation: the ‘status syndrome’ and allostatic load. *Soc. Sci. Med.* **118**, 143–151 (2014).
165. Piazza, J. R., Stawski, R. S. & Sheffler, J. L. Age, Daily Stress Processes, and Allostatic Load: A Longitudinal Study. *J Aging Heal.* 898264318788493 (2018)
doi:10.1177/0898264318788493.
166. Robertson, T. & Watts, E. The importance of age, sex and place in understanding socioeconomic inequalities in allostatic load: Evidence from the Scottish Health Survey (2008–2011). **16**, 126 (2016).
167. Logan, J. G., Barksdale, D. J., Carlson, J., Carlson, B. W. & Rowsey, P. J. Psychological stress and arterial stiffness in Korean Americans. *J. Psychosom. Res.* **73**, 53–58 (2012).
168. Matsumura, K., Noguchi, H., Rolfe, P., Yamakoshi, T. & Matsuoka, Y. Differential Effect of Two Mental Stress Tasks on Arterial Stiffness. *Jpn. Psychol. Res.* **61**, 249–261 (2019).
169. Canney, M. *et al.* Examining the utility of cystatin C as a confirmatory test of chronic kidney disease across the age range in middle-aged and older community-dwelling adults. *J. Epidemiol. Community Health* **72**, 287 LP – 293 (2018).
170. Carbone, J. T., Clift, J. & Alexander, N. Measuring allostatic load: Approaches and limitations to algorithm creation. *J. Psychosom. Res.* **163**, 111050 (2022).
171. Daly, M., Sutin, A. R. & Robinson, E. Perceived Weight Discrimination Mediates the Prospective Association Between Obesity and Physiological Dysregulation: Evidence From a Population-Based Cohort. *Psychol Sci* 956797619849440 (2019)
doi:10.1177/0956797619849440.

172. Read, S. & Grundy, E. Allostatic load and health in the older population of England: a crossed-lagged analysis. *Psychosom. Med.* **76**, 490–496 (2014).
173. Viccaro, L. J., Perera, S. & Studenski, S. A. Is timed up and go better than gait speed in predicting health, function, and falls in older adults? *J Am Geriatr Soc* **59**, 887–892 (2011).
174. Studenski, S. *et al.* Physical performance measures in the clinical setting. *J Am Geriatr Soc* **51**, 314–322 (2003).
175. Guralnik, J. M. *et al.* Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. *J Gerontol A Biol Sci Med Sci* **55**, M221–31 (2000).
176. Bohannon, R. W. Hand-grip dynamometry predicts future outcomes in aging adults. *J Geriatr Phys Ther* **31**, 3–10 (2008).
177. Manor, O., Matthews, S. & Power, C. Dichotomous or categorical response? Analysing self-rated health and lifetime social class. *Int J Epidemiol* **29**, 149–157 (2000).
178. Perez-Zepeda, M. U. *et al.* Assessing the Validity of Self-Rated Health with the Short Physical Performance Battery: A Cross-Sectional Analysis of the International Mobility in Aging Study. *PLoS One* **11**, e0153855 (2016).
179. Jylha, M. What is self-rated health and why does it predict mortality? Towards a unified conceptual model. *Soc Sci Med* **69**, 307–316 (2009).
180. Vie, T. L., Hufthammer, K. O., Holmen, T. L., Meland, E. & Breidablik, H. J. Is self-rated health a stable and predictive factor for allostatic load in early adulthood? Findings from the Nord Trøndelag Health Study (HUNT). *Soc Sci Med* **117**, 1–9 (2014).
181. von Thiele, U., Lindfors, P. & Lundberg, U. Self-rated recovery from work stress and

- allostatic load in women. *J. Psychosom. Res.* **61**, 237–242 (2006).
182. Williams, R. Scalar Measures of Fit: Pseudo R² and Information Measures (AIC & BIC). <https://www3.nd.edu/~rwilliam/stats3/L05.pdf> (2019).
 183. Scott Long, J., Freese, J. & Scott J, J. and F. *Regression Models for Categorical Dependent Variables Using Stata, 3rd Edition.* (Stata Press, 2014).
 184. Raftery, A. E. Bayesian Model Selection in Social Research. *Sociol. Methodol.* **25**, 111–163 (1995).
 185. Sallinen, J. *et al.* Hand-grip strength cut points to screen older persons at risk for mobility limitation. *J Am Geriatr Soc* **58**, 1721–1726 (2010).
 186. Pepe, M. S., Longton, G. & Janes, H. Estimation and comparison of receiver operating characteristic curves. *Stata J.* (2009) doi:10.1177/1536867x0900900101.
 187. Cleves, M. A. From the Help Desk: Comparing Areas under Receiver Operating Characteristic Curves from Two or more Probit or Logit Models. *Stata J.* **2**, 301–313 (2002).
 188. Fries, E., Hesse, J., Hellhammer, J. & Hellhammer, D. H. A new view on hypocortisolism. *Psychoneuroendocrinology* **30**, 1010–1016 (2005).
 189. Stroud, L. R., Salovey, P. & Epel, E. S. Sex differences in stress responses: social rejection versus achievement stress. *Biol. Psychiatry* **52**, 318–327 (2002).
 190. Juster, R.-P. *et al.* Sex and gender roles in relation to mental health and allostatic load. *Psychosom Med* **78**, 788–804 (2016).
 191. Howard, J. T. & Sparks, P. J. Does allostatic load calculation method matter? Evaluation of different methods and individual biomarkers functioning by race/ethnicity and educational level. *Am J Hum Biol* **28**, 627–635 (2016).

192. Berger, M. *et al.* Allostatic load is associated with psychotic symptoms and decreases with antipsychotic treatment in patients with schizophrenia and first-episode psychosis. *Psychoneuroendocrinology* **90**, 35–42 (2018).
193. Chobanian, A. V *et al.* Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertens. (Dallas, Tex. 1979)* **42**, 1206–1252 (2003).
194. Mancia, G. *et al.* 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J. Hypertens.* **31**, 1281–1357 (2013).
195. World Health Organization (WHO). *Waist Circumference and Waist–Hip Ratio*. (WHO Document Production Services, 2011).
196. World Health Organization (WHO). Body mass index - BMI. <http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi> (2020).
197. National Medicines Information Centre. Update on the management of type 2 diabetes mellitus. at <http://www.stjames.ie/GPsHealthcareProfessionals/Newsletters/NMICBulletins/NMICBulletins2011/Update on DIABETES April 2012.pdf> (2012).
198. Expert Panel on Detection and Treatment of High Blood Cholesterol in Adults, E. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* **285**, 2486–2497 (2001).

199. Donnelly, P., Dunne, H. & Conlon, P. *Kidney Disease*. (2014).
200. Brown, L. L., Zhang, Y. S., Mitchell, C. & Ailshire, J. Does Telomere Length Indicate Biological, Physical, and Cognitive Health Among Older Adults? Evidence from the Health and Retirement Study. *Journals Gerontol. Ser. A* **73**, 1626–1632 (2018).
201. Ridker, P. M. Cardiology Patient Page. C-reactive protein: a simple test to help predict risk of heart attack and stroke. *Circulation* **108**, e81-5 (2003).
202. Cohen, S., Janicki-Deverts, D. & Miller, G. E. Psychological stress and disease. *Jama* **298**, 1685–1687 (2007).
203. Puterman, E. *et al.* Lifespan adversity and later adulthood telomere length in the nationally representative US Health and Retirement Study. *Proc. Natl. Acad. Sci.* **113**, E6335 (2016).
204. Friedman, E. M., Karlamangla, A. S., Gruenewald, T. L., Koretz, B. & Seeman, T. E. Early life adversity and adult biological risk profiles. *Psychosom Med* **77**, 176–185 (2015).
205. Glei, D. A., Goldman, N., Chuang, Y. L. & Weinstein, M. Do chronic stressors lead to physiological dysregulation? Testing the theory of allostatic load. *Psychosom Med* **69**, 769–776 (2007).
206. Gallo, L. C., Jiménez, J. A., Shivpuri, S., Espinosa de los Monteros, K. & Mills, P. J. Domains of chronic stress, lifestyle factors, and allostatic load in middle-aged Mexican-American women. *Ann. Behav. Med.* **41**, 21–31 (2011).
207. Barboza Solis, C. *et al.* Adverse childhood experiences and physiological wear-and-tear in midlife: Findings from the 1958 British birth cohort. *Proc Natl Acad Sci U S A* **112**, E738–E746 (2015).
208. McLoughlin, S., Kenny, R. A. & McCrory, C. Does the choice of Allostatic Load scoring

- algorithm matter for predicting age-related health outcomes? *Psychoneuroendocrinology* **120**, 104789 (2020).
209. Krause, N., Shaw, B. A. & Cairney, J. A descriptive epidemiology of lifetime trauma and the physical health status of older adults. *Psychol. Aging* (2004) doi:10.1037/0882-7974.19.4.637.
 210. Mayfield, D., McLeod, G. & Hall, P. The CAGE questionnaire: validation of a new alcoholism screening instrument. *Am. J. Psychiatry* (1974) doi:10.1176/ajp.131.10.1121.
 211. Ewing, J. A. Detecting alcoholism. The CAGE questionnaire. *Jama* **252**, 1905–1907 (1984).
 212. Bernadt, M. W., Mumford, J., Taylor, C., Smith, B. & Murray, R. M. Comparison of questionnaire and laboratory tests in the detection of excessive drinking and alcoholism. *Lancet (London, England)* **1**, 325–328 (1982).
 213. Craig, C. L. *et al.* International physical activity questionnaire: 12-country reliability and validity. *Med. Sci. Sport. Exerc.* **35**, 1381–1395 (2003).
 214. L. F. Berkman, S. L. S. Social networks, host resistance, and mortality: a nine year follow up study of Alameda county residents. *Am. J. Epidemiol.* **109**, 186–204 (1979).
 215. Spratt, T. Why multiples matter: Reconceptualising the population referred to child and family social workers. *Br. J. Soc. Work* **42**, 1574–1591 (2012).
 216. McEwen, B. S. & Seeman, T. Protective and damaging effects of mediators of stress. Elaborating and testing the concepts of allostasis and allostatic load. *Ann N Y Acad Sci* **896**, 30–47 (1999).
 217. Matthews, K. A. & Gallo, L. C. Psychological perspectives on pathways linking socioeconomic status and physical health. *Annu. Rev. Psychol.* **62**, 501–530 (2011).
 218. Sorokin, P. A. *Social Mobility*. (Free Press, 1927).

219. Gugushvili, A., Zhao, Y. & Bukodi, E. ‘Falling from grace’ and ‘rising from rags’: Intergenerational educational mobility and depressive symptoms. *Soc. Sci. Med.* **222**, 294–304 (2019).
220. Blau, P. M. Social Mobility and Interpersonal Relations. *Am. Sociol. Rev.* **21**, 290–295 (1956).
221. Merkin, S. S., Karlamangla, A., Roux, A. V, Shrager, S. & Seeman, T. E. Life course socioeconomic status and longitudinal accumulation of allostatic load in adulthood: multi-ethnic study of atherosclerosis. *Am. J. Public Health* **104**, e48-55 (2014).
222. Green, M. J. & Popham, F. Interpreting mutual adjustment for multiple indicators of socioeconomic position without committing mutual adjustment fallacies. *BMC Public Health* **19**, 1–7 (2019).
223. Billingsley, S., Drefahl, S. & Ghilagaber, G. An application of diagonal reference models and time-varying covariates in social mobility research on mortality and fertility. *Soc. Sci. Res.* **75**, 73–82 (2018).
224. Gugushvili, A., Bulczak, G., Zelinska, O. & Koltai, J. Socioeconomic Position , Social Mobility , and Health Selection Effects on Allostatic Load in the United States Socioeconomic Position , Social Mobility , and Health Selection Effects on Allostatic Load in the United States. *PLoS One* **16**, 1–30 (2021).
225. Whelan, C. T. & Layte, R. Economic change, social mobility and meritocracy: reflections on the Irish experience. *Quarterly Economic Commentary* vol. 3 89–108 at (2004).
226. Whelan, C. T. & Layte, R. Economic boom and social mobility: The Irish experience. *Res. Soc. Stratif. Mobil.* **24**, 193–208 (2006).
227. Ó Gráda, C. & O’Rourke, K. H. The Irish economy during the century after partition. *Econ. Hist. Rev.* **75**, 336–370 (2022).

228. Callan, T. & Harmon, C. The economic return to schooling in Ireland. *Labour Econ.* **6**, 543–550 (1999).
229. Galobardes, B., Lynch, J. W. & Davey Smith, G. Childhood socioeconomic circumstances and cause-specific mortality in adulthood: systematic review and interpretation. *Epidemiol. Rev.* **26**, 7–21 (2004).
230. Hickson, D. A. *et al.* Social patterning of cumulative biological risk by education and income among African Americans. *Am. J. Public Health* **102**, 1362–1369 (2012).
231. Kubzansky, L. D., Kawachi, I. & Sparrow, D. Socioeconomic status, hostility, and risk factor clustering in the Normative Aging Study: any help from the concept of allostatic load? *Ann. Behav. Med.* **21**, 330–338 (1999).
232. Seeman, T. E. *et al.* Education, income and ethnic differences in cumulative biological risk profiles in a national sample of US adults: NHANES III (1988-1994). *Soc. Sci. Med.* **66**, 72–87 (2008).
233. van der Waal, J., Daenekindt, S. & de Koster, W. Statistical challenges in modelling the health consequences of social mobility: the need for diagonal reference models. *Int. J. Public Heal.* Vol. **62**, 1029–1037 (2017).
234. Miller, G. E., Chen, E. & Parker, K. J. Psychological stress in childhood and susceptibility to the chronic diseases of aging: moving toward a model of behavioral and biological mechanisms. *Psychol. Bull.* **137**, 959–997 (2011).
235. Kaiser, C. *DRM Diagonal Reference Model Stata*. (Open Science Framework, 2018). doi:10.17605/OSF.IO/KFDP6.
236. Luo, Y. & Waite, L. J. The impact of childhood and adult SES on physical, mental, and cognitive well-being in later life. *J. Gerontol. B. Psychol. Sci. Soc. Sci.* **60**, (2005).

237. Bulczak, G., Gugushvili, A. & Zelinska, O. How are social origin, destination and mobility linked to physical, mental, and self-rated health? Evidence from the United States. *Qual. Quant.* **56**, 3555–4585 (2021).
238. Blane, D., Harding, S. & Rosato, M. Does social mobility affect the size of the socioeconomic mortality differential?: Evidence from the Office for National Statistics Longitudinal Study. *J. R. Stat. Soc. Ser. A Stat. Soc.* **162**, 59–70 (1999).
239. Steiber, N. Intergenerational educational mobility and health satisfaction across the life course : Does the long arm of childhood conditions only become visible later in life ? *Soc. Sci. Med.* **242**, 112603 (2019).
240. Szreter, S. R. S. The Genesis of the Registrar-General ' s Social Classification of Occupations. *Br. J. Sociol.* **35**, 522–546 (1984).
241. Kirtby, P. *Celtic Tiger in Distress: Growth and inequality in Ireland*. (Palgrave Interational Political Economy, 2002).
242. Prior, L., Manley, D. & Jones, K. Stressed out? An investigation of whether allostatic load mediates associations between neighbourhood deprivation and health. *Health Place* **52**, 25–33 (2018).
243. Misiak, B. *et al.* Adverse childhood experiences and low socioeconomic status with respect to allostatic load in adulthood : A systematic review. *Psychoneuroendocrinology* **136**, (2022).
244. Wright, K. D., Lin, C., FA, C. & Williams, K. Beyond Allostatic Load. *Res. Gerontol. Nurs.* **14**, 222–224 (2021).
245. Harris, K. M. & Schorpp, K. M. Integrating Biomarkers in Social Stratification and Health Research. *Annu. Rev. Sociol.* **44**, 361–386 (2018).

246. Cornman, J. C., Gleib, D. A., Goldman, N. & Weinstein, M. Physiological Dysregulation, Frailty, and Risk of Mortality Among Older Adults. *Res. Aging* **39**, 911–933 (2017).
247. Cohen, S., Kamarck, T. & Mermelstein, R. A global measure of perceived stress. *J. Heal. Soc. Behav* **24**, 385–396 (1983).
248. Ward, M. *et al.* Linking death registration and survey data: Procedures and cohort profile for The Irish Longitudinal Study on Ageing (TILDA). *HRB Open Res.* **3**, 43 (2020).
249. Ward, M., May, P., Normand, C., Kenny, R. A. & Nolan, A. Mortality risk associated with combinations of loneliness and social isolation. Findings from the Irish Longitudinal Study on Ageing (TILDA). *Age Ageing* **50**, 1329–1335 (2021).
250. Tripska, K., Draessler, J. & Pokladnikova, J. Heart rate variability, perceived stress and willingness to seek counselling in undergraduate students. *J. Psychosom. Res.* **160**, 110972 (2022).
251. McLoughlin, S., Kenny, R. A. & McCrory, C. Psychosocial adversity and allostatic load burden in midlife and older ages. *Heal. Psychol.* **40**, 468–471 (2021).
252. Miller, G., Chen, E. & Cole, S. W. Health psychology: Developing biologically plausible models linking the social world and physical health. *Annu. Rev. Psychol.* **60**, 501–524 (2009).
253. Del Giudice, M. & Gangestad, S. W. Rethinking IL-6 and CRP: Why they are more than inflammatory biomarkers, and why it matters. *Brain. Behav. Immun.* **70**, 61–75 (2018).
254. Tang, Y., Fung, E., Xu, A. & Lan, H. Y. C-reactive protein and ageing. *Clin. Exp. Pharmacol. Physiol.* **44**, 9–14 (2017).
255. Mussap, M. *et al.* Cystatin C is a more sensitive marker than creatinine for the estimation of GFR in type 2 diabetic patients. *Kidney Int.* **61**, 1453–1461 (2002).

256. Levin, A. Cystatin C, serum creatinine, and estimates of kidney function: Searching for better measures of kidney function and cardiovascular risk. *Ann. Intern. Med.* **142**, 586–588 (2005).
257. Colangelo, L. A., Yano, Y., Jacobs, D. R. & Lloyd-Jones, D. M. Association of Resting Heart Rate with Blood Pressure and Incident Hypertension over 30 Years in Black and White Adults: The CARDIA Study. *Hypertension* **76**, 692–698 (2020).
258. Rosero-Bixby, L. & Dow, W. H. Predicting mortality with biomarkers: a population-based prospective cohort study for elderly Costa Ricans. *Popul. Health Metr.* **10**, 1–15 (2012).
259. Srikanthan, P., Seeman, T. E. & Karlamangla, A. S. Waist-Hip-Ratio as a Predictor of All-Cause Mortality in High- Functioning Older Adults. *Ann. Epidemiol.* **19**, (2009).
260. He, G. dong *et al.* A nonlinear association of total cholesterol with all-cause and cause-specific mortality. *Nutr. Metab.* **18**, 1–11 (2021).
261. Chadeau-Hyam, M. *et al.* Education, biological ageing, all-cause and cause-specific mortality and morbidity: UK biobank cohort study. *EClinicalMedicine* **29–30**, 100658 (2020).
262. Tibuakuu, M. *et al.* The association between cigarette smoking and inflammation: The Genetic Epidemiology Network of Arteriopathy (GENOA) study. *PLoS One* **12**, 1–14 (2017).
263. Ambrose, J. A. & Barua, R. S. The pathophysiology of cigarette smoking and cardiovascular disease: An update. *J. Am. Coll. Cardiol.* **43**, 1731–1737 (2004).
264. McCaffery, J. M., Marsland, A. L., Strohacker, K., Muldoon, M. F. & Manuck, S. B. Factor structure underlying components of allostatic load. *PLoS One* **7**, e47246 (2012).
265. Vineis, P. *et al.* Special Report: The Biology of Inequalities in Health: The Lifepath Consortium. *Front. public Heal.* **8**, 118 (2020).
266. Karimi, M. *et al.* Early-life inequalities and biological ageing: a multisystem Biological

Health Score approach in Understanding Society. *J Epidemiol Community Heal.* (2019)
doi:10.1136/jech-2018-212010.

267. Crimmins, E. M., Johnston, M., Hayward, M. & Seeman, T. E. Age differences in allostatic load: an index of physiological dysregulation. *Exp Gerontol* **38**, 731–734 (2003).
268. Taylor, J., McFarland, M. J. & Carr, D. C. Age, Perceptions of Mattering, and Allostatic Load. *J Aging Heal.* 898264318795805 (2018) doi:10.1177/0898264318795805.
269. Demirer, I. *et al.* Does allostatic load predict incidental coronary events differently among sexes? *Compr. Psychoneuroendocrinology* **8**, 100089 (2021).
270. Waliszewska-Prosół, M. *et al.* Allostatic load index in patients with multiple sclerosis: A case-control study. *Psychoneuroendocrinology* **142**, (2022).
271. Li, Y. & Rosemberg, M. A. S. The promise of allostatic load rests upon strategic operationalization, scoring, and targeted interventions. *Psychoneuroendocrinology* **123**, 104877 (2021).
272. Widom, C. S., Horan, J. & Brzustowicz, L. Childhood maltreatment predicts allostatic load in adulthood. *Child Abuse Negl.* **47**, 59–69 (2015).
273. McLaughlin, K. A., Sheridan, M. A., Humphreys, K. L., Belsky, J. & Ellis, B. J. The Value of Dimensional Models of Early Experience: Thinking Clearly About Concepts and Categories. *Perspect. Psychol. Sci.* **16**, 1463–1472 (2021).
274. McLaughlin, K. A., Sheridan, M. A. & Lambert, H. K. Childhood adversity and neural development: Deprivation and threat as distinct dimensions of early experience. *Neurosci. Biobehav. Rev.* **47**, 578–591 (2014).
275. Fiorito, G. *et al.* Social adversity and epigenetic aging: a multi-cohort study on socioeconomic

- differences in peripheral blood DNA methylation. *Sci. Rep.* **7**, 16266 (2017).
276. Power, C., Li, L. & Pinto Pereira, S. M. Child maltreatment (neglect and abuse) in the 1958 birth cohort: an overview of associations with developmental trajectories and long-term outcomes. *Longit. Life Course Stud.* **11**, 431–458 (2020).
 277. Lupien, S. J., King, S., Meaney, M. J. & McEwen, B. S. Can poverty get under your skin? Basal cortisol levels and cognitive function in children from low and high socioeconomic status. *Sci. Ment. Heal. Stress Brain* **9**, 37–60 (2013).
 278. Anda, R. F. *et al.* Adverse childhood experiences and smoking during adolescence and adulthood. *J. Am. Med. Assoc.* **282**, 1652–1658 (1999).
 279. Chen, E. & Miller, G. E. ‘Shift-and-Persist’ Strategies: Why Low Socioeconomic Status Isn’t Always Bad for Health. *Perspect. Psychol. Sci.* **7**, 135–158 (2012).
 280. Spatz, C. & Widom, C. S. The Cycle of Violence. *Science (80-.)*. **244**, 160–166 (1989).
 281. Hardt, J. & Rutter, M. Validity of adult retrospective reports of adverse childhood experiences: review of the evidence. *J. Child Psychol. Psychiatry.* **45**, 260–273 (2004).
 282. Colman, I. *et al.* Consistency in adult reporting of adverse childhood experiences. *Psychol. Med.* **46**, 543–549 (2016).
 283. Fosse, E. & Pfeffer, F. T. Beyond the Diagonal Reference Model : Critiques and New Directions. in *Population Association of America* 1–8 (2019).
 284. Ice, G. H., Katz-Stein, A., Himes, J. & Kane, R. L. Diurnal cycles of salivary cortisol in older adults. *Psychoneuroendocrinology* **29**, 355–370 (2004).
 285. Juster, R.-P. *et al.* Social Inequalities and the Road to Allostatic Load: From Vulnerability to Resilience. in *Developmental Psychopathology* 1–54 (2016).

doi:10.1002/9781119125556.devpsy408.

286. Rhen, T. & Cidlowski, J. A. Antiinflammatory Action of Glucocorticoids — New Mechanisms for Old Drugs. *N. Engl. J. Med.* **353**, 1711–1723 (2005).
287. Nazzaro, P., Merlo, M., Manzari, M., Cicco, G. & Pirrelli, A. Stress Response and Antihypertensive Treatment. *Drugs* **46**, 133–141 (1993).
288. Dluhy, R. G. Clinical relevance of inhaled corticosteroids and HPA axis suppression. *J. Allergy Clin. Immunol.* **101**, S447-50 (1998).
289. Kudielka, B. M., Hellhammer, D. H. & Kirschbaum, C. Sex Differences in Human Stress Response*. in *Encyclopedia of Stress (Second Edition)* (ed. Fink, G.) 469–473 (Academic Press, 2007). doi:<https://doi.org/10.1016/B978-012373947-6.00343-3>.
290. Bey, G. S., Jesdale, B. M., Ulbricht, C. M., Mick, E. O. & Person, S. D. Allostatic Load Biomarker Associations with Depressive Symptoms Vary among US Black and White Women and Men. *Healthc. (Basel, Switzerland)* **6**, 105 (2018).
291. Tampubolon, G. & Maharani, A. Trajectories of allostatic load among older Americans and Britons: Longitudinal cohort studies. *BMC Geriatr.* (2018) doi:10.1186/s12877-018-0947-4.
292. Lau, E. S. *et al.* Sex Differences in Circulating Biomarkers of Cardiovascular Disease. *J. Am. Coll. Cardiol.* **74**, 1543–1553 (2019).
293. Ferrari, M. & Quaresima, V. A brief review on the history of human functional near-infrared spectroscopy (fNIRS) development and fields of application. *Neuroimage* **63**, 921–935 (2012).
294. Balters, S. *et al.* Functional near-infrared spectroscopy brain imaging predicts symptom severity in youth exposed to traumatic stress. *J. Psychiatr. Res.* **144**, 494–502 (2021).

295. Knight, S. P. *et al.* Associations between Neurocardiovascular Signal Entropy and Physical Frailty. *Entropy* **23**, (2020).
296. Gruenewald, T. L., Seeman, T. E., Karlamangla, A. S. & Sarkisian, C. A. Allostatic load and frailty in older adults. *J Am Geriatr Soc* **57**, 1525–1531 (2009).
297. Thompson, S. C. The role of personal control in adaptive functioning. *Handbook of positive psychology*. 202–213 at (2002).
298. Kendler, K. S., Gardner, C. O. & Prescott, C. A. Personality and the experience of environmental adversity. *Psychol. Med.* **33**, 1193–1202 (2003).
299. Roberts, B. W., Kuncel, N. R., Shiner, R., Caspi, A. & Goldberg, L. R. The power of personality. *Perspect. Psychol. Sci.* **2**, 313–345 (2007).
300. De Fruyt, F., Van Leeuwen, K., Bagby, R. M., Rolland, J.-P. & Rouillon, F. Assessing and interpreting personality change and continuity in patients treated for major depression. *Psychological Assessment* vol. 18 71–80 at <https://doi.org/10.1037/1040-3590.18.1.71> (2006).
301. McEwen, B. S., Gray, J. D. & Nasca, C. Recognizing resilience: Learning from the effects of stress on the brain. *Neurobiol. Stress* **1**, 1–11 (2015).
302. Epel, E. S., McEwen, B. S. & Ickovics, J. R. Embodying Psychological Thriving: Physical Thriving in Response to Stress. **54**, (1998).
303. McEwen, B. S. Brain on stress: How the social environment gets under the skin. *Proc. Natl. Acad. Sci. U. S. A.* **109**, 17180–17185 (2012).
304. Juster, R. P., Russell, J. J., Almeida, D. & Picard, M. Allostatic load and comorbidities: A mitochondrial, epigenetic, and evolutionary perspective. *Dev. Psychopathol.* **28**, 1117–1146 (2016).

305. Brody, G. H. *et al.* Is Resilience Only Skin Deep?: Rural African Americans' Socioeconomic Status-Related Risk and Competence in Preadolescence and Psychological Adjustment and Allostatic Load at Age 19. *Psychol. Sci.* **24**, 1285–1293 (2013).
306. Singer, B. & Ryff, C. D. Hierarchies of life histories and associated health risks. *Ann N Y Acad Sci* **896**, 96–115 (1999).
307. Sheffler, J. L., Piazza, J. R., Quinn, J. M., Sachs-Ericsson, N. J. & Stanley, I. H. Adverse childhood experiences and coping strategies: identifying pathways to resiliency in adulthood. *Anxiety. Stress. Coping* **32**, 594–609 (2019).
308. King, A. L., Garnier-Villarreal, M., Simanek, A. M. & Johnson, N. L. Testing allostatic load factor structures among adolescents: A structural equation modeling approach. *Am J Hum Biol* e23242 (2019) doi:10.1002/ajhb.23242.
309. Rizvi, S., Raza, S. T. & Mahdi, F. Telomere length variations in aging and age-related diseases. *Curr. Aging Sci.* **7**, 161–167 (2014).
310. Epel, E. S. *et al.* Accelerated telomere shortening in response to life stress. *Proc. Natl. Acad. Sci. U. S. A.* **101**, 17312–17315 (2004).
311. Rentscher, K. E., Carroll, J. E. & Mitchell, C. Psychosocial stressors and telomere length: A current review of the science. *Annual Review of Public Health* vol. 41 223–245 at <https://doi.org/10.1146/annurev-publhealth-040119-094239> (2019).
312. Bell, C. G. *et al.* DNA methylation aging clocks: Challenges and recommendations. *Genome Biol.* **20**, 1–24 (2019).
313. McCrory, C. *et al.* Early life adversity and age acceleration at mid-life and older ages indexed using the next-generation GrimAge and Pace of Aging epigenetic clocks. *Psychoneuroendocrinology* **137**, 105643 (2022).

314. Hastings, W. J., Almeida, D. M. & Shalev, I. Conceptual and analytical overlap between allostatic load and systemic biological aging measures: Analyses from the National Survey of Midlife Development in the United States. *Journals Gerontol. - Ser. A Biol. Sci. Med. Sci.* (2021).
315. Baron, R. & Kenny, D. *The Moderator-Mediator Variable Distinction in Social Psychological Research*. vol. 51 (1987).
316. Kim, G. R., Jee, S. H. & Pikhart, H. Role of allostatic load and health behaviours in explaining socioeconomic disparities in mortality: a structural equation modelling approach. *J. Epidemiol. Community Health* **72**, 545 (2018).
317. D.A., G. *et al.* To what extent do biomarkers account for the large social disparities in health in Moscow? *Soc. Sci. Med.* **77**, 164–172 (2013).
318. Hu, P., Wagle, N., Goldman, N., Weinstein, M. & Seeman, T. E. The associations between socioeconomic status, allostatic load and measures of health in older Taiwanese persons: Taiwan social environment and biomarkers of aging study. *J Biosoc Sci* **39**, 545–556 (2007).
319. Akrivos, J., Zhu, C. W. & Haroutunian, V. Role of cumulative biological risk in mediating socioeconomic disparities in cognitive function in the elderly: a mediation analysis. *BMJ Open* **10**, e035847 (2020).
320. Berens, A. E., Jensen, S. K. G. & Nelson, C. A. *Biological embedding of childhood adversity: From physiological mechanisms to clinical implications*. *BMC Medicine* vol. 15 (BioMed Central Ltd., 2017).
321. Rosemberg, M.-A. S., Granner, J., Li, Y. & Seng, J. S. A scoping review of interventions targeting allostatic load. *Stress* 1–10 (2020) doi:10.1080/10253890.2020.1784136.
322. Tan, M., Mamun, A., Kitzman, H. & Dodgen, L. Longitudinal changes in all ostatic load

- during a randomized church-based, lifestyle intervention in african American women. *Ethn. Dis.* **29**, 297–308 (2019).
323. Soltani, H., Keim, N. L. & Laugero, K. D. Diet quality for sodium and vegetables mediate effects of whole food diets on 8-week changes in stress load. *Nutrients* **10**, (2018).
 324. Carroll, J. E., Irwin, M. R., Stein Merkin, S. & Seeman, T. E. Sleep and multisystem biological risk: a population-based study. *PLoS One* **10**, e0118467–e0118467 (2015).
 325. D’Alessio, L. *et al.* Reducing Allostatic Load in Depression and Anxiety Disorders: Physical Activity and Yoga Practice as Add-On Therapies. *Front. psychiatry* **11**, 501 (2020).
 326. Pascoe, M. C., Thompson, D. R. & Ski, C. F. Yoga, mindfulness-based stress reduction and stress-related physiological measures: A meta-analysis. *Psychoneuroendocrinology* **86**, 152–168 (2017).
 327. Juster, R.-P. *et al.* Social Inequalities and the Road to Allostatic Load: From Vulnerability to Resilience. in *Developmental Psychopathology, Third Edition* 1–54 (John Wiley & Sons, Inc, 2016). doi:<https://doi.org/10.1002/9781119125556.devpsy408>.
 328. Fava, G. A., Guidi, J., Semprini, F., Tomba, E. & Sonino, N. Clinical Assessment of Allostatic Load and Clinimetric Criteria. *Psychother. Psychosom.* **79**, 280–284 (2010).
 329. Fava, G. A. *et al.* Clinical characterization of allostatic overload. *Psychoneuroendocrinology* **108**, 94–101 (2019).
 330. Peng, M. *et al.* Post-COVID-19 Epidemic: Allostatic Load among Medical and Nonmedical Workers in China. *Psychother. Psychosom.* **90**, 127–136 (2021).
 331. Wild, C. P. Complementing the Genome with an “Exposome”: The Outstanding Challenge of Environmental Exposure Measurement in Molecular Epidemiology. (2005)

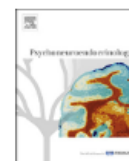
doi:10.1158/1055-9965.EPI-05-0456.

332. McDade, T. W. & Harris, K. M. From society to cells and back again: new opportunities for discovery at the biosocial interface. *Discov. Soc. Sci. Heal.* **2**, 4 (2022).



Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Does the choice of Allostatic Load scoring algorithm matter for predicting age-related health outcomes?

Sinead McLoughlin^{a,*}, Rose Anne Kenny^{a,b}, Cathal McCrory^a^a The Irish Longitudinal Study on Ageing (TILDA), Trinity Central, Trinity College Dublin, 152-160 Pearse Street, Dublin 2, Ireland^b Mercer's Institute for Successful Ageing, St James's Hospital, Dublin, Ireland

ARTICLE INFO

Keywords:

Allostatic load
Biomarkers
Walking speed
Grip strength
Self-rated health

ABSTRACT

Allostatic Load (AL) is posited to provide a measure of cumulative physiological dysregulation across multiple biological systems and demonstrates promise as a sub-clinical marker of overall health. Despite the large heterogeneity of measures employed in the literature to represent AL, few studies have investigated the impact of different AL scoring systems in predicting health. This study uses data for 4477 participants aged 50+ years participating in the Irish Longitudinal Study on Ageing (TILDA) to compare the utility of 14 different scoring algorithms that have been used to operationalise AL (i.e. count-based high-risk quartiles, deciles, two-tailed cut-points, z-scores, system-weighted indices, clinical cut-points, sex-specific scores, and incorporating medication usage). Model fit was assessed using R^2 , Bayesian Information Criterion (BIC), and the area under the Receiver Operating Characteristic curve (AUC). The measure incorporating medications predicted walking speed and SRH marginally better than others. In general, AL was not predictive of grip strength. Overall, the results suggest that the choice of AL scoring algorithm exerts a relatively modest influence in predicting a number of important health outcomes.

1. Introduction

Allostatic Load (AL) is posited to represent a sub-clinical measure of physiological wear and tear resulting from chronic exposure to life course stressors (McEwen and Stellar, 1993). In recent decades, the framework has contributed to an enhanced interdisciplinary understanding of how social, environmental, and psychological factors impact physiological functioning and shape health disparities (Beckie, 2012; Merkin et al., 2009; Upchurch et al., 2015). Despite this apparent utility, AL is beset by a number of methodological and conceptual difficulties that have hampered its potential clinical utility. These include: (1) the ongoing failure to agree a core set of biomarkers that define the construct, and (2) a plethora of different AL scoring algorithms, limiting our ability to compare results across studies. The former issue, concerning the heterogeneity of biomarkers used across studies, has been discussed at length in a number of recent reviews (Johnson et al., 2017; Juster et al., 2010), but the latter issue has received rather less attention in the literature, and is arguably just as important.

1.1. Different scoring systems for AL

Seeman et al. (1997) provided the first operational definition of AL

using a high-functioning sample of adults aged 60 years and older. They employed 10 biomarkers across the neuroendocrine, immune, metabolic and cardiovascular systems, and summed the number of parameters for which an individual had values in the highest risk quartile, based on the sample distribution (Seeman et al., 1997). This measure predicted physical and cognitive decline within the MacArthur Studies of Successful Ageing in the US, and greater incidence of cardiovascular disease over a three-year follow-up. The authors concluded that AL might perform even better in general population studies. The original scoring algorithm for AL remains a popular method today, with the aforementioned systematic review (Johnson et al., 2017) reporting that 73 % of included studies utilised this approach, despite the potential loss of information from the full risk spectrum.

Lack of consensus around an agreed biomarker panel (Johnson et al., 2017; Juster et al., 2010; Szanton et al., 2005) and scoring system (Beckie, 2012; Seplaki et al., 2005) has led to a proliferation of different means for characterising AL. Considerable heterogeneity in AL calculation exists across studies utilising the MacArthur cohort alone, including: the original count of high-risk quartiles (Seeman et al., 1997, 2004; Weinstein et al., 2003), recursive partitioning (Gruenewald et al., 2006), and use of second-order terms (Karlman et al., 2006). Alternate AL formulations from other international studies include: a sum

* Corresponding author.

E-mail address: mccloughs4@tcd.ie (S. McLoughlin).<https://doi.org/10.1016/j.psyneuen.2020.104789>

Received 6 April 2020; Received in revised form 24 June 2020; Accepted 25 June 2020

0306-4530/ © 2020 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license

(<http://creativecommons.org/licenses/by/4.0/>).

of z-scores, which may be considered more informative as it retains the continuous properties of the data (Hawkey et al., 2011; Levine and Crimmins, 2014), or the use of decile cut-points which consider only the top end of the risk distribution. Two-tailed approaches (i.e. top and bottom quartiles or deciles) for some (Hwang et al., 2014; LeBron et al., 2019) or for all biomarkers (Seplaki et al., 2006) have also been employed to account for the fact that biological risk may be non-linear.

Canonical correlation, a technique that measures the associations between sets of inter-connected variables (Karlamangla et al., 2002), and recursive partitioning, a decision-tree technique (Gruenewald et al., 2006; Singer et al., 2004), have been criticised for incorporating information on health outcomes in their derivation, which can result in the over-fitting of models and limits replication across other datasets (Seplaki et al., 2005). Clinical cut-points have also been used (Allen et al., 2019; Borrell et al., 2010; Crimmins et al., 2009; Gleib et al., 2013; Petrovic et al., 2016; Vasunilashorn et al., 2013); but, the lack of universally agreed values (e.g. cut-points for parasympathetic or immunological markers) potentially limits their application. In addition, such definitions of risk remove the potential utility of AL as a sub-clinical disease measure for identifying risk prior to the emergence of the clinical phenotype. More sophisticated attempts to develop AL measures include multivariate methods, such as grade of membership (GOM) which assesses how well an individual's scores on the set of biomarkers used to define AL correspond to a set of predefined archetypal profiles (Li et al., 2019; Seplaki et al., 2006). Interestingly, the predictive utility of AL measures calculated using GOM and count based methods are not dissimilar (Li et al., 2019). These dissimilarities, and also how the use of such complex algorithms would not be practical in clinical settings, may explain why more elaborate measures have not been adopted more widely.

1.2. Does the choice of AL scoring method matter for predicting health?

Methodological disparities in the scoring of the AL index across studies not only makes comparison of results challenging, but also hampers progress towards the use of AL as an early diagnostic screener and / or therapeutic target. This is an important theoretical and empirical matter that has not been subjected to the type of systematic investigation one might expect. Our review of the literature identified only two studies to date (Li et al., 2019; Seplaki et al., 2005) that have explicitly examined this issue.

Seplaki et al. (2005) compared the predictive utility of 9 different AL scoring algorithms (including count of high-risk quartiles/deciles, GOM, z-scores, and two-tailed quartiles/deciles, derived from two biomarker panels) in identifying poor health outcomes. Results were remarkably similar irrespective of the method used to calculate AL. They did, however, suggest that two-tailed formulations, or measures that retain the continuous properties of the biological variables, might be preferred going forward. A separate investigation by Li et al. (2019) involving the NHANES cohort compared the utility of 5 scoring algorithms (i.e. count of high-risk quartiles, z-scores, logistic regression, factor analysis, GOM) in predicting self-reported health, diabetes and hypertension. The best predictive performance was provided by a measure utilising the standardised coefficients from multivariable logistic regressions to weight individual biomarkers. However, similar to canonical correlation, health outcomes were used in the development of the scoring algorithm, which hampers replication across other populations. Li et al. (2019) recommended the original method of high-risk quartiles as a good alternative.

1.3. Should we incorporate sex differences in the calculation of the AL index?

To date, despite evidence of sex differences within the stress response (Juster et al., 2019; Verma et al., 2011), and in the downstream biological parameters associated with the stress response (Freire et al.,

2020; Goldman et al., 2004; Santos-Lozada and Howard, 2018; Stoney et al., 1988; Yang and Kozloski, 2011), there is no consensus regarding the incorporation of sex-specific risk values in the calculation of AL measures. Seplaki et al. (2006) were the first to suggest deriving an AL score using sex-specific risk definitions, with a number of others adopting this approach since (Castagné et al., 2018; Christensen et al., 2018, 2019; Duru et al., 2012; Gustafsson et al., 2012; Robertson et al., 2015). Notwithstanding the potential import of biological sex differences, a recent review of NHANES revealed that only 1/21 AL studies incorporated sex-specific risk definitions (Duong et al., 2017), and to date, no study has compared the predictive utility of an AL measures including and excluding sex-specific risk definitions with alternate calculations.

1.4. Should we incorporate medications in the calculation of the AL Index?

Whether and how doctor-prescribed medication should be incorporated into the development of the AL index is another bone of contention (Lipowicz et al., 2014). Medications can act on the biological systems to reduce observed values, reducing risk of disease (Seeman et al., 2002, 2004). On the other hand, wear and tear may already have occurred if there is a need to medicate, and this excess risk should be accounted for when calculating the score. Varied approaches to the resolution of this problem exist including: scoring an individual at high risk if taking a medication which deflates values on the biomarker (Seeman et al., 2014); adding 'medication use' as a covariate in regression models (Piazza et al., 2018); or increasing individual biomarker values in an attempt at increasing prediction accuracy (e.g. systolic and diastolic blood pressure adjusted by adding 10mmHG and 5mmHG, respectively if taking anti-hypertensives) (Robertson and Watts, 2016). To date, no study has compared the predictive utility of AL measures including medication use compared with alternate formulations.

1.5. The present study

The present study builds upon the work of Seplaki et al. (2005) and Li et al. (2019) in several important ways. Firstly, we use a sample from a nationally representative cohort of community-dwelling older persons, whereas Seplaki et al. (2005) used a militaristic sample with heavy male bias, and Li et al. (2019) used an all-female sample. Secondly, we use a number of objective measures of physical health functioning (i.e. walking speed, grip strength) as the criterion variables in the analysis. Thirdly, we incorporate sex-specific and clinical risk definitions. Finally, we examine whether included medication usage improves the predictive accuracy of AL.

2. Methods

2.1. Sample

This analysis used data from the first wave of The Irish Longitudinal Study on Ageing (TILDA), a nationally representative prospective study of over 8175 persons aged 50 years and over living in the Republic of Ireland. Sampling involved a three-stage selection process with the Irish Geodirectory as the sampling frame, where residential addresses were divided into geographical clusters, of which 640 were selected based on area level socio-economic status and location. Additional information on the sampling frame and study design is available in detail elsewhere (Whelan and Savva, 2013). Data was collected through computer assisted personal interview (CAPI) carried out by a trained interviewer, a leave behind self-completion questionnaire (SCQ), and a comprehensive clinic-based, nurse-administered health assessment. These assessments included the collection of blood samples for biomarker assessment and a battery of cognitive and physical tests. Ethical approval for the study was provided by the Faculty of Health Science Research

Ethics board in Trinity College Dublin, while informed consent is obtained from all respondents during data collection. In total, 5894 people completed either the centre or home-based health assessment. Respondents who were missing on any of the biomarkers were excluded for this study, leaving a total analytical case base of 4,477. A flow chart summarising inclusion criterion for analysis is provided in Supplementary Fig. 1.

2.2. Physiological parameters

A total of 12 biomarkers across the cardiovascular, metabolic, renal and immune systems were used to construct the various AL indices examined in this study. Biomarkers were selected to reflect the most commonly chosen systems in the AL literature (Juster et al., 2010). Two of the biomarkers - pulse wave velocity (PWV) and cystatin C (Cysc) - are relatively novel with respect to AL formulation but their inclusion was theoretically motivated. For example, there is evidence to suggest that acute and chronic stress may induce arterial dysfunction as indexed using PWV (Logan et al., 2012; Matsumura et al., 2019). Similarly, Cysc may serve as a preferred/complementary biomarker of kidney functioning compared with creatinine in older cohorts as it is less affected by declining muscle mass (Canney et al., 2018). The component biomarkers and a description of their primary function is provided in Supplementary Table 1.

In terms of the cardiovascular system, the average of two measurements of seated Systolic Blood pressure (SBP), Diastolic Blood pressure (DBP) and Resting Heart Rate (RHR) were obtained separated by a 1-minute interval using an automatic digital oscillometric blood pressure monitor (OMRON™, M10-IT). An average of two measurements between the carotid and femoral arteries was obtained using a Vicorder system, representing PWV (Skidmore Medical Ltd, Bristol, UK), a non-invasive gold standard method (Whelan and Savva, 2013). Metabolic system biomarkers included waist-hip ratio (WHR), body mass index (BMI) glycosylated haemoglobin (HbA1c), total cholesterol (TChol), and high-density lipoprotein (HDL). Weight was measured using a SECA electronic floor scales, and height was measured using a SECA 240 wall mounted measuring rod. BMI was calculated by dividing weight in kgs by height in metres squared. SECA measuring tapes were used to record WHR with measurements taken to the nearest millimetre. TChol was obtained from non-fasting blood samples, with venepuncture performed with a butterfly and a green 21-gauge Vacutainer needle and stored in EDTA tubes. A direct determination of HDL was performed using PEG-modified enzymes and dextran sulphate. HbA1c reflects blood sugar levels and metabolic functioning in the 8–12 weeks prior to blood sampling and were analysed by reverse-phase action exchange chromatography using an ADAMS A1c HA-8180 V analyser.

C-Reactive Protein (CRP) serves as our singular marker of immunological dysregulation as it was the only inflammatory marker available in the full TILDA cohort at baseline. It was measured in non-fasting blood serum on a Roche Cobas c 701 analyser using an immunoturbidimetric assay for the in vitro quantitative determination of CRP. Detection limits ranged from 0.3–350 mg/l. The two renal markers included Creatinine (Crea) and Cysc, which were measured simultaneously from frozen plasma. Crea was measured using an enzymatic method traceable to isotope-dilution mass spectrometry (Roche Creatinine plus ver.2, Roche Diagnostics, Basel Switzerland), whilst Cysc was measured using a second-generation particle enhanced immunoturbidimetric assay (Roche Tina-quant™) on a Roche Cobas 701 analyzer. This assay has a measuring range of 0.40–6.80 mg/L and is traceable to the European reference standard material (ERM-DA471/IFCC). Log transformations were applied to CRP and PWV to account for right-skewed distributions.

2.3. Calculation of summary measures

High-risk quartiles (Classic Method): To re-create the original and most commonly employed scoring algorithm across studies (Seeman et al., 1997), dichotomous indicator variables were created for each biomarker. HDL was reverse coded such that higher values represented increased risk. Empirically defined high-risk thresholds were distinguished based on the distribution of that biomarker in the sample; “1” was assigned to values falling above the 75th percentile of the distribution for each marker, and “0” was assigned to values below this threshold. These biomarkers were summed to create an index, with higher scores reflecting higher AL burden. **Two-tailed high-risk quartiles:** Seplaki et al. (2005) suggested that including risk factors at both high and low ends of the risk continuum may be more informative than simply using high-risk quartiles. To re-create this score, a value of “1” was assigned to values above the 75th percentile and below the 25th percentile of the distribution, and a value of “0” was assigned for values that fell intermediate of these thresholds. A sum of these biomarkers represented two-tailed physiological dysregulation.

Following the above methodologies, two further algorithms were created employing decile cut-points, to measure risk at more extreme levels of the distribution. **High-risk Deciles:** “1” was assigned for values above the 90th percentile, “0” was assigned to all values below this threshold, and all biomarkers were then summed. **Two-tailed high-risk deciles:** “1” was assigned for values above the 90th percentile and below 10th percentile for the measure incorporating both ends of the distribution, and “0” assigned to all values that lay intermediate between these thresholds, and scores on the individual biomarkers were then summed.

Z-scores: To create a score that retained the continuous properties of each physiological variable, each biomarker was standardised to a mean of 0 and a standard deviation of 1, and then summed to generate an overall AL score expressed in standard deviation units (Daly et al., 2019; Hawkey et al., 2011; Levine and Crimmins, 2014). **System Weighted:** It is common in the AL literature for some biological systems to be more heavily represented than others, of which metabolic system biomarkers tend to be most populous (Juster et al., 2010). A system-weighted score was therefore created to reduce this bias. Firstly, biomarkers were dichotomised following the classic methodology (Seeman et al., 1997). Secondly, each dysregulated biomarker was weighted according to the total number of biomarkers per system. System risk indices were computed as the proportion of individual biomarkers for each system for which participant values fell into high-risk quartiles (Gruenewald et al., 2012). For example, in the present study, the cardiovascular system was comprised of four biomarkers (SBP, DBP, RHR, PWV). Therefore, the sum of dysregulated biomarkers within this system were divided by 4 and expressed as a proportion ranging from 0.0–1.0. As CRP is the only immunological biomarker, no scaling occurred, hence “0” indicated no risk, whilst “1” indicated high risk. Finally, an AL score was computed as the sum of these weighted systems. This methodology has been used previously and ensures that each system is equally represented in the overall AL index (Gruenewald et al., 2012; Piazza et al., 2018; Read and Grundy, 2014).

Sex-specific cut-points: To account for variability in biomarker values according to sex, each of these 6 scoring algorithms were re-created using sex-specific cut-points (Table 2). Therefore, to create the sex-specific count of high-risk quartiles measure, individuals falling above the 75th percentile were identified using the sample distributions for men and women separately, and scores were then pooled.

High-risk quartiles (incorporating medications): To allow for the possibility that medication use was masking high values, prescription drugs were incorporated into an additional algorithm based on the classic methodology, with individuals taking medication automatically reclassified as high-risk across affected biomarkers. In TILDA, medication usage was ascertained as part of the household interview, where respondents were asked to retrieve the medicinal packaging of any

regularly taken medications and interviewers transcribed the brand/generic name of the prescription medication. The medications data was then coded in-house by pharmacologists according to Anatomic Therapeutic Classification (ATC) codes (Whelan and Savva, 2013). HbA1c was coded as high risk if individuals were currently prescribed medications of codes for insulin or analogues (A10), SBP was classified as high risk if individuals were taking anti-hypertensive medication (C02, C03, C09). RHR was recoded as high risk if taking beta-blockers (C07) or calcium blockers (C08) and finally, HDL was recoded as high risk if prescribed lipid modifying agents (C10).

Clinical: Finally, we derived a measure of AL using recognised risk definitions according to clinical guidelines (Allen et al., 2019; Borrell et al., 2010; Gruenewald et al., 2012; Prag and Richards, 2018). Clinical cut-points for each biomarker are provided in Supplementary Table 2.

2.4. Health outcomes

We utilised two objectively measured health outcomes – walking speed and grip strength (described below) – and to enable comparison with Seplaki et al. (2005), a general self-reported health measure was included.

2.4.1. Walking speed

In older adults, walking speed has been shown to be a good indicator of overall physical function (Viccaro et al., 2011), and a predictor for hospitalisation (Studenski et al., 2003) and higher morbidity (Guralnik et al., 2000). In TILDA, gait measurements were taken using a 4.88-metre computerised walkway with embedded pressure sensors (GAITRite, CIR Systems Inc., New York, NY). Participants completed two walks at their normal walking speed. The average of the two readings represents the overall walking speed expressed in centimetres travelled per second (cm/s).

2.4.2. Grip strength

Low grip strength has been robustly associated with functional decline and mortality in older adults (Bohannon, 2008) and serves as a proxy for the overall strength of the musculoskeletal system. Two measures were taken from the dominant hand using a Baseline® Hydraulic Hand Dynamometer, and the highest of the two readings in kilograms (kgs) per square inch represented the measure of grip strength used in the analysis.

2.4.3. Self-rated health

Self-rated health (SRH) is a commonly assessed item in health surveys (Manor et al., 2000), and can provide insight into the perceptions that an individual has of their own health status relevant to their peers. SRH has previously been associated with decreased physical performance (Perez-Zepeda et al., 2016) and increased mortality risk (Jylha, 2009). Previous studies have reported that lower SRH predicts higher AL (Vie et al., 2014; von Thiele et al., 2006). SRH was obtained during the CAPI with the item “In general, compared to other people your age, would you say your health is...” rated on a five-point scale of excellent, very good, good, fair, and poor.

3. Statistical analysis

All analyses were conducted in Stata (v.15; StataCorp, 2017), using TILDA dataset v.1.8.0. The outcome measures were regressed separately on each of the 14 AL scoring algorithms, adjusting for age and sex, using ordinary least squares regression with respect to walking speed and grip strength, and ordinal logistic regression for SRH. Overall model fit was assessed using the proportion of variance explained (R^2 for OLS, pseudo R^2 for ordinal logistic regression) and the Bayesian Information Criterion (BIC). An obvious advantage of using information measures is that one can compare the goodness of fit of non-nested models (Williams, 2019) as the different AL scoring algorithms are

essentially just reformulations of the same underlying set of 12 component biomarkers. The extent to which one model is preferred over another depends on the magnitude of the difference between the information measures. Higher values of R^2 and lower values of BIC indicate better model fit. BIC values were obtained using the FITSTAT package in Stata (Scott Long and Freese, 2014). Following guidelines proposed by Raftery (1995), we noted a BIC difference > 10 to indicate a better fitting model than the standard scoring algorithm. To reduce the large number of potential contrasts between the different AL scoring algorithms, we take as our reference, the overall (i.e. non-sex-specific) quartile-based risk score (hereinafter referred to as classic method) as it is the one that has been predominantly used in the AL literature.

In order to provide a comparison with Seplaki et al. (2005), binary indicator variables were created for each of the health outcomes using cut-points guided by previous literature. Grip strength was dichotomised at < 37 kg for men, and < 21 kg for women (Sallinen et al., 2010). Walking speed was dichotomised at < 120 cm/s (Studenski et al., 2011). SRH was recoded as “1” if respondents rated their health as fair/poor, “0” otherwise (Seplaki et al., 2005). Each of the binary health outcomes were treated as dependent variables in separate logistic regression models, controlling for age and sex. The area under the Receiver Operator Characteristic curve (AUC) was calculated for each health outcome for each of the 14 different AL scoring algorithms using the ROCTAB procedure (Pepe et al., 2009). Higher AUC values indicate greater classification accuracy. Comparison of AUC estimates to test the statistical significance of the difference between the classic AL algorithm and all alternative algorithms were investigated using the ROC-COMP procedure (Cleves, 2002). Finally, as age is the strongest predictor of health, we also examined which of the AL algorithms was most strongly correlated with chronological age.

4. Results

Table 1 reports sample characteristics. The mean age of the sample was 61.8 years and female respondents accounted for 53.7 % of the sample. Mean walking speed was 136.1 cm/s (SD = 20.4), and mean grip strength was 27.5 kgs (SD = 9.88). 89.0 % of the sample reported that they were in excellent/very good/good health. In total, 45.4 % of the sample were taking prescribed medications that potentially impacted values of biomarkers included in this study. Respondents included in the study were younger than those who were missing biomarker data, more educated and had, on average, a lower average count of chronic diseases. No sampling weights were applied however, as the primary focus of this study was to compare the predictive utility of various AL scoring algorithms and not to infer the relationship of AL and the health outcomes to the population. The relationship between

Table 1
Sample characteristics.

Variable	In sample (N = 4477)		Missing (N = 3697)	
	Mean	SD	Mean	SD
Sex (n, %)				
Male	2071	46.3	1673	45.3
Female	2406	53.7	2024	54.7
Age	61.8	8.4	66.3	10.8
Education (n, %)				
Primary	959	21.4	1545	41.8
Secondary	1882	42.1	1381	37.4
Tertiary	1635	36.5	768	20.8
Chronic diseases	1.6	1.4	1.8	1.5
Medications (n, %)	2033	45.4	697	18.85
Walking speed	136.1	20.4	132.5	22.0
Grip strength	27.5	9.88	25.6	9.59
SRH (n, %)				
Excellent, very good, good	3978	89.0	2922	79.2
Fair, poor	494	11.1	766	20.8

Table 2
Univariate descriptives of individual biomarkers by sex.

Biomarker	Mean	SD	Min	10 th p	25th p	Median	75th p	90 th p	Max	p
Systolic blood pressure	134.67	19.49	78.50	111.00	121.00	133.50	146.50	159.50	220.00	
Male	138.95	18.28	83.00	117.50	126.50	137.00	150.00	162.00	220.00	< 0.001
Female	130.99	19.75	78.50	107.50	117.00	129.00	143.00	158.00	208.50	
Diastolic blood pressure	82.30	11.06	51.50	68.50	75.00	82.00	89.50	96.50	132.00	
Male	83.72	10.88	53.50	70.50	76.50	83.50	90.50	97.00	132.00	< 0.001
Female	81.09	11.06	51.50	67.00	73.50	80.50	88.00	95.50	125.50	
Resting heart rate	68.78	11.37	33.00	55.50	60.50	67.50	75.50	83.50	135.50	
Male	67.81	12.00	33.00	54.00	59.50	66.50	74.50	83.50	135.50	< 0.001
Female	69.62	10.73	35.00	56.50	62.00	68.50	76.00	83.50	116.50	
Pulse wave velocity *	2.33	0.19	1.67	2.09	2.20	2.32	2.45	2.58	2.99	
Male	2.37	0.18	1.82	2.14	2.25	2.37	2.49	2.61	2.99	< 0.001
Female	2.29	0.19	1.67	2.05	2.15	2.28	2.42	2.54	2.94	
High density lipoprotein (reversed)	-1.56	0.44	-3.82	-2.13	-1.80	-1.49	-1.23	-1.07	-0.48	
Male	-1.36	0.34	-3.50	-1.80	-1.54	-1.31	-1.11	-0.99	-0.63	< 0.001
Female	-1.72	0.44	-3.82	-2.30	-1.98	-1.66	-1.41	-1.22	-0.48	
Cholesterol	5.15	1.05	1.80	3.80	4.50	5.10	5.80	6.50	12.20	
Male	4.88	1.05	1.80	3.50	4.20	4.90	5.60	6.20	9.10	< 0.001
Female	5.39	1.00	2.20	4.10	4.70	5.30	6.00	6.70	12.20	
Glycosylated haemoglobin	33.06	5.45	16.00	28.00	30.00	32.00	35.00	38.00	94.00	
Male	33.47	5.72	17.00	28.00	30.00	32.00	35.00	39.00	88.00	< 0.001
Female	32.72	5.18	16.00	28.00	30.00	32.00	34.00	37.00	94.00	
BMI	28.51	4.82	17.08	23.00	25.24	27.99	31.12	34.58	61.86	
Male	29.10	4.33	18.33	24.16	26.28	28.69	31.45	36.50	59.28	< 0.001
Female	28.00	5.15	17.08	22.33	24.47	27.24	30.69	34.66	61.86	
Waist hip ratio	0.90	0.09	0.63	0.79	0.84	0.90	0.96	1.01	1.29	
Male	0.96	0.07	0.74	0.77	0.92	0.96	1.00	1.07	1.28	< 0.001
Female	0.85	0.07	0.63	0.77	0.81	0.85	0.90	0.94	1.29	
Cystatin C	0.97	0.21	0.46	0.77	0.84	0.93	1.05	1.18	3.95	
Male	0.99	0.22	0.56	0.79	0.86	0.95	1.06	1.19	3.95	< 0.001
Female	0.95	0.20	0.46	0.76	0.83	0.92	1.03	1.18	2.97	
Creatinine	79.21	19.90	40.00	59.00	66.00	77.00	88.00	101.00	486.00	
Male	89.09	20.21	49.00	71.00	78.00	86.00	96.00	109.00	486.00	< 0.001
Female	70.71	15.13	40.00	56.00	61.00	68.00	77.00	87.00	231.00	
C-Reactive protein *	0.69	0.77	0.00	0.00	0.00	0.47	1.17	1.79	6.28	
Male	0.65	0.75	0.00	0.00	0.00	0.43	1.12	1.68	5.73	0.003
Female	0.72	0.78	0.00	0.00	0.00	0.51	1.22	1.84	6.28	

Total sample n = 4477; male = 2071, female = 2406. p = significance level determined from two sample t-test, comparisons of mean values within biomarkers between male and female respondents. *log transformed.

age and each of the AL scoring algorithms was assessed using Spearman's correlations, reported in Supplementary Table 3. The measure incorporating medications was most strongly correlated with age ($r = 0.34$), whilst the two-tailed measures revealed weak correlations with age (e.g. overall quartile ($r = 0.05$), overall decile based ($r = 0.06$)).

Univariate statistics and percentile cut-points for each of the 12 component biomarkers defining the AL construct are presented in Table 2. Two-sample t-tests revealed marked differences in biomarker values according to sex. Specifically, male respondents were characterised by significantly higher mean values for 9/12 biomarkers, whilst female respondents had significantly higher mean values for the latter 3 (RHR, CRP, Total Cholesterol). Supplementary Table 4 presents univariate statistics in respect of each of the 14 AL scoring algorithms used in the present study. Tables 3–5 report the model fit statistics for each AL scoring algorithm and the difference in model fit relative to the classic scoring algorithm for walking speed, grip strength and SRH, respectively. In this context, higher values for R^2 and lower values for BIC indicate a better fitting model compared with the standard model. In general, the results indicate that the choice of scoring algorithm has relatively modest effects on the proportion of variance explained in the health outcomes.

4.1. Walking speed

Looking first at the results for walking speed, Table 3 shows that the proportion of variance explained by the classic AL scoring algorithm (including age and sex) was 20.3 %, compared with 17.8 % for the worst (overall two-tailed quartiles and overall two-tailed deciles) and

Table 3
Model Fit Statistics for different Allostatic Load Scoring Algorithms predicting Walking Speed.

	R^2	DIFF R^2	BIC	DIFF BIC
High-risk quartiles				
Overall	0.203***	REF	38344.70	REF
Sex-specific	0.209***	0.006	38310.73	-33.97 ^a
Two-tailed quartiles				
Overall	0.178***	-0.025	38479.84	135.14
Sex-specific	0.182***	-0.021	38449.62	113.30
High-risk deciles				
Overall	0.205***	0.002	38329.40	-10.51 ^a
Sex-specific	0.207***	0.004	38322.91	-20.94 ^a
Two-tailed deciles				
Overall	0.178***	-0.025	38467.57	136.23
Sex-specific	0.180***	-0.023	38458.66	124.48
System weighted				
Overall	0.207***	0.004	38304.19	-22.17 ^a
Sex-specific	0.208***	0.005	38328.90	-27.40 ^a
Continuous				
Overall	0.204***	0.001	38337.43	-7.27
Sex-specific	0.205***	0.002	38331.71	-12.99 ^a
Medications	0.212***	0.009	38296.41	-48.29 ^a
Clinical	0.199***	-0.004	38362.26	17.56

Note: Adjusted for age and sex. R^2 = proportion of variance explained. R^2 Diff = gain in R^2 compared with the classic AL scoring algorithm. BIC = Bayesian Information Criterion. BIC Diff = Difference in BIC compared with the classic AL scoring algorithm. ^ap < 0.05, **p < 0.01, ***p < 0.001.

^a Substantial decrease in BIC compared with the classic AL scoring algorithm.

Table 4
Model Fit Statistics for different Allostatic Load Scoring Algorithms predicting Grip Strength.

	R ²	DIFF R ²	BIC	DIFF BIC
High-risk quartiles				
Overall	0.6078	REF	28968.53	REF
Sex-specific	0.6077	−0.0001	28968.90	0.37
Two-tailed quartiles				
Overall	0.6078	0.0000	28967.96	−0.57
Sex-specific	0.6078	0.0000	28968.06	−0.46
High-risk deciles				
Overall	0.6077	−0.0001	28969.34	0.82
Sex-specific	0.6076	−0.0002	28969.86	1.33
Two-tailed deciles				
Overall	0.6084**	0.0006	28960.84	−7.68
Sex-specific	0.6080*	0.0002	28965.64	−2.89
System weighted				
Overall	0.6077	−0.0001	28969.43	0.90
Sex-specific	0.6076	−0.0002	28969.74	1.21
Continuous				
Overall	0.6082*	0.0004	28963.277	−5.25
Sex-specific	0.6082**	0.0004	28963.083	−5.44
Medications				
Overall	0.6077	−0.0001	28969.45	0.92
Clinical	0.6081*	0.0003	28964.77	−3.76

Note: Adjusted for age and sex. R² = proportion of variance explained. R² Diff = gain in R² compared with the classic AL scoring algorithm. BIC = Bayesian Information Criterion. BIC Diff = Difference in BIC compared with the classic AL scoring algorithm. *p < 0.05, **p < 0.01, *** p < 0.001.

*Substantial decrease in BIC compared with the classic AL scoring algorithm.

Table 5
Model Fit Statistics for different Allostatic Load Scoring Algorithms predicting self-rated health.

	R ²	DIFF R ²	BIC	DIFF BIC
High-risk quartiles				
Overall	0.011***	REF	12156.79	REF
Sex-specific	0.013***	0.002	12133.15	−23.65*
Two-tailed quartiles				
Overall	0.002***	−0.009	12256.37	99.58
Sex-specific	0.003***	−0.008	12248.24	91.44
High-risk deciles				
Overall	0.011***	0.000	12149.79	−7.00
Sex-specific	0.011***	0.000	12158.46	1.67
Two-tailed deciles				
Overall	0.002***	−0.009	12262.80	106.00
Sex-specific	0.002***	−0.009	12262.81	106.02
System weighted				
Overall	0.012***	0.001	12139.15	−17.64*
Sex-specific	0.011***	0.000	12149.24	−7.56
Continuous				
Overall	0.010***	0.001	12163.989	7.20
Sex-specific	0.010***	0.001	12158.346	1.55
Medications				
Overall	0.019***	0.008	12052.43	−104.37*
Clinical	0.008***	−0.003	12183.01	26.21

Note: Adjusted for age and sex. R² = proportion of variance explained. R² Diff = gain in R² compared with the classic AL scoring algorithm. BIC = Bayesian Information Criterion. BIC Diff = Difference in BIC compared with the classic AL scoring algorithm. *p < 0.05, **p < 0.01, *** p < 0.001.

* Substantial decrease in BIC compared with the classic AL scoring algorithm.

21.2 % for the best (high-risk quartiles incorporating medications) fitting models. The sex-specific high-risk quartiles, high-risk decile measures, weighted measures, sex-specific z-scores, and the algorithm incorporating medications led to a strong improvement in model fit relative to the classic AL scoring algorithm, according to the BIC guidelines proposed by Raftery (1995). However, it should be acknowledged that the gain in R² was typically very modest and amounted to, at most, +0.9 %. The measures calibrated according to sex performed marginally better when predicting walking speed than

the overall measures. The two-tailed measures by contrast performed poorly, with lower values of R² and large increases in BIC compared with the classic algorithm.

4.2. Grip strength

For grip strength, Table 4 shows that the proportion of variance explained by the classic AL scoring algorithm (including age and sex) was 60.8 %, and this value did not vary substantially across the other measures; +0.06 % for the best fitting model (overall two-tailed deciles) compared with the classic model. Two-tailed decile measures, clinical and z-scores were the only AL scoring algorithms that exhibited statistically significant associations with grip strength independently of age and sex. The strength of these relationships were small, however, and the direction of these relationships differed; negative associations were noted for overall ($\beta = -0.16$, 95 % CI: $-0.27, -0.06$) and sex-specific ($\beta = -0.11$, 95 % CI: $-0.02, -0.01$) two-tailed deciles, whilst positive associations were noted for the clinical measure ($\beta = 0.13$, 95 % CI: 0.02, 0.23), as well as the overall ($\beta = 0.05$, 95 % CI: 0.01, 0.09) and sex-specific ($\beta = 0.05$, 95 % CI: 0.01, 0.09) z-score measures.

4.3. Self-rated health

Table 5 shows that the classic AL measure accounted for 1.1 % of the variance in SRH, compared with 0.02 % for the worst fitting models (overall high-risk deciles, two-tailed high-risk decile measures) and 1.9 % for the best fitting model (high-risk quartiles incorporating medications). The sex-specific high-risk quartile measure, overall weighted measure, the measure incorporating medications, and the clinical measure led to strong improvements in BIC values compared to the classic AL index, whilst the two-tailed measures performed substantially worse.

4.4. Area under the receiver operating characteristic curve (AUC)

Supplementary Table 5 reports the AUC estimates for each of the AL scoring algorithms separately for each of the three binary health outcomes. Results were consistent with what was observed when using the continuous measures. Notably, the two-tailed measures (quartiles and deciles) performed worse than the classic algorithm when predicting walking speed and SRH, whilst all measures predicted poor grip strength to the same degree of accuracy as the classic score (Fig. 1). Although a minority of AL algorithms reached statistical significance with grip strength, no substantial differences in AUC were noted between these and the classic algorithm. In addition, the count of high-risk quartiles measure incorporating medications predicted fair/ poor SRH better than the classic measure.

5. Discussion

The present study assessed the explanatory utility of a multitude of AL scoring algorithms for predicting a number of objective and subjective age-related health outcomes in an older adult population residing in Ireland. In accordance with the findings from a previous study involving a Taiwanese sample (Seplaki et al., 2005), we found that the choice of AL scoring algorithm has a relatively modest impact in terms of variance explanation and classification accuracy in the prediction of a number of important health outcomes. Although the differences between the 14 scoring algorithms were not pronounced in this study, there were, nevertheless, some subtle nuances observed.

AL was strongly associated with walking speed across all 14 scoring algorithms independently of age and sex, supporting prior findings regarding the predictive utility of AL for functional decline (Karlman et al., 2002; Read and Grundy, 2014; Singer et al., 2004; Szanton et al., 2005). Although the differences were small when compared to the classic scoring algorithm, the count of high-risk quartiles incorporating

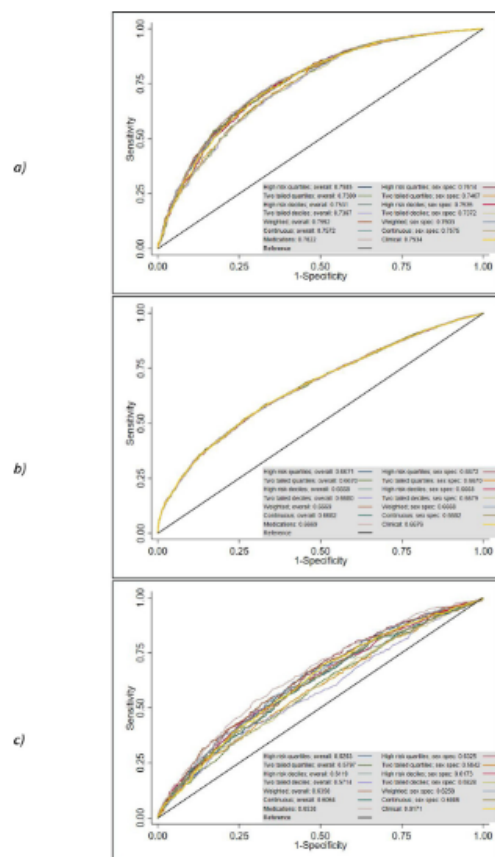


Fig. 1. AUC estimates for different scoring algorithms, predicting a) slow walking speed, b) weak grip strength and c) poor self-rated health.

medications performed marginally better. In contrast, few significant associations were observed between measures of AL and grip strength, and no algorithm fit the data significantly better than the classic method. Although few have investigated this relationship directly, grip strength shows strong age-related decline and is an important component of many frailty indices that have been found to be negatively associated with AL (Gruenewald et al., 2012; Szanton et al., 2005). The null associations of the majority of AL scoring algorithms, and the varied direction of the relationship noted for those algorithms which did statistically predict grip strength is surprising, but not without precedent. Freire et al. (2020) for example, arrived at the rather counter-intuitive conclusion that higher AL burden (classic measure) was associated with higher grip strength in a small sample of older community-dwelling adults in Brazil ($n = 256$), yet they hypothesised this contradictory result was due to survival bias. Perhaps the predominantly null results arise as there are other potential confounders that we are not controlling for in this analysis, which may help preserve muscle strength at older ages (e.g. height, occupational class etc).

In respect of SRH, results were more variable across scoring algorithms, although differences were small in absolute terms. Similar to walking speed, the algorithm incorporating medication use was the best predictor of SRH in terms of model fit. This pattern of results begs the obvious question as to whether the better predictive performance of a measure incorporating medication when using a SRH measure is simply a reflection of the individual being more aware of their 'health state' by virtue of consciously taking prescribed medications on a regular basis.

5.1. Use of one vs two-tailed risk

Notably, the AL scoring algorithms incorporating risk in both tails of the distribution of each biomarker underperformed relative to the classic one-tailed measure in this study. These findings align with results from the Hawaii Personality and Health Cohort ($n = 470$), where two-tailed measures of AL were less effective than one-tailed measures in predicting SRH and depressive symptoms. In stark contrast, however, Seplaki et al. (2005) found that two-tailed measures of risk accounted for more variance across self-reported health measures than the classic AL index. This discrepant pattern of results across studies could be explained by differences in the biomarker panels employed to represent AL. Seplaki et al.'s (2005) study included primary mediators of the stress response such as cortisol, in which both high and low values can characterize certain syndromes and diseases (Fries et al., 2005) whereas, similar to the present study, Hampson et al. (2009) did not include any markers of neuroendocrine dysregulation. Moreover, in the context of the current study, it is difficult to see how low scores for HbA1c or cystatin C would increase risk of disease, which reinforces the need to think critically about whether risk on particular biomarkers is best conceptualised as linear or curvilinear when developing AL indices.

5.2. The importance of considering sex differences

Beyond the objective of comparing the predictive utility of various AL algorithms, this study found significant differences across mean biomarker values between male and female individuals. Furthermore, the AL algorithms which were calibrated relative to sex generally performed marginally better in terms of model fit than those derived from the pooled sample with respect to walking speed and SRH. Acknowledging that men and women may react differently to stress, both psychologically and biologically (Stroud et al., 2002); we recommend that future investigations continue to examine the use of sex-specific cut-points, particularly where the distributions on the component biomarkers differ according to sex, or indeed, where there might be large sex differences (Juster et al., 2016), in the outcome measure (e.g. depression).

5.3. The importance of considering medications

The vexed question of whether to include medications in the calculation of the AL measure is a recurring feature in many critiques of the AL literature (Duong et al., 2017; Howard and Sparks, 2016; Rodriguez et al., 2019). This issue has not always been afforded the attention it arguably deserves in many empirical studies, presumably because many studies either do not capture this information, rely on self-report, or perhaps due to operational difficulties in how to treat the data if using continuous measures (e.g. z-scores). We found that including medications led to small improvements in performance relative to the classic measure with respect to walking speed and SRH. It was also the algorithm which was most strongly correlated with age. Nevertheless, we applied only one of a number of potential techniques for including medications in the development of the AL index, and future studies may wish to consider alternative approaches such as including medications as a covariate (Piazza et al., 2018) or adjusting biomarker values upward to adjust for their deflationary effect on the biomarker of interest (Robertson and Watts, 2016).

6. Strengths and limitations

This study is among the first to examine and compare the effects of various AL scoring algorithms in a community-dwelling cohort of older persons. It benefits from having a large sample pulled from a nationally representative cohort, and gold standard measures of objective physiological functioning measured using trained nurses according to

standard operating protocols. It advances the current knowledge base through the inclusion of these objective markers of physical fitness, by considering sex as an important variable in the determination of AL scores, and by accounting for medication use as a potential indicator of physiological wear and tear. Despite these strengths, this study does not have any neuroendocrine markers at baseline which is an important limitation as they are hypothesised to play a central role in the stress response. Furthermore, whilst TILDA is a nationally representative cohort study, the sample employed in this paper is not generalisable to other populations. Similarly, the results from this study are not generalisable to studies employing biomarkers different to those used here. It should also be acknowledged that although significant associations were found between measures of AL and objective health outcomes in this study, the estimated models control only for the effects of age and sex. Instead, this study provides evidence for the construction of a summary score from individual biological components to predict poor health outcomes, without assuming a causal or directional relationship.

7. Conclusion

This study was motivated by the lack of empirical insight into the effects the choice of AL scoring algorithm has on the predictive utility of poor health outcomes. Seeman et al. (2010) claimed that their original method did not represent a gold standard, yet the results of this study suggest that this classic method performs well. We therefore echo the conclusion of others (Berger et al., 2018; Li et al., 2019), that given that this is the technique used in the vast majority of papers, perhaps the notion of harmonising international work around this scoring algorithm should be considered. Nonetheless, the findings of this paper can help allay researchers concerns that the choice of scoring algorithm makes a large difference to the results, but whether the composition of biomarkers employed to reflect physiological dysregulation does remains to be elucidated.

Funding

This work was supported by the Health Research Board (HRB) of Ireland under an Emerging Investigator Award to Dr. Cathal McCrory (EIA-2017-012). TILDA was funded by Irish Life plc, the Irish Government and the Atlantic Philanthropies.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.psyneuen.2020.104789>.

References

- Allen, A.M., Thomas, M.D., Michaels, E.K., Reeves, A.N., Okoye, U., Price, M.M., Hasson, R.E., Syme, S.L., Chae, D.H., 2019. Racial discrimination, educational attainment, and biological dysregulation among midlife African American women. *Psychoneuroendocrinology* 99, 225–235. <https://doi.org/10.1016/j.psyneuen.2018.09.001>.
- Beckie, T.M., 2012. A systematic review of allostatic load, health, and health disparities. *Biol. Res. Nurs.* 14 (4), 311–346. <https://doi.org/10.1177/109800412455688>.
- Berger, M., Juster, R.-P., Westphal, S., Amminger, G.P., Bogerts, B., Schiltz, K., Bahn, S., Steiner, J., Sarney, Z., 2018. Allostatic load is associated with psychotic symptoms and decreases with antipsychotic treatment in patients with schizophrenia and first-episode psychosis. *Psychoneuroendocrinology* 90, 35–42. <https://doi.org/10.1016/j.psyneuen.2018.02.001>.
- Bohannon, R.W., 2008. Hand-grip dynamometry predicts future outcomes in aging adults. *J. Geriatr. Phys. Ther.*
- Borrell, L.N., Dallo, F.J., Nguyen, N., 2010. Racial/ethnic disparities in all-cause mortality in U.S. adults: the effect of allostatic load. *Public Health Rep* 125 (6), 810–816. <https://doi.org/10.1177/003335491012500608>.
- Canney, M., Sexton, D.J., O'Leary, N., Healy, M., Kenny, R.A., Little, M.A., O'Seaghdha, C.M., 2018. Examining the utility of cystatin C as a confirmatory test of chronic kidney disease across the age range in middle-aged and older community-dwelling adults. *J. Epidemiol. Community Health* 72 (4), 287. <https://doi.org/10.1136/jech-2017-209864> 1P-293.
- Castagné, R., Garès, V., Karimi, M., Chadeau-Hyam, M., Vineis, P., Delpierre, C., Kelly-Irving, M., Alenius, H., Avendano, M., Baltar, V., Bartley, M., Barros, H., Bochud, M., Carmeli, C., Carra, L., Costa, G., Courtin, E., Donkin, A., D'Errico, A., et al., 2018. Allostatic load and subsequent all-cause mortality: which biological markers drive the relationship? Findings from a UK birth cohort. *Eur. J. Epidemiol.* 33 (5), 441–458. <https://doi.org/10.1007/s10654-018-0364-1>.
- Christensen, D.S., Flensburg-Madsen, T., Garde, E., Hansen, A.M., Pedersen, J.M., Mortensen, E.L., 2018. Parental socioeconomic position and midlife allostatic load: a study of potential mediators. *BMC Public Health* 18 (1), 1029. <https://doi.org/10.1186/s12889-018-5956-x>.
- Christensen, D.S., Flensburg-Madsen, T., Garde, E., Hansen, A.M., Mortensen, E.L., 2019. Big five personality traits and allostatic load in midlife. *Psychol. Health* 1–18. <https://doi.org/10.1080/08870446.2019.1585851>.
- Cleves, M.A., 2002. From the help desk: comparing areas under receiver operating characteristic curves from two or more probit or logit models. *Stata J.* 2 (3), 301–313. <https://doi.org/10.1177/1536867X0200200307>.
- Crimmins, E.M., Kim, J.K., Seeman, T.E., 2009. Poverty and biological risk: the earlier "aging" of the poor. *J. Gerontol.* <https://doi.org/10.1093/gerona/gln010>.
- Daly, M., Sutin, A.R., Robinson, E., 2019. Perceived weight discrimination mediates the prospective association between obesity and physiological dysregulation: evidence from a population-based cohort. *Psychol. Sci.* <https://doi.org/10.1177/0956797619849440>. 956797619849440.
- Duong, M.T., Bingham, B.A., Aldana, P.C., Chung, S.T., Sumner, A.E., 2017. Variation in the calculation of allostatic load score: 21 examples from NHANES. *J. Racial Ethn. Health Disparities* 4 (3), 455–461. <https://doi.org/10.1007/s40615-016-0246-8>.
- Duru, O.K., Harawa, N.T., Kermah, D., Norris, K.C., 2012. Allostatic load burden and racial disparities in mortality. *J. Med. Assoc.* 104 (1–2), 89–95. [https://doi.org/10.1016/S0027-9684\(15\)30120-6](https://doi.org/10.1016/S0027-9684(15)30120-6).
- Freire, A., do, N.F., Barbosa, J.F., de, S., Pereira, D.S., Gomes, Cdos S., Guerra, R.O., 2020. Allostatic load and stress biomarkers in a sample of community-dwelling older adults. *Arch. Gerontol. Geriatr.* 87, 104006. <https://doi.org/10.1016/j.archger.2019.104006>.
- Fries, E., Hesse, J., Hellhammer, J., Hellhammer, D.H., 2005. A new view on hypothalamic-pituitary-adrenal axis. *Psychoneuroendocrinology* 30 (10), 1010–1016. <https://doi.org/10.1016/j.psyneuen.2005.04.006>.
- Glei, D.A., Goldman, N., Wu, C.H., Weinstein, M., 2013. Does exposure to stressors predict changes in physiological dysregulation? *Ann. Behav. Med.* <https://doi.org/10.1007/s12160-013-9485-7>.
- Goldman, N., Weinstein, M., Cornman, J., Singer, B., Seeman, T., Goldman, N., Chang, M.C., 2004. Sex differentials in biological risk factors for chronic disease: estimates from population-based surveys. *J. Womens Health (Larchmt)* 13 (4), 393–403. <https://doi.org/10.1089/154099904323087088>.
- Gruenewald, T.L., Seeman, T.E., Ryff, C.D., Karlamangla, A.S., Singer, B.H., 2006. Combinations of biomarkers predictive of later life mortality. *Proc. Natl. Acad. Sci. U. S. A.* 103 (38), 14158–14163. <https://doi.org/10.1073/pnas.0606215103>.
- Gruenewald, T.L., Karlamangla, A.S., Hu, P., Stein-Merkin, S., Crandall, C., Koretz, B., Seeman, T.E., 2012. History of socioeconomic disadvantage and allostatic load in later life. *Soc. Sci. Med.* 74 (1), 75–83. <https://doi.org/10.1016/j.socscimed.2011.09.037>.
- Guralnik, J.M., Ferrucci, L., Pieper, C.F., Leveille, S.G., Markides, K.S., Ostir, G.V., Studenski, S., Berkman, L.F., Wallace, R.B., 2000. Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. *J. Gerontol. A Biol. Sci. Med. Sci.* 55 (4), 221–231. <https://doi.org/10.1093/gerona/55.4.m221>.
- Gustafsson, P.E., Janlert, U., Theorell, T., Westerlund, H., Hammarstrom, A., 2012. Social and material adversity from adolescence to adulthood and allostatic load in middle-aged women and men: results from the Northern Swedish Cohort. *Ann. Behav. Med.* 43 (1), 117–128. <https://doi.org/10.1007/s12160-011-9309-6>.
- Hampson, S.E., Goldberg, L.R., Vogt, T.M., Hillier, T.A., Dubanoski, J.P., 2009. Using physiological dysregulation to assess global health status: associations with self-rated health and health behaviors. *J. Health Psychol.* 14 (2), 232–241. <https://doi.org/10.1177/1359105308100207>.
- Hawkey, L.C., Lavelle, L.A., Berntson, G.G., Cacioppo, J.T., 2011. Mediators of the relationship between socioeconomic status and allostatic load in the Chicago Health, Aging, and Social Relations Study (CHASRS). *Psychophysiology* 48 (8), 1134–1145. <https://doi.org/10.1111/j.1469-8986.2011.01185.x>.
- Howard, J.T., Sparks, P.J., 2016. Does allostatic load calculation method matter? Evaluation of different methods and individual biomarkers functioning by race/ethnicity and educational level. *Am. J. Hum. Biol.* 28 (5), 627–635. <https://doi.org/10.1002/ajhb.22843>.
- Hwang, A.C., Peng, L.N., Wen, Y.W., Tsai, Y.W., Chang, L.C., Chiou, S.T., Chen, L.K., 2014. Predicting all-cause and cause-specific mortality by static and dynamic measurements of allostatic load: a 10-year population-based cohort study in Taiwan. *J. Am. Med. Dir. Assoc.* 15 (7), 490–496. <https://doi.org/10.1016/j.jamda.2014.02.001>.
- Johnson, S.C., Cavallaro, F.L., Leon, D.A., 2017. A systematic review of allostatic load in relation to socioeconomic position: poor fidelity and major inconsistencies in biomarkers employed. *Soc. Sci. Med.* 192, 66–73. <https://doi.org/10.1016/j.socscimed.2017.09.025>.
- Juster, Robert-Paul, de Torre, Margot Barbosa, Kerr, Philippe, Kheloui, Sarah, Bourdon, Olivier, et al., 2019. Sex Differences and Gender Diversity in Stress Responses and Allostatic Load Among Workers and LGBT People. *Curr Psychiatry Rep.* <https://link.springer.com/content/pdf/10.1007%2Fs11920-019-1104-2.pdf>.
- Juster, R.P., McEwen, B.S., Lupien, S.J., 2010. Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neurosci. Biobehav. Rev.* 35 (1), 2–16. <https://doi.org/10.1016/j.neubiorev.2009.10.002>.

Appendix 1: Letter to the editor in response to the publication of Chapter 3

Psychoneuroendocrinology 123 (2021) 104877



Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen



Letter to the Editor

The promise of allostatic load rests upon strategic operationalization, scoring, and targeted interventions

The recent work by McLoughlin et al. (2020) advances the much needed conversion about the scoring algorithm of Allostatic Load (AL). They built their study upon our 2019 paper in which we compared various scoring methods of AL among a cohort of women from the NHANES data (Li et al., 2019). We agree with the authors' underscored needs on: the promise of the scoring method to predict health outcomes; accounting for medication and the consideration of sex, an understudied yet important variable for health outcomes.

We further this discussion by highlighting the need for better representations of the physiologic systems in an AL index (ALI). To date, there are inconsistencies in the inclusion of indicators to represent all the body systems (Read and Grundy, 2012). McLoughlin et al. (2020)'s study is one example of such discrepancy as their ALI lacked markers to represent the neuroendocrine system. Researchers tend to target the physiological indicators with the strongest associations with the disease outcome of interest. For example, hemoglobin A1C may be used to predict diabetes in lieu of cholesterol. However, it is important to consider the implications of the lack of representation of the all major systems (i.e., neuroendocrine, cardiovascular, immunologic, metabolic) in an ALI.

Another issue that warrants further consideration and testing is the inclusion of multiple indicators to represent one body system in an ALI. For example, in the study by McLoughlin et al. (2020), four of the 12 biomarkers represented cardiovascular functioning. Studies are needed to determine the implication of this "multi-indicator-to-one-system" approach.

Lastly, the timing of data collection is important. Given that AL represents dynamic, cumulative multisystem dysregulations, physiological indicators may need to be measured at multiple times to identify the dynamic physiological changes. The ideal time interval from baseline data collection to early detection of physiological changes or subclinical diseases remains unknown.

Only by addressing the three points above can we really be able to move toward successful interventions targeting AL (Rosemberg et al., 2020) and fully leverage allostatic load for research and clinical practice.

Declaration of Competing Interest

The authors report no declarations of interest.

References

Li, Y., Rosemberg, M.A.S., Dalton, V.K., Lee, S.J., Seng, J.S., 2019. Exploring the optimal allostatic load scoring method in women of reproductive age. *J. Adv. Nurs.* 75 (11), 2548–2558.

McLoughlin, S., Kenny, R.A., McCrory, C., 2020. Does the choice of Allostatic Load scoring algorithm matter for predicting age-related health outcomes? *Psychoneuroendocrinology* 120, 104789.

Read, S., Grundy, E., 2012. Allostatic load: a challenge to measure multisystem physiological dysregulation. National Centre for Research Methods. London School of Hygiene and Tropical Medicine and University of Cambridge.

Rosemberg, M.A.S., Granner, J., Li, Y., Seng, J.S., 2020. A scoping review of interventions targeting allostatic load. *Stress* 1–10.

Yang Li*
School of Nursing, University of Texas at Austin, Austin, TX, USA

Marie-Anne Sanon Rosemberg
School of Nursing, University of Michigan, Ann Arbor, MI, USA

* Corresponding author.
E-mail address: yang.li@nursing.utexas.edu (Y. Li).

Citation: Li, Y., & Rosemberg, M. A. S. (2021). The promise of allostatic load rests upon strategic operationalization, scoring, and targeted interventions. *Psychoneuroendocrinology*, 123, 104877. <https://doi.org/10.1016/j.psyneuen.2020.104877>

Appendix 2: Author response to the letter to the editor

Citation: McLoughlin, S., Kenny, R. A., & McCrory, C. (2021). Critiquing a study or a paradigm?



Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen



Critiquing a study or a paradigm?

In response to: The Promise of Allostatic Load Rests Upon Strategic Operationalization, Scoring, and Targeted Interventions

To the editor

We are thankful to Li and Rosenberg for their commentary on our study and for giving us the opportunity to respond. Firstly, it should be acknowledged that we agree with many of the points raised as their commentary reads more like a critique of the general Allostatic Load literature rather than a specific commentary on our paper. To briefly recap, our study was designed to compare the explanatory utility of a variety of different Allostatic Load scoring algorithms for predicting health outcomes using a panel of 12 biomarkers across 4 physiological systems using a large nationally representative sample of community-dwelling older people. Our results suggested that the choice of Allostatic Load scoring algorithm exerts a relatively modest influence in predicting several important age-related health outcomes, including walking speed and self-reported health.

Nevertheless, Li and Rosenberg seem to use our study as a springboard to underscore several common and recurring theoretical and empirical issues in the field of Allostatic Load, which arguably no single study can address. Perhaps most notably, the absence of a clear consensus about which biomarkers should be used to define an optimal measure of Allostatic Load. Such concerns have been highlighted extensively in previous reviews (Beckie, 2012; Johnson et al., 2017; Juster et al., 2010), with our own study concluding that any impact from the choice of biomarkers employed to reflect physiological dysregulation remains to be elucidated (McLoughlin et al., 2020; pg 8). This study, the first from my proposed plan of doctoral research, was not designed to directly test the impact of including/ excluding specific biomarkers/ biological systems when generating an Allostatic Load index. In fact, we believe that no singular study is optimized for doing so. We are currently working on a paper that attempts to move towards a consensus statement concerning which biomarkers are integral to Allostatic Load using multi-cohort data (including the NHANES data which Li. et al. used in their own study (Li et al., 2019)) to try to bring some clarity to this issue. The primary contribution of our study is the suggestion that the scoring method is not a major cause of concern for researchers, albeit with the proviso that future studies may wish to consider using sex-specific cut-offs and include medications when determining the overall score.

Does the non-inclusion of neuroendocrine markers invalidate the results of our study? We think not. Whilst the large heterogeneity of biomarkers employed across Allostatic Load studies limits direct comparisons, Johnson et al. (2017) noted that approximately half of the studies examined in their systematic review on socioeconomic position (SEP) and Allostatic Load similarly excluded markers of the HPA axis. The direction of the SEP-Allostatic Load relationship did not vary across these studies (Johnson et al., 2017), suggesting any impact of their inclusion is minimal. A second and related issue highlighted by Li and Rosenberg was whether an uneven number of biomarkers across physiological systems is a cause for concern. We refer readers to our original study, as this issue was addressed comprehensively; to account for inconsistencies in representation of indicators across systems, each dysregulated biomarker was weighted according to the number of biomarkers in the system (see “system weighted” scoring algorithm). Results did not suggest that the inclusion of varying quantities of indicators per system impaired the utility of the predictions. Similarly, others have reported no substantive difference in results when comparing system weighted scores with the “classic” count-based method of high risk biomarkers (Barboza Solís et al., 2016; Seeman et al., 1997).

The final issue raised by Li and Rosenberg calls attention to the need for additional prospective and longitudinal research in the field of Allostatic Load. We agree and would also welcome more research in this vein, particularly studies that explore how Allostatic Load develops over time given the growing evidence that the physiological response to stress varies by development stage, and that early childhood may represent a critical / sensitive period for the embedding of disease. A major limitation of many current epidemiologic studies is that biomarkers of Allostatic Load are collected at only one time point, which means we have little understanding of how Allostatic Load develops over time and whether changes in Allostatic Load modify disease risk. This reinforces the need to move beyond simple point in time measures. A major advantage of TILDA is that it has repeat biological measures on the same panel of individuals at each health wave sweep (although not yet available for analysis) which means that we will be able to model the functional form of change in Allostatic Load over time and examine how different Allostatic Load trajectories are related to incident disease states and cause-specific mortality, helping to provide some of the responses to concerns that Li & Rosenberg articulate in their letter.

Acknowledgement

This work was supported by the Health Research Board (HRB) of Ireland under an Emerging Investigator Award to Dr. Cathal McCrory (EIA-2017-012). TILDA was funded by Irish Life plc, the Irish Government and the Atlantic Philanthropies.

References

Barboza Solís, C., Fantin, R., Kelly-Irving, M., Delpierre, C., 2016. Physiological wear-and-tear and later subjective health in mid-life: findings from the 1958 British birth cohort. *Psychoneuroendocrinology* 74, 24–33. <https://doi.org/10.1016/j.psyneuen.2016.08.018>.

Beckie, T.M., 2012. A systematic review of allostatic load, health, and health disparities. *Biol. Res. Nurs.* 14 (4), 311–346. <https://doi.org/10.1177/1099800412455688>.

Johnson, S.C., Cavallaro, F.L., Leon, D.A., 2017. A systematic review of allostatic load in relation to socioeconomic position: poor fidelity and major inconsistencies in biomarkers employed. *Soc. Sci. Med.* 192, 66–73. <https://doi.org/10.1016/j.socscimed.2017.09.025>.

Psychoneuroendocrinology, 123, 104881. <https://doi.org/10.1016/j.psyneuen.2020.104881>

BRIEF REPORT

Psychosocial Adversity and Allostatic Load Burden in Midlife and Older Ages

Sinéad McLoughlin¹, Rose Anne Kenny^{1, 2}, and Cathal McCrory¹¹ The Irish Longitudinal Study on Ageing (TILDA), Trinity Central, Trinity College Dublin² Mercer's Institute for Successful Ageing, St. James's Hospital, Dublin, Ireland

Objective: To investigate the individual and cumulative impact of childhood and adulthood adversity on allostatic load (AL) burden. **Method:** Retrospective cross-sectional study design involving 4,165 participants from the first wave of The Irish Longitudinal study on Ageing (TILDA). AL was operationalized using 12 biomarkers across four physiological systems (cardiovascular, metabolic, renal, and immune). Measures of psychosocial adversity included poverty, abuse, loss, and illness. Negative binomial regression models estimated the relationship of individual adversities and a cumulative count of adversities with AL burden, controlling for age and sex. Multivariable models adjusted additionally for a range of other sociodemographic and lifestyle factors. **Results:** Childhood poverty, childhood physical abuse, and having a spouse/partner/child experience a life-threatening illness/accident were associated with 10% (95% CI [1.04, 1.16]), 10% (95% CI [1.01, 1.18]), and 6% (95% CI [1.01, 1.11]) greater AL burden, respectively. Cumulative adversity was associated with 3% (95% CI [1.01, 1.04]) higher AL burden. Adjusting for sociodemographic and lifestyle covariates rendered the association of childhood poverty (IRR= 1.04, 95% CI [.98, 1.09]; $p = .190$) and childhood physical abuse (IRR= 1.07, 95% CI [.99, 1.15]; $p = .081$) with AL burden nonsignificant, while the association of having an ill spouse/partner/child on AL persisted (IRR= 1.06, 95% CI [1.01, 1.11]; $p = .021$). **Conclusions:** This study provided limited support for the idea that psychosocial stress leads to higher AL, with just three out of 11 adversities associated with AL.

Keywords: adversity, allostatic load, stress, physiological dysregulation, life course

Supplemental materials: <https://doi.org/10.1037/hea0001098.supp>

Trauma, maltreatment, and socioeconomic adversity are all recognized as having a profound impact on risk of chronic disease

Sinéad McLoughlin  <https://orcid.org/0000-0002-9257-0400>

Rose Anne Kenny  <https://orcid.org/0000-0002-9336-8124>

Cathal McCrory  <https://orcid.org/0000-0001-6575-2367>

This work was supported by the Health Research Board (HRB) of Ireland under an Emerging Investigator Award to Cathal McCrory (EIA-2017-012). TILDA was funded by Irish Life plc, the Irish Government, and the Atlantic Philanthropies. The authors have no conflict of interests to report.

Sinéad McLoughlin served as a lead for conceptualization, data curation, formal analysis, methodology, and writing—original draft. Rose Anne Kenny served as supporting role for resources and writing—review & editing. Cathal McCrory serves as lead for funding acquisition and Supervision, contributed equally for writing—review & editing, and served in a supporting role for conceptualization.

Correspondence concerning this article should be addressed to Sinéad McLoughlin, The Irish Longitudinal Study on Ageing (TILDA), Trinity Central, Trinity College Dublin, 152-160 Pearse Street, Dublin 2, Ireland. Email: mcloughs4@tcd.ie

(Cohen et al., 2007). Although the mechanisms underlying this relationship remain to be fully elucidated, the allostatic load (AL) framework represents a plausible biological intermediary between psychosocial stress exposure and health. While stress is known to protect under acute circumstances, repeated or chronic activation of the stress response may lead to physiological “wear and tear,” predisposing an individual to disease (McEwen & Seeman, 1999).

Nevertheless, research to date has not been conclusive in establishing that major repeated or prolonged exposure to adverse events leads to higher burden of AL in later life. While AL is conceptualized within a life course framework, studies linking adverse experiences with dysregulation have mainly focused on isolated life stages (Friedman et al., 2015; Gleib et al., 2007; Weinstein et al., 2003), or specific life events (Dich et al., 2015; Gallo et al., 2011). Furthermore, early life may represent a critical period for the development of stress-response systems (Barboza Solís et al., 2015) but many studies exploring psychosocial adversity and AL do not include data on childhood adversities. Further scrutiny of the relative impact of individual adversities on AL burden, in lieu of the commonly employed crude counts of adversities, is warranted. This is suggested by the heterogeneity of findings across studies examining the association of isolated adverse events and

AL. For example, work stress, financial strain, relationship stress, and caregiving stress were positively associated with AL in a sample of Mexican American women, yet no association was reported between health, housing, or relationship stress and AL (Gallo et al., 2011). The purpose of this study was to examine the relationship of childhood and adulthood adversities with AL. We hypothesize that the experience of these stressors will be positively correlated with AL at midlife and older ages.

Method

Data

This analysis uses data from the first wave (2009–2011) of The Irish Longitudinal study on Ageing (TILDA), a nationally representative prospective study of over 8,175 persons aged 50+ and their spouses living in the Republic of Ireland. Data was collected through computer assisted personal interview (CAPI) carried out by a trained interviewer, a leave behind self-completion questionnaire (SCQ), and a comprehensive clinic-based health assessment (Whelan & Savva, 2013). If respondents were unable to attend the health assessment center, a trained nurse administered a subset of cognitive and physical tests in the respondent's home. Ethical approval for the study was provided by the Faculty of Health Science Research Ethics board in Trinity College Dublin, while informed consent was obtained from all respondents during data collection.

Measures

Allostatic Load

Twelve biomarkers were used to create the summary AL index encompassing four physiological systems. This includes the *cardio-vascular system*: systolic blood pressure, diastolic blood pressure, resting heart rate, pulse wave velocity; the *metabolic system*: waist-hip ratio, body mass index, glycosylated hemoglobin, high-density lipoprotein, total cholesterol; the *renal system*: creatinine, Cystatin-C; and the *immune system*: C-reactive protein. Log transformations were applied to C-reactive protein and pulse wave velocity to account for right-skewed distributions, and high-density lipoprotein was reverse coded such that higher values represented increased risk. Empirically defined high-risk thresholds were distinguished based on the distribution of that biomarker in the sample, separately for men and women. Biomarkers were dichotomized at the 75th percentile of risk and summed to create an index (range = 0–12) with higher scores reflecting higher AL. This method has been shown to work as well as alternative scoring algorithms (McLoughlin et al., 2020).

Psychosocial Stressors

Items adapted from the lifetime trauma list and administered as part of a self-completion questionnaire (SCQ; Krause et al., 2004) were used to retrospectively measure adversities experienced in childhood (i.e., parental alcohol/drug issues, physical abuse, and sexual abuse) and adulthood (i.e., experience of a fire/flood or natural disaster, spouse/child drug addiction, serious assault, personal life threatening illness, spouse/partner/child life threatening illness, and death of a child). These variables were coded "no/yes." In addition, whether a participant experienced the death of a parent in childhood was derived from dates provided during the CAPI,

and a subjectively measured item on the economic circumstances of the household prior to the age of 14 captured childhood poverty (not poor/poor). Details on the measurement of these variables is available in the [online supplemental materials](#). Cumulative counts were calculated by summing the number of adversities reported: childhood events (0–5), adulthood events (0–6), and overall exposure (0–11).

Analytical Approach

To reduce any potential bias arising from item nonresponse, we imputed for individuals missing on any of the individual adversity components and for whom we had an AL score. As the outcome variable (AL) was zero inflated and over dispersed ($M = 2.9$, variance = 4.3), we modeled the association of each adversity type with AL using negative binomial regression. Unstandardized coefficients were exponentiated and reported as incidence rate ratios (IRR), which can be interpreted as the percentage change in AL associated with the experience of each adversity type. In the base models we adjust for age and sex (Model 1) as the experience of adversity may differ between age cohorts and sexes. In secondary models we adjust for sociodemographic and lifestyle factors using hierarchical entry of covariates. Even though it is not possible to unequivocally establish relative timing for most of these variables as they were measured contemporaneously, it might still be informative to examine the degree to which their common correlation attenuates the association of adversity with AL in an exploratory way to help inform future hypothesis generation. These covariates are described in detail in the [online supplemental materials](#). Model 2 added educational attainment (primary, secondary, tertiary); Model 3 added smoking pack years, problematic alcohol consumption (four-item CAGE), and physical activity (eight-item International Physical Activity Questionnaire; low, medium, high); Model 4 added log total household income (after tax); and Model 5 added social connectedness (four-item Berkman Syme Social Network Index [SNI]). All analyses were conducted in Stata v.15 (StataCorp, 2017), using TILDA dataset v.1.8.0.

Missing Cases

The initial case base for the analysis consisted of 6,914 respondents (84.6%) who returned the SCQ. Further exclusions included 2,248 respondents who did not take part in the nurse led health assessment, and 501 missing on one or more of the AL biomarkers. Full biomarker data was available for 4,165 participants, forming the analytical sample (Supplementary Figure 1). Standard errors of estimates were adjusted to account for the clustered design effect and stratification, and data were weighted using survey weights to account for the fact that respondents who attended the health center were younger, better educated, and in better health. Multiple imputation by chained equations was conducted to estimate missing values based on observed information, assuming all data were missing at random (Little's test: $\chi^2(6,812)$, $N = 4,165$, 2974.3, $p = 1.00$). The percentage of cases for which we imputed on any individual adversity ranged from .1% to 5.1% (Supplementary Table 2). The imputation model included all variables used in the final analysis, including sociodemographic and lifestyle variables. 20 data sets were imputed with random seed to facilitate replication.

Results

Supplementary Table 1 reports the sample characteristics; mean age of participants was 63.3 years ($SD = 9.3$), and 48.2% were male. Average AL was 3.1 ($SD = 2.1$). Supplementary Table 2 reports the number of cases and survey weighted prevalence for each adversity type. Figure 1A displays the age and sex adjusted independent association of each adversity type with AL, while Figure 1B reports the full multivariable adjusted estimates. Controlling for age and sex (Supplementary Table 3, Model 1), participants who reported childhood poverty had significantly higher AL burden (IRR= 1.10, 95% CI [1.04, 1.16]; $p = .001$), as did those who reported childhood physical abuse (IRR= 1.10, 95% CI [1.01, 1.18]; $p = .021$). Participants who reported having an ill spouse or child had a 6% higher AL burden (IRR= 1.06, 95% CI [1.01, 1.11]; $p = .026$). No other individual adversity was significantly associated with AL in the base models. The cumulative count of psychosocial adversities was associated with a 3% increase in AL burden (IRR= 1.03, 95% CI [1.01, 1.04]; $p = .003$).

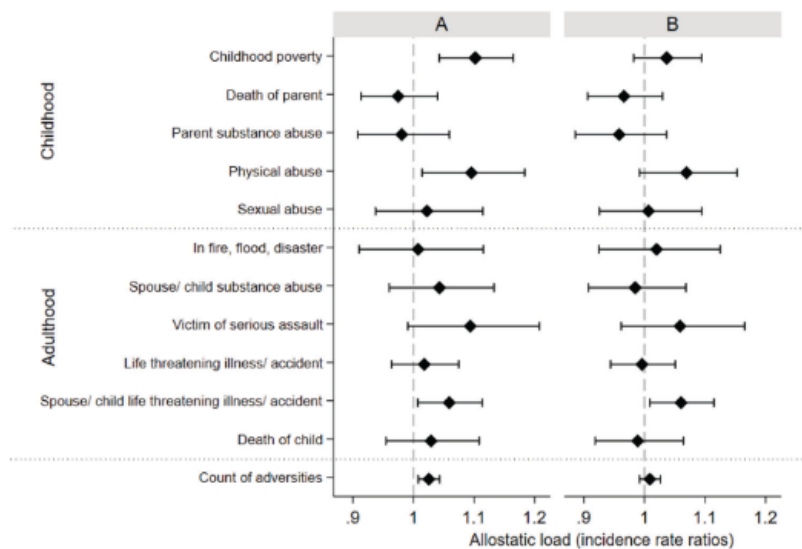
Supplementary Table 4 displays the relationships of the exposures with the covariates, and the relationships of the covariates with the outcome. The inclusion of all covariates rendered the association of childhood poverty (IRR= 1.04, 95% CI [.98, 1.09]; $p = .190$) and childhood physical abuse (IRR= 1.07, 95% CI [.99, 1.15]; $p = .081$) with AL burden nonsignificant, while the association of having an ill spouse/partner/child with AL persisted (IRR= 1.06, 95% CI [1.01, 1.11]; $p = .021$; Supplementary Table 3, Model 5). The count of adversities was not significantly associated with AL burden after multivariable adjustment (IRR: 1.01, 95%

CI [.99, 1.03]; $p = .313$). As a sensitivity check, we repeated the analyses using clinical cut-points (Supplementary Table 5) and on nonimputed data (Supplementary Table 6) but the broad pattern of results were not appreciably different. However, when we included measures of parasympathetic functioning which were available for a subset of participants ($n = 3,672$), being a victim of serious assault was now associated with higher AL burden in the base, but not the multivariable adjusted models, while the relationship of spouse/partner/child life threatening illness with AL burden was nonsignificant, possibly due to lower statistical power in this reduced sample (Supplementary Table 7).

Discussion

This study examined the association of a number of childhood and adulthood adversities with AL in a large, community-based sample of older Irish adults. The experience of adversity is common throughout life, with 57.9% experiencing at least one adversity; however, only three out of 11 adversities (childhood poverty, childhood physical abuse, spouse/partner/child life-threatening illness or accident) were associated with higher AL, albeit merely a select few from the spectrum of adversities that could be experienced during a lifetime. These findings elicit the question as to why we observe linkages between some adversity types and higher AL burden but not others. Although the majority of associations were in the positive direction, it could be conceded that these null findings with the majority of adversities and AL may result from crude measurement of the exposure (never vs. ever), which fails to capture variation in the timing, duration or severity of the event.

Figure 1
Independent Association of Each Diversity Type With Allostatic Load in the Minimally (Figure 1A) and Full Multivariable (Figure 1B) Adjusted Models



Note. Model A adjusts for age and sex. Model B = Model A + education, lifestyle factors (alcohol abuse, smoking pack years, and physical activity), income, social network index.

Unfortunately, this information is not available in TILDA, but it would be expected to moderate the impact of the stressor on AL burden. Moreover, the lack of association between many of the adulthood adversities and AL may arise because these exposures occur "more proximal" in time to the measurement of AL, and the biological consequences of exposure may only appear with a lag. In accordance with the simplistic "multiples matter" paradigm (Spratt, 2012); cumulative adversity was positively associated with greater physiological dysregulation. However, the addition of a number of sociodemographic and behavioral factors attenuated the relationship of childhood poverty, childhood physical abuse and cumulative adversity with AL burden, implicating potential pathways whereby exposure to psychosocial adversity becomes biologically embedded. Strengths include the large nationally representative sample of the community-dwelling older population of Ireland, and the range of different measures of adversity in childhood and adulthood. Limitations include the fact that the adverse events were retrospectively reported and subject to recall bias. The AL measure may be less sensitive for capturing the direct effects of HPA-axis and SAM axis dysregulation as it does not include measures of the "primary mediators" (e.g., cortisol, epinephrine, norepinephrine; McEwen & Seeman, 1999).

Conclusion

Overall, this study provides rather limited support for the idea that psychosocial stress causes physiological dysregulation, at least as indexed using the measure of AL as defined in this study. Future work should seek to broaden the variety and type of adverse events examined in the context of AL and go beyond simple dichotomies of ever versus never exposed to develop a more nuanced understanding of how timing, duration and severity impact upon one's biological health in the long run.

References

- Barboza Solís, C., Kelly-Irving, M., Fantin, R., Darnaudéry, M., Torrisani, J., Lang, T., & Delpierre, C. (2015). Adverse childhood experiences and physiological wear-and-tear in midlife: Findings from the 1958 British birth cohort. *Proceedings of the National Academy of Sciences of the United States of America*, 112(7), E738–E746. <https://doi.org/10.1073/pnas.1417325112>
- Berkman, L. F., & Syme, S. L. (1979). Social networks, host resistance, and mortality: A nine-year follow-up study of Alameda County residents. *American Journal of Epidemiology*, 109(2), 186–204. <https://doi.org/10.1093/oxfordjournals.aje.a112674>
- Bernadt, M. W., Mumford, J., Taylor, C., Smith, B., & Murray, R. M. (1982). Comparison of questionnaire and laboratory tests in the detection of excessive drinking and alcoholism. *Lancet*, 1(8267), 325–328. [https://doi.org/10.1016/S0140-6736\(82\)91579-3](https://doi.org/10.1016/S0140-6736(82)91579-3)
- Cohen, S., Janicki-Deverts, D., & Miller, G. E. (2007). Psychological stress and disease. *Journal of the American Medical Association*, 298(14), 1685–1687. <https://doi.org/10.1001/jama.298.14.1685>
- Craig, C. L., Marshall, A. L., Sjöström, M., Bauman, A. E., Booth, M. L., Ainsworth, B. E., Pratt, M., Ekelund, U., Yngve, A., Sallis, J. F., & Oja, P. (2003). International physical activity questionnaire: 12-country reliability and validity. *Medicine and Science in Sports and Exercise*, 35(8), 1381–1395. <https://doi.org/10.1249/01.MSS.0000078924.61453.Fb>
- Dich, N., Hansen, Å. M., Avlund, K., Lund, R., Mortensen, E. L., Bruunsgaard, H., & Rod, N. H. (2015). Early life adversity potentiates the effects of later life stress on cumulative physiological dysregulation. *Anxiety, Stress, and Coping*, 28(4), 372–390. <https://doi.org/10.1080/10615806.2014.969720>
- Ewing, J. A. (1984). Detecting alcoholism. The CAGE questionnaire. *Journal of the American Medical Association*, 252(14), 1905–1907. <https://doi.org/10.1001/jama.1984.03350140051025>
- Friedman, E. M., Karlamangla, A. S., Gruenewald, T. L., Koretz, B., & Seeman, T. E. (2015). Early life adversity and adult biological risk profiles. *Psychosomatic Medicine*, 77(2), 176–185. <https://doi.org/10.1097/PSY.0000000000000147>
- Gallo, L. C., Jiménez, J. A., Shivpuri, S., Espinosa de los Monteros, K., & Mills, P. J. (2011). Domains of chronic stress, lifestyle factors, and allostatic load in middle-aged Mexican-American women. *Annals of Behavioral Medicine: A Publication of the Society of Behavioral Medicine*, 41(1), 21–31. <https://doi.org/10.1007/s12160-010-9233-1>
- Glei, D. A., Goldman, N., Chuang, Y. L., & Weinstein, M. (2007). Do chronic stressors lead to physiological dysregulation? Testing the theory of allostatic load. *Psychosomatic Medicine*, 69(8), 769–776. <https://doi.org/10.1097/PSY.0b013e318157c8a6>
- Krause, N., Shaw, B. A., & Cairney, J. (2004). A descriptive epidemiology of lifetime trauma and the physical health status of older adults. *Psychology and Aging*, 19(4), 637–648. <https://doi.org/10.1037/0882-7974.19.4.637>
- Mayfield, D., McLeod, G., & Hall, P. (1974). The CAGE questionnaire: Validation of a new alcoholism screening instrument. *The American Journal of Psychiatry*, 131(10), 1121–1123. <https://doi.org/10.1176/ajp.131.10.1121>
- McEwen, B. S., & Seeman, T. (1999). Protective and damaging effects of mediators of stress. Elaborating and testing the concepts of allostasis and allostatic load. *Proceedings of the National Academy of Sciences of the United States of America*, 896(1), 30–47. <https://doi.org/10.1111/j.1749-6632.1999.tb08103.x>
- McLoughlin, S., Kenny, R. A., & McCrory, C. (2020). Does the choice of Allostatic Load scoring algorithm matter for predicting age-related health outcomes? *Psychoneuroendocrinology*, 120, 104789. <https://doi.org/10.1016/j.psyneuen.2020.104789>
- Spratt, T. (2012). Why multiples matter: Reconceptualising the population referred to child and family social workers. *British Journal of Social Work*, 42(8), 1574–1591. <https://doi.org/10.1093/bjsw/bcr165>
- StataCorp. (2017). *Stata statistical software: Release 15*. StataCorp LLC.
- Weinstein, M., Goldman, N., Hedley, A., Yu-Hsuan, L., & Seeman, T. (2003). Social linkages to biological markers of health among the elderly. *Journal of Biosocial Science*, 35(3), 433–453. <https://doi.org/10.1017/S0021932003004334>
- Whelan, B. J., & Savva, G. M. (2013). Design and methodology of the Irish Longitudinal Study on Ageing. *Journal of the American Geriatrics Society*, 61(Suppl. 2), S265–S268. <https://doi.org/10.1111/jgs.12199>

Received November 24, 2020

Revision received April 26, 2021

Accepted May 4, 2021 ■



THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Social Sciences
cite as: *J Gerontol B Psychol Sci Soc Sci*, 2023, Vol. 78, No. 1, 154–166
<https://doi.org/10.1093/geronb/gbac122>
Advance Access publication August 26, 2022



Research Article

Intergenerational Social Mobility and Allostatic Load in Midlife and Older Ages: A Diagonal Reference Modeling Approach

**Sinéad McLoughlin, MSc,^{1,*} Patrick Präg, PhD,² Mel Bartley, PhD³
Rose Anne Kenny, MD,^{1,4} and Cathal McCrory, PhD¹**

¹The Irish Longitudinal Study on Ageing (TILDA), Department of Medical Gerontology, Trinity College Dublin, Dublin, Ireland.
²Center for Research in Economics and Statistics (CREST), ENSAE, Institut Polytechnique de Paris, Palaiseau, France.
³Research Department of Epidemiology and Public Health, University College London, London, UK. ⁴Merger's Institute for Successful Ageing, St James's Hospital, Dublin, Ireland.

*Address correspondence to: Sinéad McLoughlin, The Irish Longitudinal Study on Ageing (TILDA), Trinity Central, Trinity College Dublin, 152-160 Pearse Street, Dublin 2, Ireland. E-mail: mcloughs4@tcd.ie

Received: January 21, 2022; Editorial Decision Date: August 17, 2022

Decision Editor: Jessica Kelley, PhD

Abstract

Objectives: This study aims to understand the association of life-course intergenerational social mobility with allostatic load (AL) burden in midlife and older ages in Ireland.

Methods: The study involved biological data for 3,987 older adults participating in The Irish Longitudinal Study on Ageing (TILDA). Intergenerational social mobility was characterized using the cross-classification of origin socioeconomic position (SEP; i.e., father's occupation) and destination SEP (i.e., own occupation). AL was operationalized using 12 biomarkers tapping cardiovascular, metabolic, renal, and immune system dysregulation. Diagonal reference modeling (DRM) and ordinary least square regression techniques were applied to explore the effect of social mobility on AL burden.

Results: A total of 55.5% experienced intergenerational mobility: 37.5% were upwardly mobile, 18.0% were downwardly mobile. A social gradient in AL was observed among the socially non-mobile. Destination SEP ($b = 0.74$, 95% CI = 0.57, 0.92) predominated in influence over origin, although both life stages exerted significant influence on later-life AL. Social mobility in either direction was not associated with AL burden. Mobility coefficients were substantially small across a large variety of model specifications.

Discussion: Findings provide evidence for an accumulation model of social inequalities in which disparities in health are diluted rather than increased by social mobility (i.e., gradient constraint), with the socially mobile having an AL score that is intermediate between their origin class and destination class. This implies that the effects of origin SEP on health are not immutable, but are instead responsive to changing socioeconomic circumstances across the life course.

Keywords: Diagonal reference modeling, Life course, Socioeconomic position

There exists a gradient in health across socioeconomic groups, such that the most disadvantaged experience the highest risk of morbidity and mortality (Snyder-mackler et al., 2020). It has been proposed that this social gradient in

health comes about in large part because persons of less advantaged socioeconomic position (SEP) experience greater stress exposure than their more advantaged SEP counterparts (Matthews & Gallo, 2011), with the long-term effects

© The Author(s) 2022. Published by Oxford University Press on behalf of The Gerontological Society of America.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

154

of such insults culminating in a multisystem physiological burden known as allostatic load (AL; McEwen, 1998). AL has been posited as a potential explanatory framework for understanding the biological embedding of SEP over the life course. Despite the consistent link between less advantaged SEP and high AL burden demonstrated to date (Johnson et al., 2017), the relationship is complex, and how the experience of socioeconomic dis/advantage moderates trajectories of physiological dysregulation remains to be determined.

Although life-course models are closely interrelated and difficult to disentangle statistically (Hallqvist et al., 2004), a life-course approach enables a more dynamic view of the impact of SEP on physiological functioning, recognizing the complex pathways between early-life and later-life health (Ben-Shlomo & Kuh, 2002). For instance, does the timing of socioeconomic disadvantage matter in the context of AL, such that childhood exposure results in “permanent and irreversible” scarring effects on biological systems as implied by the critical period model (Ben-Shlomo & Kuh, 2002, p. 286), or do the negative impacts of SEP disadvantage compound over time, with each additional life stage spent in less advantaged SEP adding to an ever growing health disadvantage, as suggested by the accumulation model? (Shuey & Willson, 2014). Perhaps the negative effects of disadvantaged SEP are reversible and mitigated through intergenerational or intragenerational changes, as suggested by the social mobility model (Iveson & Deary, 2017; Pudrovska & Anikputa, 2014). The classic “dissociation” hypothesis stipulates that social mobility—irrespective of upwards or downwards—is disruptive and detrimental to the well-being of individuals, leading to reduced social integration, weakened social ties, and feelings of alienation (Sorokin, 1927). These relational rifts may be experienced as stressful, thus exerting negative health implications. The “falling from grace” thesis argues that the experience of downward mobility is a more distressing experience than upward mobility, as failing to maintain the educational or occupational attainment of their parents leads to feelings of insecurity (Newman, 1999). On the other hand, the “rising from rags” thesis suggests that the positive effects of upward mobility may outweigh any negative consequences (Gugushvili et al., 2019). “Acculturation” similarly suggests that the influence of destination class on health will be stronger than that of origin (Blau, 1956). These theories have the potential to expand our understanding of how SEP impacts on biological risk over the life course.

Research to date examining the relation of different life-course models with AL has shown mixed findings, especially regarding whether origin SEP (i.e., SEP in early life), is directly associated with later-life AL. For instance, data from a Northern Swedish cohort ($n = 855$; 51.8% male) found that life-course socioeconomic disadvantage was related to a greater burden of AL. This study also revealed that origin SEP, measured using parental occupation at age 16, was a particularly sensitive period for the

embedding of socioeconomic disadvantage on AL at mid-life (age 43) among women, but not men after controlling for contemporaneous lifestyle behaviors and incorporating medication use (Gustafsson et al., 2011). Data from the Midlife in the United States (MIDUS; $n = 1,008$; 45.2% male; age range: 35–85) supported an independent effect of a composite origin SEP variable on later-life AL, adjusting for destination SEP, although the magnitude of the association was almost twice that for destination, holding age, sex and race/ethnicity constant (Gruenewald et al., 2012). In line with this, results from a longitudinal analysis of the Multi-Ethnic Study of Atherosclerosis (MESA; $n = 6135$; 47.8% male; age range 45–84) reported that the association of SEP and AL was primarily driven by destination SEP, after adjusting sociodemographic confounders and medication use (Merkin et al., 2014).

One factor that may play a role in the observed nuances across studies relates to the choice of statistical model. To date, investigations of the relative contribution of origin and destination SEP on AL have been dominated by simple linear models, estimated in a stepwise fashion. Typically, a baseline model estimates the direct effect of origin SEP on AL, and a second model controls for destination SEP (Gruenewald et al., 2012; Gustafsson et al., 2011). However, Green and Popham (2019) caution that it may be problematic to compare the effects for multiple measures of SEP on AL as independent effects, as the possible causal effects of distal SEP measures may be biased with adjustment for proximate SEP measures. The effect estimates from these models are often presented simultaneously in one table, giving the impression of equivalent interpretation, leading to the so-called “Table 2 fallacy” (Green & Popham, 2019).

Eschewing the multiple adjustment method, Robertson et al. (2014) utilized structural equation modeling (SEM) to compare the fit of different life-course models linking SEP with AL across three age cohorts (ages 35, 55, 75) using data from the West of Scotland study. When allowing effect sizes to vary between life stages, it was the accumulation model that provided the best fit to the data (Robertson et al., 2014). In relation to the social mobility model, they found that intergenerational upward mobility was associated with higher AL burden in early ($n = 740$), but not in mid ($n = 817$) or late adulthood ($n = 483$; Robertson et al., 2014), possibly due to survival bias. However, neither linear models nor SEM techniques are able to isolate the relative effects of origin and destination SEP on AL, as the influence of social mobility cannot be estimated unless the effects of past and current SEP can be separated from mobility itself (Billingsley et al., 2018).

Diagonal reference models (DRMs; Sobel, 1981) were developed to overcome the linear dependency between origin and destination SEP. The notable feature of these models is their attempt to examine the independent effect of moving between SEP groups after accounting for being in different SEP's across the life course, with the guiding

assumption that socially immobile individuals constitute the core of a social position and therefore best reflect its characteristics (Sorokin, 1959). Präg and Richards (2019) employed this technique to explicitly examine the effects of intergenerational social mobility on AL using data from *Understanding Society*, the UK Household Longitudinal Study ($n = 9851$; mean age 52.6, 44.4% male). They reported no significant associations of mobility with AL burden, a result that suggests that mobility in and of itself does not directly impact physiological dysregulation, and the weighting led to a conclusion that neither origin nor destination SEP predominate in their impact on AL (Präg & Richards, 2019). A recent U.S. based study of young adults aged 25–32 that also used DRM's arrived at a similar conclusion regarding the relative weight to be afforded to origin and destination SEP (measured using a composite of education and occupational attainment), but contrary to the UK study, there was some evidence of a mobility effect for the upwardly mobile (Gugushvili et al., 2021).

The Present Study

Aside from methodological differences, the association of social mobility with AL may differ in varying social-economic-historic environments. The Republic of Ireland provides an interesting test case for the examination of social mobility effects on physiological dysregulation as it has a strong class-based structure (Whelan & Layte, 2004, 2006). The country has undergone radical economic development in recent decades, resulting in high levels of absolute social mobility as Ireland transitioned from a predominantly agrarian to a post-industrial economy. The 1950s saw a peak in emigration and virtual stagnation of real national income, yet the decade that followed saw rapid growth as economic policy incorporated a more export-oriented strategy, attracting foreign investment and leading to the “Celtic Tiger” era at the start of the 21st century (Whelan & Layte, 2006). Opportunities for middle-class and skilled-manual work increased concomitant with diminishing agricultural trade, which impacted on the occupational structure of the country (Ó Gráda & O'Rourke, 2022). Analyzing trends in social mobility, Whelan and Layte (2002) noted that the proportion of smallholders in Ireland, or individuals who owned small farms, decreased from 20% to 10% between 1973 and 1987 (Whelan and Layte, 2002). Although the economy underperformed relative to its European counterparts who were experiencing the “Golden Age” up until the 1970s, Irish national income grew more rapidly and more dramatically, catching up with the performance of neighboring economies by the 1980s. Gross National Income (GNI) growth averaged 1.1% between 1938 and 1950, rising to 3.9% between 1960 and 1973.

Educational achievement continues to be a key mechanism in the transmission of intergenerational disadvantage (C. T. Whelan & Layte, 2002). The educational system

in Ireland went through a general restructure around the time that the current older generation of individuals were navigating their own educational attainment, including the introduction of free-secondary education. This notable reform, alongside the demand for employees with higher levels of education as the economy transformed to one based on skills and educational attainment, increased educational participation (Callan & Harmon, 1999), assisting individuals from less advantaged SEP background to be socially mobile. From 1973 to 2000, the proportion of individuals with secondary school education who held non-manual positions increased twofold, indicating a reduced capacity of higher qualifications to guarantee more advantaged positions (C. T. Whelan & Layte, 2006). The high levels of upward mobility within an aging cohort therefore allows an in-depth investigation of the long run implications of transitioning out of origin dis/advantage for AL in later life.

Method

Data Source

The Irish Longitudinal Study on Ageing (TILDA) is a nationally representative prospective cohort study of community-dwelling older persons aged 50 years or more and their spouses living in the Republic of Ireland. The sample was generated using a two-stage clustered sampling process and the Irish Geodirectory as the sampling frame, which comprises all addresses in the Republic of Ireland. The primary sampling units were 640 geographic regions selected by random selection, stratified on proportion of head of households in the professional class, proportion of the population aged ≥ 65 and older, and geographical location. The second stage involved the selection of a random sample of 40 addresses from within each primary sampling unit, resulting in an initial sample of 25,600 addresses, which were assessed for eligible participants aged ≥ 50 and older. A response rate of 62.0% was achieved at the household level, which was defined as the proportion of sampled households, including an eligible participant from whom an interview was successfully obtained. The sampling fraction is approximately 1/150 of all community-dwelling adults aged 50 years and over resident in the Republic of Ireland. Baseline data were collected between 2009 and 2011, via computer-assisted personal interviews (CAPI), leave-behind paper and pen self-completion questionnaires (SCQ; response rate = 84.6%), and a health assessment (response rate = 61.6%) comprising the collection of blood samples ($n = 5,655$) and other physiological parameters. Additional details of the study design are available elsewhere (B. J. Whelan & Savva, 2013). Ethical approval for this study was approved by the Faculty of Health Science Research Ethics board in Trinity College Dublin, while informed consent was obtained from all participants during

data collection. TILDA data are publicly available from the Irish Social Sciences Data Archive (ISSDA; <https://www.ucd.ie/issda/data/tilda/>), whereas access to the restricted researcher microdata file is available upon application (<https://tilda.tcd.ie/data/accessing-data/>).

Measurements

Outcome variable—allostatic load

Consensus is lacking regarding the optimal biomarker panel for use in the generation of AL indices, leading to large heterogeneity in biomarkers employed to date (Johnson et al., 2017). This study incorporates twelve biomarkers selected from available data based upon their representation of multiple physiological systems pertinent to disease risk, and their known association with age-related health outcomes in this cohort (McLoughlin et al., 2020). This includes the *cardiovascular system*; systolic blood pressure, diastolic blood pressure, resting heart rate, pulse wave velocity, the *metabolic system*; waist-hip ratio, body mass index, glycosylated hemoglobin, high-density lipoprotein, total cholesterol, the *renal system*; creatinine, Cystatin-C and the *immune system*; C-reactive protein. Log transformations were applied to C-reactive protein and pulse wave velocity to account for right-skewed distributions, and high-density lipoprotein was reverse coded such that higher values represented increased risk. Detailed measurement techniques for each biomarker are available elsewhere (McLoughlin et al., 2020). Each biomarker was standardized to a mean of 0 and an SD of 1 and summed to generate an overall AL score expressed in standard deviation units. Finally, this overall AL score was standardized to a mean of 0 and a SD of 1.

Exposure variable

Occupational class was drawn from retrospective data on father's occupation from childhood (age 14), and used to estimate origin SEP. Current occupation, or highest paid job if retired, was used to estimate contemporaneous or destination SEP. Following the Irish Central Statistics Office (CSO) social class coding schema and in line with previous research on Irish data, occupations for both time points were classified into five categories: professional/managerial, non-manual, skilled manual/semiskilled, unskilled and parent never worked. Participants who reported farming as origin or destination occupation were asked to provide acreage, and if they had any other paid work, and were coded into the appropriate occupation categories based on CSO criteria: farmers with 0–29 acres were assigned to the semiskilled group, 30–49 acres were assigned to the skilled manual group, 5–99 acres were assigned to the non-manual group, 100+ acres were assigned to the professional/managerial group. Farmers with unknown acreage were coded as missing. Due to small cell sizes, class was further collapsed into three categories: (a) professional/managerial, (b) non-manual/skilled manual, and (c) semiskilled/unskilled/never

worked. A series of dummy variables was generated to capture mobility trajectories (i.e., upwardly mobile, downwardly mobile, one step up, two steps up, one step down, two steps down).

Irish sociological research has a long tradition of using occupation to measure SEP because Ireland has a strong underlying social class structure (C. T. Whelan & Layte, 2004, 2006), which is correlated with other socioeconomic indicators (i.e., income, education). Occupation is often favored in social mobility research because it is an individual-level measure of SEP. Occupation serves as a key determinant of life chances and is also a measure that is in some sense transferable. As such, parental social class can be used to characterize the likely socioeconomic circumstances of children within the household growing up (Galobardes et al., 2004). Although income has been used in studies elsewhere (Gruenewald et al., 2012; Hickson et al., 2012), it is a less useful indicator in older cohorts as it may be affected by retirement status. Moreover, obtaining reliable information on the income status of the parent's generation is problematic. Education has also been used to characterize intergenerational mobility in many U.S.-based studies (Allen et al., 2019; Kubzansky et al., 1999; Seeman et al., 2008), but is arguably a less sensitive indicator in the Irish context because Ireland experienced massive educational upgrading between the 1960s and 1970s as a consequence of two educational reform acts, meaning that later-born cohorts generally have more education than earlier born cohorts. Nevertheless, we perform robustness checks on our results using education as an alternative measure of intergenerational social mobility.

Sample Exclusions

Of the baseline sample over the age of 50 ($n = 8,175$), 5,655 of these participants successfully provided blood samples and 4,477 participants had complete biological data on the biomarkers needed to construct the AL index. Of these, 490 were missing on life-course SEP variables; 319 were missing on origin SEP (including 174 farmers with unknown acreage), while 171 were missing destination SEP (including 15 farmers with unknown acreage), while 30 participants were missing SEP data on both life stages. The final analytical sample comprised 3,987 respondents. A flow chart detailing eligibility criteria and final analytical sample is detailed in [Supplementary Figure 1](#). Individuals excluded from the analyses differed to the extent that they tended to be older, with higher proportions within less advantaged SEP groups.

Analytical Strategy

Diagonal Reference Models

DRMs were estimated to test whether AL is affected by social mobility besides origin and destination (Zang et al.,

2022). DRMs model the outcome of interest (AL) as the weighted sum of the estimated mean values in the socially immobile origin group and the socially immobile destination group. We adjust in the models for age (years) and sex (male, female) as patterns of intergenerational mobility and AL burden may vary across these important demographic characteristics. We also control for a childhood self-reported health indicator (excellent, very good, good, fair, poor), as poor childhood health could set restraints on social mobility and directly affect later-life AL burden (Miller et al., 2011; Präg et al., 2022).

For ease of interpretation in the DRM analysis, age was centered around the sample mean. The constant represents the average AL burden for male respondents of average age, while the class coefficients represent the deviations from that constant. The weight parameters express the relative importance of origin and destination on AL and are constrained to range between 0 and 1. A high value of the destination weight value indicates that the relative importance of one's current SEP is greater than origin SEP with respect to AL. To test for mobility effects in DRMs, we created a series of dummy variables to represent (a) upward and downward mobility and (b) the magnitude of mobility (i.e., number of positions by which the respondent was mobile relative to origin class). For the sake of uniformity in nomenclature with the extant social mobility literature, we make use of the term "mobility effects" (Präg et al., 2022). Note that this term is used to describe a statistical association rather than imply the existence of any causal relationships. We compared the fit of these nested models with the base model using the Akaike and Bayesian Information Criteria (AIC and BIC). The DRMs were implemented in Stata using the "drm" module developed by Kaiser (2018).

Ordinary Least Square Models

To enable comparison with prior research, we also estimated a series of ordinary least square models. In separate models, we estimate first the independent associations of origin SEP and destination SEP with AL burden while adjusting for age, sex and childhood self-reported health. We then include origin and destination SEP in the same model to test for mediation (i.e. mutual adjustment). We fit a two-way interaction term between origin and destination SEP to determine whether the relationship with AL over the life course is additive or multiplicative. We examined mobility effects in ordinary least square (OLS) models using the method typified by Luo & Waite (2005) by characterizing the study population into five social mobility trajectories: stable professional/managerial, stable non-manual/skilled manual, stable semiskilled/unskilled, upwardly mobile, downwardly mobile; and comparing the conditional mean AL scores across groups (Luo & Waite, 2005). All analyses were conducted in Stata (V.15; [StataCorp, 2017]).

Results

The mean and SD values for each of the 12 biomarkers comprising the AL index are described in [Supplementary Table S2](#). [Table 1](#) reports the characteristics of the sample and the degree of intergenerational social mobility within the TILDA cohort. The mean age of the sample ($n = 3987$) was 61.8 ($SD = 8.3$), and 53.5% were female. The majority of the sample reported their childhood health to be excellent (56.4%), very good (25.3%), or good (12.7%), with <6% reporting fair or poor health. [Table 1](#) also shows that the experience of intergenerational social mobility was common, with 37.5% of the sample upwardly mobile and 18.0% of the sample downwardly mobile, leaving 44.5% non-mobile. In general, those who were mobile tended to be mobile within ± 1 occupational position around their destination, with smaller proportions mobile by ± 2 occupational positions, suggesting origin places some constraints on destination. [Table 2](#) shows the conditional means resulting from the cross-classification of origin and destination. Cells on the diagonal describe performance for individuals who were non-mobile across generations, cells below the diagonal describe those who were upwardly mobile, and cells above the diagonal describe those who were downwardly mobile. Upward mobility is associated with lower AL scores compared with class of origin, and downward mobility is associated with higher AL scores compared with class of origin.

Diagonal Reference Models

[Table 3](#) reports the parameter estimates from the DRM analysis estimating mobility effects on AL burden. The baseline model reveals that the coefficients for AL burden are smaller for people in the higher social classes, reflecting the social gradient in health amongst the socially immobile. The coefficients for the confounding variables reveal that AL burden is lower for women than men, and is positively associated with age. Poorer childhood health was associated with greater AL burden, but these effects were not significant. The subsequent models test for the effects of intergenerational mobility over and above the effects of origin and destination, allowing mobility effects to be separated from level effects. The weight parameters from [Table 3](#) indicate that the level of AL burden is closer to their non-mobile counterparts in the destination group. No significant associations of mobility trajectories with AL are reported, which is in line with the AIC and BIC values indicating that the parsimonious base model fits the data best.

Sensitivity analyses

We undertook a series of sensitivity analyses to test the robustness of the DRM findings, the rationale for which is summarized in detail in [Supplementary Table S1](#), and briefly described here. We tested for interactions of the origin weight with age, sex, and mobility status in the DRMs

Table 1. Sample Characteristics According to Origin and Destination Social Class Position and Intergenerational Social Class Mobility

	Included (<i>n</i> = 3,987)		Excluded (<i>n</i> = 4,186)	
	<i>n</i>	%	<i>n</i>	%
Age (mean, <i>SD</i>)	61.8	8.3	65.8	10.7
Female	2,134	53.5	2,296	54.9
Allostatic Load Index (mean, <i>SD</i>)	0.0	1.0	—	—
Childhood health				
Excellent	2,249	56.4	2,194	52.4
Very good	1,009	25.3	1,187	28.4
Good	497	12.5	531	12.7
Fair	172	4.3	195	4.66
Poor	60	1.50	77	1.84
Origin socioeconomic position				
Professional/managerial	871	21.9	474	14.7
Non-manual/skilled manual	1,738	43.6	1,298	40.3
Semiskilled/unskilled/never worked	1,378	34.6	1,452	45.0
Destination socioeconomic position				
Professional/managerial	1,378	34.6	818	21.8
Non-manual/skilled manual	1,785	44.8	1,509	40.1
Semiskilled/unskilled/never worked	824	20.7	1,434	38.1
Social mobility trajectories				
Downwardly mobile	716	18.0	571	19.5
Non-mobile				
Stable professional/managerial	478	12.0	197	6.7
Stable non-manual/skilled manual	881	22.1	545	18.7
Stable semiskilled/unskilled/never worked	417	10.5	654	22.4
Upwardly mobile	1,495	37.5	956	32.7
Degree of intergenerational social mobility				
Upwardly mobile 1 position	84	2.1	65	2.2
Upwardly mobile 2 positions	632	15.9	506	17.3
Downwardly mobile 1 position	1,129	28.3	786	26.9
Downwardly mobile 2 positions	366	9.2	170	5.8

Note: *SD* = standard deviation.

(Supplementary Table S3), but none of the interaction terms were statistically significant at conventional levels, suggesting that origin plays a similar role for AL burden across the life course, for the two sexes, and for those who experience mobility in their lives. To examine whether particular physiological systems were driving the observed associations and to enable comparison with previous studies, a series of separate DRM models was estimated across each of the subsystems comprising the AL composite score (i.e., cardiovascular, immune, renal, metabolic). Destination SEP exerted more influence than origin on later-life dysregulation across all systems (Supplementary Table S4).

Parameter estimates from DRMs estimating intergenerational mobility effects on a clinically derived AL index are reported in Supplementary Table S5. This alternate index was generated by summing the number of high-risk biomarkers using clinical-risk cut-points and standardizing the overall index (Supplementary Table S2). This measure incorporated medication usage in the AL score by manually scoring a biomarker as high risk if individual is taking a doctor diagnosed medication as ascertained at time of

interview. Comparison of estimates with Table 3 revealed little difference, although the weights for origin were larger in magnitude when using this alternative AL index.

Educational attainment was introduced as an alternative measure of SEP to examine whether results were dependent on the socioeconomic measure used in the analysis (Bulczak et al., 2021). Results were ostensibly similar, although the weights for destination were slightly larger in magnitude when examining education over occupational in Table 3 (Supplementary Table S6). Additionally, to assess the robustness of the 3-level SEP measure, parallel analyses were undertaken using a five-level measure (i.e., professional/managerial, non-manual, skilled manual/semiskilled, unskilled, never worked; Supplementary Table S7). On this occasion, a significant negative association was observed for each step upward from origin, suggesting that results may be sensitive to the manner in which social class groups are aggregated.

To allow a more accurate comparison to results from *Understanding Society* (Präg & Richards, 2019) and to allay suspicion that the choice of biomarkers used to

Table 2. Conditional Means for Allostatic Load Resulting From the Cross-classification of Origin and Destination Social Class Position

	Destination		
	Professional/managerial	Non-manual/skilled manual	Semiskilled/unskilled/never worked
Origin	<i>Conditional mean</i>	<i>Conditional mean</i>	<i>Conditional mean</i>
Professional/Managerial	-0.10	-0.01 (DM)	0.08 (DM)
Non-manual/skilled manual	-0.11 (UM)	0.06	0.10 (DM)
Semiskilled/unskilled/never worked	0.03 (UM)	0.18 (UM)	0.23

Notes: Adjusting for age, sex and childhood self-reported health. DM = downwardly mobile; UM = upwardly mobile. Diagonal cells reference the socially non-mobile.

generate the AL index were responsible for the different pattern of results observed between studies, an alternate measure of AL was constructed using a sum of standardized biomarkers comparable to the *Understanding Society* measure (systolic blood pressure, diastolic blood pressure, resting heart rate, waist circumference, BMI, triglycerides, total cholesterol, high-density lipoprotein, HbA1c, C-reactive protein—missing fibrinogen). Destination SEP continued to exert approximately three times the influence of origin SEP on later-life AL, and no significant associations of mobility trajectories with AL are reported (Supplementary Table S8).

To examine whether results were biased due to unmeasured confounding, additional contemporaneous sociodemographic and behavioral health variables potentially associated with both social mobility and AL burden were adjusted for in Supplementary Table S10. These included the Berkman-Syme social network index (0–4, higher values indicate higher social connectedness, derived from marital status, sociability (number and frequency of contacts with children, close relatives, and close friends); church group membership and membership in other community organizations; Berkman and Syme, 1979). Behavioral health variables included smoking status (never smoked, former smoker, current smoker), alcohol consumption frequency, and physical activity (low, moderate, high), measured using the international physical activity questionnaire (IPAQ; Craig et al., 2003). The weights for destination were larger in magnitude with the inclusion of these contemporaneous variables, and there was no association of social mobility with AL burden.

Finally, we test the robustness of our findings by taking a conservative approach to the missing biomarker data. This alternate index was generated by summing the number of high-risk biomarkers based on the 75th percentile of risk based on the sample distribution and standardizing the overall index. Participants who attended the health assessment but who were missing on <7/12 of the biomarkers were manually coded as not at risk. Supplementary Table S11 illustrates that destination SEP continued to predominate over origin SEP in terms of AL burden, and no significant associations of mobility trajectories with AL are reported.

Linear Models

The OLS models reveal a social gradient in AL burden according to both origin (Table 4A) and destination (Table 4B) class. The mutually adjusted model (Table 4C) reveals that destination mediates a substantial proportion of the effect of origin on AL burden. We examined whether the effects of origin and destination social class on AL burden were additive or multiplicative by fitting a origin × destination interaction term, but none of the individual contrasts nor the overall interaction term were significant [$F(4, 3972) = 0.61$; $p = .656$]. This result suggests that the linear combination of origin and destination social class is sufficient to describe the effects of life-course social class position on AL burden in later life. This is consistent with what we observe when we examine the conditional mean AL score for the upwardly and downwardly mobile compared with those who remained intergenerationally stable in their class position in OLS models. Figure 1 shows that the upwardly mobile ($M = -0.05$) rank intermediate between the stable professional/managerial class ($M = -0.17$) and the stable non-manual/skilled manual class ($M = 0.01$), while the downwardly mobile ($M = 0.06$) rank intermediate between the stable non-manual/skilled manual class ($M = 0.01$) and the stable semiskilled/unskilled class ($M = 0.24$).

Discussion

This study sought to examine the association of intergenerational social mobility with AL burden at midlife and older ages using a methodological technique—DRMs—that has been underutilized in public health research despite its obvious advantages relative to alternative approaches such as mutual adjustment (Green & Popham, 2019), or differentiating groups based on combinations of their origin and destination social class positions (van der Waal et al., 2017). In line with previous studies using this technique (Gugushvili et al., 2021; Präg & Richards, 2019), we observed a pronounced social gradient in AL burden among the socially immobile. The professional/managerial group had the lowest burden of AL, while the unskilled/never worked group had the highest burden of AL, with the semiskilled/non-manual group intermediate between

Table 3. Parameter Estimates From Diagonal Reference Models Estimating Mobility Effects on Allostatic Load Burden

	Base model			Upward mobility			Downward mobility			Upward steps			Downward steps		
	<i>b</i>	95% CI		<i>b</i>	95% CI		<i>b</i>	95% CI		<i>b</i>	95% CI		<i>b</i>	95% CI	
Constant	1.14***	(1.05, 1.24)		1.16***	(1.05, 1.26)		1.14***	(1.04, 1.24)		1.15***	(1.05, 1.26)		1.14***	(1.04, 1.24)	
Socially immobile															
Professional/managerial	-0.19***	(-0.24, -0.14)		-0.19***	(-0.24, -0.13)		-0.19***	(-0.24, -0.14)		-0.19***	(-0.24, -0.13)		-0.19***	(-0.24, -0.14)	
Non-manual/skilled manual	-0.00	(-0.05, 0.04)		-0.01	(-0.06, 0.04)		-0.00	(-0.05, 0.04)		-0.00	(-0.07, 0.07)		-0.00	(-0.05, 0.04)	
Semiskilled/unskilled/never worked	0.19***	(0.13, 0.25)		0.20***	(0.14, 0.25)		0.19***	(0.13, 0.25)		0.19***	(0.13, 0.26)		0.19***	(0.13, 0.25)	
Controls															
Female	-0.74***	(-0.80, -0.68)		-0.74***	(-0.80, -0.68)		-0.74***	(-0.80, -0.68)		-0.74***	(-0.79, -0.68)		-0.74***	(-0.79, -0.68)	
Age*	0.03***	(0.03, 0.03)		0.03***	(0.03, 0.03)		0.03***	(0.03, 0.03)		0.03***	(0.03, 0.03)		0.03***	(0.03, 0.03)	
Childhood health															
Excellent	Ref			Ref			Ref			Ref			Ref		
Very good	0.01	(-0.06, 0.07)		0.01	(-0.06, 0.07)		0.01	(-0.06, 0.07)		0.01	(-0.06, 0.07)		0.01	(-0.06, 0.07)	
Good	0.03	(-0.06, 0.11)		0.03	(-0.06, 0.11)		0.03	(-0.06, 0.11)		0.03	(-0.06, 0.11)		0.03	(-0.06, 0.11)	
Fair	-0.03	(-0.17, 0.10)		-0.03	(-0.17, 0.10)		-0.03	(-0.17, 0.10)		-0.03	(-0.17, 0.10)		-0.03	(-0.17, 0.10)	
Poor	0.21	(-0.02, 0.44)		0.21	(-0.02, 0.44)		0.21	(-0.02, 0.44)		0.21	(-0.02, 0.44)		0.21	(-0.02, 0.44)	
Weights															
Origin	0.26**	(0.08, 0.43)		0.37*	(0.06, 0.69)		0.25*	(0.01, 0.49)		0.33	(-0.15, 0.80)		0.24*	(0.00, 0.49)	
Destination	0.74***	(0.57, 0.92)		0.63***	(0.31, 0.94)		0.73***	(0.51, 0.99)		0.67**	(0.20, 1.15)		0.76***	(0.51, 1.00)	
Mobility status															
Upward				-0.05	(-0.16, 0.06)		-0.01	(-0.11, 0.10)							
One step upward															
Two steps upward										-0.04	(-0.17, 0.09)				
Downward										-0.02	(-0.28, 0.25)				
One step downward													-0.00	(-0.11, 0.10)	
Two steps downward													-0.03	(-0.25, 0.20)	
AIC	10,392.8			10,394.1			10,394.8			10,396.1			10,396.8		
BIC	10,462.0			10,469.6			10,470.3			10,477.8			10,478.5		
Degrees of freedom	11			12			12			13			13		

Notes: AIC = Akaike information criteria. BIC = Bayesian information criteria. 95% Confidence intervals in brackets. Age is centered around the sample mean.

* $p < .05$, ** $p < .01$, *** $p < .001$.

the two. We found significant weights of both origin and destination SEP with AL burden, indicating independent influences from both life stages on later-life physiological dysregulation. However, the relative importance of destination SEP on AL burden predominated, as approximately three times as much variance in AL burden was explained by destination compared with origin class. Social mobility was not associated with AL burden when accounting for SEP at both time points. The model fit statistics confirmed that the base model, that is, the one containing no mobility effects, provided the best fit to the data. A finding which implies that the linear combination of origin and destination is sufficient to characterize the impact of differing intergenerational social class trajectories on later-life physiological dysregulation. This interpretation is supported by the lack of a significant interaction between origin and destination in the OLS models.

The higher weights for destination compared with origin class in the DRMs, the absence of mobility effects, the stronger associations of destination compared with origin in the OLS models, and the fact that the upwardly and downwardly mobile have AL burden intermediate between their class of origin and class of destination in OLS are all consistent with an accumulation model of social inequalities in AL burden and the concept of “gradient constraint” (Blane et al., 1999). Gradient constraint refers to a process of assortment whereby social mobility moderates rather than creates or amplifies, the size of the social class differential (Blane et al. 1999). The central idea is that mobile individuals rank somewhere intermediate between the class they left and the class they join as they share characteristics in common with both. The fact that the downwardly mobile have higher AL burden than the upwardly mobile may simply reflect the greater number of years spent at a more disadvantaged level relative to class of origin, although they are still in better health than those stable at less advantaged social class positions across the span. Consistent with this interpretation, [Supplementary Table S9](#) shows that the health-related characteristics of

the upwardly mobile is comparable to those in the stable managerial/professional groups, while the health profile of the downwardly mobile is more akin to those stable at less advantaged social class positions. These mobile individuals appear to adopt characteristics of their destination group, yet carry some of the legacy of origin, which serves to dilute the destination effect.

Relation to Other Studies

Our results are consistent with the extant literature documenting that individuals of less advantaged SEP experience higher AL burden (Johnson et al., 2017). Findings from the UK Household Longitudinal Study, *Understanding Society* (Präg & Richards, 2019) found approximately equal influence from both origin and destination on later-life AL burden. This equal influence is echoed by recent results from the National Longitudinal Study of Adolescent Health (Add Health) of the United States (Gugushvili et al., 2021), although a significant and positive mobility effect was reported in this study for those who experienced upward movement from origin. Our study however, found that a higher weight was afforded to destination SEP. These disparate findings between studies regarding whether origin or destination holds more influence in determining later-life AL provoke the obvious question as to why these differences arise, as methodological disparities cannot be held responsible for inconsistencies in results across studies in this case, as all studies utilized DRM. Alternate explanations will therefore be addressed in turn, including (a) differences in biomarker composition between studies, (b) differences in cohort characteristics, (c) differences in class schema, and (d) varying patterns of social mobility.

Differences in biomarker composition

One of the longstanding criticisms of allostatic load as a concept is that there is no standard definition of the measure (Johnson et al., 2017; Juster et al., 2010) and investigators have tended to use the battery of biomarkers that are

Table 4. Independent and Mutually Adjusted Associations of Origin and Destination Social Class With Allostatic Load Burden

	Panel A		Panel B		Panel C	
	<i>b</i>	95% CI	<i>B</i>	95% CI	<i>b</i>	95% CI
Origin class						
Professional/managerial	Ref		—		Ref	
Non-manual/skilled manual	0.04	(−0.03, 0.11)	—		−0.01	(−0.08, 0.07)
Semiskilled/unskilled/never worked	0.15***	(0.08, 0.23)	—		0.08*	(0.01, 0.16)
Destination class						
Professional/managerial	—		Ref		Ref	
Non-manual/skilled manual	—		0.16***	(0.10, 0.23)	0.16***	(0.10, 0.22)
Semiskilled/unskilled/never worked	—		0.30***	(0.22, 0.38)	0.28***	(0.20, 0.36)

Notes: All models adjust for age, sex and childhood self-reported health. (A) The association of origin class with allostatic load. (B) The association of destination class with allostatic load. (C) Mutually adjusted associations of origin and destination class with allostatic load.

* $p < .05$, ** $p < .01$, *** $p < .001$.

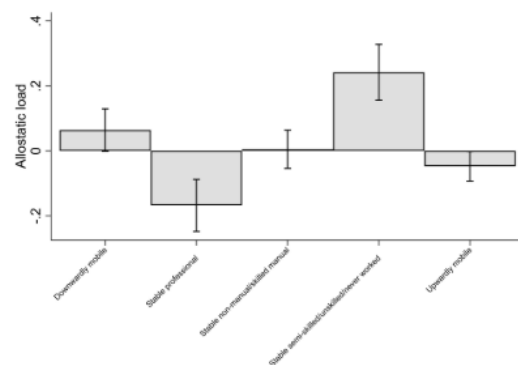


Figure 1. Conditional means for allostatic load according to intergenerational social class trajectory, adjusting for age, sex, and childhood health.

available to them in any given study to construct the index. Could the differences that we have observed regarding the relative weight to be afforded to origin as opposed to destination be due to the differing composition of the AL index between studies? This seems unlikely given the substantial overlap in the biomarkers used to define AL, with TILDA sharing 9/12 biomarkers in common with *Understanding Society*. Nevertheless, to address this possibility, we compared results for allostatic load subsystems—cardiovascular, metabolic, glucose—for which we substantially or entirely overlapped, and found that destination continued to predominate in terms of influence on later-life AL in the present study (Supplementary Table S8). Nonetheless, the lack of consensus remains a challenge with AL research, and this must be addressed to facilitate direct comparisons of results across studies and to advance the field.

Differences in sample composition

Another possibility is that the disparity in the relative weights afforded to origin and destination across studies arise due to differences in cohort characteristics. The mean age of the TILDA sample is 61.8 years, whereas *Understanding Society* and *Add Health* participants have a considerably younger age profile with a mean of 52.6 and 29 years, respectively. Allostatic load is posited to represent a measure of cumulative physiological dysregulation, so it may well be the case that the relative weights to be attached to origin and destination shift in balance over the life course as participants age (Steiber, 2019).

Differences in class schema

Of course, it is entirely tenable that differences in results may arise due to the use of different occupational coding schemas. The present study uses the Irish Central Statistic's Office (CSO) occupational social class schema which is comparable to the British Registrar General's Social Class (RGSC). This schema assumes a linear ranking

of occupations according to skill, whereas Prag and Richard (2019) use the National Statistics-Socioeconomic Classification (NS-SEC), which focuses more on the relational aspects of class, operationalizing a nonlinear social class on the basis of employment relations and conditions (Szreter, 1984). Despite these differences, it should be acknowledged that both studies documented a pronounced social gradient in AL among the socially immobile, so contrasts in the occupational coding are an unlikely explanation for the differences in the relative weight to be afforded to origin as opposed to destination observed between studies. Moreover, rates of mobility have been compared using both classification schemes using English census data and observed strong correspondence between the two measures (Bartley & Plewis, 2007).

Different levels of social mobility

The final consideration is different levels of social mobility across countries. We acknowledged previously that Ireland experienced tremendous structural mobility over the last 50 years with over half of the cohort experiencing mobility across generations. Given that the direction of mobility was predominantly in the upward direction, it is entirely plausible that the extent of structural mobility dwarves relative mobility, making it more difficult to isolate pure mobility effects on physiological dysregulation. Indeed, it has been alleged that the upgrading of Ireland's class structure in the latter half of the 20th century masked a persistent and deepening problem of blocked relative mobility (Kirtby, 2002). The same accusation could be leveled against using intergenerational educational transitions as our measure of mobility as Ireland introduced two educational reform acts during this period, with the 1967 Act introducing free-secondary level schooling for all children, and the 1972 act introducing an additional year of schooling (Callan & Harmon, 1999). This means that later-born cohorts have more education than earlier born cohorts due to a structural policy change, not necessarily mobility effects per se. An alternative possibility is that the stronger origin effects observed in *Understanding Society* reflect an older and more ingrained class system. It may also represent a cohort or period effect, as Bartley and Plewis (2007) acknowledge that the relative importance of father's social class on a person's destination has become more pronounced in the UK over recent decades. Future research should endeavor to compare results with more diverse populations, to provide insight into the potential impact of varying social mobility patterns.

Strengths and Limitations

The study has several strengths, including the use of objective biological data from an Irish sample of midlife and older adults, who grew up in an era of great social and economic change that enabled a large proportion of the population to climb the social ladder. We have already touted the

advantage of DRMs over alternative approaches such as mutual adjustment or comparing different mobility groups as they allow one to isolate pure mobility effects and allow one to parameterize the relative importance of origin and destination class regarding their impact on health.

The primary limitation of the current study is that the analyses are cross-sectional, and causal relationships cannot be assessed. Indeed, any causal effect of intergenerational social mobility would be difficult to establish, as there is no counterfactual understanding of mobility effects (Wei & Xie, 2022). When comparing individuals with the same origin and destination SEP, mobility can only go in one direction, a world in which it would go into a different direction is not conceivable. While we can assess the impact of origin and destination SEP on AL, it is outside the remit of DRMs to assess more than two generations (Zang et al., 2022), and as such may not be sensitive to detecting subtle changes in the influence of origin and destination on physiological dysregulation at varying stages of the life course. It is of course possible that this study has underestimated levels of mobility, wherein individuals have been classed as socially immobile by virtue of ending up in the same class as their origin yet were mobile between these two very broad life stages. Misclassification of class categories could also be an issue as origin class was based on a retrospective report of father's occupation. On a similar note, there has been considerable debate about the extent to which a woman's own occupation is captured as a result of traditional parental responsibilities (Bartley & Plewis, 2007).

Conclusion

Tracing the imprint of disadvantage offers a powerful tool to comprehend histories of vulnerability, and thus to inform policy on health inequalities (Prior et al., 2018). These results imply that moving up or down the social ladder does not directly influence AL burden, although individuals tend to adopt similar AL burden to those in the socioeconomic position of their destination. This does not refute the possible lasting impact of origin SEP on later-life health but offers promise that interventions channeling individuals out of early-life disadvantage to more advantageous socioeconomic circumstances may lead to a lessening of AL burden within a population.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences* online.

Funding

This work was supported by the Health Research Board (HRB) of Ireland under an Emerging Investigator Award

to C. McCrory (EIA-2017-012). TILDA was funded by Irish Life plc, the Irish Government, and the Atlantic Philanthropies. P. Präg was supported by the French National Research Agency (ANR), "Investissements d'Avenir" [LabEx Ecodec/ANR-11-LABX-0047].

Author Contributions

S. McLoughlin: conceptualization; methodology; data curation; formal analysis; writing—original draft; writing—reviewing and editing. P. Präg: writing—reviewing and editing. M. Bartley (PhD): writing—reviewing and editing. Rose Anne Kenny (MD): supervision; funding acquisition. C. McCrory: conceptualization; methodology; writing—reviewing and editing; supervision; funding acquisition. All authors had responsibility for accuracy of the final content and read and approved the final manuscript.

Acknowledgments

The authors would like to thank Dr. Caspar Kaiser for both the development of the "DRM" module in Stata, and for his helpful technical advice on its use.

Conflict of Interest

None declared.

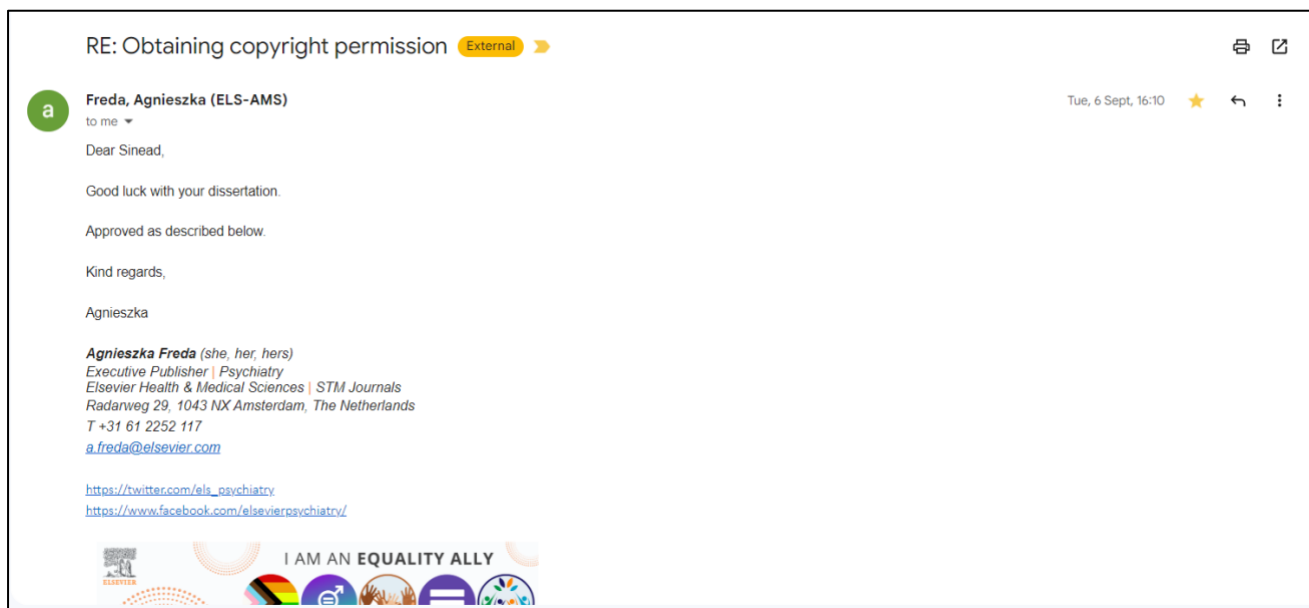
References

- Allen, A. M., Thomas, M. D., Michaels, E. K., Reeves, A. N., Okoye, U., Price, M. M., Hasson, R. E., Syme, S. L., & Chae, D. H. (2019). Racial discrimination, educational attainment, and biological dysregulation among midlife African American women. *Psychoneuroendocrinology*, 99, 225–235. doi:10.1016/j.psyneuen.2018.09.001
- Bartley, M., & Plewis, I. (2007). Increasing social mobility: An effective policy to reduce health inequalities. *Journal of the Royal Statistical Society. Series A: Statistics in Society*, 170(2), 469–481. doi:10.1111/j.1467-985X.2006.00464.x
- Ben-Shlomo, Y., & Kuh, D. (2002). A life course approach to chronic disease epidemiology: Conceptual models, empirical challenges and interdisciplinary perspectives. *International Journal of Epidemiology*, 31(2), 285–293. doi:10.1093/ije/31.2.285
- Berkman, L. F., & Syme, S. L. (1979). Social networks, host resistance, and mortality: A nine year follow up study of Alameda county residents. *American Journal of Epidemiology*, 109(2), 186–204. doi:10.1093/oxfordjournals.aje.a112674
- Billingsley, S., Drefahl, S., & Ghilagaber, G. (2018). An application of diagonal reference models and time-varying covariates in social mobility research on mortality and fertility. *Social Science Research*, 75, 73–82. doi:10.1016/j.ssresearch.2018.06.008
- Blane, D., Harding, S., & Rosato, M. (1999). Does social mobility affect the size of the socioeconomic mortality differential? Evidence from the Office for National Statistics Longitudinal Study. *Journal of the Royal Statistical Society. Series A: Statistics in Society*, 162(1), 59–70. doi:10.1111/1467-985X.00121

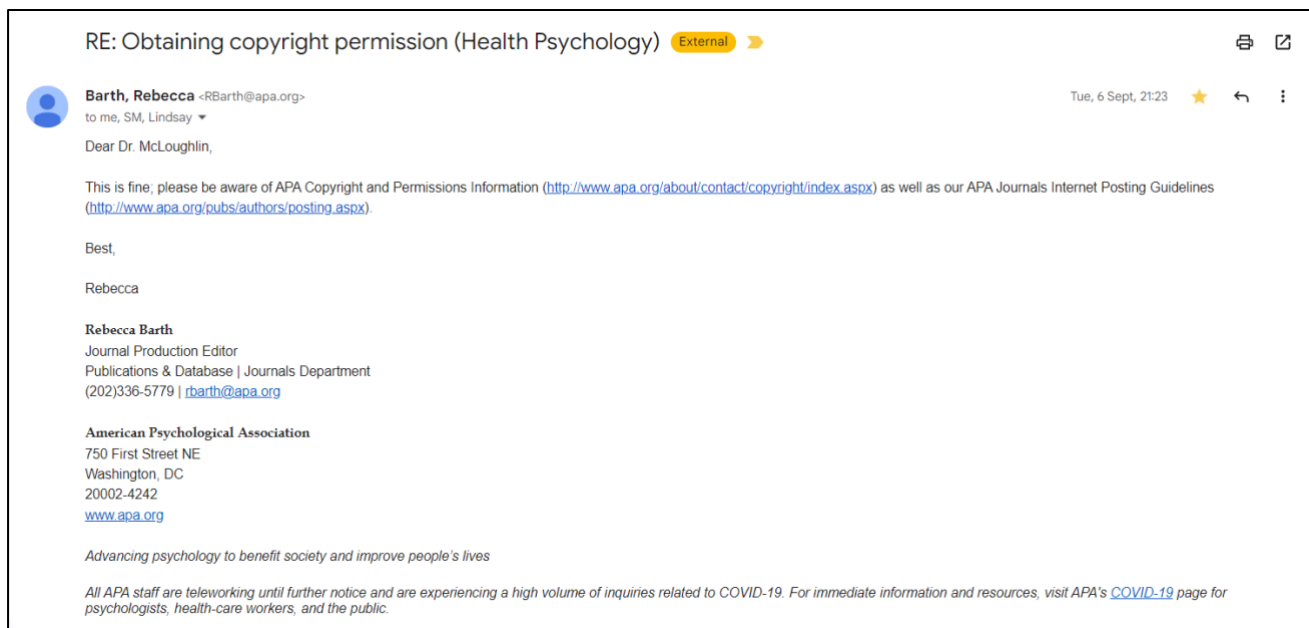
- Blau, P. M. (1956). Social mobility and interpersonal relations. *American Sociological Review*, 21(3), 290–295. doi:10.2307/2089282
- Bulczak, G., Gugushvili, A., & Zelinska, O. (2021). How are social origin, destination and mobility linked to physical, mental, and self-rated health? Evidence from the United States. *Quality and Quantity*, 56, 3555–4585. doi:10.1007/s11135-021-01286-5
- Callan, T., & Harmon, C. (1999). The economic return to schooling in Ireland. *Labour Economics*, 6(4), 543–550. doi:10.1016/S0927-5371(99)00035-4
- Craig, C. L., Marshall, A. L., Sjostrom, M., Bauman, A. E., Booth, M. L., Ainsworth, B. E., Pratt, M., Ekelund, U., Yngve, A., Sallis, J. F., & Oja, P. (2003). International physical activity questionnaire: 12-country reliability and validity. *Medicine & Science in Sports & Exercise*, 35(8), 1381–1395. doi:10.1249/01.MSS.0000078924.61453.Fb
- Galobardes, B., Lynch, J. W., & Davey Smith, G. (2004). Childhood socioeconomic circumstances and cause-specific mortality in adulthood: Systematic review and interpretation. *Epidemiologic Reviews*, 26, 7–21. doi:10.1093/epirev/mxh008
- Green, M. J., & Popham, F. (2019). Interpreting mutual adjustment for multiple indicators of socioeconomic position without committing mutual adjustment fallacies. *BMC Public Health*, 19(1), 1–7. doi:10.1186/s12889-018-6364-y
- Gruenewald, T. L., Karlamangla, A. S., Hu, P., Stein-Merkin, S., Crandall, C., Koretz, B., & Seeman, T. E. (2012). History of socioeconomic disadvantage and allostatic load in later life. *Social Science & Medicine*, 74(1), 75–83. doi:10.1016/j.socscimed.2011.09.037
- Gugushvili, A., Bulczak, G., Zelinska, O., & Koltai, J. (2021). Socioeconomic position, social mobility, and health selection effects on allostatic load in the United States socioeconomic position, social mobility, and health selection effects on allostatic load in the United States. *PLoS One*, 16(8), 1–30. doi:10.1371/journal.pone.0254414
- Gugushvili, A., Zhao, Y., & Bukodi, E. (2019). “Falling from grace” and “rising from rags”: Intergenerational educational mobility and depressive symptoms. *Social Science & Medicine*, 222, 294–304. doi:10.1016/j.socscimed.2018.12.027
- Gustafsson, P. E., Janlert, U., Theorell, T., Westerlund, H., & Hammarstrom, A. (2011). Socioeconomic status over the life course and allostatic load in adulthood: Results from the Northern Swedish Cohort. *Journal of Epidemiology & Community Health*, 65(11), 986–992. doi:10.1136/jech.2010.108332
- Hallqvist, J., Lynch, J., Bartley, M., Lang, T., & Blane, D. (2004). Can we disentangle life course processes of accumulation, critical period and social mobility? An analysis of disadvantaged socio-economic positions and myocardial infarction in the Stockholm Heart Epidemiology Program. *Social Science & Medicine*, 58(8), 1555–1562. doi:10.1016/S0277-9536(03)00344-7
- Hickson, D. A., Diez Roux, A. V., Gebreab, S. Y., Wyatt, S. B., Dubbert, P. M., Sarpong, D. F., Sims, M., & Taylor, H. A. (2012). Social patterning of cumulative biological risk by education and income among African Americans. *American Journal of Public Health*, 102(7), 1362–1369. doi:10.2105/AJPH.2011.300444
- Iveson, M. H., & Deary, I. J. (2017). Intergenerational social mobility and subjective wellbeing in later life. *Social Science & Medicine*, 188(11), 20. doi:10.1016/j.socscimed.2017.06.038
- Johnson, S. C., Cavallaro, F. L., & Leon, D. A. (2017). A systematic review of allostatic load in relation to socioeconomic position: Poor fidelity and major inconsistencies in biomarkers employed. *Social Science & Medicine*, 192, 66–73. doi:10.1016/j.socscimed.2017.09.025
- Juster, R. P., McEwen, B. S., & Lupien, S. J. (2010). Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neuroscience & Biobehavioral Reviews*, 35(1), 2–16. doi:10.1016/j.neubiorev.2009.10.002
- Kaiser, C. (2018). *DRM diagonal reference model stata*. Open Science Framework. doi:10.17605/OSF.IO/KFDP6
- Kirtby, P. (2002). *Celtic tiger in distress: Growth and inequality in Ireland*. Palgrave International Political Economy.
- Kubzansky, L. D., Kawachi, I., & Sparrow, D. (1999). Socioeconomic status, hostility, and risk factor clustering in the Normative Aging Study: Any help from the concept of allostatic load?. *Annals of Behavioural Medicine*, 21(4), 330–338. doi:10.1007/bf02895966
- Luo, Y., & Waite, L. J. (2005). The impact of childhood and adult SES on physical, mental, and cognitive well-being in later life. *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences*, 60(2). doi:10.1093/geronb/60.2.S93
- Matthews, K. A., & Gallo, L. C. (2011). Psychological perspectives on pathways linking socioeconomic status and physical health. *Annual Review of Psychology*, 62, 501–530. doi:10.1146/annurev.psych.031809.130711
- McEwen, B. (1998). Protective and damaging effects of stress mediators. *The New England Journal of Medicine*, 338(3), 171–179. doi:10.1056/NEJM199801153380307
- McLoughlin, S., Kenny, R. A., & McCrory, C. (2020). Does the choice of allostatic load scoring algorithm matter for predicting age-related health outcomes?. *Psychoneuroendocrinology*, 120, 104789. doi:10.1016/j.psyneuen.2020.104789
- Merkin, S. S., Karlamangla, A., Roux, A. V., Shrager, S., & Seeman, T. E. (2014). Life course socioeconomic status and longitudinal accumulation of allostatic load in adulthood: Multi-ethnic study of atherosclerosis. *American Journal of Public Health*, 104(4), e48–e55. doi:10.2105/ajph.2013.301841
- Miller, G. E., Chen, E., & Parker, K. J. (2011). Psychological stress in childhood and susceptibility to the chronic diseases of aging: Moving toward a model of behavioral and biological mechanisms. *Psychological Bulletin*, 137(6), 959–997. doi:10.1037/a0024768
- Newman, K. S. (1999). *Falling from grace: Downward mobility in the age of affluence* (Vol. 319). University of California Press.
- Ó Gráda, C., & O'Rourke, K. H. (2022). The Irish economy during the century after partition. *Economic History Review*, 75(2), 336–370. doi:10.1111/ehr.13106
- Präg, P., Fritsch, N. -S., & Richards, L. (2022). Intragenerational social mobility and well-being in Great Britain: A biomarker approach. *Social Forces*. doi:10.1093/sf/soab153
- Präg, P., & Richards, L. (2019). Intergenerational social mobility and allostatic load in Great Britain. *Journal of Epidemiology & Community Health*, 73, 100–105. doi:10.1136/jech-2017-210171
- Prior, L., Manley, D., & Jones, K. (2018). Stressed out? An investigation of whether allostatic load mediates associations between neighbourhood deprivation and health. *Health & Place*, 52, 25–33. doi:10.1016/j.healthplace.2018.05.003

- Pudrovska, T., & Anikputa, B. (2014). Early-life socioeconomic status and mortality in later life: An integration of four life-course mechanisms. *The Journals of Gerontology: Series B: Psychological Sciences and Social Sciences*, 69(3), 451–460. doi:10.1093/geronb/gbt122
- Robertson, T., Popham, F., & Benzeval, M. (2014). Socioeconomic position across the lifecourse & allostatic load: Data from the West of Scotland Twenty-07 cohort study. *BMC Public Health*, 14(1), 184. doi:10.1186/1471-2458-14-184
- Seeman, T. E., Merkin, S. S., Crimmins, E., Koretz, B., Charette, S., & Karlamangla, A. (2008). Education, income and ethnic differences in cumulative biological risk profiles in a national sample of US adults: NHANES III (1988–1994). *Social Science & Medicine*, 66(1), 72–87. doi:10.1016/j.socscimed.2007.08.027
- Shuey, K. M., & Willson, A. E. (2014). Economic hardship in childhood and adult health trajectories: An alternative approach to investigating life-course processes. *Advances in Life Course Research*, 22, 49–61. doi:10.1016/j.alcr.2014.05.001
- Snyder-mackler, N., Burger, J. R., Gaydos, L., Daniel, W., Noppert, G. A., Campos, F. A., Yang, Y. C., Aiello, A. E., Harris, K. M., Shively, C. A., Alberts, S. C., Biology, E., Columbia, N. B., Hill, C., Antonio, S., & Hill, C. (2020). Social determinants of health and survival in humans and other animals. *Science*, 368(6493), 37–39. doi:10.1126/science.aax9553. Social
- Sobel, M. E. (1981). Diagonal mobility models: A substantively motivated class of designs for the analysis of mobility effects. *American Sociological Review*, 46(6), 893–906. doi:10.2307/2095086
- Sorokin, P. A. (1927). *Social mobility*. Free Press.
- Sorokin, P. A. (1959). *Social and cultural mobility*. Free Press.
- StataCorp. (2017). *Stata Statistical Software: Release 15*. StataCorp LLC.
- Steiber, N. (2019). Intergenerational educational mobility and health satisfaction across the life course: Does the long arm of childhood conditions only become visible later in life? *Social Science & Medicine*, 242, 112603. doi:10.1016/j.socscimed.2019.112603
- Szreter, S. R. S. (1984). The genesis of the registrar-general's social classification of occupations, *The British Journal of Sociology*, 35(4), 522–546. doi:10.2307/590433
- van der Waal, J., Daenekindt, S., & de Koster, W. (2017). Statistical challenges in modelling the health consequences of social mobility: The need for diagonal reference models. *International Journal of Public Health Volume*, 62(9), 1029–1037. doi:10.1007/s00038-017-1018-x
- Wei, L., & Xie, Y. (2022). Social mobility as causal intervention. *SocArXiv*, 1–72. doi:10.31235/osf.io/zcg4x
- Whelan, B. J., & Savva, G. M. (2013). Design and methodology of the Irish Longitudinal Study on Ageing. *Journal of the American Geriatrics Society*, 61(Suppl. 2), S265–S268. doi:10.1111/jgs.12199
- Whelan, C. T., & Layte, R. (2002). Late industrialization and the increased merit selection hypothesis: Ireland as a test case. *European Sociological Review*, 18(1), 35–50+i. doi:10.1093/esr/18.1.35
- Whelan, C. T., & Layte, R. (2004). Economic change, social mobility and meritocracy: Reflections on the Irish experience. In *Quarterly Economic Commentary* (Vol. 3, pp. 89–108). ESRI.
- Whelan, C. T., & Layte, R. (2006). Economic boom and social mobility: The Irish experience. *Research in Social Stratification and Mobility*, 24(2), 193–208. doi:10.1016/j.rssm.2005.05.001
- Zang, E., Sobel, M. E., & Lying, L. (2022). The mobility effects hypothesis: Past, present, and future. *SocArXiv*, 06520. doi:10.31235/osf.io/d782b

Appendix 5: Copyright permission from Psychoneuroendocrinology



Appendix 6: Copyright permission from Health Psychology



Appendix 7: Copyright permission from Journals of Gerontology: Series B

RE: Obtaining copyright permission

External

Inbox x

🖨️ 📧



📧 **The Journal of Gerontology: Social Sciences**

to me, The, JAKI19@case.edu

Thu, 15 Sept, 19:38 (13 days ago)

☆ ↩️ ⋮

This is the response I got from our publisher:

No, when it comes to their own dissertations, we pretty much let authors do whatever they want. She doesn't need any special permission to publish her article in her dissertation.

Kathleen Jackson
Gerontological Society of America
Managing Editor, Journals of Gerontology
202-587-2824 | geron.org
   

Register now for the GSA 2022 [Annual Scientific Meeting](#) November 2-6 in Indianapolis, IN.