Factors that influence habitual activity in mild cognitive impairment and dementia

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Short title: Habitual activity in cognitive impairment

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Key words: Lewy bodies, Alzheimer's disease, dementia, wearables, Parkinson's disease

1. Abstract

Background: Reduced engagement with habitual activity (HA) is associated with greater risk and progression of cognitive decline and falls in older adults and people with dementia. Understanding external and intrinsic factors that affect HA may provide novel targets for non-pharmacologic interventions.

Objective: This study primarily aims to identify factors that influence HA in normal ageing and cognitive impairment, such as cognitive and motor problems and disease subtype.

Methods: 108 older adults participated in this study; 36 with cognitive impairment due to Alzheimer's Disease (AD), 30 dementia with Lewy bodies (DLB), 16 Parkinson's disease dementia (PDD) and 26 controls. A tri-axial accelerometer recorded continuous data of volume, variability and pattern of HA over seven days. Participants undertook a battery of cognitive and neuropsychological assessments.

Results: One-way analysis of variance analysis controlling for age and gender show that people with DLB and PDD engage less with HA compared to controls ($p \leq .01$), but there were no significant differences between AD and controls ($p \geq .01$). Multivariate analysis demonstrated motor disease and impairments in activities of daily living independently explained 10 - 26% of volume, variability and pattern of HA in people with cognitive impairment.

Conclusion: People with cognitive impairment have reduced HA engagement compared to controls. Motor disease and impairments in activities of daily living most strongly contribute to these findings, and may be important to consider for disease management. Wearable technology can provide a personalised picture of an individual's daily behaviours, and may be a useful tool for person-centred care.

2. Introduction

Lower levels of every-day (habitual) activities are associated with worse cognitive function [3] and wellbeing [4]. Therefore, it may be important to quantify habitual activity (HA) and target factors which influence HA when managing cognitive disorders, such as motor problems, history of falls and lack of balance confidence.

Quantification of habitual behaviours using wearable technologies provides a truer picture of a person's overall daily activity (e.g. steps per day, sum of activity counts) compared to self-report measures, and has been related to global cognitive performance [5], development of Alzheimer's disease (AD) and rate of global cognitive decline [6]. It is unclear if the presence of dementia reduces daily activity, or if reduced daily activity contributes to cognitive decline [7]. Therefore, a better understanding of the role cognition plays in facilitating daily activity in people with cognitive impairment is required.

However, total daily activity is a broad measure. Considering discrete characteristics relating to the volume, pattern and variability of HA allows a more nuanced approach to understand these data [8]. Volume refers to amount of activity such as total walking time or number of steps taken, while pattern describes length of walking bouts and the relative distribution of walking bout lengths, and variability measures the variability of bout lengths. This framework of HA allows us to understand the amount and type of activity individuals engage with, providing a novel insight into how cognitive impairment may effect a person's daily life. For example, differences in variability and pattern of walking may indicate less engagement with different types of HA and shorter bouts may reflect a more constrained environment and less time spent outside the home [9]. These novel HA characteristics have applications in the identification of frailty in older adults [10], and for the incidence and risk

of falls in different neurodegenerative disorders [11,12]. By moving beyond simply measuring total daily activity, we can provide a detailed picture of a person's functional abilities and day-to-day activity [8,12,14-16].

The majority of research into HA in dementia has simply considered volume of activity in people with cognitive impairment irrespective of disease subtype [17-21]. As of yet, factors which encourage or limit volume, variability and pattern of HA in cognitive impairment have not been identified, nor have these novel metrics been described in overarching cognitively impaired group or compared between different dementia disease subtypes, such as AD, dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD). Disease-specific differences in HA may be an important consideration for disease management and care as it may inform which disease subtypes have the greatest need for early interventions.

Therefore, this study aims move beyond the current research and describe differences in volume, pattern and variability of HA between people with cognitive impairment regardless of underlying cause and cognitively intact controls, identify factors that influence HA engagement, and consider the impact of dementia disease subtype on HA by comparing subgroups of AD, DLB and PDD. We hypothesize that (1). people with cognitive impairment of any disease subtype will engage less in HA than controls, and (2). that this will be most prominent in people with DLB and PDD as they have concurrent motor problems. We also hypothesized that (3.) volume of HA would be explained by lack of balance confidence and motor disease burden, while (4.) pattern and variability of HA will be explained by impaired cognitive functions.

3. Materials and Methods

3.1 Study participants

125 participants with probable mild cognitive impairment (MCI) and probable dementia due to AD, DLB and PD, and controls were recruited. Two independent clinicians reviewed participants' medical notes and assessments in order to verify disease diagnosis. A third clinician reviewed disagreements, providing a consensus for diagnosis. Relevant diagnostic criteria for AD, DLB and PDD [22-24] and MCI [25,26] were used; MCI due to AD and Lewy body disease (LBD) were identified as described in Donaghy, et al. [27], Thomas, et al. [28] and King, et al. [29]. Control participants of a similar age were recruited to account for effects of ageing on habitual walking behaviours.

All participants had to be over 60 years old, have capacity to consent and able to walk for two minutes, as ascertained by self-report. Participants were excluded if they had drug-induced or vascular parkinsonism, any co-existing neurological conditions or movement disorders, severe mental illness (major depression, bipolar disorder, schizophrenia), evidence of stroke affecting motor function or poor command of the English language. Controls must be cognitively intact (Mini Mental State Examination (MMSE) ≥.25), functionally independent, no diagnosis of dementia, no diagnosis of Parkinson's disease and not on any anti- dementia or Parkinson's medication.

3.2 Clinical Assessment

Age, gender, height and weight were recorded. All participants reported any falls in the last 12 months. The National Adult Reading Test (NART)[30], Cumulative Illness Rating Scale – Geriatrics (CIRS-G)[31], Movement Disorders Society Unified Parkinson's Disease Rating Scale Part III (UPDRS-III)[32], Clinical Dementia Rating Scale (CDR)[33]; Activities Balance

Confidence Scale (ABC)[34], Epworth Sleepiness Scale (ESS)[35], Geriatric Depression Scale (GDS)[36], and Bristol Activities of Daily Living Scale (BADLS) were also assessed [37].

3.3 **Cognitive assessment**

Global cognition was measured using the standardised MMSE (sMMSE) [38] and Addenbrookes Cognitive Examination III (ACE-III)[39]. The ACE-III subscales measured attention, memory, language, fluency and visuospatial function. Trail Making Task A (TMT-A) measured information processing speed [40]. The F-A-S Verbal Fluency test measured verbal fluency and executive function [41]. The simple reaction time computerised test measured attention.

3.4 **Measurement of habitual activity**

Participants were asked to wear a body-worn monitor (Axivity AX3, York, UK; dimensions 23.0 x 32.5 x 7.6 mm; weight: 11g; accuracy 20 parts per million) on their lower backs continuously for seven days. Data from the body-worn monitors was downloaded to a computer and segmented by day. Analysis was carried out using a Matlab programme. The full process from initial placement of the body-worn sensor through to data extraction and output is depicted in Figure 1. A framework of outcomes including volume, pattern and variability of walking activity were derived to aid interpretation of data [8] and are described below:

Accelerometer signals were transformed to a horizontal-vertical coordinate system and filtered with a 4^{th} order Butterworth filter at 20Hz in order to remove “noise” from the signal.

For each day, walking bouts were identified by applying selective thresholds on the magnitude of vector and the standard deviation of tri-axial acceleration signals (further detailed in [42]).

A bout is defined as any continuous period of walking. In order to enhance robustness and remain consistent with previous published findings [14,16], a minimum bout length of three consecutive steps was applied and there was no resting time threshold – if an individual stopped walking, their next three steps would be considered a new bout.

The Gaussian continuous wavelet transform of vertical acceleration was applied to smooth the data and filter out potential errors [42]. Initial contact (heel strike) and final contact (toe-off) event of the gait cycle were identified, representing a step. Total steps per bout and bout length could be calculated for each bout. Total number of bouts was calculated through identification of bouts.

3.4.1 Volume

Volume characteristics included total walk time, total steps and total bouts (individual period of walking) per day and were calculated by gathering information across all identified bouts. These were divided by number of days collected to provide average values per day.

3.4.2 Pattern

Characteristics of pattern of walking included mean length of walking bouts, and alpha. Alpha is derived by logarithmic transformation of bout density and length and is based on shape and power-law distribution [44,45]. Alpha refers to the distribution of bouts, describing the ratio of short to long walking bouts which are scaled relative to an individual's shortest walking bout. For example, a high alpha score means total walking time is made up of proportionally shorter walking bouts compared to long walking bouts.

3.4.3 Variability (S2)

Variability (S_2) refers to variability of bout length between walking bouts and was estimated using maximum likelihood technique (previously described Del Din, et al. [9],Mc Ardle, et al. [14]).This describes how widespread the data is, providing an estimation of how much an individual's bout length changed across the time period. Low variability may occur when a person engages in a low repertoire of activities, while high variability may indicate a person is engaging in a wide range of activities – driving a high variability of bout length [12,43].

<Insert Figure 1>

3.5 Data analysis

Data was assessed for normality by inspection of histograms and boxplots and the Shapiro-Wilk test. Chi-square tests were used to determine differences between groups for gender and faller status (participants with and without falls during the previous year). One-way analysis of variance analysis (ANOVAs and Kruskal Wallis tests were used to examine differences between groups ($p \leq .05$) for all demographic, cognitive and clinical variables; Fischer's Least significant difference (LSD) post-hocs and Mann Whitney U tests established where differences lay between groups in order to assess their comparability.

First, stepwise analysis of covariance (ANCOVA) assessed differences between controls and the overall cognitively impaired group for HA while controlling for age and gender. A more stringent statistical threshold of $p \leq .01$ was applied to account for multiple comparisons. Effect sizes (partial eta squared: $\boldsymbol{\eta^2}$) were calculated for key significant differences between groups. Effect sizes were interpreted according to guidelines [46]; small (.01-.06), medium (.06-.14) and large (>.14).

Following this, the relationships between HA and outcomes representing personal, cognitive, motor and mood characteristics were explored separately in controls and the cognitively impaired group using univariate regression. Only univariate regressions were considered in the control group due to the small sample size; however, significant explanatory variables were further explored in the cognitively impaired group through multivariate backwards stepwise regression. There was no cut off-applied for statistical significance and it was set to $p \leq .05$.

Finally, stepwise ANCOVA assessed differences in HA between people with AD, DLB and PDD and controls ($p \leq .01$) to address the impact of dementia disease subtype on HA engagement. Effect sizes (η^2) were calculated between groups for significant differences. Associations between personal, cognitive and motor outcomes with HA were examined in each dementia disease subtype using Spearman Rho correlations, in order to further explore disease-specific influences on HA.

4. Results

4.1 Demographics

Seventeen patients were excluded from this analysis due to withdrawal from the study (n=2), clinical diagnosis other than AD and LBD (n = 11), problems with data upload (n=2), monitor lost in the post (n=1) and refusal to wear the sensor (n=1). This left 108 participants; 82 with cognitive impairment (36 AD, 30 DLB and 16 PDD) and 26 controls. Five participants had less than seven days data collected due to hospitalisation (n = 1), discomfort (n = 1) and quality checks (n = 3). Participants were still included as data is reported as measures per day and all participants had over three days data collected; 3 - 7 days data collection is the current standard of free-living gait analysis [47].

Participants in the disease groups ranged from MCI to moderate dementia, but groups were primarily composed of mild dementia cases (see Table 1 for all clinical and demographic information). There were no significant differences for any macro gait characteristics between the MCI and dementia groups within each subtype; therefore, it was deemed feasible to include both stages of disease in each group (see Supplementary Table 1).

<Insert Table 1>

4.2 Differences in habitual activity in cognitive impairment and normal ageing

Volume: People with cognitive impairment spent significantly less time walking and took less steps per day compared to controls (see Table 2).

Pattern: People with cognitive impairment took significantly shorter walking bouts compared to controls. The distribution of their walking bouts demonstrated trends towards a greater proportion of short walking bouts compared to long (higher alpha score).

Variability: People with cognitive impairment demonstrated less variability for bout lengths compared to controls.

<Insert Table 2>

4.3 Factors that influence habitual activity in normal ageing and cognitive impairment

The significant univariate associations between HA characteristics and possible contributing factors (e.g. demographics, motor disease, cognition, balance confidence, impairments in activities of daily living) are summarised in Table 3 for the control group, and Table 4 for the

cognitively impaired group. All univariate regressions reported in Supplementary Table 2 for the control group and in Supplementary Table 3 for the cognitively impaired group.

<Insert Table 3>

<Insert Table 4>

4.3.1 Volume

In the cognitively impaired group, all volume characteristics were explained by greater motor disease severity and greater impairments in activities of daily living (ADLs), explaining 26.1% of the variance in time spent walking; 20.8% of the variance for steps taken and 17.1% of the variance for bouts taken per day (see Table 4). Motor disease severity demonstrated moderate-strong negative associations with time spent walking, steps and bouts per day in all disease subtypes (see Supplementary Table 4, 5 and 6).

Volume of HA (walk time per day, steps per day and bouts per day) was not significantly explained by any of the considered factors in the control group.

4.3.2 Pattern

In the cognitively impaired group, shorter bout lengths were greater motor disease severity, accounting for 9% of the variance (see Table 4). Higher alpha scores were explained by greater motor disease severity, and greater verbal fluency impairment demonstrated similar trends – this model explained 8.9% of the variance.

Shorter bout length was explained by greater attentional impairment (13.9 % of variance) and being female (26.5% of variance; see Table 3), while higher alpha scores were explained by being female (19.1% of variance) and older age (16.2% of variance) in controls.

4.3.3 Variability

In the cognitively impaired group, greater variability of bout length was explained by incidence of a fall within the previous year and greater balance confidence, accounting for 12.5% of the variance (see Table 4).

In the control group, less variability of bout length was explained by being female (22.5% of variance), greater attentional impairment (17.3% of variance) and slower information processing (11.6% of variance; Table 3).

4.4 The impact of disease subtype on habitual activity in people with cognitive impairment

Volume: People with DLB ($p = .003$; $\eta^2 = .161$) and PDD walked significantly less ($p = .002$; $\eta^2 = .239$)) and took less steps per day (DLB: $p = .002$, $\eta^2 = .178$; PDD: $p = .002$, $\eta^2 = .241$) compared to controls. There were no significant differences between any groups for number of bouts taken per day ($p \geq .01$), or between AD and controls or DLB for any characteristics ($p \geq .01$).

Pattern: The PDD group had a higher alpha score compared to controls ($p \leq .001$, η^2; $= .356$), AD ($p \leq .001$, $\eta^2 = .307$) and DLB ($p = .009$, $\eta^2 = .156$) see Table 2 and Figure 2) and took shorter walking bouts ($p = .003$, $\eta^2 = .174$) compared to the AD group. People with DLB ($p \leq .001$, $\eta^2 = .287$) and PDD ($p \leq .001$, $\eta^2 = .366$) also took shorter walking bouts compared to controls. There were no significant differences between AD and controls or DLB ($p \geq .01$).

Variability: People with PDD ($p \leq .001$, η^2 .366) and DLB ($p \leq .001$, $\eta^2 = .188$) were less variable in their walking bout lengths compared to controls. People with PDD were also less

variable ($p \leq .001$, $\eta^2 = .206$) compared to the AD group. There were no significant differences between AD and controls or DLB ($p \geq .01$).

<Insert Figure 2>

5. Discussion

The aim of this study was to compare HA between normal ageing and cognitive impairment, consider factors that influence HA, and explore the impact of dementia disease subtype on HA. Key findings suggest that people with cognitive impairment have lower volume, impaired patterns and less variability of HA compared to normal ageing, and this appears most prominent in people with DLB and PDD. The factors which influenced HA differed between cognitively-intact and cognitively impaired older adults.

5.1 Factors that influence habitual activity in normal ageing

This study has provided a novel overview of the differences in HA between cognitively-intact older adults and people with cognitive impairment as it goes beyond simply reporting step counts and overall activity [48]. Fitting with Hypothesis 1, cognitively-intact older adults have a greater volume and variability of HA and take proportionally more longer walking bouts compared to people with cognitive impairment. This suggests that people with cognitive impairment are less likely to engage in a variety of activities, such as housework and social calls, and may be more likely to stay within their own homes. Future research is required to provide context to these HA metrics and by doing so, allow wearable technology to provide detailed pictures of an individual's day-to-day function. This may improve our understanding of the impact of cognitive impairment on daily living and support the development of improved methods for disease management.

The influential factors of HA were different between normal ageing and cognitive impairment. In normal ageing, gender, age and cognition played a prominent role in variability and pattern of HA. The role of gender is consistent with previous literature, indicating that the distribution of bout lengths reflect traditional gender roles found in the older population [49]. Interestingly, gender did not contribute to HA engagement in people with cognitive impairment, which may be due to reduced ability to perform tasks traditionally associated with gender roles, and increased dependency and need for care. Future work should strive to look at this interaction in larger samples and consider the interaction between activity of the individual with cognitive impairment and their caregiver. By doing so, we may gain a unique insight into the loss of independence and evolution of caregiving in these populations.

Less variability and impaired pattern of HA was explained by subtle impairments in information processing and attention in controls. This may reflect limited abilities to engage cognitively with different kinds of activities in the home and community. This partially supports Hypothesis 4, however, impairments in cognitive functions did not independently contribute to the explanatory models for HA in the cognitive impairment group. Lower habitual activity has previously been associated with greater progression and risk of cognitive decline in older adults [5,6], suggesting that cognitive function plays an important role in HA engagement. However, people with cognitive impairment have a multitude of other factors which influence HA, reflecting the multi-factorial nature of MCI and dementia, and these may be more prominently associated with lower levels of HA once cognitive impairment is established. This study identified these potential factors as motor disease, impairments in activities of daily living and dementia disease subtype.

5.2 Factors that influence of habitual activity in cognitive impairment

Lower volume and impaired pattern of HA in people with cognitive impairment were strongly explained by greater motor disease severity. This somewhat supports Hypothesis 3 and previous literature in PD [8]. This relationship has not only been found in the combined cognitive impairment group; associations have similarly been found in AD, DLB and PDD when considered discretely (see Supplementary Tables 4, 5, 6). This highlights the importance of considering motor problems in treatment protocols for MCI and dementia, regardless of disease subtype. Cognitive impairment and motor problems are often considered separately in clinical practice and may therefore be neglected in individuals without visually observable motor symptoms – such as people with AD. It is also important to note that dementia disease subtypes with concurrent motor disease, such as DLB and PDD, engage less with HA compared to controls and people with AD – confirming Hypothesis 2. As motor disease may affect functional independence [50], physical interventions and advice for HA maintenance should be implemented soon after symptoms of DLB and PDD are recognised [51]. In addition to improving functional independence, this would have added benefit to well-being, mood and cognitive function [52-54].

In addition to motor disease, lower volume of HA was also explained independently by greater impairments in ADLs, which can be considered a measure of functional independence [55]. Future research should investigate if quantifying HA could act as an objective proxy marker for assessing functional independence – reducing patient burden and reliance on self-reported subjective measures, along with allowing us to explore discrepancies between objective measurements and subjective perceptions of daily living. Tailored management of ADLs, such as providing unobtrusive aids and supervision of activities [55,56], may promote

functional independence and increase or maintain HA – wearable technology could capture such outcomes [57].

5.3 **Limitations in our understanding and interpretation of free-living data**

The explanatory models of HA described in this study only explain a small amount of variance, and it is important to note there are a broad range of potential influential factors which encourage or limit HA engagement. Specific health conditions, apathy and depression, fatigue, loss of dependence, caregiver burden and health, lack of access to transportation, bad weather and environmental constraints may all act as barriers to engaging in habitual walking activities [58]. van Alphen, et al. [58] suggested that there are a range of motivators and facilitators for people with cognitive impairment to engage in activity, including dog ownership, social activities and routine.

The large range of HA in this study (see Figure 2) highlights the impact of different limiting or encouraging factors on HA. For example, the lowest volume of HA (20 minutes per day) was taken by 83 year old woman with PDD. She preferred short walking bouts (alpha: 2.04) and reported only feeling safe walking with her husband (ABC: 25/100). Her husband had taken over all household task traditionally delegated to her (BADLS: 13/60). The presence of motor disease, loss of independence, high levels of caregiving and lack of confidence in walking independently may all have influenced low engagement with HA and preference for short bouts. In contrast, the highest volume of HA (373 minutes per day) was taken by a 78 year-old man diagnosed with MCI due to LB. He reported being an active member of a walking club that meets regularly. He also had motor disease, but was confident in his balance (ABC: 98/100), functionally independent and motivated to engage in social and community-based activities.

These case studies simply highlight that one size does not fit all. Individuals have a range of personal, interpersonal, environmental, cultural and social factors that influence their engagement in behavioural activities such as walking. This must be recognised when interpreting snapshots of ambulatory activity. Free-living data is complex, personal and highly variable. Therefore, monitoring individual trajectories of change within free-living behaviours may be more clinically useful than applying thresholds of "at-risk" behaviour [59].

5.4 Considerations and implications for clinical practice

This research has direct application towards patient-centred care. Firstly, it demonstrates that the presence of MCI or dementia is not the only reason for reduced HA. Motor disease and reduced engagement with ADLs both additionally may influence lower levels of HA, and may be addressed through interventions, such as physical or occupational therapy [60] and supervision of tasks rather than direct care [56]. Additionally, future research should consider how cognition may be facilitating associations between HA, motor disease and ADLs.

Secondly, this study has demonstrated feasibility for continuously monitoring HA in different dementia disease subtypes with wearable technology. It allows us to describe more than just volume of HA, providing a detailed insight into how cognitive impairment affects a person's daily life. There is growing interest in the health industry for the use of wearable technology for improving personalised care, and monitoring disease progression and intervention efficacy [47,61-65]. In addition to providing personalised pictures of daily activity, it allows us to examine under-served areas and move beyond the need for well-controlled environments to assess models of "best-practice" [64], reducing observer bias and allowing inclusion of populations with high functional impairments. Future research should therefore use wearable technology to investigate factors that influence HA in different stages of

cognitive impairment, and in different care settings to understand how different circumstances contribute to HA engagement.

5.5 Limitations

Although this study provided novel evidence for the impact of disease subtype, cognition, functional independence and motor disease on HA, along with the feasibility of wearable technology to provide a holistic picture of habitual behaviour, it has several limitations. As it was a single centre study with a limited catchment area, a small but well-defined sample was recruited – multi-centre studies are required to boost participant numbers. The small sample size meant we considered a spectrum of cognitive impairment to improve statistical power, and did not consider disease-specific factors that influence HA in discrete dementia disease subtypes. Larger samples are therefore required to understand impact of dementia severity, and to understand disease-specific influencers of HA. Although the benefit of using wearable technology is their unobtrusive nature, no questionnaires were administered regarding daily activities or caregiver burden – this limited interpretation of results to that known in the literature and anecdotal evidence from participants. Finally, it is important to be cautious interpreting comparisons between older people with cognitive impairment and similarly-aged controls; despite detailed cognitive testing and a consensus approach to the diagnosis and categorisation of participants in this study, individuals in "prodromal" stages of MCI and dementia are difficult to detect, and may be included in control cohorts in ageing studies.

5.6 Conclusion

In conclusion, people with cognitive impairment engage less in HA compared to cognitively-intact older adults; however, impairments in cognitive functions are not the only influential factors of HA in people with MCI and dementia. Motor disease and impairments in activities

of daily living most strongly contribute to lack of HA engagement; physical and occupational interventions may therefore be useful for facilitating HA and preserving functional independence [60]. These interventions may need to implemented earlier in DLB and PDD compared to AD, but should still be a primary aim in clinical practice [51]. Wearable technology can provide a novel personalised method to measure HA in cognitively impaired populations, and may be a useful objective tool for monitoring disease progression and loss of independence. Future work is required to understand how disease severity and care settings can affect engagement with HA in people with MCI and dementia.

6. Statements

6.1 Acknowledgements

The research team acknowledges the support of the National Institute for Health Research Clinical Research Network (NIHR CRN) with the recruitment of participants, and is grateful to all the participants who took part in this study.

6.2 Statement of ethics

This study was approved by the NHS Local Research Ethics Committee, Newcastle and North Tyneside. Reference: 16/NE/005, IRAS project ID: 192941.

6.3 Disclosure statement

The authors have no conflicts of interest to declare.

6.4 Funding sources

This work is supported by the Alzheimer's Society [ADSTC2014007], Alzheimer's Research UK [ARUK-PG2015-13] and the National Institute for Health Research (NIHR) Newcastle

Biomedical Research Unit and Newcastle Biomedical Research Centre based at Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University [BH152398/PD0617]. The NIHR Clinical Research Facility provided a platform to carry out this study. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

6.5 Author contributions

RMA: Study design, acquisition of data, statistical analysis, interpretation of data, drafting and critical revision of manuscript for important intellectual content.

SDD: Data processing, critical revision of manuscript for important intellectual content

PD: Clinical diagnosis of participants, critical revision of manuscript for important intellectual content.

BG: Statistical analysis, interpretation of data, critical revision of manuscript for important intellectual content.

AT: Clinical diagnosis, interpretation of data, critical revision of manuscript for important intellectual content.

LR: Study concept and design, interpretation of data, critical revision of manuscript for important intellectual content

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