Apathy and Relational Changes in Huntington's Disease: Exploring the Caregivers' Experiences

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Thesis Portfolio Abstract

Background: Huntington's disease affects cognition, behaviour, and social and emotional functioning with reduction in self-initiated thoughts, activities, emotional responses or social activities, or apathy, a frequent and early consequence closely related to underlying neuropathological changes. Little is understood about how these changes impact on caregivers, despite emerging evidence that behavioural features of the disease and change in the caregiver/care recipient relationship are linked to perceptions of burden.

Aim: This thesis aimed to explore the experience of caregivers and the meaning-making constructed about apathy and relational change in Huntington's disease.

Methods: Semi-structured interviews analysed with reflective thematic analysis were used to investigate caregiver experience of supporting someone with Huntington's disease and apathy. Following which, a systematic review of qualitative research and thematic synthesis of caregiver experience of relational change in Huntington's disease was conducted.

Results: The qualitative study produced five themes: "What even is apathy?", "It makes my life harder", "They haven't forgotten me but they have forgotten that they ever loved me", "Grieving for someone who hasn't died yet", and "I need a safe space to say what I really feel without fear of judgement". Narratives about the invisibility and unspoken nature of both HD and caregivers were inter-woven across themes. The systematic review identified themes of: "Loss of friendship, companionship and intimacy", "Relationships built around fear", "Seeing my own future played out before me", and "HD has made us stronger".

Conclusions: This thesis portfolio highlights the emotional and interpersonal impact of Huntington's disease on caregivers. Using the theoretical framework of anticipatory grief and ambiguous loss, it

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promotes the importance of a systemic view of the impact of the disease, helping to shape future research and clinical practice.

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I would also like to thank all the HD families who have taken part in my research both as part of this thesis and everything that has come before it. I am in constant awe of the strength and fortitude you show every single day and I feel truly privileged that you have been willing to share even a tiny bit of this with me so openly and honestly.

Finally, I would like to thank my family without whom this thesis would not have been possible. To Mum, Dad and Rachel for stepping into my shoes when I have needed to elsewhere either physically or mentally. To James for always believing that I could and should do this, and to Isobel, Harry and Sophie for being, quite simply, the most amazing children I could ever have wished for.

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Glossary

Akinesia: impaired muscle movement or impairment in voluntary movement

Chorea: involuntary movements of the limbs, body or face as a result of a neurological condition, characteristically seen in Huntington's disease.

Dysarthria: difficulty speaking due to muscle weakness, resulting in slowed or slurred speech.

Dysphagia: difficulty swallowing food or drink due to muscle weakness.

Dystonia: abnormal posturing due to sustained muscle contractions.

Gait disorders: abnormal walking pattern.

Oculomotor impairment: visual problem resulting from an impairment in the brains ability to co-ordinate the eyes resulting in difficulty moving with accuracy and control.

Phenoconversion: the process by which a person transition from gene carrier status (e.g. carrying the gene expansion for Huntington's disease but showing no clinical features of the disease) to displaying clinical signs of Huntington's disease.

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Chapter 1 – Introduction

Introducing Huntington's Disease and Apathy

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Chapter 1 - Introduction

Huntington's Disease

Huntington's disease (HD) is a devastating inherited neurodegenerative disorder, estimated to affect 8.2 people per 100,000 in the UK (Furby et al., 2022). Children who have a parent with HD carry a 50% risk of having inherited the disease themselves. HD is caused by an unstable cytosine-adenosine-guanine (CAG) expansion in exon 1 of the *Huntingtin* (HTT) gene (Huntington's Disease Collaborative Research Group, 1993). Approximately 30,000 people in the US and 38,000 people in Europe live with the disease, but a further 250,000 people are at risk of having inherited this genetic mutation (Leegwater-Kim and Cha, 2004). Those at risk can test to see whether they carry the faulty gene, prior to any clinical indication of HD, but at present there is no way of predicting, for any given individual, when the disease will begin, what the earliest signs will be or the speed at which HD will progress. The psychological impact of this uncertainty is profound and far reaching, influencing life choice and affecting relationships.

HD typically presents in midlife with a combination of motor, cognitive and psychiatric problems which emerge over a decade or more, and progress steadily leading to death around 10-25 years later (Ross et al., 2014). Once considered predominantly a movement disorder, there is now greater recognition of the impact of the non-motor aspects of the disease. In a 2015 report from the US Food and Drug Administration (FDA) a person with HD (pwHD) was quoted as saying "The most significant symptoms of HD are the ones you cannot see" (FDA, 2016). Consequently, while a clinical diagnosis of HD is still made based on the presence of unequivocal motor features (Reilmann et al., 2014) a case has been made to incorporate the wider clinical profile into the diagnostic criteria (Ross et al., 2019).

Clinical Presentation of Huntington's Disease

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Motorically, HD is characterized by a distinctive chorea, dysarthria and dysphagia. Patients also exhibit dystonia, lack of coordination, akinesia, oculomotor impairment, postural instability and gait disorders. However, despite these being the most visible signs of the disease, it is the cognitive and psychological symptoms that impact pwHD and caregivers the most (Simpson et al., 2016), with the severity of the non-motor changes predicting loss of independence and the need for residential care (Dawson et al., 2004a).

Cognitive and psychiatric changes are often an early feature of HD. Cognitive impairment has been detected up to 15 years prior to motor diagnosis (Stout et al, 2011) although around 20-25% of people in the late stages of the disease still do not score within the threshold for cognitive impairment using simple cognitive screening tools (Begeti et al., 2013; Sierra et al., 2023). In the early stages of disease, pwHD exhibit a dysexecutive syndrome with impaired performance on tests of verbal fluency, working memory, response inhibition, along with problems with psychomotor slowing and attention (Stout et al., 2023). This is accompanied by changes in social cognition and decision-making (Mason et al., 2021). By the moderate stage of disease the cognitive impairment is significant and impactful with most people meeting criteria for a global dementia (Begeti et al, 2013).

Apathy

Apathy affects 11% and 64% of pwHD before the clinical diagnosis and 47% to 76% of people with a clinical diagnosis of HD reporting a degree of apathy at some point during their disease (Martinez-Horta et al., 2016; Naarding et al., 2009; Paulsen et al., 2001; Simpson et al., 2016; van Duijn et al., 2014; van Duijn et al., 2007). Unlike other clinical features of HD, apathy does not appear to be inheritable (De Souza et al., 2014) but does closely map disease progression (Kingma et al., 2008; Martinez-Horta et al., 2016; Tabrizi et al., 2009; Thompson et al., 2012; van Duijn et al., 2010) and is associated with cognitive, motor and functional decline (Hamilton et al., 2003; Thompson et al., 2012).

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Apathy can be defined as a quantitative reduction in self-initiated, goal directed behaviour (Marin, 1991). Its widely accepted to be multidimensional, and although this is conceptualised differently depending upon the model and its research methodology, most propose a tripartite structure that broadly translates to cognitive, behavioural and emotional/affective subtypes of apathy (see Radakovic and Abrahams (2014) for a review). Recently, a fourth dimension has been added which encapsulates the social elements of motivation (Ang et al., 2017) (see Table 1.1 for a summary). Evidence supporting multidimensional apathy has been reported across neurological and psychiatric disorders (Jackson & Robinson, 2022; Radakovic & Abrahams, 2014; Raffard et al., 2019).

Subtype	Description
Cognitive/executive apathy	Loss of motivation, impaired participation and perseverance in daily tasks or forming new routines, requiring prompts to initiate novel thoughts and conversations, difficulty forming new strategies or shifting behaviour.
Behavioural/initiation apathy	Loss of motivation, impaired spontaneity requiring prompts to initiate activities, reduction in self generated though.
Emotional apathy	Emotional blunting or indifference, lack of emotion or awareness of the affect of own or others behaviour.
Social apathy	A lack of drive to pursue social interactions, lack of action in own self interest, impairment in self-awareness,

Table 1.1: Description of the apathy subtypes

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Le Heron and colleagues (Le Heron et al., 2018) systematically reviewed the neuroscience literature on apathy, synthesising findings from neuroimaging studies across neurological conditions, including Parkinson's disease (PD), Alzheimer's disease (AD), HD, frontotemporal dementia (FTD), Progressive Subnuclear Palsy (PSP), Corticobasal degeneration (CBD) and stroke. They found a consistent pattern of neuroanatomical mechanisms across conditions which suggested that apathy was associated with the functional integrity of the fronto-striatal circuitry (Figure 1.1). At the core, the ventral striatum and anterior cingulate cortex play a pivotal role in apathy, with structures that are functionally and anatomically connected to these areas, such as the amygdala, anterior insula, dorsolateral prefrontal cortex, ventral tegmental area and medial prefrontal cortex, contributing to the modulation of apathy. The authors proposed a neurocognitive framework, with three distinct stages of goal-directed behaviour, conceptualised as:

(1) The ability to decide whether to engage in an action or series of actions, using a cost-benefit ratio (e.g. is the amount of effort required justified by the reward of reaching the goal?);
(2) The ability to sustain motivation long enough to achieve the goal; and
(3) Monitoring the outcome of goal-directed actions.

It is important to hold in mind however, that this framework was proposed to explain the mechanism by which neurological changes result in apathy, and not to infer any element of conscious control in the process on the part of the person with apathy.

Discourses about Apathy

When contemplating the lived experience of apathy it is important to recognise that the way we talk about apathy in everyday life does not have the same emotional neutrality that is used in the operationalised definitions produced for the clinical syndrome. In fact, apathy is often constructed in a context dependent, socio-cultural way that, in many ways carries with it a negative connotation. Historically, Christians considered apathy to be a manifestation of a lack of love and devotion to god,

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referring to it synonymously with “Sloth”, one of the Seven Deadly sins. The modern understanding of apathy emerged as people recognised and tried to make sense of the numbness and sense of disconnectedness experienced by soldiers returning from World War I, which we now understand to be “Shell Shock” or Post-Traumatic Stress Disorder (PTSD). Socially, apathy is viewed more negatively than emotions such as hate or anger. Discussions around political apathy, bystander apathy and educational apathy construct apathy as disinterest and indifference where people are not engaging in action or discussion that there is a social and moral expectation that they should. The author Leo Buscaglia summed this up perfectly when he wrote, “the opposite of love is not hate, its apathy. Its not giving a damn” (Buscaglia, 1972).

An in-depth discussion is beyond the scope of this thesis portfolio but reflection on the socially constructed discourse around apathy was a important consideration in the design of the empirical study both in the Patient and Public Involvement work that was conducted and incorporated into the study materials and in the approach to the conduct, analysis and interpretation of the results.

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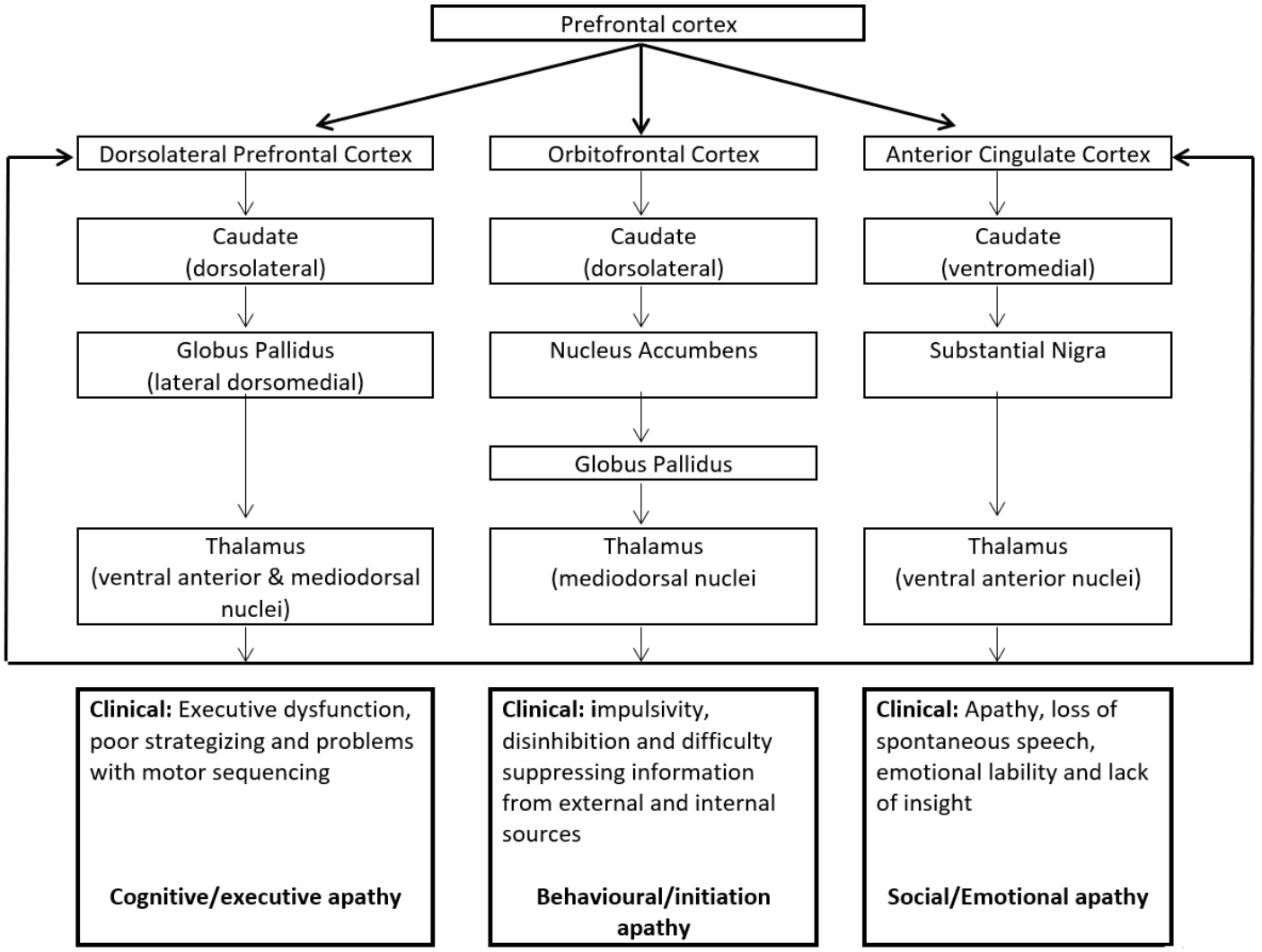

Figure 1.1 – Schematic representation of frontostriatal networks relevant to apathy reproduced and adapted from Mason (2014)

The Neuropathology of Huntington's Disease and Apathy

Early and pronounced striatal atrophy is a characteristic hallmark of HD, caused by a loss of medium-sized spiny neurons (Vonsattel & DiFiglia, 1998). Grey matter volume loss in the caudate and putamen has been reported consistently and robustly, and is present in HD gene carriers up to 20 years before their clinical diagnosis (Tan et al., 2021). Volume loss in the striatum increases in a predictable way as people get closer to clinical diagnosis and start to develop motor features (Paulsen et al., 2006), predicting phenoconversion within two years (Aylward et al., 2004). After diagnosis, extra-striatal volume loss is detectable in areas including the globus pallidus (Harris et al., 1999; Thieben et al., 2002), thalamus (Harris et al., 1999; Paulsen et al., 2006), amygdala (Dogan et al., 2013) and insula (Thieben et al., 2002). This progresses over the course of the disease to encompass most brain regions so that, by end stage disease there is on average a 30% reduction in brain weight (de la Monte et al., 1988).

Historically, there was believed to be a dorsal to ventral, anterior to posterior and medial to lateral progression of neuronal death in HD with the dorsomedial striatum affected the earliest and a relative sparing of the ventral striatum and nucleus accumbens (Bots & Bruyn, 1981; Roos et al., 1985; Vonsattel et al., 1985), however, neuroimaging studies have reported altered neural activation in the ventral striatum early in the course of HD (Enzi et al., 2012) associated with reward processing (Nickchen et al., 2017) and apathy (Davis et al., 2022). There is also evidence that HD-related apathy is associated with amygdala function, through cognitive processes connected to a blunted response to losses and impaired instrumental learning (McLauchlan et al., 2019). Functional connectivity of the amygdala is known to deteriorate prior to the onset of clinical disease and to be associated with elements of social cognition in HD (Mason et al., 2015); potentially indicating a social and emotional aspect to apathy in this patient group.

Clinical Management of HD in the UK

Despite progress, HD is currently incurable and available drug agents only provide partial relief of motor and some psychological symptoms. As such, the clinical management of HD focuses on alleviating the burden of symptoms, maintaining function and improving quality of life (Fritz et al., 2018). NICE guidelines for the treatment of HD are planned but do not currently exist in the UK (Huntington's Disease Association, 2023) therefore specialist services, although guided by International Guidelines (Bachoud-Levi et al., 2019) have grown organically (Willock et al., 2023). This has led to a disparate pattern of clinical provision across the UK, with clinics embedded in different specialties such as neurology, psychiatry, and genetics and no clear model of service provision or national picture of how services are organised, funded or resourced at a local level (Willock et al., 2023).

Despite the extensive psychological and neuropsychological symptoms of HD, access to psychological services is variable and regionally dependent. The lack of clear care pathways and the conceptualisation of HD under the medical model, means that pwHD are often referred to a neuropsychiatrist, rather than psychologist, where medication is more likely to be offered than therapy or neurorehabilitation (Simpson et al., 2016). PwHD often struggle at access generic mental health services due to the complexity of their presentation (The Neurological Alliance, 2017). Guidance recently published by the British Psychological Society recognised the lack of available research into the effectiveness of psychological interventions for pwHD and called for greater consideration of a psychological approach to be adopted by both HD researchers and clinical teams (British Psychological Society, 2021).

Clinical Management of Apathy in Huntington's Disease

PwHD and HD caregivers rate apathy as one of the three most impactful features of the disease (Simpson et al., 2016) negatively associated with quality of life. Given this and the high

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prevalence rates, it has been argued that apathy should be considered a core trait of HD (Martinez-Horta et al., 2016) and treated as a priority in the clinical care of people with the condition. To achieve this, there needs to be a greater consideration of the impact of apathy for pwHD and HD caregivers. A lack of effective pharmacological and neuropsychological treatments for apathy (Gelderblom et al., 2017) means that alternative therapeutic strategies need to be explored.

Whilst much is known about the presence and natural history of apathy in HD (Camacho et al., 2018), little is known about how apathy is experienced by the pwHD or HD caregivers. In the context of apathy, the caregiver perspective is particularly relevant since it is widely acknowledged that the pwHD is often unaware of their own apathy (Gelderblom et al., 2017) as has been found in other neurodegenerative disorders (Tondelli et al., 2021). As such, distress associated with apathy is most typically experienced by HD caregivers rather than pwHD.

Aim and Structure of the Thesis Portfolio

The overarching aim of this thesis portfolio was to develop an understanding of the HD caregiver experience of apathy, to guide the design of psychological interventions for apathy, enabling a move towards an evidence-based approach to psychological therapy in HD. To achieve this aim, the thesis portfolio presents a qualitative study of the meaning-making constructed by caregivers of pwHD and apathy in Chapters 2 and 3 and a systematic review synthesizing qualitative research that references relational change experienced by HD caregivers in Chapter 4. In Chapter 5, research findings are summarised, appraised and contextualised within the wider literature and implications for future research and clinical practice outlined.

The subject of the systematic review was identified in response to the findings from the empirical study. As such, the chapters in this portfolio have been ordered to reflect the research process in an authentic way with the empirical study presented before the systematic review.

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It is hoped that the qualitative study and systematic review of qualitative research will provoke fruitful discussion between pwHD and HD carers, clinicians and researchers and raise awareness in those unfamiliar with the disease. Embracing diversity of thinking, promoting debate and raising the profile of HD may ultimately result in the development of new and effective treatments and holistic management of the disease which is currently not standard practice in the UK. As a portfolio, this work reflects my journey as a clinician and researcher, in which completion of Doctoral training in Clinical Psychology gave me the knowledge, support and confidence to translate my clinical observations as a HD researcher into robust empirical research with integrity and pride.

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Chapter 2: Empirical Study

"They haven't forgotten me, but they have forgotten that they ever loved me" - A Qualitative Analysis of How the Meaning of Apathy is Constructed by HD Caregivers

Formatted for submission to Neuropsychological Rehabilitation*

See Appendix A for Formatting guidelines for authors

* Selected with the intention of bringing the experience of HD caregivers to a general neuropsychological audience.

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"They haven't forgotten me, but they have forgotten that they ever loved me" - A Qualitative Analysis of How the Meaning of Apathy is Constructed by HD Caregivers

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Abstract

Although one of the most prevalent and impactful features of Huntington's disease (HD), little is known about the impact of apathy on HD caregivers, although there is evidence it affects perceptions of distress and burden. Given the importance of the caregivers, we aimed to explore the lived experience of people supporting someone with HD and associated apathy. Semi-structured interviews were conducted with 11 caregivers and analysed using reflective thematic analysis, informed by a phenomenological framework. Five overarching themes were produced: (1) What even is apathy? (2) It makes my life harder: the practical impact of apathy, (3) They haven't forgotten me, but they have forgotten that they ever loved me, (4) I'm grieving for someone who hasn't died yet, and (5) I need a safe space to say what I really feel without fear of judgement. Inter-woven between these themes were complex narratives about the unspoken nature of HD, the invisibility of caregivers who felt trapped and unheard, and the one-sided nature of loving someone with the disease. Findings are discussed in relation to theoretical frameworks of anticipatory grief and ambiguous loss and situated within the wider literature on caregiving for people with a neurodegenerative condition.

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Introduction

Huntington's disease (HD) is a rare, genetic, neurodegenerative disease, (Bates et al., 2014) which affects approximately 8.2 people per 100,000 in the United Kingdom (UK) (Furby et al., 2022). It is characterised by a triad of abnormal movements (Reilmann et al., 2014), cognitive impairment (Stout et al., 2023) and psychological features (McAllister et al., 2021) which progress slowly over a 10-15 year period (Furby et al., 2022).

Although heterogeneous in nature there is increasing recognition of the impact of early cognitive and psychological changes, which include impairments in executive function (Stout et al., 2023; Tabrizi et al., 2009), social cognition (Cavallo et al., 2022; Mason et al., 2021), depression, anxiety, and apathy (Brandt, 2018; Martinez-Horta et al., 2016; Stoker et al., 2022). Despite motor features being the most obvious sign of HD, it is the severity of non-motor changes that have greatest functional impact, predicting loss of independence and need for residential care (Dawson et al., 2004b).

Due to the progressive nature of the disease, it is inevitable that someone with HD will ultimately need support to live their life (Simpson et al., 2016). With the average onset of HD occurring during midlife (Furby et al., 2022), at a time when most people are already managing considerable work, family and financial responsibilities, caring for someone with HD can be complex. In later stages of the disease, specialist care is needed, typically in institutionalised care facilities, but these are expensive (Jones et al., 2016) and few in number, often resulting in the person with HD (pwHD) being placed far from their home. Understandably, people with HD and HD caregivers prefer to manage care at home until this becomes unsustainable, with the majority of the care provided by friends and family. In addition to the financial benefit, caregivers describe this experience as rewarding and fulfilling (Roscoe et al., 2009), with evidence suggesting an association between providing care for a loved one and reduced feelings of grief later in the bereavement process

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(Boerner et al., 2004). Nevertheless, the increased physical, financial and emotional demands on caregivers are significant and when these accumulate, they can be perceived as a burden that is difficult to manage (Mitchell et al., 2015).

In the wider literature, the extent of burden experienced by caregivers of people with long term conditions has been found to be related to caregivers' own health status, the extent and nature of behavioural difficulties demonstrated by the care recipient, the frequency and extent of care required by the care recipient, and their level of dependency (Cartaxo et al., 2023); this is similar in HD. Youssov and colleagues identified an interaction between disease stage and behavioural features of HD, where highest levels of burden are reported by caregivers supporting someone with advanced disease and therefore high levels of dependency and behaviour that challenges, or, someone with early disease and high levels of depression (Youssov et al., 2022). Recent research also reported a relationship between level of apathy exhibited by people with HD and perceived burden in HD caregivers (Hergert & Cimino, 2021).

Once viewed under the umbrella of depression (Levy et al., 1998), apathy is now regarded by people with HD and HD caregivers as one of the most impactful features of the disease (Simpson et al., 2016). Up to 76% of people with HD report experiencing apathy (van Duijn et al., 2007) with symptom severity associated with cognitive, motor and functional decline (Connors et al., 2023; Hamilton et al., 2003; Thompson et al., 2002). As such, it is thought to be closely related to the underlying neuropathology of the disease (Nair et al., 2022).

Apathy is operationally defined as a quantitative reduction in self-initiated, goal-directed behaviour (Marin, 1991). But, far from a unitary construct, it has been suggested that apathy is dimensional, consisting of multiple subtypes. Although reported differently across studies and assessment tools, these broadly overlap to create four groups: cognitive/executive, behavioural/initiation, emotional and social apathy (Klar et al., 2022; Radakovic et al., 2018)

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Research on the multidimensional nature of HD-related apathy is still in its infancy, but emerging evidence supports the delineation of different apathy subtypes (Atkins et al., 2021; De Paepe et al., 2022). Whilst previous work demonstrated an association between apathy and both executive dysfunction more generally (McLauchlan et al., 2019) and decision-making specifically (Atkins et al., 2020; Morris et al., 2022), supporting the presence of executive and initiation apathy, recent studies have shown that there is a strong association between apathy and social cognition in HD (Hellem et al., 2023) endorsing the presence of emotional and social apathy. Apathy has been linked to decreased satisfaction with social roles (Fritz et al., 2018), lower emotional awareness (Lemercier et al., 2022) and poorer emotional recognition (Kempnich et al., 2018) in people with HD.

Recently, there has been a push to expand our understanding beyond the neurobiological explanation of its origin and its behavioural correlates, through investigating the lived experience of apathy (Massimo et al., 2018; Petty et al., 2019). Often, the person affected by apathy does not recognise or report being troubled by their apathy, in direct contrast to the experience of those around them (Massimo et al., 2009). The impact of apathy on HD caregivers is recognised but not yet well understood, however, feelings of isolation and loss of emotional connection, which are both consequences of social and emotional apathy, have been shown to negatively impact caregivers both in HD specifically (Aubeeluck et al., 2013; Rothing et al., 2015) and dementia more generally (Cheung et al., 2018; Manca et al., 2022). Furthermore, spousal apathy, as reported by the caregiver, has been shown to have a strong negative impact on marital relationships (de Vugt et al., 2006). Given the important role informal HD caregivers play in meeting the care needs of people with HD, understanding the impact apathy has on them is an important, yet understudied area of HD research.

The current study used qualitative semi-structured interviews and reflective thematic analysis (rTA) to explore the subjective experience and meaning-making of HD caregivers. Secondary aims were to explore the phenomenology of HD caregivers' experiences with regard to specific

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features of HD related apathy, namely proposed subtypes, with a view to consider psychological approaches to help support HD caregivers in the future.

Methods

Design

Reflective thematic analysis (rTA) (Braun & Clarke, 2019), informed by a phenomenological framework (Larsen & Adu, 2021), was used to explore the lived experience of caregivers supporting someone who has apathy associated with HD. Motivated by the notable absence of the caregiver voice in research in this area, the study aligned with the philosophical presuppositions of a phenomenological approach (Guest et al., 2012). It is acknowledged that the reality of apathy existed independently of either the caregiver or the researcher, but that both have a role in constructing knowledge about the experience of supporting someone who has apathy (Ritchie et al., 2014). As such, particular emphasis was placed upon understanding the meaning of apathy constructed by the caregiver and the reflective process of the research team, with consideration given to the impact of different subtypes of apathy on that meaning making, through the lens of a critical realist methodology.

Quality Assurance

The COREQ Consolidated criteria for reporting qualitative research (Appendix B) (Tong et al., 2007) were used to guide reporting for this study, however, it is acknowledged that these do not fully align with the philosophical underpinnings of rTA (Braun & Clarke, 2023a). As such, the "Best practice recommendations for effectively conducting and reporting thematic analysis in health psychology" (Braun & Clarke, 2023b) were used as supplemental guidelines along with Yardley's quality guidelines for rigour in qualitative research (Yardley, 2000).

Research Team

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The research team consisted of a trainee clinical psychologist (SLM), two consultant clinical neuropsychologists (CF and FG) and a consultant neurologist (RAB). The interviews were conducted by SLM, a female researcher with 17 years of HD clinical experience and 7 years of post-doctoral research experience. Expertise of qualitative research methodology was provided by FG. Reflexive analysis was used to bring the diverse experience of the multidisciplinary research team into all aspects of the study (Finlay & Gough, 2008). All authors were involved in the study design, data analysis and write up, with the first draft of the manuscript written by SLM. Recruitment was partially conducted through an HD clinic that RAB and SLM work or have worked at respectively. Four participants were known to SLM as a result of this connection. RAB only accessed anonymised data.

Ethical Approval

The study was approved by North West Liverpool Central Research Ethics Committee, the Health Research Authority in the UK and Health and Care Research Wales (REC ref 23/NW/0026, IRAS: 319976) (Appendix C).

Public and Patient Involvement (PPI)

To ensure the research was relevant and accessible to the most diverse group of HD caregivers possible, members of the HD community were approached to co-produce the language used in the recruitment tools and topic guide. A shared definition of apathy and list of common terminology used synonymously within the HD community to describe apathy was created. Further details of the PPI work reported in line with the GRIPP reporting guidelines are described in supplemental data ((Staniszewska et al., 2017))

Recruitment

Recruitment took place between March and September 2023. The study was advertised in three regional NHS HD clinics and online via the Huntington's disease Association (HDA) website and social media. Caregivers self referred online or were approached in clinics and study recruitment

documents were mailed to those who had previously consented to be contacted about research. Interested caregivers were invited to complete online consent followed by a brief demographic questionnaire which included details of their HD caregiving experience, the Zarit Caregiver Burden Scale (ZCBS) (Zarit et al., 1986) and the companions' versions of the Dimensional Apathy Scale (c-DAS) (Radakovic & Abrahams, 2014) and the Apathy Motivational Index (c-AMI) (Klar et al., 2022). Internal consistency and reliability of the c-DAS (Cronbach's alpha coefficient 0.86) (Radakovic et al., 2016), c-AMI (Cronbach's alpha coefficient 0.85) (Klar et al., 2022) and the ZCBS (Cronbach's alpha coefficient 0.92) (Hebert et al., 2000) have been established, with the c-DAS being used with HD caregivers previously (Atkins et al., 2021). This information was used to determine eligibility based on the study inclusion criteria (table 2.1). All eligible caregivers were invited to interview.

Inclusion criteria:	Abnormality cut-off scores for companion apathy scales
• Significant caring responsibilities for someone with clinically manifest HD	Companion Dimensional Apathy Scale * • Executive subscale ≥13 • Initiation subscale ≥ 16 • Emotional subscale ≥ 15
• Over 18 years of age	Companion Apathy Motivational Index **
• Scores for the pwHD supported exceed clinical cut-off for one or more subscale of the c-DAS or c-AMI	• Total ≥ 1.91 • Behavioural subscale ≥2.34 • Social subscale ≥3.17

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- Emotional subscale ≥2.31

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* Cut off scores based on (Atkins et al., 2021)

**Cut off scores based on (Ang et al., 2017) in the absence of HD specific values

Table 2.1: Inclusion Criteria for Caregiver Interviews

Sample Size

Purposive sampling was intended, to recruit a representative group of people with HD who experienced the full range of apathy subtypes in this research; however, none of the participants who completed the online questionnaires met criteria for the executive and social subtypes of apathy as set out in the inclusion criteria. Furthermore, barriers to participation described in the Results section below, made participating in interviews difficult for some caregivers. As such, a pragmatic approach using convenience sampling was adopted to recruit those willing and able to take part who met the criteria for any subtype. As the purpose of this research was to prompt discussion about the psychological impact of apathy on caregiver experiences and not to generalise to a wider population, and in line with a critical realist approach where experience is believed to be partially constructed by the individual, data saturation was not considered to be an appropriate nor achievable method of determining sample size (Braun & Clarke, 2021c).

Interviews

Semi-structured interviews lasted for one hour and were conducted online via Microsoft Teams©. Only the caregiver joined the interviewer online for the interview although, for pragmatic reasons the pwHD was often present elsewhere in the house. Where this occurred, measures were

taken to ensure interviews were conducted in a separate room where the carer would not easily be over-heard.

Care was taken to provide a safe, non-judgemental space. In the interest of establishing a good rapport, a detailed description of the interviewer's background and motivation for the research were shared before starting. At the start of every interview consent was revisited and there was a discussion about what to expect during the interview.

An interview topic guide (Appendix D) was used which focused on creating a shared understanding about what caregivers meant when they talked about apathy, how they experienced the pwHD's apathy and the meaning they constructed of it. Particular attention was given to prompting the discussion of emotional and social apathy. Caregivers were encouraged to shape the direction of the conversation through the use of open-ended questions and prompts.

Interviews were recorded and transcribed verbatim by the interviewer (SLM). Reflective notes were made at the time of the interview and used to help with the reflective process during analysis.

Analysis

The six phase process of Braun and Clarke (Braun & Clarke, 2022b) was used to reflexively analyse the interviews, with the research team iteratively moving through the following phases in a non-linear fashion: (1) familiarisation with the data, (2) generation of initial codes, (3) generation of themes, (4) reviewing potential themes, (5) defining and naming themes, and (6) producing the report. Particular attention was paid to caregivers interpretation and understanding of their lived experience.

Transcripts and video recordings of the interviews were reviewed synchronously to achieve a deep familiarity with the data. Transcripts were read and re-read. Initial coding was completed by a

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single researcher, SLM, as is good practice for reflexive thematic analysis (Braun & Clarke, 2022b) as it promotes depth and rigour of engagement and facilitates the meaning- making and interpretive process, before being discussed within the research team. A reflective diary was kept throughout to document the analysis process.

Coding was completed manually using Microsoft Word and Excel, as was the preference of the research team. Data were coded inductively initially and then deductively to ensure alignment with the research question. Semantic and latent coding were used, with semantic codes typically evolving into latent codes during the analysis process as they were adapted and augmented to capture the nuance of the caregiver perspective, as interpreted through the lens of the first author (SLM). Themes were generated based on the relationship between the codes and collaboratively reviewed within the research team to sense-check ideas and further develop the interpretation of the data and increasing the rigour of the analysis (Yardley, 2000). Consistent with a critical realist approach, caregivers were offered the opportunity to review the themes extracted from their individual interview, to check that resonance of the findings and improve the credibility of the work (L. S. Nowell et al., 2017).

Results

Participants

To characterise the sample and aid sensitivity to context (Yardley, 2000) demographic details of participants are included in Table 2.2. Details of the pwHD were not collected as the focus of the research was on the HD caregivers.

Twenty-three caregivers completed the online questionnaires. All eligible participants were invited to interview. Interviews were completed with 12 caregivers (49% of those invited) although only 11 interviews were included in the analysis due to technical issues with the sound on one interview preventing transcription. Caregiver commitments and difficulty finding a time location

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away from the pwHD were the main reasons for eligible caregivers not participating in the interviews.

Ten females and one male caregiver participated in the interviews. Of these, 10 were a spouse, and one was a parent of someone with HD. Two caregivers felt that they were able to share their caring responsibilities with someone else whilst the remaining nine where the sole carer for the pwHD. Five caregivers scored the pwHD above the clinical cut-off on the initiation apathy subscale only while six scored the pwHD above threshold on the emotional apathy subscale only. Seven caregivers scored above clinical threshold for caregiver burden based on the Zarit Caregiver Burden Scale.

	Gender	Age*	Relationship to pwHD	Years caring for pwHD	Cohabiting with pwHD	Knew the pwHD before diagnosis	Apathy subscale[$$]	Caregiver burden score **
1	F	50-59	Wife	0	Yes	Yes	Initiation	18
2	F	30-39	Fiancé	2	Yes	No	Initiation	34**
3	F	50-59	Wife	5	Yes	Yes	Emotional	23
5	F	60-69	Wife	6	Yes	Yes	Emotional	17
6	F	50-59	Wife	9	Yes	Yes	Emotional	30**
7	F	50-59	Partner	4	Yes	No	Emotional	29**

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8	F	50-59	Mother	8	Yes	No	Initiation	37**
9	F	50-59	Wife	7	Yes	No	Emotional	26**
11	F	40-49	Wife	20	Yes	Yes	Emotional	12
12	F	70-79	Wife	10	Yes	No	Initiation	26**
13	M	50-59	Husband	18	Yes	No	Initiation	36**

Table 2.2: Demographic Characteristics of Interview Participants

* Age range provided to maintain anonymity

** Zarit Caregiver burden, clinical cut-off ≥24 (Schreiner et al., 2006)

$$ Determined by scores on the c-DAS/c-AMI. All participants rated the pwHD above clinical threshold on the initiation subscale. Where they also scored above threshold for the emotional subscale they were classified in the emotional group.

$ Doesn't consider themselves to be a carer.

Key Themes

The following five key themes reflecting the caregiver experience were identified from the interviews:

(1) 'What even is apathy?'

(2) 'It makes my life harder',

(3) 'They haven't forgotten me, but they have forgotten that they ever loved me',

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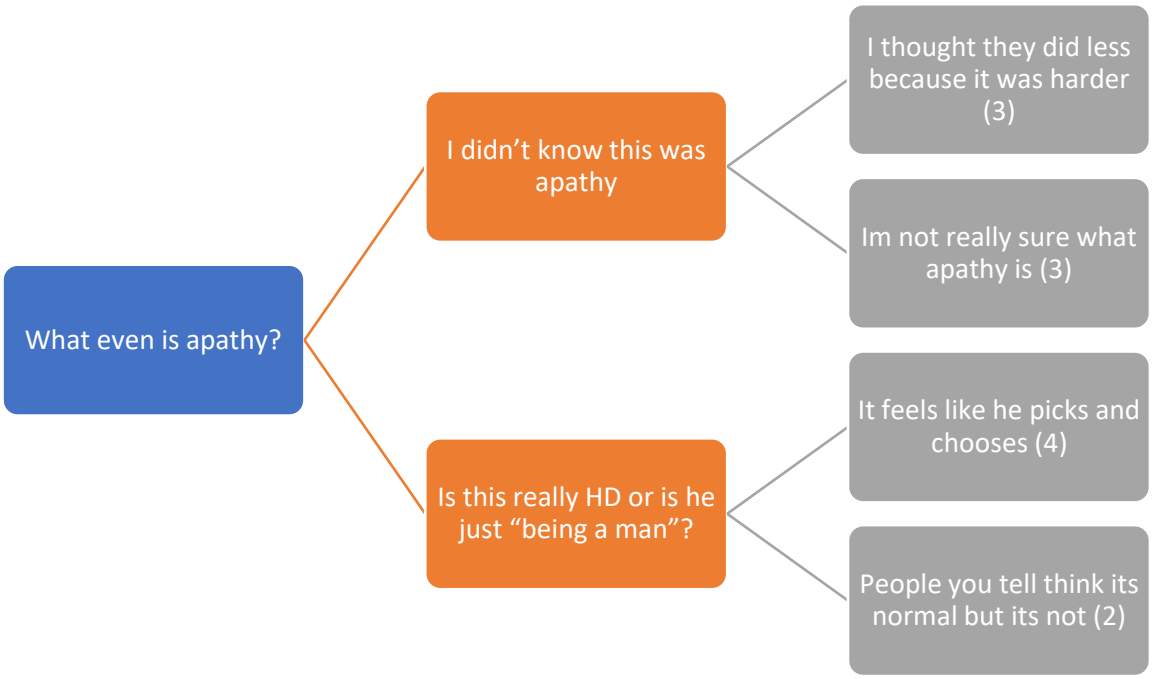
(4) ‘I’m grieving for someone who hasn’t died yet’, and

(5) ‘I need a safe space to say what I really feel without fear of judgement’.

The themes are detailed in figure 2.1 and described below.



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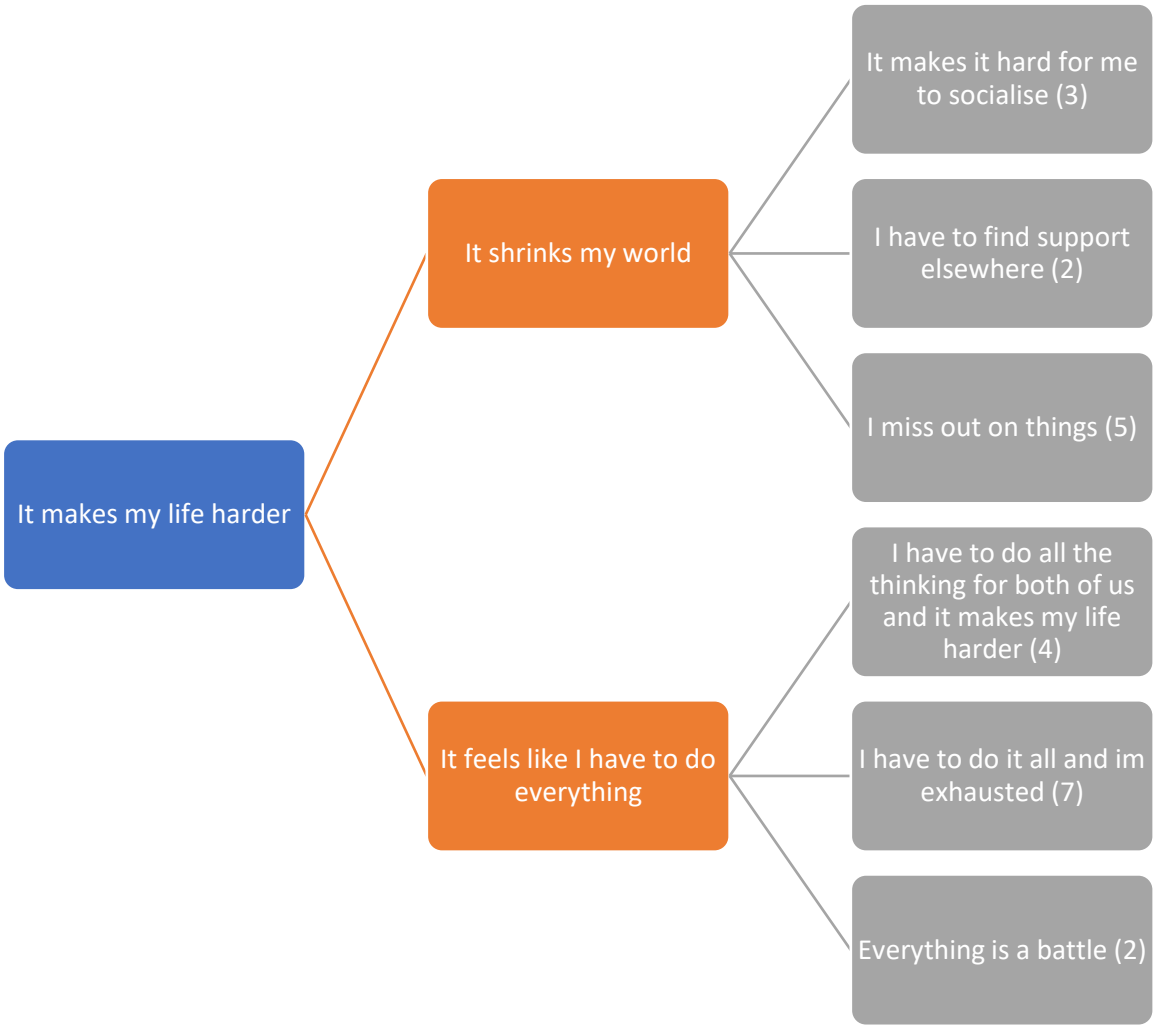

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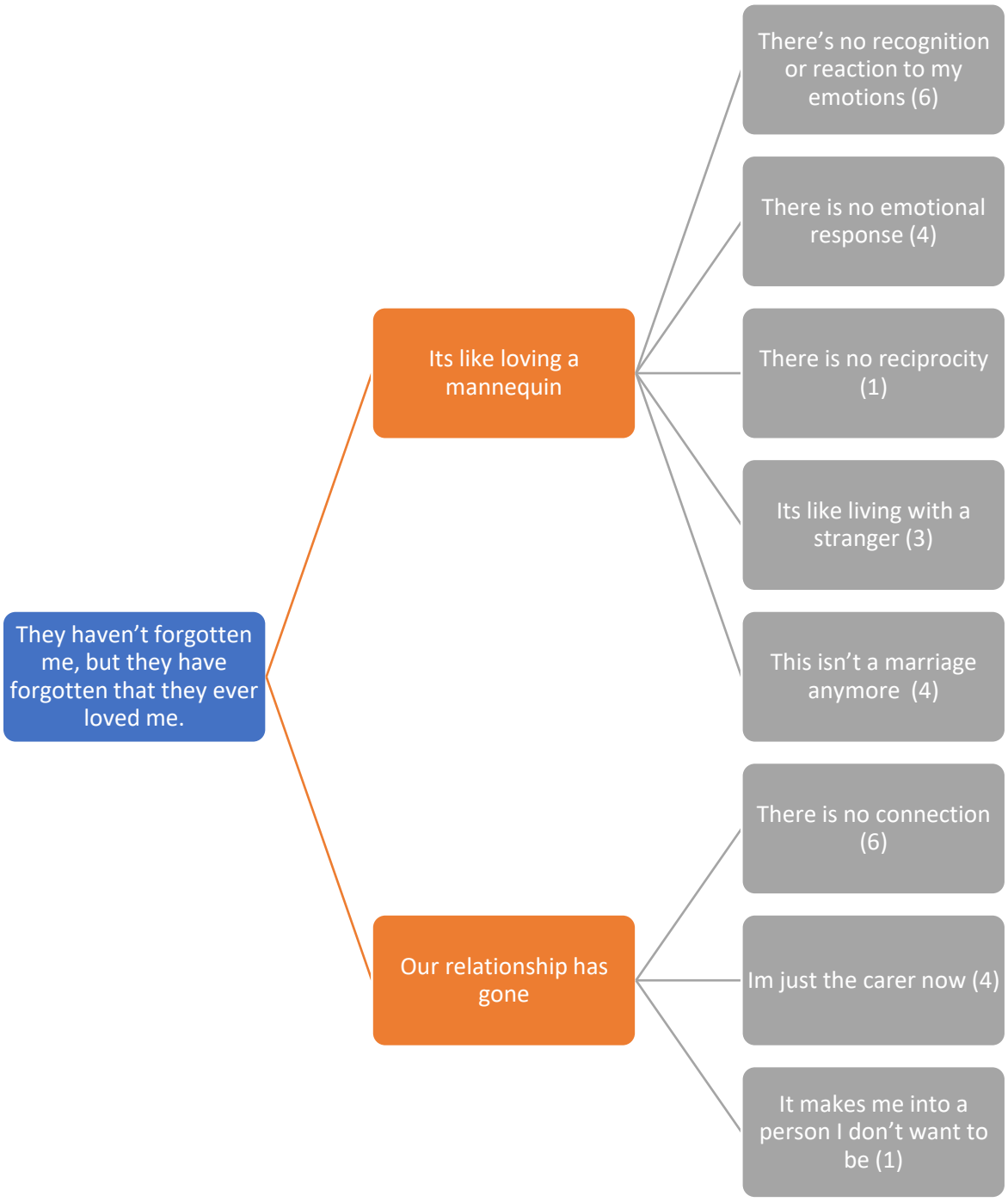

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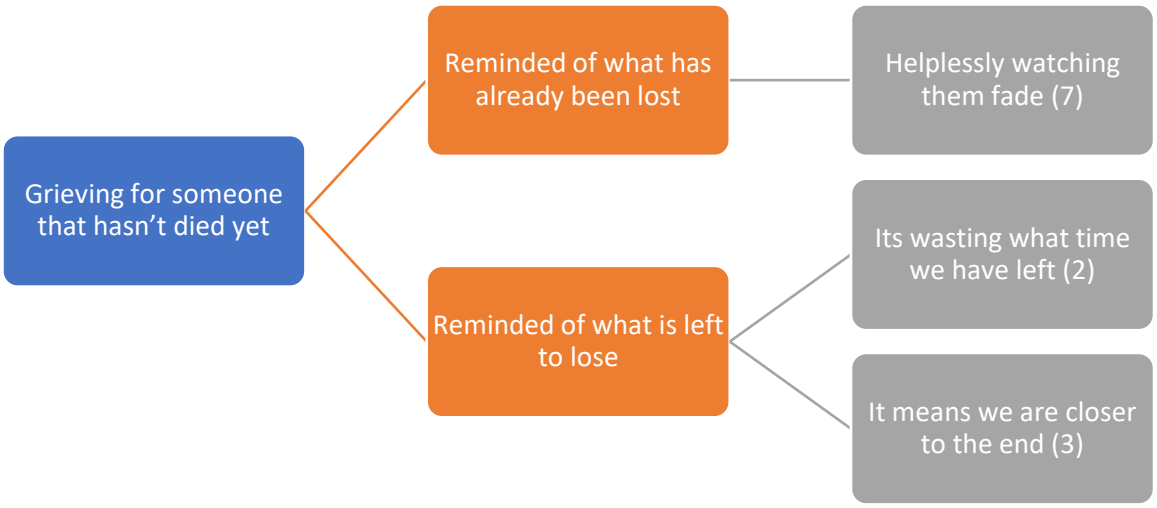

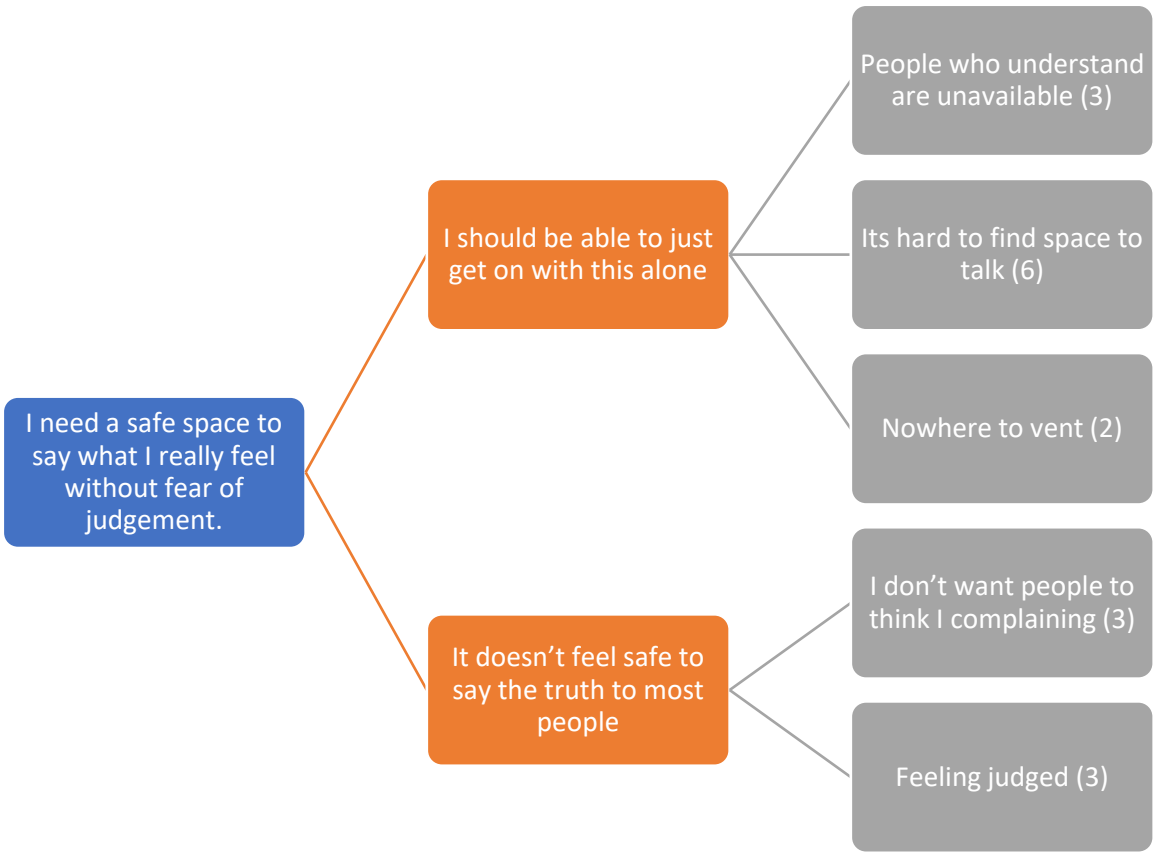

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Figure 2.1: Keys themes and sub-themes

Numbers in brackets () indicate the number of participants contributing to that sub-theme.

Theme 1: What even is apathy?

This theme draws together complex narratives about how apathy is clinically defined, subjectively experienced and socially constructed. More than just a reflection on a lack of understanding about what apathy is and is not, it combines discussions about how HD caregiver meaning making is shaped both by their own experience, the remnants of previous relationship dynamics and the influence of gendered social discourse brought by others around them. Caregivers reflected on their perceptions of the word apathy as a clinical term, with a formal definition, that they do not know. Despite eloquently describing apathy observed in the pwHD they support, caregivers often did not feel confident in their own understanding of the term "apathy", as expressed by Participant 1:

> That's a good question: What is apathy? I don't really know now, I should have looked that up really. [Participant 1].

This was especially apparent when considering behaviour that would fall within the social and emotional subtypes of apathy. Caregivers recognised traits that would fall into these subtypes but reflected on how they had not previously considered them to have been apathy:

> I probably wouldn't have thought of that as apathy but it's very much evident in him. Yes, the emotional side of him, I think we lost in his teens [Participant 8].

Interestingly, based on the c-DAS scores, five caregivers indicated that the pwHD they supported scored highly on initiation apathy, but not emotional apathy. However, four of these went on to

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discuss behaviour consistent with social and emotional apathy during their interview. Often these behaviours were made sense of as an understandable consequence of other features of HD:

> I don't think it's a lack of motivation, I think it's something… would it be cognitive? [Participant 11].

Others made sense of it as a result of the emerging symptoms of the disease impacting *"confidence in [their] own abilities"* (Participant 2), or as a way of avoiding the embarrassment felt from the awareness that other people may notice the emerging symptoms of the HD:

> He doesn't video call them, he just messages, so he's not having to present himself [Participant 2].

The narrative constructed by this participant was one of withdrawal and social avoidance as an understandable coping mechanism to deal with the shame felt as conversations became harder and choreic movements became more visible. Here the lack of understanding that apathy could result in social isolation leads her to draw upon her own feelings and emotions when observing her fiancé in social situations to make sense of his behaviour:

> I think it's his appearance in public that he worries about, although as I've said, he doesn't notice people's staring at him. [Participant 2].

Often caregivers talked about their difficulty accepting that the lack of initiation was involuntary:

> It's not because he isn't capable, 'cause he is, he's not that far gone that he can't function, but I don't know, I don't know. [Participant 1].

Many discussed the internal dilemma of trying to decide whether the lack of initiation and emotional lability they saw was a part of HD or *"just being a man"* (Participants 1, 5, 11, 12). Even if this was not

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their own understanding, caregivers described how friends and family failed to see this behaviour as apathy, or even as anything abnormal, which left the caregivers feeling invalidated and unheard:

> Sometimes you feel like you don't wanna say anything because they don't always understand what you're saying. A lot of them say, 'Ohh yeah, my husband's like that. He never knows what he wants for dinner.' And I have to say, 'Ohh yeah, I know a lot of men are like that.' But this is different. [Participant 6].

By not framing this behaviour as 'apathy,' caregivers and those around them, drew on social discourse about gender roles and intentionality to construct their meaning-making. The consequence of conceptualising the behaviour on a spectrum of "normal" male behaviour was that the impact and meaning constructed by caregivers was invisible to the rest of the world. The complex interaction between their own sense-making, the gendered social construction and the belief that their experience was trivialised by others, led to feelings of anger and frustration. This was complicated further when inconsistencies in the pwHD's behaviour fuelled the impression of choice and control on their part:

> Sometimes I just wanna scream! Sometimes I do yell, you know, just like: 'Why can't you do it? If you can push the garden mower you can push the hoover! [Participant 5].

During the interviews, some caregivers retrospectively reappraised their companion's behaviour, as a result of developing a broader understanding of the multifaceted nature of apathy. Locating the problem outside of the pwHD seemed to make the experience feel less personal:

> I was more... I liked her more than she liked me, if you know what I mean. That was what I saw. I think in her mind she was like the sort of the superior one and I sort of understood that was the dynamic of the relationship and that didn't make me feel great but I think

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> looking back, a lot of that was to do with the very early stages of the mental side of the disease. [Participant 13].

Theme 2: "It makes my life harder"

There was a general consensus that apathy made it practically harder to be a caregiver. The pwHD's lack of initiation to engage in daily activities meant that caregivers needed to do more to keep life going and several reflected on how exhausting they found it (Participant 2, 5, 6, 7, 9, 11, 12):

> Oh yeah, I'm the gardener, the painter, the cleaner. [Participant 12].

> He thinks he can sit there and I will do everything… He'll say, 'Cup of tea?' but he means he wants me to make it! [Participant 12].

> You know, I do everything at home. I go and walk the dog and then I come back in. I do tea. I clear up, I do everything on my own. I've got to, I feel like I am on my own. But then I'm looking after somebody as well. You know what I mean? So yeah, it's sort of, yeah. I just just feel weary all the time. [Participant 6].

It wasn't just having to fit more into a day that exhausted caregivers. Many talked about the impact of being the only person doing the thinking, planning and decision-making where previously this had been shared (Participants 1, 5, 7, 11). The increased mental load left some feeling like they had no mental capacity left to think, it was literally *"draining [their] brain"* (Participant 1). Juggling this on top of all of normal family life that was expected to continue, felt overwhelming, and on occasion they found their frustration difficult to contain:

> I'm thinking and doing everything for him. And I did, say, I know I shouldn't, but sometimes you can't help it, I just said 'Oh my God. You know, you're just so draining'. I know you probably, you think 'ohh dear, that's a bit harsh' but some days because, I'm at work, I'm

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> trying to support my mum, I've got my oldest, I've got my youngest son still here, I've got my daughter and we're very family orientated. God, Can someone just not drain my brain for once? Can I just please… you know? [Participant 1].

Whilst some caregivers recognised that this was part of caring for someone with HD, others found it hard to accept and tried to motivate their companion or force them to complete at least the most routine activities, such as personal hygiene. Often this resulted in conflict which left them feeling like life had become a battle:

> Sometimes I have to shout at him to get him to respond. And I say to most people, I'm not a person that wants to control. I'm not a controlling person. But I have to be, to a certain degree, and if he was to follow my instructions life would be easy. [Participant 12].

On top of making caregivers' lives busier, some felt that the apathy contributed to their feelings of being alone and unsupported. They reflect on how the lack of interest the pwHD showed towards their feelings or emotional wellbeing, left caregivers without the normal emotional support that exists within a healthy reciprocal relationship and also made it harder to find that support elsewhere:

> I don't feel I have emotional support from him at all. Not at all. That's just all gone, [Participant 1].

Several talked about how their companion's reduced engagement in social situations meant that their own social contact was reduced as a consequence:

> He didn't want people round the house so he'd say, 'Can you put your parents off this weekend' or, you know, 'I can't cope with the kids this weekend' or then he thought he couldn't cope with their kids, my grandchildren, so I didn't have them round as often [Participant 6].

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Caregivers described finding their companion's disengagement in social situations and lack of consideration for other people's feelings rude and so avoided going to social events with friends and family through fear of offending someone. Those who did try to keep up social contact described worrying that their friends would slowly drift away:

> I mean, he's not good in many social situations. He can come across quite rude, and obviously he doesn't mean it…It's like we've got friends we used to go out with quite a lot, got another couple, and I was concerned that they were gonna stop cause I felt like they were going out with other couples instead of us. And again, that's upsetting [Participant 9].

This left many caregivers feeling like they had missed out on things they wanted to do because of the apathy. Some shared feelings of being forced to live a life that they didn't chose nor, want which at times led to feelings of resentment:

> I'm retired, I should be, you know, I was fortunate enough I was able to take early retirement 'cause I had two decent pensions and I'm like, sitting here. I want to live, but I want, you know, I want to live with him as he was…I feel like my life's going too ([Participant 5].

For this caregiver, the social context of age and the expectations of retirement add to the nuance of their experience of apathy.

Theme 3: They haven't forgotten me, but they have forgotten that they ever loved me

Almost every caregiver described feeling like the relationship they had with the pwHD had diminished as a result of their apathy. The loss of the relationship was often described in a way that was consistent with the experience of a relationship breakdown:

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> I did feel the fact that she wasn't as interested in doing the same things at home as well was quite, you know, upsetting in a way because you sort of feel that, like diverging. You know, we've got nothing in common sort of feeling. [Participant 13].

The discord between social narratives around dementia and HD caregivers' experience of apathy made several caregivers feel that the loss of relationship was more personal and less understandable. They described how it made sense to them that a relationship would change if one half of a couple no longer remembered a shared past but, when the memories were still there it felt more about the relationship itself:

> It's not like the memory's gone completely, but they just see you in a different way. They sort of, yeah, relate to you in a different way. [Participant 6].

One caregiver described how this left her feeling discarded:

> You feel a little unwanted because you're not wanted in in that particular way [Participant 7].

Caregivers frequently described how the emotional cues that normally signify an intimate connection had dissipated as a result of their companions' apathy. The absence of these subtle, implicit, nuances left some caregivers feeling unloved by the pwHD, even when they were told otherwise:

> If I said to him, do you love me darling, he'll go 'course I do'. He'd say like 'yeah, absolutely'. If you asked him he'd say yeah with no doubt, I do. But he can't feel that. [Participant 5].

For one caregiver, contrasting her husband's apathy with the way he used to act towards her only highlighted what she had lost. Her experience of apathy was shaped through the lens of memories of an openly loving relationship that was no longer present:

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> When we were first together he was the one that was more keen than me, shall we say, and he showed so much affection. I know when you're young and new relationships are always all loved up, but he was the one that used to share affection more. But that's completely gone now and that's why it's probably worse [Participant 9].

For some, the lack of reciprocity or having *"no one to bounce off of"* (Participant 12) made them feel lonely and like they were sharing their life with a stranger:

> Normally it's a two-way thing, isn't it in relationships? And you know, maybe one has more in the relationship than the other but it's like it's not really a relationship anymore like that husband and wife, really. [Participant 9].

Whilst for others it was the lack of physical intimacy or physical demonstrations of affection that triggered feelings of rejection:

> If you said to me when did you last kiss? Ohh, he might give me a peck on the cheek if I'm going out without him but usually has to be forced. I have to go and kiss him, and quite often he'll back off. And not, you know, I'm say what's that about? And he'll be like, well I don't know? [Participant 5].

> It's very rare that we would even have a hug now, and there was lots of physical contact. There weren't just sex, but the physical contact. [Participant 7].

> It's hard as a mum to watch when your child has lost that ability to be affectionate. [Participant 8].

The loss of emotional reactivity was frequently interpreted as evidence of the pwHD's disengagement from the relationship and proof of its one-sided nature. For some caregivers this

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brought sadness and resignation and for others it caused anger and frustration, making them question why they continued to pour their love into an emotional void:

> When we got back to the car I had said, (so I give [her] a nice hug or something) 'this has been nice. Ohh I love when we're together on holidays', and she didn't respond. She didn't say anything… there's no interaction, you you sort of think well, why am I doing this. I'm not getting any anything back [Participant 13]

As a result, many of the caregivers described feeling like they were no longer in a reciprocal, loving marriage but had transitioned into the role of carer or acquaintance, which were both built around functionality rather than affection:

> You know, it's so I'm only doing it in the same way as, you know, if you, I suppose if you're a nurse in a hospital looking after somebody. It's it's just a job, isn't it? [Participant 13].

This came with a sense of sadness:

> I get a bit more upset now because I feel like I'm no longer his wife anymore. I'm just this person in the house that does everything for him. [Participant 6]

but also confusion, as caregivers struggled to make sense of their own identity within the relationship and to understand what role was available to them if being a wife was no longer an option given social expectations of what constitutes 'being a wife':

> Without intimacy this isn't a marriage, so what are we? [Participant 7]

Anger and resentment were commonly felt as caregivers reflected on their lack of choice in the transition. One in particular, shared a palpable sense of feeling disenfranchised and powerless in the change:

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> I don't want to be his mother. I don't want to be his carer. I don't want to be. You know. I just want to be his partner [Participant 7].

Whilst for another, it was the contrast between her own experience of caregiving and that of her sisters who supported their husbands with different illnesses, that made her reflect on the unfairness of this aspect of HD:

> My sister's both have lost their husbands. I've got two sisters. Both have lost their one had or the both had cancers, various cancers one suffered for years and years with it. But right to the end, they went up and down in their illness. But they always cared about their wives. Always was more concerned about their wives, made sure their wives were alright. Wouldn't tell them sometimes because they would be more worried. They're concerned for them and all that and. You know that's. I know I haven't got it. I know he doesn't feel like that. [Participant 12].

Theme 4: I'm grieving for someone who hasn't died yet

Throughout the interviews there was a general sense of sadness expressed by the caregivers. Many found the experience of watching the pwHD slowly drift away in front of them hard. This was mixed with a sense of hopelessness at their inability to make things better meant that even those caregivers who appeared to be composed throughout, became emotional and tearful at points:

> I joined groups all across the world trying to look for a for a cure to see if there was anything anywhere anyone had tried and made a difference. And but no, I couldn't do anything for my child and I, you know, I'm still at that stage. Where I can't make it better. And I think that's the hardest thing for me to live with [Participant 8].

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> I don't always talk about it, but, yeah, quite upset. It could get upset and it does upset me now, when I talk like that, but I don't very often and I'm not an uncaring person, but I'm not a water box. [Participant 11].

For some caregivers, the loss was very much tied up with the apathy. There was a sense that the lack of initiation, emotional reactivity and social engagement was paramount to the feeling of having already lost the person they loved and being left with a shell of their former self:

> Just feel like I've lost him somewhere in there. I think that's that's the only way I can describe it. I've lost him somewhere along the way [Participant 5].

> I thought, well, actually it's not that bad because, you know, he's still the same person. And then that was taken away. So it's sort of like a continuous grief. It's like losing somebody, you know, you lose one part of them. Then next minute you're losing something else of them [Participant 6].

For others, apathy was interpreted as the pwHD giving into the disease and giving up the fight:

> It's hard enough that the illness takes so much from HD. It takes so much away from a person with HD. Taking the motivation as well, it's kind of like giving up. And once they do that, it's like a very slippery slope [Participant 2].

Overall there was a shared belief that the presence of apathy acted as a reminder that the disease was progressing and with that, they are getting closer to the end of their HD journey:

> It's it's really difficult to watch. Um, because it's almost like. I felt I'd lost him when I got the diagnosis. And I'm and I feel like you start grieving for them. Before they've even gone. Because you know what's gonna come. And then watching every, you know, every time

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something different happens, you watch a little bit more of them go. And you just know that it's coming closer and closer to the time, when they will die [Participant 8].

Theme 5: I need a safe space to say what I really feel without fear of judgement

Talking openly and honestly about their experience of supporting someone with HD was difficult for every caregiver that took part in the study and was not something they typically made space to do. The expectation was that *"you just have to get on with it"* (Participant 1) but caregivers describe how coping alone was difficult:

> That's hard, that is hard sometimes, cause, you know you have no way of venting [Participant 5]

Some described feeling guilty and selfish for thinking about their own needs and worried that other people would think they were *"complaining"* (Participant 6):

> Sometimes what I'm saying and talking about becomes like, ohh, she's nagging again. Or she's, you know. So I try not to say certain things [Participant 12]

> Not that I want to go on about it because I don't and I'm not a person that wants to keep bringing things up [Participant 1].

Finding the time and space to talk openly was difficult. Caregivers were all sensitive to their companions' feelings and generally did not want to speak in front of the pwHD through fear of saying something that may upset them. This added to the expectation that they should suffer in silence:

> You can't open up because you think if he's listening, he's gonna be upset by what you're saying. Because sometimes you feel like you're complaining [Participant 6].

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There was a general consensus that people outside of the HD world, knew and understood very little about what HD was and what it was like to live with it:

> I've done my research and I kind of know what to expect. But until you're actually in the situation, I don't think you understand the level of how HD affects people [Participant 2].

Previous experiences had left a few caregivers feeling judged after voicing their true thoughts and feelings. There was a recognition that the complexity of caring for someone with HD made it difficult to understand and empathise for anyone who hadn't lived with HD.

> Because if you say it, it's out of your head then. And the person in front of you isn't going to judge you about it. As at some point, they might have felt exactly the same [Participant 8]

However, this was further complicated by the recognition that that whilst other HD caregivers may be the only people who truly understood their experiences, talking to them felt like burdening someone, who they knew from their own experiences, would already be dealing with so much:

> I just think, well, people have got their own crap to deal with. It's not fair to burden them with that [Participant 1].

For many, the interview provided a safe, non-judgemental space to reflect on their experience of caregiving, that they did not have elsewhere. For some, the value of such a space only became apparent during the interview:

> I would like to meet people in similar situations and I've never ever thought that until this conversation, to be honest [Participant 1].

Taking part required caregivers to explore their thoughts and feelings in a depth that many had not given themselves permission to do before:

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I do talk to my friends, but you don't talk like this, do you? Where you explain [Participant 5]

The process of collecting their thoughts and formulating them in a way that could be shared, along with being given permission to approach rather than avoid difficult feelings, appeared to help caregivers process their experiences in a therapeutic way. This prompted suggestions that access to psychological therapy may be a welcome support for caregivers:

Like talking, talking therapy, would, you know, I think would be useful [Participant 2].

Discussion

To our knowledge, this is the first study which has sought to understand HD caregivers' experience of, and the meaning they construct regarding, apathy in HD. Reflexive thematic analysis produced five main themes concerning: uncertainty about how the clinical definition, subjective experience and socially constructed meaning of apathy fit together; the practical impact of apathy, with the expectation that caregivers do more than their share of daily tasks and hold more of the mental load; the emotional impact as apathy becomes synonymous with a gradual loss of the former relationship; grief for someone who hasn't died yet; and the need for a safe space to talk openly about the impact of caring for someone with HD, without fear of judgement. Interwoven between these themes were complex narratives about the unspoken nature of HD, the invisibility of caregivers who felt trapped and unheard, and the one-sided nature of loving someone with the disease. Caregivers described feelings of sadness, frustration and anger as they reflected openly and honestly about supporting someone with HD who had apathy, despite being often unable to voice these feelings in their everyday lives in part through fear of judgement and in part through lack of time or opportunity. The nuance of caregivers' subjective experience was expressed as they shared deep and personally meaningful insights into their sense-making.

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Caregivers described in great detail and with intense emotion, how they saw apathy as synonymous with the parts of the pwHD that they had lost as a result of the disease process. Apathy was viewed as both the mechanism through which this loss occurred and a reminder that they no longer had access to the person they once knew, the companion they once shared their lives with and the future they had expected to have. These feelings were constructed as part of an early and prolonged grieving process, consistent with the concept of anticipatory grief (Chan et al., 2013).

Anticipatory grief is well understood within the field of dementia research but has only recently started to receive attention in the world of HD (Leidl et al., 2023). Between 47% and 71% of caregivers of someone with dementia report experiencing pre-death grief as a result of the "compound serial of losses" endured through the disease process (Blandin & Pepin, 2017; Large & Slinger, 2015). Lindauer and Harvath (Lindauer & Harvath, 2014) identified four components of the grief: the psychological death of the care recipient or loss of the person they used to be, the protracted and uncertain journey of dementia, difficulties communicating with the person with dementia and changes in the relationship. In the current study, all four components were discussed or alluded to as a consequence of the pwHD's apathy, not just the caregiving experience as a whole. It is unclear whether this is a distinct feature of anticipatory grief in the context of HD, but further understanding this relationship may provide an opportunity to both identify HD caregivers at risk of experiencing a more protracted grieving process and to utilise therapeutic strategies to reduce the emotional impact of apathy. Therapeutic interventions for anticipatory grief in dementia caregivers are receiving increasing attention in the empirical literature and implementation research is planned (Rupp et al., 2023). Work with HD caregivers could meaningfully contribute to this work.

The correlates of anticipatory grief in HD need to be understood. Pre-death grief has been reported at any stage of dementia, but it is typically found to be greatest in those supporting someone with moderate to severe disease (Adams & Sanders, 2016; Blandin & Pepin, 2017; Chan et

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al., 2013) where it has been shown to relate to caregiver burden (Gilsenan et al., 2023; Perez-Gonzalez et al., 2023). In the current study, caregivers were typically supporting people in the early stages of HD. There is significant evidence showing that apathy is an early feature of HD, sometimes occurring in the premanifest stages of the disease (Matmati et al., 2022) however, this is the first study to identify the importance if experiences in keeping with the concept of anticipatory grief in the context of HD related apathy. Furthermore, given that research on this issue is very limited, it is not possible to make any conclusions about the relationship between anticipatory grief and disease stage or the role of apathy, but it is perhaps an interesting observation that could be explored further.

Caregivers interpretation of the social and emotional apathy shown by the person they supported, led them to feel unloved and rejected. The absence of any emotional response or empathy for the caregiver's feelings, and lack of unprovoked signs of affection, both physical and verbal, were interpreted as disinterest and ambivalence on the part of the pwHD. Similarly, although not discussed in the context of apathy, reduced spousal intimacy is common in people who have sustained an acquired brain injury (Ponsford et al., 2012) where it is understood to be associated with the physical (Ponsford et al., 2012), cognitive and emotional consequences of the brain injury (Bowen et al., 2010). Breakdown of the loving pre-injury relationship has been associated with reduced emotional warmth and difficulties maintaining conversations (Yasmin & Riley, 2022); factors which overlap with our understanding of emotional apathy. Furthermore, the reconstruction of spousal reciprocity, partially linked to the ability to establish good patterns of communication, has been identified as a key contributing factor in marriage satisfaction following a stroke (Anderson et al., 2017).

Importantly, many caregivers described how the pwHD, when asked, still reported loving them as much as they always had. Understanding this disparity, and what leads caregivers to feel

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unloved, may help to identify ways to reduce the distress experienced by caregivers as a result of HD-related apathy. Frith and Frith (2023) suggest that "meaning" in a social context is "created through mutual adaptation and is a product of joint action". They propose that to successfully communicate meaning, both parties need to be reciprocally aligned in their verbal and non-verbal communication. Copying and responding to non-verbal actions such as eye gaze, gesture, speech sound, grammar and choice of words in a complementary way are fundamental parts of this process. People with HD typically experience difficulties understanding the actions and intentions of other people in the social world, even in the early stages of disease (Bora et al., 2016). Deficits in social cognition have been shown to relate to the social and emotional quality of life (Eddy & Rickards, 2022) and HD-related apathy (Fritz et al., 2018; Hendel et al., 2023; Kempnich et al., 2018). However, little is known, about how a pwHD expresses themselves in a social situation, or how this impacts their social relationships. In other disorders where emotional expressiveness is reduced, such as Parkinson's disease (PD) where the stoic masked face is a characteristic feature, and schizophrenia where negative symptoms are commonplace, similar feelings are reported by caregivers. A qualitative study of impaired non-verbal expressivity in people with PD found that facial masking led caregivers to think that the person with PD was emotionally unaffected by things, and unfeeling towards them. This led to reduced social connection and emotional distancing (Wootton et al., 2019). Similarly, people reported feeling less willing to engage in future interactions with someone with schizophrenia if they have reduced facial expressiveness, vocal prosody, gesturing and quality of spoken language (Riehle & Lincoln, 2017). In the neuropsychological rehabilitation literature, strategies to remediate the impact of deficits in social cognition have been described (McDonald & Cassel, 2017; Spikman et al., 2022). Although this work has not yet been applied in HD, future research is needed to determine whether similar approaches could also be effective here.

Caregivers talked about not knowing what behaviours were included in the definition of apathy and what were not. Many didn't include behaviours that would fall under the umbrella of

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social and emotional apathy, in their understanding of apathy. This is consistent with findings from a recent qualitative study which reported that people living with a neurocognitive disorder and their caregivers, were unfamiliar with the term “apathy” and also found it difficult to explain apathetic behaviour despite it being a significant feature of their condition (Burgon et al., 2023).

Regardless of which subtypes of apathy were endorsed by caregivers on the c-DAS, the impact of social and emotional apathy was discussed by every HD companion, at some level, during the interview. Here, in the absence of understanding the behaviour as apathy and/or part of the disease process, social rules and norms were used to interpret the social avoidance and lack of emotional reactivity in the same way that it would be understood in someone without HD, as a product of free will and choice. This was amplified by the incongruence between the lack of physical signs of HD and high levels of apathy seen by caregivers, which were taken as evidence that these behaviours were independent from the disease process. Situating the locus of control for social and emotional apathy, within the pwHD coupled with perceptions of conscious control, understandably led to feelings of anger and frustration.

Psychoeducation is a tool widely used in neuropsychological rehabilitation to help families understand and anticipate the specific implications of a brain injury by creating a sense of empowerment and shape realistic expectations which has been shown to improve quality of life for the family as a whole (Kitter & Sharman, 2015). Using psychoeducation to help caregivers understand apathy as a normal part of the HD disease process, including an understanding of social and emotional apathy, may help caregivers to feel more validated and develop more adaptive attributions, locating the problem firmly with the disease process.

The experience of apathy expressed in this study appeared to mirror caregivers’ experience of HD in general – never discussed, hidden from view and dealt with alone. When discussing apathy with family, friends or even healthcare professionals, HD caregivers reported feeling unheard and

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unsupported. The lack of understanding shown about their experience, left them believing that it was not "socially acceptable" to struggle in response to the apathy. Similar themes have been described by HD caregivers following the genetic testing process (Sobel & Cowan, 2003; Sobel & Cowan, 2000) (Decruyenaere et al., 2005) where the invisibility of the disease contributed to caregivers experience of disenfranchised grief (Doka, 1989). Furthermore, apathy was not even discussed between the caregiver and the pw HD with many caregivers going to great lengths to conceal their participation in the research. Although intended to shield the pwHD from the potential distress of feeling blamed for the impact of their apathy, this reluctance to talk openly about apathy within the family removes the possibility of using neuropsychological rehabilitation strategies for both the pwHD and the family to develop more adaptive patterns of behaviour to counteract the impact of apathy for the caregiver.

Talking openly about the presence and impact of apathy with people with HD and their families is a simple way of starting to breakdown this stigma. Modelling and normalising the discussion of apathy would both empower people with knowledge about what they may need to deal with in the future and help to dispel the narrative that caregivers should be expected to cope with this distressing aspect of HD alone. Exploring what the barriers are that currently prevent people from talking about apathy could facilitate this work. In particular, understanding the social discourse around apathy and whether there is a taboo or shame around judging someone to have apathy, may inform our understanding of why clinicians do not routinely discuss apathy and why friends and family try to minimalize the caregiver's experience of apathy in the pwHD.

Strengths and Limitations

The quality assurance for this work was guided by Yardley's four principles of sensitivity to context; commitment and rigour; transparency and coherence; impact and importance (Yardley, 2000). Sensitivity to the caregiver experience was integral to the design and conduct of the study,

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with adaptations made to facilitate participation and particular attention given to establishing an authentic rapport between caregivers and the researcher. Reflexivity, reflection and detailed record keeping were used throughout to attest to the rigour and transparency of the work, while the richness of the quotes included is testament to the impact and importance of the work.

Limitations of this study include the challenges of recruitment and the impact of the COVID-19 pandemic. The study was conducted following the COVID-19 pandemic, when restrictions had been eased in the UK. The impact of restrictions on social contact, on the emotional well-being of caregivers of people with dementia has been widely reported (Hanna et al., 2022; Manca et al., 2022) and should be mindfully considered when interpreting the results of this study. Wider restrictions on the social contact available to HD caregivers over an extended period of time may have changed caregivers' awareness and response to the pwHD's reduced emotional responsiveness, empathy and social behaviour. Furthermore, as a piece of qualitative research the intention was not to assume that HD caregivers are a homogeneous population nor that the findings of our study could be generalised to the wider population; however, having a larger sample, or a similar size study in a different country or socio-economic context, may have generated alternative themes that could be relevant to a wider group of HD caregivers. Specifically, due to practical constrains recruitment was limited to three UK sites, interviews were only held online and despite our best efforts, caregivers of all apathy subtypes were not represented in the sample, though it is recognised this may be a reporting artifact on the part of the caregivers rather than a true reflection of the apathy subtypes represented. It should also be acknowledged that only approximately 50% of caregivers who expressed an interest in the study were able to participate, therefore the voice of those who could not commit for practical or psychological reasons are not represented. These limitations were unavoidable in the current study but a future replication with a recruitment strategy that addresses these points would meaningfully contribute to our understanding of the impact of apathy for HD caregivers.

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Conclusion

Our study indicates that apathy makes life harder for HD caregivers. The distress they experienced was linked to an early grieving process and in particular the ambiguous loss of the relationship between caregiver and the pwHD. This was further compounded by caregivers tendency to draw upon wider social discourses about the pwHD's behaviour, and not understanding it as apathy which led to feelings of anger and frustration, as reduced social and emotional behaviour was attributed to the pwHD, rather than the disease process. Currently, apathy is an under-studied area of HD research that warrants further investigation. Future research should focus on determining whether existing strategies from the wider neuropsychological rehabilitation literature would help reduce the psychological impact of apathy on HD caregivers, including the use of couples and family therapy approaches. Co-producing this work with HD caregivers would help ensure it meets needs of this unheard and under-represented community and support services to better recognise the existential challenges experienced by caregivers.

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Chapter 3 – Extended Methodology and Reflexivity

Providing additional information on ethical considerations, recruitment, interviewing, quality assurance, philosophical stance and reflexivity

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Extended methodology

Additional information on the methodology used in the empirical paper is presented here, including further details on the qualitative research design. Discussion of my position as the researcher, how this impacted the reflexivity within the study and its role in the creation of "knowledge" are also included.

Ethical considerations

Potential for Distress

Both because the research topic had the potential to evoke strong emotions, and because of the significant strain experienced by caregivers in the study, the potential for distress was considered throughout. Using a topic guide (Appendix D) rather than an interview schedule allowed participants to determine the direction of the interview and move discussions away from areas they were unwilling or unable to touch upon. At the beginning of every interview, participants were reminded of their ability to pause or terminate the interview at any time, without providing a reason. If participants became distressed the interview was paused, they were supported and asked whether they wished to proceed. Whilst some did become distressed during the interview, no participant chose to terminate the study early. At the end of the interviews, participants were debriefed and reminded of the support that was available to them, such as their Huntington's disease (HD) clinical team, the Huntington's Disease Association carers support group and helpline, and the mental health emergency support via the GP (during office hours) and the First Response Service (outside of office hours).

Consent

Written informed consent was taken from all participants, prior to any study-related procedure being carried out. An online consenting procedure was used following the guidance in the

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HRA /MHRA joint statement on taking and documenting eConsent (Health Research Authority, 2022) (Appendix E). eConsent was chosen for pragmatic reasons, namely the capacity to read the study material at a time and place of the participants choosing. It gave caregivers the ability to fully engage in the time-consuming process of informed consent in a flexible way that they could fit around their caregiving responsibilities. Consent was revisited, verbally, at the start of every interview, and documented on the study paperwork.

Confidentiality

Attention was given to maintaining the confidentiality of participants at all times. All Personal Identifiable Data (PID) were handled in accordance with the UEA data governance policy (University of East Anglia, 2022). Correspondence was kept to a minimum and measures were taken to ensure participation was not disclosed to the person with HD (pwHD) or the HD clinic without the caregivers' consent. During the consent process, caregivers were made aware that their voice may be identifiable in the audio recordings (Appendix E) and that anonymised quotes may be used in the study manuscript.

Coercion

It was made clear throughout, that involvement in this study was voluntary and the decision to participate would not impact the clinical care provided to the pwHD (the care recipient). This was referenced in the Participant Information Sheet (Appendix F) and Consent Form (Appendix E) and emphasised verbally at the start of the interviews. Additional steps were taken to prevent coercion including a rule that no more than 3 attempts would be made to invite a participant to interview, and/or schedule an interview. Failure at either stage was taken as the participants way of communicating their wish not to participate.

Participant Recruitment

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Participant Recruitment Tools

Conversations with my supervisors CF and FG, and separately with RAB, identified the disparity between the lay and clinical meaning of the word "apathy" as a potential barrier to recruiting a diverse and inclusive group of HD caregivers to participate in the empirical study. Potential participants may have considered themselves ineligible for the study if their understanding, and our understanding of apathy did not align, and therefore not come forward for the research. To minimise the potential for the language used in the recruitment tools to inadvertently restrict recruitment, members of the HD community were approached to co-create a shared definition of apathy and common terminology for use in the study. Patient and Public Involvement has been shown to be a useful way to increase recruitment and retention into research studies (Crocker et al., 2018).

Patient and Public Involvement (PPI)

The use of PPI in this study is reported in line with the GRIPP2 reporting guidelines (Staniszewska et al., 2017):

Aim: To help create a common language to describe apathy with the intention of reducing a recruitment bias as a result of the lay perception of what is and is not apathy.

Methods: Members of the HD community were approached to share their understanding of apathy and the terminology they used synonymously with the word apathy. They were asked to complete a survey initially (Appendix G) followed by a telephone conversation if willing.

Study results: The results of the PPI questionnaires were collated and synthesised into a shared definition. The term "apathy" was preferred by the PPI group and defined as "a lack of motivation, interest or desire to take part in activities the person uses to do". This agreed language was used in all the recruitment material. An unintended result of the PPI was endorsement for the

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need and value of research into the impact of apathy in HD, which was offered, unprovoked, by several PPI members.

Discussion and conclusion: Uptake and engagement with the PPI was good with all six members of the HD community approached, agreeing to participate in the work. The consensus in the definition of apathy in HD and the agreed terminology was high.

Reflections/critical perspective: Members of the HD community were invited to participate in the PPI work but not caregivers. A shared definition of apathy, as a unitary construct, was formed however, the PPI group were not asked to consider the subtypes of apathy. In reflection, extending the work with the PPI group to include consideration of the subtypes of apathy may have helped recruitment for the initiation subtype which was absent in the empirical study.

Interviews

Topic guide

The initial iteration of the topic guide was developed through careful consideration of the empirical literature, my experience in the field of HD research and with reference to the research aim. The shared definition of apathy developed through the PPI was integrated into the proposed questions, as was the agreed language. The topic guide was reviewed and discussed with researcher RAB, an expert in HD research and clinical practice, and an independent expert apathy researcher and clinical psychologist, RR. Their feedback was integrated into the final version of the topic guide (Appendix D).

Interview design

Through collaborative discussion with the HD clinical team, and careful review of the literature relating to the conduct of interviews for rTA, the following adaptations were made to the interview design:

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(1) Interviews were offered in person at the caregivers home, online via Microsoft Teams or on the telephone (NHS England, 2023).

(2) Copies of the topic guide were offered to participants prior to the interview to reduce anticipatory stress, and allow for preparation time (Clarke & Braun, 2013). However, the additional time pressure intrinsic to preparation was acknowledged and caregivers were reassured that there was no expectation that they prepare for the interviews. Attention was paid to the necessity not to add to the burden of participation for the already time poor caregivers.

Finally, following feedback from potential participants at the start of recruitment, the option to hold interviews in a private room at the HD clinic in Cambridge, to coincide with the pwHD's clinic appointment, was introduced. This was in response to caregivers struggling to find time and space away from their caregiving responsibilities. The clinic appointment provided a unique opportunity where the pwHD was occupied without the need for the caregiver, and an environment where they would not be overheard. An amendment was submitted to REC for approval (Appendix H).

Quality Assurance

The guideline to guide good practice in rTA (Braun & Clarke, 2023b) was used to contribute toward the quality assurance of the empirical study. Furthermore, the four principles of quality assurance in qualitative research, proposed by Yardley were adhered to in the study as described in Table 3.1 below.

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Guideline	Steps taken
Sensitivity to context	• Flexibility with the location (home, HD clinic), medium (telephone, face to face, virtual) and timing (including evenings if requested) of appointments took into consideration the logistical challenges experienced by caregivers. Adaptations helped them to feel as comfortable as possible. • 1:1 interviews at times and locations that confidentiality could be assured allowed privacy when discussing their difficult experiences and personal reflection. • Genuine, authentic empathy was expressed for caregivers throughout the research process which helped them to feel safe and empowered to share their experiences (see section on "Reflexivity through the research process for further description). • Sharing the motivation for the study and my relationship to the HD community was a way of addressing the power imbalance between researcher and participant. It also helped to build trust and rapport.
Commitment and rigour	• Sampling was opportunistic • Reflexivity and reflection were used throughout, using supervision and a reflective journal to recognise and acknowledge the impact of my pre-existing experiences on the interpretation of the data (see section 3.4 for further detail). • Maintaining a commitment throughout to go against the convention of positivist research in line with the medical model.

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	• Analysis was systematic and iterative in nature. An audit trail of the analysis process was kept to promote rigour in the process.
Transparency and coherence	• Participants were offered a copy of the results, once finished, and asked to feedback their reflections on the resonance of the findings • Each stage of the analysis was document in supervision notes and the researcher's reflective diary. • Findings of the study were presented to HD research teams in Cardiff and Cambridge and their feedback used in the meaning-making process.
Impact and importance	• New knowledge about the experience of caregiving in HD has been generated, specifically regarding caregivers meaning-making around the impact of apathy. These findings provide future direction both for clinical therapeutic work and further research. • The research has provided a voice to individuals who were previously unheard. • The work can be used to draw attention to the caregiver experience in HD and promote discussions around a more systemic way of thinking about the disease.

Table 3.1: Quality Assurance – Strengths and limitations.

There are however, improvements that could have been made to the study that would have positively impacted the quality assurance. Consideration of the impact of socioeconomic factors that

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impact caregivers experience of apathy by recruiting a more culturally and geographically diverse cohort of participants would have improved the sensitivity to context of the study. Similarly, the commitment and rigour, although high in the study, could have been improved with further methodological competence that only come with experience as a qualitative researcher. Although this limitation was unavoidable it is worth acknowledging.

Philosophy and Methodology

Ontology and Epistemology

Ontology is a branch of philosophy that reflects on the nature of reality and whether or not it is theorized that an objective, measurable truth exists. Epistemology refers to the theory of knowledge and whether or not it is assumed to be possible to know the objective truth (Braun & Clarke, 2006; Clarke & Braun, 2013). Both exist on a continuum between polarised positions. A realist ontology maintains that an objective, generalisable truth exists, whereas a relativist perspective considers truth to be subjective and knowledge an individually constructed entity (Clarke & Braun, 2013). A positivist epistemology theorizes that truth is both measurable and accessible whereas constructionism considers knowledge to be context-specific, evolving and changeable depending in on both culture and experience (Madill et al., 2000).

In my previous research I adopted a realist ontology and positivist epistemology in the pursuit of scientific knowledge, as is typical in quantitative research (Braun & Clarke, 2022b). Reflecting on this work, aspects of these assumptions still resonated with me, namely, that there is a "reality" to HD that exists regardless of my perception for example, the presence of HD and, with reference to the empirical study, the presence of apathy as an objective, measurable disorder. However, my clinical and research experience led me to conclude that living with a pwHD who have apathy is both subjectively experienced and socially constructed.

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Critical realism, which is both an ontological and epistemological position (Fletcher, 2016) embodies this philosophical position. It acknowledges that a "true" reality can exist whilst also recognising that it is experienced through subjective perception (Clarke & Braun, 2013) that the researcher can only access through their own and the participants contextualised or constructed 'realities'. As such, the empirical study was designed and conducted from the position of a critical realist researcher.

Reflexivity

Reflexivity is the process through which the researcher recognises and takes responsibility for their own "situatedness" in the research (Braun & Clarke, 2019). It is the manner through which the researcher aims to "own" their own perspectives (Elliott et al., 1999) and communicate them to the reader (Braun & Clarke, 2023a). Reflexivity acts both as a strategy for quality control within qualitative research and a tool through which knowledge is generated (Berger, 2013). However, it is influence by the degree to which the researcher is "part of the researched and shares the participants' experiences" (Berger, 2013).

Researcher position can influence the research in three ways (Berger, 2013): (1) access to participants: people may be more likely to participant with a researcher they perceived to be informed and sympathetic to their situation, (2) researcher-participant relationship: there are characteristics that make people feel more comfortable to share their experiences, and (3) the background of the researcher influences the meaning-making that takes place both during and after the interview which can determine the findings of the study.

Having worked with people with HD (pwHD) and their families for a number of years prior to the empirical study, I was aware throughout that my background would have significantly shaped the empirical study. Consequently, rather than perceive this as a researcher bias as I would previously had done, I chose to use reflective Thematic Analysis to embrace, acknowledge and lean into my

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influence as a researcher on the “knowledge” constructed in this portfolio (discussed further in section.

Reflexivity through the research process

Reflections on what I brought to this work.

Prior to starting the Doctorate in Clinical Psychology, I worked first as a graduate and then postdoctoral researcher, for a combined total of seventeen years. My research focused on understanding the cognitive and psychological changes experienced by people who carried the gene for HD (Calder et al., 2010; Collins et al., 2015; Harris et al., 2019; Mason et al., 2015). As part of this work, I have always had an interest in understanding why a monogenetic disease manifests as a heterogeneous profile of cognitive and psychological symptoms. Working within a Clinical Neuroscience laboratory, much of this research focused on identification of modifiers (genetic or environmental) that could explain variability in the clinical profile of HD, in a predictable way, but this work never truly felt like it aligned with my own values as a person and a psychologist where I have always considered the nuance of individual experiences to be of the upmost importance. Over time I developed a growing insight into the challenges faced by families and the unmet needs of the HD community.

Part of my role was to provide the neuropsychological input into the NHS HD clinic where I worked clinically with people who carried the gene for HD and their families. The rare, genetic and slowly progressing nature of HD meant that there was a strong relational aspect to this work. Due to the length of the disease, people remain within the service for much longer than is typical within the NHS, for some this spans decades, providing robust continuity of care. Taken together, these factors allowed me to create a strong therapeutic alliance with both with the pwHD and members of their family. The trust and rapport that was built as a result allowed for open conversations about the impact of HD and consequently, I had the privilege of working collaboratively with pwHD, and their

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families, to design and conduct research that was clinically motivated and meaningful for the HD community. Starting the Doctorate gave me the opportunity to approach this research from a new perspective, one that embraced the experience of the individual rather than viewing them as part of a collective. This portfolio represents my journey from an experienced quantitative researcher into a newly established qualitative researcher.

Reflections during the research:

As part of this process I kept a reflexive journal throughout, two excerpts from which are provided below. The first contains my early reflections on my motivation behind the research and second, an example of my post interview reflections.

Example reflective journal entry regarding my motivation for the research:

> Working in the HD clinic I remember the desperation I saw in caregivers who were struggling to live with the person with HD who was apathetic. I also clearly recall talking to RAB about it and both recognising how the topic of apathy was avoided during clinic because of a sense of helplessness that we couldn't make it any better. It felt like understanding the problem better was a gateway to being able to make a difference.
>
> I remember one caregiver telling me a story about her husband. When she leaves for work in the morning he is sitting in his chair watching TV with the remote control in front of him. When she returns at 5pm he is still in the chair but now he is watching children's TV programs on the same channel. He has no interest in the program, has the capability to change the channel but hasn't. I distinctly recall her anger and frustration at this turn of event so I knew it has a big impact on her but I also remember feeling confused about why it caused her so much distress. Yet in other families, apathy was recognised and tolerated (at least on the surface).

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For years I have tried to understand why apathy is distressing for some caregivers and not for others. Maybe it relates to the different subtypes of apathy? Maybe it's about factors innate to the caregiver? Maybe it's about the strength of the premorbid relationship?

I have read other people's research, I have conducted my own research into the area, but the one thing I have not done is ask the caregivers… I wonder why?

Just asking (and I'm realising I have written "just asking" which I think tells me a lot about how I really feel about this at the moment!) feels unscientific, subjective and not robust but I can't think of any other way of answering this question.

Example of a reflective journal entry during the familiarisation process for Participant 8:

This is such a powerful interview. I cried so many times when listening to the recording and when reading the transcript. The pain and guilt felt by this mother and the raw grief that she so openly and honestly shared was beyond powerful.

Throughout the interview I felt compelled to find a way to share her story. To make people see how devastating HD is, how it destroys lives and how that destruction ripples out through the family.

I was conscious that I had intended to exclude JHD from this analysis however, although she met all the inclusion/exclusion criteria for the study she still viewed her son as having JHD. Interestingly, my intention in excluding JHD was because I believed that the issues and understanding would be so disparate but I was constantly surprised throughout (and commented during the interview) how much similarity there was in the relational aspects/meaning making.

GRIEF. GRIEF, GRIEF, GRIEF. I can feel her pain, it is palpable.

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Parental guilt and that feeling of always needing to be more. How can you ever make peace with knowing that your child is dying and this may be the last time that you can hold them, laugh with them, make memories with them and still find time to make your other children feel loved and valued!!!!!!!!!!!!!!!!!

I keep thinking about Isobel, Harry and Sophie [my own children] and it breaks my heart. I feel like this interview has left a stamp on me and I can't get it out of my head.

She really didn't think about the loss of emotion as apathy before this interview. I wonder if that would have helped her at the time. There feels like a real sense of grief at the loss of her son because of the loss of that emotional connection. I cannot imagine how has this has been for her.

Reflections on Analysis Process:

Braun and Clark (Braun & Clarke, 2021b) propose a six-step process to guide analysis in rTA. Analysis occurs in a sequential but iterative and non-linear way starting with an in-depth familiarisation of the data and ending with a detailed analytic narrative that is created by weaving together themes to create a "story" and situating it within the existing empirical landscape. Below an annotated account of this process is presented detailing specific aspects of data collection and coding in the current study, highlighting the reflexive process throughout the analysis (table 3.2).

1.	**Familiarisation**
	Full immersion in the data is considered to be an integral part of good qualitative data analysis (Clarke & Braun, 2013). This was achieved by reading and re-reading the

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	transcripts multiple times, both synchronously with the video recording of the interview and asynchronously (watching the video recording and reading the transcript separately). Transcription of the interviews formed part of this process. As recommended by Braun and Clark (Braun & Clarke, 2021b), I made notes of my recollection of the interview, my thoughts and feelings during the familiarisation process and initial observations of themes. The following excerpt is taken from my reflective diary following familiarisation. My thoughts and feelings following familiarisation with participants 9's interview: • She is still, very clearly very much in love with him. • She came to the interview wanting to talk about the emotional/cognitive side of HD. She felt that this was overlooked currently and want more awareness to be raised. • She did a good job of keeping her emotions contained during the interview. At times it felt very businesslike but I wonder if this was a coping strategy. She spoke a lot in general terms and held back from sharing too many personal or particular experiences. • I feel like she was one of the interviewees that I connected with the least. It took me a while to see past her barriers and to empathise with her as intuitively as some of the other participants. • She alluded to a story about how he was given the diagnosis but didn't share the details. It didn't feel like she wanted to discuss how the diagnosis came about (although I didn't ask directly) other than to say it was very difficult.

	• I noticed that her guarded nature made me feel very uncomfortable when I probed her for more information.
2.	**Coding**
	This process involves producing succinct labels across the entire dataset that captures or evokes important details from the data that relate to the research question. Coding was completed for each participant before moving onto the next. In line with the research question, coding was completed for all participants classified within the behavioural apathy subtype before moving onto the coding of participants in the emotional apathy subtype. This was a collaborative decision made by the research team to aid the immersive experience of the data analysis. An example is provided in Appendix I Initially, I approached the coding from a more positivist perspective and closely aligned to my previous research experience. I was drawn to find the 'objective' and felt very uncomfortable interpreting or seeing subjectivity as 'real' and as such focused on looking for semantic commonality rather than experiential coherence. However, I was able to recognise this through my own reflexivity and supervision. Consequently, coding was an iterative process that moved closer to a critical realist methodology each time.
3.	**Generating initial themes**
	By examining the codes and collating the data, broad patterns of meaning are produced (Braun & Clarke, 2021b). During this stage I pulled together all the data that

	pertained to each theme and considered the viability of the theme. This was done at the level of the individual before moving onto the next stage of the analysis.
4.	**Developing and reviewing themes**
	As themes emerged, the coded data was revisited and candidate themes were checked at the level of the individual and then the whole dataset. Themes were checked for their resonance and their ability to tell a story that was both faithful to the data and in line with the research question. I was aware throughout of the pull I felt towards themes that I perceived to be more consistent with and identifiable 'truth' and the discomfort I experienced when I embraced my own reflexivity in the analysis process. Reflexive journalling and supervision helped me to notice and embrace this part of the research journey.
5.	**Refining, defining and naming themes**
	These themes were then interrogated to produce a detail analysis of each theme which included an understanding of their "scope" and "focus" (Braun & Clarke, 2021b), and the story that they told. An integral part of this process was producing an informative name for each theme.
6.	**Writing up**
	Finally themes were woven together and supported by illustrative quotes from the data and situated within the existing literature to contextualise the findings.

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	Writing the manuscript was an extension of the analysis process, constructing a narrative from the themes and situating theme within the previous literature. I used my previous research and clinical experience within the HD community, reflexively, to guide this process. Throughout, I was constantly aware of my own personal pull to align the work with my former methodological position both because it felt familiar and therefore 'safe', but also because I was nervous that if I moved too far away from the conventional discourse within HD research, the work would not be recognised and accepted by the people needed to action change.

Table 3.2: reflections on the analysis process

Reflections looking back on the journey.

A detailed description of my reflections on the research process for the portfolio as a whole are contained within Chapter 5: Reflections on the Research Process.

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Chapter 4: Systematic Review and Thematic Synthesis

Huntington's disease and relational change: A systematic review and thematic synthesis of qualitative research into caregivers experiences

Formatted for submission to Journal of Huntington's Disease*

See Appendix J for Formatting guidelines for authors

* Selected with the intention of bringing the experience of HD caregivers to a specialist HD researcher and clinician audience

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Huntington's Disease and Relational Change: A Systematic Review and Thematic Synthesis of Qualitative Research into Caregivers Experiences

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Abstract

Background: Huntington's disease (HD) has been shown to impair cognitive and social functioning. Although the impact is poorly understood, clinically it is assumed that this aspect of HD contributes to the difficulties experienced by HD caregivers. Understanding the changing interpersonal dynamics between someone with HD and their caregiver as a result of the evolving disease process is an understudied but clinically important area of HD research.

Objective: This study aimed to examine caregivers subjective experience of the ways in which HD impacts interpersonal relationships.

Methods: A systematic review of the empirical qualitative literature and thematic synthesis following Thomas and Harden's framework was conducted, guided by a critical realist philosophy. Consistent with the PICO framework search terms were synonyms of the key words "Caregiver", "Huntington's disease", and "Experience" with searches of MEDLINE, CINAHL, Allied and Complementary Medicine, PsychINFO and ScienceDirect conducted between June and September 2023 and repeated in February 2024.

Results: Nine studies were identified for thematic synthesis with the experiences of 404 caregivers, 58% of whom were spouses to someone with HD, represented in the analysis. The following four analytic themes were generated: (1) Loss of friendship, companionship and intimacy, (2) Relationships built around fear, (3) "Seeing my own future played out before me", and (4) "HD has made us stronger" .

Conclusion: The results were discussed inline with the theoretical constructs of anticipatory grief and ambiguous loss, whilst drawing attention to the unique challenges presented by HD symptomatology and the shared genetic risk that challenged caregivers.

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Introduction

Huntington's disease (HD) is a rare, genetic, neurodegenerative disease (Bates et al., 2014) that affects approximately 8.2 people per 100,000 in the United Kingdon (Furby et al., 2022). Characterised by a triad of motor, psychiatric and cognitive changes, the earliest features of the disease typically emerge during midlife with the average age of diagnosis at 49 years old (Rodrigues et al., 2017). Clinical diagnosis is based on the presence of abnormal movements alone (Reilmann et al., 2014) but there is increasing recognition of the need to consider both cognitive and psychiatric features of HD in this process (Ross et al., 2019). Although the non-motor features of HD are somewhat heterogeneous, they can include the presence of cognitive changes, impaired social cognition (Cavallo et al., 2022; Mason et al., 2021), depression, anxiety, and apathy (Stoker et al., 2022) amongst others.

Features of the disease are currently irreversible and although they progress slowly, over a 10-25 year period (Ross et al., 2014), over time there is a gradual loss of independence and an increased need for support to manage activities of daily living (Simpson et al., 2016). In the early stages of HD much of this support is provided informally by family members including spouses, parents and children. As the disease advances, caregivers are often placed under increased pressure (Youssov et al., 2022). Whilst the reasons behind this are multifactorial (Roscoe et al., 2009), the severity of the non-motor features of HD are a contributing factor (Youssov et al., 2022) and have been found to predict the need for specialist care in the form of institutionalised residential care facilities (Dawson et al., 2004b) which come at a significant cost (Jones et al., 2016). It is also important to recognise that the onset of HD typically coincides with a time of life when caregivers are juggling significant work and family responsibilities (Duvall, 1988) which adds to the complexity of caring for someone with HD.

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Research to date, has focused on defining and quantifying “caregiver burden” and “quality of life” (or lack of it), and exploring how this is mediated by different aspects of the clinical presentation of HD (Mestre et al., 2018; Yu et al., 2019). Consequently, a solution-focused approach to reducing caregiver burden has been adopted introducing practical adaptations to reduce the burden on caregivers. An unintended consequence of this perspective is that it locates the “problem” firmly within the person with HD (pwHD). It does not consider the interpersonal dynamics between the pwHD and the caregiver, nor does it consider the emotional experience or social context of the caregiver. As such, it misses the opportunity to contemplate a more psychological approach to reducing caregiver distress through the use of psychological therapy or psychoeducation for example.

A recent interpretive meta synthesis of the qualitative experience of caregivers in families impacted by HD (Parekh et al., 2018) identified “Change in relationship with care recipient” as one of five themes that emerged consistently across the studies reviewed. However, to date few studies have explored the relational aspect of HD and, to our knowledge, none have been conducted with the express aim of understanding the impact of HD on inter-personal relationships, despite it being a contemporary area of research in other neurodegenerative disorders (Hochgraeber et al., 2023). Consequently, a systematic review of the empirical qualitative literature in HD was conducted, to answer the following questions:

1. How do caregivers describe the experience of providing care to someone with Huntington’s disease?
2. How do caregivers experience any change in relationship between themselves and the pwHD, as a consequence of the disease?

Method

A critical realist philosophy was adopted and used to shape the thematic synthesis methodology (Thomas & Harden, 2008). Thematic analysis (Braun & Clarke, 2021a) of the direct

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quotations and authors' interpretations was used to preserve the integrity of the original studies, and the ENTREQ statement was used to guide the reporting of the methodology (Tong et al., 2012) (Appendix K).

Search Strategy and Study Identification:

Key words were identified using the PICO framework (Richardson et al., 1995). Search terms were synonyms of the key words: (Population) "Caregiver", (Context) "Huntington's disease" and (Outcome) "Experience". The search strategy was developed for MEDLINE (Appendix L) and adapted for Cumulative Index to Nursing and Allied Health Literature (CINAHL), Allied and Complementary Medicine, PsychINFO and ScienceDirect. Main searches were conducted between June and September 2023 with a final search completed in February 2024.

The reference lists of included studies and contents pages of Journal of Huntington's disease, Movement Disorders, Neurology, and Journal of Neurology were manually searched and complementary searches of Google scholar and Research Gate were conducted.

Inclusion/Exclusion Criteria

Our aim was to synthesise adult caregiver experiences of the impact of HD on their relationships. Inclusion criteria were selected to ensure that primary, peer reviewed, qualitative research were included in the analysis, with direct quotations reported to permit analysis of raw data. Studies were included if they included experiences from the perspective of the adult caregivers, over the age of 18, who were supporting someone who developed clinical features of HD after the age of 21. It was felt that the experience of supporting someone with adult-onset HD may be different from that of caring for someone with juvenile HD, therefore inclusion criteria were selected to identify this population (Quarrell et al., 2019). Due to restricted resources that prohibited the option of translation, only research written in the English language was included. See table 4.1 for details.

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Search Outcome

The database searches yielded 152 papers for review, with a further 2 identified through the complementary searches. Papers were independently screened by SLM and AB and evaluated against the eligibility criteria using the title, abstract and full text, in a step-wise fashion. Disparities were discussed between SLM and AB, and a consensus was reached resulting in 9 papers being included in the final selection (see figure 4.1).

Quality Appraisal

Thematic synthesis is an evolving and debated field and as such, a consensus on the need for, value of and effective techniques to evaluate research quality in this process are still debated (Butler et al., 2016). Consistent with a critical realist approach, quality of the studies was assessed (Thomas & Harden, 2008) using a three-step quality assessment based on published criteria developed by (Whiffin et al., 2021). The relevance, resonance and rigour of each study was initially assessed by SLM before being discussed by the research team.

The relevance of a study referred to the degree to which the research question being addressed and findings reported in the study, aligned with that of the thematic synthesis. Resonance, referred to the richness and complexity of the data reported in the studies. Finally, the Critical Appraisal Skills Program tool, as recommended by the Cochrane collaboration (Noyes et al., 2019), was used to assess study rigour. Although not originally designed to be scores, scoring criteria developed by Butler et al. (Butler et al., 2016) was used for ease of comparison.

Consistent with the approach taken by Whiffin et al. (Whiffin et al., 2021) papers were classified as “Core, Central or Peripheral” on the basis of these evaluations (Table 4.2). Due to the limited number of papers in this area, no study was excluded as a consequence of this evaluation.

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Inclusion Criteria	Exclusion Criteria
• Qualitative research • Direct quotes included • Empirical research published in a peer reviewed journal • Research that involves the experience of someone who provides care for a pwHD e.g how does the caregiver experience the role of providing care for someone with HD • Age of the pwHD is 21 or above at the time of diagnosis to exclude juvenile onset HD • Age of the carer is 18 or above at the time of data collection • Studies published in the English Language	• Secondary research • Research where the focus is caregiver perspective of the experience of the pwHD e.g., caregivers being asked to share their opinion of how the patient experiences the symptoms of HD.

Table 4.1 : Inclusion Criteria

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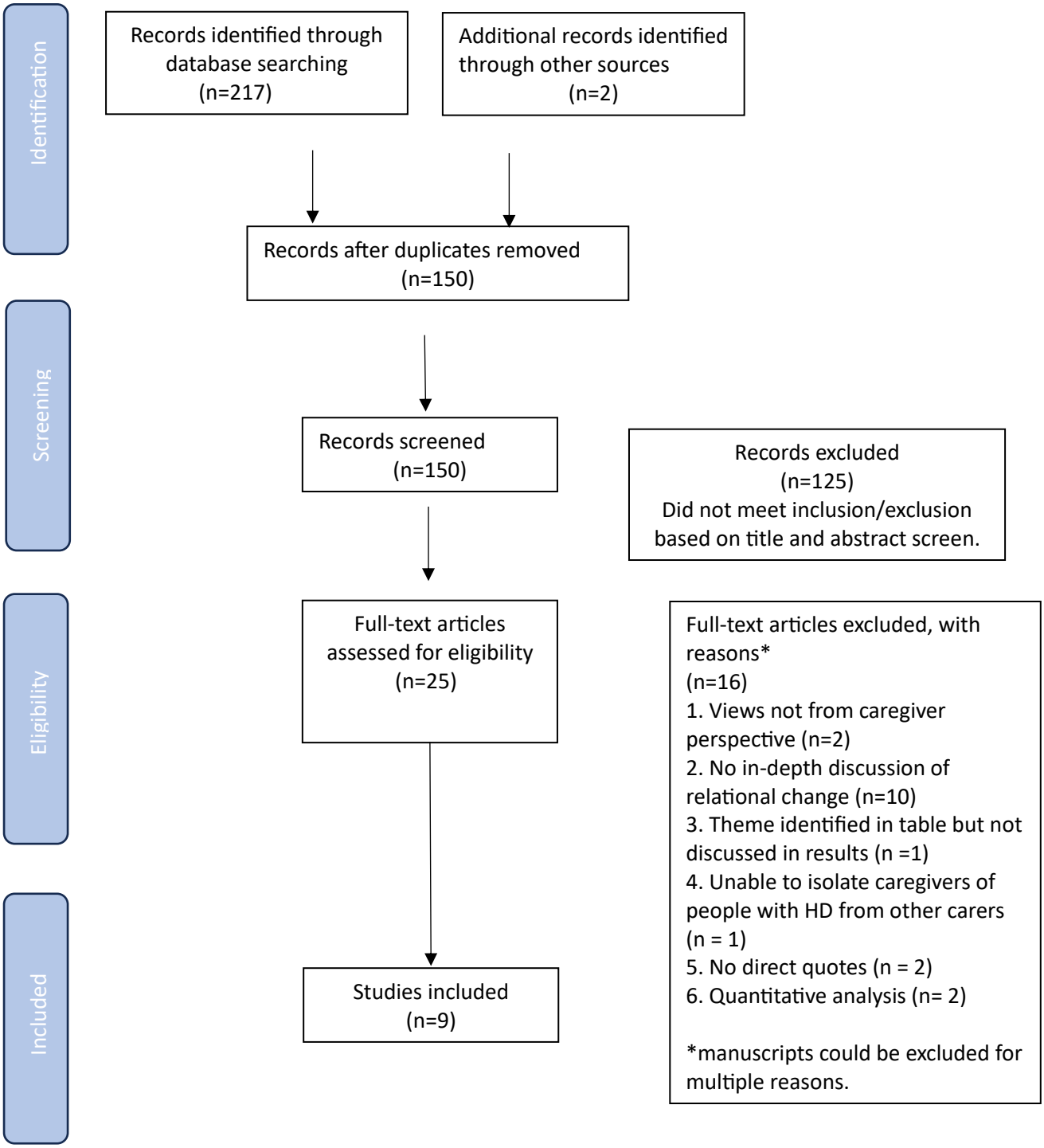
Figure 4.1 Prisma flow diagram



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Thematic Synthesis

Details of the studies were extracted and summarised by SLM and checked by AB (Table 4.3). Data for use in the analysis and thematic synthesis was defined as anything included in the sections "Results" or "Findings" and included quotations and authors reflections and interpretations.

Coding Text and Developing Descriptive Themes

The studies were read repeatedly and in detail by SLM with notes recorded in a reflective journal. Data was reviewed on a line-by-line basis and key concepts pertaining to relational change were identified and coded using Excel©. Both semantic and latent codes were used from the outset. Data and thematic codes pertaining to the key concepts were then extracted into an excel spreadsheet and organised according to descriptive themes. Coding was completed in order of quality classification and performed in an iterative way. "Core" studies were coded first, followed by "Central" and then "Peripheral". With each paper, codes previously identified were applied and where relevant, new codes were created. For completeness this process was reversed to ensure the entire codebook was reviewed for every study.

Generating Analytical Themes

Analytical themes were generated inductively. SLM, CF and FG discussed the descriptive themes and explored possible interpretations holding in mind at all times the influence of our own philosophical positions and the lens through which we were viewing the themes. Finally, the interpretation was reviewed by RAB as a way of sense-checking the meaning making.

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Core:	**Relevance:** Full alignment of empirical research questions and review question **Resonance**: Novel findings that are detailed and descriptive. Likely to make a meaningful contribution to the evidence base. **Rigour**: Robust, well documented methodology reflected in CASP scores of 7.5 or greater
Central:	**Relevance:** Relevant findings reported but empirical research questions and review question partially align. **Resonance**: Findings lack some detail and description or some may be superficial or tentative. May make a meaningful contribution to the evidence base. **Rigour**: Robust, well documented methodology reflected in CASP scores of 7.5 or greater
Peripheral:	**Relevance:** Relevant findings reported but empirical research questions and review question do not align **Resonance**: Findings lack detail and description, they may be superficial or tentative. Unlikely to make a meaningful contribution to the evidence base. **Rigour**: Questions about the robustness or the documentation of the methodology reflected in CASP scores of lower 7.5

Table 4.2: Classification of papers based on the criteria proposed by Whiffin et al (2021)

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Study ID	Research Focus	Qualitative data collection	Participants	Relationship to pwHD	HD carer characteristics	Data Analysis	Findings	CASP score (Butler et al., 2016)	Relevance to synthesis
Aubeeluck et al. (2012)	Caregiver lived experience and how they feel about caregiving	Semi-structured interview 6 Focus groups – randomly allocated (6 - 7 per group)	47 family carers, 32 fulltime, 15 part-time [e.g. had a job outside family home] Further details	26 spouses, 21 other family members	Not recorded Details withheld to maintain anonymity	Interpretive phenomenological analysis	**Themes identified:** Levels of support, dissatisfaction with caregiving role, practical aspects of caring, feelings of emotional well-being **Data relevant to relational change:**	Moderate (8)	Central

			withheld to maintain anonymity				Loss of emotional closeness, loss of the person, positive effects of HD on family relationships		
Dawson et al. (2004b)	Address paucity of knowledge about the supportive care needs of people who have HD and their	Semi-structured interview Individual interviews	19 family / informal carers Average length of time caring = 11yrs (3-21 yrs) Aged 18-80	5 supporting someone with early HD, 9 = middle/late HD, 5 = lost a relative with HD within last 12 months	Not recorded	Content analysis (Burns & Grove, 1987) and constant comparison technique (Glaser, 1967)	Six main themes: adjusting to the impact of the illness, surviving the search for essential information, gathering practical support from many sources, bolstering the spirit, choreographing	High (9)	Central

	families / carers						individual care, fearing the future		
Lowit and van Teijlingen (2005)	Gain in-depth understanding of the caregiving role and the issues that carers felt were important in the face of caring for a	Semi-structured interview, Face-to-face in carers' homes Individual interview, Sampling not discussed	10 spousal carers Age 40-89 (approx. age) Number of children per family: 0-4, 24 children in total (13 at-risk, 8 tested [5 -ve, 3+ve])	4 = husband, 6 = wife	Gender, approximate age (10 year range) All stages of HD included	Thematic analysis	5 themes identified (7 more identified but not discussed in this paper) Impact of HD, avoidance, issues around testing. Lack of support, issues around testing, Scottish Huntington's Association	Low (7)	Peripheral

family member	9/10 caring for spouse at home
	Duration of relationship 9-42 years
	Details of when they found out about HD in spouses family

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(Gibson et al., 2022)	To assess patient and caregiver perceptions on the relationship between neuropsychiatric symptoms and functional status	Semi-structured interview. In person on via telephone Individual interviews Purposive sampling – at least 1 neuropsychiatric symptom	8 caregivers Age (mean 49.4 yrs, SD 12.3 yrs, range 35-65) Gender 75% female	88% spouses	N=7 Age(mean 47.1yrs (SD = 11.7 yrs, range 35-61), Gender (71.4% female). CAG (median 43, range 40-51), TFC (median 9, range 6-12)	Descriptive content analysis	5 themes identified. Effects on daily practical functioning, impaired social interactions or relationships, negative change in personality/cognition, other negative effects of neuropsychiatric symptoms, positive coping or outcomes	Low (6.5)	Peripheral

		on Problem Behaviour Assessment Scale (PBA)			3/7 were employed				
Maxted et al. (2014)	Explore the ways in which parent/child dyads co-construct meanings of the experience of being	Semi-structured interview Dyad interviews	7 parent/child dyads	3 Mother / Daughter 2 Mother / Son 2 Father / Daughter	Parent age: range 48 – 75 (mean 61 years*, SD: 9.6 years*) Child age: range 24 – 42 (mean: 32 years*; SD: 6.9 years*)	Interpretive phenomenological analysis	Three main themes: "A spectre Hanging over us", "Us against the world", "That could be me in 50 years" Relational change: personality changes, working together/protecting	High (9.5)	Peripheral

	within a HD family								
Rothing et al. (2014)	Caregiver's experience of the impact of HD on family structure, dynamics and roles in the family	Semi-structured interview, location that was suitable to participant eg their home, office or a hotel	15 family caregivers (3 male, 12 female), aged 20 – 67yrs, Care-giving experience 11.6yrs 3 were caring for	Spouse (n=10), ex-spouse (n=1) or adult child (4).	All 5 stages	Thematic analysis	3 themes identified: Transitions of family members' roles and changes in relationships, family caretakers must adjust to mixed feelings, the family network becomes vulnerable and fragmented.	High (9.5)	Core

Part of a wider study using a thematic topic guide asking about: participant experiences of family caregiving, how they dealt with behavioural challenges/coping strategies,	multiple family members 12 had children

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		experience with health services Individual interviews							
Rothing et al. (2015)	Explore coping strategies and behaviour patterns used by caregivers to	Semi-structured interview, location that was suitable to participant eg their	15 family caregivers (3 male, 12 female), aged 20 – 67yrs, Care-giving experience 11.6yrs	Spouse (n=10), ex-spouse (n=1) or adult child (4).	All 5 stages	Thematic analysis	Results focused on responses to the question on coping strategies. 3 themes were identifies: Regulating information about the disease, towards a skewed balance and	High (9.5)	Peripheral

care for themselves	home, office or a hotel Part of a wider study using a thematic topic guide asking about: participant experiences of family caregiving, how they dealt with behavioural	3 were caring for multiple family members 12 had children	increasing isolation, increasing limitations – tolerating a life on hold.

		challenges/coping strategies, experience with health services Individual interviews								
Williams et al. (2009)	to examine the emotional experience of caregiving by family carers of	Semi-structured interview Part of a wider study	42 Family members, 27 women, mean age 52 years,	Spouse=35, Parent=6, Sibling=1	No details	Grounded theory	3 Themes: disintegration of the carers life, loss of life as it was, the ever-present shadow	Moderate (8)	Central

	people with HD	– PREDICT-HD Focus group (5-8 participants)	Only 22 participants discussed in this paper						
Williams et al. (2012)	To examine and compare the personal concerns of family members providing care for people with	Mixed methods Part of a wider study – PREDICT-HD Mailed survey with	227 Family caregivers 119 in US, 109 in UK 66% female, 71% had attended college	65% partners of someone with HD	No details	Deductive thematic analysis	3 themes: Role change, sense of isolation and concerns for children	Moderate (8.5)	Central

HD in the UK and US	narrative comments	Age range 18-80

HD = Huntington's disease; QoL = Quality of Life, CASP = Critical Appraisal Skills Program tool (Noyes et al., 2019)

* Calculated from raw data, not reported

Table 4.3: Details of studies included in thematic synthesis

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Trustworthiness

Credibility, dependability, transferability and confirmability (Lincoln & Guba, 1985) were used as markers of trustworthiness. The credibility of the thematic synthesis was established by the immersive analysis of the data and the critical reflexivity used by all authors at a personal, interpersonal, methodological and contextual level (Olmos-Vega et al., 2023). It was further supported by the independent review of the findings by RAB. The transparent reporting of the methodology used during the thematic synthesis including the operationalised, and therefore reproduceable, approach which demonstrated procedural rigour and supported the dependability of the findings. Transferability is aided through the provision of detailed, descriptive contextual information about the studies and the inclusion of rich, expressive quotes. Finally, confirmability was achieved by reporting "well-grounded" and "supportable" findings (Webster & Mertova, 2007) that were clearly derived from the data and supported by transparent reporting (L. Nowell et al., 2017).

Results

Study Characteristics

After screening was complete, nine studies were included for thematic synthesis. All studies were published between 2005 and 2022. Papers originated from UK (n= 3), USA (n = 3), Norway (n = 2) and Australia (n = 1). Semi-structed interviews were conducted to collect data which were analysed using thematic analysis (n=4), content analysis (n=2), interpretive phenomenological analysis (n= 2), and grounded theory (n= 1). Most studies used individual interviews (n=5) but two used focus groups, one used dyadic interviews and one used postal surveys with narrative comments.

Across the studies, 404 caregivers were involved, the majority of whom were female (n= 229) although the gender split was not reported, along with other demographic characteristics, in two studies due to attempts to maintain confidentiality where they were reporting data from small

samples. Whilst 58% of caregivers (n = 248) were the spouse of someone with HD, the voice of parents, children, siblings and other family members of someone with HD were also represented although the exact numbers were not recorded. Demographic characteristics of the pwHD were rarely reported although three studies included caregivers for people at any stage of HD.

Only one paper was identified as core, four as central and four as peripheral following appraisal. Whilst rigour was generally high with only two studies falling below the designated cut-off on the CASP, alignment with between the empirical study research question and the review question was low.

Themes Drawn from the Analysis

The experience of relational change in families caring for someone with HD were synthesised into four analytic themes:

1. Loss of friendship, companionship and intimacy
2. Relationships built around fear
3. "Seeing my own future played out before me"
4. "HD has made us stronger"

Loss of Friendship, Companionship and Intimacy

This theme captured rich narratives about the reasons behind, and impact of, the change in relationship and incorporated the subthemes: grieving for the lost relationship, lost friendships, "this isn't a marriage anymore", and "they are a totally different person". Almost all studies discussed the profound sense of loss felt by caregivers. The loss of friendship, companionship and intimacy was felt by many. Several talked about how the disease had turned their companion into a completely different person which left them with a sense of grief over the loss of the relationship:

> What hurts me most is that you lose the one you loved. A complete different person is sitting in the dining room today, another person than the one who was my husband years ago. (Rothing et al., 2014)

> I get these alternating feelings of sadness at the gradual passing of a warm and loving relationship with my wife, then anger at the behaviour. (Aubeeluck et al., 2012)

> I guess in a way the grieving of [loss of a husband] is over. (Dawson et al., 2004b)

The premature grieving process was both reactive and proactive. Either as a way of coping with the emotional toll of supporting someone with HD, or as a reaction to the increased need for physical care, the grief felt by the caregiver changed the nature of the relationship between the caregiver and pwHD. Spouses no longer viewed the pwHD as someone they engaged in an equal, reciprocal relationship with:

> We used to like to cook together and he'd do things…he was great helping me clean and do stuff. We're raising kids and we've got kid activities. And all of our friends do too. It's gone. I've kind of walled him off in so many ways…physical, mental…bond between a husband and wife, that's, that's gone. And I feel guilty about it, I feel horrible about that. (Williams et al., 2007)

> I've got a dependent so that's the saddest part and I miss the companionship. Having a dependent who's no longer a husband that you can talk to because you can't have conversations any more unless he's starting the conversation. (Dawson et al., 2004b)

But considered them more as a new child in the family for whom they expressed parental affection for:

> And the thing that I had learned the greatest from it was that I had to learn to fall out of love with him. And I love him dearly and I take care of him. But I've got this mother-child relationship. And that is what has helped me a great deal. I love him dearly, he's very important to me, but I'm not in love with him anymore. And that was a very hard thing to do. But I learned to do it (Williams et al., 2007)

These three quotes highlight the nuanced way in which caregivers experience and manage their grief through guilt, expressed sadness and the conscious reframing of their love and the huge personal existential effort that is required.

Feelings were often made more complicated by the physical presence of the pwHD. Unlike grief following the death of a loved one, the visible existence of the pwHD, reminded caregivers of the relationship that had been lost and left them with a sense that they had been rejected, rather than left.

> I wanted to stand by her forever, but now I realise I am not a saint who can go on giving and giving without getting any love or peace. (Williams et al., 2012)

> I feel that I am drained. I need to feel love from her but she is void of any emotions. She really does not care about my health, in fact our relationship is making us both more ill (Williams et al., 2012)

For some there was a degree of anger that, in addition to the sadness they felt at losing the relationship with the pwHD, the complexity and all-consuming nature of supporting someone with the disease acted as a barrier to finding that connection elsewhere:

> Yes, there is a lot of frustration because me and my sister were best friends, super friends, sharing everything, clothes, boyfriends, and excitements, and now she is not here, and in this process I have not been able to establish friendship of my own. (Rothing et al., 2014)

Others felt trapped in a relationship with someone they had not, and would not, chosen to spend their life with, which led to resentment and animosity:

> I miss the person that he was when I first met him, of course. Um, but then that person just disappears and you're left with somebody that you resent. Which is sad really. (Maxted et al., 2014)

The meaning making process surrounding these feelings of loss, rejection and grief was complicated and impacted on the caregiver's ability to adjust to their evolving role in support of the pwHD.

Relationship Built Around Fear

Where aggression is a symptom of HD, the impact on the caregiving relationship is often profound. Six studies discussed how once loving relationships can feel abusive and coercive as a result of the disease. Caregivers talked about "walking on eggshells" (Dawson et al., 2004b) whilst struggling to live with the unpredictability of the mood swings:

> When she is ok I almost think that there is nothing wrong and everything will be ok after all. Then she gets bad again and I just want to run a mile. It really wears me down not knowing which person I'm going to be with each day. (Aubeeluck et al., 2012)

Often the aggression was directed towards the children resulting in the relationships became tainted by fear and misunderstanding:

> *I remember when dad came visiting us, we were afraid and thought he was an alcoholic*. (Rothing et al., 2014)

> Their relationship is being affected because my son doesn't understand why his father is behaving the way he does sometimes... he [husband] refused to let him [son] know. (Williams et al., 2007)

The repercussions of this behaviour rippled through multiple layers of the family leading to a breakdown in the relationship with extended family who wanted to protect the children:

> He was hitting into the children [grandchildren], my daughter was pregnant at the time, and he was getting very aggressive and we couldn't cope with that. (Dawson et al., 2004b)

There was a general acceptance, however, that aggression was part of the disease and there was a degree of resignation that enduring this behaviour was an unavoidable part of caring for someone with HD:

> Called me names. He never hit me, but pushed or shoved, or he would do that. He actually held me somehow, not down, but against the wall and like pulled my wedding ring off and flushed it down the toilet. That was one of the worst nights, but that happens. (Gibson et al., 2022)

Unlike survivors of domestic violence, there was a clear narrative that the locus of control for the aggressive behaviour sat with the disease and was not located in either the person with HD or the caregiver. The studies in this thematic synthesis describe the impact of aggression on the caregivers' quality of life, but there was little discussion around the emotional consequences for them and few consider the implications it has on the caregiver/patient relationship although it is unanimously acknowledged that the impact is negative.

Seeing My Own Future Played out Before Me

Because of the autosomal dominant nature of HD, familial carers are often at risk of having inherited the disease themselves, this shared experience adds a unique dynamic to the caregiving relationship. Although not discussed at length in any of the empirical work, four studies described how being at risk of developing HD left caregivers feeling like they were watching their own

hypothetical futures playout when they were caring for someone with HD. Understandably, this generated fear and impacted on the relationship with the pwHD, often leading to avoidance:

> When I was helping to care for my father, I remember how difficult it was (sigh) especially looking and feeling like I was somehow seeing my own future played out before me. (Aubeeluck et al., 2012).

> It has been difficult for them, seeing their dad change and what that might mean for them. They all find it difficult to be with him...it's not just the change in their father, it's partly that, but it is also that they see what might be in store for themselves. (Lowit & van Teijlingen, 2005)

For those who had been at risk but had been found not to carry the gene for HD, the guilt of their good fortune in the face of other family members suffering changed relationships.

> Siblings talked of survivor guilt if they had a negative test result while others in the family had a positive result for Huntington's disease (Dawson et al., 2004b)

This was only highlighted in one study and although it was identified, the impact of survivor guilt on the relationship was not explored however the use of the word "guilt" implies a sense of responsibility and a need to make reparations to the pwHD. This is a unique strain on the caregiving relationship that is unlikely to be observed in other neurodegenerative diseases.

HD Has Made Us Stronger

From the outside it can often seem hard to find any positive aspects to caring from someone with a neurodegenerative disease. However, in three studies in this thematic-synthesis, caregivers reflected on how having HD in the family had led to a strengthening of the relationships within the family unit. The shared experiences of supporting someone with HD brought people closer together by creating an opportunity for openness that was unifying:

> We have to remain strong and open with our kids at all times so that they know we love them and support them and as a family we can get through whatever life's challenges are. HD has brought us closer. (Aubeeluck et al., 2012)

This was observed by researchers in one study who reflected on how the carer and the pwHD worked as a unit, noticing and reacting to each other's needs in a dynamic way. This empathic understanding of the needs of the other person creating a mutual sense of safety:

> The dynamics between the pairs interviewed often showed how the participants worked together to protect each other. For example, if one person was struggling to talk about a difficult topic, the other would often "rescue" them, or they would unconsciously collaborate in moving the conversation away from difficult topics. (Maxted et al., 2014)

Needing to adapt to the challenges of caring for someone with HD helped carers to recognise what was important to them. For some this was about being open and honest with their children to give them the knowledge and support to navigate their own HD journey in the future:

> They both know they're at risk, they know that mum has HD like grandad and our family will go through many changes. Also that our family will have to adjust to whatever mum is going through at the time some of it will be scary for them but just because mum has HD doesn't mean that either one of them will have it, but just like we teach our kids to protect themselves from diseases or from pregnancy they also have to know that this possibility is there and they need to make all the right decisions when they find that special someone. It's hard enough just being a young adult now-a-days let alone having to worry about this horrible disease but we have no choice if we deny that the disease exists what good will that do (Aubeeluck et al., 2012)

For others, having a time limit imposed on their relationship acted as a wake-up call, prompting them to stop and think about the type of spouse they had been and who they wanted to be. This is illustrated in a quote from a gentleman who had found new pleasure in the life he shares with his wife, after making the choice to become more committed to her:

> I'm very, very dedicated to my dear wife…I'm not the same person I was. And the person I am is someone who's true to his wife and enjoying…we really, we enjoy our life. (Williams et al., 2007)

It is generally assumed that the relationship between the caregiver and the pwHD will deteriorate as the disease evolves, and while this is true for many, for some the shared struggle provides a sense of unity and strength that is valued.

Discussion

Caring for someone with HD can be complex and challenging. Classically, research has focused on understanding how the disease presents practical difficulties for caregivers, with little consideration of its impact on the interpersonal dynamics between the caregivers and care recipient. This review used a narrative-synthesis approach to identify and compile caregivers' descriptions of how HD changed their relationship with the person they supported. Nine studies met the inclusion criteria and were included in the analysis with their data synthesised into four themes: (1) Loss of friendship, companionship and intimacy, (2) relationships built around fear, (3) "Seeing my own future played out before me" and (4) "HD has made us stronger". Interestingly, although empirical studies designed with the aim of understanding the relational change in HD were rare, and few reported themes connected to the impact of HD on relationships, rich descriptions of experiences and behaviour relevant to the current study were embedded within qualitative research that focused on the more general HD caregiver experience. Synthesising this data into succinct themes both

highlights the reach of relational change in HD and the extent to which it is under-recognised and seldom acknowledged in the current literature.

A recurring narrative across studies was that of loss; loss of friendship, companionship and intimacy as a result of HD. Throughout, caregivers described feelings of grief as they watched HD consume the person they were supporting, taking away everything familiar and leaving a shell of the pre-disease person. Relationship roles changes and what had once been equal and reciprocal became function and needs driven, similar to that of a parent and child. Caregivers described sadness, loneliness and rejection as they felt trapped in relationships they didn't chose and no longer wanted. In the wider empirical literature, emotional factors linked to caregiver distress have also been understood in the context of an early grieving process. Anticipatory grief, where grieving starts before the physical death of the patient (Cheung et al., 2018) describes feelings of pre-death grief which are conceptualised as the understandable response to the "multiple losses" that occur as the disease process results in loss of intimacy, companionship, personal freedom and role identity (Large & Slinger, 2013). The ambiguous and incomplete loss of intimate relationships, whereby the person is physically present but emotional absent (Boss, 2009), can cause profound sadness (Frank, 2007) and adding to the emotional burden of caregiving (Chan et al., 2013). The models of anticipatory grief and ambiguous loss have not yet been extensively applied to the field of HD research but align well with the findings of this thematic synthesis. The lack of published empirical work in this area, highlights the need for further research to understanding how HD caregivers experience and construct meaning about the losses they occur as a result of HD, with a particular focus on understanding the emotional impact of relational change. Exploring the connection between pre-loss grief and caregiver burden, where the caregiver no longer feels able to continue to support the pwHD, may provide a meaningful opportunity through with to offer psychological support and help caregivers to develop more effective coping strategies. Novel approaches to reduce the impact of

anticipatory grief in dementia caregivers are currently being explored with implementation research planned (Rupp et al., 2023). This work would be relevant to HD caregivers.

It is widely recognised that HD is associated with a range of psychiatric symptoms that vary between individuals and change time. Of these, aggression is common with between 22% and 66% of people with HD reported to display problematic levels at some point in the disease (Fisher et al., 2014). Men (Fisher et al., 2014), and those who develop HD at a younger age (Ruiz-Idiago et al., 2023) are more likely to display problematic aggressive behaviour, and while clinically it can be inferred, little is known empirically about what it feels like to be in receipt of this behaviours, especially as a caregiver. Synthesising evidence from multiple studies, the current review demonstrated that aggression affects relationships across the system around the pwHD with the impact being felt by caregivers, children and the wider family. Importantly, aggression was seen as an unavoidable part of HD, trapping caregivers in abusive and coercive relationships. Given the high prevalence of aggressive behaviour in HD, raising awareness of the consequences it has for caregivers is an important unrecognised need that should be addressed both clinically and empirically. Currently, support for caregivers is available through patient advocacy charities but this relies upon the caregiver to actively seek help themselves. We know from the literature on domestic violence that cultural norms around help-seeking (Hilbert & Krishnan, 2000) and social beliefs that devalue the legitimacy of experiences of abuse (Overstreet & Quinn, 2013), prevent victims of domestic abuse from seeking help. Evidence from the current study suggests this may be a barrier for HD caregivers. Recognising the impact of HD symptomatology on caregivers, and adopting a trauma informed approach to supporting them within routine HD services (Johnstone & Boyle, 2018) could help to reduce the impact of HD related aggression on caregivers. Using the opportunity of our routine interactions during clinic to provide signposting and access to appropriate help, along with a conscious and careful consideration of how our own interactions may inadvertently re-traumatise caregivers, could significantly reduce their distress and burden in an opportunistic way.

Finally, the genetic nature of HD gives rise to a relatively unique caregiver experience, whereby family members supporting the pwHD may themselves be at risk from the disease. Being reminded of their potential future was distressing for some and across studies caregivers describe how this led to avoidance and withdrawal from the pwHD. Whilst it was only touched upon briefly in a few studies, the impact for both the caregiver and care recipient is clear. Avoidance is a coping strategy often used in an attempt to minimise the psychological distress experienced when someone is struggling to adjust to the diagnosis (or possible diagnosis) of a long term health condition (LTC) (Carroll et al., 2022). Conceptualizing the caregivers experience in this way may open up the possibility of using psychological strategies that have been shown to be effective in other LTC's (Velazquez-Jurado et al., 2023) to help caregivers to develop strategies to manage these difficult feeling for the benefit of both themselves and the pwHD.

Further research is needed to better understand the complexity and nuance of the caregiver experience of relational change in HD. It is important both for the pwHD, and their caregiver, that the challenges of supporting someone with HD are better recognised and considered by clinicians and the wider clinical team around the HD family. Careful consideration is needed to ensure that we, as clinicians, do not inadvertently add to the burden for caregivers by tasking them with the responsibility to improve their own situation and by so doing, perpetuate the narrative that they should be managing alone. Therefore, understanding how systemic changes, including the use of peer support and social interventions, have the opportunity to significantly improve the lives of caregivers supporting people with HD should be explored clinically and empirically.

Limitations

The review was limited by the small number of studies available in the published literature and the lack of alignment with the primary focus of the research question which restricted the depth and detail of the findings. This is reflected in the quality ratings which only identified one study as

"Core", with the majority considered "Central" due to poor alignment between the aim of the study and that of the synthesis. Adopting a critical realist paradigm allowed for a pragmatic approach where methodological and theoretical differences between the qualitative studies were not considered, but consequently, the importance of methodology is not explored in this work. Finally, the caregivers' experiences included in this synthesis reflect a predominantly female perspective which should be considered when considering the context of the work. The perspectives of male caregivers and female care recipients, is not well represented.

Conclusions

The current study reviewed and synthesised caregiver experiences relating to relational change in HD. Although the data was typically embedded within wider themes, adopting this approach allowed for attention to be directed towards a relatively unacknowledged area of HD research, that, although hidden, was present in existing qualitative research. The analysis revealed themes that align with the theoretical constructs of anticipatory grief and ambiguous loss, whilst drawing attention to the unique challenges presented by HD symptomatology and the shared genetic risk that challenged caregivers. These findings both advance the evidence base and identify areas for future research and clinical development.

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Chapter 5 - Critical Appraisal and Discussion

Critical Appraisal and Discussion

This chapter brings together the findings from the empirical paper and systematic review. Their unique and combined findings are discussed in relation to their contribution to the field of clinical psychology and Huntington's disease (HD). Strengths and weaknesses of the work are considered and the wider implications of this work for clinical practice and research are summarised. My reflections on the research process undertaken in this thesis portfolio are included.

Reflections on the Research Process

Over the last few years, I have become increasingly aware that the unintended consequence of the positivist, quantitative research that is dominant in the study of HD, has been that although our understanding of the natural history of the psychological and neuropsychological aspects of the disease has developed, few advances have been made towards finding therapies to ameliorate their impact. Exciting advances in neuroscience have advanced the pursuit of disease modifying therapies over the last decade but that, in itself, has had psychological consequences for people within the HD community. Consideration of the psychological impact that this uncertainty has on someone's ability to navigate important life decisions such as if, or when, to have the genetic test for HD, get married or have children, has been lacking. As too has consideration of the impact that the constant cycle of promise and disappointment that inevitably surrounds the pursuit of novel therapeutics. Having worked with people with HD (pwHD) and their families for such a long time, I have seen firsthand the impact that this has and shared in their frustration that appropriate services are not available to offer support for the psychological distress experienced, when it is needed. It was my desire to change this that resulted in, firstly, my decision to complete the Doctorate in Clinical Psychology, and secondly, to undertake the work in this portfolio.

Despite hearing similar stories to the challenges and psychological impact of HD shared by participants in this portfolio, from many HD caregivers over the years, I found immersing myself in

the deeply personal stories shared with me during the empirical study, an intensely emotional experience and one that has forever shaped me as a researcher and clinician. I feel privileged that caregivers trusted me with their previously untold stories and a sense of responsibility to continue to help them voice their experience in the future.

As someone new to qualitative research, the empirical study in this thesis pushed me far outside my comfort zone. At times I found this overwhelming but overall, I feel that I have thrived on the experience. Developing the knowledge, skills and understanding needed to complete the qualitative research has helped me discover a path to continue my former research in a way that better aligns with my own personal values and is, I believe, meaningful for the HD community. Undertaking this work has reignited my passion for research in a way that I did not previously believe possible and cemented my interest in understanding the impact of the cognitive and psychological aspects of HD. I am excited to consider this the start of the next phase of my research journey.

Summary of Findings

This portfolio draws together existing and novel findings pertaining to the impact of HD on caregivers. It takes a step back from the dominant medicalised paradigm, that focuses on the person who carries the gene, and takes a more systemic view of the disease, documenting both the caregiver experience and focusing on the interplay between the person with HD (pwHD) and the caregiver, to consider the relational aspect of the disease.

The empirical paper aimed to gain insight into the meaning-making constructed by caregivers as they make sense of their experience supporting someone with HD who displays features of apathy. Analysis of the semi-structured interviews using reflective thematic analysis (rTA) identified five themes: “What even is apathy?”; “It makes my life harder: the practical impact of apathy”; “They haven’t forgotten me, but they have forgotten that they ever loved me”; “I’m grieving for someone who hasn’t died yet”; and “I need a safe space to say what I really feel without fear of judgement”.

Caregivers saw the apathetic behaviour as synonymous with the parts of the pwHD that they had lost as a result of the disease. It was both the conduit through which the loss occurred and a reminder of what had been lost. There was recognition that the person they had loved no longer existed but that they were still left with the status, expectations and social structure of a marriage and being a wife which left them feeling trapped and isolated. The findings resonate with the theoretical constructs of ambiguous loss and anticipatory grief which are well known in dementia research but relatively unstudied in HD, and provide a wider, nuanced insight into these and other existential challenges.

Throughout, complex narratives about the hidden and unspoken nature of the disease, the invisibility of caregivers, and the one-sided experience of loving someone with HD were interwoven. The lack of expressed emotion made caregivers feel unloved and unwanted as they reflected on how the absence of empathy and reciprocity made the pwHD seem disinterest and ambivalent towards them. Together, apathy made HD caregivers feel like they were in the combatant position of being both the main source of care and support for the pwHD and rejected by them at the same time. They shared feelings of sadness, frustration and anger that were compounded by their own lack of understanding of apathy and an absence of recognition of the impact of apathy from within the wider system around them.

In response to the empirical paper, the systematic review aimed to revisit the published qualitative literature on the caregiver experience in HD and identify embedded accounts of relational change in HD. The systematic review used thematic synthesis in line with the recommendations from Thomas and Harden (Thomas & Harden, 2008). Thematic synthesis of the findings identified four analytic themes: Loss of friendship, companionship and intimacy; Relationships built around fear; “Seeing my own future played out before me”; and “HD has made us stronger”. The most pertinent findings in the systematic review were that embedded within studies that focused on much broader questions, caregivers shared narratives about the profound sense of loss they felt. Loss of

friendship, companionship and intimacy were documented but often not discussed in any depth by the researchers. The systematic review supported the findings of the empirical paper and expanded on the experience shared by caregivers. Removing the lens of apathy provided a powerful insight into the fear felt by some caregivers due to the aggressive behaviour shown by the pwHD and the sense of resignation they experienced as they were powerless to change their situation.

Combined Discussion

The empirical study focused on understanding the meaning-making constructed by caregivers in response to apathy displayed by the pwHD, whilst the systematic review explored caregiver experience more widely. Narratives that were consistent with an early grieving process were key elements in both. The subjective experience of loss felt in relationships, friendships and emotional connections were expressed across the studies with phenomenological nuances shared that reflected societal discourses, memories of the pre-HD person and expectations of life would look like. All of which was made harder by the continued presence of the pwHD, leaving caregivers feeling like they were expected to provide love and support without receiving anything in return. This grieving process suggests the relevance of ambiguous loss and anticipatory grief, to the HD caregiver experience. Both are concepts that have emerged from the palliative care literature (Coelho & Barbosa, 2017) and have recently been applied to the caregiver experience in dementia (Boss, 2009; Chan et al., 2013).

In line with the findings of this portfolio, studies have shown that uncertainty about the progression the disease, relational changes and caregiver mental health are associated with anticipatory grief in caregivers of someone with motor neuron disease (MND) (Trucco et al., 2024). Similar findings have been reported in other long-term conditions such as end stage cancer (Fee et al., 2021). However, research on relational change in these studies has focused on perceived difficulties making the transition from spouse to caregiver or the uncertainty in relationship roles

that emerges as the disease evolves. This does not fully align with the findings of the empirical study where descriptions of relational change relate more closely with relationship breakdown. Specifically, a lack of intimacy, reciprocity and emotional alignment left caregivers feeling unloved and rejected. This loss of emotional connection may be a specific response to supporting someone with the emotional and social apathy exhibited by pwHD, highlighting a unique contribution of the work in this portfolio.

The systematic review highlights that recognition of the relational aspect of HD is still in its infancy. Of the 217 papers identified which used qualitative methodologies to investigate the HD caregiver experience, only 9 made reference to relationship changes between the caregiver and pwHD and it was not the intended focus of any of the studies included in the review. Relational change is widely recognised as a significant factor in caregiver distress in those supporting someone with dementia (Gifford et al., 2021). Studies have highlighted that the challenge of maintaining a sense of "togetherness" (Swall et al., 2020) and the stress of supporting someone with dementia reduces the perceived quality of the marital relationship for caregivers (Clare et al., 2012). Exploration of this area in HD is needed to see whether it is influenced by the unique aspects of supporting someone with the disease. Namely the earlier onset, longer duration and the genetic cause of the disease which means that, for many, HD has always been part of their relationship.

Current research focuses on applying quantitative methodologies to investigate relationship change in HD. A new self-report questionnaire has recently been created to measure the pwHD's perspective on the impact of the disease on their social relationships. It found a two-factor structure to responses, where "social motivation" (factor 1) correlated with cognition and "emotional insight" (factor 2) correlated with apathy and other behavioural features of HD (Lemercier et al., 2022). The factor "emotional insight" encapsulated items that reflected the pwHD's feelings about social

experiences with other's. To my knowledge, the work in this portfolio is the first to explore relational change in HD, qualitatively and in caregivers.

Strengths and Limitations of the Empirical Study

In this study I initially planned to explore whether caregiver experience of apathy was influenced by the subtype of apathy exhibited by the pwHD, using framework analysis (FA) (Gale et al., 2013). The study was designed with the intention of producing findings to inform future research on psychological interventions to reduce caregiver distress in response to apathy. FA provided a systematic and flexible structure through which to achieve this, and is a qualitative tool widely used in healthcare policy research (Gale et al., 2013). Failure to recruit caregivers from all four subtypes made FA less feasible. Furthermore, the process of reflexive journalling allowed me to engage with my own personal journey during the research. It helped me to recognise the sadness and anger I felt listening to caregivers and my evolving motivation for conducting the research. Therefore, I built upon the foundations of thematic analysis, which had always been an element of the FA methodology, and embraced the reflexivity in the work. rTA was identified as an alternative method of analysis that could answer the research question and provide a voice to the caregivers' untold stories. The existing design of the study aligned with recommendations for best practice rTA studies (Braun & Clarke, 2022a) and did not therefore require adaptation in response to the change from framework analysis to rTA. Changes to the methods in the empirical study are a strength of the research.

As lead researcher, my background in HD research and clinical practice was a fundamental part of the design and conduct of the study; the impact of which was considered reflexively throughout the research process (Braun & Clarke, 2023a). I used my experience to build a strong alliance during the interview which allowed me to ask meaningful questions in a genuine and unintrusive way. Sharing my experience and motivation for conducting the research with caregivers,

helped to create a safe, non-judgemental space where caregivers could reflect on their often difficult and emotive experiences. Furthermore, it shaped how I interacted with the data during the analysis and the lens through which I interpreted the caregivers' words. In rTA unlike other qualitative research, themes are considered to be a product of the interaction between the data and the researcher rather than something to be "*discovered*" within the data. As such, researcher subjectivity is considered to be a resource to be explored, understood and communicated to the reader (Braun & Clarke, 2023b) rather than a potential threat to the reliability and accuracy of the data. To achieve this transparently and robustly, I undertook a rigorous process that included reflexive journaling during the analysis process, reflexive discussions within the research team at all stages of the study and documentation of the research positions in the manuscript (Finlay & Gough, 2008). Furthermore, to support my analytic engagement in the coding process, I conducted, transcribed and analysed all interviews myself, which is considered good practice in rTA (Braun & Clarke, 2023a). Codes were developed organically and not through the use of a framework or codebook, and the process of coding continued throughout the analysis (Braun & Clarke, 2023a). The use of reflexivity in the empirical study was a further strength of the research.

However, I have been mindful throughout of the sense of responsibility I felt to share caregivers' unheard stories. As such, despite rTA embracing the role of the researcher, I have been conscious of aligning the findings as closely as possible to the caregivers' experience and not lean too heavily into my interpretation. To do this, I discussed themes extensively within the research team during the analysis, selected rich, illustrative quotes to support my interpretations and shared the results with the caregivers to check for resonance to their experience. The feedback indicated that caregivers felt their experience had been represented in the analysis and interpretation of the results. This level of engagement with the research was a final strength of the empirical study.

There were however, limitations of this work. Although difficulty recruiting caregivers from all four subtypes was identified as a potential risk during the planning stage of the study, it was not anticipated likely that this would occur. Agreement between patient and caregiver ratings of the DAS in HD has been shown to be good (Atkins et al., 2021) and my previous unpublished work suggested that all four subtypes of apathy were represented in caregiver ratings of apathy (Mason & Barker, 2022). Barriers to recruitment in the current study may be linked to the intolerance of online interviews or practical factors impacting caregiver participation such as the difficulty finding time to participate in research and the length of time the interviews took. In the design of the study, PPI was used to ensure that the language used was clear, concise and salient to the experience of caregivers (Boivin et al., 2018). Considerations were made to reduce the burden of participation on caregivers however, using PPI to explore these factors further may have identified considerations that I had not considered. Not having representation from all four subtypes of apathy was a limitation of the empirical study.

Strengths and Limitations of the Systematic Review

There are several strengths to the systematic review. As relational change is an understudied area in HD research, there is insufficient research to conduct a systematic review focussing specifically on studies of relational change in HD caregiver experience. Therefore, I adopted a broad search strategy capture any published work that might contain data pertaining to relational change embedded anywhere in the reported results, and undertook a rigorous, unautomated review of manuscripts in an attempt to include as much data relevant as possible. All stages of the process were completed by a second rater who independently competed the screening, data selection and quality appraisal stages of the systematic review and our findings were compared and amalgamated through discussion and mutual agreement. This process is considered good practice and helped to reduce researcher bias and increase study validity. Furthermore, the aim of the work in this portfolio

was to increase the visibility of the caregiver experience in HD and promote discussion about the concepts included. As such, the systematic review significantly contributes to this aim.

There are however, also limitations. A clear limitation is the lack of available data pertaining to relational change in HD which limited the scope of the systematic review and the richness and depth of the thematic synthesis. Furthermore, the small number of papers could also be argued to limit the generalisability of the findings (L Nowell et al., 2017). Whilst generalisability is often strived for in positivist research, it is not the aim of qualitative research conducted through the lens of critical realist philosophy, which focuses more on explanation and meaning, both of which were achieved in the thematic synthesis. Finally, it is a reflection of the current empirical landscape in HD, with it medical focus centred around the pwHD rather than the wider system, and was therefore unavoidable. Furthermore, a detailed description of the context of participants included for each study was provided, including demographics, country of origin, and gender information, allowing the reader to assess transferability of the findings. Information about the cultural representation and socioeconomic situation of participants was limited, which represents a limitation of the research.

Implications for Clinical Practice and Services

This portfolio highlights the importance of recognising and acknowledging the impact that HD has on caregivers. The historical conceptualisation of HD as a neurological disorder of movement, and the dominance of the medical model in our understanding of the disease, has meant that the clinical focus has centred around the person with the disease in isolation from the system around them. Consequently, the structure of HD specialist services is such that support for the caregiver is not provided within routine clinical care and many find it difficult to access (Willock et al., 2023). The experiential accounts shared in both the empirical study and the systematic review, highlighted the grief, fear and sadness of being an HD caregiver, which in some ways is similar to that of other caregivers, but in many ways unique to HD.

Both the empirical study and systematic review highlighted the absence of support for caregivers who felt unheard and judged by people outside the community. The lack of formal support overwhelmed caregivers with the sheer volume of physically and mental tasks that they were required to do. But, not having the informal support left people paralysed by social isolation and social fear as they were left existing in a space outside of friendships and the comfort of familiarity. The empirical study illuminated the importance placed on having a space to talk to someone who knew about HD but the conflicting awareness of wanting to avoid increasing the burden on other HD caregivers. Systemic approaches are common in other neurological conditions (Newby et al., 2019) and often rely on co-ordinating services in the NHS and third sector, similar may be appropriate for HD. However, adopting a systemic approach to the clinical management of the disease within existing specialist services, would go some way to address this need by utilising the experience held by clinical teams working in the field. Training existing staff in active listening skills, and ringfencing time within the current service provision to prioritise the needs of caregivers would provide some of the support needs identified by caregiver. Moreover, supporting caregivers to co-produce accessible and non-judgemental safe spaces where they can connect with others may also provide meaningful space for support.

Furthermore, restrictions imposed as a result of the COVID-19 pandemic which resulted in changes to clinical practice, have removed some forms of informal support that were previously available to caregivers. Namely, the implementation of virtual appointments means there is no longer the opportunity for casual conversations in clinic waiting rooms with other caregivers who have shared experiences, or opportunistic discussions with clinician while the pwHD is occupied elsewhere. Consideration of ways that these spaces for informal support can be reintroduce into the routine clinic visit, or recreated elsewhere would likely have a positive impact on caregivers capacity to manage and their emotional well-being. Reducing levels of caregiver depression, anxiety, burnout

and physical illness, would have positive implications for the pwHD facilitating them to be cared for at home for longer.

Finally, creating an open and inclusive narrative around the social and emotional symptoms of HD and the impact these have on those supporting someone with the disease, alongside the clinical care provided for the pwHD, would help to model what talking openly about HD looks like. Asking about this aspect of the disease, the impact on both the caregiver and their relationships, and preparing all involved for the possibility that these symptoms may emerge in the future would open a dialogue where it otherwise would go unnoticed. It would also increase knowledge and awareness about the often hidden aspects of the disease and support caregivers to recognise them as part of the disease process. Without a culture shift so that caregivers feel empowered to share, feel entitled to ask for help and don't feel guilty about complaining, wider change is unlikely to happen, as such there is a clear societal need for contextual change with services proactively advocating for the needs of caregivers.

Implications for Future Research

Among the rich and descriptive findings of the empirical study and the systematic review, the common narratives around ambiguous loss and anticipatory grief emerged as important factors in the HD caregiver experience. Future research should consider the extent to which these findings have common features across different samples, alongside exploration of the nuanced variation found across different caregiver and family circumstances, for example, with respect to the pre-diagnosis relationship and the wider societal contextual resources that may aid adaptation. Both the empirical study and the systematic review predominantly reflected the experience of female caregivers supporting male care recipients. Understanding whether their reflections were transferable to other caregiver-care recipient couplings would broaden the scope of the research. Similarly, including representation from people from a more diverse ethnic background is needed to

ensure all voices are equally represented. Newly developed, questionnaire based measures of anticipatory grief (Holm et al., 2019) may be a useful way of exploring its presence and severity in a wider population of culturally and socially diverse HD caregivers.

In the empirical study, ambiguous loss and anticipatory grief were understood as consequences of apathy. Exploring this relationship further would provide an opportunity through which to explore therapeutic options to help caregivers manage their distress. Namely, there is emerging evidence to support the efficacy of Acceptance and Commitment Therapy (ACT) as a practice that may help caregivers adjust to the losses associated with supporting someone with a long term condition (Han et al., 2021). Particularly for those caregivers supporting someone in the early stages of HD who struggle to recognise social and emotional apathy as part of the disease process, helping to reframe the loss of intimacy and connectedness may help to reduce some of the distress they experience. Evaluating the efficacy of ACT at reducing the emotional impact of apathy for HD caregivers would be an important next step. Furthermore, although HD is a degenerative process, research with survivors of acquired brain injury and their companions, has shown some therapeutic benefit following emotionally focused couples therapy (Yeates, 2013; Yeates et al., 2013). Future research may look to establish the feasibility of this approach in HD.

Wider psychological services are often not commissioned to provide support for pwHD or their caregivers due to the lack of empirical evidence supporting their involvement. Results from the empirical study suggested that future research to explore the efficacy of strategies such as psychoeducation on the role of apathy in HD and its multidimensional nature, or the use of bereavement interventions aimed at HD caregiver (Moss et al., 2021) may help to close this gap and make it easier for services to provide support where it is needed.

Finally, recognising that a significant proportion of caregivers in need of support who struggle to find the time, or find it difficult to give themselves permission to use the time for

dedicated psychological interventions, small scale service-related research or quality improvement project should look at the impact of wider system changes. Specifically, the effect of moving away from a positivist, medicalised "problem-treatment" model that disempowers caregivers and leaves them feeling isolated, guilty and trapped, towards a more constructionist model where the wider system is used to empower caregivers and create new narratives.

Overall Conclusions

This thesis portfolio aimed to develop an understanding of the HD caregiver experience of supporting someone with apathy and the wider impact of the symptoms of HD on changes in the relationship between caregivers and the pwHD. The motivation for this work was to guide the design of psychological interventions for apathy, enabling a move towards an evidence-based approach to psychological therapy in HD.

A qualitative empirical study of the meaning-making constructed by HD caregivers about apathy found that there was uncertainty about how the clinical definition, subjective experience and socially constructed meaning of apathy fit together. HD caregivers described how apathy made their lives both physically and mentally harder, with the expectation that they would do more than their share of daily tasks and hold more of the mental load. Emotionally, apathy was synonymous with a gradual loss of the former relationship between the HD caregiver and the pwHD, with many describing a grieving process even though their loved one had not died yet. Interwoven between these themes were complex narratives about the unspoken nature of HD, the invisibility of caregivers who felt trapped and unheard, and the one-sided nature of loving someone with the disease.

In response to these findings a systematic review of existing qualitative studies of the HD caregiver experience and a thematic synthesis of data pertaining to relational change was conducted to further explore the impact of HD on the interpersonal dynamics between the HD caregiver and the pwHD. Similarly, themes of loss of friendship, companionship and intimacy were identified with

caregivers describing feelings of grief as they watched the disease consume the person they once knew. Taking a wider lens on the HD caregiver experience helped to draw attention to the unique challenges presented by HD symptomatology namely, the fear and isolation that comes from supporting someone who is aggressive, and the shared genetic risk that challenged some caregivers.

Taken together, the findings highlight the under-recognised presence of ambiguous loss and anticipatory grief as factors which impact the emotional experience of HD caregivers. But beyond this, it draws attention to the profound existential challenges faced by HD caregivers many of whom expressed their feelings of guilt when talking openly about the reality of their situation. The portfolio recognises that caregivers are one element of the untold story in HD and emphasises the importance of considering this in future clinical and research practice whilst also recognising the extent of the paradigm shift needed to allow services to identify and offer support where needed.

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Appendices

Appendix A - Instructions for Authors and Formatting Instructions for Neuropsychological Rehabilitation

About the Journal

Neuropsychological Rehabilitation is an international, peer-reviewed journal publishing high-quality, original research. Please see the journal's Aims & Scope for information about its focus and peer-review policy.

Please note that this journal only publishes manuscripts in English.

Neuropsychological Rehabilitation accepts the following types of article: original articles, scholarly reviews, book reviews.

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**Usage in 2020-2022 for articles published in 2018-2022.

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All authors submitting to medicine, biomedicine, health sciences, allied and public health journals should conform to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, prepared by the International Committee of Medical Journal Editors (ICMJE).

Clinical trials: must conform to the Consort guidelines http://www.consort-statement.org. Submitted papers should include a checklist confirming that all of the Consort requirements have been met, together with the corresponding page number of the manuscript where the information is located. In addition, trials must be pre-registered on a site such as clinicaltrials.gov or equivalent, and the manuscript should include the reference number to the relevant pre-registration.

Systematic reviews: submitted papers should follow PRISMA http://www.prisma-statement.org/ guidelines and submission should also be accompanied by a completed PRISMA

checklist, together with the corresponding page number of the manuscript where the information is located.

Single-case studies: submitted papers should follow SCRIBE guidelines (http://psycnet.apa.org.uea.idm.oclc.org/fulltext/2016-17384-001.html) and include a completed SCRIBE checklist together with the corresponding page number of the manuscript where the information is located.

Observational studies: submitted papers should follow the STROBE guidelines (https://www.strobe-statement.org/index.php?id=strobe-home) and also include a completed checklist of compliance, together with the corresponding page number of the manuscript where the information is located.

Qualitative studies: should follow the COREQ guidelines (http://www.equator-network.org/reporting-guidelines/coreq/) and be accompanied by a completed COREQ checklist of compliance, together with the corresponding page number of the manuscript where the information is located.

The EQUATOR Network (Enhancing the Quality and Transparency of Health Research) website provides further information on available guidelines.

Structure

Your paper should be compiled in the following order: title page; abstract; keywords; main text introduction, materials and methods, results, discussion; acknowledgments; declaration of interest statement; references; appendices (as appropriate); table(s) with caption(s) (on individual pages); figures; figure captions (as a list).

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Spelling can be US or UK English so long as usage is consistent.

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Checklist: What to Include

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Twitter or LinkedIn). One author will need to be identified as the corresponding author, with their email address normally displayed in the article PDF (depending on the journal) and the online article. Authors' affiliations are the affiliations where the research was conducted. If any of the named co-authors moves affiliation during the peer-review process, the new affiliation can be given as a footnote. Please note that no changes to affiliation can be made after your paper is accepted. Read more on authorship.

Should contain an unstructured abstract of 200 words.

You can opt to include a **video abstract** with your article. Find out how these can help your work reach a wider audience, and what to think about when filming.

5 **keywords**. Read making your article more discoverable, including information on choosing a title and search engine optimization.

Funding details. Please supply all details required by your funding and grant-awarding bodies as follows:

For single agency grants

This work was supported by the [Funding Agency] under Grant [number xxxx].

For multiple agency grants

This work was supported by the [Funding Agency #1] under Grant [number xxxx]; [Funding Agency #2] under Grant [number xxxx]; and [Funding Agency #3] under Grant [number xxxx].

Disclosure statement. This is to acknowledge any financial interest or benefit that has arisen from the direct applications of your research. Further guidance on what is a conflict of interest and how to disclose it.

Data availability statement. If there is a data set associated with the paper, please provide information about where the data supporting the results or analyses presented in the paper can be

found. Where applicable, this should include the hyperlink, DOI or other persistent identifier associated with the data set(s). Templates are also available to support authors.

Data deposition. If you choose to share or make the data underlying the study open, please deposit your data in a recognized data repository prior to or at the time of submission. You will be asked to provide the DOI, pre-reserved DOI, or other persistent identifier for the data set.

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In order to be published in a Taylor & Francis journal, all clinical trials must have been registered in a public repository at the beginning of the research process (prior to patient enrolment). Trial registration numbers should be included in the abstract, with full details in the methods section. The registry should be publicly accessible (at no charge), open to all prospective registrants, and managed by a not-for-profit organization. For a list of registries that meet these requirements, please visit the WHO International Clinical Trials Registry Platform (ICTRP). The registration of all clinical trials facilitates the sharing of information among clinicians, researchers, and patients, enhances public confidence in research, and is in accordance with the ICMJE guidelines.

Complying With Ethics of Experimentation

Please ensure that all research reported in submitted papers has been conducted in an ethical and responsible manner, and is in full compliance with all relevant codes of experimentation and legislation. All papers which report in vivo experiments or clinical trials on humans or animals must include a written statement in the Methods section. This should explain that all work was conducted with the formal approval of the local human subject or animal care committees (institutional and national), and that clinical trials have been registered as legislation requires. Authors who do not have formal ethics review committees should include a statement that their study follows the principles of the Declaration of Helsinki.

Consent

All authors are required to follow the ICMJE requirements on privacy and informed consent from patients and study participants. Please confirm that any patient, service user, or participant (or that person's parent or legal guardian) in any research, experiment, or clinical trial described in your paper has given written consent to the inclusion of material pertaining to themselves, that they acknowledge that they cannot be identified via the paper; and that you have fully anonymized them. Where someone is deceased, please ensure you have written consent from the family or estate. Authors may use this Patient Consent Form, which should be completed, saved, and sent to the journal if requested.

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Please confirm that all mandatory laboratory health and safety procedures have been complied with in the course of conducting any experimental work reported in your paper. Please ensure your paper contains all appropriate warnings on any hazards that may be involved in carrying

out the experiments or procedures you have described, or that may be involved in instructions, materials, or formulae.

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Authors are further encouraged to cite any data sets referenced in the article and provide a Data Availability Statement.

At the point of submission, you will be asked if there is a data set associated with the paper. If you reply yes, you will be asked to provide the DOI, pre-registered DOI, hyperlink, or other persistent identifier associated with the data set(s). If you have selected to provide a pre-registered DOI, please be prepared to share the reviewer URL associated with your data deposit, upon request by reviewers.

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Updated 07-12-2023

Appendix B - COREQ (COnsolidated criteria for REporting Qualitative research) Checklist

COREQ (COnsolidated criteria for REporting Qualitative research) Checklist

A checklist of items that should be included in reports of qualitative research. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Topic	Item No.	Guide Questions/Description	Reported on Page No.
Domain 1: Research team and reflexivity			
Personal characteristics			
Interviewer/facilitator	1	Which author/s conducted the interview or focus group?	30
Credentials	2	What were the researcher's credentials? E.g. PhD, MD	28
Occupation	3	What was their occupation at the time of the study?	28
Gender	4	Was the researcher male or female?	28
Experience and training	5	What experience or training did the researcher have?	28
Relationship with participants			
Relationship established	6	Was a relationship established prior to study commencement?	28 & 30
Participant knowledge of the interviewer	7	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	30
Interviewer characteristics	8	What characteristics were reported about the inter viewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	28 & 30
Domain 2: Study design			
Theoretical framework			
Methodological orientation and Theory	9	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	27
Participant selection			
Sampling	10	How were participants selected? e.g. purposive, convenience, consecutive, snowball	29
Method of approach	11	How were participants approached? e.g. face-to-face, telephone, mail, email	28
Sample size	12	How many participants were in the study?	31
Non-participation	13	How many people refused to participate or dropped out? Reasons?	31
Setting			
Setting of data collection	14	Where was the data collected? e.g. home, clinic, workplace	30
Presence of non-participants	15	Was anyone else present besides the participants and researchers?	30
Description of sample	16	What are the important characteristics of the sample? e.g. demographic data, date	31 & 32
Data collection			
Interview guide	17	Were questions, prompts, guides provided by the authors? Was it pilot tested?	30
Repeat interviews	18	Were repeat inter views carried out? If yes, how many?	30
Audio/visual recording	19	Did the research use audio or visual recording to collect the data?	30
Field notes	20	Were field notes made during and/or after the inter view or focus group?	31
Duration	21	What was the duration of the inter views or focus group?	30
Data saturation	22	Was data saturation discussed?	29 & 30
Transcripts returned	23	Were transcripts returned to participants for comment and/or	31

Topic	Item No.	Guide Questions/Description	Reported on Page No.
		correction?	
Domain 3: analysis and findings			
Data analysis			
Number of data coders	24	How many data coders coded the data?	30 & 31
Description of the coding tree	25	Did authors provide a description of the coding tree?	34-37
Derivation of themes	26	Were themes identified in advance or derived from the data?	30-31
Software	27	What software, if applicable, was used to manage the data?	30
Participant checking	28	Did participants provide feedback on the findings?	31
Reporting			
Quotations presented	29	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	38-48
Data and findings consistent	30	Was there consistency between the data presented and the findings?	38-48
Clarity of major themes	31	Were major themes clearly presented in the findings?	38-48
Clarity of minor themes	32	Is there a description of diverse cases or discussion of minor themes?	38-48

Developed from: Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007. Volume 19, Number 6: pp. 349 – 357

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.

Appendix C – Letter of Ethical Approval for Empirical Study

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Dr Sarah Mason
Cambridge and Peterborough Foundation Trust
Elizabeth House
Fulbourn
CB21 5EF,

Email: approvals@hra.nhs.uk

24 January 2023

Dear Dr Mason,

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**A qualitative exploration of the impact of apathy on the caregiving relationship in the context of Huntington's disease.**
IRAS project ID:	**319976**
Protocol number:	**N/A**
REC reference:	**23/NW/0026**
Sponsor	**University of East Anglia**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **319976**. Please quote this on all correspondence.

Yours sincerely,
Chris King

Approvals Specialist

Email: approvals@hra.nhs.uk

Copy to: *Penny Harrison, Sponsor's Representative*

Health Research Authority

North West - Liverpool Central Research Ethics Committee
3rd Floor
Barlow House
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0207 104 8118

24 January 2023

Dr Sarah Mason
Cambridge and Peterborough Foundation Trust
Elizabeth House
Fulbourn
CB21 5EF

Dear Dr Mason,

Study title:	**A qualitative exploration of the impact of apathy on the caregiving relationship in the context of Huntington's disease.**
REC reference:	**23/NW/0026**
Protocol number:	**N/A**
IRAS project ID:	**319976**

Thank you for your letter of 20th January 2023, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved on behalf of the PR sub-committee.

Confirmation of ethical opinion

On behalf of the Research Ethics Committee (REC), I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Good practice principles and responsibilities

The UK Policy Framework for Health and Social Care Research sets out principles of good practice in the management and conduct of health and social care research. It also outlines the responsibilities of individuals and organisations, including those related to the four elements of research transparency:

1. registering research studies

2. reporting results
3. informing participants
4. sharing study data and tissue

Conditions of the favourable opinion

Confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or NHS management permission (in Scotland) should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All research should be registered in a publicly accessible database and we expect all researchers, research sponsors and others to meet this fundamental best practice standard.

It is a condition of the REC favourable opinion that **all clinical trials are registered** on a publicly accessible database within six weeks of recruiting the first research participant. For this purpose, 'clinical trials' are defined as:

- clinical trial of an investigational medicinal product
- clinical investigation or other study of a medical device
- combined trial of an investigational medicinal product and an investigational medical device
- other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice.

Failure to register a clinical trial is a breach of these approval conditions, unless a deferral has been agreed by the HRA (for more information on registration and requesting a deferral see: Research registration and research project identifiers).

If you have not already included registration details in your IRAS application form you should notify the REC of the registration details as soon as possible.

Publication of Your Research Summary

We will publish your research summary for the above study on the research summaries section of our website, together with your contact details, no earlier than three months from the date of this favourable opinion letter.

Should you wish to provide a substitute contact point, make a request to defer, or require further information, please visit:
https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/

N.B. If your study is related to COVID-19 we will aim to publish your research summary within 3 days rather than three months.

During this public health emergency, it is vital that everyone can promptly identify all relevant research related to COVID-19 that is taking place globally. If you haven't already done so, please register your study on a public registry as soon as possible and provide the REC with the registration detail, which will be posted alongside other information relating to your project. We are also asking sponsors not to request deferral of publication of research summary for any projects relating to COVID-19. In addition, to facilitate finding and extracting studies related to COVID-19 from public databases, please enter the WHO official acronym for the coronavirus disease (COVID-19) in the full title of your study. Approved COVID-19 studies can be found at:
https://www.hra.nhs.uk/covid-19-research/approved-covid-19-research/

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

After ethical review: Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study, including early termination of the study
- Final report
- Reporting results

The latest guidance on these topics can be found at
https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/.

Ethical review of research sites

The favourable opinion applies to all NHS/HSC sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" above).

Approved documents

The documents reviewed and approved by the Committee are:

Document	*Version*	*Date*
Copies of materials calling attention of potential participants to the	Version 1	09 September 2022

research [Advert]		
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		
Interview schedules or topic guides for participants [Topic guide]	Version 1	09 September 2022
IRAS Application Form [IRAS_Form_20122022]		20 December 2022
IRAS Checklist XML [Checklist_04012023]		04 January 2023
Letter from sponsor [Sponsor letter]		
Letters of invitation to participant [Invite letter]	Version 1	09 September 2022
Other [Response to REC]	Version 1	20 January 2023
Participant consent form [Consent]	Version 1	09 September 2022
Participant information sheet (PIS) [Participant Information Sheet]	Version 2	20 January 2023
Participant information sheet (PIS) [PIS_version 2.0_20.01.23_PPI added_tracked]	Version 2	20 January 2023
Referee's report or other scientific critique report [Scientific critique report]		
Research protocol or project proposal [Protocol]	Version 1	09 September 2022
Summary CV for Chief Investigator (CI) [CI CV_S Mason]	Version 1	25 November 2022
Summary CV for student [CV_SMason]	Version 1	25 November 2022
Summary CV for supervisor (student research) [Supervisor CV_RAB]	Version 1	25 November 2022
Summary CV for supervisor (student research) [Supervisor CV_CF]	Version 1	25 November 2022
Summary CV for supervisor (student research) [Supervisor CV_FG]	Version 1	25 November 2022
Summary of any applicable exclusions to sponsor insurance (non-NHS sponsors only)		
Validated questionnaire [DAS_C_apathy scale]	Version 1	09 September 2022
Validated questionnaire [AMI_C apathy scale]	Version 1	09 September 2022
Validated questionnaire [Online questionnaire]	Version 1	09 September 2022

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

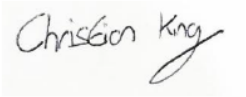
HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at:
https://www.hra.nhs.uk/planning-and-improving-research/learning/

IRAS project ID: 319976	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely



Christian King
Approvals Specialist

On behalf of

Mr Paul Mooney
Chair

Enclosures: "After ethical review – guidance for researchers"

Copy to: Penny Harrison, Sponsor's Representative

Lead Nation
approvals@hra.nhs.uk

Appendix D - Interview Topic Guide

Introduction

Thank you for agreeing to participate in the interview.

The aim of this work is to better understand what it is like to care for someone with Huntington's disease who also experiences some apathy. We are interested in your own experiences in as much detail as you feel comfortable to share. There are no right or wrong answers to any of the questions that I will ask you, and any information that you feel comfortable to share is valuable. There are no silly answers.

The interview should take approximately one hours but may be longer or shorter depending on your experiences.

As with all research, you are under no obligation to take part in this study. If you have changed your mind, you do not have to start the interview and you are free to stop at any time without providing an explanation. Your participation, or non-participation, will not influence the care that [ADD NAME OF HD PATIENT HERE] receives from the clinic in any way.

I would like to record the interview, so that I can do back to it later and make sure that I have understood everything correctly and haven't missed anything. It also means that I can give you my full attention during the interview.

Anything that you say will be kept in the strictest confidence. After the interview, our conversations will be transcribed, which means that that everything we have both said will be written down, exactly as we said it. At this time, all the identifiable information linking you to your words will be removed. It will not be possible to link anything that we use in the analysis and write up of the study back to you.

However, I need to make you aware that if you share anything during the interview that suggests that either you, or someone else is at risk of harm I will need to share this information with Prof Barker. I won't do that without your knowledge and I will talk to you about any concerns I have straight away.

Given of the above, are you happy for us to begin?

Part 1: Establishing rapport

Before we start I will explain a little about myself and my background. (Being aware of the biases that I bring and that it is likely that I will have worked with some of the participant families during my time at the VBG).

- For those people I have not worked with before I will update them on my history working with HD.

- For those people I have worked with before I will update them on the work I have been doing since leaving the VGB.

  I wonder whether you could briefly tell me a little about your history with HD?

Part 2: Experience of caring:

If you don't mind, I would like to start asking you some questions now.

Can you briefly tell me about your experiences of caring, some of the highs and some of the lows?

If they struggle, a few questions that could be asked are:

How long have you been caring for [ADD NAME OF HD PATIENT]?

How has that been for you?

How has this changed over time?

Have there been times when it has been easier? Could you tell me about that?

Have there been times when it has been harder? Could you tell me about that?

Part 3: Experience of apathy:

What do you understand by the term apathy?

Do you think apathy is one of the HD symptoms [INSERT NAME OF HD PATIENT] experiences?

Could you tell me about that? What have you noticed he/she does?

When we were designing this study we realised that the word “apathy” can mean very different things to different people. To make sure that everyone involved in this project has a shared understanding of what we mean by the term “apathy” we have put together some descriptions and examples that we think may be particularly relevant to the apathy that we see in people with Huntington’s disease. These are definitely not the only, or maybe even the best examples but they help to make sure that we are all talking about the same thing.

I would like to share these examples to you.

[READ TEXT DECIDED ON THROUGH PPI WORK HERE]

I wonder if any of these descriptions fit with anything [INSERT NAME OF HD PATIENT] does? Could you tell me about that?

How do you feel when he/she does this?

Are there any of these descriptions that surprised you?

Part 4: Impact of apathy on caregiver burden?

How do you think [INSERT NAME OF HD PATIENT]'s apathy changes the way you care for him/her?

If there was a magic tablet that that gave [INSERT NAME OF HD PATIENT] his/her motivation back how do you think your life would be different?

In your opinion, how do you think [INSERT NAME OF HD PATIENT]'s apathy impacts the way you feel about caring for him/her?

Finally, is there anything else that you feel is important for me to hear, about your experience of caring for [INSERT NAME OF PATIENT HERE]?

Part 5: Close

I would like to thank you for your time today and for being so open about your experiences. I truly value your input and you have given me so much to go away and think about.

The next stage of the research is for me to transcribe the interview that we have had today and start to analyse the data that has been collected.

Would you like to receive copies of the transcription when I have finished to check that I have understood and interpreted everything correctly?

Also, would you like to hear about the results of the study when I have finished? If so, what is the best way for me to share those with you?

Appendix E – eConsent Form for Empirical Study

(Form to be on headed paper)

IRAS ID:

Participant Identification Number for this trial:

CONSENT FORM

Title of Project: **A qualitative exploration of the impact of apathy on the caregivers relationship in the context of Huntington's disease**

Name of Researcher: Dr Sarah Mason

Please initial box

1. I confirm that I have read the information sheet dated..... (version.....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason up to the point that my interview is transcribed and anonymised, without my (or my companions) medical care or legal rights being affected. ☐

3. I understand that the interview will be recorded and stored securely on the UEA OneDrive until it has been fully transcribed. After transcription has been completed and the transcripts checked, I understand that the recording will be deleted. ☐

4. I understand that it will not be possible to fully anonymise the recording of the interview but that all efforts will be made to maintain my confidentiality. Transcripts will be fully anonymised and the recordings of the interview will be deleted once they have been transcribed and checked. ☐

5. I understand that direct quotes from my interview may be used in the analysis and write up of the study, but that all identifiable information will be removed to maintain my confidentiality. ☐

6. I understand that the recording of the interview may be sent to an external company to transcribe the data. All efforts will be made to remove any identifiable information from the recording before it is sent. Only companies who are fully compliant with UK GDPR and Data protection policies will be used. Companies will be required to fully delete all recordings after transcription has been completed and will not retain copies of the interview for any reason. ☐

7. I understand that my personal identifiable data (PID) will be held securely by the study team for the duration of the study to allow for my continued participation. However, I also understand that I am free to withdraw my permission for this at any time and request for my PID to be deleted. ☐

8. I agree to take part in the above study. ☐

_____ _____ _____

Name of Participant	Date	Signature
Name of Person seeking consent	Date	Signature

Appendix F – Participant Information Sheet for Empirical Study

University of East Anglia

A qualitative investigation of apathy in Huntington's disease: a caregivers perspective

We invite you to take part in a research study.

- Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve.
- Please take the time to read the following information carefully. Discuss it with friends and relatives if you wish.
- You are free to decide whether or not to take part in this research. If you chose not to take part, it will not affect the care that you, or the person you care for, gets from the team at the HD Clinic.
- Ask us if there is anything that is not clear or if you would like more information.

Important things that you need to know:

- We want to find out what people caring for some with Huntington's disease understand the term "apathy" to mean.
- We also want to know how and why "apathy" impacts on your ability to care for someone with Huntington's disease.
- The research will consist of individual interviews with people who care for someone with Huntington's disease who is apathetic.
- The interviews can be face-to-face or online.
- They will be run by a researcher whose job will be to make sure you can share their point of view in a friendly and safe environment.
- Questions will be asked to help direct the conversation, but there will be no pressure to answer if you don't want to or if you feel you have nothing to add.
- You can stop taking part at any time

Contents

How to contact us:

If you have any questions about this study, please talk to the researcher who organised it:
Dr Sarah Mason:
[ADD PHONE NUMBER] or SMason1@uea.ac.uk

1. Who am I?

My name is Sarah Mason, I previously worked at the HD Clinic with Prof Roger Barker and some of you may have seen me there. I am currently completing my Doctorate in Clinical Psychology and this project will form part of my thesis.

1. Why are we doing this study?

What is apathy?

The recent Task Force has defined apathy as: "a quantitative reduction in goal directed behaviour compared to a patient's previous level of functioning". But is more general terms, apathy is a lack of motivation, interest or desire to take part in activities the person uses to do.

Why do research into how caregivers experience apathy in Huntington's disease?

Patients with Huntington's disease can experience a number of changes to their thinking and motivation that evolve over the course of the disease. For example, they can appear to lose interest in the hobbies that they used to do; they may find it harder to take part in social situations or be reluctant to be around other people at all and they can also stop the necessary activities of daily living such as washing and self-care. We know from our experience in clinic that people with HD are often not troubled by these changes but we also know that they can be very distressing for those people around them who are trying to support and care for them.

Therefore, in the current project we aim to find out:

- What apathy looks like in Huntington's disease, from the eyes of the caregiver?
- How this influences the burden of caring for someone with Huntington's disease?
- What about the apathy makes it so impactful for those caring for them and what is helpful to manage it?

Why is this important?

Answering these questions will help us to understand the true impact of apathy in Huntington's disease. It will also provide some new ideas to help us start to think about ways that we can support people with Huntington's disease and their families by reducing the impact of apathy in Huntington's disease

2. Why am I being asked to take part?

You are being asked to take part because you are a caregiver for someone with Huntington's disease. We think that you are the best people to help us get the most accurate answers to the questions above.

3. What will taking part involve?

If you express an interest in taking part in this research you will first be asked to complete an online questionnaire. This questionnaire will ask some questions about you and some questions about your perspective on some of the symptoms that the person you care for may (or may not) experience.

After completing the online questionnaire, you may be asked to take part in an interview to discuss your thoughts, opinions and experiences of apathy in Huntington's disease. The conversation will be led by a researcher who will introduce different topics and questions, but the conversation will be very informal and we will aim to make it as enjoyable as possible. You should feel free to express yourself throughout the session and share any opinions you have.

Will I have to answer all the questions?

No, the researcher in charge of the interview will have a script of questions that are designed to steer the conversation, but you may feel that not all the questions apply to you. It is perfectly acceptable to answer some questions and not others. You will also be encouraged to bring your own thoughts and questions to the interview.

Will the sessions be recorded?

Yes, the discussion will be recorded in order to transcribe the data later but we will not ask you to give any of your personal information in the interview and it will not be possible to identify you from the information that will be transcribed. These recordings will be kept securely on University of East Anglia OneDrive and will be destroyed once the transcription process in complete.

How often will I need to come?

You will only need to come **once**.

How long will the research take?

The researcher leading the interview will aim to keep the sessions to about **1 hours** but if there are lots of interesting discussions, and you are willing, the session may run slightly over this time. However, as with all of our research you are free to leave at any time if you wish to.

4. Important things I should know about the data collected:

- **We, as a research team, will treat your personal identifiable data (PID) with the upmost respect and we ensure that all information collected about you during the research will be kept strictly confidential**. We fully comply with the University of East

Anglia's information governance policy regarding the collection, processing, storage and disclosure of personal information, full details of which are available on request.

- **It will not be possible for anyone outside of the research team to identify you or your comments from any of the transcripts taken from the interviews.** Despite the interview being recorded, when the conversations are transcribed you will be identified using a pseudonym and only the researchers in the study will be able to identify you from this. We will remove any information that may identify you from any direct quotes that we use in the publication of this research
- **The results of this study may be shared with collaborators and members of the wider research community upon request.** We believe that this promotes the open and transparent conduct of research by allowing others to scrutinise our work. As a result, your anonymised data (but **never any identifiable data**) may be shared with researchers abroad including those from outside the European Economic Area (EEA). Each request will be reviewed on an individual basis to ensure its integrity.

5. More information about taking part:

Where will the research be held?

You can chose between having the interview in your own home, having the interview online or, if you prefer, having the interview at confidential place that is convenient for you.

Will I get paid to take part?

We do not have any money to pay you for your time, but if you are traveling to the interview we can offer you a £10 voucher to help contribute to the cost of your transport.

Do I have to take part?

No, it is up to you to decide whether you or not to take part. We will describe the study and go through this information sheet with you. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form, which you will get a copy of. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you or your relatives receive.

6. Management of the study:

Who is sponsoring the research?

The University of East Anglia (UEA) is acting as the sponsor for this study.

Who has reviewed the study?

This study has been reviewed and given favourable ethical opinion by <<INSERT REC>>

Where should I go if I have a complaint to make about the research or the way it was conducted?

If you have concerns about the way the study has been conducted please contact:

Prof Sian Coker

Norwich Medical School

University of East Anglia

Norwich, NR 4 7TJ

Email: S.Coker@uea.ac.uk

7. How will we use your information:

We will need to use information from you for this research project.

This information will include your name and contact details. People will use this information to do the research and to check your records to make sure that the research is being done properly.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

We will keep all information about you safe and secure.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

It is our intention that transcription of the interviews will be done by the lead researcher. However, if this is not possible or practical (due to time constraints or other limitations) transcription will be outsourced to a third party. In the event that transcription is outsourced to a third party a data processing agreement (containing confidentiality obligations) will be undertaken between the sponsor (University of East Anglia) and the third party undertaking the transcription. The data processing agreement will ensure that the processing is carried out in accordance with UK GDPR. Care will be taken to ensure that the third party undertaking the

transcriptions will be based in the UK or EEA to further ensure that the processing is carried out in accordance with UK GDPR.

8. What are your choices about how the information is used?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.

If you agree to take part in this study, you will have the option to take part in future research using your data saved from this study.

9. Where you can find out more about how your information is used?

You can find out more about how we use your information

- at www.hra.nhs.uk/information-about-patients/
- by asking one of the research team
- by sending an email to dataprotection@uea.ac.uk, or
- by ringing Ellen Patterson on 07824527234

10. How to contact us:

If you have any questions about this study, please talk to the researcher who organised it: Dr Sarah Mason on: **[INSERT PHONE NUMBER HERE] or SMason1@uea.ac.uk**

Appendix G – Patient and Public Involvement Questionnaire on the understanding of apathy and common language used.

How we talk about apathy

We are in the process of designing a new study to look at the ways in which apathy can impact the lives of people with Huntington's disease and the people around them.

We are aware that we can all sometimes use different language to talk about the same concepts. This is often true where a concept is used in both a clinical setting and in everyday life, for example the word "apathy".

To make sure that we have a shared understanding when we talk and think about apathy in Huntington's disease I would like to ask you a couple of questions about the terms that we use and your understanding of them.

This information will help me to use the best language when I prepare the documents that will go out to patients and their families when we are both recruiting for and running the study.

Thank you for your time and help.

1. These are all different ways of describing the same concept. Which of them do you confidently feel like you know what it means?

- ☐ Apathy
- ☐ Demotivation
- ☐ Lack of motivation

2. Which description do you think best describes, and/or is used most often to describe the experiences of people with Huntington's disease

- ○ Apathy
- ○ Demotivation
- ○ Lack of Motivation

3. Imagine someone who experiences high levels of apathy, demotivation or a lack of motivation. In which of the following situations would you expect to see evidence of this in their behaviour?

- [ ] Taking part in social activities
- [ ] Showing affection for other people they care about
- [ ] Starting new activities
- [ ] Planning to things
- [ ] Taking part in hobbies they used to do
- [ ] Starting new hobbies
- [ ] Completing daily chores
- [ ] Self care
- [ ] Taking part in conversations
- [ ] Finishing things they have started
- [ ] Crying or being sad when they hear sad news
- [ ] Celebrating or smiling when they hear happy news
- [ ] Starting conversations
- [ ] Planning for the future

4. Imagine someone who experiences high levels of apathy, demotivation or a lack of motivation. In which of the following situations would you NOT expect to see evidence of this in their behaviour?

- [ ] Taking part in social activities
- [ ] Showing affection for other people they care about
- [ ] Starting new activities
- [ ] Planning to things
- [ ] Taking part in hobbies they used to do
- [ ] Starting new hobbies
- [ ] Completing daily chores
- [ ] Self care
- [ ] Taking part in conversations
- [ ] Finishing things they have started
- [ ] Crying or being sad when they hear sad news
- [ ] Celebrating or smiling when they hear happy news
- [ ] Starting conversations
- [ ] Planning for the future

5. In your own words, how would you describe apathy, demotivation or a lack of motivation

6. Are their better words that you use to describe describe the apathy, demotivation or lack of motivation experienced by some people with Huntington's disease? If so could you please share them below.

7. Would you mind being contacted to discuss this topic further?

- ◯ Yes
- ◯ No

Appendix H – Non-Substantial amendment to REC

Amendment Tool v1.6 06 December 2021	For office use QC: No

Section 1: Project information

Short project title*:	Impact of apathy on caregiving in HD. Version 1.
IRAS project ID* (or REC reference if no IRAS project ID is available):	319976
Sponsor amendment reference number*:	NSA 1
Sponsor amendment date* (enter as DD/MM/YY):	12 May 2023
Briefly summarise in lay language the main changes proposed in this amendment. Explain the purpose of the changes and their significance for the study. If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained (note: this field will adapt to the amount of text entered)*:	After opening recruitment, the feedback from some potential participants (Huntington's disease caregivers) was that they would like to opportunity to co-ordinate their participation in the study with their companion's (Huntington's disease patient's) clinic appointment. The reason given was that they felt uncomfortable talking openly about their experiences if their companion could hear them and, due to the advanced stage of their companions Huntington's disease), the only time they were apart was when they were at clinic. Listening to this feedback, and in the interest of recruiting a representative population of participants that was not biased by these practical constraints, we are asking for the ethical approval to be amended to include: (1) The opportunity to co-ordinate participation with their companions appointment at the NHS HD clinic. This would require permission to use a clinic room at the PIC site (Cambridge University Hospitals NHS Foundation Trust). (2) Allow for shorter interviews if necessary so as not to disrupt the NHS HD clinic in anyway. All other aspects of the conduct of the study remains unchanged. The PIC site will not be required to undertake any additional responsibilities (outside of identifying potential participants). The study documents have been amended to reflect these changes.

Project type (select):	**Specific study**			
	Research tissue bank			
	Research database			
Has the study been reviewed by a UKECA-recognised Research Ethics Committee (REC) prior to this amendment?:	**Yes**		No	
What type of UKECA-recognised Research Ethics Committee (REC) review is applicable? (select):	**NHS/HSC REC**			
	Ministry of Defence (MoDREC)			
Is all or part of this amendment being resubmitted to the Research Ethics Committee (REC) as a **modified amendment** (i.e. a substantial amendment previously given an unfavourable opinion)?	Yes		**No**	
Where is the NHS/HSC Research Ethics Committee (REC) that reviewed the study based?:	England	Wales	Scotland	Northern Ireland
	Yes	No	No	No
Was the study a clinical trial of an investigational medicinal product (CTIMP) OR does the amendment make it one?:	Yes		**No**	
Was the study a clinical investigation or other study of a medical device OR does the amendment make it one?:	Yes		**No**	
Did the study involve the administration of radioactive substances, therefore requiring ARSAC review, OR does the amendment introduce this?:	Yes		**No**	
Did the study involve the use of research exposures to ionising radiation (not involving the administration of radioactive substances) OR does the amendment introduce this?:	Yes		**No**	
Did the study involve adults lacking capacity OR does the amendment introduce this?:	Yes		**No**	
Did the study involve access to confidential patient information outside the direct care team without consent OR does the amendment introduce this?:	Yes		**No**	
Did the study involve prisoners or young offenders who are in custody or supervised by the probation service OR does the amendment introduce this?:	Yes		**No**	
Did the study involve children OR does the amendment introduce this?:	Yes		**No**	
Did the study involve NHS/HSC organisations prior to this amendment?:	**Yes**		No	
Did the study involve non-NHS/HSC organisations OR does the amendment introduce them?:	**Yes**		No	
	England	Wales	Scotland	Northern Ireland
Lead nation for the study:	**Yes**	No	No	No

Which nations had participating NHS/HSC organisations prior to this amendment?	**Yes**	No	No	No
Which nations will have participating NHS/HSC organisations after this amendment?	**Yes**	No	No	No
Was this a "single site, self sponsored" study in England or Wales prior to this amendment?	**Yes**		No	
Which nations had participating non-NHS/HSC organisations prior to this amendment?	**Yes**	No	No	No
Which nations will have participating non-NHS/HSC organisations after this amendment?	**Yes**	No	No	No

Section 2: Summary of change(s)

Please note: Each change being made as part of the amendment must be entered separately. For example, if an amendment to a clinical trial of an investigational medicinal product (CTIMP) involves an update to the Investigator's Brochure (IB), affecting the Reference Safety Information (RSI) and so the information documents to be given to participants, these should be entered into the Amendment Tool as three separate changes. A list of all possible changes is available on the "Glossary of Amendment Options" tab. To add another change, click the "Add another change" box.

Change 1	
Area of change (select)*:	Study Design
Specific change (select - only available when area of change is selected first)*:	Other minor change to study design that can be implemented within existing resource in place at participating organisations - Please specify in the free text below
Further information In particular, please describe why this change can be implemented within the existing resource in place at the participating organisations (free text - note that this field will adapt to the amount of text entered)*	(1)To allow for study related interviews to be conducted in an clinic room, adjacent to the NHS HD Clinic (PIC site), to accommodate the participant (Huntington's disease carer)'s request to co-ordinate their study participation and their companion's (Huntington's disease patient) clinic appointment. (2)To allow for shorter interviews, if necessary, to prevent any disruption to the running of the NHS HD Clinic as a result of the participants (Huntington's disease carer) interview coinciding with their companion's (Huntington's disease patients) clinic appointment.

Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	**Yes**	No	No	No
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	**All**		Some	
Where are the participating non-NHS/HSC organisations located that will be affected by this change?*:	**Yes**	No	No	No
			Remove all changes below	

Change 2	
Area of change (select)*:	Study Documents
Specific change (select - only available when area of change is selected first)*:	Other minor change to study documents (e.g. information sheets, consent forms, questionnaires, letters) that can be implemented within existing resource in place at participating organisations - Please specify in the free text below
Further information In particular, please describe why this change can be implemented within the existing resource in place at the participating organisations (free text - note that this field will adapt to the amount of text entered)*	Amendments to the protocol to reflect the changes above

Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	**Yes**	No	No	No
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	**All**		Some	
Where are the participating non-NHS/HSC organisations located that will be affected by this change?*:	**Yes**	No	No	No
			Add another change	

Section 3: Declaration(s) and lock for submission

Declaration by the Sponsor or authorised delegate

- I confirm that the Sponsor takes responsibility for the completed amendment tool
- I confirm that I have been formally authorised by the Sponsor to complete the amendment tool on their behalf

*Name [first name and surname]**:	Tracy Moulton
*Email address**:	t.moulton@uea.ac.uk

Lock for submission

Please note: This button will only become available when all mandatory (*) fields have been completed. When the button is available, clicking it will generate a locked PDF copy of the completed amendment tool which must be included in the amendment submission. Please ensure that the amendment tool is completed correctly before locking it for submission.

Lock for submission

After locking the tool, proceed to submit the amendment online. The "Submission Guidance" tab provides further information about the next steps for the amendment.

Section 4: Review bodies for the amendment

Please note: This section is for **information only**. Details in this section will complete automatically based on the options selected in Sections 1 and 2.

	Review bodies																	
	UK wide:						England and Wales:				Scotland:				Northern Ireland:			
	REC	Competent Authority MHRA - Medicines	Competent Authority MHRA - Devices	ARSAC	Radiation Assurance	UKSW Governance	REC (MCA)	CAG	HMPPS	HRA and HCRW Approval	REC (AWMA)	PBPP	SPS (RAEC)	National coordinating function	HSC REC	HSC Data Guardians	Prisons	National coordinating function	Category:
Change 1:						(Y)				(Y)									C
Change 2:						(Y)				(Y)									C
Overall reviews for the amendment:																			
Full review:						N				N									
Notification only:						Y				Y									
Overall amendment type:	Non-substantial, no study-wide review required																		
Overall Category:	C																		

IRAS 319976. Amendment

N

no-reply-IRAS <no-reply-iras@hra.nhs.uk>
To Sarah Mason (MED - Postgraduate Researcher)

Reply | Reply All | Forward | ...
Fri 12/05/2023 14:55

IRAS Project ID: 319976
Sponsor amendment reference: NSA 1

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For studies with more than one UK research site, your amendment will now be automatically shared with the R&D offices of any NHS/HSC research sites in Scotland and Northern Ireland, but you should share the amendment by email directly with those Research team/s.

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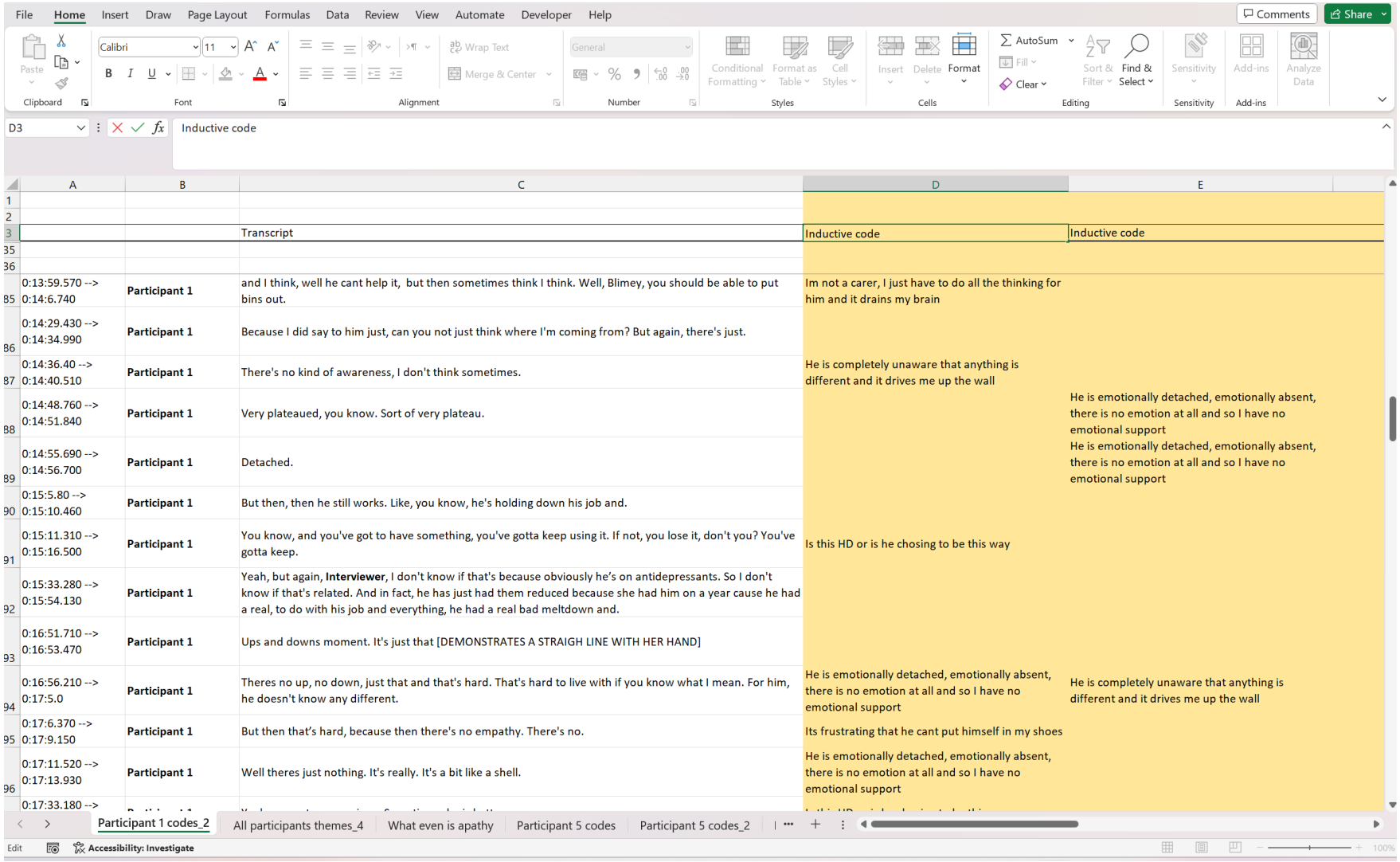

	Transcript	Inductive code	Inductive code
0:13:59.570 --> 0:14:6.740	**Participant 1**	and I think, well he cant help it, but then sometimes think I think. Well, Blimey, you should be able to put bins out.	Im not a carer, I just have to do all the thinking for him and it drains my brain	
0:14:29.430 --> 0:14:34.990	**Participant 1**	Because I did say to him just, can you not just think where I'm coming from? But again, there's just.		
0:14:36.40 --> 0:14:40.510	**Participant 1**	There's no kind of awareness, I don't think sometimes.	He is completely unaware that anything is different and it drives me up the wall	
0:14:48.760 --> 0:14:51.840	**Participant 1**	Very plateaued, you know. Sort of very plateau.		He is emotionally detached, emotionally absent, there is no emotion at all and so I have no emotional support
0:14:55.690 --> 0:14:56.700	**Participant 1**	Detached.		He is emotionally detached, emotionally absent, there is no emotion at all and so I have no emotional support
0:15:5.80 --> 0:15:10.460	**Participant 1**	But then, then he still works. Like, you know, he's holding down his job and.		
0:15:11.310 --> 0:15:16.500	**Participant 1**	You know, and you've got to have something, you've gotta keep using it. If not, you lose it, don't you? You've gotta keep.	Is this HD or is he chosing to be this way	
0:15:33.280 --> 0:15:54.130	**Participant 1**	Yeah, but again, **Interviewer**, I don't know if that's because obviously he's on antidepressants. So I don't know if that's related. And in fact, he has just had them reduced because she had him on a year cause he had a real, to do with his job and everything, he had a real bad meltdown and.		
0:16:51.710 --> 0:16:53.470	**Participant 1**	Ups and downs moment. It's just that [DEMONSTRATES A STRAIGH LINE WITH HER HAND]		
0:16:56.210 --> 0:17:5.0	**Participant 1**	Theres no up, no down, just that and that's hard. That's hard to live with if you know what I mean. For him, he doesn't know any different.	He is emotionally detached, emotionally absent, there is no emotion at all and so I have no emotional support	He is completely unaware that anything is different and it drives me up the wall
0:17:6.370 --> 0:17:9.150	**Participant 1**	But then that's hard, because then there's no empathy. There's no.	Its frustrating that he cant put himself in my shoes	
0:17:11.520 --> 0:17:13.930	**Participant 1**	Well theres just nothing. It's really. It's a bit like a shell.	He is emotionally detached, emotionally absent, there is no emotion at all and so I have no emotional support	
0:17:33.180 -->				

Appendix J – Authors Guidelines and Formatting Instructions for Journal of Huntington's disease

SUBMISSION OF MANUSCRIPT

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The article type (Research paper, Review paper, Editorial, Case Report, Letter to the Editor, etc) should be clearly mentioned in the cover letter to help the editorial process.

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The manuscript and accompanying files such as figures and tables can be submitted separately or as part of the main file. The manuscript file should be a Word document. Separate high resolution figures, supplemental material, or a supplemental video can also to be included with the submission. If the video is too large to submit, please contact jhd@iospress.com to arrange a file transfer. Further information about submitting supplementary data can be found below.

Resubmissions should include the manuscript number in the cover letter. The author's replies to the reviewer comments should be included within the revised manuscript itself (at the top). The revised paper should always be a Word document.

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Procedures involving experimentation on animal subjects should be in accord with either the guide of the institution in which the experiments were done, or with the National Research Council's guide for the care and use of laboratory animals. The author must state compliance in the cover letter and in the Methods section of the article.

Preferably patients in figures should be unrecognizable. Authors are responsible for obtaining patient permission for use of the material from all recognizable participants in photographs, videos, or other information that may be published in the Journal or on the journal's website. A statement that permission was granted by the patient must accompany the figure legend. Do not use study participants' names, initials, or hospital numbers anywhere in the manuscript (including figures).

PREPARATION OF MANUSCRIPTS

Research Reports

Organization and style of presentation

1. Manuscripts must be written in English. Authors whose native language is not English are advised to consult a professional English language editing service or a native English speaker prior to submission.

2. Manuscripts should be double spaced throughout with wide margins (2.5cm or 1in), including the abstract and references. Every page of the manuscript, including the title page, references, tables, etc., should include a page number centered at the bottom.

3. Manuscripts should be organized in the following order with headings and subheadings typed on a separate line, without indentation.

Title page

Title (should be clear, descriptive and concise).

Full name(s) of author(s).

Full affiliation(s). Delineate affiliations with lowercase letters.

Present address of author(s), if different from affiliation.

Running title (45 characters or less, including spaces).

Complete correspondence address, including telephone number and email address.

Leave the author information blank if double-blind peer review is wished for, but do include the information in the cover letter.

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When submitting the manuscript the author listing and order should be final. If any addition, deletion or rearrangement of author names in the authorship list does need to be made after submission, this can be done only before acceptance and with the Editor's approval. To request such a change, the Editor must receive the following from the corresponding author: (1) the reason for the change in author list and (2) written confirmation from all authors, including the affected author, that they agree with the addition, removal or rearrangement.

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Abstract and Keywords

-The abstract for research papers should follow the "structured abstract" format:

BACKGROUND:

OBJECTIVE:

METHODS:

RESULTS:

CONCLUSIONS:

The abstract should try to be no longer than 250 words.

- For other papers such as Reviews, the abstract should be clear, descriptive, and self-explanatory, and no longer than 250 words.

- Include a list of 4-10 keywords. These keywords should be terms from the MeSH database.

Introduction

Materials and Methods

Results

Discussion

Acknowledgments

Include individuals or companies which have assisted with your study, including advisors, administrative support and suppliers who may have donated or given materials used in the study.

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Examples for your paper's "Data Availability" statement:

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[1] Rose ME, Huerbin MB, Melick J, Marion DW, Palmer AM, Schiding JK, et al. Regulation of

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Tables

- Number according to their sequence in the text. The text should include references to all tables.
- Provide each table on a separate page of the manuscript after the references.
- Include a brief and self-explanatory title with any explanations essential to the understanding of the table given in footnotes at the bottom of the table.
- Vertical lines should not be used to separate columns. Leave some extra space between the columns instead.

Figure Legends

Figures

- Number the figures according to their sequence in the text. The text should include references to all figures.

- Figures should preferably be formatted in TIF or EPS format. JPG is also acceptable.

- A description of the statistical treatment of error analysis should be included in the figure or legend. We discourage the use of bar graphs where possible.

- Figures should be designed with the format of JHD in mind and preferable sized as they will appear when printed. A single column of the journal is 77mm and two columns are 165mm.

- Figures should be at 300 dpi or higher and be cropped to include the figure only (no blank space). CMYK is preferred for color figures.

- On figures where a scale is needed, use bar scales to avoid problems if the figure needs to be reduced.

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- Costs for color figures in the print version of the journal are as follows: 1 figure - 650 euro; 2 figures - 900 euro; 3 figures - 1050 euro; 4 figures - 1200 euro; 5 figures - 1350 euro. Cost for each additional color figure will be 150 euro. Color figures are free in the electronic version of the journal. You may opt to send in both black/white figures for print, and color figures for the online PDF (please adjust the figure legend appropriately).

Supplementary Material

Supplementary material can be submitted with the manuscript, included within the manuscript after the Figures and Tables (or otherwise after the References). Each supplementary item should have a legend and should not exceed the file size of 10MB. Supplemental videos can be submitted separately (see top of page for submission guidelines of videos). A short description of the supplementary items should be included under the header of “Supplementary Material” within the

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Review Articles

Reviews should be authoritative and topical and provide comprehensive and balanced coverage of a timely and/or controversial issue. Reviews should be prepared as detailed above for a Research Report, omitting Introduction through Discussion, and include a conclusion.

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A short communication is an article of original scholarship of unusual interest of less than 1500 words (not including references). An abstract of 100 words or less should be included with no subdivison of text into sections. References should be formatted as above. A total of two tables and/or figures are allowed.

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A hypothesis article should be a balanced and insightful consideration of a topic with novel hypotheses well presented and supported. The article should be prepared as a Research Report but without Methods or Results sections.

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Book reviews should be 750 words or less and without sections. Suggestions can be proposed to the Editors-in-Chief.

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JHD Inclusions are brief commentaries written by the authors of recent high-impact papers in the field of HD research.

The JHD Editors will reach out to authors of highly significant publications to provide a short summary of their work. This can include additional insights or interpretations on the relevant topic. Potential authors for these Inclusion commentaries are welcome to also contact one of the Editors-in-Chief to inquire about the possibility of submitting to JHD.

The Inclusion commentary can include new data of relevance to the original paper including updating reported findings or additional data excluded from the original paper due to length restrictions. In addition we recommend adding a graphical description of the key findings of the original article.

There is no formal abstract (first paragraph should be a short summary and will be used as an abstract in pubmed) Total text length should be from 750 to 1500 words (limited to less than 1,500 words) with a maximum of 3 figures/tables. Word count does not including figure legends, which should be a maximum of 150 words for each figure. Inclusions can have up to 10 references but will need to have a very clear focus on the the original paper. Inclusions will be citable in punned.

Section: Controversies

This will be a section with Pro and Con commentaries on a specific topic of interest to the HD community. Each author will generate a short opinion piece which will have a maximum of 1000 to 2000 words (with one figure and max 15 references) to make the basic argument. Both sets of authors will receive a copy of both articles, and will be given two weeks to generate a short (200 word max.) rebuttal prior to publication. It is recommended that unsolicited authors email a proposal letter and formal academic outline of the discussion to the Editors (at jhd@iospress.com) to assess the topic, before submitting manuscripts.

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- A list of at least 4-6 potential reviewers knowledgeable in the area of the study and potential reviewer conflicts.

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Appendix K - ENTREQ statement

Item No.	Guide and Description	Report Location (Reported under the heading it is presented in)
1. Aim	State the research question the synthesis addresses	Introduction
2. Synthesis methodology	Identify the synthesis methodology or theoretical framework which underpins the synthesis, and describe the rationale for choice of methodology (e.g. metaethnography, thematic synthesis, critical interpretive synthesis, grounded theory synthesis, realist synthesis, meta-aggregation, meta-study, framework synthesis)	Method Thematic synthesis Coding text and developing descriptive themes and generating analytic themes
3. Approach to searching	Indicate whether the search was pre-planned (comprehensive search strategies to seek all available studies) or iterative (to seek all available concepts until they theoretical saturation is achieved)	Pre-planned – Search strategy and study identification
4. Inclusion criteria	Specify the inclusion/exclusion criteria (e.g. in terms of population, language, year limits, type of publication, study type)	Inclusion/Exclusion criteria, Table 4.1

5. Data sources	Describe the information sources used (e.g. electronic databases (MEDLINE, EMBASE, CINAHL, psycINFO), grey literature databases (digital thesis, policy reports), relevant organisational websites, experts, information specialists, generic web searches (Google Scholar) hand searching, reference lists) and when the searches conducted; provide the rationale for using the data sources	Search strategy and study identification
6. Electronic Search strategy	Describe the literature search (e.g. provide electronic search strategies with population terms, clinical or health topic terms, experiential or social phenomena related terms, filters for qualitative research, and search limits)	Appendix L
7. Study screening methods	Describe the process of study screening and sifting (e.g. title, abstract and full text review, number of independent reviewers who screened studies)	Search outcome
8. Study characteristics	Present the characteristics of the included studies (e.g. year of publication, country, population, number of participants, data collection, methodology, analysis, research questions)	Study characteristics, Table 4.3
9. Study selection results	Identify the number of studies screened and provide reasons for study exclusion (e.g. for comprehensive searching, provide numbers of studies screened and reasons for exclusion indicated in a figure/flowchart; for	Figure 4.1

	iterative searching describe reasons for study exclusion and inclusion based on modifications to the research question and/or contribution to theory development)	
10. Rationale for appraisal	Describe the rationale and approach used to appraise the included studies or selected findings (e.g. assessment of conduct (validity and robustness), assessment of reporting (transparency), assessment of content and utility of the findings)	quality appraisal, Table 4.3
11. Appraisal items	State the tools, frameworks and criteria used to appraise the studies or selected findings (e.g. Existing tools: CASP, QARI, COREQ, Mays and Pope [25]; reviewer developed tools; describe the domains assessed: research team, study design, data analysis and interpretations, reporting)	CASP, Table 4.2, Table 4.3
12. Appraisal process	Indicate whether the appraisal was conducted independently by more than one reviewer and if consensus was required	Quality appraisal
13. Appraisal results	Present results of the quality assessment and indicate which articles, if any, were weighted/excluded based on the assessment and give the rationale	Quality appraisal, Table 4.3
14. Data extraction	Indicate which sections of the primary studies were analysed and how were the data extracted from the primary studies? (e.g. all text under the headings “results	Thematic synthesis

	/conclusions" were extracted electronically and entered into a computer software)	
15. Software	State the computer software used, if any	Coding text and developing descriptive themes
16. Number of reviewers	Identify who was involved in coding and analysis	Thematic synthesis, Coding text and developing descriptive themes, Generating analytic themes
17. Coding	Describe the process for coding of data (e.g. line by line coding to search for concepts)	Coding text and developing descriptive themes
18. Study comparison	Describe how were comparisons made within and across studies (e.g. subsequent studies were coded into pre-existing concepts, and new concepts were created when deemed necessary)	Coding text and developing descriptive themes,
19. Derivation of themes	Explain whether the process of deriving the themes or constructs was inductive or deductive	Generating analytic themes

20. Quotations	Provide quotations from the primary studies to illustrate themes/constructs, and identify whether the quotations were participant quotations of the author's interpretation	Results
21. Synthesis output	Present rich, compelling and useful results that go beyond a summary of the primary studies (e.g. new interpretation, models of evidence, conceptual models, analytical framework, development of a new theory or construct)	Results

Appendix L - Medline Search Strategy for Systematic Review:

S1	AB “Huntington’s disease” OR TI “Huntington’s disease”	31278
S2	AB “Huntington disease” OR TI “Huntington disease”	6288
S3	AB “Huntington’s chorea” OR TI “Huntington’s chorea”	800
S4	AB “Huntington chorea OR TI “Huntington chorea”	32
S5	MM “Huntington disease”	45409
S6	S1 OR S2 OR S3 OR S4 OR S5	139137
S7	AB “Caregiver” OR TI “Caregiver”	198261
S8	AB “Carer” OR TI “Carer”	123127
S9	AB “family member” OR TI “family member”	9617
S10	AB “relative” OR TI “relative”	330443
S11	(MM Caregiver) OR (MM Caregiver burden)	250860
S12	S7 OR S8 OR S9 OR S10 OR S11	8922676
S13	AB” qualitative” OR TI “qualitative”	320625
S14	AB “Interview” OR TI “Interview”	405326
S15	AB “Grounded theory” OR “TI “Grounded theory”	20081

S16	AB “Phenomenological” OR TI “Phenomenology”	17612
S17	AB “Ethnography” OR TI “Ethnography”	18043
S18	AB “Content analysis” OR TI “Content analysis”	25220
S19	(MM "Qualitative research+") OR (MM "Evaluation Studies as topic+”)	2587950
S20	(MM “Grounded Theory”)	61405
S21	(MM “Interview, psychological”)	30723
S22	S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21	7511472
S23	S6 AND S12 AND S22	126