Intraindividual cyclical variation of patient reported outcome measurements in patients with chronic health conditions

Submitted by Antoinette Francesca Davey, to the University of Exeter as a thesis for the degree of Doctor of Philosophy in Medical Studies, April 2021.

I certify that all material in this thesis which is not my own work has been identified and that no material has previously been submitted and approved for the award of a degree by this or any other University.

Signature 

Dedicated to my Nani

Thank you for your unconditional love,

strength, and light you brought to this world.

I wished you had seen the final outcome of this work.

Abstract

Background: Patient reported outcome measures (PROMs) are regularly used in research, and increasingly in clinical practice for individuals with chronic conditions, to gather patients' perspective on their experience of health. Whereas research applications have focused on the use of aggregate PROMs information, biological rhythms and other intraindividual cycles have potential implications for how patients report on their health using PROMs, and ultimately the scores that are produced, with potentially important implications for the use of PROMs at the individual level. Research on this issue is, however, sparse and results in a lack of understanding of the key concepts, methods and associated phenomena associated with individual cyclical variation in PROMs scores.

Aim: The aim of this thesis is to explore the cyclical variation in patient reported outcome measurements (PROMs) in patients with chronic conditions. Specific objectives included: a) the development of a conceptual model for researching cyclical variation of PROMs, b) the elicitation of patient perspectives on cyclical variation in PROMs, and c) the mapping, selection and use of best methods for the statistical modelling of cyclical variation.

Method: This thesis comprised of three sequential studies which informed each other to address the aims and objectives of the thesis. A mixed methods scoping review, considering both quantitative and qualitative research, was conducted to map out the knowledge on cyclical variation of patient reported outcome measurements in patients with chronic conditions. Findings from this scoping review informed the development of a conceptual model building up on established outcomes models. A longitudinal mixed methods study was conducted to understand the factors that were important in the cyclical variation of PROMs from the patients' perspective, to test the concepts within the conceptual model and to refine it. Sixteen individuals recruited with varying combinations

of asthma, depression and osteoarthritis and conducted a total of 3 interviews with each participant over a 9-month period, in order to account for seasonal changes. Finally, variation in outcome scores for a range of symptoms (aural fullness, tinnitus, dizziness, and hearing loss) in Meniere's disease was modelled by applying Fourier transformation using quantitative longitudinal data on Meniere's symptoms captured across time .

Results: The scoping review identified 33 articles which provided empirical evidence for cyclical variation in PROMs, in respiratory, musculoskeletal, mental health and neurological conditions. The hypotheses and findings in the documents were used to develop a conceptual model of cyclical variation of PROMs in chronic conditions which included the following concepts: determinants (biorhythms, timing and type of healthcare interventions), variation in outcomes (health conditions, outcomes, and time-period), a mediator (psychological health status), moderators (individual and environmental factors), and variation in scores (cognition, integration, measurement, recall and interpretation). Patient interviews confirmed both cyclical variations in outcomes as experienced by patients themselves as well as the relevance of the concepts included in the conceptual model and supported the inclusion of additional ones (sleep, partners interpretation of outcomes and salience of recent episodes and/or flare ups). Fourier analysis of the Meniere's disease data showed that the severity of symptoms was reported differently across a 24-hour period. Individuals reported the morning to be the worst time of the day for hearing loss and dizziness, tinnitus, and aural fullness peaking around 1/2pm. However, all four symptoms presented a decline in symptom severity by the evening.

Conclusion: This thesis has laid the theoretical and methodological foundation for future research on the cyclical variation of PROMs in patients with chronic health conditions. It has confirmed its existence for selected conditions based on literature

synthesis and a mixed methods study. The new conceptual model developed as part of this work, which identifies key sources of variation and hypothesises pathways that may explain intraindividual variation of PROMs, will facilitate further research. Findings from the, to my best knowledge, first longitudinal mixed methods study eliciting narratives of cyclical variation may benefit from replication in other patients and for other conditions. Finally, Fourier analyses, emerges as the analytical approach of choice to model cyclical variation of PROMs. Potential application of PROMs to monitor the impact of chronic conditions on patient's health needs to take into account cyclical variation in the selection, administration and interpretation of PROMs scores.

Contents

Acknowledgements

This work was funded by a University of Exeter Medical School College PhD scholarship. I am very much indebted to my supervisors. Professor Valderas' enthusiasm for the project, his support, encouragement and patience; Dr Mewse's support and checking in around mental wellbeing, especially during the pandemic; Professor Green's input and guidance; were all appreciated. I would like to thank all the participants who took part, without your input and voice there would not have been a PhD.

A special thank you to Gary Abel for introducing me to a new way of statistical thinking and being patient as I grasped the concepts, and for Jess Tyrrell sharing her longitudinal dataset for me use in my thesis. To my colleagues and friends in HSPRG & Primary Care, Ian, Charlotte, Joe, Jon, Jaheeda, Joy, Sarah D, Sarah W, Emily, Sinead, Raff, Emma, Mary, who supported and encouraged me throughout, helped pick up the pieces when I was overwhelmed and celebrated the victories along the way with cake! I could not have pushed through writing without my SUAW writing buddies, or Latika who was there till the end, and Tania who supported me through it all. To my best friend Sune, despite being half the world away, you were always there picking up messages and making sure I had your positive vibes for when I woke up. Craig, my old office buddy and best ever godfather to Sebastian, there are some people in this world who come into your life and I know I will never be able to replace you if you ever left.

This PhD would not be possible without the support from family. I would like to thank my parents, brother and sister for their constant support, sympathetic ear, my sister's amazing strength which fuelled my drive to complete this thesis. I am thankful for my son's patience when mummy had to work evenings and weekends, and through the multiple

lockdowns during the pandemic. I love that you wanted to “help mummy work” by joining in on the SUAW timer races. I feel lucky to have had the support from my husband who encouraged me to apply for this PhD and boosted my confidence along the way. When they say it takes a village to raise a child, I do believe it does take a village to get through a PhD, or in this case an amazing support system locally and internationally.

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Publications and conference proceedings

Publications (submitted)

Davey, A. Coombes, J. Porter, I. Green, C. Mewse, AJ. Valderas, JM. Time-dependent variation of patient reported outcome measurements (PROMs) in patients with chronic conditions: a scoping review. Submitted to Journal of Patient Reported Outcomes April 2021.

Invited talks

Davey, A. Time-dependent variation of PRO measurements in patients with chronic health conditions: A systematic scoping review. Oral presentation at the School of Health and Related Research Seminar Series, University of Sheffield 12th December 2017

Selected conference proceedings

Davey, A., Porter, I., Green, C., & Valderas, J.M Characterisation of time dependent variations of patient reported outcome measures (PROMs) in patients with chronic health conditions: a scoping review'. Oral presentation at the national Advances in Patient Reported Outcomes Research Conference, Oxford, 8th June 2017.

Davey, A., Porter, I., Coombes, J., Green, C., & Valderas, J.M. Does time of assessment matter for patient-reported outcomes in chronic health conditions. Presented at the European Biological Rhythms Society Annual meeting, Amsterdam, 31st July – 3rd August 2017

Davey, A., Porter, I., Coombes, J., Green, C., & Valderas, J.M. Time-dependent variation of PRO measurements in patients with chronic health conditions: A systematic scoping review. Presented at the International Society for Quality of Life Research Annual Conference, Philadelphia, 18th – 20th October 2017.

Davey, A., Porter, I., Green, C., & Valderas, J.M. Exploring time-dependent variation of patient-reported outcome scores across different time-points for patients with multiple conditions: A mixed methods longitudinal study. Oral presentation at International Society for Pharmacoeconomics and Outcomes Research Conference, Barcelona 12th -15th November 2018, **awarded one of the top ten student abstracts**.

Davey, A., Porter, I., Green, C., & Valderas, J.M. Exploring the variation of patient-reported outcome scores across different time-points (day, week, month) for patients with multiple conditions: Protocol for a longitudinal qualitative analysis. Presented at the national Advances in Patient Reported Outcomes Research Conference, Birmingham 20th June 2018.

Davey, A., Abel, G., Tyrell, J., Green, C. & Valderas, J.M. Using Fourier analysis to examine variations in outcome scores for individuals with Meniere's Disease. Oral presentation at the national Advances in Patient Reported Outcomes Research Conference, Leeds 13th June 2019.

Davey, A. Porter, I., Mewse, A.J., Green, C., & Valderas, J.M. Exploring the variation of patient-reported outcome scores across different time-points (day, week, month) for patients with multiple conditions. Oral presentation at the national Advances in Patient Reported Outcomes Research Conference, Leeds 13th June 2019 and the national Society for Academic Primary Care, Exeter 3rd -5th July 2019.

List of abbreviations

Term/abbreviation	Definition
AQLQ	Asthma Quality of Life Questionnaire
CASP	Critical Appraisal Skills Programme
CCM	Chronic Care Model
COPD	Chronic Obstructive Pulmonary Disorder
EMA	Ecological Momentary Assessment
EUHPID	European Community Health Promotion Indicator Development Model
FDA	Food and Drug Administration
GP	General practitioner
HRQoL	Health related quality of life
IAPT	Improving Access to Psychological Treatment
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LTC	Long term condition
MCID	Minimal Clinically Important Difference
MID	Minimal Important Difference
MS	Multiple Sclerosis
NCD	Non-communicable disease
NHS	National Health Service
PCC	Person-centred Care
PHQ	Patient Health Questionnaire
PRO	Patient reported outcome
PROM	Patient reported outcome measurement
PROMIS-10	Patient reported outcome measurement information system 10-question short form
QOF	Quality Outcomes Framework
QOL	Quality of Life
ROC	Receiver-operating characteristic
WHO	World Health Organisation
WHO ICD-11	World Health Organisation International Classification of Diseases
WOMAC	The Western Ontario and McMaster Universities Osteoarthritis Index

Authors declaration

Consistent guidance was provided mainly by the primary supervisor (Prof Jose Valderas) and the secondary supervisors (Prof Colin Green and Dr Avril Mewse) throughout the PhD. Two of the three empirical chapters of this thesis have been written up as manuscripts for publication and one is currently under review. In the thesis, these two chapters have been adapted to reflect and maintain the narrative of the thesis, and as such are not direct translations of the manuscripts used for publication.

Paper 1: Chapter 3

Davey, A., Porter, I., Coombes, J., Green, C., & Valderas, J.M. (Under review). Cyclical variation of patient reported outcome measurement (PROMs) scores in patients with chronic conditions: a scoping review.

The first empirical chapter presented in this thesis (Chapter 3) was submitted in April 2021 and is currently under review in Journal of Patient Reported Outcomes. The candidate formed the research questions, analysed the data and wrote the manuscript. Jose Valderas and Colin Green advised on the overall research questions, assisted with data screening and edited the manuscript. Ian Porter, a researcher in Exeter, and Joe Coombes, a former undergraduate student at Exeter, provided double screening for title/abstracts, full texts and data extraction and made comments on the manuscript.

Paper 2: Chapter 4

Davey, A., Porter, I., Mewse, A.J., Green, C., & Valderas, J.M. (In Preparation). Factors influencing cyclical variation in chronic health conditions: a longitudinal study.

The second empirical chapter presented in this thesis (Chapter 4) is currently being written up for publication and will be submitted for review in BMJOpen. The candidate developed the study design, and all the supporting documents attached to it under the supervision of Jose Valderas and Colin Green. The candidate carried all the data collection and analysis. Ian Porter, a researcher in Exeter, provided support in blind double coding of a sub selection of transcripts. Avril Mewse advised on the analysis of the qualitative data. Jose Valderas, Colin Green and Avril Mewse advised on the overall structure of the analyses.

Chapter 1 Introduction

1.1 Brief overview statement

Traditionally, health outcomes are assessed through objective measurements to examine physiological changes related to an individual's health condition. In recent years, the interest in subjective measurements in health outcomes has increased worldwide. In the UK, healthcare policies are taking a more patient centred approach to the management, measurement and delivery of care and aim to incorporate the patients voice alongside more traditional medical measurements. One approach to this more patient centred approach is the use of patient reported outcome measures (PROMs).

PROMs capture the patient's perception of their own health, which helps researchers and clinicians, as well as patient themselves, understand and monitor the progression of any given condition. Patients are asked to reflect on their experience of their condition and the recall period for each PROM can vary. The process by which an individual assesses their health is a complex interaction between determinants of health, the time of measurement, and the constructs measured by the instrument. There is historical evidence with physiological measurements that chronic conditions exhibit fluctuations in symptoms, and that certain conditions are more severe at different times of the day. The timing of different activities during the day (and week, month and season), can result in differences in how the impact on function is perceived. The way an individual assesses their condition at the time they complete PROMs can also potentially impact on how they report their health status. In summary, PROMs scores may change depending on the time of measurement.

1.2 Thesis aims and objectives

This thesis contributes to the evidence and understanding of the measurement of PROMs and how they are interpreted. The timing and circumstances of measurement of health outcomes should be considered, as chronic conditions exhibit cyclical variation in physiological measurements. The thesis aims to explore the cyclical variation in patient reported outcome measurement scores (PROMs).

The specific objectives are:

(1) To identify, describe and map out research and methods on cyclical variation of PROM scores for patients with chronic conditions;

(2) To develop a conceptual model of the key concepts underlying cyclical variation in PROMs

(3) To explore in depth what factors may contribute to fluctuating PROMs scores in patients with different chronic conditions through their narratives and;

(4) To identify the best statistical approaches for modelling cyclical PROMs variation and to apply it to the exploration of PROMs cyclical variation in a specific chronic condition

1.3 Structure of thesis

Following this short introduction to the thesis, Chapter 2 provides an overview of the following concepts: (a) definition, prevalence and determinants of health, (b) measurement of health outcomes, (c) patient reported outcomes measurements and the models of

health outcomes, and (d) the use of patient reported outcome measurements in chronic conditions.

Chapters 3, 4 and 6 present the empirical work undertaken to address the aims of the thesis. Chapter 3 presents the methods and results from a scoping review of literature, which aimed to identify, describe and map out the core literature on cyclical variation of PROMs in patients with chronic conditions (1st objective). The final output of this chapter is the development of a conceptual model outlining the concepts explaining cyclical variation of patient reported outcome scores (2nd objective). Chapter 4 tests the conceptual model by longitudinally exploring, from the patient's perspective, what factors influence variation in PROMS scores (2nd and 3rd objectives). Using a longitudinal mixed methods design, this study followed patients suffering from a combination of asthma, osteoarthritis and/or depression over a 9-month period interviewing them at three different times following administration of series of generic and disease specific PROMs. The process by which they evaluate and assess their health on PROMs is explored in the interviews accounting for seasonal changes at the three time points (summer, winter, and spring). The researcher's impact on the research process in the longitudinal mixed methods study will also be considered by exploring reflexivity and triangulation methods used to enhance validity and credibility of the findings (3rd objective).

Chapter 5 will explore the statistical methods used in previous research as identified in the scoping review and consider which methodological approaches would be appropriate to extract variation in PROMs scores (4th objective). This chapter will provide a rationale for using a form of spectral analysis called Fourier analysis over traditional statistical methods. Chapter 6 presents the modelling variation in PROMs scores for a specific chronic condition (Meniere's Disease) benefitting from the availability of an

international database (4th objective). This dataset contains repeated observations of tinnitus, hearing loss, dizziness, and aural fullness experience (collected with an ecological momentary assessment design) in a population with Meniere's disease, a chronic inner ear disease experienced by 13.1 per 100,000 persons-years in the UK.

The final chapter, Chapter 7, synthesises the research contributions and compares it with existing literature. Consideration is given to the implications of the main messages from the PhD and future directions of applications and research are suggested.

Chapter 2 Background to Health and Outcome Measurement

2.1 Chapter outline

The aims of this chapter are to contextualise research in support of the thesis; define and summarise the main concerns in this field of research and provide a rationale for the empirical work undertaken. Thus, that will include:

- Defining health and explaining how health measurements inform the management of chronic conditions
- Outlining the biological and environmental evidence impacting on the fluctuations of symptoms in chronic conditions
- Outlining the theoretical and conceptual underpinnings of patient outcomes and outcome measurements
- Exploring the issues of the cognitive processes involved with completing measurements

The literature review will identify gaps in health outcome measurement and the potential implications of this knowledge deficit for clinicians and researchers.

2.2 Definition of Health

In the late 1940s, the World Health Organisation (WHO) defined health as a "state" of complete physical, mental and social well-being (1). This was a shift away from the traditional medical model whereby health was defined as the absence of disease or illness. Rather the WHO definition incorporated the mental and social aspects of an individual as important factors for health (1). The term "well-being" has contributed to the debate over the difference between health and quality of life, which

will be discussed later in this chapter. Equally, the concept of defining health as a "state" has been debated as it has connotations of being permanent (2). Health is also viewed as a "process", adjusting to the demands around the individual (e.g. social and environmental), commonly referred to as determinants of health. Disease, on the other hand, has been defined as a condition that is diagnosed by a health professional and the more you have of illness or disease, the less you have of health (3).

2.2.1 Definition of chronic health conditions

Chronic health and chronic disease have often been used interchangeably in the literature and by different organisations (4), although they do not overlap completely. Diseases are either communicable or non-communicable. Communicable diseases include acute infectious diseases such as tuberculosis or measles whilst noncommunicable diseases (NCD) are chronic diseases or conditions that are caused by genetic, physiological, lifestyle, and environmental factors. According to the WHO NCDs are defined as:

"are not passed from person to person. They are of long duration and generally slow progression. The four main types … are cardiovascular diseases (like heart attacks and stroke), cancers, chronic respiratory diseases (such as chronic obstructed pulmonary disease and asthma) and diabetes" (5).

Chronic conditions on the other hand, is a generic term which incorporates not only chronic diseases but other diagnoses such as hypertension which are not a disease but rather a risk factor for cardiovascular disease (6,7). In UK health policy, chronic conditions are also referred to as long term conditions (LTC). The

Department of Health's definition of a LTC is "one that cannot currently be cured but can be controlled with the use of medication and/or other therapies" (8).

Although there is consensus that chronic conditions are of prolonged duration, the actual duration is not consistent (9). For the purposes of this thesis the term chronic conditions will be used as the term includes risk factors that have established circadian rhythms.

2.3 Determinants of health

There are a number of complex and interrelating factors that determine an individual's current state of health (known as determinants of health) and have a differential impact on a variety of conditions. However, there is a basic understanding that our health is based on our genetics, lifestyle and environment and our health care (10). Several models have been developed in order to describe and incorporate the social, economic, and physical environments which interact with individual factors shaping health status (11). The determinants of health are generally divided into three categories. Three models will be presented and explored in the next sections. The models that have been presented are the most widely used models and have framed research hypotheses around determinants of health (12)

Figure 2.1 describes how these elements (individual, social and environmental) affect health outcomes. Several models are presented in Figure 2.1 explaining what determinants affect health. Dahlgren and Whitehead's rainbow model was introduced in 1991 putting the individual as a central point introducing layers which influenced health. Meikirch's Model of Health emerged a decade later and was very similar to Dahlgren and Whitehead's rainbow model, yet viewed health as a complex adaptive system (13). Health, as presented in Meikirch's model of

health, is a state of wellbeing emerging from interactions between an individual's life demands, and social and environmental determinants, which is similar to Dahlgren and Whitehead's rainbow model of determinants of health (14).

Dahlgren and Whitehead (14), stipulated that in the centre of their model were non-modifiable individual determinants (e.g., age and sex). Within this model, individual determinants are surrounded by influences that are modifiable by policy, care delivery and individual behaviour, such as lifestyle factors, social and community networks, living and working conditions. In addition, the general socioeconomic, cultural and environmental conditions individuals live in also influence individual determinants. Their model highlights the importance of the interactions between each level. It also highlights how an individual's lifestyle is rooted in their social environment (social norms, networks, working/living conditions) and is related to the wider socioeconomic and cultural context.

The European Community Health Promotion Indicator Development Model (EUHPID), on the other hand, distinguishes between only two determinants of health: individual and environmental. This model is builds on the WHO definition of health, showing how health develops through the interaction between individual and environmental determinants (15). Here, environmental determinants of health combines the traditional concepts of social and environmental determinants of health.

2.3.1 Individual determinants of health

Bircher and Kuruvilla (2014) (14) provided a detailed explanation for each of the elements of the Meirkirch's Model of Health. The individual determinants of

health included the demands of life and potential of individuals (which included those that were biologically given to individuals and those that were acquired).

The ‘demands of life’ is further sub-divided into physiological, psychosocial and environmental demands. Physiological demands are input functions (e.g., food and oxygen intake), output (e.g., excretion), and procreation. As individuals, we deal with different conditions to meet physiological demands which vary with time and circumstances.

Psychosocial demands are related to the individual’s social development and their integration into society (e.g. social, economic and political involvement). Society determines how demands are presented to an individual and how these demands are managed. Finally, the health of individuals is affected by environmental factors, such as air quality, weather events, and workplaces. Some aspects of individual determinants of health are similar to that proposed by Bauer and colleagues (15) in their EUHPID model which includes physical (e.g. fitness), mental (e.g. sense of coherence) and the social dimensions (e.g. social support), and Dahlgren-Whiteheads inner layers of the individual and social factors.

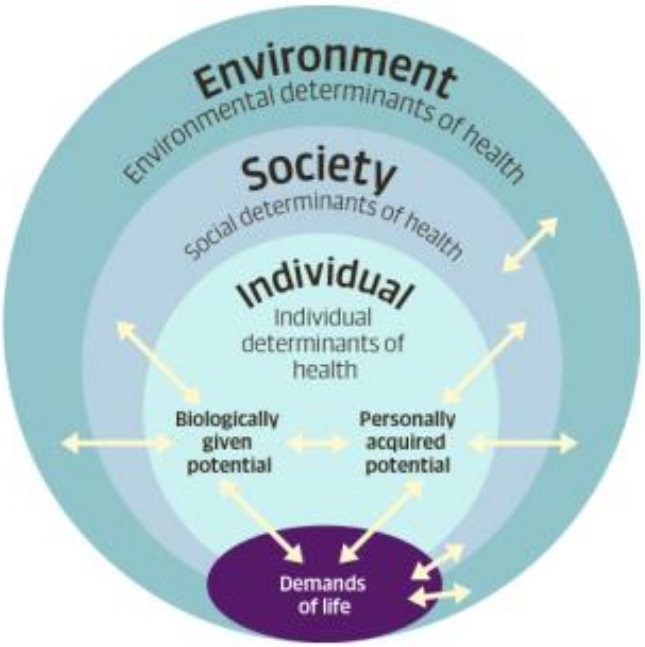
A further aspect of the Meirkirch’s model stipulates that an individual must have two levels of resource (i.e., potential) to meet the demands of life. These are, the biological element (which cannot be changed, e.g., genes) and the personally acquired potential (resources acquired during life, e.g., physiological, mental and social).

There is an interaction between the two, such that if an individual is deficient in one aspect (e.g. physical disability), they will compensate in another (e.g. become independent through their resources) in order to survive. However, these aspects of

individual determinants of health are influenced by, and affect, social and environmental determinants of health.

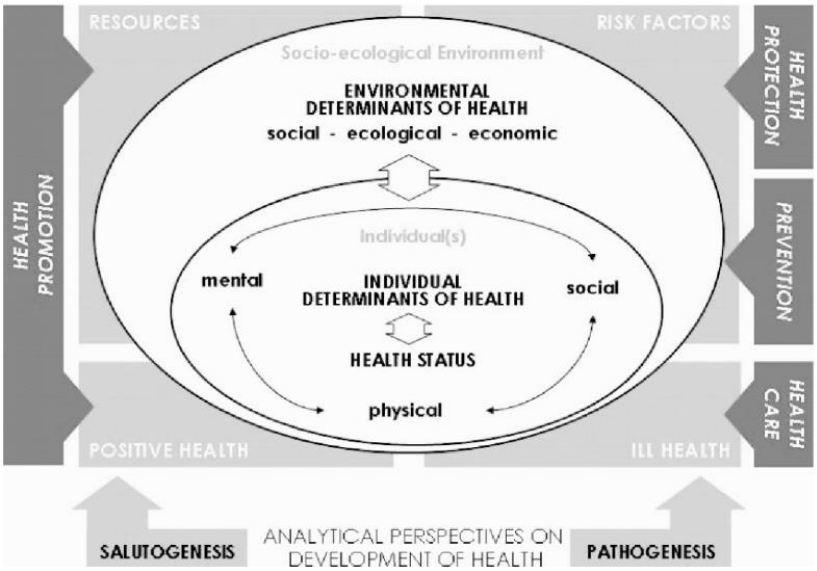
Figure 2.1 Models of determinants of health

Meikirch



Dahlgren-Whitehead

EUHPID



2.3.2 Social determinants of health

Social determinants of health broadly refer to the economic and social conditions which shape the health of an individual. The WHO has identified ten social determinants of health, which cover some of the aspects covered in both Meirkirch's and Dahlgren-Whitehead's models. These include social gradient, stress, early life, social exclusion, work, unemployment, social support, addiction, food, and transport. Additionally, the resources made available by society to its citizens, such as housing and employment, are also considered social determinants.

The social conditions people live in are known to shape their health, with individuals in lower socioeconomic group showing a greater likelihood to develop chronic illnesses. Interestingly, the EUHPID model classifies social networks as an environmental determinant of health rather than a social one. Research into social determinants of health, particularly health inequalities has been well studied and continues to be a global issue that health policies attempt to address.

2.3.3 Environmental determinants of health

The environment can directly affect our health, whether that be our living or working environment. Environmental determinants of health include not only aspects of the natural environment (e.g. air pollution, climate change), but also the conditions in which we live and work (urban versus rural). Living and working environments can directly affect health, while early exposure to indoor and outdoor pollutants may have a lasting effect on the morbidity of individuals (14).

The EUHPID model subcategorises the environmental determinants of health to include social (e.g. social networks and cultural diversity), ecological (e.g. workplace) and economic (e.g. income distribution) dimensions. There is evidence

linking income inequality to increased prevalence of health problems (16). Social deprivation impacts health, with social circumstances magnifying the stressors. Poor urban environments impacts health via higher concentrations of pollutants, and less access to nutritional food.

Research into the relationship between social and environmental determinants demonstrates a close association between certain conditions, such as asthma. Greater wealth inequality and lower socio-economic status, are important determinants of asthma amongst urban Latin American youth (17).

2.4 Management of chronic health conditions in the UK

Average life expectancy is continuing to rise worldwide, along with the number of individuals living with one or more chronic conditions. The UK, for example, has an increasing ageing population, with the median age rising 6.1 years from 1974 to 2014, and this is projected to rise even more in the next 20 years (18). As it is globally, the number of individuals living with chronic conditions in the UK is also rising and will continue to rise, with over 15 million people currently living with at least one chronic condition (19,20).

In England, the number of individuals living with more than one chronic condition is forecast to have increased from 1.9 million in 2008 to 2.9 million by 2018 (21). The quality and outcomes framework (QOF) listed the 5 most prevalent chronic conditions in primary care in England. These are asthma, depression, obesity, hypertension and diabetes (22). The QOF is an annual reward and incentive programme for all GP practices in England, whereby GP practices provide information regarding their patient population (23,24). The QOF has four

components or domains: clinical, public health, public health – additional services and quality improvement.

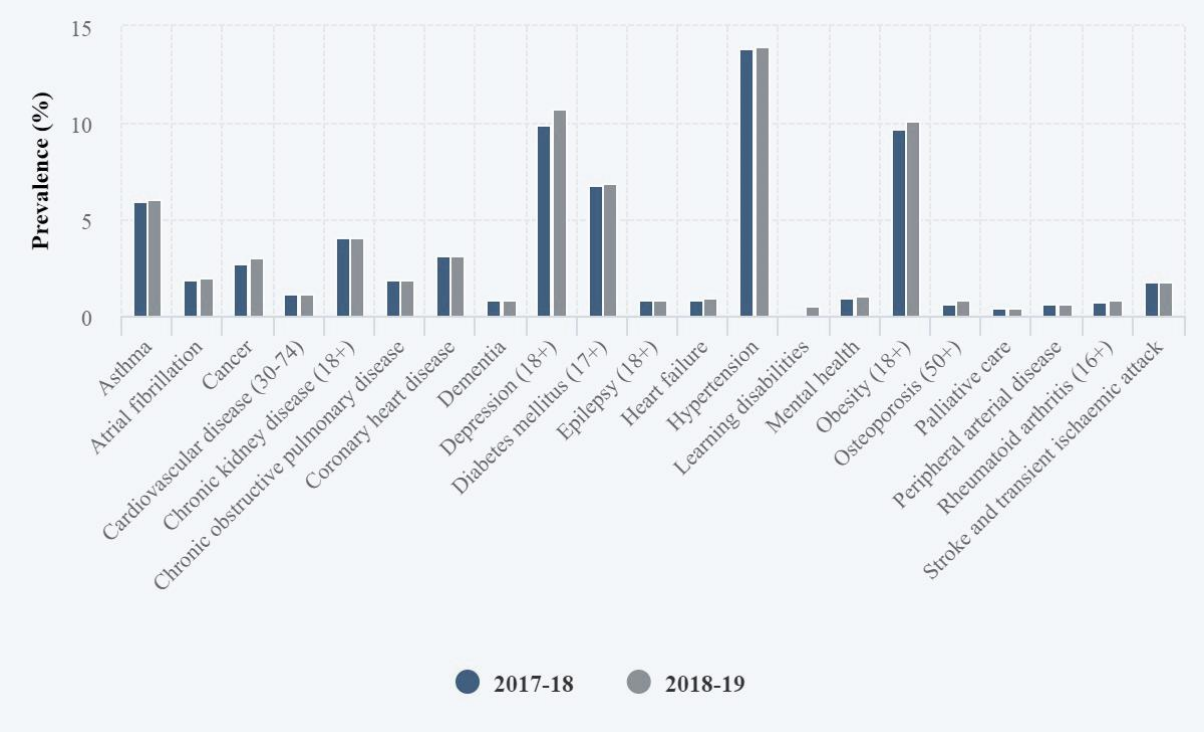
Each domain has a set of indicators whereby practices are able to score points according to their level of achievement. The aim of the QOF is to incentivise practices to deliver high quality care across a range of areas. In addition to these indicators, payments are adjusted to account for practice workload, their patient demographics and the prevalence of chronic conditions in the practice's local area (23).

Depression, as seen in Figure 2.2, is one of the top three most prevalent conditions in English primary care services and has been rising steadily over the past 5 years from just under 6% in 2012/3 to 10.7% in 2018/19 (22,25). The majority of chronic health conditions are managed through primary care services, although more specialised care for certain conditions is managed by secondary care services (26).

Increasing life expectancy has posed new challenges for health care services including delivering good quality of care to more patients with limited resources. The Chronic Care Model (CCM) (27) is geared to assisting clinicians in offering chronic disease care (28,29). The two overarching components of the model are (i) community resources and policies, and (ii) the health system. The health system includes the organisation of healthcare, system delivery, self-management and clinical information. These factors feed into productive interactions between an informed and active patient, and prepared, proactive clinical teams. Productive interactions should improve functional and clinical outcomes for disease management, which will be discussed in more detail later in this chapter.

Historically, health measurements within the NHS has been underdeveloped, with primary focus being on the prevalence of adverse outcomes (30). Clinicians have used measures to help guide and inform their practices and assess the impact of interventions administered to their patients. However, this methodology, does not provide an overall picture of the services provided to patients. Due to the variety of clinical measurements used, it is difficult to compare health impacts across different clinical specialities. As mentioned previously, clinicians and researchers rely on both subjective and objective measurements of health outcomes especially when monitoring the progression of a chronic health condition. The challenge faced by both clinicians and patients is that chronic conditions are not always stable. Symptoms may flare-up, and will affect the patient's ability to do daily tasks. This directly impacts on overall wellbeing, and general health.

Figure 2.2 QOF recorded prevalence, England 2017-18 to 2018-19



2.5 Cyclical variation of symptoms in chronic conditions

Rhythmic fluctuations of symptoms (also known as chronobiology) at different time-points have been previously reported for patients with chronic conditions. For example, there is evidence to suggest that circadian rhythms can affect the levels of pain experienced by patients with rheumatoid arthritis (31). Thus the results of diagnostic tests and impact of interventions are affected by circadian rhythms (32).

Biological rhythms in humans have varying patterns, or cycles, that continually repeat over time, such as daily and annual rhythm of activity. In human beings rhythms can be divided into three cycles: ultradian (cycles lasting less than 24 hours), circadian (cycles lasting around 24 hours) and infradian (cycles lasting more than 24 hours) (33). Within a 24-hour period there is a diurnal rhythm which is closely linked to the day/night pattern. These rhythms are governed by the external environment: day/night (light/dark), seasonal changes, the earth's rotation affecting the tidal rhythms, and changes in atmospheric pressure.

Circadian rhythmicity applies to many physiological and metabolic processes within different health conditions (34–36). Research has tended to focus on patients' responses to diagnostic tests and interventions (32). Research into cardiovascular disease, for example, and the circadian rhythm of blood pressure during the day has shown that a morning surge of blood pressure is linked to increased cardiovascular complications (37,38). Seasonal changes also have an impact on symptom severity in a number of conditions such as COPD and arthritis (39,40). Good mood may deteriorate as the day progresses and seasonal changes in baseline positivity vary with a change in daylight (41).

Cyclical variation of symptoms has also been associated with quality of life and health status. Patients with bipolar disorder experiencing a disruption in their biological rhythm have reported a decreased quality of life (42). Meanwhile circadian rhythms have been shown to be a predictor of functional impairment and severity of depression in patients with bipolar disorder (43). Poorer health status has also been attributed to night-time and early morning symptoms experienced by chronic obstructive pulmonary disease sufferers (44). Although this link between health status and circadian rhythms in chronic conditions exists, there has been a lack of focus examining how patient outcomes may be affected by these fluctuations. Exploring the impact of chronic conditions instability is important, as this variable is increasingly being used in healthcare decision making.

The way physiological changes in the body have been measured has changed over the years, with clinicians using multiple measurements to determine the status of a health condition. These measurements have shown that physiological and biochemical variables show daily rhythms which are synchronised with the human sleep-wake cycle, and which fall into two categories. The first type of rhythm peaks during the daytime and is associated with factors that affect individual activity (e.g. temperature, mental, physical and gastrointestinal activities, blood pressure and heart rate). The second rhythm shows a peak during nocturnal sleep (e.g. cortisol, melatonin). These internal mechanisms, some of which are unaffected by exogenous factors, have more recently been classified as the “body clock”, through various animal and plant studies (33).

2.6 Healthcare and measurement of outcomes

The past two decades in health care have seen a shift from relying solely on clinical and laboratory indicators of illness to incorporating the patient's point of view and voice. In 2011, with the publication of the white paper "Equity and Excellence: Liberating the NHS", there was recognition that patient's perceptions of their health and experiences of healthcare were key to providing excellent patient-centred care (45). Patient-centred care (PCC) has been at the forefront of the NHS and refers to the organisation and provision of care around the patient's needs, perspectives, experiences and preferences (46). The system is broadly based on the needs and preferences of the patient, which should be the central focus of services. However, the concept of PCC continues to evolve and change and there is no one definition that is used universally, although quality of care tends to be the main element being delivered to patients. PCC can mean different things to patients, clinicians, organisations and policy makers. In order to take patient's experiences into account, policy makers need to consider how to assess the quality of care being delivered. This means paying attention to the measurement of patient and health outcomes.

Outcomes research can be traced back to the mid-19th century and the outcomes associated with Nightingale' research on death during the Crimean War (47). The first and second world war saw further improvements in health care and the eventual creation of the National Health Service, which facilitated the organisation and centralisation of the delivery of care. However, it was not until the publication of Donabedian's paper on the framework for quality of assessment that the term outcomes was properly used (48).

Quality of care, as mentioned previously, can be defined in many ways, although one central focus of many definitions is patient outcomes. In terms of health, Porter (2010) defined outcomes as "the results of care in terms of patients'

health over time" (49). Outcomes are the end result of what has happened with the individual and focus on the individual's wellbeing can be both subjective (from the patient's perspective) or objective (assessed by the clinician) measurements. Patient outcomes are used to assess the quality of care delivered to patients and are measured at different time points during healthcare delivery. The field of clinical outcome assessment has grown since the 1980s, due to factors including the need for cost effective interventions and increased competition between health care providers to deliver the best quality of care (50).

The NHS White Paper (8), continuously states its aim to improve health outcomes without clearly defining what health outcomes are. The authors focus on the NHS outcomes framework which spans three domains of quality: the effectiveness of treatment and care provided to patients; the safety of the treatment and care provided to patients; and the broader experience patients have of the treatment and care they receive.

Health care is designed to restore or preserve patient's functioning and wellbeing related to health, which is health related quality of life. The challenge for assessing functioning or wellbeing using patient outcomes in clinical settings is that they can be modified by psychological phenomena such as health expectations (51). Thus, the way people assess their health-related quality of life can change over time which could be closely related to their way of processing living with a condition. This is known as response shift theory, which will be discussed in the subsequent sections (section 2.10.2) within the discussion of patient reported outcomes.

2.7 Models of health care and quality assessment

Donabedian's model of health care was published in the late 1960s and provided health care practitioners and researchers with a framework for performance management and improvement in health care (52). He proposed a unidirectional triad of structure, process, and outcome constructs to best evaluate quality of health care. A good structure should promote good process and eventually good outcomes for patients. Structure can be defined as the environment in which care is being delivered, the workforce delivering that care, policies within the organisation guiding and managing the care and the provision of equipment or medication used to deliver care. This should consider the social and environmental determinants of health as the interaction patients have with the clinician and clinical environment can impact on their experience of their condition. Process refers to the components of care delivered to the patients which include the technical aspect (diagnosis, interventions, medication) and the interpersonal aspect (doctor-patient interaction). The outcome is dependent on how good the structure and process is and whether the patient has the desired result of care provided by practitioners (such as patient satisfaction). Outcomes can be distinguished two ways: technical (physical and functional aspects of care), and interpersonal (patient satisfaction and patient's perception of the impact on their quality of life). Within this concept Lohr's (53) 5D's of healthcare outcomes can be considered: death, disease, disability, dissatisfaction and discomfort.

Although disease is typically measured and defined through physiologic variables, such as blood pressure (hypertension), blood glucose levels (diabetes), and forced vital capacity or forced expiratory volume (for asthma or chronic obstructive pulmonary disease), patient's experience of their condition and account of the severity of their symptoms is important, thus the measurement of disease can be seen as both subjective and objective.

2.8 Patient-reported outcomes (PROs)

The shift in the late 20th century from the traditional medical model which defined health purely as the absence of disease or illness, to a more biopsychosocial model of health incorporating the physiological, psychological and social factors in health and illness has provided some impetus to measuring health outcomes in patients. As previously discussed, health care providers use a range of clinical measurements to diagnose, monitor and inform treatment plans for patients, however these only provide half the picture of what is happening around the patient's health. Patient-reported outcomes (PROs) covers a wide range of measurable outcomes of care from the patient's perspective including symptoms, quality of life, functional status and general health perceptions (54). PROs are important to collate as they provide key information to support and enhance PCC. The collection of PRO data enhances the management of care for patients by enabling providers to better understand the impact of not only the treatment to the patient but also the impact of the condition on patient's daily lives. PRO data can assist in the discussion between the patient and health care provider, potentially improve engagement and adherence with treatment plans and improve overall outcomes. The use of patient outcomes in clinical trials has increased over the years and are used alongside physiological measurements to assess the effectiveness of treatments.

*Valderas and Alonso developed a classification system of PRO instruments (*Figure 2.3 Valderas and Alonso classification system (57)

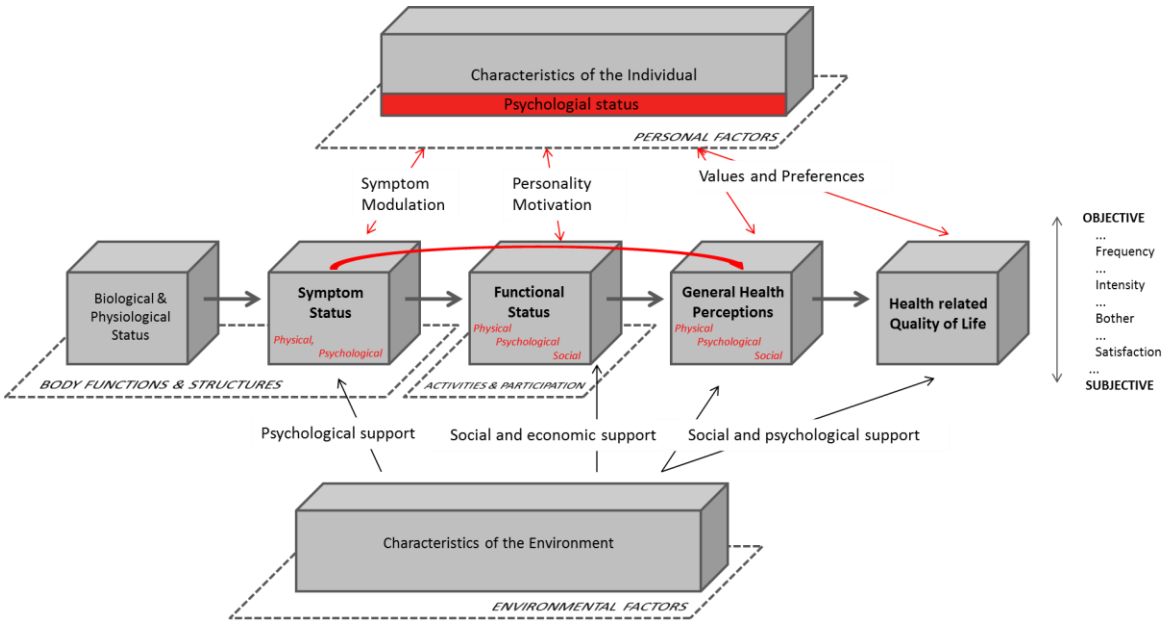


Figure 2.4) which was based on Wilson and Cleary's conceptual model of health outcomes (Figure 2.5), and the WHO international classification of functioning model (Figure 2.5) (55,56). The aim of the model was to understand the causal relationships between these factors and evaluate their contributions to the health condition examining both the biomedical paradigm (biological, physiological and clinical outcomes) and the social science paradigm (functioning and overall well-being). Through this model, it is hypothesised that physiological variables experienced in any condition influences an individual's symptom status, which then influences functional status, and functional status influences general health perceptions and finally general health perceptions influences overall quality of life. Physiological variables in this model includes the cells, organs and organ systems. This generic model has been applied to different patient population groups and has been used by health care providers to tailor the service to the particular patient population.

Figure 2.3 Valderas and Alonso classification system (57)

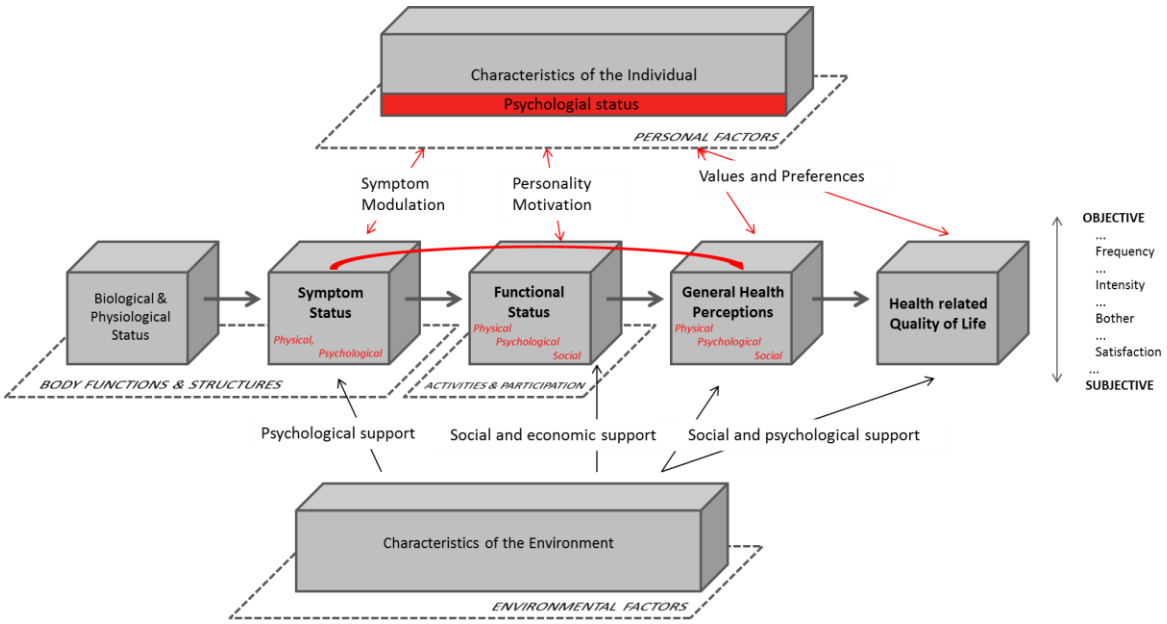


Figure 2.4 Wilson and Cleary Model for Health-Related Quality of Life (55)

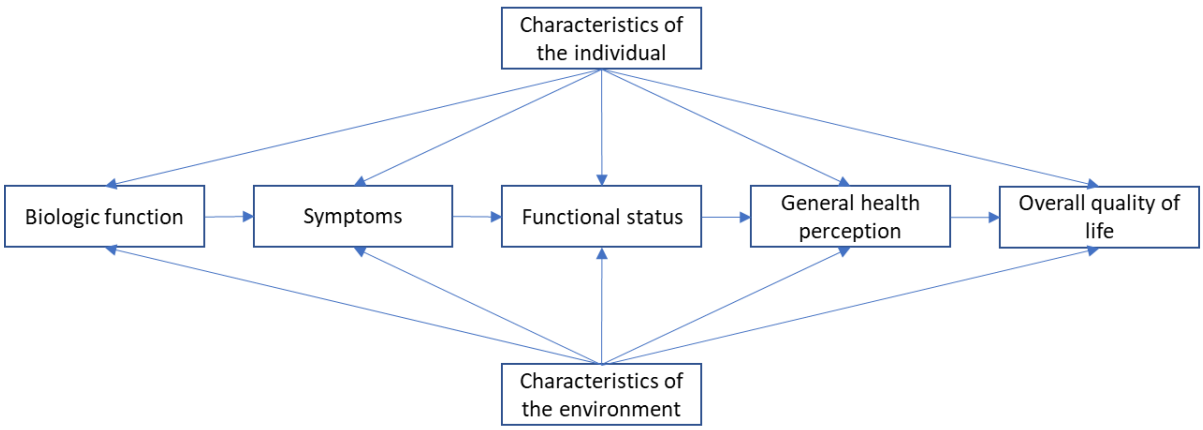
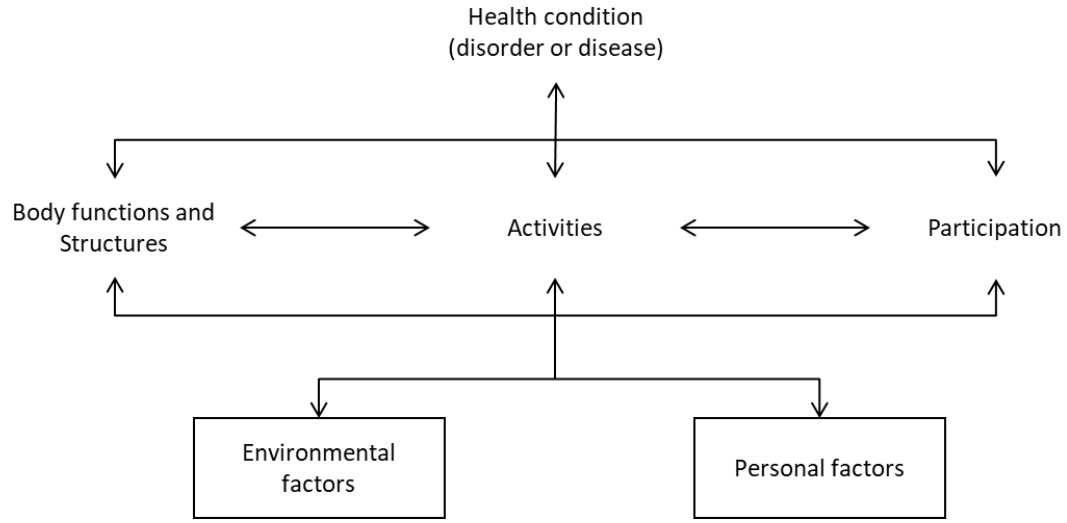


Figure 2.5 WHO International Classification of Functioning model (58)



Quality of life is a broad outcome which incorporates human experiences related to one's overall well-being and can be influenced by non-health factors such as financial status or environment (59). It was first introduced in the medical literature in the 1960s and the first QOL measure recognised in 1981 being Spitzer's QL-Index (60), despite first surfacing in the 1920s. WHO's terminology used in their definition of health in 1974 significantly contributed to discussion around the differences between quality of life and health. At the same time, the term "health-related quality of life" (HRQoL) first appeared in the medical literature with Torrance (61) first defining HRQoL as a subset of QOL relating only to the health domain. A more specific definition of health-related quality of life that is useful is "the value assigned to duration of life as modified by the impairments, functional states, perceptions, and social opportunities that are influenced by disease, injury, treatment, or policy" (62).

2.9 Patient-reported outcome measurements (PROMs)

Patient-reported outcome measurements (PROMs) are the questionnaires or instruments completed by patients to measure these outcomes (63). Patients are asked to rate their health, using either generic or disease-specific PROMs, by responding to a series of questions or items relating to symptoms, function or quality of life (63,64). PROMs attempt to measure constructs which are attributes of the individual that researchers are aiming to capture, such as pain or physical function.

The scores and any changes in scores generated from these questionnaires can then, for example , be used to assess the effectiveness of interventions, such as surgery or a pharmaceutical intervention (65,66). The majority of PROMs rely on the patient's ability to recall their health status over different periods of time. However, these scores may be influenced by recall bias (discussed in section 2.9.4), response shift (discussed in section 2.9.3) or a lack of established validity of the PROM (65).

There are thousands of PROMs available with three main types to choose from: generic, disease/condition specific, and individualised. Generic PROMs aim to measure patients' general perceptions of health and can be used within and between different patient populations, regardless of age, gender or condition (63). There are various generic PROMs available to use such as Short Form 36 (SF-36) (67), patient-reported outcomes measurement information system (PROMIS) and WHO quality of life questionnaires (WHOQOL-100 and WHOQOL-BREF) (68,69). SF-36 assesses both the physical functioning and psychological well-being of individuals, as well as evaluating overall health (70). PROMIS was designed in the United States by the National Institutes of Health to develop, validate and standardise a series of item banks that would measure key PROs such as symptoms, functioning and HRQoL (71). So far more effort, however, has been devoted to developing PROMs for specific diseases or conditions rather than generic measures (72), ranging from

common conditions such as diabetes (73), to less frequent ones, such as haemophilia (74).

2.9.1 **Measurement properties of PROMs**

The premise of PROMs is that they are used to ask questions from patients regarding constructs that cannot be obtained from other measurements, such as blood pressure readings or blood tests (63,75). As per the guidelines stipulated by the Food and Drug Administration (FDA) and International Society for Pharmaeconomics and Outcomes Research (ISPOR), most PROMs have to undergo a validation process whereby the meaning of the questions within the PROM are tested and clarified with patients (76).

There are key features that need to be considered when assessing how good a PROM is, such as reliability, validity responsiveness, and interpretability as highlighted by the COSMIN checklist (77). Individual PROMs vary with content, as they are developed to focus on either particular health conditions or aspects of health status. However, most of the instruments cover domains listed in Table 2.1 which cover the various dimensions of health (78). These aspects relate to the different determinants of health discussed earlier in this chapter, as well as Valderas and Alonso classification system. In order for clinicians and researchers to be confident that the PROMs they use to measure and, in some cases, diagnose health conditions are accurate there are certain concepts to consider, such as reliability and validity. As PROMs are used to measure change in health status with respect to an intervention the minimal important difference and the concept of response shift need to explored.

2.9.2 **Minimal important difference and minimal clinically important difference**

Patient reported outcomes are often used as primary outcomes for clinical trials evaluating new interventions or processes to investigate the effectiveness on different health conditions (30,63,65). As individuals experience changes in health or adapt to illness, their perspective and standards of well-being often fluctuate over time. Despite the validity and reliability of measures commonly used in trials, there remains an issue with the interpretability of changes in the results of PROMs in comparison to physiological measures used in clinical settings. In order to have PROMs as primary outcomes in the clinical setting, the extent to which changes in scores on the PROM reflect changes in health status that the patients would consider important is needed (30). It is recognised that there are internal and external factors that affect an individual's perception of their health, and any changes that are measured with PROMs may disappear in the noise of variability (79). This has implications on the way change in PROMs scores are analysed.

Given that health outcomes in medicine are measured through what is felt and communicated by the patient, the patient defines the difference (79). This has led to the development of the concept of minimal clinically important difference (MCID)(80). However, defining meaningful change in outcome measurements remains a challenge for researchers and clinicians for patients with any health conditions. This is due to the lack of clear guidance or clinical understanding to properly interpret what a 1-point change means on a pain or fatigue scale for example. Although creating benchmarking for outcome standardising cut-off values for quality of life scores can be difficult because of the intraindividual variation of scores.

A patient suffering from a health condition who has experienced any change in relation to how they are able to do daily tasks will regard that as meaningful change and will place great importance to that. This is considered minimal important difference (MID) as it is patient centred. MCID is used to interpret the clinical relevance of any changes in outcome measurement scores, and this may be set higher than MID. However, there has been issues around setting MID and MCID values for PROMs, with MID values differing by population or context and estimation approaches have been shown to produce highly different MIDs making triangulation difficult. In a review conducted on MIDs for fatigue PROMs, it showed that there was substantial variation in MID values for individual fatigue PROMs (81).

There are various ways of estimating MID and MCID which will either focus on comparing the individual level scores with a population level (anchor-based methods) or comparisons of certain statistical tests such as standard error of measurement, standard deviation or effect sizes (distribution method). Change criteria are often developed primarily for patient groups rather than individual patients, thus can overlook what a patient will consider a meaningful change, so although a patient sees the change as a big improvement, according to already set out criteria this is not considered meaningful. Although the criteria may be considered statistically powerful at a group level this may not be the case for an individual patient.

Anchor based methods determines individual change and is more patient-centred. It takes advantage of additional external information (anchor) taken from the patient (their perceived changes in well-being or health status) or from the clinical context (physiological measure or clinician rating) and compares this with differences on an outcome measurement from baseline (e.g. EuroQol-5 Dimension - EQ-5D, a

standardised measure of health-related quality of life) which allows us to estimate a minimal important change. The anchor which is used assigns meaning to the magnitude of change on a PROM. Historically, researchers have used the mean change of score to calculate the MID for patients, but more recently MID is being assessed using receiver-operating characteristic (ROC) curve analysis. The ROC curve approach identifies cut-off points between no change, small improvement, moderate improvement and large change depending on how they are plotted on the graph. However, there are currently no accepted standards of appraising the credibility of MID determination, which makes it difficult to confidently assume how effective an intervention is for an individual or patient group.

Distribution based methods, on the other hand, rely on the distribution of PROMs scores around the mean score to quantify the magnitude of change instead of the statistical or clinical significance of that change. However, these methods are more related to how precise the scale is rather than connecting the scores back to the patient's perspective.

Although both methods are reliable ways of measuring meaningful change, they do not consider the influence of timing. The anchor-based methods take into account patient accounts and the clinician context, however they do not take into account potential variation of scores that are determined by the timing of the assessments. The distribution method solely relies on the distribution of outcome scores around the mean score, but again this does not take into account when these measurements took place.

Intra-individual variability due to timing is not considered in the field of meaningful change unless repeated measurements are taken on a regular basis. In

a study conducted with MS patients, results showed that using both four and six point MCID cut-off points, individual MS walking scale (MSWS-12) scores were impacted by seasonal fluctuating factors including fatigue and mood which are most prevalent in patients with MS. However, when examining group differences, there were no changes in group scores of mean changes over time (82). In addition, another study examining minimal important change in Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores showed their values being extremely variable making it difficult to suggest a specific MIC value for the WOMAC for any patient population subgroup (83). Further discussion of the WOMAC instrument will be covered in Chapter 5. Upon examination into the reasoning behind the large variation of values, the authors briefly considered the potential issue of recall bias or response shift, concepts that will be discussed in the following sections.

2.9.3 **Response shift (RS)**

When interpreting any changes in PROMs scores response shift should be considered. Response shift is about changes in PROMs scores related to an individual's internal processes for dealing with living with their condition. Sprangers and Schwartz (84) built on the idea of longitudinal change in management science research and developed a theoretical model where RS was described as a response to a catalyst, such as a diagnosis, treatment or intervention. Since then, there have been advancements in the theoretical and methodological field regarding RS in terms of our understanding of adaption and appraisal processes used by individuals when interpreting and responding to items on a PROM. A common consequence of RS is that patients either over-estimate or under-estimate longitudinal change in PRO scores (further discussed in consideration to recall bias in the subsequent section) (85,86).

Patients may re-evaluate their situation through recalibration, reprioritisation or reconceptualisation. Response shift theory (RST) proposes that over time the meaning of self-reported constructs can change because of recalibration, reprioritisation, and reconceptualisation (87,88). Recalibration refers to the concept that the interpretation of one state has a different meaning for the same person on one occasion compared with other occasions due to new experiences (85). Reprioritisation occurs when patients prioritise subjective values (such as physical, social and psychological aspects of HRQoL) differently after certain experiences. Finally, reconceptualisation is when patients redefine a construct within the PROM and attach a different meaning to it.

2.9.4 **Recall bias and cognitive theory**

Recall bias is a concern for PROMs, considering that they rely on retrospective accounts from patients on their health status (85). Drawing on cognitive theory, Means et al (89) proposed that for individuals with chronic conditions which result in recurring events, people have a “generic” memory for a group of events and medical contacts and therefore have difficulty recalling specific instances. Autobiographical memory organises events in a hierarchal manner with extended periods (such as “during my employment with X), summarised events reflecting on repeated behaviours (“I coughed a lot of the time”) and specific events at the bottom (90). Thus, asking patients to recall how they felt over the past month does not match with the way these behaviours are stored in memory. In terms of chronic conditions, recall is even more problematic as symptoms fluctuate over time (91). Asking patients to recall their average level of fatigue, for example, over the past day or week will be heavily influenced by the most salient episode (worst level of fatigue) and the fatigue experienced just prior to completing the questionnaire (91–94).

The intensity of our experiences is rarely constant and the severity changes over time (95). Short term experiences, such as medical interventions, will have some intense moments and some that are not so intense, however once that experience is over we form an overall evaluation of it, capturing the remembered intensity of the experience as a whole. Cognitive science considers that much of what we recall is reconstruction, heuristic strategies used to piece together fragmented inputs of information. Experiences are encoded and retrieved if they are emotionally salient or unique whereas any routine experiences are less likely to be imprinted and are harder to access.

Many health questionnaires ask patients not only to recall information but also to aggregate and summarise their experiences. The majority of PROMs have been validated for a recall of health status over the recent past (up to 4 weeks). When patients complete these questionnaires, they use a variety of cognitive heuristics and processes of retrieval which accounts for much of the bias in recall data. Our recollections of past information are not just inaccurate, they are systematically biased and change in systematic ways which can often distort recall even for short time intervals. An individual's symptoms vary over time and situational antecedents can influence their behaviour. It has been argued that consideration should be made to how individuals recall their health and assess the quality of health care they receive (85). However, further consideration should be made as to the time in which patients are completing the assessments as this impacts on their interpretation of their health.

Recalled pain ratings suffer from recall bias and inaccuracies (96). Memory retrieval is also subject to bias by the individual's context and mental state at the time of recall. For example, individuals are more likely to retrieve negatively valenced

information when they are in a negative mood(97,98). Equally, patients experiencing pain will find it easier to recall past pain and harder to remember pain-free states, and can overestimate their past pain as well (93,99), and underestimate their pain when it is stable (100). Research in surgical settings has shown that recall did not accurately represent the average pain experienced over the interval as it was based on the most memorable moments (99,101). Thus, an individual's state and situation at the time of reporting/answering a questionnaire will influence what and how it is reported.

There is a body of literature demonstrating a relationship between current mood and mood-congruent memory bias (92,102,103). The levels of pain or anxiety experienced by chronic pain sufferers, for example, is typically quite high and changes in present pain have a greater influence on pain memory than absolute values of their current pain (92,104). A study conducted by Bryant (1993) with chronic pain sufferers confirmed that patients' memory for pain was susceptible to distortion in recall which was associated with their present levels of pain and their mood (92). Any changes in pain influenced their memory of their pain, a reported increase in pain during the study made them overestimate the strength and severity of pain at the start of the study. This highlights the importance of subjective changes in experience rather than absolute levels of pain. Chronic pain patients experience high levels of depression and salient changes in mood may influence recall of earlier levels of depression (104).

The Accessibility Model of Emotional Self-Report by (105) proposes that there are different levels of remembering experiences or events based on the principles of accessibility and it makes the distinction between momentary emotions, short-term retrospective reports and longer periods. Judgements for each timeframe is

influenced by different sources of knowledge, with short-term judgements being influenced by more episodic forms of memory biases or episodic knowledge (e.g. salient experiences, current affective state), and longer-term retrospective reports influenced by semantic forms of knowledge (e.g. beliefs, theories of self) (106).

Research has shown that sleep quality and tiredness, amongst other variables, have influenced positive affect experienced during the day (106,107), with disrupted sleep leading to low positive affect amplifying negative emotions experienced (108,109). Mill and colleagues (106) found that feelings of tiredness at the end of a day enhances the negative emotions of fear, anger, and sadness experienced, and influences retrospective ratings of emotion across two weeks. Their conclusions were that daily tiredness and personality traits systematically influence the way an individual interprets past feelings.

Another view of how patients evaluate their health is the implicit theory of change which assumes that individuals are unable to remember their previous state. Instead their judgment is based on focusing on their present state and working backwards looking for changes, improvements, deteriorations or stability of status (110). Instead of being based on an analysis of health at specific timepoints it is based on an impression of the time course. The retrospective judgement, then, of the initial state is viewed as biased. This has considerable implications on how patients' views are assessed when it comes to outcome measurements.

2.10 PROMs in clinical practice

The use of PROMs has seen a steady rise worldwide in both a research and clinical setting (72), particularly in the past decade where PROMs have been used to audit healthcare systems, assess the quality of care being delivered to patients and

manage the performance of providers and clinicians (111,112). In the UK, for instance, the performance of the health and care system at a national level explicitly includes the use of PROMs as part of the NHS Outcomes Framework (113). The NHS Outcomes Framework sets out national indicators for measuring health outcomes across the NHS services, and have a specific domain focusing on the enhancement of the quality of life for people with long term conditions measured by PROMs. Since 2009, the routine collection of PROMs data for patients having hip, knee, hernia or varicose vein elective surgery was implemented (30), with an extension to six long term conditions (including asthma, COPD, diabetes, epilepsy, heart failure and stroke) in 2010 .

Routine use of PROMs in daily clinical practice can also have potential benefits for patient management, including facilitating patient–clinician communication about issues that are important to patients, facilitating communication between health professionals around symptoms and quality of life (114,115), promoting shared decision making, and monitoring progression of a patient's illness and response to a treatment plan (116–119). PROMS have been used by primary and secondary care clinicians to screen and monitor their patient's condition, such as depression symptoms or pain severity in arthritis, in promoting patient-centred care, and assessing the patient's perspective (120). It has been suggested that PROMs increases the responsibility of clinicians, as they might detect problems that could otherwise go unnoticed (121).

How clinicians and researchers interpret PROMs scores needs to be considered due to the issues raised within the various sections in this chapter. As the use and importance of PROMs within clinical care increases, the interpretation of scores can have a potential impact on the management of chronic conditions. This

includes what course of action a clinician may decide to take depending on outcome scores. The timing of these subjective measurements are taken and what impacts on how patients assess their condition at the time of measurement becomes essential factors to consider. The following chapter considers the association between time of measurement and PROMs by exploring the literature through a scoping review.

2.11 Summary of chapter

Variation that occurs due to biological rhythms has potential implications on how patients report on their health using PROMs, and ultimately the scores that are produced. Although a change in scores could be explained through response shift theory, this theory does not consider the effect of biological rhythms on how patients evaluate their own health. There is a lack of evidence to understand the concepts to explain cyclical variation in PROMs scores when considering the instability of chronic conditions. The following chapter aims to map out the key concepts explaining cyclical variation in PROMs scores in chronic health conditions.

Chapter 3 Cyclical variation of PROMs in patients with chronic conditions: a scoping review

3.1 Chapter outline

The previous chapter provided a background to the literature on health, chronic conditions, PRO and PROMs and biological rhythms. From that chapter it was clear that cyclical variation in relation to specific periods (e.g., circadian, seasonal) of physiological phenomena has been observed for chronic conditions. The increased use of patient reported outcome measurements (PROMs) in clinical settings makes it necessary to study whether cyclical variation would impact on outcome scores used for clinical management of people with chronic conditions. However, there is a lack of literature considering cyclical variation of PROMs scores. The purpose of this chapter is to map out the key concepts on cyclical variation of PROMs in chronic health conditions, in order to clarify key definitions and conceptual boundaries, developing a conceptual framework and identifying research needs. This will help inform subsequent chapters in how time is handled in statistical models and identify gaps in research which would support the conceptual framework.

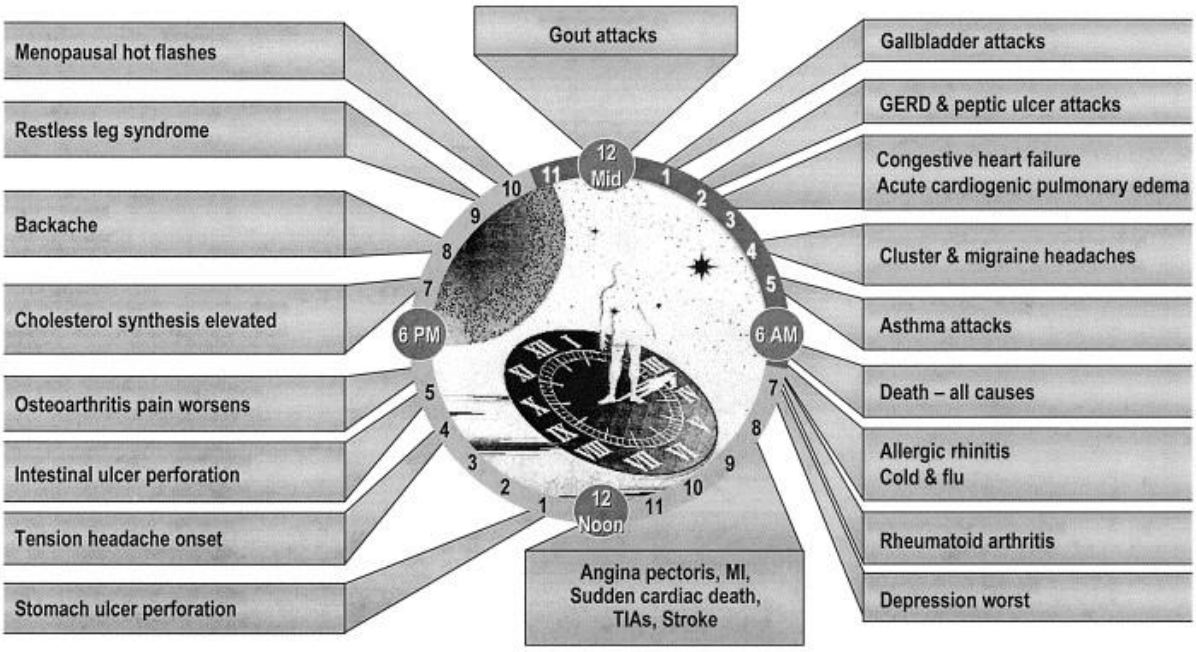
3.2 Background

3.2.1 Cyclical variation of conditions

Health conditions are rarely stable, and patients experience variation in their health outcomes over time. Cyclical variation of physiological and clinical variables has been observed in relation to biological rhythms of different periods, including both circadian (24-hour period) and longer infradian periods (e.g., circaseptan (week), circamensual (month), circannual (year)). Physiological cyclical variation has long been established for bodily temperature, blood pressure, fertility, weight, mood

and sleep (33,122). Diseases demonstrate cyclical variation in relation to physiological changes that occur, as shown in Figure 3.1, with risks increased for mortality at different hours of a 24-hour period for certain conditions (123). The risk of a cardiac event (e.g. myocardial infarction, ST-segment depression), for example, is much greater in the earlier hours of the morning due to the surge of blood pressure at waking (123). On the other hand, peak expiratory flow and forced expiratory volume is greater during the daytime and poorest at night for asthmatics, and cortisol exhibits high-amplitude circadian rhythmicity highlighting the importance of when blood samples should be tested (123).

Figure 3.1 Peak hours for disease severity and risk of morbid/mortal events in 24-hours



Smolensky and Haus (2001) – permission to use figure obtained from lead author and journal

3.2.2 **Implications of cyclical variation of health conditions on PRO scores**

Cyclical variation can be anticipated to impact on how patients reflect on their health when completing patient reported outcomes. Patient reported outcomes

(PROs) are health outcomes, which are directly reported by an individual without an interpretation of the response by a clinician or anybody else (124). PROs include the symptoms people experience, their functioning (functional status), general perceptions of their health, health related quality of life and well-being (55,56). PROs are complementary to objective outcomes that are frequently used in clinical settings (e.g. blood pressure, temperature, blood measurements). They provide unique and essential information on patients' perceptions of both the impact of conditions and their management, information that is essential for patient centred decision making (125).

Intra-individual cyclical variation has previously received little attention in the field of PROMs. PROMs were originally conceived for obtaining valid and reliable estimates of outcomes at a group level for measuring disease burden or evaluating health care interventions for populations. In this context, intra-individual cyclical variation may have become insignificant as it would be diluted when multiple individual scores are aggregated for obtaining group estimates, particularly when cyclical variation is expected to be distributed at random across different groups of patients in randomised clinical trials. However, the increased use of these measurements in clinical practice, for example in psychological services such as IAPT (Improving Access to Psychological Treatment) (126) and elective surgeries such as hip and knee replacements (127) for individual patients makes unaccounted intra-individual cyclical variation essential for establishing whether a difference in scores in a patient signals a true change in patient health status.

3.2.3 **Factors influencing patient reflections of health**

Individuals use a number of cognitive, social and emotional processes when reporting on their health. Individuals often are accurate in detecting extreme changes in their symptoms or health state which would require immediate attention. For example, people with asthma are able to recognise the need to self-medicate in extreme situations although are mostly unaware of changes to lung function on a daily basis (128). The extent to which we may recognise changes in our health is also dependent on how stimulating we find our external environment. Pain levels may be more noticeable at the end of the day when there is less stimulation to compete with our internal cues focusing on pain levels (Pennebaker 2000).

Patients with chronic conditions may have expectations about experiencing their symptoms, thus anticipating certain triggers to aggravate their condition (Crichton et al 2014). Those living with chronic conditions understand how their symptoms may fluctuate and their typical symptom levels (Broderick et al 2008). Similarly, patients have expectations for alleviation of their symptoms when they take medication and the steady increase of severity once the effects of the medication subside. Thus, individual expectations can contribute to the likelihood of seeking medical attention, which could be when health is at its most severe. Alongside external cues, patient expectation brings into question the influence of psychological status. Emotions play an important role in how patients report their health (129). Research exploring the effect of affect on symptom reporting and help-seeking behaviour has demonstrated that there is increased reporting of pain and aches following negative mood (Salovey and Birnbaum 1989). However, what is less understood is the effect of changes in mood in a day on reporting of other symptoms.

3.2.4 **Retrospective and momentary assessments of health**

PROs are usually collected using patient reported outcome measures (PROMs), typically in the form of questionnaires with standardised questions and response options. Retrospective ratings of symptom reporting is typically used in PROMs instruments, requiring individuals to retrospectively recall symptoms and their intensity over a recent period of time (recall period) (130). This requires the use of cognitive heuristics and processes of retrieval, which potentially introduces bias (126). Heuristics give disproportionate weight to the most salient episodes of peak severity when an individual constructs a recall rating (Broderick et al 2008).

Previous research has shown that retrospective ratings of health lead to an over-reporting of symptoms (131). Broderick and colleagues (2008) demonstrated a gradual decline in the correlation between momentary ratings and different reporting periods (increased from one to seven days), which indicated substantial differences between recall and momentary assessments. Individuals have a large amount of somatic information available to them, however the information that is most salient, relevant and potentially threatening is retained (131). Many PRO measurements require patients to recall their average level of fatigue, for example, over the past day or week, which may be influenced by the most salient episode (e.g. worst level of fatigue) or their current level of severity of their symptom experienced just prior to completing the questionnaire (92,132).

Because of this, other methods have become increasingly popular, such as the use of ecological momentary assessment (EMA). EMA involves repeated momentary assessment of behaviours and experiences in real time (133). However, the burden on the patients is considerably higher than cross-sectional designed

studies (134). Repeated momentary assessments of health does allow variation of health conditions to be captured and provides both researchers and clinicians with a better understanding as to how health conditions in that particular individual manifests. Other data collection methods include diaries, which can be completed at the end of the day (107), requiring patients to reflect over periods of their day. Although these methods are more reliable and less susceptible to bias, they do require additional patient time.

3.2.5 **Rationale for scoping review**

A total of 14 different types of literature reviews have been identified (135), however for the purposes of this PhD a scoping review was chosen. Unlike other reviews, which address specific questions (such as the effectiveness of an intervention), a scoping review allows the author to map out key concepts that underpin a research field (136). In addition, scoping reviews can be used to clarify working definitions, and the conceptual boundaries of a specific topic (136). Due to the lack of knowledge and understanding of this chosen topic area for the PhD, the scoping review can map out the available evidence given the broad nature of the questions being posed. The results of the review can inform future systematic reviews by specifically focusing on a set of outcomes or carefully worded questions.

The original five-step framework proposed by Arksey and O'Malley (2005) (136) has been further developed by Levac and colleagues (2010) (137) and Peters and colleagues (2015) (138), providing specific details for each of the steps. This has enabled a more rigorous process when carrying out a scoping review. Peters et al (2015) recommend defining and aligning the objective and research question followed by developing and aligning the inclusion criteria for screening the relevant

studies with the objective and research question (138). Along with Levac et al (2010) (137) who suggest using an iterative team approach when selecting studies and extracting the data, Peters et al suggest describing the planned approach in order to ensure that the process is documented (138). The final stages of the review process include searching, selecting, extracting and charting the evidence.

3.3 Objective of scoping review

The objective was to conduct a structured review of the literature to support mapping out key concepts on cyclical variation of PROMs in chronic health conditions for clarifying definitions and conceptual boundaries, developing a conceptual framework and identifying research needs.

3.4 Methods

A scoping review following current methodological standards was conducted (8). This approach is the method of choice for mapping out key concepts, and clarifying definitions, and conceptual boundaries in a relatively underexplored area of research (138,139).

3.4.1 Search strategy and selection of the literature

A search was conducted for relevant articles in four databases: MEDLINE (In-Process & Other Non-Indexed Citations and Ovid MEDLINE, 1948 to Present, accessed through OvidSP); Embase (1974 to present, accessed through OvidSP); PsycINFO (1967 to present, accessed through OvidSP); and CINAHL (from 1981 to present, accessed through EBSCO) using a model pre-defined strategy developed through an iterative process, based on published searches and with input from an information specialist. The search strategy was developed and reviewed with an information specialist from the systematic reviewing team. The strategy was tested

prior to implementation, in order to assess the types of papers emerging from the search. The final strategy combined four blocks: PROs, measurement, time, and chronic conditions (Appendix I). The search strategy was adapted to each database to comply with their terminology (140). A protocol for the scoping review was developed a priori and published on the PROSPERO website (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42017058365)

Due to the nature of the type of literature review the inclusion criteria to screen the titles, abstracts and full-text articles that was set included any record (e.g. original studies, systematic reviews, editorials, conference proceedings etc.) that met all the following criteria:

1. Reporting PROMs data (ranging from multiple scales to single items)
2. Reporting variation of PROMs across time (duration, e.g. daily, weekly, monthly, seasonally, etc.)
3. Including patients with one or more chronic conditions
4. Having been written in English

All the titles and abstracts were imported and reviewed using Rayyan, a web-based platform to facilitate the screening process (141). Any references subject to a second assessment were discussed with the main supervisor Professor Valderas (JV) and included. The inclusion criteria were tested by four reviewers (myself, an intern Joseph Coombes, Ian Porter within the research group and JV) on a selection of 20 titles and abstracts and the inter-rater reliability between the reviewers was calculated through the Cohen's Kappa value in Excel (median = 0.92). Once the titles and abstracts were screened, the inclusion criteria were tested on the full-texts

between the same reviewers (median Kappa = 0.96). Full-text screening took place following this process. Full-text articles that were not available through the University library system were obtained by emailing authors or contacting them via ResearchGate. A final list of full text articles was compiled and backwards and forwards citation searching on the included full text articles was undertaken, with the inclusion criteria applied to the identified citations.

3.4.2 **Data extraction and quality assessment**

Information was extracted into an Excel spreadsheet using a pro-forma including the characteristics of the articles, data collection methods and time periods, explicit (existing conceptual models, explicit hypotheses on cyclical variation of PROMs) and implicit assumptions (associations being explored without a priori hypotheses) (Appendix II). In order to assist in categorisation of the chronic conditions, the World Health Organisation's International Statistical Classification of Diseases and Related Health Problems guide (ICD-11) was used (142).

The quality of included articles was assessed using an adapted version of the Critical Appraisals Skills Programme (CASP) tool of observational research to assess whether articles focused on time-related variation in their studies (143) (Appendix III). The CASP tool is frequently used by systematic reviewers to assess the quality of articles and there are tools designed for a variety of study designs (e.g. qualitative, randomised controlled trials, and observational). Quality assessment methods were tested in a pilot evaluation prior to use across the literature by AD, CG and JV.

3.4.3 **Evidence synthesis**

A conceptual model was developed based on Valderas and Alonso classification model (57). The Valderas and Alonso model integrates the two main models of health outcomes, the Wilson and Cleary model (144) and the WHO International Classification of Functioning model (58) (Figure 2.4 and Figure 2.5). The developed conceptual model further elaborated on the variables and hypothesised relationships in the explicit and implicit assumptions of the studies included in the review (Appendix I).

AD and JMV conducted a pilot for the approach, AD subsequently extracted key concepts explaining time-related variation of scores from all studies. This was done by going through each of the papers and highlighting the key concepts that were mentioned (e.g. health outcomes, biorhythms). The background and discussion sections of each paper were reviewed and theoretical concepts were highlighted. Methodological approaches to studying cyclical variation were extracted from the methods sections for each paper, including study designs, data collection methods and analytical approaches. All the theoretical concepts collated from both the introduction and discussion sections were then thematically organised into hierarchal concepts explaining the sub-concepts (as seen in Appendix II). These concepts and associations were then mapped out by AD, onto a conceptual model, which was iteratively refined through discussion within the supervisory team.

3.5 Results

A total of 2420 articles were retrieved from bibliographic databases and additional 45 full-text articles were identified through forward and backward citation searchers (**Error! Reference source not found.**). A total of 33 studies were included in the final review (Figure 3.2) The quality of the studies varied from three to

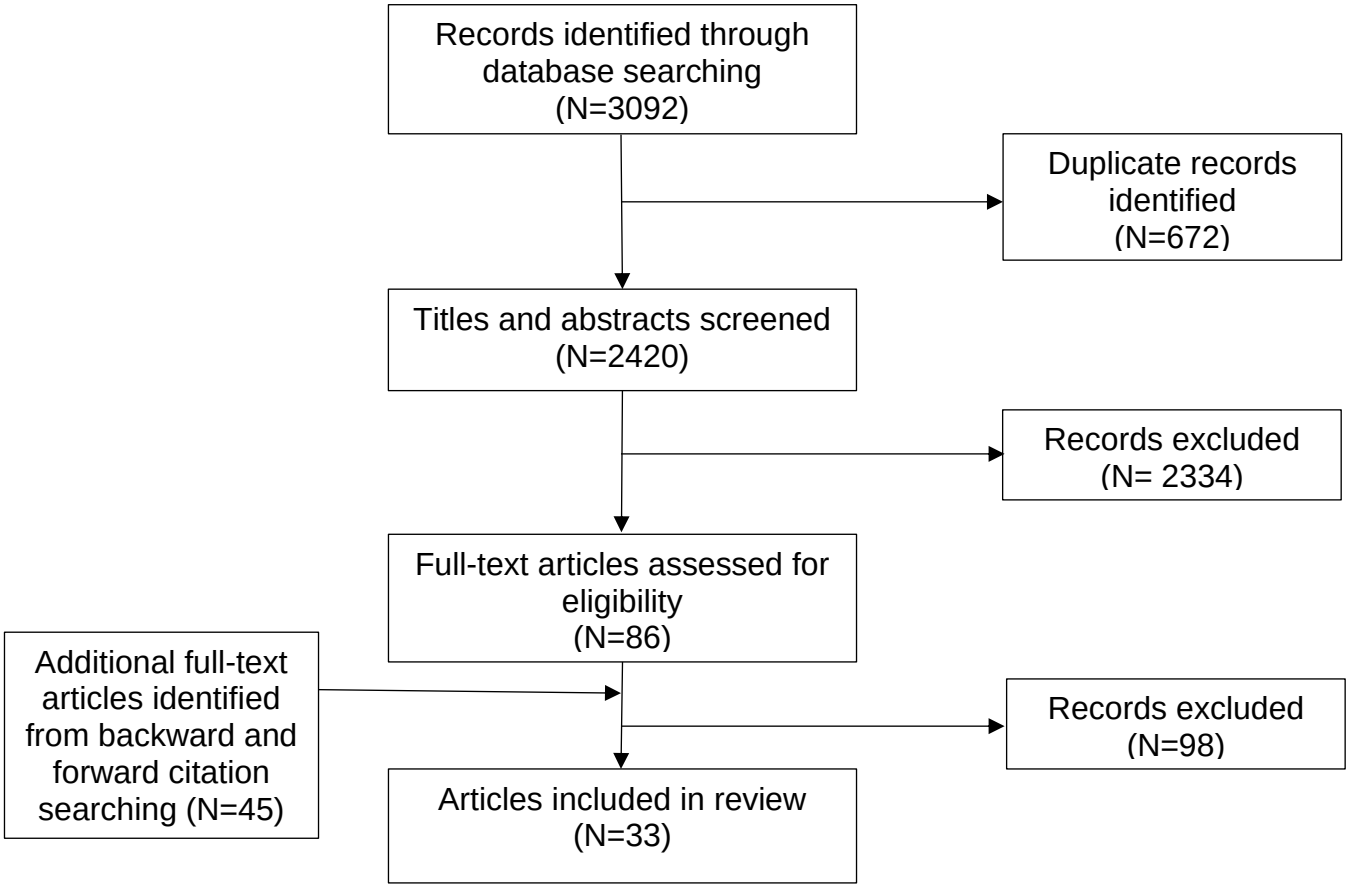
seven points (maximum) on the adapted CASP tool, with three articles achieving the maximum score of seven. Articles scoring low on the adapted CASP tool was due to not having an explicit hypothesis in relation to cyclical variation, did not recruit participants that were representative of the general population, had attrition less than 20% or did not take into account of the confounding factors related to cyclical variation of PROMs in their design/analysis.

3.5.1 **Study characteristics**

The majority of the literature was published from 2000 (145–165), with ten articles published in the last five years (145,153,157,158,161,163–168). Seventeen studies were conducted in North America (158), twelve in Europe (146,147,151,154,155,161,163,164,167,169–171), with two studies across both regions (149,152) and two further studies from Asia (166,172). Studies were conducted in patients with five broad diseases categories: mental health (n=8) (151,154,158,163–165,173,174), musculoskeletal (n=7) (146,157,159,162,168,175,176), respiratory (n=5) (149,150,155,156,170), nervous system (n=4) (152,159,160,167), and other conditions (145,148,153,161,166,169,172,177). Studies sampled mostly adult populations (n=30), with two studies focusing solely on female adults (159,177), and the remaining focusing on children (157,162,176). Studies recruited participants in specialist outpatient departments within secondary care (n=18) (145,147,148,152,155,157,159–162,166,167,169,171,172,175,176,178), primary care and the community (n=11) (146,149,150,153,154,163–165,168,173,177). The

two systematic reviews did not have any inclusion criteria relevant to specific settings.

Figure 3.2 Flow of articles in the scoping review



3.5.2 **Study designs**

Included studies in the literature collected PROMs primarily for the measurement of symptom severity (such as pain, fatigue, stiffness, shortness of breath and affect (emotions)) and functional status, including disability measures. There was a lack of quality of life measures used across the articles. Many of the studies used visual analogue scales (VAS) for pain, fatigue and stiffness

(147,150,152,157,162,175,176,179). Seven studies used single items on mood, pain and fatigue (146,153,159,161,162,167,168).

The included studies employed a range of only quantitative methodologies and designs, including observational (cross-sectional and cohort) (145–150,152–154,156,157,159–169,172–174,176,178) and experimental (randomised controlled trials) designs (155,171,175). We did not identify any studies using qualitative or mixed methods, commentaries, or editorials. Many of the studies using observational methods used the EMA approach to data collection (145,146,148,153,154,159,160,163–165,167,168,172,173,180,181). There were two systematic reviews, which focused on methodological approaches to collecting real-time data in two specific conditions (151,170). The majority of studies used a repeated measures design, collecting data from twice to eight times a day, with one study collecting data every three to four months over a 27 month period (166). Three studies were of cross-sectional design collecting data only once (149,169,174).

Table 3.1 Characteristics of the articles included in the review

Reference	Country	Design	Setting	Conditions	PROMs measurement		
					Frequency[1]	Data collection period[2]	Study quality[3]
aan het Rot et al 2012	Netherlands	Systematic Review	Various settings	Depression	Between 3 and 10	Varied	3
Abdel-Kader et al 2014	USA	Observational (Longitudinal)	Secondary care	Kidney disease	4	7 d	3
Bellamy et al 1991	Canada	RCT[4]	Secondary care	Rheumatoid arthritis	6	9 d	1
Bromberg et al 2014	USA	Observational (Longitudinal)	Secondary care	Arthritis	3	1 m	3
Claros-Salinas et al 2010	Germany	Observational (Longitudinal)	Secondary care	Multiple sclerosis	3	2 d	2
Crosby et al 2009	USA	Observational (Longitudinal)	Community	Eating disorders	6	2 w	3
Curran et al 2004	USA	Observational (Longitudinal)	Secondary care	Cancer	4	5 d	3
Dekkers et al 2000	Netherlands	Observational (Longitudinal)	Community	Rheumatoid arthritis	8 (PROMs) 9 (saliva)	2 d	2
de Wit et al 1999	Netherlands	RCT[4]	Secondary care	Cancer	2	2 m	6
Feuerecker et al 2015	Germany	Observational (Longitudinal)	Secondary care	Chronic dizziness	5	1 d	3
Feys et al 2012	USA, Spain, Belgium, Finland, Denmark	Observational (Longitudinal)	Secondary care	Multiple sclerosis	3	1 d	3

Graham-Engeland et al 2016	USA	Observational (Longitudinal)	Community	Rheumatoid arthritis	5	7 d	2
Hamilton et al 2007	USA	Observational (Longitudinal)	Secondary care	Fibromyalgia	7	2 d	2
Hardt et al 1999	Germany	Observational (Cross-sectional)	Secondary care	Chronic pain	1	1 d	5
Houtveen et al 2015	Netherlands	Observational (Longitudinal)	Community	Mental disorder	4	3 w	3
Kikuchi et al 2012	Japan	Observational (Longitudinal)	Secondary care	Headache	4	7 d	3
Kleiman et al 2017	USA	Observational (Longitudinal)	Community	Mood disorders	4	28 d	2
Kratz et al 2016	USA	Observational (Longitudinal)	Community	Chronic pain	5	7 d	5
Lavender et al 2013	USA	Observational (Longitudinal)	Secondary care	Eating Disorders	6	2 w	4
McCarley et al 2007	USA	Observational (Longitudinal)	Community	Chronic Obstructive Pulmonary Disorder (COPD)	5	8 d	7
Okifuji et al 2011	USA	Observational (Longitudinal)	Secondary care	Fibromyalgia	3	30 d	2
Partridge et al 2009	Europe and USA	Observational (Cross-sectional)	Community	Chronic Obstructive Pulmonary Disorder (COPD)	1	1 day	2
Pfaltz et al 2010	Switzerland	Observational (Longitudinal)	Community	Mood disorders	5	8 d	3
Powell et al 2017	UK	Observational (Longitudinal)	Secondary care	Multiple sclerosis	6	4 d	7
Roche et al 2013	France	Systematic Review	Various settings	Chronic Obstructive Pulmonary Disorder (COPD)	Varied	Varied	3
Schanberg et al 2005	USA	Observational (Longitudinal)	Secondary care	Polyarthritic arthritis	1	2 m	6
Schlager et al 1995	USA	Observational (Cross-sectional)	Primary care	Depression	1	1	5

Schwartz 2000	USA	Observational (Longitudinal)	Community	Cancer	1	8 w	4
Sewell et al 2010	UK	RCT[4]	Secondary care	Chronic Obstructive Pulmonary Disorder (COPD)	Twice (pre and post)	7 w (pre and post)	4
Shin and Lee 2014	Korea	Observational (Longitudinal)	Secondary care	Chronic pelvic pain	Every 2-3 months	27 m	3
Stinson 2008	Canada	Observational (Longitudinal)	Secondary care	Arthritis	3	2 w	2
Tsanas et al 2016	UK	Observational (Longitudinal)	Secondary care and community	Depression	1	3 m	2
Vernon et al 2010	USA	Observational (Longitudinal)	Primary care	Chronic cough	1	2 w	3

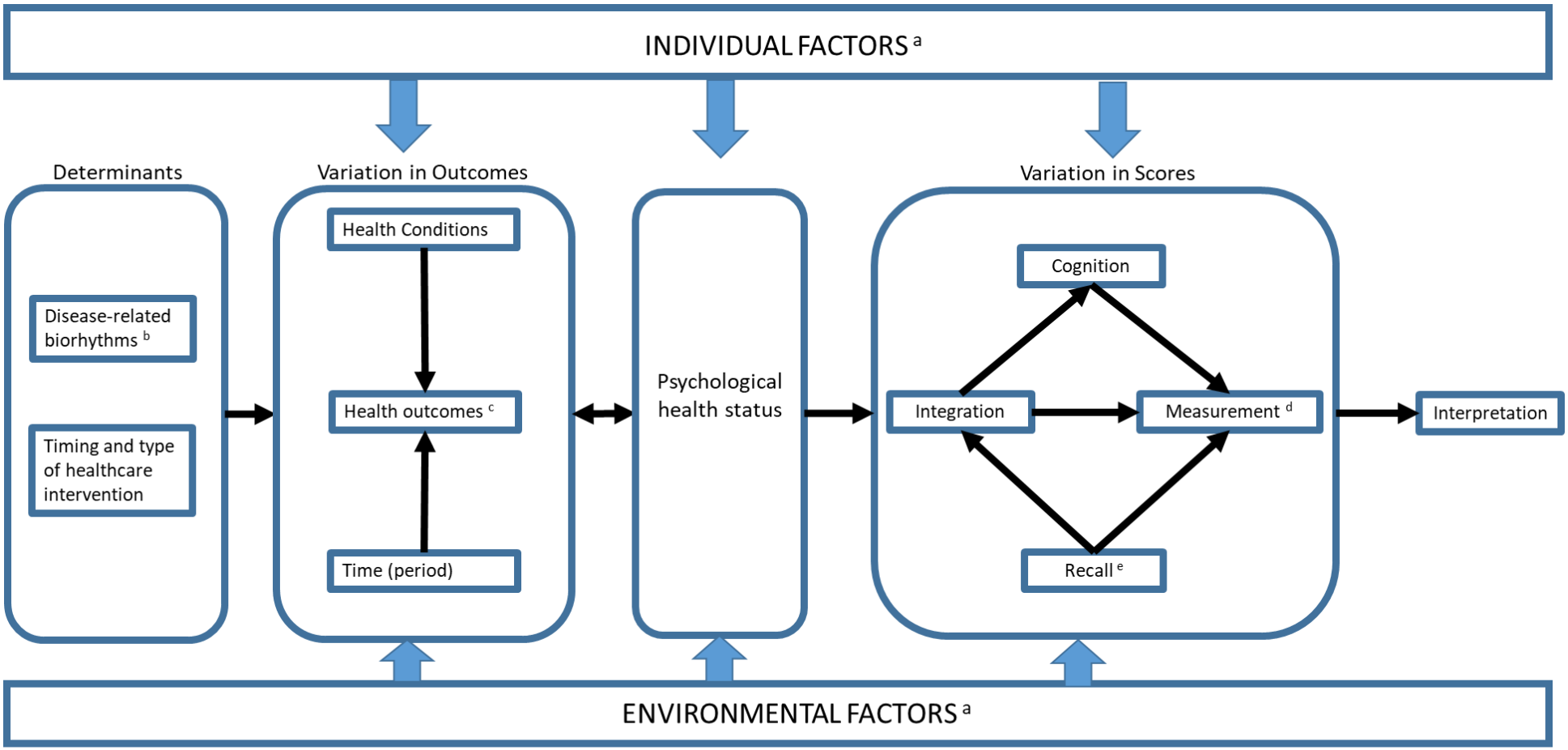
[1] The number of times measurements were completed in a day

[2] d: days; w: weeks; m: months

[3] A lower score on the CASP means article focused less on cyclical variation of PROMs (range from 0-7)

[4] Randomised Controlled trial

Figure 3.3 Conceptual model of cyclical variation of PROMs



[a] Individual factors incorporate individual determinants of health (e.g. demographics, personality, identity); environmental factors incorporate physical (urban/rural, weather) and social environment (socio-cultural, economic/political)
[b] Disease-specific biological rhythms incorporates episodic attacks and exacerbations that occur
[c] Outcomes include symptom status, functional status, general health perceptions, health related quality of life
[d] PROM characteristics including aspects around sensitivity of the instrument
[e] Recall incorporates two topics: recall bias and recall period. The recall period includes both momentary and retrospective (which can be the immediate past or longer term

3.5.3 **Conceptual model**

Two core constructs were identified (variation in health outcomes (PROs), and variation in scores (PROMs)), one key mediator (psychological status), two determinants (disease-related biorhythms, timing of biomedical interventions) and two main moderators (individual and environmental factors) for our conceptual model (Figure 3.3). The two moderators impact on the core constructs, determinants and the mediator, whilst the determinants only directly influence variation of outcomes. Psychological health status has a bidirectional relationship with variation in outcomes, in that the state of one's health can both impact on and be impacted by one's psychological state. All these results in a variation in scores, and how scores are interpreted.

3.5.4 **Determinants**

Two main sources of outcomes *va*riation are identified: disease-related biorhythms, and timing of health care interventions (including medication). Disease-related biorhythms are the natural cycles of change in the body's chemistry or function and symptoms (149), related to the health condition, which function in a rhythmic pattern. For example, those with rheumatoid arthritis present a diurnal patterning with regard to their symptoms (146,175), whilst cortisol levels that affect mood in seasonal affective disorder has a circannual rhythm (174). These biorhythms govern certain health outcomes such as symptoms and function (149), and ultimately affect health related quality of life as discussed in section 3.5.5.

The timing of medical interventions (such as the dosage and pharmacokinetics of medication) is an important factor to consider as it has significant consequences on the variation in health outcomes, due to both their

indications and adverse effects (145,149,156,172). Cancer treatments have severe effects on individuals' symptoms and functional ability. Breast cancer patients present a distinct infradian patterning of fatigue levels following chemotherapy treatments, typically highest within 24 to 48 hours following treatment (177). The type of intervention prescribed (whether that be pharmacological or not) for every condition will be different and will have varying levels of impact on an individual's overall outcome. In some conditions, the time of year an intervention is administered impacts on overall health outcomes post completion. For example, Sewell et al (155) showed that for COPD patients seasonal variations have an important impact on functional performance after pulmonary rehabilitation.

3.5.5 **Variation in health outcomes**

Variation in health outcomes depends on health conditions, the type of health outcomes (as outlined in the existing models/classification systems on health outcomes), and time (periods). The studied health conditions show cyclical patterns in their effects on health outcomes such as symptom and functional status, and health related quality of life. Individuals with musculoskeletal and nervous system conditions experience a diurnal patterning of symptoms during the day, with fatigue and pain worsening by the end of the day (146,147,152,157,159,160,162,164,167,168,172,175,176). However, individuals with respiratory conditions experience a different diurnal patterning of symptoms whereby symptoms are worse in the morning and evening(149,150,156,170). In addition, respiratory conditions have seasonal patterning with individuals reporting increased symptom severity levels over winter months (155).

Functional status, one's ability to perform daily tasks, varies with health conditions and time (153,155,157,162,164,174). It is apparent that one's functional status presents a diurnal and infradian rhythmic patterning depending on the health condition. For example, functional performance for COPD patients worsens in the winter months (155), greater functional difficulties are experienced in the mornings and on the days following nights of poorer perceived sleep quality for arthritis sufferers (157,162).

Although health related quality of life (HRQoL) was not extensively researched in the papers, there was some acknowledgement of the association between HRQoL and the symptoms and functioning experienced by individuals (147–150,152,153,162,163,166,170,180), with regard to fluctuations in symptoms and functioning across conditions being associated with lower health related quality of life. It is evident that fluctuating health outcomes has a bidirectional relationship with an individual's psychological status, in that mood is affected by and affects symptoms, functioning and health-related quality of life.

3.5.6 **Mediator: Psychological health status**

Although psychological health status is also a health outcome, it has been presented as a mediator in this model. The rationale behind this is that psychological health status strongly impacts on and is impacted by all the other concepts in the model. The mental state an individual is in appears to be determined by the two moderators as well as the other health outcomes outlined in section 3.5.5. The other concepts within the model influence the (non-observable) mediator concept (psychological health), which in turn influences variation in scores. Psychological health status incorporates mood (e.g., emotions), cognition and general

psychological and mental functions. An individual's psychological health status is determined by both the individual and environmental variables. In our model psychological health status is a mediator between variation of PROs and variation in the scores. A change in psychological status resulting in worse outcome scores has been observed for patients with MS (167), arthritis (176), or suffering mental health problems. Variations in mood have been linked to fluctuations in pain, stiffness, and fatigue in children with chronic arthritis (157). As represented in the model, the relationship between psychological status and variation of outcomes is bidirectional. Bulimic patients, for example, tended to engage more in bulimic behaviour on days where negative emotion is high, and vice versa. In addition, mood measured in a previous month predicted pain severity in the next month (168).

Psychological health status also played a role in the prediction of reduced social activities for children with chronic arthritis demonstrating the link it has with functional status (176), with lower mood and stiffness being a predictor of school attendance. The relationship between psychological status and variation of scores is unidirectional, in that lower mood at the time of completing a PROM impacts on how an individual remembers their experience of their condition, which affects the scores (168). Psychological health status also fluctuates over time, with research demonstrating a within-person fluctuations over short periods of time (158).

3.5.7 **Variation in scores**

Variation in scores is dependent on several internal processes an individual uses to complete a measurement tool. Completion of an outcome measurement is reliant on the ability of individuals to appraise their condition which involves a cognitive process. The internal processes (integration) involved for each individual

when appraising their condition is influenced by an individual's cognitive process and their recall. As completion of a PROM requires individuals to reflect on their health, there is a degree of recall involved which impacts on and is impacted by how individuals integrate their experience. All of these concepts then lead to what is completed on the measurement tool and the interpretation of outcome scores.

Within-person variance was commonly observed for different mood disorders in daily and weekly scores, including suicidal ideation (165), eating disorders (178), bipolar and borderline personality disorder (163). Cognitive decline and an increase in fatigue during the day is observed in MS patients affecting their performance to do tasks (147,152), with substantial moment-to-moment and day-to-day fluctuations in fatigue severity found in relapse-remitting MS patients (167). This decline in cognitive function can affect the internal processes involved in responding to an outcome measure, ultimately affecting the PROM score.

The sensitivity of the measurement to detect any changes in outcomes over time, and how change is defined to be clinically important within studies were important issues discussed in the articles (152,156). Diaries were more sensitive to daily score changes than measures obtained by patient interview, for pain intensity for cancer patients (171), and for young people with juvenile idiopathic arthritis (157). The timing of measurements has been shown to be of significant importance, particularly with conditions that affect cognitive performance, such as MS patients demonstrating cognitive fatigue declining as the day progresses (147).

Daily measurements of mood, in one study, impacted the evaluation of health outcomes when measuring efficacy of psychopharmacological or psychological interventions (163). However, daily measurements can also affect how individuals

report their symptoms, for example in one study, pain significantly decreased during the second week of the study, which may have been an unintentional feedback intervention resulting in changes in their appraisals or pain management (162). Although we do not know if the changes were also due to the fact that pain naturally decreased thus representing true variation in outcomes.

As defined in Section 2.9.4, recall bias is when patients remember an event or experience incorrectly (182) Retrospective accounts can lead to misclassification of symptoms (145), and an overestimation of symptoms (154,171). Psychological health status (158), symptoms at the time of recall (159), length of the recall period, and primacy or recency of information (154) all impact on how individuals appraise their condition. A systematic review of studies on major depressive disorders revealed that negative recall bias in these patients exist mostly in the underreporting of negative affect (183). Asking patients to summarise their mood over a requested period potentially overlooks clinically meaningful differences in symptom patterns which could be picked up at each moment in time (154). Although pain scores were higher in the evening and fluctuated across the weeks, pain recall was inaccurate for cancer patients with overestimation of pain reported from a previous week (171)).

3.5.8 **Moderators: Individual and Environmental factors**

One of the fundamental determinants of health is the person's individual characteristics and behaviour. When considering individual factors, part of this can be defined in terms of the demographics (e.g. age, gender) of the population being studied, their personality, motivation, values and preferences. The impact of the concepts of motivation and personality are reinforced with research conducted by Hardt et al (169) or Graham-Engeland et al (168), linking personality characteristics

such as mood-like traits to the experience of pain. An individual's level of acceptance or determination changes the way they perceive their outcomes (e.g. symptoms, functional status), for example pain acceptance was seen to buffer expected increases in pain interference and decreases in physical activity in the context of high pain for spinal cord injured patients (153). Individual thresholds could also determine changes in scores longitudinally, especially in relation to subtle changes in pain that occur for those with high pain thresholds. Multimorbidity adds to the complexity of completion and interpretation of PROMs and was an important concept to consider in the articles. Co-morbid conditions sharing similar symptoms can impact on how patients report on one particular condition, with symptoms in one condition (e.g. pain in rheumatoid arthritis) potentially triggering another condition (e.g. depression) (146,168).

Environmental determinants of health include both the physical and social environment in which individuals live and work. The physical environment includes the natural setting (e.g. weather, bioenvironmental markers, etc.) and the human setting (urban/rural). For example, temperature changes over the year can impact on symptom status for COPD sufferers exacerbating their symptoms in the winter (155) limiting their participation in activities. Furthermore, cold weather has been associated with a breakthrough of chronic prostatitis/chronic pelvic pain syndrome symptoms in the winter compared to acute symptoms reported in the summer (166). External rhythms, such as exposure to sunlight or external stimuli, have been linked to variation in outcomes and psychological status with increased sunlight linked to better outcome scores (151,174), and worsening outcomes for long exposure to external stimuli (161). Sleep quality was highlighted as a contributing factor to worsening PRO scores due to sleep disruption, triggered by numerous variables

such as stress (157,160,177) or night-time symptoms (170) and effects on symptoms such as mood upon awakening, fatigue (146,167,177), and poor overall functioning (160).

3.6 Discussion

The objectives of this scoping review were to map out key concepts of cyclical variation of chronic conditions, in order to define and identify conceptual boundaries and highlight research gaps. This scoping review provided evidence for cyclical variation in PROMs, mainly across four categories of conditions: respiratory, musculoskeletal, mental health and nervous system. This scoping review provides some evidence for cyclical variation of PROMs for certain conditions, mainly respiratory, musculoskeletal, mental health and nervous system. The literature demonstrates a range of periodic fluctuations (e.g., diurnal, circadian, infradian and seasonal) across these conditions, with key concepts influencing how patients appraise their conditions. Based on the empirical literature, we have developed a conceptual model to explain the relationships among the factors associated with cyclical variation of PROMs. The model identifies the core constructs as variation in health outcomes (PROs), and variation in scores (PROMs), a key mediator (psychological health status), determinants impacting on a core construct (disease-related biorhythms, timing of biomedical interventions) and individual and environmental factors as moderators. Variation in outcomes and scores is found to be mediated by individual/environmental factors, and psychological health status at the time of completing a PROM.

All the included studies used quantitative methods to collect momentary and retrospective accounts of patient experience. In addition, an ecological momentary

assessment approach was used to collect momentary accounts of individual experience. However, many of the articles raised issues around recall bias when collecting retrospective accounts of health, which supports existing cognitive literature (92,132). According to cognitive science, our experiences, albeit good and bad, are encoded as an overall evaluation capturing the remembered intensity of the experience (92,95) and memory is influenced by the individual's context and mental state at the time of recall.

Alongside the periods of time PROMs require patients to reflect on, the frequency with which researchers or clinicians measure health may be important to consider especially with regard to day-to-day fluctuations (176). Individual patients also exhibit different fluctuations, with individually-specific triggers and understanding this could explain these patterns in chronic conditions. This would help both patients and clinicians to efficiently manage the progression of diseases. As there were no qualitative or mixed-methods studies included in this review, explanations of how time impacts on patient's evaluations of their symptoms (scores) could not be explored. Repeated measurements and a qualitative examination into the effect of time would provide better insight into the everyday correlates of patient's symptoms and the contributing factors to fluctuations in outcome scores, such as quality of sleep or other symptoms (e.g. mood) (167).

Another factor to consider is how time was handled during the analysis of the data and what type of statistical tests were performed to analyse the data. Appropriate methodological approaches to analysing the data are necessary when attempting to examine the data in relation to time effects. It is recommended to first plot the data as a function of time and use statistical techniques for detecting periodic patterns in time-related data (184,185). Cornelissen (184) highlights that

classical study designs encouraging fewer test groups (or testing points) are not powerful enough to detect a time effect in comparison to chronobiology studies where they recommend using at least six timepoints per cycle.

3.6.1 **Limitations**

The studies included in the review used a diverse range of methodologies. Some of the authors were not fully transparent on the methods or analyses used, which proved challenging when appraising the quality of the studies. A limitation of this review is the exclusion of articles that were not published in English. Another potential limitation is the use of the terms in the search strategy and whether the list was comprehensive or sensitive enough to capture all studies of interest (e.g. qualitative). Whilst developing the layout of the concepts in the model, a degree of subjective assessment is needed, although this was an iterative exercise which was not done in isolation and the concepts were drawn from the articles.

3.6.2 **Implications**

There are various factors to consider for clinicians using PROMs in their clinical practice to assess effectiveness of interventions and/or progression of a disease. As there are thousands of PROMs instruments available for use, the type of measurement that is used should be sensitive enough to detect changes in scores for patients and this is dependent on the time (time of day or year) when a patient completes the measurement. The type of measurement and where these are taken may also impact on how patients complete them, for example before a doctor’s appointment in a healthcare setting or at home. Understanding the biorhythms of each condition and how that may affect physiological as well as self-reported data

needs to be considered when interpreting results. This will be further explored in the subsequent chapters (Chapters 4 and 5).

In addition, the frequency with which patient-reported outcome data is collected may present a fuller picture of how the condition affects patients over time. Kleiman et al (165) stipulate that no single data point should be used in making clinical decisions as, for example, variations occur in suicidal ideation over the course of a few hours. As seen in de Wit's (171) study daily diaries of pain experience showed variation of pain experience occurring on a daily basis. Multiple measurements can provide clinicians with a better understanding as to when patients are most vulnerable and intervene when patients are at a higher risk, e.g. for psychological conditions, enabling a preventative element to healthcare delivery. In addition, with multiple measurements patients would be empowered with that knowledge and understanding to better manage their conditions and present that evidence in consultations with their doctor.

Many conditions are often seen in isolation of other co-morbidities when patients visit specific specialists, despite evidence demonstrating interacting effects of each condition. With the rise of multimorbidity around the world the way healthcare is delivered should take the implications of multiple conditions on health outcomes into account. In addition, medication timing and type of medication impacts on how patients experience their condition over time, and report on that experience. Chronotherapeutics is a growing field of research demonstrating that timing of medication can alter the course or progression of a condition, which in effect can alter outcome scores.

3.7 Conclusion

The background literature in Chapter 2 presented the evidence of biological rhythms, although it highlighted a research gap to explain how these rhythms impact on PROMs scores. Existing theory within the field, such as response shift, do not account for these rhythms and how these could be reflected by PROMs scores. This scoping review has built on Chapter 2 literature by mapping out the key concepts to explain cyclical variation of PROMs in chronic conditions in the literature. There is some evidence of a systematic periodic variation in self-report PRO data at an individual level, which is important for clinical assessments. This can have profound implications for the routine use of PROMs in the care for people with chronic conditions. However, there was no qualitative research to inform on the concepts from the patients' perspective identified through the review. Thus, further research is needed to inform the conceptual model for cyclical variation of PROMs in chronic conditions, and qualitative research examining the factors influencing variation of outcome scores is needed to enhance our understanding in this area (Chapter 4). The following chapter will employ a longitudinal approach to further developing the conceptual model from a patients' perspective. Chapter 5 will critically evaluate the statistical approaches used in the scoping review articles to provide a rationale on applying a special statistical method in Chapter 6. The final empirical chapter (Chapter 6) will focus on a particular statistical approach to modelling cyclical variation using a secondary dataset that was made available.

Chapter 4 Factors influencing cyclical variation of PROMs scores: a longitudinal study

4.1 Chapter outline

The scoping review (Chapter 3) highlighted key concepts which were relevant to explaining cyclical variation in PRO scores, however there was a lack of qualitative evidence to corroborate our theoretical concepts. The purpose of this chapter is to explore how the concepts in the conceptual model from Chapter 3 contribute to the cyclical variation of chronic conditions, gathering the patient's perspectives and experiences over time

4.2 Background

There is clear evidence in the chronic health literature demonstrating that patients' experiences of their symptoms can vary at different time points. Research has tended to focus on circadian rhythm as this influences a patient's response to diagnostic tests and interventions depending on when they are administered (32). Yilmaz (40) found that patients with rheumatoid arthritis report psychological stress/mood disorder (86.1%) as the most frequent reasons for their joint symptoms and the experience of remission of symptoms was dependent on weather changes. Exacerbations in COPD symptoms has also been connected to different seasons in the year with an increased number of hospitalisations in the winter (39,186). Although there is research demonstrating variation of symptoms experienced across different conditions, there is a lack of research focusing on how this variation is captured using outcome measurements. The results of the scoping review provided a focus on which categories of conditions cyclical variation was studied in relation to outcome measurements. Coupled with the prevalence of the most common chronic

conditions in the UK, this narrowed the focus of this chapter to three main conditions: asthma, depression and osteoarthritis (OA).

4.2.1 **Prevalence and aetiology of asthma**

Asthma is one of the most common chronic conditions in the world and is one of the top five prevalent conditions being treated within UK primary care settings (187). It is an inflammatory disease of the airways of the lungs characterised by variable and recurring symptoms such as wheezing, coughing and chest tightness (188). Around 5.4 million individuals in the UK currently receive treatment for their asthma and the UK has some of the highest rates in Europe (189). Asthma is an important cause of morbidity and disability in those aged 65 and over due to the loss of control of the disease in later age and is associated with increased hospitalisations (190).

Much like other health conditions, asthma is classified as a circadian disease, with the condition worsening at night making it potentially deadly problem (Figure *3.1*) given that asthmatics are more likely to die at night from their condition than during the day (191). The Global Initiative for Asthma (GINA) guidelines have provided recommendations for the evaluation of control of the condition through the assessment of daytime symptoms, activity limitations, night-time awakenings and symptoms, lung function, exacerbations and the need for rescue treatment (192). Night-time awakenings, or sleep disruption, due to asthma symptoms have an adverse effect on an individual's daytime activities (cognitive impairment). Diurnally active individuals will display circadian variation in their pulmonary function. Individuals will have optimum lung function at around 4pm in the afternoon and equally minimal lung function at around 4am in the morning, assessed through FEV1

and PEFR. Night-time exposure to allergens found in bedding contributes to nocturnal worsening of asthma in especially sensitive individuals.

Asthma triggers vary for each individual and the varied number of patient reported triggers have been documented across studies (193–195). Generally, self-reported asthma triggers have been associated with disease severity and severe impact on the patient. Those with a higher number of triggers report a lower quality of life and this is correlated with more exacerbations, and a higher use of health care services (195). There are multiple causes of asthma symptoms which are related to environmental, economic, demographic, social, genetic, and emotional factors.

Previous research with asthmatic patients has identified a range of common triggers from the environment (including allergens, pollutants/irritants, odours, weather), social environment (stress, exercise), and individual factors (respiratory infections, medications, strong emotions) (196,197). It is more frequently reported that there is a higher prevalence of females reporting more asthma triggers than males. There has been some conflicting evidence surrounding the link between socioeconomic status and the number of triggers reported, with much of the evidence leaning towards a lower socioeconomic status linked with higher number of triggers (198,199). Emotional triggers have been associated with a higher severity of asthma, including an increased occurrence of symptoms at night, and lower quality of life (195). External triggers, such as pollen, house dust mite, drastic changes in weather have varying effects on the severity of asthma. Also, other factors such as memory, personality, gender, and cultural norms have been shown to influence perception and reporting of asthma symptoms (200).

4.2.2 **Prevalence and aetiology of depression**

Depression refers to a loss of positive affect (a loss of interest and enjoyment in ordinary things and experiences), low mood and a variety of associated emotional, cognitive, physical and behavioural symptoms (201,202). Major depression is one of the most commonly occurring disorders linked to diminished role functioning and quality of life and mortality (202), and has been predicted to be the leading cause of disease burden by 2030 (203,204). It is estimated that 1 in 6 people will experience a "common mental disorder" each week in England, such as depression or anxiety (205). Depression is one of the top five chronic conditions being treated in primary care settings, with the prevalence rate steadily rising each year (187).

Depression can occur at any stage of an individual's life, although an earlier onset of depression has been associated with worse outcomes and an increased chance of recurrence (206). There are different causal factors to first onset of depression including biological (genetic, neurological, hormonal, and neuroendocrinological mechanisms) or environmental (stress, childhood exposure to adversity) factors which can occur at different ages (206). As demonstrated in the conceptual model in Chapter 3, environmental and individual characteristics contribute to both the development of depression and severity level, whilst biological and certain other factors (e.g. outcomes) have a bidirectional relationship to depression (206).

4.2.3 **Prevalence and aetiology of osteoarthritis**

Osteoarthritis (OA) is defined as the clinical syndrome of joint pain experienced by patients which is accompanied by fluctuating levels of functional limitations and a reduced quality of life (207). According to the National Institute for

Health and Care Excellence (NICE), the number of adults in the UK diagnosed with OA has been increasing as the population ages and is the most common form of arthritis (207). However, it is difficult to record the exact incidence of osteoarthritis due to the difficulty in diagnosing the disease as the clinical syndrome of the condition does not always correspond with the structural changes usually picked up by magnetic resonance imaging (MRI). The most commonly affected joints are the hips, knees and small hand joints. Although OA is found in almost all age groups, the strongest predictive factor for the development of detectable damage is increasing age (208).

OA is the most common disability in the UK with pain, stiffness, joint deformity and loss of mobility substantially impacting individuals. Individuals with OA experience a persistence of pain which affects every aspect of their daily lives and quality of life (209–211). Mobility problems increase as their pain increases, which causes a vicious cycle resulting in a reduced quality of life.

OA has a considerable impact on health care services within the UK as well, with just over 2 million individuals visiting their GP per year due to their osteoarthritis symptoms (207). The number of consultations with primary care services increases with age, with 5% of osteoarthritis consultations recorded for those age over 45 years increasing to 10% for those aged 75 years and over. In secondary care, the number of hip and knee replacements has considerably increased with total hip replacements (THR) doubling between 1991 and 2006 (212,213), and trebling for total knee replacements (TKR) during this timeframe (213). Patients' tolerance of symptom severity, generally, has impacted on their help seeking behaviour from health professionals (214,215), leading to both underdiagnoses and under treatment of many conditions including asthma, osteoarthritis and depression (216).

4.2.4 **The effect of co-morbidities**

Comorbidities are being more recognised as important determinants of the management and prognosis of asthma as these are associated with ineffective disease control, increased health care use and poor quality of life (217). A review of the literature around asthma and co-morbidities showed that asthma is associated with an increased risk of cardiovascular disease and poor control can promote other co-morbidities such as obesity, diabetes, depression, osteoporosis and pneumonia (218). This coincides with the top five most prevalent conditions in primary care being asthma, hypertension, obesity, depression and diabetes (187). A recent retrospective study conducted with electronic medical records of the prevalence of comorbidities in people with and without asthma showed that 62.6% of adults with asthma had more than one comorbidity, and 16.3% had four or more comorbidities (219). Depression and painful conditions were two of the most prevalent comorbidities for people with asthma. It is also recognised that the number of comorbid conditions in asthma patients increases with age (218).

The comorbidity of depression and physical disorders has been recognised as a global issue since this is related to poorer quality of life and increased mortality (220). In a US multi-centre asthma trial researchers found that for their participants hypertension (35.5%) and depression (22.1%) were the most frequent co-morbid conditions (221). Findings from a WHO study reported that prevalence of depression was higher for those who had two or more chronic physical health problems in comparison to healthy controls (220). Chronic physical health problems can cause and exacerbate depression and the reverse can occur with major depression and childhood adversity being associated with risk factors related to physical health problems such as obesity, sedentary lifestyle and smoking (222). This relationship is

demonstrated in the conceptual model presented in Chapter 3, whereby health outcomes have a bidirectional relationship with psychological health status. However, there is a lack of clarity on other situational or biological factors that could be influencing this relationship, such as medication.

In a systematic review of the literature in primary care, the most frequent patterns of multimorbidity in OA was with cardiovascular and/or metabolic conditions (223). OA sufferers are more likely to develop other physical and psychological co-morbidities (224–226). The presence and number of co-morbid conditions have been associated with a functional decline in both knee and hip OA (227). Research has shown that OA sufferers often have the following comorbidities: hypertension, cardiovascular disease, peripheral vascular disease, congestive heart failure, renal function impairment, diabetes and respiratory disease (208,228,229).

4.2.5 Effect of time on medication management

Interestingly, over the past 20 years there was been increasing evidence that the consumption of prescribed medication at different times of the day yields large differences in the plasma levels (230,231). Traditional pharmacokinetic studies were always carried out in the morning and the results generalised to other times of the day, thus time of day was not considered an important factor. However, with this increasing evidence of circadian variations in the pharmacokinetics of medication this has raised a question regarding the most optimum time to treat or administer an intervention. In addition, this will enable a more patient-centred approach with the individualisation of drug treatment. Thus, the effect of time of day on health outcomes will be explored in this study with individuals.

4.2.6 **Health outcomes for asthma, osteoarthritis, and depression**

Co-morbid individuals usually experience greater impairments and more severe outcomes, for example those with arthritis and depression report greater functional impairment and worse HRQoL compared to individuals with just arthritis (232). Individuals with depression and arthritis often report that their depression exacerbates their experience of pain (232,233). It is widely acknowledged that arthritis in general negatively impacts on QoL and HRQoL, given the limitations it places on individuals' lives (232,234–237). In osteoarthritis patients, a greater number of comorbid conditions, higher levels of psychological distress and the need for walking aids were associated with worse levels of pain, function and HRQoL (225,234). Lower ratings of QoL have been shown to be affected by age, level of physical disability, and pain in osteoarthritis patients (235).

Asthma is associated with impaired HRQoL, in particular the presence of problems with anxiety/depression (238,239). The level of asthma severity is associated with varying levels of HRQoL, with severe asthma associated with significant HRQoL burden which is due to the frequency of symptoms, life-threatening attacks, increased comorbidities and the need for more pharmacological interventions (240). Decreasing levels of asthma control have also been associated with increased problems related to sleep, depression, functional impairment, and effect on work and regular activities (241).

Much of the published research has explored the impact of depression alongside a physical health condition on outcomes. However, it is also known that major depression on its own is also associated with poorer outcomes in general, especially in older adults (242,243). Major depression is linked to diminished role

functioning (e.g. work/social life), with greater sickness days and lower quality of life (202,244–247).

4.2.7 **Methodological approach**

A longitudinal study design allows researchers to assess multiple aspects of the condition they are studying. It allows analysis of changes in outcomes over time which could be associated with disease-related risk factors (248), as well as environmental factors (e.g. weather, social events). In addition, this type of study design allows examination of individual, as well as group patterns of changes in symptoms over time. Analysing temporal changes longitudinally is important for clinicians as it provides information on specific time patterns of clinical impairments (248). This is the rationale for using this type of design to document changes in outcome scores over varying periods of time in this study.

A mixed methods approach to data collection and analysis allows for the validation, interpretation and strengthening of the conceptual model developed in Chapter 3 (249). The collection of quantitative data followed by a qualitative approach can inform the further development and refinement of existing hypotheses (250,251). Researchers can then combine these findings, a process called triangulation whereby in mixed methods research it is “studying a problem using different methods to gain a more complete picture” (250). The integration of both quantitative and qualitative results can be done in various ways (252,253), and can yield insights useful for understanding cyclical variation in patient reported outcomes, and what impacts changes in outcome scores (252). Thus, a mixed methods longitudinal study design was used for this study and the integration of quantitative and qualitative results will be discussed in the methods section.

4.2.8 **Reflexive practice as a qualitative researcher**

Qualitative research is contextual in that it occurs at a specific time and place involving two or more individuals. Reflexivity has been recognised as an important strategy during the process of generating knowledge through qualitative research (254). Although the concept of reflexivity has been used interchangeably with other terms, for the purposes of this thesis the following definition will be used. It is the process by which a researcher has a continuous internal dialogue and critical self-evaluation of their theoretical positioning and recognition that this may impact on the research process as well as the analysis (255–257). Thus, reflexivity is a form of self-appraisal in research. It has been well established that this process should ensure rigour and quality in qualitative work and is a gold standard for determining the trustworthiness of findings (258). Reflexivity challenges the notion that knowledge production is solely objective and independent of the researcher developing it (255).

There is a risk that if a researcher follows a certain theoretical framework when analysing qualitative data then this limits what the researcher may see in the data. This is particularly important to consider in this thesis given that the analytical approach in this chapter was framed by the conceptual model developed in Chapter 3. Consideration of contextual factors, thus the role of self in the research process, increases the credibility of the findings and deepens our understanding of the work. A researcher's background (characteristics, experiences and academic discipline) can influence the approach they take when conducting qualitative research from the language and intonation they use whilst interviewing, how they analyse the data and how they shape and conclude their findings (255). Thus, taking these into account through the process of reflexivity researchers are able to manage their values, knowledge, and own biases which may affect the research process further enhancing credibility and transparency of the subjectivity of the researcher in the process (255,257,259,260). The subsequent sections provide a critical evaluation of myself as the researcher and how this may have impacted on the research process.

4.3 Aims and Objectives

The main aim of the longitudinal study was to explore in depth whether PROM scores varied across different time intervals, how they varied and what impacted on the variation for patients with asthma, osteoarthritis and depression. One of the objectives was to track patient-reported outcome scores for these patients across a nine-month period capturing different seasons within a year. The second objective was to gather information from patients about their perception of what impacts on how they report on their health status.

4.4 Methods

4.4.1 **Study setting and recruitment**

The focus of the study was within a primary care setting. Patients were recruited from a local GP surgery in Devon with a large list size to allow for maximum possibility of recruiting patients with asthma, osteoarthritis and depression. The practice manager of the GP surgery and lead GP for research were contacted via email and provided with an outline of the study, requirements for the GP staff and what it would involve for patients. This was followed up with a visit to the practice to discuss the project further with the lead GP and one of the administrators. Inclusion and exclusion criteria were provided to the administrator to assist in the database search for eligible patients. Patients over the age of 18 years who have been diagnosed with two or more of the three conditions (asthma, osteoarthritis, depression) and able to consent to take part were considered eligible.

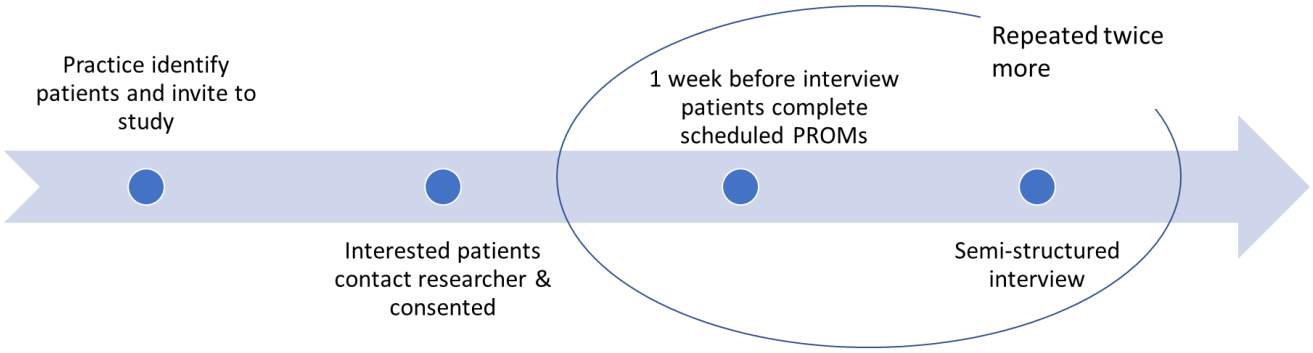
The administrator ran the database searches on the GP surgery computer system and a list of potentially eligible patients was checked by the lead GP. Once this was finalised the administrator sent an invitation pack (Appendix IV) containing: pre-prepared invitation letter on practice headed paper, the study information sheet, response form and prepaid envelope. The participant information sheet sent to the patients detailed the exact nature of the study, what it would involve, the implications and constraints of the study and if any risks were involved in taking part. It clearly stated that the participant was free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

4.4.2 **Study procedures**

Data collection occurred between the months of June 2018 and April 2019. Figure *4.1* presents the timeline of activities for the study. Patients who returned a response form agreeing to be take part were contacted either by telephone or email within two days of receipt of the form. Once contact had been established eligibility checks were made to ensure that patients had two or more of the three conditions and further information was provided. The rationale for recruiting multi-morbid patients was to allow for sufficient numbers of participants with each condition for each follow-up if retention was poor. Patients were then booked in to take part in a face-to-face interview within two weeks. A week prior to the interview, patients were asked to complete three sets of questionnaires at various times and dates. Patients had a choice as to whether they preferred an online or paper version of the questionnaires (Appendices V and VI). The questionnaires were tailored specifically to the conditions each patient had. The timings of the questionnaires were spaced out during the week to reflect both a weekday and weekend, and randomly allocated to be completed when they woke up, at noon, and when they went to bed.

At the first interview written consent was obtained from the patient and at each interview patients were reminded that their participation was voluntary, and that they could withdraw at any point not affecting their health care in any way. A copy of the signed consent form was posted to patients following the first interview. At the end of the first interview (June 2018-August 2018), patients were reminded that they would be contacted in late November 2018 (2nd interview) and again in March 2019 (3rd interview) for the following two interviews. In mid-November 2018 all patients were contacted for their second interview and a suitable time and date were organised.

Figure 4.1 Study timeline of activities



4.4.3 **Outcome measurements**

All the outcome measurements used for the study can be found in Appendix V and VI. The PROMIS initiative was born out of the United States, and is increasingly recognised as the international gold standard for patient-centred assessment (261). It is the largest resource of items covering different domains for physical, mental and social health. The PROMIS Global-10 measure is a global health assessment tool measuring symptoms, functioning, and health-care related quality of life for chronic conditions (262). It consists of 10 items that assess general domains of health and functioning which includes overall physical, mental and social health, pain, fatigue and perceived quality of life. These items have been adapted from other globally validated measurements such as SF-36 and EQ-5D, enabling the questions to be more sensitive and precise than the original items. For items Global01, 02, 03, 04, 05, 09, the scale options ranged from Excellent (5) to Poor (1). These six questions covered general health (e.g. Global01: In general, would you say your health is), psychological status (e.g. Global04: In general, how would you rate your mental health, including your mood and your ability to think?), and physical limitations (e.g. Global09: In general, please rate how well you carry out your usual social activities and roles). For Gloabl06 the scale options ranged from Completely (5) to Not at all

(1). The scale options for Global10 were Never (5) to Always (1). The scale options for Global08 were None (5) to Very Severe (1). Global07 was on a 10-point scale (ranging from 0: No pain to 10: worst imaginable pain), rather than a 5-point scale like the other items thus scores were recoded as follows: 0=5; 1, 2, or 3=4; 4,5, or 6 = 3; 7,8 or 9 = 2; 10 = 1. After recoding, the global physical health scores were a sum of Global03, Global06, Global07 and Global08. The global mental health score was a sum of Global02, Global04, Global 05 and Global10.

Physical health and mental health T-scores can then be calculated through an online scoring service provided by the Assessment Centre (263). The T-score distributions are standardised for a US population with a mean (SD) of 50(10) (261). The US sample was drawn from the 2000 United States Census and was representative of age, gender, and ethnicity (264). The higher the T-score the more the concept is being measured, for example a high (above average) global physical health T-score indicates a better than average global health compared to the mean of the US population (264). There are currently no MID published thresholds found in the literature, apart from a conference abstract in rheumatic diseases indicating a five-point difference. However, in oncology studies using the PROMIS suite a three-point difference in T-scores is deemed clinically meaningful (265). For the purposes of this PhD a range of three to five will be considered clinically meaningful. Given that the PROMIS system is becoming gold standard and sensitivity of PROMIS-10 it was decided to use this PROM in the current study.

The Patient Health Questionnaire (PHQ-9) (266) is a validated self-administered 9-item measurement focussing on depression based on the diagnostic criteria for major depressive disorders in Diagnostic and Statistical Manual Fourth Edition (DSM-IV). It assesses symptoms and functional impairment in order for

primary care clinicians to make a depression diagnosis, deriving a severity score to provide a direction for treatment. The questionnaire takes less than three minutes to complete. Each item has a scale ranging from 0 (not at all) to +3 (nearly every day). In order to derive a total score, all the items are summed up. In terms of levels of depression severity, scores between 0-4 reflect no severity, 5-9 is mild severity, 10-14 is moderate severity, 15-19 is moderately severe, and scores between 20 and 27 are considered severe. A conservative estimate of a change in scores of five or greater in the PHQ-9 was suggested to reflect a clinically relevant change in individuals with depression (267). The PHQ-9 is a commonly used PROM within Primary Care services in the UK as a screening tool for depression. GPs use this as recommended by NICE guidelines to assess depressive severity in patients presenting with depressive symptoms with the aim of determining the best course of treatment for that individual. Thus, it was determined that this was the optimum PROM to use for this study.

The Western Ontario and McMaster Universities Arthritis Index (WOMAC) is a validated, self-administered patient-reported outcome measurement widely used in the evaluation of hip and knee Osteoarthritis. It consists of 24 items divided into three subscales: Pain (5 questions), Stiffness (2 questions), and Physical Function (17 questions) and takes approximately 12 minutes to complete. The responses are on a 5-point Likert scale ranging from 0-4, corresponding to None (0), Mild (1), Moderate (2), Severe (3), and Extreme (4). Each of the three subscales is summed up with higher scores denoting worst outcomes. The range of possible scores for each subscale is: 0-20 for Pain, 0-8 for Stiffness, and 0-68 for Physical Function. A total sum of the scores for all three subscales gives a total WOMAC score. For the WOMAC, a 10–15 point change in the total score is considered a MCID, the MCID

ranged from 8 for stiffness, 9 for function to 11 for pain (268). During the PhD several osteoarthritis PROMs were assessed within our research group (Health Services Research and Policy group) using a tool that evaluated the measurement of patient-reported outcomes called EMPRO (269). EMPRO is a questionnaire completed by individual appraisers to evaluate any PROM in terms of its structure and content (e.g. conceptual framework, reliability, validity, responsiveness). From this assessment the WOMAC was determined to be the best functioning PROM for general osteoarthritis, whereas others were more specific to certain types of osteoarthritis (e.g. knee, elbow). In addition, Harris et al (2016) (270) carried out a review of osteoarthritis PROMs and found that WOMAC was one of the best performing disease specific PROM for this condition. For these reasons, it was decided that WOMAC was the best option for this study.

The Asthma Quality of Life Questionnaire with Standardised Activities (AQLQ(S)) is a validated quality of life questionnaire focusing on functional problems (physical, emotional, social and occupational) that are important to adults between the ages of 17 and 70 years with asthma (271). The AQLQ(S) is a simpler version of the original AQLQ in which the activity questions are standardised. There are various versions of the AQLQ(S), including a shortened questionnaire (mini AQLQ), a questionnaire for young people (AQLQ+12), and paediatric versions. For the purposes of this study the original questionnaire was used. The questionnaire has 32 questions separated into four domains: symptoms (12 questions), activity limitations (11 questions), emotional function (5 question) and environmental stimuli (4 questions). Patients are asked to reflect over the preceding two weeks when completing the questionnaire and respond on a 7-point scale for the questions (7 = not impaired at all - 1 = severely impaired). The questionnaire has been validated for

use in both a clinical and research setting (272). The AQLQ has responsive and longitudinal validity thus is sensitive enough to detect changes patients experience either due to an intervention or a natural fluctuation in the health condition (273). The minimal important difference (MID) for this questionnaire has been determined as 0.5 on the 7-point scale (274). In 2014, a review of the asthma PROMs identified 68 PROMs that were used for children and adults. This review demonstrated that the AQLQ was the most validated PROM to be used for an adult population and offered promise for use in clinical settings (275). It was decided that this was the best PROM to use for asthma in this study.

4.4.4 **Qualitative methods**

Semi-structured interviews were carried out with patients at three different time points using a topic guide (see Appendix VII) which was informed by the literature on patient experience of chronic conditions, and the scoping review completed prior to the longitudinal study. All interviews were audio-recorded lasting from one hour to an hour and a half. Audio-recordings were then transcribed verbatim and anonymised. All transcripts were then uploaded into NVivo software to analyse.

As the patients had completed a set of patient reported outcome measurements prior to the interview, scores were presented to the patients at the time of the interview. The first interviews focused on their scores and what potentially influenced the variation of scores at different time-points in a day or week. In addition, the interviews explored the history of their health, whether and how their symptoms varied over time and what external factors (socially determined) could have impacted on how they reported their symptoms. The topic guide was structured

with the following headings and subheadings, with questions designed to address each of the following: health status, social situation, and condition experience.

The second and third interviews primarily focused on changes since the initial interview, on their scores and what influenced their scores and how these compared to the previous interview(s). In addition, in the final interview the relationship between the conditions was explored, confirming which of their conditions was the index condition.

4.4.5 **Ethical considerations**

An ethics application was submitted with all the supporting documentation and protocol to the South Central - Oxford C NHS Research Ethics Committee for review. Following a proportionate review, ethical approval was granted in March 2018 (Ethics reference: 18/SC/0179). One of the ethical considerations brought to the attention of the committee was the potential burden of repeated interviews and completion of measurements over a nine-month period. However, patient and public involvement (PPI) was included prior to the ethics submission and the PPI members were not concerned regarding the potential overburden given the length of the data collection period.

4.4.6 **Quantitative analysis plan**

Each of the PROMs was individually calculated using the relevant scoring systems. PROMs scores were presented in a graphical form to patients at the time of their interview. To determine a change in scores, the difference between the current score and previous score was calculated and compared to existing MID/MCID scores published for each of the PROMs. The interpretation of the PROMs scores

was incorporated into the discussion of the themes within the qualitative analysis. Due to the small numbers in this study, no further statistical analysis was possible.

4.4.7 **Qualitative analysis**

A Framework method was used to analyse qualitative data at each time point for each individual, and between condition subgroups (276), using the conceptual model as a guide. The framework method sits within the family of analytical methods termed thematic or qualitative content analysis (277). The framework method is not aligned with any epistemological, philosophical or theoretical approach and is a flexible tool that can be adapted to use with multiple qualitative analytical approaches that aims to generate themes. The aim is to draw similarities and relationships between different aspects of the data to describe and/or explain certain phenomena clustered around themes (277). The difference in this method, over other qualitative analytical methods, is that data are summarised in a matrix output (using rows and columns). The rows are cases, defined as individual participants, with columns holding the relevant themes.

The method allows researchers to do an in-depth analysis of key themes across the whole dataset whilst at the same time ensuring that the voices/views of the individual participants are not lost (277). Framework analysis allows us to compare data across cases (i.e. individuals) as well as within cases (i.e. between time points for each individual).

The analytical approach taken for this study used both a deductive and inductive approach. In the deductive approach, themes were pre-selected based on the concepts from the conceptual model developed in Chapter 3. However, if another qualitative analysis approach was chosen such as Grounded Theory this would not be possible as this method is data driven (i.e. inductive). An inductive approach was

used to generate further themes from the data that would be relevant in explaining cyclical variation of PROMs in the chronic conditions being studied.

The aim for this study was to analyse the variation of themes arising within individuals at different time-points and make comparisons within individiuals across different timepoints and across individuals in the sample. The data were analysed thematically within each individual and examined by condition, then organised by themes from the conceptual model as well as any additional themes that were relevant to the interviewees.

Transcripts were coded line by line applying the thematic code which described that passage, either using the pre-existing codes or any newly generated codes. A sub-sample of the transcripts (five transcripts) were blindly coded by two other researchers within the HSPRG team (Charlotte Bramwell and Ian Porter). All the researchers met to compare and agree the codes. An analytical framework was developed following this exercise and shared with both researchers. The coding framework was applied to the remaining transcripts and continually developed through each time-period, thus making it an iterative process.

4.4.8 **Integration of quantitative and qualitative results**

The integration of the themes developed from the qualitative transcripts and the PROM scores was conducted at the analysis stage. A mixed methods matrix was created along the lines of Miles, Huberman (249) meta-matrix and further examples/guidance were drawn from O'Cathain et al (250). As described above in the qualitative analysis section (framework method), the rows represent the individual participants for which there is both qualitative and quantitative data, and the columns display different data collected on each individual. The columns corresponding to the outcomes in the conceptual model displayed the actual PROM

score for that health outcome. This helped to identify any negative cases (when a respondent's PROM score does not fit with the themes) within the qualitative analysis to facilitate understanding. Thus, if participants highlighted that a certain time of day or year was worse for them, this was not reflected in the scores, we can use the qualitative data to explore for this discrepancy in the data (as demonstrated in Table 4.1).

Table 4.1 Integration of PROMs scores and qualitative evidence

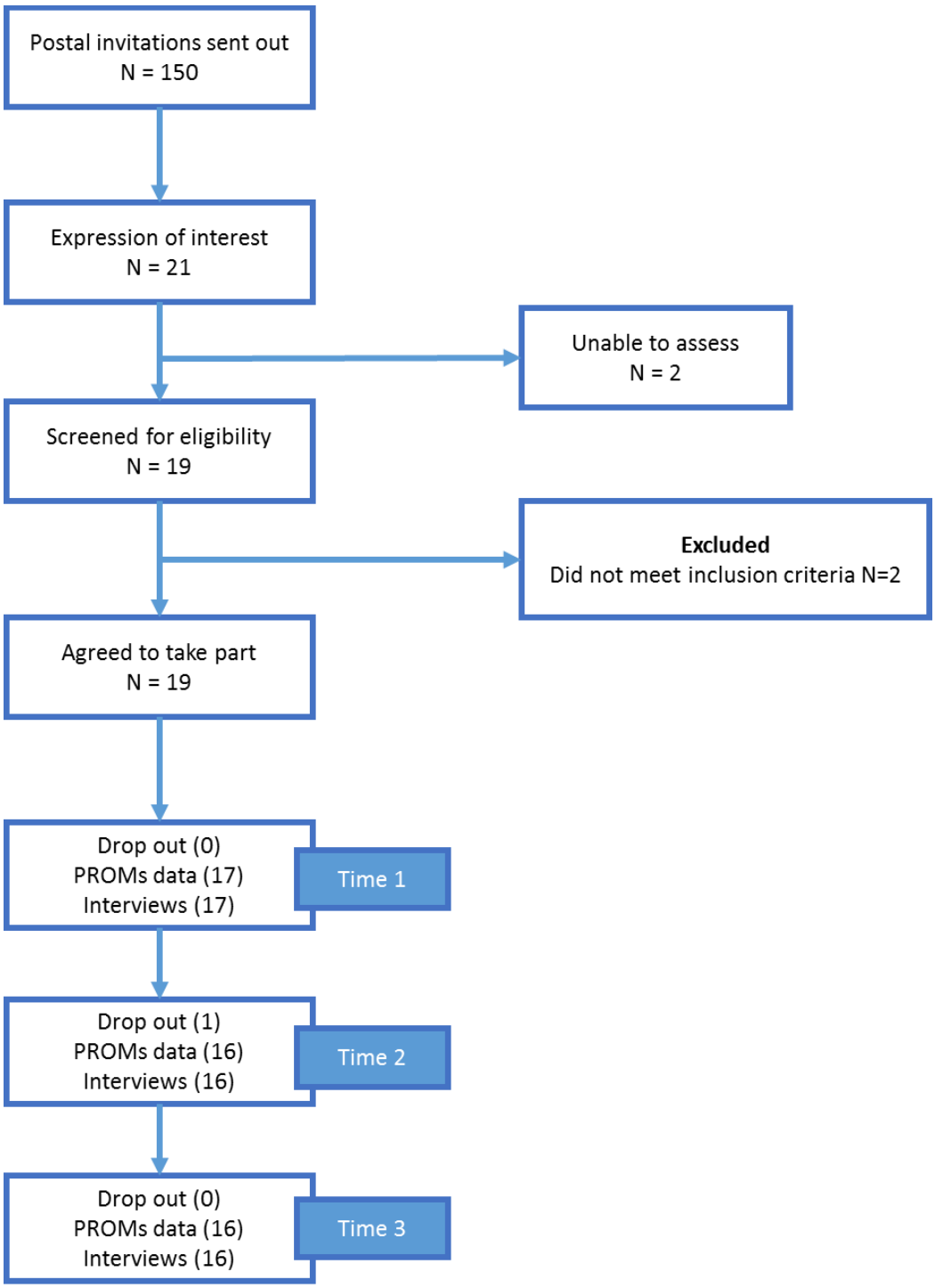
Participant	Time period	WOMAC PROM means[1]			Qualitative evidence
		Pain	Stiffness	Physical function	
Emily	Summer	4.33	2.67	21.33	"…the heat plays havoc with my hands" "so it's my hands in the summer, my feet in the winter" (soreness is the worst)
	Winter	10.00	4.00	38.67*	"Yes, and the weather's coming nicer now. Do you know what I mean? It should be easing a bit now. Getting a bit better"
	Spring	6.67	2.67	26.67*	

[1] The higher the WOMAC scores the worse the symptoms
* Denotes a significant difference from the previous score

4.5 Results

A total of 150 patients were invited to take part through postal invitations, and of those invited 21 patients responded to the study, with 17 consenting to take part. The remaining four patients were either ineligible (N=2) or failed to respond to initial phone calls/emails (N=2). A total of 16 participants were retained throughout the nine-month period, enabling a 94.1% retention rate. One participant withdrew from the study following the first interview due to time commitments and changes to work schedules (Figure 4.2). **Error! Reference source not found.** presents the sample characteristics of those who took part.

Figure 4.2 Participant flow chart



4.5.1 **Participant characteristics**

Half of the participants had osteoarthritis and depression (50%), whilst just over a third had asthma and depression (31.3%). There was almost an even split across both genders, with slightly more females in the participant sample (56.3%). Over half of the participants were retired (62.5%), with most participants being over the age of 65 years. The two participants who classed themselves as permanently sick or disabled were below the retirement age and in their 40s and 50s. There were two individuals who worked full-time, although one participant had a change in their employment status as they were made redundant by the third interview.

Some participants had additional chronic conditions, including diabetes, cancer and fibromyalgia. There was one participant who had diabetes and fibromyalgia alongside their osteoarthritis and depression. The participant with cancer did not receive any pharmacological interventions (chemotherapy) until the third interview in spring 2019. Four participants reported being treated for hypertension and currently taking medication for this condition. One participant reported having sleep apnoea and was using a CPAP machine at night.

Table 4.2 Characteristics of each participant, their conditions and medication

Pseudonym	Conditions	Years with condition	Time period worst	Gender	Age	Working status	IMD Decile*	Medication
Cathy	Osteoarthritis	15	Morning, evening & winter	Female	74	Retired	3	Ramipril, Omneprazole, Lansoprazole, Diclofenac sodium, Venotolin and Becotide
	Depression	5	Evening & winter					
Rebecca	Asthma	42	Summer & winter	Female	44	Part-time	3	Phyllocontin, symbicort inhaler, fexofenadine,
	Depression	10	Morning, evening, & weekday					
Tom	Osteoarthritis	10	Morning & evening	Male	65	Retired	6	Statins, Becotide and Ventolin
	Asthma	4	Summer & winter					
Luke	Osteoarthritis	5	Evening	Male	70	Retired	6	Ventolin, Seretide, Gabepentin, Oxycodon
	Asthma	40	Summer & winter					
Rachel	Osteoarthritis	4	Morning, evening, & winter	Female	62	Retired	7	Codeine, Becotide and Ventolin
	Asthma	1	Spring & summer					
Sarah	Asthma	All life	Weekday & summer	Female	49	Part-time	4	Ventolin and Becotide, Citalopram (stopped)
	Depression	2	Evening & weekend					
Ben	Osteoarthritis	10	Winter	Male	58	Retired	3	Nothing unless desperate
	Depression	9	Weekday & winter					
Laura	Osteoarthritis	9		Female	77	Retired	3	Levothyroxine
	Depression	18	Morning, evening, spring & winter					

Will	Asthma Osteoarthritis Depression	65 50 5	Lunchtime & summer Morning	Male	71	Retired	5	Citalopram, Tramadol, Rimipril
Emily	Osteoarthritis Depression	13 5	Morning Morning & weekend	Female	58	Part-time	6	Corticosteroid injections, HRT, Ramipril
Leo	Asthma Depression	6 4	 Evening	Male	58	Retired	3	Sertraline (T1), Mirtazapaine (T2), Pemetrexed (chemo)
Jack	Osteoarthritis Depression	10 5	Morning & winter	Male	63	Permanently sick	3	Tramadol
Olivia	Osteoarthritis Depression	2 6	Winter	Female	67	Retired	3	Citalopram
Mary	Osteoarthritis Depression	50 10	Evening	Female	75	Retired	3	Co-codamol, Omneprazole, Mastebolin
Max	Asthma Depression	10 16	Winter Lunchtime, weekday, & winter	Male	66	Permanently sick	7	Prozac, Metformane, Omeprazole, Statins
Bella	Osteoarthritis Depression Asthma	5 3 37	Evening Evening & winter	Female	47	Permanently sick	5	Amitriptyline, Co-codamol, Duloxetine, Iron tablets, Ventolin, Becotide

4.5.2 **Quantitative results**

Bearing in mind that the quantitative data presented for this chapter are based on a small sample size of participants, no definitive conclusions can be made about the analysis. However, observations on individual changes will be highlighted on the PROMs scores and the qualitative data presented in section 4.5.3 will provide further explanations for any observed changes. Appendix VIII presents graphs presented to participants of their PROMs scores over different time points.

4.5.2.1 PROMIS-10 Global-10

All participants completed this generic questionnaire (N=16). The raw summed scores for each participant at each time-point was converted into T-scores. The higher the T-scores the better the outcome for their global health and mental health. T-scores for global health ranged from 23.5 to 50.8, just above the US population average, demonstrating that reported physical health was generally lower in this study population (mean = 38.85; median = 37.4). Using the MID range of three and five points difference in timepoints, seasonal and time of day differences were observed (Table 4.3 and a Osteoarthritis; [b] Depression; [c] Asthma

Table *4.4*). There were seasonal differences in all but one participant (Max). There were no seasonal differences for Max in his disease-specific PROMs (AQLQ, PHQ-9). For six of the participants from spring to winter their physical health improved, however there were larger drops in T-score physical health means for three participants (Emily, Rachel and Mary). Six participants reported a decrease in physical health from winter to spring, whilst three reported better physical health outcomes (Sarah, Emily, Leo). Sarah and Leo's AQLQ results do not corroborate with the increased physical health T-score from Winter to Spring, however, change in Emily's WOMAC scores across these time periods match. Four out of the six

participants experienced a decline in physical health from summer to spring, with Luke and Sarah reporting an improvement. For Luke and Sarah, their asthma symptoms reported on the AQLQ similarly improved between these time periods. However this was not the case for Luke's WOMAC scores, where he reported a decline in pain and physical function (Table 4.6).

All participants barr three reported either a decline in physical health (N=6), or an increase in physical health (N=8) between the morning and afternoon. Ten participants had a difference in scores between afternoon and evening, mainly for seven who experienced an increase in physical health. Finally, only one person out of eight reported a change in their physical health for the better, Luke between the evening and morning. This coincides with his AQLQ scores, but not his WOMAC scores where they are worse in the mornings.

Table 4.3 Mean PROMIS Global-Physical health T-scores and differences across timepoints

Participant	Season T-score mean				MID season difference				Time of Day T-score mean				MID time of day difference		
	Summer	Winter	Spring		S-W[1]	W-Sp[2]	S-Sp[3]		Morning	Afternoon	Evening		M-A[4]	A-E[5]	E-M[6]
Cathy [a b]	30.33	24.9	29.6		5.43*	-4.7*	0.73		29.47	42.43	30.07		-12.96*	12.36*	0.6
Ben [a b]	43.47	40.37	42.7		3.1*	-2.33	0.77		60.53	44.65	42.7		15.88*	1.95	-17.83*
Laura [a b]	37.97	37.13	39.57		0.84	-2.44	-1.6		37.97	37.97	38.73		0	-0.76	0.76
Emily [a b]	31.1	41.13	32		-10.03*	9.13*	-0.9		33.08	39.9	34.75		-6.82	5.15*	1.67
Jack [a b]	40.33	36.3	48.3		4.03*	-12*	-7.97*		68.4	41.1	56.4		27.3*	-15.3*	-12*
Olivia [a b]	41.9	30.07	42.7		11.83*	-12.63*	-0.8		37.4	58	37.37		-20.6*	20.63*	-0.03
Mary [a b]	27.3	33.8	32.97		-6.5*	0.83	-5.67*		31	32	31.1		-1	0.9	0.1
Bella [a b]	29.56	25.1	27.14		4.46*	-2.04	2.42		49.44	26.65	27.17		22.79*	-0.52	-22.27*
Tom [a c]	55.33	45.87	54.2		9.46*	-8.33*	1.13		52.53	78.23	50.93		-25.7*	27.3*	-1.6
Luke [a c]	33.8	30.2	30.33		3.6*	-0.13	3.47*		48.4	31.1	69.4		17.3*	-38.3*	21*
Rachel [a c]	40.33	57	57.5		-16.67*	-0.5	-17.17*		73.18	65.73	56		7.45*	9.73*	-17.18*
Rebecca [b c]	28.83	26.75	35.47		2.08	-8.72*	-6.64*		30.24	29.1	30.7		1.14	-1.6	0.46
Will [b c]	49.97	40.37	49.13		9.6*	-8.76*	0.84		50.8	83.68	48.3		-32.88*	35.38*	-2.5
Sarah [b c]	59	48.3	43.5		10.7*	4.8*	15.5*		91.98	44.65	74.2		47.33*	-29.55*	-17.78*
Leo [b c]	38.75	39.95	36.3		-1.2	3.65*	2.45		50.83	37.9	37.97		12.93*	-0.07	-12.86*
Max [b c]	33.67	32.97	33.8		0.7	-0.83	-0.13		54.45	50.08	30.48		4.37*	19.6*	-23.97*

* and greyed out numbers denotes that the difference is between 3-5 points

[1] Summer to Winter; [2] Winter to Spring; [3] Summer to spring; [4] Morning to afternoon; [5] Afternoon to evening; [6] Evening to morning

[a] Osteoarthritis; [b] Depression; [c] Asthma

Table 4.4 Mean PROMIS Global-Mental health T-scores and differences across timepoints

Participant	Season T-score mean			MID season difference			Time of Day T-score mean			MID time of day difference		
	Summer	Winter	Spring	S-W[1]	W-Sp[2]	S-Sp[3]	Morning	Afternoon	Evening	M-A[4]	A-E[5]	E-M[6]
Cathy [a b]	30.33	24.9	29.6	5.43*	-4.7*	0.73	29.47	42.43	30.07	-12.96*	12.36*	0.6
Ben [a b]	43.47	40.37	42.7	3.1*	-2.33	0.77	60.53	44.65	42.7	15.88*	1.95	-17.83*
Laura [a b]	37.97	37.13	39.57	0.84	-2.44	-1.6	37.97	37.97	38.73	0	-0.76	0.76
Emily [a b]	31.1	41.13	32	-10.03*	9.13*	-0.9	33.08	39.9	34.75	-6.82*	5.15*	1.67
Jack [a b]	40.33	36.3	48.3	4.03*	-12*	-7.97*	68.4	41.1	56.4	27.3*	-15.3*	-12*
Olivia [a b]	41.9	30.07	42.7	11.83*	-12.63*	-0.8	37.4	58	37.37	-20.6*	20.63*	-0.03
Mary [a b]	27.3	33.8	32.97	-6.5*	0.83	-5.67*	31	32	31.1	-1	0.9	0.1
Bella [a b]	29.56	25.1	27.14	4.46*	-2.04	2.42	49.44	26.65	27.17	22.79*	-0.52	-22.27*
Tom [a c]	55.33	45.87	54.2	9.46*	-8.33*	1.13	52.53	78.23	50.93	-25.7*	27.3*	-1.6
Luke [a c]	33.8	30.2	30.33	3.6*	-0.13	3.47*	48.4	31.1	69.4	17.3*	-38.3*	21*
Rachel [a c]	40.33	57	57.5	-16.67*	-0.5	-17.17*	73.18	65.73	56	7.45*	9.73*	-17.18*
Rebecca [b c]	28.83	26.75	35.47	2.08	-8.72*	-6.64*	30.24	29.1	30.7	1.14	-1.6	0.46
Will [b c]	49.97	40.37	49.13	9.6*	-8.76*	0.84	50.8	83.68	48.3	-32.88*	35.38*	-2.5
Sarah [b c]	59	48.3	43.5	10.7*	4.8*	15.5*	91.98	44.65	74.2	47.33*	-29.55*	-17.78*
Leo [b c]	38.75	39.95	36.3	-1.2	3.65*	2.45	50.83	37.9	37.97	12.93*	-0.07	-12.86*
Max [b c]	33.67	32.97	33.8	0.7	-0.83	-0.13	54.45	50.08	30.48	4.37*	19.6*	-23.97*

* and greyed out denotes that the difference is between 3-5 points

[1] Summer to Winter; [2] Winter to Spring; [3] Summer to spring; [4] Morning to afternoon; [5] Afternoon to evening; [6] Evening to morning

[a] Osteoarthritis; [b] Depression; [c] Asthma

Similar to the physical health t-scores, mental health t-scores ranged from 21.2 to 59, which is slightly higher than the global health range (mean = 38.2; median = 36.3). The majority of participants (N=12) reported a change in their mental health T-scores with nine of them reporting an improvement between summer and winter. The three participants who reported a large decline in mental health were Rachel, Emily and Mary, although only Mary had a significant change in her PHQ-9 score across this period. Half of the participants experienced a change in mental health between winter and spring, with five reporting a decline. Olivia had the largest decline in mental health which does not correspond with her PHQ-9 results. There were only six participants who reported a difference between summer and spring, with two improving in mental health (Luke and Sarah). This coincides with Sarah's PHQ-9 scores improving across these seasons, however Luke's emotional function domain in the AQLQ did not reflect this.

All but three participants reported a significant change in their mental health from morning to afternoon. Eight participants reported an increase in their mental health, with score differences ranging from 4.37 to 47.33. Those who reported a decline in their mental health between the morning and afternoon had a smaller range from 12.96 to 32.88. More than half experienced a change between the afternoon and evening, with Will reporting the most improvement. Although the direction of change was the same for his PHQ-9, there was no significant change in his scores. All participants reported a decline in mental health from evening to morning on the PROMIS mental health domain. This only coincided with Jack's PHQ-9 scores, where there was a significance difference between the evening and morning scores.

4.5.2.2 WOMAC

As there were a total of 11 participants with osteoarthritis all of these participants completed the WOMAC. The higher the WOMAC score, the more severe the osteoarthritis is for participants. As mentioned in the methods section, the WOMAC PROM has three subscales, pain (0-20 score), stiffness (0-8 score), and physical function (0-68 score). Apart from Olivia, Bella, Tom, Luke, and Rachel, most of the participants did not experience difficulties in their physical function according to their WOMAC scores (Table 4.5). Generally, an increase in the WOMAC physical function score appeared to correspond with an increase in the PHQ-9. Only Bella appeared to report quite high pain scores in comparison to the other participants. However, stiffness scores varied considerably, with little variation across the day reported.

Emily, Mary, and Tom experienced a change in their pain levels from summer to winter, and further explanations from their interviews is discussed in section 4.5.4.4. Difficulty performing tasks varied with some participants (e.g. Ben, Emily, Mary) reporting seasonal differences in their ability to carry out daily tasks. Emily and Mary reported significant difficulties in the winter, whilst Ben reported the increased difficulty in the spring.

4.5.2.3 AQLQ

There were 8 participants with asthma who completed the AQLQ alongside one of the other disease-specific PROMs. The lower the score on the AQLQ, however, the worse the asthma was for that participant. AQLQ has four domains (symptoms, activity limitations, emotional function, and environmental stimuli), and a change of 0.5 on the AQLQ has been determined as a meaningful change. There were very small fluctuations in AQLQ activity limitation scores over the course of a

day, with some meaningful changes occurring between afternoon and evening (worsening) for only two participants (Luke and Rachel) (Table 4.6). Afternoons appeared to be worse for symptoms of asthma for Will and Leo, with lower scores observed than in comparison to other times of the day (Table 4.7). There were very little fluctuations during the course of the day in terms of symptom reporting. This was a similar story for how they emotionally felt, with only Leo and Luke feeling worse in the evening, Rachel feeling better in the evening and Sarah feeling better in the afternoon. Only Will and Luke reported significant impact of environmental stimuli between the afternoon and evening, whilst the other participants did not report significant changes that impacted on their asthma.

Most of the participants reported significant seasonal changes in their experience of their asthma across all four domains. Will, Luke and Sarah all reported their asthma symptoms being worst in the summer limiting their activities and affecting their emotions. Will and Luke, only, reported that there were significant environmental stimuli affecting their asthma in the summer in comparison to the other two seasons. However, Sarah reported that the winter was worse for environmental stimuli, although this may have been due to an illness that she experienced during the winter. Winter affected all four domains the worst for Rebecca and Rachel, whilst Tom and Leo reported significant increase in asthma symptoms in the spring.

4.5.2.4 PHQ-9

A total of 13 participants completed the PHQ-9. The higher the PHQ-9 scores, the worse the depressive state individuals were in, with a score of 10 or more being moderate to severe depression. A change of 5 points on the PROM is determined as meaningful. Most participants with a depression diagnosis, reported experiencing

moderate to severe depression through the study period, although this fluctuated. There were only two participants, Jack and Rebecca, who reported significant changes in their depressive state during the course of the day, whilst slight fluctuations were observed amongst the other participants. There was a significant improvement in some participants' depression (Emily, Jack, Olivia, Mary and Rebecca) between winter and spring, apart from Leo who saw a significant rise (which could have been due to the start of his chemotherapy treatment).

Table 4.5 Osteoarthritis and depression PROMs means by time period

Participant	Time period	WOMAC PROM means			PHQ-9 PROM means
		Pain	Stiffness	Physical function	
Ben	Summer	6.33	2.00	8.00	3.00
	Winter	3.67	2.33	6.33	4.33
	Spring	7.33	3.67	15.33*	2.33
	Morning	5.33	2.33	9.67	2.67
	Afternoon	5.33	3.00	9.00	3.33
	Evening	6.67	2.67	11.00	3.67
Laura	Summer	2.67	2.33	12.67	15.00
	Winter	4.00	2.67	12.67	12.00
	Spring	3.00	4.00	20.33	12.67
	Morning	2.67	2.33	13.00	13.67
	Afternoon	4.00	3.67	17.33	12.67
	Evening	3.00	3.00	15.33	13.33
Emily	Summer	4.33	2.67	21.33	13.33
	Winter	10.00	4.00	38.67*	10.00
	Spring	6.67	2.67	26.67*	3.33*
	Morning	8.67	4.00	33.33	7.00
	Afternoon	7.33	2.00	21.33*	11.33
	Evening	5.00	3.33	32.00*	8.33
Jack	Summer	10.00	4.00	35.00	1.67
	Winter	6.67	5.67	38.67	17.33*
	Spring	8.33	4.33	31.67	6.67*
	Morning	8.00	5.40	38.20	12.60
	Afternoon	10.00	5.00	37.00	10.00
	Evening	8.33	3.33	29.33*	1.33*
Olivia	Summer	10.33	5.00	41.33	6.00
	Winter	12.00	5.67	46.00	13.00*
	Spring	15.00	6.00	50.33	6.00*
	Morning	12.33	5.00	42.67	8.67
	Afternoon	13.33	5.67	47.33	8.33

	Evening	11.67	6.00	47.67	8.00
Cathy	Summer	11.33	5.33	30.00	19.33
	Winter	10.50	5.75	29.00	15.00
	Spring	10.33	5.00	36.33	16.33
	Morning	10.00	4.67	30.00	17.67
	Afternoon	14.67	5.00	34.00	18.67
	Evening	8.25	6.25	30.75	14.50
Mary	Summer	5.67	2.00	18.67	12.00
	Winter	12.67	3.33	40.00*	21.00*
	Spring	7.67	2.00	26.33*	16.00*
	Morning	8.50	2.75	26.75	15.25
	Afternoon	8.33	2.00	27.33	16.33
	Evening	9.50	2.50	33.00	18.50
Bella	Summer	15.00	6.00	53.00	19.50
	Winter	15.67	6.00	55.00	19.67
	Spring	15.89	6.00	54.22	21.56
	Morning	15.88	6.00	54.25	21.25
	Afternoon	15.50	6.00	53.25	20.00
	Evening	15.25	6.00	54.50	20.25

* Significant change from the previous score (AQLQ MCID = 0.5; PHQ-9 = 5; WOMAC stiffness = 8; WOMAC physical function = 9; WOMAC pain = 11)

Table 4.6 Asthma and Osteoarthritis PROMs means by time period

Participant number	Time period	AQLQ PROM means				WOMAC PROM means		
		Activity limitations	Symptoms	Emotional function	Environmental stimuli	Pain	Stiffness	Physical function
Tom	Summer	5.27	6.69	6.67	6.92	7.00	2.00	26.33
	Winter	5.34	6.56	6.85	6.56	11.25	3.00	34.75
	Spring	5.15	5.92*	6.40	6.17	8.00	3.33	30.00
	Morning	5.45	6.53	6.67	6.67	9.33	2.67	30.33
	Afternoon	5.18	6.50	6.90	6.58	10.00	3.00	31.67
	Evening	5.27	6.56	6.53	6.50	8.33	2.33	30.67
Luke	Summer	3.03	3.39	3.20	5.25	10.00	3.67	42.00
	Winter	5.79*	6.75*	7.00*	6.75*	10.00	3.33	40.67
	Spring	5.70	6.25	6.60	6.17	12.33	4.00	46.67
	Morning	6.05	6.67	6.90	6.63	11.50	4.00	44.50
	Afternoon	5.36	6.46	6.80	6.63	12.00	3.50	44.50
	Evening	4.15*	4.58*	4.60*	5.60*	10.00	3.60	42.00
Rachel	Summer	6.36	6.97	7.00	6.67	5.67	6.00	29.00
	Winter	5.18*	6.52	5.40	6.75	4.60	6.00	28.80
	Spring	6.36*	7.00	7.00*	7.00	5.67	6.00	31.67
	Morning	6.02	6.72	6.04	6.70	5.00	6.00	29.60
	Afternoon	6.36	6.96	7.00	6.88	5.50	6.00	30.00
	Evening	5.32*	6.75	6.20*	6.88	5.25	6.00	29.50

* Significant change from the previous score (AQLQ MCID = 0.5; PHQ-9 = 5; WOMAC stiffness = 8; WOMAC physical function = 9; WOMAC pain = 11)

Table 4.7 Asthma and depression PROMs means by time period

Participant number	Time period	AQLQ PROM means				PHQ-9 PROM means
		Activity limitations	Symptoms	Emotional function	Environmental stimuli	
Will	Summer	3.00	3.72	3.93	2.08	4.33
	Winter	3.76*	4.11	5.47*	5.25*	0.00
	Spring	4.67*	5.14*	6.67*	5.42	0.00
	Morning	3.76	4.97	5.13	4.42	1.33
	Afternoon	3.73	3.67*	5.27	3.67*	1.67
	Evening	3.94	4.33	5.67	4.67*	1.33
Leo	Summer					11.00
	Winter	4.94	5.06	4.47	5.75	10.67
	Spring	3.18	4.72	2.67*	6.08	21.00*
	Morning	4.27	4.88	3.70	6.00	13.33
	Afternoon	3.91*	4.25*	3.00*	5.50	14.67
	Evening	4.00	5.54*	4.00*	6.25	14.67
Max	Summer	5.23	6.60	6.73	6.83	9.50
	Winter	5.76	6.67	6.47	6.92	11.00
	Spring	5.82	6.83	6.00	6.92	12.67
	Morning	5.45	6.65	6.55	6.88	7.75
	Afternoon	5.52	6.79	6.40	6.94	13.75
	Evening	5.55	6.58	6.50	6.81	10.50
Rebecca	Summer	5.21	5.99	5.70	6.00	9.50
	Winter	4.84	5.19	4.60	5.63	20.00*
	Spring	6.15*	6.75*	6.60*	6.75*	13.67*
	Morning	5.25	5.88	5.49	5.93	13.29
	Afternoon	5.45	6.06	5.80	6.31	12.50*
	Evening	5.27	5.75	5.40	6.00	17.50*
Sarah	Summer	4.94	4.28	2.33	4.42	9.67

Winter	5.45*	6.81*	6.13*	6.67*	3.33*
Spring	5.18	6.47	6.20	6.17*	3.67
Morning	4.94	5.97	4.47	5.75	5.33
Afternoon	5.09	5.78	5.00*	5.58	6.00
Evening	5.55	5.81	5.20	5.92	5.33

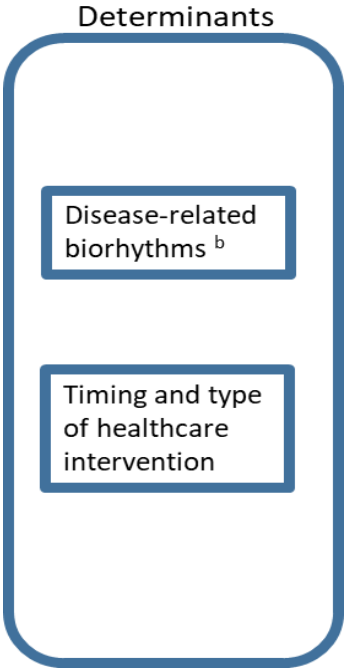
* Significant change from the previous score (AQLQ MCID = 0.5; PHQ-9 = 5; WOMAC stiffness = 8; WOMAC physical function = 9; WOMAC pain = 11)

The qualitative interviews were conducted following the completion of each set of PROMs, and the analysis of the interviews were organised according to the concepts illustrated in the conceptual model in Chapter 3 (Figure 3.3). Each of the overarching concepts within the conceptual model are presented individually in the subsequent sections along with the supporting qualitative evidence.

4.5.3 **Determinants**

There were two sub-concepts within the overarching concept of determinants within the conceptual model: disease-related biorhythms and timing and type of healthcare intervention (Figure 4.3). Each of the subthemes are discussed in the following sections.

Figure 4.3 Determinants of cyclical variation of PROMs



4.5.3.1 Disease-related biorhythms

Disease-related biorhythms are related to both the seasons of the year and time of day in terms of symptom severity across all three conditions. Depending on the individual, their biorhythms are unique to them. Participants, such as Ben and Emily, with osteoarthritis reported that stiffness was most severe in the mornings, *"I'm stiff when I get up in the morning and that finger's gone back stiff again* (Emily_T2), however once they were able to move their joints around the stiffness subsided, "*It's a little bit of stiffness, but once I'm mobile there's no problem."* (Ben_T1). This experience of morning stiffness is commonly reported in the literature highlighted in Chapter 3. In fact, any long stationary periods also resulted in increased severity of stiffness regardless of the time of year they were interviewed.

Those with asthma may experience slightly different patterns depending on which environmental conditions affect their health. Some report that mornings are more of an issue for experiencing asthma symptoms over other times of the day representing a circadian rhythm. Will recognises a pattern in his asthmatic experience, *"there is that pattern of good in the morning... it will get better, good night's sleep. It's like a bit of a wave"* (Will_T1). The likelihood of asthmatic attacks in the early hours of the morning is recognised, however some participants also reported worsening of symptoms later in a twenty-four hour period, *"during the night and in the morning yeah would be the worst time for me"* (Rebecca_T1).

Participants' asthma symptoms may be more linked to other environmental or individual factors such as stress and work environment. In addition, there is evidence to suggest that recent episodes, such as illnesses (as in Rachel's case) or hospitalisations impact on their disease pattern. *"I mean I've been I think every year for nearly almost the past ten years I'd at one point during the year had a cold which*

then ended up with this really bad cough…I tend to pick these colds up often in the spring rather than in the winter" (Rachel_T1). The rhythmic patterning of Rachel's asthma was slightly different to other participants, as it got worse in the spring (due to illness) and not the winter, and it presented as a circannual rhythm.

Depression is different for each of the participants experiencing it, and there were some participants who recognised a circadian rhythm to their depression severity. For Rebecca her depression scores are higher in the morning and her explanation for this was because she reflected on the day ahead during that time of the day, "*"that sort of time is kind of a quiet time in the morning so it's a time for probably a little bit of reflection where I'm already kind of embroiled in things at these points*" (Rebecca_T1). This is a similar situation for her in the evening, because again when her family were asleep she has the time to reflect,*" … I would say that that's right for the evening as well [low mood] because again I'm thinking about things, I've got the opportunity"* (Rebecca_T1). By the end of the day she is also feeling exhausted so that also contributes to a lower score on mood, *"…quite sort of low again because I feel sort of…you know there's so much that I haven't done that day or there's so much I need to do…I'm kind of worried about things…um and at the same time I'm so tired"* (T1).

The uncertainty of depressive episodes for participants results in a lack of awareness of the patterning of this condition for participants. Some participants discuss how their depression fluctuates for no apparent reason, which may be explained through biological changes such as cortisol fluctuations, *"Yes, but that wave of emotion that comes out-- Where does that come from? I know where the pain is, but normally, my knees are shot, so I don't understand that. No, this emotion*

is awful..." (Ben_T1). Compared to a physical condition, depression is a condition whereby some participants find it difficult to prevent changes in their mood.

4.5.3.2 Timing and type of intervention

All participants were on some prescribed medication (as seen in Appendix VIII), whether it was related to one, both or more than two conditions. The timing of when participants took their medications was dependent on the condition and purpose of the medication. For example, asthma medication such as Becotide and Ventolin was taken differently. Becotide is a preventative medication and taken less frequently, *"Yes, I use the brown one [Becotide] one each day, I always keep one or take it when I'm going away just in case I get a bad cold"* (Rachel_T3). Ventolin, on the other hand, is usually taken when symptoms are worsening*," that's the blue inhaler, instant relief, for me"* (Sarah_T1).

Most of the participants had a routine for taking their medication, whether it was at the start or end of their day. Some reported taking extra medication during the course of the day in order to alleviate their symptoms. Depending on the timeperiod of the interview (i.e. summer, winter, spring), normal medication routines are disrupted with a recent episode (e.g. illness or hospitalisation), "*I don't know if I got a wee chest cold or something but I ended up coughing all the time. I was taking more Ventolin*" (Tom_T3).

The effect of medication on an individual's symptoms and the time it takes to come into effect would influence how patients may report their experience on PROMs, *"I think you do get more good days than bad days now. They've increased the dosage and I think you're up to a level now where it's not having any more effect"* (Leo_T1). For Rebecca, an additional medication was introduced at the second interview due to increased pressures at work and she "*just broke down in the end. I*

went to the doctor's and asked for some medication. He put me on some, but it was probably about three weeks in… if you'd come here maybe two weeks ago, I would have been in tears still right now. I was that emotional still. There's obviously the increase. I've only had the increased sertraline for the last two and a half weeks" (Rebecca_T2). As seen in this quote if the interview had been scheduled earlier then Rebecca would have presented in a different way. However, this was the case for other participants whereby time of year affected their psychological status (discussed under Psychological Status and Timeperiod).

Individual's attitude to prescription medication affected how often and which medication they would be willing to take. Tom takes alternative medication to prevent the stiffness in his joints, *"I take cod liver oil every morning"* (T1) and he *"stopped a few years ago I stopped taking cod liver oil and then I was having trouble getting out of bed because I was stiff"* (T1). He used to be on stronger medication for his osteoarthritis (Diclogesic and DF18) but now only takes paracetamol. His adverseness to taking medication is evident especially when it comes to painkillers, *"I maybe should…take more than I should but unless I'm in real agony I don't tend to take them"* (T1).

Attitude to taking medication can also be linked to individual's pain thresholds and personality, as well as their length of diagnosis. Many of the participants discussed having high pain thresholds for their osteoarthritis pain, *"It's gotta hit that pinnacle when I think, "This is too much." I'll just take a couple of painkillers, a couple more if I need them later on"* (Ben_T1), and thus did not resort to taking medication unless the pain was extreme in their experience, *"That's it, I've had enough - I am taking codeine"* (Emily_T2). Those interviews that involved partners confirmed the resistance of participants in taking pain medication until the pain was unbearable,

"He waits until he's in agony before he even takes them.[tramadol and paracetamol]" (Jack_partner_T1).

The presence of partners at the interviews provided a different viewpoint of the participants' pain threshold. Partners felt this was related to the level of acceptance participants had for the amount of pain or suffering they were in "*he'd be in absolute agony after about half an hour…he won't say he's in pain. You have to make him stop and have a coffee"* (Ben_partner_T1). Pain threshold along with level of acceptance for their symptoms are important factors to consider as this affects their variation in outcomes, psychological health status and ultimately how they report on a PROM.

Participants' who had lived with their condition since childhood manage their medication in anticipation of any severe attacks (stockpiling or rationing), and this is particularly relevant for physical conditions as seen in Rebecca's case, *"I always just had a buildup on inhalers in the cupboard"* (T2). Rationing of medications only occurred with Cathy who was taking Diclofenac and was told by her GP to *"try to get by on one a day because the government don't like you prescribing them. Long-term that can bring on a heart attack, apparently. I think, "Oh God, I'll stick with one." I count them up and think, "No, you might get away with two today"* (T1). Thus, these individuals may have a heightened awareness of any subtle changes in their symptoms resulting in both an increased medication usage and changes in PROMs scores.

Although all the participants report taking either prescribed or alternative medication, many report using non-pharmacological interventions to alleviate their symptoms. These include psychological therapies such as Cognitive Behavioural

Therapy (CBT) or mindfulness (*"it was mindfulness-based cognitive therapy… that really worked well*", Max_T1), chiropractic treatment (*"What he's taught me is to manage my exceptions of what I can and can't do…He works wonders when I go"*, Tom_T1) or physiotherapy mostly, *"… it seems a lot better than it was due to recent visit to the physiotherapist"* (Laura_T2). Physiotherapy was either attended regularly in order to manage pain and stiffness levels consistently, or it was more of a reactive behaviour due to a more recent flare up or following a recent operation, "*It has come back a bit. Because that's why I thought I want to go back and see this physio again. You know, and she can see me so that's brilliant. Just for her to check it. She was so brilliant last time. Because it was horrendous"* (Laura_T1). These more recent episodes of a physical illness impact on mental health with depression and anxiety increasing, with the thought that it may impact on their physical activities, *"I've got a slight injury at the moment with my arm, I can't lift with it and this has been going on for three weeks now. I know it's only a short time span, but my thoughts are, "Is this ever going to resolve itself? Is this going to have an impact on my hockey? Am I going to have to think about retiring from the sport?" So, I totally get that if you have something that impacts on you-- So if asthma was worse for me and impacted on my daily life, then I totally get that you'd start to get low"* (Sarah_T3).

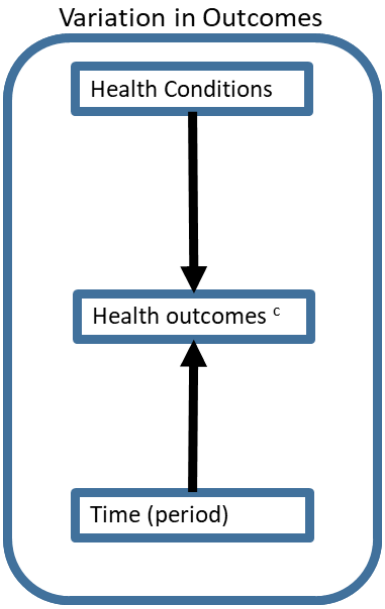
Length of diagnosis seemed to affect how in control of their health condition participants' felt, for example lifelong chronic conditions such as asthma for Sarah is *"fully under control"*, whereas depression which is a more recent diagnosis *"is not great"* (T2). Similarly, Will has had asthma and osteoarthritis most of his life and has learned to "*listen to my body*" in order to better manage his conditions (T1). This ultimately can impact on how they report their experience of their condition.

Individual and environmental factors incorporate length of diagnosis, triggers for symptoms and personality characteristics which feed into timing and type of healthcare intervention.

Taken altogether, participants were aware of the effect of their disease-related biorhythms on their experience of their condition and highlighted the varying severity over the course of the day and seasons. Participants' medication regime was dependent on their condition severity levels and recent attacks affecting their overall health outcomes.

4.5.4 **Variation in Outcomes**

Figure 4.4 Subheading of variation of outcomes



The model (Figure 3.3) developed in the scoping review outlined three main sub-themes within variation of outcomes: health conditions, health outcomes and time periods (Figure 4.4). In this study the focus was on three health conditions: asthma, depression and osteoarthritis.

4.5.4.1 Osteoarthritis and health outcomes

Participants with osteoarthritis reported pain and stiffness symptoms which fluctuated depending on weather, physical activities and biorhythms. Many reported restrictions on what activities they could participate in, and increased pain levels in the subsequent days if they had exerted themselves, *“I love doing gardening...then I know that day or the next day. It's really painful there so it won't let me do that. I have to think about what I'm doing, knowing that to try and prevent it becoming worse”* (Rachel, T1). Pain and stiffness in osteoarthritis contribute to functional limitations resulting in feelings of frustration further supporting the bidirectional relationship between variation in outcomes and psychological health status. The functional limitations that participants experienced impacted on their quality of life. Bella reflected on being “*extremely active because I come from a very industrious family. So, we were always busy, on the go, doing stuff, walking miles. We loved that sort of thing, but obviously, with all these this kicking in, you got much less quality of life"* (T1).

Although Will and Mary acknowledged that they pushed their physical boundaries affecting their fatigue levels Will stated that the increased fatigue levels ultimately *“makes me more vulnerable”* (Will_T1), whereas Mary states that *“tiredness that was making the pain"* (T1).

Length of diagnosis impacted on participants’ understanding of their condition, how they managed it and triggers to avoid, such as Emily who had osteoarthritis for 14 years reporting being *"stiff in the morning but I'm used to that now. I'm used to being seized up and all that”* (T2).

Some participants discussed having a high pain threshold, thus subtle changes in pain severity may not be recognised by these participants compared to

others. Pain thresholds are also linked to individuals' resilience and attitude to their health condition, *"I've decided that at present, I'm okay to carry on, but when the time comes, I'll what I'm going to do, as in if I'm in pain or whatever, I may take an alternative route to out"* (Leo_T2). The level of acceptance participants' had about the impact of their condition on their daily life impacted on their experience and reporting of pain levels, and ultimately their psychological health, *"I don't tend to think about the pain levels and all of that. I think I just get on with it... I got to be aware of, my pain threshold, because it could be hiding stuff" (Ben_T2)*

4.5.4.2 Asthma and health outcomes

Those with severe asthma discussed a restriction in specific activities, such as going to the gym, *"I wanted to go back to the gym at the weekend and start and… I knew I couldn't go because I would just get too wheezy and out of breath"* (Rebecca_T1), cycling and walking uphill. Stress also appeared to be a trigger for some participants, for Cathy she *"felt through that job yeah just triggered it [asthma]"* (T1).

However, for some there was some confusion as to whether symptoms experienced were those linked with asthma or anxiety*, "If I'm feeling tired and a bit down, I could start to hyperventilate very slightly. The minute I start doing that, my chest starts to tighten, but sometimes I think, "What's caused that?" More often than not, I won't think it's mood. It's got to be my reflection. I think it is.*" (Will_T1). More recent episodes, such as illnesses or hospitalisations during interviews conducted in the winter, impacted on their health condition, "*asthma is only triggered for me through illness. If I get a really bad cold..."* (Sarah_T3).

4.5.4.3 Depression and health outcomes

Depression on the other hand was very closely linked to the physical illnesses that participants experienced. Pain experience exacerbated depressive symptoms, *"It [mood] could exacerbate the feeling of pain.. maybe if I'm feeling rotten and feeling down, it could be"* (Luke_T2), and vice versa, *"Yes because I'm winding myself up. Then the pain that was missing suddenly starts hurting"* (Cathy_T2). In addition, stress from home or work environments also resulted in higher levels of depression. Many participants also reported higher levels of fatigue, which is one of the questions covered in the PHQ-9. Unlike physical conditions whereby participants knew what specifically triggered their asthma or osteoarthritis some participants were more uncertain as to why their mood fluctuated, *"I think the thing is you never know how you're going to feel"* (Laura_T1). In addition, participants reported having cognitive difficulties particularly when their mood was low.

Fatigue severity was mostly related to depression, physical activities and time of day. Tiredness impacted on how participants completed the PROMs and interpreted items on the questionnaires, *"It could be by the time later in the evening where I was feeling, really tired and exhausted and things do feel, feel worse"* (Rachel_T1).

Over the course of the day participants may be involved in different physical activities which increases their fatigue levels, thus by the end of the day fatigue levels have significantly increased. However, "*if you're not so tired you can focus more and get into actually doing something"* (Laura_T2), linking cognitive function to fatigue levels.

4.5.4.4 Time (period)

Time was a key factor in variation of outcomes across all the conditions. Appendix VIII presents which participants reported worsening symptoms according to their conditions across different time periods. Some time periods were linked to changes noticed across a 24-hour period, whilst others were longer periods such as seasonal rhythms.

All participants noticed that the time of day influenced how they experienced and reported on their health. Depending on the biorhythms of their conditions, reflection of their health varied across a 24-hour period. There was a diurnal patterning of depressive symptoms, *"first thing in the morning, I am terrible [depression]. That used to be my best time. And now yes, I think that's one of the things...So, the morning isn't the best time early on" (Laura_T2).*

This was similar for osteoarthritis symptoms, *"It [osteoarthritis pain] gets worse at the end of the night, at the end of the day when all my…when I've been walking all day, but when I come down in the morning I still have to use my… I mean I'm not holding…I'm just making sure I don't fall down the stairs, so I'm supporting myself"* (Tom_T1).

However, there was a lack of rhythmic patterning for asthma, *"depending on the conditions of the day, if it's humid, if it's wet or if there is pollution around, I can deteriorate quite quickly. By late morning I can have asthma symptoms, or hay fever symptoms or both"* (Will_T1).

The three participants who were still working noticed a weekday/weekend effect, *"evenings and Sundays, totally, are the worst"* (Sarah_T3). Whereas six of the retired participants noticed a time of week effect, with all but one recognising a

change in their depressive symptoms. Rebecca recognised that her outlook on her asthma and depression would have changed if the days that she completed the questionnaire were different, *"I was kind of tackling that I was trying to find the energy to do everything. I would've scored probably a lot higher and I know that the PHQ I probably… I was probably at the far end anyways in terms of the questions or the scores"* (T1).

Perception of health status changed depending on the time of year interviews were conducted. For example, Cathy stated that she had expected to be in poor health due to her age, *"my mind's still active but the body's sort of given up.... Everything disintegrates as you get older"* (T1).

Despite this expectation, in her second interview (during winter) she stated that she was her "own worst enemy" by getting herself "into a frazzled state" regarding her health and mortality, "*then the pain that was missing suddenly starts hurting"* (T2). This may be related to the time of year the interview was conducted, as depression levels were higher over winter. The final interview conducted in the spring, she stated that *"spring comes and I get over it. I stop hurting as much. I'm fine now. I know this sounds really stupid but by June the 20th, I can tell you how to many minutes I'm going to lose daylight"* (T3).

Almost all the participants recognised a worsening of their symptoms across the year, reinforcing a seasonal rhythm, *"…literally after Christmas, right at the very start of the new year, I could guarantee almost that I'd be in hospital... and then around this time of the year (June) my asthma would go downhill and I think pollen, the grass pollen… I would be in hospital so um sort of the second or third week of July"* (Rebecca_T1). There were various factors contributing to the increasing of

symptom severity mainly attributed to weather changes, increased illnesses, and annual events.

Seasonal effects were often expected for those with physical illnesses, and this may be due to knowledge and understanding of their conditions, for example those who had lived with their conditions since childhood (e.g. Rebecca, Sarah and Will). In terms of depression, only four participants reported a noticeable change in their mood during the winter months which they concluded was due to light exposure, a restriction in physical activities and increased isolation, *"when it's light and it's bright you can get out and you can see people. Not good living on your own shut in"* (Cathy_T1). This is not to say that depression *“goes away in the summer- but in the winter I can tend to feel more in the dumps than in the summer" (Max_T1).*

Osteoarthritic sufferers expected an increase in symptoms mainly due to a decrease in temperature, *"your arthritis is a bit worse because of the winter”* (Ben’s partner_T2). The increased pain experienced in osteoarthritic sufferers results in a change in medication regime, *"on a cold day [will take painkillers]. I'll go weeks without pain killers, but I've got them there"* (Jack_T3).

Alongside pain, participants with osteoarthritis reported feeling varying levels of stiffness. Severity of stiffness fluctuated over the course of the day, “*during the night, I struggle sometimes. I'm finding now that I'm getting up, my hips are aching as well as my spine"* (Rachel_T3) and year, with weather impacting on the seasonal rhythms, *"stiffness is worse [in the winter]…damp as well”* (Bella_T1). Stiffness levels were typically higher in the mornings, however “i*f I have a really good night's sleep and I don't move around a lot, I wake up in the morning and I'm very stiff. It takes a*

while to get the stiffness out of my joints and get going. Again, it's if I'm immobile for any period of time" (Will_T2).

There is an interaction between the symptoms experienced by osteoarthritis participants, *in the morning, there's a lot of stiffness, which obviously then produces the pain, I suppose"* (Olivia_T2). This strong link between the symptoms of pain and stiffness increases with cold weather. All of the participants recognised that the change in weather impacted on their severity levels, however the stiffness is*" not as bad in the sun"* (Cathy_T3). For some participants, preventative behaviour was demonstrated through leaving the country during the winter months in order to avoid more severe symptoms.

Asthma symptoms varied over the course of the year which was dependent on weather changes, such as *"in the summer I got a couple of wee bouts with hay fever"* (Tom_T3), and the "flu season". In the spring and summer months, pollen increases triggered asthma symptoms, whilst in the winter months sudden changes in weather and susceptibility to infectious diseases aggravated their asthma such as *"a raging chest infection…and I'm still nebulizing"* (Luke_T3). However, for some asthma sufferers unknown new triggers developed later in adulthood were not appreciated, *" I never realized I reacted to high pollen counts, I wasn't feeling great then but my mood was alright because it was daylight"* (Sarah_T2), due to psychological health status. As represented in the conceptual model in Chapter 3, changes in outcomes and psychological health status affect how participants report on their condition and could explain a variation in scores.

There is clear evidence of cyclical variation of health outcomes across the different conditions, with participants recognising changes in their symptoms,

physical function, and quality of life. Time played an important factor in these changes, with rhythmic changes presenting as circadian and seasonal. The interplay of outcomes and timing was apparent, for example in experiences of stiffness during winter or asthma symptoms increasing during the spring/summer months. Thesevariation of outcomes impact on and is impacted by how participants are feeling, i.e. their mood, which is discussed in further detail in the following section.

4.5.5 **Mediator: Psychological Health Status**

Psychological health status is often captured in the literature with anxiety and depression scores, however for the purposes of these results it relates to the current state of mind of the participant (incorporating psychological and mental functions as outlined in Chapter 3) and how that impacts on their experience and reporting of their health condition. It is evident for all participants that they "*think the mood you're in does affect your memories, doesn't it? There will be some effect" (Laura_T1).* Participants in a worsened psychological state at the time of completing a PROM may reflect inaccurately about their experience of their health condition, *"Yes, because if you had a bad day then you think it's been for the two weeks past or so and perhaps it hasn't. That's how you're feeling that day" (Olivia_T1).* Their reflection would focus *"more about the bad things than the good things. I'd be more worried about what's happened in the past that was bad" (Max_T1).* However, there is some confusion around whether the severity of the pain was an accurate reflection or that *"it [mood] could exacerbate the feeling of pain, I guess, a little bit, but because the pain was so severe than before, I don't really think that. Maybe it is. Maybe if I'm feeling rotten and feeling down, it could be. I don't know" (Luke_T2)*.

Time of day and time of year also changed their mood and how they processed their health status. Time of day seemed to affect their mental function, with some participants reporting that they can function better in the mornings. Most participants self-reported as morning chronotypes, *“I'm brighter. Anything I do in the mornings gets done better, by after tea it's getting a bit befuddled" (Cathy_T1),* thus this could explain why they felt more functional in the mornings. However, Rebecca stated that mornings were “*…a time for probably a little bit of reflection where I’m already kind of embroiled in things at these points” (T1)*, impacting on her depression scores.

Medication also impacted on psychological health status, as medication for physical symptoms improved psychological wellbeing and medication for depression removed any experience of emotions for participants. However, the effect of medication *"wears off by the end of the afternoon" (Max_T3),* which can then contribute to fluctuations in PROMs scores. Experience of symptoms impacted on their current mood, thus reinforcing the bidirectional relationship between variation in outcomes and psychological health status, *"because when you're tired, you don't take things, you don't concentrate as well, and you don't cope with things and deal with things is easy if you're tired probably. A lot of it is because I don't feel well, because I don't feel right, because I'm in pain all over. If I felt well, I'd cope with it all because I could " (Mary_T1)*.

As symptoms affected psychological health status, *"it's just everything [physical symptoms] is affected by everything. It's so darn annoying and I do get really, really low sometimes"* (Bella_T3), current mood levels also had an impact on the experience and reporting of symptoms. Current mood either diminished or exacerbated the pain participants were feeling for their osteoarthritis, *"because I'm*

winding myself up. Then the pain that was missing suddenly starts hurting" (Cathy_T2). In addition, for those with asthma, symptoms of anxiety were often confused with overlapping asthma symptoms and uncertainty if, "*they kind of feed off each other and that's what I see more than sort of just being breathless but that could just be because I'm having chest pains because I'm being anxious or it could be that my asthma is not great and I'm noticing that more than anything else*." (Rebecca_T1). The difficulty disentangling symptoms is similar with individuals with multi-morbid physical conditions (as discussed in the next section). Psychological health status is an important factor to consider when patients report on their experience of their health, thus impacting on variation in health outcomes and PROMs scores. A change in health outcomes can also affect participants' current mood.

4.5.6 **Moderator: Individual and Environmental factors**

There are two sub-themes which include individual factors and environmental factors. Individual factors tended to include resilience or general attitude, general behaviour related to their health and managing their health conditions, co-morbidities, and chronotype. Environmental factors included sub themes of physical environmental (e.g. work/home surrounding, the town they lived in and accessibility), weather, and social situation (family/friends network and annual events).

4.5.6.1 Individual factors

In terms of individual factors, there were various themes that were relevant across all participants and fed into how they experienced and reported on their health condition. General demographics of individuals are presented in **Error! Reference source not found.**, however it is interesting to note that the majority of the participants were retired. In addition to participants having co-morbid conditions

in the study, many of them had additional conditions such fibromyalgia, cancer, and obstructive sleep apnoea.

Some symptoms are similar for different conditions thus it is difficult for participants to disentangle them, *"This is where I get all confused with it because I got fibromyalgia as well. I don't know if it's, my muscles are tight and tense because I'm stressed. Is it my fibromyalgia or is it the arthritis? See, because it's a combination of the two"* (Emily_T3). For some with depression and asthma there is an inability to distinguish from asthma symptoms such as breathlessness or whether this is related to heightened anxiety, thus both conditions *“kind of feed off each other and that’s what I see more than sort of just being breathless because I’m having chest pains because I'm being anxious or it could be that my asthma is not great”* (Rebecca_T1).

Fatigue is also confused as it can be related to both lower mood and osteoarthritis. Thus, reporting on a disease specific measure such as PHQ-9 (item on fatigue) may not be accurate if the symptom is related to another condition, *"a lot of it is because I don't feel well, because I don't feel right, because I'm in pain. all over, so that is the main thing or something. If I felt well, I'd cope with it all because I could. I'd want to go out and go out for a walk. Do this and do that because I felt like it, because I get to-- It gets the afternoon " Mary_T1)*.

Equally, as Rebecca commented on above, some conditions interact with each other or as she states, “feed off each other”. Many participants commented on this interaction and how one condition affected or even triggered another, *" when it's damp and I am more breathless than I was-- than I am and it's not, but the cough. I cough and that, but I think my main problem might be arthritis and my spine that gets me down sometimes"* (Rachel_T3). This observation sometimes arose in the latter

stages of data collection period (i.e. time 3), *"on your mood. As with the heat, I've never-- Or the cold weather, but perhaps it does and I haven't recognized it enough"* (Olivia_T3), and may be an effect of the actual study methodology (repeated interviews over time) which allowed participants to reflect over their health experience, *"talking to you now, just this aura or whatever, it has got to me thinking, Yes, I hear now. Perhaps I'm having these episodes more than what I thought"* (Ben_T1).

Participants' attitude to their health conditions had a bearing on how they reported their symptoms. Level of acceptance of their conditions impacted on how severe they experienced or recalled experiencing symptoms, *"on days that my body says, you can't run, you can't keep fit. I try to be. I'm 60. I try to be, still think I'm 21"* (Jack_T1). As mentioned in the previous section (Determinants) partners who were present during the interviews were able to provide a different perspective on both participants' experience but also their general attitude to their health condition, *"If we go in on a Saturday and he's busy he's dodging people, he'd be in absolute agony after about half an hour…he won't say he's in pain. You have to make him stop and have a coffee"* (Ben's partner_T1).

Many participants described a resiliency to how they managed their conditions, *"but the arthritis, I just got on with it"* (Tom_T3). Resilience is often linked with pain threshold as some participants commented on having higher pain thresholds compared to others they know. The general attitude to life was to "*just learn how to cope and adapt and manage things"* (Sarah_T3) and persevere regardless of past or current events, and regardless of current symptom severity. Thus, this may impact on how they report their symptom severity on PROMs as their outlook on life is different.

Almost all the participants reported being more alert in the mornings, thus having a self-reported morning chronotype. Those with a morning chronotype discussed needing to *“get things done in the morning, because by afternoon, I’m hormonal. I just want to chill out and relax in the afternoon*” (Emily_T1). This may be linked to their biorhythms of their conditions, with pain increasing over the course of the day for osteoarthritis. In addition, this is also linked to the environmental factors such as working patterns, “*ideally, I'm not a morning person but I by default, I'm a morning person*” (Will_T1), and disruptions to the body clock *”was quite difficult but I'm back in a more conventional pattern now”*(Will_T1).

4.5.6.2 Environmental factors

Environmental factors contributed to variation in health outcomes and psychological health status. There were three main sub-themes which included the physical environment (e.g. town they lived in, work environment), weather and social environment (e.g. family/friends network and annual events). The physical environment seemed to affect mood rather than physical symptoms. The town in which participants lived was seasonal, I.e. from spring to autumn it was busy with tourists, *“but here, you don’t see a soul"* (Laura_T2). There were accessibility issues regarding transport links from the town to larger cities around, making some participants without transportation feeling isolated. This resulted in increased depression in some individuals who did not have a good support network around them, *“we don't see people for days or two, three days sometimes now”* (Cathy_T1).

Many people retire in this area of the country, which aligns with the range of ages for the participants in the study. Those participants with asthma have found their symptoms in this area of the country, *“are so much better near the sea… I can breathe easier, I can exercise more, so I don't ache as much. I don't get stiff as*

much… The environment triggers. I respond quite quickly" (Will_T1), compared to the city.

The work environment was a considerable trigger for participants still in employment. Some retired individuals discussed how their work did trigger some of their symptoms, but the symptoms subsided upon retirement. The triggers were either related to the actual physical environment, *"in an air conditioned office which I don't think is the best environment to be in so if a cold or something that starts at one end of the building, you know you are going to get it at some point a few days later"* (Sarah_T1), or the stress experienced, *"sometimes I start to cough and I can't stop, so I'm thinking now that it's because I'm stressed out. When I'm fine, I never ever cough. When something's happening, I cough all the time and I can't breathe"* (Emily_T2). These affected mostly those with asthma and depression, however there was limited evidence for the work environment affecting those with osteoarthritis. Stressful events started affecting sleep *"where I was waking up at three o'clock. Again, I think just the pressures of work because there'd be things going on in my head"* (Rebecca_T2).

Changes in seasons resulted in fluctuations in symptoms for those with osteoarthritis and asthma. Colder weather, specifically the damp, affected the joints, *"and then it was probably about 4 days or so, I was really in a lot of pain. I wasn't sleeping. I couldn't even sit. I had to sit and get comfortable sitting"* (Laura_T2). In terms of asthma, many participants discussed how *" it's more climate-related than anything. Unfortunately, anywhere in the UK during winter it's going to be wet and cold. My lungs don't seem to enjoy that. Well, it certainly seems to be in the winter, I get more respiratory problems. As the weather warms and summer comes on, I'm completely different"* (Rebecca_T2).

As the seasons change, symptoms change. For osteoarthritis sufferers the warmth reduced their experience of pain, but not stiffness, *" six, seven weeks where I didn't really feel anything. I don't know. I think it probably is better when it's warmer, generally, but it just doesn't-- it doesn't stop me there from walking"* (Rachel_T3). Some participants with asthma reported suffering more as spring and summer occur resulting in increased use of inhalers, which may be due to "p*ollen and things like that it gets really bad… Yeah I had to take it this morning and I had to take it [Ventolin] yesterday but I hadn't taken it before that hadn't taken it for…can't remember the last time I've taken it"* (Tom_T1).

Just under half of the participants suffering from depression highlighted how the change in light across the seasons seemed to affect their mood, associating this fluctuation to seasonal affective disorder (SAD), *"I'm not great at this end of the year, to be honest with you... I love the daylight. Going into September, October time, especially when the clocks go back, my body can't adjust very well. I go to work in the dark and I come home in the dark...For me, it's like just being in the dark all the time"* (Sarah_T1). Across the different timepoints, their mood changes and many attribute it to the change in seasons and gradual increase *"…in bright days, if I have a high of the year it would be the day the clocks go forward at the end of March. The low is when they go back"* (Sarah_T3).

The final sub-theme within the environmental factors is the social environment. This includes both the family and social support network and annual events that occur (e.g. birthdays, holidays). For a small number of individuals, the social environment resulted in increased levels of stress which then lowered their mood, *"I'm trying to juggle all of the things like that that I should be doing as opposed to just like sitting there and enjoying some time out"* (Rebecca_T2). However, for most

participants their social life was an escape from the stresses at work and home, where *"the more I interact with people, say I'm walking and my feet are painful, and I get chatting to somebody, you forget about the pain because you've got a new stimulation I suppose"* (Will_T3). Regular social events may temporarily improve their mood but *“then I come back and then it's just down to earth with a thump"* (Leo_T1).

Annual events, such as Christmas, can be either a trigger for depression or can have the opposite effect and lift someone’s mood, *"I do enjoy it because its a festive time of the year. It does bolster you up when you feel this feeling of Christmasy definitely is a lifter. Definitely but it only lasts a really short period of a few days"* (Max_T3). This is associated with stress which is either self-imposed (through the participants’ expectations) or a societal pressure of what is expected, “*if you're going to get low, it will be just before Christmas. That's because of the stress levels because everybody's on you”* (Ben_T1). For some it is a reminder of a tragic event, such as a loss of a loved one, or reinforces feelings of isolation, *"boxing day is the same. Jesus wept. I can't go another day. The day after that is the same and then it goes on to the next weekend. You're still sat there and you're still going through the same thing and you think, "No." Then you've got new year when everybody's having a new year's party and doing wonderful things and you think, "I'm sat here with my cat. What pain"* (Cathy_T3). Once the stress of the holiday period is over there is a risk that *“everything kind of catches up with you sort of health wise”* (Rebecca_T3).

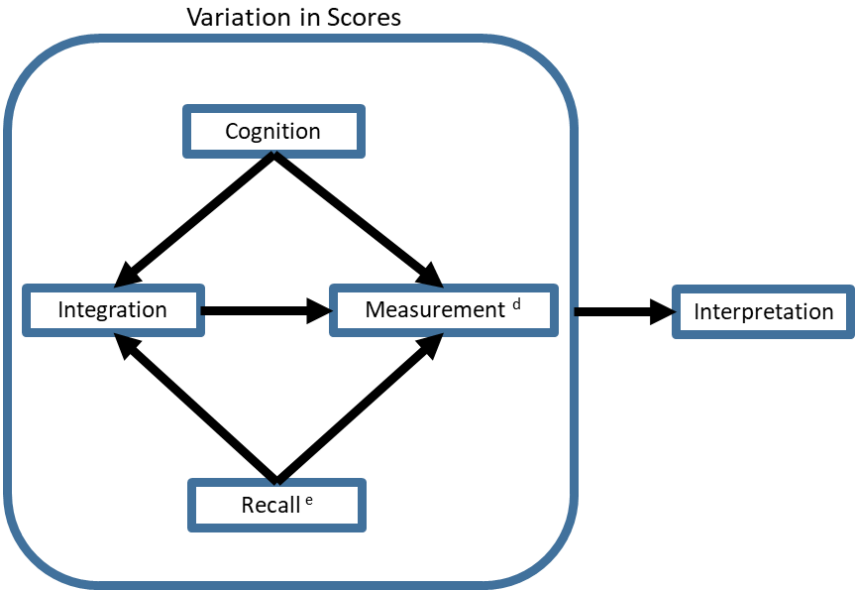
Individual and environmental factors impact on all aspects of cyclical variation of PROMs. For example, attitude to medication may prevent an individual from admitting when symptoms are severe enough to take medication alleviating their osteoarthritic pain. Environmental triggers can affect participants’ stress levels which

then has a knock-on effect on health outcomes. Thus, these are considered to be moderators in explaining cyclical variation of PROMs, impacting on overall scores.

4.5.7 **Variation in Scores**

Variation of scores incorporates the internal processing involved in interpreting PROMs questionnaires which includes how participants process the items within the questionnaires, how much they have integrated living with a chronic condition, the measurement itself and the recall issues.

Figure 4.5 Subthemes of variation of scores



4.5.7.1 Cognition

As mentioned previously, recent episodes of severe symptoms affect how patients reflect on their overall experience of their condition, *"I think it's because I had so much on. I had this bladder operation I had to go for. Then I had that appointment with the psychologist. Yes, it really wasn't a good week, to be honest. I think that probably manifested in different ways. The physical part of it, it's probably affected that as well*" (Luke_T2). In addition, psychological health status redirects the

cognitive focus on the problems participants are having, thus may intensify symptom experience and PROMs scores,*"…low mood affects memory of pain. I suppose it gives you something to focus on as well, if you're having problems. Over the last week or so, the pain in my knee has probably been what I'm focused on most, rather than my neck, rather than my back, because it's painful"* (Luke_T2).

Some participants talked of attempting to *"build a picture when I am answering those questions"* (Rebecca_T1), although how they are feeling at the time of completion affects how they reflect on their condition, "t*o be honest, I've completed questionnaires this morning with a healthy state"* (Rebecca_T2). Due to the method of reviewing their PROMs during the interviews, participants are able to take the time to reflect over their condition, "I *could see through the questionnaires. There were some double checks around that. I could see a pattern. It seems to mirror accurately what I was dealing with in the last two weeks"* (Will_T1). All the participants found the exercise of reflection and discussing their PROMs results a benefit of the study, *"I suppose these snapshots that you take they're going to be very different, aren't they? They're going to be very- depending on what's happened to people and what impacts they've had on their life and what have you. If I was to do one of those forms now, I think it would be a lot different, a lot more positive. Then, again, in a couple of weeks' time, you don't know what's going to happen, do you?"* (Will_T2). This provided them with a more in-depth understanding as to how their conditions change.

4.5.7.2 Integration

Integration represents the process an individual undertakes in an attempt to achieve a sense of balance in self-managing a chronic illness and living a meaningful life (278), *"you just learn how to cope, and adapt and manage*

things…My strategies to cope, really" (Sarah_T3). Although this looks as though Sarah has achieved integration, her strategy is to cope indicating that this is a short-term fix rather than a lifelong acceptance of her health status.

The process of integrating change involves a variety of individual factors, such as resilience, acceptance and denial. Participant's resilience to and acceptance of their health condition is integrated within and affects how they may respond to questionnaires about their health status. Participants were able to distinguish between changes in their health outcomes and their internal fine-tuning during the day. Fine-tuning involves integrating changes experienced by participants and can be influenced by internal factors such as tiredness and biorhythms, and personal characteristics of the individual as demonstrated by concepts within the conceptual model. Those in denial may not accurately respond to questions about the severity of their conditions as seen by Ben where he has to *"do it [questionnaires] with [partner], because I lie"* (T2), and his partner confirms that he would *"put "great" anyway on it, and you'd be at the "moderate" bit"* (Ben's partner_T2). However, those who feel their *"quality of life I think is good as well "*may be concerned that *"this is not the answers you normally get but it's the way I feel"* (Tom_T1), which does question the expectations of those answering PROMs in terms of what they think they should be answering for clinicians. Perception of what an individual's health should be like may be influenced by other individual factors such as age, "*I'm not sick for my age now. If I was sick, I probably wouldn't think so much. I like to think that make sense of that."* (Cathy_T2).

4.5.7.3 Recall

The PHQ9 scores for Rebecca changed significantly across the seasons, with a significant increase in the winter period. Although she noted that her mood was

significantly worse in the morning and evening, there were only slight changes in her scores at different times of the day (morning average 13.29 compared to evening average of 17.50 which is a clinically meaningful change). She did acknowledge that when answering the PHQ-9 that *“I’ve certainly taken that into account, because obviously quite a few of the questions mentioned, "over the last fortnight," don't they? Perhaps I've looked at it more over maybe four weeks rather than just focusing on the last two weeks specifically because it's all panned out for a while. I think I have tried to answer everything as I think I should for those two weeks, but maybe when it was really, really bad, maybe some of that has impinged on the way that I've answered things. To be honest, I've completed questionnaires this morning with a healthy state"* (T2).

Similarly, her asthma scores improved by the third interview. This may be due to the removal of the environmental stress she had experienced during the initial two interviews, *"just feeling that I was crap at my job and that they wanted me out. All of those things were playing on my mind massively, and that of I'll never get a job again. All of those sorts of things. I've had the extremes because of that one thing that's happened. It probably had more of an impact on the mental side of it, I would say. It has certainly played quite a big part of how I've been responding to their questions and things as well, I think"* (T3).

Despite the qualitative acknowledgement and reflection of when their symptoms were worse according to various timepoints, this did not reflect in the PROMs scores at times. This may be due to the lack of sensitivity of the PROM in terms of the rating scale, or the way participants completed the PROM, *“I suppose it could, because, that's the one first thing in the morning, because it's stiff then trying to get out of bed. It could heighten how you feel, couldn't it? You could think, ‘Well, it*

was more severe than the times at the lunch time when you've been moving around a lot more' (Rachel_T1).

4.5.7.4 Measurement

Some participants highlighted that the timeframe the PROMs ask participants to reflect on is difficult as symptoms change, *"with the better condition, two weeks is a long time because you could have lots of things"* (Bella_T2). There were various examples provided by participants of changes they experienced in their symptoms, and this was observed in PROMs scores, particularly for Emily. Although there the mean change in PHQ-9 scores were not clinically meaningful, there was a substantive increase by the afternoon Table 4.7, *"I have to get things done in the morning, because by afternoon, I'm hormonal. I just want to chill out and relax in the afternoon"* (T1). If individual scores at each time of completion was closely examined, there are considerable changes in PHQ-9 scores which were clinically meaningful. The summer PHQ-9 scores decreased from 19 to 9 over the course of a week, dropped in the winter to 3 or 4, and then increased to 10 in the final interview in the spring, *"that's the only thing that makes me down and depressed. When I think, Mother's Day. I've got five children...When it comes to a special day, two of them can't even be bothered to pick up the phone to me. That's what puts me down"* (T3).

Accuracy of participant's responses on PROMs on what they are experiencing is influenced by individual factors, as previously highlighted in section 6.5.3. Thus, the average means for some PROMs may be underestimated as mentioned previously. Perception of how much stiffness and soreness is experienced may be underestimated, "*…it's worse than what I think but maybe I'm in denial I think but I*

tried to keep myself busy because I don't want to sit around all day doing nothing you know?" (Tom_T1).

4.5.7.5 Interpretation

When reviewing Tom's PROMs scores as a graphical display, he talked about the way he answered the stiffness questions further. After completing the first questionnaire, it made him think more about when *"I was in denial I think about the stiffness…sorry about that…because until I actually…until I done the first one and I started to think about the way I felt and I thought I have got stiffness and I really up till then I was thinking I haven't got any stiffness but I have got it especially if I sit for a period a long period then get up"* (T2). Thus, if a clinician takes only one measurement of stiffness then this may not be an accurate reflection of how patients are experiencing this, especially if they are not used to this line of questioning.

The interpretation of the length of time for certain questions and the response scales for some of the PROMs was at times a difficulty for participants. In WOMAC, the question about pain whilst standing was dependent on how long one person is standing. Answering this question was difficult for Tom and he took what he was feeling at the time of completion, *"I can go on and stand at a counter for a couple of minutes…it's sore, but if I'm standing for half an hour my knees are really sore. So don't really have a time thing on this so that's why I'm not quite sure if I should be putting um…moderate or severe. I'm going to put severe because at the moment they have been quite sore"* (T1).

In addition, PROMs are completed according to Rachel's interpretation of severity levels and thresholds, which may be different compared to others, *"getting up from the settee, getting out of bed is really difficult. I say difficult. It is for me. When I was filling in the questionnaire and I saw one part I ticked severe. No, it's not*

severe because some people can't even get out of bed. That's severe" (Rachel_T1). Thus, the interpretation of response scales varies with participants, although some responses are not representative of what participants are experiencing, *"sometimes I don't find anything that exactly fits, so I just tick the nearest sort of thing"* (Laura_T2).

Although there were a small number of instances where the change in mean PROMs scores did not meet reported MID/MCID thresholds, when individual scores are examined across the different time periods the changes were greater. Current mood, changes in physiology and individual/environmental factors all explain changes in PROMs scores and need to be considered when interpreting outcomes.

4.6 Discussion

This chapter described a longitudinal mixed methods study (a) exploring the factors that could explain variation in PROMs scores from the patients perspective, (b) gathering evidence to support the themes in the conceptual model developed in Chapter 3, and (c) identifying any new emerging themes to build the model up further. The qualitative analysis highlighted the importance of the timing of PROMs administration and the impact this has on how patients interpret and report on their health condition. There is a degree of complexity when it comes to explaining variation in outcome scores as many factors need to be considered. However, variation observed in the qualitative interviews was not always replicated in overall mean PROMs scores at the different time points, which further supports the need for examining intra-individual PROMs scores.

The lack of responsiveness of a PROM in detecting changes may be due to the resiliency of the individual completing it. At the centre of Antonovsky's theory of salutogenesis where health is described as a process by which an individual moves towards either a healthy or unhealthy pole, is the sense of coherence (SOC) (279). As part of this concept there are three dimensions: comprehensibility (events that are understandable and predictable), manageability (belief that one can handle stressful situations) and meaningfulness (capacity to create and recreate meaning while managing life demands). Individuals with physical health problems appear to have a strong sense of coherence as they appear to comprehend the impact of their condition and manage flare ups. However, this is dependent on their level of acceptance of their condition, and length of their diagnosis. The uncertainty and unpredictability of depressive episodes, on the other hand, result in a lower sense of SOC for those struggling with comprehending their mental health condition.

Underestimating the impact of one's condition may be explained by their level of illness acceptance and coping abilities in managing their condition. Research has shown that the perceptions of illness for patients with chronic conditions play significant roles in psychological health, including increased anxiety and depression (280–283). Similar results were found in the participants interviewed in this study, whereby those in denial about the level of symptom severity for their physical condition experienced an impact on their psychological wellbeing. Emotional responses to changes in their symptom severity are dependent on how strong of an illness identity an individual has, how much control and understanding they have of their illness and the impact of their illness on their lives (280).

Interpretation of PROMs items is dependent on several factors such as individual threshold of symptom severity. Greenhalgh et al (2018) supported the notion patients' interpretation of PROMs items is shaped by social and cultural factors (119). The results from this study support that and adds the idea that timing of PROMs completion and psychological health status also impact on how patients interpret and complete PROMs. Graham-Engeland (2016) found that psychological status at the point of PROMs completion was associated with momentary pain and pain-related restrictions. Those who were feeling depressed are more likely to reflect and recall negative events compared to those who are not depressed (168).

The inclusion of partners in some interviews provided an alternative viewpoint, at times a more honest viewpoint, to the participant's own perception of their health. Patients develop cognitive representations of their health condition(s) which includes assumptions about the symptoms, progression, triggers, controllability or curability and the impact on their lives (284). Partners or families around patients will have their own assumptions and observations of how the patient is managing their health.

Research into dyadic illness perceptions for those with chronic health conditions has demonstrated the effect of concordance or discordance of these perceptions on overall well-being and the patients' adaptation to living with the condition (284). However, there is limited research using dyad interviews to explore how patients' illness perceptions affect responses to outcome measures.

There appeared to be an effect of repeated measurements on patient reflection. Participants had an opportunity to reflect on and examine how they perceived their health status over time. This supports the literature that the completion of PROMs prompts patients to engage in self-reflection (119). Changes in the way patients experienced their condition were noted at each timepoint accounting for the effect of time periods on health outcomes. This is one of the benefits of using a longitudinal qualitative research design (285). In addition, patients were able to take the PROMs scores to their doctors to enhance their consultation experience as well as provide information to their clinicians to consider when planning a treatment plan. Discussion of PROMs results during a clinical consultation encourages shared decision making and assists clinicians in the identification of symptomatic problems (116) resulting in better management of patients' conditions. When used appropriately, PROMS can start a dialogue between the patient and clinician, further enhancing the doctor-patient relationship (286).

Multimorbidity was common amongst this study population, which is reflective of the UK population. Patients' reported symptoms were cross cutting their conditions which made it difficult to disentangle and report on disease-specific PROMs. This could have an impact on the accuracy of PROMs scores if patients are reporting on a different condition. Videos of patients' reflection of interacting symptoms across different conditions on HealthTalk.org found similar results in that

patients were often confused around what was the cause of their experience of symptoms (287). In these videos, patients attributed the experience of symptoms to the effect of medication, other health condition or a combination of both. The co-morbid presentation of physical and mental health conditions is well established (288), however there is limited research on how patients cognitively disentangle symptoms that overlap across conditions.

Various time effects were found for health outcomes and changes in PROMs scores, particularly for time of day and time of year. Given the age groups in the sample, the day of week effect was only found for those who were still employed. Some retired participants reflected on their mood fluctuations and did recognise that they noticed a dip before the working week. Weekends and non-working days have been associated with improved well-being (289), and Sundays were found to result in the lowest well-being scores (290). However, there is limited research investigating the day of week effect on health outcomes in general.

4.6.1 **Changes to the conceptual model**

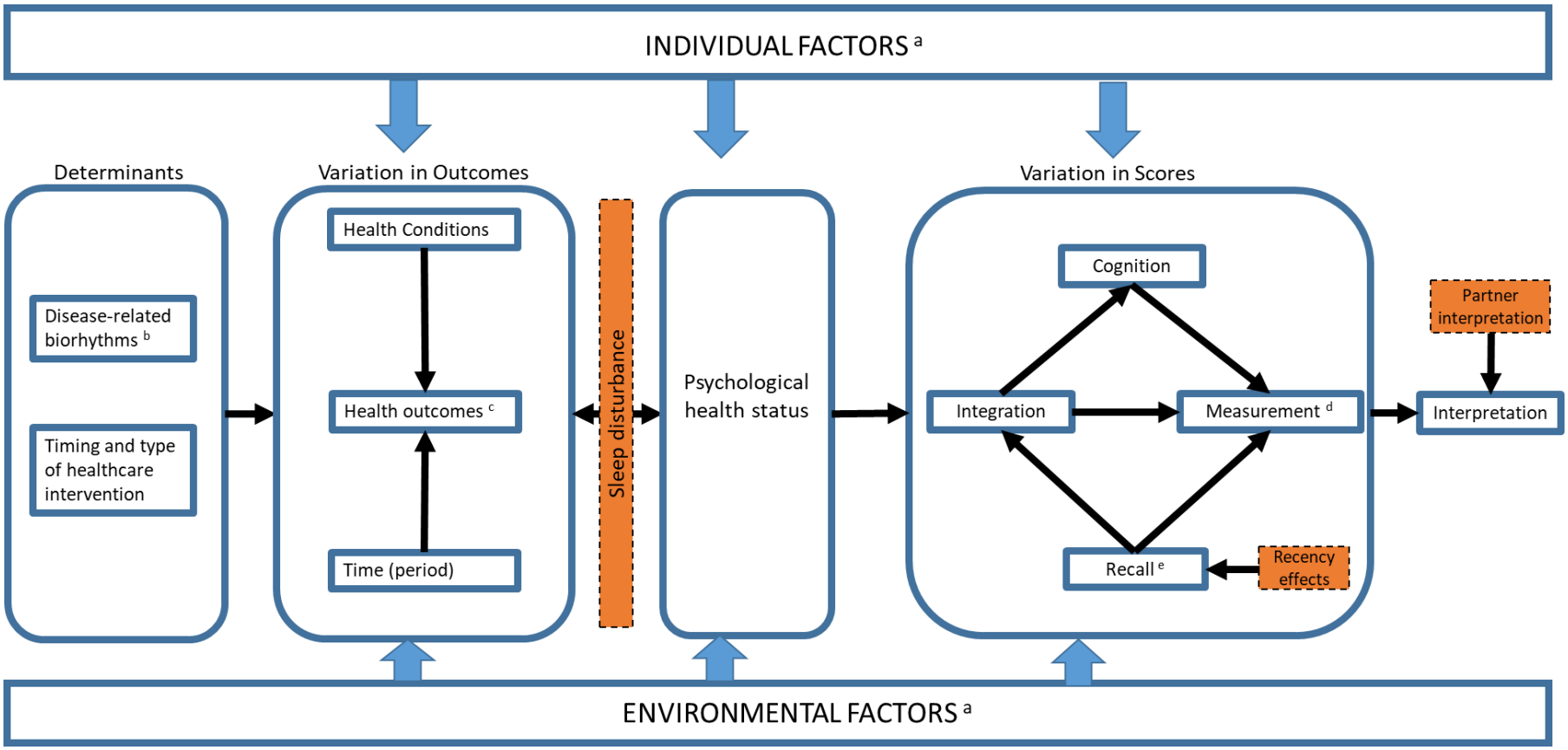
The themes developed from the interviews supported the existing conceptual model, however there were some elements that were important to consider from the patient's perspective (Figure 4.6). Firstly, the interviews demonstrated that disrupted sleep made symptoms worse. Disruption of sleep and circadian rhythmicity is a core feature of mood disorders; however, it has a bidirectional relationship with physical and emotional well-being across osteoarthritis (291–293), asthma (294,295) and depression (296,297). Poor sleep quality is related to worsened health outcomes and PROMs scores (291,298). However, psychological health status has been found to

be a mediator between sleep disturbance and heightened pain severity (299,300) and increased vigilance to pain stimuli (300).

A second important factor was recency effects on recall of health experiences by participants. As reported by Stull et al (2009), there are six factors that influence recall, including recent events (301). Recency impacts on recall of the phenomena of interest and the attributes of an experience can also influence the recall process and how participants respond to outcome measures (301). Fluctuations in the underlying phenomena of interest can affect patients' responses, and will summarise their varying experiences across the recall period (302), thus not capturing the variability.

Finally, an interesting observation was the effect of partner interpretation of their spouses' health at the time of the interview. Although there was no evidence that perceptions of partners in their daily routine would affect the cyclical patterns of patients, partner's interaction around how participants responded to PROMs was interesting. The presence of partners at the interview appeared to encourage participants to be more honest about their experience and health state, overcoming the social desirability bias effect. Research on patient–spouse concordance has been associated with better health outcomes and improved psychological well-being (303). Although this study resulted in a more honest recollection of health experience from the participant, this is dependent on the relationship between the participant and their spouse/partner. Research has shown that a lack of concordance (either overestimation or underestimation of health) has been associated with increased patient depression (304,305).

Figure 4.6 Updated conceptual model of cyclical variation of PROMs



[a] Individual factors incorporate individual determinants of health (e.g. demographics, personality, identity); environmental factors incorporate physical (urban/rural, weather) and social environment (socio-cultural, economic/political)
[b] Disease-specific biological rhythms incorporates episodic attacks and exacerbations that occur
[c] Outcomes include symptom status, functional status, general health perceptions, health related quality of life
[d] PROM characteristics including aspects around sensitivity of the instrument
[e] Recall incorporates two topics: recall bias and recall period. The recall period includes both momentary and retrospective (which can be the immediate past or longer term

4.6.2 **Strengths and limitations**

This longitudinal mixed methods study of cyclical variation in chronic conditions has some key strengths. The use of a mixed methodological approach allowed for a greater in-depth understanding into patients' responses on PROMs and the factors that influence their interpretation of PROMs items. In addition, the study provided empirical support for the conceptual model explaining cyclical variation in PROMs. This was the first study integrating PROMs scores with qualitative accounts of patients across different timepoints, capturing disease progression in both methods. Participant attrition to the study was 0%, which is difficult to achieve in longitudinal studies, providing a full dataset to analyse. There is clear evidence of subjectively perceived symptom fluctuation in the qualitative data, although sometimes this is not supported by the PROMs scores.

Repeated measurements over time had a positive benefit to both the research study and the study participants. Although time-consuming, participants were able to reflect on their conditions and account for changes in their health status. Some participants brought their PROMs scores to GP consultations to demonstrate fluctuations in their scores in an attempt to aid their GP in developing an appropriate treatment plan.

Some limitations to the study need to be acknowledged. Firstly, due to the small sample size, there is a lack of power in the quantitative element of the study, thus further statistical analyses were not possible to examine the significance of variation in scores. However, the qualitative evidence highlighted the complexity of patients' approaches in answering PROMs and interpretation of the items.

Interpretation of the results should be considered with caution as they may not be generalisable due to the small sample size.

One of the largest studies conducted most recently by the University of Manchester (306) recorded daily pain intensity in over 13,000 UK residents with chronic pain with a view of examining the impact of weather changes. Due to the large sample size researchers were able to analyse 5.1 million pain reports to demonstrate the effect of humidity on pain intensity. This was one element that was found to influence change in pain levels for participants in this study, alongside other factors. Future research should focus on other health conditions with a combined methodological approach from the Manchester study with subsequent interviews with participants.

Condition severity and length of diagnosis was not an inclusion criterion for the study. Thus, individuals who were recently diagnosed with one of the health conditions may not be aware of subtle changes in their symptoms and may attribute this to other factors or other pre-existing conditions. Individuals who had higher levels of condition severity appeared to acknowledge more subtle changes in their health condition, although this was sometimes not reflected in their PROMs scores. Subtle changes were masked by averages of PROMs scores, thus intra-individual changes on single items on PROMs were lost. This has been a concern in other studies exploring the interactions between GPs and patients whereby researchers found that aggregating patients' ratings of GP communication skills at a practice level masked considerable variation in the performance of individual GPs (307). Statistical approaches to modelling variation without losing the intra-individual changes should be considered when analysing outcome date. Chapters 6 and 7 will explore different types of statistical approaches to modelling cyclical variation and

apply this to an existing dataset. Future studies should allow for differing lengths of diagnoses to determine whether length of diagnoses affects how patients report on and interpret PROMs items.

Although representative of the local population and GP practice profile, there is a lack of diversity in the study sample. Thus, the results may not be applicable to other ethnic groups, disease groups or age groups. Future work is needed exploring cyclical variation in different disease groups and explore if there are differences in the interpretation of PROMs items across various populations.

4.6.3 **Reflexive considerations**

As a mature student doing my PhD, I had around more than 10 years of experience conducting qualitative research in a variety of settings prior to starting the PhD. I was involved in different projects focused on patient experience of GP consultations, impact of policing in the south west of England, stigmatisation and barriers experienced by prisoners upon release from prison. In addition, I am a psychotherapist thus have experience in working with individuals suffering from not only mental health problems but also physical health conditions. This prior experience in qualitative research alongside my therapeutic role in the community influenced the speed with which I built up rapport with my participants in qualitative interviewing. The approach I took with recruitment and data collection may have influenced participants to stay engaged for the lengthy period of the study.

Before conducting this study, I had some personal experience of living with a chronic condition and having family members with similar conditions. Having lived experience of the conditions I was studying was beneficial to the research process as I was able to sympathise with the participants and reinforce their own health

narrative. Knowledge of the conditions I was studying through familial experience also benefitted the interviews and the topic guide used throughout the process. However, I was aware of this influence during the data collection and analysis periods.

In order to account for this, I used two methods of triangulation: methods and investigator. Investigator triangulation is where two or more researchers provide confirmation of findings and different perspectives, adding breadth to the phenomenon of interest (308–310). During the analysis stage of the study I involved two other members of the Health Services Policy and Research Group for the purposes of triangulation of the themes being developed from the data. One was a medic thus provided a clinical perspective to the participants' reported experiences and factors impacting on their experience. The other member of the team was a non-medic and did not have prior experience of the conditions.

The second form of triangulation is methods triangulation, where the researcher used different methods of data collection in order confirm or validate their findings. In the literature it is sometimes referred to as mixed-methods research (311). There are various benefits to this method of triangulation such as it yields more comprehensive, insightful data (312), richer, more authentic data (313), and enhances validity (314). In fact a similar longitudinal mixed methods study looking to explain and better understand HRQoL in coronary artery disease examining describe, explain and understand the subjective health related quality of coronary heart disease from onset to rehabilitation found that the qualitative interviews provided an explanation for poor HRQoL when a single methodological approach would not (315).

My academic background is in psychology and most of my research has been within the field of medicine, specifically primary care. As my previous research has focused on patient experience of care, some of my interest in this study was the relationship with healthcare providers although this was not examined in the analysis. However, some of the interviewees discussed their relationship with their GPs or consultants which did impact on their help seeking behaviour regarding their health condition. The effect of the GP-patient relationship on participant PROMs scores is uncertain, however it may have resulted in a barrier for accessing help. Reduced visits to their healthcare provider may have resulted in an increased severity of their symptoms. There is a lack of literature investigating the impact of GP-patient relationships on health help-seeking behaviours, rather the focus has been on barriers to help-seeking for men (316,317), mental health problems (318–320) and young people (321,322).

The majority of my research has been conducted from within an academic institution with some focus on sensitive topics. There has been some recognition around the emotional impact of conducting research on sensitive topics, a phenomenon known as emotional labour (323). However, the impact of emotional labour research on the researcher is rarely considered, rather it has been mostly recognised in the research topics being studied. Widdowfield stated that there is a two-way effect when conducting qualitative research in that the researcher both affects and is affected by the research process (324). Therefore, it is important to consider the impact of conducting the research on the ones conducting and analysing the data. Although the topic area may not be viewed as sensitive, the impact of living with these conditions had an emotional toll on the participants which resulted in some upsetting periods in the interviews. The lives of these individuals

and the longitudinal method of monitoring their progression over a period impacted on me as a researcher. There were some stories that stayed with me and were more prevalent in my memory than others. This was particularly true for those individuals who I made a deeper connection with at each stage of data collection. At the same time, I wonder whether these connections impacted on how much information participants felt comfortable revealing during the interviews. Rapport building is an essential component of qualitative interviewing as it builds mutual trust between the researcher and interviewee and may result in fuller disclosure during the interview (325). However, the emotional impact of listening to some participant narratives can prove a burden for the researcher.

Thus, appropriate peer support is necessary for the researcher during this process. During my data collection period I did turn to peer PhD/postdoctoral researchers for support when I felt emotionally impacted by the interviews. However, there was a lack of overall support or recognition at a strategic level from the University doctoral system around this. Following the completion of the data collection I started working with a member of staff in the Doctoral College and a fellow researcher on developing a programme of work looking into the emotional impact of conducting research in sensitive topic areas and what the University can do to support them.

I do acknowledge that my academic and personal background influenced the research process, albeit in a positive way. Previous experience interviewing and having a psychotherapeutic background enabled me to establish rapport quickly and maintain engagement in the research over a long period. To ensure the credibility and transparency of the subjectivity of the researcher triangulation methods were applied during the analysis stages. In future, it would be beneficial to establish a

more formal support system for researchers focusing on sensitive topics within academia, regardless of their academic level, to reduce the likelihood of burnout and emotional impact for researchers.

4.7 Conclusions

In conclusion, this study has provided empirical support for the concepts in the conceptual model developed in Chapter 3. The empirical evidence presented has further enhanced the model with more detail to the main concepts such as sleep, effect of isolation on depression, partners interpretation and salient/recent episodes of flare ups. The subsequent chapters will focus on the quantitative elements of this field of work. As highlighted in Chapter 3, there are multiple approaches to mapping out cyclical variation in outcome scores. The sample size in Chapter 4 was too limited in size to apply any formal statistical approaches to demonstrate variation in PROMs scores. The following chapter (Chapter 6) will explore more in depth the statistical approaches presented in the articles included in the scoping review and provide a rationale for using a non-traditional approach on a longitudinal dataset in Chapter 7.

Chapter 5 Methodological approaches to exploring cyclical variation in outcome scores

5.1 Chapter overview

As stated in Chapter 1, one of the objectives is to undertake a secondary analysis of existing PROM data to explore associations between time and PROM scores. Chapter 2 presented the literature on measurement characteristics of PROMs outlining the issues around measuring and interpreting change in scores. In addition, sources of variation in measurement was discussed with particular focus on subject variation. Chapter 3 mapped out key concepts relevant to cyclical variation of PROMs with literature from the scoping review to support these concepts. However, the literature demonstrated in that chapter presented a range of statistical techniques used to explore the cyclical variation of outcome scores. This present chapter expands on the techniques presented in Chapter 3, and identifies the benefits and limitations of traditional statistical approaches to exploring fluctuations in outcome scores, whilst presenting an argument for the use of Fourier analysis in a secondary analysis of a dataset in Chapter 6.

5.2 Traditional statistical approaches to fluctuating outcomes

An important challenge in cyclical variation of PRO scores in chronic health is characterising the way our systems (physiology, symptomology) can change. These changes can be regular, as mentioned in Chapter 1, presenting certain rhythms (ultradian, circadian), or random (response to external stimuli). In many instances, prior information is available to help guide researchers in what they should measure, how often and when these measurements should occur (e.g. blood pressure upon waking up). However, this prior information may not be available thus study designs

would require a continuous monitoring of symptoms, for example, to capture changes. This further provides challenges to how this type of data is analysed in order to distinguish between signals and noise, and examining these signals for rhythmicity and cyclical variation (326).

The studies identified in the scoping review articles in Chapter 3, applied a range of statistical techniques to explore and explain variation in the data collected over a significant length of time, including ANOVA and hierarchal regression methods, as well as approaches specifically used in the field of chronobiology called spectral analysis (e.g. cosinor and Fourier analysis) . Most of the articles used momentary data in their studies, and only seven articles did not use momentary data in their analysis, yet across the studies a range of statistical techniques, particularly repeated measures (ANOVA) or multi-level modelling (MLM regression) was applied. The subsequent sections will address the benefits and limitations of the more traditional statistical analysis used by the scoping review articles and provide a rationale for using Fourier analysis in the secondary analysis in Chapter 6.

5.2.1 **Statistical approaches used in scoping review articles**

A variety of parametric and non-parametric statistical techniques were used to model the effects of time on PROMs scores (Table 5.1). Multi-level models were most frequent with time of measurement as one of the variables at the individual level (145,153,157–160,165,167,168,172–174) followed by analysis of variance to test for the effect of time on outcomes (145–148,152,155,156,162,166,169,171). Five studies used non-parametric tests such as a Kruskal-Wallis test, due to the not-normally distributed data in their results (154). Two articles used a cosinor time-series approach to describe the rhythm of outcome variables (150,175). McCarley (2007) used specific software designed to model biological rhythms in the data (150).

This software takes the approximation of the time-series data by one or more cosinor curves of a given period. The level of significance of fit of the rhythm to a cosine curve is taken from the F test of the variance. The null hypothesis is that the amplitude of the approximated curve of a specific period is zero. This software program works on all types of data, including data that are not equally spaced out in measurement. The analysis provides the following parameters per variable: mesor (rhythm-adjusted mean for 24-hr), amplitude (half of the peak-to-trough variability), and acrophase (the peak time in relation to midnight). Alongside ANOVA analysis to test the effect of time, Bellamy et al (1991) used the cosinor technique to examine individual time series for circadian variation. This was done using the least squares fitting of cosines with varying periods of 0 to 1 hours between 20 and 28 hours.

Less than a third of studies took into account confounding factors related to cyclical variation in PROMs in their analysis and/or discussion of results (15.2%), such as the effect of medication or treatment interventions (145,155,327), co-morbidities (145), time of year of intervention (155) or severity of a condition (150,166), but the vast majority did not.

Table 5.1 Statistical modelling of cyclical variation studied in the included articles

Rhythms studied	Constructs measured	PROMs	Recall period	Statistical methods used
Diurnal	Symptoms	Daytime Insomnia Scale (145)	Momentary	Linear mixed regression models with a random subject intercept and fixed time of day and dialysis day variables to examine the association of each symptom (dependent variable) with time of day and dialysis day accounting for within-subject correlations across multiple time points and days
Diurnal	Symptoms	VAS on pain and VAS on stiffness (175)	Momentary	A one way analysis of variance (ANOVA) was used to test for the effect of time. Each individual time series was analysed for circadian (about 24 hours) variation using the cosinor technique (least squares fitting of cosines with varying periods between 20 and 28 hours with 0-1 h between trial periods)
Diurnal	Symptoms Functioning	VAS pain, stiffness and fatigue intensity scales VAS from Pediatric Pain Questionnaire Activity Scale for Kids Child Activity Limitations Questionnaire (180)	Momentary	Descriptive statistics (mean and SD) used to summarise typical levels and variability of symptom intensity and symptom duration within and across days.

Diurnal	Symptoms	VAS on cognitive fatigue (147)	Momentary	Repeated measures ANOVAs performed on performance measures and subjective fatigue ratings with the within-subjects factors day (day 1 vs. day 2), time-of-day (morning vs. noon vs. afternoon) and the between subjects factor group (MS vs. stroke vs. control).
Diurnal	Symptoms	Items based on PANAS (173)	Momentary	Latent growth mixture modelling (LGMM) was used to identify distinct trajectories of daily mood patterns as reported during EMA assessments.
Diurnal	Symptoms	PANAS Single items on fatigue and pain (148)	Momentary	Repeated measures Time (4) × Group (3) analyses of variance conducted using mean FATIGUE-D, PAIN-D, and PANAS positive and negative subscale scores as dependent variables to examine group differences in overall symptom and mood levels (i.e., a Group main effect), the diurnal pattern of symptoms and mood (i.e., a Time main effect) and group differences in diurnal symptoms and mood patterns (i.e., Group × Time interaction effect).
Diurnal	Symptoms	Single items on pain, stiffness and negative mood (5-point likert). Fatigue item derived from Multidimensional Fatigue Inventory Scale (146)	Momentary	Repeated measures analysis of variance was used, with day and time of day as within-subject factors and group as between-subject factor.
Diurnal	Symptoms	Single item on dizziness intensity (0-3 scale) (161)	Momentary	For comparison of non-parametric data at different time points in one group Friedman's test was used.

Diurnal	Symptoms	VAS on fatigue (152)	Momentary	To examine the effect of time of day for subgroups with different levels of ambulatory dysfunction, a 3 time points (morning, noon, afternoon) × 2 groups (mild, moderate) repeated measures ANOVA varying walking speeds
Diurnal	Symptoms	Momentary mood (168)	Momentary	Multi-level modelling approach taken controlling for time of day and week. The EMAs were not equally spaced thus an a priori specified spatial power covariance structure which modelled time as a continuous count of elapsed minutes since the start of EMA data collection was applied. Random intercepts were specified to account for individual differences in pain levels.
Diurnal	Symptoms	Positive affect & Negative affect Stress single item Sleep single item (160)	Momentary	Multi-level modelling was used to examine variability between persons and within-person variability across time Variables measured at multiple time points were modelled as Level 1 variables and variables containing only between-persons variance were level 2 variables.
Diurnal	Symptoms	VAS on mood states and bodily complaints Single items on Fatigue and Pain (164)	Momentary	Subject--specific differences (delta scores ranging from -1.0 to 1.0) were computed per variable each assigned to the appropriate 12-hour prodromal time-window (of respectively 0-12, 13-24, 25-36, 37-48, 49-60 and 61-72 hours before the attack). Per subject this resulted in pre-attack delta scores per time window for each clustered prodromal feature.
Diurnal	Symptoms	VAS on momentary headache intensity (172)	Momentary	Multilevel modelling was used to investigate diurnal variation of headache intensity and acute headache exacerbations. Momentary headache intensity was treated as the dependent variable and time of day as the predictor. The effect of time was modelled either as fixed or random.
Diurnal	Symptoms	Suicidal ideation (not validated) (165)	Momentary	Two statistics used to quantify variability: intraclass correlations (ICCs) and root mean square of successive

				differences (RMSSD). Supplemental analyses to examine if suicidal ideation varied within a day conducting a three-level model (responses within days within people) and regressing suicidal ideation on daily observation number.
Diurnal	Symptoms	Single item on momentary pain intensity (153)	Momentary	Multilevel random effects modelling (MLM) was conducted using momentary ratings and continuous accelerometry data (level 1) nested within days (level 2) nested within individuals (level 3) nested within data collection sites (level 4).
Diurnal	Symptoms	Profile of mood states (158)	Momentary	Latent growth mixture modelling (LGMM) was used to analyse the ratings on the tension anxiety subscale of the POMS. With each participant providing several tension-anxiety ratings per day over multiple days, the number of different trajectories any single individual could experience was limited only by the number of trajectories identified in the LGMM analysis.
Diurnal	Symptoms	VAS on fatigue and dyspnea (150)	Momentary	Cosinor analysis was used to describe the rhythm for each study variable. Pearson product moment correlations between the 24-hr mean values of dyspnea, fatigue, and PEFR derived from the 8-day, multiple-time-of-day assessments. Each participant’s dyspnea, fatigue, and PEFR values for each data-collection time were correlated to obtain an 8-day mean correlation.
Diurnal	Symptoms	Single items on pain, fatigue and emotional distress (159)	Momentary	Mixed-effects analyses examining sets of lagged regressions allowing coefficients to differ across individuals (random effects) about overall population average coefficients (fixed effects) were conducted for pain, fatigue and emotional distress. For each symptom measure, a current and prior (current - 1) value was identified - and a second variable "yesterday's symptom value" was calculated (current - 1 day).

				Values obtained at the same time on the previous day were examined - time of day factor.
Diurnal	Symptoms Functioning Health status	Chronic Obstructive Pulmonary Disorder questionnaire (COPD-Q) (149)	24-hours	Bi-nomial t-test to compare the morning with other times of day in terms of when symptoms were worse than usual. Multivariate linear model regression was used to examine the relationship between individual COPD symptoms and the extent of problems with the morning routine.
Diurnal	Symptoms Functioning	Symptoms of panic attacks (154)	Momentary	Time was not taken into account in the analysis. Non-parametric Kruskal–Wallis test assessed group differences regarding the following variables: mean BSA scores, RMSSD of BSA scores, number of symptomatic episodes. Significant group effects were followed by pair-wise comparisons using two-tailed Mann–Whitney U-tests.
Diurnal	Symptoms	Single item on momentary fatigue from Brief Fatigue Inventory Momentary mood - 15 adjectives - NA/PA (167)	Momentary	3-level multilevel models were used that nested Momentary Fatigue Severity assessments within days, within individuals. Group level diurnal fatigue patterns were assessed by adding linear and quadratic fixed and random time effects, with fixed group and group-by-time interaction effects.
Diurnal	Symptoms Functioning Health status	Global Chest Symptoms Questionnaire (GCSQ) Capacity of Daily Living during the Morning (CDLM)	GCSQ – momentary CDLM – morning SGRQ – 12-month	Review of literature

		St George's Respiratory Questionnaire (SGRQ) (170)		
Diurnal	Symptoms	Single items on Brief Pain Inventory VAS on fatigue and stiffness (162)	Momentary	Repeated measures ANOVA was used to evaluate whether the means on average weekly pain intensity, unpleasantness, and interference ratings, and other symptoms (dependent variables) varied across time of day (Time Effect: morning, afternoon and evening), day of week (Day Effect: weekday versus weekend), and week (Week Effect: Weeks 1 and 2). The data were summarised over time of day, day of week and week. Time was considered as a fixed effect in the analysis.
Circadian	Symptoms	VAS on pain, fatigue, stiffness Facial affective scale (176)	Momentary	Polychotamous logistic regression (PLR) was used to evaluate various risk factors, adjusting for age and sex, for functional impairment in the winter sample.
Circadian	Symptoms	VAS on fatigue (177)	Momentary	The mean scores (SD) for each seasonal group were calculated. Analysis of variance (ANOVA) was then calculated to detect any between-group seasonal differences both at baseline and after completion of PR.
Circadian	Symptoms	Mood Zoom - 6 descriptor items (not validated) (163)	Momentary	Mixed-model analysis of variance, with group-by-time interaction serving as the primary parameter of interest.
Circadian	Symptoms Functioning Health status	Couth Severity Diary (CSD) (156)	24-hour	Subject--specific differences (delta scores ranging from -1.0 to 1.0) were computed per variable. These delta scores were assigned to the appropriate 12-hour prodromal time-window (of respectively 0-12, 13-24, 25-36, 37-48, 49-60 and 61-72 hours

				before the attack). Per subject this resulted in pre-attack delta scores per time window for each clustered prodromal feature.
Infradian (seasonal)	Symptoms	Center for Epidemiologic Studies Depression Scale (CES-D) (169)	Past week	Time was split into the factors year and month and ANCOVA analysis conducted. Autocorrelations were computed for the two time series. Therefore, mean CES-D values were correlated with moving time-lags.
Infradian (seasonal)	Symptoms Health status	Seasonal Pattern Assessment Questionnaire (SPAC) (328)	12 months	Graphical displays of subjects' daily plots of worst and average fatigue were examined for each subject and categorised according to type of pattern. When describing the different patterns of fatigue, the number of women in each category varied because not all women demonstrated the same pattern of fatigue.
Infradian (seasonal)	Symptoms Health status	Chronic Respiratory Disease Questionnaire–Self Reported (CRDQ-SF) (155)		Analysis of variance (ANOVA) was performed to analyse the differences in NIH-CPSI scores across the three seasons. Correlations between various NIHCPSI responses and seasons were calculated with Pearson's correlation coefficient
Infradian (seasonal)	Symptoms	National Institutes of Health Chronic Prostatitis Symptom Index questionnaire (NIH-CPSI) (166)	Past week	Repeated measures ANOVA was used to evaluate whether the means on average weekly e-Ouch pain intensity, unpleasantness, and interference ratings, and other symptoms (dependent variables) varied across time of day (Time Effect: morning, afternoon and evening), day of week (Day Effect: weekday versus weekend), and week (Week Effect: Weeks 1 and 2).

5.2.2 **Analysis of Variance (ANOVA)**

ANOVA is a statistical method used to determine statistically significant differences between the means of two or more independent groups. The statistical test results in the F statistic, which is a quotient of two indices of variability. These two indices of variability include variability between groups (amount of variation among different datasets), and within-group variability (or an adjusted error term, when variations are caused by differences within individual groups). When the null hypothesis is confirmed, the two indices of variability are the same resulting in an F of 1. This assumes that all means are equal and therefore there is no rhythmicity in the data. However, when F is larger than 1, the between-group variation will be larger than the within-group variation, thus assuming, the existence of rhythmicity.

ANOVA evaluates whether one or more means significantly differ from the others, however it does not evaluate the existence of a rhythmic or cyclical pattern (329). If the null hypothesis is retained, ANOVA can guide the inference about the absence of a rhythmic pattern in the data, however it cannot demonstrate the existence of any specific patterns when the null hypothesis is rejected. If the null hypothesis is rejected the test has identified a lack of uniformity in the data, although this does not necessarily confirm the existence of a rhythmic pattern. This is a drawback of the analytical method, as it fails to account for the covariance among repeated measures and assumes constant variance over time.

The type of dataset is important to consider when applying ANOVA as a potential analysis, in that the statistical technique is appropriate if the number of observations are the same for each unit of analysis at the same time points. Cross-sectional data would be inappropriate given that data are collected only once and

comparisons over different times may not be possible (see Appendix IX for an example of such an analysis). As the analytical technique focuses on comparing the mean response trend for groups over time, it is not appropriate for investigating intra-individual variation over time. Although many of the scoping review articles used momentary datasets, the authors tended to use ANOVA to examine mean differences across three categorical timepoints (morning, afternoon and evening) between different groups (147,148,152,330), rather than examining intra-individual variation. In addition, another constraint of repeated ANOVA is that it can only account for categorical repeats, hence the transformation of time from a continuous variable to a categorical one in the scoping review articles.

An issue that is faced when analysing repeated measures data (or longitudinal data) is that measurements are correlated over time. Historically, simple statistical techniques have been used to manipulate the data by reducing the range of responses for each subject to a single value and applying a univariate approach to analyse the data, as seen in the scoping review articles. Although this method may be perceived to be efficient and effective, it is sensitive to missing data as well as irregularly spaced out repeated measures. Repeated measures ANOVA treats each response as a different variable and given that you may have an unbalanced number of responses for each individual this will result in these responses being dropped in the analysis.

In addition, this method of reducing multiple responses to one single summary statistic results in a loss of information regarding the rhythm or pattern of data over time. It has been recommended that repeated-measurements ANOVA models are used if the number of repeated measurements is “small” and the distance between time points “large” and equidistant (331). This is because ANOVA is less sensitive to

non-equidistance as the normality assumption behind parametric methods such as the ANOVA, requires data to be equidistant (332).

Interestingly, in one of the articles from Chapter 3, the authors used ANOVA to detect differences in mean scores across time and then cosinor analysis to demonstrate a circadian rhythm with peak performance calculated for time of day at both an individual and group level (175). This was also repeated in another article (185) where the author combined ANOVA with Fourier analysis in order to compare periodic patterns in its entirety. Thus on its own, it is determined that ANOVA is not an appropriate method to understand cyclical variation in data. However, coupled with statistical techniques designed to explain and map our cyclical variation, such as spectral analysis, ANOVA could potentially be applied to complete datasets examining shorter rhythms.

5.2.3 **Hierarchical/Multi-level regression modelling (MLM)**

As multiple measurements for each individual in a dataset results in correlated errors, this violates the assumptions of standard ANOVA and regression models and are not suited for explicit structures within the data (333). As mentioned in the previous section, any missing data from a respondent would result in an exclusion of that respondent in the analysis. In hierarchical or multi-level regression modelling (MLM), the analysis allows for these missing data as long as it meets the “missing at random” definition. This analysis also controls for the effects of the individual using time as a continuous or categorical variable.

MLM includes both fixed effects (same for everyone) and random effects (that vary across individuals). Hierarchical modelling is flexible and can handle clustered individuals and repeated measures in the same model. Unlike ANOVA, this statistical

technique can handle unbalanced data and missing data from individuals. Longitudinal data include two aspects to sampling (inter-individuals and intra-individuals over time), and hierarchical models quantify and explain each source of variation with time-varying predictors accounting for intra-individual variance (334).

Unlike ANOVA, hierarchical modelling is advantageous to uneven spacing of repeated measurements, thus allowing for study designs which allow participants to freely respond when they can. In addition, this method is recommended for analysing EMA data (335). Mixed level models use both fixed and random effects in the same analysis. Fixed effects, such as treatments or interventions, have levels which researchers would classify as their primary interest, whereas random effects (e.g. subject effects) are levels thought of as a random selection from a larger set of levels.

There were five articles from the scoping review that used multi-level regression modelling in their analysis, however most of their analysis controlled for time as a confounding variable. Upon doing so these articles did not take into account how time related to the outcomes being examined as confounding factors could mask an actual or false association between the independent variable and outcome (336). The analytical aims proposed by Graham-Engeland et al (168) examined the effect of depression on pain levels thus they treated time of day as a confounding variable in their analysis. Hamilton (160), on the other hand, included day and time of observations as Level 1 variables to control for diurnal variation of the symptoms being measured (pain and stress). The authors recognised that there were two sources of variance in their dataset: variability between individuals and within-individuals across time. However, the data collection period for this piece of

work was two days, and the time of day effect was not reported in their analyses as their focus was on the effect of sleep quality on symptoms.

Similarly to the authors using ANOVA in their analysis, Kikuchi et al (172) categorised time of day into three-hourly blocks in their examination into the diurnal variation of tension-type headaches, thus did not use time as a continuous variable in their analysis. However, the authors did use time of day as a predictor variable and the effect of time was modelled as both fixed (same for everyone) and random (vary across individuals) effects. Participants were prompted to record their symptoms on a regular basis, allowing for evenly spaced out data collection. Kratz et al (153) also had five evenly spaced out time points whereby participants were prompted to report their pain levels. There were some limitations to the work done by Kikuchi et al (172) and Kratz et al (153) with regard to data collection and how time was managed in the analysis. Given that participants were prompted at certain times of the day, symptom intensity may have been missed and there could have been a lag between the trigger of symptoms and recording of the event. EMA recording has its benefits in its reduction in recall bias, however study designs enforcing a timeframe for when participants record their symptoms may overlook key times of the day when symptoms are at their worst.

Powell et al (167) examined the diurnal fatigue patterns by adding linear and quadratic fixed and random time effects. The analytical approach used in this study allowed the authors to detect changes in fatigue scores over the course of the day, but again they used six time-points in a 24-hour period. The difference in this study was that the authors used an algorithm randomly assigning a single prompt within each of the six consecutive 100-min periods between 10am and 8pm. However, again in this analysis, time was not a continuous variable as there were six time-

points represented over a 24-hour period. Although the authors were able to determine substantial moment-to-moment and day-to-day fluctuations in fatigue severity, they were unable to determine what factors directly affected fatigue severity scores. This may be a limitation of quantitative analysis and study designs using quantitative measurements. Further qualitative analysis exploring how individuals experienced fatigue and the factors impacting on changes in scores is needed, and this approach is explored in Chapter 4in the longitudinal mixed methods study. Thus, it can be assumed that MLM could be an approach to explore cyclical variation, however there are limitations to the way time is used or modelled in this analysis.

5.3 Spectral analytical approach to cyclical variation of outcomes

Evidence has shown that few biological variables are constant throughout a 24-hour period, or even longer periods, demonstrating the presence of rhythms (337). These rhythms differ in shape, amplitude and when peaks occur over time. An alternative approach to regression-based methods to the analysis of cyclical variation is spectral methods, such as Fourier or Cosinor analysis (338). Quantifying these rhythms can prove challenging when traditional statistical methods, such as ANOVA, are applied to this type of non-linear data. The field of chronobiology has tended to focus on describing periodic cycles, however more recently this has shifted to quantifying irregularities and studying the mechanisms underpinning this disruption and normalisation (339). Circadian variables are frequently not normally distributed thus the classical approaches to analyses applied to these variables may be limited. Understanding the distribution of the data requires adequate sample sizes across the different timepoints, which may be limited for a variety of reasons including small population samples or difficulties in data collection procedures, and increased risk of missing data. The subsequent sections will focus on two types of

statistical approaches within the field of spectral analysis which were used in some of the scoping review articles in Chapter 3: cosinor analysis and fourier analysis.

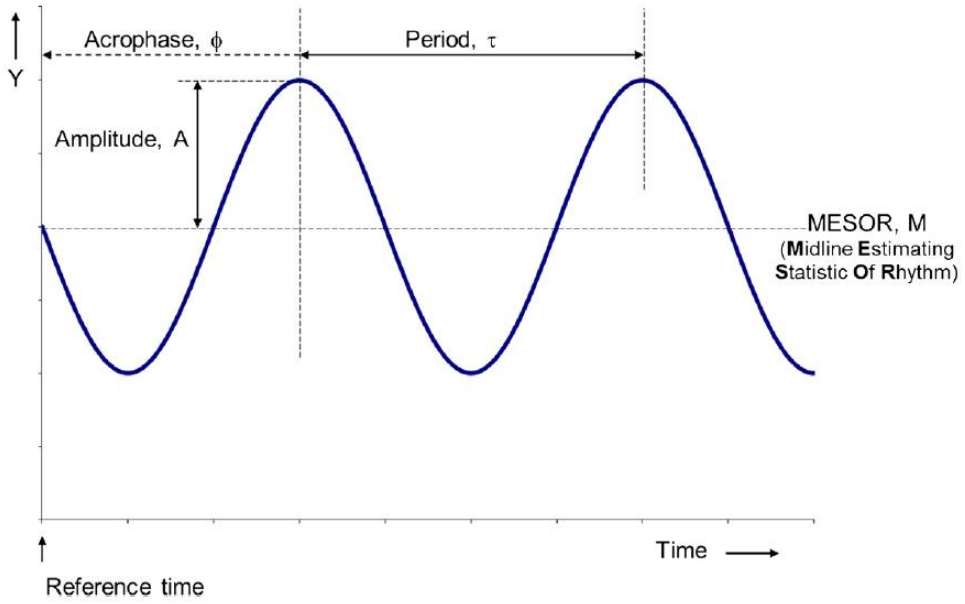
For biological rhythms, metrics of interest are usually the period (or frequency) of a cycle and some measure of a time (i.e. phase) within each cycle. To obtain these metrics, the data may be fitted with a function. There are two options: fit with an already defined parameter function (e.g. sinusoid, line, quadratic) or fit without a pre-defined function (non-parametric), such as a smoothing spline. The non-parametric requires a large dataset and averages the data at different periodicities, calculates the variance at each fit and then uses the fit with the lowest variation (340).

5.3.1 **Cosinor analysis**

Franz Halberg developed the single and population-mean cosinor techniques to handle short time-series and sparse data for the analysis of biological rhythms, when existing knowledge of potential rhythms already exists (341). Unlike AVOVA, this technique is able to handle non-equidistant and missing data. Cosinor is a regression technique which fits one or more cosine curves to the data, either separately or in parallel. This method minimises the sum of squares of the differences between the actual measurements and the fitted model (the residuals), for the period being investigated (184). Cosinor analysis can justify, or not, the existence of a given rhythm and it can calculate its parameters. The key parameters in this analytical technique are: mesor, amplitude and the acrophase (as represented in Figure 5.1). The mesor is the midline estimating statistic of rhythm. The amplitude is the extent of predictable change within a cycle. The acrophase is the timing of overall high values recurring in each cycle, expressed in (negative) degrees in relation to a reference time set to 0°. Statistical significance is determined for each of

the given metrics by an F-test with respect to the null hypothesis (zero amplitude or no-rhythm). Cosinor analysis provides an estimate of the percentage rhythm, or the proportion of variation which can be accounted for by the regression model (342).

Figure 5.1 Definition of rhythm characteristics in cosinor analysis (adapted from Cornelissen (2014) (184)



A cosine function can be fitted for each variable of interest:

$$y = M + a\cos(\frac{2\ \pi\ t}{T} + \theta) + \varepsilon$$

In this equation, *y* is the variable of interest (*e.g. patient reported outcome score)*; *T* is the time period during which the cycle occurs (e.g. circadian rhythm of 24-hours); *M* is the mesor or the mean value over the time-period; *a* is amplitude; *t* is the time period for which the value is fitted (*e.g.*, each hour of the day within a 24-hour period); *θ* is the acrophase; and *ε* is the error term. In order to transform this relationship into a linear regression model using cosinor analysis the equation may look like this (343):

$$y = M + A\cos(\frac{2\ \pi\ t}{T}) + B\sin(\frac{2\ \pi\ t}{T})$$

In this equation, $A = a\cos(\theta)$, and $B = -a\sin(\theta)$. Thus, for every hour of the day and 24-hour period, you can calculate $\cos(\frac{2\pi t}{T})$ and $\sin(\frac{2\pi t}{T})$ terms. Simple linear regression coefficients can be estimated and significant coefficients would suggest a cyclical relationship to the outcome measures being tested.

The two scoping review articles applied both the population mean cosinor analysis (150,175) and the single cosinor analysis (150). McCarley et al (150) used both the single cosinor analysis to determine the rhythm observed in each participant's dyspnea, fatigue, and PEFR values. In addition, they calculated the population mean (group) cosinors. This was done on the parameters (mesor, amplitude and acrophase) derived from the single cosinor analysis of each participant's data. The statistical significance of the fit of the rhythm to a cosine curve in McCarley et al's study (150) was obtained by the F test of the variance accounted for by the cosine curve of a given period versus a straight line. Thus a rejection of the null hypothesis demonstrated rhythmicity. The percentage of the total variance in the time series data was explained by the cosine curve approximation of the given period and the key parameters. A significant limitation of this method is that data presenting irregular patterns/cycles (i.e. not presenting any particular rhythm as described in Chapter 1) are more difficult to describe. In order to carry out cosinor analysis existing knowledge of rhythms is needed, which thus presents a significant limitation to the method when a study is attempting to demonstrate a new rhythm. Hence a different from of spectral analysis may be more appropriate to apply, such as Fourier analysis, which will be discussed in the next section.

5.3.2 **Fourier analysis**

Fourier analysis was developed in the 1800s by Jean-Baptiste-Joseph Fourier and follows the Fourier theorem which states that any time series data can be described using sine and cosine waves of various frequencies and amplitudes (329). Fourier analysis (which includes Fourier series, transform, etc) falls between time-series and regression analysis. Depending on which field an individual works from (i.e. time-series or regression person), this technique might appear to be either basic (to time-series people) or specialised (to regression individuals)(344). It is a type of spectral analysis identifying periodic patterns by partitioning the data into individual sinusoidal signals of different frequencies (345). Naturally occurring time series can be decomposed into a unique set of independent sine waves in which each wave is defined by an amplitude and frequency parameter (345), which is called a Fourier series and defined by constants known as Fourier coefficients. Fourier coefficients are the amplitudes of the sine waves at each frequency (345). The weighted sum of these component waves reconstructs the original composite time series. The objective is to calculate the coefficients up to the largest possible value of n. The greater the value of n, the more accurate the Fourier series is representative of the waveform.

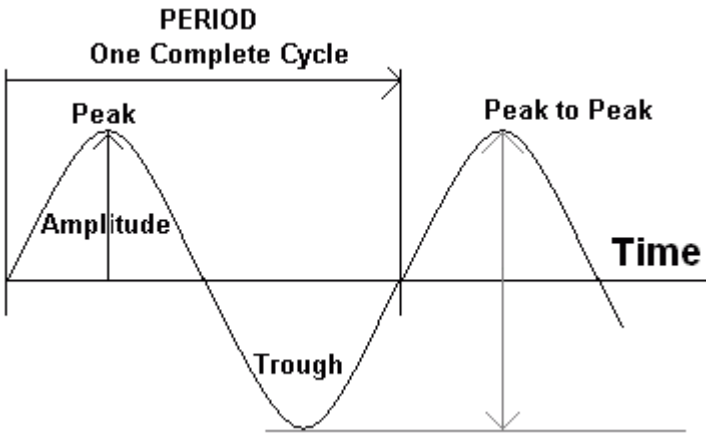
To better understand the formula of Fourier series, we need to understand sine and cosine waves. Sine waves are repeating patterns that gets through one cycle every 2 π units of time. Sine waves are represented with the following equation:

$$y = a \sin (bx + c)$$

whereby a is the amplitude of the sine curve (height), b is the period of the sine curve (length of one cycle of the curve – the natural period is 2π), and c is the phase shift of the sine curve (how much the curve shifts from 0).

In order to find periodicity in the data, we need to sample over a number of periods, i.e. multiple cycles. As mentioned above one natural period for a sine curve is 2π or 360°. Multiple periods will show us what the peaks and troughs are in the data (as demonstrated in Figure 5.2). Sine and cosine are periodic functions that return results between -1 and 1, as some angles vary. Angles are measured as the amount of rotation away from the fixed axis. The fixed axis is taken to be either horizontal (in the field of mathematics) or vertical (in the field of geography to represent a north bearing on a map) (344).

Figure 5.2 Demonstration of peaks, troughs, and complete cycles of a sine curve.



Fourier transform is commonly used in various fields of medicine and other scientific areas to detect the inherent periodic patterns of the data (185). Scientists use Fourier transform to study complex things that fluctuate in the real world, such as sound, light, heat, by separating the signal from the noise in the data collected. Any complex wave-like signal an individual measures, which fluctuates over time, can be broken down into a sum of sine waves. The Fourier Transform takes a time-

based pattern, measures every possible cycle, and returns the overall "cycle recipe" (the amplitude, offset, & rotation speed for every cycle that was found). The Fourier transform changes our perspective to asking what do I have from these data into how was this made. The Fourier transform finds the recipe for a signal and allows researchers to transform a function of time and single into a function of frequency and power enabling us to see what frequencies make up our signal and how strong these signals are. As there is noise in any dataset Fourier transform allows us to see through the noise to which frequencies matter.

Long-term patterns can be modelled more smoothly by fitting Fourier terms in a regression model. These are pairs of sine and cosine functions of time with an underlying period reflecting the full cycle being examined (e.g. circadian = 24hrs). A single sine/cosine pair will model circadian variation in the outcome as a regular wave with a single peak and trough per cycle. However, harmonics (extra sine and cosine pairs with shorter wavelengths, i.e. 12 hours, 6 hours) can be introduced which result in more flexible functions (346).

In order to better understand the mathematical underpinnings of fourier series, the next section will discuss the formula that is used to represent fourier series. A general representation of a linear model of PRO scores would be as follows:

$$O = \mu(h) + \varepsilon$$

Where *O* is the PRO score, *h* is the independent variable and ε is the random error. In any health condition the theory is that the variation of *O* with hour of day *h* is periodic. μ(*h)* can then be represented by a Fourier series in the following equation below:

$$O_h = \beta_0 + \sum_{k=1}^{l} \left[\alpha_k \sin\left(\frac{2\pi}{P_k} h\right) + \beta_k \cos\left(\frac{2\pi}{P_k} h\right) \right] + \varepsilon_h$$

O_h is the PRO score at hour h, a_k and b_k are the coefficients of the kth sine and cosine frequencies and P_k is the period (i.e. length of one cycle of the curve) for the k^{th} frequency.

5.4 Conclusions

Traditional approaches, such as ANOVA and MLM, have limitations in their ability to examine the existence of cyclical variation and the type of data needed to apply these statistical tests. ANOVA evaluates the means of variables and is unable to demonstrate the existence of cyclical variation in data. In addition, this approach is unable to handle datasets with uneven spacing. MLM, on the other hand, is most used to longitudinal datasets and accounts for uneven spacing in repeated measurements. However, the articles that used MLM in their analysis did not use time as a continuous measure, instead transforming it into a categorical variable. Fourier transform is a common approach used in medicine and physics to detect cyclical variation in data. The statistical method enables researchers to see through the noise of the data as mentioned in section 2.5 in terms of the internal or external factors that may impact on how patients respond to outcome measurements, and present patterns that are important for that condition. Chapter 6 will use the Fourier approach on a readily available longitudinal dataset to examine and visually present variation in outcome scores for Meniere's Disease.

Chapter 6 Exploring variation in outcome scores in Meniere's Disease

6.1 Chapter outline

The previous chapters presented an outline of the literature that documented fluctuations in outcome scores for chronic conditions and provided empirical evidence supporting the conceptual model. Chapter 5 explored the methodological study designs used to collect data on fluctuating outcomes scores and statistical techniques used to explore this compared to traditional methods. The present chapter will focus on applying a specific statistical technique, namely Fourier transformation, to model variation of outcome scores demonstrating a circadian rhythm in a longitudinal dataset of Meniere's disease. The purpose of Chapter 6 is to better understand how Fourier transformation can capture variation of scores in Meniere's disease. The benefits as well as the limitations of this approach will be explored in detail in this chapter.

6.2 Prevalence and Epidemiology of Meniere's disease

Meniere's disease (MD) is an inner ear disorder that is chronic, progressive, and affects both the balance and hearing functions of the inner ear. Discovered in the late 1800s, diagnostic criteria for this disease were not established until 1995. However, there is no definitive test to diagnose the condition due to the fluctuating nature of the symptoms (347). Thus, this makes it common for a misdiagnosis to occur in primary care settings (348), and for a late diagnosis to be definitively provided to patients. The ICD-11 classifies MD as an episodic vestibular syndrome which is a syndrome of "transient vertigo, dizziness, or unsteadiness lasting seconds to hours, occasionally days" (142). Individuals experience recurrent events with

repeated spells that are either triggered or spontaneous. The disease often has periods of remission and exacerbation thus making a definitive diagnosis difficult for clinicians (349). Further details about these symptoms and the impact of them on an individual are discussed later in this chapter. As the variability of the symptoms for this condition has not been researched much, there are limited data on the epidemiology of MD.

The diagnostic criteria for MD were internationally formulated across five organisations to two categories: definite MD and probable MD (350). In order to get a definite diagnosis of MD individuals need to meet a range of clinical criteria and require an observation of an episodic vertigo syndrome (lasting 20 minutes and 12 hours) which is “associated with low- to medium-frequency sensorineural hearing loss (SNHL) and fluctuating aural symptoms (hearing loss, tinnitus, and/or fullness) in the affected ear” (350). Whilst probable MD is defined by episodic vestibular symptoms (vertigo or dizziness) which are associated with fluctuating aural symptoms and occurs in a longer period from 20 minutes to 24 hours (350). Although most MD cases tend to be unilateral, i.e. experienced in one ear, as the disease progresses the incidence of bilateral cases increases with 25-40% reported in affected individuals (351,352). The average time to conversion from unilateral MD to bilateral MD was found to be 7.6 years in one study (353). Those with bilateral MD have increased vestibular symptoms which ultimately have a negative impact on their health-related quality of life (350). As the illness progresses, the severity of tinnitus and hearing loss increases (354). However, the increase in hearing loss may coincide with the natural progression of ageing.

The reported incidence of MD ranges from 8.2 to 157 per 100,000 individuals per year (355). According to a population study conducted in the UK (356) it was

estimated that the overall incidence rates were 13.1 per 100,000 persons-years. As reported in the ICD-11, MD is more common in Caucasians (of European decent), than in other populations such as Asian or African (142,350,357).Changes in society and additional stresses may have led to a gradual increase in prevalence of MD over time, especially in the female population (358). Despite earlier reports of a lack of gender difference in the prevalence of the disease (349), more recent studies have reported higher rates of diagnoses in women over men (359–361). A study using data from the UK BioBank found that of those with an MD diagnosis a higher proportion of the population were female, older (mean age of 63.4 years), and white British (96.9%) (362). This correlates with previous literature regarding the characteristics of individuals with MD. There were similar numbers of individuals with MD who were either employed or retired (362). The prevalence of this disease does increase with age. Diagnoses are most commonly made in individuals aged between 30 and 60 years of age (363,364) with the disease being more prevalent in an older population (365).

6.3 Symptomology of Meniere's disease

The most common recurrent symptoms of MD to occur include: hearing loss, vertigo, and tinnitus, often accompanied by aural fullness, with attacks to typically last for under 24 hours (350). When this set of symptoms cannot be attributed to a specific cause the syndrome is considered to be idiopathic and referred to as MD (350). Symptoms can spontaneously occur, however individuals in remission of major symptoms often experience fluctuating periods of more minor symptoms (366). Longitudinal studies have found fluctuation to be present in the early stages of MD in about 70% of patients (367). Longitudinal methodology is useful in documenting trends of fluctuations with daily recording being important, particularly in MD (367).

The benefits and limitations of using a longitudinal study design in capturing fluctuations in outcome scores was discussed in Chapter 6.

Patients with MD often report recurring episodes of vertigo lasting from around 20 minutes to several hours within a 24-hour period (349). These episodes are explained as a spinning sensation that starts and stops spontaneously, which sometimes can cause nausea. Hearing loss in MD, early in the onset of the disease may fluctuate, however, eventually some patients experience permanent hearing loss. Tinnitus is defined as a ringing, buzzing, roaring, whistling, or hissing sound in the ear. Aural fullness, is explained as a feeling of pressure in the affected ear (feeling of fullness in the ear), with symptoms lasting from a few minutes to several hours depending on certain factors such as disease progression, the individual and the environment (368). Although diagnostic criteria for MD typically mention the above symptoms, sufferers may also experience other symptoms such as nausea/vomiting, and headache during these attacks (369).

In addition, individuals report experiencing their symptoms (or attacks) in either clusters and/or several times a week, with some individuals experiencing them less frequently (every few weeks, months or years) (350). Longer disease duration has been associated with improved health satisfaction which may represent the natural disease progression and a gradual decline of the number of attacks over time (362). However, this does not coincide with the reported increased severity of tinnitus and hearing loss as documented earlier in the chapter (354). As this condition is difficult to diagnose and differentiate from other conditions with similar symptoms (e.g. migraines, ear infections or vestibular neuronitis), research on the variability of symptoms across time is limited.

6.3.1 **Triggers**

Recent research into what exacerbates the symptoms of MD demonstrated a seasonal effect (365) as well as a social environmental effect, e.g. stress (370). The effect of MD on psychological health status is discussed further in section 6.4, however it should be noted that psychological distress can also be a trigger. This supports the conceptual model presented in Chapter 3 where it shows that variation in outcomes both impacts on and is impacted by psychological health status, thus having a bidirectional effect. This is similar to psychological distress in MD whereby it can be a trigger for symptoms but also symptom severity can trigger psychological distress. Research has shown that psychological distress, such as anxiety or other emotional problems, has been considered to be an important predisposing and or triggering factor of MD (354). Attacks were found to be triggered by distressing thoughts and sensory sensations by one study (371). Stress has been found to be associated with symptoms of MD (370,372), with higher stress levels being associated with a higher chance of an MD attack and increased symptom severity (370). The physical environment can also be a trigger, visual triggers can exacerbate visual vertigo and the symptoms experienced are related to patterns of exposure to triggers (366).

6.3.2 **Meniere's disease and migraine**

Epidemiological studies have shown a link between MD and migraines (373), however some symptoms related to MD (namely fluctuating hearing loss and episodic vertigo) can also be misconstrued as symptoms for migraines. Under the episodic vestibular syndrome heading within the ICD-11, vestibular migraines can be found. The symptomology of this condition is similar to those related to MD, and

those reported by Cha et al (2007) (374). Symptoms for vestibular migraines include vertigo and dizziness and attacks can occur together or independently of other migraine symptoms such as headaches or visual aura (142). Cha and colleagues compared individuals with solely MD and those with migraine and MD (MMD). Individuals with MMD had an earlier onset of MD and migraine related symptoms, mainly episodic vertigo, and fluctuating hearing loss. The significantly lower age of onset for MMD individuals does suggest that migraines could lead to earlier susceptibility of the development of MD.

MD and migraine also share common triggering factors (as mentioned in the previous section), such as stress, weather changes and diet (369). Biorhythms, especially fluctuations in oestrogen may also be contributing factors to spreading cortical depression, which are related to both migraine and MD symptoms. Age of onset of vestibular migraine is similar to MD, later in one's life (50s) and both migraine and vestibular migraine occur more frequently in women (369).

6.4 Impact on patient outcomes

The recurrent symptoms that patients with MD experience can cause them emotional distress (22–24) as well as impact on functional status and health status (362). Episodic vertigo impairs an individual's daily function, however the uncertainty of these episodes has an immense impact on psychological status (378), preventing engagement in a range of activities (354,379). For example, a study has shown that 47% of their MD participants listed restrictions which have impacted on their social life and their employment (380). Research has shown that potential exposure to emotional stress, such as that of the threat of an attack, has increased the risk of having a subsequent vertigo attack (378). The unpredictability of MD and its

disabling symptoms can result in prolonged periods of depression for individuals (362). MD is associated with anxiety, depression, disability and adjustment disorders and dissociative disorders (375), as well as lower quality of life (366,381).

Quality of life (QoL) in MD patients has been reported to be lower than healthy adults (368). QoL scores can potentially be affected by the duration of living with the disease and the individual manages their MD (382). Poorly controlled MD results in lower quality of life scores (378). QoL in MD patients has been linked to symptom severity, psychological status, social support and an individual's coping styles (383). One study demonstrated that a lower QoL was associated with severe symptoms experienced by their population, being younger, being female, living alone and having a lower occupational status (384). The worse QoL scores for a younger population could be explained through the number of years living with this condition, in that the less amount of time an individual Is suffering with the disease may be linked to poorer management of MD.

6.5 Cyclical variation of the disease

Each of the Meniere's symptoms impacts on an individual's quality of life, with the most debilitating of symptoms (e.g. vertigo) significantly restricting physical and social activities. Due to the unpredictability of this disease, patients experience prolonged periods of depression and lower health status satisfaction (385). There is evidence to suggest, however, that the longer patients have the disease the less they experience depressive episodes (385). This could be due to patients adapting and managing their condition more effectively over time and understanding their condition better.

Few studies have been done to examine the real-time rhythmicity of this disease across different time points using outcome measurements. However, studies have prospectively documented that fluctuations occur, especially in certain symptoms (e.g. daily and weekly vertigo spells and hearing loss) (386). Research has shown fluctuations of reported experience over different seasons, with patients reporting seasonal rhythm of attacks and a peak of attacks in the spring (387). More recently, some research has been conducted into triggers of MD symptoms demonstrating both seasonal (388) and social environmental effects, e.g. stress (370), which could contribute to the fluctuating nature of the condition. In addition, increased migraine frequency has also been associated with changes in weather (e.g. low atmospheric pressure, high temperatures, low humidity) (369). However, these are limited studies that confirm these triggers and fluctuating patterns, whilst others have not been able to demonstrate any seasonal variation in MD (389). Despite this mention of fluctuations in the literature there is a lack of documented evidence demonstrating the patterns of change in outcome scores for MD. In addition, there is no research presenting the various rhythms MD supposedly exhibits in the literature, e.g. circadian, infradian.

6.6 Treatment and Management of Meniere's Disease

Given the difficulty of the diagnosis of this condition, there are various medical options available to patients with MD (390). A European position statement on treatment of MD outlined the different types of options available for MD sufferers (391). A preventative approach includes advice on diet and a low dosage of antihistamines, whilst some contradicting evidence for a second line of treatment involves steroids, and failing this future treatment being surgery (391). NICE

guidelines suggest mostly self-care management for patients presenting with MD symptoms with further treatment if self-care deteriorate (392).

The trial-and-error approach to managing and treating MD could potentially have an effect on how individuals report on their symptoms using outcome measurements, however there is a lack of research investigating this. A better understanding of how symptoms manifest over time is needed, which would then inform individuals on how to manage their condition, impacting on outcome measurement scores.

6.7Aims and research questions

The first aim is to describe the pattern of severity in symptom scores for Meniere's disease. The second aim is to examine the symptom severity profile over the course of a 24-hour period and weekly period with a specific focus on answering these three research questions. The specific research questions for this secondary analysis are:

1. Are there circadian patterns observed in MD across the four key symptoms (aura fullness, hearing loss, tinnitus, and dizziness)?
2. In a 24-hour period when are the symptoms reported to be worse and when best?
3. Are there any longer patterns observed, e.g. day of the week, across the symptoms?

6.8 Methods

This is a secondary analysis of an existing dataset collected by Tyrell (2017) (385,388) as part of a wider study monitoring the main symptoms of Meniere's disease on a daily basis, through the use of a mobile application.

6.8.1 **Background to the dataset**

During a presentation of the thesis plan at an annual postgraduate research event at the start of the PhD, one of the professors attending suggested potential access to a dataset held by Dr Jess Tyrell at the University of Exeter Medical School. Dr Tyrell developed a mobile phone application called Meniere's Monitor in 2014 to investigate the role of weather on the symptoms of MD from individuals across the world. The app was designed in collaboration between researchers at the University of Exeter Medical School, MD patients and a design company called Buzz Interactive. I met with Dr Tyrell and proposed an analytical strategy for the PhD given that cyclical variation of PROMs in MD had not been explored. There was considerable overlap in the triggers experienced by those with MD and the concepts within the conceptual model in Chapter 3, thus it seemed pertinent to use the available dataset to provide further evidence for the model.

The data collected for this dataset used an ecological momentary assessment design documenting real-time information through the mobile app. The aim was to enable patients with MD to monitor the main symptoms on a daily basis and recruitment of patients were from a range of sources (Meniere's Society, online forums, ENT clinics). This was a free app for patients to download and once installed patients were asked a range of demographic and baseline questions, details of which are described in the method section. The initial research project demonstrated that changes in weather (atmospheric pressure and humidity) and stress were associated with the worsening of symptoms for MD. These studies examined seasonal changes in symptoms due to environmental triggers, however, there have not been any studies examining diurnal patterns of symptoms.

6.8.2 **Measures and outcomes within the app**

Data were collected worldwide from participants over a four-year period from February 2014 to the end of December 2018. Participants who signed up to take part were asked a range of demographic questions including age, gender, employment status, and postcode. In addition, they were asked baseline questions about their MD which included who diagnosed their disease, what year it was diagnosed, which ear was affected, frequency of attacks, which medications they were taking for their disease and if they were experiencing migraines. Finally, individuals were asked to rate their level of severity for each of the four symptoms on a good day and a bad day on a ten-point scale.

On a daily basis, participants were asked to rate the level of severity of four symptoms on a sliding scale from 0 to 10. The questions asked about their symptoms have not been through any reliability or validity checking. At the same time, participants were able to record whether they considered themselves to have had an attack as a binary response (Yes/No). Finally, participants were questioned whether they had an unusual event on that day which could have triggered the attack or impacted on the severity of their symptoms. Optional information was collected around diet, stress levels (three questions from the Perceived Stress Scale from Cohen and Williamson [1988])(393), attack duration and severity, sleep quality and duration. GPS locations were also collected. Participants could enter this information once per 24 hours, but there was no requirement to use the app every day.

6.8.3 **Analysis plan**

6.8.3.1 Data preparation

The data were prepared in Excel prior to importing into STATA for analysis. All participants who did not provide a date of birth or provided a “fake” date of birth (i.e. date and year of completion), were deleted from the dataset. The exact time of day was recoded to hour of the day (1-24) in order to enable comparisons of symptom scores to be made by each hour of a 24-hour cycle. The original symptom scales were from 0 to 10, and these were linearly rescaled to a 0 to 100 scale (i.e. by multiplying the reported score by 10). The country of completion variable was recoded into continents in order to allow for variation in seasons due to the hemispheric influences. Countries were assigned to one of the seven continents (Asia, Africa, North America, South America, Europe, Australia, and Oceania).

6.8.3.2 Descriptive statistics

To address the first aim of the secondary analysis demographic characteristics were described for Ménière’s participants by using means and standard deviations (or medians and interquartile ranges) for quantitative variables and numbers and percentages for categorical variables. The app usage was plotted against each hour of the day to better understand how usage varied over the course of a 24-hour period. In order to obtain a graphical representation of cyclical variation of scores the mean symptom severity score for each of the four symptoms was plotted against the hour of the day using line graphs.

Prior to analysis the hour of the day variable was recoded so that 6am was the baseline reference of 0 and all other hours of the day were compared to that. This is because after examining the distribution of app usage over a 24-hour period, the least frequent use of the app was from midnight to early hours of the morning. The

mean symptom score across a 24-hour period was presented graphically for each of the four symptoms for each hour.

6.8.3.3 Assessment of change and reliability of measures

As discussed in Chapter 2, there are various ways to calculate what meaningful change in longitudinal data is. However, in this study calculations of MID/MCID or SEM were not feasible. Although baseline measures were collected, the study design did not include an additional question asking patients to indicate whether or not subsequent changes from the baseline were positive or negative.

Each symptom was measured using one item, thus the reliability of each item could not be tested as there were no comparators to evaluate each item to. Reliability is dependent on the variability between participants, thus can be context dependent, i.e. reliability will change depending on the population being studied. Despite multiple measurements collected for each participant, the circumstances in which these measurements were completed were potentially not the same as previous recordings.

6.8.3.4 Fourier transformation

A guidance document outlining the steps taken to conduct Fourier transformation with the STATA commands can be found in Appendix X. Time was represented as a patten of cosine and sine function (known as Fourier components) with variable amplitude and period. A temporal pattern of symptom severity within the 24-hour period using sine and cosine functions was tested. In addition, further analysis was conducted to examine whether the temporal pattern to model symptom severity was better described by adding cosine and sine functions with a period of 12-hours. Sine and cosine functions were tested for each of the time-periods (24-

hour, 12-hour, and 6-hour) to examine the association between the functions at each period, using a chi-square test. If there was a statistically significant association between the sine and cosine functions for each period, these would be included in the final regression model. However, once the association between the functions was not significant the model would be run excluding the non-significant time-period.

A multilevel mixed-effects linear regression was conducted with each of the symptoms (dizziness, aural fullness, tinnitus, and hearing loss) as the dependent variable and sine, cosine as independent variables with individuals as random intercepts. Confounding factors, such as age, gender, employment status, day of the week were included in the model. In order to examine the parameters of the model, with sine and cosine variables together, a Wald test of simple and composite linear hypotheses was conducted. In order to determine whether there was any difference between the sine and cosine variables and estimate the effect of various periods (24 hour, 12 hour) relative to midday, linear combinations of coefficient estimates were calculated using the “lincom” command in STATA. The lincom command computes point estimates and standard errors for each half hour of the day. All output graphs were plotted with a mid-day reference value and represented a 24-hour period.

6.8.3.5 Missing data

As the participants of the study were given the freedom to answer as and when they wanted, there is not an issue with regard to missing data. The repeated measures analyses included all available data for each participant. Those participants providing less than 10 data points were excluded from the analysis. Equally, participants who did not provide demographic data were excluded as age and gender were controlled for, and the seasonality variable required location data in order to be accurate.

6.9 Results

6.9.1 Participants

A total of 546 participants provided time-stamped data on their symptoms up to 47,598 times across a three-year period (January 2015 to September 2018). Table 6.1 presents the characteristics of the study population. The mean age was approximately 52.7 years (SD = 12.2) with a predominance of women (65.4%) and a substantial number of employed participants (68.3%). The majority of participants were from either Europe or North America (92%). The average number of years individuals have lived with Meniere's since a proper diagnosis was 8.14 years.

6.9.2 Baseline measurements

Baseline results show that a large proportion of participants reported having daily symptoms (60.3%), whilst just under a quarter had weekly symptoms (23.7%). Most participants experienced the most frequent symptoms in the left ear (37.2%) with 31.9% of participants reporting symptoms in both ears. Under half of participants frequently reported having migraines (40.8%).

6.9.3 App usage

The number of uses varied over a 24-hour period, with most usage occurring during the latter part of the day. However, there was a small percentage of reporting between midnight and 5am (6.2%). Upon further interrogation of the data, over half of participants reporting during that period were employed (70.8%), which might suggest that these were shift workers although it was not possible to confirm this theory. Around 17% of the participants reporting during this period stated that they were unable to work. The app was mostly used later in a 24-hour period, with usage

peaking at 9am and again at 9pm. The number of times participants provided data varied, with some using the app five times to over 1100 times.

Table 6.1 Characteristics of participants

		N (%)	M (S.D.)	Total N
Gender				
	Male	189 (34.6%)		546
	Female	357 (65.4%)		
Age			52.7 (12.2)	
Employment status				
	Employed	373 (68.3%)		
	Retired	56 (10.3%)		
	Unemployed	25 (4.6%)		546
	Unable to work	71 (13.0%)		
	Did not complete	21 (3.9%)		
Symptoms				
	Aural fullness		2.9 (2.7)	
	Hearing loss		4.2 (2.9)	546
	Tinnitus		4.5 (2.9)	
	Dizziness		2.3 (2.5)	
Continents				
	Europe	355 (65.6%)		
	North America	143 (26.4%)		
	South America	8 (1.5%)		
	Africa	3 (0.6%)		541
	Asia	15 (2.8%)		
	Australia	16 (2.9%)		
	Oceania	1 (0.2%)		
Baseline questions				
Which ear is affected				
	Both ears	172 (31.9%)		
	Right ear	167 (30.9%)		540
	Left ear	201 (37.2%)		
Frequency of symptoms				
	Daily	313 (60.3%)		
	Weekly	123 (23.7%)		519
	Monthly	83 (16.0%)		
Frequency of migraines				
	Daily	32 (6.1%)		
	Weekly	96 (18.4%)		
	Monthly	85 (16.3%)		522
	Rarely	170 (32.6%)		
	Never	139 (26.6%)		
Years since diagnosis			8.14 (50.6)	

6.9.4 **Symptom variability and presence of an attack**

The mean scores for the four symptoms were below 5, however the mean for tinnitus and hearing loss were closer to this ranging between 4.2 and 4.7. Most of the symptoms reported were not related to having an attack at the same time, and only a small percentage (10.6%) of observations were reported whilst having an attack. Participants assessed the severity of these attacks, with just under half (42.4%) stating the attack was quite severe (6+). For example, for the average participant, the mean score for Dizziness was 2.34, however when a participant indicated that an attack was present the score increased to 5.8. However, attacks only explain a small amount of variance because it does not happen often (up to 10% of the time).

6.9.5 **Symptom variability over time**

Figure 6.1 depicts the times participants reported symptoms by each hour of the day within a 24-hour period demonstrating variation of symptom experience across the day. The graphical display of symptom scores by hour demonstrates variation across all four symptoms. Further analyses were conducted using Fourier components and presented in 6.9.8.

6.9.6 **Symptom variability by location**

The means across all four symptoms varied by continent, however this may be due to sample size variability. The mean for tinnitus was higher in South America (M=6.1), in comparison to Europe (M=2.9). However, due to the large difference in the number of observations between the two continents, I am unable to make any comparisons between continents and countries. Table 6.2 presents the means across the different continents.

Figure 6.1 Number of observations of symptoms by hour of the day

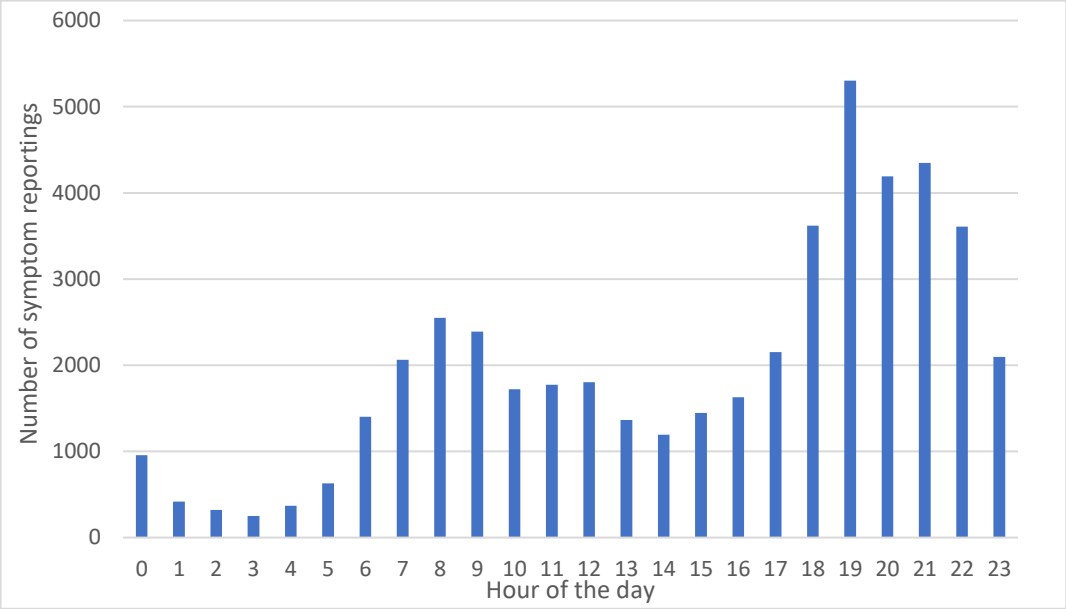


Table 6.2 Symptom means across the continents

6.9.7 **Symptom variability and participant characteristics**

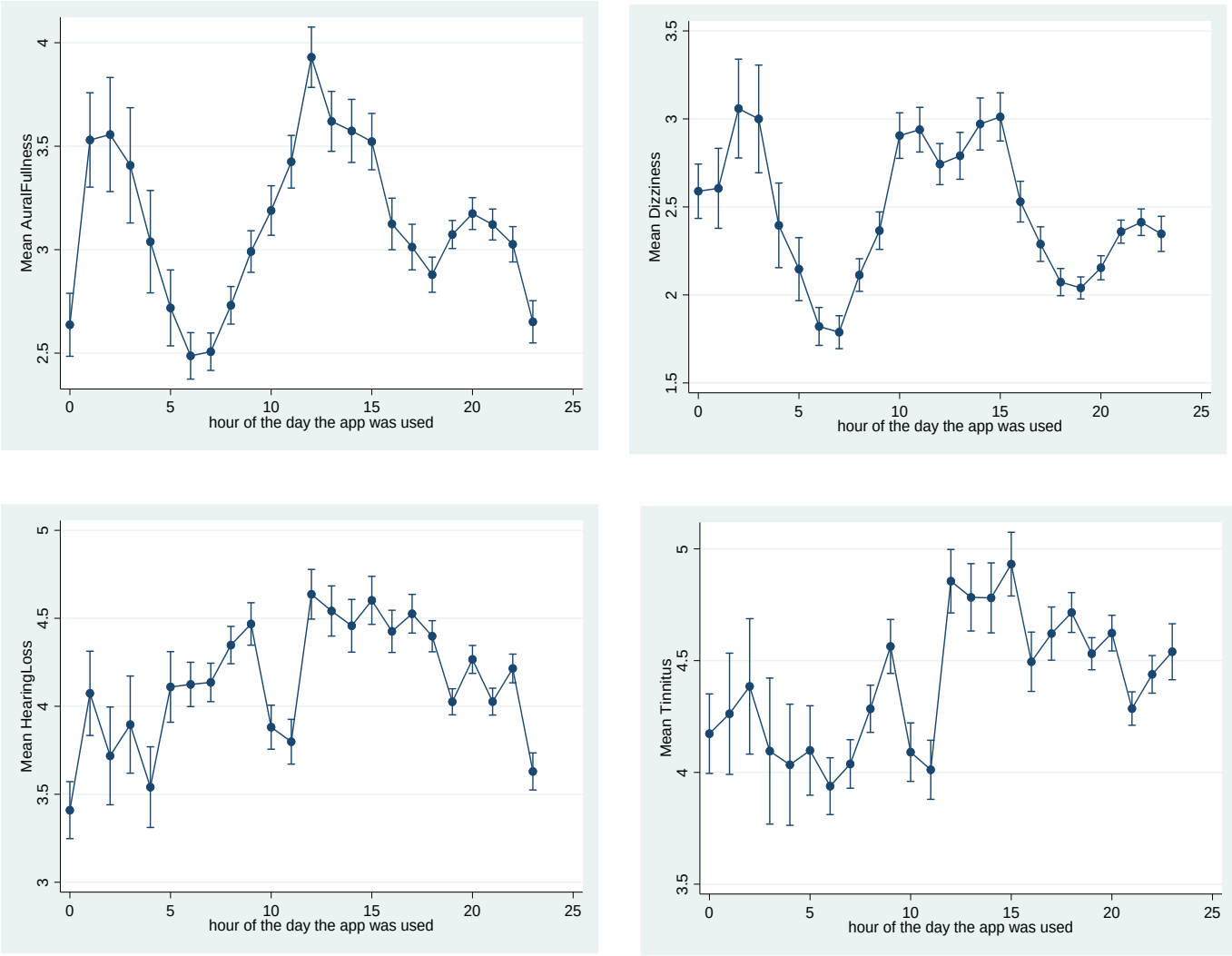
Figure 6.2 shows the mean symptom scores across each hour of the way in a 24-hour period with fluctuations occurring throughout the day. In order to test any differences in means of symptom scores across the different subgroups, t-tests were conducted with gender, and ANOVA with Bonferroni was conducted with age categories. There was a significant difference in mean scores across all the four

	Aura Fullness		**Hearing Loss**		**Tinnitus**		**Dizziness**	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Europe	2.9	2.7	4.3	2.9	4.5	2.9	2.2	2.5
North America	4.0	2.8	3.9	2.8	4.6	2.8	3.1	2.7
South America	3.0	2.3	3.1	1.9	6.1	3.5	3.6	2.9
Africa	2.2	1.4	2.1	1.4	1.3	1.2	2.1	1.6
Asia	1.7	2.0	1.5	2.1	2.5	2.6	2.2	2.4
Australia	1.1	1.2	4.3	3.3	4.5	3.1	1.3	1.5
Oceania	6.1	2.1	5.7	2.4	4.9	2.8	1.8	2.5

symptoms in men and women, with women faring worse (i.e. higher means) across

three of the four symptoms (aural fullness, dizziness, and tinnitus). Women reported only slightly worse hearing loss than men (4.31 versus 4.0), however this was still a significant difference. Examination into the differences of symptom means for different age categories, showed significant differences observed across the four symptoms.

Figure 6.2 Mean symptom scores by hour of the day



6.9.8 **Fourier analysis**

In order to determine whether there is evidence of variability in a 24-hour period a Fourier analysis was conducted whereby time of day (in hours) was converted into sine and cosine variables. Sine and cosine functions with varying periods of 24-hour, 12-hour and 6-hours were tested in the regression models until the periods were not significant at the 0.05 level. The 24-hour period and 12-hour period were statistically significant for all four symptoms, however, were not significant for the 6-hour period (Table 6.3).

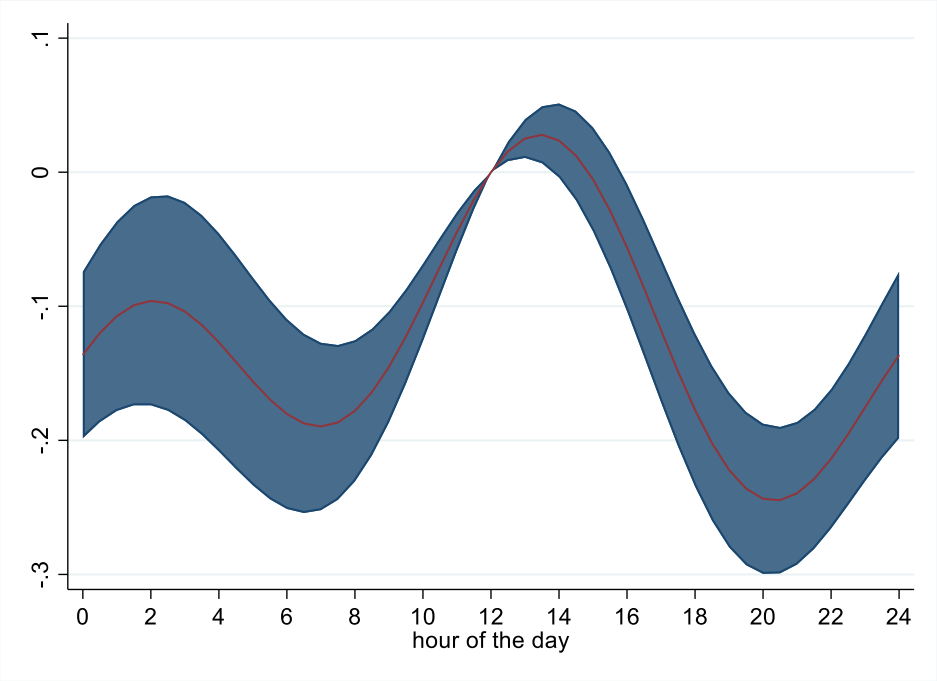
Table 6.3 Associations between sine and cosine functions across varying time periods

	24-hour period		12-hour period		6-hour period	
	χ^2	p	χ^2	p	χ^2	p
Dizziness	49.61	< 0.001	87.76	< 0.001	0.87	0.65
Tinnitus	47.38	< 0.001	17.08	< 0.001	1.89	0.39
Aural Fullness	81.95	< 0.001	38.19	< 0.001	4.63	0.10
Hearing Loss	42.42	< 0.001	42.20	< 0.001	1.26	0.53

6.9.8.1 Dizziness

Dizziness variability predicted from the model without cofounding variables is shown in Table 6.3 with changes in scores compared to mid-day in a 24-hour period. As observed in the graph (Figure 6.3), and in the output of estimates for each hour of the day, there were changes in scores observed in the 24-hour period. In comparison to midday, there were fluctuations in scores observed particularly at 8pm and 7am, albeit small. Compared to midday, there was a drop in dizziness score at 7am by 0.19, and by 8pm there was another significant drop of 0.24. Thus, participants reported less severe symptoms during the early hours of the morning and during the evening. As the day progressed participants reported an increase of dizziness scores. Appendix XI presents the coefficients and standard errors for every 30 minutes within a 24-hour period for all the symptoms. Compared to midday, there was a peak of symptom severity at 1pm for dizziness.

Figure 6.3 Dizziness predictions over a 24-hour period compared to mid-day with a 95% upper and lower bound confidence interval for a 12-hr period



There was a significant difference in symptom severity for days of the week, whereby individuals experienced worse symptoms of dizziness during the week in comparison to the weekend (range of 0.07 and .12). Females tended to report worse symptoms compared to men (0.41 higher). And compared to those in work, individuals who were not working experienced worse symptoms (1.74). Table 6.4 presents the model for dizziness and the confounding factors.

Table 6.4 Regression coefficients for dizziness and confounding factors

Variables	Coefficient	P	95% Confidence intervals	
Sine	0.00	0.91	-0.03	0.03
Cosine	-0.07	< 0.001*	-0.10	-0.04
Sine (12-hour period)	0.07	< 0.001*	0.04	0.10
Cosine (12-hour period)	0.06	0.00*	0.03	0.08
Day of week				
Monday	0.07	< 0.01*	0.02	0.12
Tuesday	0.11	< 0.001*	0.05	0.16
Wednesday	0.12	< 0.001*	0.07	0.18
Thursday	0.10	< 0.001*	0.05	0.16
Friday	0.08	< 0.001*	0.03	0.14
Saturday	0.01	0.71	-0.04	0.07
Gender				
Female	0.41	0.02*	0.07	0.75
Employment status				
Retired	0.08	0.84	-0.64	0.79
Unemployed	0.46	0.24	-0.31	1.24
Unable to work	1.80	< 0.001*	1.31	2.29
Not completed	0.14	0.75	-0.72	1.01
Age group				
26-35	0.28	0.59	-0.74	1.31
36-45	0.18	0.72	-0.78	1.14
46-55	0.15	0.75	-0.80	1.10
56-65	-0.17	0.73	-1.15	0.81
66_onwards	-0.02	0.98	-1.21	1.18

* Significance at 0.05 level

6.9.8.2 Tinnitus

As seen in Figure 6.4 Tinnitus presented in a different way in comparison to Dizziness. Higher levels of severity were reported in the early hours of the morning with a gradual decline of symptoms later in the afternoon into the evening. In comparison to midday, there were fluctuations in scores observed particularly at 4am and 9pm, albeit very small. Compared to midday, there was an increase in tinnitus

symptoms from 4am to 6am by 0.04 points, and again around 2pm, however from late afternoon (4.30pm) tinnitus severity begins to gradually drop with a sharp decrease late in the evening (9pm) by 0.15 points. Thus, the temporal pattern for tinnitus is different in comparison to dizziness with participants reporting a decrease in tinnitus symptoms during the early hours of the evening onwards. Whilst dizziness increases over the course of the day, tinnitus decreases. Appendix XI presents the coefficients and standard errors for every 30 minutes within a 24-hour period for all the symptoms.

Compared to Sunday (Table 6.5), there is a mid-week effect with individuals experiencing higher levels of severity of tinnitus on Wednesday (0.05 increase) and Thursday (0.06 increase). There were no gender differences between symptom severity across a 24-hour period. However, there was an employment status effect, whereby those who were not working (excluding those who were retired) reported higher levels of severity (between 0.99-1.64) in comparison to those who were employed. Unlike dizziness, there was an age effect in that in comparison to a younger population (aged 18-24 years), those participants aged from 26 years onwards reported higher levels of symptom severity (range from 1.13 to 2.61).

Figure 6.4 Tinnitus predictions over a 24-hour period compared to mid-day with a 95% upper and lower bound confidence interval for a 12-hr period

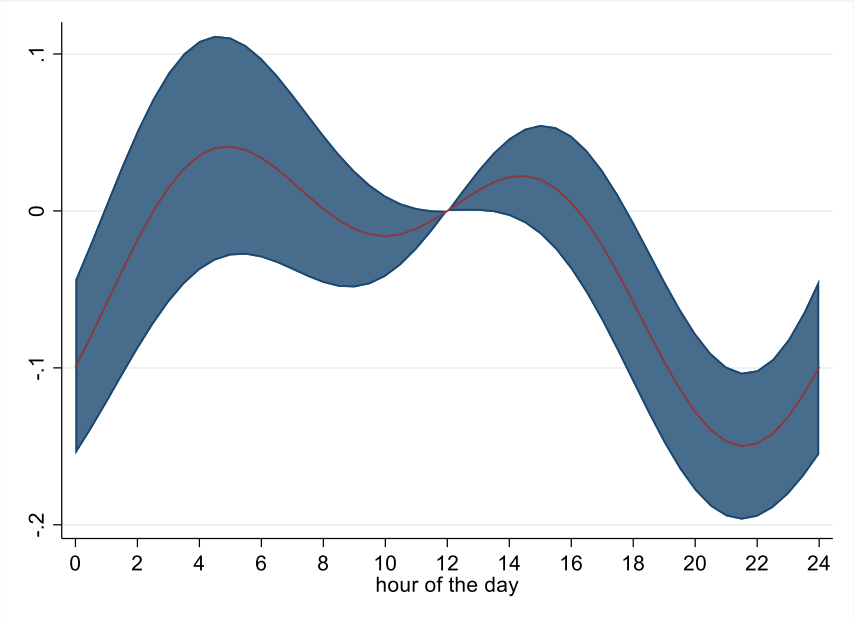


Table 6.5 Regression output for Tinnitus and confounding factors

Variables	**Coefficient**	**P**	**95% Confidence Intervals**	
Sine	0.05	< 0.001*	0.02	0.07
Cosine	-0.05	< 0.001*	-0.08	-0.02
Sine (12-hour period)	0.05	< 0.001*	0.02	0.07
Cosine (12-hour period)	-0.02	0.11	-0.04	0.00
Day of week				
Monday	0.03	0.20	-0.02	0.08
Tuesday	0.03	0.18	-0.02	0.08
Wednesday	0.06	0.02*	0.01	0.11
Thursday	0.05	0.03*	0.00	0.10
Friday	0.03	0.28	-0.02	0.08
Saturday	-0.01	0.70	-0.06	0.04
Gender				
Female	0.31	0.17	-0.13	0.75
Employment status				
Retired	0.16	0.73	-0.76	1.08
Unemployed	1.03	0.04*	0.04	2.02
Unable to work	1.47	0.00*	0.84	2.10
Not completed	0.27	0.64	-0.84	1.37
Age group				

26-35	0.97	0.15	-0.35	2.28
36-45	1.13	0.07*	-0.10	2.36
46-55	1.68	< 0.01*	0.46	2.90
56-65	1.92	< 0.001*	0.67	3.17
66_onwards	2.61	< 0.001*	1.08	4.14

* Significance at 0.05 level

6.9.8.3 Aural fullness

Temporal patterning for aural fullness was similar to that of dizziness in that reported symptom severity was lower in the morning and evenings in comparison to midday. However, the largest drop in reported symptom severity was observed in the early hours of the morning (5am), and mid-evening (8pm). The largest decrease in symptom severity was reported at 4.30am with a 0.24 drop in comparison to midday. Symptoms worsen over the course of the morning with a peak at 1pm, however as the day progresses symptoms decrease and are the lowest at 8pm with a drop of 0.27 compared to midday (Figure 6.5).

There was a day of the week significant effect, with a gradual increase of aural fullness from Tuesday to Thursday compared to Sunday (0.05 to 0.07), albeit small increases (see Table 6.6). In terms of employment status, participants who were either unemployed or unable to work reported significantly higher levels of aural fullness (0.93 to 1.75). Similarly, to tinnitus, there was no gender effect or age effect.

Figure 6.5 Aural fullness predictions over a 24-hour period compared to mid-day with a 95% upper lower bound confidence interval for a 12-hr period

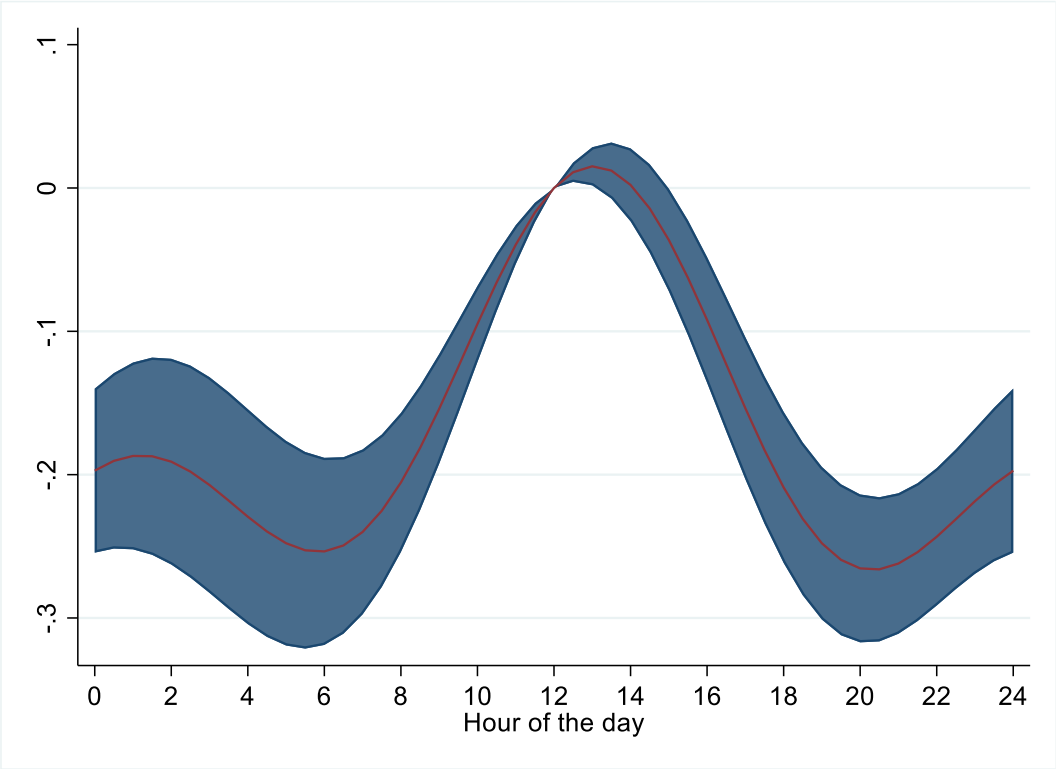


Table 6.6 Regression output for Aural fullness and confounding factors

Variables	Coefficient	P	95% Confidence intervals	
Sine	-0.02	0.08	-0.05	0.00
Cosine	-0.10	< 0.001*	-0.13	-0.07
Sine (12-hour period)	0.04	< 0.001*	0.02	0.07
Cosine (12-hour period)	0.07	< 0.001*	0.04	0.09
Day of week				
Monday	0.04	0.17	-0.01	0.09
Tuesday	0.05	0.04*	0.00	0.10
Wednesday	0.06	0.02*	0.01	0.11
Thursday	0.07	< 0.01*	0.02	0.12
Friday	0.03	0.26	-0.02	0.08
Saturday	-0.02	0.54	-0.07	0.03
Gender				
Female	0.32	0.11	-0.07	0.70
Employment status				
Retired	0.36	0.38	-0.44	1.16

Unemployed	0.93	0.04*	0.07	1.80
Unable to work	1.75	0.00*	1.20	2.30
Not completed	-0.04	0.94	-1.00	0.93
Age group				
26-35	-0.09	0.88	-1.24	1.06
36-45	-0.09	0.87	-1.17	0.98
46-55	-0.06	0.92	-1.12	1.01
56-65	0.05	0.93	-1.05	1.14
66_onwards	0.49	0.47	-0.85	1.83

* Significance at 0.05 level

6.9.8.4 Hearing loss

Fluctuations of hearing loss vary over the course of the day, albeit only slight changes can be observed (Figure 6.6). Participants reported an increase in hearing loss (0.04 points), in comparison to midday, at very early hours of the morning (2.30am). However, a small number of observations were reported at 2am (N=319) and the majority of participants who responded at this hour were employed. Due to the lack of information regarding employment details (e.g. shift workers, normal 9-5 hours) it is difficult to determine why participants provided a response during these early hours of the day. Participants reported lowest levels of hearing loss at 7.30 am (drop of 0.08 points), and 7.30pm (drop of 0.19 points), which suggests a diurnal patterning for this symptom.

There were no significant effects noticed for the day of the week or gender (Table 6.7). However, there was a significant age effect, with older participants (aged 46 onwards) reporting higher levels of hearing loss (increase of 1.37 to 2.23 points) in comparison to younger participants. This may be due to the effect of the ageing process and expected deterioration of hearing with age. Those who were retired or unable to work experienced worsening of hearing loss in comparison to those who worked (increase of 0.97 to 1.121). This may be explained through the ages of these

subgroups, as the mean for those who were retired was 68.5 years and the mean age of those who were unable to work was 52.5 years.

Figure 6.6 Hearing loss predictions over a 24-hour period compared to mid-day with a 95% upper and lower bound confidence interval for a 12-hr period

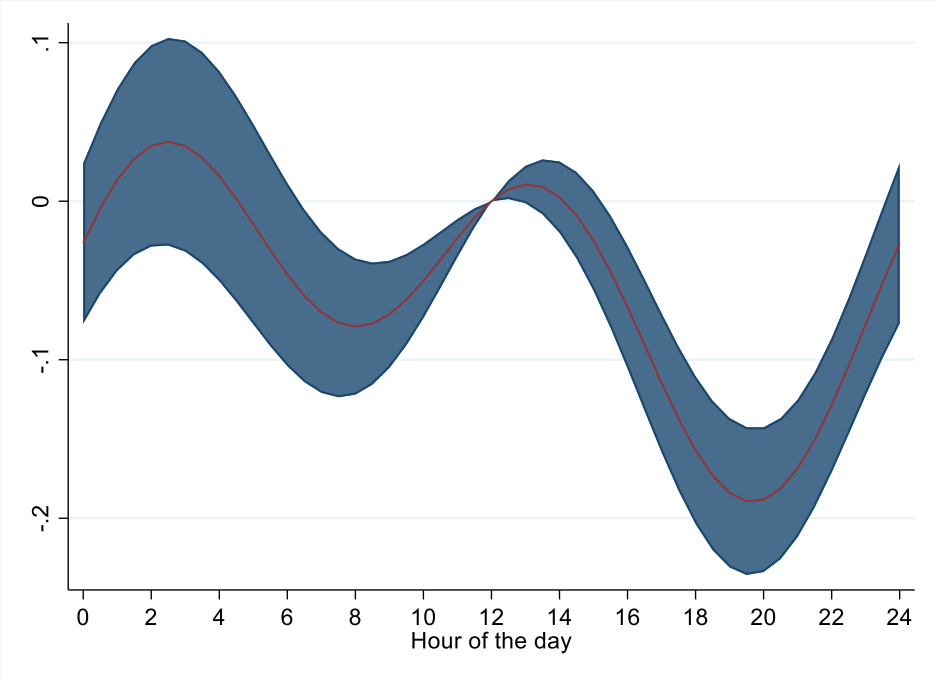


Table 6.7 Regression output for Hearing loss and confounding factors

Variables	Coefficient	P	95% Confidence intervals	
Sine	0.06	< 0.001*	0.03	0.08
Cosine	-0.01	0.30	-0.04	0.01
Sine (12-hour period)	0.06	< 0.001*	0.04	0.09
Cosine (12-hour period)	0.04	< 0.001*	0.02	0.07
Day of week				
Monday	0.03	0.15	-0.01	0.08
Tuesday	0.03	0.18	-0.01	0.08
Wednesday	0.01	0.66	-0.03	0.05
Thursday	0.03	0.19	-0.01	0.07
Friday	0.02	0.34	-0.02	0.07
Saturday	0.01	0.77	-0.04	0.05
Gender				
Female	-0.22	0.33	-0.67	0.23

Employment status				
Retired	0.97	0.04*	0.03	1.91
Unemployed	0.69	0.18	-0.32	1.71
Unable to work	1.21	< 0.001*	0.57	1.86
Not completed	0.16	0.79	-0.98	1.29
Age group				
26-35	0.74	0.28	-0.60	2.09
36-45	0.53	0.41	-0.73	1.79
46-55	1.37	0.03*	0.13	2.62
56-65	1.62	< 0.01*	0.34	2.91
66_onwards	2.23	< 0.01*	0.66	3.80

* Significance at 0.05 level

6.10 Discussion

The purpose of this chapter was to better understand how Fourier transformation can capture variation of scores in Meniere's disease. The dataset that was made available collected symptom scores for Meniere's Disease from individuals across the world through a digital app. The analysis aimed to describe both the dataset itself and the pattern of severity of the respondents. In addition, the analysis explored the severity profile over a 24-hour period (i.e. circadian patterns) and examined the existence of a weekday/end effect.

The participants providing data ranged in age, however, were mostly middle-aged which may be due to a later diagnosis of the disease as discussed in the literature (365). The average time individuals reported living with MD since a proper diagnosis was just over 8 years, however they may have been living with this disease for much longer. There was a lack of information from participants regarding the length of time they have lived with the disease (prior to diagnosis). The data presented here are representative of the reported increase of prevalence of MD with age as documented by Tyrrell et al (365).

The dataset comprised mostly of females which coincides with data from the US and the UK where MD was found to be more common in females than males (365,382). Unlike the literature, the sample in this study were predominately employed individuals and there was not an equal sample of employed and retired individuals (362). Almost all of the participants were either from North America or Europe, however details regarding their race was not collected thus it is not possible to make a comparison with existing literature regarding the distribution of participants across Caucasians and non-Caucasians (142,357,394).

Interestingly, most of the sample experienced either daily or weekly symptoms which also corresponds to the literature (350). Similarly to one study, in our sample there were more participants reporting problems in their left ear in comparison to the right ear. There is no indication in the literature as to the implications of this, thus further conclusions regarding how disease presented in one ear may affect the experiences of people with MD. There was an equal distribution of those who experienced unilateral versus bilateral MD, and there may be a link with the length of living with the disease, given that 2% to 47% of MD cases develop into a bilateral disease as the disease progresses (351,395). There were a lower number of participants in this study who experienced a frequent number of migraines in comparison to the literature (361,372). This is surprising given the established association between migraine and MD (369). However, there was a lack of data on the types of migraines experienced by our participants. As the literature focuses mostly on vestibular migraines related to MD (369,374), the data presented here do not discriminate between different types of migraines participants may have experienced.

Overall, symptom severity was observed to be higher for tinnitus and hearing loss in comparison to the other symptoms in our sample. This finding adds to existing evidence reported by Hagnebo and colleagues (354), where they reported that the longer individuals lived with MD the frequency increased of these particular symptoms they experienced. However, there is no documented research comparing the severity of symptoms experienced by MD patients. In addition, with the presence of an attack symptom severity increased across all four symptoms in our study. However, the number of incidences where participants reported a linked attack to increased severity was low.

The use of Fourier transform allowed us to determine how time (of day, week and year) affected outcome scores, which supports the conceptual model developed in Chapter 3. This has not been documented before for Meniere's Disease. Kirby and Yardley's paper on MD patients' perspectives of triggers and attacks stated that there was a time of day effect solely for vertigo and the experiences linked to this symptom (366). As demonstrated through Fourier transformation, mornings were reported by patients to be worse and severity of vertigo lessened over the course of the day. The data presented in this chapter further adds to this qualitative account for MD across a 24-hour period. Dizziness symptoms (which are linked to vertigo) were observed to be less severe in the mornings, which differs from Kirby and Yardleys' patients' accounts of vertigo (366). In addition, dizziness increased over the course of the day with a peak experienced at 1pm and decreased in the evening.

All four symptoms presented a decline in symptom severity in the evening between 8 and 9pm. However, during the day some different patterns emerged with three of the symptoms (dizziness, tinnitus and aural fullness) peaking between 1 and 2pm. Although literature has frequently reported that individuals with MD report fluctuations of tinnitus and aural fullness there was a lack of information regarding the patterns of severity (350,366). Data presented in this chapter have provided more in-depth understanding as to how tinnitus and aural fullness present in a 24-hour period. Tinnitus was reported to be worse during the morning and gradually lessened in severity in the early hours of the evening. Unlike the literature (354), the younger population in our study reported higher levels of tinnitus. This may be due to the length of time living with MD and the less amount of time participants have had to adjust to their disease.

Aural fullness presented similarly to dizziness with severity worsening over the course of the day and gradually decreasing in the afternoon to the lowest scores at 8pm. However, it should be noted with all the data presented that changes in scores were small and any conclusions should be considered carefully.

Hearing loss varied over a 24-hour period, with a peak observed in the very early hours of the morning (2.30am) and older participants reporting more severity. The characteristics of those reporting higher levels of severity coincide with the literature, however as the changes in scores were small any conclusions should be cautiously considered.

Some observations should be made with regard to the longer patterns examined in the data, i.e. weekly. Although the means of each of the symptoms did not significantly vary across the days of the week, within the regression models as a covariate the day of the week had a significant effect. This may be explained by employment status in that those who were employed had worsened symptoms during the working week compared to those who were retired, unemployed or unable to work. This coincides with findings in Chapter 4, whereby those who were employed experienced fluctuations in their outcome scores over the course of a working week. However, due to a lack of information on working patterns for participants further conclusions are unable to be made.

6.10.1 **Strengths and limitations**

To the best of our knowledge, this is the first study describing and using Fourier transformation to capture variation in MD symptom scores across different periods. The results have provided further insight into the circadian (24-hour) and infradian (longer than 24-hours) rhythms seen in MD. However, the results did only show

small changes in outcome scores and any interpretations of the results should be taken with caution. Upon saying this, the study did demonstrate that the application of the Fourier transformation on time-stamped data can map out variation in outcome scores for a chronic condition. Given that MD is a complex condition, which is not properly understood by clinicians or those suffering from it due to its fluctuating nature across time, this study has shown how the disease presents itself on daily and weekly periods.

There were some limitations to the measurements used, data analysis and interpretation of the results. As the original study did not collect specific information on the characteristics of the participants reasons as to why participants responded during the “unsocial” hours of the day, this could not be determined. More detailed information was needed to determine working patterns which may have explained reporting during these hours if participants were shift workers. In addition, the outcome measurements were not tested for reliability and validity, and there was no MCID reference point which would have been useful when interpreting changes in outcome scores. As there were no thresholds data to determine varying levels of severity (as demonstrated in the outcome measurements used in Chapter 4), I was unable to determine any meaningful comparisons between outcome scores for each symptom.

The literature demonstrated a bidirectional effect of psychological status and MD symptom severity, however as these data were not collected in this dataset this could not be examined. As this was an important concept found in other chronic conditions future research could focus on examining this bidirectional relationship as presented in the conceptual model found in Chapter 3.

6.11 Conclusions

MD is a complex disease difficult to unravel regarding pinpointing symptoms that are truly relevant to this disease. Methodological approaches to describing how symptoms fluctuate have tended to use longitudinal EMA methods, which is beneficial in capturing small changes in outcomes. Fourier transformation is a useful statistical approach to identify and map out the patterns of severity for a chronic condition over time and identify peaks during these time periods. This may be useful for clinicians to monitor the progression of their patient's disease and identify potential triggering moments in their daily lives.

Chapter 7 Discussion

7.1 Chapter overview

The thesis has established evidence supporting and explaining the key concepts of cyclical variation of PROMs (Chapter 3). Empirical work increases the relevance of these concepts, sitting them within a tested conceptual model. Longitudinal interviews with participants were key to better understanding the model's conceptual links (Chapter 4). Furthermore, the scoping review highlighted a lack of consistency, and limitations of statistical approaches to modelling cyclical variation (Chapter 5). The secondary analysis successfully modelled cyclical variation of PROMs by applying Fourier transformation to a longitudinal dataset on Meniere's Disease, drawing attention to variations in symptoms within a 24-hour period (Chapter 6). This chapter will provide a substantial overview of the thesis's main findings, in relation to how the work has contributed to existing knowledge, the strengths and limitations of the overall project, implications for clinical and research practice, and proposed recommendations for future research.

7.2 Summary of main findings

The scoping review evidenced the existence of cyclical variation of PROMs scores. Key concepts and periodic rhythms were identified in specific categories of conditions, including musculoskeletal, respiratory, nervous, and mental health. The periodic rhythms evidenced in the articles ranged from shorter diurnal (all conditions) and circadian rhythms (respiratory and mental health) to longer seasonal rhythms (respiratory and musculoskeletal). Identified concepts hypothesised by the authors of the articles were used to develop a conceptual model to explain cyclical variation of

PROMs, which is a new contribution to the area of PROMs. The concepts were categorised into four aspects within the model:

1. Core constructs
2. Moderators
3. Mediators
4. Determinants.

The first category of the core constructs were sub-categorised into:

i. *variations in health outcomes* (i.e., health conditions, health outcomes (PROs), and the time period) and;
ii. *variations in scores* focussing on the internal and external processes that are important to understanding how individuals appraise their condition (i.e., cognition, integration, measurement, recall and interpretation).

These core constructs integrated models of patient reported outcomes, with existing literature around cognition and chronobiology. The second category were two moderators: *individual and environmental factors.* The roles of the two moderators were consistent with existing theories of determinants of health and models of health outcomes discussed in Chapter 2 and Chapter 3. In relation to cyclical variation of PROMs, the third category included important determinants, *disease related biorhythms*, plus the *timing and type of healthcare intervention* individuals had had. Finally, the final category, the mediator in this model was *psychological health status*, which was the central concept in the model and directly affected all the other concepts.

A key finding from the scoping review was that patient perspectives were notably absent in the included literature. The articles used a quantitative approach to

collecting PROMs at different times thus excluded any patient explanation as to their scores and changes in scores. Patient perspectives would have reinforced the concepts raised by the authors rather than being based solely on researchers' interpretations and hypotheses of what was happening.

The longitudinal qualitative study, however, reinforced the importance of concepts developed in the scoping review, which explained cyclical variation of PROMs from the patient's perspective. The study focused on three specific conditions: depression, osteoarthritis and asthma. Participants with these conditions distinguished between changes in their health outcomes and their internal fine-tuning during the day. Fine-tuning was influenced by a variety of internal factors such as tiredness and biorhythms, as demonstrated by concepts within the conceptual model. Health outcomes were influenced by both external and internal factors, such as psychological health status and interventions participants had during data collection.

There were three additional categories that were significant in many of the interviews with participants:

i. The effect of sleep on cyclical variation of PROMs
ii. A recent episode of illness or hospitalisation
iii. The perspective of their carer/loved one.

A disruption to normal sleeping patterns affected cognitive function, resulting in variations in the usual cyclical patterns of outcomes. This, in turn, affected how they interpreted items on a PROMs questionnaire. The effect of disrupted sleep on health has received more attention in the past 20 years, with numerous studies published during the COVID-19 pandemic (396,397). Thus, findings from this PhD

not only contributes to existing knowledge of the effect of disrupted sleep on health but provides new evidence for its effect on outcome scores.

A recent episode in hospital, or severe acute illness (such as an infection), affected the cyclical variation of individuals' PROMs, where participants experienced more severe symptoms for a shorter period. This, in effect, disrupted their internal processes of appraising their condition by an overestimation of how they normally experienced their condition. This coincides with cognitive literature stating that the most salient event influences an individuals' recall of their health (91–94).

Some of the participants had their carers/loved ones present during the interviews, which introduced an alternative perspective to cyclical variation of PROMs. The carers' perception of their partner's cyclical variation was frequently at odds with the perception of the participant her/himself. Thus, a healthcare proxy may influence how participants complete and appraise their condition when completing a PROM. The current evidence around the influence of healthcare proxy on outcome scores is focused to specific health conditions, and there is a limited amount of research into the health conditions studied in this thesis (304,305). The results from this thesis therefore adds to existing knowledge, however more research into these effects are needed.

There were a range of statistical approaches to modelling cyclical variation of outcomes found in the scoping review articles. The lack of cross-referencing between the articles provides further evidence of an inconsistent approach to modelling cyclical variation. Statistical methods used by the authors, such as ANOVA, proved to be limited in its ability to handle longitudinal data and appropriately model cyclical variation of PROMs (332,333). This presented an

opportunity to develop guidance using an approach commonly used in chronobiology to model variation in PRO scores, Fourier method.

Although the Fourier method – used to map out cyclical variation of Meniere's disease – is not a new statistical technique, its application on PROMs is. Meanwhile, the guidance developed to apply Fourier when modelling cyclical variation (see Chapter 5) is a further contribution to the field (Appendix X). The use of Fourier transformation on Meniere's data (to demonstrate the peaks and troughs of symptom severity over a 24-hour period) is also new and produces previously undiscovered information. Fourier transformation can be used effectively to model cyclical variation in PROMs scores across other conditions.

7.3 Understanding cyclical variation of PROMs

There is clear evidence from the chronobiological literature demonstrating cyclical patterns of measurements for multiple chronic conditions (33,122,123). This literature mainly focuses on physiological measurements rather than patient reported outcome measurements (122). The scoping review highlighted the association between time of measurement and PROMs scores, thereby providing evidence of the existence of cyclical variations within outcome scores.

Most of the concepts important in explaining cyclical variation drawn from the scoping review articles map onto existing models of determinants of health (12,13,15). The findings from the review not only reinforce the importance of both the individual and environmental factors in explaining cyclical variation of PROMs (as demonstrated by EUHPID's model), but also highlight the influence of psychological status (15). In the Dahlgren, Whitehead and Meirkirch models, mental wellbeing was not considered, although it was incorporated in EUHPID's model.

Models of important determinants of health have been incorporated in aspects of these existing models. However, no regard had been paid to time periods, (i.e., the cyclical nature of these biological functions, (55), or consideration as to how psychological health affected individuals' cognitive processes when interpreting their health using PROMs (56).

This review further develops these existing models by explaining cyclical variation and considering the internal processes (both psychological health status and cognitive) involved in evaluating one's health. The longitudinal study progresses this knowledge further by including a patient's perspective and further supports the conceptual model with empirical evidence. Thus, the work carried out in this thesis – both within the initial scoping review and across the qualitative infrastructure used to strengthen the model – has not only added to the scope of previous work, but has crucially identified a key concept, *psychological health*, omitted from earlier models.

7.4 Factors influencing cyclical variation of PROMs

Narrative accounts of patients living with chronic health conditions have provided further insight into the impact of these conditions on individuals' lives as well as their experience of their conditions (398). However, few longitudinal qualitative studies explored the factors that underlie changes in health outcomes. Longitudinal studies can capture the changing nature of chronic conditions, while mapping the corresponding experiences of the individual (399). The evidence presented in this thesis adds to existing knowledge and understanding by providing discrete accounts of healthcare experiences across various timepoints (daily, weekly, monthly), both qualitatively and quantitatively.

Disease specific biorhythms are important in understanding the manifestation and exacerbation of chronic conditions across different time periods (400). This importance is reinforced within the conceptual model (see Figure 3.3). Furthermore, both the qualitative data and the secondary analysis of Meniere's Disease data provide empirical evidence supporting the existence of cyclical variation of PROMs and the concepts explaining this.

Seasonal symptomatic variability has been established in the asthma literature, demonstrating a worsening of PRO scores in the winter months (401), corresponding with the findings of this thesis. Literature examining variation of PROMs across different time periods, such as circadian or diurnal rhythms for asthma, however, remains limited. Circadian patterns have been well documented in individuals with osteoarthritis regarding both symptoms and functioning (175,402). Findings from this thesis corresponds with the literature and develops our understanding of the concepts impacting on these changes. Recent work has emphasized the link between seasons and symptom exacerbation in osteoarthritis (306), however this was focused again on a quantitative approach.

More recently, functional impairment of individuals who have asthma (403) and osteoarthritis (404) has been seen to affect psychological health, which corroborates the conceptual model and empirical evidence in this thesis. Individuals with depression often experience diurnal mood variation (405), while sleep disturbances exacerbate depressive symptoms (406). These data correspond with the qualitative accounts from the longitudinal study. In addition, findings from this thesis have shown that sleep disturbances not only affect health outcomes (i.e., symptoms or functioning), but also the appraisal rhythm (internal cognitive processes).

Participants perceived changes in these internal fine-tuning processes differently to those officially recorded. A new ‘marker event’ such as a hospitalisation or exacerbation of a health condition disrupted internal processing of appraisal of health. Sociological researchers view marker events as measures for individuals. By comparing their views of an ill self with other views of self, a measure of a *present self* can be achieved (407).

Illness disrupts an individual’s appraisal rhythm, introducing changes in health reporting and interpretation, as seen in the qualitative interviews. It is known from the cognitive literature that these *marker events* can introduce recall bias, as memory retrieval is affected by both context and current mental state (96–98). Current response shift theory has highlighted the importance of appraisal in explaining how individuals complete PROMs and changes in answers (408). However, the theory still overlooks the importance of the factors that explain cyclical variation of PROMs scores, such as biological rhythms.

The most recent paper by Rapkin and Schwartz (408) raises more questions regarding the effect of appraisal on QOL, which this thesis provides some answers to. The authors question the effect of psychological status on processes of appraisal. The conceptual model combined with the empirical evidence from the qualitative interviews demonstrate the important effect of psychological status on outcome scores. Psychological health both affected and was affected by health outcomes, in that a worsened mood affected how they interpreted their health and more severe symptoms affected their mood.

This thesis’s qualitative study revealed that individuals were aware of how their current situation affected their completion of the PROMs, as were their

carers/partners. The focus of much literature exploring the perspectives of healthcare proxies has tended to focus on individuals in palliative care or those who are severely cognitively impaired rather than individuals with chronic health conditions (409). Thus, findings from this thesis lend themselves to further exploration into the perspective of healthcare proxies in terms of PRO scores for different chronic conditions.

A patient's ability to accurately reflect on their health experiences, behaviour, or symptoms has a direct effect on the reliability and validity of a measure and its scores (301). The findings from this thesis show that individuals' reflections on changes raised in the interviews were noticeable when examining individual scores across the timepoints. However, these changes were lost when compared with PROMs specific MCID scores. In addition, with the items used for the Meniere's research there were no reported MCID scores, which made it difficult to determine whether the variations that were observed were clinically significant. This highlights the importance of measuring change at an individual rather than group level, given the reliance on the responsiveness of PROMs in estimating change (410–413). Responsiveness, or sensitivity, of PROMs in picking up changes in individual's health has been consistently highlighted in this thesis in both the literature review and by participants.

7.5 Modelling of cyclical variation

Cyclical variation of PROMs is not an established area of research. Thus, the scoping review presented in this thesis has built knowledge in this area by providing guidance on statistical mapping of cyclical variation. Existing articles point to an otherwise inconsistent statistical approach with limited central focus and a lack of

cross-referencing within the conditions being studied. Thus, the proposed use and practical demonstration of the Fourier analysis method – to transform and map out cyclical variation of PROMs on a longitudinal dataset – is a considerable contribution to the field. Given the limitations of other statistical approaches, such as ANOVA, in handling longitudinal data (414,415), Fourier transformation appears to offer the optimum solution.

The application of Fourier transformation on an existing dataset on Meniere's Disease provided some insight into cyclical patterning, which has not been previously documented. Kim and Cheon (416) showed seasonal variation of Meniere's with symptoms peaking in the summer and autumn, echoing similar findings to analyses conducted on the dataset used in this thesis (388). Existing research on Meniere's disease shows the impact of health outcomes (i.e. symptoms and functioning) on psychological health status (380,417), corroborating the conceptual model presented in the present research.

Although cognitive appraisal was an important concept in the conceptual model developed in this thesis, the updated Rapkin and Schwartz model considers cognitive appraisal to be central to the experience and measurement of QOL (408). Psychological health status was central to the experience and measurement of health outcomes for the model developed in this thesis. Their model accounts for catalysts and antecedents and how these affect appraisals and change in QOL which map onto moderators in my conceptual model. However, there is a lack of consideration to the impact of current psychological health status or time periods on changes in scores. The conceptual model and empirical evidence confirming the importance of these concepts in explaining cyclical variation of PROMs is a further contribution understanding change in scores.

7.6 Strengths and Limitations

There are strengths and limitations that have been highlighted within each of the empirical chapters and consideration of these in relation to the PhD as a whole will be discussed in the following sections.

7.6.1 **Strengths**

There are several strengths to this doctoral work. The development of a conceptual framework of cyclical variation, in a poorly established area of research within PROMs, has provided a guide for future researchers to develop. The conceptual framework builds on more established models of health outcomes by focusing specifically on explaining the factors affecting PRO scores.

In addition, the empirical work across depression, osteoarthritis and asthma has provided useful evidence to support the conceptual model. The importance of psychological health in explaining cyclical variation of PROMs scores adds to current theoretical models of health outcomes. This conceptual model provides a framework for future research to build on across different chronic conditions.

The proposed use and application of Fourier transformation to model cyclical variation of Meniere's Disease is ground-breaking and will help to throw light onto the rhythmic patterning of the disease. The development of a step-by-step guide with STATA commands on how to carry out the statistical method using a longitudinal dataset is a methodological contribution to the PROMs research.

7.6.2 **Limitations**

There are several limitations that have been highlighted in the preceding chapters. These centre on limitations regarding sampling, methodology, and

application. Some of the empirical work conducted in this thesis was based on previous research, mainly the scoping review and the secondary analysis. The scoping review highlighted the present lack of knowledge in the PROMs literature around cyclical variation the area, and scoped the work required to examine the field. While comprehensive, this review cannot claim to be completely exhaustive, some studies will have eluded identification.

This review also did not include expert opinions during the development of the conceptual framework, however there was input from the supervisory team who had expertise in both the clinical and patient perspective. A Delphi approach could have been used which would have incorporated the expert opinions of both clinicians and patients. However, despite these limitations, the review of the literature was systematic. No review to date has conceptualised cyclical variation of PROMs.

The dataset used in Chapter 6 centred on a chronic condition that affects a small percentage of the UK population. During the early stages of the PhD, other types of datasets were explored. One such dataset was IAPTus, used by Improving Access to Psychological Therapies (IAPT) services across England. IAPT services provide evidence-based psychological therapies to people with anxiety disorders and depression within Primary Care across England. Services are commissioned to regularly collect PROMs (specifically PHQ-9 and GAD-7). However, during discussions with several bodies (e.g., the local mental health trust and service managers) it became apparent that the administration of PROMs is prone to inconsistent timing. Data extraction from IAPT notes tend to be inaccurate as clients are asked to attend their sessions with their PROMs questionnaires completed. Thus, the date and time of completion is usually unknown. These incomplete

PROMs are then uploaded onto the IAPT systems to correspond with a patient's appointment. Thus, IAPTus data could not be considered for analysis in this PhD.

The UK PROMs programme has been collecting PROMs from elective surgeries, including patients with osteoarthritis (one of the conditions identified in the scoping review). This national programme also had serious limitations. Notably, there was no consistent approach to the administration of PROMs, while the data were again not time stamped. This suggests that their analysis would be unreliable and therefore unsuitable for this PhD.

The longitudinal study would have benefitted from a more diverse range of participants in terms of ethnicity and age. While the cohort studied was representative of the practice population for its region, it was nevertheless relatively homogenous. This may compromise face validity when data are extrapolated across national or global populations. Despite these limitations, most of the overall findings are generalisable, notably the impact of psychological health.

The concepts discussed in this thesis have provided an opening into this field of work and raised useful questions regarding the administration and interpretation of PROMs for chronic health conditions. Several future directions have been proposed in section 7.10. These will also be highlighted in the following sections (sections 7.7, 7.8, and 7.9) along with their implications for the use of PROMs in research, clinical practice and policy.

7.7 Implications for the use of PROMs in research

The study of cyclical variation in PROMs remains limited, despite the clinical evidence of its impact on health (418,419). Accordingly, the first significant theoretical contribution of the thesis is that of a conceptual model explaining cyclical

variation of PROMs. Findings from this PhD offers researchers an opportunity to refine and validate the concepts identified in the scoping review. This is important given the lack of attention cyclical variation has been given in PROMs research. The conceptual model provides researchers with a framework to better understand the effect of time of measurement on PROMs scores. Ultimately this, alongside recent work highlighting the inconsistencies in the way PROMs are administered by trial staff brings to question the impact of administration on the efficacy of interventions tested in clinical trials (420).

The model could be used to generate hypotheses for further empirical testing using a broader sample and longitudinal research methods. The thesis applied a longitudinal, qualitative approach to better understand variation in outcome scores from the patient's perspective. Longitudinal qualitative research (LQR) is an emerging methodology in health research (421). The philosophical underpinnings of LQR match with the concepts within the conceptual model as it assumes that time and change are contextual. Furthermore, the analytical approaches suggested for LQR include framework analysis which was the analytical method used in Chapter 4. The work carried out in this thesis further supports the importance of LQR in understanding health experiences over time and how that translates into changes in PROMs scores. In addition, LQR will enable researchers to study multiple time periods, from shorter diurnal periods to longer seasonal variation.

The secondary analysis further highlighted the lack of a consistent approach to modelling cyclical variation of PROMs and limitations of current statistical approaches. Cyclical variation of PROMs is rarely considered when analysing trial data. Given the evidence around variation in PROMs scores found in this thesis, this highlights potential issues in how outcomes are currently analysed in trials. The

Fourier method, however, provides researchers with a successful statistical method in modelling cyclical variation of PROMs which can be applied on clinical trial data.

The work conducted in the thesis has implications for how response shift is conceptualised. As discussed in Chapter 2, the response shift model incorporates three aspects: recalibration, reprioritization, and reconceptualization (84,408,422). However, neither the original (422) and most updated model (408) consider the effects of biorhythms or time periods on appraisal of conditions. In addition, the response shift model does not consider the bidirectional effect of psychological health on outcomes.

7.8 Implications for the use of PROMs in clinical practice

It is evident from both the literature and the empirical work conducted for this thesis that cyclical variation of PROMs exists. However, the impacts of variation on clinical practice need further consideration. For now, data from this thesis suggest that, at a minimum, cyclical variation should be incorporated within the administration processes of PROMs across primary and secondary care settings. There needs to be a consistent approach to administering and readministering PROMs when examining both the progression of a chronic condition and the effect of an intervention. For example, clinicians should collect a minimum of six PROMs questionnaires from patients over a period of a week in order to better understand how their assessments may change.

The timing of PROMs administration should be dependent on both the chronic condition being treated and the individual's own experience of the condition. Both aspects have been shown to be important when considering variation in outcomes.

The preceding empirical chapters have shown that chronic conditions can present differently in terms of cyclical variation, a contention supported by Warlteir (2004):

"*Biologic rhythms are influenced by socioecologic factors, such as jet lag and shiftwork, as well as by illness and drugs. Available clinical data have shown that signs and symptoms are not constant over time and often have cyclic patterns*" (419).

However, current GP practice limits the ability for clinicians to gather sufficient understanding of cyclical variation of PROMs of their patients during consultations. Administering PROMs during a GP consultation can introduce biases, such as timing of the consultation. As demonstrated by the findings of this thesis and literature, health conditions are affected by a multitude of internal and external factors and present in a cyclical pattern. Thus, when patients attend a GP consultation there are other factors at play when they complete a PROM during the appointment, which is not captured or taken into account. Completion of multiple time-stamped PROMs prior to a GP consultation would free up time during the consultation to discuss the results which could have positive implications for managing and treatment plan of the patient's health condition. This could be an opportunity for healthcare to use emerging technologies to collect PROMs electronically in the convenience of patients' homes.

In addition, when patients attend follow-up consultations to monitor the progression of their condition, the timing of these should considered. For example, individuals with asthma attending an annual check may not be presenting an accurate picture of their condition. However, more frequent monitoring over a 12

month period can provide clinicians with a more accurate picture of how asthma presents for that patient, impacting on treatment plans.

7.9 Implications for the policy guidance on the use of PROMs

Work being carried out by the Health Services Policy and Research Group, reviewing current NICE guidance on the use of PROMs, shows a lack of guidance linking PROMs to the management of chronic conditions (423). As this is an emerging field, more information is needed before new tools can be effectively and efficiently used. Currently in the UK, the PROMs programme – which has been underway since 2009 – does not consider cyclical variation in its administration. Evidence provided by this thesis strongly suggests that guidance should recommend a consistent approach to data collection. Currently, the only guidance provided to clinicians as to when they should administer PROMs for elective surgeries is:

"*As many providers are administering the Q1 questionnaire a number of weeks before the operation and patients may choose to complete the Q2 questionnaire at any time after receipt, there will be a range of intervals between the operation date and the Q2 completion date*" (424).

NICE guidelines for the chronic health conditions studied in this thesis do not provide clinicians with guidance on the impact of cyclical variation of outcomes (Table *7.1*). The findings from this thesis should help to improve existing practice. For example, asthma guidance updated in February 2020, only takes into account cyclical variation in clinical history, objective testing and pharmacological treatment (425). There is no mention of when to carry out these assessments despite clear biological evidence – presented in Chapter 2 – that asthma severity fluctuates within a 24-hour period. Current practice is for annual management and monitoring of

check-ups. Yet again the temporal consistency/expected variations of these check-ups are not mentioned.

Within osteoarthritis, recognition of the effect of time on joint-related stiffness is relatively new, guidance was only produced in 2014 (207). Guidelines for assessing osteoarthritis tend to be holistic, informed by many of the aspects highlighted in the conceptual model developed in Chapter 3. However, the current guidelines do not highlight the impact of seasons or time in general when providing guidance on what to cover during an annual review. The only mention of the effect of time is during the diagnostic stage of this condition.

As with asthma, there is a lack of clinical advice when addressing how patients reflect on their conditions over time and across different consultations. Although the guidance states that clinicians should monitor symptoms, there is no clear guidance on length or frequency of monitoring (e.g. hourly, once daily) or even the effect of time on symptom severity.

At the time of writing this thesis NICE guidelines on depression were being updated. The current guidelines, dating from 2009 (426), recommend that clinicians use routine outcome measurements, without offering guidance as to when they should be administered or which ones. In addition, there is no guidance around the impact of timing of diagnosis despite the evidence presented in this thesis. Similarly, there is no chronotherapeutic guidance in relation to the optimum time of day to take medication.

Table 7.1 NICE Guidance on use of PROMs for Asthma, Osteoarthritis and Depression

NICE Guidance condition	Section number	Content of guidance
Asthma	1.1 Clinical History	Take a structured clinical history in people with suspected asthma. Specifically, check for: • wheeze, cough or breathlessness, and ***any daily or seasonal variation*** in these symptoms
	1.3 Objective tests for diagnosing asthma in adults, young people and children aged 5 and over	Monitor peak flow variability ***for 2 to 4 weeks in adults*** (aged 17 and over) if there is diagnostic uncertainty after initial assessment and a FeNO test
	1.5 Principles of pharmacological treatment	Take into account the possible reasons for uncontrolled asthma, before starting or adjusting medicines for asthma in adults, young people and children. These may include: • psychosocial factors • ***seasonal or environmental factors***.
Osteoarthritis	1.1 Diagnosis	Diagnose osteoarthritis clinically without investigations if a person: • is 45 or over and • has activity-related joint pain and ***has either no morning joint-related stiffness or morning stiffness that lasts no longer than 30 minutes***. [new 2014]
	1.7 Follow-up and review	Offer regular reviews to all people with symptomatic osteoarthritis. ***Agree the timing of the reviews with the person*** (see also recommendation 1.7.2 – ***annual reviews***). Reviews should include: • monitoring the person's symptoms and the ongoing impact of the condition on their everyday activities and quality of life • monitoring the long-term course of the condition • discussing the person's knowledge of the condition, any concerns they have, their personal preferences and their ability to access services • reviewing the effectiveness and tolerability of all treatments support for self-management. [new 2014]
Depression	1.1.5 Effective delivery of interventions for depression	Use routine outcome measures and ensure that the person with depression is involved in reviewing the efficacy of the treatment
	1.4 Step 2: recognised depression	Active monitoring: arrange a further assessment, normally within ***2 weeks***
	1.8.1 Drug treatments	Increase the frequency of appointments using outcome monitoring with a validated outcome measure

7.10 Future directions and research recommendations

A conceptual model has been developed. The scoping review established the existence of cyclical variation in PROMs across different conditions and time periods. However, further systematic examination of the literature is needed to build on the results of the review. Search strategies should be refined to develop a more targeted approach with a focus on specific chronic illnesses. Such detailed knowledge would inevitably benefit patient care.

Further testing of the applicability of the model with other chronic health conditions is needed. Applying a Delphi approach gathering expert advice from stakeholders, such as clinicians and patients, would further enhance the conceptual model. In addition, input from clinicians and patients is needed to confirm the importance of the cyclical variation of PROMs. In addition, due to the limitations of the sampling in the study conducted for this thesis, the conceptual model should be tested on other populations to examine the effects of age and ethnic effects on cyclical variation of PROMs. Finally, the qualitative study highlighted differences in the time periods being studied. Consequently, comparisons of outcome variations need to be explored between, and within, the working week and weekend.

Due to the time constraints inherent within a thesis there was no opportunity to consider the implications of these findings on clinical practice, nor was there the chance to develop guidance for clinicians and researchers in terms of monitoring chronic health conditions using outcome measurements. Thus, future work could usefully focus on particular health conditions that make specific allowances for the rhythmic patterning of a given condition. An RCT comparing PROMs completion between usual care (i.e. normal practice of collecting PROMs) and different timings

(e.g. multiple times in a day, week, month) would provide us with an understanding as to the effect of time on outcome scores. This work should either match the timings of data collection and patterning or consider the implications of the patterning on outcomes.

Similarly, clinicians collecting PROMs should consider a consistent approach to information gathering (i.e., collect data at the same times of the day/week/month), and repeat measurements on a regular basis. Such an approach is likely to augment the understanding of rhythmic patterning within a patient's health condition. As part of this work it would be useful to understand the effect of sharing graphs of PROMs scores with patients as part of GP consultations. This could have an impact on how patients manage their condition, and how GPs and patients discuss PROMs scores. Future work is needed to develop guidance on measuring and interpreting PROMs longitudinally and the factors clinicians should consider when consulting their patients regarding chronic health conditions.

Future trials using PROMs to test the effectiveness of interventions should also account for the effect of administrative timing on outcome measurement scores. This would include the accurate compilation of any follow-up PROMs data within the same patient cohort. The effect of time of administration on outcomes should be considered during the analysis stage. Guidance on the use of Fourier method as applied in this thesis can be followed to examine whether there are any significant changes that occur due to time.

The use of longitudinal EMA methodology would usefully capture changes in outcomes for a chronic health condition which may help clinicians and patients better manage their conditions. This approach is sufficiently sensitive to capture data which

would be missed without some form of temporal discipline in the data collection process.

Although the longitudinal qualitative study provided insight into the patient's perspective, the concomitant quantitative data were limited. A larger, longitudinal, mixed methodological approach to studying cyclical variation of PROMs would allow PROMs scores to be explored in greater depth. This would facilitate more accurate data modelling.

In order to test statistical approaches to modelling cyclical variation, there was an exploration into the types of datasets required. This was limited to the Meniere's dataset for reasons explained earlier in this chapter. Consequently, any existing large datasets on different chronic conditions should be analysed to test the components of the conceptual framework.

Research is also needed to explore whether consistent temporal measurement of PROMs has any effect on the appraisal process. Such intervention may reduce statistical noise and amplify both individual and group effects (as suggested by some of the scoping review articles).

This thesis points to improvements in both data collection and patient knowledge. This could not only empower patients with enhanced understanding of their condition, but also could facilitate clinicians in tailoring interventions to be more effective.

7.11 Overall conclusions

In conclusion, the findings from this thesis have established the presence of cyclical variation of PROMs in some chronic health conditions and provided a conceptual approach in understanding why variation in outcome scores exist.

Several methodological contributions to the field are made by this thesis through applying different statistical techniques to model cyclical variation in outcome data. These reinforce the importance of longitudinal study designs in capturing cyclical variation.

This thesis has developed a template for future research within many chronic health conditions. Researchers can apply the conceptual framework developed during the present research and weigh the implications of cyclical variations on primary outcomes. Future investigation should look to further test and refine the conceptual model built here. It has the capacity to influence policies affecting the long-term monitoring of chronic health conditions to the potential benefit of millions.

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Appendices

Appendix I. Search strategies in Medline, EMBASE, PsychINFO and CINAHL

Domain	Medline ^	EMBASE ^	PsycINFO ^	CINAHL ^^
Patient reported outcomes (PROs)	1 health status.tw.	1 health status.tw.	1 health status.tw.	S1 TI health status or AB health status
	2 quality of life.tw. or exp quality of life/ or quality of life.mp.	2 quality of life.tw. or exp quality of life/ or quality of life.mp.	2 quality of life.tw. or exp quality of life/ or quality of life.mp.	S2 TI quality of life or AB quality of life or MH quality of life
	3 (QL or QoL or HRQL or HRQoL).tw.	3 (QL or QoL or HRQL or HRQoL).tw.	3 (QL or QoL or HRQL or HRQoL).tw.	S3 TI (QoL or HRQL or HRQoL) or AB (QoL or HRQL or HRQoL)
	4 patient-reported.tw.	4 patient-reported.tw.	4 patient-reported.tw.	S4 TI patient reported or AB patient reported
	5 (function* adj2 (status or psychological or mental or physical or social)).tw.	5 (function* adj2 (status or psychological or mental or physical or social)).tw.	5 (function* adj2 (status or psychological or mental or physical or social)).tw.	S5 TI (function* N2 (status or psychological or mental or physical or social)) or AB (function* N2 (status or psychological or mental or physical or social))
	6 disabilit*.tw.	6 disabilit*.tw.	6 disabilit*.tw.	S6 TI disabilit* or AB disability*
	7 activities of daily living.tw.	7 activities of daily living.tw.	7 activities of daily living.tw.	S7 TI activities of daily living or AB activities of daily living
	8 (wellbeing or well being).tw.	8 (wellbeing or well being).tw.	8 (wellbeing or well being).tw.	S8 TI (wellbeing or well being) or AB (wellbeing or well being)
	9 (happi* or happy).tw.	9 (happi* or happy).tw.	9 (happi* or happy).tw.	S9 TI (happi* or happy) or AB (happi* or happy)
	10 pain.tw.	10 pain.tw.	10 pain.tw.	S10 TI pain or AB pain

	11 fatigue.tw.	11 fatigue.tw.	11 fatigue.tw.	S11 TI fatigue or AB fatigue
	12 (shortness adj2 breath).tw.	12 (shortness adj2 breath).tw.	12 (shortness adj2 breath).tw.	S12 TI (shortness N2 breath) or AB (shortness N2 breath)
	13 dyspn?ea.tw.	13 dyspn?ea.tw.	13 dyspn?ea.tw.	S13 TI dyspn?ea) or AB dyspn?ea
	14 cough.tw.	14 cough.tw.	14 cough.tw.	S14 TI cough or AB cough
	15 dizz*.tw.	15 dizz*.tw.	15 dizz*.tw.	S15 TI dizz*or AB dizz*
	16 insomnia.tw.	16 insomnia.tw.	16 insomnia.tw.	S16 TI insomnia or AB insomnia
	17 anorexi*.tw.	17 anorexi*.tw.	17 anorexi*.tw.	S17 TI anorexi* or AB anorexi*
	18 nausea.tw.	18 nausea.tw.	18 nausea.tw.	S18 TI nausea or AB nausea
	19 cognitive function.tw. or exp cognitive function/ or cognitive function.mp.	19 cognitive function.tw. or exp cognitive function/ or cognitive function.mp.	19 cognitive function.tw. or exp cognitive function/ or cognitive function.mp.	S19 TI cognitive function or AB cognitive function or MH cognitive function
	20 (cognitive adj2 performance*).tw.	20 (cognitive adj2 performance*).tw.	20 (cognitive adj2 performance*).tw.	S20 cognitive n2 performance or AB cognitive n2 performance
	21 (neurobehavio* adj2 performance*).tw	21 (neurobehavio* adj2 performance*).tw	21 (neurobehavio* adj2 performance*).tw	S21 neurobehavio* n2 performance* or AB neurobehavio* n2 performance*
	22 (symptom? adj2 (assessment or index or indices or instrument? or measure? or profile? or rating? or report* or scale? or schedule? or scor* or survey?)).tw.	22 (symptom? adj2 (assessment or index or indices or instrument? or measure? or profile? or rating? or report* or scale? or schedule? or scor* or survey?)).tw.	22 (symptom? adj2 (assessment or index or indices or instrument? or measure? or profile? or rating? or report* or scale? or schedule? or scor* or survey?)).tw.	S22 TI (symptom? n2 (assessment or index or indices or instrument? or measure? or profile? or rating? or report* or scale? or schedule? or scor* or survey?)) or AB (symptom? n2 (assessment or index or indices or instrument? or measure? or

				profile? or rating? or report* or scale? or schedule? or scor* or survey?))
	23 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	23 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	23 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	S23 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22
Measurement	24 (index or indices).tw.	24 (index or indices).tw.	24 (index or indices).tw.	S24 TI (index or indices) or AB (index or indices)
	25 profile.tw.	25 profile.tw.	25 profile.tw.	S25 TI profile or AB profile
	26 rating.tw.	26 rating.tw.	26 rating.tw.	S26 TI rating or AB rating
	27 scale.tw.	27 scale.tw.	27 scale.tw.	S27 TI scale or AB scale
	28 schedule.tw.	28 schedule.tw.	28 schedule.tw.	S28 TI schedule or AB schedule
	29 survey.tw.	29 survey.tw.	29 survey.tw.	S29 TI survey or AB survey
	30 questionnaire*.tw.	30 questionnaire*.tw.	30 questionnaire*.tw.	S30 TI questionnaire* or AB questionnaire*
	31 health surveys.mp.	31 health surveys.mp.	31 health surveys.mp.	S31 TX health survey
	32 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31	32 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31	32 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31	S32 S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31
Time	33 (biolog* adj2 clock*).tw.	33 (biolog* adj2 clock*).tw.	33 (biolog* adj2 clock*).tw.	S33 TI biolog* n2 clock* or AB biolog* n2 clock*

	34 periodicity.tw.	34 periodicity.tw.	34 periodicity.tw.	S34 TI periodicity or Ab periodicity
	35 chronobiolog*.tw.	35 chronobiolog*.tw.	35 chronobiolog*.tw.	S35 TI chronobiolog* or AB chronobiology*
	36 time-of-day.tw.	36 time-of-day.tw.	36 time-of-day.tw.	S36 TI time-of-day or AB time-of-day
	37 chronotype*.tw.	37 chronotype*.tw.	37 chronotype*.tw.	S37 TI chronotype* or AB chronotype*
	38 circadian.tw.	38 circadian.tw.	38 circadian.tw.	S38 TI circadian or AB circadian
	39 (sleep-wake adj2 cycle*).tw.	39 (sleep-wake adj2 cycle*).tw.	39 (sleep-wake adj2 cycle*).tw.	S39 TI sleep-wake n2 cycle or AB sleep-wake n2 cycle
	40 twenty-four hour rhythm*.tw.	40 twenty-four hour rhythm*.tw.	40 twenty-four hour rhythm*.tw.	S40 TI twenty-four hour rhythm* or AB twenty-four hour rhythm*
	41 24-hour rhythm*.tw.	41 24-hour rhythm*.tw.	41 24-hour rhythm*.tw.	S41 TI 24-hour rhythm* or AB 24-rhythm*
	42 diurnal.tw.	42 diurnal.tw.	42 diurnal.tw.	S42 TI diurnal or AB diurnal
	43 (light dark adj2 cycle*).tw.	43 (light dark adj2 cycle*).tw.	43 (light dark adj2 cycle*).tw.	S43 TI light dark n2 cycle* or AB light dark n2 cycle*
	44 infradian.tw.	44 infradian.tw.	44 infradian.tw.	S44 TI infradian or AB infradian
	45 (tidal adj2 rhythm*).tw.	45 (tidal adj2 rhythm*).tw.	45 (tidal adj2 rhythm*).tw.	S45 TI seasonal* or AB seasonal*
	46 seasonal*.tw.	46 seasonal*.tw.	46 seasonal*.tw.	S46 TI (morning* or TI evening*) or AB (morning* or TI evening*)

	47 (morning* or evening*).tw.	47 (morning* or evening*).tw.	47 (morning* or evening*).tw.	S47 TI (awakening or waking) or AB (awakening or waking)
	48 (awakening or waking).tw.	48 (awakening or waking).tw.	48 (awakening or waking).tw.	S48 TI (nighttime or night-time) or AB (nighttime or night-time)
	49 (nighttime or night-time).tw.	49 (nighttime or night-time).tw.	49 (nighttime or night-time).tw.	S49 TI nocturnal or AB nocturnal
	50 nocturnal.tw.	50 nocturnal.tw.	50 nocturnal.tw.	S50 TI ultradian or AB ultradian
	51 ultradian.tw.	51 ultradian.tw.	51 ultradian.tw.	S51 TI time course or AB time course
	52 time course.tw.	52 time course.tw.	52 time course.tw.	S52 TI diary or AB diary
	53 diary.tw.	53 diary.tw.	53 diary.tw.	S53 TI experience sampling method* or AB experience sampling method*
	54 experience sampling method*.tw.	54 experience sampling method*.tw.	54 experience sampling method*.tw.	S54 TI ecological n2 momentary n2 assessment* or AB ecological n2 momentary n2 assessment*
	55 (ecological adj2 momentary adj2 assessment*).tw.	55 (ecological adj2 momentary adj2 assessment*).tw.	55 (ecological adj2 momentary adj2 assessment*).tw.	
	56 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55	56 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55	56 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55	S55 S33 or S44 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53 or S54

Chronic conditions	57 (chronic adj2 (illness* or condition* or disease*)).tw.	57 (chronic adj2 (illness* or condition* or disease*)).tw.	57 (chronic adj2 (illness* or condition* or disease*)).tw.	S56 MH chronic disease
	58 (long-term adj2 (illness* or condition* or disease*)).tw.	58 (long-term adj2 (illness* or condition* or disease*)).tw.	58 (long-term adj2 (illness* or condition* or disease*)).tw.	S57 TI (chronic disease or chronic illness or chronic conditions) or AB (chronic disease or chronic illness or chronic conditions)
	59 exp chronic disease/	59 exp chronic disease/	59 exp chronic disease/	58 TI (long term disease or long term condition or long term illness) or AB (long term disease or long term condition or long term illness)
	60 57 or 58 or 59	60 57 or 58 or 59	60 57 or 58 or 59	S59 S56 or S57 or S58
PROS AND MEASUREMENT AND TIME AND CHRONIC CONDITIONS	61 23 and 32 and 56 and 60	61 23 and 32 and 56 and 60	61 23 and 32 and 56 and 60	S60 S23 and S32 and S55 and S59
^ Accessed through OvidSP on 27.04.17; ^^ Accessed through EBSCO on 01.05.17; Truncation & wildcards for OvidSP based searches: * free text; ? one or none character; ? any character (for different spelling); adjn finds the words if they are within n words of one another regardless of the order in which they appear; Truncation & wildcards for CINAHL: * free text; ? any character (for different spelling); Nn finds the words if they are within n words of one another regardless of the order in which they appear.				

Appendix II Extraction of key concepts for conceptual model

Concept mapping exercise steps taken

1. Went through all the 33 articles highlighting potential concepts
2. Identified a total of 16 concepts (see appendix A)
3. Merged some of the minor concepts to a total of 5 overarching themes: Determinants, Moderators, Mediator (Psychological health), Variation in Outcomes and Variation in Scores

<u>Concepts</u>

1. Symptoms
   - Types – e.g. pain, fatigue, stiffness, affect
   - Predictability
   - Commonality across conditions
   - Severity
   - Profile
   - Order of symptom/importance (pain secondary to disability – Kratz)
2. Psychometrics
   - Validity
   - Reliability - TRT
   - Accuracy
   - Error
   - Predictive value
3. Change
   - Sensitive measurement to detect change
   - Clinical significance
   - Statistical techniques applied – e.g. std dev
4. Intervention
   - Type (pharmacological)
   - Timing
   - Loss of effect (e.g. placebo effect)
   - Implications for symptom severity and outcome scores
5. Period
   - Diurnal
   - Circadian
   - Seasonal
6. Patterns
   - “U” shape
7. Fluctuation
   - Variability of dynamic state
   - Temporality
   - Within/intra individual
   - Episodic attacks

- Exacerbations

8. Measurement
    - Subjective versus objective – quality of both types, and type of measurements used (e.g. indicators for objective measurement)
    - Momentary
    - Intervals: fixed versus random
    - Responsivity
    - Time sensitive
    - Ecological validity
    - Serial measurement
    - Misclassification
    - Respondent burden
    - Learning effect/practice effect

    Retrospective
    - Recall bias
    - Conflicting results with momentary assessment
    - Suitability of measurement to condition
    - Diagnosis – criteria
    - False positive results
    - Value of measurement
    - Guidance – WHO
    - Power, effect size, ceiling effect
9. External/Situational factors
    - Activities – daily
    - Stress
    - Psychosocial
    - Environment – temperature, humidity (bioenvironmental)
    - Setting
    - Sleep quality
    - Critical life event
    - Clock time
10. Individual factors
    - Demographics – age, gender
    - Personality – determination, acceptance/avoidance, thresholds
    - Vulnerability
    - Emotions
    - Biological/physiology
    - Co-morbidity
    - Behaviour
11. Condition
    - Types
    - Stability, progression of disease
    - Aetiology
    - Exacerbation
12. PROs

- Quality of life
- Health-related quality of life
- Health status
- Current status affecting memory (Lavendar)

13. Practical implications *affected by time of day
    - Physical, emotional and functional outcomes
    - Inform clinical practice – when to intervene (e.g. high risk)
    - Educate/Inform patients – increase patient control, self-care
14. Function
    - Limitations - disability
    - Cognitive
    - Physical
15. Disease related theoretical models
    - Psychological theory linking to health (Graham-Engeland)
16. PROMs

Appendix III. Adapted questions from the Critical Appraisals Programme (CASP) (143) observational checklist and scoring system

Criteria	Scoring
Was there an explicit hypothesis in relation to cyclical variation? Were the recruited participants representative of the general population? Was the outcome a validated measurement? Are we confident that participants completed the measurements as scheduled in the data collection procedures? Were the data available for the whole period that is relevant to the proposed rhythm (e.g. 24-hr, 7 days, weekly)? Have the confounding factors related to cyclical variation in PROMs been taken into account in the design/analysis? Is attrition less than 20%?	Yes (1) Unclear (0) No (-1)

Appendix IV. Longitudinal study patient invitation pack

PRACTICE HEADED PAPER

University of Exeter Medical School

Health Services and Research Policy Group
Smeall Building, St Lukes Campus
Exeter, EX1 2LU

<Name of patient>

<Address>

<Date>

Dear <Name of patient>,

VPRO: Variation of Patient-Reported Outcome scores across time in patients with chronic conditions

Some of the doctors at your GP surgery are working with researchers at the University of Exeter Medical School on a research study to form part of a PhD. We are interested in how time of day or how the time of year impacts on your experience of your chronic condition. The aim of the study is to explore how patients experience their conditions at different times of the day and year using both questionnaires and also face-to-face interviews. We would really appreciate your help on this research study.

We are contacting you to see if you may consider taking part. The study will involve taking part in 3 interviews. Each interview will take part for about 60 minutes. One interview will occur every 3 months. At each interview we will make sure you are happy to still happy to take part in the study. A week prior to each interview we would like to you to complete two questionnaires a day for 3 days, which should take you around 5 minutes to complete each time. We are happy for you to complete these electronically or in paper format, whichever you find easier to complete.

During the interview, we would like to go through the responses you gave on the questionnaires and explore what influenced your responses at the time.

We will ask you to sign a written consent form before we start the interview and with your permission, we would like to audio record the interview. Each interview would be conducted in a private place most convenient to you, which can be your home if you prefer.

Please take time to read the enclosed information carefully and discuss it with others if you wish. If there is anything that is not clear, or if you would like more information, please feel free to contact me – my details are on the information sheet enclosed.

If you are happy to participate, please complete the enclosed contact form and return it using the freepost envelope provided (no stamp is needed). Your response is important to the study and is greatly appreciated. We believe that the research findings will be important and helpful to clinicians when interpreting these measurements.

Many thanks for your help.

With best wishes,

Antoinette Davey

<University address & contact number>

V-PRO Qualitative Interview

PATIENT INFORMATION LEAFLET

You are being invited to take part in an interview that is being conducted by the University of Exeter. Before you decide whether or not to take part, it is important that you understand why you have been invited and what it will involve. Please read the following information carefully and discuss it with others (e.g. friends and relatives) if you wish. Ask us if there is anything that is not clear or if you would like more information. This study has been reviewed by the Oxford C Research Ethics Committee.

What is the purpose of the study?

Clinicians and researchers use patient reported outcome measurements (PROMs), patient questionnaires, to help them monitor the progress of a condition and see how effective treatments. These questionnaires are completed by patients with certain chronic conditions such as asthma, depression and osteoarthritis, sometimes as part of an annual review process within primary care. There is evidence in the literature showing that time plays an important role in our health. The time of day or even year (seasonal change) influences how patients experience their conditions. Symptoms related to asthma, depression and osteoarthritis change during the course of a 24 hour period and can vary depending on the time of year with the shift in seasons. However, this is not considered when clinicians and researchers collect patient reported outcome measurements for these conditions. The purpose of this study is to explore from a patient's perspective what influences scores on patient reported outcome measurements at different times of the day and year.

Why have I been asked to take part in an interview?

Patients who have been diagnosed with two or more of the following conditions have been asked if they would like to participate: depression, asthma and/or osteoarthritis. The information collected in the interviews will be used to better understand, from a patient's perspective, how different times of the day has an effect on the experience of their symptoms. Also we are interested in understanding how a difference in experience is captured on patient outcome measurements regularly used by clinicians to monitor the progress of a condition. We are looking to interview up to 12 patients. If we achieve that number we may come back to you and ask if you are willing to be on a reserve list.

What does taking part in the interview involve?

Before the interview starts, the researcher will ask you to read and fill in a consent form (to confirm your willingness to take part in an interview). With your permission, the researcher will audio-record the interview so that she has an accurate record of the conversation. All of the interviews that we carry out will be typed up (transcribed) so that the study researchers can look at them in detail.

Do I have to take part in an interview?

You do not have to take part in an interview for the V-PRO study. It is entirely up to you to decide whether or not you want to take part in an interview.

If you are interviewed, you can withdraw at any time without giving a reason. A decision to withdraw, or a decision not to take part, will not affect the standard of care you receive or any

of your legal rights.

What are the benefits and risks of taking part?

There is a lack of information about how time of day influences the scores on patient outcome measurements used for chronic conditions. It is important that this information is collected, so that future decisions about how clinicians design treatment plans based on these measurements can take account of potential variations in patient's experiences during a day or even year.

One possible disadvantage is the time it will take to be interviewed (up to 60 minutes) and the number of interviews you will be involved with (a maximum of 3). However, the interview will be organised for a time that suits you best.

Another possible disadvantage is that you will be asked to describe your experiences of your health condition. You may find this upsetting. However, you do not have to answer a question if you do not want to and you can stop the interview at any time. The study researcher will be able to offer support during the interview if you become upset, and they would encourage you to contact the doctor or nurse who normally provides your care, if further support was needed.

Will my taking part in an interview be kept confidential?

All information you give during the interview will be treated as confidential and will be anonymised before being included in the study analysis.

All audio recordings and interview transcripts will be kept securely during the study. The recordings will be destroyed once the research has been completed.

All personal data about patients who take part in an interview would be stored securely at the University of Exeter Medical School. You will have the right to check the accuracy of the data held about you and to correct any errors. At the end of the study, the confidential records will be kept up to 12 months and data will be kept for 4 years and then destroyed. The confidential handling, storage and disposal of your data will be compliant with research governance guidance and the Data Protection Act 1998.

What will happen to the results of the study?

The findings of the study will be published in medical journals and presented at research meetings, conferences, and in a doctoral thesis. However, your name will not be used in any written or verbal reports arising from the research. If you are interested in obtaining a summary of the results, or a copy of any publication(s), please let the study researcher know, and we can arrange to send a copy to you when the summary and/or other publication(s) are available. The results may also be presented at scientific conferences.

Who do I contact for more information?

If you would like more information or have any questions about the interview study, please contact the researcher:

Mrs Antoinette Davey
Telephone: 01392 722753
E-mail: antoinette.davey@exeter.ac.uk
or write to her at: University of Exeter Medical School, Health Services and Policy Research Group, Smeall Building, St Luke's Campus, Magdalen Road, Exeter, EX1 2LU

Thank you for reading this information sheet

VPRO: Variation of Patient-Reported Outcome scores across time in patients with chronic conditions

Patient Response Sheet

Please read the information sheet provide and if you are happy to take part in the research please read this response sheet carefully and initial the boxes if you are in agreement with the statements below:

	Please initial box
I confirm that I have read and understand the information sheet dated 20.12.2017 for the above study.	
I give permission to be contacted.	

Preferred Contact Details

When we receive your completed response sheet, a member of the research team will contact you to arrange a convenient time for the interview. Please complete your name, practice name and contact details below. Any information provided will be treated confidentially and not passed on to anyone outside the research team. Please complete the reply slip and post back to the research team in the pre paid envelope (address below).

Thank you

Full Name (Please print):	
Address	
Telephone number:	
Email address:	
Please tick your preferred type of contact:	Email ☐ Telephone ☐
Please tick when you would prefer to be contacted	AM (0900-1200) ☐ PM (1200-1800) ☐

Please post it back using the pre-paid envelope provided – no need for stamps

Appendix V Questionnaire pack for osteoarthritis and depression patients

IRAS:238523

UNIVERSITY OF EXETER | MEDICAL SCHOOL

VPRO

Variation of patient-reported outcome scores across time in patients with chronic conditions: An interview study

INSTRUCTIONS TO PARTICIPANTS

Purpose: To explore from a patient's perspective what influences scores on patient reported outcome measurements at different times of the day and year

Please complete the following questionnaires within this pack at the times instructed below. Each pack will be completed on different days and at different times of the day.

There is no need to write your name on the questionnaire

Please take your time and read each of the questions carefully

If you are unsure about how to answer a question, please give the best answer you can

There are no 'right' or 'wrong' answers – please answer as honestly as you can

PLEASE COMPLETE THIS QUESTIONNAIRE PACK ON:
SUNDAY 17th JUNE **WHEN YOU GO TO BED - NOTE THE TIME WHEN YOU COMPLETE THE QUESTIONNAIRE**

TIME COMPLETED_____

SECTION 1: OVERALL GENERAL HEALTH

This section asks you in general how you would rate your health and different aspects of your overall well-being

Global Health-
PROMIS Global Health (10) SF

	Please respond to each item by marking one box per row	Excellent	Very good	Good	Fair	Poor
Global 01	In general, would you say your health is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global 02	In general, would you say your quality of life is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global 03	In general, how would you rate your physical health?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global 04	In general, how would you rate your mental health, including your mood and your ability to think?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global 05	In general, how would you rate your satisfaction with your social activities and relationships?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global 09	In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc.)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Completely	Mostly	Moderately	A Little	Not At All
Global 08	To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In the past 7 days	Never	Rarely	Sometimes	Often	Always
Global 10	How often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		None	Mild	Moderate	Severe	Very Severe
Global 06	How would you rate your fatigue on average?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global 07	How would you rate your pain on average?	☐ 0 No Pain ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst Imaginable Pain				

Kemper-Gascon

Global Health and Well-being

1

SECTION 2: OSTEOARTHRITIS

This section asks you about symptoms related to your osteoarthritis over the past 48 hours. Please tick or cross your answers in one of the boxes

PAIN

Think about the pain you felt during the last 48 hours caused by the arthritis.

(Please mark your answers with an "✗".)

QUESTION: **How much pain have you had . . .**					Study Coordinator Use Only
1. when walking on a flat surface?					
none ❑	mild ❑	moderate ❑	severe ❑	extreme ❑	PAIN1 ____
2. when going up or down stairs?					
none ❑	mild ❑	moderate ❑	severe ❑	extreme ❑	PAIN2 ____
3. at night while in bed? (that is - pain that disturbs your sleep)					
none ❑	mild ❑	moderate ❑	severe ❑	extreme ❑	PAIN3 ____
4. while sitting or lying down?					
none ❑	mild ❑	moderate ❑	severe ❑	extreme ❑	PAIN4 ____
5. while standing?					
none ❑	mild ❑	moderate ❑	severe ❑	extreme ❑	PAIN5 ____

STIFFNESS

Think about the stiffness (not pain) you felt during the last 48 hours caused by the arthritis.

Stiffness is a sensation of **decreased** ease in moving your joint.

(Please mark your answers with an " ✗ ".)

	Study Coordinator Use Only
6. How **severe** has your stiffness been **after you first woke up** in the morning? none ❑ mild ❑ moderate ❑ severe ❑ extreme ❑	STIFF6 _____
7. How **severe** has your stiffness been after sitting or lying down or while resting **later in the day**? none ❑ mild ❑ moderate ❑ severe ❑ extreme ❑	STIFF7 _____

DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities during the last 48 hours caused by the arthritis. By this we mean **your ability to move around and take care of yourself.**

(Please mark your answers with an " ✘ ".)

QUESTION: **How much difficulty have you had . . .**					Study Coordinator Use Only
8. when going down the stairs?					
none ❑	mild ❑	moderate ❑	severe ❑	extreme ❑	PFTN8 _____
9. when going up the stairs?					
none ❑	mild ❑	moderate ❑	severe ❑	extreme ❑	PFTN9 _____
10. when getting up from a sitting position?					
none ❑	mild ❑	moderate ❑	severe ❑	extreme ❑	PFTN10 _____
11. while standing?					
none ❑	mild ❑	moderate ❑	severe ❑	extreme ❑	PFTN11 _____
12. when bending to the floor?					
none ❑	mild ❑	moderate ❑	severe ❑	extreme ❑	PFTN12 _____
13. when walking on a flat surface?					
none ❑	mild ❑	moderate ❑	severe ❑	extreme ❑	PFTN13 _____

DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities during the last 48 hours caused by the arthritis. By this we mean **your ability to move around and take care of yourself.**

(Please mark your answers with an " ✗ ".)

QUESTION: **How much difficulty have you had . . .**	Study Coordinator Use Only
14. getting in or out of a car, or getting on or off a bus? none ❑ mild ❑ moderate ❑ severe ❑ extreme ❑	PFTN14 ____
15. while going shopping? none ❑ mild ❑ moderate ❑ severe ❑ extreme ❑	PFTN15 ____
16. when putting on your socks or panty hose or stockings? none ❑ mild ❑ moderate ❑ severe ❑ extreme ❑	PFTN16 ____
17. when getting out of bed? none ❑ mild ❑ moderate ❑ severe ❑ extreme ❑	PFTN17 ____
18. when taking off your socks or panty hose or stockings? none ❑ mild ❑ moderate ❑ severe ❑ extreme ❑	PFTN18 ____
19. while lying in bed? none ❑ mild ❑ moderate ❑ severe ❑ extreme ❑	PFTN19 ____

DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities during the last 48 hours caused by the arthritis. By this we mean **your ability to move around and take care of yourself.**

(Please mark your answers with an " ✗ ".)

QUESTION: **How much difficulty have you had . . .**					Study Coordinator Use Only
20. when getting in or out of the bathtub?					
none ❑	mild ❑	moderate ❑	severe ❑	extreme ❑	PFTN20 ____
21. while sitting?					
none ❑	mild ❑	moderate ❑	severe ❑	extreme ❑	PFTN21 ____
22. when getting on or off the toilet?					
none ❑	mild ❑	moderate ❑	severe ❑	extreme ❑	PFTN22 ____
23. while doing heavy household chores?					
none ❑	mild ❑	moderate ❑	severe ❑	extreme ❑	PFTN23 ____
24. while doing light household chores?					
none ❑	mild ❑	moderate ❑	severe ❑	extreme ❑	PFTN24 ____

SECTION 3: EMOTIONAL HEALTHH

This section asks about different aspects of your emotional or mental health over the past 2 weeks

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____

=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

SECTION 4: SOME QUESTIONS ABOUT YOU

This section asks for some information about you

Q1 Are you male or female?

☐ Male ☐ Female

Q2 How old are you?

☐ Under 18 ☐ 18 to 24 ☐ 25 to 34 ☐ 35 to 44 ☐ 44 to 54

☐ 55 to 64 ☐ 65 to 74 ☐ 75 to 84 ☐ 85 or over

Q3 What is your ethnic group?

White

☐ English / Welsh / Scottish / Northern Irish /British
☐ Irish
☐ Gypsy or Irish Traveller
☐ Any other White background
☐ Please write in _____

Mixed multiple ethnic groups

☐ White and Black Caribbean
☐ White and Black African
☐ White and Asian
☐ Any other Mixed / multiple ethnic background
☐ Please write in _____

Asian Asian British

☐ Indian
☐ Pakistani
☐ Bangladeshi
☐ Chinese
☐ Any other Asian background
Please write in _____

Black African Caribbean Black British

☐ African
☐ Caribbean
☐ Any other Black / African / Caribbean background
☐ Please write in _____

Other ethnic group

☐ Arab
☐ Any other ethnic group
☐ Please write in _____

Q4 Which of these best describes what you are doing at present?

If more than one of these applies to you, please ✗ the main ONE only

☐ Full-time paid work (30 hours or more each week)
☐ Part-time paid work (under 30 hours each week)
☐ Full-time education at school, college or university
☐ Unemployed
☐ Permanently sick or disabled
☐ Fully retired from work
☐ Looking after the home
☐ Doing something else

Below is a list of common health problems. Please work down the list and, for each health problem in turn, circle 'Yes' or 'No' to indicate whether you currently have that problem.

If you **do** have a particular health problem, please indicate whether you receive medication or some other type of treatment for the problem

Health Problem	Do you have this health problem?		If you do have this health problem: do you receive treatment for it?	
Respiratory problems (including asthma, COPD)	No	Yes	No	Yes
Cardiovascular disease (including angina, heart attack)	No	Yes	No	Yes
Diabetes	No	Yes	No	Yes
Kidney disease	No	Yes	No	Yes
Hypertension (high blood pressure)	No	Yes	No	Yes
Cancer	No	Yes	No	Yes
Nervous system disease (e.g. epilepsy, Parkinson's, dementia)	No	Yes	No	Yes
Arthritis/osteoarthritis	No	Yes	No	Yes
Pain (in general)	No	Yes	No	Yes
Mental health problems	No	Yes	No	Yes
Hearing or visual impairment	No	Yes	No	Yes

Any other health problems *(please write in)*	For each health problem you list: Do you receive treatment for it?	
	No	Yes
	No	Yes
	No	Yes
	No	Yes

Thank you so much for taking the time to complete this questionnaire. Please post this back in the pre-paid envelope provided.

Appendix VI Asthma and Depression questionnaire (without the demographics section)

IRAS:238523

UNIVERSITY OF EXETER | MEDICAL SCHOOL

VPRO

Variation of patient-reported outcome scores across time in patients with chronic conditions: An interview study

INSTRUCTIONS TO PARTICIPANTS

Purpose: To explore from a patient's perspective what influences scores on patient reported outcome measurements at different times of the day and year

Please complete the following questionnaires within this pack at the times instructed below. Each pack will be completed on different days and at different times of the day.

There is no need to write your name on the questionnaire

Please take your time and read each of the questions carefully

If you are unsure about how to answer a question, please give the best answer you can

There are no 'right' or 'wrong' answers – please answer as honestly as you can

PLEASE COMPLETE THIS QUESTIONNAIRE PACK ON:
SUNDAY 10th JUNE **WHEN YOU GO TO BED - NOTE THE TIME WHEN YOU COMPLETE THE QUESTIONNAIRE**

TIME COMPLETED_____

SECTION 1: OVERALL GENERAL HEALTH

This section asks you in general how you would rate your health and different aspects of your overall well-being

Global Health-
PROMIS Global Health (10) SF

	Please respond to each item by marking one box per row	Excellent	Very good	Good	Fair	Poor
Global 01	In general, would you say your health is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global 02	In general, would you say your quality of life is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global 03	In general, how would you rate your physical health?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global 04	In general, how would you rate your mental health, including your mood and your ability to think?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global 05	In general, how would you rate your satisfaction with your social activities and relationships?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global 09	In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc.)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Completely	Mostly	Moderately	A Little	Not At All
Global 06	To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In the past 7 days	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
Global 10	How often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		None	**Mild**	**Moderate**	**Severe**	**Very Severe**
Global 08	How would you rate your fatigue on average?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global 07	How would you rate your pain on average?	☐ 0 No Pain ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst Imaginable Pain				

Kemper-Gascon

Global Health and Well-being

1

SECTION 2: ASTHMA

This section asks you about symptoms related to your asthma over the past 2 weeks. Please tick or cross your answers in one of the boxes

HOW LIMITED HAVE YOU BEEN **DURING THE LAST 2 WEEKS** IN THESE ACTIVITIES **AS A RESULT OF YOUR ASTHMA**

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A little Limitation	Not at all Limited
1. STRENUOUS ACTIVITIES (such as hurrying, exercising, running up stairs, sports)	1	2	3	4	5	6	7
2. MODERATE ACTIVITIES (such as walking, housework, gardening, shopping, climbing stairs)	1	2	3	4	5	6	7
3. SOCIAL ACTIVITIES (such as talking, playing with pets/ children, visiting friends/ relatives)	1	2	3	4	5	6	7
4. WORK-RELATED ACTIVITIES* (tasks you have to do at work)	1	2	3	4	5	6	7

* if you are not employed or self=employed, these should be tasks you have to do most days

5. SLEEPING	1	2	3	4	5	6	7

HOW MUCH **DISCOMFORT OR DISTRESS** HAVE YOU FELT **DURING THE LAST 2 WEEKS?**

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
6. How much discomfort or distress have you felt over the last 2 weeks as a result of CHEST TIGHTNESS?	1	2	3	4	5	6	7

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
7. Feel CONCERNED ABOUT HAVING ASTHMA?	1	2	3	4	5	6	7
8. Feel SHORT OF BREATH as a result of your asthma?	1	2	3	4	5	6	7
9. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO CIGARETTE SMOKE?	1	2	3	4	5	6	7
10. Experience a WHEEZE in your chest?	1	2	3	4	5	6	7
11. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF CIGARETTE SMOKE?	1	2	3	4	5	6	7

HOW MUCH **DISCOMFORT OR DISTRESS** HAVE YOU FELT **DURING THE LAST 2 WEEKS?**

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
12. How much discomfort or distress have you felt over the last 2 weeks as a result of COUGHING?	1	2	3	4	5	6	7

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
13. Feel FRUSTRATED as a result of your asthma?	1	2	3	4	5	6	7
14. Experience a feeling of CHEST HEAVINESS?	1	2	3	4	5	6	7

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
15. Feel CONCERNED ABOUT THE NEED TO USE MEDICATION for your asthma?	1	2	3	4	5	6	7
16. Feel the need to CLEAR YOUR THROAT?	1	2	3	4	5	6	7
17. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO DUST?	1	2	3	4	5	6	7
18. Experience DIFFICULTY BREATHING as a result of your asthma?	1	2	3	4	5	6	7
19. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF DUST?	1	2	3	4	5	6	7
20. WAKE UP IN THE MORNING WITH ASTHMA SYMPTOMS?	1	2	3	4	5	6	7
21. Feel AFRAID OF NOT HAVING YOUR ASTHMA MEDICATION AVAILABLE?	1	2	3	4	5	6	7
21. Feel AFRAID OF NOT HAVING YOUR ASTHMA MEDICATION AVAILABLE?	1	2	3	4	5	6	7
22. Feel bothered by HEAVY BREATHING?	1	2	3	4	5	6	7
23. Feel asthma symptoms as a RESULT OF THE WEATHER OR AIR POLLUTION OUTSIDE?	1	2	3	4	5	6	7
24. Were you WOKEN AT NIGHT by your asthma?	1	2	3	4	5	6	7
25. AVOID OR LIMIT GOING OUTSIDE BECAUSE OF THE WEATHER OR AIR POLLUTION?	1	2	3	4	5	6	7
26. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO STRONG SMELLS OR PERFUMES?	1	2	3	4	5	6	7

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
27. Feel AFRAID OF GETTING OUT OF BREATH?	1	2	3	4	5	6	7
28. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF STRONG SMELLS OR PERFUME?	1	2	3	4	5	6	7
29. Has your asthma INTERFERED WITH GETTING A GOOD NIGHT'S SLEEP?	1	2	3	4	5	6	7
18. Have a feeling of FIGHTING FOR AIR?	1	2	3	4	5	6	7

HOW LIMITED HAVE YOU BEEN **DURING THE LAST 2 WEEKS**

	Most Not Done		Several Not Done		Very Few Not Done		No Limitation
31. Think of the OVERALL RANGE OF ACTIVITIES that you would have liked to have done during the last 2 weeks. How much has your range of activities been limited by your asthma	1	2	3	4	5	6	7

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A little Limitation	Not at all Limited
32. Overall, among ALL THE ACTIVITIES that you have done during the last 2 weeks, how limited have you been by your asthma	1	2	3	4	5	6	7

SECTION 3: EMOTIONAL HEALTHH

This section asks about different aspects of your emotional or mental health over the past 2 weeks

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____

=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.

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Appendix VII Topic guide for qualitative interviews

Thank you again for taking part in this study. Have you had a chance to read through the information sheet I sent to you in the post? Do you have any questions before we begin? So as I mentioned on the phone the purpose of this study is to look at how symptoms of your condition or conditions vary over time, whether that is during a day, week or over the year and how this is captured on these questionnaires. There are no right or wrong answers, I am completely interested in your story and your experience. We can stop at any point of the interview and you can withdraw at any point of the study. So this will be the first of three interviews I will do over the next 9 months and I will check each time whether you are still happy to take part. Would it be okay to audio record our conversation so that I can focus on what you say instead of taking notes? The audio recording will be written up afterwards and then the recording will be destroyed. What I will do is make sure what I have written up is made anonymous and any identifiable information is taken out. Everything will be kept under lock and key in my office and I will only have access to the information along with my two supervisors.

Are you okay to begin recording?

So I just wanted to find out a bit more about your conditions.

1. Firstly, could you tell me about your general experience of your conditions?
    a. How long have you been diagnosed or suffering from them?
    b. Do you take any medication? When do you generally take this medication?
2. Could you tell me (PROMIS-10 = 7 days and general; PHQ-9 & AQLQ = 2 weeks; WOMAC = 48 hrs) your experience of your condition over the past 2 weeks?
    a. Has your experience been the same?
3. Could you tell me about your experience this past week when you have been completing the questionnaires?
    a. Has it been the same?
    b. How has last week compared to how you generally experience your conditions?

Thank you for that, I just wanted to talk about the questionnaires you completed the other week and I have the results here which show your responses at the three different time-points

1. What was going on for you that day when you completed the questionnaires?
2. What are your general thoughts and perceptions about the results?
    a. If they vary, explore their perceptions as to why that might be
3. How do you feel this may have or have not affected how you recalled your symptoms or experience of your condition?
4. How would you say your reported experience presented here compares to what you have said more generally or over the past 2 weeks? Are they the same or different?

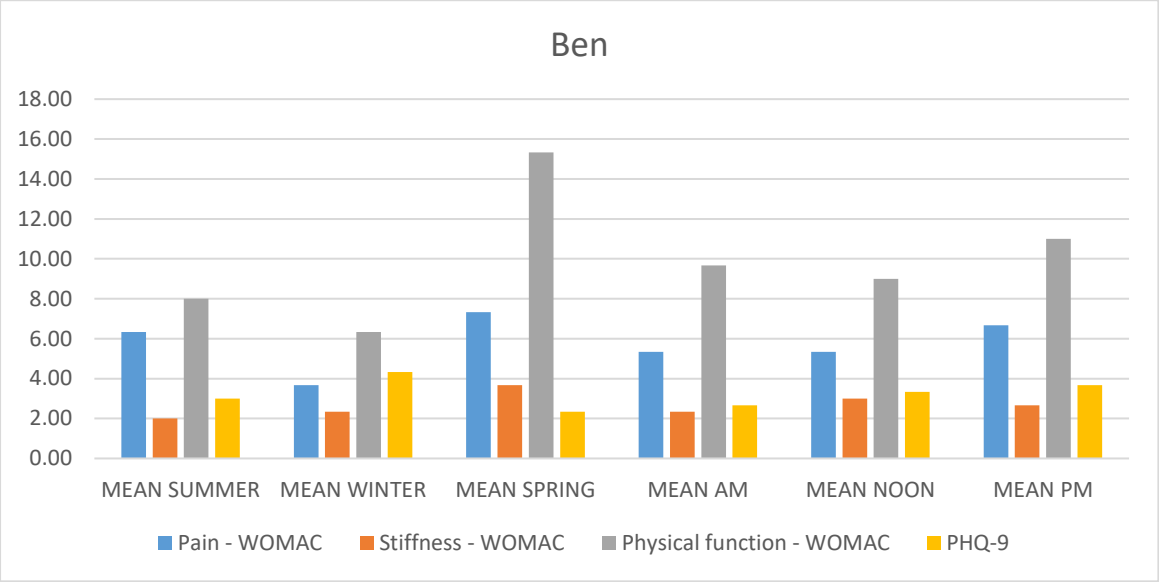
So you have said that you have had your health problems for X long

1. How does your experience of your conditions vary within a day?
    a. Do you feel it changes at all or stays the same throughout the day?
2. How about within the week?
    a. How does the weekday compare from the weekend?
3. And thinking for a longer period what about within the month?
    a. If female and still menstruating – ask if they notice their experience varies during their period or leading up to their period
4. So thinking over a 12 month period, how does your experience vary over the year, or does it stay the same throughout the year?
    a. Explore how taking holidays may or may not affect their experience
    b. Explore how annual events, religious holidays may or may not affect their change
5. What is your experience like in the different seasons, such as spring, summer, autumn and winter?
    a. Does weather impact on your experience of your conditions?
    b. What about other environmental factors?
6. In terms of personal factors
    a. Do you find that your mood impacts on how you experience your condition?
    b. How about if you feel tired, do you find that affects how you experience your condition?
    c. Do you find you a more of a morning or evening person? Is your mind the sharpest at different times of the day? Do you think that affects how you experience your conditions?
7. Do you feel there is anything else that impacts on your symptoms that I haven't mentioned?

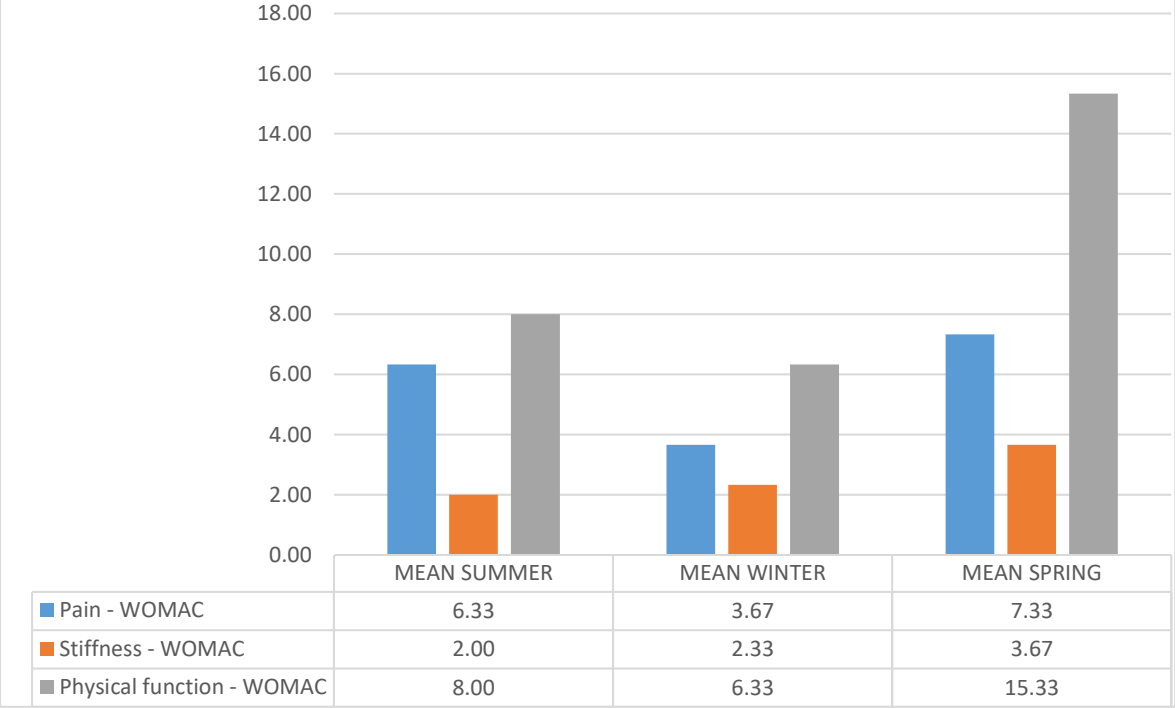
Thank you so much for taking part so far. As I mentioned this is the first of three interviews over the next 9 months. I will be in contact with you before the next interview to ask if you are still happy to take part and are happy to complete the questionnaires again. The next two interviews will be shorter as I will be focusing more on the questionnaires since I have the background information on your condition.

Appendix VIII Graphs presented to participants

Scores for Ben

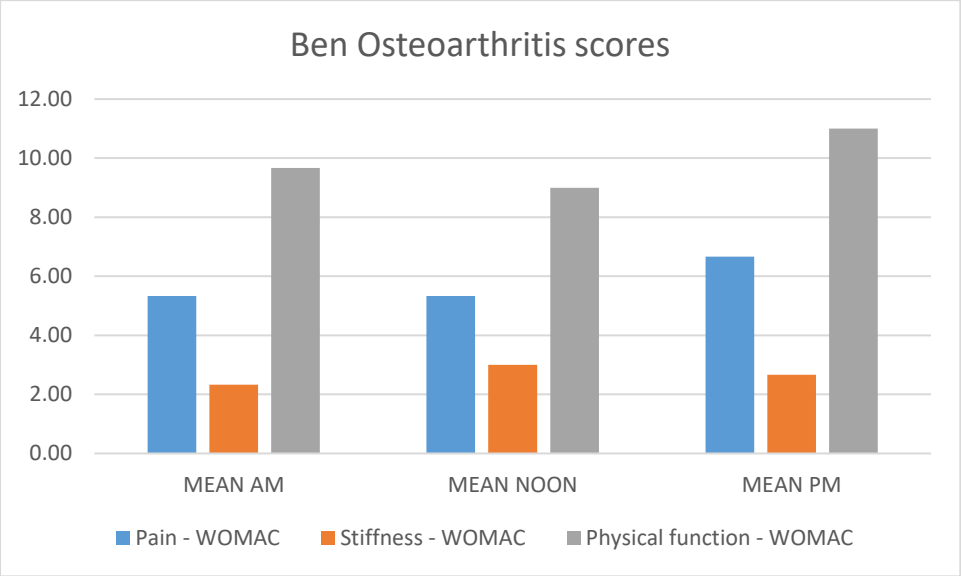


Osteoarthritis seasonal scores

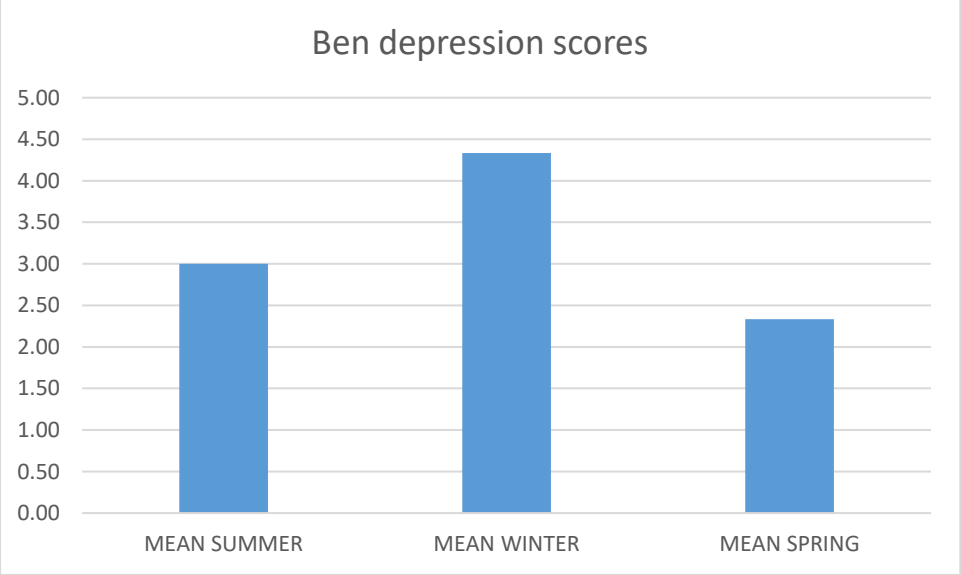


	MEAN SUMMER	MEAN WINTER	MEAN SPRING
Pain - WOMAC	6.33	3.67	7.33
Stiffness - WOMAC	2.00	2.33	3.67
Physical function - WOMAC	8.00	6.33	15.33

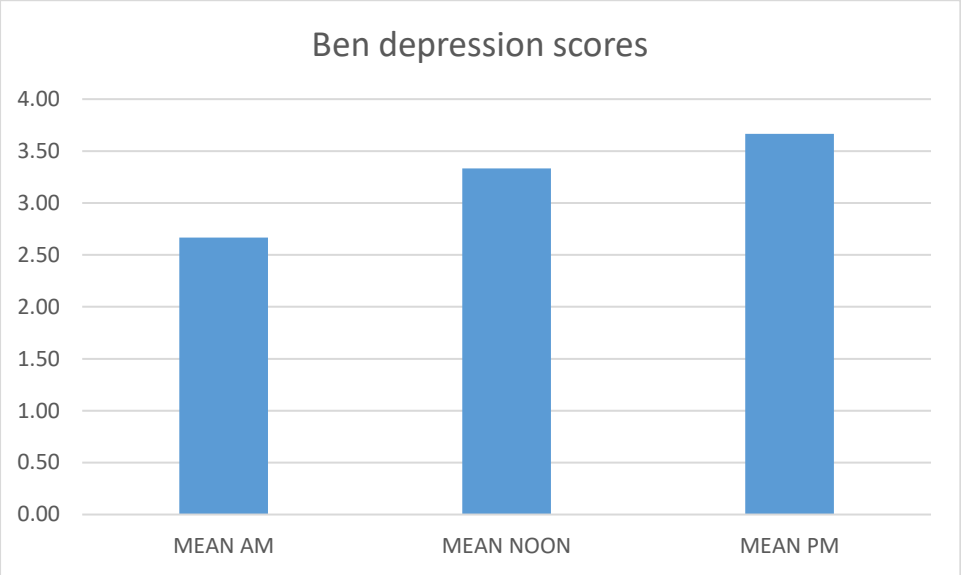
Osteoarthritis circadian scores



Depression seasonal scores



Depression circadian scores



Appendix IX WHO-QOL-BREF analysis

Background to the WHO-QOL-BREF

The WHOQOL-BREF is an abbreviated 26 item version of the WHOQOL-100, which was developed using data from the field-trial version of the WHOQOL-100, to measure quality of life in a variety of situations and populations. Although the WHOQOL instruments can be used in particular cultural settings, results are comparable across cultures. The WHOQOL-BREF produces four domain scores: physical health, psychological, social relationships and environmental. Each domain measure an area of quality of life (Table), which were tested and selected during the development of WHOQOL-100. The questionnaire has been shown to display good discriminant validity, content validity and test-retest reliability. Internal consistency of all four domains ranged from 0.68 (social relationships) to 0.82 (physical health) (Skevington et al 2004). Pearson correlations between the four domains were strong and ranged from 0.46 (physical vs social) to 0.67 (physical vs psychological) (Skevington et al 2004). Domain scores on the WHOQOL-BREF correlate at around 0.9 with WHOQOL-100 domain scores. Minimal important difference scores for the WHOQOL-BREF vary for different disease groups.

The WHOQOL-BREF includes 24 questions covering the four domains and two questions on overall quality of life and general health. All 26 questions are rated on a 1-5 scale from a low score denoting a negative score to a high score giving a positive response. In order to derive an overall domain score, the mean score of items within each domain is calculated (WHOQOL 1998). Higher domain scores denotes a higher quality of life. Means scores for each domain can then multiplied by four to make comparisons with the WHOQOL-100. Psychometric results from the field trial conducted by Skevington et al (2004) produced an overall mean score for each domain (ranged 0-20) across 23 countries. Population norms in a healthy UK population have been reported across all domains of the WHOQOL-BREF: 62 for the physical domain, 58.8 for the psychological domain, 56.8 for the social relationships domain and 56.4 for the environmental domain (Skevington et al 2004).

Table 1. Domains and areas incorporated into each domain for WHOQOL-BREF

Domain	Facets/Areas incorporated within domains
Physical Health	Activities of daily living
	Dependence on medicinal substances and medical aids
	Energy and fatigue
	Mobility
	Pain and discomfort
	Sleep and rest
	Work Capacity
Psychological	Bodily image and appearance
	Negative feelings
	Positive feelings
	Self-esteem
	Spirituality / Religion / Personal beliefs
	Thinking, learning, memory and concentration
Social Relationships	Personal relationships
	Social support
	Sexual activity
Environment	Financial resources
	Freedom, physical safety and security
	Health and social care: accessibility and quality
	Home environment
	Opportunities for acquiring new information and skills
	Participation in and opportunities for recreation / leisure activities
	Physical environment (pollution / noise / traffic / climate)
	Transport

Aim of the WHOQOL-BREF analysis

The aim of the secondary analysis was to explore the potential variation of mean scores across the four WHOQOL-BREF domains.

Methods

AtLantic Dataset

Analysis plan

A series of initial data cleaning tasks were done to prepare the database for analysis. Firstly the timestamps of each of the responses did not correspond to the actual time zone the respondent was answering from (rather it was the server time in the UK). As the respondent's country was recorded, a list of these countries was produced in SPSS and each time zone was recorded from an online search on timeanddate.com. In excel all the time zones were noted down along with formulas to calculate the addition or subtraction of the time from the server time (Timestamp + 1/24 to add an hour). A total of nine countries had multiple time zones and it was not possible to determine the exact time when the participant answered the questionnaire. Thus, these responses were excluded from the analysis (N=2183). An additional 382 records did not have a country attached to the answer and were excluded from the analysis. This left a total of 2135 records with exact times recorded corresponding with the country in which they responded from. Countries were then categorised into seven continents. The employment answers were re-coded in SPSS for analysis from a string variable to numerical format.

It is hypothesised that domain mean scores will demonstrate a circadian rhythm, meaning that scores will vary by the hour of the day (in a 24-hr period). Descriptive analyses are performed for the sample. Graphical displays of domain scores for each hour in a 24-hour period were examined for the whole sample and each chronic condition. A one-way analysis of variance (ANOVA) was performed to analyse the differences in domain scores across the different hours of the day, with statistical significance considered at $p < 0.05$. Additional examination into potential variation of domain scores by hour of the day within each chronic condition groups was carried out by graphical display. A higher score on the measure is indicative of better quality of life and a change of 3 to 5 points is considered to be clinically relevant (Kerse et al 2014). All analyses were carried out using SPSS software for Windows (version 25).

Results

Sample Characteristics

Error! Reference source not found. presents the sample characteristics of the dataset. Just over half of the sample were females (56.3%), and just under half were in full-time employment (47%). The mean age of the sample was 32.9 (SD=12.6). The mean domain scores ranged from 50.2 to 82.11 for the whole dataset. The majority of the sample did not report having one of the five stated conditions, however for those who did report having a condition the most prevalent one was depression (N=498). A small number of individuals had two or more conditions (N=73), with most confirming they suffered from two conditions (N=55).

The domain scores were plotted against each hour of the day for the whole sample and there was slight variation for physical score (see). Further plots of domain scores across a 24 hour period for each of the conditions were created to see if there was variation in scores in particular conditions (). As there was some potential variation, seen graphically, this was investigated further across the sample with an analysis of variance test.

Table 2. Characteristics of the AtLantic WHOQOL-BREF dataset

	Whole sample (N = 2135)	With one or more chronic condition(s) (N= 635)	With no chronic condition(s) (N=1500)
	N (%) or Mean (S.D.)	N (%) or Mean (S.D.)	N (%) or Mean (S.D.)
Age	32.9 (12.6)	35.1 (14.0)	32.0 (11.9)
18 to 24	636 (29.8%)	153 (24.1%)	483 (32.2%)
25 to 34	718 (33.6%)	221 (34.8%)	497 (33.1%)
35 to 44	310 (14.5%)	87 (13.7%)	223 (14.9%)
45 to 54	370 (17.3%)	124 (19.5%)	246 (16.4%)
55 to 64	65 (3.0%)	27 (4.3%)	38 (2.5%)
65 to 74	15 (0.7%)	12 (1.9%)	3 (0.2%)
75 to 84	4 (0.2%)	3 (0.5%)	1 (0.1%)

85 and above	17 (0.8%)	8 (1.3%)	9 (0.6%)
Gender			
Male	909 (43.1%)	312 (49.4%)	861 (42.7%)
Female	1206 (56.9%)	320 (50.6%)	1155 (57.3%)
Chronic condition (yes)			
Arthritis	76 (3.7%)		
Depression	498 (23.9%)		
COPD	80 (3.9%)		
Coronary heart disease	37 (1.8%)		
Diabetes	46 (2.2%)		
Employment status			
Full-time education	599 (28.1%)	149 (23.5%)	574 (28.1%)
Full-time paid work	1014 (47.5%)	262 (41.3%)	979 (48.0%)
Part-time paid work	146 (6.8%)	59 (9.3%)	142 (7.0%)
Looking after home	38 (1.8%)	13 (2.0%)	35 (1.7%)
Retired	13 (0.6%)	9 (1.4%)	12 (0.6%)
Doing something else	163 (7.6%)	54 (8.5%)	154 (7.5%)
Unemployed	132 (6.2%)	66 (10.4%)	125 (6.1%)
Permanently sick or disabled	21 (1.0%)	20 (3.1%)	16 (0.8%)
Not applicable	9 (0.4%)	3 (0.5%)	3 (0.1%)
Geographical Location			
Asia	334 (15.6%)	85 (13.4%)	249 (16.6%)

Africa	50 (2.3%)	14 (2.2%)	36 (2.4%)
North America	26 (1.2%)	6 (0.9%)	20 (1.3%)
South America	198 (9.3%)	61 (9.6%)	137 (9.1%)
Europe	1485 (69.6%)	451 (71.0%)	1034 (69.0%)
Australasia	42 (2.0%)	18 (2.8%)	24 (1.6%)
Domain Scores			
Physical Score	69.9 (15.8)	69.2 (15.8)	69.8 (15.8)
Psychological Score	50.2 (6.6)	50.2 (7.1)	50.2 (6.7)
Social Score	50.2 (8.9)	50.3 (9.1)	50.1 (8.9)
Environmental Score	82.1 (6.3)	82.2 (6.2)	82.1 (6.3)
Hour of the day completed	12.3 (7.1)	12.0 (7.0)	12.3 (7.1)

Circadian rhythm of overall mean domain scores

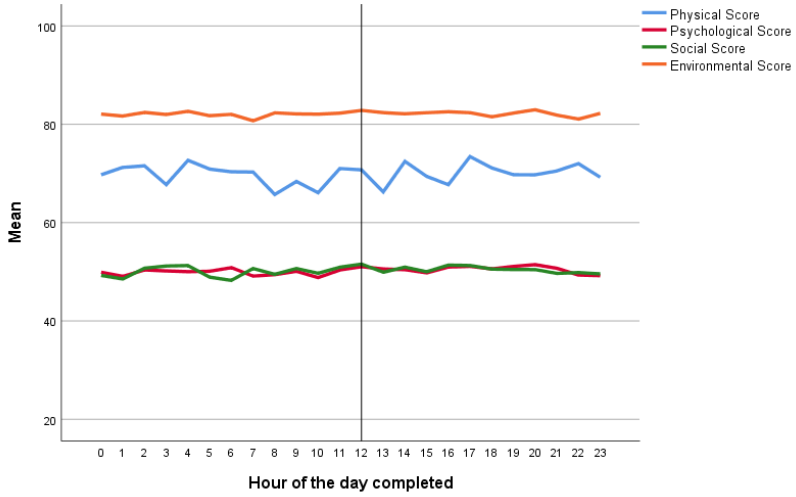
In order to explore potential variation of mean domain scores within a 24-hour period, a between-groups ANOVA was performed. The number of data points per hour was limited due to the number of responses across a 24-hour period, thus the confidence intervals varied across the hours of the day. There were no statistically significant differences between the physical domain score means and hour of the day ($F(23, 2134) = 1.46$, $p = .07$), for psychological domain score ($F(23, 2134) = 1.14$, $p = .29$), for social domain score ($F(23, 2134) = 0.90$, $p = .59$), or environmental domain score ($F(23, 2134) = .56$, $p = .95$) as determined by one-way ANOVA. All ANOVA results are presented in **Error! Reference source not found.**.

Circadian rhythm of domain scores for each condition group

In order to explore potential variation of mean domain scores in a 24-hour period within specific conditions, an ANOVA was performed on the five conditions. Using the “select cases” option in SPSS, an analysis on a particular subset of data (in this case chronic conditions) was possible. The hour of the day did not affect the mean domain scores for most of the chronic conditions. There was a statistically significant

difference in the social domain mean score for time of the day for COPD, (F (23, 80) = 1.89, p = .03). In addition, there was a statistically significant difference for psychological domain mean score for time of the day for coronary heart disease, (F (23, 37) = 5.66, p = .00).

Figure 1. Domain scores plotted against hour of the day



Discussion

To the best of our knowledge, this is the first attempt to examine how domain scores differ across a 24-hour day using WHOQOL-BREF data. The aim of the analysis was to examine any mean differences in domain score in an already collected sample of respondents to the WHOQOL-BREF, which was part of the ATLanTiC Study. The domain scores did not differ by hour of the day the sample, nor did it differ within different chronic conditions apart from two conditions. There were differences in the psychological domain score at different times of the day for those with coronary heart disease, however due to the small numbers within each hour of the day these results should be treated with caution. In addition, those with COPD reported different social domain scores at different times of the day, although the same applies for this sample as the numbers were small across the hours of the day.

Literature has demonstrated that symptom severity impacts on the limitations of activity, including social relationships for COPD sufferers (Gabriel et al 2014; Jones 2007), and time of day impacts on symptom severity and patients' ability to carry out activities (Partridge et al 2009; Roche et al 2013). More severe symptoms have been reported in the morning compared to other times of the day resulting in greater

limitations in daily activities (Partridge et al 2009; Roche et al 2013). The findings from this secondary analysis only partly support the literature, as it was not possible to make definitive conclusions regarding which hour of the day domain scores were different due to sample size. Upon examination of the graphical representations of the social domain scores across the 24-hour period, there were significant peaks observed in the early hours of the morning compared to other times of the day.

The psychological domain captures information on bodily image, feelings (both negative and positive), self-esteem, personal beliefs and cognitive function. The significant difference in scores across the day found for this domain in coronary heart disease participants is supported by the literature. Individuals with coronary heart disease commonly have co-occurring chronic conditions such as depression and cognitive impairment (Burkauskas et al 2018; Stewart et al 2017). As demonstrated in the scoping review chapter (, mood is known to fluctuate in individuals with depression with lower mood reported in the morning, rising during the day and then lowering again in the evening (Aan het Rot 2012). However, there is a lack of research examining how mood and cognitive function in heart patients differ at varying times of the day.

Summary of overall findings

The analysis conducted with the WHOQOL-BREF dataset did not result in significant differences across the different times of the day for domain scores. This finding did not support the literature presented in the scoping review describing the evidence on time-dependent variation in PRO scores for those with chronic conditions. The dataset used for this analysis only provided single time points for each individual, and an accurate assessment of any potential fluctuations for an individual was not possible. Further analysis is needed on a database with repeated measurements from the same individual to explore potential intra-individual fluctuations and determine time-dependent variation of PRO scores.

Strengths and limitations

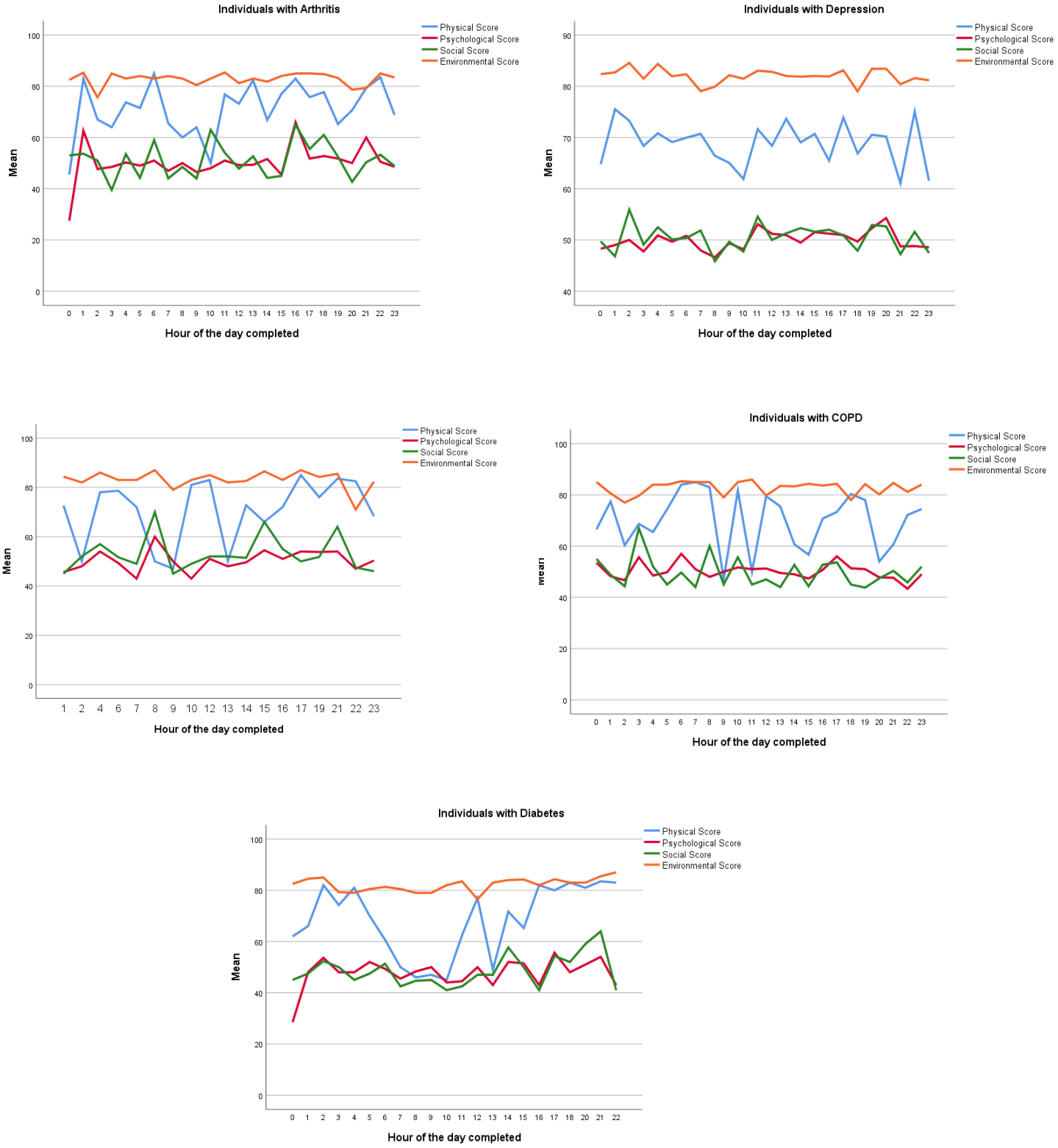
The current analysis has several limitations. Firstly, with the WHOQOL dataset, although the sample size was sufficient overall, the subsets of chronic conditions were unbalanced, with the majority of the participants having depression. Examination of each hour of the day resulted in even smaller sample sizes spread

across the 24-hour period, providing unequal group sizes to compare domain score means. Post hoc tests were not possible due to the smaller numbers representing different hours of the day for each chronic condition. The sample consisted of responses from 110 different countries, and as quality of life differs across different cultures, cross-cultural differences were unable to be performed as the numbers were small.

As the sample did not respond in the same 24-hour period this may have affected the results. The study data collection period extended over a 6-month period which covers also seasonal changes potentially affecting the responses to the questionnaire. In addition, responses varied over the day of the week and month, which could affect the responses to the facets incorporated in all the domains. Domain scores could be different depending on the day of the week (e.g. weekday versus weekend) due to social or work situations.

Finally, all the responses from participants were one-off responses, which do not reflect potential intra-individual variations that can be captured with a PROM. A database with repeated measurements across multiple time points will provide an opportunity to assess the effect of time providing more statistical power with fewer participants. Many randomised controlled trials use a repeated measures design to assess the effect of an intervention over time. However, they tend not to capture the effect of time of day which would demonstrate the presence of time dependent variation.

Figure 2. Mean domain scores for physical, social and environmental domains by hour of the day for each condition



Appendix X Guidance on using Fourier transformation on a longitudinal dataset (STATA commands)

Steps	STATA commands
1. Convert time completed to hours of the day	
2. Create two variables as sine and cosine of time of day with a 24-hour period	gen s=sin(timehh*2*_pi/24) gen c=cos(timehh*2*_pi/24)
3. Test sine and cosine variables together to see if it has worked	Test (s=0) (c=0)
4. Plot new variables against time of day: scatter plot	scatter s timehh,xline(0) xline(360) xline(720) xline(1080) xline(24) scatter c timehh,xline(0) xline(360) xline(720) xline(1080) xline(24)
5. Run the model with a mixed effects linear regression, with sine and cosine variables (indicator for day of the week and random intercept for person)	mixed [dependent variable] s c i.day_of_week i.Gender i.employment i.agegrp || personid: *independent variables have i. in front to indicate it is a categorical variable. “personid” is the respondent
If the model is not significant for a 24-hour period repeat steps 2 to 5 by splitting the periodicity to 12hour and 6 hour timeframes using the following steps until you get a significant model (12 hour is steps 7 to 10; and 6 hour is steps 11 to 14)	
6. Create a 12 hour sine and cosine variable	gen s12=sin(timehh*2*_pi/12) gen c12=cos(timehh*2*_pi/12)
7. Test these variables together	Test (s12=0) (c12=0)
8. Plot new variables against time of day	scatter s12 timehh,xline(0) xline(360) xline(720) xline(1080) xline(24) scatter c12 timehh,xline(0) xline(360) xline(720) xline(1080) xline(24)
9. Run the model with mixed effects linear regression with sine and cosine variables	mixed [dependent variable] s12 c12 i.day_of_week i.Gender i.employment i.agegrp || personid:
10. Create a 6 hour sine and cosine variable	gen s6=sin(timehh*2*_pi/6) gen c6=cos(timehh*2*_pi/6)
11. Test these variables together	test (s6=0) (c6=0)

12. Plot new variables against time of day	scatter s6 timehh,xline(0) xline(360) xline(720) xline(1080) xline(24) scatter c6 timehh,xline(0) xline(360) xline(720) xline(1080) xline(24)
13. Write out the estimates for each hour to a text file. This is to see how the scores change across each hour of the day.	mixed [dependent variable] s6 c6 i.day_of_week i.Gender i.employment i.agegrp || personid:
14. First open a file to write to	file open bob using f_output.txt,write replace
15. Write out first line – for the headings of each column	file write bob ("t") _tab ("estimate") _tab ("se") _n
16. Loop round the time of day in 30 minute intervals and use the lincom command to estimate the period effect relative to your anchor time (for MD it was midnight) and write the estimates to file	forvalues i=0(0.5)24 { local s=(sin(`i'*2*_pi/24)) local c=(cos(`i'*2*_pi/24)) local s12=(sin(`i'*2*_pi/12)) local c12=(cos(`i'*2*_pi/12)) local s6=(sin(`i'*2*_pi/6)) local c6=(cos(`i'*2*_pi/6)) lincom ((`s'*s)+(`c'*c))-((0*s)+(-1*c))+((`s12'*s12)+(`c12'*c12))-((0*s12)+(1*c12))+((`s6'*s6)+(`c6'*c6))-((0*s6)+ (1*c6)) file write bob ("`i'") _tab (r(estimate)) _tab (r(se)) _n }
17. Close file	file close bob
18. Read in a new file	insheet using f_output.txt,names clear
19. Next is to calculate the confidence intervals	gen lci=estimate-(1.96*se) gen uci=estimate+(1.96*se)
20. Plot the estimated periodicity and confidence intervals	tw (rarea lci uci t) (line estimate t), xlabel (0(4)24) legend(off)

Appendix XI Coefficients and standard errors for four symptoms for every 30-minute intervals

	Dizziness		Tinnitus		Aura fullness		Hearing Loss	
t	**estimate**	**se**	**estimate**	**se**	**estimate**	**se**	**estimate**	**se**
0	-0.14	0.03	-0.10	0.03	-0.20	0.03	-0.03	0.03
0.5	-0.12	0.03	-0.08	0.03	-0.19	0.03	0.00	0.03
1	-0.11	0.04	-0.06	0.03	-0.19	0.03	0.01	0.03
1.5	-0.10	0.04	-0.04	0.03	-0.19	0.04	0.03	0.03
2	-0.10	0.04	-0.02	0.04	-0.19	0.04	0.03	0.03
2.5	-0.10	0.04	0.00	0.04	-0.20	0.04	0.04	0.03
3	-0.10	0.04	0.01	0.04	-0.21	0.04	0.03	0.03
3.5	-0.11	0.04	0.03	0.04	-0.22	0.04	0.03	0.03
4	-0.13	0.04	0.04	0.04	-0.23	0.04	0.02	0.03
4.5	-0.14	0.04	0.04	0.04	-0.24	0.04	0.00	0.03
5	-0.16	0.04	0.04	0.04	-0.25	0.04	-0.01	0.03
5.5	-0.17	0.04	0.04	0.03	-0.25	0.03	-0.03	0.03
6	-0.18	0.04	0.03	0.03	-0.25	0.03	-0.05	0.03
6.5	-0.19	0.03	0.03	0.03	-0.25	0.03	-0.06	0.03
7	-0.19	0.03	0.02	0.03	-0.24	0.03	-0.07	0.03
7.5	-0.19	0.03	0.01	0.03	-0.23	0.03	-0.08	0.02
8	-0.18	0.03	0.00	0.02	-0.21	0.02	-0.08	0.02
8.5	-0.16	0.02	-0.01	0.02	-0.18	0.02	-0.08	0.02
9	-0.15	0.02	-0.01	0.02	-0.15	0.02	-0.07	0.02
9.5	-0.12	0.02	-0.02	0.02	-0.12	0.02	-0.06	0.01
10	-0.10	0.01	-0.02	0.01	-0.09	0.01	-0.05	0.01
10.5	-0.07	0.01	-0.01	0.01	-0.07	0.01	-0.04	0.01
11	-0.04	0.01	-0.01	0.01	-0.04	0.01	-0.02	0.01
11.5	-0.02	0.00	-0.01	0.00	-0.02	0.00	-0.01	0.00
12	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
12.5	0.02	0.00	0.01	0.00	0.01	0.00	0.01	0.00
13	0.03	0.01	0.01	0.01	0.02	0.01	0.01	0.01
13.5	0.03	0.01	0.02	0.01	0.01	0.01	0.01	0.01
14	0.02	0.01	0.02	0.01	0.00	0.01	0.00	0.01
14.5	0.01	0.02	0.02	0.02	-0.01	0.02	-0.01	0.01
15	-0.01	0.02	0.02	0.02	-0.04	0.02	-0.02	0.02
15.5	-0.03	0.02	0.01	0.02	-0.06	0.02	-0.04	0.02
16	-0.06	0.02	0.01	0.02	-0.09	0.02	-0.07	0.02
16.5	-0.09	0.03	-0.01	0.02	-0.12	0.02	-0.09	0.02
17	-0.12	0.03	-0.02	0.02	-0.15	0.03	-0.11	0.02
17.5	-0.15	0.03	-0.04	0.03	-0.18	0.03	-0.14	0.02
18	-0.18	0.03	-0.06	0.03	-0.21	0.03	-0.16	0.02
18.5	-0.20	0.03	-0.08	0.03	-0.23	0.03	-0.17	0.02
19	-0.22	0.03	-0.10	0.03	-0.25	0.03	-0.18	0.02
19.5	-0.24	0.03	-0.11	0.03	-0.26	0.03	-0.19	0.02
20	-0.24	0.03	-0.13	0.03	-0.27	0.03	-0.19	0.02
20.5	-0.24	0.03	-0.14	0.02	-0.27	0.03	-0.18	0.02

21	-0.24	0.03	-0.15	0.02	-0.26	0.03	-0.17	0.02
21.5	-0.23	0.03	-0.15	0.02	-0.25	0.02	-0.15	0.02
22	-0.21	0.03	-0.15	0.02	-0.24	0.02	-0.13	0.02
22.5	-0.20	0.03	-0.14	0.02	-0.23	0.02	-0.10	0.02
23	-0.18	0.03	-0.13	0.03	-0.22	0.03	-0.08	0.02
23.5	-0.16	0.03	-0.12	0.03	-0.21	0.03	-0.05	0.02
24	-0.14	0.03	-0.10	0.03	-0.20	0.03	-0.03	0.03