The Association between Socioeconomic Position and Biomarkers in Older Adults: Compensating for Missing Data

A thesis submitted to the University of Manchester for the degree of Doctor of Philosophy in the Faculty of Humanities

2019

GEORGIA CHATZI

School of Social Sciences – Department of Social Statistics

Table of Contents

Word count: 48,185

List of Tables

List of Figures

Abstract

High levels of inflammatory and stress-related biomarkers have been linked with several health conditions in older adults. Living in socioeconomic disadvantage may affect the levels of the biomarkers, however, previous findings are not consistent. Previous studies have used complete case analysis and ignored the high proportion of missing biomarker data in biosocial surveys. Longitudinal studies examining ageing populations are susceptible to attrition and non-random dropout and ignoring missing data can produce biased estimates due to selection processes and loss of precision.

This thesis investigated socioeconomic differences in inflammatory biomarker C-reactive protein and stress-related biomarkers cortisol and cortisone after compensating for missing data. The English Longitudinal Study of Ageing (ELSA) was used for the analyses. Complete case analyses were compared with methods considering random missingness: Inverse Probability Weighting, Full Information Maximum Likelihood, and Multiple Imputation, and non-random missingness: Diggle-Kenward and Pattern-Mixture approaches.

Differences between the least and most disadvantaged categories of education, wealth, and social class in C-reactive protein and cortisol and cortisone levels existed after adjusting for covariates. C-reactive protein levels were higher in the inverse probability weighting and multiple imputation models compared to complete case models in cross-sectional analysis. In longitudinal analysis, the C-reactive protein levels were higher in the Diggle-Kenward model compared to the other models considering random and non-random missingness. Socioeconomic differences in cortisol and cortisone levels were greater in the inverse probability weighting and multiple imputation models compared to the complete case models.

The conclusions drawn suggest that living in socioeconomic disadvantage was a significant predictor of higher levels of inflammatory and stress-related biomarkers and that complete case analyses may underestimate the socioeconomic differences in biomarkers compared to missing data approaches. This study demonstrates the importance of compensating for missingness in longitudinal biosocial studies for statistical inference.

Declaration

I, Georgia Chatzi, declare that no portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning

Copyright statement

1. The author of this thesis (including any appendices and/or schedules to this thesis) owns certain copyright or related rights in it (the "Copyright") and s/he has given The University of Manchester certain rights to use such Copyright, including for administrative purposes.
2. Copies of this thesis, either in full or in extracts and whether in hard or electronic copy, may be made **only** in accordance with the Copyright, Designs and Patents Act 1988 (as amended) and regulations issued under it or, where appropriate, in accordance with licensing agreements which the University has from time to time. This page must form part of any such copies made.
3. The ownership of certain Copyright, patents, designs, trademarks and other intellectual property (the "Intellectual Property") and any reproductions of copyright works in the thesis, for example graphs and tables ("Reproductions"), which may be described in this thesis, may not be owned by the author and may be owned by third parties. Such Intellectual Property and Reproductions cannot and must not be made available for use without the prior written permission of the owner(s) of the relevant Intellectual Property and/or Reproductions.
4. Further information on the conditions under which disclosure, publication and commercialisation of this thesis, the Copyright and any Intellectual Property

and/or Reproductions described in it may take place is available in the University IP Policy), in any relevant Thesis restriction declarations deposited in the University Library, The University Library's regulations (see http://www.library.manchester.ac.uk/about/regulations/) and in The University's policy on Presentation of Theses.

Summary of Empirical Studies

The empirical work of this thesis includes three different journal articles referred to as Chapters which are prepared to be submitted for publication.

Chapter 4 with the title “Socioeconomic position effects on inflammation in older adults: compensating for missing data” is an article prepared to be submitted to the journal of “Brain, Behavior, and Immunity”.

Chapter 5 with the title “Is social disadvantage a chronic stressor? Socioeconomic position effects on cortisol and cortisone: compensating for missing data” is an article prepared to be submitted to the journal of “Psychoneuroendocrinology”.

Chapter 6 with the title “Is the increase in social inequalities in inflammation underestimated in conventional longitudinal analyses? Socioeconomic position and repeated systemic inflammation: compensating for missing data” is an article prepared to be submitted to the “European Journal of Epidemiology”.

I am the lead author of all three articles and I am responsible for forming the research questions, conducting the statistical analyses and writing of the articles. My supervisors are listed in recognition of their contribution to the articles. My supervisors contributed to the development of the ideas and provided valuable guidance on the analyses and the interpretation of the results through the normal supervision process.

Acknowledgements

First and foremost, I would like to express my deepest gratitude to my PhD supervisors Professor Natalie Shlomo, Professor Tarani Chandola and Dr Alexandru Cernat for their support and encouragement over the past years. I will be forever grateful for giving me the opportunity to learn and grow under your guidance!

I would like to thank my internal reviewers Professor Joseph Sakshaug and Dr Tina Hannemann for their constructive feedback during the mid-year and annual reviews. I would like to extent my sincere and heartfelt obligation towards Dr Stuart Shields, for the long and helpful conversations we had about the world of academia and how to survive in it.

I extent my gratitude to the Economic and Social Research Council (ESRC) for providing funding to support my research (grant number ES/J500094/1) and also, I would like to thank the National Centre for Research Methods (NCRM) for making me feel that I am part of their team and for the free training! I would like to thank my colleagues from the department of Social Statistics for the co-operation and encouragement the past years. Particularly, I would like to thank Angelo, Jen, Rihab, Adrian, Bo, Yizhang, Sixten, and Jose.

For this great gift, I have to thank my family without whose help and support none of this would have been possible. Stavros, your love and support have been invaluable. Maria & Yiannis, thank you for letting me sleep on your couch in London while I was writing my research proposal. Uncle Dionysis and aunt Maria, your support all these years has been precious to me. Brother Yiannis, hope I can convince you someday to come and visit. Mum Kondelia and Dad Philopoemen, thank you for everything. This achievement is dedicated to you. Dad, it’s been 9 years and I miss you.

CHAPTER 1. Introduction

1.1 Importance of biosocial research from the life course perspective

Poor living conditions have been linked to poorer health. People's physical and mental health vary in society and that this calls for an approach to explain how social and biological components jointly cause specific health outcomes (Brunner, 2000). Biosocial research sets the foundation for implementing theoretical frameworks and pathways that could explain differences in morbidity and mortality rates in diseases affected by social conditions (Wilkinson & Marmot, 2003).

Later mortality and low morbidity and disability rates in socioeconomically advantaged people are observed in health studies; replicating the connection between social circumstances and disease (Syme & Berkman, 1976). Studies' findings showed evidence describing an association between undernutrition and infection sensitivity due to poor social conditions (McKeown, 1979) and not until the end of the 20th century were there stronger and consistent findings which suggested that a smaller gap between affluent and poor people is associated with greater life expectancy in populations (Wilkinson, 1996). However, a clear explanation had not been established until then. First Barker et al (1992), highlighted a primary link between poor development in utero and later chronic disease and later Kuh and Ben-Shlomo (1997) produced a secondary link to early life circumstances and adult chronic disease and developed the life course approach emphasizing the importance of early and later social and environmental influences on biological procedures.

According to the World Health Organisation the major cause of morbidity and mortality worldwide in recent decades is cardiovascular disease (CVD) affecting low and middle-income countries more than high-income ones as the population ages

(WHO, 2010). Extensive progress has been made in recent years to explore the influence of socioeconomic position (SEP) on CVD (Galobardes, 2006a; González, Artalejo, & Calero, 1998) following the association with biomarkers which indicate CVD (Loucks et al., 2010; Pollitt et al., 2008; Stringhini et al., 2013) and confirming the importance of understanding the biological procedures.

One way to investigate CVD is by using inflammatory biomarkers, since inflammation contributes to different stages in the pathogenesis of CVD and the lifelong procedure of atherogenesis causing different ischaemic outcomes (Libby, 2002; Lowe & Pepys, 2006). C-reactive protein (CRP) is an inflammatory biomarker widely collected in clinical practises from blood samples and is easily examined by standardised laboratory assays, and broadly examined in studies (Danesh et a., 2009; Pepys & Hirschfield, 2003). Stress-related biomarker cortisol activates the hypothalamic pituitary axis (HPA-axis) of the stress response system and has been found to be associated with CVD in several studies (Bhattacharyya et al., 2008; Merswolken, et al., 2013; Nijm et al., 2007; Reynolds et al., 2010). Cortisol can be converted into inactive cortisone, and examining both biomarkers may give a better insight into the cumulative amount of corticosteroids in the human body (Steward and Mason, 1995; Stalder et al., 2013; Staufenbiel et al., 2015).

Biomarker data from inflammatory and stress-related biomarkers are collected and processed in accordance with the development of longitudinal studies which follow participants over time. These studies collect sociodemographic and health-related characteristics and biomarkers and allow for the comprehensive investigation of the social effects on biological mechanisms.

1.2 The challenge of missing data in biosocial research

In biosocial research, longitudinal studies involving multiple waves of measurement and different data collections on the same individuals face a great challenge of missing data. Different reasons lead participants to drop out of the study or fail to answer questions in the questionnaire. Consequently, analyses that do not take into consideration missing values often lead to biased estimates of both model parameters and standard errors and may result in drawing misleading conclusions for the target population. Missing data in longitudinal studies unbalances the dataset over time due to the lack of repeated measurements from the same individuals. The missingness spreads in a dispersed manner over many subjects and along with the correlation of missing values and observed data leads to a loss of precision in the studies. Furthermore, a loss of data from participants with specific characteristics could lead to over or under-representation of sub-populations in the studies; making assumptions and estimating results for only a part of the population and not a representative sample of the study population.

This thesis will investigate how socioeconomic position influences the levels of inflammatory biomarker C-reactive protein and the stress-related biomarkers cortisol and cortisone and aims to fill the gap in the current knowledge related to suitable procedures and mechanisms used in biosocial research to account for missing biomarker data.

1.3 Structure of the Thesis

Chapter 2 provides a review of the existing literature focused on the association of socioeconomic position and inflammatory and stress-related biomarkers. It also gives

a brief summary of the characteristics of non-participants and reasons for non-participation in surveys. Furthermore, I define and describe comprehensively types of missing data, missing data mechanisms and the methods that have been used from other studies and have been mentioned in the literature for compensating for missing data. Chapter 3 introduces the data, presents the variables of interest and reviews the statistical methods used in this thesis.

Chapters 4, 5, and 6 are three stand-alone papers. Chapter 4 addresses three research questions and hypotheses examining the association between socioeconomic position and inflammatory biomarker C-reactive protein using data from wave 2 of the English Longitudinal Study of Ageing (ELSA). Furthermore, Chapter 4 gives a brief summary of the literature on the subject, information on the study population, and details on the statistical methods that compensate for missing data. Chapter 5 addresses four research questions and hypotheses examining the association between socioeconomic position and stress-related biomarkers cortisol and cortisone, using data from wave 6 of ELSA. Chapter 5 provides a brief summary of the literature on the subject, information on the study population, and details on the statistical methods for handling for missing data. Chapter 6 addresses three research questions and hypotheses examining the association between socioeconomic position and repeated measurements of inflammatory biomarker C-reactive protein using data from waves 2, 4, 6, and 8 of ELSA. Furthermore, Chapter 6 gives a brief summary of the literature on the subject, information on the study population, and details in the statistical methods handling for missing data.

Chapter 7 gives a summary of the main findings from the different statistical models presented in Chapters 4, 5, and 6 and addresses the overall aims of the thesis alongside answering the research questions. In addition, conclusions are drawn from the

different missing data approaches. Comparisons of the findings of this thesis with findings in the literature are also described. Furthermore, Chapter 7 provides insight into the implications, strengths and limitations of this thesis and discusses future research.

CHAPTER 2. Literature review and Methods Overview

In the first part of this chapter the existing literature on the association between socioeconomic position and inflammatory biomarker C-reactive protein and stress-related biomarkers cortisol and cortisone, is reviewed. The second part of this chapter describes the characteristics of participants who drop-out or refuse to participate in studies. The third part of this chapter refers to the identification and the mechanisms of missing data and the methods used to compensate for missing data.

2.1 Socioeconomic position effects on biomarkers of health in adulthood

Psychosocial well-being and health are affected by lifestyle and behavioural factors as well as a number of socioeconomic factors such as differences in material standards of living, inequity in access to health resources, and position in the social hierarchy. Discrepancies in exposure to social stressors may also play significant role in constructing the socioeconomic gradient in health (Elo, 2009; Lynch et al., 1994; Lynch et al., 2000; Pearlin et al., 2005)

Social inequalities in health vary during the life course. Studies suggest that socioeconomic differences in health narrow in adolescence and become wider in early adulthood (Diaz, 2002; West, 1997). Some studies suggest that social inequalities converge in later life (Bassuk et a., 2002; Beckett, 2000; Huisman et al., 2003; Knesebeck et al., 2007; Willson et al., 2007) while others suggest that inequalities in health become even wider at older ages (Acciai, 2018; Chandola et al., 2007; Sacker et al., 2005; Schöllgen, et al., 2010).

There is a broad literature examining socioeconomic inequalities in health using a great variety of biomarkers to define "health". This thesis explores social inequalities in the levels of inflammatory biomarker C-reactive protein and stress-related biomarkers cortisol and cortisone which have been linked with cardiovascular disease.

2.1.1 Socioeconomic position measurements

There are numerous ways to describe the measures of socioeconomic position (SEP) commonly used in health research and this demonstrates the complexity of the construct. "Social class", "social stratification", "social or socioeconomic status" are among the terms that have been used widely and interchangeably in the literature to describe socioeconomic position, although each term has different theoretical backgrounds and frameworks (Galobardes et al., 2006a). According to Krieger et al (1997), socioeconomic position describes the social and economic factors that can influence someone's position in the structure of society (Krieger et al., 1997).

Each socioeconomic position indicator describes different aspects of socioeconomic characteristics and can be related to different health outcomes and in different time periods of life; preferably multiple socioeconomic position indicators should be described across the life course in order to avoid residual confounding (Lawlor et al., 2004).

Among the most common socioeconomic position indicators are occupational based measures and wealth. Parental occupation or own adult occupation is significantly related to income and reflects social standing. In terms of health outcomes, this may imply particular advantages, such as better access to health care, education and material living standards in general. Moreover, occupation may reflect social networking or possible exposure to toxic environment that could influence certain

health outcomes (Galobardes et al., 2006a). However, wealth as a socioeconomic position indicator adds more information compared to income by including value of housing, cars, investments, and inheritance or pension rights. An important asset of using wealth as a socioeconomic position indicator is that it may change over the life course and it could be different among different ethnicity subgroups (Galobardes et al., 2006b). Educational level is another socioeconomic position indicator which is broadly used in the literature. It captures the transition from the family socioeconomic position to the adulthood socioeconomic position because it can determine future employment and income (Smith et al., 2000; Lynch & Kaplan, 2000). Education can have an effect on a person's cognitive functioning, resulting in a different reaction to health education messages and accessing to appropriate health services. It can be measurable in terms of "cultural literacy" and its role assessed in the association between education and health (Kaufman, 2002; Kelleher, 2002).

2.1.2 Biomarkers: definition and importance

Biomarkers can be described as "an element that is measured and evaluated as an indicator of biological or pathogenic processes" (Biomarkers Definitions Working, 2001) and it is a portmanteau of "biological marker", an objective indication of a certain medical state observed outside the patient (Strimbu & Tavel, 2010). The National Institute of Health Biomarkers Definitions Working Group defined "biomarker" as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention". The International Programme on Chemical Safety, led by the World Health Organisation defined biomarker as "any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease" (Organization & Safety, 2001). Examples

of biomarkers could be pulse and blood pressure to more complex laboratory tests of blood and tissue tests. Biomarkers are the most objective and quantifiable medical sign measured reproducibly (Strimbu & Tavel, 2010).

2.1.2.1 High-sensitivity C-reactive Protein (CRP)

C-reactive protein (CRP) is produced by the liver and cells within human coronary arteries, in the atherosclerotic intima. However, it remains controversial whether C-reactive protein simply marks inflammatory risks or has a direct role in the atherothrombotic process (Biomarkers Definitions Working, 2001). The United States Food and Drug Administration set C-reactive protein amongst the biomarkers for the use in cardiovascular risk evaluation and management (Dadu et al., 2012).

2.1.2.2 Cortisol and cortisone

Cortisol is a stress-related biomarker, broadly used in clinical and population-based studies. Cortisol has a pronounced diurnal rhythm and a short circulating half-life results in fluctuating levels of cortisol from blood samples. The measurement of cortisol from a single blood sample is an unreliable measure of chronic HPA axis activity. Instead, HPA axis status is often assessed using salivary cortisol in a number of large-scale, population-based studies, even though there are considerable issues with the sample processing and laboratory analyses of salivary cortisol (Adam & Kumari, 2009). In recent years, cortisol measured in hair samples has been increasingly employed in large population studies, partly in response to the methodological issues in processing and analysing saliva samples. Hair cortisol is believed to provide a summated measure of overall activity of the HPA axis over several weeks/months. This avoids the moment-to-moment fluctuations in blood and saliva cortisol and the drawbacks in sample collection for salivary measurements (Russell et al., 2012; Stalder & Kirschbaum, 2012). Cortisone is a metabolite of

cortisol and on some occasions, cortisol is converted into inactive cortisone by 11 beta hydroxysteroid dehydrogenase type 2. The analysis of hair cortisone in parallel to hair cortisol may provide greater insights into the amount of active and inactive corticosteroids in the body. Therefore, it is suggested to be explored together in clinical and population studies.

2.1.3 Socioeconomic position and inflammatory biomarkers

The association between socioeconomic position and levels of inflammatory biomarkers has been well-established in the literature, however, findings are not consistent and these discrepancies into findings could be related with the heterogeneity of the study populations, the use of different socioeconomic position variables to define social inequalities, and the large number of missing biomarker data in studies.

In a cross-sectional study of 19,759 people from the National Health Examination and Nutrition Survey (NHANES) it was shown that C-reactive protein levels were elevated among those with lower educational attainment and income and, also, there was a marginal trend of higher fibrinogen levels, an inflammatory biomarker which is usually tested alongside C-reactive protein, among those with lower income and education. Adults with higher educational attainment [OR=0.81(95%CI 0.67-0.97)] and with higher family income [OR=0.79(95%CI 0.67-0.93)] had lower levels of C-reactive protein compared to low educated and low-income families after controlling for potential confounders of the association. Findings from complete case analyses showed inverse association between education and family income and C-reactive protein but there was no association between SEP and fibrinogen levels. Out of 19,759 participants, 71.6% (14,015 participants) had C-reactive protein data and only 26% (5,087 participants) had fibrinogen data. The large amount of missing values could explain the different findings between the two inflammatory biomarkers in relation to

socioeconomic characteristics. Methods to address missing biomarker data were not implemented (Muennig et al., 2007).

In another study of 3,266 participants from the CARDIA (Coronary Artery Risk Development in Young Adults) study of people aged 35-55 years old and it was found that C-reactive protein levels were inversely associated with education and income level in white males [OR=1.22, $p < 0.05$ and OR=1.32, $p < 0.005$, respectively] and only with education in black females [OR=1.32,$p < 0.05$] (Gruenewald et al., 2009). Missing data in covariates (below 2.5%) were imputed by using sample mean or modes. Similar findings that produced an inverse association between occupational, education and inflammation were not consistent in middle aged Blacks compared to Whites. Missing values in education (16%) were imputed using Multiple Imputation, a well-known method to compensate for missing data when the data are assumed to be missing at random. Any missing values in the outcome variable of C-reactive protein were excluded (Pollitt et al., 2007).

A recent study examined 6,412 people from Switzerland (CoLaus) and 1,205 participants from Portugal (EPIPorto). In the CoLaus study, it was found that C-reactive protein levels were higher among those with lower education [OR=1.20(CI% 1.02-1.40)] and lower occupational position [OR=1.30 (95%CI 1.06-1.60)] after accounting for covariates. However, results were not consistent in the population from Portugal, where it was found that education [OR=1.25(95%CI 0.85-1.83) and occupation [OR=1.13(95%CI 0.80-1.60) had no effect on C-reactive protein levels (Fraga et al., 2015). Response rates of the study and missing values on biomarker data were not reported.

Findings that low education and income were linked to high inflammatory biomarkers were similar to other studies which were controlling for different covariates such as acute and chronic conditions (Alley et al., 2006), adiposity (Owen et al., 2003) and in another study which examined the association of subjective social status and C-reactive protein levels after controlling for several socioeconomic status measures (Demakakos et al., 2008). However, all the studies used cross-sectional data and none of them comprehensively reported the amount of missing data or mention any missing data handling technique in the analyses that could make results more valid.

A study used data from the Perinatal Mortality Survey (PMS) from 1958 and with a follow up at 44-45 years of age of the participants found a negative association between social class and fibrinogen. Participants lacking of information adult social class were excluded (17 out of 9,377 participants) and when examined for main effects, social class was treated as an ordinal variable while when examined as a confounding factor it was treated as a nominal categorical variable with a separate category for missing information in order to minimise attrition in mutually adjusted models. Moreover, when information about certain independent variables was unavailable, information from previous waves was used. For example, the socioeconomic position in childhood was based on father occupation in 1958 or 1965 if the data was unavailable (n=422) and if own social class when participant was 42 years old, then they used data when participant was 33 years old (n=1142). Otherwise, complete case analysis was implemented (Power et al., 2007).

A study found that parental occupation (early SEP) and own education (young adult) is predictive of early adulthood C-reactive protein and there was an association with adult C-reactive protein levels (Kivimaki et al., 2005; Loucks et al., 2010). There were similar findings for C-reactive protein using data from the population-based

Cardiovascular Risk in Young Finns Study but only for own education and not for own occupational class (Gimeno et al., 2008).

Loucks et al., (2010), used three socioeconomic position (SEP) frameworks to explain the life course approach. The study used an accumulation of risk, a social mobility and sensitive periods framework (illustrated below) and concluded that cumulative SEP was inversely associated with C-reactive protein, low socioeconomic position in both childhood and adulthood was associated with higher C-reactive protein levels and own education in young age was inverse associated with C-reactive protein in adulthood.

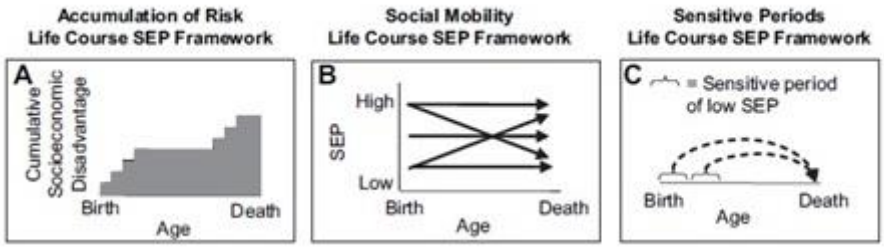


Figure 2. 1 Conceptual Frameworks for three different frameworks to conceptualize socioeconomic position (SEP) across the life course: (A) Accumulations of Risk (B) Social Mobility and (C) Sensitive Periods. (Loucks et al, 2010)

Another study indicated that increased "exposure" to adverse socioeconomic position across life course was leading to higher levels of inflammatory biomarkers (C-reactive protein and fibrinogen) in adulthood, emphasizing on the cumulative life course model. Multivariable analyses including only respondents with complete data on all variables was implemented (Tabassum et al., 2008). Findings from the 1892 Pelotas Birth Cohort study in Brazil showed that men with higher family income at birth and women with less educated mothers had higher C-reactive protein levels (Nazmi et al., 2010). While in another study was found that poorer quality housing conditions at

birth, which could be a proxy measurement for socioeconomic position, was an independent predictor of lower plasma fibrinogen (Pearce et al., 2012).

Similar findings had a study which examined the association between socioeconomic position and C-reactive protein in the Coronary Artery Risk Development in Young Adults (CARDIA) with longitudinal data and handled missing data on predictors (baseline household income and education) and standard covariates (household size for income adjustment) by substituting analogous values from the preceding CARDIA exam from a previous wave conducted two years prior (Deverts et al., 2012).

A study using data from Whitehall II showed that cumulative exposure to low socioeconomic status (SES) from childhood to middle age was related to higher C-reactive protein in adulthood. In this study, a complete case analysis has been shown to be not efficient and an imputation procedure to replace missing values on health behaviours and inflammatory biomarkers was used. Missing values in health behaviours were replaced by using information from previous waves while for biomarkers used multivariate imputation based on different covariates. Main exposure and outcome variables (Type-2 diabetes) missing values were not imputed but they used sensitivity analyses instead (Stringhini et al., 2013). Another study using data from the Atherosclerosis Risk in Communities (ARIC) examined the association of the cumulative life course and adult SES with inflammation. It was found that the increasing cumulative life course exposure to lower SES conditions for all SES measures was associated with elevated levels of adult inflammatory biomarkers. This study used multiple imputation to address the issue of missing data in the explanatory variables (Pollitt et al., 2008).

Another study using data from the UK Household Longitudinal Study (UKHLS) used a sample of adults over 25 and found that socioeconomic inequalities in C-reactive protein emerge in adults in their 30's, increase up to mid-50's and early 60's and then inequalities begin to narrow and finally converge at older ages (75 onwards). Out of 7,943 participants in the analyses, only 26.5% (n=2,106) were participants over 65 years of age. Although, survey weights have been used to account for differential non-response, mortality selection was not accounted (Davillas et al., 2017). Therefore, associations at older ages might be biased.

A very recent study using data from 4,932 participants from the English Longitudinal Study of Ageing (ELSA) and C-reactive protein biomarker data from waves 2, 4 and 6, concluded that participants with higher educational qualification ($\beta = -0.036$, $p < 0.01$) had lower C-reactive protein levels compared to those with lower educational achievements and wealthy participants had significantly lower levels of C-reactive protein ($b=-0.133$, $p<0.01$) compared to those in less wealthy categories. This study used generalised linear mixed models and joint models to compensate for missing data and account for non-random attrition. The first part of the joint model is a linear mixed model and the second part is a survival model with age, time, time squared, and random intercept. The study found no significant differences in the coefficient estimates between these two methods (Maharani, 2019).

2.1.4 Socioeconomic position and stress-related biomarkers

Living in socioeconomic disadvantage has often been conceptualised in terms of a chronic stressor that results in dysregulation of stress-responsive physiological systems such as the sympathetic nervous system and HPA axis. The HPA axis is responsible for the neuroendocrine adaptation component of the stress response to stressors, resulting in the release of cortisol several hours after encountering the

stressor. The HPA axis has an important role in social-environmental experience and physiological responses such as increased secretion of stress hormones like cortisol which may have long-term impacts on health. However, the empirical evidences linking socioeconomic position and cortisol are not consistent (Dowd et al., 2009).

However, contrary to conceptualisation of socioeconomic disadvantage as a chronic stressor, a number of studies have reported null or no significant associations with socioeconomic position (Abell et al., 2016; Bosma et al., 2015; Braig et al., 2015; Chen et al., 2013; Karlén et al., 2015; Karlén et al., 2013; O'Brien et al., 2013; Pulopulos et al., 2014; Staufenbiel et al., 2015; Vaghri et al., 2013).

In the Ulm Spatz Health Study in Germany with a small number of participants collected (n=768), it was found that lower levels of education were not related to higher levels of hair cortisol among pregnant women, however the participation rate in the study was only 49% (Braig et al., 2015). Similar results were found in a study in China examining 103 adult volunteers in China, in this study age and education were not significant determinants of higher levels of cortisol and cortisone (Chen et al., 2013). In the Netherlands Study of Depression and Anxiety (NESDA) from 760 men and women, it was found that education level was not a significant predictor of higher level of cortisol after adjusting for several confounders (Staufenbiel et al., 2015).

Earnings below the minimum wage was associated with higher levels of hair cortisol among adult volunteers in Kenya (Henley et al., 2014) similarly lower income levels and adverse changes in income were related to higher levels of hair cortisol (Serwinski et al., 2016). However, lower employment grade among London based civil servants (Abell et al., 2016) and lower objective socioeconomic status (SES) among US adults

(O'Brien et al., 2013) and lower subjective SES among Spanish adults (Pulopulos et al., 2014) were not associated with hair cortisol. The association between occupational grade and hair cortisol was actually in the reverse direction (lower cortisol among lower grade employees) in the unadjusted analyses among London civil servants (Abell et al., 2016).

The reasons for the discrepancy into findings in relation to SEP and hair cortisol are not clear. They could be related to methodological issues of the studies. Opportunistic samples (O'Brien et al., 2013) and a lack of information on the sampling frame (Chen et al., 2013), small study samples (100 participants or fewer) all make it harder to generalise to the wider population (Bosma et al., 2015; Karlén et al., 2013; Pulopulos et al., 2014; Vaghri et al., 2013) . Many studies did not report response rates from their sampling frame (Serwinski et al., 2016) or reported a very low response or participation rates (Boesch et al., 2015; Bosma et al., 2015; Karlén et al., 2015; Pulopulos et al., 2014; Staufenbiel et al., 2015; Vaghri et al., 2013) without analysing if unit non-response could have biased their reported associations. Some studies on adults used education as the measure of socioeconomic position, even though they were analysing adults in mid-life or older (Braig et al., 2015; Chen et al., 2013; Schreier et al., 2016; Staufenbiel et al., 2015) when education may not be the best indicator of SEP.

2.1.5 Methodological issues of the findings on socioeconomic position and biomarkers and methods of handling missing data

This section summarises the findings of studies assessing the association of socioeconomic position and biomarkers and whether a method of missing data was implemented to compensate for missing values. Most of the studies did not use any method of handling missing data and used complete case analysis, providing with

possible invalid results and biased estimates. Some studies used multiple imputation (MI) method for handling missing data (Pollitt et al., 2007;2008) while only one used sensitivity analysis to produce more accurate results (Stringhini et al., 2013). A study used survey weights to account for differential non-response (Davillas et al., 2017) and another one produced a missing data category and information from previous measurements to account for missing data (Power et al., 2007). Only one study used joint modelling to account for non-random dropout using longitudinal biomarker data (Maharani, 2019). However, in none of the previous studies was found a separate section describing the methodology followed for handling missing data.

2.2 Characteristics of non-participants in longitudinal surveys

Although longitudinal surveys provide plenty of information on interdisciplinary research, they are susceptible to attrition and drop-out from participants who fail to remain in the study in subsequent data or wave collections resulting in the loss of participant measurements. There is a growing body of research on survey methodology which focuses on the correlation between sample attrition and drop-out and specific characteristics of the participants (e.g. Gray et al., 1996; Hawkes & Plewis, 2006; Watson, 2003; Watson & Wooden, 2009). The reasons for attrition vary between individuals and can be due to refusal, non-consent, relocating, emigrating or attrition due to death. Certain demographic, socioeconomic and health-related characteristics are identified from non-respondent participants in surveys.

2.2.1 Gender

Almost all studies exploring survey attrition found that response rates were higher in women than in men. It was suggested that women spend more time at home compared to men and thus they were more reachable, however, even based on contact, men were less likely to participate in the surveys (Lepkowski & Couper, 2002; Nicoletti & Buck,

2003). Furthermore, a study exploring the interaction between characteristics found that unhealthy men were less likely to continue participating in surveys (Radler & Ryff, 2010).

2.2.2 Age

In general, younger and oldest participants were less likely to participate in surveys. Although, older participants were less mobile and more reachable compared to other age groups and there are studies that affirm with this (Gray et al., 1996; Lepkowski & Couper, 2002), findings from studies were not consistent. Previous studies reported that attrition increases at older ages (Becketti et al., 1988; Fitzgerald et al., 1998) and others reported the opposite (Hill & Willis, 2001), whereas yet others found unclear evidence to support any specific attrition propensity in any age group (Behr, et al., 2005; Nicoletti & Buck, 2003; Nicoletti & Peracchi, 2005). However, findings by Radler and Ryff (2010) suggested that unhealthy older people are less likely to participate in future data collection; highlighting the fact that there is an important interaction between age and health status while examining survey attrition (Radler & Ryff, 2010).

2.2.3 Ethnicity

In general, studies that focused on survey attrition between ethnic minority groups, found that people from ethnic minorities were less likely to continue in survey participation (Burkam & Lee, 1998; Uhrig, 2008; Zabel, 1998). A possible explanation could be the language barriers as in English speaking countries there were higher rates of survey nonresponse among non-English speakers (Burkam & Lee, 1998).

2.2.4 Marital status

Study findings suggested that single participants had a higher propensity to drop out compared to married ones (Gray et al., 1996; Uhrig, 2008). However, it is unclear whether this was due to the issue of lower contact rates or higher rates of refusal.

2.2.5 Housing tenure

Home ownership was associated with low attrition (Fitzgerald et al., 1998; Lepkowski & Couper, 2002; Watson, 2003; Zabel, 1998). A possible explanation of this association was the attachment to community services and activities (Gray et al., 1996; Lepkowski & Couper, 2002; Nicoletti & Peracchi, 2005).

2.2.6 Location

There were regional differences between rural and urban areas and survey response and attrition rates. Residents in large cities were less available and difficult to reach (Groves & Cooper, 1998) and had higher attrition rates in surveys (Burkam & Lee, 1998; Fitzgerald et al., 1998; Gray et al., 1996; Zabel, 1998) and a possible explanation was that social isolation in rural communities increased the cooperation rates.

2.2.7 Education

Study findings regarding the correlation between educational level and attrition propensity were consistent in the literature. Participants with higher educational achievements were more likely to appreciate the utility of research and therefore, remained in studies for longer periods (Behr et al., 2005; Fitzgerald et al., 1998; Gray et al., 1996; Lepkowski & Couper, 2002; Watson, 2003).

2.2.8 Income

Evidence on longitudinal surveys regarding income attrition probabilities were not consistent and response rates tended to be lower in participants with the lowest and

highest income levels. Some studies found that the magnitude of the estimated effects was small and found no evidence of a significant relationship (Gray et al., 1996; Lepkowski & Couper, 2002; Nicoletti & Peracchi, 2005; Zabel, 1998).

2.2.9 Employment status

Unemployed and economically inactive participants were easier to contact and hence had higher response rates compared to employed participants (Nicoletti & Peracchi, 2005; Watson & Wooden, 2009). However, in a study implementing country-specific analysis, findings similar to previous study results were reported for only 4 out of 14 countries included in the analysis. Other findings suggested that there was no evidence on significant differences between non-workers and workers on response rates (Fitzgerald et al., 1998; Zabel, 1998). Regarding attrition rates, findings suggested that lower attrition rates were found among workers (Gray et al., 1996; Lepkowski & Couper, 2002). Findings by Nicoletti and Buck (2003) reported higher cooperation propensity from economically inactive people but, on the other hand, lower contact probabilities for unemployed and economically inactive participants.

2.2.10 Health status

Evidence from a study exploring the social and health determinants of non-response in health surveys suggested that participants with poorer health had higher attrition rates compared to participants with better health (May et al., 2012). Consistent findings from other studies showed that the onset of long term conditions can decrease contactability and move people from their home in pursuit of care (Groves & Cooper, 1998; Jones et al., 2006). Furthermore, the onset of health conditions or transient health conditions can have an important effect on the willingness of participants to participate even if they are at home (Groves & Cooper, 1998). Overall, it was found that participants who were not satisfied with their health were less likely to participate

in subsequent measurements (Lepkowski & Couper, 2002). Similarly, Jones et al (2006), suggested that participants who reported poor health in Wave 1 of the British Household Panel Study (BHPS) were less likely to respond in later waves. Furthermore in the same study, it was found that participants with disabilities were less likely to continue participating in the surveys although, participants with self-reported disability had no differences in survey cooperation in relation to other healthier participants.

2.3 Introduction of missing data in studies

2.3.1 Identification of missing data

In survey analysis missing data occur for different reasons and significantly affect the validity of the results. Missing survey data can be classified by different types and patterns while for every type and pattern there is a different statistical method to compensate for missing data (Brick & Kalton, 1996; Groves et al., 2009).

Types of missing data

The most common type of missing data is total or *unit non-response* and it occurs when survey data were not collected for an element (person) in a sample (e.g. figure 2.2[1]). Refusals to take part in a survey, non-contacts and several other reasons such as language barriers, or being too ill to participate on the study contribute to total or unit non-response.

[1] "X" denotes observed value and "." denotes missing value

ID	Y_1	Y_2	Y_3	Y_4
1	X	X	X	X
2	.	.	.	.
3	X	X	X	X
4	X	X	X	X
5	X	X	X	X

Figure 2. 2 Unit non-response

Another type of missing survey data is *item non-response*; when participants fail to provide information for one or more survey items (e.g. figure 2.3[1]). It occurs when participants refuse to answer a question either because it is too sensitive, or inconsistent with other answers or even when the participant does not know the answer and the interviewers have not recorded the answer.

ID	Y_1	Y_2	Y_3	Y_4
1	X	.	X	X
2	.	X	X	X
3	X	.	X	.
4	X	X	X	X
5	X	X	X	X

Figure 2. 3 Item non-response

Missing data patterns

There are many examples of missing data patterns mentioned in several manuscripts (e.g. Little & Rubin, 2002), however, only the monotonic and intermittent missingness pattern will be further described. *Monotonic missingness* is often called *attrition* in longitudinal surveys and occurs when subjects drop out prior to the end of the study and do not return (e.g. figure 2.4[2], where $Y_{1\text{-}5}$ are different measurements). For

[2] "X" denotes observed value and "." denotes missing value

instance, participants may never return to the study either because they moved out of the country or were hospitalised; sometimes participants drop-out for unknown reasons while some other times the main reason is attrition due to death.

Y_1	Y_2	Y_3	Y_4	Y_5
x	x	x	x	x
x	x	x	x	.
x	x	x	.	.
x	x	.	.	.
x	.	.	.	.

Figure 2. 4 Monotonic missingness

Intermittent or *wave non-response* missingness occurs when participants fail to complete the interview, do not provide information for one or more waves of a panel study or when a respondent in a multiphase survey provides information for only some phases of data collection. The distinction between monotonic and intermittent missingness is that in the latter participants can return to the study and leave again at will (e.g. figure 2.5[2], where $Y_{1\text{-}5}$ are different measurements).

Y_1	Y_2	Y_3	Y_4	Y_5
x	x	x	x	x
x	.	x	x	x
x	x	x	.	.
x	x	.	.	x
x	x	x	x	.

Figure 2. 5 Intermittent missingness

[2] "X" denotes observed value and "." denotes missing value

Missing by non-coverage

Another reason for missing data occurs when elements in the population are not included in the survey's sampling frame in the first place; the missing survey data are described as "non-coverage" hence they have no chance of being selected for the sample which is under-represented. Therefore, a proportion of the study population is not represented in the sample and findings from analyses may be biased.

2.3.2 Missing data mechanisms

Rubin (1976) first described three missing data mechanisms to make assumptions about the dependence of missingness with observed and unobserved variables. Missing data mechanisms are highly important when selecting the analysis method. The different assumptions of missingness:

Missing Completely at Random (MCAR): Data are considered Missing Completely at Random when the probability of missingness is unrelated to the set of observed responses and to the values of the target unobserved variables. Equation 2.1 describes the response model under MCAR as a function of the data where R is a missing data indicator (R=1 for response and, and 0 otherwise) and ϕ is a parameter that describes the relationship between R and the data. Figure 2.6 gives a conceptualised example of the MCAR mechanism:

$$p(R|\phi) \quad (2.1)$$

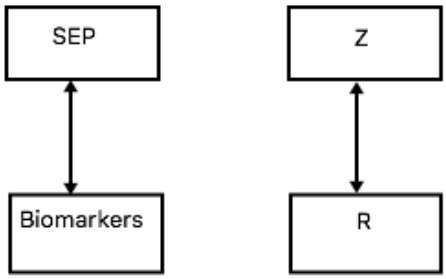


Figure 2. 6 Description of Rubin's MCAR missing data mechanism where SEP variables are completely observed for all participants and biomarkers may have some missing data. R is the missing data indicator and Z defines other measured variables. In this situation there is possible association between Z and R but not linkage with SEP and biomarkers.

Missing at Random (MAR): Data are considered Missing at Random when the probability of missingness depends on the set of observed responses but is unrelated to the values of the target unobserved variables. In example equation 2.2 Y_{obs} defines the observed parts of the data.

$$p\,(R|Y_{obs},\phi) \quad (2.2)$$

The distinction between MCAR and MAR is that missingness in MCAR, the response is independent of observed and unobserved data but in MAR the missing data is dependent on the observed data. Therefore, the analysis under MCAR can include only observed data and the unobserved data can be ignored. Figure 2.7 shows a conceptualised example of the MAR mechanism:

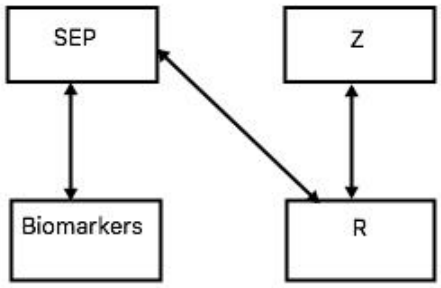


Figure 2. 7 Description of Rubin's MAR missing data mechanism where an arrow between R and SEP could describe a direct association and explain that the response may be dependent on people's SEP measurement but is independent of the missing biomarker data.

Missing Not at Random (MNAR): Data are considered Missing Not at Random when the probability of missingness depends on both the set of observed responses and the unobserved target variables. In equation 2.3 Y_{mis} defines the missing parts of the data.

$$P(R|Y_{obs}, Y_{mis}, \phi) \quad (2.3)$$

The probability of missing data is related to the values that should have been obtained. MNAR are also referred to as non-ignorable missingness. The term referred to the fact that missing data mechanisms should not and cannot be ignored. In non-ignorable missingness, future unobserved responses cannot be predicted therefore, a model for the missingness mechanism is needed. Contrary, MCAR and MAR are considered ignorable mechanisms. Figure 2.8 shows a conceptualised example of MNAR mechanism:

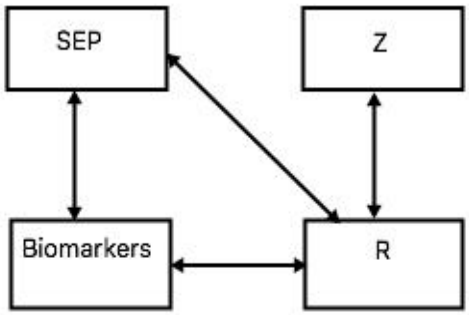


Figure 2. 8 Description of Rubin's MNAR missing data mechanism. Arrows between R and SEP and R and biomarkers explain that the probability of missing data is related to both SEP and biomarkers.

2.4 Types of methods for dealing with missing data

Little & Rubin (2002) divide the available methods that have been suggested for dealing with the issue of missing data into four categories: procedures based on completely recorded units, weighting procedures, imputation-based procedures, and model-based procedures. When considering the appropriate method of dealing with the missing data, types, patterns, and mechanisms must be taken into account to produce unbiased estimates and appropriate standard errors.

2.4.1 Procedures Based on Completely Recorded Units

The approach which is broadly used by researchers is to simply discard all cases with missing values at any measurement occasion. The approach is called Complete-Case Analysis (CCA) or Listwise Deletion (LWD) and no computational methods skills are needed. It is an ideal approach and it yields unbiased estimates only if the missingness is MCAR, otherwise the complete case could be unrepresentative for the full population. Discarding the cases with missing values could lead to substantial loss of important information over the target population and have a significant impact on reduced statistical precision and power. On some occasions if only a small part of the

sample is discarded then CCA it could be effective but in general, it is considered a problematic approach and is rarely acceptable for making reasonable assumptions.

2.4.2 Weighting Procedures (Inverse Probability Weighting)

Non-response weighting methods typically address unit-nonresponse in population-based surveys. Unit-nonresponse is an inevitable feature and by calculating survey weights that adjust the sample for potential non-response bias, the representativeness of the sample is achieved (Groves et al., 2001; Groves & Peytcheva, 2008; Little, & Rubin, 2002). Non-response weighting methods account for the participants' probability of responding and can be predicted based on information that is collected and available in the survey. In theory, each case will have a probability of responding, p. Under MCAR, it is assumed that the probability of response is equal for all participants and under MAR, it is assumed that the probability of response is equal within classes defined by the observed variables. If the response rate is low, the proportion of participants who do not respond is large and therefore under MAR, some sub-groups of the study population are not equally represented compared to the other sub-groups. In most studies, survey weights are assigned to each respondent of a survey in order to achieve unbiased estimated of parameters of the population of interest. Subsequently, it is essential, that under-represented subgroups can be accounted for given specific modelling.

Sample participants may have been selected unequal and have different probabilities of survey response. Furthermore, some participants may not be included as a sampling frame. The primary objective of weighting is to decrease bias in survey estimates by ensuring that the sample is representative to the population (Brick & Kalton, 1996).

Weighting typically increases the variances of the estimates (Kish, 1992) , however it is small price to pay to ensure that the estimates are not biased.

Survey weighting is performed in three stages. The first stage includes the production of base weights which account for the unequal probabilities of selecting participants from the sampling frame. The inverse of the probability of selecting a participant is called the design weight:

$$\Omega_i = \pi_{i-1} \quad (2.4)$$

where π_i is the probability of selecting a participant i for the sample

The second stage includes the adjustment of design weights of the respondents in order to compensate for those who were sampled but failed to respond to the survey. One way to compensate for missing data is called the weight class adjustment and it includes the separation of the sample respondents and non-respondents and categorising them into classes. Then, the inverse of the response rate is calculated in each class and multiplied by the design weight (Brick & Kalton, 1996). Individuals who do not respond are allocated a weight, $(1/p_i)$. The weight variable is calculated by dividing the inverse sampling probability of each individual in the sample by the mean of the inversed sample probabilities of all individuals in the sample (Höfler et al., 2005). It is important the non-response model be well specified and include characteristics which predict non-response.

The third stage is the method of post stratification to benchmark to known population totals typically include stratification by region, sex, and age groups. Post-stratification also adjusts further the weights of the respondents and aims to reduce bias due to incomplete coverage of the population of interest (Kalton & Kasprzyk, 1986).

2.4.3 Imputation Based Procedures

Imputation methods typically compensate for item-nonresponse which occurs when sample members refuse to answer a question (item) (Lessler & Kalsbeek, 1992). Imputation methods are procedures where each missing data value is substituted with a "filled-in" value, produced by statistical modelling. Then, following imputation, the complete dataset produced in the imputation procedure is examined with complete case methods. A variety of imputation methods exist in the literature. Imputation based procedures include single imputation and multiple imputation methods. Single imputation, such as last observation carried forward (LOCF) when analysing longitudinal data, mean imputation and hot-deck imputation are some of the single imputation methods that impute a single value for each missing item. However, the uncertainty in that value arising from the imputation model is ignored and the value is treated as a real value. This results in an underestimated uncertainty which makes the value of single imputation methods limiting. Multiple imputation methods impute multiple values for each item in order to create many complete datasets. Each value is imputed through a regression model. After this, each complete dataset is analysed and the estimates are combined according to formulae given by Rubin (1987). These methods are unbiased when data are MAR but under very specific circumstances when the imputation model is well defined by including variables which account for the selectivity of the missing data may be unbiased under MNAR (Allison, 2002; Schafer, 1997).

2.4.3.1 Single imputations

In the *single imputation* approach an incomplete observation is replaced by complete information only once. This replaced value can be obtained from a true value of an observed value or can be based on a prediction model. It is a common approach

because the analysis is easy and straightforward but methodologically may be invalid with respect to the variance estimates. One example of a single imputation approach in a longitudinal study is: *Last Observation Carried Forward* (LOCF), a well-known method of the single imputation approach. In this method, every missing value is substituted by the last observed value from the same subject. It is broadly used in pharmaceutical industry, in randomised parallel group trials and in biosocial longitudinal studies. In LOCF, it is assumed that the values of the outcome remain unchanged after missing which is unrealistic (Hedeker et al., 2007). Another approach is the *Mean Imputation* where any missing values are replaced with the mean value of the observed values. In this method, it is assumed that the mean of the variables is the appropriate estimate for any observation that has missing value in measurements but leads to the change of the variable distribution and increase complexity with the summary measures (underestimation of the standard deviation), thus it is not acceptable. Furthermore, this method requires the missing data to be MCAR. *Hot-deck imputation* is another single imputation method that replaces missing values with similar responding units in the sample (or within imputation classes in the sample) and increases some of the distortion of the variable distribution by choosing specific values to replace the missing values from the empirical distribution (Little & Rubin, 2002).

2.4.3.2 Multiple Imputation

Multiple Imputation (MI) is a general approach to the problem of missing data. It was first introduced in Rubin (1978) and (1987). In multiple imputation, every missing item is replaced by three or more acceptable values that represent a distribution of possibilities. This method produces valid inferences (such as standard errors and p-values) because the uncertainty of the missing values has been integrated. Multiple

imputation is highly efficient with a small number of imputations, particularly when the variance between imputations is not large (Rubin, 1987).

The imputation model

Multivariate imputation by chained equations (MICE) is a default method of imputing missing values using the STATA command *mi imputed* created by Raghunathan et al and Van Buuren (Raghunathan et al., 2001; van Buuren, 2007). Initially multiple imputation methods developed have assumed joint normal distribution for all the variables. MICE is a more flexible approach, where each variable with missing data is modelled conditionally upon the other variables in the data. For example, continuous variables have been modelled using linear regression and binary variables modelled using logistic regression etc. The chained equation processes include four steps which are presented with more details in Azur et al (2011). The first step includes a simple imputation of imputing the mean for every missing value in order to create a place holder. These "place holder" mean imputations are set back to missing and then these missing values are regressed on other variables in the imputation model. In the next step, the missing values are replaced with predictions from the regression models. These steps model a cycle. At the end of each imputation-cycle, every missing value has been replaced with predictions from the regression models. The number of imputation-cycles performed to impute the missing values are determined by the researchers. After the end of each imputation-cycle the final imputations are retained, resulting in several imputed datasets.

The multiple imputation method generated from Markov Chain Monte Carlo (MCMC) simulation is the default method of imputing missing data under the structural equation framework using Mplus. This method was first introduced from Rubin (1987) and Schafer (1997). The imputed dataset can be analysed in Mplus with maximum

likelihood or weighted least squares (WLS). The MCMC method creates multiple imputations by using simulations from a Bayesian prediction distribution for normal data. In the regression method of MCMC, a regression model is fitted for every variable with missing values. Each resulting regression model is added to a new regression model to produce an MCMC sequence (Rubin, 1987). Mplus runs 100 MCMC iterations and stores the imputed missing values. The process is repeated based on the desired number of imputed datasets (Asparouhov & Muthen, 2010).

Although, the literature suggests between three to five imputed data sets are efficient to produce unbiased results (e.g. Rubin, 1987; Schafer, 1997; Schafer & Olsen, 1998), **relative efficiency** quantifies more precisely the standard error in comparison to its theoretical minimum with the following equation 2.5:

$$RE = \left(1 + \frac{FMI}{m}\right)^{-1} \quad (2.5)$$

where RE is the relative efficiency, FMI is the Fraction of Missing Information (Rubin, 1987) and m is the number of imputed datasets. For instance, if the missing data rate is 60% (FMI=0.60) and the number of imputations is 20, m=20, then the RE $=\sqrt{1 + (\frac{0.60}{20})}$ = 1.01 times larger than its hypothetical minimum value, therefore 20 imputations are enough to support the validity of the results in this method.

The use of auxiliary variables

Auxiliary variables are variables which are included in the analyses but they are not part of the model of interest. An auxiliary variable is correlated with the variables of interest and the missing variables (Collins et al., 2001; Schafer, 1997). The imputation models must be built with variables that are good predictors of missingness. The

variables which are considered to predict or to be associated with the missing values should be part of the imputation model. An effective way to identify predictors of missingness is to include all variables in a model when examining the effects sizes to avoid including redundant predictors. Including many explanatory variables in the imputation model make the MAR assumption more plausible (van Buuren, 2007). It is suggested to include all variables from the model of interest – independent and dependent variables and possible confounders and additionally include the variables which were predictors of missing data and make sure the models of interest are congenial with the imputation model (Carpenter & Plewis, 2011; van Buuren, 2007). Multiple imputation can be combined with inverse probability weighting by including weight variables as covariates in imputation models to compensate for differential non-response (Kenward & Carpenter, 2007; Seaman et al., 2012).

It is suggested in the literature that any transformation in the variables should be performed before including them in the imputation model. This way incorrectly accounting for the relationship between interaction terms and untransformed variables and outcome in the imputation model is avoided (von Hippel, 2009).

2.4.4 Model-Based Procedures

Model-based procedures are broad class procedures that are generated by defining a model for the observed data and basing inferences on the likelihood or posterior distribution under that model. Parameter estimates are estimated by maximum likelihood procedures. In general, these methods are valid under MAR assumptions. Furthermore, model-based methods such as selection models and pattern mixture models which focus on the jointly estimation of a model of interest and a model of missingness, allow MNAR model assumptions (Schafer & Graham, 2002).

Expectation maximization (EM) is an iterative algorithm that detects the parameters which maximize the log likelihood when there are missing values. In general, it is applied in the case of multivariate normal data. Every iteration of EM consists of an E step (expectation step) and M step (maximization step). E-step calculates the complete data log likelihood after taking into consideration the observed data and the parameter estimates. EM is instructive because it is an iterative method that imputes estimates of the missing values by regression (Little & Rubin, 2002). It is a slow method when there is a large fraction of missing values (Nelwamondo et al., 2007).

2.4.4.1 Most commonly used methods for handling missing data in longitudinal settings

In this section the most common used methods to produce valid results in longitudinal data analysis are described (Enders, 2010; Little & Rubin, 2002; Nakai & Ke, 2011).

Latent Growth Curve Models

Methodology on MAR and MNAR models has focused on longitudinal data analyses, and specifically in growth curve models. A growth curve model describes the dependent variable as a function of an independent variable that captures the passage of time. It is built within multilevel, mixed models and the structural equation modelling framework. However, this thesis will focus only on the structural equation modelling framework.

The unconditional linear growth curve model is as follows: where Y_{ti} is the outcome score for case i at time t, $TIME_{ti}$ is the value of the temporal predictor for case i at time t, β_0 is the mean intercept, β_1 is the mean growth rate, b_{0_i} and $b_{1_i}$are residuals

(i.e. random effects) that allow the intercepts and change rates to differ in individuals, and ε_{ti} is a time-specific residual that identifies the difference between an individual's fitted linear trajectory and their observed data.

$$Y_{ti} = \beta_0 + \beta_1(TIME_{ti}) + b_{0_i} + b_{1_i}(TIME_{ti}) + \varepsilon_{ti} \quad (2.6)$$

The model in 2.6 integrates non-linear change by means of polynomial terms. For instance, the unconditional quadratic growth model is the following:

$$Y_{ti} = \beta_0 + \beta_1(TIME_{ti}) + \beta_2(TIME_{ti}^2) + b_{0_i} + b_{1_i}(TIME_{ti}) + b_{2_i}(TIME_{ti}^2) + \varepsilon_{ti} \quad (2.7)$$

where β_0 is the mean intercept, β_1 is the average linear change when *TIME* equals zero, and β_2 is the mean curvature. As above, the model uses a set of random effects to integrate individual heterogeneity into the trajectories (i.e. b_{0_i}, b_{1_i}, and b_{2_i}), and ε_{ti} is a time-specific residual.

Under the structural equation framework, the individual growth components b_{0_i}, b_{1_i}, and b_{2_i} are latent variables and their means define the average growth trajectory. Figure 2.9 illustrates a path diagram of a linear growth model with four outcome-assessments. The factor loadings for the intercept latent variable describe that the intercept is a constant component of each individual growth trajectory, and the loadings for the linear latent variable describe the timing of the assessments.

A quadratic growth curve model integrates an additional latent factor with loadings equal to the square of the linear factor loadings. Although different modelling frameworks often produce similar parameter estimates, a latent growth curve approach is more convenient for implementing MNAR models. Many of the recent software

programmes have focused on the latent variable modelling framework, and every structural equation modelling software package now implements maximum likelihood missing data handling.

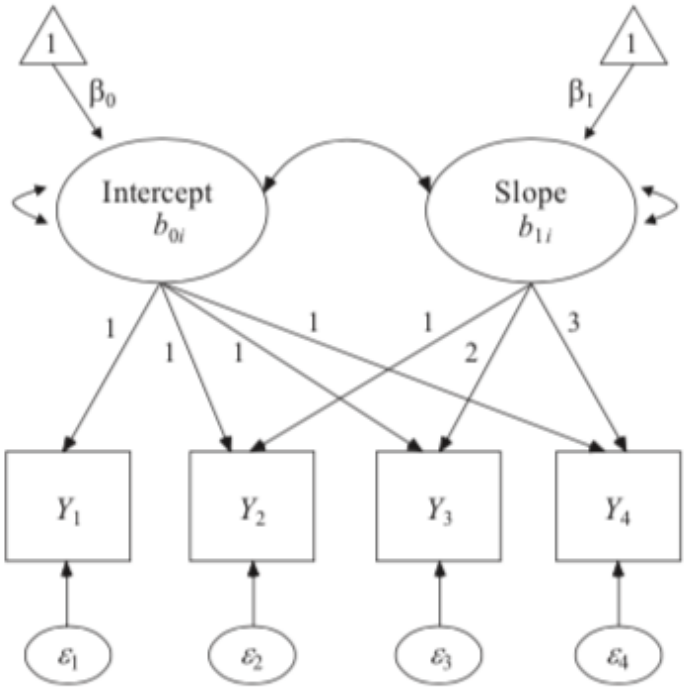


Figure 2. 9 Illustration of a path diagram of a linear growth model; β_0 =mean intercept, β_1 = mean slope; $\boldsymbol{b_{0_i}}$and $\boldsymbol{b_{1_i}}$= residuals that allow the intercepts and change rates to vary across individuals; Y_1–Y_4 = outcome variables; ε_1–ε_4 = time-specific residuals.

Full Information Maximum Likelihood

The idea of using maximum likelihood as an approach to deal with missing data dates back more than 50 years; some researchers consider maximum likelihood as a state-of-the-art missing data technique (Schafer & Graham, 2002) because it offers unbiased parameter estimates under MAR assumptions. Full Information Maximum likelihood produces more accurate parameter estimates compared to other traditional approaches. Even when the data are MCAR, maximum likelihood will still be better and more accurate to traditional techniques of complete case and available case analyses because it boosts statistical power by receiving information from observed data. However,

maximum likelihood estimation is not always the best approach under MNAR assumptions. Maximum likelihood estimation is a better option than complete and available case analyses. Furthermore, maximum likelihood is available in statistical software packages and very easy to implement.

Selection model and Pattern-Mixture Model

When missing data are MNAR then the data are called non-ignorable because ignoring missing data would yield invalid biased results. For this reason, models that can handle missing values are the selection models and pattern-mixed model.

Selection Models for Longitudinal Data

It was in the late 1970's when Heckman (Heckman, 1976; Heckman, 1979) suggested the selection model as an appropriate method to avoid bias from regression analyses with MNAR data on the dependent variable. Selection models for longitudinal data comprise a substantive model (i.e. a growth curve model) with a set of regression equations that predict missingness.

Selection models specify the model for both the longitudinal and missing process (Fitzmaurice, 2003; Little & Rubin, 2002). It is often called a parameter model because both longitudinal and missing models depend on random subject effects. As described in equation 2.8, M is a complete data model for the longitudinal outcomes and Y the probability of missingness is modelled conditionally on the potential unobserved outcomes.

$$f(M,Y|\theta,\psi)=f(Y|\theta)f(M|Y,\psi) \qquad (2.8)$$

the first part indicates the distribution of Y in the population while the second part describe the incidence of missing values as a function of Y, and θ, ψ unknown vector parameters and both are distinct (Little & Rubin, 2002). It is challenging to determine identifying restrictions that should be included in a model because the set of outcomes is restricted and the identification comes from unverifiable models for dependence of the dropout probabilities on unobserved outcomes. Therefore, it is difficult to describe how assumptions on drop out process explain assumptions about the distribution of unobserved response.

Two longitudinal models with different linkages between the repeated measures variables and the missing data indicators will be described. Wu and Carroll's (1988) model indirectly links the repeated measures variables to the response probabilities via the individual intercepts and slopes. This approach is termed as the *random coefficient selection model* or the *shared parameter model.* In contrast, Diggle and Kenward's (1994) selection model directly relates the probability of missing data at time *t* to the outcome variable at time *t.* These models have many similarities but somewhat different assumptions are required and sometimes different estimates may be produced. This thesis implemented the Diggle-Kenward selection model. Diggle and Kenward's (1994) model integrates a growth curve model with a set of regression equations that predict missingness. The probability of missing data at wave *t* depends directly on the repeated measures variables.

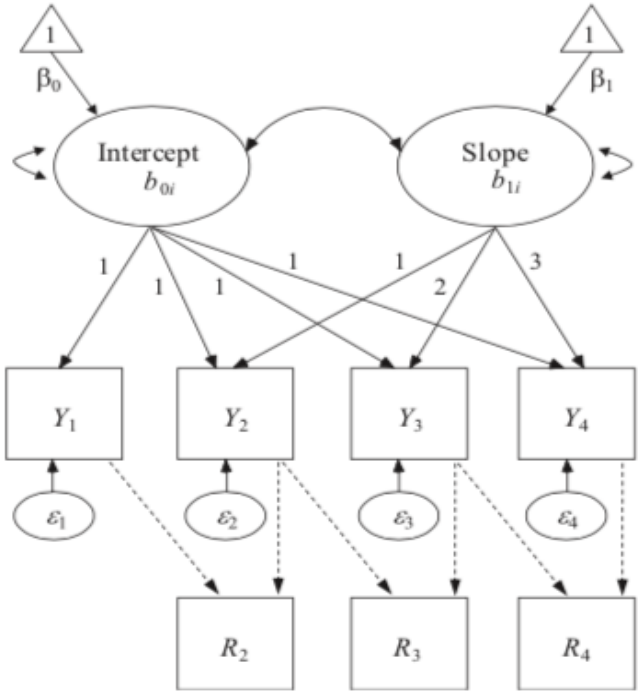


Figure 2. 10 Illustration of a path diagram for the Diggle-Kenward selection model*;* β_0 =mean intercept, β_1 = mean slope; $\boldsymbol{b_{0_i}}$and $\boldsymbol{b_{1_i}}$= residuals that allow the intercepts and change rates to vary across individuals; Y_1–Y_4 = outcome variables; ε_1–ε_4 = time-specific residuals; R_2-R_4 = missing data indicators

Figure 2.10 illustrates a path diagram of a linear Diggle and Kenward growth curve model. R_2, R_3 and R_4 are missing data indicators that describe if the outcome variable is observed or missing, and the dashed arrows show that logistic regression equations have been estimated. The probability of missing data at time *t* depends directly on the outcome variable at time *t* as well as on the outcome variable from the previous measurement. The logistic regression equations in the previous models contain details about the missing data mechanism. In Diggle and Kenward's (1994) model, a significant path between R_t and Y_t show an MNAR mechanism because dropout at wave *t* is concurrently related to the outcome. A significant association between R_t and Y_{t1} provides evidence for an MAR mechanism because dropout at time *t* is related to the outcome at the preceding measurement. If no relationship between the outcomes

and the missing data indicators exists then missing data are MCAR because dropout is unrelated to the variables in the model.

Pattern mixture model for longitudinal data

The pattern-mixture model was first described from Rubin (1976) and Little & Yau, (1996). The pattern-mixture model is also a two-part model where the first part model as Y the distribution in the strata defined by different patterns of missing data M, ξ and ω are unknown vector parameters and are distinct;

$$f(\mathrm{M},\mathrm{Y}|\xi, \omega) = f\,(\mathrm{Y}|\mathrm{M}, \xi)\, f\,(\mathrm{M}|\, \omega) \qquad (2.9)$$

the second part describes the incidence of different patterns (Little & Rubin, 2002).

Figure 2.11 illustrates a path diagram of a linear pattern mixture model. R_2, R_3 and R_4 are missing data indicators that show whether the outcome variable is observed or missing, and the dashed arrows represent that logistic regression equations that have been estimated. However, similar to Wu & Carroll's selection model the missing data indicators are regressed on the intercept and slope allowing the probability of missing data to depend on the entire set of repeated variables and the latent variables intercept and slope. The logistic regression equations in the previous models could carry information about the missing data mechanism.

The important difference between selection models and the pattern-mixture model is that the latter creates different patterns of missingness. For example, in a four-wave occasion as illustrated in Figure 2.11, complete cases would be the first pattern, participants who had the first measurement but not the second one would be the second pattern, participants who had the second measurement but not the third one the third

pattern and participants with missing data only in the last measurement would form the fourth.

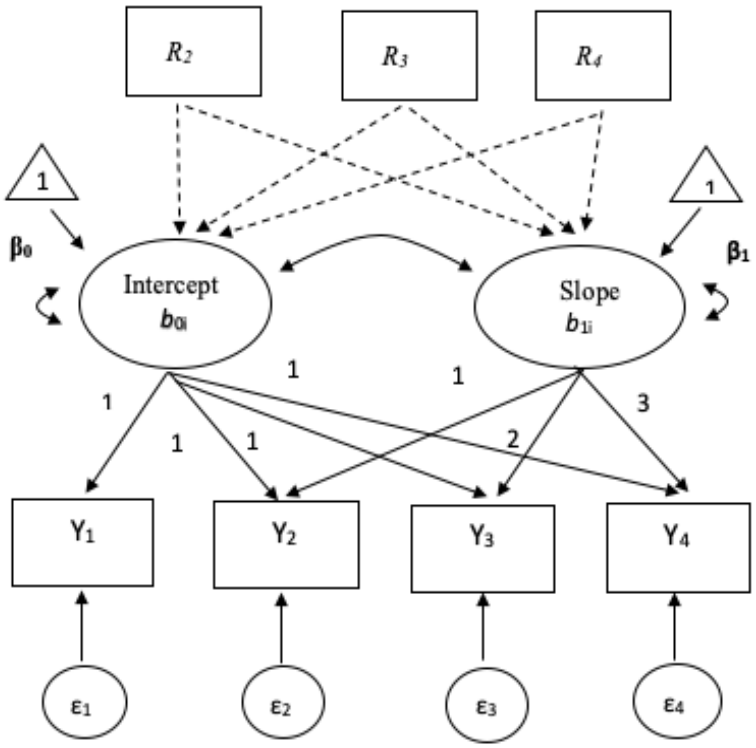


Figure 2. 11 Path diagram for Pattern-Mixture model; R_2-R_4 = missing data indicators; β_0 =mean intercept, β_1 = mean slope; $\boldsymbol{b_{0_i}}$ and $\boldsymbol{b_{1_i}}$ = residuals that allow the intercepts and change rates to vary across individuals; Y_1–Y_4 = outcome variables; ε_1–ε_4 = time-specific residuals

In the pattern-mixture model, in order to decide the best grouping of the missing data the sparseness of patterns needs to be considered, whether there are enough observations to treat them as a separate group of analysis. Moreover, the influence of missing data pattern on response variable need to be considered because in longitudinal studies intermittent observations are assumed to be randomly missing which is not always true. The accuracy of grouping observations is also important because some of them may not provide information over missing data patterns (Nakai & Ke, 2011).

Selection Model and Pattern-Mixture model assumptions

Based on Enders (2011), longitudinal selection models rely on distributional assumptions, and the accuracy of the resulting parameter estimates are dictated from the distributional assumptions. Diggle and Kenward's model require distributional assumptions for the repeated measures variables; without these assumptions, the models cannot be accurately estimated. A multivariate normal distribution for the individual intercepts and slopes or for the repeated measures variables is assumed for continuous outcomes. On the contrary, the pattern-mixture model, firstly identifies different patterns of missing data and then includes parameters in the outcomes model that describe the effect (Hedeker & Gibbons, 1997).

Similar to the selection model, the pattern mixture approach combines a model for the missing data in the analysis, but the process is completely different. A pattern mixture analysis categorises the sample into subgroups that have similar missing data pattern and estimates a growth model separately for each pattern. The different missing data groups produce unique estimates for the growth model parameters. The pattern-specific estimates are often informative but the substantive target is to estimate the population growth trajectory (Enders, 2011).

A disadvantage of the pattern-mixture model is that the accuracy of the resulting estimates cannot be examined. The need to specify values for inestimable parameters may appear to be a serious disadvantage of the pattern mixture model. However, some researchers argue that this requirement is beneficial because it forces researchers to make their assumptions explicit (Little, 1994). On the other hand, the selection model relies on implicit distributional assumptions that are not clear. This aspect of the pattern mixture model offers flexibility because it allows methodologists to explore

the sensitivity of the substantive model parameters in a number of different identification constraints. A sensitivity analysis that applies a variety of identification strategies to the same data is necessary when there are MNAR assumptions.

2.4.5 Some considerations on missing data analysis

Methodologists have broadly implemented MAR-based missing data handling procedures. The MAR assumption is related to explanatory variables, however in some occasions missingness is related to the outcome variable itself. An important problem with missing data analyses is that it is generally impossible to exclude MNAR missingness and disprove the MAR assumption (Enders, 2011; Little & Rubin, 2002; Schafer, 1997). MNAR analyses rely on untestable assumptions and even small violations of these assumptions can introduce substantial bias. A popular opinion is that sensitivity analyses that apply different models (and thus different assumptions) to the same data is necessary when MNAR analyses are implemented (Enders, 2010).

Although these models have imitations, there are options available to consider, particularly when there is outcome-related attrition. MNAR models can augment the results from an MAR-based analysis. Sensitivity analyses are useful for exploring the impact of modelling choices on key parameter estimates but the observed data do not offer any basis for model selection. Therefore, researchers should choose a model with the most justifiable set of assumptions, and this way a reasonable argument that supports this choice could be provided (Enders, 2010).

2.4.5.1 Auxiliary variables in analyses

In multiple imputation analysis, it is recommended using an extensive set of auxiliary variables. However, in a maximum likelihood analysis is challenging to be implemented as the auxiliary variables require a model specification; this means that

the number of auxiliary variables must be limited. It is challenging to specify an accurate number of auxiliary variables, but correlation between an auxiliary variable and the missing data variables largely determines the influence of an auxiliary variable. It is essential to examine the number of cases that have missing data on both the auxiliary variable and the analysis model variables. A lot of missing values in the auxiliary variables limit their contribution to the estimation process. Adding an auxiliary variable proves to be less beneficial when more than 10% of its observations are concurrently missing with one of the analysis model variables (Enders, 2008; Hardt et al., 2012). Including auxiliary variables in an analysis can reduce bias and/or increase power and thus improve the missing data handling procedure (Graham, 2003).

2.4.5.2 Differences between Multiple Imputation and Full Information Maximum Likelihood

As mentioned in Enders' (2010) the use of auxiliary variables is one of the benefits of multiple imputation potentially over maximum likelihood estimation. Graham's (2003) model is an easy approach for integrating auxiliary variables into a maximum likelihood analysis. The model borrows information from the auxiliary variables via a series of correlations between the auxiliary variables and the analysis model variables. On the other hand, multiple imputation treats auxiliary variables as additional predictors in the imputation model during the imputation phase. One advantage of the multiple imputation is that it can often accommodate a larger number of auxiliary variables than a maximum likelihood analysis (Allison, 2002, 2012; Enders, 2010).

A second advantage of multiple imputation over maximum likelihood is in the treatment of incomplete explanatory variables. In multiple imputation, there is no difference is a variable is an independent variable or a dependent variable in the

analysis. All variables in the analyses appear in the imputation regression model, regardless of their use in the subsequent analysis. On the other hand, maximum likelihood incorporates the missing data handling into the estimation process. In some situations implementing maximum likelihood estimation will result in a loss of cases (Enders, 2010).

In occasions where certain items in a questionnaire are missing, applying multiple imputations is relatively straightforward because the researcher would simply impute the missing questionnaire items and compute a scale score for each imputed data set. Maximum likelihood estimation does not fill in the data, and therefore there is no particular way to compute a single scale score that integrates the partial information at the item level (Enders, 2010).

In contrast, maximum likelihood estimation has an advantage over multiple imputation in terms of estimating interaction effects. The easiest approach for assessing interactions is to include the term in a multiple regression model (i.e., moderated multiple regression) (Aiken & West, 1991). Estimating interaction effects is straightforward in the context of maximum likelihood missing data handling because the product term is no different from any other variable. The product variable would have missing values if one of the variables involved in the product is incomplete, however, it would not be a limitation, provided that the software program allows for missing data on predictor variables (Allison, 2002; Enders, 2010).

Structural equation models represent another class of analysis where maximum likelihood estimation is generally preferable to multiple imputation. Every structural equation program offers maximum likelihood missing data handling by default. Multiple imputation is easy to implement because some structural equation modelling

programs (e.g. Mplus) have built-in facilities for automating the analysis and pooling phases (Enders, 2010).

2.5 Aims and research questions

Overall Aim:

The primary aim of this study is to examine the effect of socioeconomic position on adulthood inflammatory biomarker C-reactive protein and stress-related biomarkers cortisol and cortisone after taking into consideration the missing biomarker data. This thesis will identify missing data mechanisms as defined in Section 2.3.2 applied for the substantive topic and then a sensitivity analysis of different procedures will be applied to compensate for missing data. This study will examine which missing data technique will impact more on the analyses of the socioeconomic position and biomarkers.

2.5.1 Aim and Research Questions for Chapter 4

The aim of Chapter 4 is to investigate the effect of socioeconomic position on adulthood inflammatory biomarker C-reactive protein after taking into account the missing data using wave 2 of the English Longitudinal Study of Ageing (ELSA). This chapter will answer the following research questions:

1. What are the characteristics of participants who are less likely to have valid blood-based biomarker data?
2. What is the association of socioeconomic position and inflammation under a complete case analysis?
3. Is the association between socioeconomic position and inflammation greater after compensating for missing biomarker data?

2.5.2 Aim and research questions for Chapter 5

The aim of Chapter 5 is to investigate the effect of socioeconomic position on adulthood stress-related biomarkers cortisol and cortisone after taking into account the missing data using wave 6 of the English Longitudinal Study of Ageing (ELSA). Compared to Chapter 4, this investigation allows for higher levels of missing data. This chapter will answer the following research questions:

1. What are the differences in characteristics between participants who had a valid hair sample and those who did not?
2. What are the characteristics of participants who are less likely to have valid hair cortisol and cortisone sample?
3. Is there a negative association between socioeconomic position and levels of hair cortisol and cortisone after adjusting for confounders?
4. What is the impact that compensating for missing data approaches has on the association between socioeconomic position and hair cortisol and cortisone concentration?

2.5.3 Aim and research questions for Chapter 6

The aim of Chapter 6 is to investigate the effects of socioeconomic position on adulthood inflammatory biomarker C-reactive protein measured over time after taking into account missing data using waves 2, 4, 6, and 8 of the English Longitudinal Study of Ageing (ELSA). This chapter will answer the following research questions:

1. What are the characteristics of participants who are less likely to have inflammatory biomarker data at four, eight, and twelve years after the baseline biomarker collection?

2. How can the trajectories of repeated inflammation be explained by socioeconomic position?
3. Does accounting for missing data change the trajectory of socioeconomic position effects on repeated inflammation?

CHAPTER 3. Introduction to the data and methods

Data from the English Longitudinal Study of Ageing (ELSA) was used to address the aims of this thesis and answer the research questions mentioned in Section 2.5. Background information on ELSA is given and variables that were used to define socioeconomic position in the three empirical chapters are described. The section of this chapter describes the advantages of using ELSA to examine the association between socioeconomic position and inflammatory and stress-related biomarkers.

3.1 English Longitudinal Study of Ageing

The English Longitudinal Study of Ageing (ELSA) was established to address several questions about policy making within specific scientific frameworks. Participants are followed as they progress through middle to older ages. The design of the study provides opportunities for research which include health trajectories, disability, and healthy life expectancy. It also provides, information on socioeconomic determinants and resources in older ages and focuses on retirement and labour market activity. The study has contributed to the understanding of social networks, social support and social participation at older ages. Family and household structure are also some of the domains included in the study. However, the most important advantage is that there is opportunity, within the scope of interdisciplinary research, to link the domains together and assess their dynamic relationships. ELSA has been designed to be comparable with international longitudinal studies on ageing, such as the Survey of Health, Ageing and Retirement in Europe (SHARE) (Börsch-Supan et al., 2013) and Health and Retirement Study (HRS) in the USA (Zaninotto & Steptoe, 2019).

The English Longitudinal Study of Ageing (ELSA) is a longitudinal study that collects multidisciplinary data representative of people ages 50 and over. The sample has been

drawn from the Health Survey for England (HSE), which collects cross-sectional data of the general population annually. The sample was collected by using a multistage stratified random probability design from years 1998, 1999 and 2001 of HSE.

Some households in HSE agreed to participate in ELSA and therefore, they were re-contacted to constitute the ELSA basis sample. Every household could include two types of participants: a "core" member and a cohabiting "partner". Core members were 50 years old and older while partner participants could be aged less than 50 years. Cohabiting partners also took part in the main interviews for the purpose of conducting analyses in couples with at least one member over 50 years of age.

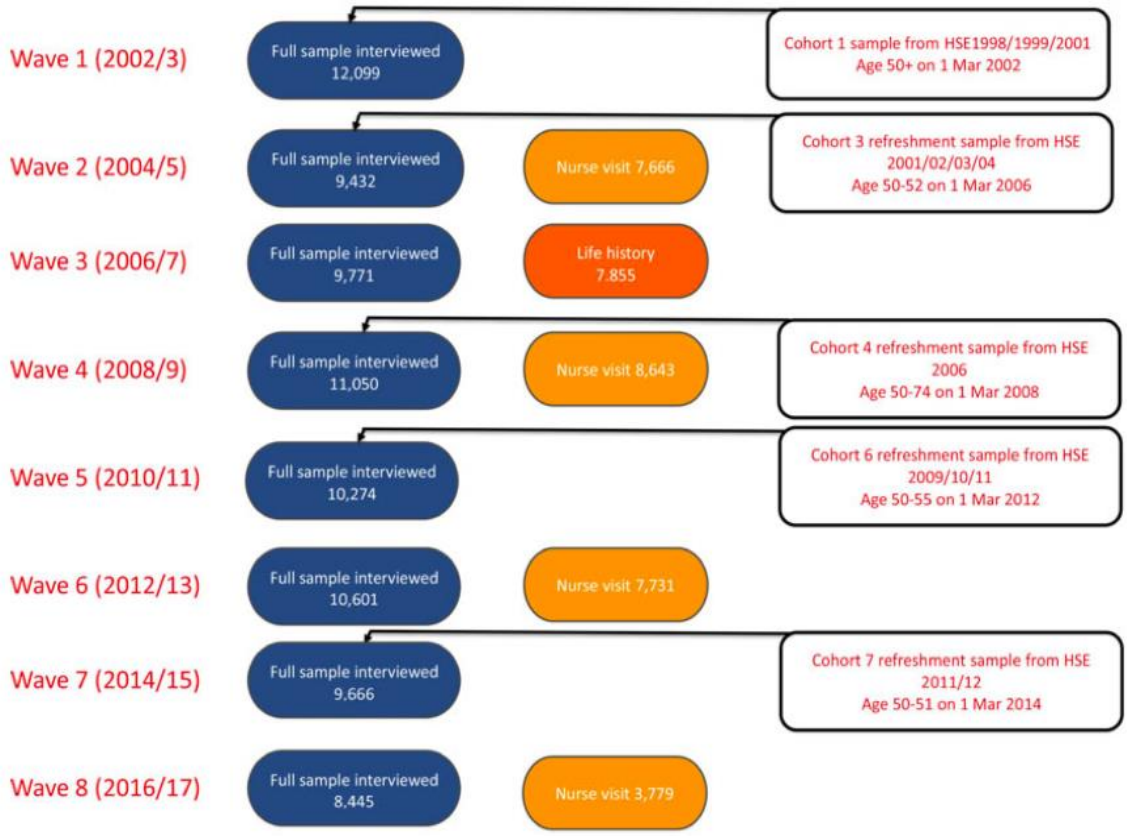


Figure 3. 1 Flowchart of the different wave collections of data in ELSA

Figure 3.1 describes the different waves and samples of data collection of the main interview. The first wave of ELSA took place in 2002/2003 and the participants were

interviewed every two years until wave 8 in 2016/2017. From the second wave and for every four years until wave 8, individuals participated in a nurse visit. In every wave, the data collection comprised a computer-assisted personal interview (CAPI) and a self-completion questionnaire.

Response rates and attrition in ELSA are complicated due to variations of responses because of differences between core and refreshment samples in waves 2,4,5, and 7 and participants who had died in the course of the study. Some individuals may accept participating in one wave but fail or refuse to take part in the subsequent wave. The maintenance of the sample representativeness is very important, therefore when carrying out analyses cross-sectional and longitudinal weights are calculated and are available in datasets.

Wave 1 included 11,391 core member participants comprised cohort 1 with a response rate (RR) of 67% from the eligible participants who were contacted. In wave 2 out of 8780 (RR=82%) core participants, 7,666 (RR=87.3%) agreed to participate in the nurse visit and 6,231 people (RR=81.2%) gave consent and were eligible to give a blood sample. In wave 3, 7,535 (RR=73%) core members were combined with a refreshment sample of 1275 (RR=61%) core member participants. The refreshment sample in wave 3 was cohort 3. Cohort 1 sample of 6,623 (RR=74%) was combined with cohort 3 sample 972 (RR=63%) and with a refreshment sample of 2,291 participants. Wave 4 refreshment sample was cohort 4. Out of a total 9,886 participants, 8218 (RR=86%) agreed to participate in the nurse visit and 6,438 (RR=78.3) had a blood sample. In wave 5 6,242 (RR=69%) were combined with 936 (RR=75%) participants from cohort 3 and 1,912 (RR=85%) participants from cohort 4. Wave 6 included 5,569 (RR=66%) participants from cohort 1, 888 (RR=73%) from cohort 3, 1,796 (RR=82%) from cohort 4 and additional 826 participants (RR=56%)

from a refreshment sample which comprised cohort 6. In the wave 6 nurse visit 7,699 (RR=88%) individuals participated and 6,180 (RR=67.4%) had blood sample collected. Wave 7 included 4,894 (RR=61%) participants from cohort 1, 787 (RR=65%) participants from cohort 3, 1,606 (RR=75%) from cohort 4, 661 (RR=82%) from cohort 4 and 301 (RR=61%) from cohort 7.

In the last available wave of ELSA, wave 8, cohort 1 included 4,219 (RR=55%) participants, cohort 3 included 723 (RR=60%), cohort 4 included 1,470 (RR=70%), cohort 6 included 582 (RR=72%) participants and cohort 7 included 229 (RR=77%) participants. Of those, 3,525 (RR=48.8%) accepted to participate in the nurse visit and 2,762 (RR=78.3%) had a blood sample collected.

3.2 Benefits of ELSA

ELSA is the first representative longitudinal study of older people in England to have a well-integrated multidisciplinary approach which measures economic circumstances, health and social aspects of people's lives, and the first in the world with emphasis on detailed economic processes and the assessment of all elements of health processes including symptoms, subjective assessments, diagnoses and biomarkers. Innovative techniques for estimating income and wealth have greatly strengthened the scope for obtaining comprehensive data on financial circumstances in a phase of life that is difficult to quantify in terms of simple indices of income. The rapid availability of data to the general research community overcomes the time delays present for many cohort studies and ensures that up to date information can be analysed (Steptoe et al., 2013).

3.3 Methods

This section describes the variables included in the models of interest in Chapters 4, 5 and 6 and the appropriate methods which were implemented to answer the research questions in every empirical chapter.

3.3.1 Variables of interest

A large number of variables have been used to answer the research questions in this thesis, however, in this section only the explanatory and outcome variables are presented.

3.3.1.1 Socioeconomic position (SEP)

This thesis examined the association between socioeconomic position and inflammatory and stress-related biomarkers.

Early adulthood SEP

Educational level was measured as the highest qualification obtained and was classified into: 1) university degree (NVQ5-4), 2) higher education but without degree, 3) high school (NVQ3-2) and 4) foreign or no qualifications. In empirical chapters 5 and 6, education level was categorised into three categories: 1) university degree (NVQ5-4) and higher education but without degree, 2) high school (NVQ3-2) and 3) foreign or no qualifications.

Late adulthood SEP:

Wealth

Total net wealth was categorized into quintiles (lowest to highest) and measured at benefit unit level. In empirical Chapters 5 and 6, wealth was categorized into tertiles.

Financial assets such savings and investments were used to estimate the wealth variable (Ploubidis, DeStavola, & Grundy, 2011).

Social class

The National Statistics Socio-Economic Classification scheme (NS-SEC) was used to measure social class which describes conditions and types of employability. Social class variable was divided into five categories: 1) Managerial and professional, 2) Intermediate, 3) Small employers and own account workers, 4) Lower supervisory and technical occupations and 5) Semi routine and routine and other occupations. In empirical chapters 5 and 6, social class was categorised into three categories: 1) Managerial and professional 2) Intermediate and 3) Semi routine and technical and other occupations. The hierarchical Register General classification considers non-manual occupations as "higher SEP" compared to manual occupations (Bartley, 2004). Employment status determined by employed, retired and not employed and not retired categories to assess the interaction with social class.

Employment status

Participants were asked to report their current employment status and the variable was categorised into three categories: 1) Employed, 2) Retired, and 3) Not employed and not retired. Employment status was used in the analyses to create an interaction term with the social class variable and therefore, nine categories were produced: 1) Managerial and professional X Employed, 2) Intermediate X Retired, 3) Intermediate X Not employed and not retired 4) Small employers X Retired, 5) Small employers X Retired, 6) Lower supervisory X Retired, 7) Lower supervisory X Not employed and not retired, 8) Semi routine X Retired, and 9) Semi routine X Not employed and not

retired. The interaction term was not applied in empirical Chapters 5 and 6 as no predicting effect on the levels of biomarkers was found.

3.3.1.2 Biomarkers

Inflammatory biomarker

Data from C-reactive protein, the inflammatory biomarker used in this thesis, were collected in waves 2, 4, 6 and 8. Biomarker data were collected from participants from a study nurse during the health assessment and nurse visit in ELSA, and serum C-reactive protein was analysed by the Department of Clinical Biochemistry at the Royal Victoria Infirmary (Newcastle-upon-Tyne, UK) using the N Latex C-reactive protein Mono Immunoassay on the Behring Nephelometer II Analyzer (Date Behring, Milton Keynes, UK). C-reactive protein concentrations was expressed in mg/L. In cross-sectional analyses in empirical Chapter 4, only one measurement of C-reactive protein was used. In longitudinal analyses in empirical Chapter 6, four different measurements of C-reactive protein from same individuals were used.

Stress related biomarkers

Data from cortisol and cortisone, the stress-related biomarkers, were collected in waves 2, 4, 6 and 8 of ELSA from blood, saliva and urine. However, in this thesis hair sample data from wave 6 of ELSA were used to measure cortisol and cortisone in participants. Hair samples were obtained as part of the visit by a study nurse. A scalp hair strand of 3 cm was collected from the posterior vertex position by cutting the hair. The samples once collected were placed onto aluminium foil, and stored in a dry, dark place before being sending to the Technische Universität Dresden, Germany. The washing procedure and steroid extraction were undertaken using high performance liquid chromatography (LC/MS) (Chen et al., 2013). Hair cortisol concentration was expressed in pg/mg. Based on an average monthly hair growth of around 1 cm, the

scalp-nearest hair segment of 3 cm represents averaged cortisol accumulated over an approximate timespan of three months prior to sampling. Cortisol is often converted into inactive cortisone (Stewart & Mason, 1995) and therefore, both biomarkers should be assessed together.

3.3.2 Methods in Chapter 4

In Chapter 4, four different methods have been implemented to examine the association between socioeconomic position and C-reactive protein. Complete case analysis was compared with inverse probability weighting, multiple imputation, and multiple imputation with attrition weights. Inverse probability weighting was used to compensate for non-response in biomarker data and it is considered to be the most appropriate method to account for differential non-response in studies when missing data are MAR (Brick & Kalton, 1996). Multiple imputation was implemented to "fill in" missing values in biomarker data. This is the most efficient method to compensate for missing data when the data are assumed to be MAR (Rubin, 1987). Multiple imputation with attrition weights was implemented to compensate for differential non-response (Kenward & Carpenter, 2007; Seaman et al., 2012).

3.3.2.1 Complete case analysis

A linear regression model was implemented to examine the association between socioeconomic position (defined by educational level, wealth, social class and the interaction term between social class and employment status) and the inflammatory biomarker C-reactive protein. The analysis was adjusted for covariates.

3.3.2.2 Inverse probability weighting

A linear regression model with non-response blood weight was implemented to examine the association between socioeconomic position and C-reactive protein. The first step for inverse probability weighting in order to reduce bias from missing data

was to choose the variables that influence the probability of being a complete case. Auxiliary variables that could act as predictors of missingness based on findings in the ELSA technical report (Scholes et al., 2008) and on the broader literature (Gustman & Steinmeier, 2004; Kho et a., 2009) were identified (paragraph 2.2 describes the literature with more details). Additional identification process by creating a binary (dichotomous) variable indicating whether participants provided C-reactive protein in the blood sampling which assumes the value of 1 and 0 otherwise, was implemented. Then a logistic regression model to investigate which variables predicted the participation in the two data collections was carried-out. Several variables were identified to predict missing C-reactive protein data.

The second step in the inverse probability weighting method included the combination of wave 2 main interview attrition weight calculated from ELSA (Scholes, 2008) with the non-response weight that was produced for those people who did not provide C-reactive protein in the blood collection. The new non-response weight was calculated as the inverse of the predicted response probabilities predicted from the previously mentioned logistic regression model with the predictors of missingness in the blood collection for C-reactive protein.

In the third step, weighted complete case analysis implementing weighted linear regression modelling was used. The weighting variable was the final non-response weight from the blood collection of C-reactive protein. The model of interest was similar to the model of unweighted complete case analysis including the interaction term between social class and employment status. The analysis was adjusted for covariates.

3.3.1.3 Multiple Imputation

A linear regression model with multiple imputed values was implemented to examine the association between socioeconomic position and C-reactive protein. Furthermore, a linear regression model with imputed values and ELSA wave 2 main interview attrition weight was implemented to examine the same association.

The imputation model consisted of the variables that are thought to predict or be associated with missing values in our data. The predictor variables from the inverse probability weighting method which were mentioned in section 3.3.2.2 and the variables from the model of interest were used to build the imputation model. Multiple imputation by chained equations to impute missing information in C-reactive protein was implemented. Fifteen imputed datasets were created based on the general pattern of the adequate number of imputations recommended (Schafer, 1999) and after assessing the relative efficiency and proportional increase in the standard error (mentioned in section 2.4.3.2) (Rubin, 1987).

The variables that were included in the models of interest (and therefore in the imputation model) were the log transformed C-reactive protein and the explanatory variables. A linear regression model was implemented to examine the association of socioeconomic position and C-reactive protein after adjusting for potential confounders along with the predictive variables of missingness.

It is generally known that transformed variables and interaction terms should be included in the imputation model in order to emphasise the relationship between the transformed variables (log transformed variables) and the interaction terms with the outcome of interest.

The second approach to compensate for missing data with multiple imputation was to implement multiple imputation with wave 2 main interview attrition weight (survey weight) which is an ELSA-derived variable. The imputation model from the aforementioned multiple imputation methods was used and the survey weight was added to adjust for attrition from the main interview.

3.3.3 Methods in Chapter 5

In Chapter 5, three different methods were implemented to examine the association between socioeconomic position and cortisol and cortisone. Complete case analyses with attrition weights were compared with two approaches of inverse probability weighting, and multiple imputation with attrition weights for each outcome variable. Complete cases analysis was implemented to account for differential non-response using wave 6 attrition weights (Brick & Kalton, 1996). The first approach for the inverse probability weighting accounted non-response in two stages. The first stage accounted for participants without hair sample and the second stage, which was conditional on having a hair sample, accounted for participants with missing biomarker data. The second approach was used to account for non-response in participants without biomarker data regardless of having hair sample or not. Multiple imputation with attrition weights was implemented with a similar approach as in Chapter 4. In all methods, missing data were assumed to be MAR.

3.3.3.1 Complete case analysis

A linear regression model with ELSA wave 6 main interview attrition weights was implemented to examine the association between socioeconomic position (defined by educational level, wealth, and social class) and the stress-related biomarker hair cortisol. The analysis was adjusted for covariates. Another linear regression model

with ELSA wave 6 main interview weights was used to examine the association between socioeconomic position and hair cortisone adjusting for the same covariates.

3.3.3.2 Inverse Probability Weighting

Three linear regression models with non-response hair cortisol and cortisone weights were used to examine the association between socioeconomic position and hair cortisol and cortisone. Two approaches for inverse probability weighting to inflate the weight for participants who were underrepresented due to missing data, were implemented.

The two-stage approach included two different models. The first model weights participants who did not have hair sample and the second model weights participants who had a hair sample but had no hair cortisol and cortisone data. The one-stage approach included only one model which weighted the participants without hair cortisol and cortisone data. These two approaches provided comprehensive information over the propensity of missingness in hair cortisol data.

Response model for hair sample (Model I of the II-stage IPW)

A dichotomous variable was created indicating those (1) who were eligible and had a hair sample and those (0) who were ineligible and did not have hair sample. Then, logistic regression was used to predict missing hair sample probabilities by including variables that were identified to be predictors of missingness.

The non-response weight was calculated as the inverse of the predicted response probabilities and was combined with the ELSA wave 6 attrition weights to create an overall weight measurement. Two linear regression models with the new non-response weight, one for each outcome variable, were implemented to examine the association

between socioeconomic position and hair cortisol and cortisone after adjusting for covariates.

Response models for hair cortisol/cortisone (Model II of the II-stage IPW)

A dichotomous variable was created on the set of eligible participants indicating those participants (1) who had hair cortisol/cortisone biomarker data and those who did not (0). A logistic regression model was used to predict absent hair cortisol and cortisone data taking into account variables which were predictors of missingness.

The final weight variable was created as the inverse of the predicted response probabilities and was combined with the non-response weight from Model I and with the ELSA wave 6 attrition weights to create an overall weight measurement.

Two linear regression models with the new non-response weight, one for each outcome variable, were implemented to examine the association between socioeconomic position and hair cortisol and cortisone after adjusting for potential confounders.

Response models for hair cortisol/cortisone (I stage IPW)

A dichotomous variable was created distinguishing those participants who had hair cortisol/cortisone biomarker data (1) and those without (0). Then, a logistic regression was implemented including predictors of missingness.

The new weight variable was created by combining the wave 6 attrition weight provided by ELSA with the new non-response weight, calculated as the inverse of the predicted response probabilities from the previously mentioned logistic regression models.

Two linear regression models with the new non-response weight, one for each outcome variable, were implemented to examine the association between socioeconomic position and hair cortisol and cortisone after adjusting for covariates.

3.3.3.3 Multiple imputation with attrition weights

A linear regression model with multiple imputed values and with ELSA main interview attrition weight was used to examine the association between socioeconomic position and hair cortisol after adjusting for covariates. Another linear regression model was used to examine the association between socioeconomic position and hair cortisone after adjusting for covariates.

The imputation model consisted of the predictor variables that are thought to predict or be associated with missing values in the data. The predictor variables from the inverse probability weighting method which were mentioned in section 3.3.3.2 and the variables from the model of interest were used to build the imputation model. Multiple imputation by chained equations to impute missing information in hair cortisol and cortisone was implemented. Twenty imputed datasets were created based on the general pattern of the adequate number of imputations recommended (Schafer, 1999) and after assessing the relative efficiency and proportional increase in the standard error (mentioned in section 2.4.3.2) (Rubin, 1987). The number of missing biomarker data was larger compared to those in Chapter 4. The variables that were included in the models of interest (and therefore in the imputation model) were the log transformed hair cortisol and cortisone and the explanatory variables. Every transformed variable was included in the imputation model in order to emphasize the relationship between the transformed variables (log transformed variables) with the outcome of interest.

Variables that were thought to predict or be associated with missing values were included in the imputation model alongside the predictor variables used from the inverse probability weighting method and the variables from the model of interest.

3.3.4 Methods in Chapter 6

In Chapter 6, five different methods were implemented to examine the association between socioeconomic position and repeated measures of C-reactive protein. Complete case analysis was compared with full information maximum likelihood, multiple imputation, Diggle and Kenward's selection model, and pattern mixture model. Full information maximum likelihood is a method which produces unbiased results when missing data are MAR (Schafer & Graham, 2002). Diggle-Kenward's (1994) selection model allowed to account for non-response by producing a logistic model which included predictors of missingness for every binary drop-out indicator. Pattern-mixture model produces three dummy drop-out indicators which are included in the model as covariates (Little & Yau, 1996; Rubin, 1976). Both Diggle-Kenward and pattern-mixture model compensate for missing data when missing data are MNAR.

3.3.4.1 Identification of the characteristics of non-response

Predictors of missingness were identified by creating three non-response models according to three different missing data patterns. For the first missing data pattern, a dichotomous variable was created indicating those participants who did not have C-reactive protein in wave 4 (labeled:1) and those who had C-reactive protein in both waves 2 and 4 (labeled:0). Using logistic regression analysis, predictors of missingness were identified. For the second missing data pattern, a dichotomous variable was created indicating those participants who didn't have C-reactive protein in wave 6 (labeled:1) and those who had C-reactive protein in both waves 2 to 6

(labeled:0). Using logistic regression analysis, predictors of missingness were identified.

For the third missing data pattern, a dichotomous variable was created indicating those participants who did not have C-reactive protein in wave 8 (labeled:1) and those who had C-reactive protein in all waves 2 - 8 (labeled:0). Using logistic regression analysis, predictors of missingness were identified.

3.3.4.2 Complete case analysis

A latent curvilinear growth curve model using maximum likelihood and listwise deletion was implemented to examine individual trajectories of change in C-reactive protein levels under the structural equation model framework. These trajectories described the intraindividual change over time by estimating the initial levels (intercept), rates of change (slope) and accelerated rates of change (quadratic slope). Measurements of C-reactive protein at four different times were used as multiple indicators of the three latent constructs of this model. The model was adjusted for covariates. Additional variables which were identified to be predictors of missingness were added as auxiliary variables.

The interindividual differences in C-reactive protein levels were estimated in relation to socioeconomic position (defined by educational level, wealth, and social class) after adjusting for covariates. Additional variables which were identified to be predictors of missingness were added as auxiliary variables.

3.3.4.3 Missing at Random (MAR) approaches

A latent curvilinear growth curve model using Full Information Maximum Likelihood (FIML) (Graham, 2003) was implemented to investigate the intraindividual change over time in C-reactive protein levels by estimating the initial levels (intercept), rates of change (slope) and acceleration in rates of change (quadratic slope). Measurements

of C-reactive protein at four different times were used as multiple indicators. Additional variables which were identified to be predictors of missingness were added as auxiliary variables.

A latent curvilinear growth curve model using Full Information Maximum Likelihood (FIML) was implemented to investigate the interindividual change over time in C-reactive protein levels by estimating the initial levels (intercept), rates of change (slope) and accelerated rates of change (quadratic slope) in relation to socioeconomic position (defined by educational level, wealth, and social class). Measurements of C-reactive protein at four different times were used as multiple indicators. The model was adjusted for covariates and additional variables which were identified to be predictors of missingness were added as auxiliary variables.

A latent curvilinear growth curve model using multiple imputation (MI) for Bayesian analysis was implemented to investigate the intraindividual change over time in C-reactive protein levels by estimating the initial levels (intercept), rates of change (slope) and acceleration in rates of change (quadratic slope). Measurements of C-reactive protein at four different times were used as multiple indicators. The imputation model included auxiliary variables which were identified to be predictors of missingness. Twenty imputed datasets were generated.

A latent curvilinear growth curve model using multiple imputation (MI) for Bayesian analysis was implemented to investigate the interindividual change over time in C-reactive protein levels by estimating the initial levels (intercept), rates of change (slope) and accelerated rates of change (quadratic slope) in relation to socioeconomic position (defined by educational level, wealth, and social class). Measurements of C-reactive protein at four different times were used as multiple indicators. The

imputation model included the variables from the model of interest, and covariates and additional variables which were identified to be predictors of missingness were added as auxiliary variables. Twenty imputed datasets were generated.

3.3.4.4 Missing Not at Random (MNAR) analyses

Diggle and Kenward's selection model is a two-part selection model. A latent curvilinear growth curve model and a selection model (logistic regression model) were implemented to investigate the intraindividual change over time in C-reactive protein levels by estimating the initial levels (intercept), rates of change (slope) and accelerated rates of change (quadratic slope). Measurements of C-reactive protein at four different times were used as multiple indicators. The selection model (logistic regression) consisted of the measurements of C-reactive protein and auxiliary variables which were identified to be predictors of missingness.

A latent curvilinear growth curve model and a selection model (logistic regression model) were implemented to investigate the interindividual change over time in C-reactive protein levels by estimating the initial levels (intercept), rates of change (slope) and accelerated rates of change (quadratic slope) in relation to socioeconomic position (defined by educational level, wealth, and social class). Measurements of C-reactive protein at four different times were used as multiple indicators. The model was adjusted for covariates. The selection model (logistic regression model) consisted of the measurements of C-reactive protein, socioeconomic position variables, covariates, and auxiliary variables which were identified to be predictors of missingness.

A Pattern Mixture Model (PMM) was used to estimate a latent curvilinear growth curve model and investigate the intraindividual change over time in C-reactive protein levels by estimating the initial levels (intercept), rates of change (slope) and

accelerated rates of change (quadratic slope). Measurements of C-reactive protein at four different times were used as multiple indicators. Additional variables which were identified to be predictors of missingness were added as auxiliary variables. In this method, three binary dummy dropout indicators were used as covariates (Muthen, 2011)

A Pattern Mixture Model (PMM) was used to estimate a latent curvilinear growth curve model and investigate the interindividual change over time in C-reactive protein levels by estimating the initial levels (intercept), rates of change (slope) and accelerated rates of change (quadratic slope) in relation to socioeconomic position (defined by educational level, wealth, and social class). Measurements of C-reactive protein at four different times were used as multiple indicators. The model was adjusted for covariates and additional variables which were identified to be predictors of missingness were added as auxiliary variables. Three binary dummy dropout indicators were used as covariates.

CHAPTER 4. Socioeconomic position effects on inflammation in older adults: compensating for missing data

Chatzi G, Chandola T, Cernat A, and Shlomo N

Abstract

In most existing studies investigating the association between socioeconomic position and inflammatory biomarkers, researchers often use complete case data for analyses and ignore the impact of missing data despite the high proportion of missing biomarker data. Ignoring missing data in surveys can produce biased estimates due to selection processes and loss of precision. This paper examines whether levels of inflammatory biomarker C-reactive protein can be explained by socioeconomic position after we compensate for missing data. We compared complete case analysis with three missing data approaches assuming Missing at Random: inverse probability weighting, multiple imputation and weighted multiple imputation.

We used cross-sectional data from men and women aged over 52 from wave 2 in the English Longitudinal Study of Ageing (ELSA) since 2004. Complete case analysis showed that people with a lower education level and working in a lower supervisory position were more likely to have higher C-reactive protein levels and therefore higher risk of inflammatory diseases. People in the lowest wealth quintile were also more likely to have higher C-reactive protein. The predicted values of C-reactive protein were higher in the inverse probability and multiple imputation methods compared to complete case analysis. The conclusions drawn suggest that it is important to account for missing biomarker data for statistical inference.

Keywords: social inequalities; inflammatory biomarker; non-response in surveys; missing data;

4.1 Introduction

Improved social conditions and health care led to significant increases in life expectancy and health outcomes in the past few decades (WHO, 2015). However, these improvements hide a wide gap in health between the most affluent and most deprived communities (Marmot, 2005).

In the UK, evidence from longitudinal studies suggest that socioeconomic position and chronic inflammation are associated, with inflammation being an important risk factor of cardiovascular disease (Na-Ek & Demakakos, 2016; Tabassum et al., 2008)

However, most of the studies on socioeconomic position and inflammation have not compensated for non-response in biomarker data that occurs due to attrition or refusal to participate in data collection. Missing data in longitudinal studies related to attrition and refusal in data collection could challenge the validity of the studies' assumptions and inferences. For example, in the English Longitudinal Study of Ageing (ELSA) with three data collections in waves 2, 4 and 6 which included a main interview, health examination and blood collection, there are multiple stages where participants give either consent or refuse to take part or may be unable or ineligible to provide a blood sample (Scholes et al., 2008). For instance, in ELSA, only 87,3% (7,666) of those who accepted to participate in the main interview (8,780), consented to participate in the health examination. Furthermore, of those 7,666 who participated in the health examination only 77% (5,899) had a blood sample with a biomarker measure.

Many studies have found that unhealthy people and people with living in socioeconomic disadvantage are more likely to drop -out of the study and refuse to participate in data collection (Banks et al., 2011; Kenny et al., 2010) which could affect the association between socioeconomic position and inflammatory outcomes.

In general, non-response in surveys can lead to bias due to selection processes and loss of precision due to the reduction of sample size (Little & Rubin, 2002); issues that have been rarely considered in studies related to biosocial research.

This study will compensate for missing data while examining the association between socioeconomic position and levels of C-reactive protein in older adults, in order to produce unbiased and accurate results. Complete case analysis, inverse probability weighting and multiple imputations will be implemented to compensate for non-response data. Section 2 provides background information based on literature findings and gives details about applied methods for missing data analyses. Furthermore, three research questions are discussed following with hypotheses based on previous study findings. Section 3 includes description of the variables and statistical modelling. Section 4 includes univariate and multivariate analysis, and presentation of the results. Section 5 includes the comparison of this study with previous studies and discussion of the findings.

4.2 Background

4.2.1 Socioeconomic effects on health in older adults

A life course approach to the association between socioeconomic position and health considers not only the possibility that early life socioeconomic position affects later life health (social causation), but also that poorer health from early in the life course affects both socioeconomic position and later health in adulthood (health - related selection) (Warren, 2009). Additionally, the association between socioeconomic position and health can be explained by specific health - related selection processes, such as “the healthy worker effect”, where unhealthier people are less likely to enter the labour force or are more likely to leave the labour force earlier than other participants (Eisen et al., 2006; Li & Sung, 1999; Shah, 2009). Such ill -health

selection effects are more prevalent among disadvantaged social groups, probably because of the higher prevalence of poorer health in those disadvantaged groups (Eisen et al., 2006).

Chronic inflammation is a biological response of the immune system associated with several health problems including cardiovascular disease (CVD) (Libby, 2006). Inflammatory biomarker C-reactive protein (CRP) is an acute-phase protein and an etiological factor in chronic inflammation and subsequently a high risk factor for developing CVD outcomes (Cesari et al., 2003; Jialal et al., 2004).

A large number of studies have examined the association of socioeconomic disparities and inflammatory biomarkers; where high levels indicate atherosclerosis (Fahdi et al., 2003) and CVD (Galobardes et al., 2006; González et al., 1998; Pearson et al., 2003). Studies using complete case analysis found that socioeconomically disadvantaged adults have higher levels of inflammatory biomarkers (Fraga et al., 2015; Gruenewald et al., 2009) while others conclude that socioeconomic disadvantages earlier in life increase the risk of inflammation in older adulthood (Packard et al., 2011; Slopen et al., 2010).

4.2.2 Characteristics of non-participation in surveys

It is important to highlight the characteristics of participants who are not responding to surveys and refuse to give consent in order to detect any differences in attrition propensities and avoid potential attrition and consent bias (Knies et al., 2012; Watson & Wooden, 2009). Existing studies suggest that men are less likely to continue to participate in studies compared to women (Lepkowski & Couper, 2002; Nicoletti & Buck, 2003; Uhrig, 2008) and that attrition increases in old age (Lepkowski & Couper, 2002; Thomas et al., 2001), although a different study suggests the opposite (Hill &

Willis, 2001). People from ethnic minorities have higher propensity to drop out (Lepkowski & Couper, 2002; Uhrig, 2008) and single people have lower contact probability compared to married people (Gray et al., 1996; Uhrig, 2008). Home owners have higher response rates (Gray et al., 1996; Lepkowski & Couper, 2002; Nicoletti & Peracchi, 2005) while people living in urban areas have higher attrition rates in some studies mostly because interviewing is more difficult in large urban areas (Burkam & Lee, 1998; Gray et al., 1996; Uhrig, 2008). Although there are studies which suggest that socioeconomic disadvantage is associated with attrition and refusal to participate in studies (Behr et al., 2005; Ekholm et al., 2010; Ferrie et al., 2009; Lepkowski & Couper, 2002), findings from a study examining three different UK surveys were inconsistent (Knies & Burton, 2014). Participants with fair health or self-assessed poorer health are less likely to participate in later waves and give consent in health-related surveys (Ferrie et al., 2009; Groves & Cooper, 1998; Knies & Burton, 2014; Lepkowski & Couper, 2002; May et al., 2012; Uhrig, 2008).

4.2.3 Applied methods for missing data analyses

An important issue that needs to be considered while selecting the appropriate method to compensate for missing data is to identify the mechanisms behind the missing data. There are three missing data mechanisms: Missing Completely at Random (MCAR) are considered the non-response data when the probability of missingness is unrelated to Y_{obs} and Y_{mis}, $p(R|\phi)$, where R is a missing data indicator (R=1 defines missingness and 0 otherwise), ϕ is a parameter that rules when R takes on the value of one or zero and Y_{obs}, Y_{mis} are the observed and unobserved parts of the data, respectively. The non-response data Missing at Random (MAR) are considered when the probability of missingness is related to Y_{obs} but not to Y_{mis}, $p(R|Y_{obs}, \phi)$ and Missing Not at Random

(MNAR) are considered the non-response data when the probability of missingness depends on Y_{obs} and Y_{mis}, $p(R|Y_{obs}, Y_{mis}, \phi)$ (R. J. A. Little & Rubin, 2002).

Although limitations in analysing missing data have been identified in the literature, few studies have used socioeconomic position in relation to inflammation which also address potential biases due to missing data. One study using data from the English Longitudinal Study of Ageing and particular wave 4 applied a causal mediation method to examine the effects of four life course SEP models on a group of combined health indicators (self-rated health, presence of longstanding illness and the presence of one or more functional limitations) and on fibrinogen, a haemostatic and inflammatory biomarker. Full Information Maximum Likelihood (FIML) (Enders & Bandalos, 2001) was used to compensate for missing values in life course SEP and mediation-confounding variables after assuming Missing at Random. This paper used Linear Structural Equation Modelling (LSEM) after FIML but did not compare results from different missing data methods (Ploubidis et al., 2014). FIML is appropriate for structural equation modelling and longitudinal data (Enders, 2010). Although, FIML and Multiple Imputation (MI) give similar results and standard errors (Newman, 2003), MI can be superior to FIML when data are not multivariate normal (Allison, 2002).

Another study using data from the Atherosclerosis Risk in Communities (ARIC) study examined the effects of cumulative life course socioeconomic status (SES) on C-reactive protein (CRP), fibrinogen, white blood cell count (WBC), von Willebrand Factor (vWF) and overall inflammatory burden. Findings suggested that cumulative life course SES is inversely associated with adult inflammatory biomarker level. This study performed multilevel modelling with imputed SES characteristics and did not compare different missing data methods (Pollitt et al., 2008).

A study using data from Whitehall II examined the association between life course socioeconomic circumstances and Type-2 diabetes (T2DM) incidence, and then extended the research if the previous association can be explained by inflammatory biomarkers of C-reactive protein (CRP) and Interleukin 6 (IL-6). Findings suggested that life course socioeconomic disadvantage is associated with the risk of having T2DM and this association was explained by the high levels of C-reactive protein and IL-6. In this study, missing information in smoking, physical activity, diet and BMI were substituted with information from previous or successive waves. For missing data in health behaviours and inflammatory biomarker multivariate imputation was implemented using limited numbers of variables in the imputation model. This study, also, did not compare different missing data methods to examine the association between life course SEP and biomarkers (Stringhini et al., 2013). Using values from previous waves to decrease non-response is not recommended and it is considered a poor strategy because it is likely to produce distorted parameter estimates since it is assumed that the values do not change in time (Cook et al., 2004; Molenberghs & Kenward, 2007).

In ELSA, there are three stages of potential unit non-response: main interview, health examination and blood sample collection. Data for the main interview was collected with Computer Assisted Personal Interviews (CAPI) and self-completion questionnaires every two years with additional nurse visits for heath examination and collection of biomarkers every four years. Multiple data collections at various time points in longitudinal studies increase the possibility of wave non-response and attrition. In particular, biomarker data collected in inflammatory measures such as C-reactive protein are collected from blood samples, which typically have lower

response rates than the rest of the health and interview data due to refusal and inability to provide blood sample (Scholes et al., 2008).

Unit-nonresponse in population-based surveys is an inevitable feature and is typically addressed by calculating survey weights that adjust the sample for potential non-response bias in order to achieve representativeness of the sample (Groves et al., 2001; Groves & Peytcheva, 2008; Little, & Rubin, 2002). Inverse probability weighting is one way to compensate for the sequential unit non-response found in the ELSA study. This method corrects the distribution of the sample observations to approximate the distribution of the population from which the sample was collected. First, the survey weights are calculated to account for the attrition arising from the previous waves (i.e. wave 1). Then, response models are developed to identify predictors of non-response in each of the subsequent stages. The estimated response propensities are used to adjust the survey weights at each stage of the health examination and blood sampling. This approach does not account for item missing data where values of variables might be missing (Scholes et al., 2008).

Alternatively, given a response to the main interview with original survey weights to account for unit non-response, the subsequent stages of response (health examination and blood samples) can themselves be treated as item non-response and therefore multiple imputation methods can be applied. In multiple imputation, every missing item is replaced by values that represent a distribution of possibilities (Carpenter et al., 2006; Seaman et al., 2012). Although, multiple imputation has been often implemented, details of how the imputation model was chosen are rare in published papers in biosocial science.

Multiple imputation is usually more efficient than inverse probability weighting when the imputation model is well defined and structured (Seaman et al., 2012). However, when many variables are missing on same individuals the imputation model can be complicated and incorrectly specified. This issue arises in longitudinal studies with multiple data collections like ELSA where whole blocks of data are missing from participants either because participants missed visits or declined to answer whole sets of related questions. In situations like this one, inverse probability weighting is preferred (Seaman et al., 2012).

The two previously mentioned approaches for compensating for missing data assume a Missing at Random non-response mechanism where the imputation models can be built by covariates identified in the dataset. However, Missing Not at Random (MNAR) occurs when the missing data depends on the unobserved variable of interest for example if participants with high levels of C-reactive protein refused to participate in the blood sampling. MNAR is the most complicated type of non-response. In general, to deal with MNAR we need to identify instrumental variables which compensate for the selectivity of the missing data and these can be included in our imputation models with sensitivity analysis carried out to test assumptions. Furthermore, using MI for MNAR could reduce bias to negligible levels (Allison, 2002; Schafer, 1997).

This study will be based on a comparison of four approaches for compensating for missing data: complete case analysis, inverse probability weighting, unweighted and weighted multiple imputation assuming Missing at Random which will be compared with complete case analysis where the non-response is considered Missing Completely at Random. We note that pairwise deletion, substitution of means, regression predictions and other forms of single imputations perform poorly apart

from under very restricted circumstances, and therefore have not been considered further (Little & Rubin, 2002).

4.2.4 Aim, research questions and hypotheses

Our study aims to examine the association between socioeconomic position and inflammation in older adults as measured by C-reactive protein after compensating for missing data. Particularly, we aim to examine the following research questions and hypotheses:

1. What are the characteristics of participants who are less likely to have valid blood-based biomarker data?

Hypothesis:

We hypothesise that there is difference between respondents and non-respondents providing biomarker data in socioeconomic characteristics and health outcomes. In particular, we hypothesise that participants from lower socioeconomic position (Behr et al., 2005; Ekholm et al., 2010; Ferrie et al., 2009; Lepkowski & Couper, 2002) and participants with poor health (Ferrie et al., 2009; R.M. Groves & Cooper, 1998; Knies & Burton, 2014; Lepkowski & Couper, 2002; Uhrig, 2008), factors that are generally found to be associated with unit-nonresponse and attrition, will be less likely to provide the study with C-reactive protein measure blood sample. We also hypothesise people in older age categories (Lepkowski & Couper, 2002; Thomas et al., 2001), people from ethnic minorities (Lepkowski & Couper, 2002; Uhrig, 2008), singles (Gray et al., 1996; Uhrig, 2008), renters (Gray et al., 1996; Lepkowski & Couper, 2002; Nicoletti & Peracchi, 2005) and people living in urban areas (Burkam & Lee, 1998; Gray et al., 1996; Uhrig, 2008) are less likely to give blood sample with C-reactive protein analyte.

2. What is the association between socioeconomic position and inflammation under a complete case analysis?

Hypothesis:

We hypothesise that there is a negative association between socioeconomic position and levels of C-reactive protein in complete case analysis. Previous work using ELSA, with different approaches to define socioeconomic circumstances, found that people living in socioeconomic disadvantage circumstances had higher levels of inflammatory biomarkers (Na-Ek & Demakakos, 2016).

3. Is the association between socioeconomic position and inflammation greater after compensating for missing biomarker data?

Hypothesis:

We hypothesise that there is a negative association between socioeconomic position and levels of C-reactive protein even after accounting for missing data (Pollitt et al., 2008; Stringhini et al., 2013). We, also, hypothesise that after accounting for non-response, the socioeconomic position differences in inflammation will be greater.

We believe that if we do not account for missing data there will be underestimation of the socioeconomic position effects on biomarker data. If people with in socioeconomic disadvantage and people with poor health are not willing to participate there will be underrepresentation of these specific groups in the association of interest and this will lead to biased results.

Based on our previous hypotheses we consider that our missing data are Missing at Random and we will implement the appropriate missing data techniques (inverse probability weighting and multiple imputations) to address potential bias for the propensity of non-response.

4.3 Methods

4.3.1 Data and study population

The English Longitudinal Study of Ageing (ELSA) is a longitudinal study which commenced in 2002 that collects multidisciplinary data every two years from 11,391 core sample members of men and women aged over 50 years old living in private households in England. The sample was collected by using a multistage stratified random probability design from years 1998, 1999 and 2001 of the cross-sectional Health Survey of England (HSE).

Waves 2, 4 and 6 of ELSA include follow up interviews and health examinations including blood sample collections from previous waves.

Health examination: In ELSA, participants who were core members and were eligible to participate in the nurse visit were 7,666 (88%) people out of 8,780 core members in the main interview. The majority of those who did not participate were mainly due to refusal. Also, a small minority could not be contacted by the nurse. Although, this could be reflected as certain circumstances, it is also suggested that it could be a hidden refusal. Several other reasons such as illness or being away at the time of the visit explain the reason for non-response (Scholes et al., 2008). Non–respondents to the nurse visit were older men and women, participants who were living in North West, West Midlands, or London, who were in the semi-routine social class, who had fair or poor self-assessed health, who were current smokers and had low frequency of physical activity (Scholes et al., 2008).

Blood sample: Out of 7,666 core members who were eligible and accepted to participate in the health examination, 6,231 people (81.2%) gave consent and were eligible to give a blood sample. Non-respondents to the blood sample were more likely

to be men over 70 years of age and women over 65 years of age, those who were living in Yorkshire and the Humber, East Midlands, East of England, London or the South West, participants in semi-routine social class, those who had good, fair or poor self-assessed health, those who had low frequency of physical activity and limiting longstanding illness (Scholes et al., 2008).

C-reactive protein sample: Out of the 6,231 participants who provided with blood sample, 5,899 (94.6%) have C-reactive protein blood sample.

For more detailed information on the general design and implementation of the health examination and blood sampling, see Scholes et al (2008).

Our study uses cross-sectional data from wave 2 (2004-2006) of ELSA. Wave 2 had three data collections: the first is the follow up interview from wave 1, the second is baseline for the health examination survey and the third is the blood sampling. The second wave of ELSA includes 9,432 participants. Of these 8,688 were core members; 7,666 accepted the health examination and 6,231 gave blood consent and were eligible to participate. The final sample in C-reactive protein was obtained from 5,899 participants (more details are presented in Figure 4.1).

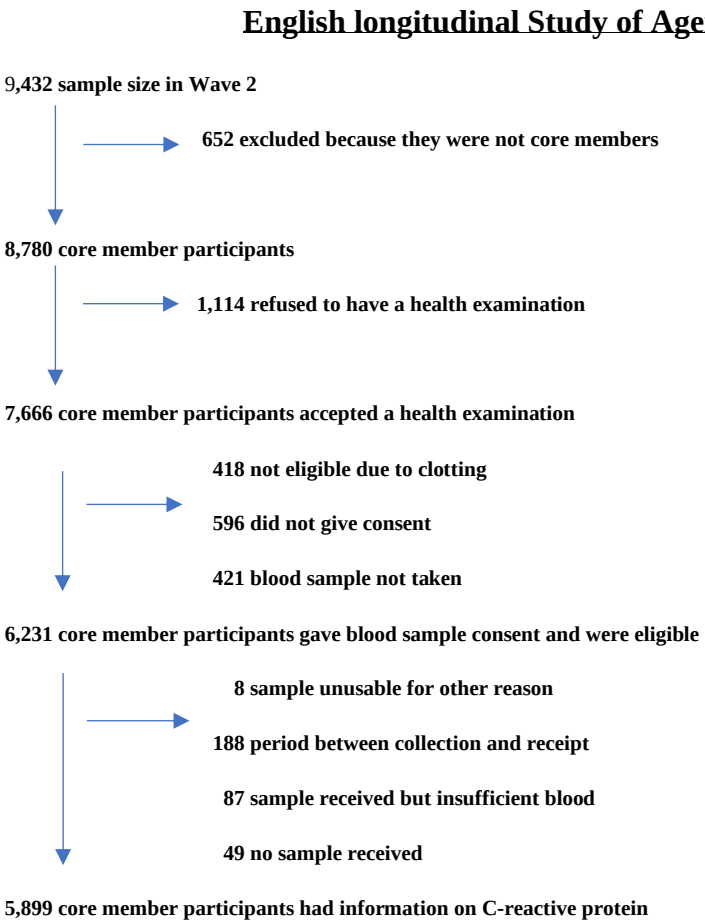


Figure 4. 1 Flowchart that shows the reduction of the sample size in different stages in the English Longitudinal Study of Ageing for wave2.

4.3.2 Measures

Inflammatory biomarker

C-reactive protein was measured from blood samples collected from the health examination. The health examination during the ELSA wave 2 was conducted by nurses who visited participants' home. The C-reactive protein variable was treated as a continuous variable and was logarithmically transformed to approach normal distribution.

Socioeconomic position

We use three different measures of socioeconomic characteristics to define the life course approach of the effects:

Early adulthood SEP: Education was measured as the highest qualification obtained and was classified into: university degree (NVQ5-4), higher education but without degree, high school (NVQ3-2) and foreign or no qualifications.

Late adulthood SEP: Total net wealth was categorized into quintiles (lowest to highest) and measured at benefit unit level. Financial assets such saving and investments were used to estimate the wealth variable (Ploubidis et al., 2011).

The National Statistics Socio-Economic Classification scheme (NS-SEC) was used to measure social class which describes conditions and types of employability. The social class variable was divided into five categories: I. Managerial & Professional, II. Intermediate, III. Small employers & own account workers, IV. Lower supervisory & Technical occupations and V. Semi routine & Routine & other occupations. The hierarchical Register General classification considers non-manual occupations as "higher SEP" compared to manual occupations (Bartley, 2004). We also use employment status determined by employed, retired and not employed and not retired categories to assess the interaction with social class.

Covariates

Age, gender, marital status (married, cohabiting, single, widowed and divorced/separated) and ethnicity (Whites and non-Whites) were taken into consideration to the analysis as could potentially confound the association of interest.

4.3.3 Statistical Modelling

This section provides details of complete case analysis and of the process used to build the response model for the inverse probability weighting procedure and develop an imputation model.

4.3.3.1 Complete case analysis

We performed linear regression modeling to examine the association between socioeconomic position and C-reactive protein. We log transformed the C-reactive protein variable to achieve normal distribution. Bivariate analysis showed that there was significant interaction between social class and employment and between age categories and gender and therefore we included the interaction term into the model of interest (Appendix A). We adjusted the model of interest for potential confounders: age, gender, age and gender interaction, marital status and ethnicity. In complete case analysis, we excluded every participant with at least one missing value in the variables included in the model of interest and in the response model (Table 4.1). The total number of the missing values in independent variables and covariates was 260 participants (see Figure 4.2).

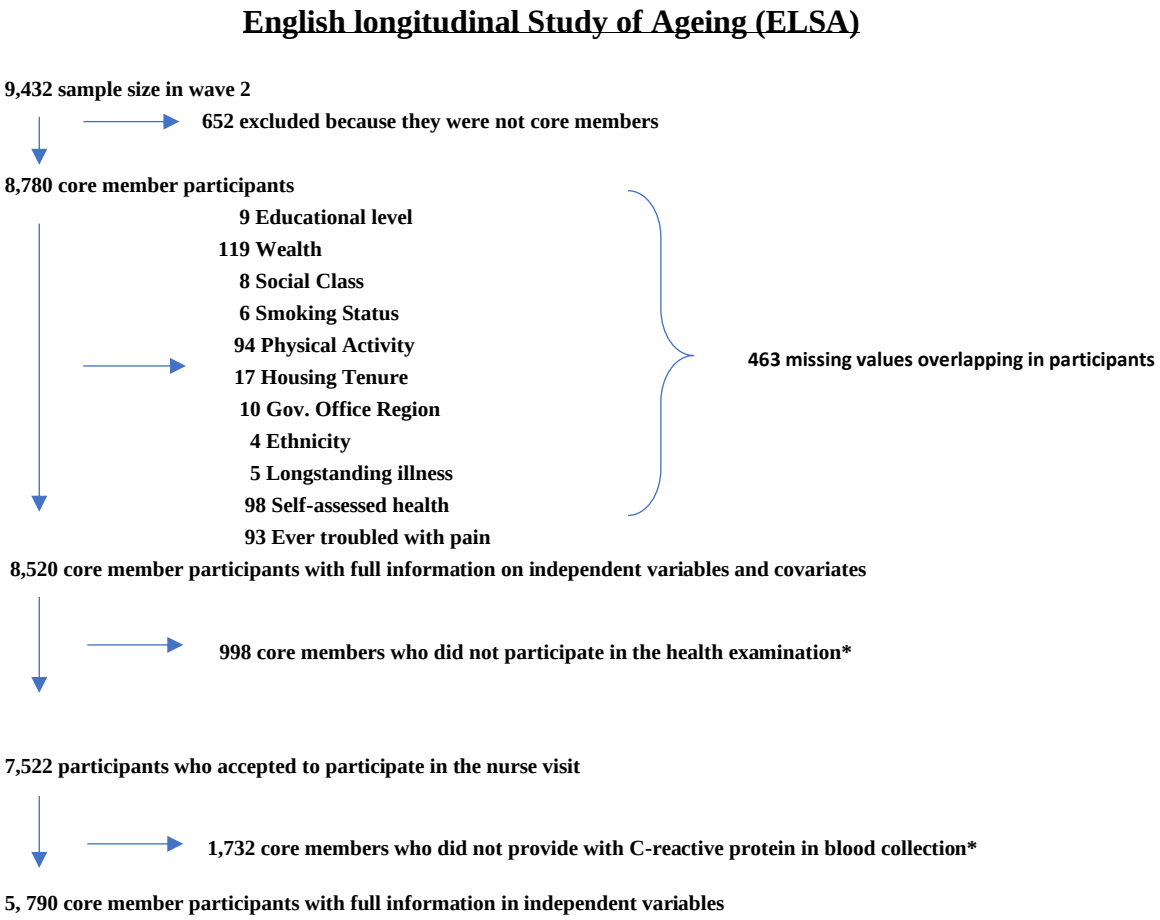


Figure 4. 2 Final sample size after deleting each participant with at least one missing value in independent variables and covariates

---

Note: 1. Missing values overlap in participants.

2. Employment status, age, gender, marital status, ever diagnosed with high blood pressure, ever diagnosed with stroke, and ever diagnosed with CVD outcomes had 0 missing values.

* more details on non-response in the Appendix B.

4.3.3.2 Inverse probability weighting methodology

The first step for inverse probability weighting to reduce bias from missing data is to choose the variables that influence the probability of being a complete case. We identified a priori candidate predictors of missingness based on findings in the ELSA technical report (Scholes et al., 2008) and on the broader literature (Gustman & Steinmeier, 2004; Kho et a., 2009) to describe those participants who did not provide C-reactive protein in the blood collection (Table 4.1). The identification process was implemented by creating a binary (dichotomous) variable indicating whether participants provided C-reactive protein in the blood sampling which assumes the

value of 1 and 0 otherwise. Then we carried out logistic regression to investigate which variables predicted the participation in the two data collections. The variables that we identified for the C-reactive blood collection are the following: social class, age and gender, smoking status, physical activity, marital status, ethnicity, housing tenure, Government Office Region, self-assessed health, asthma diagnosis, limiting long-standing illness, ever diagnosed with High Blood Pressure, ever diagnosed with Stroke, ever diagnosed with CVD and ever troubled with pain.

The weighting strategy for the wave 2 main interview constructed by the ELSA study aims to reduce bias in the sample resulting from differential non-response to the longitudinal survey. The wave 2 main interview attrition weight variable was calculated as the inverse of the predicted response probability. The variables that were found to be related to the nonresponse from wave 1 to wave 2 were the following: whether interviewed in HSE, limiting longstanding illness, social class, Government Office Region, year sampled for HSE, ethnicity, tenure, marital status, educational status, whether a current smoker, and age by sex dummy variable (Scholes et al., 2008).

The second step in inverse probability weighting included the combination of wave 2 main interview attrition weight with the non-response weight that we produced for those people who did not provide C-reactive protein in the blood collection. We calculated the new non-response weights as the inverse of the predicted response probabilities predicted from the previously mentioned logistic regression models with the predictors of missingness in the blood collection for C-reactive protein.

In the third step, we performed weighted complete case analysis implementing weighted linear regression modelling. The weighting variable was the final non-

response weight from the blood collection of C-reactive protein. The model of interest was similar to the model of unweighted complete case analysis including both interaction terms. We included log transformed C-reactive protein, educational level, wealth, social class and the interaction between social class and employment status and we adjusted for age, gender, interaction between age and gender, marital status and ethnicity.

4.3.3.3 Multiple imputation methodology

The imputation model consisted of the variables that are thought to predict or be associated with missing values in our data. We used the predictor variables from the inverse probability weighting method (Table 4.1) and we also included the variables from the model of interest. We deleted all the variables with at least one missing value because variables which themselves have missing data can limit the amount of information added in the imputation model (von Hippel, 2009). We performed multiple imputation by chained equations to impute missing information in C-reactive protein. Fifteen imputed datasets were created based on the general pattern of the adequate number of imputations recommended (Schafer, 1999). We also tested for relative efficiency (Rubin, 1987).

The variables that were included in the models of interest (and therefore in the imputation model) were log transformed C-reactive protein and independent variables. We estimated linear regression models for the association of socioeconomic position and C-reactive protein and we adjusted the model for age, gender, interaction between age and gender, marital status, ethnicity along with the predictive variables of missingness.

It is generally known that transformed variables and interaction terms should be included in the imputation model in order to emphasize the relationship between the

transformed variables (log transformed variables) and the interaction terms with the outcome of interest.

4.3.3.4 Multiple imputation with attrition weights

Another approach to compensate for missing data is to implement multiple imputation with wave 2 main interview attrition weight (survey weight) which is an ELSA-derived variable. We used the imputation model from the aforementioned multiple imputation and we weighted it using the attrition weight of wave 2 from the main interview. The survey weight was used to adjust for attrition from the main interview while missing values in C-reactive protein variable were multiply imputed.

All models were estimated in STATA V14 SE.

4.4 Results

4.4.1 Models of response to health examination and blood sample

The non-respondent analysis used demographic and health-related population characteristics from ELSA. In Table 4.1, people with a semi-routine or routine occupation were less likely [OR=0.87(95%CI=0.77 to 0.99)] to have a C-reactive protein blood sample compared with those from managerial and professional occupations. Older men [OR=0.63(95%CI=0.40 to 0.98) and women [OR=0.57(95%CI=0.39 to 0.84)] were less likely to have a C-reactive protein blood sample compared to younger men. Current smokers were less likely [OR=0.85(95%CI=0.73 to 0.98)] to have a sample compared to smokers. Those who were exercising hardly never [OR=0.71(95%CI=0.60 to 0.84)] were less likely to have sample compared to those exercising frequently. Non-white ethnic groups were less likely [OR=0.50(95%CI=0.36 to 0.68)] to have a C-reactive protein sample compared to White British people. People who lived in a rented accommodation were less likely

[OR=0.77(95%CI=0.68 to 0.88)] to have a C-reactive protein biomarker sample compared to those who lived in an owned outright accommodation. People living in Yorkshire [OR=0.75(95%CI=0.60 to 0.95)], the East Midlands [OR=0.71(95%CI=0.56 to 0.91)], the East of England [OR=0.78(95%CI=0.62 to 0.99)], London [OR=0.65(95%CI=0.51 to 0.83)] and the South West [OR=0.73(95%CI=0.58 to 0.92)] were less likely to have a C-reactive protein blood sample compared with the North East of England. People with good [0.69(0.58 to 0.83)], fair [OR=0.56(95%CI=0.46 to 0.69)] and poor [OR=0.44(95%CI=0.34 to 0.57) self-assessed health were less likely to have a C-reactive protein blood sample compared to those with excellent health. Those diagnosed with health conditions such as: High Blood Pressure [OR=0.85(95%CI=0.77 to 0.94)], Stroke [OR=0.75(95%CI=0.61 to 0.93), any of CVD outcomes [OR=0.74(95%CI=0.66 to 0.83)] were less likely to have C-reactive blood sample compared to healthier people. Those who had no trouble with pain [OR=0.82(95%CI=0.75 to 0.94)] were less likely to have C-reactive protein blood sample compared to those who had trouble.

People with asthma [OR=1.18(95%CI=1.02 to 1.36)] were more likely to have C-reactive protein biomarker data compared with people without asthma. Those with longstanding illness but not limiting [OR=1.16(95%CI=1.01 to 1.33)] were more likely to have C-reactive protein blood sample compared to those without longstanding limiting illness. Those who had trouble with pain [OR=1.13(95%CI=1.01 to 1.27)] were more likely to have C-reactive protein blood sample compared to those who had no trouble.

Table 4. 1 Non-response model to C-reactive protein blood observation

Variables	*N (%)*	*OR (SE)*	*95% Confidence Intervals*	
Social class				
Managerial & Professional	2,594(30.45)	1(ref)		
Intermediate	1,172(13.76)	0.98(0.08)	0.84	1.16
Small employers & own account	899(10.55)	1.04(0.09)	0.87	1.24
Lower supervisory	919(10.79)	1.06(0.09)	0.89	1.26
Semi-routine & routine & others	2,936(34.46)	0.87(0.05)	0.77	0.99
Age & Gender				
Male 50-54	338(3.97)	1(ref)		
Male 55-59	826(9.69)	0.75(0.11)	0.55	1.01
Male 60-64	655(7.69)	0.93(0.15)	0.68	1.28
Male 65-59	642(7.54)	0.93(0.15)	0.67	1.26
Male 70-74	549(6.44)	0.70(0.11)	0.51	0.96
Male 75-79	421(4.94)	0.67(0.11)	0.48	0.94
Male 80-84	260(3.05)	0.71(0.13)	0.49	1.03
Male 85+	140(1.64)	0.63(0.14)	0.40	0.98
Female 50-54	389(4.57)	0.77(0.13)	0.54	1.08
Female 55-59	959(11.26)	0.86(0.13)	0.63	1.15
Female 60-64	786(9.23)	0.71(0.11)	0.53	0.97
Female 65-69	732(8.59)	0.72(0.11)	0.53	0.98
Female 70-74	631(7.41)	0.67(0.11)	0.49	0.94
Female 75-79	528(6.20)	0.65(0.11)	0.47	0.90
Female 80-84	419(4.92)	0.50(0.09)	0.35	0.70
Female 85+	245(2.88)	0.57(0.11)	0.39	0.84
Smoking Status				
Non-smoker	3,091(36.28)	1(ref)		
Ex-smoker	4,133(48.51)	1.00(0.05)	0.90	1.11
Current smoker	1,296(15.21)	0.85(0.06)	0.73	0.98
Physical Activity				
More than once a week	6,565(77.05)	1(ref)		
Once a week	874(10.26)	0.96(0.08)	0.82	1.12
One to three times a month	304(3.57)	0.91(0.12)	0.71	1.18
Hardly ever or never	777(9.12)	0.71(0.06)	0.60	0.84
Marital status				
Married	5,484(64.37)	1(ref)		
Cohabiting	262(3.08)	1.23(0.18)	0.92	1.65
Single	412(4.84)	0.80(0.09)	0.65	1.01
Widowed	1,571(18.44)	0.95(0.07)	0.82	1.09
Divorced/Separated	791(9.28)	0.90(0.08)	0.76	1.06

Continued from previous page

Ethnicity				
White	8,334(97.82)	1(ref)		
Non-White	186(2.18)	0.50(0.08)	0.36	0.68
Housing Tenure				
Owners	6,978(81.90)	1(ref)		
Renters	1,428(16.76)	0.77(0.08)	0.68	0.88
Others	114(1.34)	0.92(0.19)	0.62	1.38
Government Office region				
North East	554(6.50)	1(ref)		
North West	1,109(13.02)	0.82(0.10)	0.65	1.03
Yorkshire	933(10.95)	0.75(0.09)	0.60	0.95
East Midlands	874(10.26)	0.71(0.09)	0.56	0.91
West Midlands	911(10.69)	0.92(0.11)	0.72	1.17
East of England	1,005(11.80)	0.78(0.09)	0.62	0.99
London	770(9.04)	0.65(0.08)	0.51	0.83
South East	1,355(15.90)	0.95(0.11)	0.75	1.19
South West	1,009(11.84)	0.73(0.09)	0.58	0.92
Self-assessed health				
Excellent	1,043(12.24)	1(ref)		
Very good	2,347(27.55)	0.90(0.08)	0.76	1.08
Good	2,699(31.68)	0.69(0.06)	0.58	0.83
Fair	1,762(20.68)	0.56(0.06)	0.46	0.69
Poor	669(7.85)	0.44(0.06)	0.34	0.57
Ever diagnosed with asthma				
No	7,418(87.07)	1(ref)		
Yes	1,102(12.93)	1.18(0.09)	1.02	1.36
Limiting long-standing illness				
No long-standing illness	3,614(42.42)	1(ref)		
Has long-standing illness no limiting	1,839(21.58)	1.16(0.08)	1.01	1.33
Has limiting long-standing illness	3,067(36.00)	1.10(0.08)	0.95	1.26
Ever diagnosed with high blood pressure				
No	4,731(55.53)	1(ref)		
Yes	3,789(44.47)	0.85(0.04)	0.77	0.94
Ever diagnosed with Stroke				
No	8,083(94.87)	1(ref)		
Yes	437(5.13)	0.75(0.08)	0.61	0.93
Ever diagnosed with CVD				
No	5,846(68.62)	1(ref)		
Yes	2,674(31.38)	0.74(0.04)	0.66	0.83

Continued from previous page

Whether often troubled with pain				
No	5,262(61.76)	1(ref)		
Yes	3,258(38.24)	1.13(0.06)	1.01	1.27

Notes:

1. The response was 1=had an observation of C-reactive protein (5,790) 0= did not have an observation of C-reactive protein (2,730)
2. Only 8,520 participants who were core member completing a full main interview were included
3. Only variables that were significant in the level 5% were included in the model.
4. The model R_2=0.0483
5. Odds are expressed relative to a reference category. Odds ratios greater than 1 indicate higher odds while ratios lower than 1 indicate lower odds.

4.4.2 Descriptive analysis

In Table 4.2, we present an unweighted and weighted population in categories and also unweighted and weighted means of every category in explanatory variables. We used the blood weight we created after taking into consideration the covariates mentioned in paragraph 4.4.1. The differences between weighted and unweighted means are not significant, however, the weighted means are increased compare to unweighted

Table 4. 2 Descriptive statistics of C-reactive protein with independent variables and employment status

Variables	N (%) **	N** weighted (%)	Mean (SD)	Weighted Mean (SD)
Independent variables				
Educational level				
Higher Education	730(12.9)	632(10.92)	2.99(7.49)	3.00(8.13)
Higher Education but no degree	743(12.55)	663(11.46)	3.50(6.75)	3.67(8.13)
High school	1,717(29.65)	1,616(27.91)	3.65(5.83)	3.79(6.24)
Foreign or no qualifications	2,600(44.90)	2,878(49.71)	4.93(10.5)	5.37(12.04)
Wealth quintiles				
Highest quintile	1,239(21.89)	1,092(18.87)	2.83(5.91)	2.89(6.34)
Second quintile	1,266(21.86)	1,174(20.29)	3.63(7.92)	3.85(9.37)
Third quintile	1,195(20.16)	1,159(20.02)	4.16(6.99)	4.27(7.34)
Fourth quintile	1,123(19.39)	1,134(19.60)	4.58(9.50)	5.19(13.84)
Lowest quintile	967(16.7	1,228(21.21)	5.83(11.98)	6.01(10.75)
Social class				
Managerial & Professional	1,860(32.12)	1,637(28.29)	3.43(6.65)	3.53(7.25)
Intermediate	809(13.97)	756(13.07)	4.11(10.8)	4.34(12.18)
Small employers & own account	635(10.96)	615(10.62)	3.95(7.31)	4.14(7.53)
Lower supervisory & technical	633(10.95)	664(11.47)	4.79(9.04)	5.13(10.40)
Semi routine & technical &other	1,853(32)	2,115(36.54)	4.65(9.33)	5.15(11.31)
Employment status*				
Employed	1,811(31.27)	1,718(29.68)	2.81(3.97)	2.84(4.09)
Retired	3,039(52.48)	3,061(52.88)	4.75(10.12)	5.07(10.91)
Not employed & not retired	940(16.25)	1,009(17.44)	4.61(9.36)	5.46(13.06)

Note: *Employment status variable is described for the purpose of the interaction term between social class and employment status **Total number of participants=5,790. Blood weight variable for C-reactive protein.

4.4.3 Multivariable analyses

Bivariate analysis can be found in the Appendix A.

This section compares the results of four different statistical methods compensating for missing data. Complete case analysis results are presented first then follow the results follow from inverse probability weighting and then the results from unweighted and weighted multiple imputation (Table 4.3). For all methods, participants with foreign or no qualifications had higher levels of C-reactive protein compared to participants with higher education although there is variation in the effect sizes, there is a clear gradient within the categories of the educational level in the levels of C-reactive protein.

This is also noticeable in the wealth quintiles where participants in lower quintiles have higher levels of C-reactive protein compared to those in the highest quintile. The results are statistically significant to all methods with few differences in the effects sizes.

Participants in the intermediate occupation category have lower levels of C-reactive protein compared to those in managerial and professional occupation category. The effects sizes are almost like all methods however, only in the multiple imputation the association is not significant and in the inverse probability weighting method the effect size is larger compared to the rest of the methods.

While investigating the interaction term between occupational class and employment status, we notice that only the category of participants who are in the intermediate occupational class category and currently are not employed and not retired have statistically significant higher level of C-reactive protein compared to those who are in a managerial position and currently employed. However, this association is

significant only in complete case analysis. Furthermore, participants who are small employers and belong to a lower supervisory occupational class but are not currently employed and not retired have higher levels of C-reactive protein; this association is only significant in the inverse probability weighting model.

In Figures 4.3-4.6, we present the predicted values of the independent variables on C-reactive protein in four different statistical procedures. Figures 4.3 and 4.4 show levels of C-reactive protein are higher for people with lower educational level and in lower wealth quintiles. There are also differences between the statistical methods. In MI with attrition weights, the levels of C-reactive protein are higher compared to the other methods. Figures 4.5 and 4.6 show that there is no gradient in the social class and in the interaction between social class and employment status categories. Figure 4.6 shows that retired people in lower supervisory position and people who are currently not employed and not retired but are categorised in a lower supervisory position have higher levels of C-reactive protein compared to people currently employed in managerial occupation.

Table 4. 3 Multivariable analysis in four different statistical methods adjusted for covariates

Variables	*N (%)*	*Complete case analysis*	*Inverse Probability Weighting*	*Multiple Imputation*	*Multiple imputation with attrition weights*
Independent variables		*b(SE)*			
Educational level					
Higher Education	730(12.9)	(ref)	(ref)	(ref)	(ref)
Higher Education but no degree	743(12.55)	0.15(0.06) *	0.16(0.06) **	0.14(0.05) **	0.15(0.05) **
High school	1,717(29.65)	0.16(0.05) **	0.16(0.05) **	0.14(0.05) **	0.16(0.05) **
Foreign or no qualifications	2,600(44.90)	0.23(0.05) **	0.25(0.05) **	0.22(0.05) **	0.23(0.05) **
Wealth quintiles					
Highest quintile	1,239(21.89)	(ref)	(ref)	(ref)	(ref)
Second quintile	1,266(21.86)	0.16(0.04) **	0.16(0.04) **	0.15(0.04) **	0.16(0.04) **
Third quintile	1,195(20.16)	0.34(0.05) **	0.34(0.05) **	0.34(0.04) **	0.35(0.05) **
Fourth quintile	1,123(19.39)	0.36(0.05) **	0.36(0.05) **	0.36(0.05) **	0.37(0.05) **
Lowest quintile	967(16.7)	0.51(0.05) **	0.49(0.05) **	0.52(0.05) **	0.52(0.06) **
Social class					
Managerial & Professional	1,860(32.12)	(ref)	(ref)	(ref)	(ref)
Intermediate	809(13.97)	-0.19(0.09) *	-0.20(0.08) *	-0.16(0.08)	-0.14(0.08)
Small employers & own account	635(10.96)	-0.11(0.08)	-0.11(0.08)	-0.08(0.08)	-0.10(0.08)
Lower supervisory & technical	633(10.95)	-0.03(0.09)	-0.003(0.09)	0.0003(0.09)	0.009(0.09)
Semi routine & technical &other	1,853(32.00)	-0.08(0.07)	-0.10(0.07)	-0.04(0.07)	-0.06(0.07)
Employment status					
Employed	1,811(31.27)	(ref)	(ref)	(ref)	(ref)
Retired	3,039(52.48)	0.14(0.06) *	0.16(0.06) *	0.18(0.05) **	0.18(0.06) *
Not employed & not retired	940(16.25)	0.14(0.09)	0.15(0.09)	0.19(0.09) *	0.16(0.09)
Interaction term between					
Social Class X Employment status Δ					
Managerial X Employed	894(34.46)	(ref)	(ref)	(ref)	(ref)
Intermediate X Retired	660(56.31)	0.14(0.10)	0.14(0.11)	0.10(0.10)	0.09(0.10)
Intermediate X Not employed & Not Retired	212(18.09)	0.06(0.15) *	0.05(0.15)	0.03(0.14)	0.04(0.15)
Small employers X Retired	404(44.94)	0.12(0.11)	0.11(0.11)	0.08(0.10)	0.11(0.10)
Small employers X Not employed & Not Retired	161(17.91)	0.21(0.15)	0.31(0.16) *	0.15(0.15)	0.22(0.14)
Lower supervisory X Retired	541(58.87)	0.17(0.11)	0.16(0.11)	0.13(0.11)	0.11(0.11)
Lower supervisory X Not employed & Not Retired	153(16.65)	0.27(0.17)	0.22(0.17)	0.19(0.15)	0.20(0.16)
Semi routine X Retired	1,540(52.45)	0.15(0.08)	0.16(0.08)	0.09(0.07)	0.10(0.08)
Semi routine X Not employed & Not Retired	719(24.49)	0.16(0.12)	0.23(0.12)	0.10(0.11)	0.16(0.11)

Notes: 1) * indicates significance in level 5% & ** indicates significance in level 1%

2) Models adjusted for: age, gender, age*gender, marital status and ethnicity

3) Complete Case Analysis=5,790 participants, Inverse Probability Weighting methods=5,790 participants, Multiple Imputation=8,520 participants, Weighted Multiple Imputation=8,520 participants

4) Δ Percentages are calculated in relation to the categories of social class i.e. Managerial & Professional, Intermediate etc.

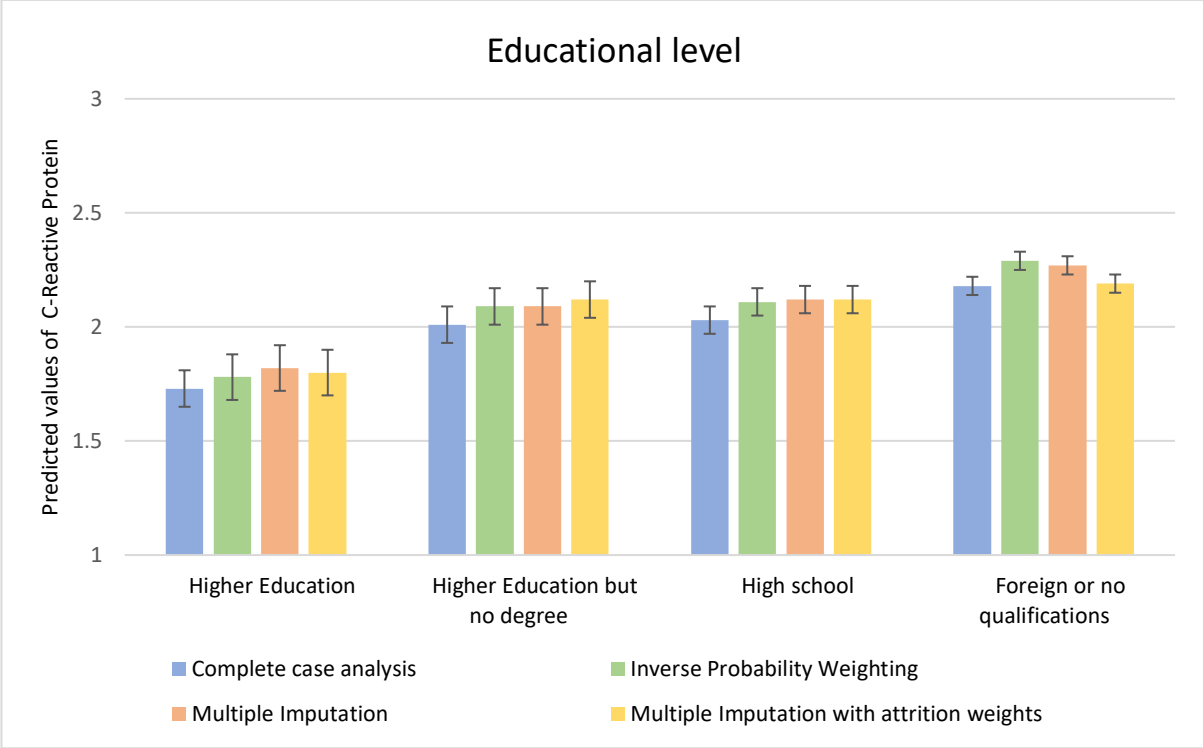


Figure 4. 3 Predicted values of C-reactive protein in educational level in four statistical methods

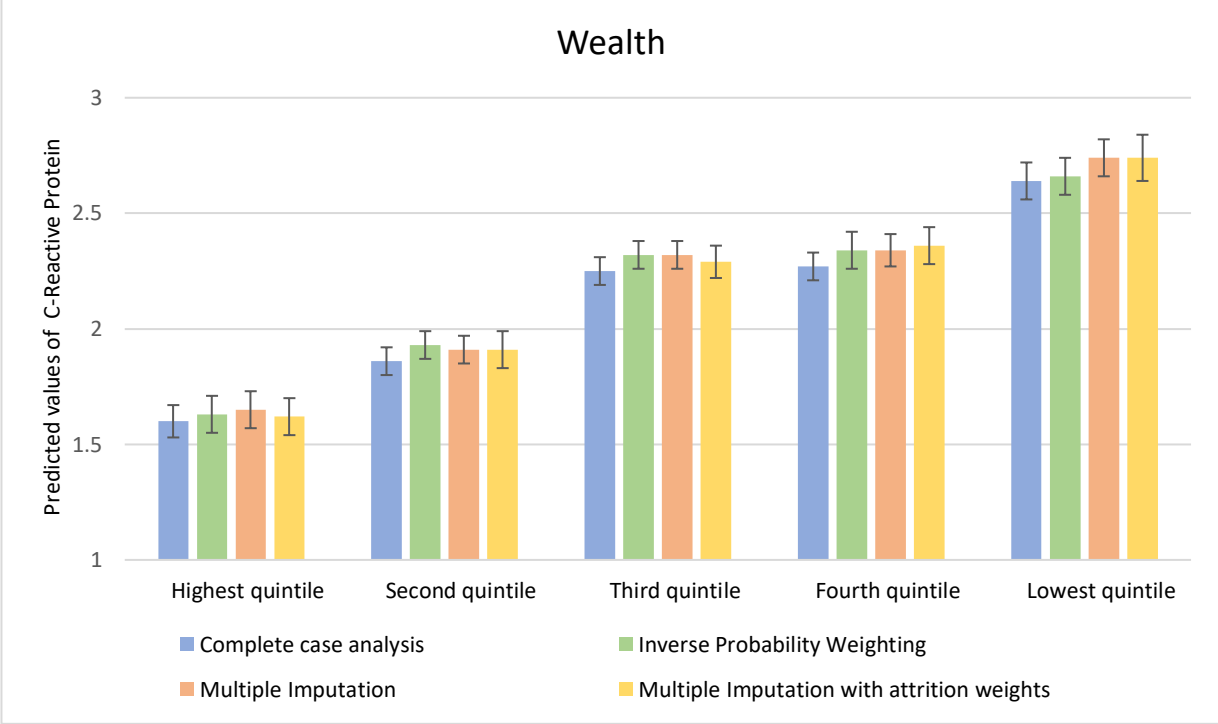


Figure 4. 4 Predicted values of C-reactive protein in wealth category in four statistical methods

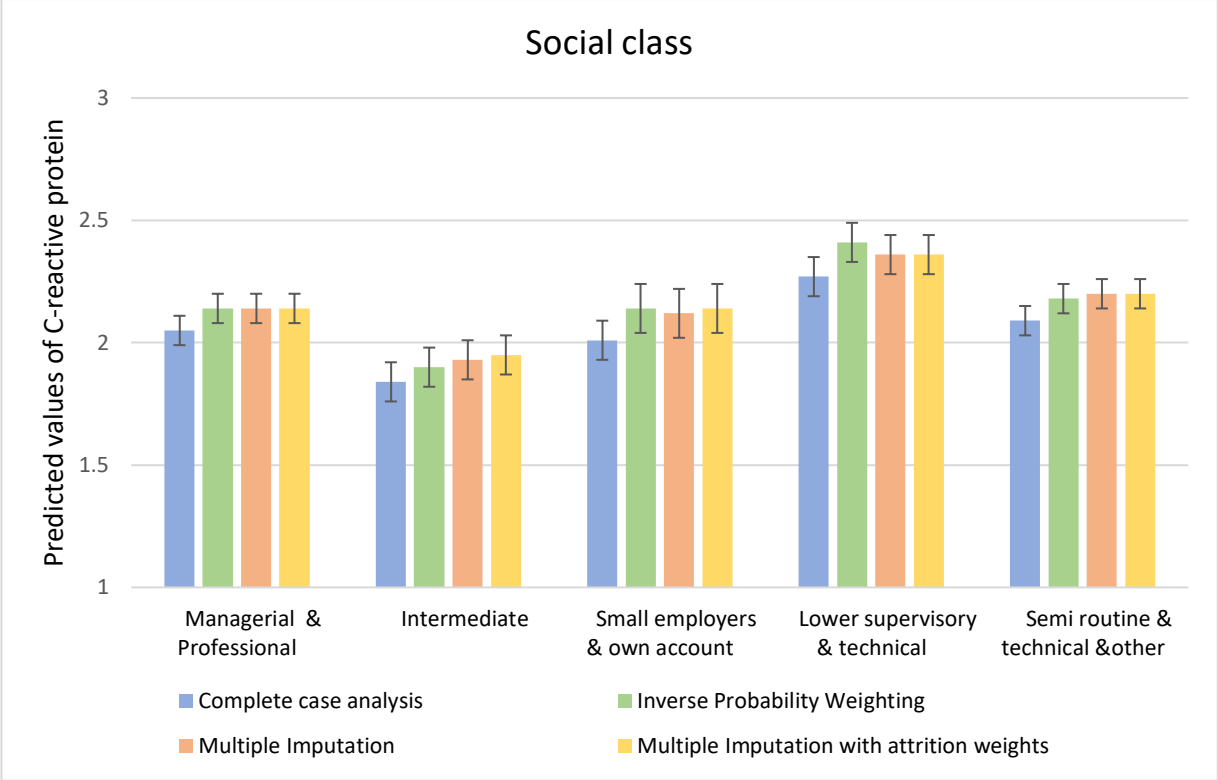


Figure 4. 5 Predicted values of C-reactive protein in social class category in four statistical methods

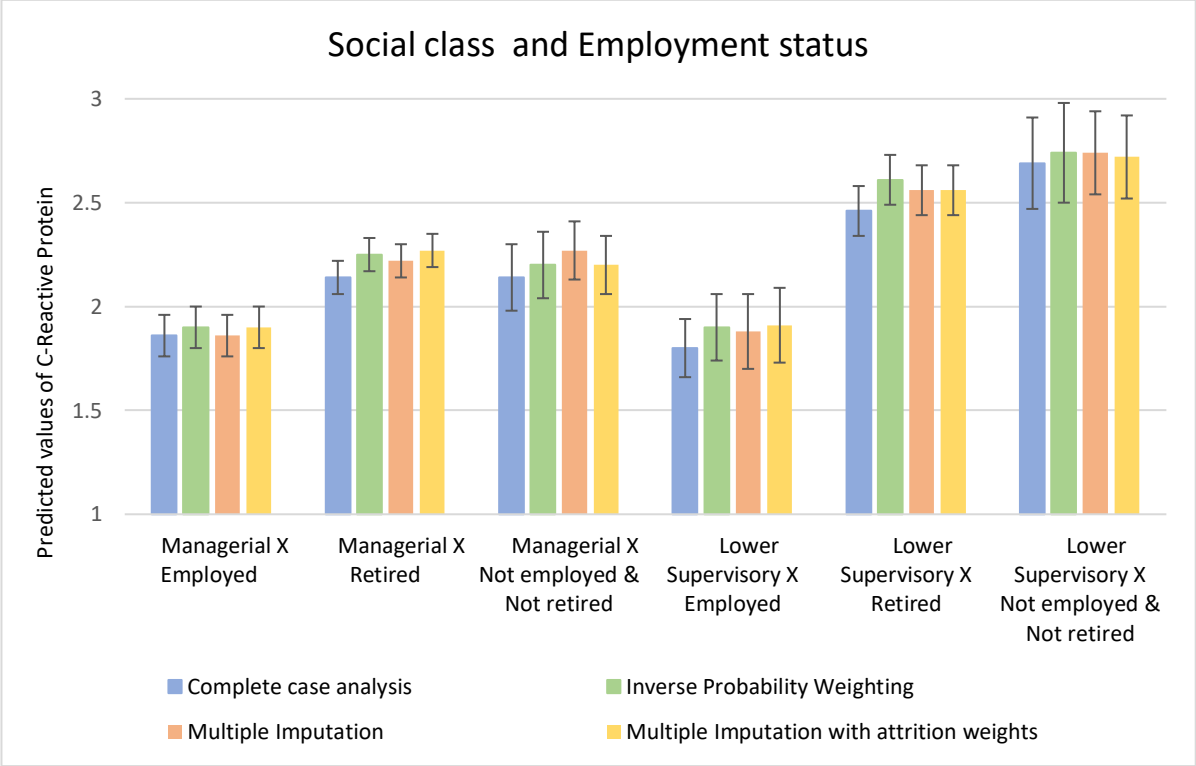


Figure 4. 6 Predicted values of C-reactive protein in the interaction between social class and employment status categories in four statistical methods. Illustration of only managerial and lower supervisory categories in social class.

4.5 Discussion

Our study findings suggest that people with social disadvantage and older men and women were less likely to have C-reactive protein biomarker data. Current smokers, renters and people who do not exercise often, people in non-white ethnic groups and those who live in urban areas were less likely have a C-reactive protein sample. In accordance with our hypothesis people with poor health were also less likely to have a C-reactive protein blood sample. Participants who have been diagnosed with certain health outcomes such as high blood pressure, stroke, CVD were less likely to have a C-reactive protein blood sample.

On the other hand, people with asthma, with longstanding but no limiting illness and people who troubled with pain were more likely to have C-reactive protein biomarker data.

Our study findings, also, suggest that there are significant associations between C-reactive protein and socioeconomic characteristics. In accordance with our hypothesis, there is a negative association between socioeconomic position and levels of C-reactive protein. People with lower educational attainment, people in lower wealth quintile and in lower social class were more likely to have higher levels of C-reactive protein, even after accounting for missing data compared to those with a university degree, in the highest wealth quintile and working in managerial and professional occupations. The results in different statistical analyses which account for missing data are similar with some variation in the estimates. However, after examining the predicted values of the C-reactive protein we can see that there is an underestimation of the effect of socioeconomic position on C-reactive protein levels. Results from the inverse probability weighting and multiple imputation models show that the levels of C-reactive protein are higher than in complete case analyses after accounting for the

characteristics of missing participants. Therefore, we suggest that by not accounting for missing data, there is high risk of losing important information from participants who have missing biomarker data.

4.5.1 Comparisons of our results with previous findings

Our findings are similar to previous studies which analysed consent bias and differences between respondent and not respondents in surveys based on socioeconomic disadvantage (Behr et al., 2005; Ekholm et al., 2010; Ferrie et al., 2009; Lepkowski & Couper, 2002). In particular, our findings were similar to studies which found that older people were less likely to give consent to participate in a survey (Gustman & Steinmeier, 2004; Lepkowski & Couper, 2002; Thomas et al., 2001). Similarly, our findings suggested that participants who were diagnosed with health conditions were less likely to have biomarker data and these findings are consistent with other studies which found that poor health status was a reason for non-consent. (Ferrie et al., 2009; Groves & Cooper, 1998; Knies & Burton, 2014; Kho et al., 2009;Lepkowski & Couper, 2002; Uhrig, 2008). Furthermore, we found that people from non-white ethnic groups (Lepkowski & Couper, 2002; Uhrig, 2008), singles (Gray et al., 1996; Uhrig, 2008), renters (Gray et al., 1996; Lepkowski & Couper, 2002; Nicoletti & Peracchi, 2005) and people living in urban areas (Burkam & Lee, 1998; Gray et al., 1996; Uhrig, 2008) are less likely to respond to health examination and blood sampling and findings were consistent with previous studies.

In accordance with previous studies which did not compensate for missing data, we found that participants living in socioeconomically disadvantaged circumstances had higher levels of C-reactive protein (Kivimaki et al., 2005; Loucks et al., 2010; Stringhini et al., 2013). Our findings were also similar with studies who compensated

for missing data although we did not follow similar statistical approaches (Ploubidis et al., 2014; Pollitt et al., 2008; Stringhini et al., 2013).

4.5.2 Methodological considerations

This study is the first to compare three different missing data methods while investigating the association between socioeconomic position and inflammatory biomarkers (i.e. C-reactive protein) in the English Longitudinal Study of Ageing. Among the strengths of our study is the use of a well-established longitudinal study that provides many variables which allow us to explore potential confounders and auxiliary variables that can predict missingness. This study used three indicators for socioeconomic position which describe comprehensively socioeconomic position characteristics.

A significant strength of our study is that we compensate for missing data using inverse probability weighting and multiple imputation and multiple imputation with attrition weights to assess the association between socioeconomic position and inflammation. Since almost a quarter of the initial sample size is lost (as seen in Figure 4.1) during the process of the health examination and the blood subsample, the application of missing data methodology was essential to draw unbiased conclusions. This study has also several limitations which are essential to be mentioned while interpreting our results. Also, based on our substantive topic, we have not taken into consideration several mediators that may affect our association such as medication usage, pre-existing high BMI and statin therapy (Ridker et al., 2005). Another limitation of our study is that we included participants with levels of C-reactive protein over 10mg/L; such high levels of C-reactive protein indicate acute inflammation (caused by cold or flu) (Pearson et al., 2003).

A further limitation of this study is the lack of a longitudinal scope of missing data in other waves of ELSA that collected biomarker data (i.e. waves 4 and 6) which could provide more information for non-response, thus better-established results for the associations of interest. However, a longitudinal approach is within our scope for future research.

With regards to the missing data processes our missing data exploration did not include sensitivity analyses which may provide evidence whether our non-response data are identified as MNAR (Little & Rubin, 2002). However, it is mentioned in the literature that MI can also consider MNAR if we include in the imputation model observed variables that could be covariates of the variable with the missing values (Allison, 2002; Schafer, 1997). For instance, we included in our imputation model variables that are related to health outcomes (i.e. ever diagnosed with High blood pressure/cancer/CVD /stroke) and variables that indicate a health statement (i.e. self-assessed health, limiting longstanding illness and ever troubled with pain) which could be covariates of the outcome variable, C-reactive protein. Although, the process of constructing an imputation model is complicated and there is always the risk of increasing parameter bias if it is done poorly, this study used many variables to produce a satisfactory imputation model.

4.5.3 Implications of our findings

Our study findings implicate the influence of socioeconomic position and health. The association between educational level, wealth and occupational class, and C-reactive protein indicates that advantaged adulthood socioeconomic circumstances play a significant role to chronic inflammation. Although, our findings while examining the interaction between occupational class and employment status are not statistically significant in the analyses, it is suggested that being currently at work is beneficial for

health. This could be explained because people with health disabilities are more likely to retire sooner due to ill health conditions (Dorn & Souza-Posa, 2004a; Madero-Cabib & Kaeser, 2016). Furthermore, people in professional and managerial occupations show more job satisfaction and less propensity to retire sooner. It is worth mentioning that the effect of health in early retirement is mediated by occupational class and education level (Dorn & Souza-Posa, 2004a).

4.5.4 Conclusion

Socioeconomic disadvantaged circumstances are associated with inflammation in adulthood after adjusting for covariates and after accounting for missing data. While associations between socioeconomic position and inflammatory markers were similar across different approaches for compensating for missing data, there were differences in the estimated coefficients and predicted estimates suggesting an underestimation of predicted C-reactive protein levels among the most disadvantaged social groups compared to the complete case analysis. We argue that it is important to account for missing biomarker data for appropriate statistical inference.

CHAPTER 5. Is socioeconomic disadvantage a chronic stressor? Socioeconomic position effects on cortisol and cortisone: compensating for missing biomarker data

Chatzi G, Chandola T, Cernat A, and Shlomo N

Abstract

Living in social disadvantage has been conceptualised as a chronic stressor, although this contradicts evidence from recent studies using hair cortisol as a measure of hypothalamus-pituitary-adrenal (HPA) axis activity. The methodological limitations of previous studies investigating the association between socioeconomic position (SEP) and hair cortisol and cortisone are taken into account in this study which examines if lower SEP is associated with higher levels of HPA axis activity as measured by hair cortisol and cortisone among older adults.

Cortisol and cortisone levels in hair samples from 2,468 participants in the 6th wave of the English Longitudinal Study of Ageing (ELSA) is examined, in relation to educational attainment, wealth, and social class. Multivariable linear regression models were used to examine the association between socioeconomic position and cortisol and cortisone levels. Inverse probability weighting and multiple imputation were used to compensate for missing data. All models were adjusted for confounders.

We found significant differences between the most and least advantaged socioeconomic groups in their levels of hair cortisol and cortisone. Further analyses that take missing data into account showed that the complete case estimates of hair cortisone in the most disadvantaged groups were underestimated compared to estimates accounting for missing data, such as inverse probability weighting and multiple imputation.

This study demonstrates that social disadvantage as measured by low SEP is correlated with increased HPA axis activity. The conceptualisation of social disadvantage as a chronic stressor may be valid and previous studies reporting no associations between SEP and hair cortisol may have some methodological limitations. Future analyses using biosocial data may need to take into account and adjust for missing data in biosocial analyses.

Keywords: social inequalities; cortisol; cortisone; stress-related biomarkers; missing data

5.1 Introduction

Socioeconomic disadvantage is hypothesized to be associated not only with the increased risk of experiencing stressful events in life but also with the limited social and material resources to buffer the effects of stressful events (Baum et al., 1999; Pearlin et al., 2005). The damaging effects of stress originate in biological mechanisms releasing high levels of cortisol, a hormone linked to the onset of pathogenic processes (Miller et al., 2007).

Previous research on documenting the association between socioeconomic discrepancies and stress-related biomarkers focused on small scale populations and ignored missing biomarker data. Non-response in longitudinal studies with multiple data collections can challenge the validity of the studies' assumptions and inferences, particularly in biosocial research where there is interplay of biology procedures, experiences through life and life style behaviours (Blane et al., 2013) and the missing data fractions are large in longitudinal studies with biomarker covariates (Ibrahim et al., 2001; Lipsitz & Ibrahim, 1998).

Item non-response can lead to selection bias when those not responding have different characteristics than those responding, leading to loss of precision due to the limited sample size. Also, potential selection criteria could be correlated with the outcome variable (Little & Rubin, 2002). In wave 6 of the English Longitudinal Study of Ageing (ELSA), only 7,699 (84.9%) of the initial 9,169 core member participants agreed to participate in the health examination. Blood samples were obtained from 6,180 (68,1%) individuals (Bridges et al., 2015) and hair cortisol and cortisone sample from only 2,558 (28.2%) and 2,502 (27.2%) participants, respectively.

Therefore, we proposed to account for missing hair cortisol and cortisone data when examining the association between socioeconomic position and cortisol/cortisone levels in order to mitigate the potential for producing biased results and underestimating the association between socioeconomic position and cortisol/cortisone. We examined the association between socioeconomic position and hair cortisol and cortisone levels which were both indicators of high stress levels in individuals after controlling for age, gender, ethnicity, marital status, hair characteristics, nurse visiting month, in wave 6 in ELSA. The analyses took into account missing data while assuming the data are missing at random. We compared the complete case analysis with different missing data compensation approaches using inverse probability weighting and multiple imputation with attrition weight approaches to compensate for missing biomarker data.

Section 5.2 provides background information based on literature findings on socioeconomic position effects on cortisol and provides details about applied methods for missing data analyses. Furthermore, three research questions are discussed following with hypotheses based on previous study findings. Section 5.3 includes a description of the variables, statistical methods and statistical modelling. Section 5.4 includes non-response models and multivariate analysis, and presentation of the results. Section 5.5 includes the comparison of this study with previous studies and discussion of the findings.

5.2. Background

5.2.1 Socioeconomic position and cortisol levels

Living in socioeconomically disadvantaged circumstances is one of the strongest predictors of morbidity and premature mortality worldwide (Mackenbach et al., 2016; Stringhini et al., 2017). Disparities in health across indicators of socioeconomic

position have been hypothesised to be caused by high levels of psychosocial disruption that increase the risk of disease by provoking the stress-elicited dysregulations of important biological and behavioural systems (Adler et al., 1999; McEwen, 1998). While acute stress can improve memory and boost immune function, chronic stress has the opposite effects and also, share co-morbidity with depression, diabetes and cognitive impairment (McEwen & Gianaros, 2011).

Pathways between stress and health are examined frequently in studies by collecting cortisol samples. Cortisol is a steroid hormone, a product from a biochemical procedure that occurs after stressors (unemployment, exams etc) activate the hypothalamus, pituitary gland and adrenal gland known as HPA axis. High levels of cortisol indicate a stress reaction (Miller et al., 2007). Cortisol levels were traditionally measured in blood, urine or saliva. However, those samples reflect short-term cortisol secretion and provide only limited information on chronic stress reactions (Hellhammer et al., 2007; Lightman et al., 2008; Young et al., 2004). Additionally, repeated measurements of cortisol which provide long-term cortisol secretion information are expensive, time-consuming and susceptible to missing data because it requires frequent availability of the study participants (Broderick et al., 2004).

Recent studies implement an alternative method which collects cortisol levels from hair samples (Meyer & Novak, 2012; Russell et al., 2012; Stalder & Kirschbaum, 2012). This non-invasive method is easily carried out by a non-health care worker and benefits from capturing cortisol production over the course of several months, capturing information on long-term cortisol secretion which related to chronic stress conditions (Russell et al., 2012). Cortisol can be converted into inactive cortisone, since cortisone is a metabolite of cortisol and the parallel assessment of both

biomarkers offer a better understanding of the biological processes of cumulative stress (Stewart and Mason, 1995;Staufenbiel et al., 2015).

Findings in some previous studies with a small number of participants suggest that there is negative association between socioeconomic position and increased levels of cortisol (Boesch et al., 2015; Gidlow et al., 2016; Henley et al., 2014; Schreier et al., 2016; Serwinski et al., 2016; Ursache et al., 2017). However, other studies conclude that there is no association (Abell et al., 2016; Braig et al., 2015; Chen et al., 2013; O'Brien et al., 2013; Pulopulos et al., 2014; Staufenbiel et al.,2013). For example, Abell and colleagues used a large observational cohort of 3,977 (63%) participants (out of initial 6,308 individuals) and suggested that there is no association between socioeconomic position and cortisol concentration level, however, only complete case analysis was implemented. These results might have underestimated the correlation between socioeconomic position and hair cortisol concentration because evidence showed that there was a significant difference in the sample selection criteria. Participants who were excluded from the analysis because they had missing values in other characteristics had almost double cortisol means compared to included participants in the study (Abell et al., 2016). Therefore, we suggest that it is crucial to compensate for non-response in order to mitigate the potential for biased results.

5.2.2 Predictors of non-participation in surveys

Missing information is not randomly distributed in analyses and some characteristics have been acknowledged to predict non-response in studies. Poor health (Ferrie et al., 2009; Groves & Cooper, 1998; Knies & Burton, 2014; Lepkowski & Couper, 2002; May et al., 2012; Uhrig, 2008) and symptoms of psychological distress have been identified as predictors of non-response in a number of studies (Volken, 2013). Premature drop-out is related to a participant's elevated psychopathology according

to health survey studies (Eaton et al., 1992; Farmer et al., 1994), although Eaton and colleagues found no association between depression diagnosis and refusal to participate in survey follow ups (Eaton et al., 1992).

Evidence from previous studies suggest that men are less likely to participate in surveys compared to women (Lepkowski & Couper, 2002; Nicoletti & Buck, 2003; Uhrig, 2008) and older people are more likely to drop out (Lepkowski & Couper, 2002; Thomas et al., 2001). People from ethnic minorities are less likely to continue participating in studies (Lepkowski & Couper, 2002; Uhrig, 2008) and single people have lower contact probability compared to married people (Gray et al., 1996; Uhrig, 2008). Home owners have higher response rates compared to renters, likely due to not having a steady address (Gray et al., 1996; Lepkowski & Couper, 2002; Nicoletti & Peracchi, 2005). People living in urban areas have higher attrition rates in some studies mostly because interviewing is more difficult in large urban areas (Burkam & Lee, 1998; Gray et al., 1996; Uhrig, 2008). Although Gray et al (1996) found that unemployed participants were more likely to participate in studies, Lepkowski and Couper, (2002) found that employed participants were strongly associated with contact propensity (Gray et al., 1996; Lepkowski & Couper, 2002). Nicoletti and Peracchi (2005), suggested that longer fieldwork periods in surveys enhanced the likelihood of getting in contact with participants and therefore there were an increase in contact probabilities.

5.2.3 Missing data analyses

This study used statistical methods for compensating: complete case analysis (assuming Missing Completely at Random), inverse probability weighting, and multiple imputation with attrition weights assuming Missing at Random.

For the inverse probability weighting, this study used two approaches. The first approach was weighting in two different stages where specific patterns of missingness were detected. First for those people whose hair sample was not collected (mainly due to a selection process) and second for people whose cortisol/cortisone biomarker sample was not obtained (mainly due to refusals). Compensating for non-response in two different stages is important to adjust for the composition of the non-responding sample and we assumed that the selection is based on different characteristics in both stages, and therefore more accurately represent the study population in Wave 6 of ELSA. The second approach used was weighting in one stage, focusing on whether participants had valid hair cortisol/ cortisone biomarker data regardless of valid hair samples. This approach is comparable to the multiple imputation approach used.

5.2.4 Aim, research questions and hypotheses

This study aims to investigate the association between socioeconomic position (SEP) and hair cortisol and cortisone concentration after compensating for missing data. Particularly, we analysed the following research questions and hypotheses:

1. What are the differences in characteristics between participants who had a valid hair sample and those who did not?

We hypothesised that men will be less likely to have valid hair sample compared to women because men are more susceptible to baldness. Furthermore, older people were less likely to have valid hair sample because they were less likely to have hair compared to younger people. Regarding other covariates, according to previous studies, participants with depressive symptoms were less likely to participate in health surveys (Eaton et al., 1992; Farmer et al., 1994).

2. What are the characteristics of the participants who are less likely to have a valid hair cortisol and cortisone sample?

Funding limitations for some of the processed hair cortisol samples in the data analysed meant that these hair samples were only processed for those who participated at all nurse visit waves of ELSA. Studies have shown that people with poor health (Ferrie et al., 2009; Groves & Cooper, 1998; Knies & Burton, 2014; Lepkowski & Couper, 2002; Uhrig, 2008), men (Lepkowski & Couper, 2002; Nicoletti & Peracchi, 2005) and older people (Lepkowski & Couper, 2002; Thomas et al., 2001) are less likely to take part in surveys.

3. Is there a negative association between socioeconomic position and levels of hair cortisol and cortisone after adjusting for confounders?

Hypothesis:

We hypothesised that there is a negative association between socioeconomic position and levels of hair cortisol and cortisone. Particularly, we suspected that people living in greater socioeconomic disadvantage were more likely to have high levels of hair cortisol and cortisone concentration. Previous studies showed that people with low educational attainment (Boesch et al., 2015; Schreier et al., 2016) and lower income (Henley et al., 2014; Serwinski et al., 2016) had higher levels of hair cortisol. Regarding covariates, men had higher levels of cortisol and cortisone than women (Dettenborn et al., 2012a; Feller et al., 2014; Manenschijn et al., 2013) while others suggested the opposite (Manenschijn et al., 2011; Raul et al., 2004). Age is an important covariate while examining population with a wide age range (Dettenborn et al., 2012; Feller et al., 2014; Stalder et al., 2013). Recent research on women suggested that single women have lower hair cortisol levels as opposed to married women (Duffy

et al., 2013). Reduced melanin content in grey or white hair of older individuals may have affected the incorporation of cortisol into hair although a previous study has not suggested an influence from hair colour (Stalder & Kirschbaum, 2012b). However, bleaching of the hair was associated with lower levels of cortisone (Staufenbiel et al., 2015). Hair exposure to UV has an impact on an individual's hair glucocorticoid contents and eventually decreases the levels of cortisol (Wester et a., 2016). Therefore, it is important to consider when the sample is collected during the year.

4. What is the impact that compensating for missing data approaches has on the association between socioeconomic position and cortisol and cortisone concentration?

We hypothesise that the association between socioeconomic position and hair cortisol and cortisone concentration is greater after accounting for missing data. We identify certain characteristics in participants who are less likely to have cortisol and cortisone thus we buffer selection bias. Previous studies which used missing data methods in biomarker data also indicated the importance of compensating for missing data, however none of them presented results from complete case analyses compared to and missing data analyses (Pollitt et al., 2007;2008; Stringhini et al., 2013).

5.3. Data and Methods

5.3.1 Data collection and study population

The English Longitudinal Study of Ageing (ELSA) collects multidisciplinary data for people 50 years and older living in England. In wave 6 of ELSA, 10,601 participants are included, of those 9,169 are core members and the remaining 1,432 are new/younger/older partners and sample members. Similar to waves 2 and 4, Wave 6 includes a health examination and blood sample. From 9,169 core members, 7,699 (83.9%) participants accepted to participate in the health examination and 6,180

(80.2%) accepted to give blood sample. Hair cortisol data was collected for the first time in wave 6 for all those who consented to the blood sample collection. Wave 2 and wave 4 include cortisol data from saliva samples.

5.3.2 Hair sample collection

This study investigated the association between socioeconomic position and the levels of hair cortisol and cortisone; therefore, it was necessary to explore the characteristics of those participants who had no hair sample and no valid hair cortisol and hair cortisone biomarker data. The hair sample was taken from close to the scalp in the posterior vertex (back area of the scalp). This particular area shows the most consistent levels of hair cortisol/cortisone compared to different areas of the scalp's hair growth (Sauvé et al., 2007).

In wave 6 out of 7,730 participants, 1,899 (24.5%) were ineligible for hair sample. Out of 1,899, the majority of them (1,826 (96.1%)) was due to short hair (at least 2cm of hair are required to examine the levels of cortisol in the past 3 months) and, the rest 3.9 % for other reasons. The hair sample was obtained from 5,267 out of 5,831 eligible hair sample participants (90.3% out of eligible individuals) as 564 participants refused to give a sample because they either were unwilling to cut their hair, ruin their hairstyle, they were concerned it would be noticeable or had time constraints. The sample of hair cortisol/cortisone was obtained from 2,588 participants out of 5,267, due to funding constrains. This selection was not random and hence it is important to explore the characteristics of participants who did not have valid hair cortisol/cortisone data. The flowchart below provides a summary of the number of participants after excluding 720 missing values in covariates[3]: educational level,

[3] The number of missing values are taken from Figure 5.1 in which a detailed flowchart is presented.

wealth tertiles, social class, employment status, ethnicity, government office region indicator, volunteering work, physical activity, depressive symptoms, accompanied in interview, limiting longstanding illness, financial type household, housing tenure, interview visit month, marital status, refreshment type, high blood pressure, cancer and psychiatric condition.

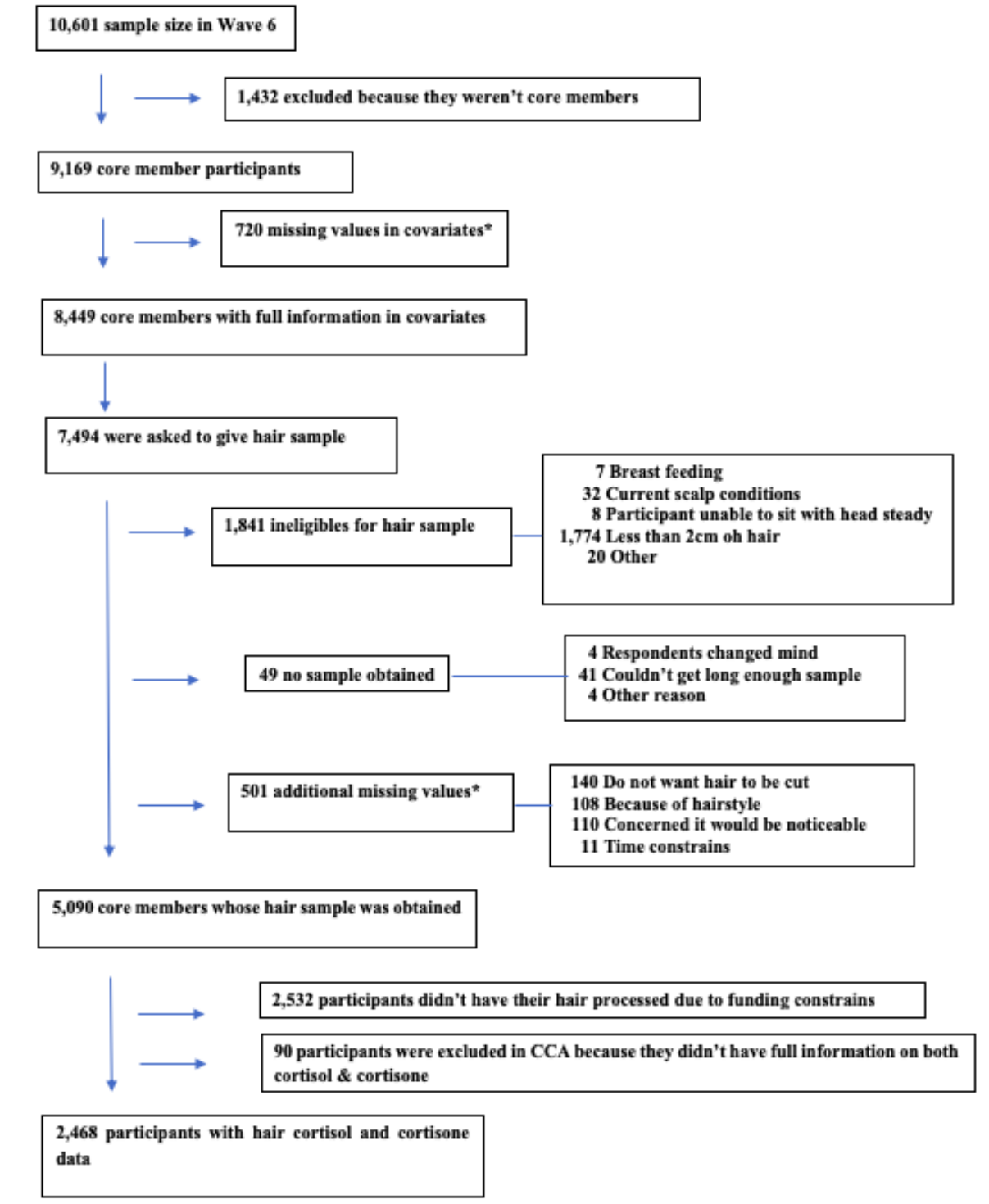


Figure 5. 1 Sample selection and final sample size in wave 6 for hair cortisol/cortisone data, the English Longitudinal Study of Ageing (ELSA)
*missing values overlap

5.3.3 Measures

Stress-related biomarkers

Hair sample collection was conducted by nurses after following particular protocols (more information can be found https://www.elsa-project.ac.uk/uploads/elsa/docs_w6/hair_sample_card.pdf & https://www.elsa-project.ac.uk/uploads/elsa/docs_w6/project_instructions_nurse.pdf). Hair cortisol and cortisone were skewed and were logarithmically transformed to approach normal distribution.

Socioeconomic position (SEP) characteristics

Early adulthood SEP: Education was measured as the highest qualification obtained classified into: i. Higher education, ii. High school and iii. Foreign or no qualifications. **Late adulthood SEP**: Total net wealth was categorised into tertiles at benefit unit level; financial assets such saving and investments were used to estimate the wealth variable (Ploubidis et al., 2011). Social class was classified into three categories: i. managerial and professional, ii. Intermediate, and iii. Semi routine and technical and other occupations. The hierarchical Register General classification considered non-manual occupations as "higher SEP" compared to manual occupations (Bartley, 2004).

Demographic and structural covariates

Age, sex, marital status (Married, Cohabiting, Single, Widowed and Divorced/Separated) and ethnicity (Whites and Non-Whites) were collected in the basic questionnaire in the main interview in wave 6. Participants were asked whether

they dyed or received any hair treatment and we recoded a dichotomous variable describing participants who either had dyed or treated their hair and otherwise. On the ELSA questionnaire, there were seven hair colour categories which describe participant's hair colour: Brown, Blonde, Red/Auburn/Ginger, White, Grey, Black, Mix of Grey and Other colours; we recoded a new variable with three categories by merging Brown/Black, Blonde/White/Red, Grey/Other/Mixed grey hair colours. Date of nurse visit, which includes the hair sample is used as indicator of season of collection; with categories for Winter (December-January-February), Spring (March-April-May), Summer (June-July-August), and Autumn (September-October-November).

5.3.4 Statistical modelling for compensating for nonresponse

5.3.4.1 Complete case analysis

Linear regression was implemented to investigate the association between socioeconomic position measures educational level, wealth, social class, and hair cortisol and cortisone after adjusting for covariates. Both cortisol and cortisone were log transformed and covariates include age, gender, interaction between age and gender, ethnicity, marital status, hair characteristics (colour, treatment, and season during collection). Every participant with missing values in covariates was excluded. The total sample size for hair cortisol and cortisone analysis was 2,468 participants.

Weighted complete case analysis using the survey weights was performed by implementing a weighted linear regression model and examining the effect of socioeconomic position on hair cortisol/cortisone after accounting for covariates.

5.3.4.2 Inverse Probability Weighting (IPW)

We implemented two approaches for inverse probability weighting to inflate the weight for participants who were underrepresented due to missing data. The two-stage

approach included two different models. The first model weighted participants who did not have hair sample and the second model weighted participants who had a hair sample but had not hair cortisol and cortisone data. The one-stage approach included only one model which weighted the participants without hair cortisol and cortisone data. These two approaches provided comprehensive information over the propensity of missingness in hair cortisol data.

Response model for hair sample (Model I of the II-stage IPW)

A dichotomous variable was created indicating those (1) who were eligible and had a hair sample (5,090 individuals) and those (0) who were ineligible and did not have hair sample (3,359 individuals). Then, logistic regression was used to predict missing hair sample probabilities, taking into account age, gender, educational level, employment status, housing tenure, ethnicity, Government Office Region, whether participants were doing volunteering work, physical activity, whether participants had depressive symptoms, were diagnosed with high blood pressure, and diagnosed with cancer (Table 5.2).

The non-response weight was calculated as the inverse of the predicted response probabilities and was combined with the ELSA Wave 6 attrition weights to create an overall weight measurement.

Response models for hair cortisol/cortisone (Model II of the II-stage IPW)

A dichotomous variable was created on the set of eligible participants (5,090 individuals) indicating those participants (1) who had hair cortisol/cortisone biomarker data (2,468 individuals) and those who did not (0) (2,622 individuals). Only

participants with valid hair sample were considered. Logistic regression was used to predict or absent cortisol/cortisone data taking into account age, gender, refreshment type in ELSA, longstanding illness, financial type household unit, whether participants were doing volunteering work, physical activity, any other person present during the interview, interview month, diagnosed with high blood pressure, and psychiatric condition were the variables which predicted missingness (Table 5.3).

The final weight variable was created as the inverse of the predicted response probabilities and was combined with the non-response weight from Model I and with the ELSA wave 6 attrition weights to create an overall weight measurement.

Weighted complete case analysis was performed implementing weighted linear regression modelling and examining the effect of socioeconomic position on hair cortisol/cortisone after accounting for covariates. The total sample size was similar to the ones in complete case analyses; for hair cortisol and cortisone analysis was on 2,468 participants.

Response models for hair cortisol/cortisone (I stage IPW)

A dichotomous variable was created distinguishing those participants (8,449 individuals) who had hair cortisol/cortisone biomarker data (1) (2,468 individuals) and those without (0) (5,981 individuals). Then, logistic regression was implemented. Age, gender, refreshment type in ELSA, longstanding illness, financial type household unit, whether participants were doing volunteering work, physical activity, any other person present during the interview, interview month, employment status, Government Office Region, volunteering work, depressive symptoms, financial unit type, ever diagnosed with high blood pressure, and diagnosed with psychiatric condition were the variables which predicted missingness (Table 5.4).

The new weight variable was created by combining the wave 6 attrition weight provided by ELSA with the new non-response weight, calculated as the inverse of the predicted response probabilities from the previously mentioned logistic regression models.

The total sample size was similar to the ones in complete case analyses; for hair cortisol and cortisone analysis was on 2,468 participants.

5.3.4.3 Multiple imputation with attrition weights

Variables that are thought to predict or be associated with missing values were included in the imputation model along with the predictor variables used from the inverse probability weighting method. We implemented multiple imputation where ELSA wave 6 attrition weights were included as explanatory variables by chained equations to impute missing information in hair cortisol and cortisone. Twenty imputed datasets were created.

The variables that were included in the dataset were the independent and dependent variables, similar to the I stage IPW of covariates and additional variables. We deleted all cases with at least one missing value apart from the variables cortisol and cortisone, hair colour, hair treatment, and nurse visiting month. We implemented multiple imputation in 8,449 participants.

All models were estimated in STATA V14 SE.

5.4 Results

5.4.1 Descriptive analysis

Table 5.1 describes the mean and standard deviation of log cortisol and log cortisone by all the variables in the analyses. There were gender differences but only for

cortisone with men having higher levels of log cortisone. Obese people had higher log cortisol and cortisone and people with fair and poor health had higher levels of log cortisol and log cortisone. Levels of cortisone were lower among those who had treated or dyed their hair, or who had blonde/red or white hair. Those in the lowest wealth tertiles had the highest levels of cortisol and cortisone. Respondents in lowest social class had the highest levels of cortisol and cortisone.

5.4.2 Models of response for participants with hair sample and cortisol/cortisone sample

Table 5.2 shows the characteristics of participants with hair sample for model I of the II stage IPW. People in age category 75-79 were more likely [OR=1.34(95%CI=1.09 to 1.64)] to have their hair sample obtained compared to younger people. Women were, almost three times more likely [OR=3.90(95%CI=3.54 to 4.31)] to have a hair sample compared to men. Participants with no qualifications or foreign qualifications were less likely to have hair sample [OR=0.83(95%CI=0.74 to 0.94)] compared to those with higher academic achievements. Non-White ethnic groups were less likely [OR=0.53(95%CI=0.41 to 0.70)] to have a hair sample compared to White British people. Retired participants were more likely to have a hair sample [OR=1.17(95%CI=1.01 to 1.35)] compared to currently employed participants. People living in the South West of England were twice more likely to have a hair sample [OR=2.11(95%=1.67 to 2.67)] compared to people living in the North East of England. Participants who were engaged in any volunteering work were more likely [OR=1.32(95%=1.19 to 1.47)] to have a hair sample compared to people without any commitment to volunteering. Those who were hardly or never exercising were less likely to have a hair sample [OR=0.78(95%CI=0.65 to 0.92)] compared to those who were exercising regularly. People with depressive symptoms were less likely to have

a hair sample [OR=0.83(95%CI=0.72 to 0.96)] compared to people without depressive symptoms. Those who were living in rented accommodation were less likely to have a hair sample [OR=0.82(95%CI=0.71 to 0.94)] compared to people living in an owned outright accommodation. Participants who were diagnosed with high blood pressure [OR=0.81(95%CI=0.67 to 0.99)] and cancer [OR=0.76(95%CI=0.57 to 1.003)] were less likely to have a hair sample compared to participants without diagnosis in those health conditions.

Table 5.3 describes the characteristics of participants with hair cortisol/cortisone measures of model II of the II-stage IPW. Those participants have had a hair sample. People in age category 60-64 were twofold more likely [OR=2.19(95%CI=1.75 to 2.74)] to have hair cortisol and cortisone measures compared to younger people while people in their 80s were less likely [OR=0.42(95%CI=0.31 to 0.46)] to have hair cortisol/cortisone measures compared to younger people. Women were less likely [OR=0.41(95%CI=0.36 to 0.47)] to have hair cortisol/cortisone measures compared to men. People who were accompanied with someone else in the room were more likely to have hair cortisol/cortisone measures [OR=1.19(95%CI=1.03 to 1.37)] compared to those who were alone during the interview. People from the refreshment sample in waves 3, 4 and 6 of ELSA were less likely [OR=0.48(95%CI=0.40 to 0.57)] to have hair cortisol/cortisone measures compared to participants who were in the ELSA since the beginning. Participants who were engaged to any volunteering work were more likely [OR=1.20(95%CI=1.05 to 1.36)] to have hair cortisol/cortisone measures compared to people without any commitment to volunteering. Those who were exercising sporadically were less likely to have hair cortisol and cortisone measures [OR=0.56(95%CI=0.38 to 0.83)] compared to those who were exercising regularly. People without limiting longstanding illness were more likely

[OR=1.26(95%CI=1.09 to 1.45)] to have hair cortisol/cortisone measures compared to people with limiting longstanding illness. People with depressive symptoms were less likely to have hair cortisol and cortisone measures [OR=0.83(95%CI=0.72 to 0.86)] compared to people without symptoms. Those who were interviewed in May and June were more likely [OR=1.81(95%CI=1.40 to 2.32)] to have hair cortisol/cortisone measures compared to people who were interviewed in January and February. Participants living in a household where couples shared joint finances were more likely to have hair cortisol/cortisone measures [OR=1.41(95%CI=1.22 to 1.63)] compared to participants in single households. Participants who were diagnosed with high blood pressure [OR=0.67(95%CI=0.50 to 0.94)] and any psychiatric condition [OR=0.61(95%CI=0.39 to 0.84)] were less likely to have hair cortisol/cortisone measures compared to participants without a diagnosis in those health conditions.

Table 5.4 shows the characteristics of participants who had hair cortisol/cortisone measures without having the restriction of having their hair sample previously obtained in the I-stage IPW. People in age category 60-64 were more likely [OR=1.93(95%CI=1.59 to 2.36)] to have hair cortisol/ cortisone measures compared to younger people while people in their 80s were less likely [OR=0.55(95%CI=0.42 to 0.73)] to have hair cortisol/cortisone measures compared to younger people. Women were more likely [OR=95%CI=1.25(1.33 to 1.39)] to have hair cortisol/cortisone measures compared to men. Non-White ethnic groups were less likely [OR=0.62(95%CI=0.44 to 0.88)] to have hair cortisol/cortisone measures compared to White British people. Retired participants were more likely to have hair cortisol/cortisone measures [OR=1.18(95%CI=1.01 to 1.36)] compared to currently employed participants. People living in the South West of England were more likely to have hair cortisol/cortisone measures [OR=1.48(95%CI=1.16 to 1.89)] compared

to people living in the North East of England. Participants who were engaged to any volunteering work were more likely [OR=1.31(95%CI=1.17 to 1.45)] to have hair cortisol/cortisone measures compared to people without any commitment to volunteering. Those who were hardly or never exercising were less likely to have hair cortisol/cortisone measures [OR=0.64(95%CI=0.52 to 0.79)] compared to those who were exercising regularly. People with depressive symptoms were less likely to have hair cortisol/cortisone measures [OR=0.83(95%CI=0.70 to 0.97)] compared to people without depressive symptoms. Those who were living in rented accommodation were less likely to have hair cortisol/cortisone measures [OR=0.85(95%CI=0.73 to 0.99)] compared to people living in an owned outright accommodation. People who were accompanied with someone else in the room were more likely to have hair cortisol/cortisone measures [OR=1.15(95%CI=1.02 to 1.30)] compared to those who were alone during the interview. People from the refreshment sample in waves 3, 4 and 6 of ELSA were less likely [OR=0.58(95%CI=0.51 to 0.67)] to have hair cortisol/cortisone measures compared to participants who were in ELSA since the beginning. People without limiting longstanding illness were more likely [OR=1.15(95%CI=1.02 to 1.29)] to have hair cortisol/cortisone measures compared to people with limiting longstanding illness. Those who were interviewed in July and August were more likely [OR=1.58(95%CI=1.32 to 1.90)] to have hair cortisol/cortisone measures compared to people who were interviewed in January and February. Participants living in a household were couple shared joint finances were more likely to have hair cortisol/cortisone measures [OR=1.32(95%CI=1.17 to 1.50)] compared to participants in single households. Participants who were diagnosed with high blood pressure [OR=0.67(95%CI=0.53 to 0.85)] and any psychiatric condition

[OR=0.67(95%CI=0.45 to 0.99)] were less likely to have hair cortisol/cortisone measures compared to participants without diagnosis of those health conditions.

Table 5. 1 Mean (SD) of log cortisol and log cortisone (log pg/mg) by all the variables in the analyses

	N (Total=2,468)	LogCortisol (pg /mg)		LogCortisone (pg /mg)	
Age categories		Mean (SD)	P-values	Mean (SD)	P-values
50-59	315	2.26(1.47)		1.90(0.85)	
60-64	613	2.07(1.61)		1.83(0.81)	
65-69	552	2.18(1.52)		1.82(0.79)	
70-74	430	2.19(1.49)	0.39	1.84(0.73)	0.65
75-79	394	2.24(1.61)		1.78(0.75)	
80+	164	2.28(1.70)		1.79(0.63)	
Gender*					
Male	1,011	2.20(1.56)	0.51	2.09(0.71)	<0.001
Female	1,457	2.16(1.58)		1.65(0.77)	
Ethnicity					
Whites	2,424	2.18(1.57)	0.84	1.83(0.78)	0.21
Non-Whites	44	2.13(1.86)		1.69(0.84)	
Marital status					
Married	1,687	2.18(1.58)		1.82(0.75)	
Cohabiting	95	2.15(1.35)		1.86(0.79)	
Single	125	2.15(1.40)	0.06	1.95(0.85)	0.22
Widowed	328	2.25(1.59)		1.77(0.79)	
Divorced/Separated	233	2.14(1.66)		1.86(0.88)	
Hair treatment*					
Yes	878	2.16(1.59)	0.56	1.52(0.78)	<0.001
No	1,590	2.19(1.56)		2.00(0.02)	
Hair colour					
Brown/Black	603	2.20(1.47)		1.88(0.79)	
Blond/White/Red	596	2.14(1.63)	0.79	1.52(0.80)	<0.001
Grey/Other/Mixed Grey	1,269	2.18(1.59)		1.95(0.72)	
Nurse visiting month					
Winter	616	2.10(1.65)		1.79(0.62)	
Spring	144	2.32(1.59)		1.88(0.83)	
Summer	627	2.24(1.59)	0.29	1.78(0.85)	0.1
Autumn	1,081	2.17(1.51)		1.86(0.81)	
Educational level					
Higher Education	785	2.18(1.54)		1.87(0.76)	
High school	814	2.15(1.61)	0.65	1.81(0.80)	0.19
Foreign or no qualifications	869	2.22(1.58)		1.81(0.78)	
Wealth tertiles					
Highest tertile	947	2.13(1.57)		1.79(0.75)	
Middle tertile	845	2.12(1.51)	<0.05	1.82(0.79)	0.02
Lowest tertile	676	2.34(1.65)		1.90(0.80)	

Continued from previous page

Social class					
Managerial & Professional	884	2.17(1.56)		1.85(0.77)	
Intermediate	691	2.10(1.55)	0.12	1.75(0.81)	<0.05
Semi routine & technical &other	893	2.26(1.60)		1.88(0.77)	

***T-test procedure otherwise ANOVA**

Table 5. 2 Response model for hair sample (n= 8,449) Part I of Two-stage approach

Variables	*N (%) Total=8,449*	*OR (SE)*	*CI%*
Age categories			
50-59	1,909(22.59)	1(ref)	1(ref)
60-64	1,581(18.71)	1.33(0.10)	1.14 to 1.55
65-59	1,609(19.04)	1.26(0.11)	1.06 to 1.50
70-74	1,215(14.38)	1.24(0.12)	1.02 to 1.50
75-79	1,098(13.00)	1.34(0.14)	1.09 to 1.64
80+	1,037(12.27)	1.25(0.13)	1.02 to 1.54
Gender			
Male	3,749(44.37)	1(ref)	1(ref)
Female	4,700(55.63)	3.90(0.19)	3.54 to 4.31
Educational class			
Higher Education	2,653(31.40)	1(ref)	1(ref)
High school	2,649(31.35)	1.02(0.06)	0.9 to 1.15
Foreign or no qualifications	3,147(37.25)	0.83(0.05)	0.74 to 0.94
Ethnicity			
White	8,173(96.73)	1(ref)	1(ref)
Non-White	276(3.27)	0.53(0.07)	0.41 to 0.70
Employment Status			
Employed	2,399(28.39)	1(ref)	1(ref)
Retired	5,175(61.25)	1.17(0.09)	1.01 to 1.35
Not employed & not retired	875(10.36)	1.17(0.11)	0.98 to 1.40
Government Office region			
North East	512(6.06)	1(ref)	1(ref)
North West	968(11.46)	1.22(0.14)	0.97 to 1.54
Yorkshire	905(10.71)	1.05(0.12)	0.83 to 1.31
East Midlands	898(10.63)	1.00(0.12)	0.79 to 1.26
West Midlands	946(11.20)	1.11(0.13)	0.88 to 1.39
East of England	1,073(12.70)	1.69(0.20)	1.35 to 2.13
London	737(8.72)	0.94(0.12)	0.73 to 1.20
South East	1,417(16.77)	1.43(0.16)	1.15 to 1.78
South West	993(11.75)	2.11(0.25)	1.67 to 2.67
Volunteering work			
No	5,948(70.40)	1(ref)	1(ref)
Yes	2,501(29.60)	1.32(0.73)	1.19 to 1.47
Physical Activity			
More than once a week	6,775(80.19)	1(ref)	1(ref)
Once a week	713(8.44)	0.94(0.08)	0.80 to 1.11
One to three times a month	249(2.95)	1.04(0.14)	0.80 to 1.36
Hardly ever or never	712(8.43)	0.78(0.07)	0.65 to 0.92

Continued from previous page

Depressive Symptoms			
CESD<4	7,320(86.64)	1(ref)	1(ref)
CESD>4	1,129(13.36)	0.83(0.06)	0.72 to 0.96
Housing Tenure			
Owners	7,057(83.52)	1(ref)	1(ref)
Renters	1,300(15.39)	0.82(0.06)	0.71 to 0.94
Others	92(1.09)	0.91(0.21)	0.58 to 1.42
Diagnosed with High Blood Pressure			
Not mentioned	7,928(93.83)	1(ref)	1(ref)
Mentioned	521(6.17)	0.81(0.08)	0.67 to 0.99
Diagnosed with Cancer			
Not mentioned	8,223(97.33)	1(ref)	1(ref)
Mentioned	226(2.67)	0.76(0.11)	0.57 to 1.003*
Constant		0.48(0.06)	0.38 to 0.60

Note: 1. the response was 1=have hair sample, 0=have not hair sample
2. 8,449 participants were included
3. Only variables that were significant in the level of 5% & 1% were included
4. Odds are expressed relative to a reference category. Odds ratio greater than 1 indicate higher odds while ratios lower than 1indicates lower odds
5. R_2=0.0996
* marginal significant statistical association

Table 5. 3 Response model for hair cortisol/cortisone biomarker data for participants who had valid hair cortisol/cortisone biomarker data (n=5,090). Part II of Two stages approach

Variables	N (%) Total=5,090	OR (SE)	CI%
Age categories			
50-59	1,029(20.22)	1(ref)	1(ref)
60-64	988(19.41)	2.19(0.25)	1.75 to 2.74
65-59	999(19.63)	1.50(0.18)	1.19 to 1.89
70-74	748(14.70)	1.70(0.21)	1.33 to 2.17
75-79	695(13.65)	1.71(0.22)	1.33 to 2.21
80+	631(12.40)	0.42(0.06)	0.31 to 0.56
Gender			
Male	1,630(32.02)	1(ref)	1(ref)
Female	3,460(67.98)	0.41(0.03)	0.36 to 0.47
Someone else present in the interview			
Not mentioned	1,290(25.34)	1(ref)	1(ref)
Mentioned	3,800(74.66)	1.19(0.09)	1.03 to 1.37
Refreshment Type			
No Refreshment	3,257(63.99)	1(ref)	1(ref)
Refreshment sample in waves 3,4 or 6	1,833(36.01)	0.48(0.04)	0.40 to 0.57
Volunteering work			
No	3,436(67.50)	1(ref)	1(ref)
Yes	1,654(32.50)	1.20(0.08)	1.05 to 1.36
Physical Activity			
More than once a week	4,209(82.69)	1(ref)	1(ref)
Once a week	395(7.76)	1.04(0.12)	0.83 to 1.31
One to three times a month	133(2.61)	0.56(0.11)	0.38 to 0.83
Hardly ever or never	353(6.94)	0.64(0.08)	0.50 to 0.83
Limiting long-standing illness			
Has limiting longstanding illness	1,760(34.58)	1(ref)	1(ref)
Longstanding but no limiting	1,061(20.84)	1.29(0.11)	1.08 to 1.53
No limiting longstanding illness	2,269(44.58)	1.26(0.09)	1.09 to 1.45
Date of the main Interview			
Jan/Feb	607(11.93)	1(ref)	1(ref)
Mar/Apr	62(1.22)	1.12(0.33)	0.63 to 2.01
May/Jun	561(11.02)	1.81(0.23)	1.40 to 2.32
Jul/Aug	1,121(22.02)	1.74(0.19)	1.40 to 2.16
Sep/Oct	1,552(30.49)	1.43(0.15)	1.17 to 1.76
Nov/Dec	1,187(23.32)	1.15(0.12)	0.93 to 1.43
Financial unit type			
Single household	1,692(33.24)	1(ref)	1(ref)
Couple but finances separate	545(10.71)	1.00(0.11)	0.80 to 1.24
Couple with joint finances	2,853(56.05)	1.41(0.10)	1.22 to 1.63

Continued from previous page

Diagnosed with High Blood Pressure			
Not Mentioned	4,814(94.58)	1(ref)	1(ref)
Mentioned	276(5.42)	0.67(0.09)	0.50 to 0.94
Diagnosed with Psychiatric condition			
Not Mentioned	4,969(97.62)	1(ref)	1(ref)
Mentioned	121(2.38)	0.61(0.14)	0.39 to 0.94
Constant		0.78(0.14)	0.54 to 1.11

Note: 1. the response was 1=have hair cortisol/cortisone data, 0=have not hair cortisol/cortisone data
2. 5,090 participants were included who had valid hair sample data
3. Only variables that were significant in the level of 5% & 1% were included
4. Odds are expressed relative to a reference category. Odds ratio greater than 1 indicate higher odds while ratios lower than 1 indicate lower odds
5. R_2=0.1146

Table 5. 4 Response model for hair Cortisol/Cortisone- One stage (n= 8,449)

Variables	N (%) Total =8,449	OR (SE)	CI%
Age categories			
50-59	1,909(22.59)	1(ref)	1(ref)
60-64	1,581(18.71)	1.93(0.19)	1.59 to 2.36
65-59	1,609(19.04)	1.42(0.16)	1.15 to 1.78
70-74	1,215(14.38)	1.52(0.18)	1.21 to 1.94
75-79	1,098(13.00)	1.60(0.20)	1.26 to 2.05
80+	1,037(12.27)	0.55(0.08)	0.42 to 0.73
Gender			
Male	3,749(44.37)	1(ref)	1(ref)
Female	4,700(55.63)	1.25(0.06)	1.13 to 1.39
Ethnicity			
White	8,173(96.73)	1(ref)	1(ref)
Non-White	276(3.27)	0.62(0.11)	0.44 to 0.88
Employment Status			
Employed	2,399(28.39)	1(ref)	1(ref)
Retired	5,175(61.25)	1.18(0.09)	1.01 to 1.36
Not employed & not retired	875(10.36)	1.05(0.11)	0.86 to 1.28
Government Office region			
North East	512(6.06)	1(ref)	1(ref)
North West	968(11.46)	1.07(0.14)	0.83 to 1.37
Yorkshire	905(10.71)	0.95(0.12)	0.74 to 1.23
East Midlands	898(10.63)	0.95(0.12)	0.74 to 1.22
West Midlands	946(11.20)	0.86(0.11)	0.66 to 1.10
East of England	1,073(12.70)	1.34(0.17)	1.05 to 1.71
London	737(8.72)	0.82(0.12)	0.62 to 1.08
South East	1,417(16.77)	1.23(0.15)	0.97 to 1.56
South West	993(11.75)	1.48(0.18)	1.16 to 1.89
Volunteering work			
No	5,948(70.40)	1(ref)	1(ref)
Yes	2,501(29.60)	1.31(0.07)	1.17 to 1.45
Physical Activity			
More than once a week	6,775(80.19)	1(ref)	1(ref)
Once a week	713(8.44)	1.02(0.09)	0.85 to 1.22
One to three times a month	249(2.95)	0.78(0.13)	0.57 to 1.07
Hardly ever or never	712(8.43)	0.64(0.07)	0.52 to 0.79
Depressive Symptoms			
CESD<4	7,320(86.64)	1(ref)	1(ref)
CESD>4	1,129(13.36)	0.83(0.07)	0.70 to 0.97

Continued from previous page

Housing Tenure			
Owners	7,057(83.52)	1(ref)	1(ref)
Renters	1,300(15.39)	0.85(0.07)	0.73 to 0.99
Others	92(1.09)	1.02(0.25)	0.64 to 1.65
Someone else present in the interview			
Not mentioned	2,169(25.67)	1(ref)	1(ref)
Mentioned	6,280(74.33)	1.15(0.07)	1.02 to 1.30
Diagnosed with High Blood Pressure			
Not mentioned	7,928(93.83)	1(ref)	1(ref)
Mentioned	521(6.17)	0.67(0.08)	0.53 to 0.85
Diagnosed with Psychiatric condition			
Not mentioned	8,254(97.69)	1(ref)	1(ref)
Mentioned	195(2.31)	0.67(0.13)	0.45 to 0.99
Refreshment type			
No refreshment	5,207(61.63)	1(ref)	1(ref)
Refreshment in waves 3, 4 & 6	3,242(38.37)	0.58(0.04)	0.51 to 0.67
Limiting longstanding illness			
Limiting longstanding illness	2,969(35.14)	1(ref)	1(ref)
Longstanding but not limiting	1,705(20.18)	1.23(0.09)	1.07 to 1.41
No limiting longstanding illness	3,775(44.68)	1.15(0.07)	1.02 to 1.29
Date of the main interview			
Jan/Feb	1,013(11.99)	1(ref)	1(ref)
Mar/Apr	132(1.56)	0.87(0.21)	0.54 to 1.39
May/Jun	889(10.52)	1.57(0.17)	1.27 to 1.93
Jul/Aug	1,763(20.87)	1.58(0.15)	1.32 to 1.90
Sep/Oct	2,644(31.29)	1.29(0.11)	1.08 to 1.53
Nov/Dec	2,008(23.77)	1.10(0.10)	0.93 to 1.32
Financial Unit Type			
Single	2,766(32.74)	1(ref)	1(ref)
Couple, but finances separate	913(10.81)	1.01(0.10)	0.83 to 1.21
Couple with joint finances	4,770(56.46)	1.32(0.08)	1.17 to 1.50
Constant		0.15(0.03)	0.10 to 0.21

Note: 1. The response was 1=have hair cortisol/cortisone sample 0=have no hair cortisol/cortisone sample
2. 8,449 participants were included
3. Only variables that were significant in the level of 5% & 1% were included
4. Odds are expressed relative to a reference category. Odds ratio greater than 1 indicate higher odds while ratios lower than 1 indicate lower odds
5.R^2=0.0749

5.4.3 Multivariable analyses

This section shows results of the complete case analysis with the five statistical methods compensating for missing data for hair cortisol and cortisone biomarker data. Complete case analyses results are presented first, then follows the results from inverse probability weighting in two stages and in one stage approaches follows and then the results from the multiple imputations with attrition weights (Tables 5.5-5.6). Information on covariates' estimates can be found in Appendices C- H.

For the dependent variable cortisol, participants with foreign or no qualifications had higher levels of cortisol in all methods compared to participants with higher education. Although, the effect sizes in the inverse probability weighting methods were higher compared to complete case analysis and multiple imputation, there was no statistical difference in the association between educational level and cortisol. Participants living in the lowest wealth tertiles had higher levels of cortisol in all methods compared to participants in the highest tertiles, although only in complete case analysis and in the multiple imputation analysis was the association difference between those tertiles was significantly different. Participants in a semi routine and technical and other occupations had higher levels of cortisol compared to people in a managerial and professional position. However, this positive association was not significantly different in any of the five methods.

For the dependent variable cortisone, participants with foreign or no qualifications had higher levels of cortisone compared to participants with higher education. This association was significantly different only in the multiple imputation method. In all other methods, the effect sizes were lower and not statistically different. Participants living in the lowest wealth tertiles had higher levels of cortisone in all methods compared to participants in the highest tertile, although in the inverse probability

weighting methods the effects sizes were larger compared to complete cases analysis and multiple imputation. People in disadvantaged social class positions had lower levels of cortisone compared to people in managerial and professional occupations. These associations were significant in all methods, however, the effects sizes in multiple imputation were larger compared to complete case analysis and inverse probability weighting.

In Figures 5.1-5.6, we present the predicted values of cortisol and cortisone in educational level, wealth, and social class in complete case analysis, inverse probability (I stage) and multiple imputation with attrition weights. Figure 5.1 and 5.2 illustrate the effect of educational level on cortisol and cortisone in three statistical methods. Both figures showed that the predicted values in the inverse probability weighting and multiple imputation were higher than in complete case analyses in both cortisol and cortisone. Similar findings are illustrated in Figures 5.3 and 5.4 which described the effects of wealth tertiles on cortisol and cortisone in three statistical methods. In all wealth tertiles categories, the predicted values in the inverse probability weighting and in the multiple imputation were higher than in complete case analyses in both cortisol and cortisone. Figures 5.5 and 5.6 showed the effect of social class on cortisol and cortisone in three statistical methods. In almost all categories and in both cortisol and cortisone, the predicted values were higher in the inverse probability weighting and in multiple imputation.

Table 5. 5 Multivariable analysis in five different statistical methods and three SEP models adjusted for covariates††† for hair cortisol (2,468 participants in CCA, IPW1, IPW2 & IPW3 and 8,449 in Multiple Imputation)

	Complete case analysis (N=2,468)		Inverse Probability Weighting (1 out of 2 stages) (N=2,468)		Inverse Probability Weighting (2 out of 2 stages) (N=2,468)		Inverse Probability Weighting (1 stage) (N=2,468)		Multiple Imputation with attrition weights (N=8,449)	
Independent variables	b	SE	b	SE	b	SE	b	SE	b	SE
Educational level*										
Higher Education	(ref)		(ref)		(ref)		(ref)		(ref)	
High school	-0.05	0.08	-0.01	0.09	-0.02	0.10	0.00	0.10	-0.05	0.10
Foreign or no qualifications	0.06	0.08	0.10	0.09	0.08	0.10	0.09	0.11	0.06	0.08
Wealth tertiles										
Highest tertile	(ref)		(ref)		(ref)		(ref)		(ref)	
Middle tertile	-0.02	0.08	-0.03	0.08	0.01	0.09	-0.01	0.10	-0.05	0.08
Lowest tertile	**0.23†**	**0.08**	0.19	0.10	0.17	0.11	0.19	0.11	**0.22†**	**0.09**
Social class**										
Managerial & Professional	(ref)		(ref)		(ref)		(ref)		(ref)	
Intermediate	-0.05	0.08	-0.06	0.10	-0.11	0.12	-0.11	0.12	-0.05	0.11
Semi routine & technical &other	0.10	0.08	0.12	0.09	0.05	0.10	0.06	0.10	0.10	0.09

*Model 1: Educational level + covariates †††

**Model 2: Wealth tertiles + covariates†††

***Model 3: Social class + covariates†††

†indicate statistical significance in 5%

†††Covariates: age, gender, ageXgender, ethnicity, marital status, hair colour, hair treatment, visiting nurse season

Table 5. 6 Multivariate analysis in five different statistical methods and three SEP models adjusted for covariates††† for hair cortisone (2,468 participants in CCA, IPW1, IPW2 & IPW3 and 8,449 in Multiple Imputation)

	Complete case analysis (N=2,468)		Inverse Probability Weighting (1 out of 2 stages) (N=2,468)		Inverse Probability Weighting (2 out of 2 stages) (N=2,468)		Inverse Probability Weighting (1 stage) (N=2,468)		Multiple Imputation with attrition weights (N=8,449)	
Independent variables	b	SE	b	SE	b	SE	b	SE	b	SE
Educational level*										
Higher Education	(ref)		(ref)		(ref)		(ref)		(ref)	
High school	0.00	0.04	-0.01	0.04	-0.02	0.05	-0.02	0.05	0.02	0.05
Foreign or no qualifications	0.06	0.04	0.06	0.04	0.06	0.05	0.06	0.05	**0.11**††	**0.04**
Wealth tertiles**										
Highest tertile	(ref)		(ref)		(ref)		(ref)		(ref)	
Middle tertile	0.05	0.03	0.07	0.04	0.08	0.04	0.08	0.05	0.06	0.04
Lowest tertile	**0.13**††	**0.04**	**0.16**††	**0.04**	**0.15**††	**0.05**	**0.17**††	**0.05**	**0.15**††	**0.05**
Social class**										
Managerial & Professional	(ref)		(ref)		(ref)		(ref)		(ref)	
Intermediate	0.01	0.04	-0.01	0.05	-0.01	0.06	0.00	0.06	0.03	0.04
Semi routine & technical &other	**0.10**††	**0.04**	**0.09**††	**0.04**	**0.09**†	**0.04**	**0.10**††	**0.04**	**0.13**††	**0.04**

*Model 1: Educational level + covariates†††

**Model 2: Wealth tertiles + covariates †††

***Model 3: Social class + covariates†††

†indicate statistical significance in 5% and †† in 1%

†††Covariates: age, gender, ageXgender, ethnicity, marital status, hair colour, hair treatment, visiting nurse season

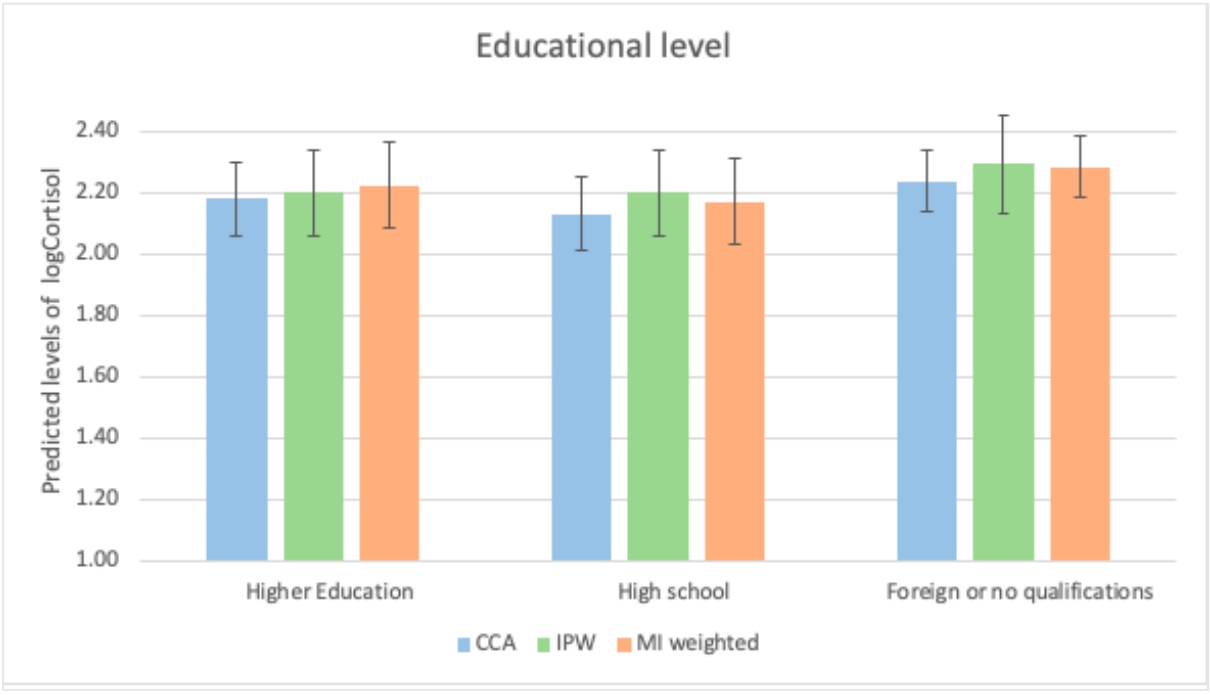


Figure 5. 2 Predicted levels of log cortisol by educational level estimated from Table 5.5

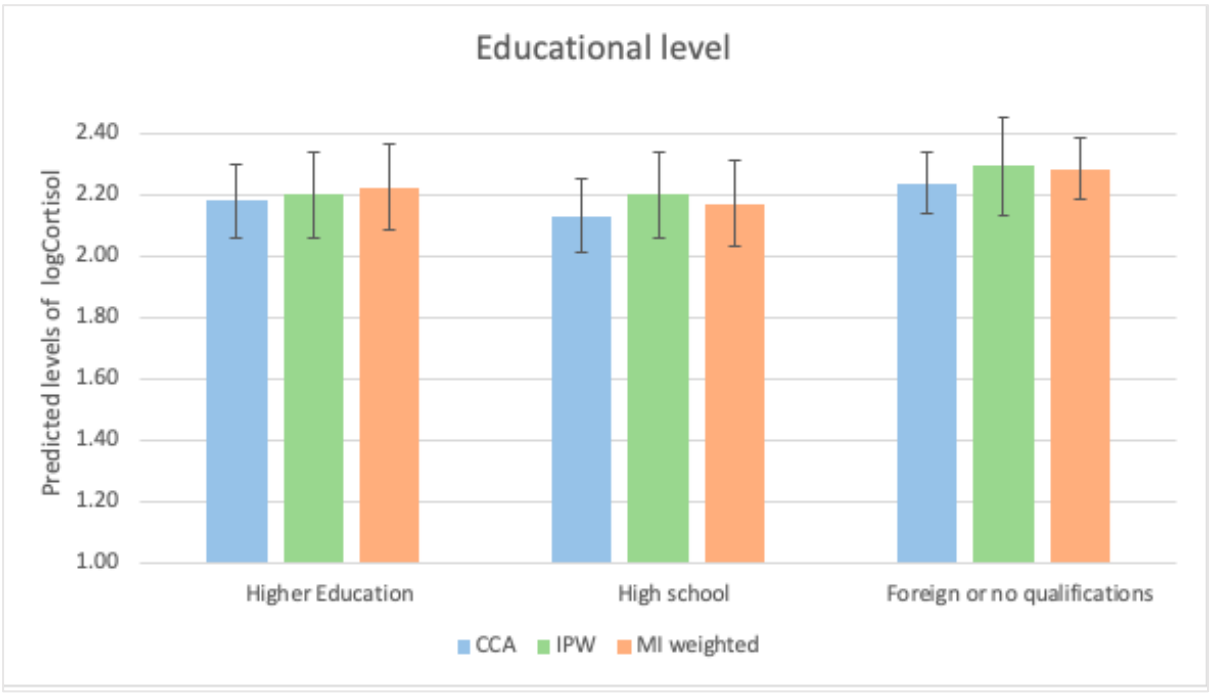


Figure 5. 3 Predicted levels of log cortisone by educational level estimated from Table 5.6

Figure 5. 4 Predicted levels of log cortisol by wealth tertiles estimated from Table 5.5

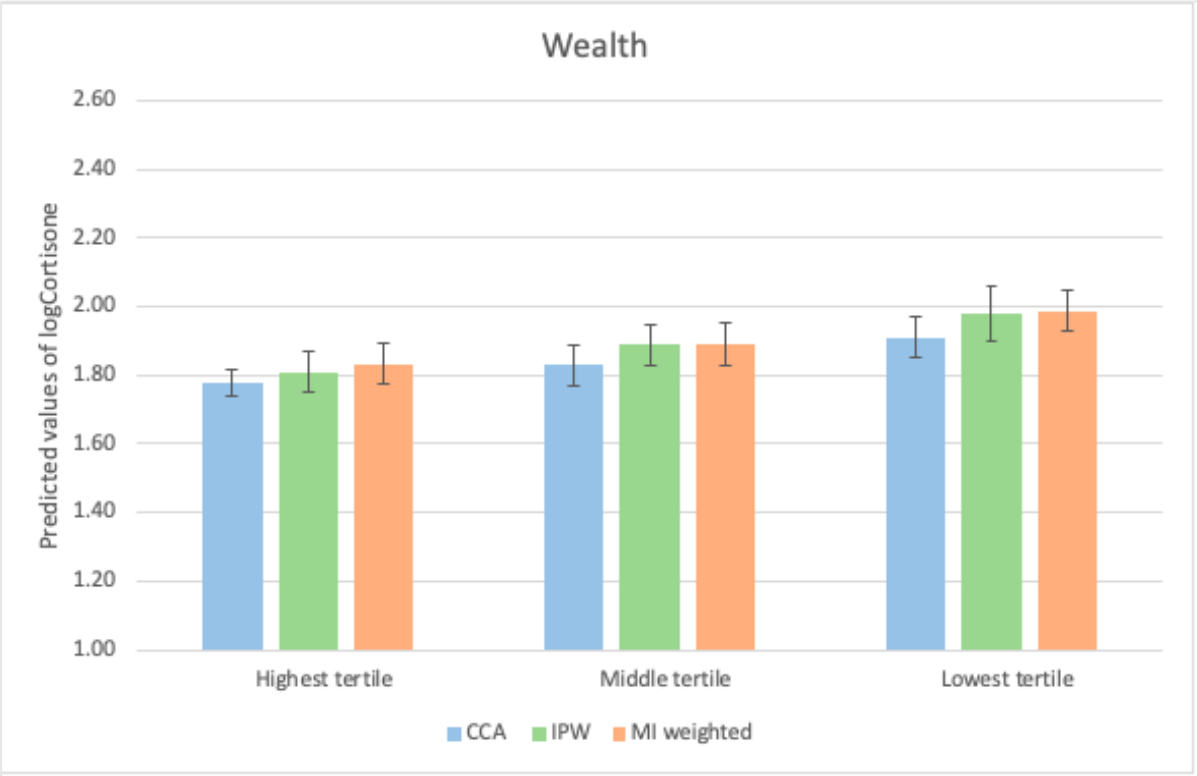


Figure 5. 5 Predicted levels of log cortisone by wealth tertiles estimated from Table 5.6

Figure 5. 6 Predicted levels of log cortisol by social class estimated from Table 5.5

Figure 5. 7 Predicted levels of log cortisone by social class estimated from Table 5.6

5.5 Discussion

The focus of this study was to evaluate the association between socioeconomic position and levels of hair cortisol and cortisone data after compensating for missing data. Our study findings suggest that there are significant associations between cortisol and cortisone in relation to socioeconomic characteristics. In accordance with our hypotheses there is a negative association between socioeconomic position and levels of cortisol/cortisone.

People with foreign or no qualifications, in lower wealth tertiles and people in semi-routine and technical and other manual occupations were more likely to have higher levels of cortisol and cortisone compared to people in higher education, in higher wealth tertiles and those in managerial and professional occupations. The results are consistent in all statistical methods to compensate for non-response although the association becomes either stronger or loses significance depending on which missing data approach was used.

5.5.1 Comparison of results with findings in the literature

Our findings are consistent with findings for people who had lower educational attainment (Boesch et al., 2015; Schreier et al., 2016), and were living in lower socioeconomic position tertiles conceptualised by education and income (Serwinski et al., 2016). It is worth mentioning that previous studies used small populations and/or excluded participants with missing biomarker data resulting in inconsistent or not significant results. To our knowledge, no other studies that have examined socioeconomic position effects on hair cortisol and cortisone concentrations have also compensated for missing biomarker data, making the study the first of its kind.

The results suggest that people with low educational attainment and with physical and mental health conditions are less likely to have a hair sample. Furthermore, in accordance with our hypotheses older people and people with poor health were less likely to have valid stress-related biomarker data. In accordance with our hypothesis, women were more likely to have a hair sample compared to men. Women were also more likely to have biomarker data but only in the one-stage approach of the response model.

5.5.2 Methodological considerations

The current study compared four different missing data methods with complete case analysis while investigating the association between socioeconomic position and stress-related biomarkers. Among the strengths of our study is that we compensated for missing data using two different inverse probability weighting approaches (a two-stages and one-stage approach) and multiple imputation approach with attrition weights to assess the association between socioeconomic position and stress. By identifying predictors of missingness, we investigated the reasons behind missing biomarker data and we implemented different statistical methods compensating for missing data in an attempt to mitigate bias from nonresponse while implementing complete case analyses.

Our study highlights that there is a correlation between socioeconomic position and hair cortisol and cortisone even after accounting for important confounders such as age, sex ethnicity, marital status and hair characteristics. Our findings are consistent with previous studies suggesting that men have higher levels of cortisol and cortisone than women (Dettenborn et al., 2012a; Feller et al., 2014; Manenschijn et al., 2013). Furthermore, our findings were similar with other studies which suggested that age is an important predictor for stress-related biomarkers and subsequently for increased

stress, particularly when examining populations with a wide age range (Dettenborn et al., 2012; Feller et al., 2014; Stalder et al., 2013). Reduced melanin content in the grey or white hair of older individuals may affect the incorporation of cortisol into hair although a previous study has not suggested an influence on hair colour (Stalder & Kirschbaum, 2012b), we found a negative association between participants with blonde-white-red hair and hair cortisone levels in all SEP models and all methods compensating for missing biomarker data. Recent research suggests that bleaching of the hair was associated with lower levels of cortisone (Staufenbiel et al., 2015) and our findings were consistent in all SEP models and in almost all methods compensating for missing biomarker data. Most dye and bleach products penetrate the hair matrix and could have a direct effect on incorporated cortisol and cortisone. Furthermore, hair treatment could increase hair mass, which could result in decreased hair cortisol concentrations (Manenschijn et al., 2011). Although, previous research on hair cortisol levels suggested that in winter, hair cortisol levels were lower compared to other seasons (Staufenbiel et al., 2015) another study suggests that mood and diurnal rhythm (a biological rhythm repeating cyclically throughout 24 hours) change during winter leading to an altered HPA axis activity (Magnusson & Boivin, 2003) our findings suggest that during summer and during autumn, the cortisol and cortisone levels, respectively are higher.

Potential limitations of the current study relate to the fact that our sample includes only adults aged over 50 years old and therefore the findings may not be representative for younger adults. A further limitation of this study is that the analysis is based on cross-sectional data from ELSA wave 6 and does not take into account patterns of missingness from previous waves of ELSA. However, the previous waves of ELSA did not measure hair cortisol/cortisone; only ELSA wave 6 provides data on hair

cortisol and cortisone thus a longitudinal approach using hair cortisol sample is not possible.

5.5.3 Conclusion

Socioeconomic disadvantage in later life is associated with higher levels of biomarkers related with stress after adjusting for covariates and accounting for missing data. Associations between socioeconomic position and stress biomarkers were similar across different approaches compensating for missing data, however, there are noticeable differences in the coefficient estimates suggesting that there is underestimation of biomarkers of stress among disadvantaged social groups in contrast to the complete case analysis. We conclude that it is important to account for missing biomarker data for statistical inference on associations between the socioeconomic position and stress related biomarkers.

CHAPTER 6. Is the increase in social inequalities in inflammation underestimated in conventional longitudinal analyses? Socioeconomic position and repeated systemic inflammation: compensating for missing data

Abstract

The association between socioeconomic adversity and systemic inflammation is well documented in cross-sectional studies, however, the association between living in socioeconomic disadvantage and repeated systemic inflammation in older adults has not been examined in detail, particularly taking into account longitudinal patterns of missingness. Inference from longitudinal analyses of ageing populations is susceptible to biases arising from attrition and non-random dropout.

4,574 men and women aged 52 years and older from the English Longitudinal Study of Ageing (ELSA) wave 2 onwards were analysed. C-reactive protein levels were measured in waves 2, 4, 6, and 8 (2004-2016). Latent growth curve models estimated the relationship between different measures of socioeconomic position (education, wealth, and social class) and C-reactive protein, compensating for missing data under different assumptions: complete case analysis, full information maximum likelihood, multiple imputation, Diggle-Kenward selection model, and pattern-mixture model.

Differences between the most and least affluent categories of socioeconomic position were found. Participants with foreign or no qualifications, participants in the lowest wealth tertile, and participants in manual occupations had increased levels of C-reactive protein compared to the most advantaged categories of education, wealth, and social class. Differences between the Diggle-Kenward and other methods for compensating for missing data suggest that the missing completely at random and

missing at random analyses underestimated socioeconomic differences in C-reactive protein.

This study demonstrates that living in socioeconomic disadvantage is associated with higher C-reactive protein levels over time and that the social discrepancies in health between the most and least affluent socioeconomic groups persist at older ages. It also highlights the importance of compensating for missingness in longitudinal studies with ageing participants who are susceptible to non-random drop out.

Keywords: socioeconomic inequalities; inflammation; biomarkers; missing data; non-random drop out

6.1 Introduction

Improved living conditions and health care had led to significant increases in life expectancy and health outcomes in the past few decades (WHO, 2015). However, a growing body of evidence suggest that there is a wide gap in health between the most and least affluent communities (e.g. Marmot, 2005).

Socioeconomically disadvantaged people are susceptible to ill-health and high mortality and disability rates are observed in many studies; highlighting the connection between living in poor social circumstances and disease (e.g. Syme & Berkman, 1976).

Early life exposure to socioeconomically adverse conditions and cumulative social adversity in adult life have been linked with higher levels of inflammatory biomarkers and thus, a higher risk of cardiovascular disease (CVD) in later life (Pollitt et al., 2008; Pollitt et al., 2005). However, these findings were not consistently significant for C-reactive protein, an important biomarker used for identifying systemic inflammation. We suggest that the findings may have been inconsistent due to the nature of cross-sectional data and we suggest examining the effect of living at a socioeconomic disadvantage on systemic inflammation while using longitudinal data from an English prospective study.

Longitudinal studies in biosocial research include repeated observations of biomarkers of an individual over a period of time to explore the characteristics of the emergence, development, and change over time. In contrast to cross-sectional analysis, a longitudinal study contains information on measurements that vary over time. However, multiple data collections at various time points increase the possibility of wave non-response and attrition.

In the English Longitudinal Study of Ageing (ELSA), there are three stages of potential unit non-response: main interview, health examination and blood sample collection. Data for the main interview were collected with Computer Assisted Personal Interviews (CAPI) and self-completion questionnaires every two years with additional nurse visits for heath examination and collection of biomarkers every four years.

In particular, biomarker data collected in inflammatory measures such as C-reactive protein are collected from blood samples, which typically have lower response rates than the rest of the health and interview data due to the refusal and inability to provide blood samples. For example, in ELSA, participants give either consent or refuse to take part or may be unable or ineligible to provide a blood sample (Scholes et al., 2008).

This study compares five different missing data methods that assume that missing data are missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR). We present results from participants who had CRP data in all waves (complete case analysis – maximum likelihood) and from participants who had at least one CRP measurement with full information maximum likelihood, multiple imputation, Diggle-Kenward selection model, and pattern mixture model.

Section 6.2 provides background information based on the literature findings on socioeconomic position effects on C-reactive protein details about applied methods for missing data analyses. Furthermore, three research questions are discussed following with hypotheses based on previous study findings. Section 6.3 includes a description of the variables, statistical methods and statistical modelling. Section 6.4 includes non-response models and multivariate analysis, and presentation of the

results. Section 6.5 includes the comparison of this study with previous studies and discussion of the findings.

6.2 Background

6.2.1 Socioeconomic effects on health in adulthood

The elderly population has increased significantly in the UK and will continue to increase with the improvement of living and working conditions, and healthcare services (Artazcoz & Rueda, 2007). However, health in elderly populations is a rather salient issue, as older adults are more susceptible to disease and disability (Wolff et al, 2002).

A large number of epidemiological studies have examined the association of socioeconomic disparities and inflammatory biomarkers and CVD in older adults (Galobardes et al., 2006; González et al., 1998; Pearson et al., 2003). Studies using complete case analysis and cross sectional data found that socioeconomically disadvantaged adults had higher levels of inflammatory biomarkers (Fraga et al., 2015; Gruenewald et al., 2009). Moreover, studies focused on a life-course approach concluded that cumulative socioeconomic disadvantage throughout life increase the levels of inflammatory biomarkers in adulthood (Kivimaki et al., 2005; Loucks et al., 2010) and similar findings had two studies which used two repeated measures of inflammatory biomarker C-reactive protein using data from the Whitehall II study (Gimeno et al., 2007; Stringhini et al., 2013) and data from the ELSA study (Stringhini et al., 2018). Another study used longitudinal data from three waves of ELSA and after accounting non-random attrition found that SEP measures defined as income, social class and education have significant effects on C-reactive protein levels in older adults (Maharani, 2019).

6.2.2 Characteristics of non-participation in longitudinal surveys

Previous studies in survey methodology, suggest the importance of considering participants who are less likely to respond to surveys and refuse to give consent in order to identify any differences in attrition propensities and avoid potential attrition, selection, and consent bias (Knies et al., 2012; Watson & Wooden, 2009).

Other studies suggest that socioeconomic disadvantage is associated with attrition and refusal to participate in studies (Behr et al., 2005; Ekholm et al., 2010; Ferrie et al., 2009; Lepkowski & Couper, 2002).

Studies suggest that attrition propensities increase at older ages (Lepkowski & Couper, 2002; Thomas et al., 2001) that men are less likely to continue to participate in studies compared to women (Lepkowski & Couper, 2002; Nicoletti & Buck, 2003; Uhrig, 2008). People from ethnic minorities have a higher propensity to drop out of the study (Lepkowski & Couper, 2002; Uhrig, 2008) and married people are less likely to leave the study (Gray et al., 1996; Uhrig, 2008). Home owners have higher response rates (Gray et al., 1996; Lepkowski & Couper, 2002; Nicoletti & Peracchi, 2005) while people living in urban areas have higher attrition rates in some studies mostly because interviewing is more difficult in large urban areas (Burkam & Lee, 1998; Gray et al., 1996; Uhrig, 2008). Participants with fair health or self-assessed poorer health are less likely to participate in later waves and give consent in health surveys (Ferrie et al., 2009; Groves & Cooper, 1998; Knies & Burton, 2014; Lepkowski & Couper, 2002; May et al., 2012; Uhrig, 2008).

Attrition due to death is an important challenge to consider in longitudinal studies and especially in studies which focus on ageing and health as participants grow older. It is strongly suggested to account for the deceased participants in analyses by

implementing joint modelling as it would prove to be informative for the longitudinal responses and the probability of survival (Brilleman et al, 2010; Diehr et al., 2001).

6.2.3 Modelling missing data

The choice of methods to handle missing data is dependent on the mechanisms that lead to missing data and missing data patterns. Little and Rubin's (2002) missing data mechanisms are: The unobserved data are considered Missing Completely at Random (MCAR) when the probability of missingness is unrelated to Y_{obs} (observed data) and Y_{mis} (unobserved data) , where R is a missing data indicator (R=1 defines missingness and 0 otherwise), ϕ is a parameter that rules when R takes on the value of one or zero (equation 6.1).

$$p(R|\phi) \qquad (6.1)$$

The unobserved data are considered Missing at Random (MAR) when the probability of missingness R is related to Y_{obs} but not to Y_{mis} (equation 6.2)

$$p(R|Y_{obs,}\, \phi) \qquad (6.2)$$

and unobserved data are considered Missing Not at Random (MNAR) when the probability of missingness R depends on Y_{obs} and Y_{mis} (equation 2.3)

$$p(R|Y_{obs}, Y_{mis}, \phi) \qquad (2.3)$$

Figure 6.1 presents the three missing data mechanisms adapted from similar figures in Schafer & Graham (2002) and Enders (2010) and illustrates the possible associations between missingness R and data, as described in equations 6.1-6.3.

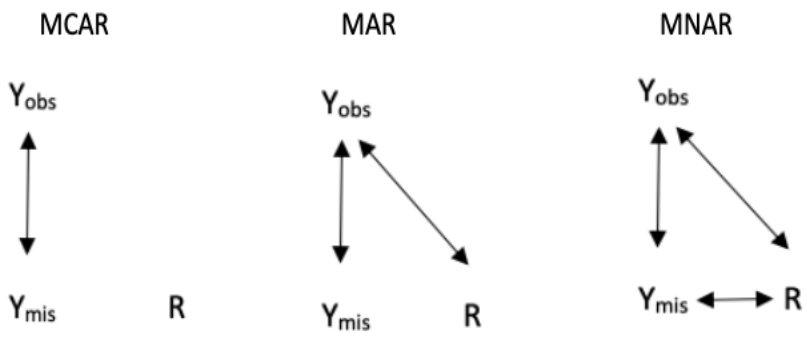


Figure 6. 1 Illustration of Rubin's missing data mechanisms. Double-headed arrows indicate statistical associations between R, Y_{obs} and Y_{mis}.

A common problem with analysing longitudinal data is that subjects may have dropped out of the study prematurely in such a way that ignoring the mechanism for drop out will lead to biased estimates. In such situations the mechanism is called "non-ignorable". The distinction between ignorable and non-ignorable missing data depends on the type of missingness based on the missing data mechanisms. Missing data literature often describes the missing mechanism MAR as ignorable missingness because there is no need to consider the parameters of the missing data distribution. In contrast, MNAR mechanism implies that assessing for missing data assuming that carry important information about the substantive model parameters, and, therefore, a MAR model produces biased parameter estimates (Rubin, 1976). In such cases different statistical techniques such as selection, pattern mixture, and shared parameter models are available to produce unbiased parameters after taking into account the joint distribution of the data and the probability of missingness (Enders, 2011b).

MAR and MNAR models make fundamentally different predictions about the unobserved score values (Molenberghs & Kenward, 2007). The MNAR models attempt to avoid bias by integrating a model that describes the propensity for missing

data into the analysis. For example, the selection model augments the growth curve analysis with a set of logistic regressions that describe the probability of missing data at each occasion (Diggle & Kenward, 1994). The pattern mixture model produces estimates separately within each missing data pattern and subsequently averages these estimates over the missing data patterns (Muthén et al, 2011; Roy, 2003; Roy & Daniels, 2008) .

6.2.3.1 Latent growth models for dealing with missing data

A Latent Growth Model (LGM) describes the outcome variable as a function of predictor variable that captures the passage of time, at least over the time interval of interest, under the Structural Equation Modelling (SEM) framework; an amalgamate regression analysis. In order to introduce the LGM models, path diagrams with four time points representing repeated measures of C-reactive protein in waves 2 to 8 are presented in Figures 6.2-6.4. The intercept is a constant for any given individual across time, the slopes represents the C-reactive protein linear and quadratic trajectories, determined by the four repeated C-reactive protein measures.

i. Full information Maximum Likelihood

Maximum Likelihood Missing Data Handling (ML) or Full Information Maximum Likelihood (FIML) is a missing data technique which can produce unbiased parameter estimates under a MAR assumption. It is a highly recommended procedure even under MCAR assumptions where complete case methods fail to produce accurate parameter estimates (Schafer & Graham, 2002). FIML repeatedly produces different combinations of population estimates until it detects the values with the highest log likelihood. Model fit information is based on complete cases since in FIML model's fit information is derived from a summation across fit function for individual cases.

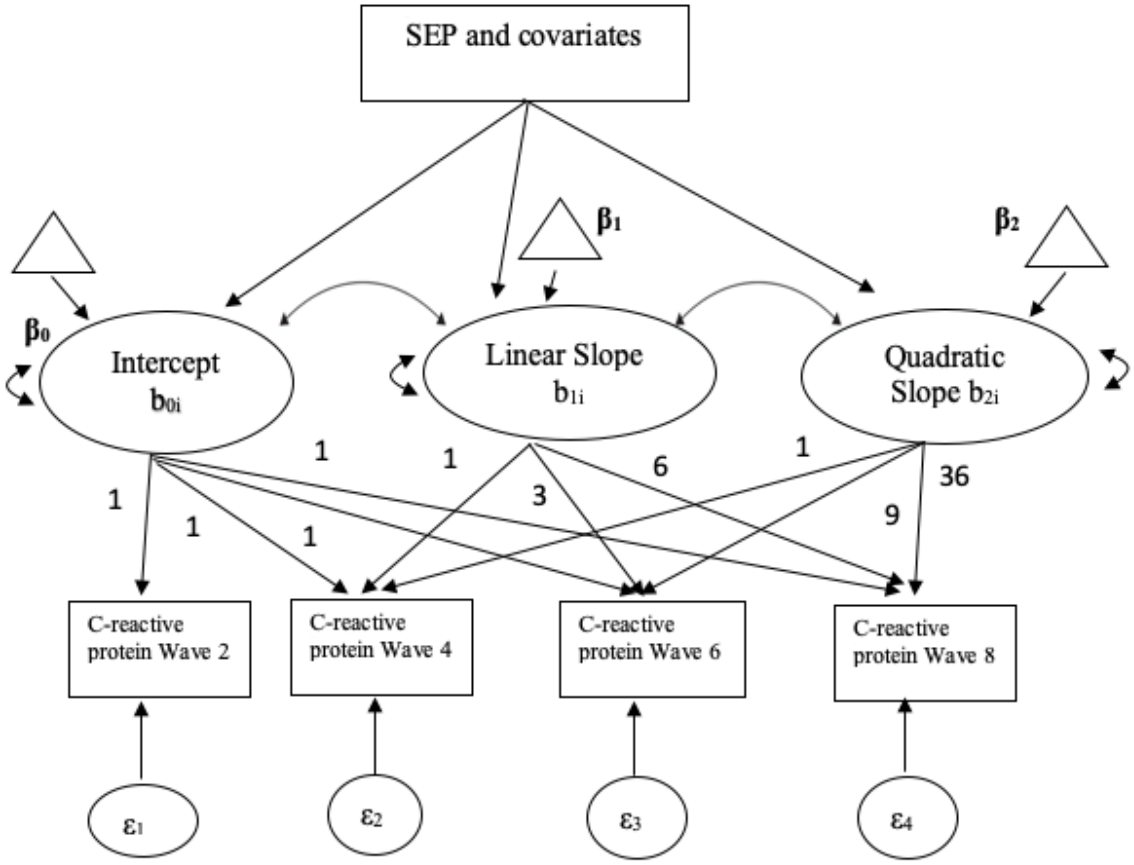


Figure 6. 2 Path diagram of a latent growth model (FIML and MI) where β_0 = mean intercept; β_1 = mean growth rate; β_2=mean quadratic growth rate; b_{0i}, b_{1i} and b_{2i} = residuals that allow the intercepts and the change rates to vary for every individual; C-reactive protein in four waves; SEP and covariates; ε_1-ε_3 = time-specific residuals (Enders, 2011b)

ii. Multiple imputation

Under the structural equation framework, multiple imputations of missing data can be generated from a Markov Chain Monte Carlo (MCMC) simulation. This method was first implemented from Rubin (1987) and Schafer (1997). In multiple imputation, multiple copies of the dataset are created in which missing values are replaced by imputed values that represent a distribution of possibilities estimated from partially observed data. Each imputed dataset estimates are combined. A multiple imputation

model should identify and include variables associated with the probability of the data being missing (Carpenter et al., 2006; Seaman et al., 2012).

iii. Diggle-Kenward selection model

Diggle and Kenward's (1994) selection model is a model with two components which combines the latent growth analysis with an additional set of regression equations that predict response probabilities. The Diggle and Kenward selection model describes the joint distribution of the data and the probability of missingness p(Y,R) as seen in Equation 6.1:

$$p(Y,R) = p(R|Y)p(Y) \quad (6.1)$$

where p(R|Y) is the conditional distribution of missingness, given the Y and p(Y) is the marginal distribution of the data. The conditional distribution describes an individual's probability to have missing values with a specific score and the marginal distribution describes the probability of having different scores. To illustrate, path diagram 6.3 shows the R1-R3 missing data indicators which indicate whether the outcome is observed or missing; the dashed arrow indicates logistic regression equations for every missing data indicator.

iv. Pattern Mixture Models

The Pattern Mixture model (Little, 1993, 1994) is, also, a two-part model consisted of a substantive model and a model of different missing data patterns, as seen in Equation 6.2.

$$P(Y,R|\theta, \varphi) = P(Y|R,\theta)\, p(R|\varphi) \quad (6.2)$$

Where $P(Y|R,\theta)$ is the conditional distribution of Y and $p(R|\varphi)$ is the marginal distribution of missing data, θ is a set of parameters that describe the distribution of

Y, and φ contains parameters that describe the propensity of missing data on Y. The sample is stratified into groups that share the common missing data pattern and estimate the substantive growth model separately within each pattern. For example, in a four-wave study like this one with monotone missing pattern, a pattern will be formed for the complete cases, another pattern for those participants who left after wave 2, another pattern for participants who left after wave 4 and a final pattern for those participants who left after wave 6.

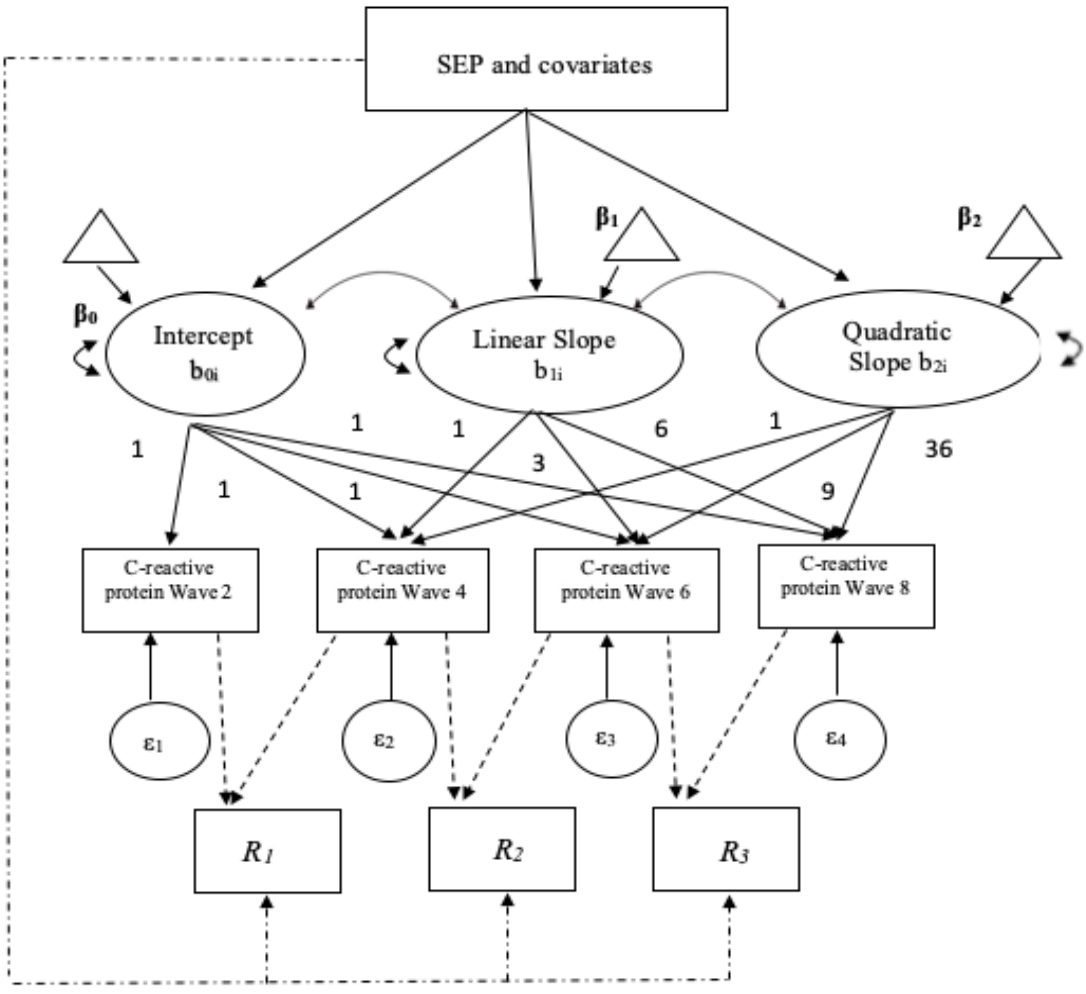


Figure 6. 3 Path diagram of the Diggle and Kenward selection model. β_0 = mean intercept; β_1 = mean linear growth rate; β_2=mean quadratic growth rate; b_{0i}, b_{1i} and b_{2i} = residuals that allow the intercepts and the change rates to vary for every individual; C-reactive protein in four waves; SEP and covariates; ε_1-ε_4 = time-specific residuals; and R1 to R4 = missing data indicators (Diggle & Kenward, 1994)

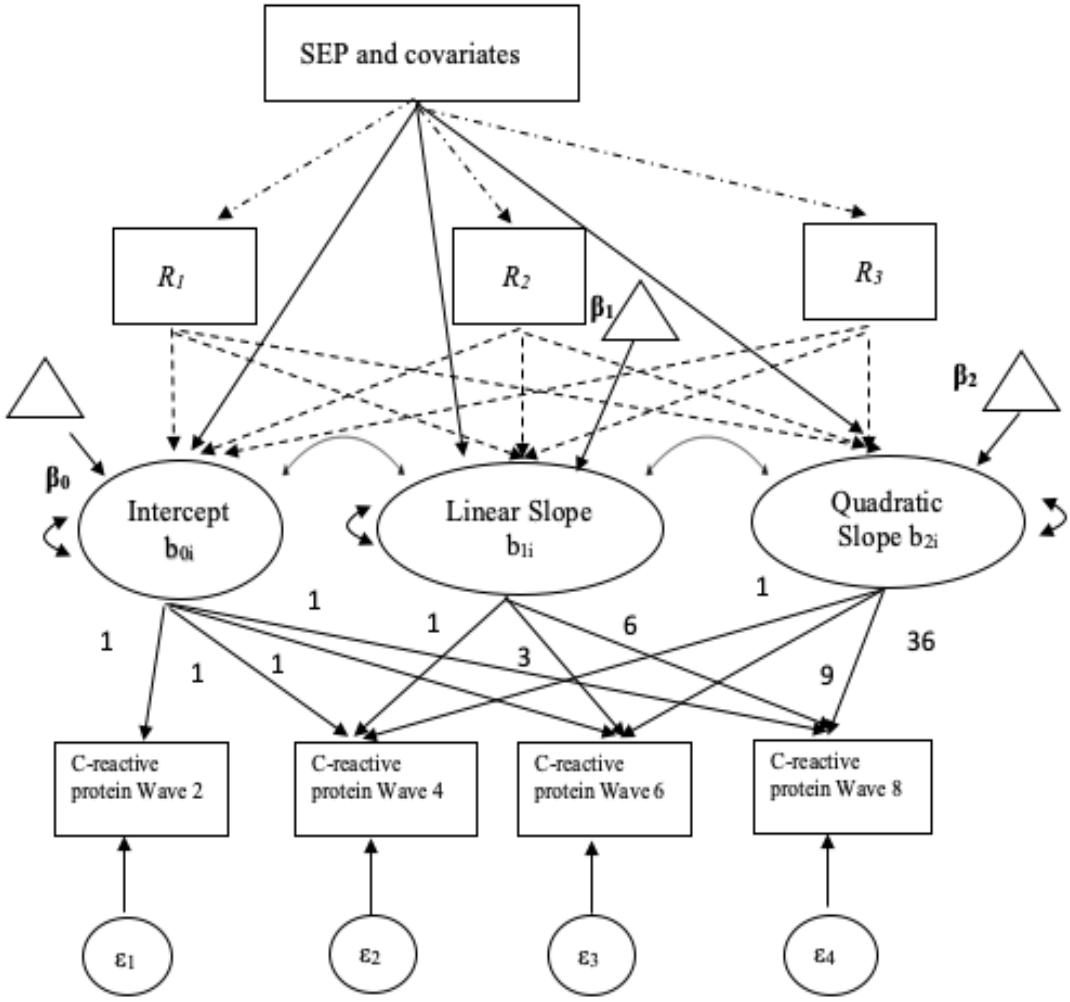


Figure 6. 4 Path diagram of pattern-mixture model. β_0 = mean intercept; β_1 = mean linear growth rate; β_2=mean quadratic growth rate;b_{0i}, b_{1i} and b_{2i} = residuals that allow the intercepts and the change rates to vary for every individual; C-reactive protein in four waves; ε_1-ε_4 = time-specific residuals; SEP and covariates; and R1 to R3 = missing data indicators added as covariates.

6.2.4 The gap in the literature

Most of the studies examining socioeconomic position and inflammation ignored non-response in biomarker data that occurs due to attrition or refusal to participate in data collections (e.g. Gruenewald et al., 2009; Jousilahti et al, 2003; Na-Ek & Demakakos, 2016). A recent study used longitudinal data of ELSA and three measurements of C-reactive protein to examine repeated systemic inflammation in relation to income,

social class and educational level. In this study a generalised mixed model and a joint survival model were compared but no significant differences between the two methods were found (Maharani, 2019). Our study contributes to the current literature by including one additional measurement of C-reactive protein and comparing five different methods accounting for missing data. We will implement latent growth modelling to examine socioeconomic position effects on repeated inflammation in older adults and compensate for missing data using maximum likelihood in complete data, full information maximum likelihood, multiple imputation, the Diggle-Kenward selection model and the pattern mixture models. The advantage of these models is that are used to evaluate change over time by using latent variables referred as growth factors (Muthén & Curran, 1997).

6.2.5 Aim of the study, research questions, and hypotheses

This study aims to describe changes of socioeconomic position effects on inflammation in older adults measured over time after compensating for missing data which are missing completely at random, missing at random, and missing not at random. Particularly, we aim to examine the following research questions and hypotheses:

Research questions and hypotheses

1. What are the characteristics of ELSA participants who are less likely to have inflammatory biomarker data at four, eight and twelve years after the baseline biomarker collection?

Studies have shown that people living at socioeconomic disadvantage are more likely to drop out the study in later waves (Behr et al., 2005; Ekholm et al., 2010; Ferrie et al., 2009; Lepkowski & Couper, 2002). Missingness in longitudinal studies is also

correlated with poorer health (Ferrie et al., 2009; Groves & Cooper, 1998; Knies & Burton, 2014; Lepkowski & Couper, 2002; May et al., 2012; Uhrig, 2008). We hypothesise that people at socioeconomic disadvantage are more likely to be missing in Waves 4, 6 and 8, and people who have poorer self-perceived health are more likely to be missing from the study. We also hypothesise older people (Lepkowski & Couper, 2002; Thomas et al., 2001), people from ethnic minorities (Lepkowski & Couper, 2002; Uhrig, 2008), never-married (Gray et al., 1996; Uhrig, 2008), renters (Gray et al., 1996; Lepkowski & Couper, 2002; Nicoletti & Peracchi, 2005) and people living in urban areas (Burkam & Lee, 1998; Gray et al., 1996; Uhrig, 2008) are less likely to have C-reactive protein in later waves.

2. How can the trajectories of repeated inflammation be explained by socioeconomic position?

We hypothesise that people living in socioeconomic disadvantage will have higher levels of C-reactive protein compared to people living in socioeconomic advantaged circumstances and that these higher levels will remain over time (Gimeno et al., 2007; Stringhini et al., 2013; Maharani, 2019)

3. Does accounting for missing data change the trajectory of socioeconomic position effects on repeated inflammation?

We hypothesise that there will be differences in estimates between complete data and missing data analyses as missing data analyses consider variables which explain missingness in later waves, and non-random drop-out. We hypothesise that complete case analysis will underestimate the effect of socioeconomic position on C-reactive protein.

6.3. Methods

6.3.1 Data population

The English Longitudinal Study of Ageing (ELSA) is a longitudinal study that collects multidisciplinary data every two years and commenced in 2002 from 11,391 core sample members of men and women aged over 50 years old living in private households in England. The sample was collected by using a multistage stratified random probability design from years 1998, 1999 and 2001 of the cross-sectional Health Survey for England (HSE) (White et al, 1993).

Waves 2-8 of ELSA include follow up interviews and health examinations including blood sample and biomarker collections.

6.3.2 Measures

Inflammatory biomarker

C-reactive protein was measured from blood samples collected from the health examination. The health examinations during the ELSA waves 2-8 were conducted by nurses who visited participants' homes following the main interview. C-reactive protein variables were treated as continuous variables and were logarithmically transformed to approach the normal distribution.

Socioeconomic position

We used three different measures of time-invariant socioeconomic characteristics from Wave 2 main interview to define socioeconomic position:

Early adulthood SEP: Educational level was measured as the highest qualification obtained and was classified into: higher education, high school and foreign or no qualifications.

Late adulthood SEP: Total net wealth was categorized into tertiles (lowest to highest) and measured at benefit unit level; financial assets such as saving and investments were used to estimate the wealth variable (White, Nicolaas, Foster, Browne, & Carey, 1993).

The National Statistics Socio-Economic Classification scheme (NS-SEC) was used to measure occupational class which describes conditions and types of employability. The social class variable was divided into three categories: Managerial & Professional, Intermediate, and Semi routine and technical and other occupations.

Demographic and structural covariates

Age (coded in three categories), gender, ethnicity (Whites and non-Whites) and marital status (married, cohabiting, single, widowed and divorced/separated) were included in the analysis as could potentially confound the association of interest. These variables were time-invariant and were taken from the wave 2 main interview.

6.3.3 Statistical Modelling

Table 6.1 presents the core member participants who participated in three data collections (main interview, health examination, and blood sample) and had C-reactive protein measurement in four waves of ELSA.

Since the Diggle and Kenward (1994) approach requires monotonic missingness to account for non-ignorable drop-out between data collections, we present here the results assuming a monotonic missing data pattern. We note that pattern–mixture approach performs well with both monotonic and intermittent missing data patterns and, therefore, we include the same analyses with intermittent missing data pattern in the Appendices L-N.

Table 6. 1 Core member participants in waves 2, 4, 6 and 8 (participated in four waves)

ELSA Waves	Main interview	Health examination	Blood sample	C-reactive protein
Wave 2 (2004/5)	8,780	7,666	6,231	5,899
Wave 4 (2008/9)	6,623	5,625	4,391	4,195
Wave 6 (2012/14)	5,659	4,743	3,698	3,528
Wave 8 (2016/17)	4,219	2,483	1,897	1,840

We excluded participants with no C-reactive protein measurement in wave 2 but had C-reactive protein in waves 4, 6 and 8 and consider this number of participants as the baseline sample. Therefore, we included 5,368 participants in wave 2, 3,410 in Wave 4, 2,321 in wave 6 and 1,281 in Wave 8 in the analyses. Furthermore, we excluded every participant with missing values in covariates. Every participant with at least one measurement of CRP>10 mg/L in any wave was excluded since levels of CRP over 10mg/L indicate acute inflammation (i.e. caused by flu and cold) and not chronic inflammation (Pearson et al., 2003)

Therefore, the analyses were conducted in 1,083 participants for the complete case analysis and 4,574 participants for the FIML, Multiple Imputation, Diggle-Kenward and Pattern-Mixture Model approaches. Figure 6.5 illustrates the sample size in all waves of ELSA before and after the exclusion criteria.

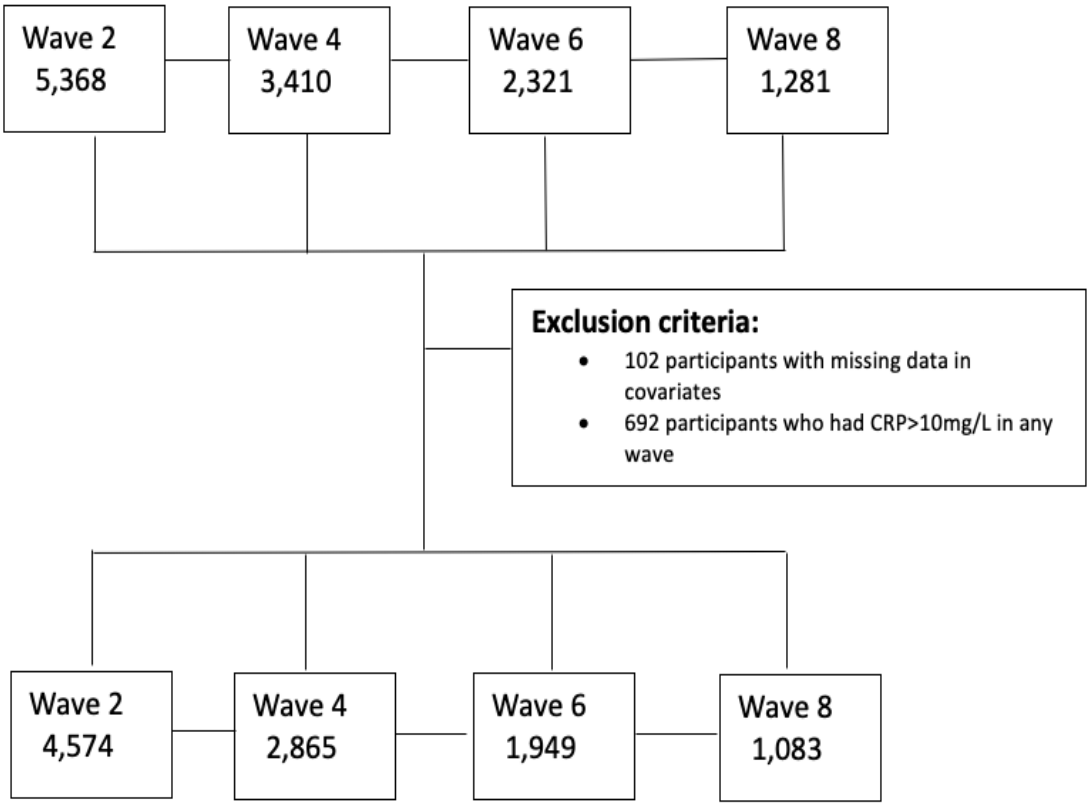


Figure 6. 5 Sample sizes in ELSA waves before and after exclusion criteria

6.3.3.1 Non-response models and patterns of missing data

We identified predictors of missingness by creating three non-response models according to missing data patterns. For the first missing data pattern, a dichotomous variable was created indicating those participants who did not have C-reactive protein in wave 4 (labeled:1) and those who had C-reactive protein in both waves 2 and 4 (labeled:0), as seen in Table 6.2. Using logistic regression analysis, we identified the predictors of missingness: age, sex, education, wealth, occupation, marital status, self-assessed health, physical activity, smoking status, government office region and whether there was cancer diagnosis. For the second missing data pattern, a dichotomous variable was created indicating those participants who didn't have C-reactive protein in wave 6 (labeled:1) and those who had C-reactive protein in both waves 2 to 6 (labeled:0), as seen in Table 6.3. Using logistic regression analysis, we identified the predictors: age, sex, educational level, social class, marital status, self-

assessed health, physical activity, smoking status, government office region, and whether there was cancer and CVD diagnosis as predictors of missingness.

For the third missing data pattern, a dichotomous variable was created indicating those participants who did not have C-reactive protein in wave 8 (labeled:1) and those who had C-reactive protein in all waves 2 - 8 (labeled:0), as seen in Table 6.4. Using logistic regression analysis, we identified the predictors: age, sex, educational level, social class, marital status, self-assessed health, physical activity, smoking status, government office region, and whether there was cancer and CVD diagnosis as predictors of missingness.

6.3.3.2 Missing at Random (MAR) approaches

Full Information Maximum Likelihood (FIML) and Multiple Imputation (MI) were implemented to investigate the association between socioeconomic position, measured as educational level, wealth, and social class and repeated measures of C-reactive protein after adjusting for covariates. Covariates included age, sex, ethnicity, and marital status. We included in our models the predictors of missingness as auxiliary variables.

6.3.3.3 Missing Not at Random (MNAR) analyses

As described in section 2.3.3, Diggle and Kenward's approach is a two-part selection model which also considers missing data by creating a separate logistic regression model consisting of auxiliary variables that are predictors of missingness. We used the auxiliary variables that were identified from the logistic regression models in section 6.3.3.1 and in Tables 6.3, 6.4 and 6.5. Although, the assumptions in the pattern mixture model are not based on a regression model we used the same auxiliary variables to describe the correlation structure as in the latent growth model.

We used STATA V14 SE for cleaning and preparing the data and for descriptive statistics analysis. All growth models were estimated in Mplus V8.0.

6.4 Results

6.4.1 Descriptive analysis

Table 6.2 describes the means and the standard deviations of C-reactive protein measurements in four waves of ELSA by SEP measures and covariates (age, gender, ethnicity, marital status and self-assessed health). C-reactive protein levels increased in subsequent waves while C-reactive levels decreased in wave 2 and 4 when we exclude deceased participants in the analysis.

Participants who died or dropped-out of the study between the waves had higher levels of C-reactive protein compared to participants who remained in the study. Participants who died between the waves had higher C-reactive protein levels compared to those participants who dropped-out in a subsequent wave. People with foreign or no qualifications had a higher mean of C-reactive protein in wave 2 compared to people in other educational level categories. The results were similar in wave 4, however, in wave 6, people in the higher but no degree category had the highest C-reactive protein mean. People in the lowest wealth tertile had the highest C-reactive protein mean in all three waves compared to the other wealth categories. In wave 2, participants in the lower categories of social class had higher C-reactive protein mean compared to managerial positions, however, these differences become narrower in the subsequent waves 4, 6 and 8.

Older people had higher C-reactive protein mean in all waves, although the sample size of older people was noticeably reduced in wave 8. Female participants had higher a C-reactive protein mean compared to men in waves 2 and 4 but this changes in waves

6 and 8. Non-White British had lower C-reactive protein mean in all waves. Widowers had higher C-reactive protein mean in all three waves compared to the other categories in marital status. People with poor health in wave 2 had the higher levels of C-reactive protein in waves 2 and 4 but not in wave 6 and 8, where people with those who reported fair self-assessed health had higher C-reactive protein levels compared to the other categories. This difference can be explained by the rapid reduction of the sample size of participants with poor health in wave 2. The sample size is reduced by 89.5% from wave 2 to wave 8 compared to only a 65.2% reduction of the sample size for participants who considered their health as excellent in wave 2.

6.4.2 Non-response models for participants with a C-reactive protein sample

Table 6.3, Table 6.4, and Table 6.5 shows the characteristics of participants who were more or less likely to be missing thus not to have C-reactive protein in wave 2 to waves 4, 6 and 8. Respondents with foreign or no qualifications were 39% (OR=1.39 CIs 1.14 to 1.69) more likely to be missing in wave 4, 52% (OR=1.52 CIs 1.27 to 1.83) in wave 6 and 56% (OR=1.56 CIs 1.29 to 1.88) in wave 8 compared to people with higher education skills.

Participants in the lowest wealth tertile were 26% (OR=1.26 CIs 1.03 to 1.53) more likely to be missing compared to people in the highest wealth tertile in wave 4.

Participants in a semi-routine and technical and other social class were 22% (OR=1.22 CIs 1.02 to 1.46) more likely in wave 4 to be missing compared to managerial and professional occupations.

Older respondents aged over 70 were 27% (OR=1.27; 95% CI 1.07 to 1.50) more likely to be missing in wave 4, almost threefold more likely to be missing in wave 6 (OR=2.87 CIs 2.40 to 3.43) and fourfold more likely to be missing in wave 8

(OR=3.82 CIs 3.09 to 4.74) compared to younger respondents. Female respondents were 21% (OR=0.79 CIs 0.68 to 0.90) less likely to be missing in wave 4, 19% (OR=0.81 CIs 0.71 to 0.93) in wave 6 and 15% (OR= 0.85 CIs 0.73 to 0.99) in wave 8 compared to men.

Table 6. 2 Descriptive C-reactive protein mean (SD) of covariates in waves 2, 4, 6 and 8 of ELSA

	C-reactive protein in Wave 2(N= 4,574)			C-reactive protein in Wave 4(N=2,865)			C-reactive protein in Wave 6(N=1,949)			C-reactive protein in Wave 8(N=1,083)		
	N	Mean (SD)	P-values	N	Mean (SD)	P-values	N	Mean (SD)	P-values	N	Mean (SD)	P-values
Mean CRP (SD) - total		2.44(2.09)			2.33(2.03)			1.99(1.80)			1.91(1.85)	
Mean CRP(SD)												
Respondents	2,865	2.29(1.99)		1,949	2.26(2.00)		1,083	1.89(1.74)		1,083	1.91(1.85)	
Deceased in later waves	487	3.04(2.49)	<0.001	127	2.88(2.36)	<0.01	NA	NA	<0.01	NA	NA	NA
Drop-outs in later waves	1,222	2.56(2.13)		789	2.42(2.05)		866	2.14(1.86)		NA	NA	
Mean CRP (SD) - after excluding decedents in later waves	3,960**	2.37(2.03)		2,738	2.31(2.01)		1,949	1.99(1.80)		1,083	1.91(1.85)	
Educational level												
Higher education	1,176	2.09(1.92)		845	2.02(1.94)		626	1.78(1.71)		366	1.66(1.80)	
High school	1,376	2.40(2.12)	<0.001	900	2.32(2.02)	<0.001	631	1.98(1.84)	<0.001	369	1.92(1.85)	<0.001
Foreign or no qualifications	2,022	2.68(2.16)		1,120	2.57(2.10)		692	2.22(1.81)		348	2.15(1.87)	
Wealth tertiles												
Highest tertile	1,708	2.01(1.83)		1,188	2.01(1.89)		833	1.73(1.66)		495	1.63(1.70)	
Middle tertile	1,581	2.60(2.18)	<0.001	982	2.55(2.16)	<0.001	677	2.12(1.78)	<0.001	384	2.05(1.88)	<0.001
Lowest tertile	1,285	2.81(2.22)		695	2.57(2.05)		439	2.32(2.00)		204	2.31(2.03)	
Social class												
Managerial & Professional	1,481	2.23(1.99)		1,024	2.13(1.90)		731	1.84(1.78)		422	1.66(1.74)	
Intermediate	1,144	2.27(2.08)	<0.001	722	2.27(2.04)	<0.001	496	1.91(1.70)	<0.001	263	1.99(1.99)	<0.001
Semi routine & technical &other	1,949	2.71(2.17)		1,119	2.56(2.14)		722	2.22(1.86)		398	2.11(1.85)	

Continued from previous page

Age categories												
50-59	1,448	2.22(2.01)		1,041	2.22(1.95)		798	1.90(1.77)		489	1.85(1.79)	
60-69	1,570	2.36(2.09)	<0.001	1,070	2.23(2.00)	<0.001	757	1.91(1.73)	<0.001	449	1.88(1.87)	0.1863
70+	1,556	2.73(2.16)		754	2.63(2.18)		394	2.37(1.94)		145	2.20(1.95)	
Gender*												
Male	2,082	2.34(2.06)	0.0034	1,254	2.18(1.93)	<0.001	850	1.88(1.74)	0.0016	473	1.78(1.80)	0.018
Female	2,492	2.53(2.13)		1,611	2.45(2.11)		1,099	2.09(1.84)		610	2.01(1.88)	
Ethnicity*												
Whites	4,505	2.44(2.10)	0.933	2,832	2.33(2.04)	0.7275	1,926	2.00(1.79)	0.9308	1,071	1.91(1.85)	0.4962
Non-Whites	69	2.44(2.04)		33	2.49(2.18)		23	2.17(2.34)		12	1.5(1.70)	
Marital status												
Married	3,074	2.36(2.06)		1,989	2.26(1.99)		1,376	1.91(1.73)		820	1.81(1.77)	
Cohabiting	161	2.08(1.70)		100	2.49(2.13)		73	2.00(1.85)		42	1.78(1.88)	
Single	202	2.60(2.18)	<0.001	119	2.33(2.08)	0.0054	79	2.36(2.19)	<0.001	36	1.65(2.11)	<0.001
Widowed	754	2.83(2.20)		391	2.74(2.29)		229	2.48(2.03)		95	2.40(2.14)	
Divorced/Separated	383	2.42(2.19)		266	2.21(1.90)		192	1.95(1.71)		90	2.44(1.94)	
Self-assessed health												
Excellent	650	1.93(1.86)		476	1.95(1.84)		349	1.64(1.60)		226	1.57(1.63)	
Very Good	1,434	2.21(1.90)		990	2.22(1.99)		690	1.87(1.65)		399	1.83(1.74)	
Good	1,434	2.52(2.13)	<0.001	885	2.42(2.08)	<0.001	595	2.10(1.80)	<0.001	314	2.11(2.06)	<0.001
Fair	826	2.87(2.26)		424	2.76(2.19)		272	2.53(2.20)		120	2.22(1.88)	
Poor	230	3.34(2.51)		90	2.79(1.85)		43	2.27(1.88)		24	2.08(2.07)	

Notes: *t-test otherwise ANOVA

** This number refers to the sum of participants after excluding those who died in any later wave of the study. Total number of participants in wave 2 is 4,574 and total number of participants who died in later waves is 614 (487+127), therefore, the total number of participants would be 3,960.

Table 6. 3 Non-response model for CRP for wave 2 and 4. Total sample size is 4,574, 0= observed values of C-reactive protein for wave 2 to 4 (n=2,865) and 1= missing participants from wave 2 to 4 (n=1,709)

	N	Odds Ratio	Std. Err.	P>|z|	[95% Conf.	Interval]
Educational level						
Higher education	1,176	1(ref)				
High school	1,376	1.16	0.11	0.118	0.96	1.41
Foreign or no qualifications	2,022	1.39	0.14	0.001	1.14	1.69
Wealth tertiles						
Highest tertile	1,708	1(ref)				
Middle tertile	1,581	1.18	0.10	0.041	1.01	1.39
Lowest tertile	1,285	1.26	0.13	0.022	1.03	1.53
Social class						
Managerial & Professional	1,481	1(ref)				
Intermediate	1,144	1.16	0.11	0.124	0.96	1.39
Semi routine & technical &other	1,949	1.22	0.11	0.026	1.02	1.46
Age categories						
50-59	1,448	1(ref)				
60-69	1,570	1.15	0.10	0.105	0.97	1.35
70+	1,556	2.23	0.20	<0.001	1.87	2.66
Gender						
Male	2,082	1(ref)				
Female	2,492	0.79	0.06	0.001	0.68	0.90
Ethnicity						
Whites	4,505	1(ref)				
Non-Whites	69	2.02	0.53	0.007	1.21	3.37
Marital status						
Married	3,074	1(ref)				
Cohabiting	161	1.28	0.23	0.168	0.90	1.81
Single	202	1.02	0.16	0.922	0.74	1.39
Widowed	754	1.05	0.10	0.643	0.86	1.27
Divorced/Separated	383	0.70	0.09	0.005	0.54	0.89
Self-assessed health						
Excellent	650	1(ref)				
Very Good	1,434	1.09	0.12	0.428	0.88	1.35
Good	1,434	1.38	0.15	0.003	1.12	1.71
Fair	826	1.78	0.21	<0.001	1.41	2.25
Poor	230	2.45	0.43	<0.001	1.74	3.46

Continued from previous page

Physical activity						
More than once a week	3,646	1(ref)				
Once a week	458	1.30	0.14	0.014	1.06	1.61
One to three a month	153	1.13	0.20	0.509	0.79	1.60
Hardly ever or never	317	2.00	0.26	<0.001	1.55	2.58
Smoking Status						
Non-smoker	1,733	1(ref)				
Ex-smoker	2,233	1.14	0.08	0.067	0.99	1.32
Current smoker	608	1.37	0.14	0.003	1.11	1.68
Government Office region						
North East	295	1(ref)				
North West	604	2.00	0.31	<0.001	1.47	2.73
Yorkshire	492	1.22	0.20	0.228	0.88	1.68
East Midlands	444	1.14	0.19	0.427	0.82	1.59
West Midlands	515	1.03	0.17	0.878	0.74	1.41
East of England	533	1.27	0.21	0.149	0.92	1.75
London	369	1.43	0.25	0.044	1.01	2.02
South East	811	1.25	0.19	0.156	0.92	1.69
South West	511	1.56	0.25	0.007	1.13	2.14
Ever diagnosed with cancer						
No	4,259	1(ref)				
Yes	315	1.30	0.16	0.035	1.02	1.67
Constant		0.14	0.03	<0.001	0.10	0.21

*sample size = 4,574
0 = observed CRP in waves 2 & 4 = 2,865

1 = missing CRP = 1,709

R_2 = 0.08

Participants with poor self-assessed health were twofold (OR=2.45 CIs 1.74 to 3.46) more likely to be missing in wave 4, almost three times (OR=2.89 CIs 1.95 to 4.29) more likely to be missing in wave 6 and two times (OR=2.34 CIs 1.44 to 3.79) more likely to be missing in wave 8 compared to participants who consider their health to be excellent in wave 2.

Participants who were diagnosed with cancer in wave 2 were 30% (OR=1.30 CIs 1.02 to 1.67) more likely to be missing in wave 4 and 38% (OR=1.38 CIs 1.06 to 1.79) in wave 6 compared to healthier participants who were not diagnosed with cancer in wave 2.

Participants diagnosed with CVD in wave 2 were 25% (OR=1.25 CIs 1.08 to 1.46) more likely to be missing in wave 6 and 49% (OR=1.49 CIs 1.23 to 1.80) less likely to be missing in wave 8 compared to participants who were not diagnosed with CVD in wave 2.

Table 6. 4 Non-response model for C-reactive protein for wave 2 and 6. Total sample size is 4,574, 0= observed values of C-reactive protein for wave 2 to 6 (n=1,949) and 1= missing participants from wave 2 to 6 (n=2,625)

	N	Odds Ratio	Std. Err.	P>|z|	[95% Conf.	Interval]
Educational level						
Higher education	1,176	1(ref)				
High school	1,376	1.21	0.11	0.032	1.02	1.45
Foreign or no qualifications	2,022	1.52	0.14	<0.001	1.27	1.83
Social class						
Managerial & Professional	1,481	1(ref)				
Intermediate	1,144	1.12	0.10	0.217	0.94	1.34
Semi routine & technical &other	1,949	1.27	0.11	0.007	1.07	1.50
Age categories						
50-59	1,448	1(ref)				
60-69	1,570	1.22	0.09	0.01	1.05	1.42
70+	1,556	2.87	0.26	<0.001	2.40	3.43
Gender						
Male	2,082	1(ref)				
Female	2,492	0.81	0.06	0.003	0.71	0.93
Marital status						
Married	3,074	1(ref)				
Cohabiting	161	1.16	0.20	0.375	0.83	1.63
Single	202	1.04	0.17	0.825	0.76	1.42
Widowed	754	1.03	0.10	0.752	0.85	1.26
Divorced/Separated	383	0.73	0.09	0.006	0.58	0.91
Self-assessed health						
Excellent	650	1(ref)				
Very Good	1,434	1.11	0.11	0.315	0.91	1.34
Good	1,434	1.29	0.13	0.011	1.06	1.58
Fair	826	1.55	0.18	<0.001	1.23	1.95
Poor	230	2.89	0.58	<0.001	1.95	4.29
Physical activity						
More than once a week	3,646	1(ref)				
Once a week	458	1.18	0.13	0.134	0.95	1.47
One to three a month	153	0.87	0.16	0.444	0.61	1.24
Hardly ever or never	317	2.03	0.31	<0.001	1. 50	2.74
Smoking Status						
Non-smoker	1,733	1(ref)				
Ex-smoker	2,233	1.09	0.08	0.22	0.95	1.25
Current smoker	608	1.30	0.14	0.013	1.06	1.59

Continued from previous page

Government Office region						
North East	295	1(ref)				
North West	604	1.73	0.27	0	1.27	2.35
Yorkshire	492	1.04	0.17	0.797	0.76	1.42
East Midlands	444	0.97	0.16	0.866	0.71	1.34
West Midlands	515	1.01	0.16	0.965	0.74	1.37
East of England	533	1.17	0.18	0.32	0.86	1.59
London	369	1.50	0.26	0.017	1.07	2.10
South East	811	1.05	0.15	0.724	0.79	1.40
South West	511	1.18	0.19	0.307	0.86	1.60
Ever diagnosed with cancer						
No	4,259	1(ref)				
Yes	315	1.38	0.18	0.016	1.06	1.79
Ever diagnosed with CVD						
No	3,318	1(ref)				
Yes	1,256	1.25	0.10	0.003	1.08	1.46
Constant		0.39	0.07	<0.001	0.28	0.55

*sample size = 4,574

0 = observed CRP in waves 2 & 4 & 6= 1,949

1 = missing CRP = 2,625

R_2 = 0.09

Table 6. 5 Non-response model for CRP for wave 2 and 8. Total sample size is 4,574, 0= observed values of CRP for waves 2 to 8 (n=1,083) and 1= missing participants from wave 2 to 8 (n=3,491)

	N	Odds Ratio	Std. Err.	P>|z|	[95% Conf.	Interval]
Educational level						
Higher education	1,176	1(ref)				
High school	1,376	1.17	0.11	0.085	0.98	1.41
Foreign or no qualifications	2,022	1.56	0.15	<0.001	1.29	1.88
Age categories						
50-59	1,448	1(ref)				
60-69	1,570	1.19	0.10	0.037	1.01	1.39
70+	1,556	3.82	0.42	<0.001	3.09	4.74
Gender						
Male	2,082	1(ref)				
Female	2,492	0.85	0.07	0.035	0.73	0.99
Self-assessed health						
Excellent	650	1(ref)				
Very Good	1,434	1.25	0.13	0.037	1.01	1.54
Good	1,434	1.50	0.17	<0.001	1.21	1.86
Fair	826	1.94	0.27	<0.001	1.48	2.55
Poor	230	2.34	0.58	0.001	1.44	3.79
Physical activity						
More than once a week	3,646	1(ref)				
Once a week	458	1.29	0.18	0.059	0.99	1.69
One to three a month	153	0.70	0.14	0.067	0.47	1.03
Hardly ever or never	317	2.10	0.45	0.001	1.38	3.21
Smoking Status						
Non-smoker	1,733	1(ref)				
Ex-smoker	2,233	1.01	0.08	0.943	0.86	1.18
Current smoker	608	1.38	0.17	0.01	1.08	1.76
Housing Tenure						
Owners	3,922	1(ref)				
Renters	594	1.36	0.19	0.027	1.04	1.77
Others	58	0.76	0.25	0.399	0.40	1.44
Government Office region						
North East	295	1(ref)				
North West	604	1.63	0.30	0.009	1.13	2.35
Yorkshire	492	1.00	0.18	0.984	0.70	1.44
East Midlands	444	0.81	0.15	0.263	0.57	1.17
West Midlands	515	0.97	0.18	0.88	0.68	1.39
East of England	533	0.92	0.17	0.646	0.65	1.31
London	369	1.53	0.31	0.038	1.02	2.28

Continued from previous page

South East	811	1.06	0.18	0.729	0.76	1.48
South West	511	1.25	0.23	0.24	0.86	1.80
Ever diagnosed with CVD						
No	3,318	1(ref)				
Yes	1,256	1.49	0.14	<0.001	1.23	1.80
Constant		1.00	0.19	0.991	0.69	1.46

*sample size = 4,574

0=observed CRP in Waves 2-8 = 1,083

1=missing CRP = 3,491

R_2= 0.10

6.4.3 Multivariable analyses

Table 6.6 presents the null model from five different approaches with latent growth models. Latent variables show the within individual (intra-individual level) change over time. In complete case analysis, the intercept coefficient (i.e. initial level of C-reactive protein in wave 2) is 0.388 and there is 0.004 average rate of change over time but there is a curvilinear (non-linear) decline (b=-0.022) in C-reactive protein levels over the two last waves. In FIML, MI, DK and PMM the intercept coefficient is larger compared to complete case but the linear effect is negative in all methods which indicates that C-reactive protein levels decreased in later ELSA waves, however, this decline was not statistically significant. The quadratic effect was negative in all methods and statistically significant which indicates that there was an accelerated decline in C-reactive protein levels over time.

Table 6. 6 Latent variables of null model in five different methods of compensating from missing data – intra-individual level

	Complete case analysis (1,083)			**Full Information Maximum Likelihood (4,574)**			**Multiple Imputation (4,574)**		
	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values
Mean intercept	**0.388**	**0.029**	**<0.001**	**0.516**	**0.014**	**<0.001**	**0.519**	**0.013**	**<0.001**
Mean linear slope	0.004	0.028	0.884	0.003	0.019	0.861	0	0.02	0.853
Mean quadratic slope	**-0.022**	**0.009**	**0.012**	**-0.026**	**0.007**	**0.001**	**-0.025**	**0.006**	**0.001**
Variance intercept	**0.816**	**0.073**	**<0.001**	**0.701**	**0.051**	**<0.001**	**0.712**	**0.047**	**<0.001**
Variance linear slope	**0.267**	**0.081**	**0.001**	**0.207**	**0.007**	**0.002**	**0.227**	**0.059**	**<0.001**
Variance quadratic slope	**0.013**	**0.006**	**0.047**	0.011	0.006	0.087	**0.013**	**0.005**	**0.015**

	Diggle-Kenward model (4,574)			**Pattern Mixture models (4,574)**		
	Coef	SE	P-values	Coef	SE	P-values
Mean intercept	**0.516**	**0.014**	**<0.001**	**0.516**	**0.014**	**<0.001**
Mean linear slope	-0.003	0.019	0.885	0.003	0.021	0.877
Mean quadratic slope	**-0.023**	**0.007**	**0.002**	**-0.026**	**0.008**	**0.001**
Variance intercept	**0.612**	**0.044**	**<0.001**	**0.702**	**0.051**	**<0.001**
Variance linear slope	**0.171**	**0.064**	**0.008**	**0.218**	**0.066**	**0.001**
Variance quadratic slope	0.702	0.051	0.002	0.011	0.006	0.081

Figures 6.6 - 6.11 illustrate the result estimates of five different approaches and the predicted values of C-reactive protein from the latent growth modelling analyses (further information on coefficient estimates and covariates in Appendices I – K). The predicted values from the complete case analysis are presented first, followed by the predicted values from FIML and MI assuming MAR and DK selection model and PMM assuming MNAR.

In the complete case graph, (Figure 6.6) the intercept, linear and quadratic slope in the high school category were not statistically significant, but the intercept coefficient in other methods was statistically significant. In foreign and no qualifications category the intercept estimates were statistically significant in all methods which indicated that those in this category of educational level had higher levels of C-reactive protein compared to those participants in higher education. In the complete case analysis, the linear slope was statistically significant and negative which indicated that C-reactive protein levels decreased in time but the quadratic slope was positive which indicated an accelerated increase over time. Overall, there were no significantly differences between the methods.

Figure 6.7 illustrates the predicted values of C-reactive protein and educational level. In the complete case analysis, the predicted values of C-reactive protein were lower in all categories of educational level compared to the other methods. The predicted levels of C-reactive protein in the foreign and no qualifications educational level category were higher in the DK model compared to FIML, MI and PMM. The predicted levels of C-reactive protein in the DK model were higher in the foreign and no qualifications category compared to the higher education category.

Figure 6.8 shows no statistically significant differences between the methods, but the DK model had larger intercept coefficients for both the middle and lowest wealth tertiles which indicates that people in lower wealth tertiles had higher levels of C-reactive protein compared to participants in the highest wealth tertile. In the complete case model the intercept coefficient in the lowest wealth tertile was not statistically significant in contrast to the other methods where we found statistical significant differences between the least and most advantaged wealth categories. Linear slopes were statistically significant only in the middle wealth tertile, although negative in all methods apart from the complete case. The DK model had the lowest linear slope coefficient compared to all the methods. On the contrary, the quadratic slope was positive and statistically significant in all methods and MI quadratic slope coefficient was lower compared to the other methods.

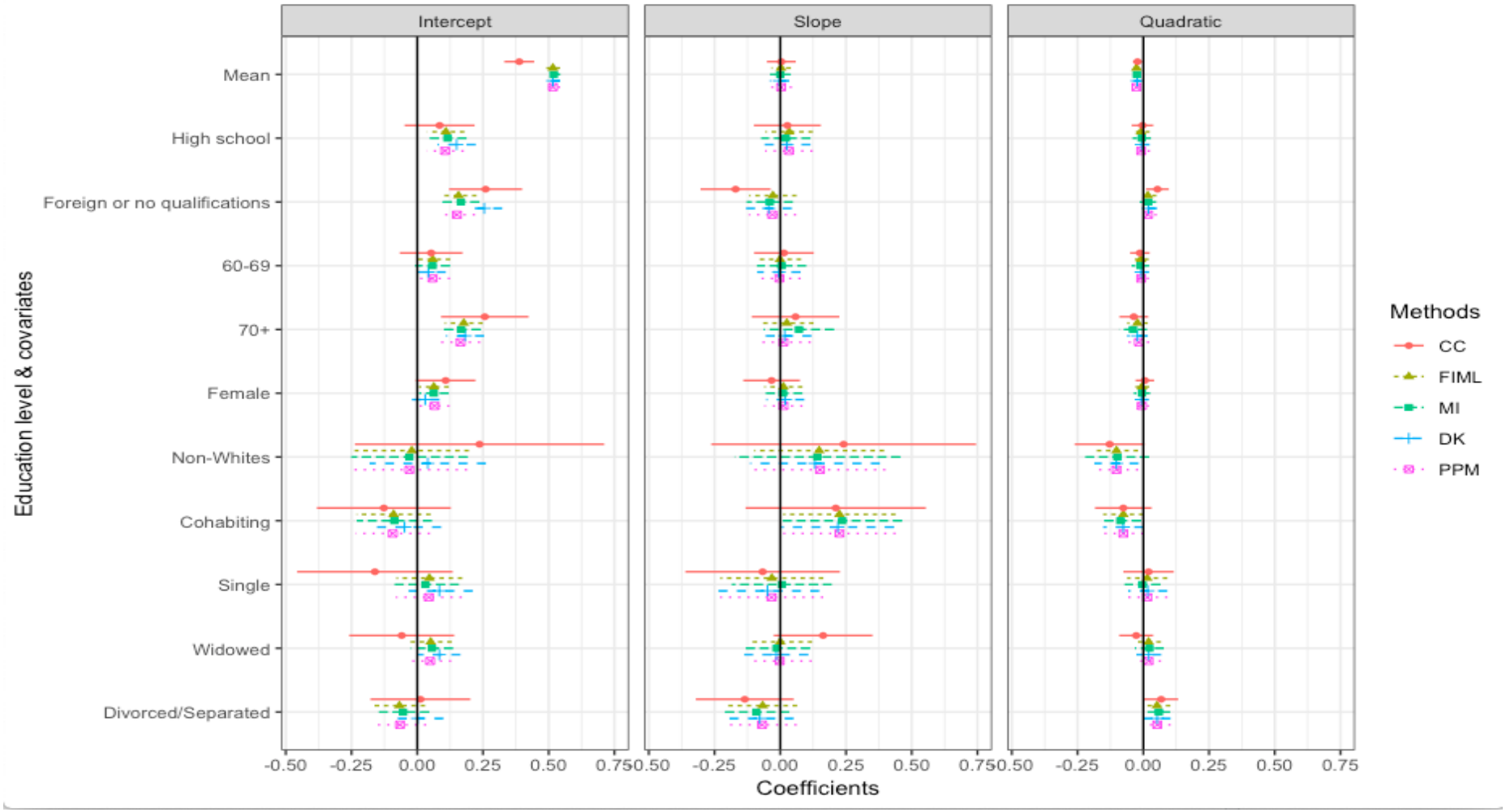


Figure 6. 6 Illustration of the C-reactive protein coefficients in the intercept, linear and quadratic slope in educational level (Reference categories: higher education, age 50-59, male, Whites, and married.

The predicted values of C-reactive protein by wealth are shown in Figure 6.9. The complete case graph had lower predicted levels of C-reactive protein in all wealth categories compared to the other methods. Participants in the middle tertile had higher predicted values compared to the lowest and highest wealth tertiles in all methods apart from the DK model. In the DK model the predicted levels of C-reactive protein were higher in the lowest wealth tertile. In the MI graph, the predicted levels of C-reactive protein in the middle and lowest tertiles were very similar, however, the predicted levels of C-reactive protein in the lowest wealth tertile were higher in subsequent waves compared to the affluent wealth categories

Figure 6.10 showed no statistically significant differences between the methods, but the DK model had larger intercept coefficients in the lowest social class category which indicated that participants in semi-routine, technical and other occupations had higher levels of C-reactive protein compared to participants in the managerial and professional social class. In the complete case analysis, the intercept coefficient was negative indicating that participants in the intermediate social class category were more likely to have higher levels of C-reactive protein, however, none of the associations were statistically significant in any of the methods. There were no statistically significant differences between the linear slopes in all methods. On the contrary, the quadratic slopes had positive coefficients but again not significantly different in all methods.

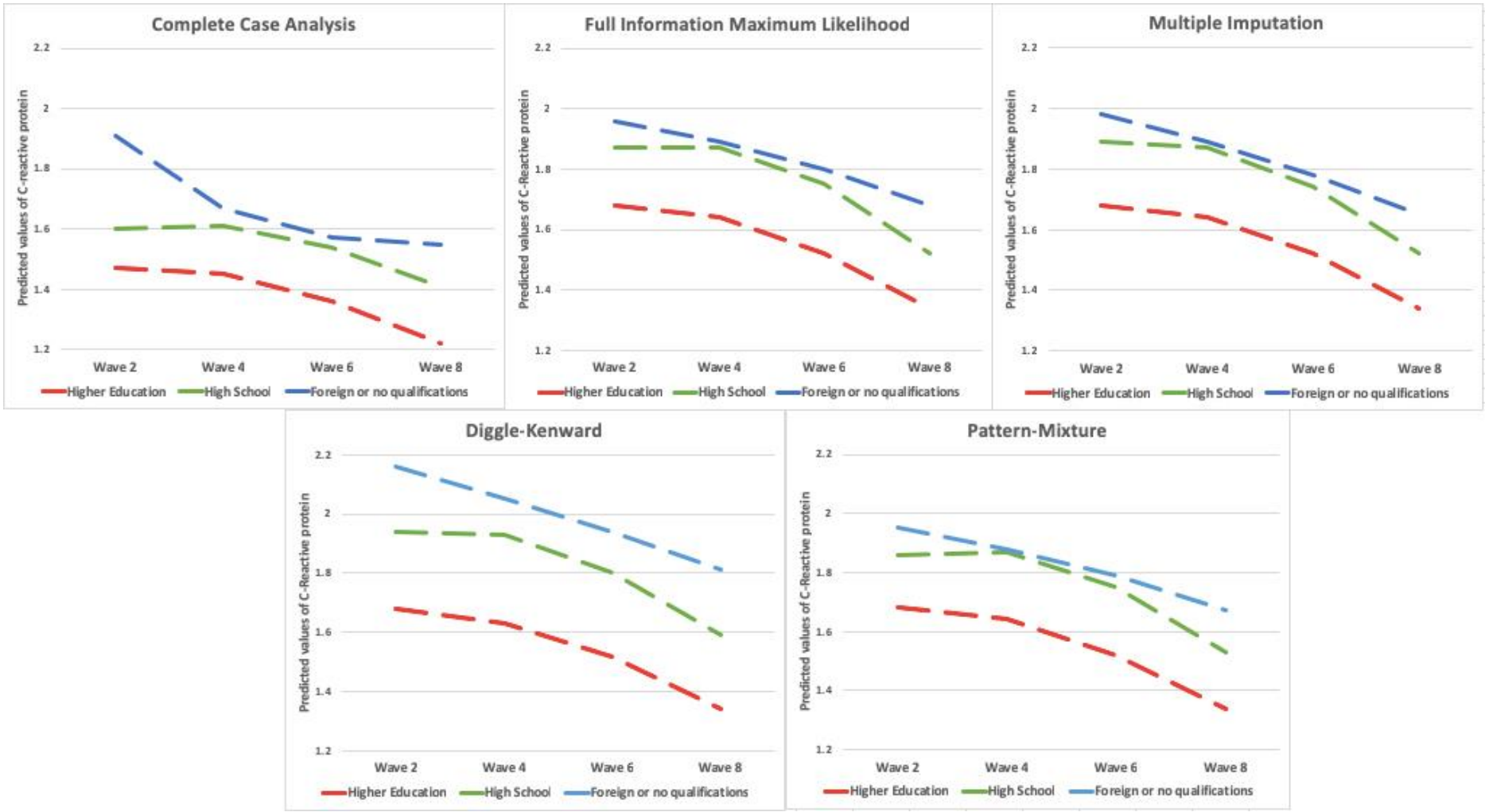


Figure 6. 7 Predicted values of C-reactive protein and educational level in five methods

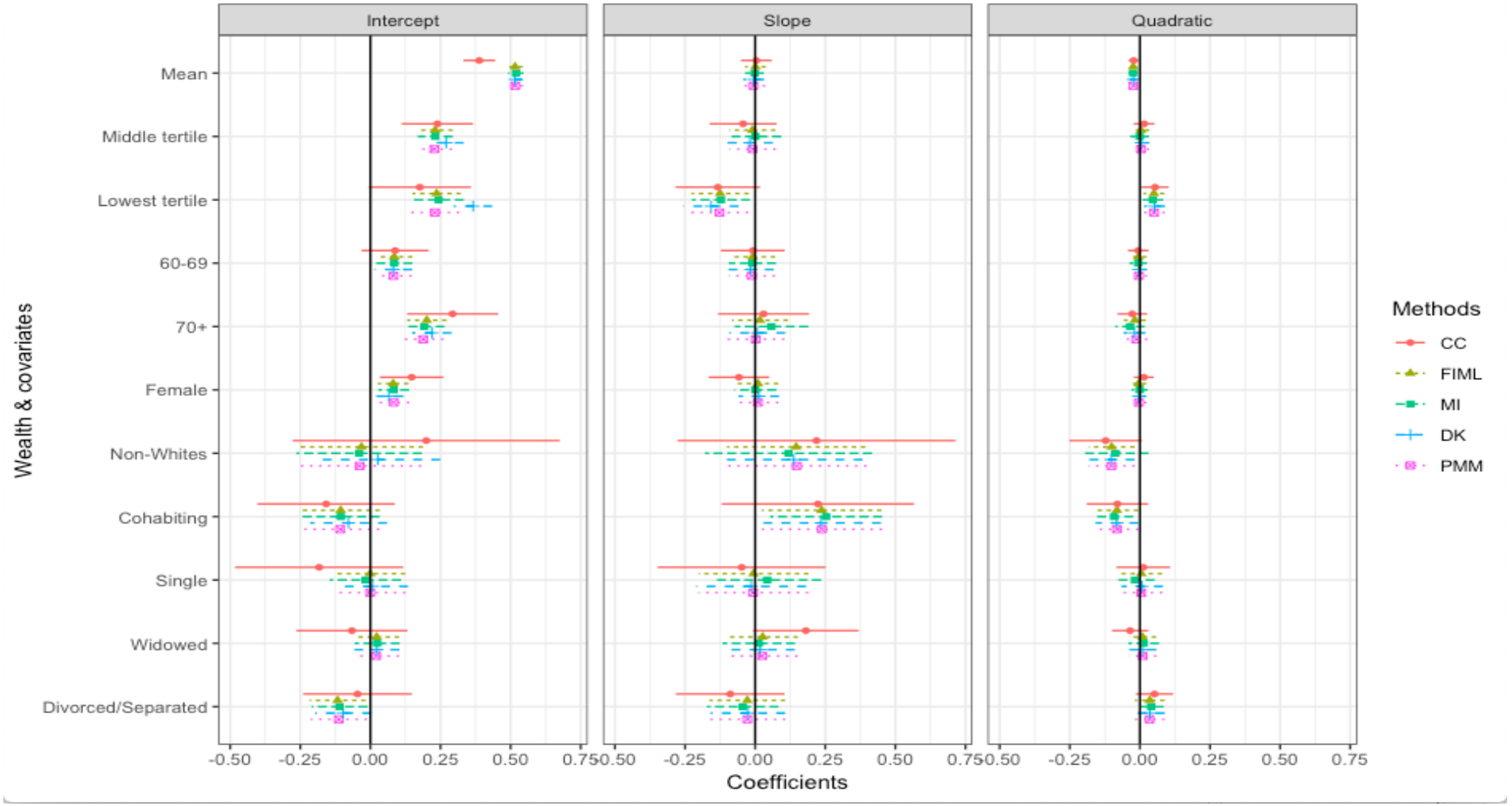


Figure 6. 8 Illustration of the CRP coefficients in intercept, linear and quadratic slope in wealth tertiles (Reference categories: highest wealth tertile, age 50-59, male, Whites, and married)

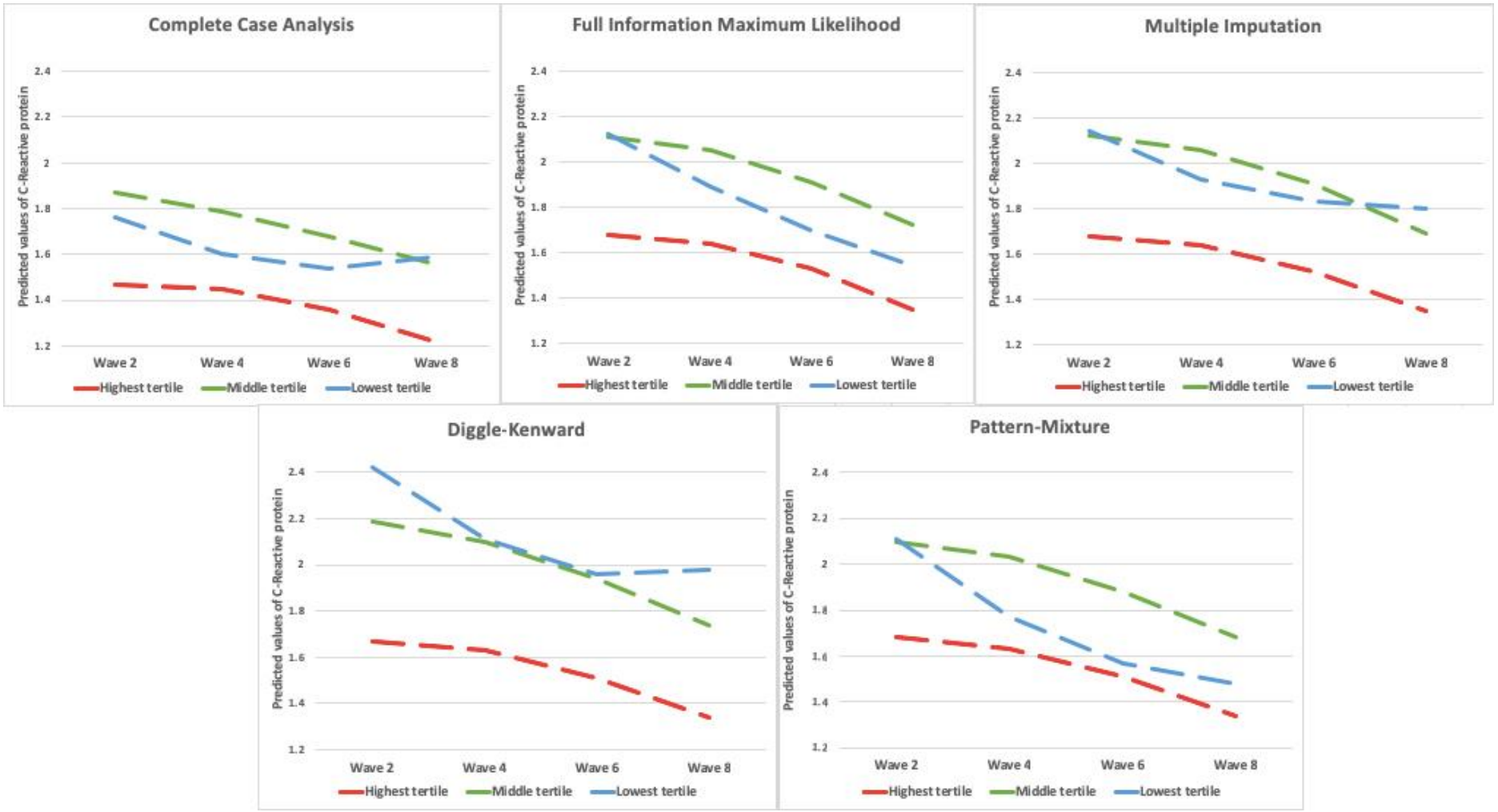


Figure 6. 9 Predicted values of C-reactive protein and wealth tertiles in five methods

Predicted levels of C-reactive protein and social class in Figure 6.11 showed that the complete case model had lower predicted levels of C-reactive protein in all social class categories compared to the other methods. Participants in the semi routine and technical occupations category had higher levels of C-reactive protein in all methods compared to the managerial and professional category of social class. In the DK method the predicted values were higher for the lowest social class category compared to all other methods. FIML, MI and PMM show almost similar predicted values in all categories for social class.

We extended our analyses and we dropped deceased participants but we could not identify any differences as the patterns of results remained unchanged. Moreover, we performed analysis using the same statistical methods in participants with intermittent missingness (participants who left the study and returned in subsequent wave) and our findings were similar to those with monotone missingness. There were no significant differences in the coefficient estimates.

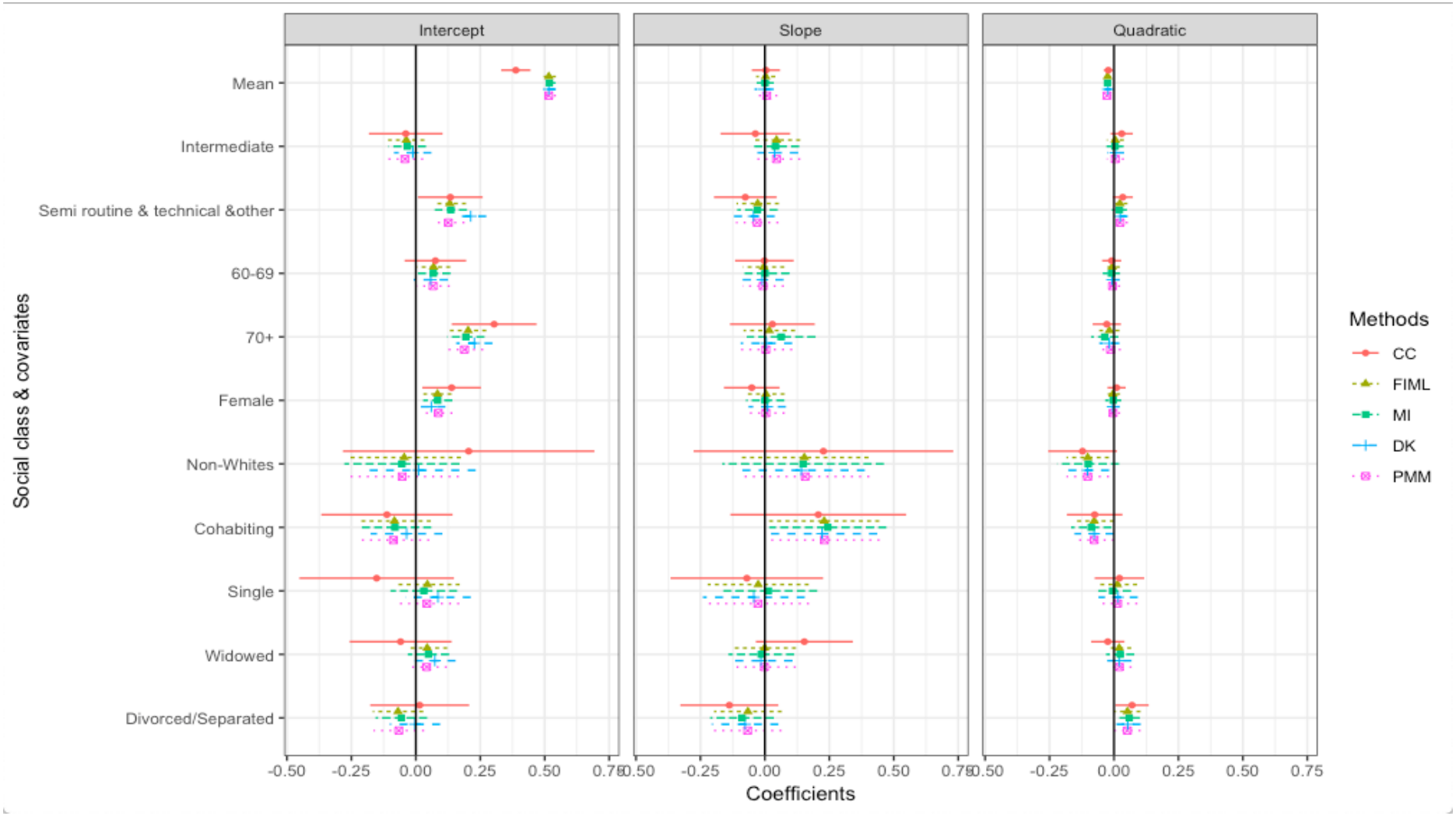


Figure 6. 10 Illustration of the C-reactive protein coefficients in intercept, linear and quadratic slope in social class (Reference categories: managerial and professional, age 50-59, male, Whites, and married)

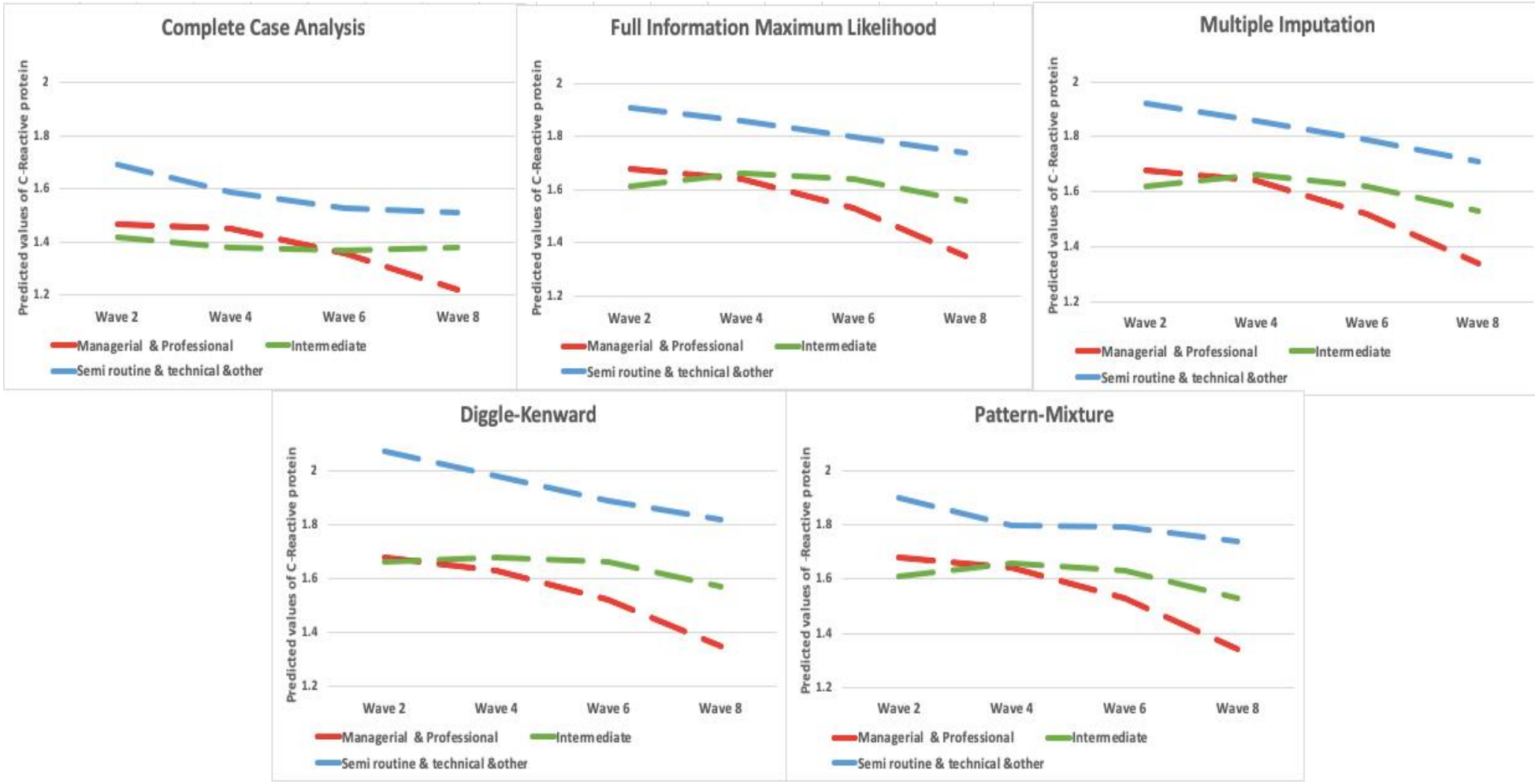


Figure 6. 11 Predicted values of C-reactive protein and social class in five methods

6.5 Discussion

Our study findings suggest that wave 2 ELSA respondents living at a socioeconomic disadvantage who were older and men were less likely to have a measure of C-reactive protein in subsequent waves. Respondents who were divorced and separated were less likely to have a C-reactive protein measurement in subsequent waves. Participants living in rented accommodation and participants living in urban areas were less likely to have C-reactive protein measurement. Participants with poorer health, physically inactive and current smokers were also less likely to have a C-reactive protein sample in subsequent waves. Furthermore, ELSA wave respondents living in social housing and in urban areas were more likely to be missing in the subsequent waves.

This study focused on evaluating the association between socioeconomic position and repeated systemic inflammation using methods that consider two different assumptions of random and informative (non-random) attrition. In this representative sample of older population in England, three indicators of socioeconomic position were associated with higher levels of C-reactive protein in four waves of ELSA. Educational level, wealth, and social class were significantly associated with higher levels of C-reactive protein in almost all methods and the association was not significantly different between the methods.

Our findings are consistent with cross-sectional longitudinal studies that have examined the role of socioeconomic position and inflammatory biomarkers, however we also consider missingness under different missing data assumptions and compare the results of five different methods. Therefore, our findings provide further information on the socioeconomic differences in the levels of inflammation as older adults age in four waves of ELSA.

6.5.1 Comparison of the results with previous studies

In accordance with previous studies using cross-sectional data and also with our hypotheses, we found that people living in socioeconomic disadvantage had higher levels of C-reactive protein (Kivimaki et al., 2005; Loucks et al., 2010; Pollitt et al., 2008), Our findings were similar with a longitudinal study using ELSA participants which accounted for non-random attrition but found no significant differences between the complete case analysis and the joint modelling analysis which accounted for non-random drop-out (Maharani, 2019).

Our results suggest that older people were more likely to be missing and thus not have a measure of C-reactive protein sample in the subsequent waves. This is consistent with previous findings which suggested that older people were susceptible to attrition in follow-up (Gustman & Steinmeier, 2004; Lepkowski & Couper, 2002). Men were also more likely to be missing from future measurements (Nicoletti & Buck, 2003; Uhrig, 2008). Furthermore, according to our hypothesis people living at a social disadvantage (Behr et al., 2005; Ekholm et al., 2010; Ferrie et al., 2009), people with poor health (Groves & Cooper, 1998; Kho et al, 2009; Uhrig, 2008) and smokers were more likely to be missing in follow-up studies.

Contrary to the literature which suggests that C-reactive protein levels increase with age (Singh & Newman, 2011; Varadhan et al., 2014; Wyczalkowska-Tomasik et al., 2016), our findings suggested that C-reactive protein levels decreased after the baseline ELSA wave, although older ELSA participants had higher levels of C-reactive protein. Differences in our findings regarding the C-reactive protein levels could be explained by the selective loss of follow up of unhealthy and sensitive participants and inclusion of healthy participants known as the “healthy survivor effect” (Arrighi & Hertz-Picciotto, 1994).

There is a debate in the literature on whether socioeconomic differences in health in older adults decline or increase with advancing age. This could be also be explained by the "healthy survivor effect" that was mentioned above. Another possible explanation of different findings could be the use of the different measures for the socioeconomic position for the elderly populations (Huisman et al., 2003; Knesebeck et al., 2007; Robert & House, 1996). Some studies suggest that income, education, and occupational class are not appropriate measures to describe socioeconomic circumstances in older ages (Adler & Ostrove, 1999; Allin et al., 2009; Duncan et al., 2002; Grundy & Holt, 2001; Robert & House, 1996) and other studies argued that wealth is the appropriate indicator to determine socioeconomic status in older adults (e.g. Huisman et al., 2003; Lynch & Kaplan, 2000; Robert & House, 1996; Smith & Kington, 1997; Willson et al., 2007). Compared to income, wealth is more dispersed in older adults (Allin et al., 2009) and although income decreases as older adults retire, wealth seems to reach its peak (Smith & Kington, 1997). In this study, we used educational level, wealth and social class in order to describe the mid and the later adulthood socioeconomic position.

We suggest that the observed decline in socioeconomic differences with advancing age is biased since our findings suggest that the differences between socioeconomic position categories persist and become wider when we compensate for missing data.

6.5.2 Methodological considerations

This study compared five missing data methods after assuming that missing data were MCAR, MAR, and MNAR. Although we found no statistically significant differences between the methods, the DK model had larger predicted levels of C-reactive protein compared to the other methods. The Diggle-Kenward (1994) model is a two-part selection model, it is comprised of a growth model and a logistic regression model

which takes into account variables correlated with missing values. The DK and PMM method assume that missing data are MNAR. However, the predicted values in PMM are lower compared to those in the DK method. Unlike the DK method, the PMM does not produce a logistic regression model but creates different missing data patterns and includes binary dummy dropout indicators as covariates in the model of interest. FIML and MI assume both that missing data are MAR and although both methods include auxiliary variables in their models, there were differences in the coefficient estimates and predicted values compared to the DK method which considers that missingness is associated with the C-reactive protein levels.

Among the strengths of our study is that we compensated for missing data by implementing MNAR methodology and particularly joint modelling which also accounts the probability of survival. Our study highlights that there is correlation between socioeconomic position and systemic inflammation even after accounting for important confounders such as age, sex, ethnicity, and marital status. We used three indicators for socioeconomic position which comprehensively describe the mid and the later life socioeconomic circumstances. We also included in our imputation model and in joint modelling covariates that predict missingness and indicate health statement (i.e. self-assessed health), mobility (i.e. physical activity), health behaviours (i.e. smoking status), and health outcome (i.e. cancer, CVD) which could be covariates of C-reactive protein. We excluded participants with C-reactive protein levels of 10mg/L in order to avoid including participants with acute inflammation and focus only in the assessment of chronic inflammation.

The main limitation of our study is that our findings in five different methods are only based on assumptions in different mechanisms of missing data. It is impossible to identify the mechanisms of missing data and whether non-random drop out exists in

our data without implementing a simulation study. A potential limitation of the current study is that although we compensate for missing data by using different methods assuming MAR and MNAR, it is not possible to identify which model fits the data best because there is no a unique selection criterion. As mentioned in Zinn and Gnambs (2018), criteria such as Bayesian information criterion (BIC) and Akaike information criteria (AIC) could not be implemented because of the different dimensionality of the outcome variables. For instance, in the MI method the dimension of the outcome variable equals the observed and unobserved cases in the data but on the other hand in FIML the dimension of the outcome variables corresponds to the observed values. To our knowledge, there is no coherent cross-validation approach or selection criteria that could allow a decision about which model fits data best, however, Zinn and Gnambs (2018) suggest that applying sensitivity analysis by comparing estimated effects is the only currently available solution.

6.5.3 Conclusion

Socioeconomically disadvantaged circumstances in the mid- and late-adulthood are associated with repeated inflammation in adulthood after controlling for covariates and after assuming missing data as MAR and MNAR. This study demonstrated that the social discrepancies in health between the most and least affluent socioeconomic groups persist at older ages. It also highlights the importance of compensating for missingness in longitudinal studies in biosocial research with ageing participants who are susceptible to non-random drop out.

CHAPTER 7. Discussion and conclusions

This thesis' findings confirm that socioeconomic position (described as educational level, wealth, and social class) is associated with the inflammatory biomarker C-reactive protein and stress-related biomarkers cortisol and cortisone in the cross-sectional analysis. Furthermore, the findings using longitudinal analysis confirm the association between socioeconomic position and repeated measures of C-reactive protein. The results varied between socioeconomic position measures and between methods used to compensate for non-response in biomarker data.

7.1 Main findings

7.1.1 Socioeconomic position effects on inflammation in older adults: compensating for missing data

According to the first hypothesis in Chapter 4, the findings suggest that there were differences in the characteristics between respondents and non-respondents in providing biomarker data. Participants from living in socioeconomic disadvantage and participants diagnosed with specific health conditions were less likely to provide a C-reactive protein measure blood sample. The findings were consistent with the second hypothesis that there was a negative association between socioeconomic position and levels of C-reactive protein after adjusting for possible confounders. The results varied by socioeconomic position measure and categories of the interaction term between social class and employment status. According to the third hypothesis, it is suggested that the association between socioeconomic position and C-reactive protein was expected to be greater after considering the influence of missing data. In the inverse probability weighting and multiple imputation methods in which predictors of missingness were considered either by producing a non-response model to create non-response weight or by adding them into an imputation model, the effects sizes were

larger in comparison with complete case analyses. Participants in the lowest educational category were more likely (b=0.23, p<0.001) compared to those with higher education in complete case model, however, in the inverse probability weighting model the effect was larger (b=0.25, p<0.001). Participants in the lowest wealth quintile were more likely (b = 0.51, p<0.001) to have higher levels of C-reactive protein compared to those in the most affluent wealth quintile in complete case model, however the effect was larger in multiple imputation model (b=0.52, p<0.001) and in the multiple imputation with attrition weights model (b=0.52, p<0.001).

7.1.2 Is social disadvantage a chronic stressor? Socioeconomic position effects on cortisol and cortisone: compensating for missing biomarker data

According to the first hypothesis in Chapter 5, there were differences between the characteristics of participants who had valid hair cortisol and cortisone data and those who did not have it. Living in socioeconomic disadvantage, having poorer health, and other demographic characteristics explained the missingness in hair sample and biomarker data. The findings were consistent with the second hypothesis that there was a negative association between socioeconomic position and cortisol and cortisone biomarker data after adjusting for possible confounders. The results varied between socioeconomic position measures and the two biomarker measurements. Consistent with the third hypothesis, the findings suggest a negative association between socioeconomic position and stress-related biomarkers after compensating for missing data. The results varied by socioeconomic position measures, the two biomarkers and missing data methods. While assessing the educational level effects on cortisone, it was found that only multiple imputation estimates were statistically significant compared to the estimates from complete case analysis and inverse probability

weighting. Participants in foreign or no qualification category had no significant differences (b=0.06, p>0.005) in the levels of hair cortisone compared to those in the higher education category in complete case model, however, in the multiple imputation with attrition weights model, there were statistically significant differences (b=0.11, p<0.001).

7.1.3 Is the increase in social inequalities in inflammation underestimated in conventional longitudinal analyses? Socioeconomic position and repeated systemic inflammation: compensating for missing data

The study findings were consistent with the first hypothesis in Chapter 6, that participants living in socioeconomic disadvantage and participants with poorer health and other demographic characteristics were more likely to drop out of the study in later waves of ELSA. Additionally, findings suggest that dropped out participants who had dropped out and those who became deceased in subsequent waves had higher levels of C-reactive protein in earlier wave measurements. The findings were consistent with the second hypothesis that living in socioeconomic disadvantage influenced intercepts and linear and quadratic slopes of C-reactive protein in complete case analysis. Education level was a significant predictor of C-reactive protein intercept and linear and quadratic slope. Although, wealth was a significant predictor of C-reactive protein intercept and quadratic slope, wealth was not a significant predictor of the linear slope. Although social class had an effect on C-reactive intercept, social class did not have an effect on linear and quadratic slopes after accounting for possible confounders, in complete case analysis.

In line with the third hypothesis, the findings suggested that missing data methods produced different results compared to complete case analysis. Results varied between socioeconomic position measures. For the social class and wealth variables, the

socioeconomic position effect was much larger on C-reactive protein intercept and slopes for all of the estimates derived after compensating for missing data compared to the complete case estimates.

7.2 Comparison of the study with previous studies

7.2.1 Socioeconomic position effects on inflammation in older adults: compensating for missing data

The findings are similar to previous studies which analysed consent bias and differences between respondents and non-respondents in surveys based on socioeconomic disadvantage (Behr et al., 2005; Ekholm et al., 2010; Ferrie et al., 2009; Lepkowski & Couper, 2002). In particular, the findings were similar to studies which found that older people were less likely to give consent to participate in a survey (Gustman & Steinmeier, 2004; Lepkowski & Couper, 2002; Thomas et al., 2001). Similarly, the findings suggested that participants who were diagnosed with health conditions were less likely to have biomarker data and these findings are consistent with other studies which found that poor health status was a reason for non-consent. (Ferrie et al., 2009; Groves & Cooper, 1998; Knies & Burton, 2014; Kho et al., 2009;Lepkowski & Couper, 2002; Uhrig, 2008). Furthermore, it was found that people from non-white ethnic groups (Lepkowski & Couper, 2002; Uhrig, 2008), singles (Gray et al., 1996; Uhrig, 2008), renters (Gray et al., 1996; Lepkowski & Couper, 2002; Nicoletti & Peracchi, 2005) and people living in urban areas (Burkam & Lee, 1998; Gray et al., 1996; Uhrig, 2008) were less likely to respond to health examination and blood sampling and findings were consistent with previous studies.

In accordance with previous studies which did not compensate for missing data, it was found that participants living at socioeconomic disadvantaged circumstances had higher levels of C-reactive protein (Kivimaki et al., 2005; Loucks et al., 2010;

Stringhini et al., 2013). The study findings were also similar to studies that compensated for missing data although different statistical approaches were followed (Pollitt et al., 2008; Stringhini et al., 2013).

7.2.2 Is social disadvantage a chronic stressor? Socioeconomic position effects on cortisol and cortisone: compensating for missing biomarker data

In accordance with the second hypothesis in Chapter 5, adults with depressive symptoms and psychiatric condition were less likely to have a hair sample and cortisol and cortisone biomarker data (Eaton et al., 1992; Farmer et al., 1994; Volken, 2013). Furthermore, participants with poorer health were less likely to have biomarker data (Ferrie et al., 2009; Groves & Cooper, 1998; Knies & Burton, 2014; Kho et al., 2009;Lepkowski & Couper, 2002; Uhrig, 2008).

The study findings were consistent with findings for people who had lower educational attainment (Boesch et al., 2015; Schreier et al., 2016), and were living in lower socioeconomic position tertiles measured by education and income (Serwinski et al., 2016).

7.2.3 Is the increase in social inequalities in inflammation underestimated in conventional longitudinal analyses? Socioeconomic position and repeated systemic inflammation: compensating for missing data

In accordance with previous studies using cross-sectional data and also with the hypotheses, it was found that people living in socioeconomic disadvantage had higher levels of C-reactive protein (Kivimaki et al., 2005; Loucks et al., 2010; Pollitt et al., 2007; 2008). Three studies used two measurements of C-reactive protein (Gimeno et al., 2007; Stringhini et al., 2013; Stringhini et al,.2018) and only one study accounted for non-random missingness using three measurements of C-reactive protein in the ELSA. This study implemented a linear mixed model with random effects and found that people with lower educational attainment and people in the poorest wealth tertile

had higher levels of C-reactive protein over time. When a joint model to account for non-random dropout was implemented, no significant differences in the coefficient estimates were found (Maharani, 2019). It is suggested that the joint model which was part a linear mixed model and part a survival model with age, time, time squared and the random intercepts from the linear model, was poorly estimated as predictors of missingness were not included and therefore no information about the characteristics of participants who non-randomly drop out of the study were included in the model.

The results suggest that older people were more likely to be missing and thus not have a measure of C-reactive protein sample in the subsequent waves. This is consistent with previous findings which suggested that older people were susceptible to attrition in follow-up (Gustman & Steinmeier, 2004; Lepkowski & Couper, 2002). Men were also more likely to be missing from future measurements (Nicoletti & Buck, 2003; Uhrig, 2008). Furthermore, according to our hypothesis, people living at a social disadvantage (Behr et al., 2005; Ekholm et al., 2010; Ferrie et al., 2009), people with poor health (Groves & Cooper, 1998; Kho et al, 2009; Uhrig, 2008) and smokers were more likely to be missing in follow-up studies.

Contrary to the literature which suggests that C-reactive protein levels increase with age (Singh & Newman, 2011; Varadhan et al., 2014; Wyczalkowska-Tomasik et al., 2016), the findings suggested that C-reactive protein levels decreased after the baseline ELSA wave, although there still remained large differences between the least and most advantaged groups. Differences in our findings regarding the C-reactive protein levels could be explained by the selective loss of follow up of unhealthy and sensitive participants and inclusion of healthy participants known as the “healthy survivor effect” (Arrighi & Hertz-Picciotto, 1994).

7.3 Contribution of this thesis to the literature

This thesis contributed to the existing literature by examining social inequalities in health and in older adults living in England, using data from a longitudinal prospective study. The methodological challenges originating from missing data were also examined. In this thesis, it was found that participants living in socioeconomic disadvantage and with certain health conditions (i.e. CVD, stroke, high blood pressure, cancer, asthma, depressive symptoms etc) were less likely to have a biomarker sample. This is very important particularly if the aim of the study is to examine social inequalities in health. If missing data are ignored then conclusions for only the well-off and healthy participants are drawn and subsequently social inequalities in health are underestimated. In order to examine if this underestimation existed, several methods for compensating for missing data were implemented. It was found that there is an underestimation of the effect of socioeconomic circumstances on health and thus it is important to consider missing data in the analyses. Furthermore, this thesis provided details on the sensitivity analyses of the methods considering random missingness in Chapters 4 and 5, and details on the sensitivity analysis of the methods considering random and non-random missingness in Chapter 6.

Data from the inflammatory biomarker C-reactive protein and stress-related biomarkers cortisol and cortisone were used. Both biomarkers have been referred to as biomarkers of health in the literature and have been associated with cardiovascular disease. Furthermore, both biomarkers had large numbers of missing data. In Chapter 4, C-reactive protein data were used from wave 2 of ELSA and it was found that from those participants who had a main interview, only 70% had a C-reactive protein sample. In Chapter 5, hair cortisol and cortisone data were used from wave 6 of ELSA and it was found that only 40% of the participants who agreed to have a main interview

had a hair cortisol and cortisone sample. In Chapter 6, from those participants who had a C-reactive protein sample in wave 2, only 24% had a C-reactive protein sample in wave 8. It would be interesting to explore the changes in the trajectories of hair cortisol and cortisone in time, however, there is no longitudinal collection of hair sample in ELSA.

7.4 Initial motivation for the thesis

Although living conditions and access to health care has been improved in the last decades, certain sub-populations still remain widely susceptible to ill-health. Certain health conditions such as cardiovascular disease has been linked with higher levels of specific inflammatory and stress-related biomarkers which on some occasions can predict the disease onset. Therefore, it is important to acknowledge the predictors of high biomarker measurements in order to avoid the disease onset and subsequently to improve people's wellbeing.

Previous research in social epidemiology focused on exploring the social inequalities in health and targeted specific inflammatory and stress-related biomarkers to explain the socioeconomic position discrepancies in the levels of these biomarkers. Findings in the literature exploring socioeconomic position effects on C-reactive protein and hair cortisol were inconsistent and there are some methodological considerations that could explain the variations in the results. In many longitudinal surveys, which collect biomarker data, participants who accepted to participate in the main interview often refuse to participate in nurse visits and additionally refuse to give blood sample resulting in the loss of valuable biomarker data. Survey methodologists highlighted the fact that participants with certain characteristics are less likely to participate in biomarker collections leaving surveys susceptible to selection bias. Producing results

and create assumptions for only part of the population is biased and threatens the study validity.

Another issue that threatens the validity of observational studies is the attrition and non-random drop out. Participants living in poor socioeconomic conditions and with poorer health are less likely to stay for a long time in the study and therefore in the course of study, remaining participants are well-off and healthier. Furthermore, in an ageing study like ELSA in which participants are over 50 and older grow older during the study, death is a leading cause for attrition.

Missing data in observational studies is often ignored and this work suggests that ignoring missing data is the leading cause for the inconsistencies in findings in other observational studies while exploring social inequalities and health.

Although, recently there has been a focus on missing data methods in the social epidemiology literature, the exact steps that have been followed in missing data methodology have been rarely described and it is difficult to assess whether it is the appropriate one for the data. Missing data methods can be implemented in different statistical packages such as STATA, R, SPSS, Mplus, and SAS and more recently with machine learning.

7.4.1 Application of missing data methods

In this thesis, several statistical methods were considered to address the missing data limitations. Inverse probability weighing, full information maximum likelihood, multiple imputations, selection model, and pattern mixture model were compared with complete case analysis.

Inverse probability weighting, multiple imputation and full information maximum likelihood are methods which consider that missing data are MAR. After applying

sensitivity analysis in Chapters 4, 5 and 6, it was shown that missing biomarker data are not missing completely at random, since there were differences in the values of the biomarkers in different methods. Therefore, it was necessary to compensate for missing biomarker data. In Chapter 6, methods which considered that missing data were MCAR, MAR and MNAR were implemented. It was found that the Diggle-Kenward selection model which considers MNAR produced larger values of C-reactive protein compared to other methods which considered missing data as MCAR and MAR. Therefore, it could be assumed that participants with high C-reactive protein levels were more likely to be missing from the study.

In this thesis, an important component of the methods assuming MAR and MNAR was considered. This important component was to identify predictors of missingness often called "auxiliary variables" which would help build comprehensive profiles of the participants who were less likely to have biomarker data either in particular waves examined in cross sectional analyses or during the study's course in the longitudinal analysis. The survey methodology literature and multidisciplinary data collected from ELSA helped to identify variables with strong predictive power over missing biomarker data. Furthermore, the non-response analyses in Chapters 4, 5 and 6, identified additional predictors of missingness which were not mentioned in the literature. Participants with certain health conditions such as CVD, stroke, asthma, feeling pain, disabilities (limiting longstanding illnesses), high blood pressure, cancer and depressive symptoms were less likely to have biomarker data.

It is important to include variables with a minimum of missing values themselves as missingness in auxiliary variables proved to be less helpful. In the second step, these auxiliary variables were used to build a logistic regression model and to calculate the non-response weight from the inverse of the predicted response probabilities from the

same logistic regression model. Further, attrition weights which accounted for differential non-response from the previous wave were combined with the new non-response weight to produce the final cross-sectional blood weight in our analysis.

These auxiliary variables were also included in the imputation model of the multiple imputation method. The imputation model consisted of the model of interest and auxiliary variables. It is important while implementing multiple imputation with chained equations to model every variable in the imputation model with the correct type of regression. Since, regression models for every variable are produced; all binary variables should be in the logistic regression category and all ordinal variables in the logit regression category etc. The number of imputations is also very important as the literature suggests different numbers depending on the percentage of missingness. There is a general rule of thumb that a minimum 20 imputations are sufficient to avoid bias and increase power, however, it is highly recommended to always check the relative efficiency equation and thus have information on the magnitude of the multiple imputation standard error (and therefore sampling variance) in relation to its theoretical minimum. In our analyses, results from 15-20 imputations were presented as adding more imputations did not alter our results significantly.

Full information maximum likelihood (FIML) benefits from the use of auxiliary variables as a correlation matrix is produced and information from the auxiliary variables help estimate the coefficients and standard errors. This thesis has implemented the Diggle-Kenward selection model assuming non-ignorable missing data. The DK benefits from the use of auxiliary variables and regresses these variables into the selection model. On the other hand, the pattern mixture model does not benefit from auxiliary variables and they were not modelled in the analyses. However, all

variables that predicted missingness were included in the model using the "with" command in Mplus.

In this thesis, a simulation study has not been carried out to evaluate which missing data method performed better; the identification and inclusion of auxiliary variables in the models which are related to the outcome of interest, demonstrates the great importance of implementing MAR and MNAR methods compared with the complete case analysis assuming MCAR.

7.5 Research implications

In ELSA, the wealth variable has remained a very strong predictor of higher levels of inflammatory and stress-related biomarkers. On the other hand, educational level and social class were not consistently good predictors of higher levels of biomarkers in different methods compensating for missing data. Previous research has suggested that wealth which is the accumulation of assets over time is a recommended indicator to describe comprehensively the socioeconomic circumstances in older adults (Lynch, 1996). Educational level and social class are traditional indicators of socioeconomic position, however, they provide only a partial view of socioeconomic inequalities in health (Galobardes et al., 2007). This thesis tested whether paternal social class when the participants were 14 years old, which was retrospectively collected, was associated with the biomarkers of interest. No association was found and therefore it was not included as a predictor in any analyses. By including the wealth variable, any family assets and resources such as an inheritance can be captured and therefore indirectly family socioeconomic circumstances are described (Halaby & Weakliem, 1993; Wright & Halaby, 1993).

In this thesis, socioeconomic position has been modelled in two different ways. In Chapter 4, educational level, wealth, and social class and interaction between social class and employment status have been inserted in the models simultaneously and were adjusted for possible confounders. In Chapters 5 and 6, educational level, wealth and social class have been re-categorised and inserted in the models independently and were adjusted for possible confounders. No interaction term was added in the substantive model in Chapters 5 and 6 as no predicting effect on the levels of biomarkers was found. With these two different approaches, I highlighted the importance of exploring the indicators of socioeconomic position when simultaneously and independently modelled, since the indicators have overlapping properties and may also be independently correlated with biomarkers at older ages.

The thesis highlighted the importance of exploring the characteristics of participants who fail to participate in subsequent data collections and wave measurements. It also highlighted the importance of compensating for missing data in surveys otherwise certain sub-populations will be over or under-represented in analyses.

Figures in Chapters 4, 5, and 6 showing predicted values of C-reactive protein and cortisol and cortisone indicate that differences exist between methods. In the analysis in Chapter 4, simultaneously assessing the socioeconomic position effects on C-reactive protein, some differences in the coefficient estimates between the statistical methods compensating for missing method were found. The differences in the coefficients were not large, however, the differences in the predicted values were larger between the methods, as shown in Figures 4.3-4.6. In Chapter 5, Table 5.6 shows differences between socioeconomic position variables and cortisone in different methods. In particular, the educational level was a strong predictor of higher levels of cortisone only in multiple imputation and not in complete case analysis and inverse

probability weighting methods. Wealth was a significant predictor of higher levels of cortisone, however the effect sizes were larger in inverse probability weighting methods and multiple imputation compared to complete case analysis. Social class was also a significant predictor in all methods, but multiple imputation results had larger effects sizes compared to complete cases and inverse probability weighting methods.

For the longitudinal analysis in Chapter 6, five different latent growth models were compared: complete case analysis with maximum likelihood, full information maximum likelihood, multiple imputation, Diggle-Kenward selection model and pattern mixture model. All socioeconomic position indicators were significant predictors of higher levels in C-reactive protein intercept. However, only educational level was a strong predictor of C-reactive protein linear and quadratic slopes. There were differences in all socioeconomic position indicators and across different methods in longitudinal analysis. In particular, the effect sizes and predicted values in Diggle-Kenward method were much larger compared to the other methods.

In general, similar conclusions under the different methods were found in this thesis. Differences in the magnitude of the effect sizes were found under the different methods, however, the overall conclusions did not change much. While examining the effect of education on cortisone, statistically significant results and larger effect sizes were found only in the multiple imputation method. The differences in the magnitude of the effect sizes highlighted the importance of compensating for missing data and the importance of identifying appropriate predictors of missingness. Otherwise, there would be an underestimation of the socioeconomic position effect on biomarkers and this would lead to inconsistent and inaccurate results, and misleading and erroneous conclusions.

The development of missing data methods in different statistical software programs makes methods for dealing with missing data such as inverse probability, full information maximum likelihood, multiple imputation, selection models and pattern mixture models relatively easy to be implemented. However, there are always pitfalls and drawbacks when preparation is not appropriately considered. It is very important to identify strong predictors of missingness which are strongly associated with the missing outcome variable. In this thesis, every participant with missing values in independent variables, possible confounders and auxiliary variables were excluded to avoid creating additional noise by trying to compensate for missingness in covariates as it has proved to be unhelpful if you have good amount of missingness in the outcome of interest (Thoemmes & Rose, 2014). While running the different missing data methods, time must be taken into consideration as sometimes models take long to converge. Therefore, the right choice of covariates is necessary to produce reliable results.

Although, both full information maximum likelihood and multiple imputation work under the assumption of MAR there are several differences between the methods. Based on Allison et al (2012) arguments, full information maximum likelihood is simpler when the appropriate software is available (e.g. Mplus, R). Multiple imputation requires more details from auxiliary variables for the imputation model to be accurately specified and properly built.

Another issue with multiple imputation is that the imputation model must be congenial with the model of interest. The two models do not have to be identical, but they cannot have major inconsistencies.

One other benefit of FIML is that it produces a deterministic result. On the other hand, multiple imputation gives different results every time you run the models because random draws are a crucial part of the process. The variability can be reduced by imputing more data sets, however, the number of data sets should always be tested for relative efficiency. One disadvantage of FIML is the necessity of a specially designed software to be implemented.

Although there is a significant increase in missing data methodology research in latest decades (Carpenter & Kenward, 2012; Enders, 2011; Little et al., 2012; Muthén et al., 2011), some issues are unresolved regarding the challenging matter of selection bias in longitudinal research. To begin with, there is no unique model selection criteria that would allow for decisions which model fits data best. Some standard methods for model comparison such as information criteria and/or cross validation cannot be applied. Zinn and Gnambs (2018) argue that sometimes it is possible to compare selection models and pattern-mixture models with AIC and BIC, however, different likelihood specifications and numbers of observations in FIML and MI make these methods unlikely to be compared. Moreover, missing data models cannot be compared because there is no coherent cross-validation approach. Zinn and Gnambs (2018) argue that at least for the moment only logical reasoning and comparing estimated effects could help to assess which missing data approach fits the data best.

7.6 Strengths and limitations

The English Longitudinal Study of Ageing is the first representative study of the older population in England. It is a multidisciplinary study which measures economic, health, and social aspects of people's lives. ELSA provides a broad range of

socioeconomic and health measurements in time and, therefore, facilitates the longitudinal analysis in biosocial research (Steptoe et al., 2013).

An important strength of this study is the use of three different socioeconomic indicators to define socioeconomic position in older adults. There is a broad literature exploring which is the most suitable socioeconomic indicator to describe best the socioeconomic profile in older adults and therefore the most appropriate indicators were explored. Educational level describes the early adulthood socioeconomic position, wealth describes the accumulative assets through the life course and the social class gives information on occupational classification at the moment of measurement.

Another strength of this study is that two different biomarkers to explore the socioeconomic position effects on older adult health were used. In particular, biomarker data from C-reactive protein collected from four ELSA waves, over a period of twelve years provided sufficient data to explore the C-reactive protein trajectories. Additionally, biomarker data from hair cortisol and cortisone were used in contrast with other studies that have assessed cortisol sample from saliva, serum or urine. Hair cortisol can be converted into inactive hair cortisone, and therefore a parallel assessment is necessary. Additionally, information on multiple measurements of C-reactive protein in a 12-year follow up to explore the health trajectories were used.

The most important strength of this study is the missing data methodology for accounting for missing biomarker data. Missing data are a very significant matter particularly in biosocial research were participants with certain characteristics are found to have missing biomarker data. Both socioeconomic measurements and

biomarker data are susceptible to ignorable and non-ignorable drop-out. Therefore, analysing the complete cases only would lead to ignoring certain sub-populations with certain characteristics. In this study, the cases would be people living in socioeconomic disadvantaged circumstances and people with higher levels of biomarkers and thus worse health. In only complete cases were taken into account then conclusions on well-off and healthier participants could be drawn.

Three main methods under the MAR assumptions were implemented. Inverse probability weighting and multiple imputation for cross-sectional analyses and full-information maximum likelihood and multiple imputation for the longitudinal analysis. Two methods under the MNAR assumption were implemented. The Diggle-Kenward selection model and pattern-mixture model were implemented after considering monotonic missingness. The Diggle-Kenward selection model originally designed for permanent attrition (i.e. monotonic missingness). To adjust for monotonic and intermittent missingness Enders et al (2011b), suggested options to account for intermittent missingness by creating unique missing data indicators. However, because intermittent missingness is not an event of interest, these options assume that the values are consistent with an MAR mechanism. In order to simplify our analyses only monotonic missingness has been presented[4].

This thesis did not investigate methodology of MNAR in cross-sectional settings since data that are MNAR may depend on current and future observations and lacking this information could make MNAR methods less accurate.

Another limitation of this study is that assumptions for the nature of data missingness were made. Hence, there is lack of information whether the data are MAR or MNAR.

[4] Results considering intermittent missingness can be found in the Appendices L-N

There is a strong debate whether missing data in longitudinal settings are MAR or MNAR. For instance, if missingness in biomarker data in subsequent waves is related to higher biomarker measurement in a previous wave, missing data are categorised as MAR. In contrast, if missingness in biomarker data is related to hypothetically higher biomarker data in the current wave, missing data are categorised as MNAR.

A simulation study could be implemented to reveal the true nature of missing data and provide an answer to these assumptions; however, simulations studies are based on observed datasets and therefore, certain limitations are unavoidable.

Mediators that lie on the causal pathway can give additional information on the effects of socioeconomic position on health. Since our findings are based on observational data, the association between socioeconomic position and health was tested and any assumptions about causality cannot be made. This approach was beyond the scope of this thesis as an important aim was to explore the missing data in biosocial research. Further work focused on identifying potential mediators and creating appropriate statistical models is necessary to explain the pathways between socioeconomic position and health.

7.7 Future Research

Exploring the potential pathways from the socioeconomic position to health can help to understand the effect of socioeconomic position on health. Potential mediators can be related to health behaviours such as smoking status, alcohol consumption, physical activity, diet while other mediators can be health-related measures such as Body Mass Index, hip-to-waist ratio, cognitive ability etc. From the findings of this thesis it is not possible to test how socioeconomic position influences higher levels of biomarkers and subsequently ill-health. There is broad literature exploring the socioeconomic

position effects on health behaviours and the effects of health behaviours on the levels of specific health-related biomarkers, however, the pathways that exist between socioeconomic position and health are rarely examined. Furthermore, there is a great gap in the literature for exploring these pathways whilst focusing on missing biomarker data.

Future work can include research on socioeconomic trajectories across the life course and levels of health-related biomarkers whilst maintaining focus on missing data. Since participants in ageing studies are getting older, missing data due to drop out and attrition due to death is very common. Considering these methodological limitations may prove informative on the extension of social inequalities in health in ageing populations while examining socioeconomic transitions.

7.8 Conclusions

The results suggest that socioeconomic position affects inflammation and HPA activity in older adults. Findings were different across socioeconomic position measures and missing data methods but the conclusions remained similar. The thesis highlighted the fact that compensating for missing biomarker data in biosocial research is important in order to tackle methodological limitations originating from the loss of information. The use of inverse probability weighting and multiple imputation in cross-sectional settings and joint modelling in longitudinal settings are plausible methods to compensate for missing biomarker data. A sensitivity analysis is essential to compare the estimates from the different applied methods. However, statistical modelling should always be applied with caution and due regard for the underlying assumptions.

References

Abell, J. G., Stalder, T., Ferrie, J. E., Shipley, M. J., Kirschbaum, C., Kivimäki, M., & Kumari, M. (2016). Assessing cortisol from hair samples in a large observational cohort: The Whitehall II study. *Psychoneuroendocrinology*, *73*, 148–156. https://doi.org/10.1016/j.psyneuen.2016.07.214

Acciai, F. (2018). The age pattern of social inequalities in health at older ages: Are common measures of socio-economic status interchangeable? *Public Health*, *157*, 135–141. https://doi.org/10.1016/j.puhe.2018.01.002

Adam, E. K., & Kumari, M. (2009). Assessing salivary cortisol in large-scale, epidemiological research. *Psychoneuroendocrinology*, *34*(10), 1423–1436. https://doi.org/10.1016/j.psyneuen.2009.06.011

Adler, N. E., & Ostrove, J. M. (1999). Socioeconomic status and health: What we know and what we don't. *Annals of the New York Academy of Sciences*, *896*, 3–15.

Alley, D. E., Seeman, T. E., Ki Kim, J., Karlamangla, A., Hu, P., & Crimmins, E. M. (2006). Socioeconomic status and C-reactive protein levels in the US population: NHANES IV. *Brain Behav Immun*, *20*(5), 498–504. https://doi.org/10.1016/j.bbi.2005.10.003

Allin, S., Masseria, C., & Mossialos, E. (2009). Measuring Socioeconomic Differences in Use of Health Care Services by Wealth Versus by Income. *American Journal of Public Health*, *99*(10), 1849–1855. https://doi.org/10.2105/AJPH.2008.141499

Allison, P. D. (2002). *Missing Data*. SAGE Publications.

Allison, P. D. (2012). Handling Missing Data by Maximum Likelihood.

An, K., Salyer, J., Brown, R. E., Kao, H.-F. S., Starkweather, A., & Shim, I. (2016). Salivary Biomarkers of Chronic Psychosocial Stress and CVD Risks: A Systematic Review. *Biological Research For Nursing*, *18*(3), 241–263. https://doi.org/10.1177/1099800415604437

Arrighi, H. M., & Hertz-Picciotto, I. (1994). The Evolving Concept of the Healthy Worker Survivor Effect. *Epidemiology*, *5*(2), 189–196. Retrieved from https://www.jstor.org/stable/3702361

Artazcoz, L., & Rueda, S. (2007). Social inequalities in health among the elderly: A challenge for public health research. *Journal of Epidemiology and Community Health*, *61*(6), 466–467. https://doi.org/10.1136/jech.2006.058081

Azur, M. J., Stuart, E. A., Frangakis, C., & Leaf, P. J. (2011). Multiple Imputation by Chained Equations: What is it and how does it work? *International Journal of Methods in Psychiatric Research*, *20*(1), 40–49. https://doi.org/10.1002/mpr.329

Banks, J., Muriel, A., & Smith, J. P. (2011). Attrition and health in ageing studies: Evidence from ELSA and HRS. *Longitudinal and Life Course Studies*, *2*(2), 101–126. https://doi.org/10.14301/llcs.v2i2.115

Barker, D. J., Meade, T. W., Fall, C. H., Lee, A., Osmond, C., Phipps, K., & Stirling, Y. (1992). Relation of fetal and infant growth to plasma fibrinogen and factor VII concentrations in adult life. *BMJ*, *304*(6820), 148–152. https://doi.org/10.1136/bmj.304.6820.148

Bartley, M. (2004). *Health Inequality: An Introduction to Concepts, Theories and Methods*. Wiley.

Bassuk, S. S., Berkman, L. F., & Amick, B. C. (2002). Socioeconomic status and mortality among the elderly: Findings from four US communities. *American Journal of Epidemiology*, *155*(6), 520–533.

Baum, A., Garofalo, J. P., & Yali, A. M. (1999). Socioeconomic status and chronic stress. Does stress account for SES effects on health? *Annals of the New York Academy of Sciences*, *896*, 131–144.

Beckett, M. (2000). Converging health inequalities in later life—An artifact of mortality selection. *Journal of Health and Social Behavior*, *41*(1), 106–119.

Becketti, S., Gould, W., Lillard, L., & Welch, F. (1988). The Panel Study of Income Dynamics after Fourteen Years: An Evaluation. *Journal of Labor Economics*, *6*(4), 472–492. https://doi.org/10.1086/298192

Behr, A., Bellgardt, E., & Rendtel, U. (2005). Extent and Determinants of Panel Attrition in the European Community Household Panel. *European Sociological Review*, *21*(5), 489–512.

Ben-Shlomo, Y., & Kuh, D. (2002). A life course approach to chronic disease epidemiology: Conceptual models, empirical challenges and interdisciplinary perspectives. *Int J Epidemiol*, *31*(2), 258–293.

Benzeval, M., Green, M. J., & Leyland, A. H. (2011). Do social inequalities in health widen or converge with age? Longitudinal evidence from three cohorts in the West of Scotland. *BMC Public Health*, *11*(1), 947. https://doi.org/10.1186/1471-2458-11-947

Bhattacharyya, M. R., Molloy, G. J., & Steptoe, A. (2008). Depression is associated with flatter cortisol rhythms in patients with coronary artery disease. *Journal of Psychosomatic Research*, *65*(2), 107–113. https://doi.org/10.1016/j.jpsychores.2008.03.012

Biomarkers Definitions Working, G. (2001). Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. *Clin Pharmacol Ther*, *69*(3), 89–95. https://doi.org/10.1067/mcp.2001.113989

Blane, D., Kelly-Irving, M., d'Errico, A., Bartley, M., & Montgomery, S. (2013). Social-biological transitions: How does the social become biological? *Longitudinal and Life Course Studies*, *4*(2), 136–146. https://doi.org/10.14301/llcs.v4i2.236

Boesch, M., Sefidan, S., Annen, H., Ehlert, U., Roos, L., Uum, S. V., … Marca, R. L. (2015). Hair cortisol concentration is unaffected by basic military training, but related to sociodemographic and environmental factors. *Stress*, *18*(1), 35–41. https://doi.org/10.3109/10253890.2014.974028

Börsch-Supan, A., Brandt, M., Hunkler, C., Kneip, T., Korbmacher, J., Malter, F., … Zuber, S. (2013). Data Resource Profile: The Survey of Health, Ageing and Retirement in Europe (SHARE). *International Journal of Epidemiology*, *42*(4), 992–1001. https://doi.org/10.1093/ije/dyt088

Bosma, H., Golsteyn, B., Groffen, D., Schils, T., Stalder, T., Syurina, E., … Feron, F. (2015). The socioeconomic patterning of perceived stress and hair cortisol in Dutch 10-12 year olds. *International Journal of Public Health and Epidemiology*, *4*(8), 195–197. Retrieved from https://cris.maastrichtuniversity.nl/portal/en/publications/the-socioeconomic-patterning-of-perceived-stress-and-hair-cortisol-in-dutch-1012-year-olds(c5881044-b21f-4645-b29e-fa76e6ce1f9f).html

Braig, S., Grabher, F., Ntomchukwu, C., Reister, F., Stalder, T., Kirschbaum, C., … Rothenbacher, D. (2015). Determinants of maternal hair cortisol concentrations at delivery reflecting the last trimester of pregnancy. *Psychoneuroendocrinology*, *52*(Supplement C), 289–296. https://doi.org/10.1016/j.psyneuen.2014.12.006

Brick, J. M., & Kalton, G. (1996). Handling missing data in survey research. *Statistical Methods in Medical Research*, *5*(3), 215–238. https://doi.org/10.1177/096228029600500302

Bridges, S., Hussey, D., & Blake, M. (2015). *The dynamics of ageing. The 2012 English Longitudinal Study of Ageing (Wave 6). Technical Report*. NatCen.

Brilleman, S. L., Pachana, N. A., & Dobson, A. J. (2010). The impact of attrition on the representativeness of cohort studies of older people. *BMC Medical Research Methodology*, *10*, 71. https://doi.org/10.1186/1471-2288-10-71

Broderick, J. E., Arnold, D., Kudielka, B. M., & Kirschbaum, C. (2004). Salivary cortisol sampling compliance: Comparison of patients and healthy volunteers. *Psychoneuroendocrinology*, *29*(5), 636–650. https://doi.org/10.1016/S0306-4530(03)00093-3

Brunner, E. J. (2000). Towards a new social biology. In L. K. Berkman (Ed.), *Social Epidemiology*. Retrieved from http://discovery.ucl.ac.uk/24059/

Brunner, E., Shipley, M. J., Blane, D., Smith, G. D., & Marmot, M. G. (1999). When does cardiovascular risk start? Past and present socioeconomic circumstances and risk factors in adulthood. *J Epidemiol Community Health*, *53*(12), 757–764. Retrieved from ://000083878200008

Burkam, D. T., & Lee, V. E. (1998). Effects of Monotone and Nonmonotone Attrition on Parameter Estimates in Regression Models with Educational Data: Demographic Effects on Achievement, Aspirations, and Attitudes. *The Journal of Human Resources*, *33*(2), 555–574. https://doi.org/10.2307/146441

Carpenter, J., & Plewis, I. (2011). Analysing longitudinal studies with non-response: Issues and statistical methods. In M. Williams & P. Vogt (Eds.), *The SAGE handbook of Innovation in Social Research Methods* (pp. 498–523). Retrieved from http://researchonline.lshtm.ac.uk/179961/

Carpenter, J. R., Kenward, M. G., & Vansteelandt, S. (2006). A comparison of multiple imputation and doubly robust estimation for analyses with missing data. *Journal of the Royal Statistical Society: Series A (Statistics in Society)*, *169*(3), 571–584. https://doi.org/10.1111/j.1467-985X.2006.00407.x

Carpenter, James, & Kenward, M. (2012). *Multiple Imputation and its Application*. John Wiley & Sons.

Cesari, M., Penninx, B. W. J. H., Newman, A. B., Kritchevsky, S. B., Nicklas, B. J., Sutton-Tyrrell, K., … Pahor, M. (2003). Inflammatory markers and onset of cardiovascular events: Results

from the Health ABC study. *Circulation*, *108*(19), 2317–2322. https://doi.org/10.1161/01.CIR.0000097109.90783.FC

Chandola, T., Ferrie, J., Sacker, A., & Marmot, M. (2007). Social inequalities in self reported health in early old age: Follow-up of prospective cohort study. *BMJ*, *334*(7601), 990. https://doi.org/10.1136/bmj.39167.439792.55

Chen, Z., Li, J., Zhang, J., Xing, X., Gao, W., Lu, Z., & Deng, H. (2013). Simultaneous determination of hair cortisol, cortisone and DHEAS with liquid chromatography–electrospray ionization-tandem mass spectrometry in negative mode. *Journal of Chromatography B*, *929*(Supplement C), 187–194. https://doi.org/10.1016/j.jchromb.2013.04.026

Cook, R. J., Zeng, L., & Yi, G. Y. (2004). Marginal Analysis of Incomplete Longitudinal Binary Data: A Cautionary Note on LOCF Imputation. *Biometrics*, *60*(3), 820–828. https://doi.org/10.1111/j.0006-341X.2004.00234.x

Dadu, R. T., Nambi, V., & Ballantyne, C. M. (2012). Developing and assessing cardivascular biomarkers. *Transl Res*, *159*(4), 256–276.

Danesh John, & Pepys Mark B. (2009). C-Reactive Protein and Coronary Disease. *Circulation*, *120*(21), 2036–2039. https://doi.org/10.1161/CIRCULATIONAHA.109.907212

Davey Smith, G., Gunnell, D., & Ben-Shlomo, Y. (2000). Life-course approaches to socioeconomic differentials in cause-specific adult mortality. In D. Leon & G. Walt (Eds.), *Poverty, Inequality and Health: An International Perspective.* (pp. 88–124). Oxford:Oxford University Press.

Demakakos, P., Nazroo, J., Breeze, E., & Marmot, M. (2008). Socioeconomic status and health: The role of subjective social status. *Soc Sci Med*, *67*(2), 330–340. https://doi.org/10.1016/j.socscimed.2008.03.038

Dettenborn, L., Tietze, A., Kirschbaum, C., & Stalder, T. (2012). The assessment of cortisol in human hair: Associations with sociodemographic variables and potential confounders. *Stress (Amsterdam, Netherlands)*, *15*(6), 578–588. https://doi.org/10.3109/10253890.2012.654479

Dettenborn, Lucia, Muhtz, C., Skoluda, N., Stalder, T., Steudte, S., Hinkelmann, K., … Otte, C. (2012). Introducing a novel method to assess cumulative steroid concentrations: Increased hair cortisol concentrations over 6 months in medicated patients with depression. *Stress (Amsterdam, Netherlands)*, *15*(3), 348–353. https://doi.org/10.3109/10253890.2011.619239

Deverts, D. J., Cohen, S., Kalra, P., & Matthews, K. A. (2012). The prospective association of socioeconomic status with C-reactive protein levels in the CARDIA study. *Brain Behav Immun*, *26*(7), 1128–1135. https://doi.org/10.1016/j.bbi.2012.07.017

Diaz, M. D. M. (2002). Socio-economic health inequalities in Brazil: Gender and age effects. *Health Economics*, *11*(2), 141–154.

Diehr, P., Patrick, D. L., Spertus, J., Kiefe, C. I., McDonell, M., & Fihn, S. D. (2001). Transforming self-rated health and the SF-36 scales to include death and improve interpretability. *Medical Care*, *39*(7), 670–680.

Diggle, P., & Kenward, M. G. (1994). Informative Drop-Out in Longitudinal Data Analysis. *Journal of the Royal Statistical Society. Series C (Applied Statistics)*, *43*(1), 49–93. https://doi.org/10.2307/2986113

DizdarevicBostandic, A., Burekovic, A., VelijaAsimi, Z., & Godinjak, A. (2013). Inflammatory Markers in Patients with Hypothyroidism and Diabetes Mellitus Type 1. *Medical Archives*, *67*(3), 160. https://doi.org/10.5455/medarh.2013.67.160-161

Dorn, D., & Souza-Posa, A. (2004a). *Motives for Early Retirement: Switzerland in an International Comparison*.

Dowd, J. B., Simanek, A. M., & Aiello, A. E. (2009). Socio-economic status, cortisol and allostatic load: A review of the literature. *International Journal of Epidemiology*, *38*(5), 1297–1309. https://doi.org/10.1093/ije/dyp277

Duffy, A. R., Groer, M., Kane, B., & Williams, S. (2013). 133. Relationships between hair cortisol and marital status in female veterans. *Brain, Behavior, and Immunity*, *32*(Supplement), e39. https://doi.org/10.1016/j.bbi.2013.07.145

Duncan, G. J., Daly, M. C., McDonough, P., & Williams, D. R. (2002). Optimal Indicators of Socioeconomic Status for Health Research. *American Journal of Public Health*, *92*(7), 1151–1157. https://doi.org/10.2105/AJPH.92.7.1151

Eaton, W. W., Anthony, J. C., Tepper, S., & Dryman, A. (1992a). Psychopathology and attrition in the epidemiologic catchment area surveys. *American Journal of Epidemiology*, *135*(9), 1051–1059.

Eaton, W. W., Anthony, J. C., Tepper, S., & Dryman, A. (1992b). Psychopathology and attrition in the epidemiologic catchment area surveys. *American Journal of Epidemiology*, *135*(9), 1051–1059.

Eisen, E. A., Picciotto, S., & Robins, J. M. (2006). Healthy Worker Effect. In *Encyclopedia of Environmetrics*. https://doi.org/10.1002/9780470057339.vah007.pub2

Ekholm, O., Gundgaard, J., Rasmussen, N. K. R., & Hansen, E. H. (2010). The effect of health, socio-economic position, and mode of data collection on non-response in health interview surveys. *Scandinavian Journal of Public Health*, *38*(7), 699–706. https://doi.org/10.1177/1403494810382474

Elo, I. T. (2009). Social Class Differentials in Health and Mortality: Patterns and Explanations in Comparative Perspective. *Annual Review of Sociology*, *35*(1), 553–572. https://doi.org/10.1146/annurev-soc-070308-115929

Enders, C. K. (2008). A Note on the Use of Missing Auxiliary Variables in Full Information Maximum Likelihood-Based Structural Equation Models. *Structural Equation Modeling: A Multidisciplinary Journal*, *15*(3), 434–448. https://doi.org/10.1080/10705510802154307

Enders, C. K. (2010). *Applied missing data analysis*. Guilford Press.

Enders, C. K. (2011a). Analyzing longitudinal data with missing values. *Rehabilitation Psychology*, *56*(4), 267–288. https://doi.org/10.1037/a0025579

Enders, C. K. (2011b). Missing not at random models for latent growth curve analyses. *Psychological Methods*, *16*(1), 1–16. https://doi.org/10.1037/a0022640

Enders, C. K., & Bandalos, D. L. (2001). The Relative Performance of Full Information Maximum Likelihood Estimation for Missing Data in Structural Equation Models. *Structural Equation Modeling: A Multidisciplinary Journal*, *8*(3), 430–457. https://doi.org/10.1207/S15328007SEM0803_5

Fahdi, I. E., Gaddam, V., Garza, L., Romeo, F., & Mehta, J. L. (2003). Inflammation, infection, and atherosclerosis. *Brain, Behavior, and Immunity*, *17*(4), 238–244. https://doi.org/10.1016/S0889-1591(03)00052-7

Farmer, M., Locke, B., Liu, I., & Moscicki, E. (1994). Depressive symptoms and attrition: The NHANES I epidmiologic follow-up study. *International Journal of Methods in Psychiatric Research*, *4*, 19–27.

Feller, S., Vigl, M., Bergmann, M. M., Boeing, H., Kirschbaum, C., & Stalder, T. (2014). Predictors of hair cortisol concentrations in older adults. *Psychoneuroendocrinology*, *39*(Supplement C), 132–140. https://doi.org/10.1016/j.psyneuen.2013.10.007

Ferrie, J. E., Kivimäki, M., Singh-Manoux, A., Shortt, A., Martikainen, P., Head, J., … Shipley, M. J. (2009). Non-response to baseline, non-response to follow-up and mortality in the Whitehall II cohort. *International Journal of Epidemiology*, *38*(3), 831–837. https://doi.org/10.1093/ije/dyp153

Fitzgerald, J., Gottschalk, P., & Moffitt, R. (1998). *An Analysis of Sample Attrition in Panel Data: The Michigan Panel Study of Income Dynamics* (Working Paper No. 220). https://doi.org/10.3386/t0220

Fitzmaurice, G. M. (2003). Methods for Handling Dropouts in Longitudinal Clinical Trials. *Statistica Neerlandica*, *57*(1), 75–99. https://doi.org/10.1111/1467-9574.00222

Fraga, S., Marques-Vidal, P., Vollenweider, P., Waeber, G., Guessous, I., Paccaud, F., … Stringhini, S. (2015). Association of socioeconomic status with inflammatory markers: A two cohort comparison. *Prev Med*, *71*, 12–19. https://doi.org/10.1016/j.ypmed.2014.11.031

Galobardes, B., Smith, G. D., & Lynch, J. W. (2006). Systematic review of the influence of childhood socioeconomic circumstances on risk for cardiovascular disease in adulthood. *Ann Epidemiol*, *16*(2), 91–104. https://doi.org/10.1016/j.annepidem.2005.06.053

Galobardes, Bruna, Lynch, J., & Smith, G. D. (2007). Measuring socioeconomic position in health research. *British Medical Bulletin*, *81–82*(1), 21–37. https://doi.org/10.1093/bmb/ldm001

Galobardes, Bruna, Shaw, M., Lawlor, D. A., Lynch, J. W., & Smith, G. D. (2006a). Indicators of socioeconomic position (part 1). *Journal of Epidemiology and Community Health*, *60*(1), 7–12. https://doi.org/10.1136/jech.2004.023531

Galobardes, Bruna, Shaw, M., Lawlor, D. A., Lynch, J. W., & Smith, G. D. (2006b). Indicators of socioeconomic position (part 2). *Journal of Epidemiology and Community Health*, *60*(2), 95–101. https://doi.org/10.1136/jech.2004.028092

Gidlow, C. J., Randall, J., Gillman, J., Silk, S., & Jones, M. V. (2016). Hair cortisol and self-reported stress in healthy, working adults. *Psychoneuroendocrinology*, *63*, 163–169. https://doi.org/10.1016/j.psyneuen.2015.09.022

Gimeno, D., Ferrie, J. E., Elovainio, M., Pulkki-Raback, L., Keltikangas-Jarvinen, L., Eklund, C., … Kivimaki, M. (2008). When do social inequalities in C-reactive protein start? A life course perspective from conception to adulthood in the Cardiovascular Risk in Young Finns Study. *Int J Epidemiol*, *37*(2), 290–298. https://doi.org/10.1093/ije/dym244

Gimeno, David, Brunner, E. J., Lowe, G. D. O., Rumley, A., Marmot, M. G., & Ferrie, J. E. (2007). Adult socioeconomic position, C-reactive protein and interleukin-6 in the Whitehall II prospective study. *European Journal of Epidemiology*, *22*(10), 675–683. https://doi.org/10.1007/s10654-007-9171-9

González, M. A., Artalejo, F. R., & Calero, J. del R. (1998). Relationship between socioeconomic status and ischaemic heart disease in cohort and case-control studies: 1960–1993. *International Journal of Epidemiology*, *27*(3), 350–358. https://doi.org/10.1093/ije/27.3.350

Graham, J. W. (2003). Adding Missing-Data-Relevant Variables to FIML-Based Structural Equation Models. *Structural Equation Modeling: A Multidisciplinary Journal*, *10*(1), 80–100. https://doi.org/10.1207/S15328007SEM1001_4

Gray, R., Campanelli, P., Deepchand, K., & Prescott-Clarke, P. (1996). Exploring Survey Non-Response: The Effect of Attrition on a Follow-Up of the 1984-85 Health and Life Style Survey. *The Statistician*, *45*(2), 163–183. Retrieved from https://www.researchgate.net/publication/270251778_Exploring_Survey_Non-Response_The_Effect_of_Attrition_on_a_Follow-Up_of_the_1984-85_Health_and_Life_Style_Survey

Groves, R.M., & Cooper, M. P. (1998). *Nonresponse in household Interview Surveys.* John Wiley & Sons, New York.

Groves, Robert M., Dillman, D. A., Eltinge, J. L., & Little, R. J. A. (2001). *Survey Nonresponse*. Retrieved from http://www.wiley.com/WileyCDA/WileyTitle/productCd-0471396273.html

Groves, Robert M., Jr, F. J. F., Couper, M. P., Lepkowski, J. M., Singer, E., & Tourangeau, R. (2009). *Survey Methodology*. John Wiley & Sons.

Groves, Robert M., & Peytcheva, E. (2008). The Impact of Nonresponse Rates on Nonresponse Bias: A Meta-Analysis. *Public Opinion Quarterly*, *72*(2), 167–189. https://doi.org/10.1093/poq/nfn011

Gruenewald, T. L., Cohen, S., Matthews, K. A., Tracy, R., & Seeman, T. E. (2009). Association of socioeconomic status with inflammation markers in black and white men and women in the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Soc Sci Med*, *69*(3), 451–459. https://doi.org/10.1016/j.socscimed.2009.05.018

Grundy, E., & Holt, G. (2001). The socioeconomic status of older adults: How should we measure it in studies of health inequalities? *Journal of Epidemiology & Community Health*, *55*(12), 895–904. https://doi.org/10.1136/jech.55.12.895

Gustman, A. L., & Steinmeier, T. L. (2004). Social security, pensions and retirement behaviour within the family. *Journal of Applied Econometrics*, *19*(6), 723–737. https://doi.org/10.1002/jae.753

Halaby, C. N., & Weakliem, D. L. (1993). Ownership and authority in the earnings function: Nonnested tests of alternative specifications. *American Sociological Review; Washington*, *58*(1), 16. Retrieved from https://search.proquest.com/docview/218815995/abstract/429703F8F7284D95PQ/1

Hardt, J., Herke, M., & Leonhart, R. (2012). Auxiliary variables in multiple imputation in regression with missing X: A warning against including too many in small sample research. *BMC Medical Research Methodology*, *12*, 184. https://doi.org/10.1186/1471-2288-12-184

Hawkes, D., & Plewis, I. (2006). Modelling non-response in the National Child Development Study. *Journal of the Royal Statistical Society: Series A (Statistics in Society)*, *169*(3), 479–491. https://doi.org/10.1111/j.1467-985X.2006.00401.x

Heckman, J. J. (1976). The common structure of statistical models of truncation, sample selection and limited dependent variables and a simple estimator for such models. *Annals of Economics and Social Measurement*, *5*, 475–492. Retrieved from https://ci.nii.ac.jp/naid/10014824205/

Heckman, J. J. (1979). Sample Selection Bias as a Specification Error. *Econometrica*, *47*(1), 153–161. https://doi.org/10.2307/1912352

Hedeker, D., & Gibbons, R. D. (1997). Application of random-effects pattern mixture models for missing data in longitudinal studies. *Psychological Methods*, *2*(1), 64–78. https://doi.org/10.1037/1082-989X.2.1.64

Hedeker, D., Mermelstein, R. J., & Demirtas, H. (2007). Analysis of binary outcomes with missing data: Missing = smoking, last observation carried forward, and a little multiple imputation.

Addiction (Abingdon, England), *102*(10), 1564–1573. https://doi.org/10.1111/j.1360-0443.2007.01946.x

Hellhammer, J., Fries, E., Schweisthal, O. W., Schlotz, W., Stone, A. A., & Hagemann, D. (2007). Several daily measurements are necessary to reliably assess the cortisol rise after awakening: State- and trait components. *Psychoneuroendocrinology*, *32*(1), 80–86. https://doi.org/10.1016/j.psyneuen.2006.10.005

Henley, P., Lowthers, M., Koren, G., Fedha, P. T., Russell, E., VanUum, S., … Bend, J. R. (2014). Cultural and socio-economic conditions as factors contributing to chronic stress in sub-Saharan African communities. *Canadian Journal of Physiology and Pharmacology*, *92*(9), 725–732. https://doi.org/10.1139/cjpp-2014-0035

Hill, D. H., & Willis, R. J. (2001). Reducing Panel Attrition: A Search for Effective Policy Instruments. *The Journal of Human Resources*, *36*(3), 416–438. https://doi.org/10.2307/3069625

Huisman, M., Kunst, A. E., & Mackenbach, J. P. (2003). Socioeconomic inequalities in morbidity among the elderly; a European overview. *Social Science & Medicine (1982)*, *57*(5), 861–873.

Ibrahim, J. G., Chen, M.-H., & Lipsitz, S. R. (2001). Missing responses in generalised linear mixed models when the missing data mechanism is nonignorable. *Biometrika*, *88*(2), 551–564. https://doi.org/10.1093/biomet/88.2.551

Jialal, I., Devaraj, S., & Venugopal, S. K. (2004). C-reactive protein: Risk marker or mediator in atherothrombosis? *Hypertension (Dallas, Tex.: 1979)*, *44*(1), 6–11. https://doi.org/10.1161/01.HYP.0000130484.20501.df

Jones, A. M., Koolman, X., & Rice, N. (2006). Health-related non-response in the British Household Panel Survey and European Community Household Panel: Using inverse-probability-weighted estimators in non-linear models. *Journal of the Royal Statistical Society: Series A (Statistics in Society)*, *169*(3), 543–569. https://doi.org/10.1111/j.1467-985X.2006.00399.x

Jousilahti, P., Salomaa, V., Rasi, V., Vahtera, E., & Palosuo, T. (2003). Association of markers of systemic inflammation, C-reactive protein, serum amyloid A, and fibrinogen, with socioeconomic status. *J Epidemiol Community Health*, *57*(9), 730–733. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12933781

Kalton, G., & Kasprzyk, D. (1986). The treatment of missing survey data. *Survey Methodology*, *12*(1), 1–16.

Karlén, J., Frostell, A., Theodorsson, E., Faresjö, T., & Ludvigsson, J. (2013). Maternal Influence on Child HPA Axis: A Prospective Study of Cortisol Levels in Hair. *Pediatrics*, *132*(5), e1333–e1340. https://doi.org/10.1542/peds.2013-1178

Karlén, J., Ludvigsson, J., Hedmark, M., Faresjö, Å., Theodorsson, E., & Faresjö, T. (2015). Early Psychosocial Exposures, Hair Cortisol Levels, and Disease Risk. *Pediatrics*, *135*(6), e1450–e1457. https://doi.org/10.1542/peds.2014-2561

Kaufman, J. S. (2002). Whad'ya know? Another view on cultural literacy. *Epidemiology (Cambridge, Mass.)*, *13*(5), 500–503. https://doi.org/10.1097/01.EDE.0000024137.49946.F5

Kelleher, J. (2002). Cultural literacy and health. *Epidemiology (Cambridge, Mass.)*, *13*(5), 497–500. https://doi.org/10.1097/01.EDE.0000024136.78650.04

Kenny, R. A., Whelan, B. J., Cronin, H., Kamiya, Y., Kearney, P., O'Regan, C., & Ziegel, M. (2010). *The design of the Irish Longitudinal Study on Ageing*. Dublin: Trinity College.

Kenward, M. G., & Carpenter, J. (2007). Multiple imputation: Current perspectives. *Statistical Methods in Medical Research*, *16*(3), 199–218. https://doi.org/10.1177/0962280206075304

Kho, M. E., Duffett, M., Willison, D. J., Cook, D. J., & Brouwers, M. C. (2009). Written informed consent and selection bias in observational studies using medical records: Systematic review. *BMJ*, *338*, b866. https://doi.org/10.1136/bmj.b866

Kish, L. (1992). Weighting for Unequal Pi. *Journal of Official Statistics*, *8*(2), 183–200.

Kittleson MM, M. L., Wang NY, Chu AY, Ford DE, Klag MJ. (2006). Asssociation of Childhood Socioeconomic Status with Subsequent Coronary Heart Disease in Physicians. *Arch Intern Med*, *166*, 2356–2361.

Kivimaki, M., Lawlor, D. A., Juonala, M., Smith, G. D., Elovainio, M., Keltikangas-Jarvinen, L., … Raitakari, O. T. (2005). Lifecourse socioeconomic position, C-reactive protein, and carotid intima-media thickness in young adults: The cardiovascular risk in Young Finns Study. *Arterioscler Thromb Vasc Biol*, *25*(10), 2197–2202. https://doi.org/10.1161/01.ATV.0000183729.91449.6e

Knesebeck, O. V. D., Wahrendorf, M., Hyde, M., & Siegrist, J. (2007). Socio-economic position and quality of life among older people in 10 European countries: Results of the SHARE study. *Ageing & Society*, *27*(2), 269–284. https://doi.org/10.1017/S0144686X06005484

Knies, G., & Burton, J. (2014). Analysis of four studies in a comparative framework reveals: Health linkage consent rates on British cohort studies higher than on UK household panel surveys. *BMC Medical Research Methodology*, *14*, 125. https://doi.org/10.1186/1471-2288-14-125

Knies, G., Burton, J., & Sala, E. (2012). Consenting to health record linkage: Evidence from a multi-purpose longitudinal survey of a general population. *BMC Health Services Research*, *12*, 52. https://doi.org/10.1186/1472-6963-12-52

Krieger, N., Williams, D. R., & Moss, N. E. (1997). Measuring social class in US public health research: Concepts, methodologies, and guidelines. *Annual Review of Public Health*, *18*, 341–378. https://doi.org/10.1146/annurev.publhealth.18.1.341

Kuh, D., & Shlomo, Y. B. (1997). *A Life Course Approach to Chronic Disease Epidemiology*. OUP Oxford.

Kuh, D., & Shlomo, Y. B. (2004). *A Life Course Approach to Chronic Disease Epidemiology*. OUP Oxford.

Lawlor, D. A, Ben-Shlomo, Y., & Leon, D. A. (2004). Pre-adult influences on cardiovascular disease. In D. Kuh & Y. Ben-Shlomo (Eds.), *A life course approach to chronic disease epidemiology* (2nd ed., pp. 41–76). New york: Oxford University Press.

Lawlor, Debbie A, Davey Smith, G., & Ebrahim, S. (2004). Socioeconomic Position and Hormone Replacement Therapy Use: Explaining the Discrepancy in Evidence From Observational and Randomized Controlled Trials. *American Journal of Public Health*, *94*(12), 2149–2154. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1448605/

Lepkowski, J. M., & Couper, M. P. (2002). Nonresponse in the Second Wave of Longitudinal Household Surveys. In R.M. Groves, D. A. Dillman, J. L. Eltinge, & R. J. A. Little (Eds.), *Survey Nonresponse*. John Wiley & Sons, New York.

Li, C.-Y., & Sung, F.-C. (1999). A review of the healthy worker effect in occupational epidemiology. *Occupational Medicine*, *49*(4), 225–229. https://doi.org/10.1093/occmed/49.4.225

Libby, P. (2002). Inflammation in atherosclerosis. *Nature*, *420*(6917), 868–874. https://doi.org/10.1038/nature01323

Libby, P. (2006). Inflammation and cardiovascular disease mechanisms. *The American Journal of Clinical Nutrition*, *83*(2), 456S-460S. Retrieved from http://ajcn.nutrition.org/content/83/2/456S

Lightman, S. L., Wiles, C. C., Atkinson, H. C., Henley, D. E., Russell, G. M., Leendertz, J. A., … Conway-Campbell, B. L. (2008). The significance of glucocorticoid pulsatility. *European Journal of Pharmacology*, *583*(2–3), 255–262. https://doi.org/10.1016/j.ejphar.2007.11.073

Lipsitz, S. R., & Ibrahim, J. G. (1998). Estimating equations with incomplete categorical covariates in the Cox model. *Biometrics*, *54*(3), 1002–1013.

Little, R. J. A. (1993). Pattern-Mixture Models for Multivariate Incomplete Data. *Journal of the American Statistical Association*, *88*(421), 125–134. https://doi.org/10.1080/01621459.1993.10594302

Little, R. J. A. (1994). A Class of Pattern-Mixture Models for Normal Incomplete Data. *Biometrika*, *81*(3), 471–483. https://doi.org/10.2307/2337120

Little, R. J. A., & Rubin, D. B. (2002). *Statistical Analysis with Missing Data*. John Wiley & Sons.

Little, R. J. A., Rubin, D. B., Little, R. J. A., & Rubin, D. B. (2002). Introduction. In *Statistical Analysis with Missing Data* (pp. 1–23). Retrieved from http://onlinelibrary.wiley.com/doi/10.1002/9781119013563.ch1/summary

Little, R. J., D'Agostino, R., Cohen, M. L., Dickersin, K., Emerson, S. S., Farrar, J. T., … Stern, H. (2012). The Prevention and Treatment of Missing Data in Clinical Trials. *New England Journal of Medicine*, *367*(14), 1355–1360. https://doi.org/10.1056/NEJMsr1203730

Little, R., & Vartivarian, S. (2004). Does Weighting for Nonresponse Increase the Variance of Survey Means? *The University of Michigan Department of Biostatistics Working Paper Series*. Retrieved from http://biostats.bepress.com/umichbiostat/paper35

Loucks, E. B., Pilote, L., Lynch, J. W., Richard, H., Almeida, N. D., Benjamin, E. J., & Murabito, J. M. (2010). Life course socioeconomic position is associated with inflammatory markers: The Framingham Offspring Study. *Soc Sci Med*, *71*(1), 187–195. https://doi.org/10.1016/j.socscimed.2010.03.012

Lowe, G. D. O., & Pepys, M. B. (2006). C-reactive protein and cardiovascular disease: Weighing the evidence. *Current Atherosclerosis Reports*, *8*(5), 421–428.

Lynch, J. (1996). Social Position and Health. *Annals of Epidemiology*, *1*(6), 21–23. Retrieved from https://www.infona.pl//resource/bwmeta1.element.elsevier-a7ba0dd8-60cc-34a1-b417-b0a8e7575dcc

Lynch, J., & Kaplan, G. (2000). Socioeconomic position. In L. F. Berkman & I. Kawachi (Eds.), *Social Epidemiology* (1st ed., pp. 13–15). Oxford:Oxford University Press.

Lynch, J. W., Kaplan, G. A., Cohen, R. D., Wilson, T. W., Smith, N. L., Kauhanen, J., & Salonen, J. T. (1994). Childhood and adult socioeconomic status as predictors of mortality in Finland. *Originally Published as Volume 1, Issue 8896*, *343*(8896), 524–527. https://doi.org/10.1016/S0140-6736(94)91468-0

Lynch, J. W., Kaplan, G. A., Gohen, R. D., Kauhanen, J., & Wilson, A. (1994). Childhood and adult socioeconomic status as predictors of mortality in Finland. *Lancet*, *343*(8896), 524–527.

Lynch, J. W., Smith, G. D., Kaplan, G. A., & House, J. S. (2000). Income inequality and mortality: Importance to health of individual income, psychosocial environment, or material conditions. *BMJ (Clinical Research Ed.)*, *320*(7243), 1200–1204.

Mackenbach, J. P., Kulhánová, I., Artnik, B., Bopp, M., Borrell, C., Clemens, T., … de Gelder, R. (2016). Changes in mortality inequalities over two decades: Register based study of European countries. *BMJ (Clinical Research Ed.)*, *353*, i1732.

Madero-Cabib, I., & Kaeser, L. (2016). How voluntary is the active ageing life? A life-course study on the determinants of extending careers. *European Journal of Ageing*, *13*(1), 25–37. https://doi.org/10.1007/s10433-015-0355-y

Magnusson, A., & Boivin, D. (2003). Seasonal Affective Disorder: An Overview. *Chronobiology International*, *20*(2), 189–207. https://doi.org/10.1081/CBI-120019310

Manenschijn, L., Schaap, L., van Schoor, N. M., van der Pas, S., Peeters, G. M. E. E., Lips, P., … van Rossum, E. F. C. (2013). High long-term cortisol levels, measured in scalp hair, are associated with a history of cardiovascular disease. *The Journal of Clinical Endocrinology and Metabolism*, *98*(5), 2078–2083. https://doi.org/10.1210/jc.2012-3663

Manenschijn, Laura, Koper, J. W., Lamberts, S. W. J., & van Rossum, E. F. C. (2011). Evaluation of a method to measure long term cortisol levels. *Steroids*, *76*(10), 1032–1036. https://doi.org/10.1016/j.steroids.2011.04.005

Marmot, M. (2005). Social determinants of health inequalities. *The Lancet*, *365*(9464), 1099–1104. https://doi.org/10.1016/S0140-6736(05)71146-6

Marmot, M. G., Shipley, M. J., Hemingway, H., Head, J., & Brunner, E. J. (2008). Biological and behavioural explanations of social inequalities in coronary heart disease: The Whitehall II study. *Diabetologia*, *51*(11), 1980–1988. https://doi.org/10.1007/s00125-008-1144-3

May, A. M., Adema, L. E., Romaguera, D., Vergnaud, A.-C., Agudo, A., Ekelund, U., … Peeters, P. H. (2012). Determinants of non- response to a second assessment of lifestyle factors and body weight in the EPIC-PANACEA study. *BMC Medical Research Methodology*, *12*, 148. https://doi.org/10.1186/1471-2288-12-148

McEwen, B. S. (1998). Protective and Damaging Effects of Stress Mediators. *New England Journal of Medicine*, *338*(3), 171–179. https://doi.org/10.1056/NEJM199801153380307

McEwen, B. S., & Gianaros, P. J. (2011). Stress- and Allostasis-Induced Brain Plasticity. *Annual Review of Medicine*, *62*, 431–445. https://doi.org/10.1146/annurev-med-052209-100430

McKeown, T. (1979). *The Role of Medicine: Dream, Mirage, or Nemesis?* Princeton University Press.

Merswolken, M., Deter, H.-C., Siebenhuener, S., Orth-Gomér, K., & Weber, C. S. (2013). Anxiety as predictor of the cortisol awakening response in patients with coronary heart disease. *International Journal of Behavioral Medicine*, *20*(3), 461–467. https://doi.org/10.1007/s12529-012-9233-6

Meyer, J. S., & Novak, M. A. (2012). Minireview: Hair cortisol: a novel biomarker of hypothalamic-pituitary-adrenocortical activity. *Endocrinology*, *153*(9), 4120–4127. https://doi.org/10.1210/en.2012-1226

Miller, G. E., Chen, E., & Zhou, E. S. (2007a). If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. *Psychological Bulletin*, *133*(1), 25–45. https://doi.org/10.1037/0033-2909.133.1.25

Miller, G. E., Chen, E., & Zhou, E. S. (2007b). If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. *Psychological Bulletin*, *133*(1), 25–45. https://doi.org/10.1037/0033-2909.133.1.25

Molenberghs, G., & Kenward, M. G. (2007a). *Missing data in clinical studies*. Retrieved from http://onlinelibrary.wiley.com/book/10.1002/9780470510445

Molenberghs, G., & Kenward, M. G. (2007b). *Missing data in clinical trials*. West Sussex: UK: Wiley.

Muthén, B., Asparouhov, T., Hunter, A., & Leuchter, A. (2011). Growth Modeling with Non-Ignorable Dropout: Alternative Analyses of the STAR*D Antidepressant Trial. *Psychological Methods*, *16*(1), 17–33. https://doi.org/10.1037/a0022634

Muthén, B., Kaplan, D., & Hollis, M. (1987). On structural equation modeling with data that are not missing completely at random. *Psychometrika*, *52*(3), 431–462. https://doi.org/10.1007/BF02294365

Na-Ek, N., & Demakakos, P. (2016). Social mobility and inflammatory and metabolic markers at older ages: The English Longitudinal Study of Ageing. *J Epidemiol Community Health*, jech-2016-207394. https://doi.org/10.1136/jech-2016-207394

Nakai, M., & Ke, W. (2011). Review of the Methods for Handling Missing Data in Longitudinal Data Analysis. *ResearchGate*, *5*(1), 1–13. Retrieved from https://www.researchgate.net/publication/228531247_Review_of_the_Methods_for_Handling_Missing_Data_in_Longitudinal_Data_Analysis

Nazmi, A., Oliveira, I. O., Horta, B. L., Gigante, D. P., & Victora, C. G. (2010). Lifecourse socioeconomic trajectories and C-reactive protein levels in young adults: Findings from a Brazilian birth cohort. *Soc Sci Med*, *70*(8), 1229–1236. https://doi.org/10.1016/j.socscimed.2009.12.014

Nelwamondo, F. V., Mohamed, S., & Marwala, T. (2007). Missing Data: A Comparison of Neural Network and Expectation Maximisation Techniques. *ArXiv:0704.3474 [Stat]*. Retrieved from http://arxiv.org/abs/0704.3474

Newman, D. A. (2003). Longitudinal Modeling with Randomly and Systematically Missing Data: A Simulation of Ad Hoc, Maximum Likelihood, and Multiple Imputation Techniques. *Organizational Research Methods*, *6*(3), 328–362. https://doi.org/10.1177/1094428103254673

Nicoletti, C., & Buck, N. (2003). Explaining Contact and Refusals in the British and German Household Panels. In N. Buck, C. Nicoletti, A. McCulloh, & J. Burton, *Repost in Attrition Analysis and Item Non-response* (Chintex Working Paper no. 16).

Nicoletti, C., & Peracchi, F. (2005). *Survey Response and Survey Characteristics: Microlevel Evidence from the European Community Household Panel*. *168*, 63–70.

Nijm, J., Kristenson, M., Olsson, A. G., & Jonasson, L. (2007). Impaired cortisol response to acute stressors in patients with coronary disease. Implications for inflammatory activity. *Journal of Internal Medicine*, *262*(3), 375–384. https://doi.org/10.1111/j.1365-2796.2007.01817.x

O'Brien, K. M., Tronick, E. Z., & Moore, C. L. (2013). Relationship between hair cortisol and perceived chronic stress in a diverse sample. *Stress and Health: Journal of the International Society for the Investigation of Stress*, *29*(4), 337–344. https://doi.org/10.1002/smi.2475

Organization, W. H., & Safety, I. P. on C. (2001). *Biomarkers in risk assessment: Validity and validation*. Retrieved from http://www.who.int/iris/handle/10665/42363

Owen, N., Poulton, T., Hay, F. C., Mohamed-Ali, V., & Steptoe, A. (2003). Socioeconomic status, C-reactive protein, immune factors, and responses to acute mental stress. *Brain Behav Immun*, *17*(4), 286–295. https://doi.org/10.1016/s0889-1591(03)00058-8

Packard, C. J., Bezlyak, V., McLean, J. S., Batty, G. D., Ford, I., Burns, H., … Tannahill, C. (2011). Early life socioeconomic adversity is associated in adult life with chronic inflammation, carotid atherosclerosis, poorer lung function and decreased cognitive performance: A cross-sectional, population-based study. *BMC Public Health*, *11*, 42. https://doi.org/10.1186/1471-2458-11-42

Pearce, M. S., Ahmed, A., Tennant, P. W., Parker, L., & Unwin, N. C. (2012). Lifecourse predictors of adult fibrinogen levels: The Newcastle Thousand Families Study. *Int J Cardiol*, *155*(2), 206–211. https://doi.org/10.1016/j.ijcard.2010.09.053

Pearlin, L. I., Schieman, S., Fazio, E. M., & Meersman, S. C. (2005). Stress, health, and the life course: Some conceptual perspectives. *Journal of Health and Social Behavior*, *46*(2), 205–219. https://doi.org/10.1177/002214650504600206

Pearson, T. A., Mensah, G. A., Alexander, R. W., Anderson, J. L., Cannon, R. O., Criqui, M., … Vinicor, F. (2003). Markers of Inflammation and Cardiovascular Disease. *Circulation*, *107*(3), 499–511. https://doi.org/10.1161/01.CIR.0000052939.59093.45

Pepys, M. B., & Hirschfield, G. M. (2003). C-reactive protein: A critical update. *The Journal of Clinical Investigation*, *111*(12), 1805–1812. https://doi.org/10.1172/JCI18921

Ploubidis, G. B., Benova, L., Grundy, E., Laydon, D., & DeStavola, B. (2014). Lifelong Socio Economic Position and biomarkers of later life health: Testing the contribution of competing hypotheses. *Social Science & Medicine*, *119*, 258–265. https://doi.org/10.1016/j.socscimed.2014.02.018

Ploubidis, G. B., DeStavola, B. L., & Grundy, E. (2011). Health differentials in the older population of England: An empirical comparison of the materialist, lifestyle and psychosocial hypotheses. *BMC Public Health*, *11*(1), 1–11. https://doi.org/10.1186/1471-2458-11-390

Pollitt, R. A., Kaufman, J. S., Rose, K. M., Diez-Roux, A. V., Zeng, D., & Heiss, G. (2007). Early-life and adult socioeconomic status and inflammatory risk markers in adulthood. *Eur J Epidemiol*, *22*(1), 55–66. https://doi.org/10.1007/s10654-006-9082-1

Pollitt, R. A., Kaufman, J. S., Rose, K. M., Diez-Roux, A. V., Zeng, D., & Heiss, G. (2008). Cumulative life course and adult socioeconomic status and markers of inflammation in adulthood. *J Epidemiol Community Health*, *62*(6), 484–491. https://doi.org/10.1136/jech.2006.054106

Pollitt, Ricardo A., Rose, K. M., & Kaufman, J. S. (2005). Evaluating the evidence for models of life course socioeconomic factors and cardiovascular outcomes: A systematic review. *BMC Public Health*, *5*, 7. https://doi.org/10.1186/1471-2458-5-7

Power, C., Atherton, K., Strachan, D. P., Shepherd, P., Fuller, E., Davis, A., … Stansfeld, S. (2007). Life-course influences on health in British adults: Effects of socio-economic position in childhood and adulthood. *Int J Epidemiol*, *36*(3), 532–539. https://doi.org/10.1093/ije/dyl310

Pulopulos, M. M., Hidalgo, V., Almela, M., Puig-Perez, S., Villada, C., & Salvador, A. (2014). Hair cortisol and cognitive performance in healthy older people. *Psychoneuroendocrinology*, *44*, 100–111. https://doi.org/10.1016/j.psyneuen.2014.03.002

Radler, B. T., & Ryff, C. D. (2010). Who Participates? Accounting for Longitudinal Retention in the MIDUS National Study of Health and Well-Being. *Journal of Aging and Health*, *22*(3), 307–331. https://doi.org/10.1177/0898264309358617

Raghunathan, T. E., Lepkowski, J. M., Hoewyk, J. V., & Solenberger, P. (2001). *A multivariate technique for multiply imputing missing values using a sequence of regression models. Survey Methodology 27*.

Raul, J.-S., Cirimele, V., Ludes, B., & Kintz, P. (2004). Detection of physiological concentrations of cortisol and cortisone in human hair. *Clinical Biochemistry*, *37*(12), 1105–1111. https://doi.org/10.1016/j.clinbiochem.2004.02.010

Reynolds, R. M., Labad, J., Strachan, M. W. J., Braun, A., Fowkes, F. G. R., Lee, A. J., … Edinburgh Type 2 Diabetes Study (ET2DS) Investigators. (2010). Elevated fasting plasma cortisol is associated with ischemic heart disease and its risk factors in people with type 2 diabetes: The Edinburgh type 2 diabetes study. *The Journal of Clinical Endocrinology and Metabolism*, *95*(4), 1602–1608. https://doi.org/10.1210/jc.2009-2112

Ridker, P. M., Libby, P., & Buring, J. E. (2015). Risk markers and the primary prevention of cardiovascular disease. In D. L. Mann, D. P. Zipes, P. Libby, R. O. Bonow, & E. Braunwald (Eds.), *Braunwald's heart disease: A textbook of cardiovascular medicine* (10th ed., pp. 891–933). Philadelphia PA: Elsevier/Saunders.

Ridker, Paul M, Cannon, C. P., Morrow, D., Rifai, N., Rose, L. M., McCabe, C. H., … Braunwald, E. (2005). C-Reactive Protein Levels and Outcomes after Statin Therapy. *New England Journal of Medicine*, *352*(1), 20–28. https://doi.org/10.1056/NEJMoa042378

Robert, S., & House, J. S. (1996). SES Differentials in Health by Age and Alternative Indicators of SES. *Journal of Aging and Health*, *8*(3), 359–388. https://doi.org/10.1177/089826439600800304

Roy, J. (2003). Modeling Longitudinal Data with Nonignorable Dropouts Using a Latent Dropout Class Model. *Biometrics*, *59*(4), 829–836. https://doi.org/10.1111/j.0006-341X.2003.00097.x

Roy, J., & Daniels, M. J. (2008). A General Class of Pattern Mixture Models for Nonignorable Dropout with Many Possible Dropout Times. *Biometrics*, *64*(2), 538–545. https://doi.org/10.1111/j.1541-0420.2007.00884.x

Rubin, D. B. (1976). Inference and missing data. *Biometrika*, *63*(3), 581–592. https://doi.org/10.1093/biomet/63.3.581

Rubin, D. B. (2004). *Multiple Imputation for Nonresponse in Surveys*. Hoboken, N.J: Wiley-Interscience.

Russell, E., Koren, G., Rieder, M., & Van Uum, S. (2012). Hair cortisol as a biological marker of chronic stress: Current status, future directions and unanswered questions. *Psychoneuroendocrinology*, *37*(5), 589–601. https://doi.org/10.1016/j.psyneuen.2011.09.009

Sacker, A., Clarke, P., Wiggins, R. D., & Bartley, M. (2005). Social dynamics of health inequalities: A growth curve analysis of aging and self assessed health in the British household panel survey 1991-2001. *Journal of Epidemiology and Community Health*, *59*(6), 495–501. https://doi.org/10.1136/jech.2004.026278

Sauvé, B., Koren, G., Walsh, G., Tokmakejian, S., & Uum, S. H. V. (2007). Measurement of cortisol in human Hair as a biomarker of systemic exposure. *Clinical & Investigative Medicine*, *30*(5), 183–191. https://doi.org/10.25011/cim.v30i5.2894

Schafer, J. L. (1997). *Analysis of Incomplete Multivariate Data*. CRC Press.

Schafer, J. L. (1999). Multiple imputation: A primer. *Statistical Methods in Medical Research*, *8*(1), 3–15. https://doi.org/10.1177/096228029900800102

Schafer, J. L., & Olsen, M. K. (1998). Multiple Imputation for Multivariate Missing-Data Problems: A Data Analyst's Perspective. *Multivariate Behavioral Research*, *33*(4), 545–571. https://doi.org/10.1207/s15327906mbr3304_5

Schafer, Joseph L., & Graham, J. W. (2002). Missing data: Our view of the state of the art. *Psychological Methods*, *7*(2), 147–177.

Scholes, S., Taylor, R., Cheshire, H., Cox, K., & Lessof, C. (2008). *Technical report (ELSA wave 2): Retirement, health and relationships of the older population in England*. Retrieved from https://www.ifs.org.uk/publications/4359

Schöllgen, I., Huxhold, O., & Tesch-Römer, C. (2010). Socioeconomic status and health in the second half of life: Findings from the German Ageing Survey. *European Journal of Ageing*, *7*(1), 17–28. https://doi.org/10.1007/s10433-010-0140-x

Schreier, H. M. C., Enlow, M. B., Ritz, T., Coull, B. A., Gennings, C., Wright, R. O., & Wright, R. J. (2016). Lifetime exposure to traumatic and other stressful life events and hair cortisol in a multi-racial/ethnic sample of pregnant women. *Stress*, *19*(1), 45–52. https://doi.org/10.3109/10253890.2015.1117447

Seaman, S. R., White, I. R., Copas, A. J., & Li, L. (2012). Combining Multiple Imputation and Inverse-Probability Weighting. *Biometrics*, *68*(1), 129–137. https://doi.org/10.1111/j.1541-0420.2011.01666.x

Serwinski, B., Salavecz, G., Kirschbaum, C., & Steptoe, A. (2016). Associations between hair cortisol concentration, income, income dynamics and status incongruity in healthy middle-aged

women. *Psychoneuroendocrinology*, *67*, 182–188. https://doi.org/10.1016/j.psyneuen.2016.02.008

Shah, D. (2009). Healthy worker effect phenomenon. *Indian Journal of Occupational and Environmental Medicine*, *13*(2), 77–79. https://doi.org/10.4103/0019-5278.55123

Singh, T., & Newman, A. B. (2011). Inflammatory markers in population studies of aging. *Ageing Research Reviews*, *10*(3), 319–329. https://doi.org/10.1016/j.arr.2010.11.002

Slopen, N., Lewis, T. T., Gruenewald, T. L., Mujahid, M. S., Ryff, C. D., Albert, M. A., & Williams, D. R. (2010). Early life adversity and inflammation in African Americans and whites in the midlife in the United States survey. *Psychosom Med*, *72*(7), 694–701. https://doi.org/10.1097/PSY.0b013e3181e9c16f

Smith, J. P., & Kington, R. (1997). Demographic and economic correlates of health in old age. *Demography*, *34*(1), 159–170. https://doi.org/10.2307/2061665

Stalder, T., & Kirschbaum, C. (2012a). Analysis of cortisol in hair—State of the art and future directions. *Brain, Behavior, and Immunity*, *26*(7), 1019–1029. https://doi.org/10.1016/j.bbi.2012.02.002

Stalder, T., & Kirschbaum, C. (2012b). Analysis of cortisol in hair—State of the art and future directions. *Brain, Behavior, and Immunity*, *26*(7), 1019–1029. https://doi.org/10.1016/j.bbi.2012.02.002

Stalder, T., Kirschbaum, C., Alexander, N., Bornstein, S. R., Gao, W., Miller, R., … Fischer, J. E. (2013). Cortisol in hair and the metabolic syndrome. *The Journal of Clinical Endocrinology and Metabolism*, *98*(6), 2573–2580. https://doi.org/10.1210/jc.2013-1056

Staufenbiel, S. M., Penninx, B. W. J. H., de Rijke, Y. B., van den Akker, E. L. T., & van Rossum, E. F. C. (2015). Determinants of hair cortisol and hair cortisone concentrations in adults. *Psychoneuroendocrinology*, *60*(Supplement C), 182–194. https://doi.org/10.1016/j.psyneuen.2015.06.011

Staufenbiel, S. M., Penninx, B. W. J. H., Spijker, A. T., Elzinga, B. M., & van Rossum, E. F. C. (2013). Hair cortisol, stress exposure, and mental health in humans: A systematic review. *Psychoneuroendocrinology*, *38*(8), 1220–1235. https://doi.org/10.1016/j.psyneuen.2012.11.015

Steptoe, A., Breeze, E., Banks, J., & Nazroo, J. (2013). Cohort Profile: The English Longitudinal Study of Ageing. *International Journal of Epidemiology*, *42*(6), 1640–1648. https://doi.org/10.1093/ije/dys168

Stewart, P. M., & Mason, J. I. (1995). Cortisol to cortisone: Glucocorticoid to mineralocorticoid. *Steroids*, *60*(1), 143–146. https://doi.org/10.1016/0039-128X(94)00024-7

Strimbu, K., & Tavel, J. A. (2010). What are biomarkers? *Curr Opin HIV AIDS*, *5*(6), 463–466. https://doi.org/10.1097/COH.0b013e32833ed177

Stringhini, S., Batty, G. D., Bovet, P., Shipley, M. J., Marmot, M. G., Kumari, M., … Kivimaki, M. (2013). Association of lifecourse socioeconomic status with chronic inflammation and type 2 diabetes risk: The Whitehall II prospective cohort study. *PLoS Med*, *10*(7), e1001479. https://doi.org/10.1371/journal.pmed.1001479

Stringhini, Silvia, Carmeli, C., Jokela, M., Avendaño, M., Muennig, P., Guida, F., … Zins, M. (2017). 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. *The Lancet*, *389*(10075), 1229–1237. https://doi.org/10.1016/S0140-6736(16)32380-7

Stringhini, Silvia, Zaninotto, P., Kumari, M., Kivimäki, M., & Batty, G. D. (2016). Lifecourse socioeconomic status and type 2 diabetes: The role of chronic inflammation in the English Longitudinal Study of Ageing. *Scientific Reports*, *6*, 24780. https://doi.org/10.1038/srep24780

Stringhini, Silvia, Zaninotto, P., Kumari, M., Kivimäki, M., Lassale, C., & Batty, G. D. (2018). Socio-economic trajectories and cardiovascular disease mortality in older people: The English Longitudinal Study of Ageing. *International Journal of Epidemiology*, *47*(1), 36–46. https://doi.org/10.1093/ije/dyx106

Syme, S. L., & Berkman, L. F. (1976). Social class, susceptibility and sickness. *American Journal of Epidemiology*, *104*(1), 1–8.

Tabassum, F., Kumari, M., Rumley, A., Lowe, G., Power, C., & Strachan, D. P. (2008). Effects of socioeconomic position on inflammatory and hemostatic markers: A life-course analysis in the 1958 British birth cohort. *Am J Epidemiol*, *167*(11), 1332–1341. https://doi.org/10.1093/aje/kwn055

Thoemmes, F., & Rose, N. (2014). A Cautious Note on Auxiliary Variables That Can Increase Bias in Missing Data Problems. *Multivariate Behavioral Research*, *49*(5), 443–459. https://doi.org/10.1080/00273171.2014.931799

Thomas, D., Frankenberg, E., & Smith, J. P. (2001). Lost but Not Forgotten [Product Page]. Retrieved April 27, 2017, from https://www.rand.org/pubs/reprints/RP965.html

Uhrig, S. (2008). *The Nature and Causes of Attrition in the British Household Panel Survey*. University of Essex.

Ursache, A., Merz, E. C., Melvin, S., Meyer, J., & Noble, K. G. (2017). Socioeconomic status, hair cortisol and internalizing symptoms in parents and children. *Psychoneuroendocrinology*, *78*, 142–150. https://doi.org/10.1016/j.psyneuen.2017.01.020

Vaghri, Z., Guhn, M., Weinberg, J., Grunau, R. E., Yu, W., & Hertzman, C. (2013). Hair cortisol reflects socio-economic factors and hair zinc in preschoolers. *Psychoneuroendocrinology*, *38*(3), 331–340. https://doi.org/10.1016/j.psyneuen.2012.06.009

van Buuren, S. (2007). Multiple imputation of discrete and continuous data by fully conditional specification. *Statistical Methods in Medical Research*, *16*(3), 219–242. https://doi.org/10.1177/0962280206074463

Varadhan, R., Yao, W., Matteini, A., Beamer, B. A., Xue, Q.-L., Yang, H., … Walston, J. (2014). Simple biologically informed inflammatory index of two serum cytokines predicts 10 year all-cause mortality in older adults. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *69*(2), 165–173. https://doi.org/10.1093/gerona/glt023

Volken, T. (2013). Second-stage non-response in the Swiss health survey: Determinants and bias in outcomes. *BMC Public Health*, *13*, 167. https://doi.org/10.1186/1471-2458-13-167

von Hippel, P. T. (2009). How to impute interactions, squares and other transformed variables. *Sociological Methodology*, *39*(39), 265–291.

Warren, J. R. (2009). Socioeconomic Status and Health across the Life Course: A Test of the Social Causation and Health Selection Hypotheses. *Social Forces; a Scientific Medium of Social Study and Interpretation*, *87*(4), 2125–2153. https://doi.org/10.1353/sof.0.0219

Watson, D. (2003). Sample Attrition between Waves 1 and 5 in the European Community Household Panel. *European Sociological Review*, *19*, 361–378.

Watson, N, & Wooden, M. (2009). Identifying factors affecting longitudinal survey response. In P. Lynn (Ed.), *Methodology of longitudinal studies.* (Chichester: Wiley, pp. 157–181).

Watson, Nicole, & Wooden, M. (2009). Identifying Factors Affecting Longitudinal Survey Response. In *Methodology of Longitudinal Surveys* (pp. 157–181). https://doi.org/10.1002/9780470743874.ch10

West, P. (1997). Health inequalities in the early years: Is there equalisation in youth? *Social Science & Medicine (1982)*, *44*(6), 833–858.

Wester, V. L., van der Wulp, N. R. P., Koper, J. W., de Rijke, Y. B., & van Rossum, E. F. C. (2016). Hair cortisol and cortisone are decreased by natural sunlight. *Psychoneuroendocrinology*, *72*, 94–96. https://doi.org/10.1016/j.psyneuen.2016.06.016

White, A., Nicolaas, G., Foster, K., Browne, F., & Carey, S. (1993). *Health Survey for England 1991* (No. 1993 Series HS no.1). London.

WHO. (2015). *World Report on Ageing and Health*. Luxembourgh.

WHO | Global status report on noncommunicable diseases 2010. (n.d.). Retrieved August 7, 2016, from WHO website: http://www.who.int/nmh/publications/ncd_report2010/en/

Wilkinson, R. G. (1996). *Unhealthy Societies: The Afflictions of Inequality*. Routledge.

Wilkinson, R. G., & Marmot, M. (2003). *Social Determinants of Health: The Solid Facts*. World Health Organization.

Willson, A. E., Shuey, K. M., & Elder, Jr., Glen H. (2007). Cumulative Advantage Processes as Mechanisms of Inequality in Life Course Health. *American Journal of Sociology*, *112*(6), 1886–1924. https://doi.org/10.1086/512712

Wilson, T. W., Kaplan, G. A., Kauhanen, J., Cohen, R. D., Wu, M., Salonen, R., & Salonen, J. T. (1993). Association between Plasma-Fibrinogen Concentration and 5 Socioeconomic Indexes in the Kuopio Ischemic-Heart-Disease Risk Factor Study. *American Journal of Epidemiology*, *137*(3), 292–300. Retrieved from ://A1993KZ18400004

Wolff, J. L., Starfield, B., & Anderson, G. (2002). Prevalence, Expenditures, and Complications of Multiple Chronic Conditions in the Elderly. *Archives of Internal Medicine*, *162*(20), 2269–2276. https://doi.org/10.1001/archinte.162.20.2269

Wright, E. O., & Halaby, C. N. (1993). Typologies, scales, and class analysis: A comment on Halaby and Weakliem's "Ownership and Authority in the Earnings Function"--Comment/Reply.

American Sociological Review; Washington, *58*(1), 31. Retrieved from https://search.proquest.com/docview/218810255/abstract/BE421CF9DF314DB1PQ/1

Wu, M. C., & Carroll, R. J. (1988). Estimation and Comparison of Changes in the Presence of Informative Right Censoring by Modeling the Censoring Process. *Biometrics*, *44*(1), 175–188. https://doi.org/10.2307/2531905

Wyczalkowska-Tomasik, A., Czarkowska-Paczek, B., Zielenkiewicz, M., & Paczek, L. (2016). Inflammatory Markers Change with Age, but do not Fall Beyond Reported Normal Ranges. *Archivum Immunologiae et Therapiae Experimentalis*, *64*, 249–254. https://doi.org/10.1007/s00005-015-0357-7

Young, E. A., Abelson, J., & Lightman, S. L. (2004). Cortisol pulsatility and its role in stress regulation and health. *Frontiers in Neuroendocrinology*, *25*(2), 69–76. https://doi.org/10.1016/j.yfrne.2004.07.001

Zabel, J. E. (1998). An Analysis of Attrition in the Panel Study of Income Dynamics and the Survey of Income and Program Participation with an Application to a Model of Labor Market Behavior. *The Journal of Human Resources*, *33*(2), 479–506. https://doi.org/10.2307/146438

Zaninotto, P., & Steptoe, A. (2019). English Longitudinal Study of Ageing. In D. Gu & M. E. Dupre (Eds.), *Encyclopedia of Gerontology and Population Aging* (pp. 1–7). https://doi.org/10.1007/978-3-319-69892-2_335-1

Zinn, S., & Gnambs, T. (2018). Modeling competence development in the presence of selection bias. *Behavior Research Methods*, *50*(6), 2426–2441. https://doi.org/10.3758/s13428-018-1021-z

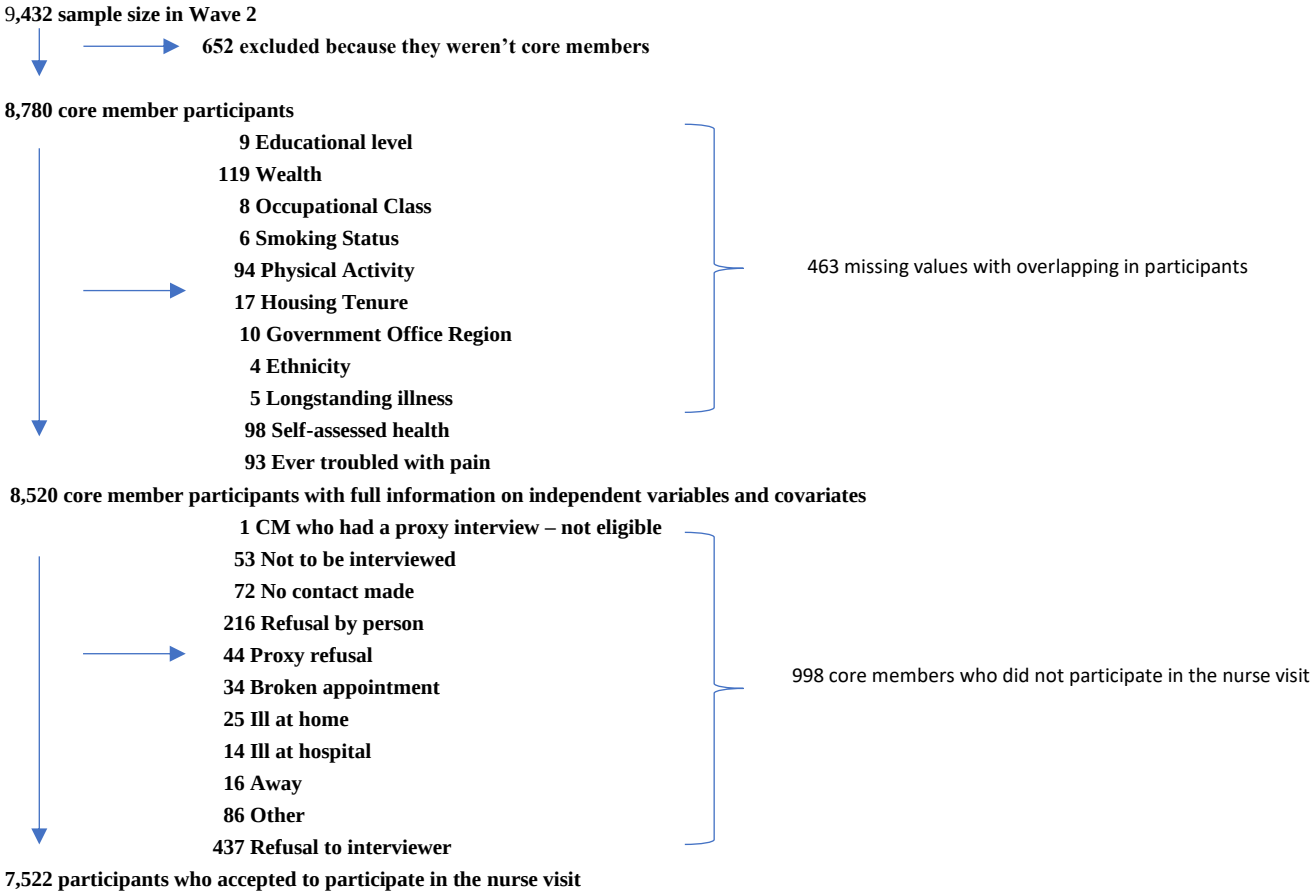
Appendices

Appendix A Bivariate analysis with interaction term between social class and employment status

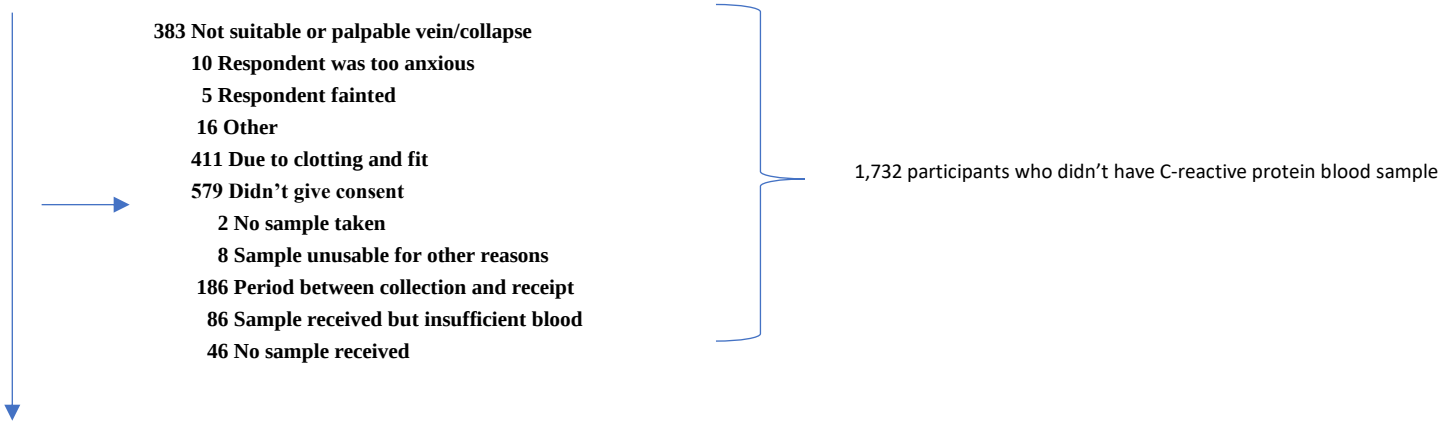
Variables	N(%)	Mean (SD)	Coef(SE)	95% Confidence Interval
Independent variables				
Educational level				
Higher Education	730(12.9)	2.99(7.49)	(ref)	(ref)
Higher Education but no degree	743(12.55)	3.50(6.75)	0.25(0.05)	0.14 to 0.36
High school	1,717(29.65)	3.65(5.83)	0.3(0.05)	0.21 to 0.40
Foreign or no qualifications	2,600(44.90)	4.9(10.5)	0.54(0.05)	0.45 to 0.63
Wealth quintiles				
Highest quintile	1239(21.89)	2.83(5.91)	(ref)	(ref)
Second quintile	1266(21.86)	3.63(7.92)	0.20(0.04)	0.11 t 0.28
Third quintile	1195(20.16)	4.16(6.99)	0.42(0.04)	0.33 to 0.51
Fourth quintile	1123(19.39)	4.58(9.50)	0.47(0.04)	0.38 to 0.56
Lowest quintile	967(16.7)	5.83(11.98)	0.67(0.04)	0.58 to 0.77
Occupational class				
Managerial & Professional	1860(32.12)	3.43(6.65)	(ref)	(ref)
Intermediate	809(13.97)	4.11(10.8)	0.06(0.04)	-0.02 to 0.15
Small employers & own account	635(10.96)	3.95(7.31)	0.07(0.05)	-0.02 to 0.17
Lower supervisory & technical	633(10.95)	4.79(9.04)	0.35(0.05)	0.25 to 0.45
Semi routine & technical &other	1853(32)	4.65(9.33)	0.31(0.03)	0.24 to 0.38
Employment status				
Employed	1811(31.27)	2.81(3.97)	(ref)	(ref)
Retired	3039(52.48)	4.75(10.12)	0.37(0.03)	0.31 to 0.44
Not employed & not retired	940(16.25)	4.61(9.36)	0.38(0.04)	0.29 to 0.47
Interaction term between				
Occupational class X Employment status				
Managerial X Employed			(ref)	(ref)
Intermediate X Retired			0.11(0.10)	-0.08 to 0.32
Intermediate X Not employed & Not Retired			-0.05(0.15)	-0.35 to 0.24
Small employers X Retired			0.13(0.10)	-0.07 to 0.35
Small employers X Not employed & Not Retired			0.20(0.15)	-0.10 to 0.51
Lower supervisory X Retired			0.18(0.11)	-0.04 to 0.40
Lower supervisory X Not employed & Not Retired			0.23(0.17)	-0.09 to 0.57
Semi routine X Retired			0.17(0.08)	0.01 to 0.33
Semi routine X Not employed & Not Retired			0.13(0.11)	-0.09 to 0.36

Appendix B Flowchart of missing values in wave 2 ELSA

English longitudinal Study of Ageing (ELSA)



7,522 participants who accepted to participate in the nurse visit



5, 790 core member participants with full information in independent variables

Extended figure 3.3 Final sample size after deleting each participant with at least one missing value in independent variables and covariates

---

Note: 1. Missing values overlap in participants.
2. Employment status, age, gender, marital status, ever diagnosed with high blood pressure, ever diagnosed with stroke, and ever diagnosed with CVD outcomes had 0 missing values.

Appendix C: Multivariate analysis in five different statistical methods adjusted for covariates for hair cortisol and educational level (2,468 participants in CCA, IPW1, IPW2 & IPW3 and 8,449 in Multiple Imputation)

	Complete case analysis (N=2,468)			Inverse Probability Weighting (1 out of 2 stages) (N=2,468)			Inverse Probability Weighting (2 out of 2 stages) (N=2,468)			Inverse Probability Weighting (1 stage) (N=2,468)			Multiple Imputation with attrition weights (N=8,449)		
Independent variables	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values
Educational level															
Higher Education	(ref)			(ref)			(ref)			(ref)			(ref)		
High school	-0.05	0.08	0.554	-0.01	0.09	0.887	-0.02	0.10	0.879	0.00	0.10	0.991	-0.05	0.10	0.568
Foreign or no qualifications	0.06	0.08	0.468	0.10	0.09	0.296	0.08	0.10	0.469	0.09	0.11	0.380	0.06	0.08	0.475
Covariates															
Age categories															
50-59	(ref)			(ref)			(ref)			(ref)			(ref)		
60-64	-0.30	0.16	0.068	-0.29	0.16	0.077	-0.26	0.18	0.15	-0.28	0.18	0.123	-0.19	0.15	0.236
65-69	0.22	0.17	0.201	0.17	0.19	0.378	0.20	0.22	0.342	0.17	0.21	0.424	0.07	0.16	0.652
70-74	0.20	0.18	0.266	0.06	0.18	0.731	0.06	0.20	0.747	0.06	0.21	0.762	0.05	0.20	0.793
75-79	0.32	0.18	0.077	0.32	0.21	0.124	0.39	0.24	0.098	0.36	0.24	0.131	0.15	0.16	0.375
80+	0.40	0.24	0.097	0.43	0.29	0.136	0.38	0.30	0.216	0.36	0.31	0.245	0.23	0.20	0.263
Gender															
Male	(ref)			(ref)			(ref)			(ref)			(ref)		
Female	0.28	0.19	0.141	0.23	0.22	0.291	0.30	0.23	0.195	0.32	0.24	0.186	-0.01	0.16	0.963
Age categories X Gender															
Male 50-59	(ref)			(ref)			(ref)			(ref)			(ref)		
Female 60-64	0.17	0.22	0.447	0.21	0.24	0.395	0.16	0.27	0.55	0.17	0.27	0.532	0.13	0.17	0.462
Female 65-69	-0.53	0.23	0.019	-0.47	0.26	0.066	-0.56	0.28	0.046	-0.55	0.28	0.051	-0.11	0.17	0.531
Female 70-74	-0.50	0.24	0.035	-0.36	0.25	0.153	-0.37	0.27	0.169	-0.40	0.28	0.147	-0.10	0.19	0.610
Female 75-79	-0.64	0.24	0.008	-0.67	0.28	0.015	-0.79	0.30	0.008	-0.80	0.30	0.008	-0.19	0.18	0.285
Female 80+	-0.70	0.31	0.024	-0.71	0.36	0.049	-0.74	0.37	0.043	-0.77	0.37	0.039	-0.18	0.18	0.312
Ethnicity															
White	(ref)			(ref)			(ref)			(ref)			(ref)		
Non-White	-0.16	0.24	0.522	-0.25	0.39	0.533	0.09	0.48	0.846	0.17	0.48	0.719	-0.12	0.29	0.683
Marital status															
Married	(ref)			(ref)			(ref)			(ref)			(ref)		
Cohabiting	0.01	0.17	0.951	-0.05	0.15	0.766	-0.06	0.21	0.784	-0.02	0.22	0.944	-0.02	0.20	0.933
Single	-0.03	0.15	0.845	-0.09	0.14	0.524	-0.02	0.15	0.884	-0.04	0.15	0.791	0.01	0.15	0.961
Widowed	0.09	0.10	0.364	0.02	0.11	0.889	0.05	0.12	0.669	0.07	0.12	0.562	0.05	0.12	0.650
Divorced/Separated	-0.04	0.11	0.739	0.03	0.17	0.867	0.05	0.20	0.788	0.03	0.20	0.870	-0.05	0.13	0.701
Hair treatment															
Yes	(ref)			(ref)			(ref)			(ref)			(ref)		
No	0.05	0.09	0.552	0.06	0.10	0.577	0.01	0.12	0.962	0.03	0.11	0.787	0.02	0.12	0.862
Hair colour															
Brown/Black	(ref)			(ref)			(ref)			(ref)			(ref)		
Blond/White/Red	-0.09	0.09	0.316	-0.06	0.11	0.559	-0.06	0.12	0.625	-0.05	0.13	0.717	-0.03	0.09	0.706
Grey/Other/MixedGrey	-0.05	0.09	0.564	-0.07	0.10	0.495	-0.02	0.13	0.865	-0.03	0.13	0.823	-0.06	0.09	0.544
Nurse visiting month															
Winter	(ref)			(ref)			(ref)			(ref)			(ref)		
Spring	0.27	0.15	0.068	0.26	0.16	0.097	0.25	0.19	0.185	0.22	0.19	0.245	0.22	0.19	0.258
Summer	0.14	0.09	0.131	0.33	0.11	0.003	0.16	0.13	0.21	0.16	0.14	0.230	0.11	0.09	0.248
Autumn	0.07	0.08	0.405	0.17	0.09	0.071	0.09	0.11	0.403	0.09	0.11	0.430	0.06	0.11	0.568
Constant	2.05	0.18	<0.001	2.00	0.19	<0.001	2.06	0.20	<0.001	2.04	0.17	<0.001	2.18	0.17	<0.001

Appendix D: Multivariate analysis in five different statistical methods adjusted for covariates for hair cortisone and educational level (2,468 participants in CCA, IPW1, IPW2 & IPW3 and 8,449 in Multiple Imputation)

	Complete case analysis (N=2,468)			Inverse Probability Weighting (1 out of 2 stages) (N=2,468)			Inverse Probability Weighting (2 out of 2 stages) (N=2,468)			Inverse Probability Weighting (1 stage) (N=2,468)			Multiple Imputation with attrition weights (N=8,449)		
Independent variables	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values
Educational level															
Higher Education	(ref)			(ref)			(ref)			(ref)			(ref)		
High school	0.00	0.04	0.905	-0.01	0.04	0.884	-0.02	0.05	0.714	-0.02	0.05	0.709	0.02	0.05	0.707
Foreign or no qualifications	0.06	0.04	0.107	0.06	0.04	0.156	0.06	0.05	0.247	0.06	0.05	0.212	**0.11**	**0.04**	**0.013**
Covariates															
Age categories															
50-59	(ref)			(ref)			(ref)			(ref)			(ref)		
60-64	-0.06	0.08	0.412	0.00	0.08	0.993	-0.02	0.09	0.786	-0.04	0.09	0.676	-0.05	0.05	0.366
65-69	-0.04	0.08	0.614	0.00	0.09	0.955	-0.04	0.10	0.704	-0.04	0.10	0.653	-0.05	0.08	0.486
70-74	-0.02	0.08	0.827	0.03	0.09	0.752	0.00	0.09	0.97	0.01	0.10	0.913	-0.03	0.07	0.691
75-79	-0.14	0.09	0.095	-0.09	0.09	0.309	-0.13	0.10	0.18	-0.14	0.10	0.156	-0.11	0.08	0.204
80+	-0.22	0.11	0.051	-0.17	0.09	0.061	-0.21	0.10	0.04	-0.21	0.10	0.034	-0.06	0.10	0.532
Gender															
Male	(ref)			(ref)			(ref)			(ref)			(ref)		
Female	-0.28	0.09	0.002	-0.20	0.11	0.064	-0.24	0.12	0.053	-0.22	0.12	0.083	-0.26	0.06	<0.001
Age categories X Gender															
Male 50-59	(ref)			(ref)			(ref)			(ref)			(ref)		
Female 60-64	0.01	0.10	0.928	-0.02	0.12	0.877	0.05	0.13	0.702	0.05	0.13	0.693	-0.01	0.07	0.895
Female 65-69	-0.02	0.10	0.845	-0.06	0.13	0.627	0.01	0.14	0.938	-0.01	0.14	0.963	-0.02	0.07	0.797
Female 70-74	-0.04	0.11	0.686	-0.12	0.12	0.338	-0.06	0.14	0.645	-0.10	0.14	0.471	-0.04	0.08	0.577
Female 75-79	0.07	0.11	0.557	-0.01	0.13	0.967	0.06	0.14	0.656	0.05	0.14	0.753	0.01	0.08	0.93
Female 80+	0.22	0.14	0.133	0.20	0.14	0.158	0.29	0.15	0.064	0.25	0.15	0.109	0.02	0.08	0.778
Ethnicity															
White	(ref)			(ref)			(ref)			(ref)			(ref)		
Non-White	-0.23	0.11	0.045	-0.17	0.16	0.285	-0.07	0.19	0.694	-0.07	0.19	0.725	-0.19	0.11	0.108
Marital status															
Married	(ref)			(ref)			(ref)			(ref)			(ref)		
Cohabiting	0.07	0.08	0.391	0.08	0.09	0.385	0.00	0.10	0.985	0.00	0.10	0.961	0.06	0.09	0.501
Single	0.06	0.07	0.392	0.08	0.08	0.338	0.01	0.10	0.94	0.03	0.10	0.758	0.11	0.10	0.27
Widowed	0.07	0.05	0.159	0.08	0.06	0.127	0.10	0.06	0.107	0.13	0.06	0.041	0.06	0.04	0.164
Divorced/Separated	0.11	0.05	0.034	0.11	0.08	0.137	0.12	0.09	0.162	0.12	0.09	0.184	0.09	0.07	0.172
Hair treatment															
Yes	(ref)			(ref)			(ref)			(ref)			(ref)		
No	0.29	0.04	<0.001	0.31	0.05	<0.001	0.31	0.06	<0.001	0.32	0.06	<0.001	0.36	0.04	<0.001
Hair colour															
Brown/Black	(ref)			(ref)			(ref)			(ref)			(ref)		
Blond/White/Red	-0.31	0.04	<0.001	-0.29	0.05	<0.001	-0.27	0.06	<0.001	-0.27	0.06	<0.001	-0.19	0.05	<0.001
Grey/Other/MixedGrey	-0.10	0.04	0.015	-0.10	0.05	0.037	-0.06	0.06	0.296	-0.05	0.06	0.42	-0.06	0.05	0.04
Nurse visiting month															
Winter	(ref)			(ref)			(ref)			(ref)			(ref)		
Spring	0.13	0.07	0.051	0.12	0.08	0.152	0.09	0.09	0.279	0.11	0.09	0.228	0.09	0.08	0.236
Summer	-0.01	0.04	0.862	0.05	0.05	0.309	0.01	0.05	0.812	0.00	0.06	0.95	-0.03	0.05	0.584
Autumn	0.07	0.04	0.048	0.12	0.04	0.002	0.13	0.05	0.008	0.13	0.05	0.007	0.06	0.04	0.114
Constant	1.90	0.08	<0.001	1.80	0.09	<0.001	1.82	0.10	<0.001	1.80	0.11	<0.001	1.89	0.08	<0.001

Appendix E: Multivariate analysis in five different statistical methods adjusted for covariates for hair cortisol and wealth tertiles (2,468 participants in CCA, IPW1, IPW2 & IPW3 and 8,449 in Multiple Imputation)

	Complete case analysis (N=2,468)			Inverse Probability Weighting (1 out of 2 stages) (N=2,468)			Inverse Probability Weighting (2 out of 2 stages) (N=2,468)			Inverse Probability Weighting (1 stage) (N=2,468)			Multiple Imputation with attrition weights (N=8,449)		
Independent variables	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values
Wealth tertiles															
Highest tertile	(ref)			(ref)			(ref)			(ref)			(ref)		
Middle tertile	-0.02	0.08	0.814	-0.03	0.08	0.742	0.01	0.09	0.951	-0.01	0.10	0.928	-0.05	0.08	0.553
Lowest tertile	**0.23**	**0.08**	**0.007**	0.19	0.10	0.058	0.17	0.11	0.123	0.19	0.11	0.107	**0.22**	**0.09**	**0.016**
Covariates															
Age categories															
50-59	(ref)			(ref)			(ref)			(ref)			(ref)		
60-64	-0.30	0.16	0.066	-0.30	0.17	0.068	-0.27	0.18	0.146	-0.29	0.19	0.116	-0.15	0.15	0.333
65-69	0.23	0.17	0.185	0.17	0.20	0.394	0.20	0.22	0.348	0.17	0.22	0.434	0.11	0.17	0.5
70-74	0.22	0.18	0.221	0.08	0.18	0.671	0.08	0.20	0.696	0.08	0.21	0.71	0.10	0.20	0.635
75-79	0.31	0.18	0.091	0.31	0.21	0.143	0.39	0.24	0.104	0.36	0.24	0.135	0.18	0.16	0.276
80+	0.39	0.24	0.106	0.43	0.29	0.148	0.37	0.31	0.229	0.35	0.31	0.263	0.26	0.20	0.196
Gender															
Male	(ref)			(ref)			(ref)			(ref)			(ref)		
Female	0.24	0.19	0.212	0.19	0.22	0.381	0.27	0.24	0.252	0.28	0.24	0.248	-0.02	0.16	0.915
Age categories X Gender															
Male 50-59	(ref)			(ref)			(ref)			(ref)			(ref)		
Female 60-64	0.20	0.22	0.355	0.25	0.25	0.321	0.19	0.27	0.486	0.21	0.28	0.458	0.13	0.17	0.455
Female 65-69	-0.49	0.23	0.03	-0.43	0.26	0.102	-0.52	0.29	0.07	-0.50	0.29	0.082	-0.09	0.17	0.586
Female 70-74	-0.46	0.24	0.05	-0.32	0.26	0.209	-0.34	0.28	0.225	-0.36	0.29	0.207	-0.08	0.19	0.66
Female 75-79	-0.58	0.24	0.016	-0.61	0.28	0.028	-0.75	0.31	0.014	-0.76	0.31	0.015	-0.16	0.18	0.364
Female 80+	-0.66	0.31	0.035	-0.67	0.37	0.069	-0.70	0.37	0.061	-0.72	0.38	0.059	-0.17	0.18	0.359
Ethnicity															
White	(ref)			(ref)			(ref)			(ref)			(ref)		
Non-White	-0.14	0.24	0.576	-0.24	0.39	0.546	0.10	0.49	0.831	0.18	0.48	0.703	-0.13	0.29	0.646
Marital status															
Married	(ref)			(ref)			(ref)			(ref)			(ref)		
Cohabiting	-0.02	0.17	0.925	-0.07	0.15	0.629	-0.09	0.22	0.679	-0.05	0.22	0.824	-0.06	0.20	0.782
Single	-0.08	0.15	0.6	-0.13	0.14	0.339	-0.06	0.15	0.668	-0.09	0.15	0.575	-0.07	0.15	0.662
Widowed	0.05	0.10	0.648	-0.02	0.12	0.85	0.02	0.12	0.889	0.03	0.12	0.786	0.00	0.12	0.993
Divorced/Separated	-0.13	0.11	0.258	-0.04	0.17	0.816	-0.01	0.20	0.979	-0.03	0.20	0.884	-0.14	0.13	0.3
Hair treatment															
Yes	(ref)			(ref)			(ref)			(ref)			(ref)		
No	0.04	0.09	0.646	0.04	0.10	0.666	0.00	0.12	0.974	0.02	0.11	0.858	0.01	0.12	0.919
Hair colour															
Brown/Black	(ref)			(ref)			(ref)			(ref)			(ref)		
Blond/White/Red	-0.09	0.09	0.356	-0.05	0.11	0.641	-0.05	0.13	0.662	-0.04	0.13	0.754	-0.03	0.09	0.735
Grey/Other/MixedGrey	-0.05	0.09	0.597	-0.06	0.10	0.543	-0.02	0.13	0.886	-0.03	0.13	0.845	-0.06	0.10	0.563
Nurse visiting month															
Winter	(ref)			(ref)			(ref)			(ref)			(ref)		
Spring	0.28	0.15	0.06	0.27	0.16	0.094	0.26	0.19	0.169	0.23	0.19	0.221	0.22	0.19	0.249
Summer	0.13	0.09	0.152	0.32	0.11	0.003	0.16	0.13	0.216	0.16	0.14	0.234	0.11	0.09	0.257
Autumn	0.06	0.08	0.429	0.16	0.09	0.082	0.09	0.11	0.395	0.09	0.11	0.413	0.06	0.11	0.597
Constant	2.02	0.18	<0.001	2.00	0.19	<0.001	2.04	0.20	<0.001	2.04	0.21	<0.001	2.13	0.17	<0.001

Appendix F: Multivariate analysis in five different statistical methods adjusted for covariates for hair cortisone and wealth tertiles (2,468 participants in CCA, IPW1, IPW2 & IPW3 and 8,449 in Multiple Imputation)

	Complete case analysis (N=2,468)			Inverse Probability Weighting (1 out of 2 stages) (N=2,468)			Inverse Probability Weighting (2 out of 2 stages) (N=2,468)			Inverse Probability Weighting (1 stage) (N=2,468)			Multiple Imputation with attrition weights (N=8,449)		
Independent variables	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values
Wealth tertiles															
Highest tertile	(ref)			(ref)			(ref)			(ref)			(ref)		
Middle tertile	0.05	0.03	0.133	0.07	0.04	0.082	0.08	0.04	0.072	0.08	0.05	0.074	0.06	0.04	0.131
Lowest tertile	**0.13**	**0.04**	**0.001**	0.16	0.04	<0.001	0.15	0.05	0.003	**0.17**	**0.05**	**0.001**	**0.15**	**0.05**	**0.002**
Covariates															
Age categories															
50-59	(ref)			(ref)			(ref)			(ref)			(ref)		
60-64	-0.06	0.08	0.391	0.00	0.08	0.953	-0.03	0.09	0.768	-0.04	0.09	0.649	-0.02	0.05	0.631
65-69	-0.04	0.08	0.623	-0.01	0.09	0.918	-0.04	0.10	0.701	-0.04	0.10	0.657	-0.03	0.08	0.711
70-74	-0.02	0.08	0.848	0.03	0.09	0.719	0.01	0.09	0.929	0.02	0.10	0.862	0.00	0.07	0.985
75-79	-0.15	0.09	0.079	-0.10	0.09	0.252	-0.14	0.10	0.164	-0.14	0.10	0.145	-0.09	0.08	0.306
80+	-0.23	0.11	0.041	-0.18	0.09	0.046	-0.21	0.10	0.032	-0.22	0.10	0.027	-0.04	0.10	0.685
Gender															
Male	(ref)			(ref)			(ref)			(ref)			(ref)		
Female	-0.30	0.09	0.001	-0.22	0.11	0.036	-0.27	0.13	0.035	-0.24	0.13	0.054	-0.26	0.07	<0.001
Age categories X Gender															
Male 50-59	(ref)			(ref)			(ref)			(ref)			(ref)		
Female 60-64	0.03	0.10	0.769	0.01	0.12	0.943	0.08	0.13	0.567	0.08	0.13	0.546	-0.01	0.07	0.931
Female 65-69	0.00	0.10	0.986	-0.03	0.12	0.812	0.04	0.14	0.785	0.02	0.14	0.87	-0.01	0.07	0.924
Female 70-74	-0.02	0.11	0.882	-0.08	0.12	0.493	-0.03	0.14	0.832	-0.06	0.14	0.654	-0.03	0.08	0.675
Female 75-79	0.09	0.11	0.401	0.03	0.13	0.823	0.09	0.14	0.514	0.08	0.14	0.594	0.03	0.08	0.759
Female 80+	0.25	0.14	0.089	0.23	0.14	0.104	0.32	0.16	0.043	0.28	0.16	0.073	0.04	0.08	0.604
Ethnicity															
White	(ref)			(ref)			(ref)			(ref)			(ref)		
Non-White	-0.22	0.11	0.053	-0.16	0.16	0.307	-0.06	0.19	0.752	-0.05	0.19	0.805	-0.19	0.12	0.106
Marital status															
Married	(ref)			(ref)			(ref)			(ref)			(ref)		
Cohabiting	0.06	0.08	0.472	0.06	0.09	0.519	-0.02	0.10	0.831	-0.03	0.10	0.781	0.04	0.09	0.631
Single	0.03	0.07	0.671	0.04	0.08	0.625	-0.03	0.10	0.78	-0.01	0.10	0.932	0.07	0.10	0.47
Widowed	0.04	0.05	0.385	0.05	0.06	0.342	0.07	0.06	0.251	0.10	0.06	0.132	0.04	0.04	0.4
Divorced/Separated	0.06	0.05	0.241	0.06	0.08	0.424	0.08	0.09	0.398	0.07	0.09	0.454	0.05	0.07	0.508
Hair treatment															
Yes	(ref)			(ref)			(ref)			(ref)			(ref)		
No	0.28	0.04	<0.001	0.31	0.05	<0.001	0.31	0.06	<0.001	0.31	0.06	<0.001	0.35	0.04	<0.001
Hair colour															
Brown/Black	(ref)			(ref)			(ref)			(ref)			(ref)		
Blond/White/Red	-0.31	0.04	<0.001	-0.29	0.05	<0.001	-0.27	0.06	<0.001	-0.26	0.06	<0.001	-0.19	0.05	<0.001
Grey/Other/MixedGrey	-0.09	0.04	0.017	-0.10	0.05	0.047	-0.06	0.06	0.32	-0.05	0.06	0.449	-0.03	0.05	0.36
Nurse visiting month															
Winter	(ref)			(ref)			(ref)			(ref)			(ref)		
Spring	0.13	0.07	0.05	0.12	0.08	0.148	0.10	0.09	0.248	0.12	0.09	0.195	0.09	0.08	0.228
Summer	-0.01	0.04	0.793	0.04	0.05	0.349	0.01	0.05	0.816	0.00	0.06	0.941	-0.03	0.05	0.585
Autumn	0.07	0.04	0.05	0.12	0.04	0.002	0.13	0.05	0.007	0.13	0.05	0.006	0.06	0.04	0.124
Constant	1.89	0.08	<0.001	1.77	0.09	<0.001	1.77	0.10	<0.001	1.75	0.10	<0.001	1.86	0.08	<0.001

Appendix G: Multivariate analysis in five different statistical methods adjusted for covariates for hair cortisol and social class (2,468 participants in CCA, IPW1, IPW2 & IPW3 and 8,449 in Multiple Imputation)

	Complete case analysis (N=2,468)			Inverse Probability Weighting (1 out of 2 stages) (N=2,468)			Inverse Probability Weighting (2 out of 2 stages) (N=2,468)			Inverse Probability Weighting (1 stage) (N=2,468)			Multiple Imputation with attrition weights (N=8,449)		
Independent variables	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values
Social class															
Managerial & Professional	(ref)			(ref)			(ref)			(ref)			(ref)		
Intermediate	-0.05	0.08	0.573	-0.06	0.10	0.564	-0.11	0.12	0.349	-0.11	0.12	0.359	-0.05	0.11	0.637
Semi routine & technical &otl	0.10	0.08	0.189	0.12	0.09	0.147	0.05	0.10	0.587	0.06	0.10	0.566	0.10	0.09	0.237
Covariates															
Age categories															
50-59	(ref)			(ref)			(ref)			(ref)			(ref)		
60-64	-0.29	0.16	0.075	-0.29	0.17	0.089	-0.25	0.19	0.181	-0.27	0.19	0.149	-0.17	0.15	0.264
65-69	0.21	0.17	0.209	0.16	0.20	0.411	0.20	0.22	0.352	0.17	0.22	0.438	0.08	0.16	0.62
70-74	0.20	0.18	0.263	0.06	0.18	0.75	0.07	0.21	0.729	0.07	0.22	0.746	0.06	0.20	0.766
75-79	0.32	0.18	0.083	0.31	0.21	0.138	0.40	0.24	0.1	0.37	0.24	0.13	0.15	0.16	0.369
80+	0.41	0.24	0.091	0.44	0.29	0.128	0.39	0.31	0.205	0.37	0.31	0.233	0.24	0.20	0.231
Gender															
Male	(ref)			(ref)			(ref)			(ref)			(ref)		
Female	0.27	0.19	0.159	0.21	0.22	0.323	0.29	0.24	0.214	0.31	0.24	0.202	-0.01	0.16	0.97
Age categories X Gender															
Male 50-59	(ref)			(ref)			(ref)			(ref)			(ref)		
Female 60-64	0.17	0.22	0.433	0.22	0.25	0.378	0.17	0.27	0.532	0.18	0.28	0.513	0.12	0.17	0.479
Female 65-69	-0.51	0.23	0.023	-0.45	0.26	0.081	-0.54	0.28	0.058	-0.52	0.29	0.067	-0.10	0.17	0.542
Female 70-74	-0.48	0.24	0.043	-0.33	0.26	0.197	-0.35	0.28	0.211	-0.38	0.29	0.19	-0.09	0.19	0.654
Female 75-79	-0.61	0.24	0.012	-0.63	0.28	0.023	-0.76	0.30	0.012	-0.77	0.31	0.013	-0.17	0.18	0.355
Female 80+	-0.69	0.31	0.027	-0.70	0.36	0.054	-0.73	0.37	0.05	-0.75	0.38	0.047	-0.16	0.18	0.359
Ethnicity															
White	(ref)			(ref)			(ref)			(ref)			(ref)		
Non-White	-0.14	0.24	0.562	-0.23	0.40	0.564	0.11	0.49	0.823	0.19	0.49	0.699	-0.12	0.29	0.695
Marital status															
Married	(ref)			(ref)			(ref)			(ref)			(ref)		
Cohabiting	0.00	0.17	0.991	-0.06	0.15	0.688	-0.08	0.21	0.72	-0.04	0.22	0.873	-0.01	0.20	0.946
Single	-0.03	0.15	0.857	-0.09	0.14	0.494	-0.02	0.15	0.885	-0.04	0.15	0.799	0.00	0.15	0.997
Widowed	0.08	0.10	0.432	0.00	0.11	0.99	0.04	0.12	0.738	0.06	0.12	0.616	0.04	0.12	0.706
Divorced/Separated	-0.05	0.11	0.682	0.02	0.17	0.911	0.05	0.21	0.792	0.04	0.21	0.865	-0.06	0.13	0.651
Hair treatment															
Yes	(ref)			(ref)			(ref)			(ref)			(ref)		
No	0.04	0.09	0.617	0.05	0.10	0.642	0.00	0.12	0.969	0.02	0.11	0.859	0.02	0.12	0.854
Hair colour															
Brown/Black	(ref)			(ref)			(ref)			(ref)			(ref)		
Blond/White/Red	-0.09	0.09	0.326	-0.05	0.11	0.614	-0.05	0.13	0.667	-0.04	0.13	0.76	-0.03	0.09	0.712
Grey/Other/MixedGrey	-0.05	0.09	0.579	-0.06	0.10	0.547	-0.02	0.13	0.9	-0.02	0.13	0.863	-0.06	0.09	0.543
Nurse visiting month															
Winter	(ref)			(ref)			(ref)			(ref)			(ref)		
Spring	0.27	0.15	0.066	0.26	0.16	0.105	0.25	0.19	0.199	0.21	0.19	0.265	0.22	0.19	0.26
Summer	0.14	0.09	0.126	0.33	0.11	0.003	0.17	0.13	0.205	0.17	0.14	0.224	0.11	0.09	0.252
Autumn	0.06	0.08	0.415	0.16	0.09	0.08	0.09	0.11	0.416	0.08	0.11	0.444	0.06	0.11	0.591
Constant	2.03	0.18	<0.001	2.00	0.19	<0.001	2.08	0.2	<0.001	2.08	0.21	<0.001	2.15	0.17	<0.001

Appendix H: Multivariate analysis in five different statistical methods adjusted for covariates for hair cortisone and social class (2,468 participants in CCA, IPW1, IPW2 & IPW3 and 8,449 in Multiple Imputation)

	Complete case analysis (N=2,468)			Inverse Probability Weighting (1 out of 2 stages) (N=2,468)			Inverse Probability Weighting (2 out of 2 stages) (N=2,468)			Inverse Probability Weighting (1 stage) (N=2,468)			Multiple Imputation with attrition weights (N=8,449)		
Independent variables	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values
Social class															
Managerial & Professional	(ref)			(ref)			(ref)			(ref)			(ref)		
Intermediate	0.01	0.04	0.797	-0.01	0.05	0.848	-0.01	0.06	0.789	0.00	0.06	0.96	0.03	0.04	0.518
Semi routine & technical &other	**0.10**	**0.04**	**0.003**	0.09	0.04	0.017	0.09	0.04	0.033	**0.10**	**0.04**	**0.028**	**0.13**	**0.04**	**0.001**
Covariates															
Age categories															
50-59	(ref)			(ref)			(ref)			(ref)			(ref)		
60-64	-0.06	0.08	0.406	0.00	0.08	0.98	-0.02	0.09	0.83	-0.03	0.09	0.716	-0.04	0.05	0.439
65-69	-0.05	0.08	0.545	-0.01	0.09	0.887	-0.04	0.10	0.672	-0.05	0.10	0.626	-0.05	0.08	0.525
70-74	-0.02	0.08	0.778	0.02	0.09	0.794	0.00	0.09	0.971	0.01	0.10	0.915	-0.02	0.07	0.74
75-79	-0.15	0.09	0.08	-0.10	0.09	0.281	-0.13	0.10	0.178	-0.14	0.10	0.155	-0.11	0.08	0.213
80+	-0.21	0.11	0.056	-0.17	0.09	0.071	-0.19	0.10	0.052	-0.20	0.10	0.045	-0.05	0.10	0.64
Gender															
Male	(ref)			(ref)			(ref)			(ref)			(ref)		
Female	-0.28	0.09	0.001	-0.21	0.11	0.054	-0.25	0.13	0.049	-0.22	0.13	0.079	-0.26	0.06	<0.001
Age categories X Gender															
Male 50-59	(ref)			(ref)			(ref)			(ref)			(ref)		
Female 60-64	0.01	0.10	0.893	-0.01	0.12	0.916	0.05	0.13	0.682	0.06	0.13	0.673	-0.01	0.07	0.874
Female 65-69	-0.01	0.10	0.924	-0.05	0.13	0.704	0.02	0.14	0.876	0.00	0.14	0.978	-0.01	0.07	0.837
Female 70-74	-0.03	0.11	0.796	-0.10	0.12	0.428	-0.04	0.14	0.746	-0.08	0.14	0.565	-0.03	0.08	0.668
Female 75-79	0.09	0.11	0.447	0.02	0.13	0.89	0.09	0.14	0.55	0.07	0.15	0.641	0.02	0.08	0.773
Female 80+	0.22	0.14	0.122	0.20	0.14	0.147	0.29	0.16	0.068	0.25	0.16	0.113	0.03	0.08	0.667
Ethnicity															
White	(ref)			(ref)			(ref)			(ref)			(ref)		
Non-White	-0.22	0.11	0.051	-0.16	0.16	0.316	-0.06	0.19	0.744	-0.05	0.19	0.779	-0.19	0.12	0.116
Marital status															
Married	(ref)			(ref)			(ref)			(ref)			(ref)		
Cohabiting	0.06	0.08	0.404	0.07	0.09	0.449	-0.01	0.10	0.888	-0.02	0.10	0.854	0.06	0.09	0.497
Single	0.06	0.07	0.378	0.08	0.08	0.361	0.00	0.10	0.983	0.03	0.10	0.792	0.10	0.10	0.294
Widowed	0.06	0.05	0.218	0.08	0.05	0.166	0.09	0.06	0.147	0.12	0.06	0.057	0.05	0.04	0.218
Divorced/Separated	0.10	0.05	0.041	0.11	0.08	0.171	0.12	0.09	0.188	0.12	0.10	0.213	0.09	0.07	0.191
Hair treatment															
Yes	(ref)			(ref)			(ref)			(ref)			(ref)		
No	0.28	0.04	<0.001	0.31	0.05	<0.001	0.31	0.06	<0.001	0.32	0.06	<0.001	0.36	0.04	<0.001
Hair colour															
Brown/Black	(ref)			(ref)			(ref)			(ref)			(ref)		
Blond/White/Red	-0.31	0.04	<0.001	-0.29	0.05	<0.001	-0.27	0.06	<0.001	-0.26	0.06	<0.001	-0.19	0.05	<0.001
Grey/Other/MixedGrey	-0.10	0.04	0.016	-0.10	0.05	0.048	-0.06	0.06	0.346	-0.04	0.06	0.486	-0.05	0.05	0.34
Nurse visiting month															
Winter	(ref)			(ref)			(ref)			(ref)			(ref)		
Spring	0.14	0.07	0.045	0.12	0.08	0.16	0.10	0.09	0.269	0.11	0.09	0.219	0.09	0.08	0.234
Summer	-0.01	0.04	0.851	0.05	0.05	0.318	0.01	0.05	0.786	0.01	0.06	0.918	-0.03	0.05	0.575
Autumn	0.07	0.04	0.051	0.12	0.04	0.002	0.13	0.05	0.008	0.13	0.05	0.007	0.06	0.04	0.135
Constant	1.90	0.06	<0.001	1.79	0.09	<0.001	1.79	0.10	<0.001	1.78	0.1	<0.001	1.87	0.08	<0.001

Appendix I: Educational level and (log transformed) C-reactive protein in five methods with covariates – monotonic missingness

	Complete case analysis (1,083)			Full Information Maximum Likelihood (4,574)			Multiple Imputation (4,574)			Diggle-Kenward model (4,574)			Pattern Mixture Models (4,574)		
Intercept															
Educational level	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values
Higher education	(ref)														
High school	0.085	0.068	0.213	**0.109**	**0.036**	**0.003**	**0.115**	**0.037**	**0.002**	**0.15**	**0.037**	**<0.001**	**0.106**	**0.036**	**0.004**
Foreign or no quali	**0.26**	**0.071**	**<0.001**	**0.157**	**0.035**	**<0.001**	**0.166**	**0.036**	**<0.001**	**0.255**	**0.035**	**<0.001**	**0.151**	**0.035**	**<0.001**
Covariates															
Age categories															
50-59	ref														
60-69	0.053	0.061	0.381	0.059	0.034	0.076	0.058	0.034	0.085	0.042	0.034	0.222	0.058	0.034	0.085
70+	0.257	0.085	0.002	0.177	0.037	<0.001	0.167	0.038	<0.001	0.182	0.037	<0.001	0.165	0.038	<0.001
Gender															
Male	ref														
Female	0.108	0.058	0.063	0.063	0.029	0.029	0.063	0.029	0.03	0.03	0.028	0.288	0.066	0.029	0.022
Ethnicity															
Whites	ref														
Non-Whites	0.237	0.242	0.328	-0.021	0.111	0.848	-0.03	0.113	0.788	0.04	0.113	0.719	-0.03	0.112	0.79
Marital status															
Married	ref														
Cohabiting	-0.127	0.13	0.329	-0.09	0.072	0.211	-0.087	0.073	0.228	-0.048	0.071	0.503	-0.093	0.072	0.194
Single	-0.161	0.151	0.284	0.046	0.064	0.475	0.031	0.065	0.633	0.084	0.065	0.198	0.044	0.064	0.488
Widowed	-0.059	0.102	0.564	0.051	0.041	0.21	0.056	0.041	0.174	0.084	0.041	0.04	0.049	0.041	0.224
Divorced/Separate	0.012	0.097	0.902	-0.068	0.05	0.175	-0.054	0.051	0.285	0.002	0.05	0.974	-0.066	0.051	0.194
												D1	0.073	0.037	0.05
Slope												D2	0.018	0.041	0.655
Educational level												D3	0.026	0.04	0.518
Higher education	(ref)														
High school	0.027	0.065	0.672	0.034	0.046	0.459	0.021	0.048	0.659	0.025	0.046	0.59	0.033	0.046	0.468
Foreign or no quali	**-0.17**	**0.068**	**0.013**	-0.028	0.046	0.545	-0.04	0.045	0.369	-0.044	0.045	0.336	-0.03	0.046	0.504
Covariates															
Age categories															
50-59															
60-69	0.014	0.058	0.807	-0.001	0.041	0.979	0.005	0.048	0.916	-0.005	0.042	0.897	-0.003	0.041	0.936
70+	0.058	0.085	0.494	0.025	0.052	0.626	0.071	0.068	0.294	0.017	0.052	0.744	0.012	0.053	0.813
Gender															
Male															
Female	-0.033	0.055	0.554	0.012	0.037	0.748	0.01	0.038	0.789	0.019	0.037	0.618	0.012	0.037	0.744
Ethnicity															
Whites															
Non-Whites	0.241	0.257	0.35	0.148	0.126	0.242	0.141	0.161	0.38	0.132	0.126	0.297	0.151	0.127	0.235
Marital status															
Married															
Cohabiting	0.211	0.175	0.229	0.225	0.109	0.039	0.236	0.116	0.042	0.219	0.109	0.044	0.225	0.109	0.038
Single	-0.067	0.15	0.656	-0.032	0.1	0.747	0.006	0.097	0.949	-0.049	0.101	0.629	-0.033	0.1	0.739
Widowed	0.163	0.096	0.088	0	0.062	0.996	-0.014	0.065	0.833	-0.015	0.062	0.815	-0.002	0.062	0.974
Divorced/Separate	-0.135	0.095	0.156	-0.067	0.067	0.312	-0.091	0.064	0.152	-0.078	0.066	0.238	-0.069	0.067	0.303
												D1	-0.017	0.017	0.304
Quadratic term												D2	0.087	0.05	0.079
Educational level												D3	0.017	0.053	0.753
Higher Education															
High school	-0.003	0.021	0.895	-0.009	0.017	0.605	-0.006	0.018	0.751	-0.007	0.016	0.681	-0.008	0.017	0.62
Foreign or no quali	**0.054**	**0.022**	**0.013**	0.017	0.017	0.316	0.018	0.016	0.276	0.019	0.017	0.258	0.018	0.017	0.279
Covariates															
Age categories															
50-59															
60-69	-0.013	0.019	0.488	-0.009	0.015	0.557	-0.011	0.017	0.51	-0.008	0.015	0.588	-0.008	0.015	0.594
70+	-0.036	0.028	0.192	-0.022	0.02	0.276	-0.039	0.027	0.153	-0.022	0.02	0.276	-0.017	0.02	0.408
Gender															
Male															
Female	0.006	0.018	0.717	-0.005	0.014	0.692	-0.005	0.016	0.759	-0.007	0.014	0.631	-0.006	0.014	0.684
Ethnicity															
Whites															
Non-Whites	-0.128	0.068	0.061	-0.102	0.042	0.016	-0.099	0.062	0.111	-0.102	0.043	0.018	-0.102	0.042	0.016
Marital status															
Married															
Cohabiting	-0.076	0.055	0.168	-0.076	0.039	0.05	-0.087	0.04	0.031	-0.076	0.039	0.051	-0.076	0.039	0.05
Single	0.02	0.049	0.688	0.015	0.039	0.706	-0.003	0.035	0.924	0.017	0.038	0.65	0.015	0.039	0.696
Widowed	-0.027	0.033	0.401	0.02	0.024	0.417	0.023	0.028	0.401	0.021	0.024	0.392	0.02	0.024	0.399
Divorced/Separate	0.068	0.033	0.036	0.052	0.026	0.041	0.059	0.022	0.006	0.053	0.026	0.037	0.053	0.026	0.039
												D1	0.005	0.004	0.227
												D2	-0.033	0.015	0.034
												D3	-0.007	0.023	0.755
Mean intercept	**0.388**	**0.029**	**<0.001**	**0.516**	**0.014**	**<0.001**	**0.519**	**0.013**	**<0.001**	**0.516**	**0.014**	**<0.001**	**0.516**	**0.014**	**<0.001**
Mean slope	0.004	0.028	0.884	0.003	0.019	0.861	0	0.02	0.853	-0.003	0.019	0.885	0.003	0.021	0.877
Mean quadratic term	**-0.022**	**0.009**	**0.012**	**-0.026**	**0.007**	**0.001**	**-0.025**	**0.006**	**0.001**	**-0.023**	**0.007**	**0.002**	**-0.026**	**0.008**	**0.001**

Appendix J: Wealth and (log transformed) C-reactive protein in five methods with covariates – monotonic missingness

	Complete case analysis (1,083)			Full Information Maximum Likelihood (4,574)			Multiple Imputation (4,574)			Diggle-Kenward model (4,574)			Pattern Mixture Models (4,574)		
Intercept	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values
Wealth tertiles															
Highest tertile	(ref)														
Middle tertile	**0.239**	**0.065**	**<0.001**	**0.231**	**0.032**	**<0.001**	**0.231**	**0.032**	**<0.001**	**0.27**	**0.032**	**<0.001**	**0.228**	**0.032**	**<0.001**
Lowest tertile	0.176	0.093	0.059	**0.236**	**0.044**	**<0.001**	**0.243**	**0.046**	**<0.001**	**0.366**	**0.035**	**<0.001**	**0.23**	**0.044**	**<0.001**
Covariates															
Age categories															
50-59	(ref)														
60-69	0.088	0.061	0.146	0.085	0.033	0.01	0.085	0.033	0.011	0.082	0.034	0.015	0.082	0.033	0.013
70+	0.293	0.083	<0.001	0.201	0.036	<0.001	0.192	0.037	<0.001	0.219	0.036	<0.001	0.188	0.037	<0.001
Gender															
Male	(ref)														
Female	0.147	0.058	0.012	0.081	0.028	0.004	0.083	0.028	0.004	0.065	0.027	0.018	0.083	0.028	0.003
Ethnicity															
Whites	(ref)														
Non-Whites	0.199	0.243	0.412	-0.032	0.112	0.777	-0.04	0.114	0.729	0.026	0.114	0.818	-0.039	0.112	0.728
Marital status															
Married	(ref)														
Cohabiting	-0.158	0.125	0.207	-0.106	0.071	0.135	-0.106	0.071	0.136	-0.078	0.07	0.265	-0.108	0.071	0.125
Single	-0.183	0.153	0.231	-0.001	0.064	0.993	-0.018	0.065	0.783	0.007	0.065	0.915	-0.001	0.064	0.988
Widowed	-0.066	0.101	0.512	0.022	0.041	0.592	0.024	0.041	0.57	0.023	0.041	0.576	0.021	0.041	0.608
Divorced/Separat	-0.046	0.099	0.643	-0.117	0.051	0.021	-0.11	0.051	0.032	-0.097	0.051	0.058	-0.113	0.051	0.026
Slope												D1	0.07	0.037	0.058
												D2	0.022	0.041	0.594
Wealth tertiles												D3	0.024	0.04	0.552
Highest tertile	(ref)														
Middle tertile	-0.043	0.061	0.487	-0.01	0.042	0.81	0.001	0.047	0.986	-0.019	0.042	0.64	-0.009	0.042	0.827
Lowest tertile	-0.133	0.077	0.082	**-0.125**	**0.052**	**0.016**	**-0.122**	**0.053**	**0.023**	**-0.157**	**0.05**	**0.002**	**-0.127**	**0.052**	**0.015**
Covariates															
Age categories															
50-59	(ref)														
60-69	-0.008	0.058	0.897	-0.009	0.041	0.828	-0.01	0.043	0.821	-0.016	0.042	0.694	-0.012	0.042	0.777
70+	0.03	0.083	0.722	0.017	0.051	0.736	0.058	0.067	0.386	0.008	0.051	0.874	0.002	0.052	0.965
Gender															
Male	(ref)														
Female	-0.058	0.055	0.288	0.01	0.037	0.786	0.001	0.038	0.975	0.013	0.037	0.719	0.01	0.037	0.788
Ethnicity															
Whites	(ref)														
Non-Whites	0.219	0.253	0.386	0.146	0.126	0.248	0.119	0.152	0.432	0.138	0.125	0.27	0.148	0.127	0.243
Marital status															
Married	(ref)														
Cohabiting	0.224	0.175	0.202	0.237	0.109	0.03	0.253	0.102	0.014	0.235	0.109	0.032	0.238	0.109	0.029
Single	-0.048	0.153	0.756	-0.006	0.1	0.956	0.043	0.098	0.665	-0.014	0.1	0.886	-0.007	0.1	0.947
Widowed	0.181	0.096	0.059	0.027	0.064	0.675	0.013	0.066	0.839	0.018	0.063	0.773	0.025	0.064	0.694
Divorced/Separat	-0.089	0.099	0.368	-0.028	0.069	0.687	-0.044	0.065	0.502	-0.026	0.068	0.701	-0.028	0.069	0.68
Quadratic term												D1	-0.03	0.017	0.072
												D2	0.089	0.05	0.075
												D3	0.021	0.053	0.696
Wealth tertiles															
Highest tertile	(ref)														
Middle tertile	0.015	0.019	0.456	0.004	0.015	0.817	-0.001	0.017	0.959	0.005	0.015	0.762	0.003	0.015	0.824
Lowest tertile	**0.054**	**0.025**	**0.028**	**0.05**	**0.019**	**0.009**	**0.046**	**0.019**	**0.017**	**0.052**	**0.019**	**0.006**	**0.051**	**0.019**	**0.007**
Covariates															
Age categories															
50-59	(ref)														
60-69	-0.006	0.019	0.754	-0.005	0.015	0.721	-0.006	0.016	0.695	-0.004	0.015	0.776	-0.004	0.015	0.774
70+	-0.027	0.027	0.32	-0.018	0.02	0.354	-0.035	0.027	0.194	-0.019	0.02	0.349	-0.013	0.02	0.532
Gender															
Male	(ref)														
Female	0.014	0.018	0.42	-0.004	0.014	0.791	-0.001	0.015	0.945	-0.004	0.014	0.759	-0.004	0.014	0.791
Ethnicity															
Whites	(ref)														
Non-Whites	-0.122	0.066	0.066	-0.101	0.042	0.016	-0.087	0.06	0.149	-0.103	0.043	0.016	-0.101	0.042	0.016
Marital status															
Married	(ref)														
Cohabiting	-0.08	0.056	0.149	-0.082	0.039	0.037	-0.092	0.035	0.009	-0.082	0.039	0.038	-0.082	0.039	0.037
Single	0.012	0.049	0.804	0.005	0.038	0.9	-0.018	0.036	0.626	0.008	0.038	0.843	0.005	0.038	0.89
Widowed	-0.035	0.033	0.281	0.009	0.025	0.716	0.014	0.028	0.634	0.01	0.025	0.684	0.01	0.025	0.696
Divorced/Separat	0.052	0.034	0.133	0.035	0.027	0.185	0.04	0.023	0.076	0.036	0.027	0.181	0.035	0.027	0.183
												D1	0.007	0.004	0.071
												D2	-0.031	0.015	0.045
												D3	-0.009	0.023	0.707
Mean intercept	**0.388**	**0.029**	**<0.001**	**0.516**	**0.014**	**<0.001**	**0.519**	**0.014**	**<0.001**	**0.516**	**0.014**	**0.001**	**0.516**	**0.014**	**<0.001**
Mean slope	0.004	0.028	0.889	0.001	0.019	0.979	-0.002	0.017	0.867	-0.005	0.019	0.794	-0.006	0.021	0.778
Mean quadratic term	**-0.022**	**0.009**	**0.012**	**-0.024**	**0.007**	**0.001**	**-0.024**	**0.008**	**0.001**	**-0.023**	**0.007**	**0.003**	**-0.023**	**0.008**	**0.004**

Appendix K: Social class and (log transformed) C-reactive protein in five methods with covariates – monotonic missingness

	Complete case analysis (1,083)			Full Information Maximum Likelihood (4,574)			Multiple Imputation (4,574)			Diggle-Kenward model (4,574)			Pattern Mixture Models (4,574)		
Intercept	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values
Social class															
Managerial & Profession	(ref)														
Intermediate	-0.039	0.073	0.594	-0.037	0.036	0.298	-0.033	0.037	0.372	-0.012	0.037	0.746	-0.042	0.036	0.25
Semi routine & technical	**0.134**	**0.064**	**0.036**	**0.132**	**0.032**	**<0.001**	**0.136**	**0.032**	**<0.001**	**0.213**	**0.031**	**<0.001**	**0.126**	**0.032**	**<0.001**
Covariates															
Age categories															
50-59	(ref)														
60-69	0.076	0.061	0.211	0.069	0.033	0.039	0.068	0.034	0.042	0.058	0.034	0.085	0.067	0.033	0.046
70+	0.304	0.084	<0.001	0.203	0.036	<0.001	0.194	0.037	<0.001	0.227	0.036	<0.001	0.189	0.037	<0.001
Gender															
Male	(ref)														
Female	0.139	0.058	0.018	0.084	0.028	0.003	0.085	0.029	0.003	0.06	0.028	0.031	0.087	0.028	0.002
Ethnicity															
Whites	(ref)														
Non-Whites	0.205	0.249	0.411	-0.045	0.112	0.688	-0.054	0.114	0.635	0.011	0.113	0.921	-0.053	0.112	0.634
Marital status															
Married	(ref)														
Cohabiting	-0.112	0.13	0.391	-0.083	0.072	0.244	-0.081	0.072	0.263	-0.036	0.071	0.61	-0.087	0.071	0.222
Single	-0.152	0.153	0.319	0.045	0.064	0.477	0.031	0.066	0.633	0.086	0.065	0.184	0.043	0.064	0.495
Widowed	-0.059	0.101	0.559	0.044	0.04	0.281	0.049	0.041	0.235	0.074	0.041	0.07	0.042	0.04	0.3
Divorced/Separated	0.015	0.098	0.881	-0.069	0.05	0.168	-0.056	0.051	0.274	-0.003	0.05	0.96	-0.066	0.05	0.188
Slope												D1	0.079	0.037	0.033
												D2	0.023	0.041	0.573
Social class												D3	0.032	0.04	0.43
Managerial & Profession	(ref)														
Intermediate	-0.037	0.069	0.589	0.045	0.047	0.34	0.041	0.047	0.383	0.037	0.047	0.43	0.045	0.047	0.343
Semi routine & technical	-0.076	0.062	0.221	-0.028	0.042	0.504	-0.029	0.04	0.469	-0.044	0.042	0.299	-0.03	0.042	0.482
Covariates															
Age categories															
50-59	(ref)														
60-69	-0.002	0.058	0.977	-0.005	0.041	0.905	0.001	0.048	0.985	-0.01	0.042	0.801	-0.007	0.041	0.859
70+	0.029	0.084	0.733	0.017	0.051	0.737	0.063	0.068	0.352	0.006	0.051	0.904	0.004	0.052	0.935
Gender															
Male	(ref)														
Female	-0.051	0.055	0.353	0.004	0.037	0.916	0.001	0.038	0.979	0.009	0.037	0.812	0.004	0.037	0.922
Ethnicity															
Whites	(ref)														
Non-Whites	0.227	0.257	0.377	0.153	0.127	0.227	0.148	0.16	0.353	0.141	0.126	0.266	0.156	0.127	0.221
Marital status															
Married	(ref)														
Cohabiting	0.207	0.174	0.235	0.23	0.109	0.034	0.244	0.116	0.035	0.222	0.109	0.041	0.231	0.109	0.034
Single	-0.07	0.151	0.645	-0.026	0.1	0.798	0.013	0.097	0.893	-0.043	0.101	0.668	-0.027	0.101	0.79
Widowed	0.153	0.096	0.111	-0.001	0.062	0.994	-0.014	0.065	0.826	-0.015	0.062	0.805	-0.002	0.062	0.974
Divorced/Separated	-0.138	0.097	0.154	-0.066	0.067	0.325	-0.089	0.063	0.157	-0.077	0.066	0.246	-0.067	0.067	0.316
Quadratic term												D1	-0.011	0.017	0.517
												D2	0.086	0.05	0.086
Social class												D3	0.013	0.053	0.802
Managerial & Profession	(ref)														
Intermediate	0.03	0.022	0.17	0.005	0.017	0.79	0.004	0.017	0.79	0.006	0.017	0.715	0.005	0.017	0.776
Semi routine & technical	0.034	0.02	0.089	0.023	0.015	0.137	0.021	0.015	0.162	0.024	0.015	0.115	0.024	0.015	0.125
Covariates															
Age categories															
50-59	(ref)														
60-69	-0.009	0.019	0.644	-0.007	0.015	0.619	-0.01	0.017	0.554	-0.007	0.015	0.661	-0.006	0.015	0.663
70+	-0.028	0.028	0.316	-0.018	0.02	0.356	-0.036	0.027	0.182	-0.018	0.02	0.359	-0.013	0.02	0.514
Gender															
Male	(ref)														
Female	0.01	0.018	0.553	-0.004	0.014	0.775	-0.003	0.016	0.841	-0.005	0.014	0.719	-0.004	0.014	0.775
Ethnicity															
Whites	(ref)														
Non-Whites	-0.122	0.068	0.071	-0.102	0.042	0.015	-0.1	0.061	0.105	-0.103	0.043	0.016	-0.102	0.042	0.015
Marital status															
Married	(ref)														
Cohabiting	-0.075	0.055	0.173	-0.077	0.039	0.046	-0.088	0.04	0.028	-0.077	0.039	0.048	-0.077	0.039	0.046
Single	0.021	0.049	0.672	0.013	0.039	0.731	-0.005	0.036	0.893	0.016	0.039	0.673	0.014	0.039	0.721
Widowed	-0.024	0.033	0.459	0.02	0.024	0.413	0.024	0.028	0.396	0.021	0.024	0.382	0.021	0.024	0.397
Divorced/Separated	0.07	0.033	0.034	0.052	0.026	0.042	0.059	0.021	0.006	0.053	0.026	0.038	0.052	0.026	0.041
												D1	0.003	0.004	0.423
												D2	-0.033	0.016	0.036
												D3	-0.006	0.023	0.784
Mean intercept	**0.388**	**0.029**	**<0.001**	**0.516**	**0.014**	**<0.001**	**0.518**	**0.012**	**<0.001**	**0.516**	**0.014**	**<0.001**	**0.516**	**0.014**	**<0.001**
Mean slope	0.004	0.028	0.887	0.003	0.019	0.862	0.001	0.017	0.873	-0.003	0.019	0.887	0.007	0.021	0.748
Mean quadratic term	**-0.022**	**0.009**	**0.012**	**-0.025**	**0.007**	**0.001**	**-0.025**	**0.007**	**0.001**	**-0.023**	**0.007**	**0.002**	**-0.027**	**0.008**	**0.001**

Appendix L: Educational level and (log transformed) C-reactive protein in five methods with covariates – intermittent missingness

	Complete case analysis (1,083)			Full Information Maximum Likelihood (5,025)			Multiple Imputation (5,025)			Diggle-Kenward model (5,025)			Pattern Mixture Models (5,025)		
Intercept															
Educational level	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values
Higher education	(ref)														
High school	0.085	0.068	0.213	**0.106**	**0.035**	**0.002**	**0.113**	**0.035**	**0.001**	**0.152**	**0.035**	**<0.001**	**0.103**	**0.035**	**0.003**
Foreign or no qualification	**0.26**	**0.071**	**<0.001**	**0.157**	**0.033**	**<0.001**	**0.167**	**0.034**	**<0.001**	**0.263**	**0.033**	**<0.001**	**0.151**	**0.034**	**<0.001**
Covariates															
Age categories															
50-59	ref														
60-69	0.053	0.061	0.381	0.073	0.032	0.023	0.073	0.032	0.022	0.056	0.032	0.085	0.071	0.032	0.026
70+	0.257	0.085	0.002	0.178	0.036	<0.001	0.175	0.037	<0.001	0.179	0.035	<0.001	0.165	0.037	<0.001
Gender															
Male	ref														
Female	0.108	0.058	0.063	0.057	0.027	0.037	0.055	0.028	0.048	0.026	0.027	0.327	0.06	0.027	0.028
Ethnicity															
Whites	ref														
Non-Whites	0.237	0.242	0.328	-0.012	0.104	0.906	-0.022	0.106	0.832	0.056	0.106	0.594	-0.016	0.105	0.875
Marital status															
Married	ref														
Cohabiting	-0.127	0.13	0.329	-0.102	0.069	0.138	-0.1	0.069	0.149	-0.069	0.069	0.317	-0.107	0.069	0.12
Single	-0.161	0.151	0.284	-0.01	0.064	0.88	-0.019	0.065	0.766	0.032	0.065	0.624	-0.013	0.063	0.842
Widowed	-0.059	0.102	0.564	0.046	0.039	0.239	0.049	0.04	0.223	0.079	0.04	0.045	0.044	0.039	0.266
Divorced/Separated	0.012	0.097	0.902	-0.059	0.048	0.217	-0.046	0.049	0.345	0.013	0.048	0.793	-0.058	0.048	0.233
												D1	0.075	0.035	0.032
Slope												D2	0.024	0.041	0.557
Educational level												D3	0.035	0.036	0.334
Higher education	(ref)														
High school	0.027	0.065	0.672	0.024	0.043	0.578	0.004	0.041	0.93	0.018	0.043	0.681	0.024	0.043	0.576
Foreign or no qualification	**-0.17**	**0.068**	**0.013**	-0.022	0.043	0.606	-0.04	0.04	0.32	-0.045	0.043	0.294	-0.023	0.043	0.589
Covariates															
Age categories															
50-59															
60-69	0.014	0.058	0.807	-0.028	0.039	0.466	-0.04	0.045	0.373	-0.031	0.039	0.429	-0.029	0.039	0.45
70+	0.058	0.085	0.494	0.008	0.049	0.878	0.006	0.051	0.913	-0.001	0.049	0.989	0.002	0.05	0.968
Gender															
Male															
Female	-0.033	0.055	0.554	0.015	0.035	0.675	0.018	0.045	0.691	0.021	0.035	0.543	0.014	0.035	0.682
Ethnicity															
Whites															
Non-Whites	0.241	0.257	0.35	0.15	0.124	0.225	0.114	0.17	0.502	0.116	0.123	0.346	0.152	0.124	0.22
Marital status															
Married															
Cohabiting	0.211	0.175	0.229	0.215	0.1	0.032	0.229	0.082	0.005	0.206	0.101	0.041	0.216	0.101	0.032
Single	-0.067	0.15	0.656	-0.003	0.093	0.976	0.039	0.098	0.694	-0.011	0.093	0.906	-0.002	0.093	0.979
Widowed	0.163	0.096	0.088	0.001	0.059	0.982	0.005	0.057	0.926	-0.004	0.058	0.946	0.001	0.059	0.99
Divorced/Separated	-0.135	0.095	0.156	-0.08	0.063	0.202	-0.119	0.064	0.062	-0.09	0.063	0.153	-0.08	0.063	0.204
												D1	-0.024	0.015	0.112
Quadratic term												D2	0.052	0.052	0.316
Educational level												D3	-0.005	0.051	0.929
Higher Education															
High school	-0.003	0.021	0.895	-0.007	0.016	0.652	0.001	0.015	0.963	-0.006	0.016	0.702	-0.007	0.016	0.657
Foreign or no qualification	**0.054**	**0.022**	**0.013**	0.012	0.016	0.434	0.019	0.014	0.187	0.016	0.016	0.316	0.013	0.016	0.408
Covariates															
Age categories															
50-59															
60-69	-0.013	0.019	0.488	-0.003	0.014	0.821	0.001	0.016	0.935	-0.002	0.014	0.864	-0.003	0.014	0.844
70+	-0.036	0.028	0.192	-0.017	0.019	0.348	-0.016	0.021	0.444	-0.017	0.019	0.373	-0.015	0.019	0.43
Gender															
Male															
Female	0.006	0.018	0.717	-0.003	0.013	0.792	-0.005	0.017	0.774	-0.005	0.013	0.728	-0.003	0.013	0.791
Ethnicity															
Whites															
Non-Whites	-0.128	0.068	0.061	-0.104	0.041	0.011	-0.084	0.059	0.157	-0.1	0.041	0.015	-0.104	0.041	0.011
Marital status															
Married															
Cohabiting	-0.076	0.055	0.168	-0.077	0.037	0.037	-0.082	0.029	0.005	-0.075	0.037	0.041	-0.077	0.037	0.037
Single	0.02	0.049	0.688	0.005	0.035	0.894	-0.017	0.034	0.621	0.003	0.035	0.927	0.005	0.035	0.893
Widowed	-0.027	0.033	0.401	0.01	0.023	0.648	0.006	0.021	0.794	0.01	0.023	0.653	0.011	0.023	0.636
Divorced/Separated	0.068	0.033	0.036	0.052	0.024	0.03	0.064	0.022	0.003	0.052	0.024	0.029	0.051	0.024	0.031
												D1	0.006	0.003	0.094
												D2	-0.018	0.016	0.259
												D3	0	0.023	0.992
Mean intercept	**0.388**	**0.029**	**<0.001**	**0.512**	**0.013**	**<0.001**	**0.512**	**0.013**	**<0.001**	**0.512**	**0.013**	**<0.001**	**0.512**	**0.013**	**<0.001**
Mean slope	0.004	0.028	0.884	0.006	0.018	0.736	0	0.017	0.876	-0.001	0.018	0.96	0.005	0.006	0.784
Mean quadratic term	**-0.022**	**0.009**	**0.012**	**-0.027**	**0.007**	**<0.001**	**-0.024**	**0.007**	**<0.001**	**-0.024**	**0.007**	**<0.001**	**-0.026**	**0.007**	**<0.001**

Appendix M: Wealth and (log transformed) C-reactive protein in five methods with covariates – intermittent missingness

	Complete case analysis (1,083)			Full Information Maximum Likelihood (5,025)			Multiple Imputation (5,025)			Diggle-Kenward model (5,025)			Pattern Mixture Models (5,025)		
Intercept	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values
Wealth tertiles															
Highest tertile	(ref)														
Middle tertile	**0.239**	**0.065**	**<0.001**	**0.259**	**0.031**	**<0.001**	**0.262**	**0.031**	**<0.001**	**0.295**	**0.031**	**<0.001**	**0.256**	**0.031**	**<0.001**
Lowest tertile	0.176	0.093	0.059	**0.266**	**0.042**	**<0.001**	**0.27**	**0.043**	**<0.001**	**0.395**	**0.033**	**<0.001**	**0.261**	**0.042**	**<0.001**
Covariates															
Age categories															
50-59	(ref)														
60-69	0.088	0.061	0.146	0.098	0.032	0.002	0.1	0.032	0.002	0.097	0.032	0.002	0.096	0.031	0.002
70+	0.293	0.083	<0.001	0.198	0.035	<0.001	0.196	0.036	<0.001	0.213	0.034	<0.001	0.185	0.036	<0.001
Gender															
Male	(ref)														
Female	0.147	0.058	0.012	0.074	0.027	0.006	0.074	0.027	0.007	0.06	0.026	0.022	0.076	0.027	0.005
Ethnicity															
Whites	(ref)														
Non-Whites	0.199	0.243	0.412	-0.028	0.105	0.792	-0.038	0.107	0.719	0.037	0.107	0.731	-0.03	0.105	0.772
Marital status															
Married	(ref)														
Cohabiting	-0.158	0.125	0.207	-0.124	0.068	0.068	-0.122	0.068	0.073	-0.104	0.067	0.122	-0.128	0.068	0.059
Single	-0.183	0.153	0.231	-0.054	0.063	0.397	-0.067	0.065	0.299	-0.041	0.064	0.519	-0.055	0.063	0.38
Widowed	-0.066	0.101	0.512	0.014	0.039	0.714	0.014	0.04	0.734	0.015	0.04	0.704	0.013	0.039	0.749
Divorced/Separated	-0.046	0.099	0.643	-0.111	0.049	0.022	-0.104	0.049	0.034	-0.09	0.049	0.066	-0.108	0.049	0.026
Slope												D1	0.069	0.035	0.047
												D2	0.029	0.041	0.481
Wealth tertiles												D3	0.03	0.036	0.396
Highest tertile	(ref)														
Middle tertile	-0.043	0.061	0.487	-0.041	0.039	0.291	-0.046	0.038	0.224	-0.049	0.039	0.213	-0.04	0.039	0.308
Lowest tertile	-0.133	0.077	0.082	**-0.146**	**0.049**	**0.003**	**-0.159**	**0.053**	**0.003**	**-0.173**	**0.047**	**<0.001**	**-0.147**	**0.049**	**0.003**
Covariates															
Age categories															
50-59	(ref)														
60-69	-0.008	0.058	0.897	-0.037	0.039	0.337	-0.051	0.044	0.252	-0.043	0.039	0.269	-0.039	0.039	0.319
70+	0.03	0.083	0.722	0.003	0.048	0.957	0.001	0.05	0.986	-0.009	0.048	0.855	-0.005	0.049	0.915
Gender															
Male	(ref)														
Female	-0.058	0.055	0.288	0.014	0.035	0.68	0.014	0.044	0.751	0.017	0.035	0.625	0.014	0.035	0.686
Ethnicity															
Whites	(ref)														
Non-Whites	0.219	0.253	0.386	0.153	0.122	0.21	0.127	0.171	0.458	0.125	0.121	0.304	0.154	0.122	0.208
Marital status															
Married	(ref)														
Cohabiting	0.224	0.175	0.202	0.231	0.101	0.022	0.245	0.081	0.003	0.224	0.101	0.027	0.232	0.101	0.022
Single	-0.048	0.153	0.756	0.029	0.093	0.76	0.077	0.099	0.438	0.028	0.093	0.768	0.028	0.093	0.76
Widowed	0.181	0.096	0.059	0.031	0.06	0.6	0.04	0.057	0.486	0.032	0.06	0.595	0.03	0.06	0.612
Divorced/Separated	-0.089	0.099	0.368	-0.036	0.065	0.576	-0.065	0.066	0.323	-0.035	0.065	0.591	-0.036	0.065	0.581
Quadratic term												D1	-0.015	0.015	0.322
												D2	0.061	0.052	0.24
												D3	0.001	0.051	0.99
Wealth tertiles															
Highest tertile	(ref)														
Middle tertile	0.015	0.019	0.456	0.01	0.014	0.487	0.013	0.013	0.314	0.011	0.014	0.445	0.01	0.014	0.501
Lowest tertile	**0.054**	**0.025**	**0.028**	**0.05**	**0.018**	**0.005**	**0.055**	**0.017**	**0.001**	**0.052**	**0.018**	**0.003**	**0.051**	**0.018**	**0.004**
Covariates															
Age categories															
50-59	(ref)														
60-69	-0.006	0.019	0.754	<0.001	0.014	0.991	0.005	0.016	0.743	0.001	0.014	0.926	0.001	0.014	0.957
70+	-0.027	0.027	0.32	-0.015	0.018	0.406	-0.014	0.021	0.504	-0.014	0.018	0.45	-0.012	0.019	0.525
Gender															
Male	(ref)														
Female	0.014	0.018	0.42	-0.002	0.013	0.852	-0.003	0.016	0.866	-0.003	0.013	0.826	-0.002	0.013	0.853
Ethnicity															
Whites	(ref)														
Non-Whites	-0.122	0.066	0.066	-0.105	0.04	0.009	-0.089	0.06	0.135	-0.102	0.041	0.012	-0.105	0.041	0.009
Marital status															
Married	(ref)														
Cohabiting	-0.08	0.056	0.149	-0.083	0.037	0.025	-0.088	0.029	0.002	-0.081	0.037	0.028	-0.083	0.037	0.025
Single	0.012	0.049	0.804	-0.006	0.035	0.86	-0.029	0.034	0.382	-0.008	0.035	0.818	-0.006	0.035	0.863
Widowed	-0.035	0.033	0.281	-0.001	0.023	0.979	-0.006	0.022	0.778	-0.001	0.023	0.972	0	0.023	0.996
Divorced/Separated	0.052	0.034	0.133	0.035	0.025	0.161	0.045	0.022	0.045	0.035	0.025	0.159	0.034	0.025	0.164
												D1	0.003	0.003	0.322
												D2	-0.023	0.016	0.152
												D3	-0.002	0.023	0.93
Mean intercept	**0.388**	**0.029**	**<0.001**	**0.512**	**0.013**	**<0.001**	**0.515**	**0.013**	**<0.001**	**0.512**	**0.013**	**<0.001**	**0.512**	**0.013**	**<0.001**
Mean slope	0.004	0.028	0.889	0.003	0.018	0.873	-0.001	0.018	0.875	0.005	0.019	0.897	0.005	0.02	0.811
Mean quadratic term	**-0.022**	**0.009**	**0.012**	**-0.026**	**0.007**	**<0.001**	**-0.024**	**0.007**	**<0.001**	**-0.024**	**0.007**	**0.001**	**-0.026**	**0.008**	**0.001**

Appendix N: Social class and (log transformed) C-reactive protein in five methods with covariates – intermittent missingness

	Complete case analysis (1,083)			Full Information Maximum Likelihood (5,025)			Multiple Imputation (5,025)			Diggle-Kenward model (5,025)			Pattern Mixture Models (5,025)		
Intercept	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values	Coef	SE	P-values
Social class															
Managerial & Professional	(ref)														
Intermediate	-0.039	0.073	0.594	-0.031	0.034	0.372	-0.025	0.035	0.466	0	0.035	0.99	-0.034	0.034	0.32
Semi routine & technical &oth	**0.134**	**0.064**	**0.036**	**0.136**	**0.03**	**<0.001**	**0.14**	**0.031**	**<0.001**	**0.224**	**0.03**	**<0.001**	**0.131**	**0.03**	**<0.001**
Covariates															
Age categories															
50-59	(ref)														
60-69	0.076	0.061	0.211	0.081	0.032	0.01	0.083	0.032	0.01	0.072	0.032	0.025	0.079	0.032	0.012
70+	0.304	0.084	<0.001	0.203	0.035	<0.001	0.202	0.036	<0.001	0.224	0.034	<0.001	0.189	0.036	<0.001
Gender															
Male	(ref)														
Female	0.139	0.058	0.018	0.079	0.027	0.004	0.077	0.028	0.005	0.057	0.027	0.035	0.081	0.027	0.003
Ethnicity															
Whites	(ref)														
Non-Whites	0.205	0.249	0.411	-0.033	0.105	0.752	-0.043	0.107	0.685	0.031	0.107	0.773	-0.037	0.106	0.728
Marital status															
Married	(ref)														
Cohabiting	-0.112	0.13	0.391	-0.099	0.069	0.149	-0.097	0.069	0.163	-0.062	0.069	0.369	-0.105	0.069	0.128
Single	-0.152	0.153	0.319	-0.01	0.063	0.878	-0.019	0.065	0.768	0.034	0.065	0.594	-0.013	0.063	0.833
Widowed	-0.059	0.101	0.559	0.039	0.039	0.323	0.041	0.04	0.299	0.069	0.039	0.081	0.036	0.039	0.36
Divorced/Separated	0.015	0.098	0.881	-0.061	0.048	0.204	-0.048	0.049	0.325	0.008	0.048	0.864	-0.059	0.048	0.218
Slope												D1	0.08	0.035	0.021
												D2	0.03	0.041	0.457
Social class												D3	0.042	0.036	0.243
Managerial & Professional	(ref)														
Intermediate	-0.037	0.069	0.589	0.042	0.044	0.342	0.03	0.042	0.483	0.036	0.044	0.417	0.043	0.044	0.336
Semi routine & technical &oth	-0.076	0.062	0.221	-0.024	0.04	0.537	-0.031	0.039	0.42	-0.042	0.04	0.285	-0.025	0.04	0.537
Covariates															
Age categories															
50-59	(ref)														
60-69	-0.002	0.058	0.977	-0.031	0.039	0.422	-0.043	0.044	0.331	-0.036	0.039	0.363	-0.032	0.039	0.406
70+	0.029	0.084	0.733	0.001	0.048	0.979	-0.002	0.049	0.97	-0.011	0.048	0.814	-0.004	0.049	0.93
Gender															
Male	(ref)														
Female	-0.051	0.055	0.353	0.007	0.035	0.836	0.01	0.045	0.832	0.011	0.035	0.751	0.007	0.035	0.85
Ethnicity															
Whites	(ref)														
Non-Whites	0.227	0.257	0.377	0.153	0.123	0.215	0.123	0.17	0.471	0.119	0.123	0.331	0.154	0.123	0.211
Marital status															
Married	(ref)														
Cohabiting	0.207	0.174	0.235	0.221	0.1	0.028	0.233	0.082	0.005	0.212	0.101	0.036	0.222	0.101	0.027
Single	-0.07	0.151	0.645	0.004	0.093	0.967	0.044	0.098	0.654	-0.004	0.094	0.964	0.004	0.093	0.962
Widowed	0.153	0.096	0.111	0.002	0.059	0.971	0.006	0.057	0.92	-0.004	0.059	0.95	0.002	0.059	0.978
Divorced/Separated	-0.138	0.097	0.154	-0.076	0.063	0.225	-0.116	0.064	0.069	-0.086	0.063	0.169	-0.076	0.063	0.228
Quadratic term												D1	-0.019	0.015	0.214
												D2	0.053	0.052	0.31
Social class												D3	-0.008	0.051	0.871
Managerial & Professional	(ref)														
Intermediate	0.03	0.022	0.17	0.003	0.016	0.863	0.007	0.014	0.623	0.004	0.016	0.811	0.003	0.016	0.862
Semi routine & technical &oth	0.034	0.02	0.089	0.019	0.014	0.184	0.02	0.013	0.124	0.021	0.014	0.144	0.02	0.015	0.179
Covariates															
Age categories															
50-59	(ref)														
60-69	-0.009	0.019	0.644	-0.002	0.014	0.879	0.002	0.016	0.877	-0.001	0.014	0.94	-0.002	0.014	0.906
70+	-0.028	0.028	0.316	-0.015	0.018	0.421	-0.013	0.021	0.528	-0.013	0.019	0.47	-0.012	0.019	0.516
Gender															
Male	(ref)														
Female	0.01	0.018	0.553	-0.002	0.013	0.875	-0.003	0.017	0.852	-0.003	0.013	0.833	-0.002	0.013	0.881
Ethnicity															
Whites	(ref)														
Non-Whites	-0.122	0.068	0.071	-0.103	0.041	0.011	-0.086	0.06	0.149	-0.1	0.04	0.014	-0.104	0.041	0.011
Marital status															
Married	(ref)														
Cohabiting	-0.075	0.055	0.173	-0.078	0.036	0.033	-0.082	0.029	0.004	-0.076	0.037	0.036	-0.078	0.036	0.033
Single	0.021	0.049	0.672	0.003	0.035	0.938	-0.018	0.034	0.587	0.001	0.035	0.978	0.003	0.035	0.938
Widowed	-0.024	0.033	0.459	0.01	0.023	0.663	0.005	0.021	0.802	0.01	0.023	0.661	0.01	0.023	0.651
Divorced/Separated	0.07	0.033	0.034	0.05	0.024	0.034	0.064	0.022	0.003	0.051	0.024	0.032	0.05	0.024	0.035
												D1	0.004	0.003	0.198
												D2	-0.021	0.016	0.208
												D3	0.001	0.023	0.972
Mean intercept	**0.388**	**0.029**	**<0.001**	**0.512**	**0.013**	**<0.001**	**0.515**	**0.013**	**<0.001**	**0.512**	**0.013**	**<0.001**	**0.512**	**0.013**	**<0.001**
Mean slope	0.004	0.028	0.887	0.006	0.018	0.737	0.001	0.019	0.897	-0.001	0.018	0.962	0.008	0.02	0.68
Mean quadratic term	**-0.022**	**0.009**	**<0.001**	**-0.027**	**0.007**	**<0.001**	**-0.025**	**0.005**	**<0.001**	**-0.024**	**0.007**	**<0.001**	**-0.027**	**0.008**	**<0.001**